STATE OF NORTH CAROLINA **Department of State Treasurer** NC State Health Plan for Teachers and State Employees	**REQUEST FOR INFORMATION NO.** 270-20240419GLP Due Date: May 31, 2024, 2:00 PM ET
Refer ALL Inquiries to: Kimberly Alston, Contracting Agent	Issue Date: April 19, 2024 Commodity: 851017 Health Administration Services
E-Mail: Kimberly.Alston@nctreasurer.com with a copy to SHPContracting@nctreasurer.com	Using Agency Name: NC State Health Plan for Teachers and State Employees

MAILING INSTRUCTIONS: Respondents shall submit one (1) signed, original paper response, and one (1) electronic copy on a flash drive and one (1) redacted electronic copy on a flash drive, if applicable pursuant to Section 3.0.D. The address label shall clearly note the RFI number as shown below. It is the responsibility of the submitting entity to have the RFI in this office by the specified time and date of opening.

DELIVERY ADDRESS
RFI NO. 270-20240419GLP NC Department of State Treasurer State Health Plan Division Attn: Kimberly Alston, Contracting Agent 3200 Atlantic Avenue, Raleigh, NC 27604

NOTICE TO RESPONDENTS

Responses to this RFI will be received at the address above until May 31, 2024, 2:00 PM ET.

QUESTIONS

Email written questions no later than April 30, 2024, 5:00 PM ET to Kimberly.Alston@nctreasurer.com with a copy to SHPContracting@nctreasurer.com.

EXECUTION

RESPONDENT NAME: Virta Medical PC	E-MAIL: Ryan.andrews@virtahealth.com	
STREET ADDRESS: 655 Montgomery St Suite 810	P.O. BOX:	ZIP: 94111
CITY & STATE: San Francisco, California	TELEPHONE NUMBER: 401-644-8157	TOLL FREE TEL. NO:
TYPE OR PRINT NAME & TITLE OF PERSON SIGNING: Ryan Andrews, Head of Public Sector	FAX NUMBER:	
AUTHORIZED SIGNATURE:	DATE: 5/21/2024	

1.0 EXECUTIVE SUMMARY

The North Carolina State Health Plan for Teachers and State Employees ("Plan"), a division of the North Carolina Department of State Treasurer, provides health care coverage to more than 740,000 teachers and school personnel, State Employees, retirees, current and former lawmakers, state university and community college personnel, and their dependents. The mission of the State Health Plan is to improve the health and health care of North Carolina teachers, State Employees, retirees, and their dependents, in a financially sustainable manner, thereby serving as a model to the people of North Carolina for improving their health and well-being.

2.0 PURPOSE AND OBJECTIVES OF THE REQUST FOR INFORMATION

The Plan's net spend on glucagon-like peptides (GLP-1s) and gastric inhibitory polypeptide (GIP) agonists for weight loss exceeded $100 million in 2023 and was projected to exceed $170 million in 2024. In order to limit this financially unsustainable expense, the Board of Trustees for the State Health Plan for Teachers and State Employees ended coverage of GLP-1s, GIP-GLP-1 agonists and other similar molecular entities used for weight loss as a benefit effective April 1, 2024.

The Board further directed Plan staff to explore options that may allow members who need these medications the most to obtain them, informed by medical necessity and long-term cost effectiveness, under a fiscally sustainable model, budgeted over at least the next five years. To that end, the Plan is issuing this Request for Information (RFI) to gather ideas and solutions from the marketplace.

This RFI is intended to collect information, recommendations, and potential solutions for the Plan to consider respecting the feasibility of providing benefit coverage to Plan members to use GLP-1, GIP-GLP-1 agonists, and other similar new molecular entities, for the purpose of weight loss in a manner that is financially sustainable for the Plan.

The Plan is seeking responses outlining detailed solutions that would address the following:

A. Permit the Plan to provide benefit coverage to Plan members to use GLP-1, GIP-GLP-1 agonists, and other similar new molecular entities, for the purpose of weight loss.

B. Establish a pricing framework that would permit the Plan to provide such benefit coverage in a fiscally responsible manner in order to maintain financial sustainability. For example, the Plan seeks the ability to:

    1. Pay for varying percentages of the unit cost according to medical necessity considerations.
    2. Receive the same effective net price if the Plan only choses to pay for a medication for an additional FDA indication without paying for it for all other indications.
    3. Audit claims, rebates, and prior authorizations for accuracy and compliance with applicable laws and regulations.

C. Potential for establishing a program outlining certain eligibility requirements, parameters, or other prerequisites for Plan members to follow in order to receive benefit coverage of GLP-1, GIP-GLP-1 agonists, and other similar new molecular entities, for weight loss. As a result, the Plan seeks the ability to:

1. Require that an approved weight loss program or nutrition classes be completed before approval of payment for the medication.
2. Develop step therapies involving lower cost medications.
3. Require that medications be prescribed by a practitioner with appropriate levels of expertise.
4. Prohibit Body mass index (BMI) measurements from being estimated via telehealth visit to ensure accuracy and accountability, while enabling a data collection process that supports the successful implementation of the benefit.

D. Potential for establishing a program wherein the Plan has the flexibility to establish parameters for utilization management of GLP-1, GIP-GLP-1 agonists, and other similar new molecular entities for weight loss, which may include considerations such as, but not limited to:

1. BMI;
2. Current weight;
3. Documented history of lifestyle modifications, which may include reduced calorie intake and increased physical activity;
4. Documented enrollment and measurable participation in other nutritional or dietary programs;
5. Consideration of evidence for one or more comorbid conditions or other obesity-related medical conditions;
6. Data analytics and reporting tools supporting successful claims adjudication and program evaluation;
7. Requirements for in-person treatment visits to verify efficacy of medications for individuals; or
8. Any other considerations or parameters that would support a program to achieve the Plan's objectives of serving the members who need these medications the most.

E. Provide cost, price structures, or other relevant expense information related to the recommendations and potential solutions submitted.

3.0 RFI PROCEDURES

A. Schedule

Responses must be received by the date, time and the location specified on the cover sheet of this RFI. Respondents may be requested to present and discuss their submissions at the Plan's offices in-person or remotely. If the Plan requests such a presentation, respondents will be notified of the specific date and time at least two weeks in advance of any presentation.

B. Clarification Questions

Clarification questions will be accepted until April 30, 2024, 5:00 PM ET as specified on the cover sheet of this RFI (the "Clarification Period"). All questions must be submitted in writing. Responses to all questions received shall be addressed and issued as an addendum to this RFI. During the Clarification Period, respondents are strongly encouraged to raise any and all

questions or concerns about the RFI. Any questions or concerns not raised during this period are considered waived by the respondent.

Question submittals should include a reference to the applicable RFI section and be submitted in the format shown below:

No.	Reference	Respondent Question
1.	RFI Section, Page Number	Respondent Question . . . ?

C. Response

The Plan recognizes that considerable effort will be required in preparing a response to this RFI. However, please note this is a request for information only, and not a request for services. The respondent shall bear all costs for preparing this RFI. **Under no circumstances will any documents, information, recommendations, or potential solutions submitted in response to this RFI, or any communications between the Plan and a respondent, create a binding agreement or contract, or expectation thereof, between the Plan and respondent or between the State of North Carolina and respondent.**

1. Content and Format

The Plan expects a comprehensive, detailed explanation of the workings of each component of the response. Each component of the response will explain how it will operate to address the needs and objectives of the Plan as identified in Section 2.0. The Plan is not interested in brochures or "boilerplate" responses. Instead, responses should clearly define how the proposed solution(s) would meet the Plan's needs. Any issues or exceptions to the Plan's requirements should also be identified and explained.

The response may include charts, graphs, or other visuals that assist in demonstrating how a component of a response operates or how that component would meet the Plan's objectives.

A comprehensive, detailed equipment list including software, applications and other information technology components required for the proposed solution should be provided. The Plan is not interested in participating in any field trials of new equipment or software.

The response should define all services that would be required by the proposed solution. The response should also include:

- The respondent's understanding of the project and services by addressing the Plan's objectives; and
- An estimated total cost of ownership for the solution including continued compliance with emerging industry standards.

2. Multiple Responses

Multiple responses, or alternative individual solutions will be accepted from a single respondent provided that each response is comprehensive, meets all of the Plan's requirements, and is truly unique. If submitting multiple responses, place each response in a separate envelope and clearly mark responses as "Response #1, Response #2, etc.

D. Confidentiality

Responses obtained by the Plan under this RFI and items derived therefrom are subject to the State Public Records Act, Chapter 132 of the North Carolina General Statutes (the "SPRA").

If a response contains any proprietary or confidential information protected from public disclosure under the SPRA, the respondent shall submit a redacted electronic copy on a flash drive to the Plan with its response. Any proprietary or confidential information under the SPRA must be clearly redacted by the respondent in black markings fully covering and obscuring such information within the redacted electronic copy of the RFI response. By submitting a redacted electronic copy, respondent warrants that it has a good faith opinion that the redacted information in fact meet the requirements of the SPRA and the SPRA prevents their public disclosure. Blanket assertions of confidentiality are not permitted.

In the Plan's unfettered discretion and without notification to any respondent, the Plan may post any responses obtained by the Plan under this RFI, and items derived therefrom, on the Plan's public website (www.shpnc.org). In posting such items to the Plan's website, the Plan will post the redacted version of such items, if respondent has provided redactions in compliance with this section. If no redacted version of such items has been provided to the Plan in compliance with this section, the Plan will post such items on the Plan's website in the manner they were provided to the Plan.

Redacted copies provided by respondents to the Plan may be released in response to SPRA requests without notification to the respondent. Further, respondent's information that cannot be shown to be prohibited from disclosure by the SPRA may be subject to public disclosure under the terms of the SPRA.

If a legal action is brought to compel the Plan to disclose any of the respondent's redacted information, the Plan will notify the respondent of such action and consent to intervention of the respondent in the action and to the respondent's defense of the confidential status of the redacted information. In such legal action, the duty and responsibility to defend such information shall solely be the respondent's, and the Plan shall have no liability to the respondent for the Plan's failure to defend such action.

E. Respondent Materials

All responses, inquiries, or correspondence relating to or referenced in this RFI, and all documentation submitted by the various respondents shall become the property of the Plan when received. Ideas, approaches, information, recommendations, potential solutions, and options (but not proprietary material) presented by respondents may be used in whole or in part by the Plan in developing a future solicitation, should the Plan decide to proceed with a solicitation. Further, combinations of various responses from respondents may also become part of a solicitation, based on the needs of the Plan.

REQUEST FOR INFORMATION NUMBER:270-20240419GLP
ADDENDUM NUMBER:1

REQUEST FOR INFORMATION (RFI) ADDENDUM

Issuing Agency:	North Carolina State Health Plan for Teachers and State Employees
RFI Number:	270-20240419GLP
RFI Description:	GLP-1 Solutions
RFI Opening Date and Time:	May 31, 2024, 2:00 PM ET
Addendum Number:	1
Addendum Date:	May 6, 2024
Purchasing Agent:	Kimberly Alston

FAILURE TO RETURN THIS ENTIRE ADDENDUM MAY SUBJECT YOUR RESPONSE TO REJECTION.

1. Addendum Number 1 is in response to questions submitted. Responses to questions begin on the next page.

2. Return one signed copy of this Addendum with your RFI response.

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Execute Addendum Number 1, RFI Number 270-20240419GLP:

Respondent: Virta Medical PC

Authorized Signature: _____

Name and Title (Print): Ryan Andrews

Head of Public Sector

Date: 5/21/2024

Question #	Document Section	Respondent Question	State's Response
1	General	Since [Our Business] and the procedure of endoscopic sleeve gastroplasty (ESG) isn't a GLP-1 or manufacturer, what is your suggestion for us re: the RFI? We believe that ESG would be an excellent option for the NCSHP to consider.	Pursuant to RFI Section 3.0 C. 2. "Multiple Responses," the Plan requests that you submit any information, potential solutions, or alternatives relevant to the matter of weight loss benefits/solutions, for the Plan's review and consideration as a response to the RFI.
2	General	What is the timeline for a potential decision? What is the desired go-live date?	This is a request for information only, and not a request for services. There is not a set timeline for any decisions. In the Plan's sole discretion, the Plan may take any feasible and financially sound steps to address the fiscal issues of coverage for GLP-1 and GIP-GLP-1 agonists for weight loss, including other potential weight loss alternatives for Plan members.
3	General	Who is North Carolina State Health Plan for Teachers and State Employees pharmacy benefit manager? Is RX carved in or out of the health plan?	The Plan's Pharmacy Benefit Manager (PBM) is CVS Caremark. Pharmacy is carved out from the medical benefit. The Plan's current third-party administrator is Blue Cross Blue Shield of North Carolina.
4	Section 1.0, Page 2	Is there a current vendor providing these services? If so, how may I obtain copies of any incumbent contract documents?	The Plan discontinued coverage for GLP-1s, GIP-GLP-1 agonists, and other similar new molecular entities, for the purpose of weight loss effective April 1, 2024. These benefits were provided through the Plan's PBM Contract. No current vendor provides services that includes these molecular entities as a covered benefit for weight loss. The Plan follows the provisions of the North Carolina Public Records Act for public documents with requests submitted to PublicRecords@nctreasurer.com.
5	Section 2.0, Page 2	Who/what type of physician was prescribing the majority weight loss drugs?	There were no limitations on the type of provider with prescribing authority that can prescribe these medications. That is true for all medications. The requirement is only that the member have a valid prescription and meet the utilization management requirements (if applicable).
6	Section 2.0, Page 2	If this RFI greenlights a solicitation, what is the estimated time frame for procurement?	This is a request for information only, and not a request for services. There is not a set timeline for any decisions. In the Plan's sole discretion, the Plan may take any feasible and financially sound steps to address the fiscal issues of coverage for GLP-1 and GIP-GLP-1 agonists for weight loss, including other potential weight loss alternatives for Plan members.

Question #	Document Section	Respondent Question	State's Response
7	Section 2.0, Page 2	What is the anticipated contract value?	This is a request for information only, and not a request for services. We do not have an anticipated contract value at this time.
8	Section 2.0, Page 2	What is the number of patients who were taking GLP-1 and GIPs for weight loss in 2023? What is the estimated growth year over year? Goals for the program for the next 5 years?	There were approximately 24,750 utilizers in calendar year 2023. The estimated growth year over year is 51.2% in 2024; 28.6% in 2025 and 14.8% in 2026. The Plan's goal is to have a solution in place that permits benefit coverage for Plan Members in a financially sustainable manner.
9	Section 2.0 B.1., Page 2	B. Establish a pricing framework that would permit the Plan to provide such benefit coverage in a fiscally responsible manner in order to maintain financial sustainability. For example, the Plan seeks the ability to: 1. Pay for varying percentages of the unit cost according to medical necessity considerations. Can you please elaborate on what this is referring to (i.e., GLP-1)?	Under this cost model, the member's cost share for the medication would vary based on need. For example, a member with a lower BMI and no chronic conditions would have a higher cost share than someone with a BMI of 40 and multiple comorbidities.
10	Section 2.0 B., Page 2	Is there a list of medications that ideally would be included for weight loss? Will the state consider "off-label" prescriptions i.e., Ozempic for weight loss instead of Wegovy or Moujaro instead of Zepbound? Is the state open to alternative options such as sterile compounding for these medications while they're on the FDA shortage list?	The specific brand names may expand over time but currently include Saxenda, Wegovy, and Zepbound. The Plan is aware of the possibility for off label use by prescribers and have put specific utilization management guidelines in place to avoid this. The Plan is not interested in off labeled use of a GLP-1, GIP-GLP-1 agonist FDA approved for diabetes (Ozempic, Mounjaro, etc) within our current PBM framework. Consequently, any off labeled use would have to be fully separate from the existing pharmacy benefit administrative processes. The Plan is open to reviewing all legal, feasible, and fiscally sound solutions. Any solution would have to be structured such that it would be administratively feasible.

Question #	Document Section	Respondent Question	State's Response
11	Section 2.0 C., Page 2	What were the specific parameters for coverage for GLP-1 and GIPs for weight loss before they were removed from the plan? Is there any data from when the meds were covered on efficacy of certain programs or requirements?	The Plan was using the standard utilization management guidelines for the GLP-1 and GIP-GLP-1s for weight loss provided by our PBM (CVS Caremark). This included a prior authorization in line with FDA approved BMI criteria, participation in a comprehensive weight management program for at least 6 months prior to using drug therapy, and quantity limits. Prior to 1/1/2024 this prior authorization permitted attestation from providers and did not require documentation. CVS Caremark updated the standard UM beginning 1/1/2024. This update requires documentation of BMI and comorbid conditions (if applicable). However, the update does not require documentation for participation in a weight management program - CVS permits an attestation. Grandfathered members eligible after 1/1/2024 that had prior authorizations due between 1/1/2024-4/1/2024 were subject to these new guidelines.
12	Section 2.0 C.1., Pages 2 and 3	Would group sessions, virtual coaching or webinar format be allowable for lifestyle coaching options? Will you allow any health coaches who are not certified NBC-HW? (National board-certified health wellness)	Pursuant to RFI Section 3.0 C. 2. "Multiple Responses," the Plan is open to reviewing all alternatives and potential solutions.
13	Section 2.0 C.4., Page 3	Please explain the prohibition on BMI measurements via telehealth. Given the rural nature of North Carolina, in person measurement requirement is likely a very large barrier to care.	The Plan begins within a frame of reference that a provider should meet with the patient to assess BMI and clinical necessity. However, solutions that meet the objective of ensuring an accurate and medically appropriate diagnosis and include components to subsequently ensure correct measurements that maintain accountability for continuation of therapy would be welcomed.
14	Section 2.0 D.1., Page 3	Is a waist to height or waist to hip ratio acceptable in lieu of BMI for program qualification?	The Plan prefers to use BMI for program qualifications if for no other reason than it is used by the FDA for indication, but the Plan would be open to multiple measures that represent alternative thinking.

Question #	Document Section	Respondent Question	State's Response
15	Section 2.0 D.3., Page 3	Are there any specific qualifications or components required for the weight loss lifestyle management?	There are on specific requirements, but documentation of participation and completion will be required. Attestations will not be sufficient.
16	Section 2.0 E., Page 3	What are the determinants of the program decision in terms of weighted value? -Price -Patient experience -Overall value -Small business/Local NC business	There are no set determinants for making program decisions at this time. The Plan will review all submissions for feasibility and achieving the Plan's fiscal goals solutions.

virta

1.0 Executive Summary

Virta is the leading virtual clinic for reversing metabolic disease no matter where a member is on the spectrum of metabolic health (overweight, obese, prediabetic or type 2 diabetic). Members with metabolic disease have carbohydrate intolerance and insulin resistance- Virta addresses the root case of metabolic disease through personalized nutrition therapy paired with advanced telehealth. Virta focuses on lasting behavior change and safe medication deprescription inclusive of GLP-1s and GIP agonists (weight loss drugs). Virta has clinicians licensed in all 50 states and every member has a Virta clinician watching over them, deprescribing medications in real time as clinically appropriate. Virta's telehealth model uses continuous remote monitoring—we provide members with everything they need to be successful in our treatment, a connected blood glucose and ketone monitor, connected scale, blood pressure cuff, strips, lancets, alcohol pads and more.

Our members watch in disbelief as their blood sugar stabilizes, their ketones rise and they start shedding weight immediately after making nutritional changes. All aspects of Virta are personalized to each member based on their food preferences, aversions, religious restrictions, budget and holistic personal situation. Our members interact with their Virta team two to three times per day over the first three months, and almost daily after that. Virta has shown the same clinical outcomes across all racial and ethnic boundaries and socioeconomic status (Health Equity Attachments 1-3). At two years Virta showed 12% sustained weight loss from baseline weight. Virta has also found that the majority of members, when educated about GLP-1s opt for a drug free alternative, NOT GLP-1 drugs.

Virta released the first clinical study of its kind (attachments Sustained weight loss and GLP-1s and Virta in the GLP-1 folder) where members came into Virta already on a GLP-1 drug, and presumably already experiencing weight loss. Then they started Virta and lost another 13.6% of their body weight. Subsequently, through shared decision making (member and Virta clinician), we eliminated GLP-1 drugs for members. Unlike the GLP-1 clinical trials where we would expect to see regain of the majority weight lost in the next 12 months, our members were still 12.7% below their baseline weight (when they entered Virta) at 6 months post GLP-1 elimination and still 12.1% below their Virta baseline weight 12 months post GLP-1 elimination.

Virta is pleased to present our response to the North Carolina State Health Plan for Teachers and State Employees ("Plan") RFI below. For your convenience, Virta has numbered sections corresponding to the RFI to address each point in section 2.0.

virta

2.0 Needs and Objectives

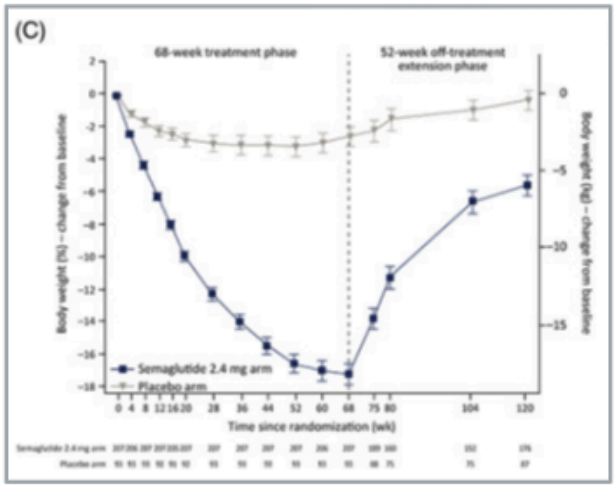
From the Plan's narrative provided in RFI 270-20240419GLP it is clear that the Plan is balancing the cost of covering GLP-1s and GIP agonists for weight loss versus the clinical outcomes members achieve and the long-term sustainability of those outcomes.

Virta has over 10 years of experience deprescribing GLP-1s in the context of type 2 diabetes reversal and weight loss. Our members have found, when educated about GLP-1s and GIP agonists, more than half of members seek out a drug-free alternative instead. Additionally, Virta published the first of its kind peer reviewed research showing that when GLP-1s are paired with Virta's lifestyle intervention, members sustain weight loss 12 months after removing the GLP-1.

The illustration below shows members coming into Virta already on a GLP-1 (and presumably having already lost weight). Then members start Virta and lose an additional 13.6% of their body weight. Through shared decision making with their Virta clinician, the member stops the GLP-1- the interesting thing is that rather than a member experiencing weight regain (the dotted red line- most studies show at least ⅔ of any weight loss is regained 12 months after stopping GLP-1s & GIP agonists) -

After GLP-1 tapers off, weight regain occurs

STEP 1 trial results



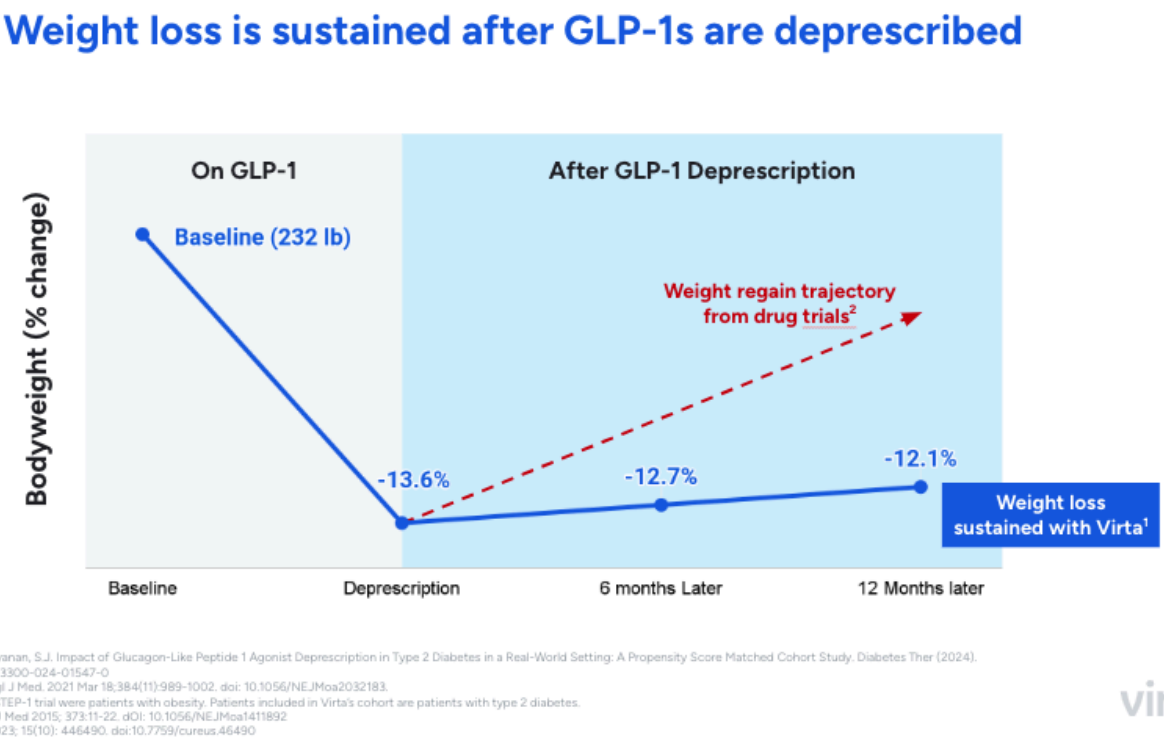
Even after patients follow strict calorie restriction and exercise, most experience a steep regression in outcomes: [1]

- **65%** of weight lost is regained
- **80%** decline in blood sugar improvements

1 Wilding JPH, Batterham RL, Davies M, et al. Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension. Diabetes Obes Metab. 2022;24(8):1553-1564.

through Virta's lasting personalized nutritional therapy that addresses the root cause of

metabolic disease, the member sustains their weight loss 12 months after stopping the GLP-1 (still 12.1% below their baseline when entering Virta).



1 McKenzie, A.L., Athinarayanan, S.J. Impact of Glucagon-Like Peptide 1 Agonist Deprescription in Type 2 Diabetes in a Real-World Setting: A Propensity Score Matched Cohort Study. Diabetes Ther (2024). https://doi.org/10.1007/s13300-024-01547-0
2 Wilding JPH, et al. N Engl J Med. 2021 Mar 18;384(11):989-1002. doi: 10.1056/NEJMoa2032183.
Note: Participants in the STEP-1 trial were patients with obesity. Patients included in Virta's cohort are patients with type 2 diabetes.
Pi-Sunyer X, et al. N Engl J Med 2015; 373:11-22. dOI: 10.1056/NEJMoa1411892
Kubota M, et al. Cureus 2023; 15(10): 446490. doi:10.7759/cureus.46490

Even given all of the above, some Plan members are still only looking for what is perceived as a "miracle drug" or "silver bullet" and are not open to lifestyle change- they only want the weight loss drugs they've heard so much about. For this subset of the Plan's membership, Virta can be the responsible prescriber of GLP-1s and GIP agonists, ensuring members titrate dosage up properly to ensure maximum weight loss, monitor side-effects and complications, and safely deprescribe when clinically indicated, once a member achieves their desired weight loss goal and/or through shared decision making with the member. Many members cannot tolerate these GLP-1s and GIP agonists long term so even if they do not achieve their weight loss goals they start looking for drug free alternatives at which point Virta's nutritional therapy would be reintroduced to the member.

Virta is uniquely positioned to ensure members understand and take into account all aspects of GLP-1s and GIP agonist drugs and drug-free weight loss alternatives that can be even more effective and impactful for weight loss while ensuring that those members who choose to embrace weight loss drugs have sustained weight loss outcomes, not short term weight loss which is regained once they discontinue GLP-1s and GIP agonists.

A. With fifty percent of adult Americans projected to be obese by 2030, traditional obesity care is not working. Virta is different from traditional obesity care vendors of

the past decade who have too often underwhelmed in outcomes and savings, many of whom are now “innovating” by prescribing GLP-1s and GIP agonists. Overall, Virta's goal is to provide members excellent choices for how to manage their weight- whether it be a drug free weight loss alternative, combination therapy or solely drug induced weight loss- while providing the Plan with a significantly more cost effective alternative with outcomes on par with weight loss drugs.

First, Virta has found that with effective conversation and education around GLP-1s and GIP agonists, more than half of members decide a drug free alternative is the best approach for them. For those interested in GLP-1 drugs, Virta can assist the Plan to educate members about weight loss drugs so they’re making an informed decision about utilizing drugs as a path to weight loss. For members that want to embrace weight loss drugs and are open to personalized nutrition therapy, Virta’s combination therapy where we use nutrition in concert with weight loss drugs can help members reach their weight loss goals faster, get them off of weight loss drugs sooner and their weight loss is sustained longer (Sustained weight loss and GLP-1s and Virta). For those those only seeking to embrace weight loss drugs, Virta can be the closed prescriber network to ensure specific criteria are met (ie participation in Virta for at least 6 months before weight loss drugs would be covered under the plan) and that members are not obtaining weight loss drugs “off-label”.

Now, shifting to outcomes:

virta

When it comes to Virta's outcomes, please see the above image and the attached Peterson Health Technology Institute (PHTI) report to see how Virta stands out in the market. PHTI is an organization dedicated to evaluating digital health technologies. PHTI aims to improve health and reduce costs through rigorous, evidence-based research. It assesses the clinical benefits, economic impact, and effects on health equity, privacy, and security of digital health solutions. Out of the 8 companies analyzed, Virta Health is proud to be highlighted as the only solution that delivers meaningful health improvement and economic impact. PHTI concluded "current evidence does not support broader adoption" for the other 7 companies. While this study was diabetes management specific, members with obesity and prediabetes have the same carbohydrate intolerance and insulin resistance as their counterparts with type 2 diabetes, however their metabolic health has not deteriorated to the point where they have a type 2 diabetes diagnosis...yet. The PHTI study also emphasizes Virta's commitment to validated research and outcomes.

Additionally, Virta has released 13 peer review papers with most stemming from our clinical trial we conducted BEFORE launching commercially. Please see Virta's research page (and included in Clinical Studies attachments) for our applicable peer reviewed papers. Virta has demonstrated and published 12% weight loss at 1 year and 11% weight loss at 2 years in our clinical trial. Through our book of business data, Virta shows 5% weight loss at 10 weeks and 10% weight loss sustained at 1 year (without adding GLP-1s). The results are consistent for members with Obesity, Prediabetes, and Type 2 Diabetes in large part because care is individualized, taking into consideration dietary preferences, budget, access to food, allergies, and cultural dietary considerations. Through our clinical trial consisting of members with prediabetes, many of whom also have obesity, Virta has achieved an average of 11% weight loss over 2 years, with 75% member retention, and 97% of members in our prediabetes program do not progress to type 2 diabetes (typically 15% of members diagnosed with prediabetes progress to type 2 diabetes over a 2 year period) .

Again, Virta stands out in many ways in the market but our sustained outcomes after deprescription may be one of our biggest differentiators. Virta conducted a first of its kind study demonstrating sustained weight loss and A1c reduction after GLP-1s are deprescribed. For patients continuing on Virta's nutrition therapy after being deprescribed from their GLP-1, weight was not regained at 6 and 12 months following deprescription. There was no difference between the matched cohorts (1. deprescribed from a GLP-1 and 2. continued their GLP-1) in weight regain and HbA1c at 6 and 12 months after deprescription/index date.

Virta addresses weight loss strategies in three ways.

virta

1. Nutrition Therapy and Behavior Modification

Virta is different in that we effectively address the root cause of obesity and broken metabolism—nutrition. We believe that obesity is a disease and that many, if not most, members do not want to go on another drug to manage their disease. They also do not want yet another ineffective diet and exercise program that sets them up for failure. Virta's nutrition therapy is different in that the therapy addresses insulin resistance and carbohydrate intolerance. Virta helps members adopt a low carbohydrate, moderate protein, high fat diet personalized to each member's specific situation. We're helping members teach their body to burn fat for energy, NOT carbs. When following Virta's personalized nutrition therapy, members stop having cravings and constant feelings of hunger. This, combined with the high touch care team support and rapid outcomes, allows 69% of Virta members to remain enrolled in treatment one year after starting—significantly higher than most competing weight loss solutions and medications. Virta's evidence-based nutrition therapy and behavioral modification solution delivers weight loss results on par with GLP-1s, but without those drugs (and side-effects), and at a fraction of the cost. From our clinical trial, members with obesity on Virta lost 13% of body weight at one year, without drugs. The same clinical trial tracked longer-term impact with data out to 3.5 years showing 9.3% sustained weight loss.

2. Adjunct to GLP-1s with Drug Offramp

When used in combination with GLP-1s and GIP agonists, Virta provides a path to provider-assisted deprescription, and sustained weight loss without drugs. Virta is the only company with research showing deprescription of GLP-1s and GIP agonists with sustainable weight loss after 1 year (GLP-1s folder). These results demonstrate that CRNT (carbohydrate restriction nutritional therapy) in a continuous remote care model provides an effective GLP-1 and GIP agonists off-ramp and maintenance therapy, allowing members to discontinue GLP-1s and GIP agonists while maintaining body weight loss and glycemia below therapeutic targets. To increase the likelihood of GLP-1s and GIP agonists ever being cost effective at their current price, a highly-effective lifestyle, nutrition, and behavioral modification intervention should be used in combination with the drug (per manufacturer's instructions- Employers and targeted obesity care attachment):

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No matter the GLP-1 coverage or member BMI:

Lifestyle programs are foundational

	BMI 25–26.9 kg/m²	BMI 27–29.9 kg/m²	BMI 30–34.9 kg/m²	BMI 35–39.9 kg/m²	BMI 40+ kg/m²
Lifestyle Modification	✓	✓	✓	✓	✓
Pharmacotherapy /Medications & Lifestyle Modification		with comorbidity	✓	✓	✓
Bariatric Procedures			certain procedures with comorbidity	certain procedures with comorbidity	✓

Figure 2: Recommended Treatments by BMI (Summarized from Treatment Guidelines)

Source: Milliman, Employers and Targeted Obesity Care: Exploring the Concept of an Obesity Center of Excellence, February 2024

Virta believes the combination of its industry-leading drug-free weight loss of 13% at one year, and being the only solution with published data showing outcomes sustainability following the GLP-1 and GIP agonists deprescription puts Virta in a category of our own that gives health plans and employers confidence that members can see the short-term positive impact of weight loss drugs, come off, and maintain the outcomes at a fraction of the cost of staying on these weight loss drugs long-term.

As members make progress in controlling their weight through Virta's nutritional intervention, Virta providers aim to safely de-prescribe medications in a sequence that reflects published clinical guidelines and shared decision making with the member.

3. Gatekeeper and Responsible Access

Virta has the ability to serve as the front-end gatekeeper to weight loss drugs, ensuring weight loss drugs are only prescribed to the small fraction of members with demonstrated clinical necessity, or those who are unresponsive to lifestyle therapy. Our philosophy is to treat drugs as the last resort in most cases, and only prescribe after behavioral modification has been attempted. For those who do truly need the drugs, we aim to enroll them in Virta as a co-therapy, with the ultimate goal of de-prescribing the GLP-1s while sustaining weight loss results.

If the Plan wishes to cover GLP-1s and GIP agonists for weight loss, then a trusted prescriber is recommended to enable greater control over prescribing behavior, utilization, and cost. This Virta-recommended model does require integration with the

Plan's PBM, with the PBM placing an NPI-block on all non-Virta prescribers. This approach would be an add-on at no additional cost to Sustainable Weight Loss, called Responsible Prescribing, and enables us to effectively bypass the complexities of Prior Authorization, while ensuring appropriate medication access and maintenance of a positive member experience. Members prescribed a GLP-1 by a non-Virta provider would receive a rejection notice when filling the medication and would be instructed to visit Virta, where they would be provided all of weight management options, including non-drug and combination therapy for those ready to participate in a more intensive and effective lifestyle intervention (see more information on our Trusted Prescriber Network below). Virta enrollment advisors and intake Providers have experience effectively triaging members to lifestyle and nutrition therapy as a first-line therapy.

Virta's Philosophy Towards GLP-1s for Obesity

1. Obesity is a serious disease, and GLP-1s are the right answer for some patients, as an adjunct to behavioral modifications.
2. That said, GLP-1s are not the right answer for every patient. Individual preference and health risk should dictate the course of treatment.
3. Very few patients on GLP-1s will want to take the drugs forever, and thus need a viable offramp that ensures sustainable weight control.

With the Responsible Prescribing add-on, Virta's Sustainable Weight Loss solution offers three distinct pathways for members based upon their clinical need and readiness for lifestyle change:

- **Nutrition Therapy:** An intensive, provider-led, behavior-based nutrition program with clinically significant weight loss, without drugs
- **Nutrition Therapy + GLP-1/GIP Agonists:** Virta's classic behavior-based nutrition program used in conjunction with Virta prescribed GLP-1s and GIP agonists, with a path to deprescription
- **Lifestyle + GLP-1/GIP agonists:** Screening, responsible prescribing, and dose optimization of GLP-1s and GIP agonists to people who could benefit from weight loss drugs

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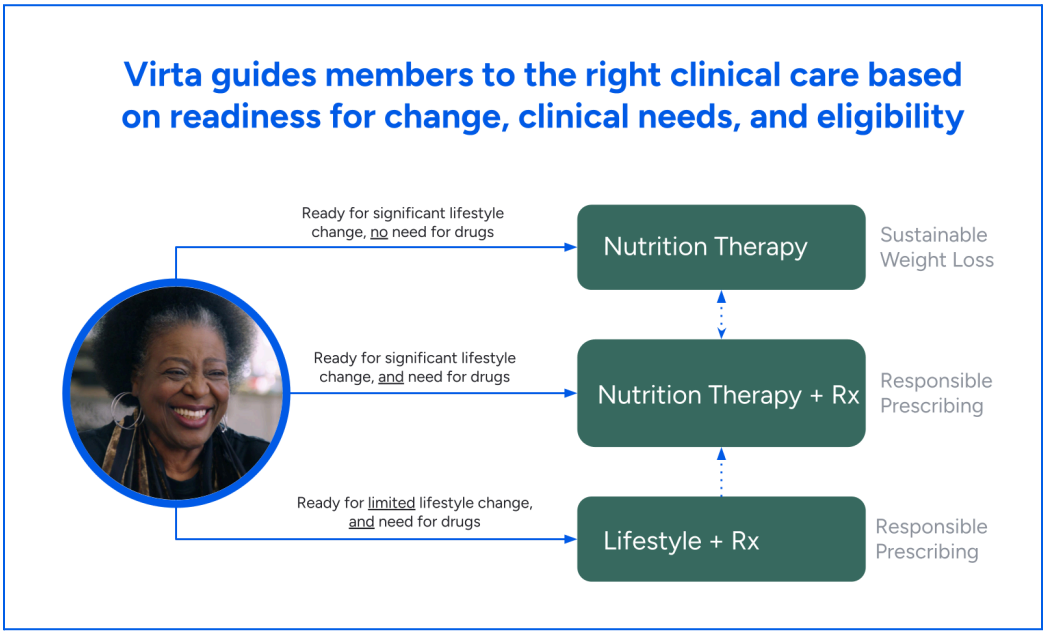
- **Weight Maintenance:** An intensive, provider-led, behavior-based nutrition program to maintain weight loss after GLP-1s are deprescribed



B. Virta has a pricing framework that is beneficial for the Plan from both a financial and clinical standpoint. Virta puts 100% of Virta's fees at risk tied to significant clinical outcomes. The BMI threshold for eligibility in Virta's clinical weight loss program can be set at BMI ≥ 25 or BMI ≥ 30 (or anything in between) based on the Plan's discretion. Virta can follow the Plan's eligibility criteria and FDA guidelines to prescribe GLP-1s. All Virta fees are paid as preventative medical claims through the Plan's TPA and hit the self-funded pool of funds used to pay claims. Please find Virta's fee schedule to follow. Virta is positioned as a covered benefit for plan members.

a. **Sustainable Weight Loss:** $170 PPPM
   i. Includes Weight Management and Prediabetes
   ii. Responsible Prescribing as an optional add-on

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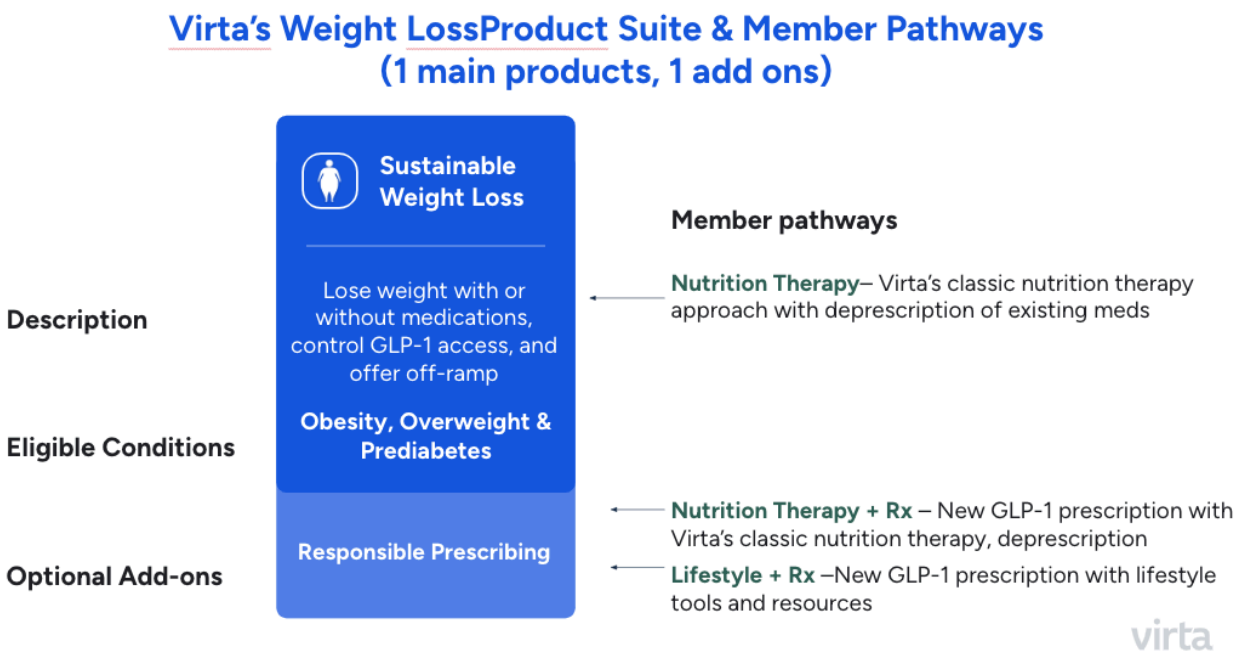

Virta's Performance Guarantee (PG) structure for our Sustainable Weight Loss solution offers 100% of year one fees at risk tied to:

- 5% Average Weight Loss—Max Refund of 100% of fees

PG's are measured at the end of the first year. All members who have been in treatment for a minimum of 180 days will be included in the analysis, with a 50 member minimum eligible per category although the claims fees for ALL members are at risk. Virta would welcome the opportunity to further discuss what options the Plan feels is best to accommodate the goals of cost containment versus sustained clinical outcomes from embracing weight loss drugs. Below please find guardrails Virta has put in place when it comes to prescribing GLP-1s and GIP agonists.

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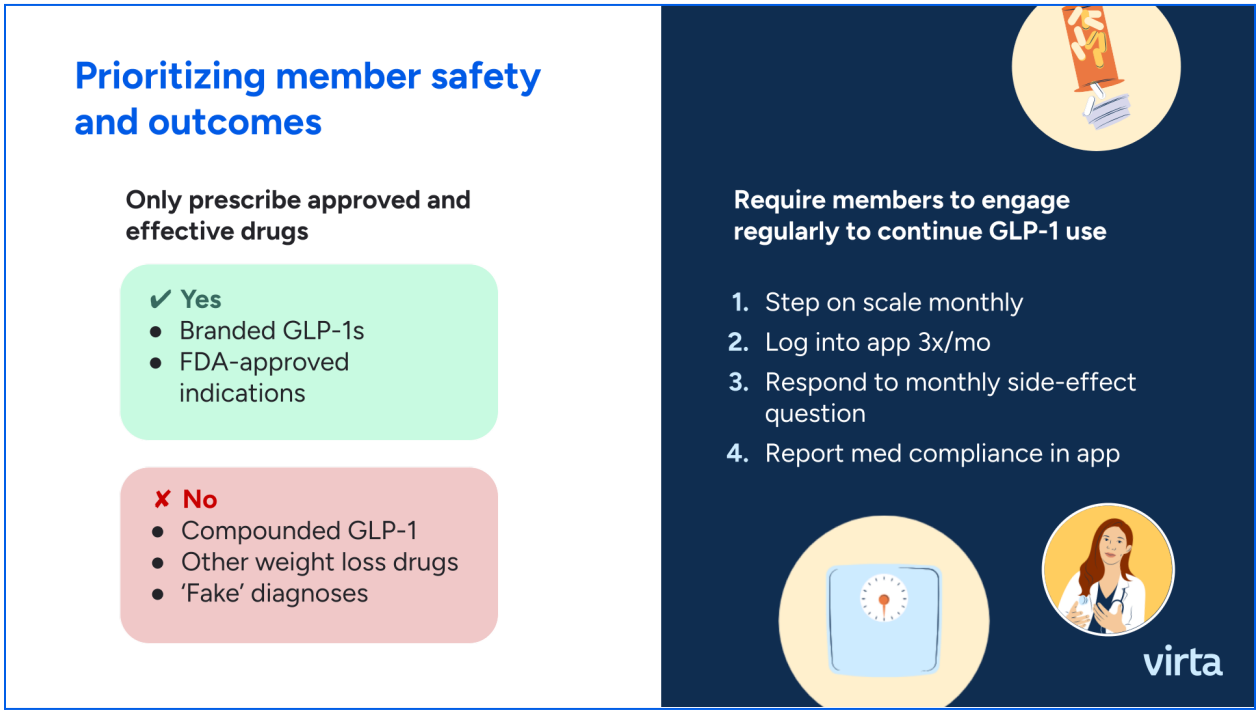
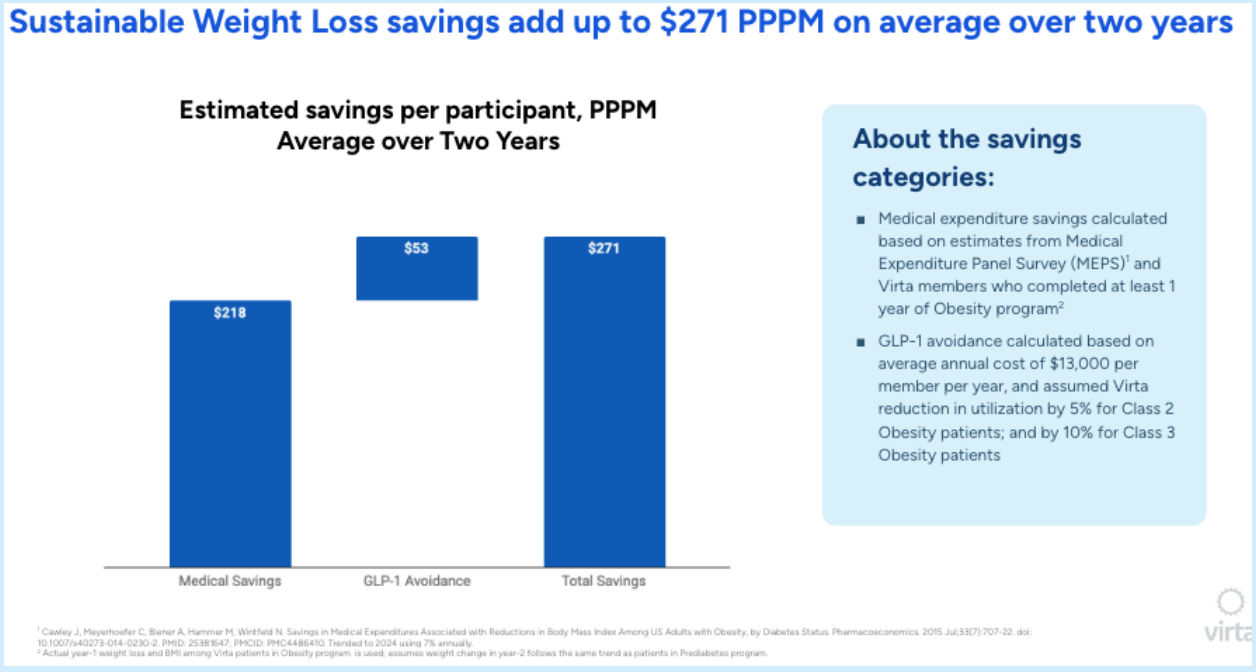


Please see below for a comprehensive list of all services/enhancements/equipment included in the base fee/per participant rate:

- Daily remote provider oversight monitoring blood sugar and medication
- Unlimited health coach interactions with a dedicated health coach
- Intensive unlimited 1:1 health coaching
- Virta individualized nutrition therapy
- Clinical intake/screening
- Behavioral health content
- Medication deprescription
- Communication to PCP
- Connected scale
- Blood pressure cuff
- Blood Glucose/Ketone monitor
- Glucose Strips
- Ketone Strips
- Lab testing (included through LabCorp or Quest- alternatively Virta has the ability to ingest recent labs for members)
- App-based educational content (550+ articles/videos, 600+ recipes, lists of restaurants with Virta-friendly menu suggestions, shopping on a budget list suggestions, and more)
- In-app member community

- Implementation Support
- Reporting
- Fees at risk

For Sustainable Weight Loss (personalized nutrition therapy- no GLP-1s added), our ROI analysis projects savings on a per-member basis by comparing healthcare costs for a Virta member with obesity/prediabetes versus the same member with usual care. Through Virta's care, obesity savings add up to $271 PPPM- please note, there is no “soft dollar” productivity included in this ROI calculation



on average over two years (for prediabetes savings $296 PPPM- please note, there is no “soft dollar” productivity included in this ROI calculation either.)

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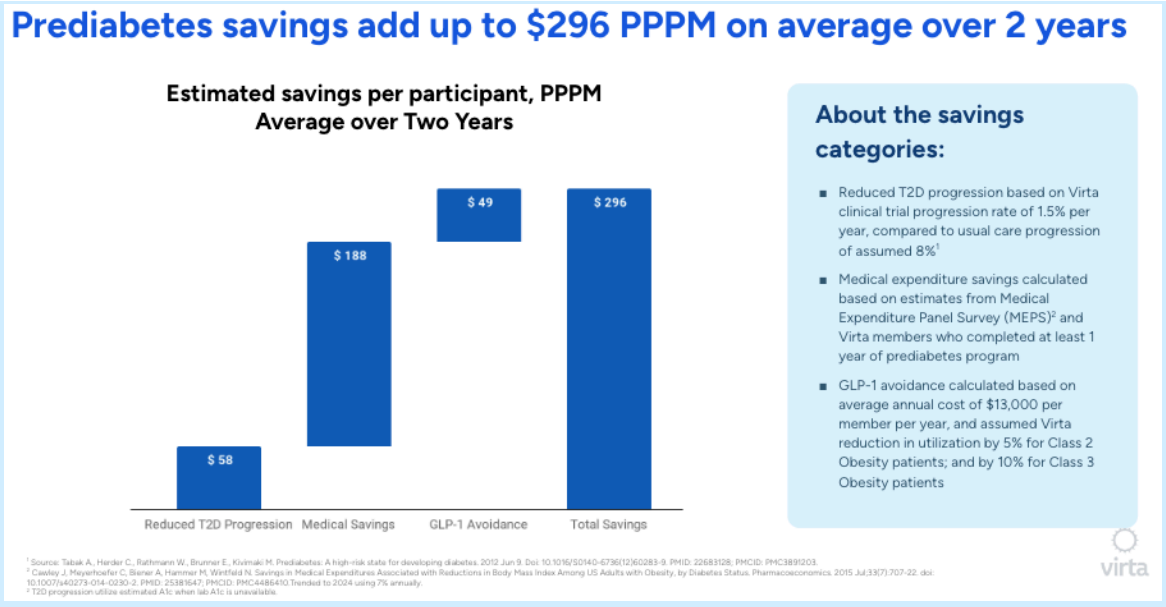

Medical expenditure savings calculated based on estimates from Medical Expenditure Panel Survey (MEPS) and Virta members who completed at least 1 year of Virta's Sustainable Weight Loss program; GLP-1 avoidance calculated based on average annual cost of $13,000 per member per year, and assumed Virta reduction in utilization by 5% for Class 2 Obesity members; and by 10% for Class 3 Obesity members. Below please find the ROI analysis for Sustainable Weight Loss (including both Obesity and Prediabetes Reversal assuming 740,000 total plan members). Assumptions are based on North Carolina State prevalence rates (45% for obesity and 34.6% for prediabetes) and 50% of members seeking a GLP-1 opting for nutrition (assumed a low 20% enrollment rate of all obese and prediabetic members to take into consideration overlap between the obese and prediabetic populations). Virta also has the ability to decrease BMI eligibility down to 25 to address metabolic syndrome sooner for those members looking to improve their metabolic health earlier in their journey. Virta recommends not offering GLP-1 drugs and GIP agonists below the FDA guidelines (currently BMI of 27).

Netting out Virta's fees the ROI for the Plan is over $317 million over two years. We broke out year 1 and 2 ROI for each respective cohort (weight loss and prediabetes) so you can see the impact on each respective population and then show the cumulative impact of Virta's programs. The overall ROI is 1.7 to 1 over a two year period. Please keep in mind that his analysis takes into account only those choosing the non-drug alternative as we do not believe there is any positive ROI from GLP-1s and GIP agonists due to their prohibitively expensive cost and lack of long term clinical outcomes. Weight loss drugs will help a subgroup of members get on the track to better metabolic health, however when they are not paired with effective lifestyle change programs members tend to regain most if not all weight lost.

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	Sustainable Weight Loss		Prediabetes	
Estimated Prevalence	45%		35%	
Projected Enrollment	20%		20%	
Number Enrolled	66,600		51,208	
	Year 1	Year 2	Year 1	Year 2
Total Gross Savings	$216,317,000	$217,449,000	$166,375,000	$197,560,000
Cost of Virta	$135,864,000	$135,864,000	$104,464,000	$104,464,000
Net Savings	**$80,453,000**	**$81,585,000**	**$61,911,000**	**$93,096,000**
ROI	**1.6**	**1.6**	**1.6**	**1.9**
Net Savings at 2 years	**$162,038,000**		**$155,007,000**	
ROI at 2 years	**1.6**		**1.7**	

	Virta	
	Year 1	Year 2
Total Gross Savings	$382,692,000	$415,009,000
Cost of Virta	$240,328,000	$240,328,000
Net Savings	**$142,364,000**	**$174,681,000**
ROI	**1.6**	**1.7**
Net Savings at 2 years	**$317,045,000**	
ROI at 2 years	**1.7**	

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For those embracing GLP-1 drugs, there is no savings given the cost of these drugs. However when GLP-1s are paired with Virta we see over 13% ADDITIONAL weight loss and sustain that weight loss 12 months after getting off the GLP-1 drugs.

Validation

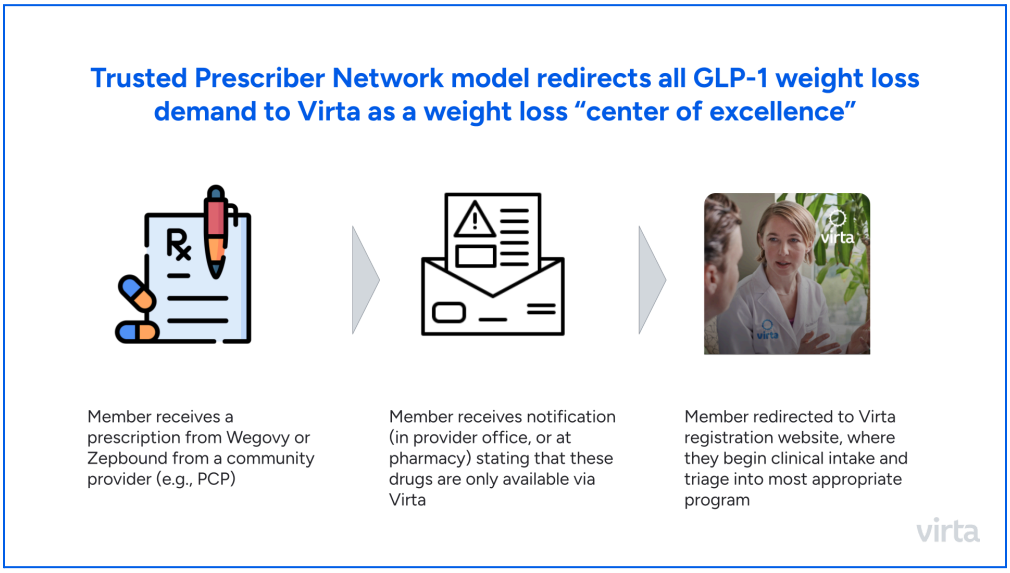
Virta's outcomes, ROI and program have all been validated by the Validation Institute (see Validation Institute Folder). We have also found that many seeking GLP-1s become nonadherent around 6 months at which point they seek effective weight loss alternatives (Virta's Sustainable Weight Loss).

For our *Nutrition Therapy + GLP-1 pathway* (combo therapy), we have the capability of setting up avenues for members based on certain criteria (i.e. see examples below in section D of eligibility requirements).

- With this pathway, Virta offers utilization management and supports PBM integration. There are multiple ways to operationalize this, but most clients are seeking a Trusted Prescriber Network due to lower implementation costs and better control of drug spend. Virta is open to working with the Plan on other models that best meet the needs of your members if this option is not desired. See more on step therapy below.
    - **Trusted Prescriber Network [Recommended]**
        - Under this model, only Virta providers—not community providers— may prescribe GLP-1 drugs for weight loss. Virta providers are practitioners with appropriate licensure and we have numerous board certified Obesity Medicine providers on the team. The Plan will provide members with proactive information on Virta as the sole prescriber of GLP-1s, in addition to Virta's non-drug weight loss options. The PBM loads Virta's list of prescriber NPIs and only those members receiving a prescription from a Virta provider may fill that script. Members receiving prescriptions for GLP-1s from a community provider will receive a rejection notice, with instructions to enroll in Virta to access GLP-1 drugs and other non-drug weight loss options. Once members apply to Virta, they undergo a medical evaluation by our provider team to ensure they are clinically eligible for GLP-1 drugs. They may also enroll in Virta's nutrition therapy with or without GLP-1 medications. Members must remain engaged in their care to receive prescription refills.

          To set up a Trusted Prescriber Network, Virta will work with the Plan and the PBM to establish the allowable Virta provider NPIs and member messaging.

The benefit of this approach is that Virta can serve as the trusted gatekeeper for GLP-1 drugs, ensure responsible prescribing behavior, and ensure that all members receiving GLP-1 drugs are actively engaged in Virta's care. **This approach is not expected to impact prescription drug rebates; PBM should not charge a rebate decrement.**



Under our recommended Trusted Prescriber Network, **prior authorization is not required.** That being said, Virta will both closely manage new starts and continuation of GLP-1s. New starts will follow the Plan—Virta solution based upon FDA BMI threshold and the Trusted Prescriber Network model. Continuation will be at the discretion of Virta providers, and demonstrated continued engagement. At all times, members must meet the following minimum program adherence requirements (note we are flexible in this criteria):

- Injection logging: 3x / month
- Weight logging: 1x / month
- Side effect logging: 1x / month
- Ketone Logging: 12x / month
- Weight loss achieved: 2% @ 6 months

- **Step therapy options**, while Virta has the capability to set up this method, we have not done so as of yet with any of our partners due to the agreed member friction it causes. An example of how we've done this in the past, Virta sets up pathways for members to join Virta as part of a step therapy approach before

bariatric surgery. With this, Virta did see a portion of those members opt out of bariatric surgery after a few months of Virta's care. If the Plan prefers a step therapy option for their members, we would welcome additional discussion about this pathway as we are very flexible with our approach in understanding that each organization and population has varying complexities to consider.

1. Virta feels that members paying varying percentages of GLP-1s and GIP agonists corresponding to medical necessity considerations is more a function of a TPA/PBM. Virta is happy to talk about this in greater detail if desired by the Plan.
2. Virta feels pricing around GLP-1s and GIP agonists and FDA indications is a function of your PBM, however would be happy to discuss further if desired by the Plan.
3. Virta feels auditing claims, rebates and prior authorizations around GLP-1s and GIP agonists for accuracy and compliance with applicable laws and regulations is a function of your PBM. However Virta would be happy to discuss further if desired by the Plan.

C. With Virta as your partner, the Plan will have the flexibility to establish parameters for utilization management of GLP-1s and GIP agonists for weight loss, specifically around eligibility requirements, prerequisites for Plan members to follow to receive benefit coverage for GLP-1s and GIP agonists and other similar new molecular entities for weight loss.

1. Using the Trusted Prescriber Network (closed network previously mentioned) Virta has the ability to require members enroll in and actively engage in Virta's drug-free Sustainable Weight Loss for a period of time prior to becoming eligible for GLP-1s and GIP agonists coverage under the Plan. Until the Plan's requirement is satisfied, the Virta clinical team would not prescribe weight loss drugs to plan members.
2. Regarding therapies involving lower cost medications- Virta is focused on nutrition first, however we would be open to utilizing lower cost medications when clinically appropriate to achieve weight loss. Drugs such as metformin when used in a clinically appropriate manner can result in modest weight loss for those that are overweight/obese and may be prediabetic or have type 2 diabetes.
3. Virta always requires that medications be prescribed by a Virta clinician using shared decision making with the member based on medically objective clinical criteria and the latest standards of medicine.
4. Regarding prohibiting BMI measurements from being estimated via telehealth, Virta ensures that BMI is accurate through the continuous remote monitoring members participate in. Through the combination of biomarkers we collect (weight, blood glucose and ketones, and more), the member's care team will be able to confirm the member is actively engaging and progressing. For members that are not engaging or seeing progress, we utilize a combination of Machine Learning and personalized content from a human coach to re-engage them or troubleshoot why progress is not being made. If a member is disengaged for 30 days, we discharge them from our care and stop billing the Plan.

Virta also sends members to Quest Diagnostics or LabCorp to get initial biomarkers taken so we have a baseline of each member coming into the program. Members self-report height and weight at the time of enrollment which is confirmed via Virta's cellularly connected scale. BMI is assessed and we enroll in Virta based upon this information.

D. With Virta as your partner, the Plan will have the flexibility to establish parameters for utilization management of GLP-1s and GIP agonists for weight loss, specifically around eligibility requirements, prerequisites for Plan members to follow to receive benefit coverage for GLP-1s and GIP agonists and other similar new molecular entities for weight loss.

1. The most common consideration is setting up a BMI threshold. Most of our partners select a BMI ≥ 25 but Virta can set this criteria based on the Plan's discretion (i.e. BMI ≥ 27 or 30).
2. Current weight is not a consideration Virta has used as eligibility criteria but we have the capability to set that up if the Plan desires. We are happy to talk through this in greater detail.
3. We do not currently ingest documentation around lifestyle modifications such as reduced calorie intake or increased physical activity as this information tends to be unreliable, there is a high probability for inaccuracy and we believe it should not be considered when addressing coverage around GLP-1s and GIP agonists.
4. Documentation and active participation in Virta's Sustainable Weight Loss (personalized nutrition therapy) for a period of time can be utilized as a consideration for the Plan to cover GLP-1s and GIP agonists. As mentioned earlier, members will have to regularly log biomarkers showing they are engaging in the Virta program they sign up for. If they are not engaging, Virta will try to re-engage quickly and if the member does not, we will disenroll them from the program and stop billing the Plan
5. Virta follows FDA guidelines when the Trusted Prescriber Network (closed prescriber network) is chosen. Virta always guides members to nutrition first, however if a member was not interested in personalized nutrition therapy and only was interested in GLP-1/GIP agonists, subject to any additional requirements, Virta clinicians currently would not require comorbidities or other obesity related medication conditions to prescribe weight loss drugs. Virta's clinical trial and focus was originally on type 2 diabetes and reversing that condition. While our mission is still to reverse type 2 diabetes in 100 million people, we've found that Virta improves a wide range of comorbidities such as prediabetes, obesity, blood pressure, sleep, kidney function, knee pain, depression and more (see attached clinical studies). Virta has shown through research and our book of business outcomes that we can significantly help multiple conditions and can work with the Plan to set up certain comorbidities eligibility criteria based on the Plan's preferences.

6. Virta provides reporting at 90, 180 and 365 days (annually after there) around the number of applicants, enrollments, weight loss, GLP-1/GIP agonists deprescription and sustained weight loss after deprescribing weight loss drugs. These reports enable the Plan to easily see the impact Virta is having on Plan member's lives both from the clinical and human perspectives.
7. As a telemedicine and remote-first company, we do not usually require any in-person visits as members can log all of their biomarkers more conveniently through the app on their phone. However, we do have members get baseline lab testing to identify eligible members and confirm diagnosis for both safety and eligibility along with follow up labs every 6 months to confirm engagement and verify efficacy of medications. These are obtained at no extra cost through Virta at LabCorp or Quest. Additionally, through members logging biomarkers it is extremely obvious who is following the treatment and who is not following the treatment. Members cannot "cheat" their biomarkers. For example, if a member is non-adherent to the Virta program, his biomarkers will tell that story, increased blood glucose readings, very low or no blood ketones present. Weight loss will also not occur. Again, if members become disengaged for 30 days, they are discharged from Virta's care, transitioned back to the previous provider and Virta stops billing the Plan.
8. Virta's medical team performs medical intake during the enrollment process. At that time, Virta is gathering information on medical conditions which might warrant consideration for GLP-1 in the setting of obesity. Since Virta is a medically supervised program, we can focus on nutrition and prescribe GLP-1s when it is clinically/medically appropriate to do so.

E. Virta's cost for Sustainable Weight Loss (and all corresponding modules) is simple- $170 per actively engaged member. Virta defines active engagement as members logging biomarkers or interacting with their care team. Our fee is a bundled fee encompassing unlimited interactions, all durable medical equipment and regular labs. If a member becomes disengaged for 30 days, self-graduates, or drops out of the program, the Plan stops getting billed. The Plan only pays for what it uses.

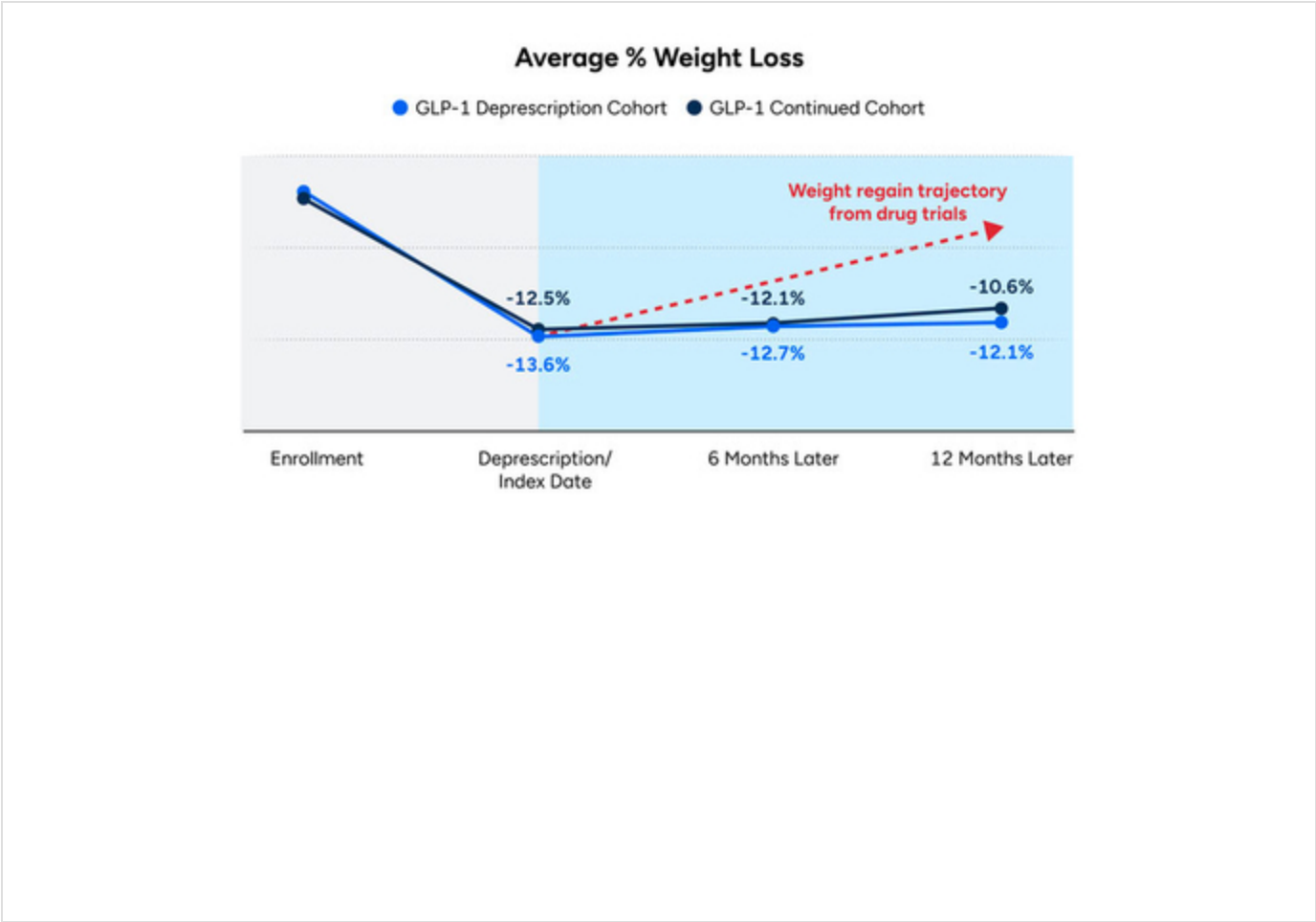
Virta has been deprescribing GLP-1s and GIP agonists for over 10 years in the type 2 diabetes and obesity space. Virta started with a 2 year clinical trial (which was extended out to 5 years- all peer reviewed clinical publications attached/included) before launching commercially. Virta has 13 peer reviewed publications ranging from outcomes reversing type 2 diabetes to reduction in knee pain, better sleep, improved mental health and more (all attached).

That being said, GLP-1s and GIP agonists for weight loss are new to everyone and all public sector organizations are weighing the hefty cost of their drugs against the clinical outcomes and whether members need to and can tolerate being on these drugs in perpetuity. Virta is uniquely positioned to be a drug-free alternative to GLP-1s and GIP agonists at a fraction of the cost of those drugs. Virta can also help those who are looking to embrace weight loss drugs

but are also open to nutrition therapy achieve greater weight loss, be an off-ramp from weight loss drugs and achieve sustained weight loss. Finally, for those only looking to embrace weight loss drugs, Virta can help them effectively achieve their weight loss goals and when they're ready sustain their weight loss by making lasting behavior change.

Virta Health Announces First-of-its-Kind Peer-Reviewed Study Proving Its Approach Is an Effective Off-Ramp From GLP-1s for Sustained Weight Loss

Company builds on nearly 10 years of GLP-1 experience, expanding its Sustainable Weight Loss solution to deliver medication-free and medication-assisted weight loss



Following GLP-1 deprescription, weight did not significantly increase at 6 or 12 months post deprescription, compared to many well-known drug trials (in red) where patients regain up to 2/3rds of weight loss after discontinuing the drug. (Graphic: Business Wire)

February 29, 2024 09:00 AM Eastern Standard Time

DENVER--(BUSINESS WIRE)--Virta Health has released first-of-its-kind, peer-reviewed data demonstrating the company's approach to personalized nutrition therapy results in sustained weight loss after the discontinuation of glucagon-like peptide-1 receptor agonists (GLP-1s), including Ozempic. Published today in *Diabetes Therapy*, the data demonstrates Virta is a powerful and sustainable off-ramp from GLP-1s.

These outcomes stand in stark contrast to other real-world results of GLP-1 weight loss treatments. Discontinuing the medications has been shown to lead to rapid worsening of blood sugar and weight regain, even when accompanied by physical activity and calorie restriction. Additionally, as many as two out of three people on GLP-1s stop within a year and quickly regain the weight they lost, underscoring the need for an effective medication-free alternative and off-ramp from the medications to achieve sustainable results.

The study assessed weight loss in two groups of Virta members with type 2 diabetes: those for whom (a) GLP-1s were fully deprescribed and (b) GLP-1s were continued. At one year follow-up, both groups achieved significant and sustained improvement in weight loss, with no differences between the groups. For those eliminating GLP-1 use, there was no change or regain in body weight, a result previously unheard of.

Virta's prior clinical trials and real-world outcomes showed significant and sustained weight loss through a medication-free approach, demonstrating members who never started on GLP-1s were able to achieve and sustain similar weight loss to those who received GLP-1 therapy. These results, combined with today's findings in *Diabetes Therapy*, demonstrate the company's approach to personalized nutrition therapy serves as both a powerful alternative to and off-ramp from GLP-1s.

“GLP-1 drugs are not a long-term or silver bullet solution to America’s obesity crisis. In addition to their numerous side effects, they can cost anywhere from $900 to $1,300 per month, and are only effective if taken continuously over a lifetime,” said Sami Inkinen, co-founder and CEO of Virta Health. “Many companies claim their solutions can be used to maintain weight loss, but Virta is the first and only to provide data proving we can deliver drug-like impact without the drugs, and through provider-led personalized nutrition. Our approach – which is built on a decade of experience working with and without GLP-1’s to reverse type 2 diabetes – enables members to lose weight sustainably and maintain their results."

In line with these new findings, Virta announced the expansion of its Sustainable Weight Loss solution, a comprehensive approach to weight loss that enables employers and payers to offer responsible and individualized use of GLP-1s. The new features will include personalized journeys, providing members with safe and responsible access to the medications, as well as individualized nutrition plans. Virta will also place its fees at risk for all customers, regardless of the members’ individual journey, with performance targets connected to deprescription of GLP-1’s, as well as sustained weight loss after deprescription.

Members can achieve clinical weight loss without the use of medications, or with medications in combination with Virta's personalized nutrition therapy. Members can also decide they don’t want to be on GLP-1s long term and use Virta as a safe and sustainable off-ramp to the drugs while maintaining a healthy weight.

Additional Resources

- *Diabetes Therapy:* Impact of Glucagon-Like Peptide 1 Agonist Deprescription in Type 2 Diabetes in a Real-World Setting: A Propensity Score Matched Cohort Study
- Webinar on Health Plan Executive Survey on GLP-1 Cost Crisis

About Virta Health

Virta Health is redefining the standard of care for metabolic diseases such as obesity, type 2 diabetes, and prediabetes. Our approach combines personalized nutrition therapy with continuous support from providers and coaches, empowering members to achieve lasting outcomes and take back their lives. Virta has earned the trust of the nation’s largest employers and payers, including organizations like AutoZone, US Foods, Banner Aetna, and Blue Cross Blue Shield plans throughout the country. To learn more, visit www.virtahealth.com.

Notes to GLP-1 Study Image

Wilding JPH, et al. N Engl J Med. 2021 Mar 18;384(11):989-1002. doi: 10.1056/NEJMoa2032183.
Note: Participants in the STEP-1 trial were patients with obesity. Patients included in Virta’s cohort are patients with type 2 diabetes.
Pi-Sunyer X, et al. N Engl J Med 2015; 373:11-22. dOI: 10.1056/NEJMoa1411892
Kubota M, et al. Cureus 2023; 15(10): 446490. doi:10.7759/cureus.46490

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PETERSON HEALTH TECHNOLOGY INSTITUTE

ANNOUNCEMENT

New Report Finds That Digital Diabetes Management Tools Fail to Deliver Meaningful Health Benefits to Patients While Increasing Spending

For Release
MARCH 21, 2024

Media Contact
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Independent evaluation from Peterson Health Technology Institute recommends new directions for digital diabetes solutions

NEW YORK — Peterson Health Technology Institute (PHTI), an independent organization that evaluates healthcare technologies to improve health and lower costs, today released a new evaluation of digital diabetes management tools. These solutions are used by millions of Americans and have been funded by $58 billion of investment and mergers and acquisitions, yet the evidence shows that the technologies do not deliver meaningful clinical benefits, and result in increased healthcare spending.

The analysis, conducted by a team of health technology assessment experts and informed by clinical advisors, evaluated eight widely used digital tools that people with type 2 diabetes use to track and manage blood glucose using a noncontinuous glucometer.

The report found that people who use these tools achieve only small reductions in hemoglobin A1c (HbA1c) compared to those who do not, and these reductions are not sufficient or sustained enough to change the trajectory of their health, care or long-term prognosis, including cardiovascular risks. The solutions also result in increased overall healthcare costs. One promising solution, Virta, supports nutritional ketosis to achieve diabetes remission in patients who follow the rigorous diet modifications.

“When these digital diabetes management tools launched more than a decade ago, they promised to improve health outcomes for people with diabetes and deliver savings to payers. Based on the scientific evidence, these solutions have fallen short, and it is time to move toward the next generation of innovation,” said Caroline Pearson, executive director of PHTI. “Patients with diabetes invest time, energy, and resources

in these tools, and they deserve to experience meaningful, positive benefits for their health. The healthcare sector as a whole needs transparent, accurate information about the clinical and economic impact of these digital tools that are taking up precious healthcare dollars."

PHTI's rigorous analysis incorporated an evidence-based assessment framework and review of more than 1,100 articles, including 120 submitted to PHTI by companies evaluated in the report. PHTI's ratings are at the category level, including **remote patient monitoring** solutions that support providers, and **behavior and lifestyle modification** solutions that engage users to improve their diet, exercise, and self-management.

HbA1c is the standard form of measurement of glycemic control in diabetics. The studies show that these digital tools deliver small reductions in HbA1c of 0.23 to 0.60 percentage points compared to usual care. These results are generally below industry standards for Minimal Clinically Important Difference (MCID) of 0.50 percentage points. Further, the evidence indicates that this small improvement is not durable because the reduction is not sustained over time.

Additionally, PHTI's analysis did not find evidence to demonstrate that digital diabetes management tools improve other health factors, including weight loss, body mass index, blood pressure, cholesterol, or other common conditions impacting people with diabetes. The analysis also concluded that, despite the disproportionate impact of diabetes on low-income and racially and ethnically diverse communities, these tools are not currently being deployed in ways that improve health equity.

PHTI's evaluation further determined that these tools increase net healthcare spending. This is due to the fact that price for the solutions exceeds the associated healthcare cost savings, because the minimal clinical benefit does not enable the patient to avoid other care or treatments. For patients using tools in the remote patient monitoring category, annual spending is projected to increase by $2,002 for commercial insurance patients, by $1,011 for Medicare patients, and by $723 for Medicaid patients, as a result of higher provider payments. For patients using tools in the behavior and lifestyle modification category, annual spending is estimated to increase by $484 for commercial insurance patients, by $513 for Medicare patients, and by $574 for Medicaid patients. For all payers, the increased spending associated with virtual diabetes solutions has a significant impact on total spending given how many people are eligible to use the solutions, including 4.3% of those with commercial insurance, 17.0% of those with Medicare, and 4.8% of those with Medicaid.

In addition to its scientific literature review, PHTI proactively engaged the companies included in the report and provided an opportunity for them to share data and product information. Companies in PHTI's evaluation include DarioHealth, Glooko, Omada, Perry Health, Teladoc (Livongo), Verily (Onduo), Vida, and Virta. The evaluation considered evidence about which populations stand to benefit the most from using the technology, as well as the durability of clinical impacts given the importance of sustained glucose control to achieve health benefits. The economic analysis modeled expected healthcare savings resulting from improved glycemic control for patients using digital diabetes management solutions who are enrolled in Medicare, Medicaid, and commercial insurance.

PHTI identified two potential bright spots for digital diabetes management tools. Initial data showed that Virta users are much more likely to achieve clinically meaningful benefits in glycemic control, including diabetes remission and the ability to reduce or eliminate their diabetes medications, if they can maintain the rigorous dietary requirements of the intervention. The other area of greater potential is among patients with higher starting HbA1c levels who are newly starting insulin. By engaging these patients at an early critical transition point in their care, digital solutions could have more impact by helping establish good self-management habits among these higher-risk patients.

The following summarizes the evaluation's category-level ratings:

Exhibit 19
PHTI CATEGORY-LEVEL RATINGS FOR DIGITAL DIABETES MANAGEMENT SOLUTIONS

● Positive ● Moderate ● Negative
● Higher Evidence Certainty ○ Lower Evidence Certainty

	Clinical Effectiveness	Economic Impact[a]	Summary Rating[b]
Remote Patient Monitoring Glooko	**Results:** Small but not clinically meaningful reduction in HbA1c **Evidence Certainty:** Higher	Net increase in spending — current provider reimbursement exceeds cost savings from avoided care	**Current evidence does not support broader adoption**
Behavior and Lifestyle Modification DarioHealth, Omada, Perry Health, Teladoc (Livongo), Verily (Onduo), Vida[c]	**Results:** Small but not clinically meaningful reduction in HbA1c[d] **Evidence Certainty:** Higher	Net increase in spending — current solution pricing exceeds cost savings from avoided care	**Current evidence does not support broader adoption**
Nutritional Ketosis Virta	**Results:** Clinically meaningful reduction in HbA1c sufficient to achieve remission in some patients[e] **Evidence Certainty:** Lower	Initial net increase in spending with potential for long-term savings	**Evidence supports broader adoption with ongoing evidence generation**

Source: PHTI, Digital Diabetes Management Solutions Assessment, March 2024. See full PHTI report on digital diabetes management solutions for complete assessment, methods, and recommendations.
a Economic impact for remote patient monitoring based on standard provider reimbursement using remote patient monitoring (RPM) codes. Economic impact for behavior and lifestyle modification category assumes a $64 per user per month product price.
b Summary rating reflects the combination of clinical and economic results.
c Not all solutions have clinical data that meet the inclusion standards for this report. Based on the similarity of approaches and the consistency of clinical outcomes across the category, it is fair to assume that companies without solution-specific data perform in line with the category. Purchasers and users will have to make their own assumptions about performance.
d Potential for improved and meaningful clinical benefits in populations with higher starting HbA1c who are newly starting insulin.
e Key questions for nutritional ketosis involve generalizability of evidence and adherence rates among real-world users.

In the United States, about one in seven adults—more than 38 million living in the U.S.—has Type 2 diabetes, which is the eighth leading cause of death. At over $400 billion of total healthcare spending annually, diabetes is the most expensive chronic condition to treat and manage. Given the critical role of patient self-management, investment in digital health tools has surged in recent years.

Throughout the assessment process, PHTI worked with a range of independent evaluation partners, clinical advisors, patients with Type 2 diabetes, and other stakeholders. Report contributors and reviewers included:

- Curta: assessed the clinical and economic impact of these technologies using the published ICER-PHTI Assessment Framework for Digital Health Technologies, including the systematic literature review and budget impact assessment
- Charm Economics: identified what technologies cost to deliver, how they work, and their impact on patients and purchasers
- Institute for Clinical and Economic Review (ICER): co-developed the ICER-PHTI Assessment Framework for Digital Health Technologies, and was consulted to review its implementation in this report
- Ami Bhatt, MD, *Chief Innovation Officer of the American College of Cardiology*
- Richard Milani, MD, *Chief Clinical Innovation Officer, Sutter Health; former innovation lead at Ochner Health System*
- Karen Rheuban, MD, *Co-Founder and Director of the University of Virginia Center for Telehealth*
- Focus groups and interviews with patients with Type 2 diabetes who had experience with digital diabetes management solutions

"Managing diabetes is complex and essential to future cardiovascular health. Patients will gain agency and drive better clinical benefit if they direct their time and effort towards effective interventions rather than tools that provide marginal or no benefit," said report contributor Ami Bhatt, MD, chief innovation officer of the American College of Cardiology.

"New diabetes technologies need to be easier to use, by the people who need them most, at lower cost than standard care, and provide real health benefits," said report contributor Richard Milani, MD, chief clinical innovation officer at Sutter Health. "This evaluation suggests there is room for new innovations that deliver for patients and address worrying increases in healthcare spending."

The PHTI report provides recommendations and best practices for innovators, providers and payers. The next generation of diabetes management solutions should aim for clinically meaningful improvements in glycemic control, potentially integrating continuous glucose monitors and new GLP-1 obesity medications. Solutions should also generate sufficient evidence to support broader adoption, and they should prioritize access for populations who need them most. Providers of diabetes care should have clarity about the performance of these digital solutions when recommending them to their patients. Payers, including health plans and employers, should adapt their contracting approach to require transparency about the solution's usage and benefits within their covered population and to include financial performance guarantees tied to clinical outcomes.

"PHTI is filling an important role in delivering actionable and market-facing information to digital health purchasers about what solutions will make a meaningful impact on health outcomes for members, making them worth investment," said Peter Long, PhD, executive vice president, Strategy and Health Solutions at Blue Shield of California and a PHTI Advisory Board member. "Having an organization like PHTI cut through the noise of digital health options helps payers make faster and more effective decisions for members to that we can focus on the big work of transforming the healthcare system."

PHTI has announced that future assessment areas include virtual physical therapy, blood pressure monitoring, and mental health tools.

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About the Peterson Health Technology Institute

The Peterson Health Technology Institute (PHTI) provides independent evaluations of innovative healthcare technologies to improve health and lower costs. Through its rigorous, evidence-based research, PHTI analyzes the clinical benefits and economic impact of digital health solutions, as well as their effects on **health equity, privacy, and security.** These evaluations inform decisions for providers, patients, payers, and investors, accelerating the adoption of high-value technology in healthcare. PHTI was founded in 2023 by the Peterson Center on Healthcare. For more information, please visit PHTI.com.

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Hope for Health Equity (Part I): Addressing Disparities in Type 2 Diabetes Care

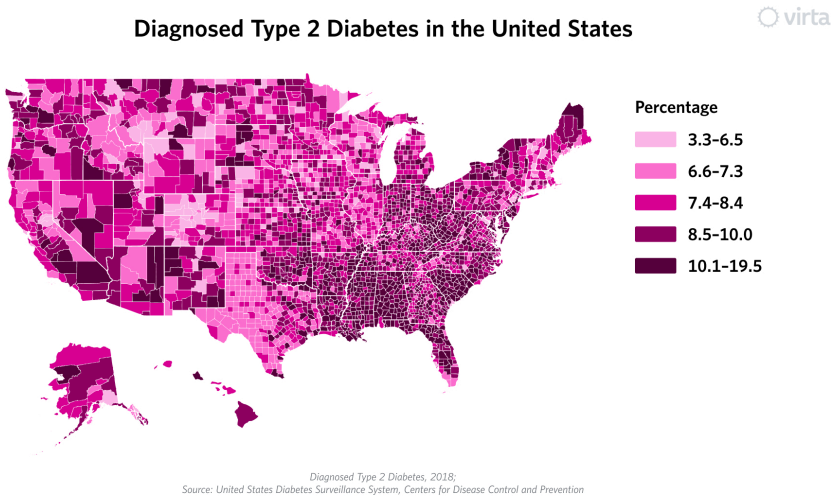
Published on November 1, 2022

Virta Health

This is Part I of a three part series on health equity. Our series continues with an exploration of Virta patient outcomes in Part II: Outcomes by Socioeconomic Status and Part III: Outcomes by Race and Ethnicity.

Nowhere are health equity issues more apparent than in type 2 diabetes, obesity, and metabolic health. For those in disadvantaged communities, and for certain racial and ethnic minority groups (in particular Black, Native American, Hispanic, and Pacific Islander populations), rates of diabetes far surpass the national average. These populations are also more likely to be on medications to manage their diabetes, and to experience worse outcomes, including death or severe complications such as amputation and blindness.

One of the clearest examples of current disparities is in the Deep South, where rates of type 2 diabetes are among the highest in the U.S. and many of the hardest-hit communities are Black and low-income. In one zip code in South Carolina, for example, amputation rates are nearly *40 times* greater than other Deep South communities. Stunningly, on a national basis, 52-80% of patients who receive a lower-leg amputation will die within five years. This is horrifying and has to stop.



Rates of type 2 diabetes in the U.S. vary significantly across geographies

Social determinants of health—factors that include access to food, housing, education and healthcare—play a key role in these disparities. Lack of access to healthy and affordable foods can increase the likelihood of developing type 2 diabetes. Lack of access to quality healthcare might mean that diabetes progression accelerates to an uncontrolled state, which increases the chances of catastrophic outcomes, including preventable disability and death.

This then begs the question: what is the healthcare industry doing about this? To fix the problem first requires being able to measure and understand it. Clinical trial data may identify the number of patients by race and ethnicity subgroups, but the outcomes by subgroup are not always reported, which can mask important differences and hide disparities. Further, those who have measured outcomes by population sub-groups seem reluctant to publish such data.

Until now, that included Virta. This year, we initiated an effort to more deeply understand how Virta affects patients from different backgrounds. Specifically, we looked at outcomes by Area Deprivation Index to approximate socioeconomic conditions of the area in which one lives and by self-reported race and ethnicity. We've decided to share this data, in part because we are excited about the results, but also because we believe there is much we and others can learn from it. Moreover, it presents opportunities for us all to better understand how to do even more to mitigate the effects of this devastating condition.

In observance of National Diabetes Awareness Month, we'll share what we are seeing in our patient population, and we encourage other diabetes-focused providers to do the same. In doing so, we'll uncover both what's

working well and where we need to improve. We are early in our health equity journey, but by sharing an early look at our data, we hope to start a discussion on how to accelerate the delivery of world-class metabolic health care to everyone who needs it.

Our series continues with an exploration of Virta patient outcomes in Part II: Outcomes by Socioeconomic Status and Part III: Outcomes by Race and Ethnicity.

Learn more about Virta's health equity work here. Watch a replay of our recent webinar on Closing Health Equity Gaps in diabetes care, which includes a deep dive on Virta's Health Equity Research Study.

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Virta's newest board member

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Hope for Health Equity (Part II): Virta Patient Outcomes by Socioeconomic Status

Published on November 2, 2022

Virta Health

This is Part II of a three part series on health equity. Part I summarized the disparities that exist in type 2 diabetes care. The series concludes with Part III: Outcomes by Race and Ethnicity.

In Part I of our series on health equity, we summarized the disparities that exist for people living with type 2 diabetes. In Part II, we begin to explore Virta patient outcomes, specifically through the lens of socioeconomic advantage or disadvantage.

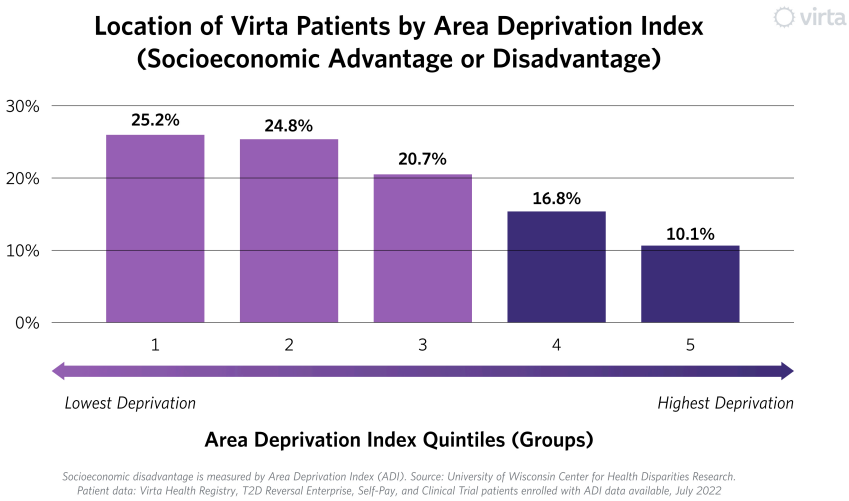
In our exploration, we first asked a simple question: are we moving the needle for those hardest hit by type 2 diabetes?

To answer this question, we first looked at our outcomes based on where our population lives. Where someone lives is a strong indicator of a person's risk of having diabetes and experiencing complications. Social determinants of health (SDOH)—income, housing, education, occupation, access to care, social structure and supports, and more—play a critical role in diabetes care and outcomes, and can vary substantially even for geographies that are in close proximity.

To help compare outcomes across geographies, we turned to the Area Deprivation Index (ADI). ADI is increasingly used as a strong proxy for socioeconomic conditions within a specific geographic area. Using census block groups or zip code, U.S. geographic areas are ranked by level of deprivation, then split into quintiles (five equal-sized groups). Group "1" includes the nation's least disadvantaged areas, and group "5" includes the most disadvantaged areas.

Where do Virta patients live?

The first thing we noticed when we used ADI to look at our population living with type 2 diabetes is that we enroll people who live in all types of neighborhoods—from the most socioeconomically advantaged to the most disadvantaged. In fact, 27% of our patients come from the two most disadvantaged groups in the country.[1]



27% of Virta patients are in the two most disadvantaged areas of the country

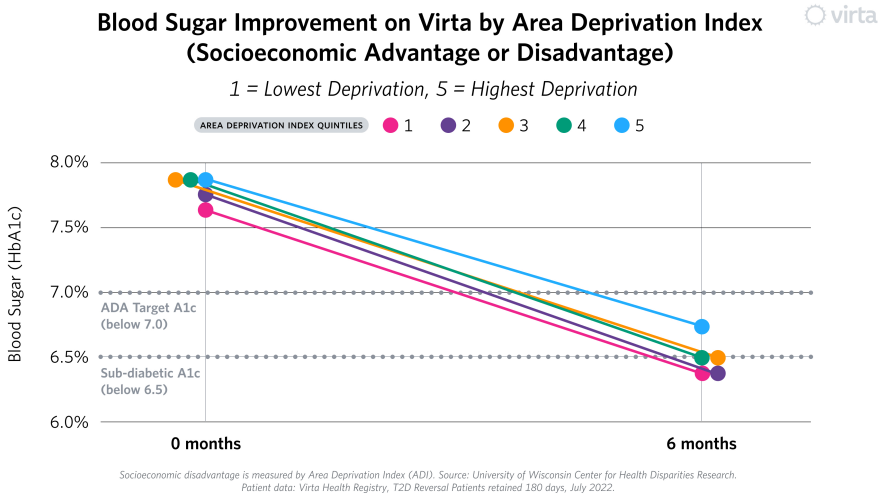
Today we skew toward more advantaged communities, and see an opportunity to increase our population in the more disadvantaged locations. One potential reason for the skew is that we have a small but non-trivial group of patients who self-pay. These individuals may be more likely to reside in advantaged groups. Our self-pay group will become a smaller portion of our overall population as more entities offer Virta as a covered benefit.

In addition, our population could be skewed to the higher quintiles because most of our patients receive Virta through employer-sponsored health insurance, where by definition they are employed and have insurance. Given that seven out of 10 patients with diabetes in the U.S. are covered by public programs, the most significant way we can accelerate a population shift is

through partnering with more government-sponsored health plans and programs—a strategic focus for Virta.

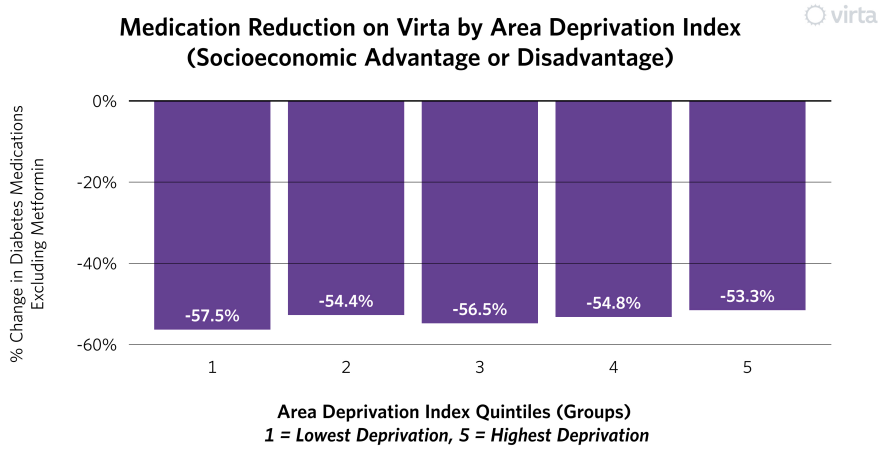
The outcomes: Virta's impact by Area Deprivation Index

Next, we looked at patient outcomes, and discovered that **Virta patients achieve life-changing health improvement, irrespective of where they live**. All ADI groups experienced at least a one point improvement in HbA1c (blood sugar) on average.[2] This threshold is important, as each one percentage point drop is associated with reduced risk of complications, including heart attacks, strokes, kidney disease, eye disease and more.



All ADI groups experienced at least a one point improvement in blood sugar (HbA1c)

All groups on average achieved results below the American Diabetes Association goal for blood sugar, and some groups even achieved blood sugar (HbA1c) levels below 6.5%—the level used to diagnose type 2 diabetes. Further, these results were achieved while *reducing or even eliminating medications*. Each group experienced at least a 50% reduction in diabetes prescriptions (excluding metformin).[3] This stands in stark contrast to typical diabetes care, where patients often require more medication, especially over longer periods of time.[4-5]



All groups significantly reduced blood sugar while reducing the need for medications

Much gets written about the power of telemedicine to democratize health care and narrow disparities by enabling high-quality care wherever someone lives. Virta has been a fully-virtual intervention from the beginning. Our results embody telemedicine's biggest aspirations. Viewing our outcomes through the ADI lens is one way to test this statement, and we are encouraged by what we are seeing.

We suspect one reason we see this level of consistency is that we built individualization into our treatment since day one. We personalize care to each person's religious and cultural background, food preferences, ability to access and afford healthy food, and medical needs.

This is not to say we've fully "cracked the code." Rather, we are continually asking how we can make these results better, and how we can optimize our approach to better recognize each individual journey. Initiatives already underway—from updating marketing and treatment materials to deepening our cultural competency training to continuing to improve the diversity of our coaching staff—can play a key role. For now though, we are encouraged, even as we recognize that there is important work ahead.

Our health equity series continues in Part III: Outcomes by Race and Ethnicity. In case you missed it, Part I summarizes the disparities that exist in type 2 diabetes care.

Learn more about Virta's health equity work here. Watch a replay of our recent webinar on Closing Health Equity Gaps in diabetes care, which includes a deep dive on Virta's Health Equity Research Study.

Citations

1. Patient data: Virta Health Registry, T2D Reversal Enterprise, Self-Pay, and Clinical Trial patients enrolled with ADI data available, July 2022. Groups 4 and 5 represent people living in the top 40% most disadvantaged areas of the United States.
2. Population includes patients enrolled in Virta's type 2 diabetes reversal program as of July 2022 who are retained for more than 180 days.
3. Data displays percent change in the number of diabetes medications other than metformin 180 days into treatment compared to enrollment
4. Hallberg SJ, McKenzie AL, Williams PT, et al. Effectiveness and Safety of a Novel Care Model for the Management of Type 2 Diabetes at 1 Year: An Open-Label, Non-Randomized, Controlled Study. Diabetes Therapy. 2018; 9:583–612.
5. The Look Ahead Research Group. Long-term Effects of a Lifestyle Intervention on Weight and Cardiovascular Risk Factors in Individuals with Type 2 Diabetes Mellitus - Four-year results of the Look AHEAD Trial. Arch Intern Med. 2010; 170: 1566-1575.

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Hope for Health Equity (Part I): Addressing Disparities in Type 2 Diabetes Care

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Hope for Health Equity (Part III): Virta Patient Outcomes by Race and Ethnicity

Published on November 3, 2022

Virta Health

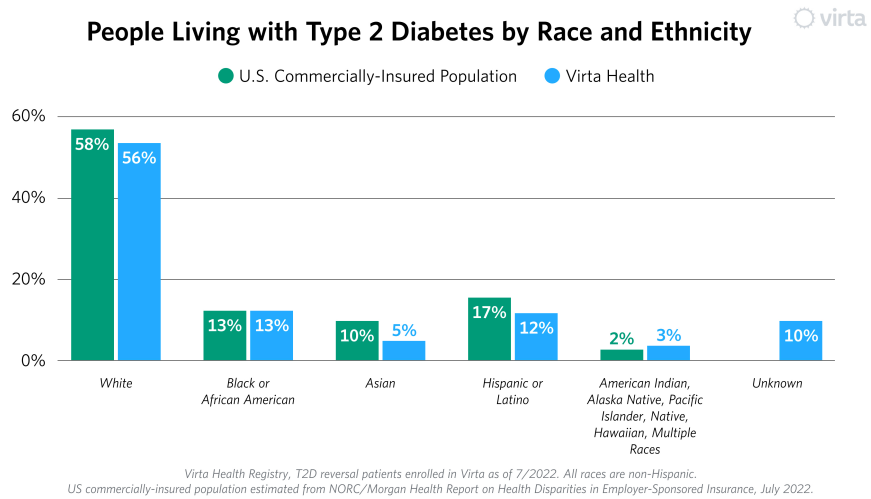
In Part I of this series, we outlined how type 2 diabetes is inherently a health equity issue: patients with socioeconomic challenges and people from many racial and ethnic minority groups are not only more likely to have type 2 diabetes, they also experience severe complications and poor outcomes at significantly higher rates. In Part II, we looked at how Virta is able to deliver consistent, world-class health outcomes to patients living in areas across a wide range of socioeconomic conditions. In Part III, we now look at Virta's outcomes by race and ethnicity.

Across healthcare, examining data by race and ethnicity—the foundation of understanding and improving disparities—presents significant hurdles. Public programs in particular suffer from "a critical lack of complete, standardized, self-identified race and ethnicity data" according to a recent NCQA report.

Further, people are often unwilling to share personal information for fear of discrimination, or because they don't identify with the options provided.

Health equity experts we've spoken with echo these challenges, underscoring how much work is to be done throughout the healthcare system. Virta addressed these challenges by adopting race and ethnicity data collection categories that better align to federal standards. We also undertook a rigorous data collection effort with our commercial population. This gave us insight into patients across our business, which primarily comes from more than 300 self-insured employers and commercial health plans that are our partners.

It is unsurprising, then, that the race and ethnicity composition closely mirrors that of the broader commercially-insured population nationally (with some notable exceptions, where today we under-index among non-Hispanic Asian and Hispanic or Latino populations).[1]



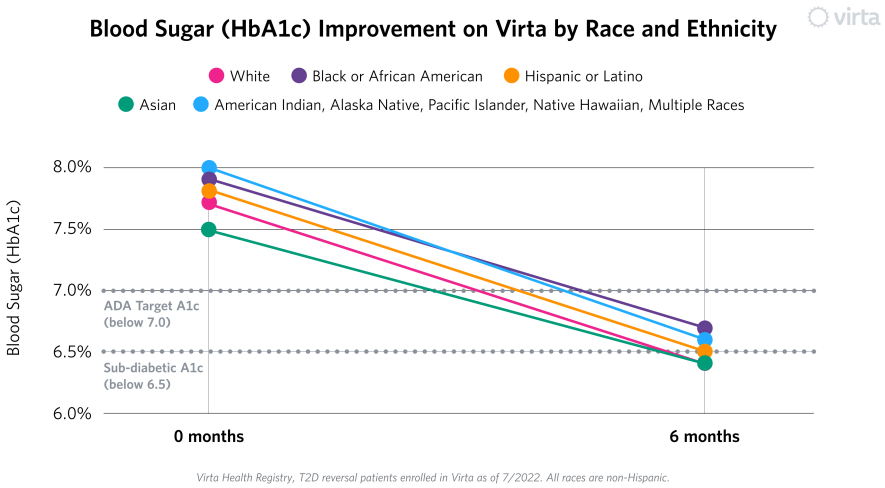
Virta's population reflects the U.S. commercially-insured population, with some exceptions

In raw numbers, one third of our patients come from racial and ethnic minority groups. Many of these groups experience higher than average prevalence of type 2 diabetes, and we see an opportunity to increase enrollment among the communities that are most affected. Some of this will happen organically, as Virta begins to work with more government-sponsored plans and programs that provide Virta as a covered benefit. We also see the opportunity to implement additional programs that expand our reach in these communities.

Virta Patient Outcome by Race and Ethnicity

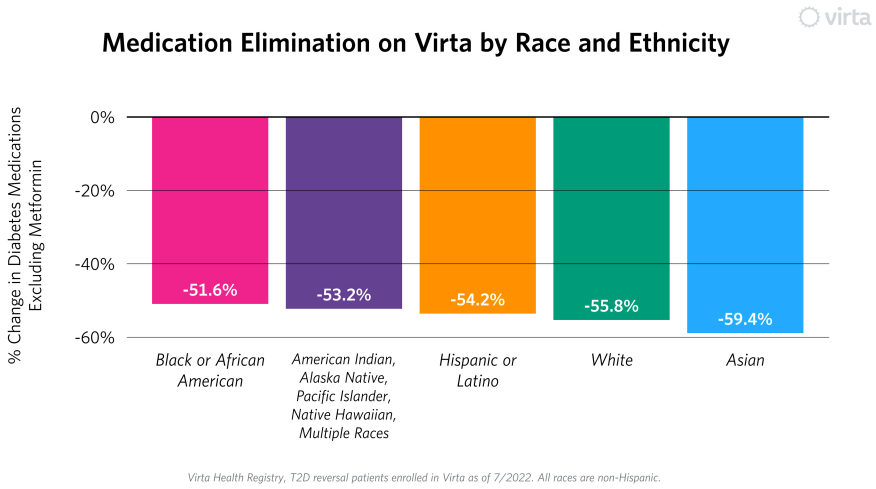
With that context, let's look at the results. Much like the ADI groups highlighted in Part II, **all racial and ethnic groups had at least a one point drop in HbA1c (blood sugar), ranging from 1.1% to 1.4%.**[2] This is clinically important, as every percentage point decrease in HbA1c is associated with a lower risk of complications (heart attack, stroke, kidney disease, eye disease

and more). Notably, all groups met or fell below the American Diabetes Association treatment target of blood sugar below 7.0%. Some groups even reached an average HbA1c below 6.5%, the level for diagnosis for type 2 diabetes.



All groups experienced more than a one point drop in blood sugar (HbA1c)

Critically, once again these improvements happened with significantly fewer medications, ranging from 52% to 59% reduction in overall use of diabetes prescriptions, excluding metformin.[2] This is counter to what typically happens within usual diabetes care, where there has been no improvement in population-level outcomes over a 10-year period, and emphasis is placed on medication *adherence*, not reduction in need.



All groups significantly reduced blood sugar while reducing the need for medications

In summary, **Virta's outcomes materially improve the health of our patients, through better blood sugar levels and less need for medication, irrespective of self-reported race and ethnicity**. Mere "management" by chasing A1c

with more and more medication fails to reverse the devastating trends in prevalence and cost that have been marching upward for decades.

And still, there is much more to be done. Although the results are clinically significant across all groups, differences remain. For example, non-Hispanic White people achieve sub-diabetic blood sugar at slightly higher rates than other groups.

We don't yet know exactly why this is, and much of the next phase of our work is asking why we see the results we do, so we can better inform our clinical roadmap to limit gaps and further increase effectiveness for all patients. Even so, there are things we are doing now that can help. For example, we have already increased the diversity of our coaches, and can continue to do so. Similarly, we can expand our cultural competency training initiatives, provide more culturally relevant content from marketing to enrollment to treatment, and more.

While we acknowledge the work ahead, we also celebrate the results we see within our diverse patient population. We see promise to help people with diabetes achieve profound health transformation, no matter where they live, their socioeconomic situation, or their race or ethnicity. More than ever, we are dedicated to making this a reality, and excited to build on this data to develop a roadmap to guide our future and the care we provide. And, we look forward to continuing to share what we learn along the way.

This concludes our three-part health equity series. In case you missed it, Part I summarized the disparities that exist in type 2 diabetes care. Part II examined Virta patient outcomes by socioeconomic status.

Learn more about Virta's health equity work here. Watch a replay of our recent webinar on Closing Health Equity Gaps in diabetes care, which includes a deep dive on Virta's Health Equity Research Study.

Citations

1. Population is from Virta's Enterprise deployments and Self-Pay and Clinical Trial patients who were enrolled in Virta's type 2 diabetes reversal program as of July 2022. All races reflected on the graph are non-Hispanic. Proportion of US commercially-insured population with T2D identifying as each race and ethnicity was estimated from data contained in the NORC/Morgan Health Report on Health Disparities in Employer-Sponsored Insurance among working age individuals (25-64 years of age) with private insurance, July 2022.
2. Population includes patients enrolled in Virta's type 2 diabetes reversal program who were treated for more than 180 days as of July 2022.
3. Data displays percent change in the number of diabetes medications other than metformin prescribed to the group 180 days into treatment compared to enrollment.

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virta + ValidationInstitute

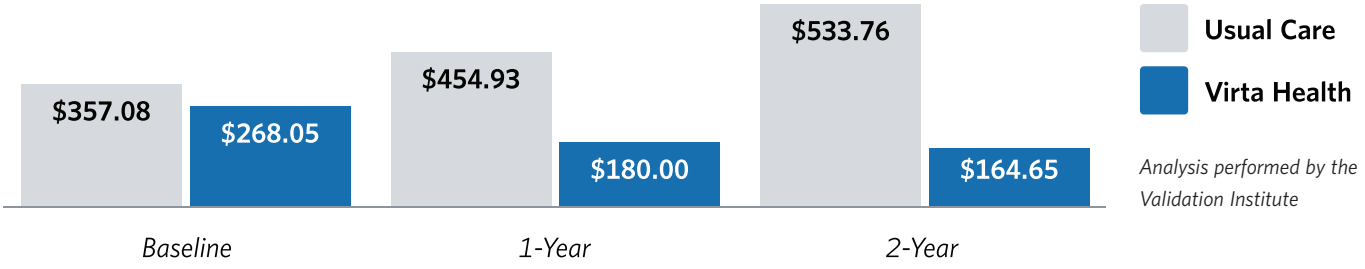
Virta is the only diabetes vendor to achieve outcomes, savings, and program validations.

Diabetes and prediabetes affect nearly 50% of Americans.[1] In addition to the devastating personal costs of the disease—nearly $400B is spent on diabetes every year.[2] So unsurprisingly, there are no shortage of health solutions making big claims that they can make a dent in this epidemic. But consistent measurement and validation of impact is lacking, making it difficult to understand a basic question—does this solution actually work?

Our outcomes and savings claims are backed by years of research and one of the longest clinical trials in digital diabetes interventions. But don't take our word for it.

The Validation Institute has now awarded Virta three distinct validations: level 1 savings validation, level 2 outcomes validation, and the comprehensive program validation.

Level 1 Validation: Virta Reduces Rx Spend



Analysis performed by the Validation Institute

KEY TAKEAWAY: Virta reduces Rx spend by $280 per patient per month over two years[3] (2 year difference – baseline difference). When following usual care, patients are often prescribed more and more medication to manage their diabetes, but with Virta, the opposite happens. Rx costs go down consistently, year after year.

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Level 2 Validation: Virta Produces Real Health Outcomes

	IMPROVEMENT VS. BASELINE	
Measure	**At One Year**	**At Two Years**
HbA1c	-1.3	-0.9
Weight (kg)	-14.29	-11.94
Weight (%)	-11.80%	-10.40%
T2D Medication Excl Metformin (% of pts)	Decrease from 56.9% → 29.7%	Decrease from 56.9% → 26.8%

Athinarayanan et al, Long-Term Effects of a Novel Continuous Remote Care Intervention Including Nutritional Ketosis for the Management of Type 2 Diabetes: A 2-Year Nonrandomized Clinical Trial. Frontiers in Endocrinology (2019) 10:348. Mean change in HbA1c and weight were derived using an intent-to-treat analysis from a linear mixed effect model.

KEY TAKEAWAY: Virta meaningfully moves the needle on several key outcomes for patients with Type 2 diabetes, including clinically significant weight loss and A1c reductions, and medication deprescription.

Virta is the only digital health solution to achieve level 1 and 2 validations, plus the newly developed Program Validation.

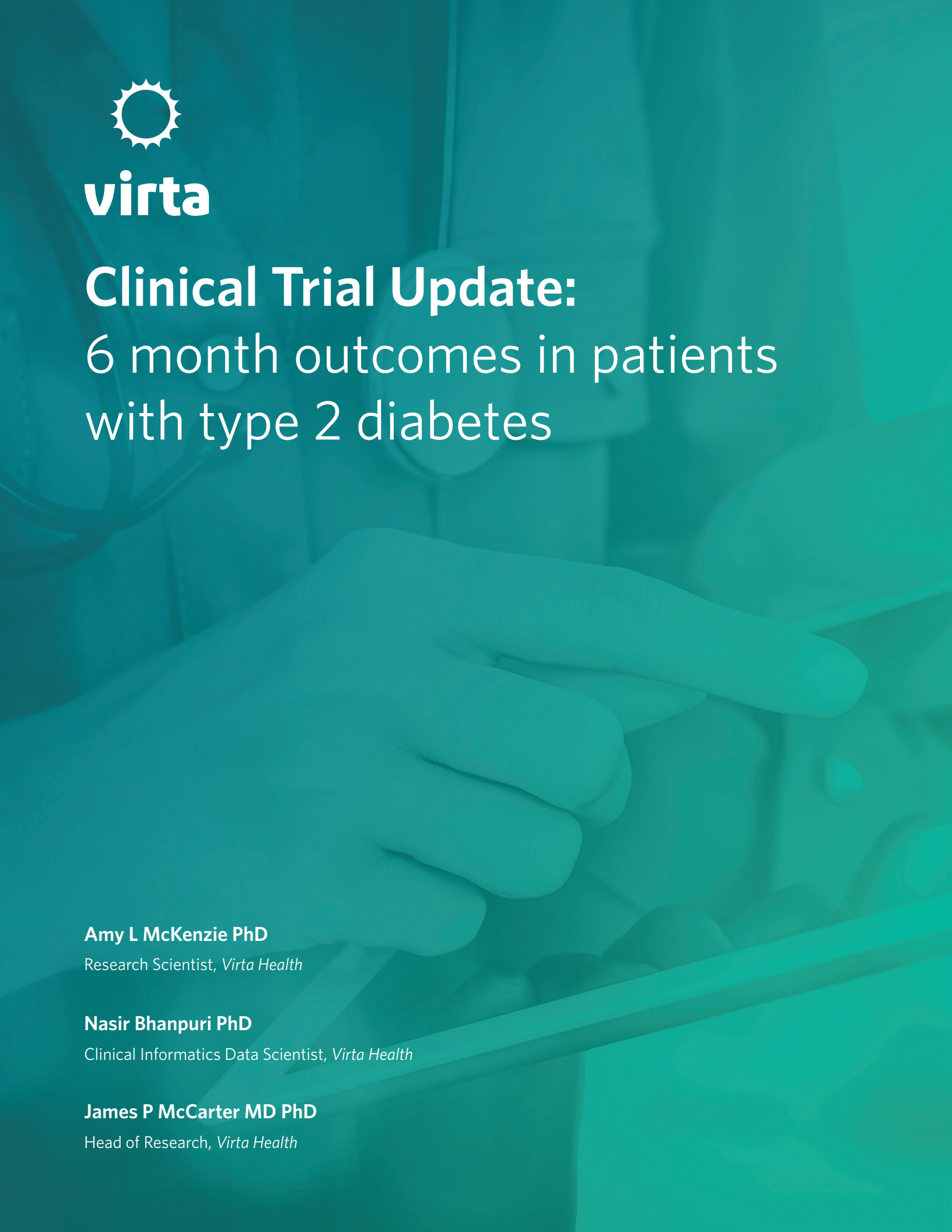
In addition to achieving level 1 and level 2 validations, Virta is the first digital health solution to receive the newly-developed Program Validation. This validation recognizes Virta for the rigorous, evidence-based research underlying its diabetes reversal treatment, and its best-in-class financial and health outcomes for employer customers.

PROGRAM VALIDATION
Must prove clinical rigor using one of five gold standard evaluation methodologies. Further, companies must first achieve both savings and outcomes validations.

$50K GUARANTEE

LEVEL ONE: SAVINGS
Can produce a reduction of health care spending including the cost of the provider. Product/solution has produced, and replicated a lower cost for healthcare overall or a specific component of healthcare.

LEVEL TWO: OUTCOMES
Product/solution has measurably "moved the needle" on an outcome (risk, HbA1c, events, employee retention, etc.) of importance.



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Clinical Trial Update:
6 month outcomes in patients with type 2 diabetes

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Clinical Trial Update: 6 month outcomes in patients with type 2 diabetes

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Virta Health

Nearly 30 million Americans[1] and over 400 million people worldwide[2] live with type 2 diabetes (T2D), a condition that is considered chronic and progressive with no cure[3]. While capable of improving glycemic control, pharmacological therapy and bariatric surgery are often accompanied by side effects[4], reduced quality of life[5], and economic burden[6], highlighting the critical need for interventions with better outcomes without the negative impact.

Intensive lifestyle interventions and nutritional medicine often improve health outcomes for people living with diabetes in the short term, but evidence for their sustainability over the long term is limited.[7] Another challenge for treatment of chronic conditions is the need for continuous care, which is difficult to provide in an outpatient setting.[8]

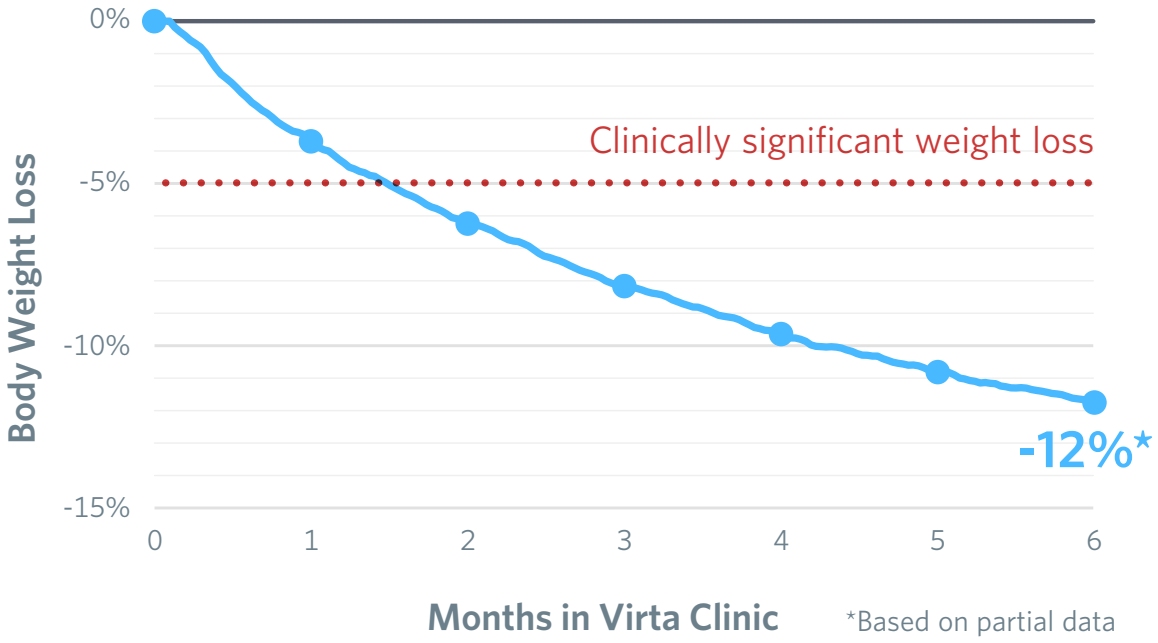
At the Virta Clinic, we hope to address these challenges by providing patients with intensive, personalized interventions backed by continuous support from our remote care team of health coaches and physicians. Our research efforts will evaluate the efficacy, safety, sustainability, and economic impact of care within the Virta Clinic for people living with T2D. Our ongoing research will allow us to continuously improve our personalized care plans to positively impact health outcomes for patients.

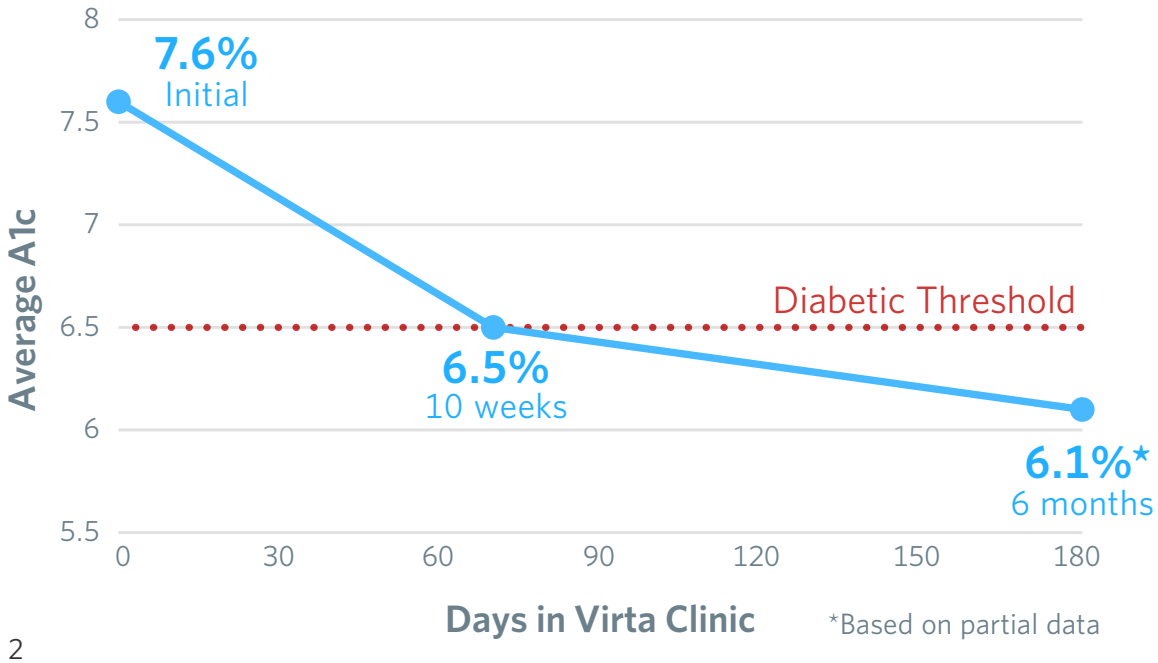
In partnership with Indiana University Health Arnett, we have undertaken a clinical trial to evaluate the efficacy of the personalized care plans utilized at the Virta Clinic for 262 patients with a diagnosis of T2D (baseline characteristics, mean±SD—age: 54±8 y, body mass: 117±26 kg, BMI: 41±9 $kg \cdot m^{-2}$, 66.8% (175/262) women, HbA1c: 7.6±1.5%, with 89% prescribed at least 1 glycemic control medication). At the Virta clinic, each patient receives an individualized plan for nutritional ketosis, behavioral and social support, biomarker tracking tools, and ongoing care from a health coach with medication management by a physician.

Recently, we published short-term, 10 week health outcomes for these patients.[9] On average, patients reduced their HbA1c 1.1% from 7.6% at enrollment with 91% retention. Fifty-six percent (147 of 262) of participants achieved an HbA1c <6.5% at follow up, and 97% (143 of 147) of those participants achieved this without an increase in the number or dosage of diabetic medications. Further, 64% of insulin, sulfonylurea, SGLT-2 inhibitor, DPP-4 inhibitor, and thiazolidinedione prescriptions were

eliminated in 10 weeks. The average patient lost 7.2% of their body weight—75% of completers attained clinically significant weight loss during this time (more than 5% of their body weight).

After 6 months, 89% of participants were still enrolled in the study. Glycosylated hemoglobin was reduced to 6.1±0.7% from 7.5±1.3% in a sample of 108 participants who elected to test HbA1c at 6 months. Twenty-two of the 108 started with a HbA1c <6.5%, and at 6 months, 82 of 108 (76%) reduced their HbA1c below the threshold for diabetes diagnosis (6.5%). Patients lost 11.5±8.8% of their body weight; 81% (212 of 262) patients attained clinically significant weight loss. Most medication eliminations were maintained through 6 months concurrently with reduced HbA1c and weight.





Discussion

Improvements in glycemic control and lipid profiles in adults with T2D have been associated with weight loss of greater than 5%[10], making weight loss a desired component of many T2D treatment plans. The assumption in this paradigm is often that weight loss leads to the improvements in glycemic control, but it's possible that improvements in glycemic control occur simultaneously with or before significant weight loss is achieved. In our 10 week outcomes, weight and HbA1c reduction seemingly occur simultaneously, but with significant reductions in HbA1c occurring even before the full life cycle of red blood cells (approximately 100 days). Other research demonstrates improvements in glycemic control occur prior to significant weight loss. Patients with T2D who consumed a low carbohydrate (21g per day) diet had significantly improved insulin sensitivity concurrent with significantly lower plasma glucose and HbA1c, but only 2kg (1.8%) weight loss after two weeks[11]. This early improvement in glycemic control is further highlighted by how quickly insulin and some oral anti-diabetic medications must be reduced or eliminated when a low carbohydrate diet is begun, with most reductions and eliminations occurring in the first 3 weeks[11,12]. This suggests weight loss may not be the driver of improved glycemic control, but rather a positive side effect that is achieved concurrently with a well-formulated, very low carbohydrate diet.

Glycosylated hemoglobin and weight changes after 6 and 12 months were evaluated in a systematic review and meta-analysis of 11 studies involving intensive lifestyle interventions for adults with T2D who were also overweight or obese[10]. HbA1c was not evaluated at 6 months in any of these studies, but at 1 year, changes in HbA1c ranged from +0.2% to -1.2% with only 4 interventions eliciting a reduction greater than 0.5%. Interventions utilizing meal replacements, reduced energy intake, and a diet containing <25% of caloric intake from carbohydrates helped patients lose more than 5% of their weight in 6 months. In all but 2 studies, patients regained weight between 6 and 12 months; weight loss was maintained within 0.1% in the remaining 2 investigations. Published earlier this year, a small RCT evaluated 32 week (8 month) health outcomes following the online delivery of a low-carbohydrate intervention with lifestyle recommendations compared to the American Diabetes Association's "Create Your Plate" diet in adults with T2D who were "ready to change" and "conscientious", as defined by the researchers.[13] After 8 months, participants in the low carbohydrate intervention group reduced HbA1c by 0.8% from 7.1% at enrollment and reduced body weight 11.6% from 110 kg at baseline. In summary, most interventions were not successful at achieving clinically significant weight loss in 6 months and were accompanied by a range of responses in HbA1c. However, the online program utilizing a low carbohydrate diet[13] was the most impactful on both HbA1c and body weight in this timeframe.

It's important to note that reductions in HbA1c and weight were achieved in these studies through the delivery of special programs or intensive interventions with patients, not from one-time instruction. However, none of these programs are available outside of research studies to help adults with T2D

follow through on clinical advice. On the other hand, commercially available weight loss programs have recently been adapted specifically for adults with T2D; one such program was compared to the standard of care in an RCT.[14] At 6 months, this program helped patients reduce HbA1c 0.7% and lose 4% of body weight, compared to only 2% weight loss and no change in HbA1c in the standard of care control group. Although it is difficult to compare our results directly to interventions in separate RCTs, patients with T2D receiving care at the Virta Clinic lost nearly three times as much weight in 6 months, with a loss of 11.5%, compared to this commercially available program, and over 5 times as much as the standard of care group in this study.

Maintaining these health outcomes is a known and ongoing challenge for many intensive interventions. The team at Virta is focused on evaluating long-term outcomes and sustainability in our patients, committed to learning from our research and the research of others, and constantly evolving care plans to meet individual patient goals and needs. While six months is early in long-term maintenance, we look forward to sharing our 1- and 2- year outcomes and learnings in the peer-reviewed literature as the data become available.

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ORIGINAL RESEARCH

Effectiveness and Safety of a Novel Care Model for the Management of Type 2 Diabetes at 1 Year: An Open-Label, Non-Randomized, Controlled Study

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ABSTRACT

Introduction: Carbohydrate restriction markedly improves glycemic control in patients with type 2 diabetes (T2D) but necessitates prompt medication changes. Therefore, we assessed the effectiveness and safety of a novel care model providing continuous remote care with medication management based on biometric feedback combined with the metabolic approach of nutritional ketosis for T2D management.

Methods: We conducted an open-label, non-randomized, controlled, before-and-after 1-year study of this continuous care intervention (CCI) and usual care (UC). Primary outcomes were glycosylated hemoglobin (HbA_{1c}), weight, and medication use. Secondary outcomes included fasting serum glucose and insulin, HOMA-IR, blood lipids and lipoproteins, liver and kidney function markers, and high-sensitivity C-reactive protein (hsCRP).

Results: 349 adults with T2D enrolled: CCI: $n = 262$ [mean (SD); 54 (8) years, 116.5 (25.9) kg, 40.4 (8.8) kg m^2, 92% obese, 88% prescribed T2D medication]; UC: $n = 87$ (52 (10) years, 105.6 (22.15) kg, 36.72 (7.26) kg m^2, 82% obese, 87% prescribed T2D medication]. 218 participants (83%) remained enrolled in the CCI at 1 year. Intention-to-treat analysis of the CCI (mean ± SE) revealed HbA_{1c} declined from

Enhanced content To view enhanced content for this article go to https://doi.org/10.6084/m9.figshare.5803119.

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59.6 ± 1.0 to 45.2 ± 0.8 mmol mol^{-1} ($7.6 \pm 0.09\%$ to $6.3 \pm 0.07\%$, $P < 1.0 \times 10^{-16}$), weight declined 13.8 ± 0.71 kg ($P < 1.0 \times 10^{-16}$), and T2D medication prescription other than metformin declined from $56.9 \pm 3.1\%$ to $29.7 \pm 3.0\%$ ($P < 1.0 \times 10^{-16}$). Insulin therapy was reduced or eliminated in 94% of users; sulfonylureas were entirely eliminated in the CCI. No adverse events were attributed to the CCI. Additional CCI 1-year effects were HOMA-IR -55% ($P = 3.2 \times 10^{-5}$), hsCRP -39% ($P < 1.0 \times 10^{-16}$), triglycerides -24% ($P < 1.0 \times 10^{-16}$), HDL-cholesterol $+18\%$ ($P < 1.0 \times 10^{-16}$), and LDL-cholesterol $+10\%$ ($P = 5.1 \times 10^{-5}$); serum creatinine and liver enzymes (ALT, AST, and ALP) declined ($P \leq 0.0001$), and apolipoprotein B was unchanged ($P = 0.37$). UC participants had no significant changes in biomarkers or T2D medication prescription at 1 year.

Conclusions: These results demonstrate that a novel metabolic and continuous remote care model can support adults with T2D to safely improve HbA_{1c}, weight, and other biomarkers while reducing diabetes medication use.

ClinicalTrials.gov Identifier: NCT02519309.

Funding: Virta Health Corp.

PLAIN LANGUAGE SUMMARY

Treatments for type 2 diabetes (T2D) have improved, yet T2D and being overweight are still significant public health concerns. Blood sugar in patients with T2D can improve quickly when patients eat significantly fewer dietary carbohydrates. However, this demands careful medicine management by doctors, and patients need support and frequent contact with health providers to sustain this way of living. The purpose of this study was to evaluate if a new care model with very low dietary carbohydrate intake and continuous supervision by a health coach and doctor could safely lower HbA1c, weight and need for medicines after 1 year in adults with T2D. 262 adults with T2D volunteered to participate in this continuous care intervention (CCI) along with 87 adults with T2D receiving usual care (UC) from their doctors and diabetes education program. After 1 year, patients in the CCI, on average, lowered HbA1c from 7.6 to 6.3%, lost 12% of their body weight, and reduced diabetes medicine use. 94% of patients who were prescribed insulin reduced or stopped their insulin use, and sulfonylureas were eliminated in all patients. Participants in the UC group had no changes to HbA1c, weight or diabetes medicine use over the year. These changes in CCI participants happened safely while dyslipidemia and markers of inflammation and liver function improved. This suggests the novel care model studied here using dietary carbohydrate restriction and continuous remote care can safely support adults with T2D to lower HbA1c, weight, and medicine use.

Keywords: Beta-hydroxybutyrate; Carbohydrate restriction; HbA1c; Ketosis; Type 2 diabetes; Weight loss

Abbreviations

ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ApoB	Apolipoprotein B
AST	Aspartate aminotransferase
BHB	Beta-hydroxybutyrate
BUN	Blood urea nitrogen
CBC	Complete blood count
CCI	Continuous care intervention
CCI-onsite	Subset of participants who selected on-site education
CCI-web	Subset of participants who selected web-based education
CMP	Complete metabolic panel
DPP-4	Dipeptidyl peptidase-4 inhibitor
eGFR	Estimated glomerular filtration rate
FT4	Free T4
GLP-1	Glucagon-like peptide 1 receptor agonists
HOMA-IR	Homeostatic model assessment of insulin resistance
hsCRP	High-sensitivity C-reactive protein
PCP	Primary care provider
SGLT-2	Sodium glucose co-transporter 2 inhibitors
T2D	Type 2 diabetes

TSH	Thyroid stimulating hormone
UC	Usual care
VLCD	Very low energy diet

INTRODUCTION

The number of people living with diabetes worldwide nearly quadrupled since 1980, estimated at 422 million in 2014 [1]. In the USA, the Centers for Disease Control reports 30.3 million adults presently live with diabetes, and it is among the leading causes of death [2]. Treatment modalities for type 2 diabetes (T2D) have demonstrated varying success. Intensive lifestyle interventions are effective treatments for obese individuals with T2D when weight loss is achieved and sustained [3]. Evidence for improved cardiovascular outcomes in patients with T2D prescribed glucagon-like peptide 1 receptor agonists (GLP-1) and sodium glucose co-transporter 2 inhibitors (SGLT-2) is increasing [4, 5]. Forty percent of patients undergoing bariatric surgery demonstrate substantial improvements in glycemic control after 1 year and many achieve T2D remission [6]. Despite advancements in treatment options, cost, side effects, adherence, and disease progression remain barriers.

Guidelines for T2D management recommend lifestyle change and weight loss [7, 8]. However, a fraction of individuals are successful at long-term weight loss maintenance and true disease remission is uncommon [3, 9]. Mediterranean-style, DASH, and plant-based diets, sometimes with prescribed energy restriction, are recommended, but effectiveness data are limited [7] and low fat diets have not been shown to be superior for weight loss [10]. Commercially available weight loss programs have demonstrated short-term success in glycemic control, but continued success at 1 year is uncommon [11].

Glycemic control can be achieved quickly with carbohydrate restriction via very low energy diets (400–800 kcal day^{-1}; VLCD) [12]. However, VLCD are necessarily temporary and outcomes often revert when patients resume former dietary patterns. Alternatively, nutritional ketosis, achieved by consuming moderate protein and greatly reduced carbohydrate, results in similarly increased serum beta-hydroxybutyrate (BHB) concentrations as observed during VLCD, which signifies a shift to using fat as the body's primary fuel source [12]. This nutritional therapy may help patients achieve sustainable glycemic control without prescribed energy restriction. Benefit may accrue from decreased circulating glucose and insulin [13], ketone signaling [14, 15], or eventual weight loss. Studies utilizing carbohydrate restriction observed improved glycemic control and cardiometabolic markers, but were often short-term trials of small groups, excluded subjects prescribed insulin, or infrequently monitored or achieved ketosis [16–20].

The chronic nature of diabetes care presents an additional challenge requiring sustained behavioral change that is difficult to support with traditional medical care including infrequent provider contact [21]. Adherence to lifestyle changes may be poor in the absence of support from providers and peers. We therefore hypothesized that a comprehensive care model that supports patients to achieve sustained nutritional ketosis while eating to satiety may have robust benefits in T2D management. This intervention utilizes continuous care through intensive, digitally enabled support including telemedicine access to a medical provider (physician or nurse practitioner), health coaching, nutrition and behavior change education and individualized care plans, biometric feedback, and peer support via an online community. Thus, the purpose of this study was to assess the effectiveness and safety of a novel care model (Virta Clinic, Virta Health; San Francisco, CA, USA) for the management of T2D after 1 year. Secondary aims were (1) to determine if a difference in primary outcomes existed between participants who self-selected on-site versus web-based education delivery and (2) explore the time course of biomarker change at 70 days and 1 year into the CCI. Primary endpoints to assess effectiveness of the intervention were change in glycosylated hemoglobin (HbA_{1c}), body weight, and medication prescription after 1 year. Secondary outcomes, including clinical biomarkers of

associated physiological systems and adverse events, were assessed to determine safety of the intervention.

METHODS

We utilized an open-label, non-randomized, controlled, before-and-after study design with a cohort of patients who self-selected to participate in the metabolic and continuous care intervention (CCI) for T2D and a comparison group of patients who self-selected to participate while receiving their usual care (UC) from their own medical providers and diabetes education program (Clinicaltrials.gov Identifier NCT02519309). Adults diagnosed with T2D were recruited via clinical referrals, local advertisements, and word of mouth in Lafayette, Indiana, USA and surrounding region from August 2015 through March 2016. This study was approved by the Franciscan Health Lafayette Institutional Review Board. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Continuous Care Intervention

Participants in the CCI underwent history and physical exam followed by laboratory testing to ensure they met inclusion and exclusion criteria (Supplementary Materials A). Upon qualifying, CCI participants received biomarker tracking tools including a cellular-connected body weight scale (BT003, Body Trace; New York, NY, USA), a finger-stick blood glucose and ketone meter (Precision Xtra, Abbott; Alameda, CA, USA), and a blood pressure cuff if hypertension was diagnosed (BP742 N, Omron Healthcare, Inc.; Lake Forest, IL, USA). Access to a web-based software application (app) was provided for biomarker reporting and monitoring, education, and communication with remote care team (via telemedicine) consisting of a health coach and medical provider (physician or nurse practitioner) for advice and medication management. Social support was provided via an online peer community. Participants in the CCI retained their primary care provider (PCP) for conditions other than metabolic disease, and care coordination between the PCP and CCI provider occurred as needed. Frequency and type of biomarker tracking were individualized on the basis of care needs and recorded by participants in the app; initial participant instructions were to weigh and measure blood BHB concentration daily, and to measure blood glucose one to three times daily. The remote care team monitored this information; a medical provider made medication changes as indicated by the participant-reported biomarkers (Supplementary Materials B).

Participants were provided individualized nutrition recommendations that allowed them to achieve and sustain nutritional ketosis with a goal of 0.5–3.0 mmol L^{-1} blood BHB. Participants were encouraged to report daily hunger, cravings, energy, and mood on a four-point Likert scale. These ratings and BHB concentrations were utilized to adjust nutritional guidance. With the insulin resistance characteristic of T2D, patients typically require total dietary carbohydrates to be restricted to less than 30 g day^{-1} to achieve nutritional ketosis. Health coaches monitored blood BHB concentrations logged by participants and worked with participants individually to adjust dietary carbohydrate intake to a level that would allow them to achieve nutritional ketosis. Daily protein intake was initially targeted to a level of 1.5 g kg^{-1} of reference (i.e., medium-frame "ideal") body weight and adjusted as necessary to aid participants in achieving nutritional ketosis based on participant-logged blood BHB concentrations. Participants were coached to incorporate dietary fats to satiety. Participants were advised to consume adequate intake of omega-3 (eicosapentaenoic acid and docosahexaenoic acid) and omega-6 (linoleic acid) polyunsaturated fats [22], while it was recommended that the remainder of their intake from fat come from both monounsaturated and saturated sources. Other aspects of the diet were individually prescribed to ensure safety, effectiveness, and

satisfaction, including consumption of 3–5 servings of non-starchy vegetables and adequate mineral and fluid intake for the ketogenic state. At onset of dietary changes, participants were advised to consume a multivitamin, 1000–2000 IU vitamin D3, and up to 1000 mg omega-3 daily. If participants exhibited signs of magnesium depletion (e.g., muscle twitches or cramps), daily supplementation (500 mg magnesium oxide or 200 mg magnesium chloride) was suggested. If participants exhibited headaches, constipation, or lightheadedness, adequate sodium and fluid intake was recommended. BHB concentrations were also utilized as a marker of adherence to nutritional ketosis. Behavior change strategies were utilized by the remote care team and tailored to the needs of each participant to help achieve glycemic control. Examples of techniques utilized include education of natural consequences, shaping knowledge, goal setting, self-monitoring, feedback, monitoring and reinforcement from health coach and medical provider, self-belief, social support, relapse prevention, associations, and repetition.

Participants in the CCI self-selected how they would receive most of their education: (1) via on-site group education classes that met weekly for 12 weeks, bi-weekly for 12 weeks, and monthly for 6 months ($n = 136$; CCI-on-site) or (2) via web-based, recorded educational content viewed independently through the app ($n = 126$; CCI-web). Educational content was the same regardless of delivery method (Supplementary Materials C), and all other aspects of care were the same. During on-site classes, health coaches presented educational content and medical providers met with participants individually. Participants receiving web-based education could schedule visits with the CCI medical provider if desired. Apart from education delivery, both groups received remote care from health coaches.

Usual Care

Participants in the UC group were patients with diagnosed T2D who were recently referred to the local diabetes education program by their primary care physician or endocrinologist where they were counseled by registered dietitians on diabetes self-management, nutrition, and lifestyle [7]. Medical care for their T2D was provided by their primary care physician or endocrinologist. No modification to the care that they received for their T2D was made by the study. This group was observed at baseline and 1 year as reference for typical disease treatment and progression over 1 year within the same geographical, health care, and laboratory locations. UC participants attended a separate information session and informed consent was obtained followed by laboratory testing to ensure they met all inclusion and exclusion criteria. Patients were informed that the trial also had an intervention arm and could participate in that group if they chose to do so.

Outcome Measures

In-clinic vital signs and anthropometrics were obtained at baseline, 70-days (CCI only [23]), and 1-year follow-up. Height was assessed via stadiometer for calculation of body mass index. In-clinic weight for all participants was measured to the nearest 0.1 lb (Model 750, Detecto; Webb City, MO, USA) and converted to kg. In-clinic blood pressure was obtained manually by trained staff after participants rested in a seated position for 5 min. Adverse events were reported to the Principal Investigator and reviewed by the Institutional Review Board.

Fasted blood draws occurred at baseline, 70-days (CCI only [23]), and 1-year follow up. Blood analytes were determined via standard procedures at a Clinical Laboratory Improvement Amendment (CLIA) accredited laboratory on the day of sample collection or from stored serum (Supplementary Materials D).

Statistical Analysis

Statistical analyses were performed using JMP software (version 5.1, SAS Institute; Cary, SC, USA) for all analyses except multiple imputation, for which we used Stata software (version 11, StataCorp; College Station, TX, USA). Multiple imputation was used to estimate means

Table 1 Baseline characteristics of the recruited sample, completers, and participants with missing data by treatment arm

	All		Completers with data		Dropout or missing data		Completers-Dropouts Mean ± SE
	N	Mean (SD) or ±SE	*N*	Mean (SD) or ±SE	*N*	Mean (SD) or ±SE	
Age (years)							
CCI-all education[a]	262	53.75 (8.35)	218	54.09 (8.35)	44	52.09 (8.25)	2.0 ± 1.37
Usual care[a]	87	52.33 (9.52)	78	51.71 (9.62)	9	57.78 (6.85)	− 6.07 ± 2.53*
CCI-all vs. usual care[b]		1.42 ± 1.14		2.38 ± 1.23*		− 5.69 ± 2.6*	
Female (%)							
CCI-all education[a]	262	66.79 ± 2.91	218	65.14 ± 3.23	44	75.0 ± 6.53	− 9.86 ± 7.28
Usual care[a]	87	58.62 ± 5.28	78	60.26 ± 5.54	9	44.44 ± 16.56	15.81 ± 17.47
CCI-all vs. usual care[b]		8.17 ± 6.03		4.88 ± 6.41		30.56 ± 17.8	
African American (%)							
CCI-all education[a]	262	6.87 ± 1.56	218	5.96 ± 1.6	44	11.36 ± 4.78	− 5.4 ± 5.05
Usual care[a]	87	0.0 ± 0.0	78	0.0 ± 0.0	9	0.0 ± 0.0	0.0 ± 0.0
CCI-all vs. usual care[b]		6.87 ± 1.56§		5.96 ± 1.6‡		11.36 ± 4.78*	
Years with type 2 diabetes							
CCI-all education[a]	261	8.44 (7.22)	217	8.4 (7.28)	44	8.61 (6.97)	− 0.21 ± 1.16
Usual care[a]	71	7.85 (7.32)	71	7.85 (7.32)		Not collected	
CCI-all vs. usual care[b]		0.59 (0.9)		0.56 ± 1.0			
Beta-hydroxybutyrate (mmol L^{-1})							
CCI-all education[a]	248	0.17 (0.15)	186	0.17 (0.15)	62	0.19 (0.16)	− 0.02 ± 0.02
Usual care[a]	79	0.15 (0.13)	59	0.14 (0.12)	20	0.17 (0.15)	− 0.03 ± 0.03
CCI-all vs. usual care[b]		0.02 ± 0.02		0.02 ± 0.02		0.02 ± 0.04	
Hemoglobin A_{1c} (mmol mol^{-1})							
CCI-all education[a]	262	59.55 (16.4)	204	58.35 (15.3)	58	63.49 (19.57)	− 28.66 ± 2.73
Usual care[a]	87	59.99 (19.24)	72	61.08 (19.89)	15	54.52 (14.87)	− 16.97 ± 4.48
CCI-all vs. usual care[b]		− 0.44 ± 2.3		− 2.73 ± 2.62		8.96 ± 4.59*	
Hemoglobin A_{1c} (%)							
CCI-all education[a]	262	7.60 (1.50)	204	7.49 (1.4)	58	7.96 (1.79)	− 0.47 ± 0.25
Usual care[a]	87	7.64 (1.76)	72	7.74 (1.82)	15	7.14 (1.36)	0.60 ± 0.41
CCI-all vs. usual care[b]		− 0.04 ± 0.21		− 0.25 ± 0.24		0.82 ± 0.42*	
Fasting glucose (mmol L^{-1})							
CCI-all education[a]	258	8.92 (3.41)	202	8.8 (3.28)	56	9.36 (3.83)	− 0.55 ± 0.56
Usual care[a]	86	8.67 (4.03)	71	8.71 (3.96)	15	8.5 (4.5)	0.21 ± 1.25
CCI-all vs. usual care[b]		0.25 ± 0.48		0.1 ± 0.52		0.86 ± 1.27	

Table 1 continued

	All		Completers with data		Dropout or missing data		Completers-Dropouts Mean ± SE
	N	Mean (SD) or ±SE	*N*	Mean (SD) or ±SE	*N*	Mean (SD) or ±SE	
Insulin all (pmol L^{-1})							
CCI-all education[a]	248	198.35 (165.85)	186	197.65 (167.17)	62	200.5 (163.21)	− 2.85 ± 24.1
Usual care[a]	79	202.17 (172.58)	59	206.68 (187.93)	20	188.77 (119.18)	17.99 ± 36.18
CCI-all vs. usual care[b]		− 3.82 ± 22.09		− 9.1 ± 27.36		11.74 ± 33.75	
C-peptide (nmol L^{-1})							
CCI-all education[a]	247	1.45 (0.71)	185	1.47 (0.72)	62	1.39 (0.69)	0.07 ± 0.1
Usual care[a]	79	1.38 (0.82)	59	1.35 (0.82)	20	1.49 (0.84)	− 0.14 ± 0.22
CCI-all vs. usual care[b]		0.07 ± 0.1		0.12 ± 0.12		− 0.09 ± 0.21	
HOMA-IR (insulin derived), all							
CCI-all education[a]	244	11.8 (13.14)	179	11.19 (12.75)	65	13.48 (14.12)	− 2.3 ± 1.99
Usual care[a]	78	10.64 (9.12)	56	11.31 (10.05)	22	8.94 (6.03)	2.36 ± 1.86
CCI-all vs. usual care[b]		1.16 ± 1.33		− 0.12 ± 1.65		4.54 ± 2.17	
HOMA-IR (insulin derived), excluding exogenous users							
CCI-all education[a]	172	11.77 (13.87)	129	11.00 (13.53)	43	14.09 (14.76)	− 3.08 ± 2.55
Usual care[a]	43	9.40 (8.25)	25	9.36 (9.39)	18	9.45 (6.61)	− 0.09 ± 2.44
CCI-all vs. usual care[b]		2.37 ± 1.64		1.64 ± 2.22		4.63 ± 2.74	
HOMA-IR (C-peptide derived)							
CCI-all education[a]	239	11.52 (7.15)	170	11.44 (6.26)	69	11.72 (9.04)	− 0.28 ± 1.19
Usual care[a]	72	11.16 (7.26)	47	10.56 (7.70)	25	12.29 (6.33)	− 1.73 ± 1.69
CCI-all vs. usual care[b]		0.36 ± 0.97		0.88 ± 1.22		− 0.56 ± 1.67	
Weight-clinic (kg)							
CCI-all education[a]	257	116.51 (25.94)	184	115.42 (24.62)	73	119.25 (29.01)	− 3.83 ± 3.85
Usual care[a]	83	105.63 (22.15)	69	106.79 (22.18)	14	99.94 (21.86)	6.84 ± 6.42
CCI-all vs. usual care[b]		10.87 ± 2.92§		8.63 ± 3.23†		19.3 ± 6.76†	
BMI (kg m^{-2})							
CCI-all education[a]	257	40.43 (8.81)	184	39.87 (7.88)	73	41.82 (10.75)	− 1.94 ± 1.39
Usual care[a]	83	36.72 (7.26)	69	37.14 (7.62)	14	34.66 (4.8)	2.48 ± 1.58
CCI-all vs. usual care[b]		3.7 ± 0.97‡		2.73 ± 1.09†		7.15 ± 1.8§	
Systolic blood pressure (mmHg)							
CCI-all education[a]	260	131.94 (14.09)	187	132.51 (14.54)	73	130.47 (12.84)	2.05 ± 1.84
Usual care[a]	79	129.8 (13.61)	67	128.72 (12.65)	12	135.83 (17.49)	− 7.12 ± 5.28
CCI-all vs. usual care[b]		2.14 ± 1.76		3.8 ± 1.88*		− 5.37 ± 5.27	

Table 1 continued

	All		Completers with data		Dropout or missing data		Completers-Dropouts Mean ± SE
	N	Mean (SD) or ±SE	*N*	Mean (SD) or ±SE	*N*	Mean (SD) or ±SE	
Diastolic blood pressure (mmHg)							
CCI-all education[a]	260	82.09 (8.25)	187	81.59 (8.05)	73	83.37 (8.67)	− 1.78 ± 1.17
Usual care[a]	79	82.0 (8.93)	67	81.1 (8.07)	12	87.0 (11.95)	− 5.9 ± 3.59
CCI-all vs. usual care[b]		0.09 ± 1.13		0.49 ± 1.15		− 3.63 ± 3.6	
Total cholesterol (mmol L^{-1})							
CCI-all education[a]	247	4.76 (1.07)	186	4.68 (1.03)	61	4.99 (1.15)	− 0.31 ± 0.17
Usual care[a]	79	4.76 (1.19)	59	4.72 (1.26)	20	4.88 (0.93)	− 0.16 ± 0.27
CCI-all vs. usual care[b]		− 0.0 ± 0.15		− 0.04 ± 0.18		0.11 ± 0.26	
LDL-cholesterol (mmol L^{-1})							
CCI-all education[a]	232	102.51 (32.89)	172	100.08 (32.56)	60	109.47 (33.13)	− 9.39 ± 4.94
Usual care[a]	70	101.50 (36.16)	48	100.38 (37.93)	22	103.95 (32.67)	− 3.58 ± 8.86
CCI-all vs. usual care[b]		1.01 ± 4.83		− 0.29 ± 6.01		5.51 ± 8.17	
Apo B (g L^{-1})							
CCI-all education[a]	248	1.05 (0.29)	186	1.03 (0.28)	62	1.1 (0.31)	− 0.06 ± 0.04
Usual care[a]	79	1.07 (0.28)	59	1.06 (0.3)	20	1.11 (0.24)	− 0.05 ± 0.07
CCI-all vs. usual care[b]		− 0.02 ± 0.04		− 0.02 ± 0.04		− 0.01 ± 0.07	
HDL-C (mmol L^{-1})							
CCI-all education[a]	247	1.09 (0.35)	186	1.1 (0.36)	61	1.08 (0.32)	0.02 ± 0.05
Usual care[a]	79	0.97 (0.29)	59	0.96 (0.29)	20	1.02 (0.29)	− 0.06 ± 0.08
CCI-all vs. usual care[b]		0.12 ± 0.04†		0.14 ± 0.05†		0.06 ± 0.08	
Triglycerides (mmol L^{-1})							
CCI-all education[a]	247	2.23 (1.62)	186	2.27 (1.73)	61	2.11 (1.25)	0.15 ± 0.2
Usual care[a]	79	3.2 (4.53)	59	3.36 (5.17)	20	2.72 (1.56)	0.64 ± 0.76
CCI-all vs. usual care[b]		− 0.97 ± 0.52*		− 1.09 ± 0.68		− 0.61 ± 0.38*	
Total/HDL-cholesterol							
CCI-all education[a]	247	4.72 (1.7)	186	4.65 (1.72)	61	4.93 (1.65)	− 0.28 ± 0.25
Usual care[a]	79	5.37 (2.42)	59	5.44 (2.63)	20	5.17 (1.72)	0.27 ± 0.52
CCI-all vs. usual care[b]		− 0.65 ± 0.29*		− 0.79 ± 0.36*		− 0.24 ± 0.44	
hsC-reactive protein (nmol L^{-1})							
CCI-all education[a]	249	81.33 (138.0)	193	85.62 (153.05)	56	66.76 (62.1)	18.86 ± 13.81
Usual care[a]	85	84.67 (82.1)	70	86.95 (86.95)	15	73.81 (73.81)	13.14 ± 19.14
CCI-all vs. usual care[b]		− 3.24 ± 12.48		− 1.33 ± 15.05		− 7.05 ± 18.19	

Table 1 continued

	All		Completers with data		Dropout or missing data		Completers-Dropouts Mean ± SE
	N	Mean (SD) or ±SE	*N*	Mean (SD) or ±SE	*N*	Mean (SD) or ±SE	
ALT (μkat L^{-1})							
CCI-all education[a]	257	0.51 (0.38)	201	0.52 (0.41)	56	0.47 (0.27)	0.05 ± 0.05
Usual care[a]	86	0.46 (0.33)	71	0.45 (0.34)	15	0.51 (0.29)	− 0.05 ± 0.09
CCI-all vs. usual care[b]		0.05 ± 0.04		0.07 ± 0.05		− 0.04 ± 0.08	
AST (μkat L^{-1})							
CCI-all education[a]	257	0.4 (0.25)	201	0.41 (0.28)	56	0.36 (0.15)	0.04 ± 0.03
Usual care[a]	86	0.4 (0.32)	71	0.39 (0.35)	15	0.42 (0.16)	− 0.03 ± 0.06
CCI-all vs. usual care[b]		− 0.0 ± 0.04		0.01 ± 0.05		− 0.06 ± 0.05	
Alkaline phosphatase (μkat L^{-1})							
CCI-all education[a]	256	1.24 (0.37)	200	1.24 (0.37)	56	1.23 (0.36)	0.01 ± 0.05
Usual care[a]	86	1.29 (0.44)	71	1.31 (0.45)	15	1.22 (0.38)	0.09 ± 0.11
CCI-all vs. usual care[b]		− 0.05 ± 0.05		− 0.07 ± 0.06		0.01 ± 0.11	
Serum creatinine (μmol L^{-1})							
CCI-all education[a]	258	77.79 (21.22)	202	77.79 (20.33)	56	81.33 (24.75)	− 3.54 ± 3.54
Usual care[a]	86	80.44 (22.1)	71	78.68 (20.33)	15	86.63 (25.64)	− 7.07 ± 7.07
CCI-all vs. usual care[b]		− 1.77 ± 2.65		− 1.77 ± 2.65		− 5.3 ± 7.07	
BUN (mmol L^{-1})							
CCI-all education[a]	258	6.03 (2.34)	202	6.06 (2.15)	56	5.9 (2.96)	0.16 ± 0.42
Usual care[a]	86	5.73 (2.23)	71	5.59 (1.86)	15	6.38 (3.52)	− 0.79 ± 0.94
CCI-all vs. usual care[b]		0.3 ± 0.28		0.47 ± 0.27		− 0.47 ± 0.99	
eGFR (mL s^{-1} m^{-2})							
CCI-all education[a]	258	1.34 (0.23)	202	1.35 (0.22)	56	1.33 (0.25)	0.02 ± 0.04
Usual care[a]	86	1.32 (0.23)	71	1.34 (0.22)	15	1.26 (0.28)	0.08 ± 0.08
CCI-all vs. usual care[b]		0.02 ± 0.03		0.02 ± 0.03		0.03 ± 0.08	
Anion gap (mmol L^{-1})							
CCI-all education[a]	257	6.83 (1.67)	201	6.79 (1.7)	56	6.98 (1.53)	− 0.19 ± 0.24
Usual care[a]	86	6.93 (1.82)	71	6.92 (1.82)	15	7.0 (1.89)	− 0.08 ± 0.53
CCI-all vs. usual care[b]		− 0.1 ± 0.22		− 0.12 ± 0.25		− 0.02 ± 0.53	
Uric acid (μmo L^{-1})							
CCI-all education[a]	261	347.99 (86.85)	202	348.58 (86.25)	59	346.2 (89.82)	2.38 ± 13.09
Usual care[a]	85	333.12 (87.44)	71	330.74 (85.66)	14	345.01 (98.75)	− 14.28 ± 28.55
CCI-all vs. usual care[b]		14.87 ± 10.71		17.25 ± 11.9		1.19 ± 29.15	

Table 1 continued

	All		Completers with data		Dropout or missing data		Completers-Dropouts Mean ± SE
	N	Mean (SD) or ±SE	*N*	Mean (SD) or ±SE	*N*	Mean (SD) or ±SE	
TSH (mIU L^{-1})							
CCI-all education[a]	259	2.32 (1.74)	200	2.31 (1.79)	59	2.38 (1.55)	− 0.07 ± 0.24
Usual care[a]	85	1.97 (1.16)	70	2.09 (1.16)	15	1.38 (1.03)	0.71 ± 0.3*
CCI-all vs. usual care[b]		0.36 ± 0.17*		0.21 ± 0.19		1.0 ± 0.33†	
Free T4 (pmol L^{-1})							
CCI-all education[a]	260	11.84 (2.19)	202	11.84 (2.32)	58	11.58 (2.19)	0.26 ± 0.39
Usual care[a]	86	11.33 (3.73)	71	11.33 (3.86)	15	10.94 (2.32)	0.39 ± 0.77
CCI-all vs. usual care[b]		0.51 ± 0.39		0.51 ± 0.51		0.64 ± 0.64	
Any diabetes medication, excluding metformin (%)							
CCI-all education[a]	262	56.87 ± 3.06	218	55.50 ± 3.37	44	63.64 ± 7.25	− 8.13 ± 8.00
Usual care[a]	87	66.67 ± 5.05	73	68.49 ± 5.44	14	57.14 ± 13.23	11.35 ± 14.32
CCI-all vs. usual care[b]		− 9.80 ± 5.91		− 12.99± 6.39*		6.49 ± 15.08	
Sulfonylurea (%)							
CCI-all education[a]	262	23.66 ± 2.63	218	24.31 ± 2.91	44	20.45 ± 6.08	3.86 ± 6.74
Usual care[a]	87	24.14 ± 4.59	73	23.29 ± 4.95	14	28.57 ± 12.07	− 5.28 ± 13.05
CCI-all vs. usual care[b]		− 0.48 ± 5.29		1.02 ± 5.74		− 8.12± 13.52	
Insulin (%)							
CCI-all education[a]	262	29.77 ± 2.82	218	28.44 ± 3.06	44	36.36 ± 7.25	− 7.92 ± 7.87
Usual care[a]	87	45.98 ± 5.34	78	50.0 ± 5.66	9	11.11 ± 10.48	38.89 (1.91)‡
CCI-all vs. usual care[b]		− 16.21 ± 6.04†		− 21.56 ± 6.43‡		25.25 ± 12.74*	
Thiazolidinedione (%)							
CCI-all education[a]	262	1.53 ± 0.76	218	1.83 ± 0.91	44	0.0 ± 0.0	1.83 ± 0.91*
Usual care[a]	87	1.15 ± 1.14	73	1.37 ± 1.36	14	0.0 ± 0.0	1.37 ± 1.36
CCI-all vs. usual care[b]		0.38 ± 1.37		0.46 ± 1.64		0.0 ± 0.0	
SGLT-2 (%)							
CCI-all education[a]	262	10.31 ± 1.88	218	10.55 ± 2.08	44	9.09 ± 4.33	1.46 ± 4.81
Usual care[a]	87	13.79 ± 3.7	73	15.07 ± 4.19	14	7.14 ± 6.88	7.93 ± 8.06
CCI-all vs. usual care[b]		− 3.48 ± 4.15		− 4.52 ± 4.68		1.95 ± 8.13*	
DPP-4 (%)							
CCI-all education[a]	262	9.92 ± 1.85	218	10.09 ± 2.04	44	9.09 ± 4.33	1.0 ± 4.79
Usual care[a]	87	8.05 ± 2.92	73	8.22 ± 3.21	14	7.14 ± 6.88	1.08 ± 7.60
CCI-all vs. usual care[b]		1.87 ± 3.45		1.87 ± 3.81		1.95 ± 8.13	

Table 1 continued

	All		Completers with data		Dropout or missing data		Completers-Dropouts Mean ± SE
	N	Mean (SD) or ±SE	*N*	Mean (SD) or ±SE	*N*	Mean (SD) or ±SE	
GLP-1 (%)							
CCI-all education[a]	262	13.36 ± 2.1	218	12.84 ± 2.27	44	15.91 ± 5.51	− 3.07 ± 5.96
Usual care[a]	87	14.94 ± 3.82	73	16.44 ± 4.34	14	7.14 ± 6.88	9.30 ± 8.14
CCI-all vs. usual care[b]		− 1.58 ± 4.36		− 3.59 ± 4.89		8.77 ± 8.82	
Metformin (%)							
CCI-all education[a]	262	71.37 ± 2.79	218	71.56 ± 3.06	44	70.45 ± 6.88	1.11 ± 7.53
Usual care[a]	87	60.92 ± 5.23	73	61.64 ± 5.69	14	57.14 ± 13.23	4.50 ± 14.40
CCI-all vs. usual care[b]		10.45 ± 5.93		9.92 ± 6.46		13.31 ± 14.91	

See Table S1 (electronic supplemental material) for CCI-web, CCI-onsite, and additional comparisons

[a] Mean and standard deviations for continuous variables, percentages and standard errors for categorical variables

[b] Difference between means or percentages ± 1 standard error of the difference. Significant baseline difference between means or percentages at $0.05 > P \geq 0.01$ (*); $0.01 > P \geq 0.001$ (†); $0.001 > P \geq 0.0001$ (‡); and $P < 0.0001$ (§)

and standard errors that include the variability between imputations. Missing values were estimated from 700 imputations from multivariate normal regression. The number of missing data points for each measure can be determined from the difference between all participants and completers in Tables 1 and S1. Across all biomarkers, 4% of baseline values and 24% of 1-year values were missing (due to dropout, incalculable values, or inability to procure timely samples) and thus imputed to conduct the intention-to-treat analysis. Two-sample *t* tests were used to test whether baseline differences and differences between 1-year biomarker changes were significant. Within-group changes were tested using paired *t* test and analysis of covariance (ANCOVA) when adjusted for baseline covariates (sex, age, baseline BMI, insulin use versus non-use, and African-American race). Although tables present triglyceride and hsCRP summary statistics in clinical units, significance levels were obtained from log-transformed values to reduce skewness. For completer analysis, percent change was calculated as the mean difference (Table 2) divided by the mean baseline value (Table 1). Significant changes in medication use and the proportion of patients with HbA_{1c} at least 48 mmol mol^{-1} (≥ 6.5%) were tested using McNemar test with continuity correction in completers, and linear regression of the changes in the dichotomous states when missing outcome data were imputed. Standard deviations are presented within parentheses and standard errors following "±". Nominal significance levels (*P*) are presented in tables; however, a significance level of $P < 0.0017$ ensures simultaneous significance at $P < 0.05$ with Bonferroni adjustment for the 30 variables examined. Results presented are intention-to-treat analyses (all), where missing values were estimated by imputation, unless otherwise noted. Participants who withdrew or lacked biomarkers at 1 year were not included in the analyses of completers.

RESULTS

Participant Characteristics

Table 1 presents baseline characteristics of the 262 CCI and 87 UC participants. At baseline, 88% of CCI participants were prescribed

Table 2 Mean changes in biomarkers between baseline and 1-year for participants receiving the CCI and UC

	Completers						All starters (dropouts imputed)[d]		
	Unadjusted				Adjusted for baseline[c]		Unadjusted		
	N	Difference (SD) or ± SE	1 Year	Significance[e]	Difference ±SE	Significance[e]	Difference ± SE	1 Year	Significance[e]
Beta-hydroxybutyrate (mmol L^{-1})									
CCI-all education[a]	186	0.14 (0.36)	0.31 (0.35)	2.2×10^{-5}	0.13 ± 0.02	2.8×10^{-7}	0.12 ± 0.02	0.3 ± 0.02	5.8×10^{-7}
Usual care[a]	59	0.04 (0.23)	0.18 (0.21)	0.24	0.06 ± 0.05	0.18	0.03 ± 0.04	0.18 ± 0.03	0.38
CCI-all vs. usual care[b]		0.1 (0.0)		0.01	0.06 ± 0.05	0.24	0.09 ± 0.04		0.04
Hemoglobin A_{1c} (mmol mol^{-1})									
CCI-all education[a]	204	− 14.1 (14.43)	44.25 (10.28)	$<10^{-16}$	− 14.43 ± 0.98	$<10^{-16}$	− 14.21 ± 0.98	45.23 ± 0.77	$<10^{-16}$
Usual care[a]	72	2.19 (14.76)	63.27 (19.89)	0.21	2.4 ± 1.75	0.17	2.19 ± 1.64	62.18 ± 2.08	0.18
CCI-all vs. usual care[b]		− 16.29 ± 1.97		4.4×10^{-16}	− 16.83 ± 2.08	4.4×10^{-16}	− 16.4 ± 1.86		$<10^{-16}$
Hemoglobin A_{1c} (%)									
CCI-all education[a]	204	− 1.29 (1.32)	6.20 (0.94)	$<10^{-16}$	− 1.32 ± 0.09	$<10^{-16}$	− 1.30 ± 0.09	6.29 ± 0.07	$< 10^{-16}$
Usual care[a]	72	0.20 (1.35)	7.94 (1.82)	0.21	0.22 ± 0.16	0.17	0.20 ± 0.15	7.84 ± 0.19	0.18
CCI-all vs. usual care[b]		− 1.49 ± 0.18		4.4×10^{-16}	− 1.54 ± 0.19	4.4×10^{-16}	−1.50 ± 0.17		$< 10^{-16}$
Fasting glucose (mmol L^{-1})									
CCI-all education[a]	202	− 1.96 (3.2)	6.84 (1.87)	$<10^{-16}$	− 2.02 ± 0.26	6.0×10^{-15}	− 1.95 ± 0.23	6.98 ± 0.17	$< 10^{-16}$
Usual care[a]	71	0.59 (4.59)	9.3 (4.74)	0.28	0.81 ± 0.45	0.07	0.63 ± 0.49	9.29 ± 0.49	0.2
CCI-all vs. usual care[b]		− 2.55 ± 0.59		1.5×10^{-5}	− 2.83 ± 0.53	7.9×10^{-8}	− 2.58 ± 0.54		2.1×10^{-6}
Insulin, all (pmol L^{-1})									
CCI-all education[a]	186	− 75.01 (178.49)	122.58 (169.6)	9.9×10^{-9}	− 91.4 ± 12.15	5.5×10^{-14}	− 73.62 ± 12.5	126.26 ± 12.5	4.3×10^{-9}
Usual care[a]	59	12.15 (210.23)	218.91 (239.46)	0.66	36.88 ± 29.66	0.21	5.97 ± 24.52	206.27 ± 26.11	0.81
CCI-all vs. usual care[b]		− 87.23 (29.86)		0.004	− 127.58 ± 32.43	0.0009	− 79.59 ± 27.5		0.004

Table 2 continued

	Completers						All starters (dropouts imputed)[d]		
	Unadjusted				Adjusted for baseline[c]		Unadjusted		
	N	Difference (SD) or ± SE	1 Year	Significance[e]	Difference ±SE	Significance[e]	Difference ± SE	1 Year	Significance[e]
C-peptide (nmol L^{-1})									
CCI-all education[a]	185	− 0.36 (0.57)	1.11 (0.59)	$<10^{-16}$	− 0.34 ± 0.05	1.1×10^{-13}	− 0.33 ± 0.04	1.11 ± 0.04	2.2×10^{-16}
Usual care[a]	59	0.08 (0.77)	1.43 (0.92)	0.41	0.02 ± 0.09	0.79	0.06 ± 0.09	1.44 ± 0.1	0.5
CCI-all vs. usual care[b]		− 0.44 ± 0.11		5.4×10^{-5}	− 0.37 ± 0.1	0.0004	− 0.4 ± 0.1		5.3×10^{-5}
HOMA-IR (insulin derived), all									
CCI-all education[a]	179	− 5.54 (12.19)	5.65 (8.71)	1.2×10^{-9}	− 5.87 ± 0.92	2.2×10^{-10}	− 5.58 ± 0.86	6.16 ± 0.69	7.5×10^{-11}
Usual care[a]	56	1.65 (12.46)	12.96 (12.9)	0.32	2.4 ± 1.76	0.17	1.82 ± 1.49	12.2 ± 1.42	0.22
CCI-all vs. usual care[b]		− 7.19 (1.9)		0.0002	− 8.27±2.04	4.9×10^{-5}	− 7.4 ± 1.72		1.6×10^{-5}
HOMA-IR (insulin derived), e × cluding e × ogenous insulin users									
CCI-all education[a]	129	− 6.03 (10.67)	4.98 (5.69)	1.4×10^{-10}	− 6.13 ± 0.98	4.2×10^{-10}	− 6.82 ± 0.9	5.61 ± 0.51	3.2×10^{-5}
Usual care[a]	25	3.99 (12.76)	13.35 (14.71)	0.12	4.1 ± 2.34	0.08	1.84 ± 1.96	13.3 ± 1.56	0.35
CCI-all vs. usual care[b]		− 10.01 ± 2.72		0.0002	− 10.23 ± 2.56	6.3×10^{-5}	− 8.65 ± 2.16		6.0×10^{-5}
HOMA-IR (C-peptide derived)									
CCI-all education[a]	170	− 3.53 (5.59)	7.9 (3.89)	2.2×10^{-16}	− 3.53 ± 0.55	1.2×10^{-10}	− 3.45 ± 0.46	8.25 ± 0.4	1.0×10^{-13}
Usual care[a]	47	1.94 (10.54)	12.49 (10.46)	0.21	1.77 ± 1.12	0.11	1.65 ± 1.13	12.6 ± 1.11	0.14
CCI-all vs. usual care[b]		− 5.47 (1.6)		0.0006	− 5.29 ± 1.28	3.3×10^{-5}	− 5.11 ± 1.22		3.0×10^{-5}
Weight-clinic (kg)									
CCI-all education[a]	184	− 14.24 (10.29)	101.17 (22.06)	$<10^{-16}$	− 13.81 ± 0.63	$<10^{-16}$	− 13.8 ± 0.71	102.72 ± 1.5	$< 10^{-16}$
Usual care[a]	69	0.04 (5.94)	106.82 (22.52)	0.95	− 1.11 ± 1.06	0.29	− 0.16 ± 0.84	107.31 ± 2.55	0.85
CCI-all vs. usual care[b]		− 14.29 ± 1.04		$<10^{-16}$	− 12.7 ± 1.26	$<10^{-16}$	− 13.65 ± 1.1		$< 10^{-16}$

Table 2 continued

	Completers						All starters (dropouts imputed)[d]		
	Unadjusted				Adjusted for baseline[c]		Unadjusted		
	N	Difference (SD) or ± SE	1 Year	Significance[e]	Difference ±SE	Signif-icance[e]	Difference ± SE	1 Year	Significance[e]
Systolic blood pressure (mmHg)									
CCI-all education[a]	187	− 6.77 (16.3)	125.84 (13.22)	1.3×10^{-8}	− 6.52 ± 1.24	1.6×10^{-7}	− 6.36 ± 1.12	125.57 ± 0.91	1.3×10^{-8}
Usual care[a]	67	0.25 (17.8)	128.57 (11.82)	0.91	− 0.45 ± 2.15	0.83	− 0.9 ± 2.07	129.01 ± 1.72	0.67
CCI-all vs. usual care[b]		− 7.02 (2.4)		0.005	− 6.07 ± 2.55	0.02	− 5.46 ± 2.36		0.02
Diastolic blood pressure (mmHg)									
CCI-all education[a]	187	− 3.59 (9.33)	78.0 (7.55)	1.4×10^{-7}	− 3.5 ± 0.7	6.2×10^{-7}	− 3.51 ± 0.65	78.58 ± 0.56	7.2×10^{-8}
Usual care[a]	67	− 0.12 (10.15)	80.99 (9.59)	0.92	− 0.39 ± 1.21	0.75	− 0.9 ± 1.2	81.12 ± 1.08	0.45
CCI-all vs. usual care[b]		− 3.47 ± 1.42		0.01	− 3.10±1.44	0.03	− 2.61 ± 1.37		0.06
Total cholesterol (mmol L^{-1})									
CCI-all education[a]	186	0.24 (0.93)	4.92 (1.18)	0.0004	0.24 ± 0.08	0.004	0.21 ± 0.07	4.97 ± 0.08	0.006
Usual care[a]	59	0.00 (1.60)	4.72 (1.62)	0.99	0.0 ± 0.16	0.98	− 0.04 ± 0.18	4.69 ± 0.18	0.83
CCI-all vs. usual care[b]		0.25 ± 0.22		0.26	0.25 ± 0.18	0.17	0.24 ± 0.19		0.2
LDL-C ($mmol^{-1}$)									
CCI-all education[a]	172	0.28 (0.83)	2.87 (0.98)	7.7×10^{-6}	0.28 ± 0.07	2.6×10^{-5}	0.26 ± 0.06	2.94 ± 0.07	5.1×10^{-5}
Usual care[a]	48	− 0.28 (0.97)	2.32 (0.8)	0.05	−0.28 ± 0.13	0.03	− 0.28 ± 0.12	2.32 ± 0.12	0.02
CCI-all vs. usual care[b]		0.56 ± 0.15		0.0003	0.56 ± 0.15	0.0002	0.54 ± 0.14		0.0001
Apo B (g L^{-1})									
CCI-all education[a]	186	− 0.01 (0.24)	1.03 (0.29)	0.69	− 0.0 ± 0.02	0.82	− 0.02 ± 0.02	1.04 ± 0.02	0.37
Usual care[a]	59	0.02 (0.37)	1.07 (0.39)	0.75	0.0 ± 0.04	0.9	0.0 ± 0.04	1.06 ± 0.04	0.95
CCI-all vs. usual care[b]		− 0.02 (0.05)		0.66	− 0.01 ± 0.05	0.83	− 0.02 ± 0.05		0.67

Table 2 continued

	Completers						All starters (dropouts imputed)[d]		
	Unadjusted				Adjusted for baseline[c]		Unadjusted		
	N	Difference (SD) or ± SE	1 Year	Significance[e]	Difference ±SE	Significance[e]	Difference ± SE	1 Year	Significance[e]
HDL-C (mmol L^{-1})									
CCI-all education[a]	186	0.20 (0.31)	1.29 (0.41)	$<10^{-16}$	0.19 ± 0.02	$<10^{-16}$	0.2 ± 0.02	1.29 ± 0.03	$< 10^{-16}$
Usual care[a]	59	− 0.04 (0.23)	0.92 (0.32)	0.15	− 0.02 ± 0.04	0.69	− 0.03 ± 0.03	0.95 ± 0.04	0.41
CCI-all vs. usual care[b]		0.24 ± 0.04		1.7×10^{-10}	0.2 ± 0.05	9.9×10^{-6}	0.23 ± 0.04		1.3×10^{-8}
Triglycerides (mmol L^{-1})									
CCI-all education[a]	186	− 0.56 (1.9)	1.71 (1.64)	$<10^{-16}$	− 0.56 ± 0.18	9.3×10^{-15}	− 0.54 ± 0.14	1.67 ± 0.13	$< 10^{-16}$
Usual care[a]	59	0.34 (3.40)	3.7 (5.67)	0.22	− 0.35 ± 0.32	0.48	0.32 ± 0.37	3.45 ± 0.55	0.43
CCI-all vs. usual care[b]		− 0.9 ± 0.46		1.4×10^{-7}	− 0.92 ± 0.38	7.5×10^{-6}	− 0.86 ± 0.39		9.9×10^{-7}
Total/HDL-cholesterol									
CCI-all education[a]	186	− 0.47 (1.41)	4.18 (1.71)	4.1×10^{-6}	− 0.45 ± 0.16	0.005	− 0.53 ± 0.12	4.19 ± 0.13	1.7×10^{-5}
Usual care[a]	59	0.52 (3.45)	5.96 (4.27)	0.24	0.44 ± 0.29	0.13	0.42 ± 0.36	5.73 ± 0.43	0.24
CCI-all vs. usual care[b]		− 1.00 ± 0.46		0.03	− 0.89 ± 0.33	0.008	− 0.95 ± 0.38		0.01
hsC⁻reactive protein (nmol L^{-1})									
CCI-all education[a]	193	− 31.71 (127.15)	53.81 (67.24)	$<10^{-8}$	− 29.43 ± 9.14	$<10^{-16}$	− 34.29 ± 10.0	52.86 ± 5.24	$< 10^{-16}$
Usual care[a]	70	12.48 (126.86)	99.43 (139.91)	0.94	8.48 ± 16.1	0.88	12.48 ± 14.1	97.72 ± 14.76	0.93
CCI-all vs. usual care[b]		− 44.29 (17.14)		1.2×10^{-6}	− 37.91 ± 18.55	3.0×10^{-5}	− 46.76 ± 17.24		9.3×10^{-7}
ALT (μkat L^{-1})									
CCI-all education[a]	201	− 0.16 (0.4)	0.36 (0.19)	9.5×10^{-9}	− 0.16 ± 0.03	9.4×10^{-10}	− 0.15 ± 0.02	0.36 ± 0.01	2.4×10^{-10}
Usual care[a]	71	0.01 (0.28)	0.47 (0.34)	0.67	0.02 ± 0.05	0.67	0.01 ± 0.03	0.47 ± 0.04	0.77
CCI-all vs. usual care[b]		− 0.18 (0.04)		5.1×10^{-5}	− 0.18 ± 0.05	0.0009	− 0.16 ± 0.04		4.6×10^{-5}

Table 2 continued

	Completers						All starters (dropouts imputed)[d]		
	Unadjusted				Adjusted for baseline[c]		Unadjusted		
	N	Difference (SD) or ± SE	1 Year	Significance[e]	Difference ±SE	Signif-icance[e]	Difference ± SE	1 Year	Significance[e]
AST (μkat L^{-1})									
CCI-all education[a]	201	− 0.09 (0.27)	0.32 (0.11)	2.8×10^{-6}	− 0.09 ± 0.02	1.3×10^{-5}	− 0.08 ± 0.02	0.32 ± 0.01	5.1×10^{-7}
Usual care[a]	71	0.01 (0.32)	0.4 (0.27)	0.79	0.01 ± 0.04	0.69	0.01 ± 0.03	0.41 ± 0.03	0.72
CCI-all vs. usual care[b]		− 0.1 (0.04)		0.02	− 0.1 ± 0.04	0.02	− 0.09 ± 0.04		0.01
Alkaline phosphatase (μkat L^{-1})									
CCI-all education[a]	200	− 0.16 (0.24)	1.07 (0.35)	$<10^{-8}$	− 0.17 ± 0.02	$<10^{-16}$	− 0.16 ± 0.02	1.08 ± 0.02	$< 10^{-16}$
Usual care[a]	71	0.0 (0.22)	1.31 (0.45)	0.94	0.02 ± 0.03	0.61	0.01 ± 0.03	1.3 ± 0.05	0.67
CCI-all vs. usual care[b]		− 0.17 (0.03)		6.3×10^{-8}	− 0.18 ± 0.03	1.4×10^{-7}	− 0.17 ± 0.03		3.1×10^{-8}
Serum creatinine (μmol L^{-1})									
CCI-all education[a]	202	− 3.54 (14.14)	73.37 (18.56)	0.0001	− 3.54 ± 0.88	0.001	− 3.54 ± 0.88	74.26 ± 0.88	0.0001
Usual care[a]	71	− 0.88 (18.56)	77.79 (18.56)	0.56	− 2.65 ± 1.77	0.15	− 1.77 ± 1.77	78.68 ± 1.77	0.29
CCI-all vs. usual care[b]		− 2.65 ± 2.65		0.32	− 0.88 ± 2.65	0.73	− 1.77 ± 2.65		0.49
BUN (mmol L^{-1})									
CCI-all education[a]	202	0.76 (2.49)	6.82 (2.78)	1.5×10^{-5}	0.75 ± 0.17	1.6×10^{-5}	0.79 ± 0.17	6.81 ± 0.19	5.5×10^{-6}
Usual care[a]	71	0.07 (2.15)	5.66 (2.11)	0.78	0.06 ± 0.3	0.85	− 0.01 ± 0.27	5.72 ± 0.26	0.97
CCI-all vs. usual care[b]		0.69 (0.29)		0.03	0.69 (0.32)	0.05	0.8 ± 0.32		0.01
eGFR (mL s^{-1} m^{-2})									
CCI-all education[a]	202	0.03 (0.15)	1.38 (0.2)	0.003	0.03 ± 0.01	0.009	0.03 ± 0.01	1.38 ± 0.01	0.005
Usual care[a]	71	0.01 (0.19)	1.34 (0.22)	0.51	0.02 ± 0.02	0.36	0.01 ± 0.02	1.34 ± 0.02	0.48
CCI-all vs. usual care[b]		0.03 ± 0.02		0.28	0.01 ± 0.02	0.61	0.02 ± 0.02		0.51

Table 2 continued

	Completers						All starters (dropouts imputed)[d]		
	Unadjusted				Adjusted for baseline[c]		Unadjusted		
	N	Difference (SD) or ± SE	1 Year	Significance[e]	Difference ±SE	Significance[e]	Difference ± SE	1 Year	Significance[e]
Anion gap (mmol L^{-1})									
CCI-all education[a]	201	0.29 (2.02)	7.08 (1.75)	0.04	0.28 ± 0.15	0.06	0.28 ± 0.14	7.13 ± 0.12	0.04
Usual care[a]	71	0.83 (2.44)	7.75 (1.97)	0.004	0.84 ± 0.26	0.001	0.81 ± 0.26	7.75 ± 0.22	0.002
CCI-all vs. usual care[b]		− 0.54 (0.3)		0.09	− 0.56 ± 0.31	0.07	− 0.53 ± 0.3		0.08
CO_2 (mmol L^{-1})									
CCI-all education[a]	202	0.12 (2.26)	28.06 (2.29)	0.45	0.16 ± 0.18	0.38	0.18 ± 0.16	27.94 ± 0.16	0.27
Usual care[a]	71	0.17 (2.97)	28.23 (2.58)	0.63	− 0.2 ± 0.3	0.51	0.04 ± 0.33	28.12 ± 0.29	0.9
CCI-all vs. usual care[b]		− 0.05 (0.3)		0.9	0.36 ± 0.36	0.32	0.14 ± 0.37		0.71
Uric acid (μmol L^{-1})									
CCI-all education[a]	202	0.59 (70.79)	349.18 (91.01)	0.91	1.78 ± 4.76	0.72	1.78 ± 4.76	349.77 ± 5.95	0.67
Usual care[a]	71	− 10.71 (64.24)	320.03 (85.06)	0.15	− 16.66 ± 8.92	0.06	− 11.9 ± 7.73	322.41 ± 10.11	0.13
CCI-all vs. usual care[b]		11.3 ± 8.92		0.21	18.44 ± 10.11	0.07	13.68 ± 8.92		0.13
TSH (mIU L^{-1})									
CCI-all education[a]	200	− 0.41 (1.62)	1.9 (1.1)	0.0004	− 0.4 ± 0.11	0.0002	− 0.42 ± 0.1	1.91 ± 0.08	5.3×10^{-5}
Usual care[a]	70	− 0.09 (0.99)	2.01 (0.99)	0.47	− 0.09 ± 0.19	0.64	0.0 ± 0.12	1.96 ± 0.12	0.98
CCI-all vs. usual care[b]		− 0.33 ± 0.16		0.05	− 0.31 ± 0.22	0.15	− 0.42 ± 0.16		0.01
Free T4 (pmol L^{-1})									
CCI-all education[a]	202	0.13 (2.32)	11.97 (2.45)	0.7	0.0 ± 0.26	0.83	0.13 ± 0.13	11.97 ± 0.13	0.58
Usual care[a]	71	0.26 (4.25)	11.58 (2.83)	0.7	0.26 ± 0.39	0.48	0.26 ± 0.39	11.46 ± 0.26	0.61
CCI-all vs. usual care[b]		− 0.13 (0.0)		0.8	− 0.26 ± 0.39	0.43	− 0.13 ± 0.51		0.78

Table 2 continued

	Completers						All starters (dropouts imputed)[d]		
	Unadjusted				Adjusted for baseline[c]		Unadjusted		
	N	Difference (SD) or ± SE	1 Year	Significance[e]	Difference ±SE	Signif-icance[e]	Difference ± SE	1 Year	Significance[e]
Any diabetes medication, e × cluding metformin (%)									
CCI-all education[a]	218	− 27.52 (49.65)	27.98 ± 3.05	2.2×10^{-16}	− 27.66 ± 3.21	$<10^{-16}$	− 27.19 ± 3.14	29.68 ± 2.94	$< 10^{-16}$
Usual care[a]	78	6.85 (34.68)	75.34 ± 5.08	0.09	7.54 ± 5.87	0.2	5.99 ± 4.31	72.66 ± 5.0	0.09
CCI-all vs. usual care[b]		− 34.37 ± 5.27		7.0×10^{-11}	− 35.36 ± 6.83	2.3×10^{-7}	− 33.19 ± 5.34		9.0×10^{-9}
Sulfonylurea (%)									
CCI-all education[a]	218	− 24.31 (43.0)	0.0 ± 0.0	$<10^{-16}$	− 24.23 ± 2.86	$<10^{-16}$	− 23.67 ± 2.7	0.0 ± 0.0	$< 10^{-16}$
Usual care[a]	78	2.74 (37.17)	26.02 ± 5.17	0.53	2.56 ± 5.24	0.63	1.91 ± 4.23	26.02 ± 5.17	0.65
CCI-all vs. usual care[b]		− 27.05 ± 5.23		2.4×10^{-7}	− 26.85 ± 6.07	9.7×10^{-6}	− 25.58 ± 5.02		3.3×10^{-7}
Insulin (%)									
CCI-all education[a]	218	− 13.3 (35.37)	15.14 ± 2.43	2.8×10^{-8}	− 15.5 ± 2.0	9.3×10^{-15}	− 13.03 ± 2.22	16.74 ± 2.4	4.3×10^{-9}
Usual care[a]	78	1.37 (31.15)	52.05 ± 5.89	0.71	8.46 ± 3.65	0.02	3.17 ± 3.68	49.18 ± 5.45	0.39
CCI-all vs. usual care[b]		− 14.67 ± 4.36		0.0008	− 23.89 ± 4.24	1.8×10^{-8}	− 16.19 ± 4.3		0.0002
Thiazolidinedione (%)									
CCI-all education[a]	218	− 1.38 (15.12)	0.46 ± 0.46	0.18	− 1.47 ± 0.9	0.1	− 1.1 ± 0.91	0.42 ± 0.49	0.23
Usual care[a]	78	0.0 (0.0)	1.37 ± 1.37		0.26 ± 1.64	0.87	0.22 ± 0.51	1.27 ± 1.26	0.67
CCI-all vs. usual care[b]		− 1.38 ± 1.02		0.18	− 1.78 ± 1.91	0.35	− 1.31 ± 1.04		0.21
SGLT−2 (%)									
CCI-all education[a]	218	− 9.63 (29.57)	0.92 ± 0.65	1.5×10^{-6}	− 9.96 ± 2.04	1.1×10^{-6}	− 9.26 ± 1.88	0.92 ± 1.88	9.0×10^{-7}
Usual care[a]	78	0.0 (28.87)	15.07 ± 4.22	1	1.13 ± 3.72	0.76	0.87 ± 3.17	15.07 ± 4.21	0.78
CCI-all vs. usual care[b]		− 9.63 ± 3.93		0.01	− 11.0 ± 4.32	0.01	− 10.13 ± 3.69		0.006

Table 2 continued

	Completers						All starters (dropouts imputed)[d]		
	Unadjusted				Adjusted for baseline[c]		Unadjusted		
	N	Difference (SD) or ± SE	1 Year	Significance[e]	Difference ±SE	Significance[e]	Difference ± SE	1 Year	Significance[e]
DPP^{-}4 (%)									
CCI-all education[a]	218	− 3.67 (34.42)	6.42 ± 1.66	0.12	− 3.69 ± 2.21	0.09	− 3.52 ± 2.21	6.29 ± 1.66	0.11
Usual care[a]	78	2.74 (23.41)	10.96 ± 3.68	0.32	2.97 ± 4.05	0.46	2.64 ± 2.92	10.74 ± 3.51	0.37
CCI-all vs. usual care[b]		− 6.41 ± 3.6		0.07	− 6.64 ± 4.7	0.16	− 6.16 ± 3.66		0.09
GLP^{-}1 (%)									
CCI-all education[a]	218	0.92 (34.6)	13.76 ± 2.34	0.7	1.15 ± 2.31	0.62	0.98 ± 2.3	14.4 ± 2.29	0.67
Usual care[a]	78	2.74 (33.22)	19.18 ± 4.64	0.48	2.09 ± 4.23	0.62	2.94 ± 3.84	17.02 ± 4.39	0.44
CCI-all vs. usual care[b]		− 1.82 ± 4.54		0.69	− 0.99 ± 4.91	0.84	− 1.96 ± 4.48		0.66
Metformin (%)									
CCI-all education[a]	218	− 7.34 (46.45)	64.22 ± 3.25	0.02	− 7.14 ± 3.0	0.02	− 6.34 ± 3.06	65.18 ± 3.14	0.04
Usual care[a]	78	0.0 (37.27)	61.64 ± 5.73	1	0.83 ± 5.5	0.88	− 0.08 ± 4.55	60.67 ± 5.61	0.99
CCI-all vs. usual care[b]		− 7.34 ± 5.38		0.17	− 7.95 ± 6.38	0.21	− 6.26 ± 5.48		0.25

See Table S2 (electronic supplemental material) for CCI-web, CCI-onsite, and additional comparisons

[a] Imputed values based on 700 iterations from multivariate normal regression

[b] Adjusted for sex, age, baseline BMI, baseline insulin use (user vs. non-user), and African-American race

[c] A significance level of $P < 0.0017$ ensures overall simultaneous significance of $P \leq 0.05$ over the 30 variables using Bonferroni correction

[d] Means (standard deviations) are presented. Sample sizes, means, and significance levels refer to subjects with baseline and 1-year measurements for completers, and to 349 subjects (262 intervention and 87 usual care) for all starters. Significance levels for completers refer to one-sample *t* test with or without adjustment. Untransformed triglyceride and hsC-reactive protein values are presented; however, their statistical significances were based on their log-transformed values. CCI-all refers to the CCI-web and CCI-onsite combined

[e] Mean differences ± one standard error. Significance levels refer to two-sample *t* test or analysis of covariance for the differences

diabetes medication (57% were prescribed a diabetes medication other than metformin, 30% prescribed insulin) and 93% were obese. Eighty-seven percent of participants in UC at baseline were prescribed diabetes medication (46% prescribed insulin), and 82% were obese. Forty-four participants (16.8%) withdrew from the CCI, 22 from each education delivery mode. Baseline characteristics of CCI dropouts did not differ significantly from the 218 completers except none of the five thiazolidinedione users were dropouts (Table 1). At baseline, characteristics of CCI participants who self-selected web-based versus on-site education were not significantly different after accounting for multiple comparisons (see Table S1 in the electronic supplementary material). Compared to the 78 UC participants who completed the study, the nine that withdrew tended to be older (58 versus 52 years old), had lower TSH, and fewer were prescribed insulin, SGLT-2, DPP-4, GLP-1, or blood pressure medications (Table 1).

Effectiveness

Table 2 presents mean 1-year changes in biomarkers. In the CCI, HbA_{1c} was significantly reduced 17%, from 60 ± 1.0 mmol mol^{-1} ($7.6 \pm 0.09\%$) at baseline to 45 ± 0.8 mmol mol^{-1} ($6.3 \pm 0.07\%$) after 1 year (nominal significance $P < 1.0 \times 10^{-16}$; Fig. 1). Eighty-five percent (174/204) of CCI participants completing 1-year HbA_{1c} testing observed a decline greater than 2.2 mmol mol^{-1} ($> 0.2\%$) in the measure. When adjusted for multiple comparisons, significant within-CCI reductions were observed in fasting glucose (-22%, $P < 1.0 \times 10^{-16}$), fasting insulin (-43%, $P = 6.7 \times 10^{-16}$), C-peptide (-23%, $P = 2.2 \times 10^{-16}$), HOMA-IR derived from fasting insulin excluding exogenous users (-55%, $P = 3.2 \times 10^{-5}$), HOMA-IR derived from C-peptide (-29%, $P = 1.0 \times 10^{-13}$), weight from clinic measurements (-12%, $P < 1.0 \times 10^{-16}$), weight from home scales (-13%, $P < 1.0 \times 10^{-16}$, Fig. 2), triglycerides (-24%, $P < 1.0 \times 10^{-16}$), high-sensitivity C-reactive protein (-39%, $P < 1.0 \times 10^{-16}$), ALT (-30%, $P = 2.4 \times 10^{-10}$), AST (-21%, $P = 5.1 \times 10^{-7}$), and alkaline phosphatase (-13%, $P < 1.0 \times 10^{-16}$). HDL-cholesterol increased 18% ($P < 1.0 \times 10^{-16}$) and calculated LDL-cholesterol increased 10% ($P = 5.1 \times 10^{-5}$) while apolipoprotein B (ApoB) concentration was unchanged ($P = 0.37$) for participants in the CCI. There were no significant differences in mean biomarker changes between CCI-web and CCI-onsite (see Table S2 in the electronic supplementary material). In contrast to the CCI, patients enrolled in UC for 1 year showed no Bonferroni-adjusted significant change for any of the biomarkers measured (Table 2).

Following 1 year of CCI, usage of all diabetes medications combined (excluding metformin) was reduced significantly ($56.9 \pm 3.1\%$ to $29.7 \pm 3.0\%$, $P < 1.0 \times 10^{-16}$) through decreased prescriptions for DPP-4 (9.9–6.3%, $P = 0.11$), insulin (29.8–16.7%, $P = 4.3 \times 10^{-9}$), SGLT-2 inhibitors (10.3–0.9%, $P = 9 \times 10^{-7}$), sulfonylureas (23.7–0%, $P < 1.0 \times 10^{-16}$), and thiazolidinediones (1.5–0.4%, $P = 0.23$) (Fig. 3). GLP-1 prescriptions were statistically unchanged (13.4% at baseline to 14.4% at 1 year, $P = 0.67$), and metformin decreased slightly (71.4–65.0%, $P = 0.04$) for CCI participants. Forty percent (31/78) of CCI participants who began the study with insulin prescriptions (average dose of 64.2 units) eliminated the medication, while the remaining 60% (47/78) of insulin users reduced daily dosage from 105.2 to 53.8 units ($P < 0.0001$). Patients enrolled in UC for 1 year showed no Bonferroni-adjusted significant change for prescription of medication. For the 34 UC participants that continued using insulin, the average daily dose increased from 96.0 to 111.9 units.

The proportion of participants in the total imputed CCI group with HbA_{1c}below 48 mmol mol^{-1} ($< 6.5\%$) increased from $19.5 \pm 2.4\%$ to $69.8 \pm 3.1\%$. Of those in the CCI with HbA_{1c} reported at 1 year, 72% (147/204) achieved HbA_{1c} below 48 mmol mol^{-1} (6.5%) and 60.3% (123/204) of participants achieved HbA_{1c} below 48 mmol mol^{-1} ($< 6.5\%$) while taking no diabetes medication or only metformin. Of those in the CCI with HbA_{1c} below 48 mmol mol^{-1} ($< 6.5\%$) at 1 year, 42.3% (52/123) were prescribed no diabetes medication and 57.7% (71/123) were prescribed metformin only. The proportion of the total imputed CCI group with

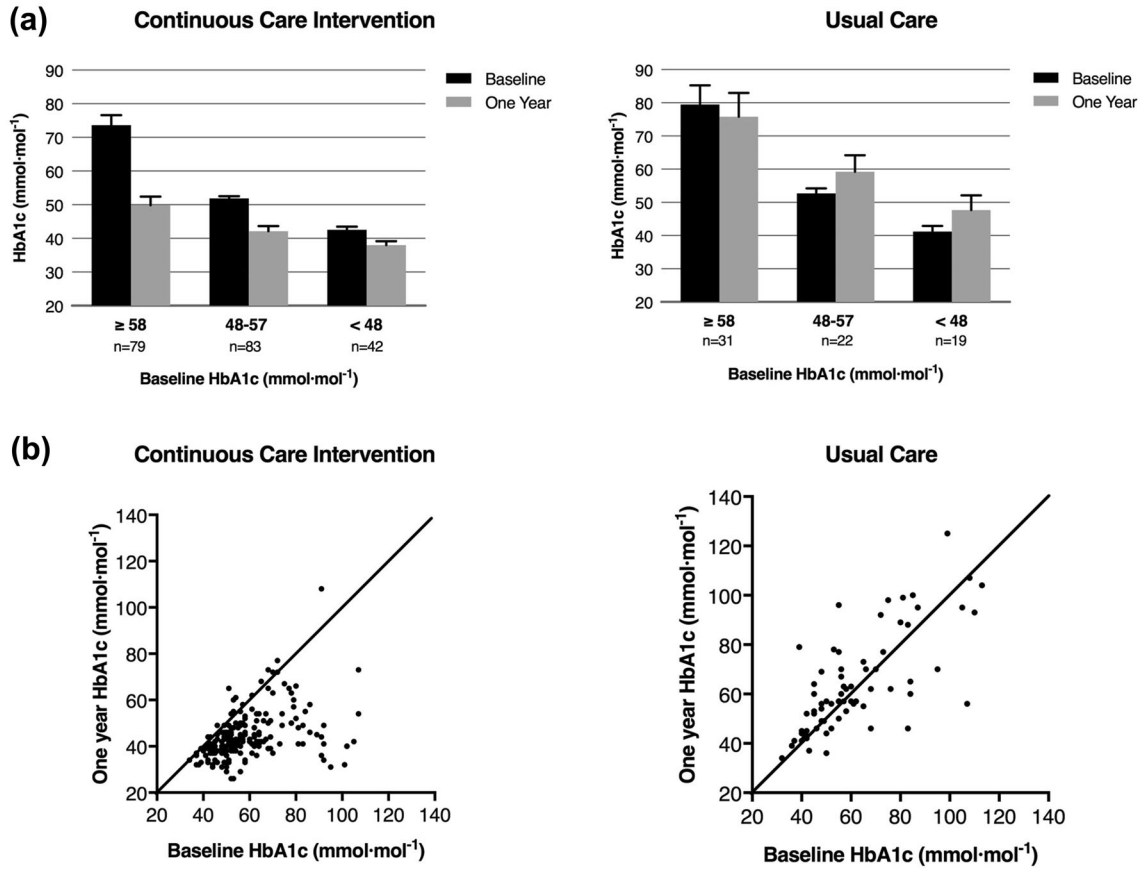

Fig. 1 Change in HbA_{1c} over the course of 1 year for CCI and UC groups. **a** Mean (95% CI) in HbA_{1c} based on starting value at baseline and 1 year for completers in both groups. **b** Individual changes in HbA_{1c} over 1 year for completers in both groups

fasting glucose below 6.99 mmol L^{-1} at 1 year increased from 34.9 ± 3.3% to 58.4 ± 3.9%, and the proportion with class III obesity decreased from 45.5 ± 3.1% to 19.6 ± 2.8%.

Compared to UC, the CCI showed significant Bonferroni-adjusted ($P < 0.0017$) net reductions in HbA_{1c} (nominal significance for the two-group comparison, $P < 10^{-16}$; Fig. 1), fasting glucose ($P = 2.1 \times 10^{-6}$), fasting insulin excluding exogenous users ($P = 4.6 \times 10^{-5}$), C-peptide ($P = 5.3 \times 10^{-5}$), HOMA-IR derived from insulin excluding exogenous users ($P = 6.0 \times 10^{-5}$) or derived from C-peptide ($P = 3.0 \times 10^{-5}$), weight ($P < 10^{-16}$), triglycerides ($P = 1.0 \times 10^{-6}$), hsCRP ($P = 9.3 \times 10^{-7}$), ALT ($P = 4.6 \times 10^{-5}$), and alkaline phosphatase ($P = 3.1 \times 10^{-8}$). All of these group differences remained significant when adjusted for the baseline age, sex, insulin medication use, and body mass index (Table 2). The CCI decrease in diabetes medication use was significantly greater than the changes in the UC group for all diabetes medications ($P < 10^{-16}$) and all diabetes medications excluding metformin ($P = 9.0 \times 10^{-9}$), including sulfonylurea ($P = 3.3 \times 10^{-7}$) and insulin ($P = 0.0002$) (Fig. 3).

The CCI-web and CC-onsite sub-cohorts provide replication of the above results. Specifically, Table S2 (see electronic supplementary material) shows that within-group Bonferroni significance was achieved separately for the mean 1-year reductions in HbA_{1c}, fasting glucose, fasting insulin, C-peptide, HOMA-IR, triglycerides, and hsCRP, and the significant increases in HDL-cholesterol and LDL-cholesterol. The Bonferroni-adjusted significant differences from the UC cohort were also

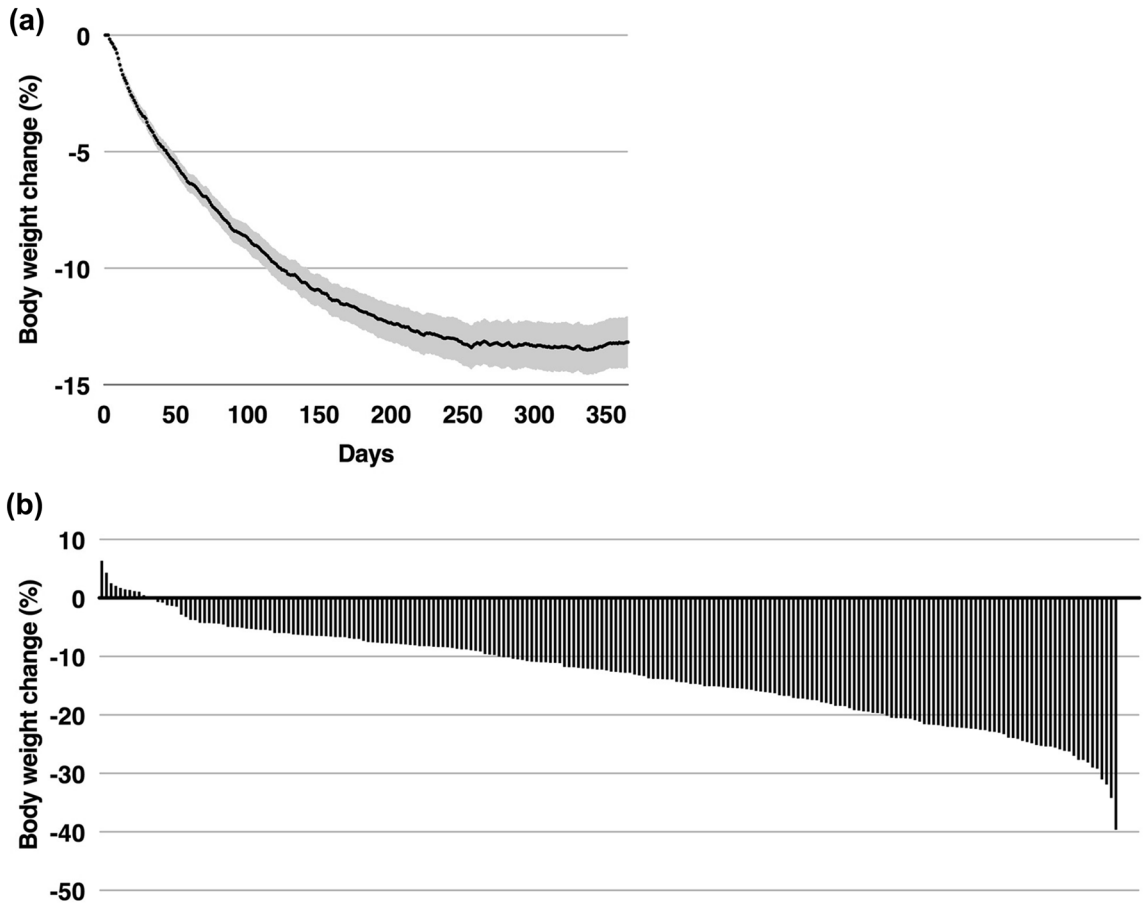

Fig. 2 Body weight change over the course of 1 year in CCI completers. **a** Mean (95% CI) change in body weight for completers over the course of 1 year. For each individual, weight on a given day was computed as the 3-day trailing mean (to reduce day-to-day variation). On dates where no weights were recorded during the 3-day time window for a given participant, the most recent 3-day mean preceding the date was used. **b** Histogram depicting individual body weight changes at 1 year

replicated by the two educational sub-cohorts for HbA_{1c}, fasting glucose, insulin-derived HOMA-IR, weight, HDL-cholesterol, LDL-cholesterol, triglycerides, hsCRP, and alkaline phosphatase, with or without adjustment for baseline covariates.

Time Course of Biomarker Change in CCI

Over the course of the intervention at baseline, 70 days [23], and 1 year, the proportion of participants in the total imputed CCI with HbA_{1c} below 48 mmol mol^{-1} (< 6.5%) increased from 19.5 ± 2.4 to 60.7 ± 3.1 to 69.8 ± 3.1%; the proportion with fasting glucose below 6.99 mmol L^{-1} (< 126 mg dL^{-1}) increased from 34.9 ± 3.3 to 55.5 ± 3.3 to 58.4 ± 3.9%, and the proportion with class III obesity decreased from 45.5 ± 3.1, to 30.2 ± 3.1, to 19.6 ± 2.8%.

The time course of biomarker changes also differed by variable (see Table S3 in the electronic supplementary material). Most of the 1-year improvements in diabetes risk factors were achieved during the first 70 days of the intervention including 84% of the HbA_{1c} decrease, 90% of the fasting glucose decrease, 73% of the fasting insulin decrease, 64% of the C-peptide decrease, and 87% and 74% of the decreases in HOMA-IR as estimated from fasting insulin and C-peptide concentrations, respectively. Improvements in blood pressure also mostly

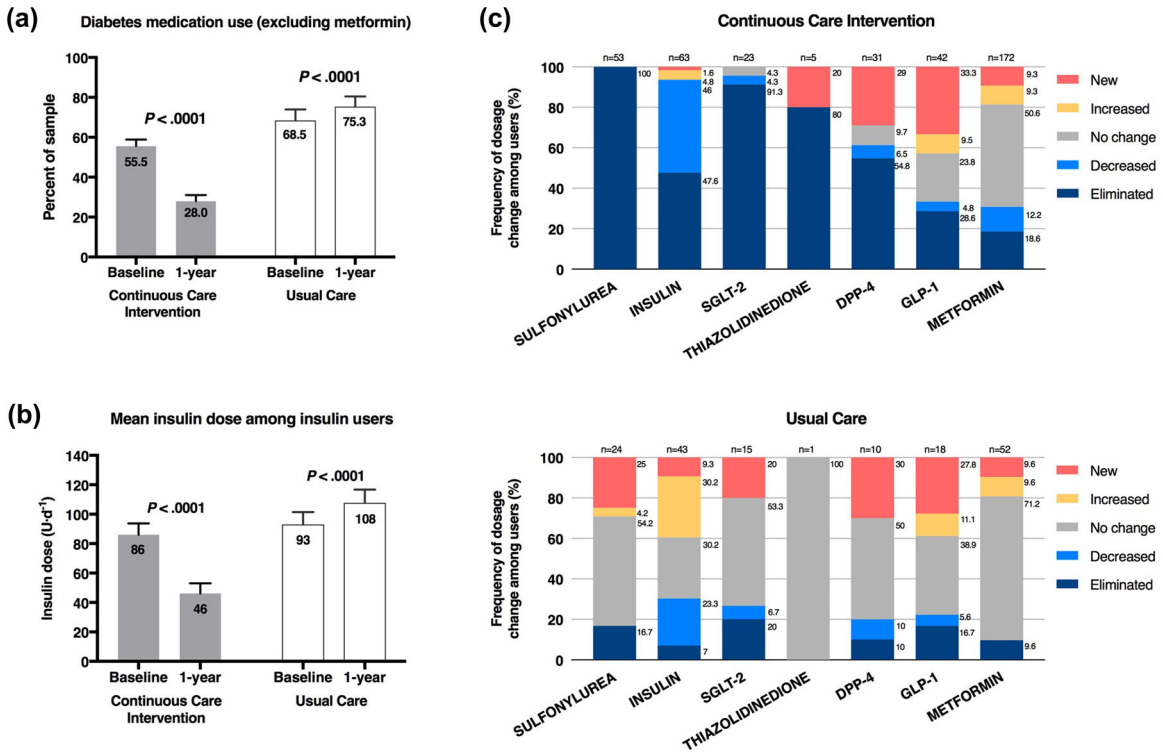

Fig. 3 Medication changes over the course of 1 year in completers of the CCI and UC groups. **a** Proportion of completers prescribed diabetes medications other than metformin. **b** Mean ± SE prescribed dose among insulin users. **c** Frequency in change of medication dosage among prescribed users by diabetes medication class in both groups

occurred in the initial 70 days, as did reductions in alkaline phosphatase, serum creatinine, and eGFR. Most of the plasma triglyceride decrease occurred during the first 70 days (87%), whereas essentially all the substantial increase in HDL-cholesterol occurred between the initial 70 days of the intervention and 1 year (99%). About 60% of weight loss occurred in the first 70 days.

Retention and Adherence in CCI

Eighty-three percent of participants remained enrolled in the CCI at 1 year. Nearly all CCI participants (96%) reported at least one BHB reading of 0.5 mmol L^{-1} or more by handheld measure, and among completers, the group mean at 70 days by laboratory measure was over threefold the baseline (0.54 ± 0.04 versus 0.17 ± 0.01 mmol L^{-1}). Laboratory-measured BHB at 1 year (0.31 ± 0.03 mmol L^{-1}) was nearly double the baseline value (Fig. 4). The intention-to-treat analysis yielded similar results, with an increase in average from baseline (0.17 ± 0.01 mmol L^{-1}) to 70 days (0.54 ± 0.04 mmol L^{-1}), followed by a decrease at 1 year (0.30 ± 0.02 mmol L^{-1}), though still nearly twofold the baseline concentrations.

Safety and Adverse Events

For CCI participants, acid–base physiology was normal; no cases of metabolic acidosis were observed. One CCI patient (0.38% of starters) had a clinically significant rise in serum creatinine, but group mean declined at 1 year. Mean blood urea nitrogen increased significantly in the CCI group, possibly indicating increased dietary protein consumption although high protein intake was not recommended. Mean uric acid in the CCI rose transiently at 70 days, but was unchanged at 1 year; no new cases of gout were diagnosed. Mean free T4 level was

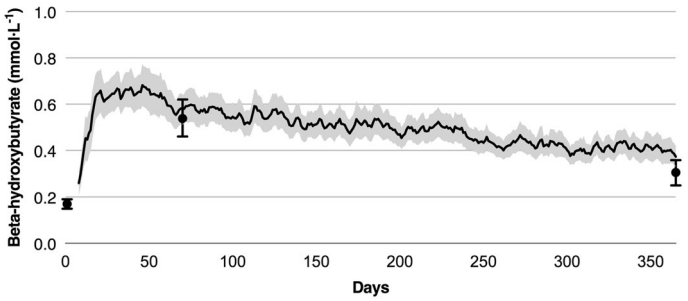

Fig. 4 Beta-hydroxybutyrate concentrations of CCI completers. Note: For each individual in the graph, the BHB concentration on a given day was computed as the 3-day trailing mean (to reduce day-to-day variation). On dates where no BHB concentrations were recorded during the 3-day time window for a given participant, the most recent 3-day mean preceding the date was used. Line graph depicts mean (95% CI) over time for BHB measured at home and reported via the app. Dots and error bars represent the mean ± SE from laboratory measured BHB at baseline, 70 days, and 1 year

unchanged, and TSH was significantly lower at 1 year; two new cases of subclinical hypothyroidism were observed (0.76% of starters) in the CCI [24].

Adverse events occurred in 6/262 CCI participants including one non-ST-segment myocardial infarction, one inferior myocardial ischemia by electrocardiogram, one metastatic neuroendocrine carcinoma, one malignant cancer with multiple brain lesions and lung tumor, and death from renal hemorrhage and failure and hyperkalemia. Also, one episode of hypoglycemia occurred following a motor vehicle accident and medical records indicated the patient was not taking insulin as prescribed; no other episodes of symptomatic hypoglycemia requiring assistance were reported. None of the adverse events were attributed to the intervention.

Adverse events were reported in 6/87 UC participants, including one percutaneous coronary intervention (PCI) to left anterior descending stenosis, one PCI to right coronary artery, two carotid endarterectomies (one of which was successful), multifactorial encephalopathy, and diabetic ketoacidosis with pulmonary emboli.

DISCUSSION

This study evaluated the effectiveness and safety of an alternative treatment model for T2D that utilized continuous remote care to provide a high level of outpatient support combined with individualized nutrition enabling long-term maintenance of behavioral and metabolic change via nutritional ketosis. This trial prospectively observed adults with T2D undergoing treatment via this novel care model and a comparison group of adults with T2D undergoing usual care treatment. Following 1 year of CCI, participants achieved a 14 mmol mol^{-1} (1.3 ± 0.1%) decline in HbA_{1c} concurrent with 12% weight loss and reduction in medication use. Consistent conclusions were reached with intention-to-treat analysis and analysis of completers. A usual care group showed no change in diabetes status or related biomarkers over the year.

Effectiveness

The CCI reduced HbA_{1c} by 14 mmol mol^{-1} (1.3%) at 1 year. HbA_{1c} reductions up to 7 mmol mol^{-1} (0.6%) via intensive lifestyle intervention [25] and 11 mmol mol^{-1} (1.0%) via an energy-restricted low-carbohydrate diet with partial food provision delivered via an outpatient setting [26] were previously reported. The present intervention achieved 12% weight loss at 1 year; previously studied interventions elicited 4–9% weight loss in patients with T2D [25, 26]. The regular monitoring of weight, glucose, and BHB as biometric feedback

for participant, health coach, and medical provider may have provided behavior reinforcement. Further, it seems plausible that this multicomponent care model allowed for greater improvements compared to interventions that provided a subset of components. A recent primary care-led weight management intervention utilizing a 3–5 month VLCD resulted in a 10 mmol mol^{-1} (0.9%) reduction in HbA_{1c} and 10% weight loss at 1 year; 46% of participants achieved HbA_{1c} below 48 mmol mol^{-1} (< 6.5%) while taking no medications [27]. While only 25% of participants in the present investigation achieved this measure of diabetes remission, the protocol for the present investigation discontinued metformin prescription only because of contraindication, intolerance, or patient request given its efficacy for T2D prevention and recommended use in certain populations [7]. An additional 35% of participants in the present investigation were able to attain HbA_{1c} below 48 mmol mol^{-1} (< 6.5%) while taking only metformin. The longer duration of T2D and baseline insulin prescription to 30% of participants might be factors influencing the proportion of participants in which glycemic control medications could be discontinued in this investigation.

HbA_{1c} improved concurrent with medication reductions prescribed for blood glucose-lowering. For each medication class, the sum percentage of eliminations and reductions of prescriptions at 1 year exceeded that observed at 70 days [23]. Improved glycemic control via a predominantly pharmaceutical approach has demonstrated paradoxical increased cardiovascular risk [28]. Tight glycemic control can elicit symptomatic hypoglycemia [29] or weight gain [30], neither of which was observed in CCI. Thus, it is likely the treatment method by which glycemic control is achieved (e.g., pharmacological, surgery, lifestyle intervention) is important to health outcomes and risk.

Most changes in HbA_{1c}, glucose, insulin, C-peptide, and HOMA-IR occurred in the first 70 days with further improvement observed at 1 year. While the mechanism for improved insulin sensitivity in ketosis is not fully understood, early improvements in HbA_{1c} and HOMA-IR indicate rapid restoration of liver and peripheral insulin sensitivity and are consistent with improvements observed within 2 weeks of ketosis when measured by euglycemic hyperinsulinemic clamp [13]. Utilization of blood BHB for self-monitoring with reinforcement by clinicians may have contributed to sustained HbA_{1c} improvement. Further, BHB acts as a signaling molecule, reducing inflammation and oxidative stress [14, 15]; therefore, mild ketonemia may benefit multiple organs and systems. With appropriate dietary formulation, benefits of nutritional ketosis are observed in mouse models of longevity and health span [31, 32]. Participant mean BHB levels are of similar magnitude to those observed with SGLT-2 inhibitor treatment ($\sim$ 0.5 mmol L^{-1}) [33]. Recent trials [5, 34] demonstrate cardiovascular benefits to two SGLT-2 inhibitors; mild ketosis was postulated as a mechanism [33]. Nutritionally achieved ketosis may have long-term cardiovascular benefits without the pharmaceutical risk profile [34]. Further, presence of glucose and palmitate has been associated with beta cell apoptosis [35]. Given the reduced levels of glucose and palmitate observed during nutritional ketosis [36], it is plausible that ketosis might play a role in attenuating glucolipotoxicity-induced beta cell death.

Beyond achieving improved glycemic control concurrent with medication and weight reductions, the CCI had broad positive impact on blood pressure, liver enzymes, hsCRP, triglycerides, and HDL-C. Elevated ALT, AST, and ALP are associated with non-alcoholic fatty liver disease and non-alcoholic steatohepatitis [37]; these enzymes were significantly reduced with intervention. Rapid reduction in triglycerides and gradual rise in HDL-C observed following CCI are consistent with previously studied carbohydrate-restricted interventions and carbohydrates are well known to increase triglycerides [38]. Of the 108 CCI completers with elevated baseline triglycerides ($\geq$ 1.69 mmol L^{-1}), 54% were in normal range at 1 year. Rise in LDL-C at 1 year, occurring with significant triglyceride decrease, was expected as there is less exchange via cholesteryl ester transfer protein [39]. However, this exchange would not affect particle number and ApoB was unchanged, suggesting an overall neutral

impact on LDL lipoprotein-associated cardiovascular risk. In epidemiological studies, utilization of dietary saturated fat in place of carbohydrate was associated with beneficial impact on lipid profile, cardiovascular outcomes, and mortality despite higher LDL-C [40, 41]. Transiently increased total and LDL cholesterol were also associated with mobilization of adipose cholesterol stores during major weight loss [42].

Consistent with population-level studies that observed very low rates of diabetes remission [43], the UC group had no change in HbA_{1c} and other indicators of glycemic status and insulin resistance but a net increase in diabetes medication use. Laboratory tests were generally unremarkable with biomarkers not changing significantly. The same facilities and methodologies were used for both the CCI and UC participants indicating that the changes observed in CCI participants not observed in the UC participants are unlikely to be due to methodological changes in clinical or laboratory data capture.

Despite independent recruitment of the CCI and UC groups, most of their baseline characteristics including HbA_{1c} and years since diabetes diagnosis were not significantly different. To enable a comparison between the CCI and UC groups, covariate adjustment was utilized to adjust for differences in baseline characteristics including sex, age, baseline BMI, baseline insulin use (user vs. non-user), and African-American race. With or without baseline adjustment, the change over 1 year elicited in the CC and UC groups differ in all primary outcomes—HbA_{1c}, medication use, and weight—and most secondary outcomes including lipid profile, inflammation, and liver function. In general, the favorable changes observed in the CCI were not observed in the UC cohort. For example, of patients who obtained HbA_{1c} measurements at 1 year, 60% of CCI participants achieved a HbA_{1c} below 48 mmol mol^{-1} (< 6.5%) while taking no diabetes medications or metformin only, whereas only 10% of UC participants achieved this status.

One interpretation of these results is that the differences in observed outcomes over the year are due to advantages of the CCI over usual care. This suggests a need to incorporate carbohydrate restriction and comprehensive, continuous remote care as options in current guidelines for patients with diabetes as evidence accumulates [44]. However, alternative explanations are possible that may account for the large degree of difference observed. For instance, patients entering the CCI were recruited knowing that they were making a commitment to lifestyle change, while the UC participants were identified as recent referrals to local diabetes education programs and may not have had similar motivation or expectations of effort as the CCI participants. However, even when motivation is controlled for upon recruitment as an inclusion criterion for participation, additional factors may play a role in retention as evidenced by a recent study with randomization [45]. Also, the CCI and UC cohorts may also have differed in baseline characteristics that were not captured such as socioeconomic status.

Additionally, the treatment intensity of the two cohorts was not equal. The UC participants had one or more meetings with a registered dietitian and were under the medical supervision of their primary care provider or endocrinologist with periodic medical visits. In contrast, the CCI participants received a comprehensive and individualized continuous remote care intervention (and in one subgroup, the addition of on-site group classes). A more intensive intervention might have delivered somewhat better results than the investigation's UC group. For instance, a recent in-person group-based intervention for weight loss in T2D adults reduced HbA_{1c} by 3 mmol mol^{-1} (0.3%) and weight by 4.0% after a year and medications were reduced in 26% of participants [46]. Future research might compare interventions of similar intensity with different treatment strategies to begin to understand the contribution of each component of the intervention to the overall effect.

Adherence to CCI

Eighty-three percent of CCI participants were retained through 1 year; patient perceived

benefits of favorable health outcomes, individualized continuity of care, relationship with health coach, ongoing education, biometric feedback, and peer support may have aided retention. Most participants achieved nutritional ketosis during CCI and maintained elevated BHB at 1 year, indicating sustainability and was possibly enabled by the novel use of blood BHB as daily biofeedback for adherence.

Safety of CCI

No episodes of ketoacidosis, no hypo- or hyperglycemic events requiring assistance, and no adverse events were attributable to the CCI. With improvements or no change in liver, kidney, and thyroid function, safety of the intervention appears favorable. The absence of hypoglycemic events requiring assistance despite relatively tight glucose control may be due to the careful medical provider prescription management, especially rapid downward titration of insulin and sulfonylurea preventing hypoglycemia following dietary changes. Additionally, elevated BHB may have offered protection against hypoglycemic events, as starvation-adapted humans with elevated BHB have demonstrated full preservation of central nervous system function despite profound hypoglycemia induced by exogenous insulin [47].

Study Strengths and Weaknesses

Prior studies have demonstrated favorable improvements in T2D status following carefully managed ketogenic diets as case series [48] or in small short-term randomized trials [45]. This study's strengths include its prospective design, large cohort, high retention, duration, replication of findings between the CCI-onsite and CCI-web groups, and the collection of multiple time points in the intervention group allowing assessment of how biomarkers changed over time. This study also included participants prescribed insulin and with long-standing T2D, which were often exclusion criteria for prior studies. The means of recruitment, outpatient setting, and lack of food provision may enhance the real-world application of this study.

Weaknesses of this study include that it occurred at a single site and participants were mostly Caucasian. Socioeconomic and psychosocial status and genetics data were not collected. The study was not of sufficient size and duration to measure hard endpoints (e.g., mortality). Future trials could include a multisite randomized controlled trial with greater racial and ethnic diversity, broader age range, and greater disease severity.

CONCLUSIONS

This study demonstrated that a T2D intervention combining technology-enabled continuous remote care with individualized care plans encouraging nutritional ketosis can significantly reduce HbA_{1c}, medication use, and weight within 70 days [23], and that these outcomes can be maintained or improved through 1 year. Most intervention participants with HbA_{1c} reported at 1 year achieved glycemic control in the sub-diabetes range with either no medication or the use of metformin alone. Related health parameters improved including blood pressure, lipid-lipoprotein profile, inflammation, and liver function. Ongoing research will determine the continued sustainability, effectiveness, and safety of these behavioral and metabolic changes.

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Compliance with Ethics Guidelines. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Data Availability. The data sets analyzed during the current study are available from the corresponding author on reasonable request.

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ORIGINAL ARTICLE

Effectiveness of a ketogenic diet and virtual coaching intervention for patients with diabetes: A difference-in-differences analysis

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Abstract

Aim: To test the effectiveness of a ketogenic diet and virtual coaching intervention in controlling markers of diabetes care and healthcare utilization.

Materials and Methods: Using a difference-in-differences analysis with a waiting list control group—a quasi-experimental methodology—we estimated the 5-month change in HbA1c, body mass index, blood pressure, prescription medication use and costs, as well as healthcare utilization. The analysis included 590 patients with diabetes who were also overweight or obese, and who regularly utilize the Veterans Health Administration (VA) for healthcare. We used data from VA electronic health records from 2018 to 2020.

Results: The ketogenic diet and virtual coaching intervention was associated with significant reductions in HbA1c (−0.69 [95% CI −1.02, −0.36]), diabetes medication fills (−0.38, [−0.49, −0.26]), body mass index (−1.07, [−1.95, −0.19]), diastolic blood pressure levels (−1.43, [−2.72, −0.14]), outpatient visits (−0.36, [−0.70, −0.02]) and prescription drug costs (−34.54 [−48.56, −20.53]). We found no significant change in emergency department visits (−0.02 [−0.05, 0.01]) or inpatient admissions (−0.01 [−0.02, 0.01]).

Conclusions: This real-world assessment of a virtual coaching and diet programme shows that such an intervention offers short-term benefits on markers of diabetes care and healthcare utilization in patients with diabetes.

KEYWORDS
dietary intervention, health economics, type 2 diabetes, weight control

1 | INTRODUCTION

The prevalence of diabetes is disproportionately high among US veterans. Approximately 25% of veterans have a diabetes diagnosis in comparison with 9% of the general population.[1] The Veterans Health Administration (VA) incurs more than $200 million in outpatient expenditure and more than $1 billion in inpatient expenditure for veterans with diabetes.[2] In light of these serious health and financial consequences, the VA recently undertook a test of effectiveness of a ketogenic diet and virtual coaching (KD-VC) intervention among patients with diabetes.

Lifestyle interventions and medical nutrition therapy are cornerstones of non-pharmacological treatment for patients with diabetes. In particular, some virtual diet interventions with coaching

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components have been shown to be effective in achieving short-term weight loss and improving glucose control,[3-11] although less is known about the impact of coaching programmes with a specific ketogenic (keto) diet component.[12] One virtual diabetes coaching programme with a keto diet component has been previously evaluated. Virta Health (San Francisco, CA) conducted a non-randomized clinical trial testing the impact of a combined individualized keto diet and telehealth medical care model on overweight and obese adults with diabetes relative to a usual care arm. This programme's coaching component also includes an emphasis on diabetes medication management. Over a 2-year intervention period, HbA1c declined by 0.9% and 62% of participants reduced or eliminated insulin use.[13-15] However, these results remain subject to bias because of the non-randomized design and the absence of a similarly motivated comparison group.

Furthermore, while the short-term clinical benefits of keto and other non-keto virtual diet interventions are promising for diabetes, there is little information on such programmes regarding healthcare utilization or costs. Increasing use of telehealth interventions may help to unburden healthcare systems of some care and treatment costs. Understanding whether virtual care interventions improve utilization and cost outcomes in diabetes is critical for healthcare system resource allocation.

Using a quasi-experimental approach, the current study was designed to estimate the effectiveness of the KD-VC programme among veterans with diabetes enrolled in VA healthcare. We conducted a difference-in-differences analysis with a waiting list control group to answer the following question: What is the impact of the KD-VC programme over 5 months on (a) markers of glucose control and metabolic health, (b) outpatient and inpatient utilization, and (c) prescription drug utilization and costs?

2 | MATERIALS AND METHODS

2.1 | Study design

We used a difference-in-differences approach to estimate the impact of the KD-VC programme on key diabetes outcomes using VA electronic health records from 2018 to 2020. A difference-in-differences approach uses observational data to compare changes in outcomes between a treatment and control group, both before and after an intervention is delivered.[16-18] The study was reviewed and considered exempt research by the VA Boston Healthcare System Institutional Review Board.

2.2 | Virta telehealth and keto coaching intervention

The Virta Health programme is an online telehealth and coaching intervention in which participants are counselled to adhere to a keto diet.[13] The programme also includes education components and management of medications for patients with diabetes. In April 2019, VA initiated a pilot programme in which 454 veterans were given access to the Virta KD-VC programme on a first-come-first-serve basis until enrolment capacity was reached in October 2019. An additional 867 veterans who wished to enrol after capacity was reached did not have the opportunity to do so. For the purposes of this report, this group is referred to as the control group but is equivalent to a waiting list control group because of motivation comparable with the treatment group.

Veterans were required to meet several inclusion criteria. These included enrolment in medical benefits through VA, a current diabetes diagnosis (defined as HbA1c greater than or equal to 6.5%) and at least one current diabetes medication other than, or in addition to, metformin. The latter criterion was designed to exclude enrolment by patients taking metformin alone for diabetes prevention or other non-diabetes indications. Exclusion criteria included active duty status, veterans living abroad, and a list of special conditions including, but not limited to, type 1 diabetes, end stage renal disease, heart failure, active chemotherapy treatment and others. All applicants completed an initial screening based on self-report. Treatment patients were required to provide VA benefit cards, HbA1c results and prescriptions for physician validation of inclusion criteria. Control group participants did not undergo physician validation of self-reported data.

2.3 | Data

We used data from the VA Corporate Data Warehouse, which contains electronic health records and information on sociodemographic characteristics, chronic conditions, medications and vital signs, as well as VA outpatient, inpatient and emergency department utilization. Data on diabetes medication costs to the VA were provided by VA's Pharmacy Benefits Management Services. Data were extracted from September 2018 to August 2020.

2.4 | Matching and screening

Virta Health collected information on name, address, social security number and telephone number for all patients. These data were provided to the research team and used to match to VA patient records for analysis. Because the treatment and control groups underwent different screening processes, we imposed uniform treatment inclusion criteria using VA data to create comparable treatment and control samples with regard to underlying health status and motivation. Specifically, we screened VA data on all participants for a diabetes diagnosis within a year of application date, at least one active non-metformin diabetes medication and an HbA1c level greater than or equal to 6.5% within the prior 6 months.

2.5 | Measurements

2.5.1 | Outcome variables

We identified 10 outcomes of interest related to diabetes care: HbA1c, body mass index (BMI), systolic blood pressure (SBP), diastolic

blood pressure (DBP), emergency department (ED) visits, outpatient visits, inpatient admissions, number of insulin prescriptions, number of diabetes prescriptions and the costs of diabetes prescriptions. Outcomes were captured up to 5 months postapplication date. This window was selected because, at 6 months, patients from the waiting list began to enrol in the intervention and the COVID-19 pandemic began to impact utilization rates in the control group. When subjects had multiple observations per month, monthly averages were calculated, dropping observations that were greater than three standard deviations from the monthly subject-specific average.

2.5.2 | Primary independent variable

The KD-VC programme effect is the primary covariate of interest, and is the interaction term between an indicator variable for treatment status (coded as 1 if treated and 0 if control) and an indicator variable for postapplication time period (coded as 1 for post-KD-VC programme application months and 0 for preapplication months). Because control participants do not have a treatment date, we used the application month as the relevant postperiod for ease of comparison.

2.5.3 | Covariates

Sociodemographic characteristics included gender, age, race/ethnicity and urban/rural residence. Also included were Charlson co-morbidity index[19] and an indicator for VA enrolment priority status (a proxy for socioeconomic status). As is standard in difference-in-differences analyses, we also include month-specific time indicators (fixed effects).

2.6 | Statistical analysis

We first conducted a descriptive analysis of baseline characteristics of treatment and control participants before their KD-VC programme application date using *t* tests for binary or continuous variables and chi-squared tests for categorical variables. We then estimated a difference-in-differences equation of the following multivariate linear specification:

$$y_{it} = \alpha + \beta_1 T_i + \beta_2 Post_{it} + \beta_3 (T * Post)_{it} + \theta X_i' + \gamma_t + \varepsilon_{it}, \quad (1)$$

where y_{it} is one of eight outcomes for individual, i, in month, t; β_3 is the change in outcome associated with receiving the KD-VC programme, T_i, in the postperiod, $Post_{it}$; X_i are covariates and γ_t are month fixed effects. Huber-White robust standard errors were calculated at the patient level.[20]

Causal inference in the difference-in-differences framework relies on the assumption that the trends in the outcomes evolved similarly between treatment and control groups in the preapplication period and would have continued to evolve similarly in the absence of the treatment. This parallel-trends assumption allows inferences that the difference-in-differences estimates (β_3) are attributable to the KD-VC programme, and not to other factors that may have influenced treatment uptake. To test the parallel trends assumption, we estimated regressions of the outcomes with interactions between the relative month indicator and treatment indicator for each outcome. Joint chi-squared tests of the interactions failed to reject zero differences in the trends of these outcomes between the control and treatment groups in the preapplication period.

As an additional robustness check, we examined the differential missingness of data between treatment and control patients for five outcomes: HbA1c, BMI, SBP/DBP (combined), ED visits and outpatient visits. This robustness check is designed to detect for any documentation bias in the electronic health record specifically related to treatment. We created an indicator for outcome-specific missingness (1 if missing, 0 if non-missing) and regressed this new variable on the variables in Equation (1). In this specification, a positive value of β_3 would indicate the percentage point probability that treatment status is associated with outcome-specific missingness. For outcomes for which there was evidence of differential missingness, we ran weighted regressions, where weights were calculated as the inverse probability of having an observed outcome in the postapplication period.[21]

3 | RESULTS

3.1 | Matching and screening processes

Virta Health provided 1328 patient records to the VA research team. Seven of these records were removed because of duplicate entries or blank records. Of the viable records, 454 were marked as treatment patients and 867 were marked as control patients. Figure 1 shows how the analytical sample was derived. Using a combination of patient identifiers, 84.7% of Virta Health records were successfully matched to VA records. The match rate was higher in the treatment group (99.3%) than in the control group (77.0%). The somewhat higher match rate in the treatment group is probably because these participants were actively screened for eligibility by Virta Health staff whereas control group participants were not. After matching patient records, we imposed uniform inclusion criteria using VA data on HbA1c, diabetes diagnosis and prescription medications. Of the matched sample, 52.7% met all three inclusion criteria: 61.0% in the treatment group and 47.2% in the control group. The final analytical sample contained 590 patients: 275 in the treatment group and 315 in the control group.

3.2 | Baseline characteristics

The baseline characteristics of the treatment and control groups are presented in Table 1. Treatment patients were more probable to be male and non-Hispanic White, and each of these variables are

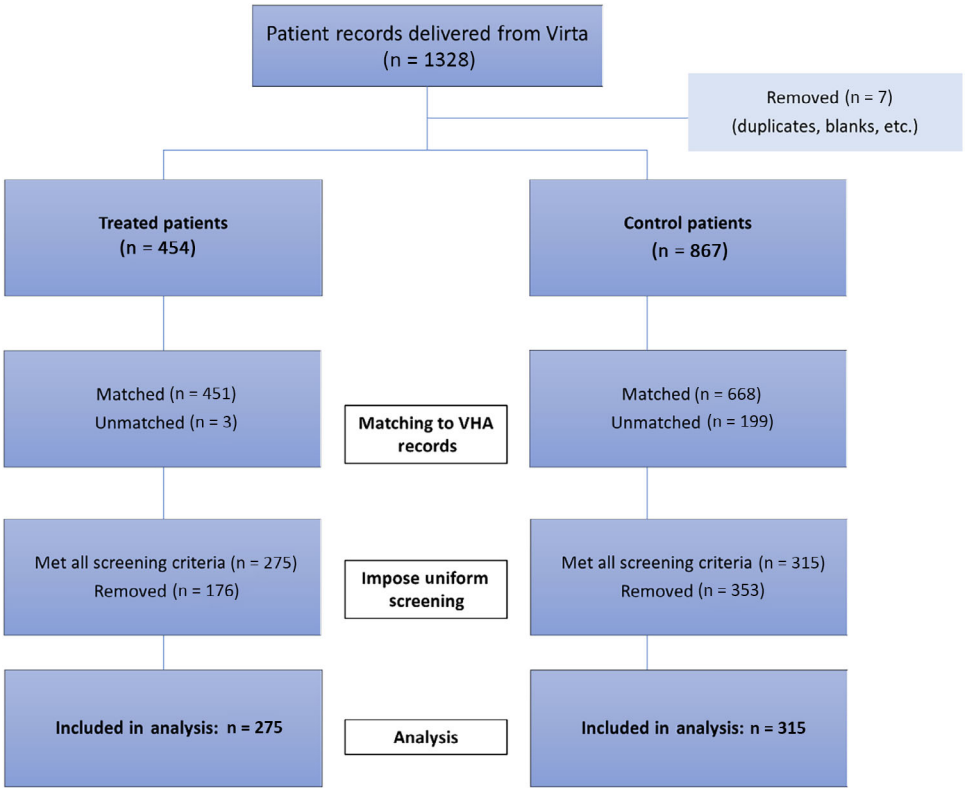

FIGURE 1 Flow diagram of veterans in the analytical sample. VHA, Veterans Health Administration

controlled for in the regression models. The treatment group had slightly lower baseline HbA1c and monthly insulin prescriptions, and slightly higher prior participation in VA weight-loss programmes. However, the trends in these variables between treatment and control groups were statistically indistinguishable during the preapplication period, supporting the assumption of parallel trends. All other measures of sociodemographic variables, healthcare utilization, health status and prescriptions were evenly distributed between treatment and control groups.

3.3 | Impacts of the keto diet and virtual coaching programme

The difference-in-differences estimates comparing health outcomes before and after KD-VC programme application dates are reported in Table 2 and are shown graphically in Figure 2. The KD-VC programme was associated with a −0.69% (standard error [SE]: 0.168) decline in HbA1c and BMI was reduced by −1.07 (SE: 0.447) during the 5-month study period. Significant reductions were noted in the number of monthly insulin prescriptions and all monthly diabetes-related medications. The reduction in average monthly diabetes-related medication costs was −$34.54 (SE: 7.135) per patient. Treatment was associated with a small reduction in the number of monthly outpatient visits. No significant changes in inpatient admissions or ED visits were detected.

For all outcomes, results did not vary significantly with the inclusion of baseline covariates and/or time fixed effects in the models. Unadjusted differences in outcomes are presented in Appendix SA and month-specific treatment effects are included in Appendix SB.

3.4 | Tests for differential missingness in outcomes

We tested for differential missingness in outcomes between treatment and control groups for HbA1c, BMI, SBP/DBP (combined), ED visits and outpatient visits (Appendix SC). Only one outcome, BMI, showed evidence of differential attrition. Treatment group patients were 5% more probable to have a missing BMI value and 4% more probable to have a missing BP value in the post-application period, relative to control group patients. We then weighted the observations in the primary difference-in-differences specification using the inverse of the probability of having a non-missing BMI value in the postapplication period. Results from this analysis were not meaningfully different from the results in the primary specifications (Appendix SD).

4 | DISCUSSION

In this quasi-experimental study using a difference-in-differences analysis with a waiting list control group, we found that a KD-VC programme was associated with significant reductions in HbA1c, diabetes medication fills, prescription medication costs, BMI, DBP and outpatient visits over 5 months among overweight and obese veterans with diabetes. Results were also robust when assessed for differential

TABLE 1 Baseline characteristics of veterans enrolled in the ketogenic diet and virtual coaching programme and in the waiting list control group, 2018-2020

Baseline variables	Treatment (n = 275)	Control (n = 315)	*P* value
Sociodemographic characteristics			
Males (%)	85.8	92.7	.007
Age, y (average)	58.1	57.7	.577
Urban resident (%)	66.2	72.7	.086
Race/ethnicity (%)			
Black, non-Hispanic	13.8	19.4	.02
White, non-Hispanic	68.4	56.2	
Hispanic	7.3	11.8	
Other, non-Hispanic	7.3	10.5	
Missing	3.3	2.2	
Priority status (%)			
1-3	73.5	70.8	.732
4-6	16.4	18.7	
7-8	10.2	10.5	
VA utilization			
Outpatient visits (monthly average)	3.8	3.5	.167
Emergency department visits (monthly average)	0.07	0.07	.931
Inpatient admissions (monthly average)	0.02	0.02	.977
Health status			
Co-morbidity index (average)	1.0	1.2	.204
BMI (kg/m^2, average)[a]	35.2 (n = 260)	35.0 (n = 298)	.842
HbA1c (%, average)	8.8	9.1	.048
Prescriptions (Rx)			
Metformin (%)	73.1	67.9	.172
Insulin (monthly average)	0.5	0.6	.042
Diabetes medications (monthly average)	1.1	1.1	.607
Total no. of non-metformin prescriptions	6.2	6.5	.371
Average cost of diabetes prescriptions (monthly average)	92.8	89.8	.696

Note: P values were computed using two-sample *t* tests for differences in continuous variables, and chi-square tests for categorical variables.
Abbreviations: BMI, body mass index; Rx, number of fills; VA, Veterans Health Administration.
[a]The number of observations for BMI are smaller because of missingness in the variable. Sample sizes for this metric are presented in parentheses next to group averages.

missingness of data. These findings support a role for this programme as a lifestyle intervention for patients with diabetes.

The magnitude of the changes we observed are consistent with prior research investigating the efficacy of other virtual diet programmes for diabetes care, irrespective of dietary guidelines.[22] With respect to HbA1c, we found that the KD-VC programme reduced HbA1c by 0.69%. Reductions of this magnitude are considered clinically meaningful by clinicians and regulatory agencies.[23] Other named diet virtual programmes that advocate the restriction of certain foods or macronutrients report short-term HbA1c reductions in the range of 0.8%-1.1%, although there is substantial variation in the strengths of study designs.[3-5,12] Named virtual diet programmes that promote healthy eating based on national dietary guidelines, national diabetes guidelines or caloric restriction either report no impact on HbA1c or reductions of up to 0.6%-0.9%.[6-11] However, many of these reports did not include a control group for comparison.

We found that participation in the KD-VC programme led to an estimated 1.07 kg/m^2 reduction in BMI, which is approximately 3% of the average preapplication BMI in the control group. This treatment effect is comparable with previously published studies of virtual diabetes programmes, which report BMI reductions associated with programme participation of 2.5%-8%.[3,6-8,10,13-15,24-28] Although we observed differential missingness in the BMI outcome, with treatment group participants being 5% more probable to have a missing outcome in the postapplication period, the use of inverse probability weighting models did not change the magnitude or precision of the results.

TABLE 2 Five-month changes in diabetes outcomes for veterans in the ketogenic diet and virtual coaching programme and control groups, before and after Virta application dates

Variable	Outcomes									
	HbA1c	Body mass index	Systolic blood pressure	Diastolic blood pressure	Outpatient visits (no.)	Inpatient admissions (no.)	ED visits (no.)	Insulin prescriptions (no.)	Any diabetes prescriptions (no.)	Prescription drug costs
Treatment*postperiod (DiD estimator)[a]	−0.69***	−1.07*	−0.78	−1.43*	−0.36*	−0.01	−0.02	−0.21***	−0.38***	−34.54**
	(0.168)	(0.447)	(1.245)	(0.658)	(0.175)	(0.008)	(0.015)	(0.041)	(0.059)	(7.135)
Treatment group indicator	−0.23	0.52	−0.63	0.84	0.28	0.002	0.0033	−0.030	0.024	8.897
	(0.148)	(0.655)	(1.197)	(0.647)	(0.206)	(0.0051)	(0.014)	(0.050)	(0.060)	(8.796)
Postperiod indicator	−0.24	−0.15	−0.37	0.26	0.57**	0.002	−0.0079	−0.0034	0.054	3.281
	(0.178)	(0.573)	(1.382)	(0.701)	(0.197)	(0.008)	(0.014)	(0.045)	(0.070)	(8.568)
Observations	1548	2459	2794	2794	7080	7080	7080	7080	7080	7080
Adjusted R^2	0.104	0.046	0.019	0.107	0.086	0.010	0.009	0.028	0.022	0.011

[a]The treatment*postperiod difference-in-difference (DiD) indicator estimates the impact of Virta treatment. Robust standard errors are displayed in parentheses. All regression models included variables for male, age, co-morbidity index, urban, race/ethnicity, priority status and calendar month fixed effects, not shown here. Full regression results are presented in Appendices SA and SB. The number of observations are reported at the patient-month level.

*$P < 0.01$. **$P < 0.05$. ***$P < 0.001$.

A novel contribution of this study is its use of administrative data to examine the impact of a KD-VC programme on healthcare utilization and costs. We found that the intervention led to a 0.36 reduction in the average number of monthly outpatient visits per patient and a 0.38 reduction in the average number of monthly diabetes medication fills over the 5-month period. The 34.5% reduction in diabetes medication fills from the baseline (preapplication period) is similar to that reported by other virtual diabetes programmes, in which declines in medication usage are in the 5%-40% range.[4-7,10] Savings attributable to the reduction in diabetes-related medications were approximately $35 per patient per month, which represents approximately 10% of the monthly programme cost. These cost reductions are probably conservative relative to other healthcare systems. Prescription drug prices within the VA are lower than private sector costs, as the VA negotiates medication purchase prices and uses a unified list of covered drugs, and discounts are defined by law.

This study has some limitations that may impact its generalizability. The study was conducted in a real-world environment and randomization was not performed. We worked to overcome this by simulating inclusion criteria with administrative data, and this produced study groups that approached being matched on observable characteristics. After imposing uniform screening criteria, we found no significant differences in pretreatment trends among study participants. We were unable to control for motivational differences between treatment and control groups, so it is possible that some veterans who initially expressed interest in the KD-VC programme would not have enrolled or completed the treatment if offered the chance. The study design also did not allow us to monitor KD-VC programme adherence in the treatment group or dietary changes in the control group.

It remains unclear whether the favourable effects observed operate through the personalized coaching component, the keto diet, patient motivation, or some combination of these. Given that adherence to the keto diet may be difficult and that the long-term effects of the diet are as of yet unknown, it is important to understand the differential impacts of various components of virtual diabetes programmes.[12] Because we relied on administrative data for outcome measures, there was potential for differential missingness. Although we observed greater postapplication missingness for some data in the treatment group, models that used inverse probability of observation weighting produced similar findings to the main results. Finally, it is important to note that we cannot comment on the durability of these results. The postapplication study period was 5 months, and therefore we cannot infer that results with a KD-VC programme are sustainable over longer periods of time.

In this study we showed that a lifestyle intervention involving a KD-VC programme produced clinically meaningful effects over 5 months on biochemical markers and healthcare utilization in patients with diabetes. As patients' personal and cultural preferences for diets are probable to vary, future research may seek to test the efficacy and appropriateness of a variety of diet options with or without coaching.[22] This research could inform how virtual diet programmes could be used to meet the needs of patients with

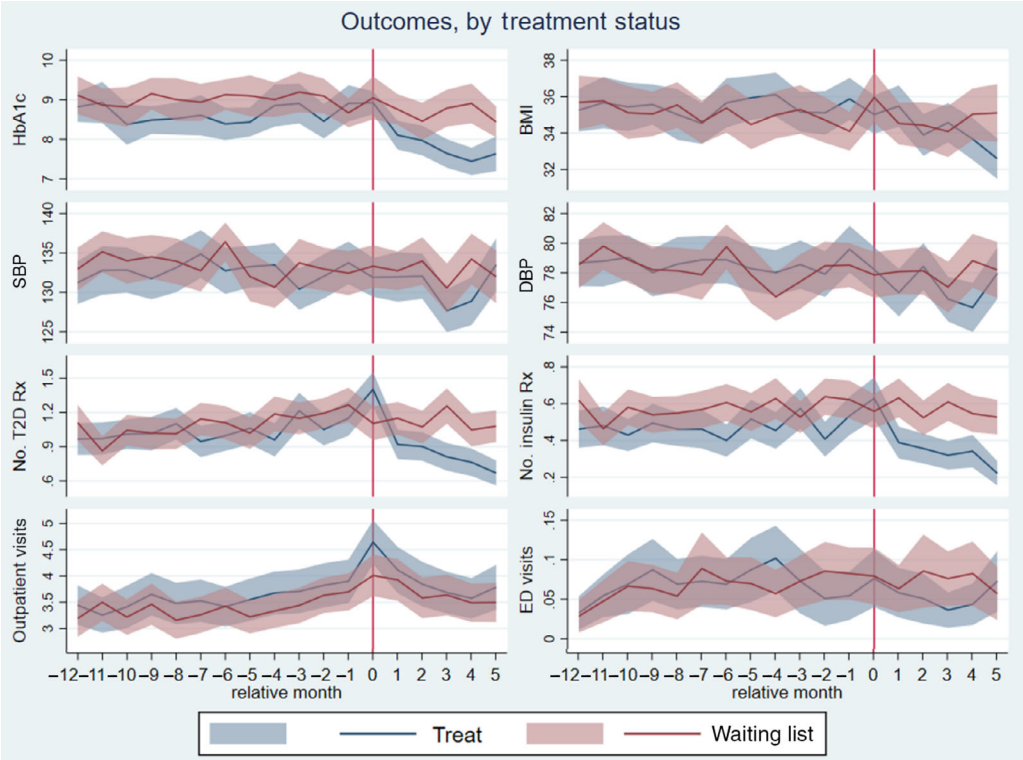

FIGURE 2 Difference-in-differences graphs for 5-month changes in diabetes outcomes for veterans in the ketogenic diet and virtual coaching treatment and control groups, before and after Virta application dates. Shown are the average monthly trends in eight different outcome measures (HbA1c, body mass index [BMI], systolic blood pressure [SBP], diastolic blood pressure [DBP], number of diabetes medication fills [No. T2D Rx], number of insulin medication fills [No. insulin Rx], number of Veterans Health Administration [VA] outpatient visits and number of VA emergency department [ED] visits) for the Virta treatment group and the waiting list control group. Virta application month is indexed at month zero

diabetes. Compiling a scientifically rigorous evidence base with long-term follow-up data, attention to possible untoward effects and appropriate control groups is critically important as we continue to seek innovative approaches to diabetes prevention and treatment.

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CONFLICT OF INTEREST

The authors have no potential conflicts of interest relevant to this article to disclose.

AUTHOR CONTRIBUTIONS

K.L.S., S.D.P. and A.B.F. conceived the idea for the study. K.L.S., J.L., N.J.N., S.D.P. and A.B.F. contributed to the study design and analysis plan. K.L.S. and J.L. conducted the statistical analysis. All authors contributed to and approved the final manuscript. K.L.S. takes responsibility for the contents of the article.

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DATA AVAILABILITY STATEMENT

Authors elect not to share data and the reason is: VA data is restricted to authorized VA researchers.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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Long-Term Effects of a Novel Continuous Remote Care Intervention Including Nutritional Ketosis for the Management of Type 2 Diabetes: A 2-Year Non-randomized Clinical Trial

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Purpose: Studies on long-term sustainability of low-carbohydrate approaches to treat diabetes are limited. We previously reported the effectiveness of a novel digitally-monitored continuous care intervention (CCI) including nutritional ketosis in improving weight, glycemic outcomes, lipid, and liver marker changes at 1 year. Here, we assess the effects of the CCI at 2 years.

Materials and methods: An open label, non-randomized, controlled study with 262 and 87 participants with T2D were enrolled in the CCI and usual care (UC) groups, respectively. Primary outcomes were retention, glycemic control, and weight changes at 2 years. Secondary outcomes included changes in body composition, liver, cardiovascular, kidney, thyroid and inflammatory markers, diabetes medication use and disease status.

Results: Reductions from baseline to 2 years in the CCI group resulting from intent-to-treat analyses included: HbA1c, fasting glucose, fasting insulin, weight, systolic blood pressure, diastolic blood pressure, triglycerides, and liver alanine transaminase, and HDL-C increased. Spine bone mineral density in the CCI group was unchanged. Use of any glycemic control medication (excluding metformin) among CCI participants declined (from 55.7 to 26.8%) including insulin (-62%) and sulfonylureas (-100%). The UC group had no changes in these parameters (except uric acid and anion gap) or diabetes medication use. There was also resolution of diabetes (reversal, 53.5%; remission, 17.6%) in the CCI group but not in UC. All the reported improvements had $p < 0.00012$.

Conclusion: The CCI group sustained long-term beneficial effects on multiple clinical markers of diabetes and cardiometabolic health at 2 years while utilizing less medication.

The intervention was also effective in the resolution of diabetes and visceral obesity with no adverse effect on bone health.

Clinical Trial Registration: Clinicaltrials.gov NCT02519309

Keywords: type 2 diabetes, nutritional ketosis, HbA1c, body composition, reversal and remission

INTRODUCTION

Type 2 diabetes (T2D), obesity, and metabolic disease impact over one billion people and present a challenge to public health and economic growth (1, 2). In the United States, over 30 million people have diabetes and it is recognized among the leading causes of morbidity and mortality, especially through increased cardiovascular disease (CVD) (3). The remission rate under usual care is 0.5–2% (4) while an intensive lifestyle intervention resulted in remission rates (both partial and complete) of 11.5 and 9.2% at 1 and 2 years (5). When lifestyle interventions are insufficient, medications are indicated to manage the disease and slow progression (6, 7).

When T2D care directed at disease reversal is successful, this includes achievement of restored metabolic health, glycemic control with reduced dependence on medication, and in some cases disease remission. Three non-pharmaceutical approaches have demonstrated high rates of at least temporary T2D diabetes reversal or remission: bariatric surgery, very low calorie diets (VLCD), and nutritional ketosis achieved through carbohydrate restriction (8–10). In controlled clinical trials, each approach has demonstrated improved glycemic control and CVD risk factors, reduced pharmaceutical dependence, and weight loss. The three approaches show a similar time-course with glycemic control preceding weight loss by weeks or months, suggesting potential overlap of mechanisms (11, 12).

With bariatric surgery, up to 60% of patients demonstrate T2D remission at 1 year (13). Outcomes at 2 years and beyond indicate ∼50% of patients can achieve ongoing diabetes remission (13, 14). The second Diabetes Surgery Summit recommended using bariatric surgery to treat T2D with support from worldwide medical and scientific societies (15), but both complications associated with surgery and cost limit its widespread use (16, 17). VLCDs providing <900 kcal/day allow rapid discontinuation of most medications, improved glycemic control, and weight loss. This approach is necessarily temporary, however, with weight regain and impaired glucose control typically occurring within 3–6 months of reintroduction of substantial proportions of dietary carbohydrates (9, 18–20).

A third approach to diabetes reversal is sustained dietary carbohydrate restriction. Low-carbohydrate diets have consistently elicited improvements in T2D, metabolic disease, and obesity up to one year (21, 22), however, longer-term studies and studies including patients prescribed insulin are limited. A low-carbohydrate Mediterranean diet caused remission in 14.7% of newly diagnosed diabetes patients at 1 year vs. 4.1% with a low-fat diet (23), and a small randomized trial utilizing a ketogenic diet demonstrated improved weight and diabetes control at 1 year (24). Systematic reviews also corroborate the effectiveness of a low-carbohydrate diet for T2D (25, 26) and it has recently become a consensus recommended dietary option (27–29). Nonetheless, sustained adherence to carbohydrate restriction is considered challenging (27, 28) and an LDL-C increase is sometimes observed (30–33). Given that total LDL-particles (LDL-P), small LDL-P, and ApoB tend to improve or remain unchanged, the impact of an increase in LDL-C on CVD risk in the context of this dietary pattern is unknown.

We have previously reported 1 year outcomes of an open-label, non-randomized, controlled, longitudinal study with 262 continuous care intervention (CCI), and 87 usual care (UC) participants with T2D (10). The CCI included individualized support with telemedicine, health coaching, and guidance in nutritional ketosis using an individualized low-carbohydrate diet. Nutritional guidance encouraged sustained nutritional ketosis; patients were counseled on preparation of a low-carbohydrate diet adapted to meet their life circumstances. Eighty-three percent of CCI participants remained enrolled at 1 year and 60% of completers achieved an HbA1c <6.5% while prescribed metformin or no diabetes medication. Weight was reduced and most CVD risk factors improved (33).

Long-term studies of low-carbohydrate dietary approaches to treat type 2 diabetes and obesity are limited, particularly among those that are delivered and supported remotely. Here we assess longer-term outcomes in CCI participants with T2D at 2 years, as well as the effects on body composition and related comorbidities. The primary aims were to investigate the effect of the CCI on retention, glycemic control, diabetes status, and weight. Secondary aims included: (1) investigating the effect of the CCI on bone mineral density, visceral fat composition, cardiovascular risk factors, liver, kidney, thyroid and inflammatory markers, and related disease outcomes (e.g., metabolic syndrome); and (2) comparing 2-year outcomes between the CCI and UC groups.

Abbreviations: CCI, continuous care intervention; UC, usual care; T2D, type 2 diabetes; HbA1c, hemoglobin A1c; CVD, cardiovascular disease; VLCD, very low calorie diet; BMI, body mass index; BHB, beta-hydroxybutyrate; BMD, bone mineral density; CAF, central abdominal fat; A/G, android:gynoid ratio; LELM, lower extremity lean mass; HDL, high density lipoprotein; LDL, low density lipoprotein; LDL-C, LDL cholesterol; LDL-P, LDL particle; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; NAFLD, nonalcoholic fatty liver disease; NLF, NAFLD liver fat score; NFS, NAFLD fibrosis score; TSH, thyroid stimulating hormone; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; hsCRP, high sensitive C-reactive protein; WBC, white blood cells; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; SGLT-2, sodium-glucose cotransporter-2 inhibitors; DPP-4, dipeptidyl peptidase-4 inhibitors; GLP-1, glucagon-like-peptide 1 receptor agonists; FFM, fat-free mass; VAT, visceral adipose tissue; GLM, generalized linear model; LMM, linear mixed-effect model; ADA, American Diabetes Association;

MATERIALS AND METHODS

Study Design and Participants

The comprehensive study design was previously published with the 1 year outcomes (10, 33), and the results presented here are the follow-up 2-year results from the same ongoing five-year clinical trial (*Clinical trials.gov identifier: NCT02519309*). This is an open-label, non-randomized, outpatient study, and results presented here are based on data from the first 2 years of the trial collected from August, 2015 to May, 2018. Participants aged 21 to 65 years with a confirmed diagnosis of T2D and a body mass index (BMI) >25 kg/m^2 self-selected to receive either the CCI or usual care (UC). Major exclusion criteria are listed in the previous publication (10, 33). All study participants provided written informed consent and the study was approved by the Franciscan Health Lafayette Institutional Review Board, Lafayette, IN, USA.

Study Interventions

Continuous Care Intervention (CCI)

For the intervention group, participants were advised to achieve and sustain nutritional ketosis (blood BHB level of 0.5–3.0 mmol L^{-1}) through sufficient carbohydrate restriction (initially <30 g day^{-1} but gradually increased based on personal carbohydrate tolerance and health goals). Participants' daily protein intake was initially targeted at a level of 1.5 g kg^{-1} of a medium-frame ideal weight body and further individualized based on biomarkers. Participants were instructed to include sufficient dietary fat in meals to achieve satiety without tracking energy intake. Nutrition education directed consumption of monounsaturated and saturated fat with sufficient intake of omega-3 and omega-6 polyunsaturated fats. The participants were also encouraged to consume sufficient fluid, vitamins and minerals including sodium and magnesium, especially if signs of mineral deficiency were encountered (e.g., decreased circulating volume) (10).

The CCI participants were provided access to a web-based software application (app), which was used to provide telemedicine communication, online resources and biomarker tracking tools. The participants used the app to upload and monitor their reportable biomarkers including body weight, blood glucose and beta-hydroxybutyrate (BHB). Biomarkers allowed for daily feedback to the care team and individualization of patient instruction. Frequency of reporting was personalized over time based on care needs. The web-based app was also used by participants to communicate with their remote care team consisting of a health coach and a medical provider. The remote care team provided education and support regarding dietary changes, behavior modification techniques for maintenance of lifestyle changes, and directed medication changes for diabetes and antihypertensive medications. Education modules covered core concepts related to the dietary changes for achieving nutritional ketosis, and adaptation to and maintenance of the diet (10). Participants selected their preferred education mode (CCI-virtual, $n = 126$ or CCI-onsite, $n = 136$) during recruitment. The CCI-virtual group received care and education primarily via app-based communication. The CCI-onsite group also received care and education via clinic-based group meetings (weekly for 12 weeks, bi-weekly for 12 weeks, monthly for 6 months, and then quarterly in the second year). All participants had access to the app for communication with their care team, online resources, biomarker tracking and the opportunity to participate in an online peer community for social support.

Usual Care (UC)

The participants recruited for usual care (UC) received care from their primary care physician or endocrinologist and were counseled by a registered dietician as part of a diabetes education program. These participants received the American Diabetes Association (ADA) recommendations on nutrition, lifestyle and diabetes management. No modification of their care was made for the study and routine biomarkers (weight, glucose and ketones) were not collected from these participants. This group was used as a reference control to study the effect of disease progression over 2 years in a cohort of participants prospectively recruited from the same geography and healthcare system.

Figure 1 depicts the study flow from recruitment to 2 years post-enrollment.

Outcomes

Primary Outcomes

The primary outcomes were retention, HbA1c, HOMA-IR derived from insulin or c-peptide (formulas listed in **Supplementary Table 1**), fasting glucose, fasting insulin, c-peptide and weight.

Secondary Outcomes

Long-term body composition changes assessed in CCI participants included bone mineral density (BMD), abdominal fat content (CAF and A/G ratioC), and lower extremity lean mass (LELM). Body composition was not assessed in UC participants. Cardiovascular-related markers included resting blood pressure (systolic and diastolic), triglycerides, total cholesterol, HDL-C and calculated LDL-C (Friedewald equation, **Supplementary Table 1**). Liver-related markers included the liver enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP), bilirubin, and two calculated liver scores: non-alcoholic liver fat score (NLF) and non-alcoholic liver fibrosis score (NFS) (formulas in **Supplementary Table 1**). Kidney-related markers included serum creatinine, uric acid, anion gap, blood urea nitrogen (BUN), and estimated glomerular filtration rate (eGFR). Thyroid-related markers included thyroid stimulating hormone (TSH) and free T4. Inflammatory markers included high sensitive C-reactive protein (hsCRP) and white blood cell count (WBC). Changes in overall diabetes medication use, use by class, and insulin dose were tracked over the 2 years of the trial.

The prevalence and resolution of T2D (diabetes reversal, partial and complete remission), metabolic syndrome, liver steatosis, and fibrosis were evaluated at baseline and 2 years using the criteria provided in **Supplementary Table 2**. Assignment of metabolic syndrome was based on the presence of three of

CLIA, Clinical Laboratory Improvement Amendments; IRB, Institutional Review Board; DXA, dual-energy X-ray absorptiometry.

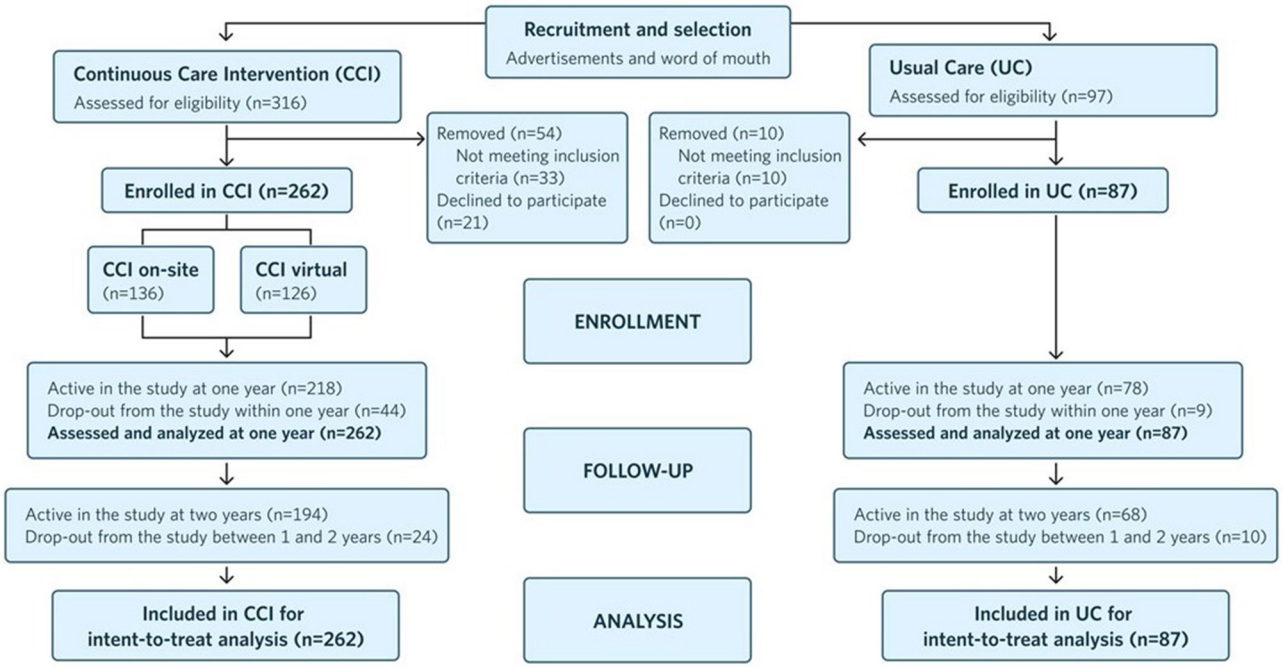

FIGURE 1 | Flow chart of participants in each stage of the study from recruitment to 2 years post-enrollment and analysis.

the five defined criteria according to measured laboratory and anthropometric variables (34, 35) and pharmacological treatment for any of the conditions was not considered in the assignment (**Supplementary Table 2**).

Adverse events encountered in the study were reported to the Principal Investigator and reviewed by the Institutional Review Board (IRB).

Laboratory Measures

Clinical anthropometrics and laboratory blood analyte measurements were obtained at baseline, 1 year, and 2 years from the CCI and UC participants. Details of the methods were previously published (10). All blood analytes were measured at a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory.

Body Composition Measures

The CCI participants' total body composition was measured at baseline, 1 year and 2 years using dual-energy X-ray absorptiometry (DXA) (Lunar GE Prodigy, Madison, WI). Participants were scanned while wearing light clothing using standard clinical imaging procedures. The scans obtained were analyzed using GE Encore software (v11.10, Madison, WI). In many obese patients, full body scans were not obtained due to the scanner not accommodating the patient's complete body resulting in issues such as cropping of the arms and/or overlapping of arms with the chest (36, 37). To address these limitations, changes in bone density and fat and lean mass were assessed using subregions rather than the full body scan. We assessed changes in the bone mass by evaluating total spine bone mineral density (BMD) from baseline to 2 years (38). For assessment of fat mass, we manually selected the central abdominal fat (CAF) region using the software and evaluated the changes in CAF over time, as previously suggested for overweight individuals (36, 39). Furthermore, we assessed changes in the android:gynoid (A/G) ratio by time. Due to lack of proper arm lean mass measurement, we analyzed the lower extremity lean mass (LELM) to assess weight-related changes in lean mass over time (40, 41).

Statistical Analyses

All analyses were conducted using SPSS statistical software (Version 25.0, Armonk, NY). First, we examined the assumptions of normality and linearity. According to Kline's (2011) guidelines (42), 14 outcomes (i.e., fasting insulin, insulin and C-peptide-derived HOMA-IR scores, triglycerides, ALT, AST, bilirubin, N-LFS, BUN, serum creatinine, TSH, Free T4, hsCRP, and BHB) were positively skewed. We explored two approaches to handling the skewed variables: natural log-transformations and removing the top 1% of values. For N-LFS, which includes both positive and negative values, a modulus log-transformation was performed instead of a natural log-transformation (43). For most variables, both approaches resulted in new skew and kurtosis values within the acceptable range. One variable (triglycerides) was only corrected via log-transformation, whereas two variables (C-peptide-derived HOMA-IR and TSH) were only corrected by removing the top 1% of values. For the other variables, we conducted sensitivity analyses to compare the two approaches. Because the results did not differ between the approaches and because interpretation of outcomes is more difficult with transformed variables, we report results from the approach of removing the top 1% of values for all variables except

TABLE 1 | Baseline characteristics.

	All		Completers with data		Dropout or missing data		Completers-Dropouts
	N	Mean (SD) or ± SE	*N*	Mean (SD) or ± SE	*N*	Mean (SD) or ± SE	Mean ± SE
Age (years)							
CCI-all education	262	53.8 (8.4)	194	54.4 (8.2)	68	51.9 (8.7)	2.5 ± 1.2
Usual Care	87	52.3 (9.5)	68	51.4 (9.4)	19	55.6 (9.5)	−4.2 ± 2.4
CCI-all vs. usual care		1.4 ± 1.1		3.0 ± 1.2		−3.6 ± 2.4	
African American (%)							
CCI-all education	262	6.9 ± 1.6	194	6.2 ± 1.7	68	8.8 ± 3.5	−2.6 ± 3.6
Usual Care	87	0.0 ± 0.0	68	0.0 ± 0.0	19	0.0 ± 0.0	—
CCI-all vs. usual care		6.9 ± 1.6*		6.2 ± 1.7*		8.8 ± 3.5	
Body mass index (kg m^{-2})							
CCI-all education	257	40.42 (8.81)	190	40.41 (8.42)	67	40.46 (9.90)	−0.05 ± 1.25
Usual Care	83	36.72 (7.26)	64	36.90 (7.41)	19	36.11 (6.89)	0.79 ± 1.91
CCI-all vs. usual care		3.70 ± 1.07*		3.51 ± 1.18		4.34 ± 2.43	
Female (%)							
CCI-all education	262	66.79 ± 2.92	194	65.98 ± 3.41	68	69.12 ± 5.64	−3.14 ± 6.66
Usual Care	87	58.62 ± 5.31	68	60.29 ± 5.98	19	52.63 ± 11.77	7.66 ± 12.90
CCI-all vs. usual care		8.17 ± 6.06		5.69 ± 6.76		16.49 ± 12.35	
Waist circumference (in)							
CCI-all education	218	49.02 (5.64)	159	49.04 (6.40)	59	48.97 (6.89)	0.06 ± 1.00
Usual Care	83	46.41 (5.64)	64	46.33 (5.63)	19	46.67 (5.82)	0.34 ± 1.48
CCI-all vs. usual care		2.61 ± 0.81		2.71 ± 0.92		2.30 ± 1.75	
Years since type 2 diabetes diagnosis							
CCI-all education	261	8.44 (7.22)	193	8.15 (7.02)	68	9.25 (7.75)	−1.1 ± 1.02
Usual Care	71	7.85 (7.32)	63	7.90 (7.41)	8	7.38 (7.05)	0.53 ± 2.77
CCI-all vs. usual care		0.59 ± 0.97		0.25 ± 1.03		1.88 ± 2.87	
GLYCEMIC							
Hemoglobin A1c (%)							
CCI-all education	262	7.6 (1.5)	194	7.5 (1.41)	68	7.9 (1.7)	−0.4 ± 0.2
Usual Care	87	7.6 (1.8)	68	7.7 (1.9)	19	7.41 (1.4)	0.3 ± 0.5
CCI-all vs. usual care		−0.0 ± 0.2		−0.2 (0.3)		0.45 ± 0.43	
C-Peptide (nmol L^{-1})							
CCI-all education	248	4.36 (2.15)	185	4.40 (2.15)	63	4.25 (2.17)	0.15 ± 0.31
Usual Care	79	4.18 (2.48)	62	3.86 (2.22)	17	5.35 (3.08)	−1.50 ± 0.80
CCI-all vs. usual care		0.18 ± 0.29		0.54 ± 0.32		−1.10 ± 0.80	
Fasting glucose (mg/dL)							
CCI-all education	258	160.77 (61.37)	191	158.01 (60.77)	67	168.64 (62.86)	−10.63 ± 8.81
Usual Care	86	156.20 (72.60)	67	162.07 (78.71)	19	135.47 (39.85)	26.60 ± 13.27
CCI-all vs. usual care		4.57 ± 8.01		−4.06 ± 10.57		33.17 ± 15.25	
Fasting Insulin (mIU L^{-1})							
CCI-all education	248	28.56 (23.88)	185	27.37 (22.33)	63	32.06 (27.86)	−4.70 ± 3.87
Usual Care	79	29.11 (24.85)	62	25.54 (21.87)	17	42.12 (30.95)	−16.58 ± 6.58
CCI-all vs. usual care		−0.55 ± 3.12		1.83 ± 3.26		−10.05 ± 7.79	
HOMA-IR (insulin derived), all							
CCI-all education	220	8.96 (6.17)	168	8.92 (6.19)	52	9.10 (6.14)	−0.19 ± 0.98
Usual Care	78	10.64 (9.12)	61	9.56 (8.35)	17	14.52 (10.88)	−4.96 ± 2.85
CCI-all vs. usual care		−1.68 ± 1.11		−0.65 ± 1.17		−5.41 ± 2.77	
HOMA-IR (insulin derived), excluding exogenous users							
CCI-all education	157	8.80 (5.64)	121	8.62 (5.74)	36	9.41 (5.31)	−0.78 ± 1.07
Usual Care	42	9.41 (8.35)	32	7.95 (6.53)	10	14.09 (11.77)	−6.15 ± 2.90
CCI-all vs. usual care		−0.61 ± 1.36		0.68 ± 1.17		−4.68 ± 3.82	

(Continued)

TABLE 1 | Continued

	All		Completers with data		Dropout or missing data		Completers-Dropouts
	N	Mean (SD) or ± SE	*N*	Mean (SD) or ± SE	*N*	Mean (SD) or ± SE	Mean ± SE
HOMA-IR (C-peptide derived), all							
CCI-all education	244	11.73 (7.40)	182	11.52 (6.55)	62	12.33 (9.51)	−0.80 ± 1.09
Usual Care	78	11.10 (7.56)	61	10.63 (7.64)	17	12.80 (7.23)	−2.17 ± 2.07
CCI-all vs. usual care		0.62 ± 0.97		0.89 ± 1.01		−0.47 ± 2.49	
METABOLIC AND BODY COMPOSITION							
Diabetes reversal (%)[a]							
CCI-all education	262	12.2 ± 2.0	194	12.9 ± 2.4	68	10.3 ± 3.7	2.6 ± 4.6
Usual Care	87	20.7 ± 4.4	68	19.1 ± 4.8	19	26.3 ± 10.4	−7.2 ± 10.6
CCI-all vs. usual care		−8.5 ± 4.8		−6.2 ± 5.4		−16.0 ± 11.0	
Metabolic syndrome (%)							
CCI-all education	262	88.6 ± 2.0	194	88.7 ± 2.3	68	88.2 ± 4.0	0.4 ± 4.5
Usual Care	81	91.4 ± 3.1	62	93.6 ± 3.2	19	84.2 ± 9.0	9.3 ± 9.2
CCI-all vs. usual care		−2.8 ± 4.0		−4.9 ± 3.9		4.0 ± 8.7	
Weight-clinic (kgs)							
CCI-all education	257	116.50 (25.94)	190	115.97 (24.94)	67	117.98 (28.72)	−2.00 ± 3.69
Usual Care	83	105.63 (22.14)	64	105.32 (21.81)	19	106.67 (23.82)	−1.35 ± 5.82
CCI-all vs. usual care		10.87 ± 3.17*		10.65 ± 3.50		11.32 ± 7.21	
Spine bone mineral density (g/cm^2)							
CCI-all education	238	1.20 (0.16)	178	1.20 (0.15)	60	1.21 (0.18)	−0.01 ± 0.03
Central abdominal fat (kg)							
CCI-all education	237	5.77 (1.69)	177	5.72 (1.69)	60	5.94 (1.72)	−0.22 ± 0.25
Android: gynoid ratio							
CCI-all education	238	1.27 (0.33)	178	1.26 (0.33)	60	1.31 (0.34)	−0.06 ± 0.05
Lower extremity lean mass (kg)							
CCI-all education	238	18.45 (4.05)	178	18.42 (3.94)	60	18.53 (4.40)	−0.11 ± 0.61
CARDIOVASCULAR							
Systolic blood pressure (mmHg)							
CCI-all education	260	131.9 (14.1)	192	132.2 (14.2)	68	131.1 (13.8)	1.2 (2.0)
Usual Care	79	129.8 (13.6)	61	129.0 (13.6)	18	132.7 (13.5)	−3.7 (3.7)
CCI-all vs. usual care		2.1 ± 1.8		3.3 ± 2.1		−1.6 ± 3.6	
Diastolic blood pressure (mmHg)							
CCI-all education	260	82.1 (8.3)	192	81.7 (8.0)	68	83.4 (8.9)	−1.7 ± 1.2
Usual Care	79	82.0 (8.9)	61	82.1 (8.8)	18	81.8 (9.6)	0.3 ± 2.4
CCI-all vs. usual care		0.1 ± 1.1		−0.4 ± 1.2		1.6 ± 2.4	
Total cholesterol (mg/dL)							
CCI-all education	247	183.6 (41.2)	184	181.9 (40.3)	63	188.7 (43.6)	−6.8 ± 6.0
Usual Care	79	183.8 (45.8)	62	186.5 (49.3)	17	174.0 (28.7)	12.5 ± 12.5
CCI-all vs. usual care		−0.2 ± 5.5		−4.6 ± 6.3		14.7 ± 11.2	
LDL-cholesterol (mg/dL)							
CCI-all education	232	102.5 (32.9)	173	101.1 (33.0)	59	106.6 (32.6)	−5.5 ± 5.0
Usual Care	70	101.5 (36.2)	56	103.8 (38.3)	14	92.3 (24.8)	11.5 ± 10.8
CCI-all vs. usual care		1.0 ± 4.6		−2.7 ± 5.3		14.3 ± 9.3	
HDL-cholesterol (mg/dL)							
CCI-all education	247	42.2 (13.4)	184	42.5 (13.7)	63	41.3 (12.7)	1.1 ± 2.0
Usual Care	79	37.6 (11.2)	62	38.3 (11.5)	17	35.2 (10.1)	3.0 ± 3.1
CCI-all vs. usual care		4.6 ± 1.7		4.2 ± 1.9		6.1 ± 3.3	

(Continued)

TABLE 1 | Continued

	All		Completers with data		Dropout or missing data		Completers-Dropouts
	N	Mean (SD) or ± SE	*N*	Mean (SD) or ± SE	*N*	Mean (SD) or ± SE	Mean ± SE
Triglycerides (mg/dL)							
CCI-all education	247	197.2 (143.4)	184	200.7 (153.5)	63	187.1 (109.0)	13.5 ± 21.0
Usual Care	79	282.9 (401.2)	62	283.7 (443.6)	17	280.0 (185.0)	3.7 ± 110.5
CCI-all vs. usual care		−85.7 ± 46.1		−83.0 ± 57.5		−92.9 ± 46.9	
LIVER							
ALT (Units/L)							
CCI-all education	257	30.65 (22.77)	190	31.65 (24.54)	67	27.79 (16.63)	3.86 ± 3.23
Usual Care	86	27.74 (19.81)	67	28.31 (21.30)	19	25.74 (13.59)	2.58 ± 5.17
CCI-all vs. usual care		2.90 ± 2.75		3.34 ± 3.38		2.05 ± 4.17	
AST (Units/L)							
CCI-all education	257	23.69 (15.19)	190	24.37 (16.79)	67	21.76 (9.08)	2.61 ± 2.16
Usual Care	86	23.90 (19.39)	67	24.25 (21.36)	19	22.63 (10.02)	1.62 ± 5.07
CCI-all vs. usual care		−0.20 ± 2.04		0.12 ± 2.57		−0.87 ± 2.42	
ALP (Units/L)							
CCI-all education	256	74.11 (22.14)	189	74.32 (22.32)	67	73.54 (21.79)	0.78 ± 3.15
Usual Care	86	77.36 (26.29)	67	78.25 (27.67)	19	74.21 (21.08)	4.04 ± 6.86
CCI-all vs. usual care		−3.25 ± 2.90		−3.94 ± 3.39		−0.67 ± 5.62	
Bilirubin (mg/dL)							
CCI-all education	256	0.54 (0.21)	189	0.55 (0.21)	67	0.49 (0.18)	0.06 ± 0.03
Usual Care	86	0.55 (0.28)	67	0.54 (0.27)	19	0.59 (0.29)	−0.05 ± 0.07
CCI-all vs. usual care		−0.02 ± 0.03		0.01 ± 0.04		−0.11 ± 0.05	
NAFLD-Liver fat score							
CCI-all education	243	3.43 (3.84)	181	3.26 (3.62)	62	3.92 (4.44)	−0.65 ± 0.62
Usual Care	74	3.10 (3.63)	57	2.49 (3.00)	17	5.14 (4.80)	−2.65 ± 1.23
CCI-all vs. usual care		0.33 ± 0.50		0.78 ± 0.53		−1.23 ± 1.24	
NAFLD-Fibrosis score							
CCI-all education	238	−0.23 (1.36)	177	−0.25 (1.37)	61	−0.18 (1.35)	−0.07 ± 0.20
Usual Care	75	−0.80 (1.41)	58	−0.82 (1.47)	17	−0.71 (1.20)	−0.11 ± 0.39
CCI-all vs. usual care		0.56 ± 0.18		0.57 ± 0.21		0.53 ± 0.36	
KIDNEY							
Anion gap (mmol L^{-1})							
CCI-all education	257	6.83 (1.67)	190	6.76 (1.68)	67	7.03 (1.62)	−0.27 ± 0.24
Usual Care	86	6.93 (1.82)	67	6.82 (1.86)	19	7.32 (1.67)	−0.50 ± 0.47
CCI-all vs. usual care		−0.10 ± 0.21		−0.06 ± 0.25		−0.29 ± 0.42	
BUN (mg/dL)							
CCI-all education	258	16.88 (6.55)	191	17.17 (6.05)	67	16.06 (7.81)	1.11 ± 0.93
Usual Care	86	16.05 (6.25)	67	15.81 (6.28)	19	16.89 (6.24)	−1.09 ± 1.63
CCI-all vs. usual care		0.84 ± −0.81		1.37 ± 0.87		−0.84 ± 1.95	
eGFR (mL s^{-1} m^{-2}) CCI-all education	258	80.48 (13.62)	191	80.36 (13.53)	67	80.84 (13.96)	−0.48 ± 1.94
Usual Care	86	79.17 (13.73)	67	79.39 (13.72)	19	78.42 (14.11)	0.97 ± 3.59
CCI-all vs. usual care		1.31 ± 1.70		0.97 ± 1.93		2.42 ± 3.64	
Serum creatinine (mg/dL)							
CCI-all education	258	0.88 (0.24)	191	0.88 (0.23)	67	0.90 (0.26)	−0.02 ± 0.03
Usual Care	86	0.91 (0.25)	67	0.91 (0.25)	19	0.90 (0.22)	0.004 ± 0.06
CCI-all vs. usual care		−0.02 ± 0.03		−0.03 ± 0.03		−0.01 ± 0.07	

(Continued)

TABLE 1 | Continued

	All		Completers with data		Dropout or missing data		Completers-Dropouts
	N	Mean (SD) or ± SE	*N*	Mean (SD) or ± SE	*N*	Mean (SD) or ± SE	Mean ± SE
Uric acid (mg/dL)							
CCI-all education	261	5.85 (1.46)	193	5.88 (1.45)	68	5.77 (1.48)	0.11 ± 0.21
Usual Care	85	5.60 (1.47)	67	5.58 (1.34)	18	5.70 (1.92)	0.12 ± 0.39
CCI-all vs. usual care		0.25 ± 0.18		0.30 ± 0.20		0.07 ± 0.42	
THYROID							
TSH (mIU L^{-1})							
CCI-all education	259	2.32 (1.74)	192	2.31 (1.81)	67	2.36 (1.52)	−0.05 ± 0.25
Usual Care	86	3.80 (17.07)	68	4.37 (19.17)	18	1.65 (1.05)	2.72 ± 4.54
CCI-all vs. usual care		−1.48 ± 1.84		−2.06 ± 2.33		0.71 ± 0.38	
Free T4 (ng/dL)							
CCI-all education	260	0.92 (0.17)	193	0.92 (0.18)	67	0.91 (0.17)	0.01 ± 0.02
Usual Care	86	0.88 (0.29)	68	0.87 (0.31)	18	0.89 (0.16)	−0.02 ± 0.08
CCI-all vs. usual care		0.04 ± 0.03		0.05 ± 0.03		0.02 ± 0.04	
OTHER							
Beta-hydroxybutyrate (mmol L^{-1})							
CCI-all education	248	0.17 (0.15)	185	0.17 (0.15)	63	0.19 (0.16)	−0.03 ± 0.02
Usual Care	79	0.15 (0.13)	62	0.14 (0.11)	17	0.20 (0.18)	−0.06 ± 0.04
CCI-all vs. usual care		0.02 ± 0.20		0.03 ± 0.18		−0.01 (0.04)	
hsC-reactive protein (nmol L^{-1})							
CCI-all education	249	8.54 (14.49)	186	8.92 (16.35)	63	7.44 (6.41)	1.48 ± 2.12
Usual Care	85	8.89 (8.62)	67	9.08 (8.91)	18	8.18 (7.64)	0.90 ± 2.30
CCI-all vs. usual care		−0.34 ± 1.67		−0.16 ± 2.10		−0.74 ± 1.79	
White blood cell (k/cumm)							
CCI-all education	260	7.24 (1.89)	193	7.12 (1.82)	67	7.57 (2.08)	−0.45 ± 0.27
Usual Care	86	8.14 (2.39)	67	8.15 (2.30)	19	8.08 (2.73)	0.07 ± 0.62
CCI-all vs. usual care		−0.90 ± 0.28		−1.03 ± 0.31*		−0.51 ± 0.58	
DIABETES MEDICATION							
Any diabetes medication, excluding metformin (%)							
CCI-all education	262	56.87 ± 3.07	194	55.67 ± 3.58	68	60.29 ± 5.98	−4.62 ± 7.00
Usual Care	87	66.67 ± 5.08	68	66.18 ± 5.78	19	68.42 ± 10.96	−2.25 ± 12.37
CCI-all vs. usual care		−9.80 ± 5.94		−10.51 ± 6.80		−8.13 ± 12.71	
Sulfonylurea (%)							
CCI-all education	262	23.66 ± 2.63	194	25.77 ± 3.15	68	17.65 ± 4.66	8.13 ± 5.62
Usual Care	87	24.14 ± 4.61	68	22.06 ± 5.07	19	31.58 ± 10.96	−9.52 ± 11.19
CCI-all vs. usual care		−0.47 ± 5.28		3.71 ± 6.11		−13.93 ± 11.91	
Insulin (%)							
CCI-all education	262	29.77 ± 2.83	194	29.38 ± 3.28	68	30.88 ± 5.64	−1.50 ± 6.47
Usual Care	87	45.98 ± 5.37	68	48.53 ± 6.11	19	36.84 ± 11.37	11.69 ± 12.91
CCI-all vs. usual care		−16.21 ± 6.07		−19.15 ± 6.93		−5.96 ± 12.25	
Thiazolidinedione (%)							
CCI-all education	262	1.53 ± 0.76	194	1.55 ± 0.89	68	1.47 ± 01.47	0.08 ± 1.74
Usual Care	87	1.15 ± 1.15	68	1.47 ± 1.47	19	0.00 ± 0.00	1.47 ± 2.79
CCI-all vs. usual care		0.38 ± 1.48		0.08 ± 1.74		1.47 ± 2.79	
SGLT-2 (%)							
CCI-all education	262	10.31 ± 1.88	194	9.79 ± 2.14	68	11.77 ± 3.94	−1.97 ± 4.30
Usual Care	87	14.94 ± 3.84	68	14.71 ± 4.33	19	15.79 ± 8.59	−1.08 ± 9.36
CCI-all vs. usual care		−4.64 ± 4.28		−4.91 ± 4.83		−4.03 ± 8.71	

(Continued)

TABLE 1 | Continued

	All		Completers with data		Dropout or missing data		Completers-Dropouts
	N	Mean (SD) or ± SE	*N*	Mean (SD) or ± SE	*N*	Mean (SD) or ± SE	Mean ± SE
DPP-4 (%)							
CCI-all education	262	9.92 ± 1.85	194	9.28 ± 2.09	68	11.77 ± 3.94	−2.49 ± 4.23
Usual Care	87	8.05 ± 2.93	68	5.88 ± 2.87	19	15.79 ± 8.59	−9.91 ± 9.06
CCI-all vs. usual care		1.88 ± 3.63		3.40 ± 3.92		−4.03 ± 8.71	
GLP-1 (%)							
CCI-all education	262	13.36 ± 2.11	194	13.40 ± 2.45	68	13.24 ± 4.14	0.17 ± 4.81
Usual Care	87	16.09 ± 3.96	68	19.12 ± 4.80	19	5.26 ± 5.26	13.85 ± 7.13
CCI-all vs. usual care		−2.73 ± 4.31		−5.72 ± 5.39		7.97 ± 8.33	
Metformin (%)							
CCI-all education	262	71.37 ± 2.80	194	71.65 ± 3.24	68	70.59 ± 05.57	1.06 ± 6.39
Usual Care	87	60.92 ± 5.26	68	60.29 ± 5.98	19	63.16 ± 11.37	−2.86 ± 12.81
CCI-all vs. usual care		10.46 ± 5.96		11.36 ± 6.80		7.43 ± 12.12	

SD, standard deviation; SE, standard error; CCI, continuous care intervention; UC, usual care; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; NAFLD, nonalcoholic fatty liver disease; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rates; TSH, thyroid stimulating hormone; SGLT-2, Sodium glucose co-transporter 2 inhibitor; DPP-4, Dipeptidyl peptidase-4 inhibitor; GLP-1, Glucagon-like peptide 1 receptor agonist.

Ns slightly differs for each variable depending on the patients' compliance to complete their laboratory, body composition assessments and clinic visits within the specified time-frame.

[a]*Meeting diabetes reversal criteria at baseline was defined as HbA1c <6.5% and no use of medication for glycemic control other than metformin.*

[*]*A significance level of $P < 0.0012$ ensures overall simultaneous significance of $P < 0.05$ over the 43 variables using Bonferroni correction.*

triglycerides. For triglycerides, analyses were performed and *p*-values reported on the log-transformed variable but the means and standard errors reported were computed from the untransformed variable. Next, we ran independent sample *t*-tests to examine differences in baseline characteristics between CCI and UC, and completers and dropouts.

We performed linear mixed-effects models (LMMs) to assess (1) within-group changes in the continuous study outcomes from baseline to 2 years and (2) between-group differences (CCI vs. UC) in the study outcomes at 2 years. The LMMs included fixed effects for time, group (CCI vs. UC), and a time by group interaction. Covariates included baseline age, sex, race (African American vs. other), BMI, and insulin use. This maximum likelihood-based approach uses all available repeated data, resulting in an intent-to-treat analysis. An unstructured covariance structure was specified for all models to account for correlations between repeated measures.

Within-group changes and between-group differences in dichotomous disease outcome variables [i.e., diabetes reversal, diabetes remission (partial or complete) and complete remission (44), metabolic syndrome (34, 35), steatosis (45), fibrosis (46)] were assessed, controlling for baseline age, sex, race, time since diagnosis, BMI, and insulin use. For this set of analyses, multiple imputation was used to replace missing values from baseline and 2 years with a set of plausible values, facilitating an intent-to-treat analysis (all ns = 262). Missing values were estimated from 40 imputations (47) from logistic regression. Within-group changes from baseline to 2 years and between-group differences at 2 years were assessed using generalized estimating equations with binary logistic models and unstructured covariance matrices.

We also examined changes in participants' diabetes medication use. First, we compared the rates of diabetes medication use within groups from baseline to 2 years using McNemar's test with continuity correction when appropriate. Next, we calculated the proportion of participants in each group with each diabetes medication class eliminated, reduced, not changed, increased, or added. Paired *t*-tests were used to assess within-group changes in insulin dosages from baseline to 2 years among participants taking insulin at baseline and among participants taking insulin at both baseline and 2 years.

We conducted a second set of analyses with 2-year completers only. Results of the completers-only analyses appear in **Supplementary Table 3**. Given that 2 different modes (virtual and onsite) were utilized for delivery of the CCI group educational content, we also conducted another set of analyses to assess whether differences existed between the groups on all analyses of primary outcomes. As in our prior time points (10, 48), no group differences were found; thus, the data from the two CCI educational groups were combined for this report. For all study analyses, nominal significance levels (P) are presented in the tables. A significance level of $P < 0.0012$ ensures overall simultaneous significance of $P < 0.05$ over the 43 variables using Bonferroni correction.

RESULTS

Participant Characteristics

Table 1 presents baseline characteristics of the 262 CCI and 87 UC participants. Participants did not differ between groups in demographic characteristics, except the proportion of African

Americans was higher in the CCI group. Baseline characteristics were well-matched between the groups, except for mean weight and BMI, which were higher in the CCI group. There were no differences between completers and dropouts on baseline characteristics for either group.

Retention and Long-Term Dietary Adherence

One hundred ninety four participants (74% of 262) remained enrolled in the CCI at 2 years (**Figure 1**), as did 68 UC group participants (78% of 87). CCI-participant-reported reasons for dropout included: intervening life events (e.g., family emergencies), difficulty attending or completing laboratory and clinic visits associated with the trial, and insufficient motivation for participation in the intervention. At both 1 and 2 years, laboratory-measured blood BHB was 0.27 ± 0.02 mmol L^{-1}, 50% higher than the baseline value (0.18 ± 0.01 mmol L^{-1}). The mean laboratory BHB level was stable from 1 to 2 years, and 61.5% ($n = 161$) of participants uploaded a blood BHB measurement >0.5 mmol L^{-1} in the app at least once between 1 and 2 years.

Glycemic Control

HbA1c improved at 2 years (0.9% unit decrease, $P = 1.8 \times 10^{-17}$; **Figure 2A**) among CCI participants and was lower than the UC group. Related markers including C-peptide, fasting glucose, fasting insulin (**Figure 2B**), insulin-derived HOMA-IR excluding exogenous insulin users, and c-peptide-derived HOMA-IR also significantly decreased after correction for multiple comparisons in the CCI group at 2 years and were lower than the UC group (except C-peptide); no changes from baseline to 2 years were observed in the UC group (**Supplementary Figures 1A,B**; **Table 2**).

Within the CCI, reduction in glycemia occurred concurrently with reduced medication use (**Supplementary Table 3**). The proportion of CCI completers taking any diabetes medication (excluding metformin) decreased at 2 years (**Figure 3A**). The mean dose among CCI participants prescribed insulin at baseline decreased by 81% at 2 years (from 81.9 to 15.5 U/day), but not among UC participants (+13%; from 96.6 to 109.3 U/day) (**Figure 3B**). For participants who remained insulin-users at 2 years, mean dose also decreased in the CCI by 61% (from 104.3 to 40.2 U/day, $P = 9.2 \times 10^{-5}$) but not in UC participants (+19% from 103.8 to 123.5 U/day, $P = 0.29$). Among completers prescribed each diabetes medication class, the proportion with each dosage change (eliminated, reduced, unchanged, increased or newly added) at 2 years in each group appears in **Figure 3C**.

Diabetes Status

All within-group changes and between-group differences in diabetes status among the CCI and UC group participants appear in **Supplementary Table 4** (intent-to-treat analyses were conducted, all below ns = 262). The proportion of participants meeting the defined criteria for diabetes reversal at 2 years increased to 53.5% from baseline in the CCI group, whereas no change was observed in the UC group. Diabetes remission (partial or complete) was observed in 46 (17.6%) participants in the CCI group and two (2.4%) of the UC participants at 2 years. Complete remission was observed in 17 (6.7%) CCI participants and none (0%) of the UC participants at 2 years.

Weight and Body Composition Outcomes

At 2 years, the mean weight reduction from baseline was −10% (**Figure 4A**) in the CCI group, whereas no change was observed in the UC group (**Supplementary Figure 1C**). Among CCI patients, 74% had ≥5% weight loss compared to only 14% of UC patients (**Supplementary Figure 2**; completers analysis, $n = 193$). Consistent with the weight loss observed, the CCI group had reductions in abdominal fat content with decreases in CAF (**Figure 4B**) and the A/G ratio from baseline to 2 years (**Table 2**). Total spine BMD within the CCI remained unchanged from baseline to 2 years after correction for multiple comparisons, whereas the average LELM was reduced from baseline to 2 years (**Table 2**).

Cardiovascular Risk Factor Outcomes

Decreases in systolic (**Figure 4C**) and diastolic (**Figure 4D**) blood pressures and triglycerides were observed in the CCI but not UC group at 2 years (**Table 2**; **Supplementary Figures 3A,B**). The CCI group's HDL-cholesterol and LDL-cholesterol both increased from baseline to 2 years, whereas no changes were observed in the UC group (**Table 2**). No changes in total cholesterol were observed in either the CCI or UC group. At 2 years, the CCI group had higher HDL-cholesterol, higher LDL-cholesterol, and lower triglycerides than UC. No between-group differences were observed at 2 years in systolic or diastolic blood pressure or total cholesterol (**Table 2**).

Liver-Related Outcomes

Reductions were observed in liver-related outcomes including ALT (**Figure 4E**), AST, ALP, NLF and NFS in the CCI group, whereas no changes were observed in the UC group (**Table 2**, e.g., ALT; **Supplementary Figure 3C**). No Bonferroni-corrected group differences were observed for bilirubin, ALT, or AST at 2 years (**Table 2**).

Kidney, Thyroid, and Inflammation Outcomes

The eGFR increased in the CCI but not UC group at 2 years (**Table 2**). The UC but not CCI group had increased anion gap and decreased uric acid. No bonferroni-corrected within-group changes in BUN, serum creatinine, TSH, or Free T4 were observed in either the CCI or UC group from baseline to 2 years. No between-group differences were observed for any thyroid- or kidney-related markers at 2 years (**Table 2**).

From baseline to 2 years, decreases in the CCI group's hsCRP (**Figure 4F**) and white blood cells were observed. No changes were observed in the UC group (**Supplementary Figure 3D**). At 2 years, both markers of inflammation were lower in the CCI group compared to the UC group (**Table 2**).

Related Comorbidities

All within-group changes and between-group differences in comorbidities status among the CCI and UC group participants appear in **Supplementary Table 4** (intent-to-treat analyses were

TABLE 2 | Adjusted mean changes over time.

	Baseline		1 Year				2 Years			
	Mean ± SE	P	Mean ± SE	*P*	Change from baseline	*P*	Mean ± SE	*P*	Change from baseline	*P*
GLYCEMIC										
Hemoglobin A1c (%)										
CCI-all education	7.7 ± 0.1		6.3 ± 0.1		−1.3 ± 0.1	6.6×10^{-38}	6.7 ± 0.1		−0.9 ± 0.1	1.8×10^{-17}
Usual Care	7.5 ± 0.2		7.6 ± 0.1		0.2 ± 0.2	0.31	7.9 ± 0.2		0.4 ± 0.2	0.02
CCI-all vs. usual care	0.2 ± 0.2	0.28	−1.3 ± 0.2	2.7×10^{-14}			−1.2 ± 0.2	1.3×10^{-9}		
C-Peptide (nmol L^{-1})										
CCI-all education	4.33 ± 0.13		3.27 ± 0.14		−1.06 ± 0.13	7.3×10^{-14}	3.16 ± 0.12		−1.17 ± 0.13	2.2×10^{-16}
Usual Care	4.39 ± 0.24		4.38 ± 0.25		−0.004 ± 0.24	0.99	3.89 ± 0.22		−0.49 ± 0.24	0.04
CCI-all vs. usual care	−0.06 ± 0.28	0.84	−1.12 ± 0.28	9.8×10^{-5}			−0.73 ± 0.26	5.0×10^{-3}		
Fasting glucose (mg/dL)										
CCI-all education	163.67 ± 3.90		127.29 ± 3.62		−36.39 ± 4.47	1.0×10^{-14}	134.58 ± 4.13		−29.10 ± 4.88	6.8×10^{-9}
Usual Care	151.21 ± 6.93		160.58 ± 6.17		9.38 ± 7.61	0.22	172.89 ± 7.00		21.68 ± 8.28	0.01
CCI-all vs. usual care	12.47 ± 8.02	0.12	−33.30 ± 7.24	6.3×10^{-6}			−38.31 ± 8.21	4.8×10^{-6}		
Fasting Insulin (mIU L^{-1})[a]										
CCI-all education	27.73 ± 1.26		16.47 ± 1.13		−11.26 ± 1.28	3.2×10^{-16}	16.02 ± 1.02		−11.71 ± 1.25	2.2×10^{-18}
Usual Care	27.57 ± 2.29		26.47 ± 2.06		−1.10 ± 2.30	0.63	24.17 ± 1.84		−3.40 ± 2.22	0.13
CCI-all vs. usual care	0.16 ± 2.63	0.95	−10.00 ± 2.38	3.6×10^{-5}			−8.15 ± 2.14	1.7×10^{-4}		
HOMA-IR (insulin derived), all[a]										
CCI-all education	9.09 ± 0.41		4.85 ± 0.39		−4.24 ± 0.45	3.5×10^{-18}	5.27 ± 0.44		−3.82 ± 0.49	3.8×10^{-13}
Usual Care	9.58 ± 0.73		10.33 ± 0.73		0.75 ± 0.81	0.35	9.95 ± 0.77		0.37 ± 0.83	0.66
CCI-all vs. usual care	−0.49 ± 0.85	0.57	−5.48 ± 0.84	2.9×10^{-10}			−4.67 ± 0.89	3.4×10^{-7}		
HOMA-IR (insulin derived), excluding exogenous users[a]										
CCI-all education	9.08 ± 0.46		4.56 ± 0.44		−4.53 ± 0.47	6.5×10^{-18}	5.25 ± 0.38		−3.83 ± 0.49	2.7×10^{-13}
Usual Care	8.66 ± 0.92		10.87 ± 0.98		2.21 ± 1.02	0.03	8.26 ± 0.75		−0.40 ± 0.94	0.68
CCI-all vs. usual care	0.43 ± 1.03		−6.31 ± 1.08	2.2×10^{-8}			−3.01 ± 0.85	5.4×10^{-4}		
HOMA-IR (C-peptide derived), all[a]										
CCI-all education	11.25 ± 0.37		8.07 ± 0.38		−3.19 ± 0.39	1.8×10^{-14}	7.88 ± 0.35		−3.37 ± 0.39	1.1×10^{-15}
Usual Care	11.04 ± 0.67		11.81 ± 0.71		0.77 ± 0.72	0.28	10.62 ± 0.64	2.5×10^{-4}	−0.42 ± 0.70	0.55
CCI-all vs. usual care	0.21 ± 0.77	0.78	−3.75 ± 0.81	5.8×10^{-6}			−2.74 ± 0.74			
METABOLIC AND BODY COMPOSITION										
Weight-clinic (kg)										
CCI-all education	114.56 ± 0.60		100.27 ± 0.86		−14.29 ± 0.71	9.7×10^{-56}	102.62 ± 1.10		−11.94 ± 0.96	8.8×10^{-28}
Usual Care	111.07 ± 1.09		111.71 ± 1.47		0.64 ± 1.17	0.58	112.35 ± 1.90		1.28 ± 1.63	0.43
CCI-all vs. usual care	3.49 ± 1.27	0.01	−11.44 ± 1.71	1.4×10^{-10}			−9.73 ± 2.20	1.5×10^{-5}		

(Continued)

TABLE 2 | Continued

	Baseline		1 Year				2 Years			
	Mean ± SE	**P**	**Mean ± SE**	***P***	**Change from baseline**	***P***	**Mean ± SE**	***P***	**Change from baseline**	***P***
Spine bone mineral density (g/cm^2)										
CCI-all education	1.21 ± 0.01	—	1.22 ± 0.01	—	0.01 ± 0.01	0.11	1.22 ± 0.01	—	0.01 ± 0.01	0.02
Central abdominal fat (kg)										
CCI-all education	5.89 ± 0.07	—	4.62 ± 0.08	—	−1.27 ± 0.07	1.3×10^{-42}	4.99 ± 0.10	—	−0.90 ± 0.08	1.6×10^{-21}
Android: gynoid ratio										
CCI-all education	1.27 ± 0.02	—	1.18 ± 0.02	—	−0.09 ± 0.1	2.4×10^{-13}	1.20 ± 0.02	—	−0.07 ± 0.01	4.7×10^{-8}
Lower extremities lean mass (kg)										
CCI-all education	18.74 ± 0.16	—	17.41 ± 0.15	—	−1.33 ± 0.10	5.9×10^{-31}	17.38 ± 0.17	—	−1.36 ± 0.12	1.3×10^{-21}
CARDIOVASCULAR										
Systolic blood pressure (mmHg)										
CCI-all education	131.7 ± 0.9		125.3 ± 0.9		−6.5 ± 1.1	3.3×10^{-8}	125.9 ± 1.0		−5.8 ± 1.2	2.4×10^{-6}
Usual Care	130.3 ± 1.6		129.5 ± 1.6		−0.9 ± 1.9	0.66	129.9 ± 1.8		−0.5 ± 2.1	0.83
CCI-all vs. usual care	1.4 ± 1.8	0.43	−4.2 ± 1.8	0.02			−3.9 ± 2.1	0.06		
Diastolic blood pressure (mmHg)										
CCI-all education	81.8 ± 0.5		78.1 ± 0.6		−3.7 ± 0.7	5.4×10^{-8}	78.7 ± 0.6		−3.1 ± 0.7	3.3×10^{-5}
Usual Care	82.1 ± 1.0		81.3 ± 1.0		−0.8 ± 1.1	0.47	81.6 ± 1.1		−0.6 ± 1.3	0.65
CCI-all vs. usual care	−0.3 ± 1.1	0.76	−3.2 ± 1.1	0.41			−2.8 ± 1.3	0.03		
Total cholesterol (mg/dL)										
CCI-all education	184.4 ± 2.7		192.8 ± 3.4		8.4 ± 3.1	0.01	194.1 ± 3.5		9.7 ± 3.6	0.01
Usual Care	181.2 ± 4.9		179.4 ± 6.1		−1.8 ± 5.5	0.75	180.9 ± 6.2		−0.3 ± 6.4	0.96
CCI-all vs. usual care	3.3 ± 5.7	0.57	13.5 ± 7.0	0.06			13.3 ± 7.2	0.07		
LDL-cholesterol (mg/dL)										
CCI-all education	103.5 ± 2.2		114.1 ± 2.5		10.6 ± 2.5	2.5×10^{-5}	114.6 ± 2.8		11.1 ± 2.8	1.1×10^{-4}
Usual Care	100.0 ± 4.2		88.9 ± 4.9		−11.2 ± 4.7	0.02	90.9 ± 5.1		−9.1 ± 5.1	0.08
CCI-all vs. usual care	3.6 ± 4.8	0.46	25.2 ± 5.6	8.9×10^{-6}			23.7 ± 5.9	7.0×10^{-5}		
HDL-cholesterol (mg/dL)										
CCI-all education	41.8 ± 0.9		49.5 ± 0.9		7.8 ± 0.8	4.4×10^{-19}	49.5 ± 1.0		7.8 ± 0.9	2.7×10^{-16}
Usual Care	38.7 ± 1.4		37.2 ± 1.7		−1.5 ± 1.4	0.3	42.5 ± 1.7		3.8 ± 1.6	0.02
CCI-all vs. usual care	3.1 ± 1.6	0.06	12.4 ± 2.0	1.1×10^{-9}			7.1 ± 2.0	4.1×10^{-4}		
Triglycerides (mg/dL)[b]										
CCI-all education	197.2 ± 9.1		148.9 ± 10.1		−48.3 ± 13.7	7.4×10^{-16}	153.3 ± 10.4		−43.9 ± 14.0	6.2×10^{-9}
Usual Care	282.9 ± 45.1		314.5 ± 61.4		31.6 ± 74.6	0.35	209.5 ± 18.5		−73.4 ± 55.9	0.75
CCI-all vs. usual care	−85.7 ± 30.1	0.09	−165.5 ± 39.0	1.5×10^{-8}			−56.2 ± 19.0	7.1×10^{-5}		

(Continued)

TABLE 2 | Continued

	Baseline		1 Year				2 Years			
	Mean ± SE	P	Mean ± SE	*P*	Change from baseline	*P*	Mean ± SE	*P*	Change from baseline	*P*
LIVER										
ALT (Units/L)[a]										
CCI-all education	29.16 ± 0.97		21.53 ± 0.88		−7.63 ± 1.02	7.7×10^{-13}	23.00 ± 0.91		−6.16 ± 0.95	4.0×10^{-10}
Usual Care	25.84 ± 1.72		26.98 ± 1.51		1.14 ± 1.73	0.51	26.80 ± 1.57		0.96 ± 1.62	0.56
CCI-all vs. usual care	3.31 ± 1.99	0.1	−5.45 ± 1.77	0.002			−3.80 ± 1.84	0.04		
AST (Units/L)[a]										
CCI-all education	22.50 ± 0.64		19.07 ± 0.58		−3.43 ± 0.69	1.1×10^{-6}	19.78 ± 0.57		−2.72 ± 0.66	5.1×10^{-5}
Usual Care	21.51 ± 1.13		23.37 ± 1.00		1.86 ± 1.19	0.12	23.19 ± 0.99		1.68 ± 1.14	0.14
CCI-all vs. usual care	0.99 ± 1.31	0.45	−4.30 ± 1.17	2.8×10^{-4}			−3.41 ± 1.16	3.5×10^{-3}		
ALP (Units/L)										
CCI-all education	74.13 ± 1.42		64.34 ± 1.44		−9.78 ± 0.98	1.9×10^{-20}	64.50 ± 1.58		−9.63 ± 1.19*	1.8×10^{-14}
Usual Care	78.55 ± 2.53		79.05 ± 2.55		0.50 ± 1.65	0.76	82.47 ± 2.76		3.92 ± 2.00	0.05
CCI-all vs. usual care	−4.42 ± 2.94	0.13	−14.71 ± 2.97	1.2×10^{-6}			−17.97 ± 3.22	5.1×10^{-8}		
Bilirubin (mg/dL)[a]										
CCI-all education	0.53 ± 0.01		0.53 ± 0.02		−0.001 ± 0.01	0.92	0.52 ± 0.02		−0.01 ± 0.01	0.45
Usual Care	0.55 ± 0.02		0.57 ± 0.03		0.03 ± 0.02	0.16	0.52 ± 0.03		−0.03 ± 0.02	15
CCI-all vs. usual care	−0.01 ± 0.03	0.64	−0.04 ± 0.03	0.18			0.01 ± 0.03	0.8		
NAFLD-Liver fat score[a]										
CCI-all education	3.29 ± 0.21		1.34 ± 0.19		−1.95 ± 0.22	2.0×10^{-16}	0.71 ± 0.20		−2.58 ± 0.22	2.9×10^{-25}
Usual Care	3.20 ± 0.38		3.79 ± 0.35		0.59 ± 0.40	0.14	3.02 ± 0.37		−0.17 ± 0.40	0.66
CCI-all vs. usual care	0.09 ± 0.44	0.83	−2.45 ± 0.40	4.2×10^{-9}			−2.32 ± 0.43	1.6×10^{-7}		
NAFLD-Fibrosis score										
CCI-all education	−0.31 ± 0.06		−0.95 ± 0.07		−0.64 ± 0.06	4.0×10^{-22}	−0.78 ± 0.08		−0.47 ± 0.08	2.3×10^{-9}
Usual Care	−0.45 ± 0.11		−0.19 ± 0.12		0.27 ± 0.12	0.01	−0.24 ± 0.14		0.21 ± 0.14	0.12
CCI-all vs. usual care	0.14 ± 0.13	0.27	−0.77 ± 0.14	4.4×10^{-8}			−0.54 ± 0.16	0.001		
KIDNEY										
Anion gap (mmol L^{-1})										
CCI-all education	6.83 ± 0.11		7.12 ± 0.13		0.29 ± 0.15	0.05	7.29 ± 0.13		0.46 ± 0.14	0.003
Usual Care	6.92 ± 0.19		7.74 ± 0.22		0.82 ± 0.25	0.001	7.80 ± 0.22		0.88 ± 0.24	3.2×10^{-4}
CCI-all vs. usual care	−0.09 ± 0.22	0.68	−0.63 ± 0.25	0.01			−0.51 ± 0.25	0.04		
BUN (mmol L^{-1})[a]										
CCI-all education	16.40 ± 0.32		18.46 ± 0.37		2.06 ± 0.36	3.8×10^{-8}	17.41 ± 0.40		1.01 ± 0.43	0.02
Usual Care	16.18 ± 0.56		15.83 ± 0.63		−0.35 ± 0.61	0.57	16.21 ± 0.68		0.03 ± 0.72	0.97
CCI-all vs. usual care	0.22 ± 0.65	0.74	2.63 ± 0.74	4.0×10^{-4}			1.20 ± 0.90	0.14		
eGFR (mL s^{-1} m^{-2})										
CCI-all education	80.53 ± 0.78		82.50 ± 0.78		1.97 ± 0.67	0.004	83.26 ± 0.80		2.73 ± 0.72	1.6×10^{-4}

(Continued)

TABLE 2 | Continued

	Baseline		1 Year				2 Years			
	Mean ± SE	P	Mean ± SE	*P*	Change from baseline	*P*	Mean ± SE	*P*	Change from baseline	*P*
Usual Care	78.70 ± 1.39		79.56 ± 1.36		0.86 ± 1.13	0.45	79.12 ± 1.39		0.42 ± 1.21	0.73
CCI-all vs. usual care	1.82 ± 1.61	0.26	2.94 ± 1.59	0.07			4.14 ± 1.63	0.01		
Serum creatinine (μmol L^{-1})[a]										
CCI-all education	0.88 ± 0.01		0.83 ± 0.01		−0.04 ± 0.01	5.3×10^{-6}	0.85 ± 0.01		−0.03 ± 0.01	0.003
Usual Care	0.90 ± 0.02		0.87 ± 0.02		−0.03 ± 0.02	0.07	0.88 ± 0.02		−0.01 ± 0.02	0.39
CCI-all vs. usual care	−0.02 ± 0.02	0.37	−0.04 ± 0.02	0.12			−0.04 ± 0.02	0.12		
Uric acid (μmo L^{-1})										
CCI-all education	5.83 ± 0.09		5.82 ± 0.10		−0.01 ± 0.08	0.9	5.72 ± 0.10		−0.11 ± 0.09	0.2
Usual Care	5.67 ± 0.16		5.44 ± 0.18		−0.24 ± 0.14	0.09	5.13 ± 0.18		−0.54 ± 0.16	6.2×10^{-4}
CCI-all vs. usual care	0.16 ± 0.19	0.39	0.39 ± 0.21	0.06			0.59 ± 0.21	0.005		
THYROID										
TSH (mIU L^{-1})[a]										
CCI-all education	2.16 ± 0.08		1.89 ± 0.07		−0.28 ± 0.07*	1.3×10^{-4}	1.90 ± 0.08		−0.22 ± 0.09	0.01
Usual Care	1.94 ± 0.14		1.92 ± 0.13		−0.01 ± 0.12	0.92	2.04 ± 0.14		0.11 ± 0.16	0.49
CCI-all vs. usual care	0.23 ± 0.16	0.15	−0.04 ± 0.15	0.79			−0.10 ± 0.16	0.52		
Free T4 (pmol L^{-1})[a]										
CCI-all education	0.91 ± 0.01		0.92 ± 0.01		0.01 ± 0.01	0.04	0.93 ± 0.01		0.01 ± 0.01	0.01
Usual Care	0.85 ± 0.02		0.89 ± 0.02		0.04 ± 0.02	0.53	0.90 ± 0.02		0.05 ± 0.02	0.25
CCI-all vs. usual care	0.06 ± 0.02	0.003	0.03 ± 0.03	0.23			0.02 ± 0.03	0.34		
Other										
Beta-hydroxybutyrate (mmol L^{-1})[a]										
CCI-all education	0.18 ± 0.01		0.27 ± 0.02		0.09 ± 0.02	6.8×10^{-7}	0.27 ± 0.02		0.09 ± 0.02	4.7×10^{-5}
Usual Care	0.14 ± 0.02		0.17 ± 0.03		0.03 ± 0.03	0.43	0.18 ± 0.04		0.03 ± 0.04	0.38
CCI-all vs. usual care	0.03 ± 0.02	0.11	0.10 ± 0.04	0.01			0.09 ± 0.04	0.03		
hsC-reactive protein (nmol L^{-1})[a]										
CCI-all education	7.45 ± 0.42		5.01 ± 0.46		−2.44 ± 0.40	2.4×10^{-9}	4.69 ± 0.40		−2.76 ± 0.37	6.9×10^{-13}
Usual Care	9.03 ± 0.75		9.06 ± 0.81		0.03 ± 0.69	0.96	8.38 ± 0.74		−0.65 ± 0.65	0.32
CCI-all vs. usual care	−1.58 ± 0.87	0.07	−4.05 ± 0.94	2.1×10^{-5}			−3.69 ± 0.86	2.3×10^{-5}		
White blood cell (k/cumm)										
CCI-all education	7.22 ± 0.12		6.52 ± 0.13		−0.70 ± 0.10	6.6×10^{-11}	6.68 ± 0.15		−0.54 ± 0.13	4.3×10^{-5}

(Continued)

TABLE 2 | Continued

	Baseline		1 Year			2 Years			
	Mean ± SE	P	Mean ± SE	P	Change from baseline	P	Mean ± SE	P	Change from baseline	P
Usual Care	8.12 ± 0.22		8.16 ± 0.23		0.04 ± 0.17	0.82	8.07 ± 0.27		−0.05 ± 0.23	0.82
CCI-all vs. usual care	−0.90 ± 0.26	5.3×10^{-4}	−1.64 ± 0.27*	2.3×10^{-9}			−1.39 ± 0.32	1.6×10^{-5}		

Ns for continuous care intervention = 262 and Ns for usual care = 87. Unless otherwise noted, estimates reported were obtained from linear mixed-effects models which provide adjusted means and mean changes, controlling for baseline age, sex, race, body mass index, and insulin use. This maximum likelihood-based approach uses all available repeated data, resulting in an intent-to-treat analysis. A significance level of $P < 0.0012$ ensures overall simultaneous significance of $P < 0.05$ over the 43 variables using Bonferroni correction. Abbreviations: SE, standard error; CCI, continuous care intervention; UC, usual care; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; NAFLD, nonalcoholic fatty liver disease; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rates; TSH, thyroid stimulating hormone.

[a]Variable was positively skewed and after removing the top 1% of values, skew and kurtosis values fell within acceptable ranges. Analyses were conducted on data excluding the top 1% of values for each variable, although due to the maximum likelihood approach all cases were still included in the analyses.

[b]Variable was positively skewed and a natural log transformation was performed. The linear mixed-effects model analysis including covariates was conducted on the transformed variable and significance values provided are from the transformed analysis. However, because transformed numbers are difficult to interpret, non-transformed and unadjusted means, mean changes, and standard errors for participants who completed the study visit were computed and provided in the table.

conducted, all below ns = 262) and **Supplementary Table 5** (per-protocol analyses). At 2 years, 27.2% of CCI participants ($P = 4.9 \times 10^{-15}$) and 6.5% of UC patients showed resolution of metabolic syndrome. The proportion of CCI patients with suspected steatosis was reduced from 95.8 to 67.4% ($P < 0.0 \times 10^{-36}$), whereas no change occurred in UC at 2 years. The proportion of patients without suspected fibrosis increased from 18.3 to 30.8% ($P = 1.4 \times 10^{-5}$) in the CCI, but did not change in the UC at 2 years.

Adverse Events

In the CCI group, there were no reported adverse events between 1 and 2 years related to the intervention or that resulted in discontinuation, including no reported episodes of ketoacidosis or severe hypoglycemia requiring assistance. Limited or no change in kidney and thyroid functions were seen in the CCI at 2 years. Adverse events occurring in the first year of intervention ($n = 6$) were previously reported (11); during the second year of intervention, nine adverse events were reported including: one breast cancer diagnosis, one mycosis fungoides, one onset of atrial fibrillation (Afib) with heart failure, one onset of migraine, two cases of chest pain (one resulting in stent placement), one pulmonary effusion, and two pulmonary embolisms (one following orthopedic surgery and one with benign ovarian mass/Afib) in the CCI group. In the UC group, adverse events occurring in the first year ($n = 6$) were previously reported (11), and in the second year, adverse events occurred in six participants: one death from liver cancer, one hospitalization from recurrent seizure, one ureteropelvic junction obstruction from kidney stone, one cerebrovascular accident with left side weakness and sensory disturbances, one chest pain requiring percutaneous coronary intervention, and one deep vein thrombosis.

DISCUSSION

Following 2 years of a remote continuous care intervention supporting medical and lifestyle changes, the CCI participants demonstrated improved HbA1c, fasting glucose and insulin, and HOMA-IR. Pharmaceutical interventions of 1.5 to 3 years duration report HbA1c reductions of 0.2 to 1.0% with DPP-4 inhibitors, SGLT-2 inhibitors and GLP-1 agonists (6, 7, 49). The HbA1c reduction of 0.9% with this CCI is comparable to that observed in pharmaceutical trials, but is achieved while discontinuing 67.0% of diabetes-specific prescriptions including most insulins and all sulfonylureas that engender risks for weight gain and hypoglycemia (50, 51). Comparable improvements in glycemic control and reduced medication were not observed in UC participants recruited from the same healthcare system, suggesting that the CCI improves diabetes management relative to usual care. Other interventions using carbohydrate restriction reported variable long-term glycemic improvement outcomes (52–57). The 0.9% absolute (12% relative) HbA1c reduction observed at 2 years is consistent with low carbohydrate studies reporting HbA1c reductions of 8–15% at 2 to 3.5 years (52, 55–57) with medication reduction. Two other studies reported no

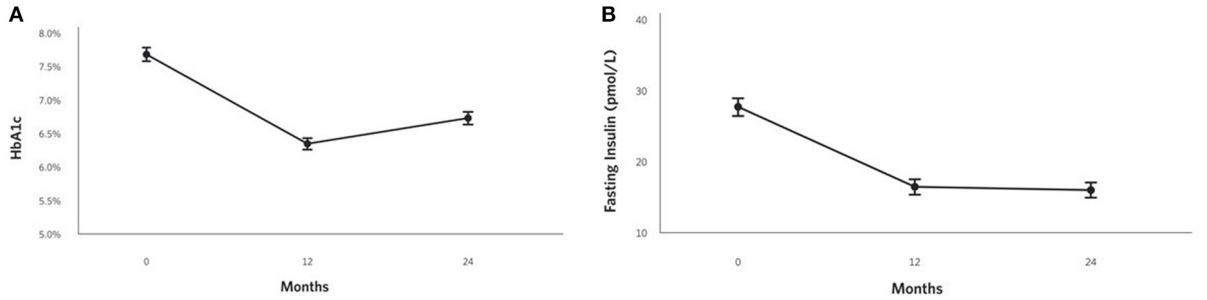

FIGURE 2 | Adjusted mean changes from baseline to 2 years in the CCI group for **(A)** HbA1c (−12% relative to baseline, $P = 1.8 \times 10^{-17}$), **(B)** Fasting insulin (−42% relative to baseline, $P = 2.2 \times 10^{-18}$).

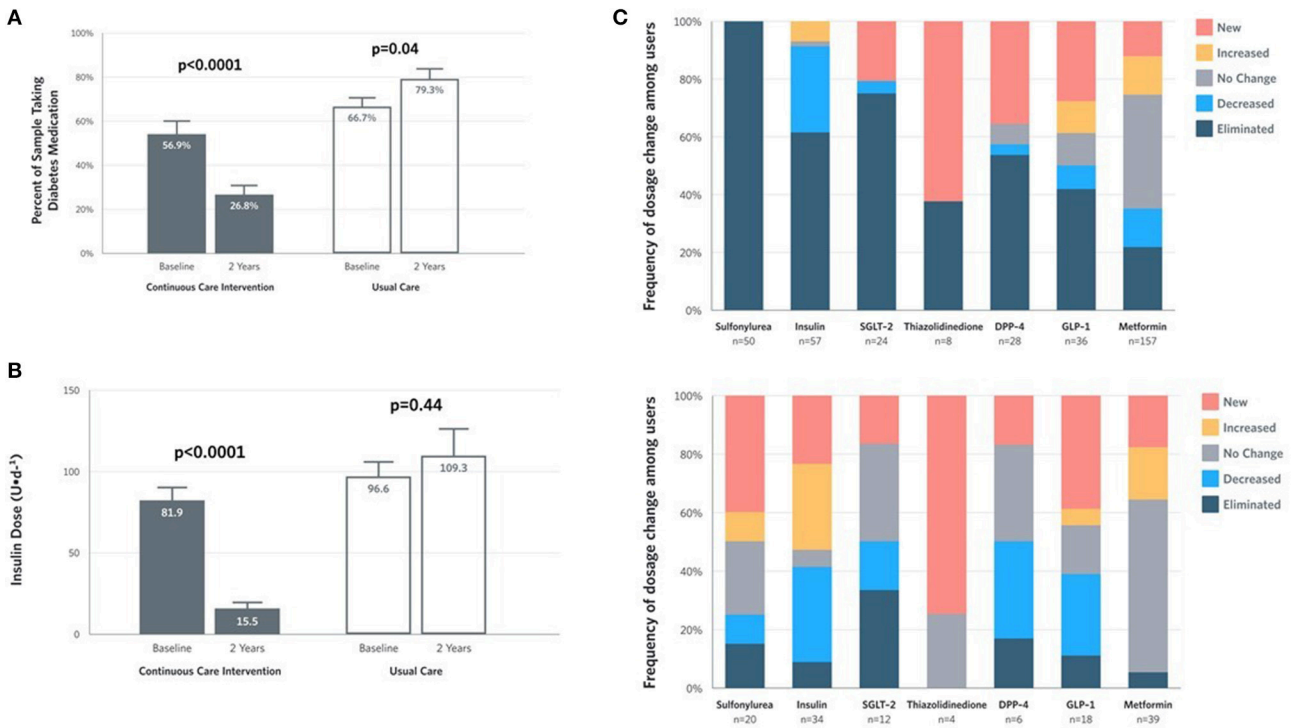

FIGURE 3 | Medication and insulin dose changes from baseline to 2 years for CCI and UC group completers. **(A)** Percent of completers taking diabetes medications, excluding metformin. **(B)** Mean ± SE prescribed insulin dose among baseline users. **(C)** Frequency of medication dosage and use change among prescribed users by diabetes medication class.

changes in HbA1c from baseline to 2 years, even though the low-carbohydrate arm reduced HbA1c in the first 6 months (53, 54).

Criticisms of low-carbohydrate diets relate to poor adherence and long-term sustainability (25, 26, 28). In this CCI, self-monitoring combined with continuous remote-monitoring and feedback from the care team, including behavioral support and nutrition advice via the app, may have improved accountability and engagement (58). In addition to glucose and weight tracking, dietary adherence was monitored by blood ketones. The 2 year BHB increase above baseline demonstrates sustained dietary modification. While laboratory BHB levels were increased from baseline, the encouraged range of nutritional ketosis (≥0.5 mM) was observed in only a minority (14.1%) of participants at 2 years. On average, patient-measured BHB was ≥0.5 mM for 32.8% of measurements over the 2 years (**Supplementary Figure 4**). This reveals an opportunity to increase adherence to nutritional ketosis for patients not achieving their desired health outcomes while prompting future research investigating the association between dietary adherence and health improvements.

A majority of the CCI participants (53.5%) met criteria for diabetes reversal at 2 years while 17.6% achieved diabetes remission (i.e., glycemic control without medication use) based on intent-to-treat with multiple imputation. The percentage of all CCI enrollees ($N = 262$) with verified reversal and remission requiring both completion of 2 years of the trial

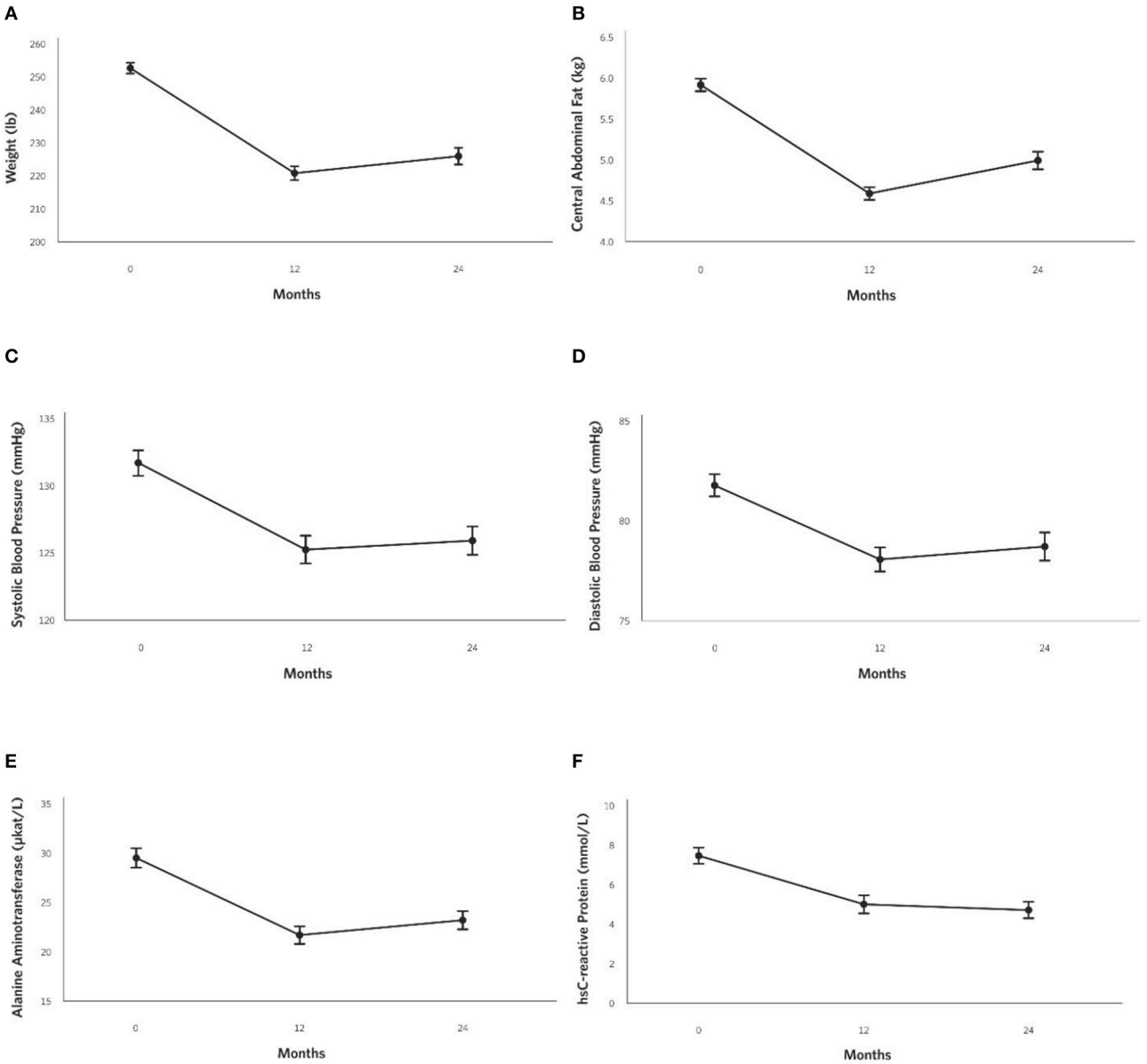

FIGURE 4 | Adjusted mean changes from baseline to 2-years in the CCI group for **(A)** Weight (−10% relative to baseline, $P = 8.8 \times 10^{-28}$), **(B)** Central Abdominal Fat [CAF] (−15% relative to baseline, $P = 1.6 \times 10^{-21}$), **(C)** Systolic Blood Pressure (−4% relative to baseline, $P = 2.4 \times 10^{-6}$), **(D)** Diastolic Blood Pressure (−4% relative to baseline, $P = 3.3 \times 10^{-5}$) **(E)** Alanine aminotransferase [ALT] (−21% relative to baseline, $P = 4.0 \times 10^{-10}$), and **(F)** High sensitive C-reactive protein [hsCRP](−37% relative to baseline, $P = 6.9 \times 10^{-13}$).

and an obtained laboratory value for HbA1c were 37.8 and 14.9%, respectively. CCI diabetes reversal exceeds remission as prescriptions for metformin were usually continued given its role in preventing disease progression (10, 59), preserving β-cell function (59) and in the treatment of pre-diabetes per guidelines (28). Partial and complete remission rates of 2.4 and 0.2% per year, respectively, were reported in 122,781 T2D patients receiving standard diabetes care (4). The 2 year remission rate (both partial and complete) in the CCI (17.6%) is higher than that achieved through intensive lifestyle intervention (ILI) in the Look AHEAD trial (9.2%) (5). Greater diabetes remission in the CCI vs. Look AHEAD ILI could result from differences in the dietary intervention (23), patients' ability to self-select their lifestyle change or effectiveness of continuous remote care. Length of time with a T2D diagnosis is a factor in remission, with longer time since diagnosis resulting in lower remission (4, 5, 9). Despite a mean and median of 8.4 and 7 years since diagnosis among CCI participants, the remission rate was higher than the Look AHEAD trial where its participants had a median of 5 years (4) since diabetes diagnosis.

Participants in the CCI achieved 10% mean weight loss (−11.9 kg) at 2 years. CCI weight loss was comparable to observed weight loss following surgical gastric banding (−10.7 kg) at 2 years (59). Previous studies consistently report that weight loss increases the likelihood of T2D remission (4, 5, 9). CCI participants also improved blood pressure, triglycerides, and HDL-cholesterol. Total cholesterol was unchanged and LDL-cholesterol was increased at 2 years, but was not different from the LDL-cholesterol level observed at 1 year (+0.51 mg/dL, $P = 0.85$). Despite the rise in LDL-cholesterol, the CCI cohort improved in 22 out of 26 CVD markers at 1 year (33). These changes included a decrease in small LDL-particles and large VLDL-P and an increase in LDL-particle size partitioning with no changes in ApoB (33), a marker considered a better predictor of CVD risk than LDL-cholesterol (33, 60). Non-elevated LDL cholesterol values together with higher triglycerides and lower HDL-cholesterol are common in patients with abdominal obesity, T2D, and metabolic syndrome (61, 62); these individuals often still have elevated atherogenic lipoproteins such as non-HDL (63), small LDL particles (62, 64), and VLDL (62, 64). In the CCI group, non-HDL cholesterol did not change from baseline to 2 years (141.7 ± 2.6 at baseline to 143.7 ± 3.1 mg/dl, $P = 0.51$) and several cardiovascular risk factors improved, suggesting that the rise in LDL-cholesterol may not be associated with increased atherogenic risk (65).

The CCI group had a reduction in visceral fat content, CAF and A/G ratio. This is consistent with other low-carbohydrate interventions reporting visceral fat reduction as a component of weight loss (30, 56, 66–68). Anatomical distribution of fat around the abdominal area ("android" obesity) is associated with T2D (69) and other comorbidities such as metabolic syndrome (70) and NAFLD (71). The alleviation of visceral fat in the CCI group was concurrent with resolution of metabolic syndrome at 2 years, while sustaining 1 year improvements of liver enzymes (10), steatosis, and fibrosis (72). The comprehensive effect of reduced visceral fat and improvement in associated comorbidities was previously reported (68, 73, 74). Rat studies have shown that removal of visceral adipose tissue increases insulin sensitivity while delaying T2D (75), and prevents metabolic syndrome and NAFLD (76). Resolution of liver steatosis and fibrosis may protect against other T2D macrovascular and microvascular complications such as cardiovascular disease and nephropathy (77). Furthermore, abdominal adiposity and NAFLD are frequently associated with altered inflammatory pathways in T2D patients (71). Excess free fatty acids from visceral adipose tissue may initiate chronic low-grade inflammation and activate nuclear factor kappa B signaling (71, 77). CCI participants also improved inflammatory status (hsCRP and WBC) at 1 year (10) and 2 years.

While some studies in animal models (78, 79) and children treated with ketogenic diets (80, 81) have suggested retardation in skeletal development and reduction in BMD, in this study of adults with T2D the CCI group had no change in total spine BMD over 2 years. Our results are consistent with other adult ketogenic dietary studies that reported no bone mass loss in short-term (66) or long-term follow-up of 2 (67, 82) and 5 (83) years. The differing findings of ketogenic diet on bone mass between adults and children could be due to differential effects on developed and mineralized vs. developing bones (84). In this study, the CCI group had a reduction (7.0%, 1.3 kg) in the calculated LELM. Most lean mass loss was encountered in the first year without further reduction in year 2. Studies have reported that obese adults have about 20% higher thigh muscle mass than those with normal weight (85). The reduced upper body load burden achieved through weight loss might explain the reduction of LELM. This reflects an appropriate weight loss-related reduction in muscle mass rather than muscle deficiency (86, 87). Weight loss (∼10%) induced by energy restriction resulted in slightly higher lean mass loss than the CCI (8.4% appendicular lean mass and 7.6% total lean mass loss at 20 weeks) (88). Total lean mass loss from 10% weight reduction by bariatric surgery is reported in the range of 7.3 to 15.9% from baseline (89, 90). Greater weight is associated with more lean mass loss (91, 92). Approximately 25% of diet-induced weight loss (without exercise) often arises from lean mass (93). In the present intervention, lean mass loss contributed an estimated 14% to the lower extremity weight loss. The lower proportion of lean mass loss in the CCI group, despite higher percentage of weight loss, may be due to the adequate dietary protein recommendations (94, 95). Since ∼73% of lean mass is water, the observed reduction of LELM in the first year of intervention may have arisen from natriuresis and water loss that occurs during keto-adaptation (96, 97).

Strengths and Limitations

This study's strengths include its size and prospective, longitudinal data collection from two participant groups (CCI and UC) which allowed statistical analysis by linear mixed effects model to investigate intervention time and treatment effects. The UC group was prospectively recruited from the same healthcare system. While not randomized, the participants' self-selection of intervention may contribute to the observed high retention and predicts real-life clinical management of chronic disease. The study also included patients prescribed insulin and with long-standing disease, groups often excluded from prior studies. The multi-component aspect of the intervention involving regular biomarker monitoring and access to a remote care team may have improved the long-term dietary adherence and engagement. The dietary advice including encouraging participants to restrict carbohydrates, moderate protein intake, and eat to satiety may also help in maintaining long-term effectiveness. Weaknesses of this study include the lack of randomization and racial diversity limiting generalization of the results to all T2D patients. Interpretation of DXA body composition was limited to subregion analyses due to the scanner not accommodating the patients' complete body.

CONCLUSIONS

At 2 years, the CCI, including remote medical management with instruction in nutritional ketosis, was associated with improvements in blood glucose, insulin, HbA1c, weight, blood pressure, triglyceride, liver function, and inflammation and reduced dependence upon medication. These long-term benefits were achieved concurrent with reduced prevalence of metabolic

syndrome, and visceral adiposity. The CCI had no adverse effect on bone mineral density. The CCI group also had a higher prevalence of diabetes reversal and remission compared to the UC group following a standard diabetes care program. These results provide evidence that sustained improvement in diabetes status can be achieved through the continuous remote monitoring and accountability mechanisms provided by this multi-component CCI including recommendations for low-carbohydrate nutrition.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Franciscan Health Lafayette Institutional Review Board with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Franciscan Health Lafayette Institutional Review Board.

AUTHOR CONTRIBUTIONS

SA, RA, and JM drafted the manuscript. SA, RA, AM, NB, and SH participated in data acquisition and compiling. RA and SA analyzed the data. JM, AM, NB, WC, RA, SA, SH, SP, and JV edited the manuscript. All authors approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2019.00348/full#supplementary-material

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Cardiovascular Diabetology

ORIGINAL INVESTIGATION

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Impact of a 2-year trial of nutritional ketosis on indices of cardiovascular disease risk in patients with type 2 diabetes

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Abstract

Background: We have previously reported that in patients with type 2 diabetes (T2D) consumption of a very low carbohydrate diet capable of inducing nutritional ketosis over 2 years (continuous care intervention, CCI) resulted in improved body weight, glycemic control, and multiple risk factors for cardiovascular disease (CVD) with the exception of an increase in low density lipoprotein cholesterol (LDL-C). In the present study, we report the impact of this intervention on markers of risk for atherosclerotic cardiovascular disease (CVD), with a focus on lipoprotein subfraction particle concentrations as well as carotid-artery intima-media thickness (CIMT).

Methods: Analyses were performed in patients with T2D who completed 2 years of this study (CCI; n = 194; usual care (UC): n = 68). Lipoprotein subfraction particle concentrations were measured by ion mobility at baseline, 1, and 2 years and CIMT was measured at baseline and 2 years. Principal component analysis (PCA) was used to assess changes in independent clusters of lipoprotein particles.

Results: At 2 years, CCI resulted in a 23% decrease of small LDL IIIb and a 29% increase of large LDL I with no change in total LDL particle concentration or ApoB. The change in proportion of smaller and larger LDL was reflected by reversal of the small LDL subclass phenotype B in a high proportion of CCI participants (48.1%) and a shift in the principal component (PC) representing the atherogenic lipoprotein phenotype characteristic of T2D from a major to a secondary component of the total variance. The increase in LDL-C in the CCI group was mainly attributed to larger cholesterol-enriched LDL particles. CIMT showed no change in either the CCI or UC group.

Conclusion: Consumption of a very low carbohydrate diet with nutritional ketosis for 2 years in patients with type 2 diabetes lowered levels of small LDL particles that are commonly increased in diabetic dyslipidemia and are a marker for heightened CVD risk. A corresponding increase in concentrations of larger LDL particles was responsible for higher levels of plasma LDL-C. The lack of increase in total LDL particles, ApoB, and in progression of CIMT, provide supporting evidence that this dietary intervention did not adversely affect risk of CVD.

Keywords: Type 2 diabetes, Nutritional ketosis, Cardiovascular risk, Lipoprotein sub-fractionation, Atherogenic lipoprotein phenotype

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Background

Global incidence of diabetes is rising substantially, with the expectation of a 50% increase between 2015 and 2040 [1]. The leading cause of death in patients with diabetes is cardiovascular disease (CVD) [2] and mitigating CVD risk has become a principal focus of current diabetes

guidelines [3, 4]. Multiple studies have found that therapeutic carbohydrate restriction significantly improves a number of CVD risk factors [5–7], including elevated triglycerides and small dense LDL, low HDL-C, and markers of non-alcoholic fatty liver disease [8, 9]. These factors contribute to residual risk of CVD following statin treatment for lowering of LDL-cholesterol (LDL-C) [10].

Although LDL-C has been a mainstay for CVD risk prediction and management for decades, it is not characteristically elevated in patients with diabetes. Rather, the most common dyslipidemia in type 2 diabetes (T2D) consists of high triglycerides (TG), low HDL-cholesterol (HDL-C), and a preponderance of small dense LDL particles [11, 12]. This trait which is a central feature of metabolic syndrome, has been designated the atherogenic lipoprotein phenotype (ALP) or atherogenic dyslipidemia [11–14]. Multiple studies have shown beneficial effects of carbohydrate restriction on this phenotype [15–17]. Recently, very low carbohydrate diets that achieve nutritional ketosis have been shown to be of benefit in diabetes management, with effects including improvements in weight, HbA1c, triglycerides and HDL-C [5, 18]. However, such diets often result in increased concentrations of LDL-C [18, 19], which has raised concerns regarding an adverse effect on CVD risk.

While LDL-C is taken to reflect the role of LDL particles in the development of CVD, it has been shown that measurement of LDL particles [20, 21] and ApoB, which is a measure of the number of all atherogenic particles (LDL, IDL, VLDL, lipoprotein (a), chylomicron remnants) [20, 22] can provide superior assessment of CVD risk, most notably when there is discordance between LDL-C and LDL particle concentrations [22]. This discrepancy is commonly due to increased levels of small, dense, cholesterol-depleted particles, as is the case for the dyslipidemia of T2D. There is increasing evidence that levels of small, dense LDL are predictive of CVD incidence independent of LDL-C [23–27], whereas in general levels of large LDL show weak or absent associations with CVD risk [27]. Properties of small LDL that may underlie this risk include increased circulation time due to decreased receptor-mediated uptake, increased vascular wall binding, and increased susceptibility to oxidation and glycation [28]. Assessment of other lipoprotein particle subclasses, including those within VLDL and HDL, has provided the ability to further assess CVD risk [20].

We previously reported that 2 years of treatment with a continuous care intervention (CCI) produced significant improvements in weight, blood glucose, HbA1c, liver function, and inflammatory markers with no adverse effects on kidney markers [29]. Participants in the CCI group had a 0.9% mean absolute reduction in HbA1c and a 10% average weight loss at 2 years [29]. CCI is a personalized carbohydrate restriction (CR) intervention with guidance encouraging nutritional ketosis that is delivered and supported remotely using a telemedicine-approach, via one-to-one health coaching and physician-led treatment. At 1 year, the intervention resulted in substantial improvements in multiple cardiometabolic risk markers including triglycerides, HDL-C, ApoA1, ApoB: ApoA1 ratio, and blood pressure [30, 31]. However, there was an increase in LDL-C that was maintained through 2 years despite sustained improvements in TG and HDL-C [30]. To further characterize changes in LDL and other lipoproteins at 1 and 2 years, we have here utilized the technique of ion mobility (IM) which directly measures concentrations of lipoprotein particle subclasses across the full diameter spectrum from HDL to VLDL. The primary aims were to investigate the effect of the CCI and UC on lipoprotein subfractions and carotid intima-media thickness (CIMT). Secondary aims included: (1) investigating the effect of CCI and UC on T2D atherogenic dyslipidemia using both principal component analyses and assessment of LDL subclass phenotypes and (2) among the CCI participants, comparing the 2-year changes of lipoprotein subclasses and CIMT between individuals in the highest and lowest quartiles of either LDL-C or ApoB responses. Other ancillary aims included assessing potential relationships between adiposity and beta-hydroxybutyrate (BHB) with changes in lipids, lipoproteins and LDL phenotype.

Materials and methods

Study design and intervention

The data analyzed for this study are measurements of CVD risk markers obtained at baseline and after 1 and 2 years of follow-up in participants in the clinical trial NCT02519309. This is an open-label, non-randomized controlled trial of the effects of carbohydrate restriction including nutritional ketosis conducted in a cohort of patients with T2D. The study design, comprehensive details of the study intervention, and major exclusion criteria were previously published [29, 31]. Briefly, the trial recruited participants with an established diagnosis of T2D and a body mass index (BMI) > 25 kg/m^2, who self-selected to receive either the CCI or usual care (UC). All study participants were informed and consented to participate in the study, and the study was approved by the Franciscan Health Lafayette Institutional Review Board. Patients in the CCI group received nutritional advice on carbohydrate restriction to achieve and sustain nutritional ketosis. They were initially advised to consume < 30 g of carbohydrates, approximately 1.5 g protein per kg reference body weight, and fat to satiety each day. Blood beta-hydroxybutyrate (BHB) was used as

a marker of carbohydrate restriction, with BHB ≥ 0.5 mM [32] indicating nutritional ketosis. Over time, BHB and dietary intake targets were modified according to patient health needs, goals, and values. The patients had access to a web-interfaced software application (app) that they used to communicate with their remote care team and receive telemedicine-based treatment. The app was used to upload selected biomarkers for monitoring adherence to nutritional intervention and health-related progress including body weight, blood glucose, and BHB. The frequency of reporting glucose and BHB was adjusted to each participant's preferences and current health needs. Participants with a confirmed history of hypertension additionally received an automatic sphygmomanometer, blood pressure readings were uploaded in the app for assessment by the care team. The reported blood glucose and blood pressure readings were evaluated routinely by the physician who adjusted diabetic and anti-hypertensive prescriptions as needed. Via the app, participants had access to online resources and the opportunity to participate in an online social support community.

Patients who chose UC comprised a reference group that was recruited from the same geographical and healthcare system. They continued with their existing care team without modification and received nutritional and lifestyle advice as recommended by the American Diabetes Association (ADA) between August 2015 and May 2018 [3]. No study-specific modification of treatment or care was made but the participants in the UC arm were required to obtain annual tests for measurement of clinical biomarkers.

Anthropometric measures

Anthropometric measures were obtained for both CCI and UC participants in the clinic at baseline, 1 year, and 2 years. Body weight and height were measured using a stadiometer and calibrated scale, respectively and the values were used to calculate body mass index (BMI). Manual blood pressure measurements were performed by trained staff. Dual-energy X-ray absorptiometry (DXA; Lunar GE Prodigy, Madison, WI) was utilized to measure total body composition and to estimate central abdominal fat (CAF), as previously described [29], in the CCI group only.

Lipid analyses

An accredited Clinical Laboratory Improvement Amendment (CLIA) laboratory was used to analyze all the standard blood analytes. For the determination of total cholesterol, HDL-C, TG, ApoA1, and ApoB, an enzymatic, colorimetric method was employed using FDA approved Cobas c501 (Roche Diagnostics; Indianapolis, IN, USA) assays. LDL cholesterol (LDL-C) levels were calculated using the Friedewald equation, except if the TG level exceeded 400 mg/dL, in which case LDL-C was not determined (n = 15, 8, 8 in CCI and n = 9, 10, 6 in UC at baseline, 1 year and 2 years, respectively). ApoB: ApoA1 ratios were computed. Non-HDL cholesterol was calculated as total minus HDL cholesterol and remnant cholesterol was assessed as total cholesterol minus (HDL-cholesterol plus LDL-cholesterol).

Lipoprotein analyses

Particle concentrations of VLDL, IDL, LDL, and HDL subfractions were analyzed in specific particle-size intervals using ion mobility (IM), which uniquely allows for direct particle quantification as a function of particle diameter [21] following a procedure to remove other plasma proteins [24]. The IM instrument utilizes an electrospray to create an aerosol of particles which then pass through a differential mobility analyzer coupled to a particle counter. Particle concentrations (nmol/L) were measured in 11 size intervals (Å): VLDL: large (424.0 to 547.0), medium (335.0 to 424.0), small (296.0 to 335.0); IDL: large (250.0 to 296.0) and small (233.3 to 250.0); LDL: large LDL I (224.6 to 233.3), medium LDL IIa (220.0 to 224.6), and LDL IIb (214.1 to 220.0), small LDL IIIa (208.2 to 214.1) and LDL IIIb (204.9 to 208.2), very small LDL IVa (199.0 to 204.9), LDL IVb (190.0 to 199.0) and LDL IVc (180.0 to 190.0); HDL: large HDL 2b (105.0 to 145.0) and smaller HDL 2a + 3 (76.5 to 105.0). In addition, particles in the size range between LDL and HDL (145.0 to 180.0 Å) were measured (designated midzone). Peak LDL diameter was determined as described [22]. Interassay variation was reduced by the inclusion of two in-house controls in each preparatory process and triplicate analysis. Inter- and intra-assay coefficients of variability were < 15% for lipoprotein subclass concentrations and < 0.8% for LDL peak diameter. In addition, LDL subclass phenotypes were determined as described previously [33]: phenotype A (predominance of larger LDL particles with LDL peak diameter > 21.88 nm), phenotype B (predominance of small LDL particles with LDL peak diameter < 21.55 nm), or intermediate phenotype I (with LDL peak diameter between 21.55 and 21.88 nm).

Carotid intima-media thickness (CIMT) measurement

Ultrasound assessment CIMT was performed in both CCI and UC participants. A high-resolution B mode carotid ultrasound was used (Philips EPIQ5 system; Amsterdam, Netherlands) and the scans were performed by trained and blinded technicians. The participants were placed in a supine position, and both right and left carotid arteries were evaluated with grayscale, spectral, and color Doppler images. The images were taken 1 cm distal to the carotid bulb, below its bifurcation limit. As

previously published [30], three imaging planes, anterior, lateral, and posterior, were captured for each participant. These images were then analyzed using the edge detection software (Carotid Analyzer for Research, Medical Imaging Application, Coralville, IA) by a trained and blinded analyst. Any images that were classified "poor" and those with missing planes were removed from all the time points, before the right and left mean CIMT and diameter were calculated from the images. The right and left CIMT average measurements were then used to calculate the overall mean CIMT.

Statistical analyses

Analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp, Armonk, N.Y., USA). All were first examined for normality and linearity using the skewness and kurtosis cut-offs suggested by Kline's 2011 guidelines [34]. Four outcomes were positively skewed (i.e., triglycerides, LDL IVa, LDL IVb, and LDL IVc), these variables were normalized by either removal of the top 1% of values or natural log transformations (as specified in the tables' footnotes). Between-group and between completers versus dropouts' differences in baseline data were analyzed using independent sample t-tests.

All analyses were based on the per-protocol principle including only participants with available data at baseline and 2 years. We used linear mixed-effects models (LMMs) to analyze all the primary endpoints. The models included fixed effects of time, treatment group, and time-by-group interaction to estimate the adjusted means at each time point and to assess the time-effect of the treatments (baseline to 2 years) and between-treatment group differences (CCI versus UC). All models were adjusted for baseline age, sex, BMI, insulin use, statin use, HDL 2 + 3a, and mid-zone. BMI, insulin-use, HDL 2 + 3a and mid-zone were included as co-variates because they differed significantly between CCI and UC groups at baseline. A sensitivity analysis was conducted using data including all participants (262 CCI and 87 UC participants) based on the intent-to-treat principle. The estimation of the missing data in the LMMs was based on the maximum likelihood approach and an unstructured (UN) covariance structure was used to account for within-group correlation over time. The changes in the proportion of participants' use of lipid-lowering and antihypertensive medications between baseline versus 2 years in both CCI and UC were analyzed using McNemar's test with continuity correction when appropriate. Logistic generalized estimating equations (GEE) analysis with an unstructured covariance matrix were used to analyze the time-effect of each treatment group (CCI and UC) on the trichotomous categorical variable, LDL phenotype pattern (Pattern A, B and I). Covariates included baseline age, sex, BMI, insulin use, statin use, HDL 2 + 3a, and mid-zone.

Individual differences in the changes of LDL-C and ApoB between baseline and 2 years were assessed using hypo- and hyper-responder categories. For the classification of LDL-C and ApoB hypo- versus hyper-responders, we generated quartiles using the calculated delta LDL-C and delta ApoB from baseline to 2 years. The lowest (greatest decrease) and highest (greatest increase) quartiles were classified as hypo- and hyper-responders, respectively. A-one-way MANOVA was performed to assess the differences in the multivariate lipoprotein profiles at 2 years for the LDL-C and ApoB hypo- versus hyper-responders. Lipoprotein variables that failed the Shapiro–Wilk test of normality were log-transformed before inclusion in the MANOVA to meet the multivariate normality and outliers' assumptions. The 2-year differences in mean CIMT between the LDL-C or ApoB hypo- and hyper-responder groups were assessed using independent T-tests.

Finally, measures of adiposity and BHB were tested as predictors of changes in lipids and lipoproteins. Linear and multiple linear regression analyses were used to assess the relationships between changes in BMI and CAF with lipids and lipoproteins. BHB values that were uploaded in the app by the CCI participants were treated as count data, where the number of days participants reported a BHB value of ≥ 0.5 mM over the past 24 months was modeled using negative binomial regression for association with lipids, lipoproteins, and LDL phenotype shift.

A strict Bonferroni correction was applied to the LMM and MANOVA analyses, where $P < 0.0015$ and $P < 0.003$, respectively indicated statistical significance. For all other exploratory analyses, $P < 0.05$ was used to determine statistical significance.

Principal component analysis

There was a strong inter-correlation and dependency between the lipoprotein subclasses and lipid variables. To simplify analysis, principal component analysis (PCA) was performed on the 16 lipoproteins and 3 traditional lipids to reduce the variables by generating a new independent combination of the variables that explains the variance of the data. Separate PCAs were performed on baseline and 2-year follow-up data in the CCI and UC treatment groups. Three steps were used: (1) Identification and extraction of major principal components, (2) Rotation of the principal components to identify relevant loading factors, and (3) Interpretation of the principal components and its associated variance. First, we assessed the data for sampling adequacy and its suitability for factor analysis using the Kaiser–Meyer–Olkin

(KMO) statistic (cut-off > 0.6) and the Barlett test of sphericity (P < 0.001). Then, we performed PCA on the baseline CCI (n = 223) and UC (n = 70), and 2-year follow-up CCI (n = 140) and UC (n = 46) data, separately. The major principal components represented in each dataset were extracted after assessing the scree plots, and an eigenvalue of 1 was used as a cut-off to select and retain the principal components. We used both varimax and promax rotation methods to identify loading factors for each principal component and a loading value cut-off > 0.40 was used to determine the individual lipoproteins and lipids represented in each component. The individual extracted principal components and their associated variance at baseline and 2-years follow-up were qualitatively assessed. The variance of the individual PCs at baseline and 2-years explains how much of the information in the data is captured by the respective PCs. A PC with the highest variance contribution represents the most information in the data, while a PC with less variance captures less information in the data. Changes in the rank of the PCs were assessed at baseline and 2 years.

Results

Participant characteristics

This study enrolled 262 CCI and 87 UC participants, with 194 CCI and 68 UC participants remaining enrolled for 2 years. As previously reported [20], baseline demographic characteristics of the two treatment groups were similar except for the proportion of African Americans. Baseline anthropometric measures, CVD risk markers, and average CIMT were similar between CCI and UC, except for BMI (Additional file 1: Table S1). Baseline levels of lipoprotein subclasses were similar between CCI and UC groups, except for mid-zone and small HDL 2a + 3 which were significantly lower in the CCI group. At baseline, 50% of CCI and 59% of UC participants were on statin treatment ($P = 0.16$). There were no significant differences in baseline characteristics of those who dropped out of the study versus those remaining, except for the baseline proportion of LDL phenotypes in UC (Additional file 1: Table S1).

Changes in primary laboratory and clinical outcome measures

Within the UC group, no changes over time in lipids, lipoproteins, apoproteins, blood pressure, CIMT and lipid-lowering and anti-hypertensive medications were observed. Among CCI participants at 1 and 2 years, mean LDL-C and HDL-C increased, mean TG and blood pressure decreased, and total cholesterol was unchanged, as previously reported [20] (Additional file 1: Table S2, Figure S1). Lower blood pressures were observed concurrent with reduced use of antihypertensive medication ($P = 1.0 \times 10^{-3}$), particularly diuretics ($P = 7.0 \times 10^{-3}$) at 2 years (Additional file 1: Table S3). The use of statin medication was unchanged at 2 years, but the use of other lipid-lowering medications (bile acid sequestrants, fibrates, niacin and omega-3 fatty acid ethyl esters) decreased ($P = 8.0 \times 10^{-3}$) from a small baseline population of 9.3%.

Among CCI participants, remnant cholesterol decreased at 1 and 2 years (− 22.4% at 2 years, $P = 3.1 \times 10^{-7}$), and ApoA1 increased (+ 10.9% at 2 years, $P = 1.4 \times 10^{-7}$; Additional file 1: Table S2). Non-HDL, ApoB, ApoB: ApoA1 ratio, and CIMT were unchanged (Additional file 1: Table S2). No significant changes in total LDL, total IDL, total VLDL, and total HDL particles were seen in the CCI and UC groups. Among lipoprotein subfractions, VLDL subclasses and IDL I were unchanged at 2 years, while IDL II increased (+ 24.6% at 2 years, $P = 2.0 \times 10^{-10}$, Table 1, Additional file 1: Figure S1) and was greater than UC ($P = 5.1 \times 10^{-8}$). Large LDL I increased at one and 2 years (+ 29.1% at 2 years, $P = 2.4 \times 10^{-8}$) concurrent with increases in LDL peak diameter (+ 2.0% at 2 years, $P = 1.9 \times 10^{-10}$); both were greater compared to UC ($P = 2.0 \times 10^{-6}$ and $P = 1.2 \times 10^{-4}$, respectively). LDL IIa and IIb were unchanged. Small LDL IIIa and IIIb decreased at 1 year, with LDL IIIb maintaining significance at 2 years (− 23.1% at 2 years, $P = 1.0 \times 10^{-3}$) where it was lower compared to UC ($P = 1.0 \times 10^{-3}$) (Table 1), while the reduction in LDL IIIa at 2 years was of borderline significance after Bonferroni correction ($P = 3.0 \times 10^{-3}$). There were non-significant decreases in very small LDL (IVa–c). Particles in the mid-zone were lower at 1 and 2 years (− 6.8% at 2 years, $P = 7.4 \times 10^{-7}$) and compared to UC ($P = 1.0 \times 10^{-3}$). No significant differences in HDL subfractions were observed in either CCI or UC groups. An intent-to-treat sensitivity analysis using all available data revealed results consistent with the per-protocol (completers) analysis (Additional file 1: Table S4).

Changes in principal components and LDL subclass phenotypes

Principal component analysis was performed on the baseline and 2-year data separately in the CCI and UC groups. At baseline data, for the CCI group, three major principal components (PC1, PC2, PC3) were extracted accounting for 39.9%, 24.8%, and 12.7% of the total variance (77.4%), respectively. PC1 consisted of contributions from small LDLs (LDL IIIa to LDL IVc), large VLDL, medium VLDL, and TG in the positive direction and HDL-C in the negative direction (Additional file 1: Table S5). Major contributors of PC2 were large and medium LDLs (LDL I to LDL IIb), IDLs, VLDL small, and LDL-C in a positive direction. Finally, contributors of

Table 1 Adjusted means and changes in lipoproteins over time by treatment group among completers

Variables	Visit	Continuous care intervention (n = 194)		Usual care (n = 68)		Between group effect	
		Mean ± SE	Change from baseline (Mean, CI)	Mean ± SE	Change from baseline (Mean, CI)	Mean difference	95% CI
Total VLDL (nmol/L)	Baseline	138.6 ± 5.7		144.0 ± 8.4		− 5.3	− 25.4 to 14.8
	1 year	128.7 ± 5.8	− 9.9, − 25.8 to 5.9	146.9 ± 8.7	3.0, − 20.3 to 26.2	− 18.2	− 39.0 to 2.5
	2 years	129.3 ± 5.9	− 9.3, − 25.3 to 6.6	144.1 ± 8.7	0.2, − 23.0 to 23.4	− 14.8	− 35.7 to 6.0
VLDL large (nmol/L)	Baseline	23.9 ± 1.0		22.2 ± 1.7		1.7	− 2.3 to 5.7
	1 year	19.1 ± 1.0	− 4.8, − 7.6 to − 2.0*	22.7 ± 1.8	0.5, − 4.3 to 5.2	− 3.6	− 7.7 to 0.6
	2 years	20.3 ± 1.0	− 3.6, − 6.4 to − 0.8	21.9 ± 1.7	− 0.3, − 5.0 to 4.4	− 1.6	− 5.7 to 2.4
VLDL medium (nmol/L)	Baseline	57.3 ± 1.8		55.2 ± 3.1		2.1	− 5.2 to 9.3
	1 year	52.3 ± 1.8	− 5.0, − 10.0 to 0.0	54.6 ± 3.2	− 0.5, − 9.1 to 8.0	− 2.4	− 9.8 to 5.1
	2 years	52.5 ± 1.8	− 4.7, − 9.7 to 0.3	54.7 ± 3.1	− 0.5, − 8.9 to 7.9	− 2.2	− 9.4 to 5.1
VLDL small (nmol/L)	Baseline	59.3 ± 1.5		55.8 ± 2.6		3.4	− 2.6 to 9.5
	1 year	63.2 ± 1.5	3.9, − 0.3 to 8.1	55.0 ± 2.7	− 0.8, − 8.0 to 6.3	8.2	2.0 to 14.4
	2 years	59.2 ± 1.5	− 0.1, − 4.3 to 4.1	54.9 ± 2.6	− 0.9, − 8.0 to 6.1	4.3	− 1.8 to 10.4
Total IDL (nmol/L)	Baseline	256.6 ± 8.0		255.1 ± 11.9		1.6	− 27.0 to 30.1
	1 year	285.1 ± 8.3	28.4, 5.9 to 50.9	256.1 ± 12.3	1.1, − 32.0 to 34.1	28.9	− 0.6 to 58.4
	2 years	288.9 ± 8.4	32.2, 9.6 to 54.9 †	261.5 ± 12.3	6.4, − 26.5 to 39.4	27.3	− 2.3 to 57.0
IDL 1 (nmol/L)	Baseline	136.2 ± 3.3		129.2 ± 5.7		7.0	− 6.2 to 20.1
	1 year	139.4 ± 3.3	3.2, − 5.9 to 12.3	128.8 ± 5.9	− 0.4, − 15.9 to 15.0	10.6	− 2.9 to 24.1
	2 years	136.4 ± 3.3	0.2, − 8.9 to 9.2	128.3 ± 5.7	− 0.9, − 16.1 to 14.3	8.0	− 5.1 to 21.1
IDL 2 (nmol/L)	Baseline	122.1 ± 3.8		113.3 ± 6.5		8.8	− 6.3 to 23.8
	1 year	152.1 ± 3.8	30.0, 19.6 to 40.4*	112.0 ± 6.7	− 1.3, − 19.0 to 16.4	40.1*	24.6 to 55.5*
	2 years	156.3 ± 3.8	34.2, 23.9 to 44.6*	114.0 ± 6.5	0.7, − 16.7 to 18.1	42.3*	27.2 to 57.3*
Total LDL (nmol/L)	Baseline	991.8 ± 25.9		1028.7 ± 40.8		− 36.9	− 132.7 to 58.9
	1 year	962.7 ± 26.8	− 29.1, − 101.9 to 43.7	1026.5 ± 43.1	− 2.2, − 117.2 to 112.8	− 63.8	− 164.4 to 36.8
	2 years	1002.0 ± 27.0	10.3, − 62.8 to 83.4	1022.1 ± 42.3	− 6.6, − 120.2 to 107.0	− 20.0	− 119.6 to 79.6
LDL I (nmol/L)	Baseline	163.5 ± 6.0		155.6 ± 10.3		7.9	− 16.0 to 31.8
	1 year	207.7 ± 6.1	44.2, 27.6 to 60.7*	146.1 ± 10.7	− 9.6, − 37.7 to 18.6	61.7*	37.1 to 86.2*
	2 years	211.1 ± 6.0	47.6, 31.1 to 64.0*	152.9 ± 10.3	− 2.8, − 30.4 to 24.9	58.2*	34.3 to 82.1*
LDL IIa (nmol/L)	Baseline	137.8 ± 4.7		135.8 ± 8.0		2.0	− 16.6 to 20.5
	1 year	153.4 ± 4.7	15.6, 2.7 to 28.4	126.5 ± 8.3	− 9.3, − 31.1 to 12.5	26.9	7.8 to 45.9
	2 years	156.1 ± 4.7	18.3, 5.5 to 31.1 †	129.2 ± 8.0	− 6.6, − 28.0 to 14.8	26.9†	8.4 to 45.4†
LDL IIb (nmol/L)	Baseline	176.0 ± 5.6		170.1 ± 9.5		6.0	− 16.1 to 28.0
	1 year	169.7 ± 5.6	− 6.3, − 21.6 to 9.0	166.0 ± 9.9	− 4.1, − 30.0 to 21.9	3.7	− 19.0 to 26.3
	2 years	174.9 ± 5.6	− 1.1, − 16.3 to 14.2	171.4 ± 9.5	1.3, − 24.3 to 26.9	3.6	− 18.5 to 25.7
LDL IIIa (nmol/L)	Baseline	191.5 ± 7.3		169.8 ± 12.6		21.7	− 7.4 to 50.8
	1 year	157.4 ± 7.4	− 34.0, − 54.2 to − 13.9*	187.2 ± 13.0	17.4, − 16.7 to 51.6	− 29.8	− 59.6 to 0.1
	2 years	161.1 ± 7.3	− 30.3, − 50.4 to − 10.3†	193.5 ± 12.6	23.8, − 9.9 to 57.4	− 32.4	− 61.5 to − 3.3
LDL IIIb (nmol/L)	Baseline	87.8 ± 4.4		84.7 ± 7.6		3.1	− 14.6 to 20.7
	1 year	66.5 ± 4.5	− 21.2, − 33.5 to − 9.0*	98.0 ± 7.9	13.3, − 7.5 to 34.1	− 31.5*	− 49.6 to − 13.4*
	2 years	67.5 ± 4.4	− 20.3, − 32.5 to − 8.1*	96.5 ± 7.6	11.8, − 8.7 to 32.2	− 29.0*	− 46.6 to − 11.3*
LDL IVa (nmol/L)[a]	Baseline	89.1 ± 3.2		95.0 ± 5.6		− 5.9	− 18.7 to 6.9
	1 year	76.4 ± 3.2	− 12.7, − 21.4 to − 4.0†	93.1 ± 5.9	− 1.9, − 17.4 to 13.6	− 16.7	− 30.0 to − 3.4
	2 years	76.9 ± 3.2	− 12.2, − 20.9 to − 3.6	89.9 ± 5.6	− 5.1, − 20.2 to 10.1	− 13.1	− 25.9 to − 0.2
LDL IVb (nmol/L)[a]	Baseline	78.3 ± 1.8		82.8 ± 3.2		− 4.5	− 11.8 to 2.8
	1 year	71.6 ± 1.8	− 6.7, − 11.7 to − 1.7	82.7 ± 3.3	− 0.1, − 8.8 to 8.6	− 11.1†	− 18.6 to − 3.6†
	2 years	73.2 ± 1.8	− 5.1, − 10.1 to − 0.2	81.5 ± 3.2	− 1.3, − 9.9 to 7.5	− 8.3	− 15.6 to − 1.0

Table 1 (continued)

Variables	Visit	Continuous care intervention (n = 194)		Usual care (n = 68)		Between group effect	
		Mean ± SE	Change from baseline (Mean, CI)	Mean ± SE	Change from baseline (Mean, CI)	Mean difference	95% CI
LDL IVc (nmol/L)[a]	Baseline	88.9 ± 1.3		89.6 ± 2.2		− 0.6	− 5.8 to 4.5
	1 year	83.6 ± 1.3	− 5.3, − 8.8 to − 1.7[Ī]	88.6 ± 2.3	− 0.9, − 7.1 to 5.2	− 5.0	− 10.3 to 0.3
	2 years	84.0 ± 1.3	− 5.0, − 8.5 to − 1.4	85.7 ± 2.2	− 3.8, − 9.8 to 2.2	− 1.8	− 6.9 to 3.4
Mid-zone (nmol/L)	Baseline	875.3 ± 8.6		892.2 ± 14.7		− 16.9	− 50.9 to 17.1
	1 year	828.6 ± 8.6	− 46.6, − 70.2 to − 23.1*	890.5 ± 15.2	− 1.7, − 41.8 to 38.3	− 61.8*	− 96.7 to − 26.9*
	2 years	815.4 ± 8.6	− 59.9, − 83.4 to − 36.4*	876.0 ± 14.7	− 16.2, − 55.6 to 23.2	− 60.6*	− 94.6 to − 26.5*
Total HDL	Baseline	22.9 ± 0.3		25.1 ± 0.5		− 2.2	− 3.4 to − 0.9
	1 year	22.8 ± 0.4	− 0.2, − 1.1 to 0.8	24.8 ± 0.5	− 0.3, − 1.7 to 1.1	− 2.0	− 3.3 to − 0.7
	2 years	22.8 ± 0.4	− 0.1, − 1.1 to 0.9	25.3 ± 0.5	0.2, − 1.2 to 1.6	− 2.5	− 3.8 to − 1.2
HDL 2b (μmol/L)	Baseline	6.0 ± 0.1		6.0 ± 0.1		0.0	− 0.3 to 0.2
	1 year	6.3 ± 0.1	0.4, 0.1 to 0.6[Ī]	6.0 ± 0.1	− 0.0, − 0.4 to 0.4	0.3	0.0 to 0.7
	2 years	6.3 ± 0.1	0.3, 0.1 to 0.5	6.1 ± 0.1	0.1, − 0.3 to 0.5	− 0.1	− 0.2 to 0.5
HDL 2a + 3 (μmol/L)	Baseline	17.3 ± 0.2		18.0 ± 0.3		− 0.7	− 1.3 to − 0.1
	1 year	16.8 ± 0.2	− 0.5, − 0.9 to − 0.0	17.5 ± 0.3	− 0.5, − 1.2 to 0.3	− 0.7	− 1.4 to − 0.0
	2 years	17.0 ± 0.2	− 0.3, − 0.8 to 0.1	17.8 ± 0.3	− 0.2, − 0.9 to 0.6	− 0.8	− 1.5 to − 0.2
LDL peak diameters (Å)	Baseline	215.2 ± 0.5		215.0 ± 0.8		0.2	− 1.7 to 2.1
	1 year	219.6 ± 0.5	4.4, 3.1 to 5.7*	215.1 ± 0.8	0.1, − 2.1 to 2.3	4.5*	2.6 to 6.5*
	2 years	219.5 ± 0.5	4.3, 3.0 to 5.6*	215.8 ± 0.8	0.8, − 1.4 to 3.0	3.7*	1.8 to 5.6*

Adjusted means and mean changes were obtained from an analysis using linear mixed-effects model (LMM) controlling for baseline age, sex, race, body mass index, HDL 2 + 3a, mid-zone, insulin use and statin use

SE standard error, *CI* 95% confidence interval, *LDL* low density lipoprotein, *HDL* high-density lipoprotein, *IDL* intermediate density lipoprotein, *VLDL* very low-density lipoprotein, *CIMT* carotid intima-media thickness

[a] Variables normalized by removing the top 1% of values. Analyses were conducted excluding the top 1% values, although all cases were included using the maximum likelihood approach

[b] Variables normalized by natural log transformation. Non-transformed and unadjusted means, mean changes, CI and standard errors were provided in the table, but the significance level is calculated from the transformed analysis

* $P < 0.0015$ ensures overall simultaneous significance of $P < 0.05$ over the 33 variables using Bonferroni correction

Ī $P < 0.005$

PC3 were HDL subclasses (HDL 2b and HDL 2a + 3), the mid-zone fraction and very small LDL IVc in the positive direction. From the 2-year data in the CCI group, four principal components were extracted explaining 82.7% of the overall variance. The major component explained 39.9% of the total variance and was consistent with PC2 of baseline data (Additional file 1: Table S5). The next two components were both consistent with PC1 of baseline data and were therefore designated PC1a and PC1b, accounting for 22.9% and 13.9% of the variance, respectively. Small and very small LDLs contributed to both PC1a and PC1b with a greater contribution from small LDLs (LDL IIIa and IIIb) in PC1a and very small LDLs (LDL IVa to LDL IVc) in PC1b. PC1a was also represented by all VLDLs (mainly medium and large) and TG in a positive and HDL-C in a negative direction. PC1b was strongly represented by the mid-zone fraction and was also moderately associated with TG, and medium and large VLDLs. The last extracted component explained 6.1% of the variance and corresponded closely to PC3 of the baseline data (Additional file 1: Table S5). PCA on both baseline and follow-up UC data consistently extracted three components which corresponded closely to the PCs extracted from the baseline CCI data, except that HDL-C was not loaded in PC3 in the 2-year follow-up data. The distribution of variance explained by each component was similar at baseline and 2 years.

The distribution of LDL peak diameter and its associated LDL subclass phenotypes among the CCI and UC participants at baseline, 1 and 2 years (Fig. 1) generally indicates a bimodal distribution consistent with the previous categorization of these phenotypes [24]. In the CCI group there was a shift in the proportion of LDL

phenotypes from B to A while no changes were seen in the UC group (Fig. 1; Additional file 1: Table S6).

Changes in lipoprotein subfractions and CIMT in LDL-C and ApoB hypo- and hyper-responders

CCI participants in the quartiles of greatest decrease and increase in LDL-C and in ApoB from baseline to 2 years were categorized into hypo- and hyper-responder groups. One-way MANOVA of the lipoprotein subclasses and LDL peak diameter in LDL-C hypo- versus hyper-responders revealed a significant difference in the overall lipoprotein profile (Pillai's Trace = 0.66; F = 5.09, $P = 6.0 \times 10^{-6}$). LDL-C hyper-responders had significantly greater VLDL medium, VLDL small, IDL I, IDL II, LDL I, IIa, and IIb compared to hypo-responders at 2 years (Additional file 1: Table S7). There were no significant differences in the lipoprotein profile between ApoB hypo- and hyper-responders (Pillai's Trace = 0.37; F = 1.75, $P = 0.37$) Additional file 1: Table S8). No differences in mean CIMT at 2 years between the LDL-C ($P = 0.49$) and ApoB ($P = 0.43$) hypo- versus hyper-responders were observed.

Relationships between BMI, CAF, and nutritional ketosis with lipids and lipoprotein subclasses and phenotypes

Univariate linear regression analyses revealed significant positive associations of 2 year change in BMI with TG, large VLDL, LDL IIIa, and LDL IIb, and inverse correlations with HDL-C, IDL II, and HDL2b. Changes in CAF were positively associated with TG, large VLDL, midzone, LDL IVa, LDL IIIa, LDL IIIb, and LDL IIb, and

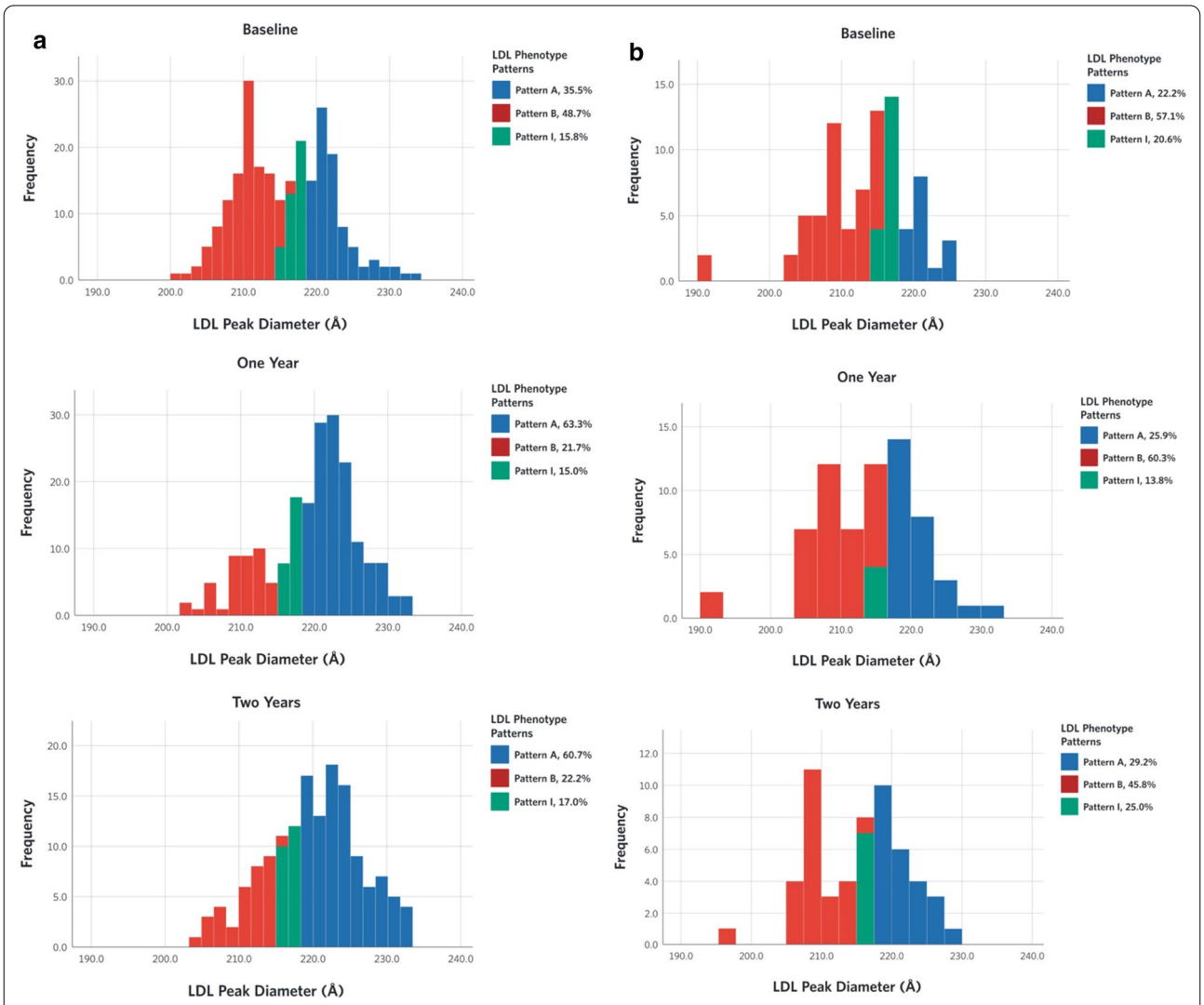

Fig. 1 Distribution of LDL phenotype pattern and LDL peak diameters (Å) at baseline, 1 and 2 years. **a** Continuous care intervention, **b** usual care

negatively associated with HDL-C, IDL II, LDL I and HDL2b (Additional file 1: Table S9). Including both BMI and CAF in the multiple linear regression model revealed that only change in BMI was positively associated with TG and LDL IIIa explaining 39.0% and 32.0% of variance, respectively, and change in CAF was inversely associated with HDL-C, IDL II, and HDL 2b, explaining 55.0%, 34.0% and 29.0% of the variance, respectively (Additional file 1: Table S9).

More frequent reporting of nutritional ketosis (BHB $\geq$ 0.5 mM) over 2 years was associated with greater increases in HDL-C, IDL II, and LDL I, and greater decreases in TG and the mid-zone particle fraction (Additional file 1: Table S10). Additionally, there was a significant association between more frequent reporting of nutritional ketosis with LDL phenotype B to A conversion (Additional file 1: Table S11).

Discussion

Here, we present analyses of changes in CVD risk markers in patients with type 2 diabetes following a 2-year intervention with a very low carbohydrate diet aimed at achieving nutritional ketosis. We demonstrated that, compared with usual care, the very low carbohydrate diet reduced levels of very small LDL IIIb and increased concentrations of large LDL and the closely related IDL-2 species [35], with no significant change in total LDL particles and ApoB, a measure of all atherogenic lipoproteins. The results demonstrate a sustained improvement of the atherogenic lipoprotein phenotype characteristic of type 2 diabetes that comprises elevated plasma triglyceride and small, dense LDL particles, and reduced HDL-cholesterol [11, 12]. Therapies targeting this dyslipidemia have been reported to mitigate CVD residual risk and decrease CVD events among patients with diabetes [13, 14, 36].

Notably, the significant increase in LDL-C in the CCI group was primarily attributed to an increase in larger cholesterol enriched LDL particles. This is consistent with the finding that, among LDL subfractions, only larger LDL I and medium-sized LDL II, but not smaller particles, were significantly greater at 2 years in those in the upper versus lower quartile of dietary LDL-C response. The increase in larger LDL is likely due, at least in part, to high saturated fat intake, which has been shown to preferentially increase levels of these particles, particularly in the context of reduced carbohydrate intake [15, 16, 37]. Since there is a growing consensus that concentrations of LDL particles and ApoB are superior to LDL-C as predictors of CVD, particularly when there is discordance between LDL-C and the particle measures [22, 38], the present findings, including a lack of increase in total LDL particles and ApoB, provide reassurance that the increase in LDL-C with the dietary intervention does not signify an increase in CVD risk. This inference aligns with the observation in the PURE study, where higher dietary saturated fat consumption was associated with higher LDL-C, but not with higher all-cause or CVD mortality [39]. Furthermore, this supposition is consistent with lack of progression of atherosclerosis in our study as assessed by CIMT. Given the stronger association of small versus large LDL particles with CVD risk [23–26], it remains possible that the reduction of very small LDL and other features of atherogenic dyslipidemia in the CCI group might lead to improvement in atherosclerosis measures with a longer-term intervention. A benefit of the dietary intervention on CVD risk might also be predicted by the observed reductions in remnant cholesterol [28], as well as the increases in HDL-C and the HDL protein ApoAI [40, 41], although recent studies have called into question whether reduced CVD risk can be reliably inferred by an increase in HDL-C [42, 43].

Given the evidence for multiple metabolic relationships among the various lipoprotein classes, we turned to PCA to determine whether the effect of the very low carbohydrate diet could be defined by one or more independent clusters of inter-related changes in lipoprotein subfractions. From the baseline data of both the CCI and UC groups, we identified three independent PCs, all corresponding to PCs previously identified in healthy individuals [26]. The major component in the present study (PC1) is consistent with PC2 in the earlier report, which in turn, closely reflects features of the atherogenic lipoprotein phenotype [26]. Notably, this PC has been associated with increased CVD risk [26] and with chronic kidney disease [44]. Moreover, it has been associated with a 22% increase in the odds of coronary artery calcification (CAC) in individuals with diabetes and metabolic syndrome [45] and with CAC in those with reduced kidney function [44]. With dietary intervention in the CCI group, we found that PC1 shifted from the largest variance contributor at baseline to a secondary variance component. Furthermore, it could then be separated into two sub-components (PC1a and PC1b). Interestingly, small LDL IIIa and IIIb were relatively more strongly loaded onto PC1a, along with triglycerides and medium and large VLDL (positively) and HDL-C (negatively). In contrast, very small LDL IVa to LDL IVb were more strongly loaded onto PC1b, along with moderate loading of triglycerides and medium and large VLDL. These distinctions suggest that the very low carbohydrate intervention may have exposed effects on two independent components of the atherogenic lipoprotein phenotype, involving small and very small LDL particles, respectively. The diet-induced shift in PC1 from the primary to the secondary contributor to the overall variance is consistent with

conversion from small LDL phenotype B to phenotype A in a high proportion of the CCI participants. This finding is in line with other studies reporting the reversal of phenotype B to A through down-titration of carbohydrate intake relative to fat intake in healthy individuals [16] and in those with metabolic syndrome treated with an isocaloric low carbohydrate, high fat diet [17].

PC2 in the present study is consistent with the main PC (PC1) previously identified in healthy individuals [26] and is represented by LDL-C as well as large and medium LDL, IDL and small VLDL. Consistent with the increase in LDL-C in the CCI group, we showed that the associated variance in PC2 shifted from a secondary to the major contributor at 2 years. While the implications of this shift for CVD remain uncertain, it is notable that this PC was not found to be associated with CVD risk in healthy individuals [26] or with CAC in those with diabetes or metabolic syndrome [45].

Finally, the minor PC3, which was associated with reduced CVD risk in healthy individuals [26] and represents a spectrum of particles ranging from small HDL2a + 3 and large HDL2b to the smallest LDL species (LDL IVc), was not affected significantly by the dietary intervention. However, there was a trend toward increased HDL2b, which might have contributed to the observed increase in HDL-C and ApoAI.

The ion mobility analysis also identified a novel particle fraction in the size range between LDL and HDL, designated mid-zone, which was significantly reduced in the CCI group. The loading of this fraction onto PC1b suggests that it may represent a feature of this component of the atherogenic lipoprotein phenotype. However, it was also represented in PC3, raising the possibility that it may be heterogeneous, representing contributions from both LDL and HDL, and perhaps other particles in this size range. Further studies will be required to characterize this fraction and determine its metabolic significance and possible relation to CVD risk.

The findings from this study raise the question as to the extent to which reduced body weight and central adiposity may have contributed to the lipoprotein changes induced by the very low carbohydrate diet [15, 46]. Although the study design makes it difficult to disentangle these influences, we found that weight loss, abdominal fat reduction, and ketosis were differentially associated with specific lipoprotein particle changes. Both reduction in BMI and more frequent ketosis were correlated with improvement in TG, and reduced BMI was associated with lower levels of small LDLs. On the other hand, ketosis was related to increased large LDL I and conversion of LDL phenotype B to A, and, along with reduced central adiposity, to increased IDL 2 (closely related to large LDL [35]) and HDL-C. We speculate that carbohydrate restriction in conjunction with weight loss either through additive or synergistic actions may reduce the availability of the hepatic triglyceride pool for production of VLDL precursors of small LDLs [15]. On the other hand, more frequent ketosis may reflect greater carbohydrate restriction and higher intake of fat, including saturated fat which, as noted above, preferentially increases level of larger LDL particles in conjunction with reduced carbohydrate intake [15, 16, 37]. One or both of these dietary effects may enhance the conversion of LDL phenotype B to A [16, 47]. Interestingly, a study performed in obese patients who underwent laparoscopic adjustable gastric banding failed to show significant changes in LDL levels and LDL subfractions despite a substantial weight loss of 13.4% at 13 months [48]. Together, these observations, along with earlier studies [15, 17] suggest that carbohydrate restriction and nutritional ketosis may contribute significantly to the observed lipoprotein changes independent of changes in adiposity.

A strength of this study is its 2-year duration, the longest to evaluate lipoprotein changes in response to a very low carbohydrate diet including nutritional ketosis. While free-living ad libitum food consumption among participants who self-selected their intervention enhances the generalizability of the study by mimicking patient choice in lifestyle intervention for diabetes treatment. Within the CCI group, long term tracking of blood BHB as a marker of carbohydrate restriction provided the opportunity to explore the relationship between frequency of reported nutritional ketosis status and shift from LDL subclass phenotype B to A.

A limitation of this study is the lack of randomization and lack of tight control over the food consumed by the CCI and UC groups. In addition, the fact that the study participants were mostly Caucasian limits the generalizability of the study to other races and ethnic groups. Finally, the lack of changes in CIMT in the two groups could be due to insufficient duration of the study or to variation in image acquisition and interpretation among the individuals performing this technique. Furthermore, the CIMT analysis did not include carotid plaque assessment.

Conclusion

In conclusion, these results demonstrate that in patients with type 2 diabetes, consumption of a very low carbohydrate diet with nutritional ketosis for 2 years was associated with sustained improvement in the atherogenic lipid and lipoprotein profile that is characteristic of this condition. This finding was reinforced by the use of an unbiased principal component analysis that identified this profile as one of three independent clusters of lipoprotein fractions, another of which accounted for the

diet-induced increase in LDL-C. While the implications of these effects for CVD outcomes will require future long-term studies, both the lack of increase in total LDL particle number and carotid intima-media thickness point to the cardiovascular safety of a very low carbohydrate diet in the context of a substantial benefit for management of type 2 diabetes [18].

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12933-020-01178-2.

Additional file 1: Figure S1. Change in lipids and lipoprotein subclasses in CCI at baseline, one and two years. **Table S1.** Baseline characteristics. **Table S2.** Adjusted means and changes in lipids, blood pressure and CIMT over time by treatment group among completers. **Table S3.** Lipid lowering and anti-hypertensive medication use over time among completers. **Table S4.** Adjusted means and changes in lipids, lipoproteins, apoproteins, blood pressure, and CIMT over time by treatment group (intent-to-treat analysis). **Table S5.** Principal Components and Respective Loading of Each Lipoprotein/Lipid from Baseline and Two-year Follow-up Data. **Table S6.** Estimated mean proportions and standard errors in the change of LDL phenotype patterns from baseline to two years. **Table S7.** Multivariate analysis of variance (MANOVA) of lipoprotein subclasses in LDL-C hypo- versus hyper-responders. **Table S8.** Multivariate analysis of variance (MANOVA) of lipoprotein subclasses in ApoB hypo- versus hyper-responders. **Table S9.** Relationships between change in BMI and central abdominal fat with lipids and lipoproteins. **Table S10.** Association between frequency of participants reporting BHB $\geq$ 0.5mM with change in lipids and lipoproteins from baseline to 2 years. **Table S11**. LDL phenotype conversions and their associations with frequency of participants reporting BHB $\geq$ 0.5mM from baseline to 2 years.

Abbreviations

CCI: Continuous care intervention; UC: Usual care; T2D: Type 2 diabetes; CVD: Cardiovascular disease; BMI: Body mass index; BHB: Beta-hydroxybutyrate; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; TG: Triglycerides; IDL: Intermediate density lipoprotein; VLDL: Very large density lipoprotein; ApoB: Apolipoprotein B; ApoA1: Apolipoprotein A1; ALP: Atherogenic lipoprotein phenotype; CR: Carbohydrate restriction; CAF: Central abdominal fat; IM: Ion mobility; CIMT: Carotid-artery intima-media thickness; DXA: Dual-energy X-ray absorptiometry; LMM: Linear mixed-effect model; PCA: Principal component analysis; PC: Principal component; MANOVA: Multivariate analysis of variance; ADA: American Diabetes Association.

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Authors' contributions

SJH is the principal investigator of the study. RMK and SJH conceived the idea of performing lipoprotein analyses. SJA, ALM, SMK and SJH participated in data acquisition and compiling. SJA analyzed the data. SJA, RMK, ALM and SJH drafted the manuscript. RMK, ALM, SJA, SJH, SDP, JSV, KL, and JPM edited the manuscript. All authors provided critical feedback. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All study participants were informed and consented to participate in the study, and the study was approved by the Franciscan Health Lafayette Institutional Review Board (Clinical trials.gov NCT02519309).

Consent for publication

Not applicable.

Competing interests

Employees, consultants, founders and advisors of Virta Health Corp participated in the study design, data collection, analysis and interpretation of the data.SJA, SJH, ALM, and SDP are employed by Virta Health Corp and were offered stock options. SDP and JSV are founders of Virta Health Corp. JPM is a shareholder and RMK is an advisor for Virta Health Corp. SMK and KL have no conflict of interests to declare.

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Publisher's Note

Original Paper

A Novel Intervention Including Individualized Nutritional Recommendations Reduces Hemoglobin A1c Level, Medication Use, and Weight in Type 2 Diabetes

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Abstract

Background: Type 2 diabetes (T2D) is typically managed with a reduced fat diet plus glucose-lowering medications, the latter often promoting weight gain.

Objective: We evaluated whether individuals with T2D could be taught by either on-site group or remote means to sustain adequate carbohydrate restriction to achieve nutritional ketosis as part of a comprehensive intervention, thereby improving glycemic control, decreasing medication use, and allowing clinically relevant weight loss.

Methods: This study was a nonrandomized, parallel arm, outpatient intervention. Adults with T2D (N=262; mean age 54, SD 8, years; mean body mass index 41, SD 8, $kg \cdot m^{-2}$; 66.8% (175/262) women) were enrolled in an outpatient protocol providing intensive nutrition and behavioral counseling, digital coaching and education platform, and physician-guided medication management. A total of 238 participants completed the first 10 weeks. Body weight, capillary blood glucose, and beta-hydroxybutyrate (BOHB) levels were recorded daily using a mobile interface. Hemoglobin A_{1c} (HbA_{1c}) and related biomarkers of T2D were evaluated at baseline and 10-week follow-up.

Results: Baseline HbA_{1c} level was 7.6% (SD 1.5%) and only 52/262 (19.8%) participants had an HbA_{1c} level of <6.5%. After 10 weeks, HbA_{1c} level was reduced by 1.0% (SD 1.1%; 95% CI 0.9% to 1.1%, P<.001), and the percentage of individuals with an HbA_{1c} level of <6.5% increased to 56.1% (147/262). The majority of participants (234/262, 89.3%) were taking at least one diabetes medication at baseline. By 10 weeks, 133/234 (56.8%) individuals had one or more diabetes medications reduced or eliminated. At follow-up, 47.7% of participants (125/262) achieved an HbA_{1c} level of <6.5% while taking metformin only (n=86) or no diabetes medications (n=39). Mean body mass reduction was 7.2% (SD 3.7%; 95% CI 5.8% to 7.7%, P<.001) from baseline (117, SD 26, kg). Mean BOHB over 10 weeks was 0.6 (SD 0.6) $mmol \cdot L^{-1}$ indicating consistent carbohydrate restriction. Post hoc comparison of the remote versus on-site means of education revealed no effect of delivery method on change in HbA_{1c} ($F_{1,260}$=1.503, P=.22).

Conclusions: These initial results indicate that an individualized program delivered and supported remotely that incorporates nutritional ketosis can be highly effective in improving glycemic control and weight loss in adults with T2D while significantly decreasing medication use.

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KEYWORDS

type 2 diabetes; ketosis; Hb A1c; weight loss; mobile health

Introduction

Type 2 diabetes is generally regarded as a chronic, progressive disease that can be slowed by the vigorous use of lifestyle changes and medications but eventually results in vascular damage and end-organ failure [1,2]. Current medical treatment interventions result in virtually no disease remission, as seen in a study within the Kaiser health care population where the spontaneous remission rate is 0.5% [3]. As the disease progresses, it has been shown that glucose-lowering medication use, health care costs, and complications all rise. At 9 years, less than 25% of patients are able to control their blood glucose level with only one medication [4], and 10-15 years after the diagnosis of type 2 diabetes, more than 50% of patients will require insulin [5].

Despite the overall paucity of type 2 diabetes remission data, there exist three notable treatment exceptions. Bariatric surgery, such as gastric bypass, is effective at reversing type 2 diabetes, with 40%-60% of surgical patients demonstrating remission 1 year after the surgery. The most comprehensive study of surgical intervention to prevent or reverse type 2 diabetes is the Swedish Obese Subjects Trial [6], demonstrating an 8-fold reduction in the incidence of the disease at 2 years. However, further out into the postoperative experience, many of these patients regain weight and relapse into diabetes, and they are at risk of developing nutritional deficiencies as well [7].

There have been many reports of short-term improvement in glycemic control with very low-calorie diets (VLCDs) consisting of either common foods or chemically defined formulas, ranging in energy from 400-800 kcal·day^{-1}. Bistrian et al [8] administered a common-food 600-800 kcal·day^{-1} VLCD to 7 insulin-using subjects with type 2 diabetes for inpatient and outpatient durations of 2-12 months. All 7 subjects achieved rapid improvement in glycemic control despite the cessation of insulin therapy, and 6 of 7 subjects experienced substantial weight loss. Bauman et al [9] hospitalized 64 patients with type 2 diabetes, including 42 patients taking insulin, and administered a VLCD for a mean of 23 days. After 19 months, 10 patients remained in remission. Wing et al [10] randomized 93 obese individuals with type 2 diabetes to either a low-calorie diet or an intermittent formula VLCD for 1 year. The VLCD group achieved greater initial weight loss and greater hemoglobin A_{1c} (HbA_{1c}) reductions, but these differences between the 2 diet arms were not sustained over the duration of the study. In a recent study by Steven et al [11], 13 of 30 individuals with type 2 diabetes but not using insulin achieved normal blood glucose values after 8 months of lifestyle intervention. In this case, a chemically defined, liquid, low-carbohydrate VLCD was prescribed for 8 weeks, followed by 6 months of an unspecified energy maintenance diet.

These 4 studies [8-11] used VLCDs to control blood glucose level while stopping or reducing diabetes medications. The limitation of using a VLCD to manage a chronic disease is that this type of diet is necessarily temporary, given that it provides less than 800 kcal·day^{-1} and thus is unsustainable in the long term.

Alternatively, nutritional ketosis, defined as a dietary regimen resulting in serum beta-hydroxybutyrate (BOHB) levels between 0.5 and 3.0 mmol·L^{-1} [12], may yield similar or better results over longer periods of time by not explicitly prescribing caloric restriction. Nutritional ketosis is often achieved by reduced carbohydrate, moderate protein, and increased fat intake. In this setting, moderately reduced energy intake may occur in association with the proportionately high fat intake, reduced circulating insulin due to reduced carbohydrate consumption, and potential metabolic benefits of mild ketonemia. For example, Boden et al [13] reported that in patients with type 2 diabetes fed a ketogenic diet to satiety improved insulin sensitivity by 75% within 2 weeks. When given free access to a ketogenic buffet, daily energy intake dropped by about one-third, resulting in a total weight loss of 2 kg over 2 weeks. The authors concluded that this modest weight loss in and of itself could not explain the improved insulin sensitivity.

There have been a number of studies using low-carbohydrate, high-fat dietary strategies in the management of type 2 diabetes [14-20], but these group sizes have been small and often excluded subjects taking insulin. In addition, the dietary interventions used in these studies frequently were not sufficiently low in carbohydrate or protein to induce sustained nutritional ketosis. However, multiple studies of ketogenic diets prescribed without energy restriction have demonstrated both tolerability and effectiveness of this dietary approach to improve a broad range of cardiometabolic markers in prediabetic and dyslipidemic outpatients [21-23]. And finally, recent studies have identified BOHB in the nutritional ketosis range as a potent epigenetic signal that decreases oxidative stress [24], hepatic glucose output [25], and insulin resistance [26].

We therefore hypothesized that a comprehensive program with individualized nutritional recommendations that supports participants in achieving sustained nutritional ketosis while eating to satiety may have unique benefits in the management of type 2 diabetes. Specifically, this study was designed to assess the practical utility of an intensive digital intervention supported by medical management, continuous digital health coaching, nutrition education, behavioral support, biometric feedback, and peer support via an online community. We refer to this technology-enabled medical service as the Virta Clinic.

Methods

Subjects

Adults with type 2 diabetes between the ages of 21 and 65 years were recruited via clinical referrals, media advertising, and word of mouth in the greater Lafayette, Indiana, region. Exclusion criteria included advanced renal, cardiac, and hepatic dysfunction, history of ketoacidosis, dietary fat intolerance, or pregnancy or planned pregnancy.

The Virta Clinic

Virta utilizes a technology-enabled, full-service clinic model for metabolic recovery from type 2 diabetes including medical management by physicians, health coaching, nutrition and behavior change education, biometric feedback, and peer support. Physicians and health coaches were trained in the basic principles of achieving and maintaining nutritional ketosis based on previous published works [21,22,27]. In this study, educational content was delivered via either on-site weekly 90-minute group-based classes or Web-based recorded educational content, and participants self-selected their preferred mode of content delivery. The same educational content was provided by each delivery method. Educational content included discussion of the pathophysiology of diabetes, practical management of carbohydrate restriction while consuming protein in moderation and increasing fat intake, the utilization of ketones as a biofeedback mechanism, and appropriate utilization of behavior change techniques. No modifications to participants' physical activity were encouraged in the first 10 weeks of the intervention.

Remote support was provided to each subject through tracking of daily biometrics, the assignment of a personal health coach available daily via one-on-one texting for advice and problem solving, support via an online community of his or her peers, and physician supervision. Subjects were instructed to monitor and report glucose level via the Web to the care team 1-3 times per day, and a physician made medication changes as appropriate. Additionally, the medication status of each participant was reviewed by the care team and the principal investigator weekly.

Nutritional Ketosis

The Virta Clinic includes individualized nutritional recommendations to sustain nutritional ketosis by titrating carbohydrate and protein intake to the patient's individual tolerance [27]. With the insulin resistance characteristic of type 2 diabetes, subjects typically require total dietary carbohydrates to be restricted to <30 g·day^{-1}. Daily protein intake was targeted to a level of 1.5 g·kg^{-1} of reference (ie, medium-frame "ideal") body weight and participants were coached to incorporate dietary fats to satiety. Other aspects of the diet were individually prescribed to ensure safety, effectiveness, and satisfaction, including consumption of 3-5 servings of nonstarchy vegetables and adequate mineral and fluid intake for the ketogenic state. BOHB was monitored routinely via finger-stick blood monitoring using a handheld device (Abbott Precision Xtra Blood Glucose and Ketone Monitoring System, Alameda, CA, USA) and participants were encouraged to obtain BOHB readings ≥0.5 mmol·L^{-1}.

Outcome Measures and Testing Procedures

Type 2 diabetes status was determined by HbA_{1c} level at baseline and again at 10-11 weeks into the program. A value of 6.5% or greater, or HbA_{1c} level <6.5% but taking at least one hypoglycemic medication, was considered indicative of type 2 diabetes. Secondary outcome measures included assessment of (1) body weight determined daily on a cellular-connected scale (BodyTrace BT003 cellular-connected scale, New York, New York, USA); (2) medication use for control of diabetes; and (3) blood pressure obtained in the seated position. Fasting blood was analyzed for total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, C-reactive protein, total white blood cell count, and kidney and liver functions. All laboratory test results were analyzed by standard procedures. Hunger was assessed using a 4-point Likert scale from 1 (no) to 4 (always), representing the participant's subjective level of hunger over the previous 24-hours.

Statistical Analysis

Descriptive statistics were calculated for each variable as mean (SD). Baseline and 10- to 11-week follow-up measures were compared with paired-sample *t* tests to evaluate for significant differences in primary (HbA_{1c} level) and secondary outcome variables over time, following implementation of carbohydrate restriction per the Virta Clinic. Statistical significance was set a priori at $P<.05$; for secondary outcome variables, we applied a Bonferroni adjustment for multiple comparisons, setting $P<.003$ as the level of significance for those outcome measures. McNemar test with continuity correction and Bonferroni adjustment for multiple comparisons was utilized to assess for a difference in the proportion of participants who were prescribed each of the 7 medication classes at baseline compared with follow-up, setting $P<.007$ as the level of significance. We utilized an intention-to-treat analysis with the last observation carried forward for analyses of all participants; separate subanalyses were performed for participants who completed follow-up testing (completers). Given that 2 different modes were utilized for delivery of educational content, we performed a post hoc analysis on the primary outcome measure to determine if differences existed between groups.

Institutional Review Board Approval

The protocol was reviewed and approved by the Institutional Review Board at Franciscan Health Lafayette East, Lafayette, Indiana. Subjects were informed of the purpose and possible risks of the investigation before signing an informed consent document approved by the institutional review board.

Results

Characteristics of Subjects

A total of 262 subjects with diagnosis of type 2 diabetes were enrolled in this study. The mean age was 54 (SD 8) years and 66.8% (175/262) were female. Additional baseline data are provided in Table 1.

Table 1. Participant characteristics at baseline and follow-up.

Characteristics	n[a]	Baseline	Follow-up	Mean difference		t_{n-1}	P[b]
		Mean (SD)	Mean (SD)	Mean (SD)	95% CI		
Hemoglobin A_{1c} (%)							
All	262	7.6 (1.5)	6.6 (1.1)	−1.0 (1.1)	−1.1 to −0.9	14.9	<.001
Completers	238	7.6 (1.5)	6.5 (1.0)	−1.1 (1.1)	−1.2 to −1.0	15.6	<.001
Fasting glucose ($mg \cdot dL^{-1}$)							
All	259	162 (61)	131 (37)	−30 (56)	−37 to −25	8.68	<.001
Completers	236	163 (62)	129 (34)	−33 (58)	−41 to −26	8.8	<.001
Body mass index ($kg \cdot m^{-2}$)							
All	262	40.8 (8.9)	37.9 (8.5)	−2.9 (1.2)	−3.1 to −2.7	30	<.001
Completers	238	40.7 (8.5)	37.7 (8.0)	−3.1 (1.5)	−3.3 to −2.9	31.3	<.001
Weight (kg)							
All	262	117 (26.3)	109 (24.9)	−8 (4.6)	−9 to −8	29.1	<.001
Completers	238	117 (25.7)	109 (24.3)	−9 (4.5)	−9 to −8	30.7	<.001
Systolic blood pressure (mm Hg)							
All	260	132 (16)	126 (15)	−6 (19)	−8 to −4	5.29	<.001
Completers	236	132 (17)	125 (15)	−7 (20)	−9 to −4	5.32	<.001
Diastolic blood pressure (mm Hg)							
All	260	82 (10)	78 (10)	−4 (12)	−5 to −2	5.22	<.001
Completers	236	82 (10)	78 (9)	−4 (12)	−6 to −3	5.25	<.001
Total cholesterol ($mg \cdot dL^{-1}$)							
All	262	177 (41)	172 (41)	−5 (31)	−9 to −1	2.64	.009
Completers	238	177 (41)	172 (41)	−6 (33)	−10 to −1	2.64	.009
LDL-C[c] (calculated; $mg \cdot dL^{-1}$)							
All	245	97 (33)	99 (36)	2 (25)	−2 to 5	0.987	.32
Completers	223	98 (34)	99 (37)	2 (27)	−2 to 5	0.987	.32
HDL-C[d] ($mg \cdot dL^{-1}$)							
All	262	44 (13)	44 (13)	0.5 (8)	−0.5 to 1	0.966	.33
Completers	238	44 (14)	45 (13)	0.5 (8)	−0.5 to 1.5	0.966	.33
Triglycerides ($mg \cdot dL^{-1}$)							
All	262	185 (127)	147 (87)	−37 (107)	−50 to −24	5.61	<.001
Completers	238	185 (129)	145 (84)	−41 (112)	−55 to −27	5.64	<.001
Serum creatinine ($mg \cdot dL^{-1}$)							
All	259	0.88 (0.24)	0.85 (0.22)	−0.03 (0.12)	−0.04 to −0.01	3.61	<.001
Completers	236	0.88 (0.24)	0.85 (0.22)	−0.03 (0.13)	−0.05 to −0.01	3.61	<.001
ALT[e] ($units \cdot L^{-1}$)							
All	259	31 (23)	26 (16)	−4 (19)	−7 to −2	3.82	<.001
Completers	236	31 (24)	26 (16)	−5 (20)	−7 to −2	3.83	<.001
AST[f] ($units \cdot L^{-1}$)							
All	259	24 (15)	21 (9)	−3 (13)	−4 to −1	3.31	<.001
Completers	236	24 (16)	21 (9)	−3 (14)	−5 to −1	3.31	<.001

Characteristics	n[a]	Baseline	Follow-up	Mean difference		t_{n-1}	P[b]
		Mean (SD)	Mean (SD)	Mean (SD)	95% CI		
Alkaline phosphatase (units·L^{-1})							
All	259	74 (22)	68 (20)	−6 (11)	−8 to −5	9.78	<.001
Completers	236	75 (22)	67 (20)	−8 (11)	−9 to −6	9.96	<.001
C-reactive protein (mg·L^{-1})							
All	247	8.1 (8.2)	9.2 (11.5)	1.2 (7.5)	−0.2 to 2.1	2.45	.01
Completers	225	8.2 (8.1)	9.6 (12.1)	1.4 (8.1)	−0.3 to 2.1	2.6	.01
Total WBC[g] (x10^{9} ·L^{-1})							
All	236	7.2 (1.9)	6.7 (1.9)	−0.5 (1.3)	−0.6 to −0.3	5.37	<.001
Completers	234	7.2 (1.8)	6.7 (1.9)	−0.5 (1.3)	−0.6 to −0.3	5.36	<.001

[a]Reductions in the number of participants (n) are due to missed laboratory orders, except in the case of LDL-C, where LDL-C was incalculable.

[b]We set P<.003 as the level of significance for multiple comparisons.

[c]LDL-C: low-density lipoprotein cholesterol.

[d]HDL-C: high-density lipoprotein cholesterol.

[e]ALT: alanine aminotransferase.

[f]AST: aspartate aminotransferase.

[g]WBC: white blood cell.

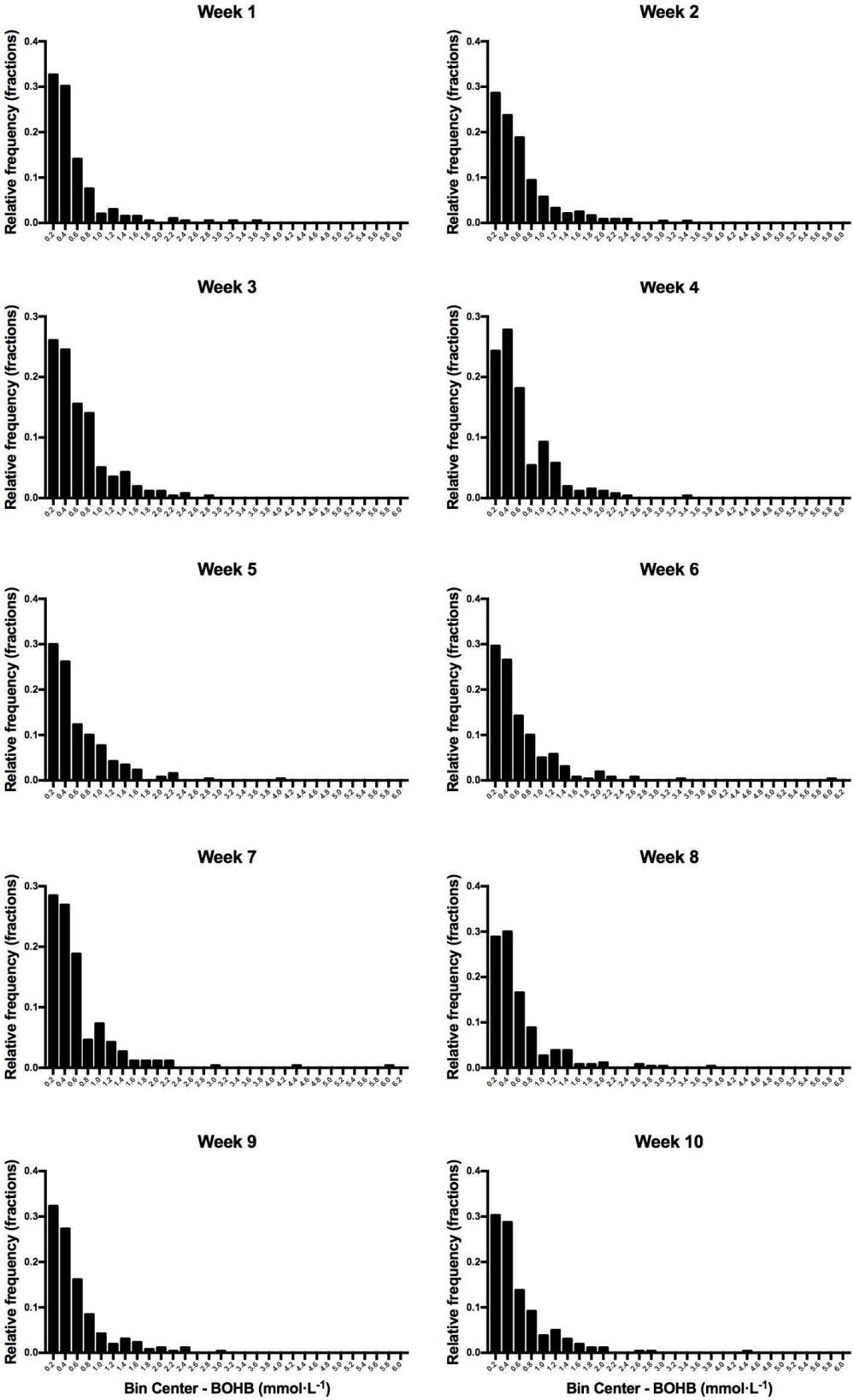
Retention

At 11 weeks, 21 of the 262 subjects had dropped out and 3 had not obtained the follow-up laboratory test results, yielding 238 or 90.8% retention for this phase of the study. Among the noncompleters, the most common reasons to leave the study were as follows: removed for noncompliance (n=6), unrelated health issue took priority (n=3), family illness or other issues (n=3), cost of medical appointments (n=2), and undisclosed personal choice (n=2). The age and sex distributions did not differ between noncompleters and completers.

Program Adherence

Daily BOHB level averaged over 10 weeks of the program was 0.6 (SD 0.6) mmol·L^{-1} (see Figure 1). This range is indicative of a modest state of nutritional ketosis in most of the subjects, with highest value similar to levels observed during fasting. There were no cases of diabetic ketoacidosis (ie, hyperglycemia concurrent with serum BOHB level >6 mmol·L^{-1}).

Figure 1. Relative frequency distribution of participant weekly average beta-hydroxybutyrate (BOHB) concentrations. An observed weekly average BOHB concentration on the border of 2 bins is placed in the bin holding the larger values. Evidence of carbohydrate restriction exhibited by elevated ketones was present in the first week in the majority of subjects and maintained for the duration of the study. All reported BOHB concentrations greater than 3.0 were in participants taking a sodium-glucose cotransporter-2 inhibitor, except for one (4.4 mmol•L−1) in which we suspect elevated BOHB due to increased exercise and another (6.0 mmol•L−1) in which we suspect participant data entry error. Excluding this 1 value, average BOHB concentrations for this participant ranged from 0.4 to 1.4 mmol•L^{-1}.

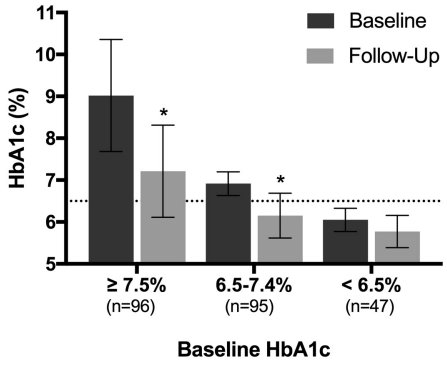


Hemoglobin A1c

Baseline HbA_{1c} level was 7.6% (SD 1.5%) and 210/262 (80.2%) participants had an HbA_{1c} level of ≥6.5%. After 10 weeks, HbA_{1c} level was reduced by 1.0% (SD 1.1%; 95% CI 0.9% to 1.1%, *P*<.001), and 56.1% (147/262) achieved an HbA_{1c} level of <6.5%. HbA_{1c} level for the 238 completers was similarly reduced from 7.6% (SD 1.5%) at baseline to 6.5% (SD 1.0%; 95% CI of mean difference −1.2% to −1.0%, *P*<.001) at 10-11 weeks into the Virta Clinic program. The varying responses of HbA_{1c} based upon starting level are shown in Figure 2. Of the 147 participants who achieved an HbA_{1c} level of less than 6.5%, 143 (97.3%) reached this goal without an increase in the number or dosage of diabetes medications. At follow-up, 47.7% of participants (125/262) achieved an HbA_{1c} level of less than 6.5% while taking metformin only (n=86) or no diabetes medications (n=39).

Post hoc analysis of method of educational content delivery revealed there was no significant interaction between delivery method and time for HbA_{1c} ($F_{1,260}$=0.18, *P*=.67), nor was there an effect of delivery method ($F_{1,260}$=1.503, *P*=.22). Baseline HbA_{1c} level was similar (on-site: mean 7.7%, SD 1.6%, digital: mean 7.5%, SD 1.4%; mean difference = 0.2%, 95% CI of mean difference: −0.2% to 0.5%; t_{520}=0.94, *P*=.69), and HbA_{1c} reductions of 1.0% (SD 1.1%) and 1.0% (SD 1.0%) for the on-site and digital content delivery methods, respectively, were achieved with no difference between delivery methods at follow-up (mean difference = 0.2%, 95% CI of mean difference: −0.2% to 0.6%; t_{520}=1.29, *P*=.39).

Figure 2. Hemoglobin A1c (HbA1c) changes by baseline level. Error bars represent SD; the dotted line represents the threshold for diagnosis of type 2 diabetes. Significant reductions in HbA1c level from baseline to follow-up were observed in subjects whose baseline HbA1c level was ≥7.5% (mean 9.0%, SD 1.3% to 7.2%, SD 1.1%, *P*<.001) and between 6.5% and 7.4% (mean 6.9%, SD 0.3% to 6.2%, SD 0.5%, *P*<.001). For those whose baseline HbA1c level was <6.5%, HbA1c level was improved but not significantly after correcting for multiple comparisons (mean 6.1%, SD 0.3% to 5.8%, SD 0.4%, *P*=.03). *Represents significant difference from baseline.



Hypoglycemic Medications

The majority of participants (234/262, 89.3%) were taking at least one diabetes medication at baseline. Both the number and dosage of most diabetes medications were reduced substantially in the first 10-11 weeks of the Virta Clinic program (Table 2, Figure 3). As shown in Table 2, of the initial 262 subjects, 112 (42.7%) experienced a decrease in their medications with another 21 (8.0%) having their medications eliminated. Only 13 (5.0%) of the 262 subjects were prescribed a new class or increased dose of medication. Of the 262 participants, 88 (33.6%) had no change in their medications and 28 (10.7%) were taking no hypoglycemic medications at entry into the study or at follow-up.

Table 2. Change in prescription of medication class or dose between baseline and follow-up.

Change in medication prescription or dose between baseline and follow-up	n	HbA_{1c}[a] <6.5% at follow-up, n (%)	Baseline HbA_{1c} (%), mean (SD)	Follow-up HbA_{1c} (%), mean (SD)
Increase	13	4 (31)	8.5 (2.0)	7.4 (1.4)
No change	88	57 (65)	7.2 (1.2)	6.5 (1.0)
Decrease	112	47 (42)	8 (1.6)	6.8 (1.1)
Complete elimination of medications	21	17 (81)	6.7 (0.9)	6.1 (0.5)
No medications prescribed	28	22 (79)	7.3 (1.3)	6.3 (1.1)

[a]HbA_{1c}: hemoglobin A_{1c}.

Figure 3 shows the changes in the 7 common classes of hypoglycemic medication prescribed to the subjects in this study. For sulfonylureas, sodium-glucose cotransporter-2 inhibitors, and thiazolidinediones, the vast majority of subjects discontinued these medications (90.3%, 86.2%, and 75.0%, respectively). To a lesser degree, this was also the case for dipeptidyl peptidase-4 inhibitors (56.7%), insulin (35.9%), and glucagon-like peptide-1 receptor agonists (27.9%). The exception to this trend was metformin. The proportion of participants who were prescribed insulin, sulfonylureas, and sodium-glucose cotransporter-2 inhibitors was significantly different at follow-up compared with baseline (all *P*<.007, see Figure 3). Given the reduced risk for hypoglycemia with the glucagon-like peptide-1 receptor agonists relative to insulin and sulfonylureas, the former was added in some cases in order to withdraw the latter two. In the case of metformin, given its modest but significant efficacy in the prevention of diabetes, its continued use in this cohort was encouraged (ie, 186 users at baseline and 181 at follow-up).

Figure 4 shows changes in HbA_{1c} level over 10-11 weeks in subjects whose insulin dosage was increased, unchanged, reduced, or eliminated. Only 5% (4 of 78 initial users) had their dosage increased in order to manage their initial HbA_{1c} value of 8.3% (SD 0.4%). For the other 74 subjects who entered the study while taking insulin, the HbA_{1c} values declined significantly despite the same, reduced, or eliminated insulin dosages.

Figure 3. Frequency of medication dose changes by drug class. Bars represent total users of each drug with the type of dose change (increase, no change, decrease, or elimination) stacked within the bar and the relative frequency noted next to each section. The total number of users is noted at the top of each bar. The proportion of participants who were prescribed the drug was significantly different between baseline and follow-up for insulin ($\chi2_1$=21.4, *P*<.001), sulfonylureas ($\chi2_1$=54.0, *P*<.001), and sodium-glucose cotranporter-2 (SGLT-2) inhibitors ($\chi2_1$=17.9, *P*<.001) but not for dipeptidyl peptidase-4 (DPP-4) inhibitors ($\chi2_1$=6.9, *P*=.009), thiazolidinediones ($\chi2_1$=1.3, *P*=.25), glucagon-like peptide-1 (GLP-1) receptor agonists ($\chi2_1$=0.5, *P*=.50), or metformin ($\chi2_1$=0.8, *P*=.36).

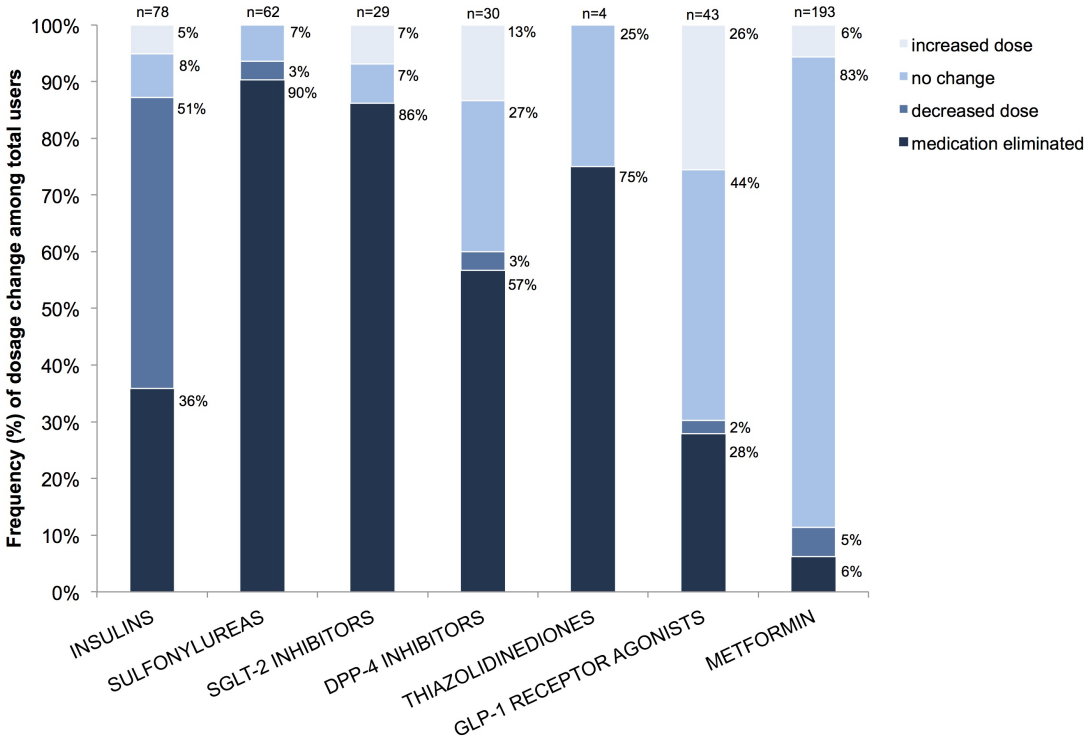
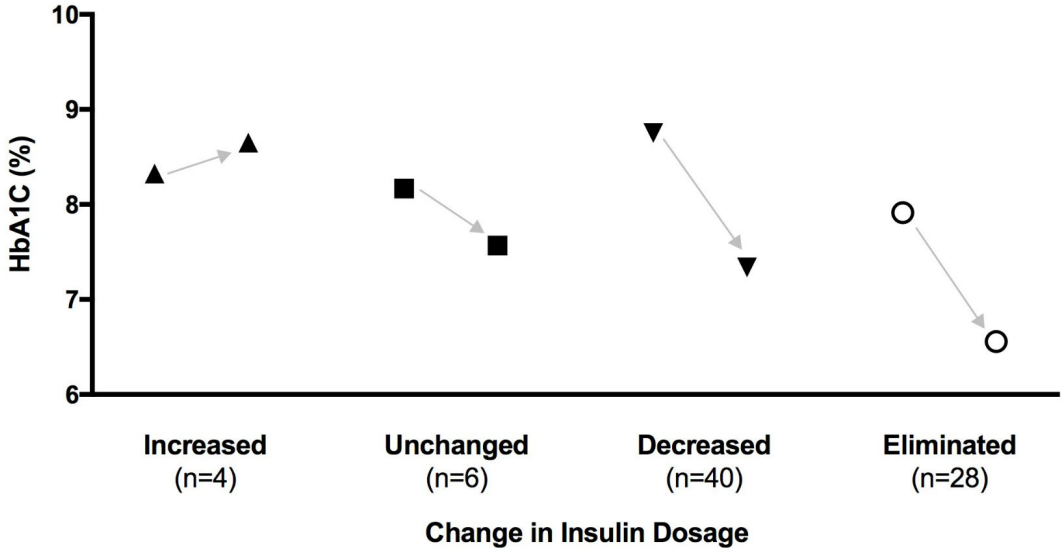


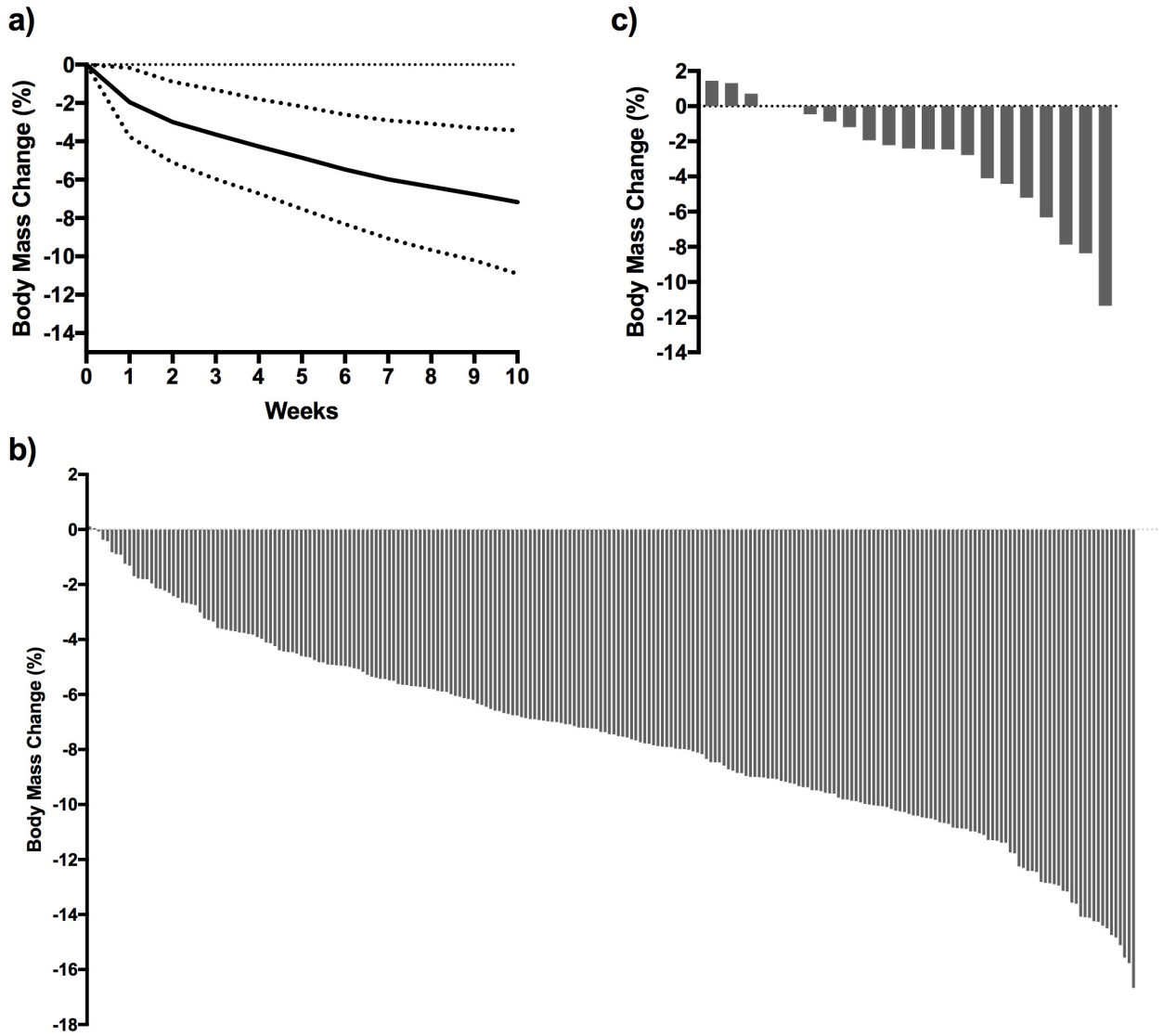
Figure 4. Hemoglobin A1c (HbA1c) level at baseline and 10-11 weeks per change in insulin dosage. Insulin users who were able to eliminate or reduce their use of the drug also significantly reduced their HbA1c level (7.9%, SD 1.5%, to 6.6%, SD 0.9%, P<.001 and 8.8%, SD 1.8%, to 7.4%, SD 1.2%, P<.001, respectively). Six users with no change in insulin dose achieved a reduction in HbA1c level, although it was not statistically significant (8.2%, SD 1.8%, to 7.6%, SD 1.2%, P=.25). Despite an increased insulin dosage in 4 users, HbA1c level increased but the difference was not significant (8.3%, SD 0.4%, to 8.7%, SD 0.8%, P=.61).



Body Weight

Weight and body mass index (BMI) changes from baseline to 10 weeks are presented in Table 1, and the mean weight change (as percentage of starting weight) over time is shown in Figure 5 (part “a”). Figure 5 (parts “b” and “c”) also shows individual subjects’ weight change over 10 weeks for completers and at the time of dropout for noncompleters. Mean weight loss at 10 weeks for completers was 7.2% (SD 3.7%) of initial body weight. Only 5 out of 262 subjects (2 completers, 3 noncompleters) registered a weight gain, and 75% of completers lost 5% or more of their initial body weight in this time period.

Figure 5. Participant weight loss over 10 weeks. Part “a”—weight change over 10 weeks for all participants. Solid line represents the mean; dotted lines represent one standard deviation from the mean. Part “b”—individual body weight changes as percentage of starting body weight at 10 weeks for completers (n=238). Part “c”—individual body weight changes as percentage of starting body weight for each noncompleter at the time of removal from study. For the 21 dropouts, time to drop out was 6 (SD 3) weeks (n=3 participants are still enrolled in the study but did not complete 10-week follow-up testing).



Laboratory Test Results and Measures

Consistent with the HbA_{1c} changes, the fasting glucose level (Table 1) declined markedly despite reduced hypoglycemic medication usage. There were no significant changes in total, low-density lipoprotein, or high-density lipoprotein cholesterol levels, nor were any changes made to statin prescriptions during this time. Triglycerides were significantly reduced by 20%. There were modest but significant reductions in both systolic and diastolic blood pressure. Although not elevated at baseline, the mean serum creatinine, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase levels were all significantly reduced at 10-11 weeks. Biomarkers of inflammation were mixed. While C-reactive protein was unchanged, total white blood cell count decreased significantly after 10 weeks of the ketogenic diet.

Baseline hunger on a scale from 1 (no) to 4 (always) was 1.6 (SD 0.6). At 10 weeks, subjective hunger was 1.3 (SD 0.4; 95% CI of mean difference: −0.4 to −0.2, t_{134}=5.58, P<.001). Furthermore, 46/135 (34.1%) subjects at baseline reported no hunger, increasing to 78/135 (57.8%) at 10 weeks.

Side Effects

One subject withdrew from the study in the first 70 days because of a dietary side effect (diarrhea due to fat intolerance). There were no serious adverse events in this time period and, specifically, no serious symptomatic hypoglycemic events requiring medical intervention.

Discussion

Although the American Diabetes Association has recently relaxed its advocacy for severe dietary fat restriction, the current paradigm for the management of type 2 diabetes is to prescribe a diet containing about 40% of energy from carbohydrates (eg, a Mediterranean diet) and then adjust medications as necessary to maintain glycemic control [28]. The Virta Clinic manages

type 2 diabetes from the perspective that it is a disease of carbohydrate intolerance. Given that this investigation is a nonrandomized demonstration study without measurement against standard of care, no statistical comparisons are made. However, these data demonstrate that when participants were supported through a novel, individualized program including instruction for limiting dietary carbohydrates to <30 $g \cdot day^{-1}$, medications could be substantially reduced or eliminated in most subjects, overall glycemic control was improved, and clinically relevant weight loss (5% or greater) was achieved in a majority of participants.

Other group-based and digitally delivered programs have demonstrated improvements in HbA_{1c} level with modest or no reduction in weight and often without a reduction in medication. A recent in-person group-based intervention for weight loss in adults with type 2 diabetes reduced HbA_{1c} level by 0.7% and weight by 3.3% after 12-13 weeks [29], while our investigation reduced HbA_{1c} level by 1.0% and weight by 7.2% in 10-11 weeks. Digitally delivered programs have elicited a range of improvements in HbA_{1c} (from none to significant) [30]; however, these results were often achieved by increased medication use due to improved adherence and without a reduction in weight [31]. This study demonstrated that these results (reduced HbA_{1c} level, weight, and medication use) can be achieved concurrently. Specifically, 147 (56.1%) of the initial 262 subjects in this initial study of the Virta Clinic registered HbA_{1c} values <6.5% at 10- to 11-week follow-up. Of these, 39 participants were able to achieve these results without taking any diabetes medication and 86 participants were able to achieve these results taking only metformin. Considering the equilibration time for HbA_{1c} is approximately 120 days, the significant decrease after 70-77 days reported here is a conservative estimate of the true improvement in glucose metabolism.

Achieving an HbA_{1c} value under 6.5% is considered "tight control" for type 2 diabetes. There are two commonly reported side effects of tight control—weight gain [32,33] and symptomatic hypoglycemia [28,33,34]. Paradoxically, in this study, we observed very consistent weight loss while observing no severe symptomatic hypoglycemic events. In addition to the very close mobile communication between the participant, coach, and physician in the Virta Clinic, this absence of severe hypoglycemic episodes despite very tight glucose control may be due to the protection of central nervous system function by circulating levels of BOHB. Two studies of starvation-adapted humans have demonstrated full preservation of central nervous system function despite profound hypoglycemia induced by exogenous insulin administration [35,36].

As it pertains to weight loss, it is all the more interesting that the Virta Clinic instructs its participants to strictly limit carbohydrates and eat protein in moderation but to eat fat to satiety. In daily Web-based questionnaires, patients reported reduced hunger once adapted to the ketogenic diet. This subjective decrease in hunger, albeit modest in magnitude, may have allowed the majority of subjects to experience significant weight loss. This concurrent combination of weight loss and reduced hunger is particularly interesting given that significant weight loss by caloric restriction typically increases hunger [37]. However, in light of the recent reports of epigenetic effects of BOHB reducing oxidative stress [24,38] and improving insulin sensitivity [26], it is possible that these paradoxical results can be ascribed to a combination of the metabolic and epigenetic effects of mild nutritional ketosis.

Although we have not calculated the economic implications of improved glycemic control with reduced medications, the removal of diabetes medications combined with clinically significant weight loss [39] has been shown to generate health care cost savings. The timing of these cost savings is immediate in the case of the medication reductions and could accrue over time because of the effect of lowering BMI. As for the HbA_{1c} reduction observed in this study, when changes of this magnitude are attained with intensive medication use, this tends to increase both drug costs and adverse events [40]. However, given that a 0.5% reduction in HbA_{1c} level was associated with a 17% reduction in diabetic vascular complications following aggressive medication management [2], our 1.0% HbA_{1c} level reduction with less medication has the potential to yield even greater savings in the cost of complications over time.

In conclusion, we demonstrated for the first time that biomarkers of type 2 diabetes can be reversed in a substantial fraction of participants using a comprehensive digitally delivered intervention, including medical management by physicians, health coaching, nutrition education emphasizing individualized carbohydrate intake to induce nutritional ketosis, behavioral support, biometric feedback, and peer support. In contrast to current intensive pharmaceutical management strategies, the positive results were achieved with less use of medication and substantial weight loss. The brief duration of this initial study cannot predict the long-term outcomes or sustainability of the nutrition recommendations used by the Virta Clinic. Early results demonstrate markedly improved glycemic control with less medication and modest changes in blood pressure, total white blood cell count, and liver and kidney functions. Ongoing work will evaluate the efficacy and sustainability of this intervention over 2 years.

Acknowledgments

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Conflicts of Interest

Virta Health Corp. funded this study, and all authors have a financial relationship with the study sponsor. ALM, SJH, BCC, BMV, TML, MKA, RMG, JPM, and SJP are employed by Virta. JSV serves as a consultant to Virta. JSV and SDP are cofounders of Virta. All authors have stock options in Virta. The organization contributed to study design, the collection, analysis, and interpretation of data, and approval of the final manuscript. Potentially related conflicts of interest are as follows: SDP serves as a consultant to Atkins Nutritionals and has received royalties as an author of two science-based low-carbohydrate books published by Beyond Obesity LLC. JSV serves as a consultant to Atkins Nutritionals, Metagenics, and UCAN, has received grants from the National Dairy Council and Malaysian Palm Oil Board, and has received royalties as an author of two science-based low-carbohydrate books published by Beyond Obesity LLC. SJH serves as a consultant to Atkins Nutritionals.

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Abbreviations

BMI: body mass index
BOHB: beta-hydroxybutyrate
HbA1c: hemoglobin A1c
VLCD: very low-calorie diet

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OR: NUTRITION—CLINICAL | JUNE 01 2022

29-OR: Impact of Carbohydrate-Restricted Nutrition Therapy Delivered via Continuous Remote Care on Metabolic Markers in Veterans with Type 2 Diabetes: A Nationwide, Real-World Study

FREE

MICHELLE VANTIEGHEM; AMY L. MCKENZIE; ROBERT E. RATNER

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Type 2 Diabetes (T2D) affects one in four Veterans and often occurs with dyslipidemia, chronic kidney disease, and nonalcoholic fatty liver disease (NAFLD) . In a pilot program, the Veterans Health Administration partnered with Virta Health to provide carbohydrate restricted nutrition therapy via continuous remote care to Veterans to reverse T2D by reducing glucose and dependence on medication, as demonstrated in prior research. This retrospective analysis assessed the 1- and 2-year effects on lipids and renal and hepatic markers in a real-world sample of Veterans with T2D using medical record data. Changes in metabolic markers from enrollment to 1- and 2- years (E, 1y, 2y) were assessed with paired t-tests with Holm-Bonferroni correction for multiple comparisons. Veterans retained at least two years at time of analysis were included (n=254, 58.5% of 434 eligible enrolled, 60±8 years, 12% female) . HDL-C (E: 42±16, 1y: 46±12, 2y: 44±mg/dl; ps<0.001) and triglycerides (E: 205±168, 1y: 186±184, 2y: 160±1mg/dl; 2y p<0.05) improved. Total cholesterol (E: 165±46 mg/dl) and nonHDL-C (E: 124±46 mg/dl) were unchanged. Serum creatinine (E: 1.0±0.3 mg/dl) and eGFR (E: 85±18 ml/min/1.73m2) were stable; BUN increased (E: 17.3±6.1; 1y: 19.6±8.4, 2y: 18.9±7.6 mg/dl, ps<0.05) but remained within normal limits. Liver enzymes (ALP at E: 77.8±24.6 U/L; ALT at E: 32.3±17.1 U/L) were within normal limits and unchanged except AST decreased (E: 26.6±14.1, 1y: 21.7±8.7, 2y: 21.8±9.3 U/L, 2y p<0.05) . Veterans with T2D who underwent two years of diabetes reversal treatment improved atherogenic dyslipidemia and AST with no adverse effects on other markers of NAFLD and renal function, suggesting long term broad metabolic health benefit of this care model in the real world.

Disclosure

M.Vantieghem: Employee; Virta Health Corp., Stock/Shareholder; Virta Health Corp. **A.L.Mckenzie:** Employee; Virta Health Corp., Stock/Shareholder; Virta Health Corp. **R.E.Ratner:** Employee; Virta Health Corp.

Carbohydrate Intervention Including Nutritional Ketosis in Patients with Type 2 Diabetes

Differentiation of Diabetes by Pathophysiology, Natural History, and Prognosis

Metabolic Endotoxemia Initiates Obesity and Insulin Resistance

From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus

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Article Navigation

LB: PSYCHOSOCIAL / BEHAVIORAL MEDICINE | JUNE 01 2022

50-LB: Perceived Control over Eating Improves following Initiation of Carbohydrate-Restricted Nutrition Therapy in a Continuous Remote Care Model FREE

REBECCA N. ADAMS; MICHELLE VANTIEGHEM; BRITTANIE M. VOLK; SHAMINIE J. ATHINARAYANAN; AMY L. MCKENZIE

Diabetes 2022;71(Supplement_1):50-LB

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Background: Nutrition is an important component of metabolic disease prevention and treatment, yet eating and perceived control over eating (PCOE) are complex behaviors. Most people who attempt lifestyle changes have setbacks that can interfere with confidence and motivation for sustained change. The Virta Health virtual clinic provides medically-supervised nutrition therapy for metabolic disease focused on carbohydrate restriction and provides education and tools to: (1) understand how foods impact metabolic health; (2) facilitate autonomy for food choices; and (3) disentangle physiological and emotional food cues, to foster patients' eating confidence even if they struggle with adherence. This analysis explored whether Virta patients' PCOE improved during early treatment as these concepts were taught.

Methods: As part of standard clinical care, Virta patients (N=5940, Mean (M) age = 54 years, 72% white, 61% female, 73% T2D, M BMI = 36) responded to 4 items (total score range 4-20) assessing PCOE before the dietary intervention and at follow-up (M days = 60, SD = 15) . Paired t-tests were conducted to assess changes in PCOE over time among all patients and separately within subgroups based on dietary adherence (M ketones during treatment ≥ or < 0.5 mM) .

Results: PCOE improved from pre-treatment (M=13.3, "slightly" in control) to the first follow-up (M=15.7, "somewhat" in control) in all patients ($p<0.0001$) and within both subgroups of dietary adherence (more-adherent group: +3.0 from 13.3, $p<0.0001$; less-adherent group: +1.7 from 13.3, $p<0.0001$) .

Conclusions: Consistent with treatment aims, patients' PCOE improved. Importantly, patients who did not meet dietary adherence targets still gained confidence for controlling eating, though to a lesser extent. We predict that a healthier relationship with food, which includes greater PCOE, will help patients maintain motivation and get back on track following a setback; future research should

investigate whether greater PCOE is associated with long-term adherence and metabolic health outcomes.

Disclosure

R. N. Adams: Employee; Virta Health Corp. **M. Vantieghem:** Employee; Virta Health Corp., Stock/Shareholder; Virta Health Corp. **B. M. Volk:** Employee; Virta Health Corp., Stock/Shareholder; Virta Health Corp. **S. J. Athinarayanan:** Employee; Virta Health Corp. **A. L. Mckenzie:** Employee; Virta Health Corp., Stock/Shareholder; Virta Health Corp.

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OR: CLINICAL THERAPEUTICS / NEW TECHNOLOGY—DIABETES PREVENTION | JUNE 01 2022

59-OR: Long-Term Sustainability and Durability of Diabetes Prevention via Nutritional Intervention FREE

AMY L. MCKENZIE; SHAMINIE J. ATHINARAYANAN; MICHELLE VANTIEGHEM; BRITTANIE M. VOLK; REBECCA N. ADAMS; CAROLINE G.P. ROBERTS; BRANDON FELL; ROBERT E. RATNER; JEFF VOLEK; STEPHEN PHINNEY; SARAH HALLBERG

Diabetes 2022;71(Supplement_1):59-OR

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The national Diabetes Prevention Program (nDPP) failed to translate the efficacy of the Diabetes Prevention Program (DPP) into real world effectiveness. We initiated a prevention program, previously publishing outcomes on 96 patients with prediabetes over two years with 75% retention. This single center observational trial examines the effectiveness of a very low carbohydrate intervention (VLCI) including nutritional ketosis delivered via a continuous remote care (CRC) model; here, we report sustainability and durability at 5 years. At completion of the 2-year trial, 58 of the original cohort (80%) renewed consent and 78% completed the 5 year follow-up. At baseline, all had prediabetes, with mean weight 1kg and mean BMI 38.9 kg/m^2. Using intention to treat analysis at 5 years, 22% regressed to normoglycemia, 13% progressed to diabetes, and 65% remained prediabetes. A1c remained unchanged (mean 5.9%) , and mean fasting glucose fell from 112 to 1mg/dl (p=NS) . Weight fell from 1to 103 kg (p<0.001) , with insulin resistance falling from a HOMA-IR of 6.1 to 4.7 (p<0.05) . The nDPP utilizes 5% weight loss as a surrogate outcome for prevention. Forty-eight percent of the sample met that criteria at 5 years, with 19% achieving a 5-9.9% weight loss, 19% a 10-19.9% weight loss, and 10% with at least 20% weight loss. There was a 30% reduction in class 3 obesity (BMI ≥40) , contributing to a 2.7 fold increase in those now overweight (BMI 25-29.9) . These results show that a VLCI delivered via CRC is sustainable in prediabetes, resulting in normalization of A1c without medication in over 20% with limited glycemic deterioration to the diabetes threshold. No other real world intervention has presented glycemic data on diabetes prevention, but only reported surrogate weight change as an outcome. Over 5 years, almost half of the cohort achieved that surrogate with significant population shifts to lower obesity classes. The promise of the DPP is met via telehealth-supported VLCI and is sustainable over the long term.

Disclosure

A.L.Mckenzie: Employee; Virta Health Corp., Stock/Shareholder; Virta Health Corp. **S.Phinney:** Employee; Virta Health Corp. **S.Hallberg:** Advisory Panel; Atkins Nutritionals Inc., Employee; Virta

Health Corp., Stock/Shareholder; Virta Health Corp. **S.J.Athinarayanan:** Employee; Virta Health Corp. **M.Vantieghem:** Employee; Virta Health Corp., Stock/Shareholder; Virta Health Corp. **B.M.Volk:** Employee; Virta Health Corp., Stock/Shareholder; Virta Health Corp. **R.N.Adams:** Employee; Virta Health Corp. **C.G.P.Roberts:** Employee; Virta Health Corp., Stock/Shareholder; Virta Health Corp. **B.Fell:** Employee; Virta Health Corp., Stock/Shareholder; Virta Health Corp. **R.E.Ratner:** Employee; Virta Health Corp. **J.Volek:** Advisory Panel; Abbott Diagnostics, Simply Good Foods, Stock/Shareholder; Virta Health Corp.

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Type 2 Diabetes Prevention Focused on Normalization of Glycemia: A Two-Year Pilot Study

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Abstract: The purpose of this study is to assess the effects of an alternative approach to type 2 diabetes prevention. Ninety-six patients with prediabetes (age 52 (10) years; 80% female; BMI 39.2 (7.1) kg/m^2) received a continuous remote care intervention focused on reducing hyperglycemia through carbohydrate restricted nutrition therapy for two years in a single arm, prospective, longitudinal pilot study. Two-year retention was 75% (72 of 96 participants). Fifty-one percent of participants (49 of 96) met carbohydrate restriction goals as assessed by blood beta-hydroxybutyrate concentrations for more than one-third of reported measurements. Estimated cumulative incidence of normoglycemia (HbA1c < 5.7% without medication) and type 2 diabetes (HbA1c $\geq$ 6.5% or <6.5% with medication other than metformin) at two years were 52.3% and 3%, respectively. Prevalence of metabolic syndrome, class II or greater obesity, and suspected hepatic steatosis significantly decreased at two years. These results demonstrate the potential utility of an alternate approach to type 2 diabetes prevention, carbohydrate restricted nutrition therapy delivered through a continuous remote care model, for normalization of glycemia and improvement in related comorbidities.

Keywords: prediabetes; remote continuous care; low carbohydrate; metabolic syndrome; obesity

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1. Introduction

The United States faces a significant public health challenge with one in three adults living with prediabetes [1], a population at increased risk for progression to type 2 diabetes [2]. Patients with prediabetes often live with obesity and metabolic syndrome (MetS), each an independent predictor of type 2 diabetes [3,4], and the number of comorbidities is associated with increased risk of type 2 diabetes [5]. Each of these chronic conditions is associated with increased risk of cardiovascular disease, and evidence suggests microvascular damage may be present in patients with prediabetes prior to the development of obvious macrovascular disease. This demonstrates the need to initiate treatment for this high-risk state aimed at reversal of the condition to healthy or lower risk state to prevent or delay the onset of type 2 diabetes.

Intensive lifestyle intervention in the landmark Diabetes Prevention Program (DPP) reduced the incidence of type 2 diabetes by 58% [6], and use of behavioral interventions like the DPP are recommended by the United States Preventive Services Task Force to reduce risk [7]. Following the successful translation of the DPP into a community setting [8], the

Centers for Disease Control (CDC) established the National Diabetes Prevention Program (NDPP) to make low-cost lifestyle interventions widely available, and the Centers for Medicare and Medicaid Services (CMS) determined that the NDPP met criteria for expansion to and reimbursement for Medicare participants [9]. For full CDC recognition and CMS reimbursement, NDPPs must meet specific operational criteria, including 5% average weight loss among participants enrolled at least nine months [10]. However, retention in these programs is severely challenged. The recent study by Cannon et al. of the NDPP observed only 31.9% retention at 10 months concurrent with a strong association between retention and weight loss [11]. These findings highlight the imminent need to reconsider the diabetes prevention strategy to ensure that meaningful health improvements are achieved more broadly across this high-risk population [12].

We developed an outcomes-driven program, focused on reducing hyperglycemia and normalization of glycemia to delay or prevent the progression to type 2 diabetes, rather than the 5% weight loss goal utilized in the NDPP. This intervention utilized carbohydrate-restricted nutrition therapy delivered through a remotely delivered continuous care model. In this pilot study among 96 patients with prediabetes, we aimed to assess the impact of this alternate approach to type 2 diabetes prevention on retention, adherence, and change in the metabolic condition status of prediabetes and related comorbidities over two years.

2. Materials and Methods

2.1. Design and Participants

Adults with medical record diagnoses of prediabetes and metabolic syndrome (n = 116) were enrolled in a single-arm, prospective, longitudinal study to assess the effects of the continuous care intervention on markers of metabolic health (Clinicaltrials.gov (accessed on 19 February 2021) Identifier NCT02519309). For the purpose of this analysis, prediabetes was defined as HbA1c < 6.5% concurrent with metformin use or HbA1c between 5.7% and 6.4%, inclusive, without the use of glycemic control medication to align with the American Diabetes Association Standards of Medical Care, given that metformin is recommended in patients with prediabetes [13]. Participants whose characteristics did not meet the defined criteria for prediabetes at baseline testing (n = 20) were excluded from the following analyses; this included patients whose baseline HbA1c was <5.7% without medication and patients who were found to be taking an antihyperglycemic medication other than metformin during the baseline history and physical assessment (Supplemental Figure S1). Ninety-six participants were included in the analysis.

Participants between the ages of 21 and 65 years were recruited via clinical referrals, local media advertising, and word of mouth in Lafayette, Indiana and the surrounding area between August 2015 and March 2016. Individuals with advanced renal, hepatic, or cardiac dysfunction, dietary fat intolerance, or who were pregnant or planned to become pregnant were excluded from the study. The Franciscan Health Lafayette Institutional Review Board approved this study. All participants provided written informed consent.

2.2. Intervention

Details pertaining to the continuous care intervention were previously published [14–16]. In brief, participants accessed a mobile web-based application (app) which connected them to their remote care team consisting of a health coach who provided support for nutrition and behavior change and a medical provider who monitored the biomarkers and managed diabetes and hypertension medications. Participants self-selected to receive their education via either regularly scheduled on-site group classes consisting of presentations and group discussions or via web-based education modules consisting of videos and written materials viewed online at the participant's choice of time and pace. The app also provided educational resources and access to peer social support via an online community regardless of the education delivery modality selected. Initial nutrition guidance included restricting dietary carbohydrates to fewer than 30 g per day, consumption of 1.5 g dietary protein per kg reference body weight daily, and consumption of dietary fat to satiety

with the goal of achieving nutritional ketosis defined as blood beta-hydroxybutyrate (BHB) $\geq$ 0.5 mmol/L. The majority of dietary carbohydrates consisted of non-starchy vegetables, dairy, and/or nuts; participants selected individual foods based on their dietary preferences and philosophies. To monitor adherence to carbohydrate restriction and allow providers to manage medications, participants recorded blood glucose and BHB (Precision Xtra, Abbott; Alameda, CA, USA) and blood pressure (BP742 N, Omron Healthcare, Inc.; Lake Forest, IL, USA), if hypertension was diagnosed, in the app. Body weight was recorded in the app via cellular-connected scale (BT003, Body Trace; New York, NY, USA). Initially, participants measured and recorded biomarkers daily, and the care team adjusted the BHB target and frequency of reporting over time to meet individual health needs and goals.

2.3. Assessments

Participants underwent a history and physical examination and laboratory testing to obtain baseline and one- and two-year follow-up measures. Trained clinic staff assessed height, waist circumference, and blood pressure. Weight was uploaded to the app via a cellular connected scale provided to each participant. Trained staff at a Clinical Laboratory Improvement Amendment (CLIA) certified laboratory obtained blood from participants in a fasting state and analyzed blood samples for glucose, insulin, HDL-cholesterol (HDL-C), triglycerides, alanine transaminase (ALT), and aspartate aminotransferase (AST) on the day of sample collection or from stored serum.

We assigned the presence of conditions as follows: normoglycemia: HbA1c < 5.7% without glycemic control medication; prediabetes: HbA1c < 6.5% concurrent with metformin use or HbA1c between 5.7% and 6.4%, inclusive; type 2 diabetes: HbA1c $\geq$ 6.5% with or without glycemic control medication or HbA1c < 6.5% with glycemic control medication other than metformin; MetS: presence of three of five diagnostic criteria (BMI > 30 kg/m^2 was substituted for waist circumference when it was not available) [17,18]; obesity $\geq$ class II: BMI $\geq$ 35 kg/m^2; suspected hepatic steatosis: NAFLD-Liver Fat Score > $-$0.640 [19].

2.4. Statistical Methods

In this pilot study, we assessed the retention in the intervention and adherence to nutrition guidance. We assessed the outcome variables for assumptions of normality and linearity using Kline's guidelines [20] and transformed variables as noted in the tables. We performed independent sample t-tests to examine the differences in baseline characteristics between those who selected on-site versus web-based education and between completers versus dropouts.

We calculated crude incidence of first occurrence of type 2 diabetes diagnosis and normoglycemia per 100 person-years and used the Kaplan–Meier approach to estimate the cumulative incidence [21] of type 2 diabetes and normoglycemia at two years. We assessed the changes in dichotomous outcome variables over time using generalized estimating equations (GEE) with binary logistic models and unstructured covariance matrices, and we estimated the missing values with 40 imputations [22] from logistic regression to allow intent-to-treat analysis. For continuous outcome variables, we utilized linear mixed effects models (LMM) to obtain the estimated marginal means and assess changes over the two-year follow-up period. The LMM uses an intent-to-treat principle which includes all available data and estimates the model parameters through a maximum-likelihood approach. An unstructured covariance matrix was specified. Covariates in GEE and LMM included baseline age, sex, race, and metformin use. LMM and chi-square were also utilized to assess the two-year clinical biomarker and retention differences, respectively, between those who selected on-site and web-based education. Significance level was set at 0.05 and was adjusted in each analysis with related variables to account for the number of contrasts using the Bonferroni method. We performed statistical analyses with SPSS statistical software (version 25.0, Armonk, NY, USA). Means are reported with (standard deviation) or $\pm$standard error.

3. Results

3.1. Participant Characteristics, Retention, and Adherence

Participants with prediabetes were 52(10) years of age with a BMI of 39.24(7.06) kg/m^2 at enrollment. Most participants were female (80%) and white/Caucasian (96%); four percent were African-American. Clinical characteristics among those who selected on-site versus web-based education were not different at baseline or two years ($p > 0.05$, Supplemental Tables S1 and S2), nor was two-year retention (77.8% on-site vs. 71.4% web-based, X^2 (1, n = 96) = 0.508, p = 0.476), so subsequent analyses were performed on the combined cohort. Metformin was prescribed to 15, 13, and 15 participants at baseline, one year, and two years, respectively, and thus was included as a covariate in statistical analyses.

Eighty percent of participants (77 of 96) remained enrolled in the intervention at one year, and 75% (72 of 96) at two years. Baseline clinical characteristics of two-year completers and dropouts were not different (Supplemental Table S3). Fifty-one percent of participants (49 of 96) obtained BHB $\geq$ 0.5 mmol/L for more than one-third of their reported measurements. Participants reported 205 $\pm$ 160 BHB measurements over two years.

3.2. Incidence of Normoglycemia and Type 2 Diabetes

Estimated cumulative incidence of normoglycemia at two years was 52.3%. The crude incidence for first occurrence of reversion from prediabetes to normoglycemia was 47.6 cases per 100 person-years. One new case of type 2 diabetes each year was observed in the population under study, resulting in a crude incidence of type 2 diabetes diagnosis of 1.5 cases per 100 person-years. The estimated cumulative incidence of type 2 diabetes at two years was 3%.

3.3. Change in Metabolic Condition Status

Prevalence of normoglycemia significantly increased, while prevalence of prediabetes, MetS, and suspected hepatic steatosis significantly decreased at one and two years (Table 1). The proportion of participants with class II and III obesity also significantly decreased (Figure 1). Prevalence of type 2 diabetes was unchanged from baseline after correction for multiple comparisons.

Table 1. Prevalence of metabolic condition status over two years.

Metabolic Condition	Baseline		1 Year			2 Years		
	n	**Mean $\pm$ SE**	***n***	**Mean $\pm$ SE**	***p***	***n***	**Mean $\pm$ SE**	***p***
Prediabetes (%)	96	100.0 $\pm$ 0.0	70	54.0 $\pm$ 6.0	<0.001	63	67.0 $\pm$ 5.9	<0.001
Normoglycemia (%)	96	0.0 $\pm$ 0.0	70	46.0 $\pm$ 6.0	<0.001	63	33.0 $\pm$ 5.9	<0.001
Type 2 Diabetes (%)	96	0.0 $\pm$ 0.0	70	4.0 $\pm$ 2.7	0.04	63	5.0 $\pm$ 3.1	0.02
Metabolic Syndrome (%)	94	94.0 $\pm$ 2.5	65	30.0 $\pm$ 5.7	<0.001	47	49.0 $\pm$ 7.1	<0.001
Obesity $\geq$ Class II (%)	96	67.0 $\pm$ 4.8	77	38.0 $\pm$ 5.5	<0.001	72	43.0 $\pm$ 5.6	<0.001
Suspected Steatosis (%)	89	88.0 $\pm$ 3.5	58	41.0 $\pm$ 6.1	<0.001	42	48.0 $\pm$ 6.5	<0.001

Note: n indicates the available data at the time point. Multiple imputation was utilized to facilitate intent-to-treat analysis. Contrasts compared follow-up to baseline. Statistical significance is indicated by $p < 0.004$ following Bonferroni correction for multiple comparisons.

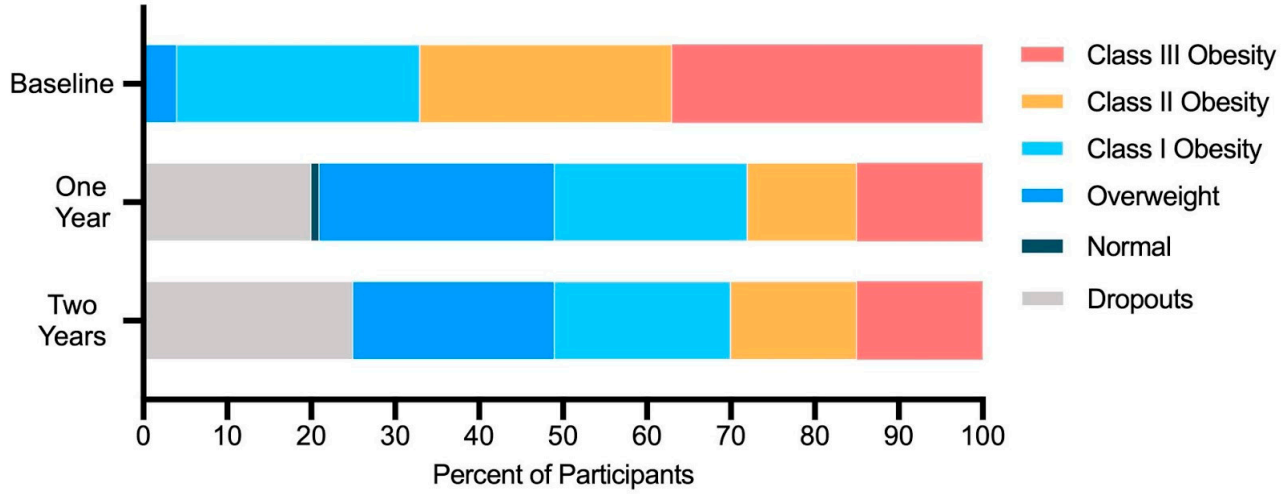

Figure 1. Prevalence of obesity classes and body mass index categories among participants over time.

3.4. Change in Clinical Markers Associated with Metabolic Conditions

Clinical markers related to diabetes, obesity, and MetS improved except for blood pressure, in which a significant improvement was observed only in systolic pressure following one year (Table 2). At one and two years, 64% and 53% of participants enrolled, respectively, lost at least 5% body weight, and 54% and 47% lost at least 7%. Components of the NAFLD-Liver Fat Score (fasting insulin, aspartate aminotransferase, and alanine aminotransferase) for suspected steatosis significantly improved at one and two years except for aspartate aminotransferase, which was statistically unchanged.

Table 2. Change in metabolic condition clinical markers compared to baseline.

	Baseline		**1 year**			**2 years**		
	n	EMM ± SE	*n*	EMM ± SE	*p*	*n*	EMM ± SE	*p*
HbA1c (%)	96	5.95 ± 0.02	70	5.63 ± 0.03	<0.001	64	5.73 ± 0.04	<0.001
HbA1c (mmol/mol)	96	41.5 ± 0.2	70	38.3 ± 0.3	<0.001	64	39.3 ± 0.4	<0.001
Fasting Glucose (mmol/L)	95	6.11 ± 0.08	69	5.61 ± 0.08	<0.001	63	5.64 ± 0.08	<0.001
Fasting Insulin (pmol/L)	90	164.80 ± 10.21	67	94.73 ± 6.53	<0.001	58	104.59 ± 7.22	<0.001
SBP (mmHg)	95	129.9 ± 1.4	62	123.1 ± 1.5	<0.001	48	127.3 ± 1.8	0.18
DBP (mmHg)	95	82.5 ± 0.8	62	79.2 ± 1.0	0.01	48	80.5 ± 1.1	0.11
Weight (kg)	96	109.6 ± 2.2	77	95.7 ± 1.9	<0.001	72	97.2 ± 1.9	<0.001
BMI (kg/m^2)	96	39.08 ± 0.72	77	34.11 ± 0.63	<0.001	72	34.62 ± 0.62	<0.001
Waist Circumference (cm)	74	118.9 ± 1.6	52	107.8 ± 1.7	<0.001	42	110.9 ± 2.7	0.002
HDL-cholesterol (mmol/L)	90	1.28 ± 0.03	67	1.45 ± 0.04	<0.001	58	1.46 ± 0.05	<0.001
Triglycerides (mmol/L)	90	1.81 ± 0.09	67	1.38 ± 0.09	<0.001	58	1.28 ± 0.08	<0.001
ALT (µkat/L) †	95	0.46 ± 0.02	69	0.37 ± 0.02	<0.001	63	0.37 ± 0.02	<0.001
AST (µkat/L) †	95	0.37 ± 0.02	69	0.34 ± 0.02	0.03	63	0.33 ± 0.01	0.04
NAFLD-Liver Fat Score	89	1.84 ± 0.24	58	−0.78 ± 0.20	<0.001	42	−0.35 ± 0.24	<0.001

Note: *n* indicates the available data at the time point. Contrasts compared follow-up to baseline. Statistical significance is indicated by $p < 0.002$ following Bonferroni correction for multiple comparisons. Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase, NAFLD, non-alcoholic fatty liver disease. † Variable failed normality (positively skewed). Analyses were conducted on data excluding the top 1% of values and treating these values as missing in the LMM model.

4. Discussion

These results demonstrate the potential utility of an alternate approach to type 2 diabetes prevention, carbohydrate restricted nutrition therapy delivered through a continuous remote care model, for reversion of prediabetes and improvement of related comorbidities. Seventy-five percent of participants were retained in the program for two years, with an estimated cumulative incidence of normoglycemia of 52% and of progression to type 2 diabetes of 3%. Prevalence of MetS, class II and III obesity, and suspected hepatic steatosis within this cohort significantly declined.

Retention in the present investigation was 80% and 75% at one and two years, respectively, far exceeding the 32% at 10 months [11] and 13.2% at one year [23] published in two different analyses of the NDPP. A number of factors may contribute to the differences observed. A remote delivery method may facilitate higher retention, as observed in another virtually delivered intervention [24]. Other factors include continuous access to a remote care team for support, daily focus on blood BHB goals rather than weight, and the magnitude of mean weight loss (12.7%) achieved in the first year. A relationship between weight loss and retention has been observed in both the NDPP and commercial weight loss programs [11,23,25]. Greater weight loss in the first year was associated with long-term weight loss maintenance of 5% or more, regardless of initial treatment, throughout the DPP and DPPOS [26].

Among participants in the present intervention, 64% and 53% achieved the $\geq$5% weight loss goal established by the CDC at one and two years, respectively, exceeding the 36% observed in the NDPP [23]. Nearly half of participants in the present study maintained $\geq$7% weight loss at two years, similar to the 24-week findings of the DPP, which declined to 38% at an average of 2.8 years follow-up [6]. Given the tendency for weight regain commonly observed across weight loss interventions, long-term retention and greater early weight loss in programs may play a critical role in helping participants maintain improved health status.

Achieving the 5% weight loss goal through a low fat, low calorie diet and physical activity goals has been the cornerstone of the NDPP given the relationship between weight loss and reduced risk of progression to type 2 diabetes in the DPP [27]. However, transient regression to normoglycemia in the first three years of the DPP was associated with significantly lower risk of progressing to type 2 diabetes during the 6–7 years of follow-up during the DPP Outcomes Study (DPPOS) [28]. The estimated cumulative incidence of reversion to normoglycemia (52%) in this study exceeded the approximately 35% observed at two years with intensive lifestyle intervention in the DPP [28]. Relatedly, incidence of progression to type 2 diabetes was low at 1.5 cases per 100 person-years, relative to 4.8 and 7.8 cases per 100-person years observed in the DPP lifestyle intervention and metformin groups [6]. These findings indicate that alternative short-term targets focused on normalization of glycemia, such as through dietary carbohydrate restriction, may provide viable alternatives to short-term diet and physical activity targets and longer-term weight loss (and weight loss maintenance) goals for diabetes prevention.

Reversion to normoglycemia is associated with positive health benefits beyond type 2 diabetes prevention or delay. Risk of cardiovascular disease, myocardial infarction, stroke, and all-cause mortality was reduced in a Chinese cohort of patients with prediabetes who reverted to normoglycemia within two years compared to those who progressed to type 2 diabetes over nearly nine years of follow-up [29]. In the DPPOS, achieving transient regression to normoglycemia also reduced odds of developing aggregate microvascular disease (retinopathy, nephropathy, and neuropathy), as well as retinopathy and nephropathy individually [30]. Prevalence of microvascular complications among the three DPP groups (lifestyle, metformin, and placebo) was similar at 15-years post-randomization as mean HbA1c across the groups converged to within 0.3% and above 6.0%, but prevalence of microvascular complications was 28% lower among those who did not progress to type 2 diabetes compared to those who did [31]. This may suggest a key role for long-term maintenance of normoglycemia or prevention of progression to type 2 diabetes for maximum

benefit. Considering the high rates of retention and normalization of glycemia observed in this study combined with the remote delivery and monitoring methods utilized, this intervention may have the potential to address a critical need in this high-risk population, and future research should assess its long-term effects on prevention of type 2 diabetes and its complications.

Although meeting a particular weight loss target was not a stated goal for participants in this intervention, the majority of enrolled participants met the 5% benchmark at two years. Lifestyle intervention independent of weight loss predicted regression to normoglycemia in the DPP [32], and hyperglycemia can be resolved prior to significant weight loss following bariatric surgery [33]. Further, carbohydrate restriction in the absence of weight loss has been demonstrated to reverse metabolic syndrome [34]. Taken together, this may suggest that weight loss can be an effect of metabolic health improved by other means, rather than a primary driver, further highlighting the potential for alternate goals related to the ultimate outcome of diabetes prevention.

Accompanying normalization of glycemia and weight loss, prevalence of MetS and suspected hepatic steatosis declined following this intervention. Reduction in the prevalence of MetS (−45%) exceeded that of the DPP, where prevalence declined from 51 to 43% [35] and was similar to a four-week low-carbohydrate feeding study [34], which demonstrated that MetS resolution is possible with carbohydrate restriction even in the absence of weight loss. Similarly, a study in patients with NAFLD demonstrated that liver fat was reduced significantly following just one day of consuming a ketogenic diet due to reduced de novo lipogenesis and increased beta oxidation [36], providing a potential explanation for the decreased prevalence of suspected hepatic steatosis observed in this study. The inverse trend in some biomarkers between one and two years is of unknown significance given the significant improvement maintained at two years compared to baseline and existing evidence demonstrating that even transient normalization of glucose can have long-term positive health benefit.

Strengths of this study include its two-year follow-up period and assessment of incident type 2 diabetes, which is lacking in the NDPP. Limitations include the predominance of females enrolled in the study (although this is similar to enrollment in the NDPP), the lack of racial diversity, and that the study was not designed to test the contribution of each component of the intervention to outcomes, nor to evaluate equivalence or superiority to alternate interventions or care models. Data were analyzed conservatively according to intent-to-treat principles and included participants who did not fully adhere to the intervention components; thus, these outcomes are likely to reflect what might be expected in a real-world setting.

As observed in the DPP, clinical outcomes are often tied to program retention and adherence, but focus should remain on achieving and sustaining clinically meaningful outcomes. Historically in the context of prediabetes, outcomes have focused on a 5% weight loss goal through adhering to a low fat, low calorie diet and physical activity targets, but evidence now demonstrates that metabolic health can be improved by focusing on alternate targets, such as achievement of normoglycemia through nutrition therapy. Remote delivery methods may provide another strategy for improving retention and facilitating improved health outcomes in a larger proportion of individuals.

5. Conclusions

This pilot study demonstrated that the majority of patients with prediabetes who chose to enroll in this intervention achieved normoglycemia and maintained clinically meaningful weight loss through two years, suggesting this intervention utilizing carbohydrate restricted nutrition therapy delivered through a continuous remote care model may provide an additional and alternative approach for type 2 diabetes prevention. Future research may evaluate the effectiveness of this care model versus alternatives for the prevention or delay of progression to type 2 diabetes.

Supplementary Materials: The following are available online at https://www.mdpi.com/2072-6643/13/3/749/s1. Figure S1: Participant Flow Diagram, Table S1: Baseline characteristics of participants who selected on-site versus web-based education delivery, Table S2: Characteristics of participants who selected on-site versus web-based education delivery after two-years treatment, Table S3: Baseline characteristics of participants and comparison of completers and dropouts.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data are not publicly available due to privacy concerns.

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Conflicts of Interest: A.L.M., S.J.A., J.M., R.N.A., J.P.M., S.D.P., and S.J.H. have been employed by Virta Health Corp and were offered stock options. S.D.P. and J.S.V. are founders of Virta Health Corp. M.K. declares no conflict of interest.

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P: COMPLICATIONS—KIDNEY—CLINICAL AND TRANSLATIONAL RESEARCH | JUNE 20 2023

410-P: Two-Year (2y) eGFR Slope in People with Type 2 Diabetes (T2D) Receiving a Very Low Carbohydrate Diet (VLCD) Intervention

FREE

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A VLCD including nutritional ketosis is an effective T2D intervention, but its use is cautioned in renal disease. We compared eGFR slope among people with T2D with varying renal function who received a VLCD intervention via continuous remote telemedicine care (CCI, n=262) or Usual Care without carbohydrate restriction (UC, n=87) over two years. Four ketosis trajectory classes (KTs) were identified within CCI using latent class trajectory modeling. We compared eGFR slopes for CCI KTs using a linear mixed effect model with UC as the reference. The eGFR slope was positive in all CCI KTs and negative in UC (Table 1). eGFR slope improved in CCI (p=0.045), in sustained nutritional ketosis (SNK) group (p=0.01), and in those with baseline eGFR <90 (p<0.001) compared with UC. KT with higher blood ketones (SNK and MDNK) had greater eGFR rise. These results show that eGFR slopes rose in people with T2D on CCI and declined in UC. Rise of eGFR slope appears to have a dose-dependent relationship with endogenous ketone concentration and duration of maintenance of ketosis, including those with stage 2 chronic kidney disease, suggesting nutritional ketosis VLCD may provide benefit rather than risk in early renal disease.

Table 1. Two-year eGFR slopes in whole CCI cohort, CCI sub cohort with baseline eGFR<90, CCI participants divided into four ketosis trajectory classes (KT) and in UC (control) used as a reference category in the linear mixed effect model

	eGFR slope (mL/min/1.73m²/year)		
Whole cohort	**Mean + SE**	**Slope Difference**	**p-value**
CCI, n=248	0.84 ± 0.42		
UC (control), n=87	-0.68 ± 1.26	**1.52 ± 0.84**	**0.045**
CCI divided into 4 ketosis trajectory classes			
Time * Group interaction			0.11
Sustained nutritional ketosis (consistently ~ 1mM), SNK (N=17)	3.38 ± 2.35	**4.06 ± 1.63**	**0.01**
Moderately declining nutritional ketosis (~0.7mM followed by ~0.5mM), MDNK (N=99)	1.09 ± 1.68	1.78 ± 0.96	0.07
Low nutritional ketosis (consistently ~ 0.3mM to 0.4mM), LNK (N=105)	0.20 ± 1.69	0.88 ± 0.97	0.36
Unsustained nutritional ketosis (~0.3mM followed by ~ 0.1mM), UNK (N=27)	0.22 ± 2.32	0.91 ± 1.60	0.57
UC (control)	-0.69 ± 0.72		
	eGFR slope (mL/min/1.73m²/year)		
Subcohort analysis, baseline eGFR< 90	**Mean + SE**	**Slope Difference**	**p-value**
CCI, n=111	2.99 ± 0.73		
UC (control), n=44	1.06 ± 2.13	**1.93 ± 1.40**	**<0.001**
CCI divided into 4 ketosis trajectory classes			
Time * Group interaction			0.47
SNK (N=8)	6.28 ± 4.35	5.22 ± 3.16	0.10
MDNK (N=47)	3.26 ± 2.83	2.21 ± 1.64	0.18
LNK (N=47)	2.40 ± 2.81	1.34 ± 1.62	0.41
UNK (N=11)	2.38 ± 3.69	1.33 ± 2.50	0.60
UC (control)	1.05 ± 1.19		

Disclosure

S.J.Athinarayanan: Employee; Virta Health Corp. **C.G.P.Roberts:** Employee; Virta Health Corp. **R.N.Adams:** Employee; Virta Health Corp. **B.M.Volk:** Employee; Virta Health Corp., Stock/Shareholder; Virta Health Corp. **S.D.Phinney:** Board Member; Virta Health Corp., Employee; Virta Health Corp., Stock/Shareholder; Virta Health Corp. **J.Volek:** Stock/Shareholder; Virta Health Corp. **A.L.Mckenzie:** Employee; Virta Health Corp., Stock/Shareholder; Virta Health Corp.

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P: CLINICAL THERAPEUTICS / NEW TECHNOLOGY—OTHER THERAPEUTIC AGENTS | JUNE 01 2022

834-P: Two-Year Effects of Carbohydrate-Restricted Nutrition Therapy Delivered via Continuous Remote Care among Veterans with Type 2 Diabetes: A Nationwide, Real-World Study FREE

AMY L. MCKENZIE; MICHELLE VANTIEGHEM; BRANDON FELL; ROBERT E. RATNER

Diabetes 2022;71(Supplement_1):834-P

https://doi.org/10.2337/db22-834-P

Type 2 diabetes (T2D) affects about one in four Veterans, a rate nearly three times the general population, and diabetes medications and supplies constitute about one quarter of these Veterans' pharmacy spend. The Veterans Health Administration partnered with Virta Health to provide carbohydrate restricted nutrition therapy via a continuous remote care model to Veterans in a pilot program. Five-month outcomes demonstrated significant reductions in HbA1c, BMI, diabetes medications and cost, and outpatient visits, but long term sustainability in this population is unknown. This retrospective, real-world, longitudinal analysis assessed the 1- and 2-year effects of the treatment on glycemia, diabetes medications, and body weight using medical record data. Veterans retained at least two years at time of analysis were included (n=254, 58.5% of 434 eligible enrolled, 60±8 years, 12% female) . With initiation of nutritional intervention, glycemia fell necessitating medication titration and elimination to prevent hypoglycemia. The number of diabetes medications prescribed to each person significantly decreased from 2.4±0.9 to 1.3±0.9 and 1.6±0.8 at one and two years, respectively (ps<0.0001) . Despite this significant reduction in pharmacologic therapy, HbA1c was significantly reduced at one year (-0.7±1.6%, p<0.0001) and two years (-0.6±1.7%, p<0.0001) compared to enrollment (8.1±1.5%) . Body weight also declined from 241.1±50.1 lb to 223.2±44.4 lb at one year and 222.1±46.8 lb at two years (ps<0.0001) , reflecting 6.8±7.6% and 7.0±9.4% weight loss per person at one and two years, respectively. These findings demonstrate that sustained improvement in glycemia concurrent with medication deprescription and clinically significant weight loss are achievable in the real world among Veterans who choose this therapy.

Disclosure

A.L.Mckenzie: Employee; Virta Health Corp., Stock/Shareholder; Virta Health Corp. **M.Vantieghem:** Employee; Virta Health Corp., Stock/Shareholder; Virta Health Corp. **B.Fell:**

Employee; Virta Health Corp., Stock/Shareholder; Virta Health Corp. **R.E.Ratner:** Employee; Virta Health Corp.

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P: CLINICAL THERAPEUTICS / NEW TECHNOLOGY—OTHER THERAPEUTIC AGENTS | JUNE 01 2022

832-P: Five-Year Weight and Glycemic Outcomes following a Very-Low-Carbohydrate Intervention Including Nutritional Ketosis in Patients with Type 2 Diabetes FREE

SHAMINIE J. ATHINARAYANAN; MICHELLE VANTIEGHEM; AMY L. MCKENZIE; SARAH HALLBERG; CAROLINE G.P. ROBERTS; BRITTANIE M. VOLK; REBECCA N. ADAMS; ROBERT E. RATNER; JEFF VOLEK; STEPHEN PHINNEY

Diabetes 2022;71(Supplement_1):832-P

https://doi.org/10.2337/db22-832-P

Objective: We previously reported long term effectiveness of a very low carbohydrate intervention including nutritional ketosis (VLCI) delivered via continuous remote care (CRC) for improving weight and glycemia at 2 years in people with type 2 diabetes (T2D) . We assessed 5-year changes to determine if the intervention is sustainable, durable, and effective over a longer period of time.

Research Design and Methods: Patients with T2D who were initially enrolled in a 2 year non-randomized, controlled clinical trial received a CRC emphasizing a VLCI. These patients were offered to continue for an additional 3 years of prospective follow-up. Of the 200 patients completing 2 years, 169 (84.5%) patients consented to the extension and 122 (72.2%) were retained at 5 years. Among those who extended, baseline versus 5 year differences in weight and glycemic outcomes were assessed using linear mixed effects models in an intent-to-treat analysis. P-values were adjusted using Holm-Bonferroni correction.

Results: At five years, there were persistent improvements in weight from 116.4 to 107.6 kg (-8.8 kg, 95%CI [-11.0, -6.6]) , fasting insulin from 25.8 to 24.5 mIU/L (-7.9 mIU/L, 95%CI [-10.0, -5.8]) , and HOMA-IR from 9.1 to 6.6 (-2.5, 95%CI [-3.5, -1.5]) (all adjusted p-values <0.05) . Total diabetes medications were reduced 46.6%, and 59.9% excluding metformin were deprescribed. The percent of patients prescribed diabetes medications significantly decreased at 5 years (from 85.2% to 71.3%; p<0.01) , including patients taking sulfonylureas (from 27.0% to 4.9%) , insulin (from 26.2% to 13.1%) , and SGLT2i (from 10.7% to 2.5%) . Despite less medication use, HbA1c improved from 7.5 to 7.2% (-0.3%, 95%CI [-0.6, 0.0], unadjusted p-value<0.05) .

Conclusions: Over 5 years follow-up, the VLCI with CRC showed excellent retention, sustained clinically significant weight loss, and stable glycemic control with reduced dependency on antidiabetes medications.

Disclosure

S.J.Athinarayanan: Employee; Virta Health Corp. **S.Phinney:** Employee; Virta Health Corp. **M.Vantieghem:** Employee; Virta Health Corp., Stock/Shareholder; Virta Health Corp. **A.L.Mckenzie:** Employee; Virta Health Corp., Stock/Shareholder; Virta Health Corp. **S.Hallberg:** Advisory Panel; Atkins Nutritionals Inc., Employee; Virta Health Corp., Stock/Shareholder; Virta Health Corp. **C.G.P.Roberts:** Employee; Virta Health Corp., Stock/Shareholder; Virta Health Corp. **B.M.Volk:** Employee; Virta Health Corp., Stock/Shareholder; Virta Health Corp. **R.N.Adams:** Employee; Virta Health Corp. **R.E.Ratner:** Employee; Virta Health Corp. **J.Volek:** Advisory Panel; Abbott Diagnostics, Simply Good Foods, Stock/Shareholder; Virta Health Corp.

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Virta Health Highlights Lasting, Transformative Health Improvements In 5-Year Diabetes Reversal Study

Published on June 5, 2022

Virta Health

years

"Through Virta, I not only reversed my diabetes and lost over 50 pounds, I got my life back." — Jane Ann Dimitt, who lowered her A1c from 11.4% to 5.5% while removing medications

SAN FRANCISCO (JUNE 6, 2022)—Virta Health, the leader in type 2 diabetes reversal, revealed preliminary five-year results from its landmark clinical trial at the American Diabetes Association 82nd Scientific Sessions. Presenting four unique abstracts, Virta highlighted myriad, lasting health improvements for people with type 2 diabetes and prediabetes, including blood sugar control, clinically-significant weight loss, reduced inflammation, and improvements in other markers of cardiometabolic health.

These transformative health outcomes coincided with medication reduction or elimination for many trial patients, including Jane Ann Dimitt.

For over two decades, Jane Ann was prescribed increasing levels of medications

Ann lowered her blood sugar to 5.5% (below even the prediabetes threshold) and lost over 50 pounds, while drastically *reducing* her reliance on medications. She also saw improved mobility, decreased inflammation and neuropathy, and now has the energy to play with her grandchildren—all without needing the insulin doctors said was imminent.

The outcomes of Jane Ann and Virta's other trial patients contradict the belief that progression of diabetes—and a lifetime of increasing medications—is inevitable. One-fifth of Virta patients completing five years of treatment saw full remission (A1c <6.5% without any diabetes medications for at least 3 months). One-third of patients achieved A1c below 6.5% without any diabetes medications, or only requiring Metformin. Notably, inflammatory markers, triglycerides, and HDL cholesterol all improved significantly.

These outcomes, in conjunction with previous research demonstrating improvements in cardiovascular disease risk

disease epidemic. In the U.S., costs are rising as patient outcomes continue to worsen, including surges in amputations, hyperglycemic events, and diabetes-related deaths during the COVID-19 pandemic.

Meanwhile, getting patients to stick with an intervention remains a significant challenge in diabetes therapy. Rates of medication adherence—that is, whether patients take their medications as prescribed—fall as low as 34% over the first three years for those starting insulin. For the National Diabetes Prevention Program, considered the gold standard in lifestyle interventions, only 13% of patients were retained at one year.

In contrast, in Virta's trial nearly 50% of participants with type 2 diabetes were retained at five years. Of those who continued past year two, 72% remained for an additional three years to year five. For Kim Shepherd, who lost 55 pounds, eliminated 10 different medications, reversed her diabetes, and even saw her GERD (acid reflux) and plantar fasciitis

this disease can rob you of your whole life, it can take your eyes, your feet, and your kidneys. I have 4 kids and 9 grandkids to keep up with. I've learned to love hiking and biking. Nothing is worth losing all of that and going back to how I was before."

Additional key outcomes demonstrating the success of Virta's approach at five years include:

- **Sustained blood sugar control.** Virta patients experienced persistent improvements in blood sugar on average, while requiring significantly fewer medications.
- **Medication deprescription.** Half of patients prescribed insulin at the start of the trial no longer needed it at five years. Across all diabetes drugs, prescriptions were reduced by nearly 50%.
- **Weight loss**. Average weight among Virta participants decreased by 7.6%, exceeding the 5% benchmark for clinically significant weight loss by more than 50%.

showed encouraging signs in reversing the progression of chronic kidney disease.

"Virta's patients are helping redefine what long-term success can look like in type 2 diabetes care," said Dr. Alan Moses, former Senior Vice President and Global Chief Medical Officer of Novo Nordisk, and Virta advisor. "The patient outcomes set a new standard for real-world applications of diabetes treatment."

Trial participants with prediabetes also saw meaningful improvements, with progression rates far below what has been demonstrated in other studies. Further, Virta patients sustained 6% weight loss over five years, exceeding the clinically-significant benchmark for diabetes prevention and far surpassing the 2% weight loss observed in the NIH Diabetes Prevention Program lifestyle intervention.

The study is also notable for its longevity. Five-year published results are extremely rare in digital health, where most studies follow populations for no more than a year,

health but overall mood, quality of life, and outlook on the future.

Says patient Denise Lamb, who has maintained diabetes reversal alongside a nearly 70 pound weight loss, “My journey has been phenomenal. The Virta program has not only helped me achieve healthy blood glucose, but also attain a far better weight, normal blood pressure, and better understanding of my body. Virta’s lifestyle changed my lifestyle!”

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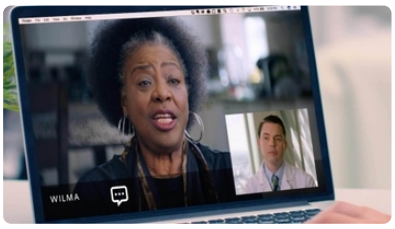

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P: EPIDEMIOLOGY—NUTRITION | JUNE 01 2022

1176-P: A Population Shift in Meeting Glycemic Targets Following Five Years of a Very-Low-Carbohydrate Intervention (VLCI) and Continuous Remote Care (CRC) FREE

BRITTANIE M. VOLK; AMY L. MCKENZIE; SHAMINIE J. ATHINARAYANAN; MICHELLE VANTIEGHEM; REBECCA N. ADAMS; CAROLINE G.P. ROBERTS; ROBERT E. RATNER; JEFF VOLEK; STEPHEN PHINNEY; SARAH HALLBERG

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Background: We previously reported 1- and 2-year effectiveness of a VLCI via CRC. Here we assess the long term effectiveness of the treatment via achievement of A1c ≤6.5%, <7%, and <8% with and without antidiabetes medications at 5 years.

Research Design and Methods: Patients with T2D who initially enrolled in a 2-year non-randomized, controlled clinical trial and received a VLCI via CRC were offered 3 additional years of prospective follow-up. Of the 200 patients completing 2 years, 169 (84.5%) consented to extend; 122 (72.2%) were retained at 5 years. Among those who extended, McNemar's test was used to assess the change in percent of patients meeting glycemic targets from baseline to 5 years among completers and on an intent-to-treat basis.

Results: At 5 years, the percent of completing patients meeting glycemic goals improved across all defined targets (Table 1) . Of completing patients, 20% achieved diabetes remission, while 32.5% achieved an A1c <6.5% without the use of antidiabetes medications with the exception of metformin.

Conclusions: One fifth of completing patients achieved the international consensus criteria for diabetes remission at 5 years, which is unique among lifestyle interventions. The proportion of people at A1c goal increased, suggesting the VLCI delivered via CRC may be an effective, long-term strategy to improve population health.

Table 1. Prevalence of Diabetes Remission and Achievement of ADA and AACE Glycemic Targets in Adults with T2D Treated with a Very Low Carbohydrate Intervention via Continuous Remote Care at 5 years

	Completers only n=120		ITT missing data LOCF n=169		ITT missing data imputed n=169	
	Baseline n (%)	5 years n (%)	Baseline n (%)	5 years n (%)	Baseline n (%)	5 years n (%)
Remission: HbA1c <6.5%, no meds ≥3 months	0 (0.0)	24 (20.0)	0 (0.0)	34 (20.1)	0 (0.0)	50 (29.6)
HbA1c <6.5%, no anti-diabetes meds or only metformin	14 (11.7)	39 (32.5) ***	19 (11.2)	59 (34.9) ***	19 (11.2)	64 (37.9) ***
AACE glycemic target: HbA1c ≤6.5%	28 (23.3)	50 (41.7) ***	39 (23.1)	79 (46.7) ***	39 (23.1)	76 (45.0) ***
HbA1c <7.0%, no anti-diabetes meds or only metformin	9 (7.5)	28 (23.3) ***	14 (8.3)	38 (22.5) ***	14 (8.3)	50 (29.6) ***
ADA glycemic target: HbA1c <7%	62 (51.7)	67 (55.8)	85 (50.3)	102 (60.4) *	85 (50.3)	90 (53.2)
HEDIS guidance: HbA1c <8.0%	87 (72.5)	91 (75.8)	123 (72.8)	130 (76.9)	123 (72.8)	113 (66.9)

*** p-value <0.001; ** p-value <0.01; * and p-value <0.05. The statistical significance was assessed using McNemar's test for baseline versus 5 years, except for the diabetes remission category.

HbA1c available in 120 of 122 completers

LOCF, missing value imputed as last observation carried forward

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Disclosure

B.M.Volk: Employee; Virta Health Corp., Stock/Shareholder; Virta Health Corp. **S.Hallberg:** Advisory Panel; Atkins Nutritionals Inc., Employee; Virta Health Corp., Stock/Shareholder; Virta Health Corp. **A.L.Mckenzie:** Employee; Virta Health Corp., Stock/Shareholder; Virta Health Corp. **S.J.Athinarayanan:** Employee; Virta Health Corp. **M.Vantieghem:** Employee; Virta Health Corp., Stock/Shareholder; Virta Health Corp. **R.N.Adams:** Employee; Virta Health Corp. **C.G.P.Roberts:** Employee; Virta Health Corp., Stock/Shareholder; Virta Health Corp. **R.E.Ratner:** Employee; Virta Health Corp. **J.Volek:** Advisory Panel; Abbott Diagnostics, Simply Good Foods, Stock/Shareholder; Virta Health Corp. **S.Phinney:** Employee; Virta Health Corp.

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Post hoc analyses of surrogate markers of non-alcoholic fatty liver disease (NAFLD) and liver fibrosis in patients with type 2 diabetes in a digitally supported continuous care intervention: an open-label, non-randomised controlled study

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ABSTRACT

Objective One year of comprehensive continuous care intervention (CCI) through nutritional ketosis improves glycosylated haemoglobin(HbA1c), body weight and liver enzymes among patients with type 2 diabetes (T2D). Here, we report the effect of the CCI on surrogate scores of non-alcoholic fatty liver disease (NAFLD) and liver fibrosis.

Methods This was a non-randomised longitudinal study, including adults with T2D who were self-enrolled to the CCI (n=262) or to receive usual care (UC, n=87) during 1 year. An NAFLD liver fat score (N-LFS) >−0.640 defined the presence of fatty liver. An NAFLD fibrosis score (NFS) of >0.675 identified subjects with advanced fibrosis. Changes in N-LFS and NFS at 1 year were the main endpoints.

Results At baseline, NAFLD was present in 95% of patients in the CCI and 90% of patients in the UC. At 1 year, weight loss of ≥5% was achieved in 79% of patients in the CCI versus 19% of patients in UC (p<0.001). N-LFS mean score was reduced in the CCI group (−1.95±0.22, p<0.001), whereas it was not changed in the UC (0.47±0.41, p=0.26) (CCI vs UC, p<0.001). NFS was reduced in the CCI group (−0.65±0.06, p<0.001) compared with UC (0.26±0.11, p=0.02) (p<0.001 between two groups). In the CCI group, the percentage of individuals with a low probability of advanced fibrosis increased from 18% at baseline to 33% at 1 year (p<0.001).

Conclusions One year of a digitally supported CCI significantly improved surrogates of NAFLD and advanced fibrosis in patients with T2D.

Trial registration number NCT02519309; Results.

Strengths and limitations of this study

- This is a longitudinal study including 262 continuous care intervention and 87 usual care patients with type 2 diabetes who have higher risk in developing non-alcoholic fatty liver disease (NAFLD).
- This study performed exploratory association analyses to demonstrate the relationship between glycaemic improvements and improvements in alanine aminotransferase levels.
- The assessment of resolution of steatosis and fibrosis is limited by the sensitivity and specificity of the non-invasive markers used in the study.
- The patients were restricted in their carbohydrate intake and monitored for their nutritional ketosis state, but dietary energy, macronutrient and micronutrient intakes were not assessed.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is an important cause of chronic liver disease, hepatocellular carcinoma and liver transplant worldwide and is associated with increased risk of heart disease, diabetes, chronic kidney disease and malignancies.[1–4] NAFLD is highly prevalent (~70%) among patients with obesity and type 2 diabetes (T2D).[5] T2D is usually associated with the more aggressive form of NAFLD, including non-alcoholic steatohepatitis (NASH; indicating significant hepatocellular injury) and advanced fibrosis[6] and is linked with high risk for all-cause and liver-related mortality.[7–10] Currently, there are no approved pharmacological interventions for NASH. Weight loss (WL) via lifestyle changes including dietary modification and exercise is the first-line intervention used in treating and improving NAFLD/NASH.[11 12] However, the majority of patients do not achieve or

sustain targeted WL goals.[11 13] Previous studies show a close relationship between the degree of weight reduction and improvements in most of the NASH-related features, including steatosis, inflammation, fibrosis, insulin resistance and elevated liver enzymes, irrespective of the type of diet consumed.[13–22] However, there is an intense debate about what types of diet are most effective for treating NASH and, to date, the optimal degree of energy restriction and macronutrient composition of dietary interventions in subjects with NASH and T2D are not well defined.[12]

Low-carbohydrate, high-fat (LCHF) and ketogenic diets have demonstrated a superior WL effect to low-fat, high-carbohydrate diets in adults with overweight and obesity[23–26] and short-term interventions with very low carbohydrate diets are associated with improved insulin sensitivity and glycaemic control.[27 28] Lower consumption of carbohydrate, LCHF and ketogenic diets improve appetite control, satiety and/or reduce daily food intake helping to limit dietary energy consumption while maintaining patient-perceived vigour.[29] In patients with NAFLD, the beneficial effects of LCHF diets on liver enzymes and intrahepatic lipid content (IHLC) have been explored with contradictory results. Among studies with varied carbohydrate intakes, some reported a significant reduction of aminotransferases,[16 30–32] while others did not report significant changes in these enzymes.[17 33 34] A recent meta-analysis of pooled data from 10 clinical trials reported that low carbohydrate diet (LCD) in patients with NAFLD led to a significant reduction in IHLC.[35]

We recently demonstrated that 1 year of a telemedicine-based comprehensive continuous care intervention (CCI) with carbohydrate restriction-induced ketosis and behaviour change support significantly reduced glycosylated haemoglobin (HbA1c) level and medication usage in patients with T2D.[36] The effectiveness of the CCI relies in maintaining a carbohydrate-restricted diet and monitoring compliance with the dietary regimen by assessing the patient's nutritional ketosis by blood tests during the year. We also demonstrated that 1 year of the CCI was effective in improving liver enzymes, where mean alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) were reduced by 29%, 20% and 13%, all p<0.01, respectively. These findings highlight the beneficial effect of the CCI on diabetes management and in ameliorating the liver-related injury. These changes were not reported in the usual care (UC) patients receiving standard diabetes care treatment. Therefore, in the current post hoc analysis, we assessed 1 year within-group and between-group (CCI vs UC) differences in non-invasive liver markers of steatosis (NAFLD liver fat score (N-LFS)) and fibrosis (NAFLD fibrosis score (NFS)) in the full study sample (CCI and UC cohorts). In addition, we assessed these outcomes in the subgroup of patients with abnormal ALT at baseline (ALT levels of >30 U/L in men and >19 U/L in women). Among all patients, ancillary aims included assessing if changes in weight and HbA1c were associated with ALT and metabolic parameter improvements and potential relationships between changes in the ALT with other metabolic parameters.

METHODS

The design and primary results of this study were previously published, and the current results are based on a 1-year post hoc analysis using the data collected from the same cohort in that clinical study (*Clinicaltrials.gov identifier: NCT02519309*).[36] A brief description of the study design, participants and interventions are listed in the online supplementary appendix (methods section). Briefly, this was a non-randomised and open-label controlled longitudinal study, including patients 21–65 years of age with a diagnosis of T2D and a body mass index (BMI) of >25 kg/m^2. Furthermore, patients were excluded if they had significant alcohol intake (average consumption of three or more alcohol-containing beverages daily or consumption of more than 14 standard drinks per week), presence of any other cause of liver disease or secondary causes of NAFLD and decompensated cirrhosis.

Patient and public involvement

Patients were not involved in the design and implementation of the study. Patient participants have been thanked for their participation in all resulting manuscripts and will receive information on publications on study completion.

Study recruitment and intervention

Patients participating in the CCI had access to a remote care team consisting of a personal health coach and medical providers (physician or nurse practitioner). The participants in the CCI self-selected between two different educational modes, either via on-site education classes (n=136, CCI on-site) or via web-based educational content (n=126, CCI virtual). The CCI patients were routinely assessed for nutritional ketosis based on blood beta-hydroxybutyrate (BHB) concentrations. We also recruited and followed a cohort of UC patients with T2D (n=87) who received a standard diabetes care treatment from their primary care physician or endocrinologist without modification.[36 37]

Outcomes

Primary outcomes: NAFLD liver fat and liver fibrosis by non-invasive surrogate markers

N-LFS is a surrogate marker of fatty liver that includes the presence of the metabolic syndrome, T2D, fasting serum insulin, AST and the AST/ALT ratio. An N-LFS cut-off of >−0.640 predicts liver fat (>5.56% of hepatocytes) with a sensitivity of 86% and specificity of 71%.[38 39] NFS is a widely validated biomarker for identifying patients at different risks of fibrosis severity. NFS is derived from age, BMI, hyperglycaemia, the AST/ALT ratio, platelet and albumin. The NFS threshold of <−1.455 can reliably exclude patients with advanced fibrosis (negative predictive value ≈92%) and >0.675 can accurately detect

subjects with advanced fibrosis (positive predictive value ≈85%).[40–42] The equations for calculating both scores are displayed in the online supplementary appendix (methods section).

Ancillary outcomes: other biochemical markers

Results from other metabolic (HbA1c, fasting glucose, fasting insulin, homeostatic model assessment-insulin resistance (HOMA-IR), triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol and low-density lipoprotein cholesterol), liver (ALT, AST and ALP), kidney (creatinine and estimated glomerular filtration rate (eGFR)), BHB and high-sensitivity C reactive protein parameters were previously published in the full CCI and UC cohort.[36] These additional biochemical markers were assessed in the subset analyses of patients with abnormal ALT at baseline.[43]

Statistical analyses

First, we examined the assumptions of normality and linearity. According to Kline's guidelines,[44] seven outcomes (ie, N-LFS, ALT, AST, fasting insulin, triglycerides, C reactive protein and BHB) were positively skewed. We explored two approaches to handling the skewed variables: natural log-transformations and removing the top 1% of values. For N-LFS, which includes both positive and negative values, a modulus log-transformation[45] was performed instead of a natural log-transformation. For every variable except triglycerides, both approaches resulted in new skew and kurtosis values falling within the acceptable range. We conducted sensitivity analyses related to our first aim to compare the two approaches. The results did not differ between the two approaches, and to make interpretation feasible, we report results from the approach of removing the top 1% of values for the linear mixed-effects model (LMM) analyses. For triglycerides, analyses were performed on the log-transformed variable; p values reported are based on analyses with the transformed variable, but the means and SEs reported were computed from the original variable without any adjustments. For both analysis of covariance (ANCOVA) and correlation analyses, the natural or modulus log-transformed variables were used to determine the association.

The first aim of the study was to examine: (1) within-group changes in the study outcomes from baseline to 1 year and (2) between-group differences (CCI vs UC) in the study outcomes at 1 year. The on-site and virtual CCI patients were grouped together for analyses since no significant differences were observed in biochemical markers between these two modes of educational delivery.[36] We performed LMMs in SPSS statistics software to estimate the within-group and between-group differences. The LMMs included fixed effects for time, group (CCI vs UC) and time by group interaction. Covariates included baseline age, sex, race (African-American vs other), diabetes duration, BMI and insulin use. This maximum likelihood-based approach uses all available repeated data, resulting in an intent-to-treat analysis. An unstructured covariance structure was specified for all models to account for correlations between repeated measures. Most analyses were conducted on a subsample of participants with abnormal (>30 U/L in men and >19 U/L in women)[46] ALT at baseline (195 of 347; 157 CCI and 38 UC). We also conducted analyses assessing changes in N-LFS, NFS, albumin and platelets on the full study sample because results were not previously reported. In addition, we examined changes in the proportions of participants meeting clinically relevant cut-offs for N-LFS, NFS and ALT. Within-group changes in the proportions from baseline to 1 year were assessed using McNemar's test. Between-group differences in proportions were assessed using χ^2 test. For this set of analyses, multiple imputation (20 imputations) was used to replace missing values from baseline and 1 year with a set of plausible values, facilitating an intent-to-treat analysis.

The second study aim was to explore relationships between: (1) changes in WL and HbA1c categories and its associations with ALT and metabolic parameters improvements and (2) changes in ALT and metabolic variables. Multiple imputation was also used to handle missing data for aim two analyses. We performed one-way longitudinal ANCOVA analyses for comparisons between different cutoffs of WL (<5%, 5%–10% and >10%) and with changes in diabetes-related and liver-related continuous variables. Covariates included baseline value of the dependent variables and BMI. Trend analyses were performed using Mantel-Haenszel χ^2 tests to assess changes in the proportions of patients meeting clinical cut-offs (for ALT, N-LFS and NFS normalisation) within different weight and HbA1c categories. An adjusted OR was calculated to measure the strength of association between HbA1c changes and ALT normalisation using logistic regression. The logistic regression analysis was adjusted by BMI, age, gender and baseline dependent covariates. Unadjusted and adjusted Pearsons' correlations were performed to identify relationships between changes in ALT levels and changes in metabolic-related and lipid-related parameters from baseline to 1 year. Adjusted correlations were also performed while controlling for baseline dependent covariates, baseline age, sex, race (African-American vs other), diabetes duration, BMI and insulin use. All CIs, significance tests and resulting p values were two sided, with an alpha level of 0.05. A Bonferroni correction was applied to each set of analyses (LMM or ANCOVA) to control the family-wise error rate. The Bonferroni adjusted p value=0.05/19 variables=0.0025 was used to determine statistical significance for each set of hypothesis-driven analyses.

RESULTS

Baseline features of participants

Recruitment and baseline results were published previously.[36] Briefly, between August 2015 and April 2016, 262 and 87 patients were enrolled in the CCI and UC groups,

respectively. Online supplementary figure 1 shows the flow of patients through the study. At baseline, average age was 53.4±8.7 years and 226 participants (65%) were female. The average time since T2D diagnosis was 8.3±7.2 years and 314 subjects (90%) were obese with a mean BMI of 39.5.[36] Two hundred and ninety-three participants (84%) were on medication for diabetes, and 118 (34%) were insulin users.[36] The proportion of patients with abnormal ALT was higher in CCI (58%) compared with the UC (44%). At baseline, 330 subjects (95%) had suspicion of NAFLD and fewer patients (69 of 349 (20%)) had a NFS threshold of <−1.455 indicating low probability of advanced fibrosis. Compared with UC, mean baseline BMI was significantly higher in patients in the CCI. The remaining patient demographics and baseline features were generally not different between the two groups.[36 47]

Influence of intervention and time on 1-year study endpoints

Non-invasive markers of steatosis (N-LFS) and NAFLD fibrosis (NFS)

After 1 year, the CCI decreased N-LFS and NFS for the full cohort and among patients with abnormal ALT at baseline, whereas no changes were observed in the UC full cohort or subset (table 1). There were significant between group (CCI vs UC) differences in N-LFS and NFS observed in both the full and abnormal baseline ALT cohort at 1 year (table 1). Notably, the proportion of patients with suspected steatosis reduced from 95% to 75% at 1 year in the CCI, whereas no change occurred in UC. At 1 year, the proportion of patients without fibrosis increased from 18% to 33% in CCI group, p<0.001, but no change occurred in the UC. Similar to the full cohort, the proportion of patients with suspected steatosis was reduced from 99% to 76%, p<0.001,and proportion of those without fibrosis increased from 20% to 37%, p<0.001, through 1 year among CCI patients with abnormal ALT levels (table 2). Between-group (CCI vs UC) differences at 1 year are listed in table 1.

Metabolic parameters

At 1 year, beneficial changes observed in the metabolic parameters of the full CCI cohort[36 47] were also reported in the subset of patients with abnormal baseline ALT, including reduction of HbA1c, fasting glucose, fasting insulin, HOMA-IR, triglycerides (all p<0.001) and increase of HDL cholesterol (p<0.001) (table 1). No changes in metabolic parameters were observed in the UC group. Between-group (CCI vs UC) differences at 1 year are listed in table 1.

Other liver-related, kidney function tests and parameters

Among CCI patients with abnormal ALT at baseline, significant reductions in the liver enzymes were observed (table 1), as previously reported in the full CCI cohort. No changes in liver-related tests were observed in the UC group. Among patients with increased ALT levels at baseline, 93 (61%) of 153 participants enrolled in the CCI versus 3 (8%) of 38 patients in UC had ALT normalisation at 1 year (table 2). Significant within-CCI changes were observed for albumin and platelet in the full CCI cohort, whereas in the subsample of patients with abnormal baseline ALT, there was only a significant decrease in the platelet (table 1). As reported in the full CCI cohort,[36] significant changes in C reactive protein and BHB concentrations were found in the subset of CCI patients with abnormal baseline ALT over 1 year. These changes were not found in the UC group. When adjusted for multiple comparisons, no significant changes in creatinine or eGFR were found in either the CCI or UC group. Between-group differences at 1 year are listed in table 1.

Associations between WL and study outcomes in the CCI group

At 1 year, WL of ≥5% was achieved in 79% of CCI patients with 54% achieving WL of ≥10%. The proportion of patients losing weight was lower in the UC group with only 17 UC participants (19.5%) achieving ≥5% WL and only 4 (6%) with ≥10% WL (online supplementary figure 2). In the CCI group, there was a trend towards greater mean percentage WL by higher baseline BMI classification, especially in patients losing more than 5% or 10% of body weight (online supplementary table 1). As shown in table 3, there were relationship trends between the degree of 1 year of WL (%) and changes in liver, metabolic and non-invasive markers of steatosis and fibrosis among CCI participants. At 1 year, the CCI patients who achieved WL ≥10% showed the greatest reductions in N-LFS (p<0.001) and NFS (p<0.001), whereas no statistically significant differences were found between patients with WL from 5% to 10% versus <5%. Similarly, patients who achieved WL ≥10% also showed decreases in HbA1c (p<0.001) and triglycerides (p<0.001) from baseline to 1 year. The 1-year probability of suspected fatty liver (N-LFS >−0.64) was lower (66%) among patients with WL ≥10% compared with the other WL groups (<5% (85%) and 5%–10% (86%)). The proportion of patients with low likelihood of fibrosis at 1 year was higher among patients with WL ≥10% (41%) versus patients with WL of 5%–10% (26%) and <5% (22%).

Correlation analyses between changes in ALT levels with changes in metabolic parameters in the CCI group

In the CCI group, changes in HbA1c, weight and fasting glucose from baseline to 1 year were associated with changes in ALT levels in the full cohort (HbA1c: r=0.148, p=0.03; weight: r=0.198, p=0.004; fasting glucose: r=0.176, p=0.004) and among patients with abnormal levels of ALT at baseline (HbA1c: r=0.253, p=0.005; weight: r=0.278, p=0.003, fasting glucose: r=0.305, p<0.001) (table 4). Changes in other lipid markers did not correlate with changes in ALT levels (table 4). Figure 1A–D displays 1-year associations between change in HbA1c and normalisation of ALT levels. In the full CCI group, 141 (70%) of 201 patients with HbA1c reductions of ≥ 0.5% at 1 year had normal ALT levels (figure 1A). Among CCI patients with abnormal ALT levels at baseline, 77 (65%) of 119 patients

Table 1 Estimated marginal means and mean changes in metabolic, liver-related and non-invasive markers at baseline and after 1 year of the CCI and UC interventions

	Baseline		1 year		Change	
Variables	**Mean±SE**	**P value**	**Mean±SE**	**P value**	**Mean difference±SE**	**P value**
Full cohort (CCI, n=262 and UC, n=87)						
Non-invasive biomarker						
NAFLD-LFS*†						
CCI	3.26±0.21		1.30±0.19		−1.95±0.22	3.3×10^{-16}
UC	3.25±0.38		3.71±0.35		0.47±0.41	0.26
CCI versus UC	0.01±0.44	0.44	−2.41±0.41	9.8×10^{-9}		
NAFLD fibrosis score*						
CCI	−0.32±0.06		−0.97±0.07		−0.65±0.06	6.5×10^{-22}
UC	−0.45±0.11		−0.19±0.12		0.26±0.11	0.02
CCI versus UC	0.13±0.13	0.31	−0.78±0.14	4.3×10^{-8}		
Liver-related tests						
Albumin (g/dL)*						
CCI	4.43±0.02		4.51±0.02		0.08±0.02	4.7×10^{-6}
UC	4.42±0.04		4.42±0.03		−0.01±0.03	0.87
CCI versus UC	0.01±0.04	0.84	0.09±0.04	0.02		
Platelet ($\times 10^9$)*						
CCI	250.52±3.86		227.60±3.69		−22.92±2.28	1.6×10^{-20}
UC	252.96±6.91		241.87±6.53		−11.09±3.88	0.005
CCI versus UC	−2.44±8.03	0.76	−14.27±7.62	0.06		
Abnormal ALT cohort (CCI: n=153 and UC: n=38)						
Non-invasive biomarker						
NAFLD-LFS‡†						
CCI	3.96±0.28		1.46±0.26		−2.50±0.30	1.5×10^{-13}
UC	4.44±0.58		4.53±0.57		0.09±0.66	0.9
CCI versus UC	−0.48±0.65	0.46	−3.06±0.63	2.7×10^{-6}		
NAFLD fibrosis score‡						
CCI	−0.43±0.08		−1.14±0.09		−0.71±0.08	7.5×10^{-15}
UC	−0.62±0.17		−0.35±0.18		0.26±0.17	0.12
CCI versus UC	0.19±0.19	0.33	−0.79±0.20	0.0002		
Metabolic parameters						
HbA1c (%)‡						
CCI	7.50±0.10		6.16±0.10		−1.35±0.11	3.6×10^{-25}
UC	7.10±0.21		7.32±0.18		0.22±0.23	0.33
CCI versus UC	0.41±0.23	0.08	−1.16±0.20	3.4×10^{-8}		
Fasting glucose (mg/dL)‡						
CCI	158.34±4.42		124.05±3.94		−34.29±5.10	2.4×10^{-10}
UC	139.79±9.15		152.13±8.08		12.34±10.37	0.24
CCI versus UC	18.55±10.19	0.07	−28.09±9.05	0.02		
Fasting insulin (m/UL)‡†						
CCI	30.16±1.75		18.01±1.56		−12.15±1.78	3.0×10^{-10}
UC	32.15±3.63		30.01±3.41		−2.14±3.82	0.58
CCI versus UC	−1.99±4.04	0.62	−12.00±3.77	0.002		
HOMA-IR‡						
CCI	9.57±0.60		5.18±0.70		−4.38±0.78	8.7×10^{-8}
UC	11.51±1.18		13.73±1.43		2.22±1.56	0.16
CCI versus UC	−1.95±1.33	0.14	−8.56±1.60	3.7×10^{-7}		

Continued

Table 1 Continued

	Baseline		1 year		Change	
Variables	**Mean±SE**	**P value**	**Mean±SE**	**P value**	**Mean difference±SE**	**P value**
Triglycerides (mg/dL)‡§						
CCI	197.54±8.74		162.59±15.85		−34.95±17.35	2.7×10^{-9}
UC	232.18±24.87		267.29±47.90		35.11±51.34	0.62
CCI versus UC	−34.64±21.50	0.12	−104.70±39.84	0.0001		
Cholesterol (mg/dL)‡						
CCI	181.58±3.35		197.13±4.46		15.55±4.05	0.0001
UC	178.91±7.02		182.69±9.51		3.78±8.68	0.66
CCI versus UC	2.67±7.82	0.73	14.44±10.53	0.17		
HDL cholesterol (mg/dL)‡						
CCI	41.67±1.10		50.18±1.30		8.51±1.15	9.2×10^{-12}
UC	36.60±2.30		33.45±2.77		−3.15±2.46	0.2
CCI versus UC	5.07±2.56	0.05	16.73±3.07	1.8×10^{-7}		
LDL cholesterol (mg/dL)‡						
CCI	100.31±2.85		117.16±3.42		16.86±3.26	8.7×10^{-7}
UC	98.12±6.23		90.22±7.87		−7.90±7.56	0.3
CCI versus UC	2.19±6.88	0.75	26.94±8.60	0.002		
Liver-related tests						
ALT (U/L)‡†						
CCI	37.00±1.24		23.55±1.32		−13.44±1.59	2.7×10^{-14}
UC	37.86±2.56		38.04±2.68		0.18±3.23	0.96
CCI versus UC	−0.86±2.86	0.76	−14.49±3.01	3.5×10^{-6}		
AST (U/L)‡†						
CCI	27.11±0.97		19.77±0.83		−7.34±1.00	8.9×10^{-12}
UC	27.69±2.03		28.55±1.73		0.86±2.09	0.68
CCI versus UC	−0.59±2.26	0.8	−8.78±1.93	1.1×10^{-5}		
ALP (U/L)‡						
CCI	74.07±2.00		64.53±2.02		−9.55±1.33	2.5×10^{-11}
UC	79.79±4.16		81.02±4.18		1.23±2.68	0.65
CCI versus UC	−5.72±4.64	0.22	−16.49±4.67	0.0005		
Albumin (g/dL)‡						
CCI	4.50±0.02		4.56±0.02		0.06±0.02	0.004
UC	4.52±0.05		4.48±0.05		−0.04±0.05	0.35
CCI versus UC	−0.02±0.05	0.64	0.08±0.05	0.11		
Platelet ($\times10^9$)‡						
CCI	247.45±5.21		225.87±5.06		−21.57±3.11	9.8×10^{-11}
UC	249.46±10.84		240.78±10.48		−8.69±6.30	0.17
CCI versus UC	−2.02±12.09	0.87	−14.90±11.71	0.21		
Kidney function tests						
Creatinine (mg/dL)‡						
CCI	0.86±0.02		0.82±0.01		−0.05±0.01	0.0005
UC	0.83±0.03		0.83±0.03		−0.01±0.03	0.85
CCI versus UC	0.03±0.03	0.39	−0.01±0.03	0.71		
eGFR (CKD-EPI)‡						
CCI	81.53±0.90		83.32±0.88		1.79±0.75	0.02
UC	82.26±1.86		81.72±1.81		−0.54±1.53	0.72
CCI versus UC	−0.73±2.08	0.72	1.60±2.03	0.43		
Other parameters						

Continued

Table 1 Continued

Variables	Baseline Mean±SE	P value	1 year Mean±SE	P value	Change Mean difference±SE	P value
CRP (mg/dL)‡†						
CCI	6.85±0.50		4.51±0.50		−2.34±0.48	2.4×10^{-6}
UC	9.41±1.03		9.84±1.04		0.43±0.97	0.66
CCI versus UC	−2.56±1.15	0.03	−5.33±1.16	8.2×10^{-6}		
BHB (mmol/L)‡†						
CCI	0.17±0.01		0.26±0.02		0.09±0.02	7.3×10^{-5}
UC	0.15±0.03		0.12±0.04		−0.03±0.04	0.45
CCI versus UC	0.02±0.03	0.5	0.14±0.04	0.002		

Unless otherwise noted, estimates reported were obtained from linear mixed-effects models that provide marginal means and mean changes, adjusting for baseline age, gender, race, diabetes duration, body mass index and insulin use.
This maximum likelihood-based approach uses all available repeated data, resulting in an intent-to-treat analysis.
Multiple comparisons were adjusted for Bonferroni corrections (P<0.0025).
However, because transformed numbers are difficult to interpret, non-transformed and unadjusted means, mean changes, and standard errors for participants who completed the study visit were computed and provided in the table.
*Full sample analysis.
†Variable was positively skewed and after removing the top 1% of values, skew and kurtosis values fell within acceptable ranges. Analyses were conducted on data excluding the top 1% of values for each variable, although due to the maximum likelihood approach all cases were still included in the analyses.
‡Subgroup analysis of participants with abnormal ALT at baseline. Abnormal ALT refers to >19 U/L for women and 30 U/L for men.
§Variable was positively skewed and a natural log transformation was performed. The linear mixed-effects model analysis including covariates was conducted on the transformed variable and significance values provided are from the transformed analysis.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BHB, beta-hydroxybutyrate; CCI, continuous care intervention; CKD-EPI, chronic kidney disease-epidemiological collaboration equation; CRP, C reactive protein; eGFR, estimated glomerular filtration rates; HbA1c, glycosylated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LFS, liver fat score; NAFLD, non-alcoholic fatty liver disease; UC, usual care.

with a reduction of ≥ 0.5% in HbA1c showed normalisation of ALT levels (figure 1B). One-year reduction of ≥0.5% in HbA1c increased the odds of ALT normalisation 2.4-fold (95% CI 1.09 to 5.3) after controlling for baseline levels of HbA1c, BMI, ALT, diabetes duration, insulin use and WL (%) at 1 year. Given that weight reductions

Table 2 Resolution of abnormal ALT, steatosis and fibrosis (as estimated using non-invasive liver markers cut-off) from baseline to 1 year in continuous care intervention (CCI) and usual care (UC)

Variables	CCI Baseline	CCI 1 year	CCI P value*	UC Baseline	UC 1 year	UC P value*	Between-groups p values†
Full cohort	**n=262**			**n=87**			
Abnormal ALT, n (%)‡	153 (58)	60 (23)	8.1×10^{-11}	38 (44)	35 (40)	0.664	0.006
NAFLD-LFS							
>−0.640, n (%)	250 (95)	197 (75)	7.9×10^{-10}	80 (92)	79 (91)	0.678	0.002
NAFLD fibrosis score							
<−1.455, n (%)	46 (18)	87 (33)	3.9×10^{-7}	23 (26)	22 (25)	1.0	0.139
Abnormal ALT at baseline	**n=153**			**n=38**			
NAFLD-LFS							
>−0.640, n (%)	151 (99)	117 (76)	1.8×10^{-7}	35 (92)	37 (97)	0.625	0.007
NAFLD fibrosis score							
<−1.455, n (%)	30 (20)	56 (37)	4.1×10^{-5}	11 (29)	11 (29)	1.0	0.266

NAFLD-LFS cut-off >−0.640 for detecting liver fat >5.56% (sensitivity: 86% and specificity: 71%).
NAFLD fibrosis score <−1.455 corresponds with low probability of advanced fibrosis (NPV ≈ 92%) and >0.675 indicates high probability of advanced fibrosis (PPV ≈ 85%).
*McNemar's test.
†χ^2 tests were used when appropriated.
‡Abnormal ALT refers to >19 U/L for women and 30 U/L for men.
ALT, alanine aminotransferase; LFS, liver fat score; NAFLD, non-alcoholic fatty liver disease; NPV, negative predictive value; PPV, positive predictive value.

Table 3 One-year associations between weight loss (%) and changes in liver-related and diabetes-related variables

Variables	CCI cohort, n=262 ≤5% n=54	5%–10% n=65	>10% n=143	P value
Liver-related parameters				
Δ ALT (U/L)*	−3.99±2.83	−7.30±2.32	−12.52±2.41	0.01
Δ Platelet ($\times 10^9$)*	−20.36±5.32	−25.33±4.38	−23.5±3.24	0.656
Δ ALP (U/L)*	−4.36±2.18	−9.70±1.93	−11.45±1.45†	0.007
Metabolic-related parameters				
Δ HbA1c (%)*	−0.92±0.21	−1.25±0.16	−1.58±0.13†	0.002
Δ Triglycerides (mg/dL)*	−6.25±39.3	−34.63±25.8	−63.8±13.9†	0.007
Δ Cholesterol (mg/dL)*	1.34±7.22	- 0.17±5.78	10.07±3.83	0.134
Δ HDL cholesterol (mg/dL)*	−0.84±1.8	6.17±1.51‡	10.41±1.07†	4.6×10^{-8}
Δ LDL cholesterol (mg/dL)*	3.42±8.14	0.53±5.15	12.41±3.79	0.183
Kidney function parameters				
Δ Creatinine (mg/dL)*	−0.023±0.022	−0.008±0.019	−0.065±0.017	0.039
Non-invasive biomarkers				
Δ NAFLD-LFS*	−0.197±0.86	−1.291±0.65	−2.805±0.44†	2.5×10^{-7}
>−0.640§, n (%)	46 (85%)	56 (86%)	95 (66%)	0.001
Δ NAFLD fibrosis score*	0.055±0.13	−0.351±0.10	−1.014±0.08†	2.6×10^{-15}
<−1.455§, n (%)	14 (26%)	14 (22%)	59 (41%)	0.007
Other parameters				
Δ CRP (mg/dL)*	−0.506±1.66	−2.831±1.0	−3.970±1.42	0.012
Δ BHB (mmol/L)*	0.017±0.06	0.061±0.03	0.203±0.03†	3.8×10^{-4}

Intention-to-treat analysis.
The sign means± SEs. P values represent difference between groups. Δ means change from baseline.
*Analysis of covariance (ANCOVA) while controlling by BMI and baseline values for each analysed covariate.
†Significant difference (p<0.001) between WL >10% as compared with WL 5%–10% and <5%.
‡Significant difference (p<0.001) between WL >10% and WL 5%–10% as compared with WL <5%.
§For categorical variables, p value for the Mantel-Haenszel χ^2 test for trend and for continuous variables.
All ANCOVA analyses were adjusted by Bonferroni test for multiple comparisons (p <0.0025).
ALT, alanine aminotransferase; ALP, alkaline phosphatase; BHB, beta-hydroxybutyrate; BMI, body mass index; CCI, continuous care intervention; CRP, C reactive protein; HbA1c, glycosylated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LFS, liver fat score; NAFLD, non-alcoholic fatty liver disease; WL, weight loss.

Table 4 Correlations change in ALT and changes in metabolic parameters

Variable	*Full CCI cohort* n=262 Unadjusted *r*	P value*	Adjusted *r*	P value*	*CCI cohort with abnormal baseline ALT levels* n=153† Unadjusted *r*	P value*	Adjusted *r*	P value*
Δ Body weight (%)	0.191	0.043	0.198	0.004	0.253	0.056	0.278	0.003
Δ Fasting glucose (mg/dL)	0.124	0.118	0.176	0.004	0.184	0.051	0.305	1.2×10^{-4}
Δ HbA1c (%)	0.176	0.043	0.148	0.033	0.220	0.018	0.253	0.005
Δ Triglycerides (mg/dL)	0.032	0.741	0.025	0.490	0.091	0.428	0.106	0.163
Δ Cholesterol (mg/dL)	−0.076	0.375	−0.031	0.563	−0.046	0.663	−0.020	0.605
Δ HDL cholesterol (mg/dL)	−0.115	0.160	−0.069	0.219	−0.145	0.182	−0.118	0.207
Δ LDL cholesterol (mg/dL)	−0.049	0.526	−0.022	0.476	−0.042	0.669	−0.032	0.690

ΔMeans change from baseline.
*Unadjusted and adjusted Pearson's correlations. Adjustments while controlling for individual baseline covariate levels, age, sex, race (African-American vs other), diabetes duration, body mass index and insulin use.
†ALT levels >19 in women and >30 in men.
ALT, alanine aminotransferase; CCI, continuous care intervention; HbA1c, glycosylated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

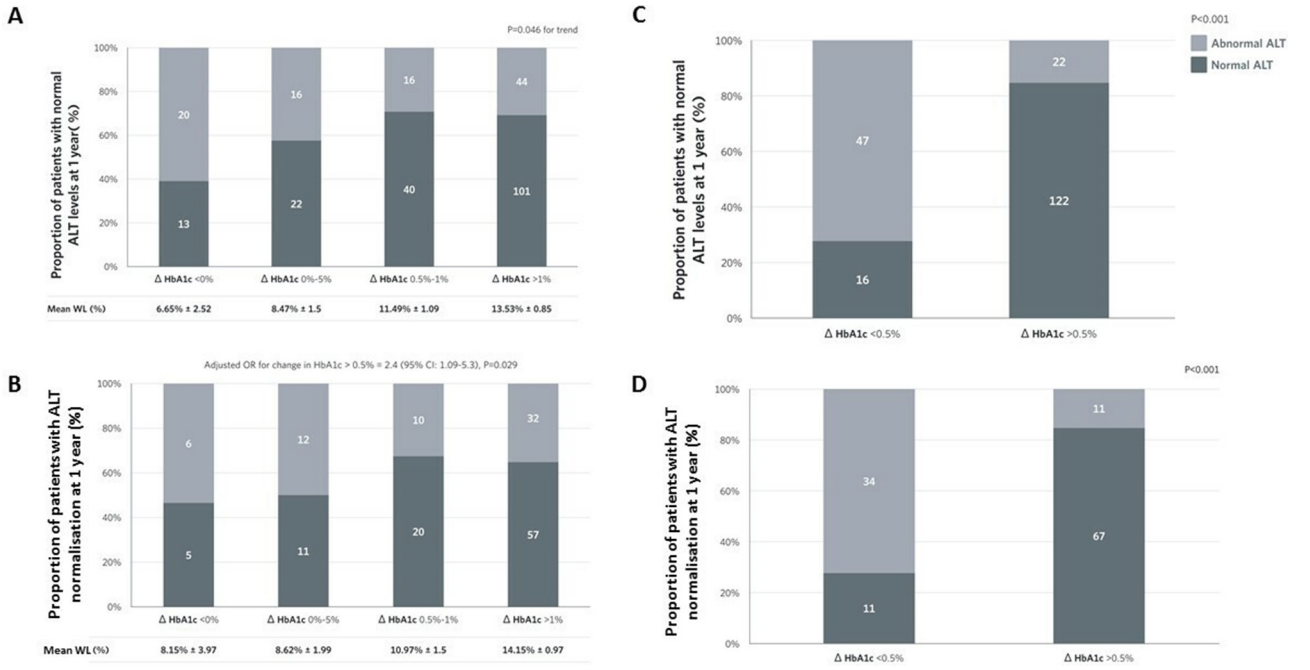

Figure 1 Association between reduction in HbA1c (%) and normalisation of ALT* levels at 1 year of intervention in CCI group. (A) Full CCI cohort (n=272). Higher proportion of patients with ALT normalisation were observed in HbA1c (%) reduction categories 0.5%–1.0%; 71% and >1.0%; 70%. (B) CCI patients with increased levels of ALT at baseline (n=153). higher proportion of patients with ALT normalisation were observed in HbA1c (%) reduction categories 0.5%–1.0%; 67% and >1.0%; 64%. Adjusted OR for change in HbA1c >0.5%=2.4 (95% CI 1.09 to 5.3), p=0.029. (C) CCI patients with weight loss ≥5% (n=207). Among patients with weight loss >5%, higher levels of ALT normalisation (85%) were observed in patients with HbA1c (%) reduction of >0.5%. (D) CCI patients with increased levels of ALT at baseline and weight loss ≥5% (n=123). Among patients with weight loss >5% and abnormal ALT levels at baseline, higher levels of ALT normalisation (86%) were observed in patients with HbA1c (%) reduction of >0.5%. *ALT levels <19 in women and <30 in men. ALT, alanine aminotransferase; CCI, continuous care intervention; HbA1c, glycosylated haemoglobin.

(≥ 5%) can be associated with changes in HbA1c level, we sought to explore whether a reduction of ≥ 0.5% in HbA1c was still associated with ALT normalisation, independent of WL (≥5%) (figure 1C,D). A reduction of ≥0.5% in HbA1c was associated with higher rates of ALT normalisation, regardless of whether or not 5% WL was achieved (p<0.001).

Safety

Adverse events during this trial were previously reported.[36] Mean platelet count was reduced in the CCI (−22.9±2.3, p<0.001) versus UC group (−11.1±3.9, p=0.005); however, the proportion of patients with a platelet count below 150×10^9L was not different between groups. There was no hepatic decompensation (variceal haemorrhage, ascites or hepatic encephalopathy) or ALT flare-up (>5 times the upper limit of normal) reported during the trial in either the CCI or UC group.

DISCUSSION

The findings of the current analysis show that 1 year of a digitally supported CCI reduced risk of fatty liver and advanced liver fibrosis in overweight and obese adults with T2D. Improvements were concurrent with improved glycaemic status, reduction in cardiovascular risk factors and decreased use of medications for diabetes and hypertension.[36 47] The beneficial effects extended to patients with increased levels of aminotransferase, thus indicating that remote care medically supervised ketosis is also effective in patients at risk of liver disease progression. The influence of carbohydrate restriction and nutritional ketosis on liver histology of patients with biopsy-proven NASH remains largely unexplored in the context of a well-designed randomised controlled trial. A pilot study including five patients with biopsy-proven NASH showed that 6 months of ketogenic diet (KD) (less than 20 g per day of carbohydrate) induced significant WL (mean of 13 kg) and four of five patients reduced liver fat, inflammation and fibrosis.[33] The current study provides evidence that a remote-care medically supervised KD can improve NASH and even fibrosis. A recent meta-analysis of 10 studies reported the effects of LCD on liver function tests in patients with NAFLD and concluded that LCD reduced IHLC but did not improve liver enzymes,[35] although heterogeneity among NAFLD populations and interventions were observed across the included studies.

Among CCI participants, correlations were also found between the improvements in HbA1c and ALT changes, even after controlling for WL and changes in insulin use. Among subjects with abnormal ALT levels at baseline, a reduction of ≥0.5% in HbA1c was associated with increased rates of ALT normalisation. This finding suggests that

liver enzyme improvements may be related to improvements in glycaemic control and insulin concentration in addition to WL. Importantly, few studies have directly compared the metabolic advantages of different diets for the treatment of NAFLD,[15 32 48] and the impact of dietary macronutrient composition remains largely unknown. Three studies have shown that low-carbohydrate and low-fat diets reduced liver fat, transaminases and insulin resistance to similar degrees,[15 21 48] whereas another study reported that a moderate hypocaloric LCD in insulin-resistant patients improved ALT levels more than a hypocaloric low-fat diet, despite equal WL.[48] Among patients with T2D, a 'moderate-carbohydrate modified Mediterranean diet' (35% carbohydrates, 45% high monounsaturated fat) showed greater ALT reductions than two other higher carbohydrate hypocaloric diets including the 2003 recommended American Diabetes Association (ADA) or low glycaemic index diets.[49]

Our results also demonstrated that non-invasive risk scores for fatty liver and fibrosis were improved in patients who underwent CCI as compared with the UC control, and greater reductions were observed in patients with the largest reductions in body weight (≥10%). Our results are consistent with previous studies reporting that LCD reduce intrahepatic lipid accumulation.[15 16 21 32 33] Likewise, 1 year liver fibrosis as assessed by NFS improved in the CCI group, and the proportion of patients with low likelihood of fibrosis increased from 18% to 33% at 1 year of intervention. Similar to previous studies addressing the impact of WL on NASH-related fibrosis,[13 50] we showed a relationship between the degree of WL and improvements in NFS.

LCD or KD have been proposed to more effectively reduce all features of the metabolic syndrome, which is present in approximately 80% of patients with NAFLD, compared with low-fat diets[51 52]; however, the physiological mechanisms are not fully established.[53–55] In line with our findings, Holland *et al*[56] showed that irrespective of physical exercise, rats fed a ketogenic formulation had lower liver triglycerides and lower activation of the proinflammatory Nuclear factor kappa Beta (NF-kB) pathway compared with rats fed Western and standard chow diets. Likewise, a recent human study using a 2-week isocaloric carbohydrate restricted diet demonstrated a drastic reduction of hepatic steatosis and a shift in lipid metabolism pathway from de novo lipogenesis to ß-oxidation and increased BHB production.[57] This shift in the lipid homeostasis following a short-term ketogenic diet occurred in conjunction with a shift in gut microbia towards increased folate production as well as decreased expression of key serum inflammatory markers.[57]

Strengths and weaknesses of this clinical trial have been previously described.[36] Some strengths of this study include a large cohort of patients with T2D and high suspicion of NAFLD, an intervention with 1 year of digitally supported continuous care including monitored adherence to nutritional ketosis and a control group of patients with T2D provided UC with standard nutritional recommendations.[36] Relative to prior outpatient interventions, the current study is unusual in the degree of health coach and physician support, the degree of prescribed carbohydrate restriction and the use of BHB as a blood biomarker of dietary adherence. These attributes may contribute to superior outcomes observed in the intervention group when compared with UC patients. The multicomponent approach used in the intervention encouraged the patient to adapt carbohydrate restriction through continuous monitoring of nutritional ketosis and provided behavioural support through interaction with their health coaches.

Some weaknesses of this study include the absence of imaging-proven or biopsy-proven NAFLD or NASH diagnosis and lack of random allocation to assign patients to intervention and control groups. Food was not provided for participants so dietary macronutrient and micronutrient contents and sources were not strictly controlled.

In conclusion, 1 year of a digitally supported CCI including individualised nutritional ketosis led to significant improvement in non-invasive markers of liver fat and fibrosis together with sustained WL in overweight and obese patients with T2D. A relationship was observed between the degree of WL and improvements in liver-related and non-liver-related outcomes with greater benefits in patients losing more than 10% of body weight. A reduction of ≥0.5% in HbA1c was independently associated with ALT normalisation even after controlling for WL. Medical interventions incorporating ketogenic diets appear effective for improving NAFLD and therefore may be an effective approach for reversing the natural history of NAFLD progression, although further studies are needed to confirm potential beneficial effect in patients with biopsy-confirmed NASH.

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Contributors EV-G, SJA, RNA, JPM and NC wrote the manuscript. ALM, NHB, SJH and SJA participated in data acquisition. EV-G and SJA analysed the data. NC, SJH, NHB, ALM, WWC, JPM, SDP and JSV supervised this particular analysis and edited the manuscript. All authors approved the final version of the manuscript.

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Competing interests SJA, SJH, NHB, ALM, RNA, JPM and SDP are employees of Virta Health Corp and have been offered stock options. SDP and JSV are founders of Virta Health Corp. EV-G, WWC and NC have nothing relevant to declare.

Patient consent Obtained.

Ethics approval Franciscan Health Lafayette Institutional Review Board.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data sets and statistical code used for the current study are available from the corresponding author on reasonable request.

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virta

The Cardiovascular Benefits of the Virta Treatment

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Summary

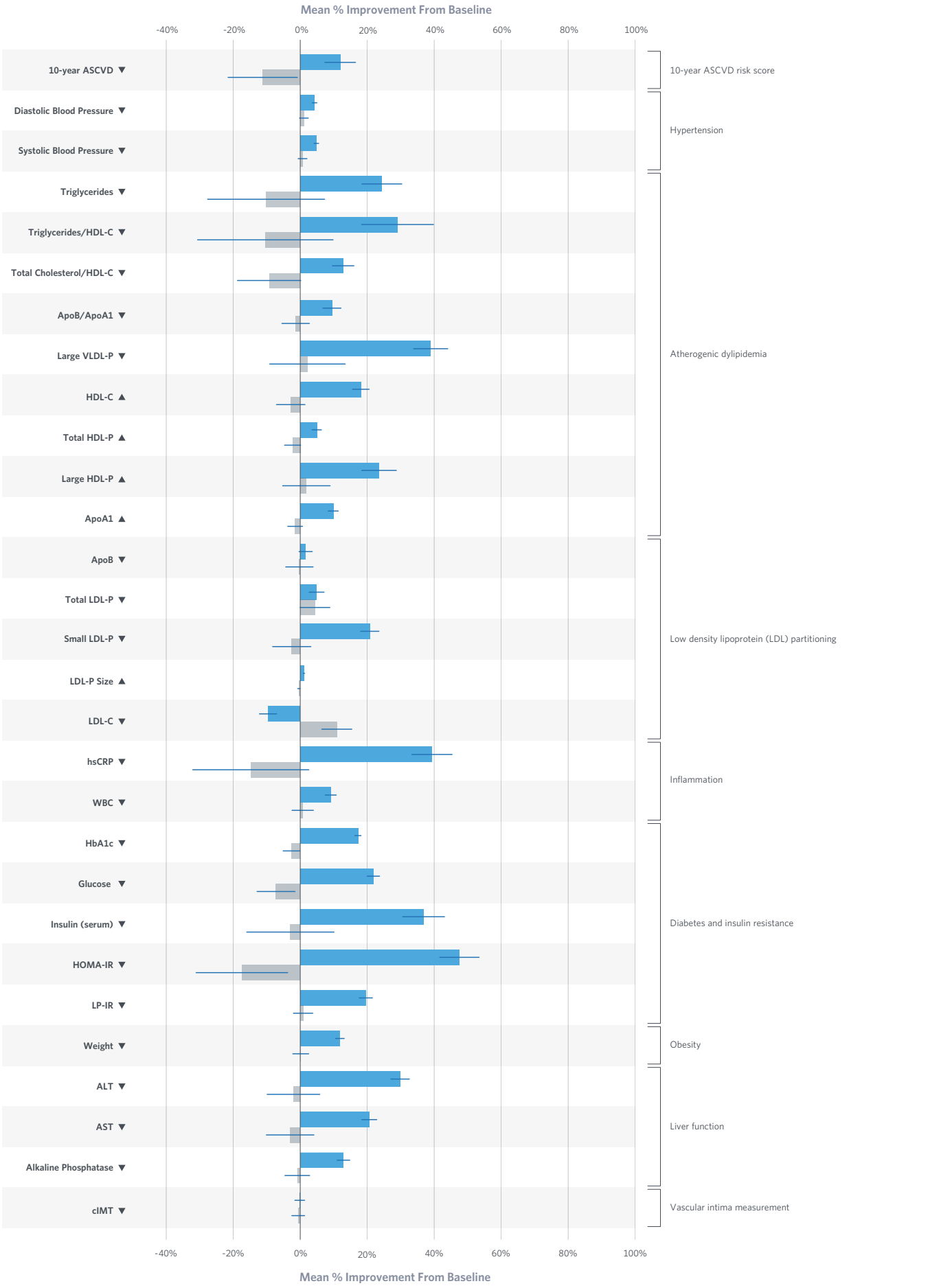
Cardiovascular disease (CVD) is the number one cause of morbidity and mortality in patients with type 2 diabetes (T2D) (Gregg et al., 2007). Virta Health provides the first clinically-proven treatment to reverse type 2 diabetes and other chronic metabolic diseases without the use of added medications or surgery. At one year, 60% of patients in the Virta clinical trial achieved diabetes reversal, defined as hemoglobin A1c (HbA1c) <6.5% without medication other than metformin. 94% of insulin users reduced or eliminated usage altogether and 83% of patients remained active in the trial (Hallberg et al., 2018; McKenzie et al., 2017). In addition to T2D improvements, patients demonstrate dramatic improvement in many cardiovascular risk factors indicating an opportunity to substantially reduce CVD complications in T2D populations (Bhanpuri et al., 2018).

Here, we systematically review 29 parameters associated with CVD which were tracked in the clinical trial, 25 of which show statistically significant improvement following 1-yr of Virta treatment. A usual care group by contrast saw no significant improvement in the 29 parameters.

These parameters can be grouped into the following categories:

1. 10-year ASCVD risk score (which improved by 11.9% following Virta treatment)
2. hypertension
3. atherogenic dyslipidemia
4. low density lipoprotein (LDL) partitioning
5. inflammation
6. diabetes and insulin resistance
7. obesity
8. liver function
9. vascular intima measurement
10. Medication usage for hypertension, cholesterol and diabetes was also tracked and substantial prescription reduction was demonstrated following Virta treatment

Together these findings provide a robust case for both near-term and projected long-term improvement in CVD outcomes in T2D patients with the Virta treatment.


Virta
Usual Care
Mean % Improvement From Baseline
-40%
-20%
0%
20%
40%
60%
80%
100%
10-year ASCVD ▼
Diastolic Blood Pressure ▼
Systolic Blood Pressure ▼
Triglycerides ▼
Triglycerides/HDL-C ▼
Total Cholesterol/HDL-C ▼
ApoB/ApoA1 ▼
Large VLDL-P ▼
HDL-C ▲
Total HDL-P ▲
Large HDL-P ▲
ApoA1 ▲
ApoB ▼
Total LDL-P ▼
Small LDL-P ▼
LDL-P Size ▲
LDL-C ▼
hsCRP ▼
WBC ▼
HbA1c ▼
Glucose ▼
Insulin (serum) ▼
HOMA-IR ▼
LP-IR ▼
Weight ▼
ALT ▼
AST ▼
Alkaline Phosphatase ▼
cIMT ▼
10-year ASCVD risk score
Hypertension
Atherogenic dylipidemia
Low density lipoprotein (LDL) partitioning
Inflammation
Diabetes and insulin resistance
Obesity
Liver function
Vascular intima measurement

Introduction

In August of 2015, Virta Health and Indiana University Health (IUH) began a 2-yr prospective longitudinal non-randomized controlled clinical trial (n=465) to determine efficacy, safety and sustainability of the Virta treatment for 262 T2D patients and 116 pre-diabetes patients with an additional 87 T2D patients receiving usual care. Virta treatment patients received online continuous remote care support including telemedicine, health coaching, individualized education for nutrition and behavior change (including nutritional ketosis), biometric feedback and peer support. Usual care patients were seen by an endocrinologist and met with a registered dietitian and diabetes educator. A description of the trial is provided by Bhanpuri et al., 2018; Hallberg et al., 2018; McKenzie et al., 2017 including 70-day and 1-yr outcomes for T2D patients. (Outcomes for pre-diabetes patients will be described in a future publication.) The trial is registered at Clinicaltrials.gov, Identifier NCT02519309.

Methods

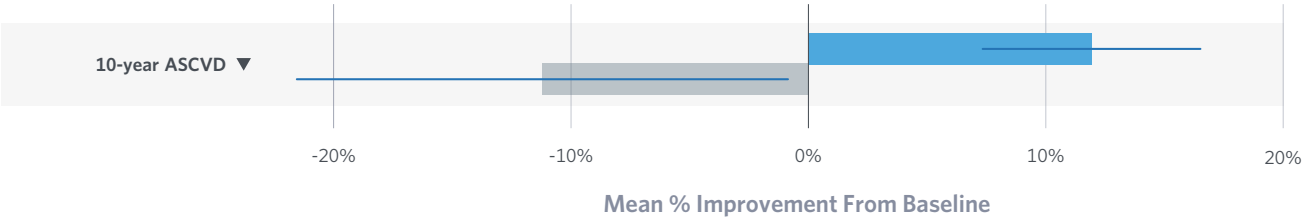
The statistical significance of biomarker changes for T2D patients following Virta treatment (n=262) or usual care (n=87) was determined by comparing baseline and 1-yr values. Two-sample t-tests were used for comparisons between groups and ANCOVA and paired t-tests were used for comparisons within groups. Both intent-to-treat with multiple imputation (provided here) and completers analysis were conducted with Bonferroni adjustment for the number of variables examined ($p<0.0017$) (Hallberg et al., 2018) ($p<0.0019$) (Bhanpuri et al., 2018). Most of the improvements in CVD risk observed in the Virta Health trial have precedence in the published literature describing the application of dietary changes including nutritional ketosis under medical supervision for T2D, pre-diabetes and metabolic syndrome patients. Examples are cited below with more extensive citations available in reviews by Feinman et al., 2015; Noakes and Windt, 2017. It should be noted that the biomarkers described here have varying degrees of validation from changes correlated with mortality in clinical trials, to correlations with mortality in epidemiological studies, to experimental support. Some are tightly correlated with one another whereas others are independent. Together, they provide a global picture of cardiometabolic change.

Results

A review of all scores, biomarkers, and medication use shows statistically significant improvement in 25 of 29 factors along with decreased medication use during the first year of the Virta treatment. For each measure, the forest plot shows the Virta treatment first in blue followed by the usual care in gray. Position of the bar indicates population mean and the black line indicates standard error. Movement to the right is considered favorable (i.e. improved biomarker status, decreased medication use) and movement to the left is considered unfavorable. Results are from the intention-to-treat analysis with missing values imputed. Next, we present these changes in ten sections.

1. Aggregate Cardiovascular Disease Risk Score Improves

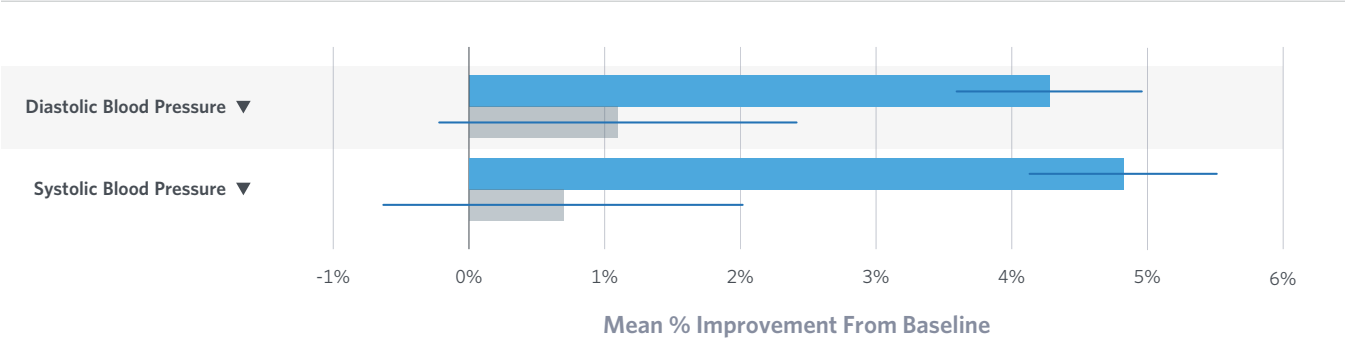
The aggregate atherosclerotic cardiovascular disease (ASCVD) risk score was developed by the American Heart Association and American College of Cardiology to estimate the 10-year and lifetime risks for atherosclerotic cardiovascular disease (ASCVD), defined as coronary death, nonfatal myocardial infarction, or fatal or nonfatal stroke based on the aggregation of systolic blood pressure, total, LDL and HDL cholesterol, along with diabetes history, medication use, age, sex, and race (Goff et al., 2014). Following 1-yr of the Virta treatment, the mean patient 10-year ASCVD risk score decreased 11.9% ($P=4.9x10^{-5}$) indicating a potential reduced risk of myocardial infarction or stroke. Usual care mean ASCVD risk increased 10.4% (P=0.17). Therefore, relative to the usual care group, the Virta treatment showed a trend toward greater risk reduction (net percent change of -22.3%, P=0.008) (Bhanpuri et al., 2018). (Note that taking a conservative approach, diabetes status was scored as unchanged in the calculation despite improvements observed in the Virta treatment group.)



A meta-analysis of 17 trials comparing low carbohydrate versus low fat diets showed a greater 10-yr ASCVD risk score improvement with the low carbohydrate groups (Sackner-Bernstein et al., 2015).

2. Hypertension Improves

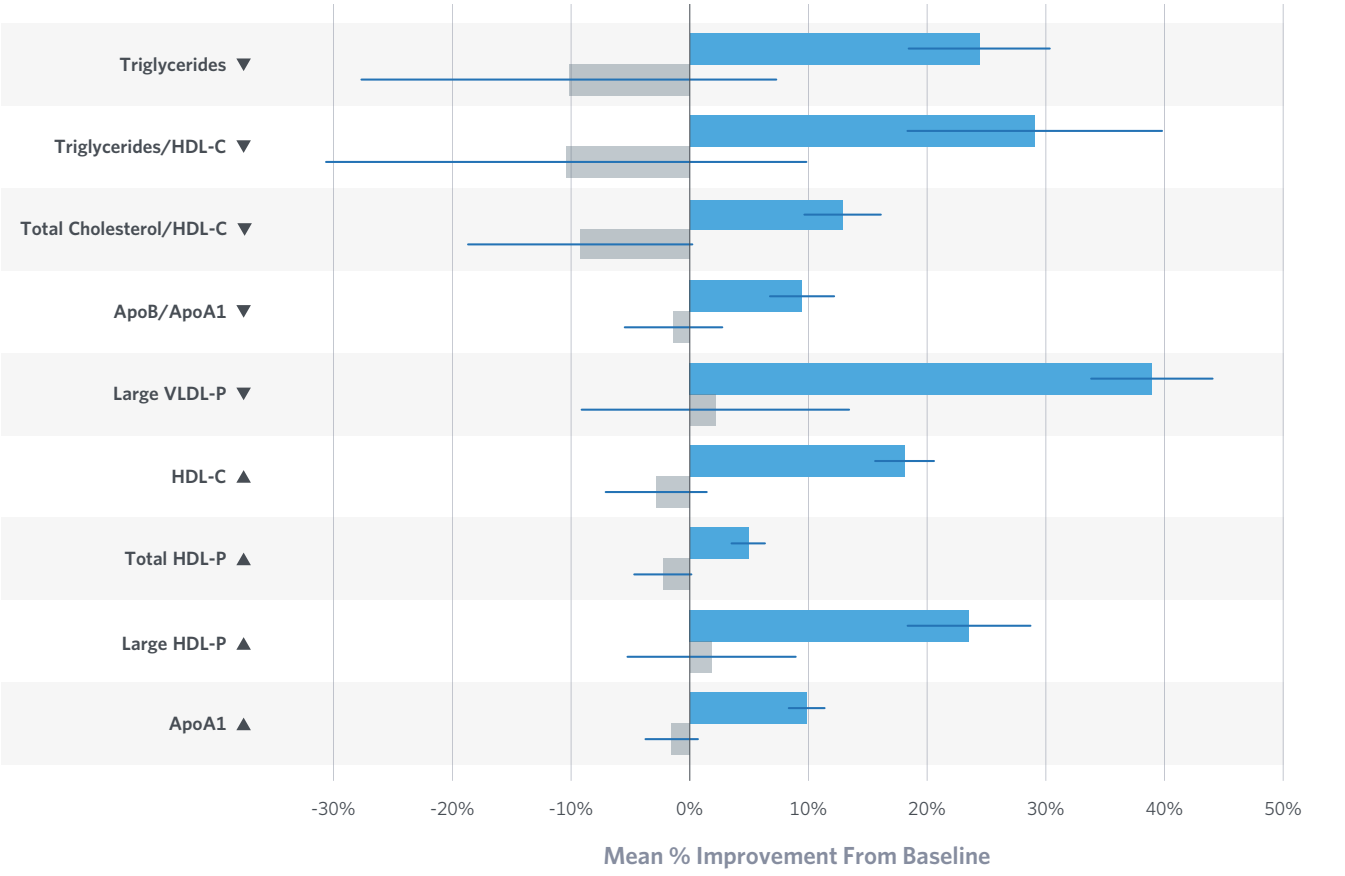
Strong evidence exists that hypertension is a primary cardiovascular risk factor; reduction in blood pressure (BP) is therefore a major target for medical therapy (Ettehad et al., 2016). Revised 2017 guidelines from the ACC/AHA task force recommend treatment, through lifestyle modification and/or medication, should begin at 130/80 mm Hg rather than 140/90 (Whelton et al., 2017). Following 1-yr of the Virta treatment, the mean patient systolic BP decreased 4.8% from 132 to 126 ($P=1.3x10^{-8}$) while mean patient diastolic BP decreased 4.3% from 83 to 79 ($P=7.2x10^{-8}$) (Bhanpuri et al., 2018). Blood pressure reductions in the Virta treatment group occurred simultaneous with reduced overall use of antihypertensive medication (-17.0%) and especially diuretics (-24.8%) as described in detail below (section 10). The usual care group showed no statistically significant change in BP at one year; 130/82 to 129/81 (P=0.67 and 0.45, respectively), and no reduction in use of antihypertensive medication.



Blood pressure reductions following carbohydrate restriction and/or nutritional ketosis have been demonstrated in several trials (Ballard et al., 2013; Shai et al., 2010; Tay et al., 2014).

3. Atherogenic Dyslipidemia Improves

Atherogenic dyslipidemia, a known risk factor for CVD (Fruchart et al., 2008) is highly prevalent in patients with T2D (Arca et al., 2012). The condition is characterized by lipid profile abnormalities including increased triglycerides and decreased high-density lipoprotein cholesterol (HDL-C). Furthermore, evidence suggests that elevated large very low-density lipoprotein particles (large VLDL-P) may be one of the key underlying abnormalities in atherogenic dyslipidemia (Adiels et al., 2008). In addition to impacting the eight factors shown here, atherogenic dyslipidemia also results in increased small LDL-P described below (section 4). Following 1-yr of the Virta treatment, mean fasting triglyceride was reduced 24.4% ($P<10^{-16}$), triglyceride/HDL-C ratio was reduced 29.1% ($P<10^{-16}$), total cholesterol/HDL-C ratio was reduced 11.2% ($P=1.7x10^{-5}$), ApoB/ApoA1 ratio was reduced 9.5% ($P=1.9x10^{-7}$),

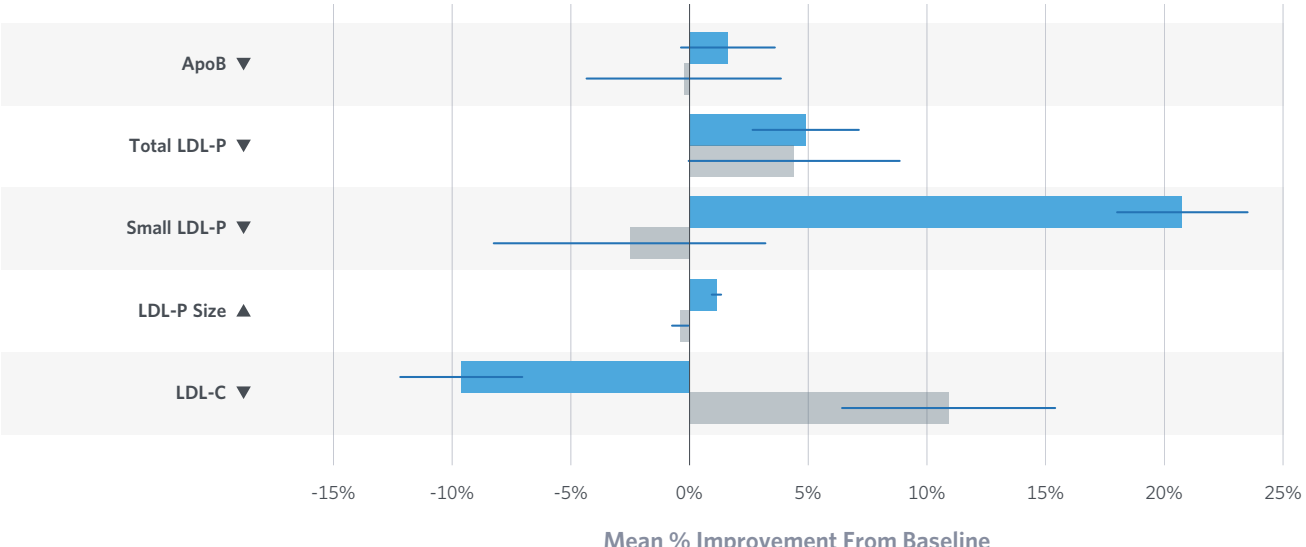


large VLDL-P was reduced 38.9% ($P=4.2x10^{-15}$), HDL-C increased 18.1% ($P<10^{-16}$), total HDL particles (HDL-P) increased 4.9% ($P=5.6x10^{-6}$), and large HDL-P increased 23.5% ($P=1.2x10^{-11}$). Apolipoprotein A1 (Apo A1), a marker of HDL particles, also increased 9.9% ($P<10^{-16}$) (Bhanpuri et al., 2018; Hallberg et al., 2018). All of these changes are favorable and together indicate an improvement of atherogenic dyslipidemia following the Virta treatment. The usual care group showed no statistically significant change in these parameters; triglyceride +10.1% (P=0.43), triglyceride/HDL-C ratio +9.8% (P=0.24), total cholesterol/HDL-C ratio +7.9% (P=0.24), ApoB/ApoA1 ratio +2.8% (P=0.58), large VLDL-P +0% (P=0.77), HDL-C -2.6% (P=0.41), total HDL-P -2.3% (P=0.23), large HDL-P +2.6% (P=0.74), and Apo A1 -1.4% (P=0.37).

Greater improvement of atherogenic dyslipidemia in low carbohydrate versus low fat diets have been reproduced in many trials measuring triglycerides and HDL-C including Westman et al., 2008 (T2D), Volek et al., 2008 (metabolic syndrome), Hussain et al., 2012 (T2D), Tay et al., 2014 (T2D), and Bazzano et al., 2014 (obesity) and confirmed in a meta-analysis of eleven trials (Mansoor et al., 2016).

4. LDL Particles Shift Toward the Non-atherogenic Fraction

While higher calculated low-density lipoprotein cholesterol (LDL-C) has traditionally been associated with increased CVD risk (Giugliano et al., 2017; Law et al., 2003), LDL-C has recently been correlated with improved survival in two large prospective studies and a systematic review (Orozco-Beltran et al., 2017; Ravnskov et al., 2016; Zuliani et al., 2017). The pattern is especially apparent in elderly cohorts. Studies also indicate tracking Apolipoprotein B (ApoB) (Barter et al., 2006) or LDL-P particle number (Otvos et al., 2011) provides a better CVD risk measure. Further, the subfraction distribution of LDL particles is likely more important with small, dense LDL particles (small LDL-P) associated with atherogenesis while large, buoyant LDL particles appear relatively neutral in their effect on CVD risk (Gardner et al., 1996; Rizzo and Berneis, 2007; Superko, 2001). Following 1-yr of the Virta treatment, while mean LDL-C rises (+9.6%, $P=4.9x10^{-5}$), overall LDL particle number is unchanged as measured by both Apo B (-1.9%, P=0.37) and LDL-P (-4.9%, P=0.02). The distribution of LDL particles shifts

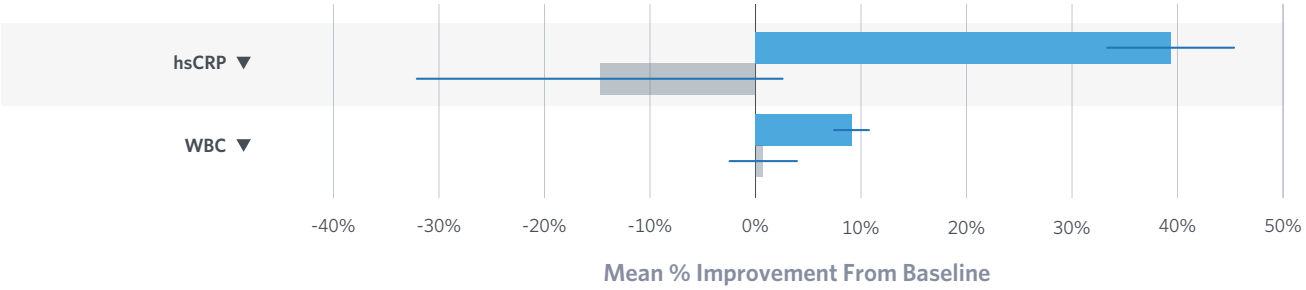


significantly away from small LDL-P (-20.8%, P=1.2x10^{-12}) and the mean LDL particle size rises (+1.1%, P=6.0x10^{-10}) (Bhanpuri et al., 2018). While counter to the traditional metric, the overall picture is of a potentially beneficial change in the LDL profile. The usual care group showed no statistically significant change in LDL parameters; LDL-C (-11.0%, P=0.02), Apo B (+0%, P=0.95), LDL-P (-4.4%, P=0.31), small LDL-P (+2.5%, P=0.67) and mean LDL-P size (-0.3%, P=0.25).

While higher saturated fat consumption can result in an LDL-C rise, it does not result in an increase in CVD risk (Chowdhury et al., 2014; Mente et al., 2017; Ramsden et al., 2016; Siri-Tarino et al., 2010a), contradicting the diet-heart hypothesis (Noakes and Windt, 2017; Siri-Tarino et al., 2010b). Low carbohydrate and nutritional ketosis trials often show a rise in LDL-C (Mansoor et al., 2016; Nordmann et al., 2006), but trials also show a consistent reduction in the small, dense LDL particles and a corresponding increase in large, buoyant LDL particles relative to low fat diets (Aude et al., 2004; Forsythe et al., 2010; Volek et al., 2008; R. J. Wood et al., 2006). A reasonable interpretation of the evidence is that LDL-C is not a useful marker of CVD risk in the context of a ketogenic diet where fat is the primary fuel source, the LDL profile is dominated by large non-atherogenic LDL particles (T. R. Wood et al., 2016), and other CVD risk factors are showing favorable changes.

5. Inflammation Improves

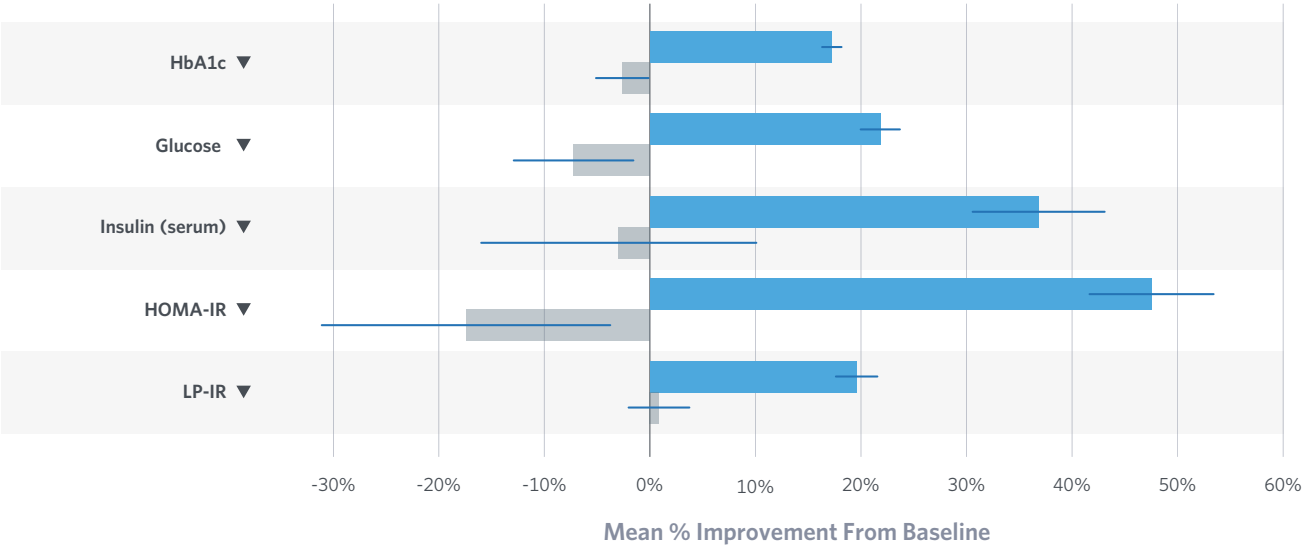
Inflammation is an independent CVD risk factor involved in all stages of atherogenesis (Libby et al., 2009). High-sensitivity C-reactive protein (hsCRP) and white blood cell count (WBC) are widely accepted markers of inflammation and risk factors for CVD (Folsom et al., 2002; Kannel et al., 1992). Following 1-yr of the Virta treatment, hsCRP was reduced 39.3% (P<10^{-16}) and WBC was reduced 9.1% (P<3.2x10^{-11}) indicating a substantial reduction in inflammation (Bhanpuri et al., 2018). The usual care group showed no statistically significant change in hsCRP (+14.4%, P=0.93) or WBC (-1.2%, P=0.76).



Reductions in inflammation through carbohydrate restriction and/or nutritional ketosis have been demonstrated in several prior clinical trials. Forsythe found significant decreases in inflammatory markers following twelve weeks of a low carbohydrate diet in overweight adults including hsCRP (-23%) and significantly larger decreases than a low fat diet for TNF-a, IL-8, MCP-1, E-selectin and I-CAM (Forsythe et al., 2007). Shai observed a significant decrease in hsCRP (-29%) following a 2-yr low carbohydrate diet (Shai et al., 2008).

6. Type 2 Diabetes Status Improves

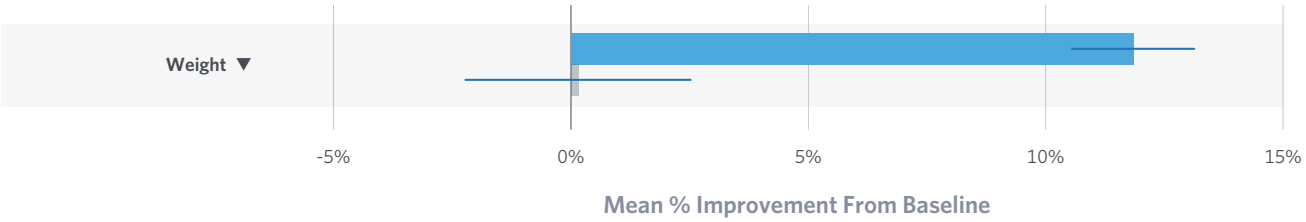
Diabetes itself is a major CVD risk factor. CVD risk increases two to four-fold with a diagnosis of T2D (Martín-Timón et al., 2014) and risk is reduced with lowered HbA1c (Eeg-Olofsson et al., 2016). T2D status following one year of Virta treatment improves based on mean HbA1c decrease of 17% ($P<1.0x10^{-16}$) (from 7.6% to 6.3%), fasting glucose decrease of 22% ($P<1.0x10^{-16}$), fasting insulin decrease of 43% ($P=6.7x10^{-16}$), homeostatic model assessment of insulin resistance (HOMA-IR) decrease of 55% ($P=73.2x10^{-5}$) (Hallberg et al., 2018) and NMR-derived lipoprotein insulin resistance score (LP-IR) decrease of 19.6% ($P<10^{-16}$) (Bhanpuri et al., 2018). Additionally, 69.8% of Virta patients achieved a 1-yr HbA1c below the diabetes threshold of 6.5%. Diabetes status improvements in the Virta treatment group occurred simultaneous with reduced use of diabetes medications other than metformin (-47.8% of all prescriptions discontinued) and especially insulin (94% of prescriptions reduced or discontinued) as described in detail below (section 10). 60% of patients had a 1-yr HbA1c <6.5% while taking no diabetes medications or metformin only, a metric used by Virta for "diabetes reversal". Virta manages toward long-term reversal through continued nutritional and behavior change. The usual care group showed no improvement in diabetes status; mean changes included HbA1c +2.6% (P=0.18), fasting glucose +7.3% (P=0.2), fasting insulin +3.0% (P=0.81), HOMA-IR +17.5% (P=0.22), and LP-IR -1.4% (P=0.74). Aggregate scores are described by Matthews et al., 1985 for HOMA-IR and by Shalaurova et al., 2014 for LP-IR, a combination of six lipoprotein measures.



Improvements in T2D status through nutritional ketosis under medical supervision have been demonstrated previously in short-term randomized in-patient experiments (Boden et al., 2005), in randomized out-patient trials of up to one year (Goday et al., 2016; Saslow, 2017; Saslow et al., 2017; 2014; Westman et al., 2008) in trial follow-up of over 3 years (Nielsen and Joensson, 2008), in non-randomized trials (Hussain et al., 2012), and in clinical case series (Dashti et al., 2007).

7. Obesity Improves

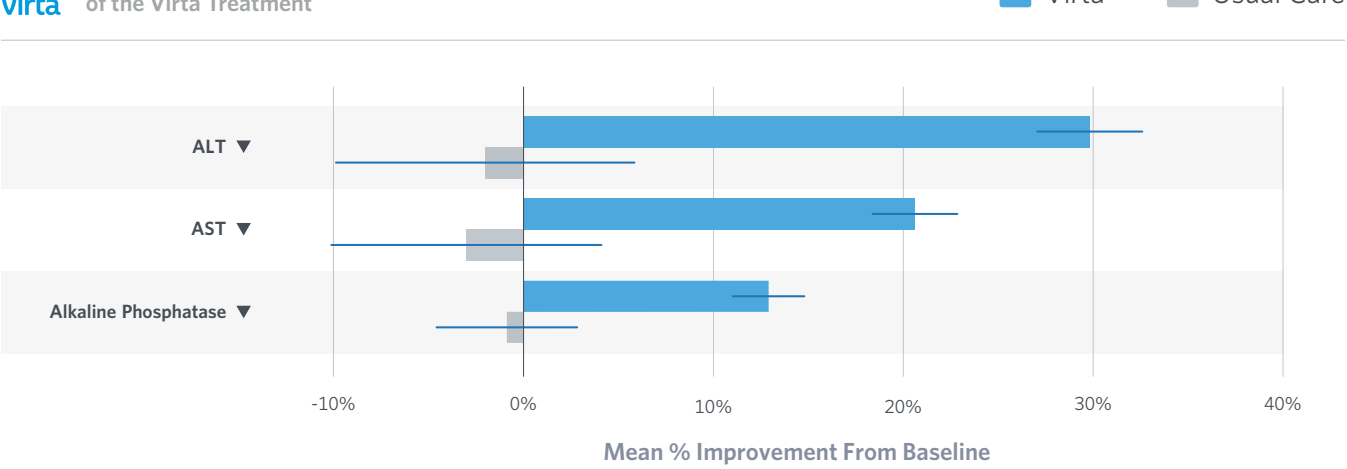
Obesity is an important independent CVD risk factor (GBD 2015 Obesity Collaborators et al., 2017; Hubert et al., 1983). Virta intervention trial participants had a mean starting weight of 116.5 kg (256.9 lbs.), mean body mass index (BMI) of 40.4 kg/m^2, 93% were obese and 45.6% had class III (high risk) obesity. Following 1-yr of the Virta treatment, the mean patient weight declined 12% ($P<1.0x10^{-16}$) or 30.8 lbs, mean BMI declined 4.8 to 35.6 kg/m^2, and class III obesity was reduced to 19.6% of the cohort (Hallberg et al., 2018). The usual care group had a mean starting weight of 105.6 kg (232.9 lbs), mean BMI of 36.7, and 82% were obese; no improvement in mean weight was observed at 1-yr (-0.15%, P=0.85), and BMI and obesity class distribution were also unchanged.



Improvements in obesity through carbohydrate restriction or nutritional ketosis have been demonstrated in numerous clinical trials including Bazzano et al., 2014; Gardner et al., 2007; Moreno et al., 2014; Shai et al., 2008; Yancy et al., 2005. It should be noted that few trials have obtained the degree of weight loss achieved by the Virta treatment at one year possibly because expectations around dietary changes were less intensive (e.g. mild carbohydrate restriction versus monitored nutritional ketosis) or support for behavior change was less effective (e.g. group instruction versus individualized online health coaching and telemedicine) (Gardner et al., 2018).

8. Liver Function Improves

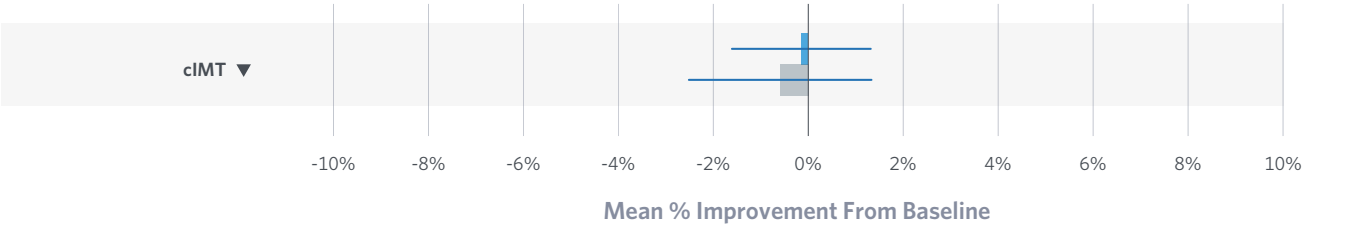
Non-alcoholic fatty liver disease (NAFLD) is highly prevalent among obese and T2D patients (Portillo-Sanchez et al., 2015) and is associated with increased CVD risk (Adams et al., 2017). NAFLD can progress to non-alcoholic steatohepatitis (NASH), advanced fibrosis, cirrhosis and hepatocellular carcinoma (HCC). Elevated serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) are often observed in NAFLD; elevated ALT and ALP are CVD risk factors (Targher and Byrne, 2015). ALT and AST are used in calculating NAFLD liver fat score (NAFLD-LFS) and NAFLD fibrosis score (NFS) (Angulo et al., 2007; Kotronen et al., 2009). Following 1-yr of the Virta treatment, mean patient ALT declined 29.4% ($P=2.4x10^{-10}$), AST declined 20.0% ($P=5.1x10^{-7}$) and ALP declined 12.9% ($P<1.0x10^{-16}$) (Hallberg et al., 2018). The usual care group showed no significant change in enzymes; ALT +2.2% (P=0.77), AST +2.5% (P=0.72) and ALP +1.0% (P=0.67).



Few studies have examined liver enzymes and liver fat in long-term ketogenic diets. A two-year study of a low carbohydrate diet with weight loss resulted in statistically significant reduction in ALT (-9.2%) (Shai et al., 2008). A caloric restriction diet resulting in weight loss with or without mild carbohydrate restriction (38% or 53% carbohydrate) reduced ALT from elevated levels (de Luis et al., 2010). Short-term (two week) carbohydrate restriction (<20 g/day) resulted in sharp reduction in liver fat (Browning et al., 2011) and improved cardiometabolic risk factors in NAFLD patients (Mardinoglu et al., 2018).

9. Carotid Intima Media Thickness is Unchanged

Carotid intima media thickness (cIMT) is a non-invasive measure of atherosclerosis that is significantly associated with CVD morbidity (Doneen and Bale, 2013). However, a recent meta-analysis found that cIMT progression over an average of 3.6 years in 3,902 T2D patients did not correlate with increased CVD events (Lorenz et al., 2015). Following 1-yr of the Virta treatment or usual care there was no significant change in cIMT from baseline (P=0.65 and 0.87, respectively) (Bhanpuri et al., 2018).



Change in cIMT following long-term use of a ketogenic diet for epilepsy control has been examined in small cohorts. In 13 patients over two years (Kapetanakis et al., 2014) and 10 patients over a decade (Heussinger et al., 2017), no significant change in cIMT was observed. Progression or regression of cIMT may take many years to manifest and may require a larger cohort to achieve statistical significance. In summary, there is currently no cIMT evidence of vascular harm or benefit from long-term nutritional ketosis.

10. Medication use for Hypertension and Diabetes is Decreased

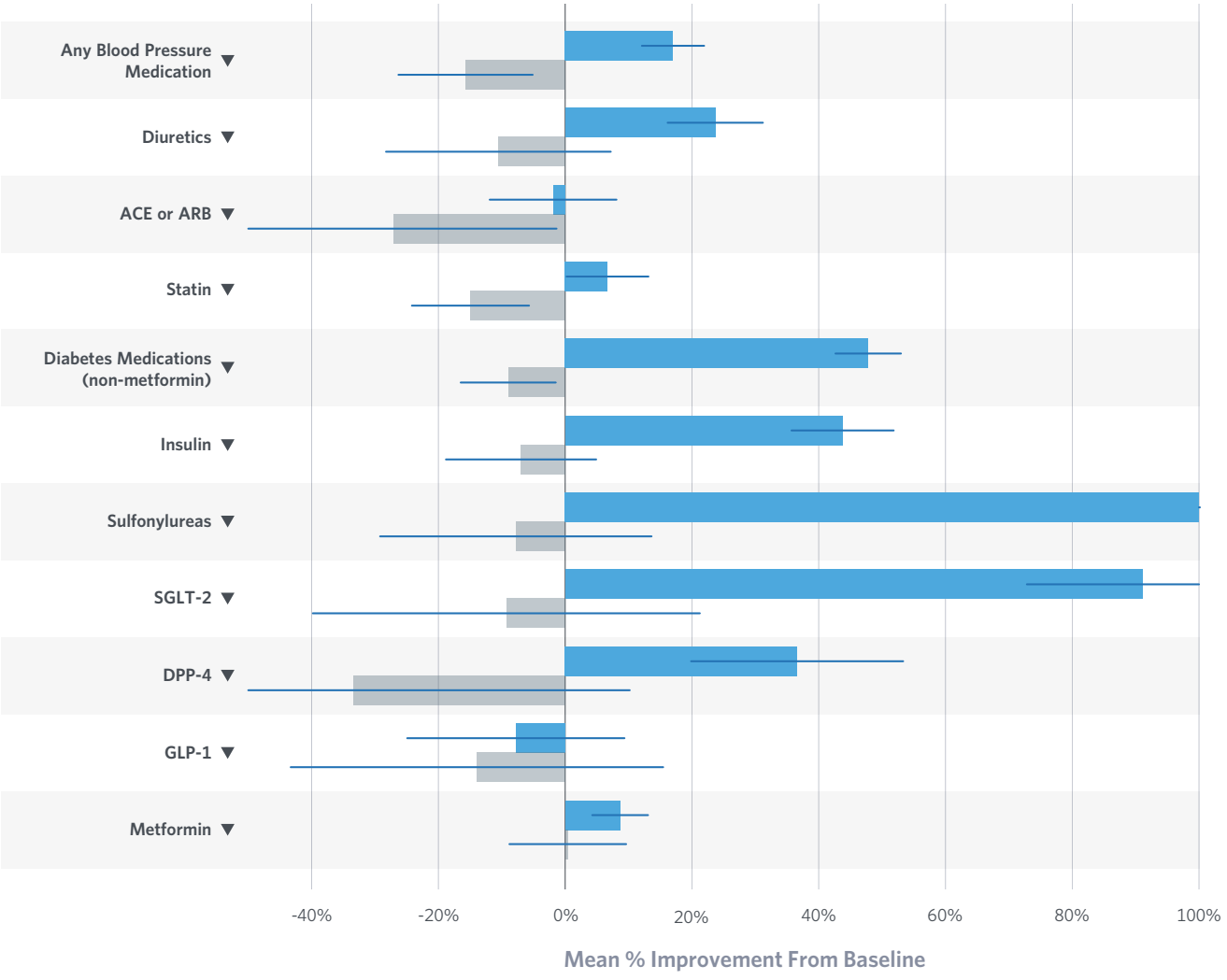
Prescription medications have powerful physiological impacts that come with substantial risk of iatrogenic effect so that reduced medication use when pharmaceutical treatment is no longer required can be beneficial (Gnjidic et al., 2012; Iyer et al., 2008). Negative effects of medications can result from side effects, allergic reactions, incorrect doses and timing, missed doses, overdose, drug-drug interactions (polypharmacy), physician and pharmacy mistakes, and product quality control issues (Classen et al., 2011; Ernst and Grizzle, 2001; Garfinkel et al., 2015; Poudel et al., 2017). Medications for hypertension can be problematic for hypotension and syncope especially in elderly patients (Williamson et al., 2016). Diabetes medications, especially insulin and sulfonylureas, can cause hypoglycemia and syncope (Abdelhafiz and Sinclair, 2017; Action to Control Cardiovascular Risk in Diabetes Study Group et al., 2008; McCoy et al., 2016). Insulin use also results in weight gain (Henry et al., 1993) and tight glycemic control achieved with pharmaceuticals is associated with a paradoxical increase in cardiovascular mortality (the ACCORD Study Group, 2011). Therefore, in both hypertension and diabetes care, an excellent rationale exists for removing medications when the health conditions can be managed effectively with individualized nutrition and behavior change.

Virta has developed physician-directed guidance for patient medication reductions and eliminations as blood pressure and blood glucose measurements and symptoms allow (Bhanpuri et al., 2018; Hallberg et al., 2018). Following resolution of hypertension, diuretics and beta blockers are often discontinued first. Angiotensin-converting-enzyme inhibitors (ACEs) and angiotensin II receptor blockers (ARBs) are generally continued due to known renal protection with diabetes (Jafar et al., 2001; Schmieder et al., 2011). Glycemic medications are reduced or eliminated to safely adjust for targeted decreases in glucose concentrations with a primary focus on preventing episodes of symptomatic hypoglycemia. Medication eliminations typically occur by first discontinuing sulfonylureas and SGLT-2 inhibitors, followed by short-acting, and then long-acting insulin. Thiazolidinediones, DPP-4 inhibitors, and GLP-1 are discontinued later. Metformin, given its effectiveness, low cost, tolerability and recommendation for use in pre-diabetes (American Diabetes Association, 2018), is often continued.

Following 1-yr of the Virta treatment, antihypertensive medication use declined 17.0% (from 67.2 to 55.8% of the population prescribed any BP medication, ($P=5.3\times10^{-5}$) and diuretic use declined 24.8% (from 40.8 to 31.2%, P=0.0004). Changes in ACE or ARB use (+2.0%, from 29.4 to 30.0%, P=0.76) were not significant. Statin use did not change significantly (-6.6%, from 50.0 to 46.7%, P=0.15) (Bhanpuri et al., 2018). The use of any diabetes medication other than metformin declined 47.8% (from 56.9 to 29.7%, $P<1.0\times10^{-16}$). Use of individual diabetes prescriptions changed as follows: sulfonylureas, -100% (from 23.7% to 0%, $P<1.0\times10^{-16}$), SGLT-2 inhibitors -91.3% (10.3% to 0.9%, $P=9\times10^{-7}$), thiazolidinediones -73.3% (from 1.5%

to 0.4%, P=.23), insulin -44.0% (from 29.8% to 16.7%, P=4.3x10^{-9}), DPP-4 -36.4% (from 9.9 to 6.3%, P=.11), metformin -9.0% (71.4% to 65.0%, P=.04) and GLP-1 +7.5% (from 13.4% to 14.4%, P=.67). Reductions in sulfonylureas, SGLT-2 inhibitors and insulin use were statistically significant. Patients who continued to use insulin reduced daily dosage significantly (-48.9%, from 105.2 to 53.8 units, P<0.0001) (Hallberg et al., 2018). The usual care group showed a trend toward increased medication use at 1-yr; any antihypertensive (+15.7%, P=0.09), diuretics (+10.4%, P=0.44), ACE/ARBs (+27.2%, P=0.13), statins (+15.0%, P=0.04), any diabetes medication other than metformin (+9.0%, P=0.09), sulfonylureas (+7.9%, P=0.65), SGLT-2 inhibitors (+6.1%, P=0.78), thiazolidinediones (+21.0%, P=0.67), insulin (+6.9%, P=0.39), DPP-4 (+32.6%, P=0.37), metformin (+0.1%, P=0.99), and GLP-1 (+20.9%, P=0.44). For the usual care participants who continued using insulin, the average daily dose increased significantly (+16.6% from 96.0 to 111.9 units, P<0.0001).

Medication eliminations following initiation of a ketogenic nutrition plan in T2D patients has been previously demonstrated for sulfonylureas and DPP-4 inhibitors at three months and one year (Saslow et al., 2017; 2014). Hussain et al., 2012 also report medication reductions and eliminations upon initiation of a ketogenic diet in T2D patients.



Conclusions

In published 1-yr results of a prospective longitudinal clinical trial comparing 262 intervention subjects and 87 usual care subjects with type 2 diabetes, the Virta treatment has demonstrated substantial and sustained beneficial impact on cardiovascular risk factors including improvement in the 10-year ASCVD risk score, hypertension, atherogenic dyslipidemia, LDL partitioning, inflammation, diabetes and insulin resistance, obesity and liver function. Simultaneously, medication usage for hypertension and diabetes was significantly reduced. Usual care subjects showed no improvements in CVD risk factors and no medication reductions. Numerous published studies of nutritional ketosis and carbohydrate restriction provide precedence for the observed CVD risk factor improvements. Together these findings provide a robust case for both near-term and projected long-term improved CVD outcomes in Virta's T2D patients.

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Original Article

Improvement in patient-reported sleep in type 2 diabetes and prediabetes participants receiving a continuous care intervention with nutritional ketosis

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ABSTRACT

Objective: Sleep disruption is frequently associated with type 2 diabetes (T2D) and hyperglycemia. We recently reported the effectiveness of a continuous care intervention (CCI) emphasizing nutritional ketosis for improving HbA1c, body weight and cardiovascular risk factors in T2D patients. The present study assessed the effect of this CCI approach on sleep quality using a subjective patient-reported sleep questionnaire.

Methods: A non-randomized, controlled longitudinal study; 262 T2D and 116 prediabetes patients enrolled in the CCI and 87 separately recruited T2D patients continued usual care (UC) treatment. Patients completed the Pittsburgh Sleep Quality Index (PSQI) questionnaire. A PSQI score of >5 (scale 0 to 21) was used to identify poor sleepers.

Results: Global sleep quality improved in the CCI T2D ($p < 0.001$) and prediabetes ($p < 0.001$) patients after one year of intervention. Subjective sleep quality (component 1), sleep disturbance (component 5) and daytime dysfunction (component 7), also showed improvements in the CCI T2D ($p < 0.01$ for sleep quality and sleep disturbance; and $p < 0.001$ for daytime dysfunction) and prediabetes patients ($p < 0.001$ for all three components); compared to the UC T2D group after one year. The proportion of patients with poor sleep quality was significantly reduced after one year of CCI (T2D; from 68.3% at baseline to 56.5% at one year, $p = 0.001$ and prediabetes; from 77.9% at baseline to 48.7% at one year, $p < 0.001$).

Conclusion: This study demonstrates improved sleep quality as assessed by PSQI in patients with T2D and prediabetes undergoing CCI including nutritional ketosis but not in T2D patients receiving UC. The dietary intervention benefited both sleep quality and the severity of T2D symptoms suggesting that nutritional ketosis improves overall health via multiple mechanisms.

Abbreviations: CCI, continuous care intervention; UC, usual care; T2D, type 2 diabetes; BMI, body mass idex; PSQI, Pittsburgh Sleep Quality Index; OSA, obstructive sleep apnea; HbA1c, hemoglobin A1c; CPAP, continuous positive airway pressure; AHI, apnea and hypopnea indices; KD, ketogenic diet; REM, rapid eye movement; SWS, slow wave sleep; BHB, beta-hydroxybutryrate; HOMA-IR, homeostatic model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein.

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1. Introduction

Sleep disruption is associated with obesity and type 2 diabetes (T2D), yet the bidirectional relationship between sleep and glucose metabolism is not fully understood. It is linked to increased diabetes prevalence in both experimental [1–4] and epidemiological studies [5–7]. In addition, the severity of hyperglycemia in individuals with diabetes is associated with poor sleep quality [8–11], short sleep duration [8,9,12,13] and a greater tendency to develop sleep disorders including obstructive sleep apnea (OSA) [14,15]. Both the International Diabetes Federation (IDF) and American Diabetes Association (ADA) recommend evaluating T2D patients for sleep breathing problems especially OSA and strongly encourage treatment when found [16,17].

Weight loss has demonstrated effectiveness to improve sleep quality, quantity [18,19] and to treat OSA in obese patients. Lifestyle intervention induced weight loss showed significant reduction in the apnea and hypopnea indices (AHI) in conjunction with a decrease in hemoglobin A1c (HbA1c) levels in a randomized controlled trial of obese OSA patients with comorbid diabetes [20]. Further, weight loss following bariatric surgery is effective at improving glycemic control and improving AHI in OSA patients [21]. Intervention studies specifically targeting sleep disruption in OSA patients without any effect on weight, such as continuous positive airway pressure (CPAP) treatment, have shown contradictory results for glycemic control. Most CPAP intervention studies in T2D reported no glycemic benefit from the treatment [22,23], but one study demonstrated a slight reduction in HbA1c [24]. In contrast, CPAP studies on prediabetic OSA patients showed improvements in insulin sensitivity and glucose tolerance [25,26]. It is not clear from these studies whether improvement of glycemic control in conjunction with weight loss improves sleep quality or vice-versa.

A few studies have investigated the impact of dietary macronutrient composition on sleep duration and quality. Two studies reported reduction of slow wave sleep (SWS) and elevation of rapid eye movement (REM) sleep in individuals consuming higher carbohydrates (600 g carbohydrate or 80% energy from carbohydrate) [27,28]. Another study reported the effect of a high carbohydrate (56% energy from carbohydrate) diet in reducing sleep onset latency when compared to a control diet [29]. Studies investigating low carbohydrate diets showed the opposite effect; reduced REM [30], increased REM onset latency [31] and increased SWS [30], even after 4 h of administering a very low carbohydrate meal [30]. Collectively, these findings signify dietary carbohydrate content as an important factor in modulating sleep architecture, but extrapolation from these studies is limited since they were conducted in experimentally controlled conditions with small numbers of healthy individuals in a short time-span and with diets administered at specific time points.

Population and intervention-based studies on the overall impact of carbohydrate intake on sleep indices or sleep quality are very limited. Katagiri et al., showed reduced sleep quality in individuals consuming more carbohydrates as measured by a subjective sleep measure, the Pittsburgh Sleep Quality Index (PSQI) [32]. Studies investigating the effect of ketogenic diet (KD) in children with sleep problems showed improvement in daytime sleepiness [33,34] as well as positive changes in sleep architecture [34,35]. However, in one of these studies, sleep improvements were suggested to be due to weight loss rather than the KD [35]. Despite restricted carbohydrate intake concurrent with sleep improvement in these children, SWS decreased [35] and REM increased [34,35] which contradicts studies on carbohydrate intake and sleep architecture in adults [27,28,30]. Carbohydrate restriction and ketogenic diets are widely used in the clinical management of obesity and diabetes, but studies assessing the effect of this diet on sleep are currently limited. We recently demonstrated a continuous remote care treatment for T2D including nutritional ketosis significantly improved glycemic control, weight, and cardiovascular disease risk factors and reduced diabetes medication use at one year [36–38].

The purpose of this study was to assess the effect of the intervention by time-interval on the global PSQI and its seven component scores as well as compared its changes with different intervention and disease categories. We also assessed the relationship between changes in the sleep parameters versus key biochemical parameters, and also investigated the correlation of pain, circadian rhythm disruption and CPAP usage versus patient-perceived sleep status. We hypothesized that the global sleep indexes would improve analogously, as improvement in other key biochemical parameters observed in the intervention.

2. Materials and methods

2.1. Study participants and design

This study is part of a clinical trial (*Clinical trials.gov identifier:* NCT02519309) that was approved by the Franciscan Health Lafayette Institutional Review Board. Patients between age 21 and 65 years with either a diagnosis of T2D and a BMI >25 kg/m^2 or prediabetes and a BMI >30 kg/m^2 were included in this study. Detailed study design including the inclusion and exclusion criteria were previously reported [36,37]. Briefly, the trial was an open-label, non-randomized, controlled, longitudinal study with patients divided into three groups. The T2D and pre-diabetes patients in the continuous care intervention (CCI) regimen self-selected either on-site (CCI-onsite) or web-based (CCI-web) education delivery. Educational content and medical treatment was the same for both CCI-onsite and CCI-web. As there were no significant differences in outcomes including PSQI scores, between educational groups, they are combined for further analysis [36,37]. Both T2D and prediabetes CCI patients had access to a mobile health application (app) that enabled them to communicate and be continuously monitored by a team of healthcare professionals including a personal health coach and physician or nurse practitioner. Patients received individualized guidance in achieving nutritional ketosis, typically including restriction of daily dietary carbohydrates to less than 30 g. Patients were encouraged to measure and input weight, blood glucose and blood beta-hydroxybutyrate (BHB) concentrations daily in the app. These measurements were used by the health care team for monitoring the patient's condition (weight and glucose) and assessing carbohydrate restriction (BHB).

Separately recruited usual care (UC) T2D patients were participants in a local diabetes education program including care by their primary care physician or endocrinologist and counseling by registered dietitians; no modification to their care was made for the study. This group was observed at baseline and one year as reference for typical disease treatment and progression within the same geography and health system. UC patients were informed that the trial had an intervention arm and could participate in that group if they chose to do so.

2.2. Demographic and clinical variables

Patient demographic and clinical data were collected at baseline, 70 days and one year. Laboratory measures were assessed at a Clinical Laboratory Improvement (CLIA) certified laboratory. These data were initially analyzed to evaluate the safety and effectiveness of the CCI in improving diabetes status (glycemic control and medication use), weight and other metabolic factors in T2D [36,37] and prediabetes patients [38] (unpublished data, manuscript in

preparation). Some of the clinical variables – weight, fasting blood glucose, HbA1c, homeostatic model assessment of insulin resistance (HOMA-IR), BHB and high sensitivity C-reactive protein (hsCRP) – were included for further analyses in this study. Usual care T2D patients were not continuously monitored for weight, blood glucose, or BHB; clinical and laboratory measures were obtained for this group only at baseline and one year.

2.3. Pittsburgh Sleep Quality Index (PSQI)

CCI patients were administered a set of questionnaires, including the PSQI, during visits at baseline, 70 days and one year; UC participants completed questionnaires at baseline and one year. The PSQI consists of 19 validated questions assessing sleep quality and efficiency [39]. The global PSQI score is calculated from seven component scores on subjective sleep quality (component 1), sleep latency (component 2), sleep duration (component 3), habitual sleep efficiency (component 4), sleep disturbances (component 5), use of sleep medication (component 6) and daytime dysfunction (component 7). Each question within the component is scored on a 4-point Likert scale of 0–3, with 3 indicating worse outcomes and the mean was calculated for each component score. The sum of the component score means generates the global PSQI score that ranges from 0 to 21. Higher global PSQI scores indicate poorer sleep. A patient with a global PSQI score $\leq$5 is considered a "good sleeper" and >5 is categorized as a "poor sleeper" [40]. Change in the PSQI score over time was calculated using the formula below:

$$\text{Delta PSQI} = \frac{(\text{Post} - \text{intervention PSQI} - \text{Baseline PSQI})}{\text{Baseline PSQI}}$$

2.4. Pain, shifted sleep chronotype and CPAP usage

Patients were classified into "pain" and "non-pain" groups based on their response to pain-related questions in both the PSQI (question 5i) and a separate questionnaire used to calculate the knee injury and osteoarthritis outcome score (KOOS). Overall KOOS results will be reported in a separate publication. Classification of patients under circadian rhythm "disrupted" and "non-disrupted" groups was based on the wake time and bedtime responses for PSQI questions 1 and 3 for compilation of component 4 (sleep efficiency). Patients were classified as having a shifted wake-up time if they reported typically waking between 11am and 2am, while those with bedtimes between 12am and 6pm were bedtime shifted. These arbitrary bedtime and wake time cut-off ranges were selected based on evening and night shift workers schedule (second shift – 3pm to 11pm and third shift- 11pm to 7am); which causes these workers to have sleep patterns that deviate from a normal chronotype. Patients were also surveyed regarding CPAP usage and discontinuation, however detailed usage information such as CPAP pressure settings and usage compliance were not obtained making it difficult to interpret the patients OSA treatment status.

2.5. Statistical analyses

The questionnaires were administered by research personnel and completed by patients on paper. Paper questionnaires were scanned and responses were transcribed in duplicate by an independent contract data entry firm. The patterns of missing data were assessed using Little's MCAR test [41] and were found to be missing at random (MAR). Missing data were imputed by Multivariate Imputation by Chained Equations (MICE) [42], and Intent to treat (ITT) analyses were performed. Normality of the global PSQI and component scores was evaluated using Lilliefors test. Even after transformation, the data failed the normality test (ie there was a skew toward lower PSQI scores and a long tail of higher scores) (Supplemental Fig. 1A–C); therefore, nonparametric tests were used for analyses of PSQI scores. Results from continuous variables were expressed as mean ± standard deviation. Comparisons between groups were performed using the Kruskal–Wallis test, and comparisons within groups were performed using the Wilcoxon Sign Rank test. Tukey's honest significant difference test was used to analyze pairwise differences among significant results from omnibus tests. McNemar's test was used for assessing statistical significance of transitioning between 'good' and 'poor' sleeper among the CCI and UC cohorts.

Adjusted Pearson's and Spearman correlations were calculated between changes from baseline in global PSQI and changes in metabolic-parameters. Adjusted correlations were performed while controlling for age, gender and BMI at baseline. All participants in the CCI group were stratified by sleep improvement status based on their baseline and one year global PSQI scores. Patients that were initially considered "poor sleepers" with a baseline PSQI >5 but whose score after one year decreased to at or below the threshold of 5 were classified as improved. Those patients who were considered "good sleepers" at both baseline and one year were classified as maintained. Finally, those patients whose 1 year PSQI score was >5 (regardless of their baseline score) were classified as not improved. Stepwise analyses of covariance (ANCOVA) were performed between the three different CCI sleep status groups at one year with the change of the glucose-related, ketone and inflammatory markers, while controlling by age, gender and years living with diabetes. Statistical tests were performed with MATLAB R2017b using the Statistics and Machine Learning Toolbox [43] and the R statistical program version 3.5.0 [44].

3. Results

3.1. Baseline participant characteristics

Details on the recruitment and extensive baseline characteristics of the CCI and UC T2D patients were previously published [36,37]. The demographic, glycemic, inflammatory and sleep baseline characteristics of the participants that were included for assessments of sleep are presented in Table 1. One-hundred forty-three (54.6%) CCI T2D, 61 (54%) CCI prediabetes, and 53 (62.3%) UC T2D patients completed the PSQI at all expected time points. The number of patients who completed the trial at one year were slightly higher than those who completed the PSQI questionnaires. Some of the patients completed the study period and laboratory analysis but were unable to attend the clinic for their 70-days and one-year follow-up visits, where they are required to complete their corresponding questionnaires. The proportion of missing PSQI data were similar across the three groups with 77.61% of CCI T2D, 79.06% of CCI prediabetes and 79.24% of UC T2D completed the PSQI in all expected time points. There were no significant differences between completers and non-completers on baseline characteristics for either group at one year of the intervention (Supplemental Table 1). The global PSQI and component scores did not differ significantly among the groups (CCI T2D, CCI prediabetes and UC T2D) at baseline. The proportion of participants with overall poor sleep quality was higher in the CCI prediabetes group (77.9%) compared to the CCI T2D (68.3%) and UC T2D (68.2%) groups.

3.2. Effect of intervention on sleep

3.2.1. Global PSQI and component scores

Overall sleep quality as assessed by the global PSQI score, improved in CCI T2D (median change from 7 to 6; $p < 0.001$) and

Table 1
Baseline characteristics of participants included in the study. Baseline data were calculated using intent-to-treat (ITT) data.

Patient Cohorts	CCI Type 2 Diabetes	CCI Prediabetes	UC Type 2 Diabetes
Starters, Completers, PSQI Available (n)	262, 218, 143	116, 113, 61	87, 78, 53
	mean (S.D.)	mean (S.D.)	mean (S.D.)
Age (years)	53.8 (±8.4)	51.9 (±9.4)	52.7 (±9.3)
Male/female (ratio)	87/175 (1:2)	29/84 (1:3)	35/50 (2:3)
Body weight (kg)	116.4 (±26.1)	109.9 (±23.6)	108.3 (±25.1)
BMI (kg/m^2)	40.4 (±8.9)	38.8 (±7.1)	38.2 (±9.1)
Fasting glucose (mg/dL)	160.78 (±61.32)	109.58 (±15.20)*	157.08 (±72.48)
HbA1c (%)	7.60 (±1.50)	5.91 (±0.24)*	7.67 (±1.77)
HOMA-IR	11.8 (±13.1)	7.1 (±7.4)*	13.7 (±17.8)
high sensitivity C-reactive protein (nmol/L)	9.31 (±19.31)	7.46 (±7.51)	9.34 (±9.10)
Beta-hydroxybutyrate (mmol/L)	0.17 (±0.15)	0.14 (±0.13)	0.15 (±0.12)
Global PSQI Score	7.72 (±3.72)	7.96 (±3.43)	7.92 (±3.85)
Subjective sleep quality	1.18 (±0.75)	1.22 (±0.73)	1.25 (±0.79)
Sleep latency	1.09 (±0.93)	1.33 (±0.958)	1.05 (±0.89)
Sleep duration	1.23 (±0.92)	1.27 (±0.96)	1.14 (±0.94)
Habitual sleep efficiency	0.68 (±0.99)	0.61 (±0.89)	0.71 (±1.04)
Sleep disturbances	1.64 (±0.63)	1.66 (±0.68)	1.75 (±0.74)
Use of sleep medication	0.69 (±1.16)	0.66 (±1.11)	0.85 (±1.26)
Daytime dysfunction	1.22 (±0.77)	1.21 (±0.76)	1.17 (±0.86)
Poor sleepers N (%)	179 (68.3)	88 (77.9)	58 (68.2)
Good sleepers N (%)	83 (31.7)	25 (22.1)	27 (31.8)

Note. Subjective sleep quality, component 1; sleep latency, component 2; sleep duration, component 3; habitual sleep efficiency, component 4; sleep disturbances, component 5; use of sleep medication, component 6, and daytime dysfunction, component 7.
*p-value <0.001.

prediabetes (median change from 7 to 5; $p < 0.001$) groups after one year of the intervention (Fig. 1). No significant change in the global PSQI score was observed in UC T2D (median change from 7 to 8, $p = 0.245$). At one year, global PSQI scores in the CCI T2D ($p < 0.001$) and prediabetes ($p < 0.01$) were significantly lower than in the UC T2D, whereas no differences were observed at baseline (Supplementary Fig. 2A). Among patients characterized as poor sleepers at baseline (global PSQI >5), one year global PSQI score was lower in the CCI T2D ($p < 0.001$) and prediabetes ($p < 0.001$) than in the UC T2D (Supplementary Fig. 2B). Greater reduction in the global PSQI score was observed in CCI T2D (median change of −1, $p < 0.01$) and CCI prediabetes groups (median change of −2, $p < 0.001$) compared to the UC T2D group (Supplementary Fig. 3). Further assessment of the PSQI component scores revealed three of the seven components showed significant change at one year for CCI T2D and prediabetes groups. Subjective sleep quality ($p < 0.01$ CCI T2D; $p < 0.001$ CCI prediabetes), sleep disturbance ($p < 0.01$ CCI T2D; $p < 0.001$ CCI prediabetes) and daytime dysfunction ($p < 0.001$ CCI T2D; $p < 0.001$ CCI prediabetes) scores were lower in the CCI T2D and prediabetes patients compared to the UC T2D group at one year (Fig. 2 A–C).

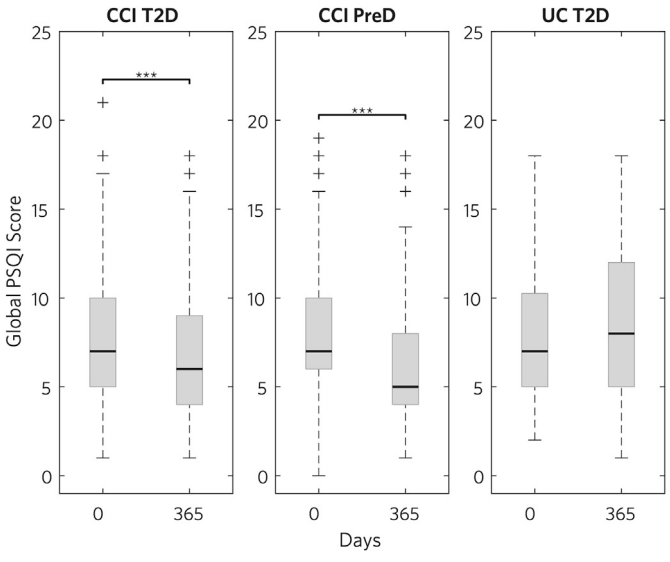

Fig. 1. Distribution of global PSQI scores at baseline and 365 days in CCI T2D, CCI PreD and UC T2D. Global PSQI score was significantly reduced in the CCI T2D and CCI PreD groups but not in the UC T2D group after 365 days. Boxplot descriptors (Figs. 1 and 2; Supplementary Figs. 3 and 4) Horizontal line within the box indicates median; upper and lower boundaries of the box represent the 25th and 75th percentiles; whiskers of the box indicate the range and "+++" signs represent outlier values. ** p-value <0.01; *** p-value <0.001.

3.2.2. Resolution of poor sleep quality

There were 179 (68.3%) T2D and 88 (77.9%) prediabetes patients categorized as "poor sleepers" in the CCI at baseline. The proportions of "poor sleepers" in the CCI were reduced after one year of the intervention, with 56.5% of T2D ($p = 0.001$) and 48.7% ($p < 0.001$) of prediabetes patients categorized as "poor sleepers" at one year. In the UC cohort, the proportion of patients categorized as "poor sleepers" did not change after one year (68.2% at baseline to 69.4% at one year).

3.2.3. Association within the CCI group between changes in global PSQI with metabolic and inflammatory markers

Table 2 shows correlations between changes in the global PSQI score with changes in glucose-related, ketone and inflammatory markers in the CCI. In the prediabetes group, changes in fasting glucose ($r = 0.23$, $p = 0.02$) and HOMA-IR ($r = 0.32$, $p < 0.001$) were correlated to changes in PSQI scores after controlling for baseline age, sex and weight. Increased ketone concentrations in the prediabetes participants were also associated with reduction of global PSQI scores ($r = -0.242$, $p = 0.01$). These correlations observed in the prediabetes group were not present in the CCI T2D group and changes in the HbA1c and hsCRP did not correlate with changes in global PSQI scores in either group. Change in mean weight ($p = 0.04$) and HOMA-IR ($p = 0.01$) were the only variables independently and significantly associated between the three different sleep status (improved, maintained and not improved sleep status) at one year of the intervention. No statistically significant differences were found in weight loss changes between patients with

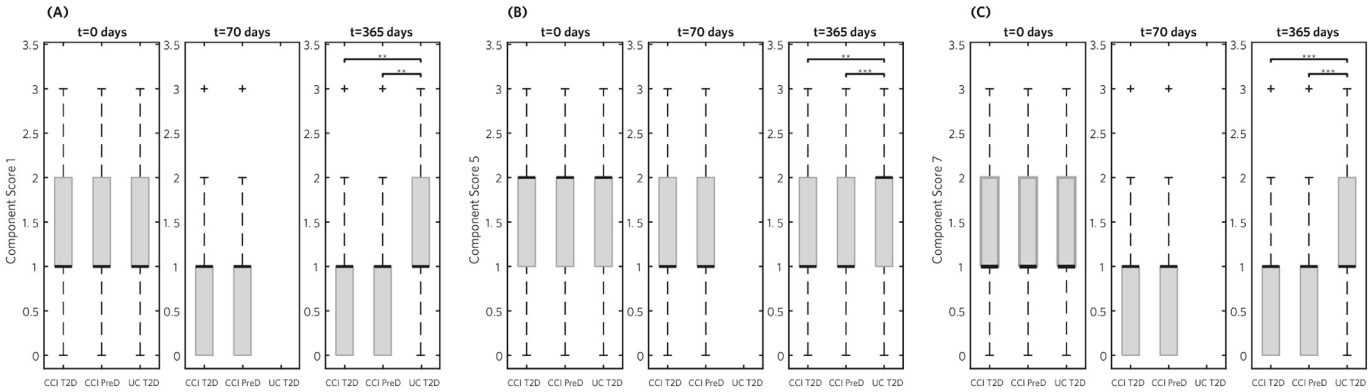

Fig. 2. Distribution of PSQI components subjective sleep quality, sleep disturbances and daytime dysfunction in CCI T2D, CCI PreD and UC T2D groups at three different timepoints (0, 70 and 365 days). Subjective sleep quality (A), sleep disturbances (B), and daytime dysfunction (C) were significantly lower in the CCI T2D and CCI PreD groups when compared to UC T2D group at 365 days. Boxplot descriptors (Figs. 1 and 2; Supplementary Figs. 3 and 4) Horizontal line within the box indicates median; upper and lower boundaries of the box represent the 25th and 75th percentiles; whiskers of the box indicate the range and "+++" signs represent outlier values.** p-value <0.01; *** p-value <0.001.

Table 2
Correlation analyses between change in the global PSQI score and change in metabolic parameters after one year of CCI.

Variable	CCI T2D Cohort N = 262				CCI Prediabetes Cohort N = 113			
	rho	P value*	Adjusted r	P value+	rho	P value*	Adjusted r	P value+
Δ Fasting glucose (mg/dl)	0.032	0.60	0.008	0.90	0.240	0.01	0.226	0.018
Δ HbA1c (%)	−0.037	0.55	−0.049	0.44	−0.024	0.80	−0.032	0.74
Δ HOMA-IR	−0.060	0.34	−0.069	0.27	0.314	0.0008	0.323	0.0006
Δ BHB	−0.003	0.96	−0.044	0.49	−0.297	0.002	−0.242	0.011
Δ hsCRP	−0.067	0.29	−0.008	0.90	−0.022	0.82	−0.032	0.74

*Spearman and +Adjusted Pearson's correlations. Adjustments while controlling for age, sex and baseline weight.

improved, maintained and not improved sleep status. Patients who maintained sleep showed highest reductions of HOMA-IR (−6.94 ± 0.86), with statistically significant difference than those who did not improve sleep, after one year of the intervention ($p = 0.02$). Improvements in HOMA-IR among patients in the improved sleep (−4.17 ± 0.86) and not improved sleep status (−4.24 ± 0.55) did not differ significantly.

3.3. Effect of persistent pain on sleep improvement

We further assessed the effect of pain on sleep improvement in the CCI by classifying the patient's pain status using response retrieved from questions specifically related to pain in the sleep and knee (KOOS) questionnaires. As illustrated in Supplementary Fig. 4, patients with pain had higher global PSQI scores, indicating poorer sleep, compared to those categorized under "non-pain" group at all three time points. Both patients in the "non-pain" (Supplementary Fig. 5A, $p < 0.001$). and "pain" group (Supplementary Fig. 5B, $p < 0.01$) had reductions in their global PSQI score at 70 days and one year.

3.4. Effect of shifted sleep chronotype on sleep improvement

We also assessed the effect of shifted sleep chronotype on the global PSQI score improvement. Patients were classified as having shifted sleep chronotype based on their self-reported wake-up times and bedtimes as defined in the methods. There were 18, 27, and 96 patients in the CCI cohort classified as both wake-up time and bedtime shifted, wake-up time shifted only or bedtime shifted only respectively. Patients with shifted bedtimes, had reduced global PSQI scores ($p < 0.01$), as did those with normal chronotype ($p < 0.001$) (Supplementary Fig. 6A and B). However, those patients with shifted wake-up times (Supplementary figures 6C) did not show a change in their global PSQI score after one year of the intervention. Those with both shifted wake-up times and bedtimes also did not show a change in their global PSQI score after one year of the intervention.

3.5. Effect of CPAP usage on sleep improvement

At baseline, there were a total of 140 participants in both CCI and UC treatment groups with CPAP equipment prescribed for sleep. Among CPAP users, 91 were in the CCI T2D group, 31 in the CCI prediabetes and 18 in the UC T2D group. Fifteen (13 CCI T2D and two UC T2D) of the 140 participants discontinued using CPAP at one year. Only six (46%) of the 13 CCI T2D participants discontinued due to patient-reported improvement in sleep quality from the CCI and reduction of weight; the remaining seven reported discontinuation due to discomfort or personal choice. Global PSQI scores among the CPAP users at baseline and one year did not show a significantly different distribution pattern than what was observed in the full cohort of participants.

4. Discussion

This study is one of the first designed to assess the effect of carbohydrate restriction and nutritional ketosis on sleep quality in individuals with hyperglycemia and insulin resistance. Improved patient-reported sleep quality as assessed by global PSQI suggests that CCI including nutritional ketosis benefited sleep quality in both patients with T2D and prediabetes. The proportion of patients categorized as "poor sleepers" at one year was significantly reduced in the CCI groups but not in the UC group. Furthermore, these results demonstrate that the sleep quality improvement observed in the whole intervention population was due in part to 17% of baseline "poor sleepers" being reclassified as "good sleepers" at one year. Our results are consistent with previous findings that showed improved overall sleep quality in children consuming ketogenic diets [33,34].

Improvement in the global PSQI score of patients undergoing the CCI was mainly due to significant changes in three PSQI components: subjective sleep quality, sleep disturbance and daytime dysfunction. Both objective and subjective sleep quality impairment are frequently reported in diabetes patients and positively associated with severity of hyperglycemia [8–11]. Likewise, correlation between poor sleep quality and increased carbohydrate intake [32] has also been previously reported. These observed patterns of association between sleep quality with hyperglycemia and carbohydrate intake may explain why this carbohydrate restriction intervention improved subjective sleep quality. The sleep disturbance component of the global PSQI score is associated with poor glycemic control among T2D patients [45]. One study reported a significant correlation between sleep disturbance and HbA1c level [46]. Night time sleep disturbance in T2D patients can be related to a wide range of conditions such as nocturnal polyuria, pain, and breathing problems, especially in those with OSA. In our study, we also showed that patients encountering persistent pain, including knee pain, had a higher median global PSQI score, while one year of the intervention effectively improved global PSQI scores in these patients despite the persistence of reported pain in some patients. It is possible that improvement in the sleep disturbance of the CCI patients contributed to the glycemic control improvement in these patients. The effectiveness of the intervention in improving sleep in those with pain, further emphasizes its' applicability in alleviating sleep disturbance.

Furthermore, there was a significant improvement in the daytime dysfunction component of the global PSQI score in the CCI group. Excessive daytime sleepiness and dysfunction are reported commonly in T2D [47,48], and weight loss through bariatric surgery has a positive resolving effect on daytime dysfunction and sleepiness [49,50]. In the present investigation, the majority of CCI patients achieved weight loss of $\geq$10%, which could have contributed to the significant improvement observed in daytime function. In addition, we also evaluated the effect of the intervention on a subcohort of patients with a self-reported pattern of shifted non-standard bedtimes and wake-up times that were not aligned to the light dark cycle, which likely affects daytime functioning. Circadian rhythm disruption is frequently associated with metabolic alterations, especially in an insulin resistant state [51,52]. While patients with a normal sleep chronotype benefited the most, the intervention also improved the sleep of patients with time shifted bedtimes. A similar advantage of the intervention was not observed in patients with shifted wake-up times, though this may be due to the limited number of patients in this subgroup ($n = 27$).

The improvement in the global PSQI score observed in CCI patients occurred concurrently with weight reduction and glycemic control improvement [36,37]. Martin et al., [53] reported a direct correlation between degree of weight loss and global PSQI score improvement in healthy nonobese adults receiving an energy restricted diet, while Chaput et al., [54] reported an improvement in global PSQI score following the initial 5-kg weight loss, but no additional improvement with subsequent weight loss. A study using a ketogenic diet in children alleviated abnormal sleep architecture; however, weight loss was suggested as the main determinant of improved sleep [35]. These studies collectively imply a direct association between weight loss and improved PSQI score. Likewise, long-term maintenance of weight loss was associated with better sleep quality and quantity [18] while the degree of weight loss reduction is directly correlated with OSA improvement [19]. Alternately, some studies also demonstrate the efficacy of anti-glycemic medications for improving PSQI score concurrent with improved glycemic control [55]. This study identified associations between HOMA-IR and weight reductions with stratification of patients' sleep status in the full CCI cohort even though there were no significant differences in weight loss and insulin resistance reduction levels between those who had improved sleep and those who did not. Patients with good sleep quality at the beginning of the intervention benefited the most in reducing insulin resistance. Improvement in fasting glucose and HOMA-IR were only positively associated with improved PSQI score in prediabetes patients.

It is not clear if nutritional ketosis achieved by substantial carbohydrate restriction augmented the effect of the intervention on sleep or if weight loss and/or improved glycemic control generated from the intervention contributed to sleep quality improvements. We showed a significant correlation between blood beta-hydroxybutryrate (BHB) levels and PSQI improvement in the prediabetes cohort. While the effect of and mechanism of BHB in sleep are not clear, a positive correlation between blood BHB levels and carbon dioxide (CO_2) response was previously reported in patients with obesity related hypoventilation syndrome that had reduced CO_2 response [56]. A continuous state of ketosis through carbohydrate restriction and fat intake also induces the postprandial release of a satiety hormone, cholecystokinin (CCK) [30,57,58]. When administered in rats, CCK was shown to promote slow wave activity and NREM sleep [59]. CCK was also shown to induce sleep when administered in diabetic rats [60]. Therefore, it is possible that one mechanism of improved sleep with a ketogenic diet that increases BHB levels is through CCK induction.

There are several limitations of our study. The study was designed mainly to assess the impact of the CCI on glycemic control, medication use, weight, and cardiovascular disease risk factors. Patient-reported outcomes for quality of life measures including sleep were included as secondary endpoints. It is difficult to determine the causality among the intervention, related to improvement in primary outcomes and improvement in sleep from this study. A major limitation of this study is the use of subjective sleep measures as self-reported sleep assessment is subject to limited self-knowledge of sleep behavior and inconsistency in reporting. Changes in architecture were not included in the study. Therefore, future studies that use randomized controlled trial designs and objective sleep measures are needed to confirm our results. In addition, patients with an established diagnosis of a sleep disorder such as OSA were not separated in the analysis since complete records of their CPAP usage were not collected in the questionnaire. Patient compliance with CPAP usage is essential for making interpretations about the status of their OSA treatment and its effect on sleep and glycemic control. The study also lacked recruitment of prediabetes patients in the UC group for direct comparison of the treatment effect between UC and CCI on sleep in these patients.

In conclusion, these results demonstrate that overall sleep quality significantly improved in T2D and prediabetes patients undergoing remote CCI including nutritional ketosis but not in T2D patients in the UC group. The sleep improvement was concurrent with weight reduction and glycemic control improvement. The PSQI components that improved were sleep quality, sleep disturbance and daytime dysfunction. These results suggest that nutritional ketosis benefits overall health through improved glycemic control as well as improved sleep quality.

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Author contributions

S.J.A, M.S, C.J.V and J.P.M drafted the manuscript. A.L.M, N.H.B, S.J.H and S.J.A participated in data acquisition and compiling. M.S and S.J.A analyzed the data. C.J.V supervised this particular analysis,

J.P.M, A.L.M, S.J.H, N.H.B, W.W.C, S.D.P and J.S.D edited the manuscript. W.W.C. proposed measuring subjective sleep quality as part of the parent Continuous Care Intervention clinical trial. All authors approved the final version of the manuscript.

Conflict of interest

SJA, SJH, ALM, NHB, JPM, and SDP are employed by Virta Health Corp and were offered company's stock options. SDP and JSV are founders of Virta Health Corp. CJV, MJS and WWC have no conflict of interest to declare.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.12.014.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2018.12.014.

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Table 1. Two-year eGFR slopes in whole CCI cohort, CCI sub cohort with baseline eGFR<90, CCI participants divided into four ketosis trajectory classes (KT) and in UC (control) used as a reference category in the linear mixed effect model

	eGFR slope (mL/min/1.73m^2/year)		
Whole cohort	**Mean + SE**	**Slope Difference**	**p-value**
CCI, n=248	0.84 ± 0.42		
UC (control), n=87	-0.68 ± 1.26	**1.52 ± 0.84**	**0.045**
CCI divided into 4 ketosis trajectory classes			
Time * Group interaction			0.11
Sustained nutritional ketosis (consistently ~ 1mM), SNK (N=17)	3.38 ± 2.35	**4.06 ± 1.63**	**0.01**
Moderately declining nutritional ketosis (~0.7mM followed by ~0.5mM), MDNK (N=99)	1.09 ± 1.68	1.78 ± 0.96	0.07
Low nutritional ketosis (consistently ~ 0.3mM to 0.4mM), LNK (N=105)	0.20 ± 1.69	0.88 ± 0.97	0.36
Unsustained nutritional ketosis (~0.3mM followed by ~ 0.1mM), UNK (N=27)	0.22 ± 2.32	0.91 ± 1.60	0.57
UC (control)	-0.69 ± 0.72		
	eGFR slope (mL/min/1.73m^2/year)		
Subcohort analysis, baseline eGFR< 90	**Mean + SE**	**Slope Difference**	**p-value**
CCI, n=111	2.99 ± 0.73		
UC (control), n=44	1.06 ± 2.13	**1.93 ± 1.40**	**<0.001**
CCI divided into 4 ketosis trajectory classes			
Time * Group interaction			0.47
SNK (N=8)	6.28 ± 4.35	5.22 ± 3.16	0.10
MDNK (N=47)	3.26 ± 2.83	2.21 ± 1.64	0.18
LNK (N=47)	2.40 ± 2.81	1.34 ± 1.62	0.41
UNK (N=11)	2.38 ± 3.69	1.33 ± 2.50	0.60
UC (control)	1.05 ± 1.19		

Note. CCI ketosis trajectory classes were identified using latent class trajectory modeling (LCTM) with non-structured matrix of variance-covariance and class-specific variance-covariance structure. A total of 248 CCI participants were included in the LCTM, participants who stayed in the intervention up to 10 weeks and those who had ketone loggings at least in two time points. To identify ketosis trajectory classes, the percentage of days logging ketone ≥ 0.3mM was modeled over time using non-Gaussian distribution. eGFR slope estimates were obtained from linear mixed-effects models controlling for baseline age, sex, race, insulin use, and diabetes duration. The maximum-likelihood based approach uses all available data, resulting in an intent-to-treat analysis.
Abbreviations. eGFR, estimated glomerular filtration rate; CCI, continuous care intervention; UC, usual care; SNK, sustained nutritional ketosis; MDNK, moderately declining nutritional ketosis; LNK, low nutritional ketosis; UNK, unsustained nutritional ketosis

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P: EPIDEMIOLOGY—OTHER | JUNE 01 2022

1245-P: Outcomes among Veterans with T2D at Time of Departure from Virtual Clinic: A Nationwide, Real World Study FREE

BRANDON FELL; MICHELLE VANTIEGHEM; AMY L. MCKENZIE; ROBERT E. RATNER

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Lifestyle interventions for type 2 diabetes (T2D) typically have poor retention, and drop out is often assumed to indicate treatment failure. A partnership between the Veterans Health Administration and Virta Health allows Veterans with T2D to enroll in Virta's clinic, which provides carbohydrate restricted nutrition therapy via continuous remote care. We sought to assess change in clinical outcomes upon clinic departure using medical record data. Percent change in clinical outcomes on a per patient basis from enrollment to time of departure were assessed with one sample t tests. Among 677 enrolled Veterans, 270 (40.0%) departed the clinic within 2 years (283±184 days in treatment; enrollment: age 58±9y, 13% female, 235±47 lb, 179±86 mg/dl glucose, 2.3±0.9 T2D medications) . Weight was significantly reduced at time of departure in all groups initiating nutrition therapy ($p<0.05$) , although clinically significant weight loss was only achieved among those who left after one year (Table 1) . Percent change in blood glucose was unchanged ($p>0.05$) despite lower mean glucose which occurred concurrent with medication deprescription in most groups ($p<0.05$) . These results show that Veterans initiating therapy experienced clinical improvements prior to clinic departure and return to standard care, particularly in weight after one year of treatment and in reduced need for medication to maintain glycemia.

Table 1. Change in Clinical Outcomes at Time of Clinic Departure

Days in Clinic at Time of Departure	n	%	Per Patient Percent Change in Weight		Per Patient Percent Change in Glucose		Per Patient Percent Change in Diabetes Medications	
			n	Mean [95% CI]	n	Mean [95% CI]	n	Median [IQR]
0-180 did not initiate nutrition therapy	50	17.2	21	-1.3 [-2.7,0]	10	-0.5 [-27.9,27]	50	0 [0]
0-180 initiated nutrition therapy	58	19.9	55	-2.8 [-4.5,-1.2]**	54	-5.8 [-14.8,3.2]	58	0 [33.3]***
181-365	70	24.1	69	-3.8 [-5.1,-2.5]***	70	0.5 [-9.1,10.1]	70	-50.0 [50.0]***
366-545	58	19.9	57	-5.4 [-7.8,-3.1]***	56	3.7 [-7.3,14.7]	58	-33.3 [50.0]***
546-730	34	11.7	34	-5.6 [-9,-2.2]**	34	-2.4 [-16.8,12]	34	-50.0 [66.7]**

*** p <0.001; ** p <0.01; * and p <0.05

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Disclosure

B.Fell: Employee; Virta Health Corp., Stock/Shareholder; Virta Health Corp. **M.Vantieghem:** Employee; Virta Health Corp., Stock/Shareholder; Virta Health Corp. **A.L.Mckenzie:** Employee; Virta Health Corp., Stock/Shareholder; Virta Health Corp. **R.E.Ratner:** Employee; Virta Health Corp.

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classes. The molecular programs contributing to disease pathogenesis in CA are still poorly characterized, largely restricted to the identification of somatic mutations in *USP8* in 40-60% of CD adenomas. To more fully characterize the mutational and transcriptional landscape driving both classes of CA, we performed whole-exome sequencing and RNA-seq in 19 CD and 16 AS adenomas. We identified *USP8* mutations in 53% of CD (10/19) and 6% of AS (1/16) samples. Strikingly, in 19% of AS tumors (3/16), all exhibiting an unusually aggressive disease course, including two cases with brain metastases, we identified recurrent somatic pathogenic mutations in *TP53* and novel loss-of-function mutations in telomere maintenance genes *DAXX* and *ATRX*. Furthermore, while all tumors with *USP8* mutations (regardless of CD/AS status) exhibited no chromosomal abnormalities as measured by copy-number variation (CNV) and loss of heterozygosity (LOH) analysis, 33% of CD (4/12, including 1 tumor with a *DAXX* mutation) and 36% of AS (4/11, including all *DAXX/ATRX*-mutated cases) samples exhibited profound chromosomal instability, characterized by hyperdiploidy, widespread whole-chromosome LOH events, and arm-level breakpoints. Using transcriptome analysis (n=22), we identified three classes of tumors (C1-C3), reflecting these distinct somatic alteration profiles. C1 tumors (n=6) are characterized by chromosomal stability, includes exclusively *USP8*-mutated CD, and exhibits upregulation of genes involved in metabolic processes and protein acetylation. C2 tumors (n=10) are comprised exclusively of AS (including all *TP53*- and/or *DAXX/ATRX*-mutated cases), are characterized by chromosomal instability, and exhibits concordant upregulation of cell cycle programs. Finally, C3 (n=6) contains a mixture of AS and CD cases (including CD without mutations in *USP8*) and features an expression profile that partly overlap with C1 tumors, but also exhibit higher expression of inflammatory genes. Taken together, our data suggest that CD and AS are distinct molecular subtypes of CA, highlighting the dominant role of *USP8* mutations in driving a unique transcriptional program and illustrate for the first time that unlike most cases of CD, AS cases are characterized by profound genomic instability and cell cycle activation, features associated with a more aggressive disease course.

Diabetes Mellitus and Glucose Metabolism

DIABETES DIAGNOSIS, TREATMENT AND COMPLICATIONS

A Continuous Remote Care Intervention Utilizing Carbohydrate Restriction Including Nutritional Ketosis Improves Markers of Metabolic Risk and Reduces Diabetes Medication Use in Patients With Type 2 Diabetes Over 3.5 Years

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SUN-LB113

Novel lifestyle, pharmaceutical, and/or surgical therapies for type 2 diabetes (T2D) are under study to assess lasting impact on metabolic risk. Among them, carbohydrate restriction including nutritional ketosis (CR) has emerged as a safe and effective nutrition therapy for reducing hyperglycemia in patients with T2D[1], yet longer term effects are unknown. At the conclusion of a 2-year study assessing a continuous remote care intervention utilizing CR (CCI) among patients who selected this therapy, intervention participants were offered the opportunity to consent to participate in a 3-year extension assessing outcomes at 3.5- and 5-y following initial enrollment. 143 of 169 extension-consented participants provided data at 3.5-y follow up. Among 3.5-y completers, linear mixed effects models were used to assess change over time in diabetes-related outcomes and McNemar's tests were used to assess for a difference in the proportion of participants meeting certain criteria at baseline compared to follow-up. At enrollment, 3.5-y completers were (mean±SE) 55±1 y of age, 40.8±0.7 kg/m^2, and 8±1 y since diagnosis. Following treatment with the CCI for 3.5 y, significant improvements compared to baseline were observed in HbA1c (-0.6±0.1 from 7.4±0.1%; $P = 1.9\text{x}10^{-5}$), weight (-10.9±1.1 from 117.4 kg; $P = 6.9\text{x}10^{-17}$), nonHDL-C (-10±4 from 139±3 mg/dL; $P = 0.005$), triglycerides (-41±11 from 189±10 mg/dl; $P = 2.1\text{x}10^{-4}$), and HDL-C (+9±1 from 43±1 mg/dl; $P = 3.0\text{x}10^{-11}$); total cholesterol and LDL-C were statistically unchanged. The percentage of participants prescribed diabetes medication decreased from 84.6 to 67.1% ($P = 5.0\text{x}10^{-6}$), while 50.2% of diabetes medications and 71.4% of diabetes medications other than metformin were discontinued. The percentage of participants treated with no pharmaceuticals or monotherapy increased from 52.5 to 81.9% ($P = 1.3\text{x}10^{-8}$). 45.5% (65/143) of participants achieved HbA1c <6.5% with either no medication (34/65, 52%) or only metformin (31/65, 48%) at 3.5 y; 37.8% of participants maintained this status from 1 through 3.5 y of treatment. 22% of participants achieved diabetes remission at 3.5 y, and 17.5% of participants maintained remission status from 2 through 3.5 y of treatment. This demonstrates that clinically meaningful improvements across multiple markers of metabolic risk can be sustained in patients with T2D who selected treatment with this CCI for 3.5 y. Improvements in metabolic risk markers reduced the need for diabetes medication, allowing some patients to achieve and sustain diabetes remission. This ongoing trial will assess 5-y effects.

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Genetics and Development (including Gene Regulation)

GENETICS AND DEVELOPMENT AND NON-STEROID HORMONE SIGNALING I

Association of Receptor for Advanced Glycation End Product (RAGE) Gene Polymorphisms & Serum Levels of Soluble RAGE (sRAGE) With Metabolic Syndrome (MS) in Mexican Population

Diana Elizabeth Gonzalez-Guerrero, PhD[1], Armando Rojas-Rubio, PhD[2], Maria-Luisa Lazo-de-la-Vega-Monroy, PhD[1], Armando Gomez-Ojeda, PhD[1], Claudia Luevano-Contreras, PhD[1], Maciste Macias-Cervantes, PhD[1], Martha Eugenia Fajardo-Araujo, PhD[1], Ma Eugenia Garay-Sevilla, MD,PhD[1].

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ORIGINAL RESEARCH

Impact of Glucagon-Like Peptide 1 Agonist Deprescription in Type 2 Diabetes in a Real-World Setting: A Propensity Score Matched Cohort Study

Amy L. McKenzie · Shaminie J. Athinarayanan

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ABSTRACT

Introduction: Glucagon-like peptide 1 receptor agonists (GLP-1) elicit substantial reductions in glycemia and body weight in people with type 2 diabetes (T2D) and obesity, but existing data suggest the therapy must be continued indefinitely to maintain clinical improvements. Given the high cost and poor real-world persistence of GLP-1, an effective therapy that enables deprescription with sustained clinical improvements would be beneficial. Thus, the purpose of this real-world study was to assess the effect of GLP-1 deprescription on glycemia and body weight following co-therapy with carbohydrate restricted nutrition therapy (CRNT) supported via telemedicine in a continuous remote care model.

Methods: A retrospective, propensity score matched cohort study among patients with T2D at a telemedicine clinic was conducted. Patients in whom GLP-1 were deprescribed (DeRx; $n=154$) were matched 1:1 with patients in whom GLP-1 were continued (Rx). HbA1c and body weight at enrollment in clinic (pre-CRNT), at date of deprescription or index date (derx/ID), and at 6 and 12 months (m) post-derx/ID were utilized in this study.

Results: No regression in weight was observed following deprescription with >70% maintaining ≥5% weight loss 12 m post-derx/ID. HbA1c rose 6 m and 12 m post-derx/ID in both DeRx and Rx cohorts, but most patients maintained HbA1c < 6.5%. HbA1c and body weight measured 6 m and 12 m following derx/ID did not significantly differ between cohorts and were improved at derx/ID and at follow-up intervals compared to pre-CRNT.

Conclusion: These results demonstrate the potential for an alternate therapy, such as CRNT supported via telemedicine, to enable maintenance of weight loss and glycemia below therapeutic targets following discontinuation of GLP-1 therapy.

Keywords: Type 2 diabetes; Ketogenic diet; GLP-1 receptor agonists; Weight; Hemoglobin A1c; Deprescription; Real-world

Amy L. McKenzie and Shaminie J. Athinarayanan contributed equally to this article.

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Key Summary Points

Why carry out this study?

In clinical trials, glucagon-like peptide 1 receptor agonists (GLP-1) have demonstrated significant reductions in glycemia and body weight among patients with type 2 diabetes and obesity with rapid regression of clinical improvements upon discontinuation of the medication even with persistent caloric restriction and exercise counseling, suggesting the drug must be continued indefinitely.

Cost and poor persistence of the GLP-1 therapy pose real-world challenges to maintaining improved health outcomes long-term, so therapies that enable deprescription with maintenance of clinical improvements are needed.

What was learned from the study?

Body weight did not rise in the 12 months following deprescription of GLP-1 therapy when patients continued carbohydrate restricted nutrition therapy supported via telemedicine in a continuous remote care model.

Hemoglobin A1c rose but on average remained below the diagnostic threshold for type 2 diabetes.

There was no difference between discontinued and continued GLP-1 therapy cohorts in body weight or HbA1c over 12 months following GLP-1 deprescription or matched index date.

This study informs clinical practice, showing that improved glycemia and weight loss can be maintained following GLP-1 deprescription among patients undergoing CRNT supported by continuous remote care, potentially mitigating the need for lifetime, continuous use of the pharmaceutical.

INTRODUCTION

About one in seven adults in the USA lives with type 2 diabetes (T2D) [1], and 78% also live with excess weight or obesity [2]. Prevalence of T2D, excess weight, and obesity continues to grow [3, 4] alongside the cost of healthcare for these conditions [5, 6], particularly through introduction of high cost medications associated with significant weight loss, such as glucagon-like peptide 1 receptor agonists (GLP-1) [7, 8].

Recent pharmaceutical advancements among incretin mimetics like GLP-1 show great potential, having elicited substantial glucose-lowering effects in T2D [9–16] and weight loss nearing that which is achieved through surgical intervention among people with excess weight or obesity without T2D [17, 18]. However, clinical trial evidence to date demonstrates the high efficacy and high cost drugs must be continued indefinitely to sustain improved clinical outcomes [19, 20].

Lifestyle intervention, as the cornerstone of T2D and obesity care, may serve as an effective combination and sequential therapy to pharmaceuticals to enable eventual deprescription—particularly among interventions demonstrated to elicit significant weight loss, regression of prediabetes to normoglycemia, and remission of T2D, such as carbohydrate restricted nutrition therapy (CRNT) [21, 22]. To date, no studies have assessed the use of CRNT as an adjunct lifestyle intervention with GLP-1 and its effect on maintaining outcomes after discontinuation of GLP-1.

Virta Health, a nationwide telemedicine clinic in the USA, specializes in treating adults with T2D, prediabetes, and obesity through a medically supervised intervention focused on delivering CRNT. Patients engage with this system through a mobile health application (app) which offers educational resources, tracking of biomarkers, direct communication with a healthcare team that includes health coaches and licensed medical professionals, and an optional social community for peer interaction. Using real-world data from the clinic, we assessed the impact of GLP-1 deprescription (DeRx) on glycemia and body weight among

people with T2D and excess weight or obesity compared to a matched cohort of patients who continued (Rx) GLP-1 therapy.

METHODS

Study Population and Design

This retrospective, real-world analysis utilized de-identified data obtained from medical records among patients of Virta Health. The use of de-identified data, in compliance with the Health Insurance Portability and Accountability Act (HIPAA) standards, exempts this study from the need for ethics committee approval, as it does not involve identifiable human subjects. Patients in the clinic are initially counseled to achieve and sustain nutritional ketosis (blood beta-hydroxybutyrate (BHB) 0.5–3.0 mmol/L). The initial guidance is to restrict carbohydrate less than 30 g per day (or less than 50 g if consuming a vegan eating pattern), protein intake around 1.5 g/kg of reference body weight, and fat intake is titrated to achieve satiety while enabling weight loss if that is a goal of the patient. Level of carbohydrate restriction and ketones are later individualized on the basis of the patient's personal carbohydrate tolerance and health goals. Patients were encouraged to continue CRNT for the entire period while they are under care in the telemedicine clinic. Frequency of follow-up with patients regarding biomarkers and the nutrition therapy is individualized on the basis of patient outreach and health need and can be as often as daily. Weight is tracked regularly using a cellular-connected scale (Body Trace BT003, New York, USA) which automatically uploads data to the app. Additionally, patients are advised to consistently upload their fingerstick blood glucose and BHB measurements to track their treatment progression. As a component of the clinic's care protocol, patients who are enrolled in the clinic are encouraged to complete regular laboratory assessments, including hemoglobin A1c (HbA1c), in line with the recommended frequency by care standards.

In this study, we identified patients with a diagnosis of T2D who were established on GLP-1 therapy prior to enrollment in the clinic where they then initiated CRNT as a co-therapy and whose GLP-1 was subsequently deprescribed following improved glycemia to HbA1c < 6.5% within 3–9 months of beginning CRNT (GLP-1 DeRx cohort) to assess change in glycemia and weight following deprescription. To assess HbA1c and weight changes after deprescription compared to continued GLP-1 therapy, a matched cohort of patients who were established on GLP-1 prior to enrollment and improved glycemia to HbA1c < 6.5 but remained on GLP-1 therapy concurrent with CRNT (GLP-1 Rx cohort) was identified.

Outcomes and Study Measures

The retrospective analysis primarily aimed to assess change in HbA1c and body weight 6 and 12 months following GLP-1 deprescription. This study also aimed to determine if HbA1c or body weight differed in the year following deprescription or index date (derx/ID) between the GLP-1 DeRx and GLP-1 Rx cohorts. In addition to HbA1c and body weight, diabetes medication data, demographics and app data, including gender, age, race and ethnicity, and app-uploaded fingerstick blood BHB (a biomarker of adherence to the CRNT) were obtained from medical records for this analysis.

Statistical Methods

To adjust for confounders and minimize bias, propensity score matching was used to match each patient in the GLP-1 DeRx cohort (reference cohort) 1:1 with a patient in the GLP-1 Rx cohort. The reference cohort was matched using propensity scores estimated from a multivariate regression model and the nearest neighbor method without any replacement. For matching, enrollment and index date covariates included age, gender, race and ethnicity, HbA1c, body mass index (BMI), number of diabetes medications, and distribution of follow-up HbA1c and weight data availability and the GLP-1 drug prescribed prior to enrollment in the clinic. To assess balance between the cohorts after matching, baseline covariates were assessed using analysis of variance

(ANOVA) or chi-squared test and standardized differences between cohorts.

Longitudinal and between matched cohort differences in HbA1c and weight were assessed at enrollment in the clinic (pre-CRNT), derx/ID, and 6 and 12 months post-derx/ID using linear mixed effects models. Additionally, we repeated the analyses in two medication subgroups with sufficient sample size (semaglutide and dulaglutide). Recognizing the effect of diabetes medications on HbA1c and body weight, we included the number of diabetes medications for each patient at enrollment and derx/ID in the propensity score matching to adjust for confounding factors. Further, two sensitivity analyses were performed: (1) after removing patients on sodium/glucose cotransporter 2 (SGLT2) inhibitors, and (2) after removing patients on any diabetes medication other than metformin.

We assessed longitudinal changes in BHB in the matched cohorts using two different methods. First, the daily BHB measurements were compiled as count data where percentage days of logging BHB ≥ 0.3 mM (indicative of carbohydrate restriction and low levels of nutritional ketosis) were calculated for the four main time intervals: enrollment to derx/ID, derx/ID ± 3 months, and 6 ± 3 and 12 ± 3 months post-derx/ID. We then used generalized estimating equations (GEE) with an unstructured correlation matrix, logarithmic link, and Poisson distribution to assess longitudinal changes and rate of change in frequency of BHB ≥ 0.3 mM between the two cohorts. Second, mean BHB was calculated for the four main time intervals and a linear mixed effect model was used to assess longitudinal changes in mean BHB and the rate of mean BHB changes between the two cohorts.

All analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria) version 4.2.2 (2022-10-31) and IBM SPSS statistics (version 29.0.1.0). Two-sided p values less than 0.05 were considered statistically significant.

RESULTS

Following GLP-1 deprescription in 154 individuals meeting inclusion criteria for the primary cohort, HbA1c increased at 6 months (0.4% [95% CI 0.2, 0.6], $p < 0.001$) and 12 months (0.6% [95% CI 0.3, 0.8]) compared to time of deprescription, though the mean remained within the non-diabetic range (6.0% at 6 months; 6.2% at 12 months). Weight did not significantly increase at 6 or 12 months following deprescription ($p > 0.05$). Compared to pre-CRN therapy, HbA1c and weight remained significantly lower up to 12 months following deprescription.

Patient characteristics of the propensity score matched cohorts are described in Table 1. No significant differences were observed between matched cohorts, and cohorts were balanced according to absolute standardized differences. Within the GLP-1 DeRx cohort, the medication most frequently utilized by patients prior to enrollment in the clinic was dulaglutide (43.5%), followed by semaglutide (29.2%), liraglutide (17.5%), and exenatide (7.1%); following deprescription, one patient was prescribed no diabetes medication, 132 patients continued on only metformin, and 21 patients continued on a diabetes medication other than metformin. The mean duration of care in both cohorts was at least 18 months.

HbA1c and body weight measured 6 and 12 months following derx/ID did not significantly differ between cohorts (Fig. 1). In all cohorts, HbA1c and body weight improved significantly at time of derx/ID and at follow-up intervals compared to levels at enrollment in the clinic, prior to adding CRNT as co-therapy. In both the DeRx and Rx cohorts, HbA1c at 6 and 12 months follow-up rose relative to derx/ID ($p < 0.001$). HbA1c for most individuals in both cohorts remained below 6.5% up to 12 months following derx/ID (DeRx, 64.8%; Rx, 64.1%), including 20.4%, and 20.3% of the GLP-1 DeRx, and Rx cohorts who maintained normoglycemia (HbA1c < 5.7%) 12 months following derx/ID. No significant change in body weight following derx/ID was observed in any cohort (p values > 0.05). More than 70% of patients in each of the matched cohorts maintained at least 5% body weight loss 12 months following derx/ID (Fig. 2). Subgroup analyses of semaglutide and dulaglutide were consistent with the full cohort and HbA1c and body

Table 1 Characteristics of the matched cohorts

	GLP-1 deprescription cohort ($n = 154$)	Continued GLP-1 therapy cohort ($n = 154$)
Age, mean (SD), years	55.9 (8.7)	55.3 (8.4)
Gender, *n* (%)		
Female	77 (50.0)	90 (58.4)
Male	77 (50.0)	64 (41.6)
Race and ethnicity (*n*,%)		
Non-Hispanic White	100 (64.9)	108 (70.1)
Non-Hispanic Black or African American	9 (5.8)	19 (12.3)
Hispanic	29 (18.8)	19 (12.3)
Non-Hispanic American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, or Multiple Races	7 (4.5)	8 (5.2)
Enrollment BMI mean (SD), kg/m^2	35.7 (6.9)	36.5 (7.2)
Enrollment HbA1c mean (SD), %	7.3 (1.2)	7.4 (1.4)
Distribution of diabetes medication classes at deprescription or index date (*n*, %)		
GLP-1	0 (0)	154 (100)
SGLT2i	10 (6.5)	0 (0)
Sulfonylureas	1 (0.6)	0 (0)
DPP4	4 (2.5)	0 (0)
Insulin	4 (2.6)	0 (0)
Thiazolidinediones	2 (1.3)	3 (1.9)
Metformin	149 (96.8)	49 (31.8)

weight changes by medication are described in Supplementary Fig. 1. Sensitivity analyses removing patients who were prescribed (1) SGLT2 inhibitors and (2) any diabetes medication other than metformin, from the analysis, were consistent with the overall findings.

Frequency of achieving BHB ≥ 0.3 mM via CRNT declined more rapidly among the GLP-1 Rx cohort compared to the DeRx cohort ($p = 0.037$), and mean BHB of the GLP-1 Rx cohort was lower compared to the DeRx cohort at all time intervals ($p < 0.05$; Supplementary Fig. 2).

DISCUSSION

Results of this real-world analysis demonstrate that GLP-1 can be discontinued without weight regain following initiation of successful co-therapy with carbohydrate restricted nutrition within this care model. While glycemia increased marginally, the mean remained below the diagnostic threshold for diabetes. No differences in glycemia or body weight were observed up to 12 months following deprescription of GLP-1 compared to a matched cohort in whom

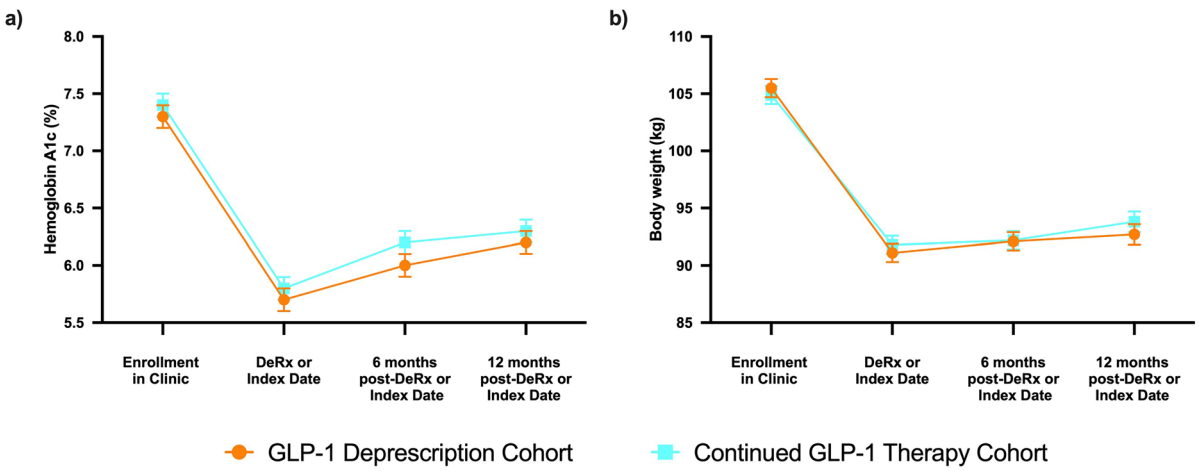

Fig. 1 Comparison of HbA1c and body weight. Longitudinal and between-group change in estimated mean **a** hemoglobin A1c (HbA1c, %) and **b** body weight (kg) from enrollment to 12 months following deprescription or index date in GLP-1 deprescription and continued GLP-1 therapy cohorts

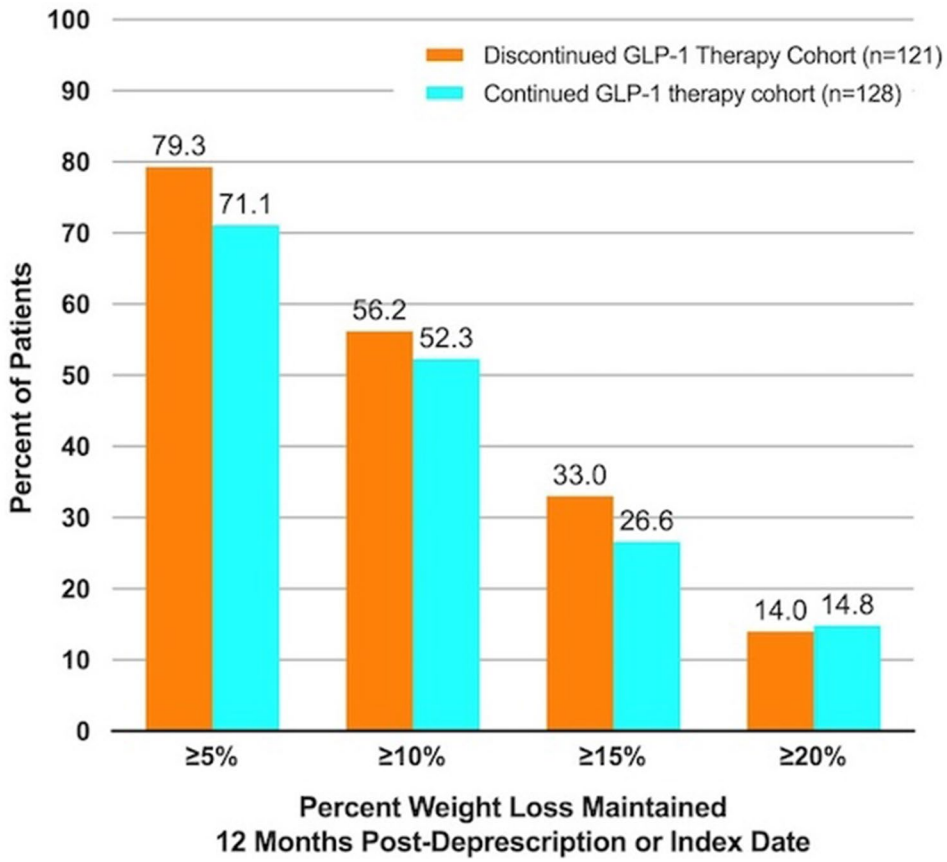

Fig. 2 Proportion of patients maintaining weight loss targets at 12 months post-deprescription or index date by cohort

GLP-1 therapy was continued. Taken together, these results suggest that CRNT supported via telemedicine in a continuous remote care model may be used in combination with GLP-1 therapy to enable stepping off GLP-1 therapy in some individuals, and continuing CRNT (often with concurrent metformin therapy) may provide an effective maintenance therapy, particularly for weight loss. More frequent maintenance of nutritional ketosis achieved through CRNT (indicating more consistent carbohydrate restriction) was observed in the DeRx cohort during the pre-deprescription time interval compared to the GLP-1 Rx cohort, suggesting adherence to CRNT may assist clinical decision-making regarding the feasibility of deprescription for individual patients.

The STEP 1 trial extension showed rapid regression in glycemia and body weight following withdrawal of semaglutide administered in conjunction with a physical activity and caloric restriction lifestyle intervention [19]. One year after therapy withdrawal, participants regained 64% of weight lost and 80% of the decline in HbA1c that had been achieved. A similar regression in weight as well as fasting plasma glucose among individuals with T2D following the withdrawal of a GLP-1 drug was observed in the SCALE trial [23]. Results from the present real-world analysis contrast prior research, showing less regression of outcomes—only 15% of the body weight lost and 36% of the HbA1c decline achieved with combination GLP-1 and CRNT prior to GLP-1 deprescription was regained in the year following discontinuation of the medication, despite being in a group with more progressive insulin resistance. Specifically, among those deprescribed semaglutide, there was no regression in body weight 1 year following discontinuation and a 40% regression in the HbA1c decline. Although the effects of GLP-1 therapy as an adjunct to lifestyle intervention prior to enrollment in the clinic are unknown, it is reasonable to expect GLP-1 therapy resulted in HbA1c and body weight reductions prior to those achieved by adding CRNT and continuous remote care, suggesting the overall regression in HbA1c and body weight in the context of GLP-1 deprescription and continued CRNT may be less than what can be observed in these data.

The STEP 4 and SURMOUNT 4 trials assessed withdrawal of GLP-1 therapy, but not lifestyle intervention, and showed regain of about half of the weight lost during combination therapy over the next 11–12 months while lifestyle intervention was continued [20, 24]. The lifestyle intervention studied in these trials focused on caloric restriction and exercise with monthly in-person or telephone counseling, while the lifestyle intervention in the present real-world study focuses primarily on carbohydrate restriction and eating until satiety with continuous remote support, suggesting that the type of nutrition therapy and degree of support utilized as a combination and sequential therapy may play a role in the ability to maintain weight loss following discontinuation of the GLP-1.

One potential reason dietary carbohydrate restriction, and nutritional ketosis in particular, may provide an advantage for weight loss maintenance following GLP-1 deprescription is through reduced hunger and appetite—an effect shared by both the drug and the nutrition therapy. Participants in a clinical trial evaluating the effects of the CRNT utilized in the present study reported reduced perceptions of hunger after 10 weeks of therapy concurrent with mean blood BHB of 0.6 mM [25], and blood BHB concentrations are associated with lower concentrations of the hunger hormone ghrelin and higher concentrations of satiety hormones glucagon-like peptide 1 and cholecystokinin [26].

Longitudinal changes in HbA1c did not differ between DeRx and Rx cohorts, though the frequency of achieving BHB $\geq$ 0.3 mM with CRNT and mean BHB was higher within the DeRx cohort. Carbohydrate restriction results in less glycemic variability [27], particularly post-meal—an effect similar to that which is achieved with GLP-1 therapy through delayed gastric emptying [28, 29]. Further, reduced carbohydrate intake may to some degree replace the need for glucose-dependent insulin secretion with GLP-1 therapy. Past research has also shown that more frequent maintenance of nutritional ketosis is associated with improvements in atherogenic dyslipidemia, glycemia, body weight, and markers of renal function [30–32]. Given the differences in BHB concentrations and frequency with which nutritional ketosis

was maintained between the cohorts, blood BHB concentrations appear to support clinical decision-making regarding GLP-1 deprescription in real-world clinical practice in addition to supporting patients in their daily nutrition choices and may be a useful indicator of likelihood of success in maintaining clinical improvements upon deprescription.

Another noteworthy observation from this study was that patients established on GLP-1 therapy prior to enrollment in the clinic achieved 13% weight loss and 1.6% reduction in HbA1c following initiation of CRNT in combination with GLP-1 therapy. Further improvement in glycemia and weight elicited with this combination therapy exceeds effects observed in other real-world studies among those who switched to injectable semaglutide from less potent GLP-1 [33, 34]. Further, the weight loss achieved with carbohydrate restriction and GLP-1 combination therapy was on par or greater than weight loss observed in STEP 2 among people with T2D treated with 2.4 mg and 1.0 mg semaglutide [10] and in the real world across 10 clinics [35], suggesting there may be benefit to pairing GLP-1 with CRNT therapy to achieve greater weight loss when clinically indicated or to enable greater weight loss when higher doses are poorly tolerated.

Additionally, cost and side effects are important considerations in GLP-1 therapy, and may contribute to the rates of uptake, adherence, and persistence observed throughout the USA today. For example, real-world persistence of GLP-1 therapy at 1 year is approximately 50% [36]. This suggests multiple therapeutic options must be accessible to enable the desired clinical outcomes for individual patients with unique preferences and circumstances.

Strengths of this analysis include its use of real-world data from a nationwide clinic, broadening the applicability of its findings, and that it is, to the best of the authors' knowledge, the first study to assess glycemia and weight outcomes following withdrawal of GLP-1 in T2D under free-living, real-world conditions. Use of real-world data also has limitations given its retrospective and observational nature, even though differences between cohorts were reduced using matched cohort analysis. Duration of GLP-1 use prior to enrollment in the clinic, response to GLP-1 and prior lifestyle therapy prior to enrollment in the clinic, and adherence to GLP-1 therapy could not be accounted for. Application of these findings is limited to the medications utilized by the patient population included in this analysis. Future research should evaluate the effect of GLP-1 deprescription including medications which have recently come to market as indicated for T2D or for excess weight or obesity without T2D and include data from time of GLP-1 therapy initiation.

CONCLUSION

Results of this real-world analysis demonstrate that GLP-1 can be deprescribed without negative effects on glycemia and body weight following initiation of co-therapy with CRNT within this care model. These real-world data contrast clinical trial evidence in which rapid weight regain was observed following discontinuation of GLP-1 therapy even when traditional caloric restriction and physical activity counseling persisted and suggest that CRNT and continuous care may provide an appropriate glycemia and body weight maintenance therapy following deprescription, to mitigate the need for lifelong, continued GLP-1 therapy.

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Data Availability. Data may be obtained from a third party and are not publicly available.

Declarations

Conflict of Interest. Amy L McKenzie holds stock in Virta Health Corp. She was employed by Virta Health at initiation of the study; she is now affiliated with Abbott, Lingo Germany GmbH, Wiesbaden, Germany. Shaminie J Athinarayanan is employed and holds stock in Virta Health Corp.

Ethical Approval. This retrospective, real-world data exclusively utilized de-identified data and we determined that formal ethics approval is not required. All patient information used in this study was anonymized in accordance with the Health Insurance Portability and Accountability Act (HIPAA) regulations, ensuring that individual privacy rights and confidentiality are maintained. The study was compliant with the Helsinki Declaration of 1964, and its later amendments.

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Employers and targeted obesity care: Exploring the concept of an obesity center of excellence

Assessing benefits, financial structures, and operational considerations

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Commissioned by Eli Lilly and Company

Milliman

A targeted obesity care model combined with a risk-sharing financial component may align provider and employer incentives for treatment of obesity.

Introduction

Obesity has become a significant public health concern in the United States (U.S.), with its prevalence increasing dramatically over the past few decades. According to the Centers for Disease Control and Prevention (CDC), the rate of obesity among adults in the U.S. is 41.9% as of 2020, an increase from 30.5% in 2000.[1] The pathology of obesity is complex, involving a combination of genetic, behavioral, metabolic, and environmental factors.[2] Individuals with obesity have a higher rate of certain comorbidities, including type 2 diabetes (T2D), cardiovascular diseases, metabolic syndrome, chronic kidney disease, depression, and others.[3] The impact of obesity in the workplace has resulted in less overall productivity and increased absenteeism, relative to employees who do not have obesity.[4,5] Moreover, individuals with obesity have a greater risk of all-cause mortality and cardiovascular-related mortality.[6]

Studies have shown weight loss for individuals with obesity leads to decreased health risks and therapeutic benefits for comorbidities.[7,8,9] However, in the current landscape of obesity treatment and management, several challenges exist. Stigma and negative stereotypes regarding obesity can influence the judgment and behavior of providers toward affected patients, potentially affecting the quality of care provided.[10] This stigma can lead to patients with obesity experiencing stress, avoiding care, mistrusting doctors, and having poor adherence to treatments.[10] Additionally, treatment approaches for obesity often lack coordination among providers, with patients having inadequate short- and long-term support. From a group health insurance point of view, employers have inconsistent coverage of obesity-related treatments, such as bariatric procedures and glucagon-like peptide-1 (GLP-1) agonist medications. According to recent studies of large employers, it is estimated that 45% of employers currently provide coverage for bariatric surgery,[11] and an anticipated 43%[12] to 49%[13] of employers will provide coverage in 2024 for GLP-1 medications indicated for chronic weight management. Comparatively, 92% of large employers currently cover GLP-1s for T2D.[13] More than half of the employers surveyed were “very concerned” about the long-term cost implications of GLP-1s.[13]

Currently, there exist a variety of programs and businesses targeted at the treatment of obesity. Employer wellness programs are aimed at promoting healthy behaviors and frequently include weight management components, but studies reveal mixed reviews on the ability of wellness programs to significantly impact health and economic outcomes for patients and employers.[14] Alternately, obesity telehealth programs have emerged as a way of offering targeted and individualized obesity care for employees. These programs typically include a virtual care model, diet and activity planning, metric tracking, and health coaching. The most popular obesity telehealth platforms have monthly per-subscriber fees, but the cost of medical services (e.g., labs) and prescription drugs are often not included in the fees.[15,16,17]

Given the current challenges related to the treatment of obesity and management of related costs, this white paper explores financial and operational considerations for creating a best-in-class treatment center for obesity, in the form of a center of excellence (CoE). The CoE would incorporate financially at-risk components associated with obesity treatment and outcomes, with a goal of consistent and appropriate care, sustainable patient outcomes, and long-term reductions in overall healthcare costs. By exploring the dynamics of an obesity CoE, this white paper aims to provide a conceptual solution for employers that aligns incentives among stakeholders in the treatment and management of obesity.

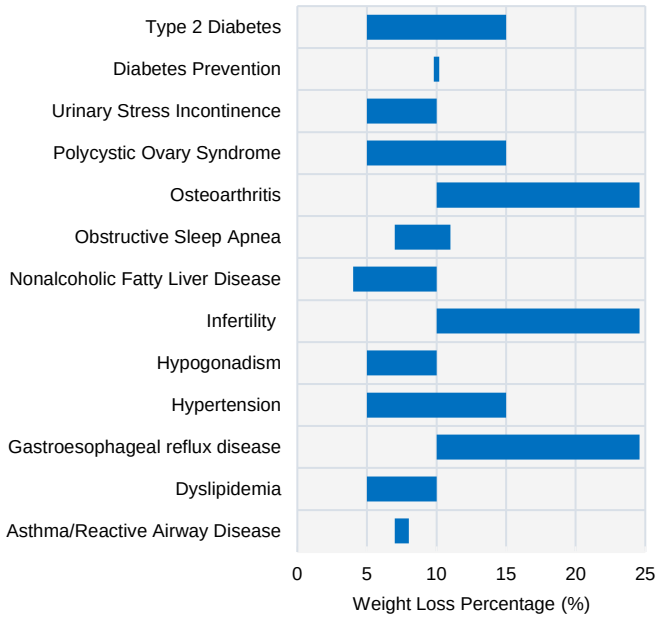
Note that the framework discussed herein is oriented toward an obesity CoE model for self-insured employers and their

employees; however, the model may be applicable to other types of payers and insurers as well.

Benefits of weight loss and obesity management

The American Association of Clinical Endocrinology (AACE) and the American College of Endocrinology (ACE) published obesity clinical practice guidelines in 2016. According to the guidelines, for most obesity-related conditions a loss of 5% to 10% of body weight can result in therapeutic benefits. Figure 1 summarizes the weight loss required for therapeutic benefits of 13 comorbidities related to obesity, as noted in the AACE/ACE guidelines.[18] Note that improvements due to weight loss for congestive heart failure and cardiovascular disease were ongoing or in the planning phase at the time of the AACE/ACE guidelines, and thus these diseases are not included in Figure 1.

FIGURE 1: WEIGHT LOSS (%) REQUIRED FOR THERAPEUTIC BENEFIT OF COMORBIDITIES (SUMMARIZED FROM AACE/ACE GUIDELINES[18])



Note: Additional therapeutic benefits may be seen at weight loss levels higher than what is displayed in this figure; the percentages in Figure 1 are supported by studies included in the AACE/ACE guidelines.

Therapeutic benefits of weight loss are numerous, including decreased blood pressure, decreased hemoglobin A1c levels, and improvements in inflammation, joint stress mechanics, and ovulation.[9] In one study, individuals with a body mass index (BMI) of 40 kg/m^2 who lost weight (median of 13% weight loss) had risk reductions for T2D of 41%, sleep apnea of 40%, hypertension of 22%, dyslipidemia of 19%, and asthma of 18%.[8]

The AACE/ACE guidelines recommend lifestyle modifications as a first line of treatment for obesity, which includes diet, physical activity, and behavioral modifications. Under certain circumstances, the guidelines also recommend medication-assisted weight loss in conjunction with lifestyle therapy, or bariatric procedures to help meet goals for clinical outcomes. Figure 2 summarizes recommended treatment guidelines across increasing BMI classes.

FIGURE 2: RECOMMENDEDED TREATMENTS BY BMI (SUMMARIZED FROM TREATMENT GUIDELINES[18,19])

CONSIDERATIONS FOR EMPLOYERS

From an employer's healthcare cost perspective, the financial implications of obesity can be significant. Adults ages 20 to 65 with obesity are estimated to incur annual medical expenses that are twice as high as those of adults with a normal weight. Additionally, average expenditures increase as BMI increases. Compared to a normal-weight cohort, annual medical expenditures are 1.7 times higher for class 1 obesity (BMI 30.0-34.9), 2.2 times higher for class 2 obesity (BMI 35.0-39.9), and 3.3 times higher for class 3 obesity (BMI ≥ 40.0).[20] Over 30 units of BMI, each one-unit BMI increase is associated with an additional cost of $253 per person per year (in 2019 dollars).[21]

Weight loss can lead to potential healthcare savings for employers. According to a publication that estimated weight-loss-associated decreases in medical care expenditures in a commercially insured population, individuals with obesity and chronic conditions can have estimated reductions in total medical expenditures ranging from $238 to $752 in annual savings for each one-point decrease in BMI unit.[22] Note that these savings estimates do not include the incremental cost of the care plan and/or treatment to achieve the BMI decreases.

In the workplace, weight loss can result in reduced job absenteeism, as individuals with obesity are estimated to miss three more days of work annually due to injury or illness compared to individuals with normal weight (5.3 days missed versus 2.3 days missed, respectively).[5] Presenteeism may also be improved with weight loss, given employees with a BMI ≥ 35 experience greater health-related work limitations—such as needing additional time to complete tasks and lower ability to perform physical job

demands—than the average worker.[23] More generally, employers who provide comprehensive healthcare coverage and offer wellness programs to their employees have been shown to increase employee job satisfaction levels and productivity, and decrease their likelihood of seeking other employment opportunities.[24,25]

Exploration of an obesity CoE model

A CoE is a dedicated facility or team within a healthcare organization that provides exceptional care and leadership in a specific area of medicine. It is characterized by a high concentration of specialized skills and resources, coupled with a commitment to research, education, and quality. A CoE typically aims to provide high-quality patient outcomes, advance medical knowledge, and reduce healthcare costs in its area of focus.

The concept of a CoE model is familiar to U.S. payers. CoEs have been implemented to improve value in multiple conditions and medical episodes from cancer to knee replacement.[26,27] The CoEs where providers are willing to take on risk for outcomes are typically targeted at conditions that are acute in nature or have a defined treatment period (e.g., oncology, kidney, musculoskeletal).[17,26,28] The CoEs that treat chronic conditions (e.g., diabetes or chronic obstructive pulmonary disease)[29,30] are often structured around a fee-for-service (FFS) payment model. Additionally, CoEs typically treat conditions prevalent in older populations, where Medicare may be able to benefit from longer-term clinical improvements due to the lower rate of member turnover or churn compared to commercial insurance. Lastly, CoEs typically have a physical facility where they see patients and may add telehealth services as additional support. For obesity treatment and management, a CoE provides best-in-class care through a specific provider network. An obesity CoE has a few key differences from typical CoE models in place today:

- Obesity is a chronic, long-term condition that requires ongoing support, even after weight-loss goals are achieved.
- A longer time horizon may be needed to realize cost savings associated with weight loss and other therapeutic benefits.
- Obesity and weight-related outcomes are generally easy to self-measure. Thus, an obesity CoE could provide treatment and support primarily through a telehealth platform, with referrals to in-person specialists, as needed.
- Individuals with obesity often have other conditions that are already being managed by a primary care provider or specialist. Thus, continuity of care and coordination among providers both within and outside of the CoE are essential.
- Obesity affects individuals of all ages, with the highest prevalence in older age groups.[1] However, Medicare is currently prohibited from covering weight-loss medications[31] and only covers bariatric surgery in certain circumstances related to severe obesity.[32] Thus, an obesity CoE would likely target care for employee populations and commercially insured individuals.

FEATURES OF AN OBESITY COE

Comprehensive obesity care. Conceptually, an obesity CoE provides comprehensive care with a holistic approach that incorporates obesity treatment protocols (such as those described within the AACE/ACE guidelines) to provide the most effective care for patients. The goals are to develop a personalized treatment plan that is tailored to a patient's risk, provide support for short-term and long-term weight management success, and align incentives for all stakeholders. This approach would result in a patient receiving the most appropriate and beneficial treatment for their specific situation, while, ideally, the employer benefits from shared financial accountability. Elements of this holistic approach are already being implemented in some healthcare settings. These existing organizations are paving the way for a more integrated and comprehensive approach to obesity treatment, demonstrating the feasibility and effectiveness of such a model.

Lifestyle support. One of the key components of obesity comprehensive care is lifestyle support. This includes dietary and exercise guidance, as well as psychological support to help patients make and maintain healthy lifestyle changes. It could even provide financial counseling to help patients plan for or manage the costs associated with purchasing healthier food options or enrolling in wellness classes. The CoE could also interact with existing wellness benefits such as lifestyle management and fitness programs that employers are offering. This allows for a more holistic approach to obesity treatment, addressing not just the physical aspects of the condition, but also the behavioral factors that contribute to it.

Pharmaceutical and procedural interventions. In addition to lifestyle support, the CoE may also prescribe anti-obesity medications (AOMs) or recommend bariatric procedures, depending on the patient's individual needs and circumstances. Independent studies suggest pairing AOMs with an obesity-centric care program can lead to more patient engagement, greater weight loss, and better adherence to the medication than average.[33,34]

From an employer's perspective, AOM prescription coverage and bariatric procedures could be limited to the CoE provider network through medical network and pharmacy coverage policies. Therefore, only patients who are participating in the program and have been evaluated as appropriate would be able to receive pharmaceutical treatments for obesity. This strategy safeguards against misuse or off-label use of AOM interventions by

restricting treatment to patients who meet the clinical obesity indication requirements. Simultaneously, it combines AOM usage with continuous care from the CoE to promote lifestyle changes that contribute to greater adherence and longer-term success.

Breadth of care. A CoE for obesity requires expertise in all areas of obesity—professionals ranging from bariatricians to dieticians to sleep experts who are well-versed in the complexities of obesity and are equipped to provide comprehensive care to patients. Access to these professionals would be made easier through the CoE, given its foundation in telehealth. Patients could access expert care and ongoing support without needing to travel to a healthcare facility. This would make treatment more convenient and accessible, even for employees living in rural areas and other areas with limited access to healthcare professionals. However, recognizing that the journey to a healthier lifestyle is a long-term commitment that requires continuous encouragement and guidance, there can and should still be coordinated, in-person engagement opportunities, likely through community or patient support groups.

Integration with primary care and other specialists. Given the overlap between obesity and other conditions, coordination among providers both within and outside of the CoE is important. A CoE model should provide continuity of care with the patient's current primary and specialty providers. A coordinated care model may facilitate collaboration among healthcare providers, resulting in more efficient healthcare spend—such as not duplicating labs across multiple providers—and personalized treatment plans that consider a patient's underlying conditions (e.g., mental health). Furthermore, it enables the patient's primary care provider to be engaged in the patient's care plan, which provides additional accountability and support to the patient outside the CoE.

POTENTIAL DRAWBACKS OF AN OBESITY COE

There are potential drawbacks to consider when evaluating an obesity CoE as well. The capacity to support all acuities of obesity, including the ability to engage with patients long-term, may be a challenge. It is particularly important to ensure that certain populations, especially those without access to telehealth or technology, are not disadvantaged. To address this, an additional fee could be included to offset this disparity, such as an employer paying for necessary equipment like scales or other remote monitoring devices or providing access to computers or tablets for virtual visits. Finally, depending on the financial model and incentives associated with treatment at the CoE, it may be prudent for employers to structure their benefit designs to drive utilization to the CoE through reduced member cost sharing or other incentives. However, this could result in limiting patient choice and access to providers outside the CoE.

Operationalization of an obesity CoE

ESTABLISHING AN OBESITY COE

The formation of an obesity CoE requires defining the scope of services and care plans that will be offered, identifying clinical characteristics of patients eligible to be treated within the CoE, setting up the provider network and ensuring proper credentialing, and development of a platform tailored to the CoE.

Scope of services. One of the first steps to setting up an obesity CoE is determining the scope of services provided under the network. Ideally, the CoE network would provide comprehensive obesity care, including medical services (e.g., healthcare provider visits, bariatric procedures), prescription drugs (e.g., AOMs), coordination of care (e.g., connecting patients to specialists for comorbidities), and non-billable service (e.g., support groups). Measures for sustainable weight loss should be agreed upon and incorporated into the care plans so they can be adequately monitored and tracked over the performance period. This includes defining care pathways that outline the patient's journey from initial diagnosis and treatment to long-term maintenance. It also involves prescribing AOMs or bariatric procedures as part of a comprehensive treatment plan, when appropriate. These elements together ensure that the CoE provides a well-rounded, effective approach to obesity care.

Patient eligibility. The next step is establishing the clinical characteristics—such as BMI, body fat percentage, and presence of comorbidities—that would be necessary for an individual to qualify for care through the CoE. Treatment guidelines, such as the ACE/AACE guidelines,[18] may be considered when defining the criteria for the CoE-eligible population. The CoE should assess stratification of members based on the severity of obesity and the presence of any comorbidities, as well as consider how to manage long-term member alignment for ongoing weight maintenance support.

CoE credentialing and provider network. Once the scope of services and patient eligibility criteria has been determined, the CoE can initiate creating the provider network and ensuring proper credentialing. Providers must have or obtain state licensure to ensure they meet the necessary qualifications and standards to treat patients in each state, particularly given the nationwide telehealth-based platform of the CoE. The CoE may include providers that are employed by the CoE as well as third-party providers that are contracted to provide specific services under the CoE network, such as bariatric surgeons.

Platform development. Lastly, the CoE can develop or acquire a patient engagement telehealth platform that enables seamless patient interaction, data collection, and care coordination across the various professionals and services offered within the CoE. This could be built in-house by the CoE development team, outsourced to an external development team, or purchased from a large telehealth provider and customized to the CoE's needs. The platform should automate the specific care model for the CoE, with the care pathways integrated into the website and app.

COE AND EMPLOYER CONTRACTING

CoEs may offer various options for financial structures, member attribution methods, tracking and monitoring, and ongoing reassessments. The CoE and employers may negotiate and contract on terms for each population of interest (e.g., newly treated versus maintenance individuals). The employer could contract directly with the CoE, or the contracting could be through an insurance company, pharmacy benefit manager (PBM), or the employer's third-party administrator (TPA). The contract would reflect the agreed-upon financial model, as well as the terms for any risk-sharing or quality metrics. At a minimum, the employer would include the CoE as an in-network provider to enable patient access to the specialized provider network.

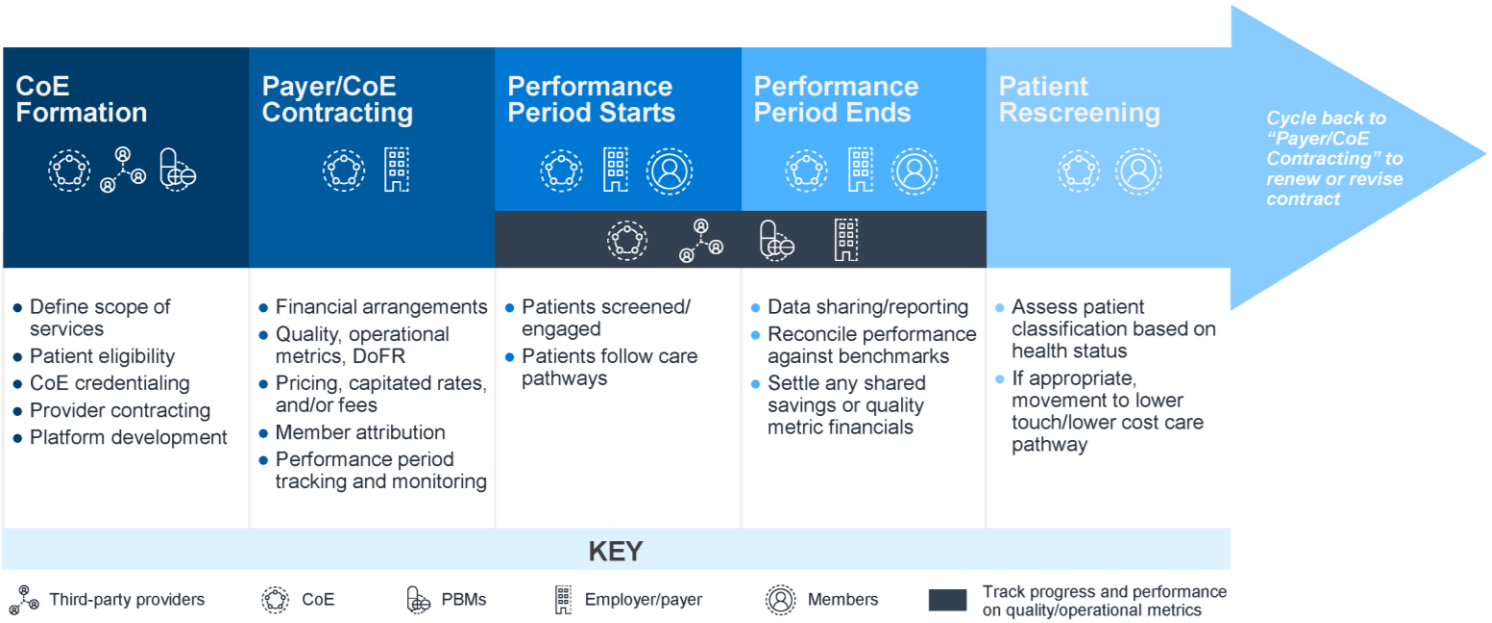
Figure 3 summarizes the timeline, key activities, and stakeholders associated with the development and operationalization of a CoE.

Financial structures and contracting. Financial structures and pricing for the CoE's services can take different forms based on the CoE's capacity for risk sharing and the employer's preferences for partnering with the CoE. The goal is to achieve a balanced and fair payment system that considers the quality, quantity, and cost of the care provided, including care and management that is not reimbursable through typical provider contracts. It is practical for the CoE to offer different financial models that align their incentives with the employers' needs to ensure both parties benefit from the partnership. Depending on the features of the chosen financial model, the CoE and employer may need to align on a division of financial responsibility (DoFR) and/or outcomes and quality metrics to ensure transparency and accountability among the contracting parties. Pricing, such as fee-for-service rates, capitated payments, bundled payments, and other fees, should also be included in the contract terms.

Setting up data-sharing pipelines and business associate agreements (BAAs) with employers, TPAs, providers, and PBMs is a key step to facilitate the efficient and secure exchange of information, promoting collaboration and coordination among all parties involved in the patients' care. Additionally, cooperation with PBMs or pharmaceutical manufacturers is crucial to ensure the appropriate management of, and access to, AOMs.

Member attribution. Attributing qualified members to the obesity CoE should be a systematic process based on objective criteria and analytics. Attribution can be performed either prospectively or retrospectively. Under a prospective approach, potential members undergo a screening process to assess their health status and determine their suitability for the program. The screening process could be triggered upon an overweight or obesity diagnosis being identified in claims data, or if an individual has diagnosed comorbidities that are typically associated with obesity, even if obesity has not directly been identified in claims data. Individuals may also choose to self-elect or may be referred by their healthcare provider to participate in the screening process. Following the screening, the eligibility of the members is determined based on specific criteria set by the CoE or employer. Once deemed eligible, members can elect to be enrolled in the CoE treatment program.

FIGURE 3: TIMELINE AND STAKEHOLDERS ASSOCIATED WITH OPERATIONALIZATION OF A COE



Under a retrospective approach, there may not be an up-front screening process for individuals who are deemed eligible to receive treatment through the CoE. Rather, any employee can choose to seek care through the obesity CoE. At the end of the performance period, the CoE-treated employee population would be assessed to identify the individuals who met certain criteria or received certain types of service. Only those individuals would be included in the attributed population for the financial modeling and outcomes or quality payment calculations.

Tracking and monitoring. Tracking progress and monitoring outcomes is a crucial aspect if quality/outcome payments or financial risk-sharing is involved. This involves the use of measurable operational and quality metrics to assess the effectiveness of the care provided, such as prevalence and incidence of obesity-related complications, percentage weight change, and overall health costs and outcomes.

There is also the potential for the CoE to collect patient-reported measures, such as patient experience, self-esteem, absenteeism, mobility, and impact on quality of life, to provide insight into indirect outcomes associated with obesity treatment. These metrics provide tangible data on the performance of the CoE, allowing for continuous improvement, refinement of the care model, and execution of outcomes contracting. They also provide valuable insights into the patients' progress, helping to guide future treatment decisions.

A recent study on measurable metrics in obesity assessed multiple obesity-related measures within 10 healthcare organizations and found that there were certain operational and quality performance measures that were useful for obesity tracking and outcomes. These measures included prevalence of overweight/obesity in the organization and within the targeted clinics, diagnosis and assessment of obesity-related complications, documentation of obesity diagnosis, percentage weight change in a 15-month period, and prescriptions for AOMs.[35]

The CDC has also published guidance on employer evaluation measures for planning of obesity prevention and control programs, which includes measurement categories such as worker productivity, healthcare costs, health outcomes, and organization changes (e.g., workplace programming).[36] It should be noted that tracking and measuring clinical outcomes over time should be normalized for the continual flux of new versus maintenance patients to limit the potential skew in overall outcomes that may result from new patients being added.

FIGURE 4: ASSESSMENT OF POTENTIAL FINANCIAL MODELS FOR AN OBESITY COE

	FFS	FFS + Quality	Shared Savings	Specialty Capitation	Full Capitation
Financial model definition	Each service has an associated payment to the provider with no link to quality or value	Each service has an associated payment and bonuses are issued to the provider for achieving quality metric goals	Total cost is compared to a benchmark and a portion of savings or losses are shared with the provider	An amount is paid to the provider to cover all services within a specialty category, shifting the risk of these services to the provider	An amount is paid to the provider to cover all services, shifting the risk of all services to the provider
Key aspects of the financial model as it applies to an obesity CoE	• FFS rate structure for obesity-related services and drugs (e.g., medical/ pharmacy claims, nutritional coaching, coordinated care) • Employers who send their members to the CoE providers pay a negotiated rate for services	• FFS rate structure for obesity-related services and drugs, supplemented with payouts associated with meeting particular quality measures, such as weight loss, patient engagement, and adherence to medication • Potentially lower FFS negotiated rates for obesity drugs and services versus FFS-only model	• CoE providers share in profit (or losses) based on total cost of care (i.e., not limited to obesity-related incurred costs) compared to benchmarks. • Shared savings measurements should be on total cost of care for there to be an opportunity for savings. The obesity CoE would take risk on total cost of care but only be responsible for managing obesity	• Capitated rate covers certain medical and drug expenditures specifically identified as being related to obesity. Incentivizes providers to not overutilize or overprescribe • Capitated rate is set in advance, potentially with premium rates varying by treatment protocol	• Capitated rate covers all medical and drug expenditures, not just those specifically identified as being related to obesity. The CoE must have large network to take risk on total cost of care • Capitated rate is set in advance, potentially with premium rates varying by treatment protocol
Assessment of financial models for an obesity CoE	**Does not mitigate volume or cost risk:** There are no outcomes-oriented risk components, nor cost containment **Easy model to implement today:** All drugs and services are paid on a fee-for-service basis	**Aligns incentives:** Provider network is oriented to obesity management and provider payments are contingent upon positive outcomes **Fairly easy model to implement today:** Requires clear outcomes/quality measures. Good precedence for this model among other condition-specific CoEs	**Accounts for total cost of care:** Shared savings/loss is possible if the CoE is willing to take risk on total cost of care, even without having a direct relationship with the provider networks managing other comorbidities **Difficult model to implement today:** Requires a clear member attribution method, multi-year tracking, and access to all medical and pharmacy claims	**Offers predictability, for a premium:** This model works for obesity CoE, but only if the PMPM rate is high enough to mitigate treatment disincentives and employers are willing to pay the higher premiums **Difficult model to implement today:** Requires a clear member attribution method, agreement on the division of financial responsibilities and premium rates	**Requires robust network of specialties and providers:** A full capitation model requires a large provider network and may limit patient choice **Difficult model to implement today:** Requires a clear member attribution method, a wide provider network, and access to all medical and pharmacy claims

Ongoing reassessments. Lastly, in a typical CoE, patients "graduate" from the CoE when they have successfully completed their treatment plan and no longer require the intensive support of the CoE. For obesity care, studies have shown that individuals with continued clinical support are more successful at maintaining their initial weight loss.[37] For this reason, an obesity CoE may elect to use an acuity-based care model that enables ongoing engagement with individuals who have met their weight loss goals and encourages continued adherence to lifestyle changes and medications (if applicable). Therefore, payments and quality measures that are tailored to short-term and long-term treatment of obesity are important for sustainability of the program. For example, the employer should not be overpaying for maintenance services, nor should the CoE be subject to quality measures that are not applicable for a treated population in the maintenance phase of treatment. The financial and quality measures must ensure that patients who require long-term care continue to receive the support they need, while also preserving the financial sustainability of the CoE.

Financial models for an obesity CoE

CoEs perform many services that replace those performed by other healthcare providers, while also performing additional services that may not be submitted or captured within the healthcare claims process. Payment contracts can be set up on a financial risk spectrum from FFS (i.e., no financial risk is shifted from the employer to the CoE) to full capitation (i.e., financial risk for total cost of care of enrolled patients is shifted to the CoE). Figure 4 describes each financial model, as well as the benefits and drawbacks for employers and providers focused on managing obesity. Of these five financial models, "FFS + Quality" and "Specialty Capitation" will be explored further in the next section, given the shared financial risk between employers and CoEs, feasibility, and likely interest of employers in such models for treatment and management of obesity.

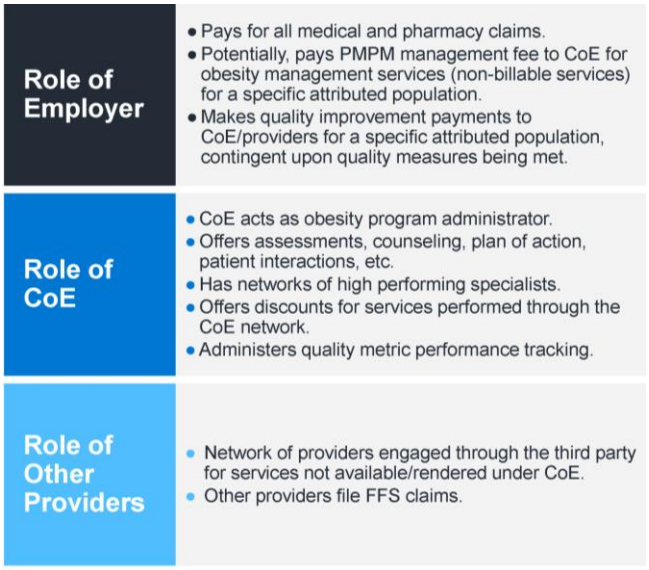
DEEPER DIVE: "FFS + QUALITY" MODEL

Figure 5 presents the role of the employer, the CoE, and other providers as it relates to the "FFS + Quality" model.

The key benefits of a "FFS + Quality" financial model are that it offers a network of physicians who are accountable for outcomes associated with obesity care and weight loss management and may also provide reduced FFS rates for obesity care services and drugs. The key drawback of this model is that employer costs increase as the volume of services, prescriptions, or adherence to AOMs increase.

The CoE and employers executing a "FFS + Quality" model must align on the fee schedule and quality payments. For instance, the obesity CoE may offer lower fees for obesity services compared to other providers, with additional quality/outcome payments made contingent on successfully meeting agreed-upon measures. Thus, providers are incentivized to meet quality/outcome goals to receive the contingent payment(s). Quality measures and outcome goals should vary depending on the population being measured, such as a newly treated population versus a maintenance population. Under the "FFS + Quality" model, the employer or its TPA will also be responsible for the monitoring and auditing of healthcare utilization. This offers another layer of oversight for the employer to confirm the CoE is not overutilizing treatment.

FIGURE 5: "FFS + QUALITY" STAKEHOLDER ROLES



DEEPER DIVE: "SPECIALTY CAPITATION" MODEL

Figure 6 presents the roles of the employer, the CoE, and other providers as they relate to the "Specialty Capitated" model.

Key benefits of a "Specialty Capitation" financial model are that it provides per-individual cost stability to the employer for the year related to obesity treatment and incentivizes providers to provide efficient care at lower costs to retain revenue from the per member per month (PMPM) capitation rate.

A drawback of this model is that the CoE providers are financially at-risk for all obesity-related care. The provider is responsible for balancing the management of healthcare costs with providing appropriate care and maintaining quality outcomes. Additionally, because direct healthcare savings from weight loss are usually linked to improvements in obesity-related comorbidities, a provider in an obesity CoE may have limited opportunities for cost savings because the healthcare cost offsets would occur outside the CoE's remit. A capitated payment model stabilizes an employer's cost exposure for an individual member, but it does not necessarily incentivize providers to drive toward particular outcomes or quality care. Therefore, it may be necessary to incorporate quality metrics into the "Specialty Capitation" model to offset the potential disincentives for providing more expensive care (when appropriate).

Furthermore, the capitation amount may be difficult to set without accounting for the mix of obesity severity levels within the employer population. Depending on the size of the employer,

experience may not be sufficient to set a credible capitation rate without using a market benchmark. Patients with more severe obesity may have a care plan that includes higher-cost AOMs and/or bariatric procedures, while patients with less severe obesity may have a care plan focused on lifestyle and nutrition management. For these reasons, the capitation rate will need to be set high enough so there is not a disincentive for providing care. However, this may make it less attractive to employers if the rate is higher compared to what is spent on obesity care today. The CoE may need to work with actuaries and other pricing experts to help determine appropriate capitation rates for each employer contract.

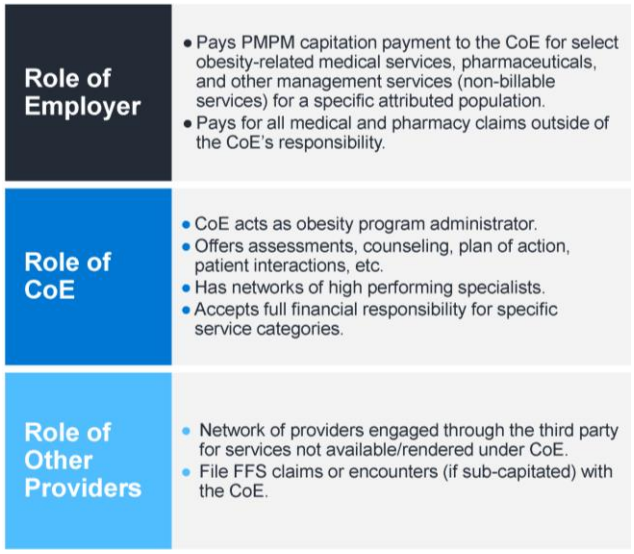
The attribution of patients and determination of appropriate capitation rates are critical in the "Specialty Capitation" model. There may be different capitation rate cells given a patient's characteristics, which would be assessed during the screening process. Furthermore, the employer and CoE must agree upon the DoFR to align on the services for which the CoE is responsible under the capitation.

Under the "Specialty Capitated" model, the employer is incentivized to drive all obesity care through the CoE. For example, if the obesity CoE is responsible for the costs of AOMs within the capitation, but an individual receives an AOM outside of the CoE, then the employer would likely be responsible for those costs. A benefit of this restriction is that the employer has confidence that obesity treatments, like AOMs, are being prescribed appropriately (i.e., no off-label use). However, this restriction may limit patient access and treatment choice. For example, if a patient with T2D was being treated with a GLP-1 drug outside of the CoE and wanted to begin treatment for obesity through the CoE, an employer might prefer that the individual switch to a GLP-1 medication indicated for obesity because the AOM costs would be included within the capitated rate. Thus, the "Specialty Capitated" model may unintentionally prefer certain GLP-1 medications.

The capitation rate needs to be high enough to ensure providers can appropriately and adequately treat each patient, but low enough that employers are willing to pay to direct all obesity care to the CoE. The employer or its TPA will be responsible for the monitoring and auditing of healthcare utilization, with the goal of verifying the CoE is appropriately using its options according to the treatment guidelines and the contracting terms to ensure the providers are not underutilizing certain treatments, such as bariatric procedures or AOMs.

Bundled payments, also known as episode-based payments, are another form of specialty capitation. A bundled payment is a fixed-price agreement for a predefined episode of care, commonly consisting of a procedure and all related services or all care for a medical condition. Bundled payments eliminate the risk to the CoE that an attributed member will receive higher-cost services early in the capitation period and then leave the program or the employer.

FIGURE 6: "SPECIALTY CAPITATION" STAKEHOLDER ROLES



Conclusion

The current landscape of obesity treatment presents several challenges, including lack of care coordination, inadequate patient support, and inconsistent coverage of treatments. This paper explored and presented key considerations for operationalizing a CoE for obesity treatment. The program should provide comprehensive, coordinated care with a goal of appropriate, efficient, and effective care. The implementation of an obesity CoE would require careful planning, including defining the scope of care, setting up data-sharing pipelines, and tracking progress and outcomes. Financially, the CoE may offer a variety of models that can shift or share the financial risk between the CoE providers and the employer. Employers that want to drive toward positive obesity outcomes may favor a financial model with payments contingent on quality or outcomes, while employers that desire predictable costs may favor a capitated pricing model. In summary, a CoE for obesity could potentially align financial and treatment incentives for obesity care, benefiting employees, employers, and healthcare providers.

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Limitations

Milliman was engaged by Eli Lilly to support exploring the concept of an obesity CoE. This paper was supported by research and Milliman subject matter experts familiar with disease management programs, CoEs, and risk-sharing models. This white paper outlines typical and/or the most relevant types of programs that may be applicable to an obesity CoE; it is not intended to be a comprehensive study of every type of program or model available.

While this report provides a guide for operationalizing a center of excellence, entities interested in creating a CoE model for obesity should engage with the appropriate professionals to address specific financial and operational nuances. The comprehensive obesity CoE model described in this white paper, to our knowledge, is not yet in existence. Therefore, the process and financial models outlined here are intended to provide thought leadership as a conceptual solution for obesity treatment. Actual experience for operationalizing an obesity CoE may vary from what has been described herein.

Guidelines issued by the American Academy of Actuaries require actuaries to include their professional qualifications in all actuarial communications. Austin Barrington and Jessica Naber are members of the American Academy of Actuaries and meet the qualification standards for authoring this report.

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