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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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-hydroxybutryrate; BMD, bone mineral density; CAF, central abdominal fat; A/G, android:gynoid ratio; LELM, lower extremities lean mass; HDL, high density lipoprotein; LDL, low density lipoprotein; 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; CLIA, Clinical Laboratory Improvement Amendments; IRB, Institutional Review Board; DXA, dual-energy X-ray absorptiometry

ABSTRACT

OBJECTIVE: Studies on long-term sustainability of low-carbohydrate approaches to treat diabetes are limited. We aim to assess the effects of a continuous care intervention (CCI) on retention, glycemic control, weight, body composition, cardiovascular, liver, kidney, thyroid, inflammatory markers, diabetes medication usage and disease outcomes at 2 years in adults with type 2 diabetes (T2D).

RESEARCH DESIGN 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.

RESULTS: Significant changes from baseline to 2 years in the CCI group included: HbA1c (-12% from 7.7±0.1%); fasting glucose (-18% from 163.67±3.90 mg/dL); fasting insulin (-42% from 27.73±1.26 pmol L^{-1}); weight (-10% from 114.56±0.60 kg); systolic blood pressure (-4% from 131.7±0.9 mmHg); diastolic blood pressure (-4% from 81.8±0.5 mmHg); triglycerides (-22% from 197.2±9.1 mg/dL); HDL-C (+19% from 41.8±0.9 mg/dL), and liver alanine transaminase (-21% from 29.16±0.97 U/L). Spine bone mineral density in the CCI group was unchanged. Glycemic control medication use (excluding metformin) among CCI participants declined (from 56.9% to 26.8%, $P=1.3x10^{-11}$) including prescribed insulin (-62%) and sulfonylureas (-100%). The UC group had no significant changes in these parameters (except uric acid and anion gap) or diabetes medication use. There was also significant resolution of diabetes (reversal, 53.5%; remission, 17.6%) in the CCI group but not in UC. All the reported improvements had p-values <0.00012.

CONCLUSIONS: The CCI 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.

TRIAL REGISTRATION

Clinicaltrials.gov NCT02519309

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,S34). In the United States, over 30 million people have diabetes and it is a leading cause of morbidity and mortality, especially through increased cardiovascular disease (CVD)(2). The remission rate under usual care is 0.5 - 2%(3) while intensive lifestyle intervention resulted in remission rates (both partial and complete) of 11.5% and 9.2% at 1 and 2 years(4). When lifestyle intervention is insufficient, medications are indicated to manage the disease and slow progression.

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(5,6,7). 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(8,S35,S36).

With bariatric surgery, up to 60% of patients demonstrate T2D remission at 1 year(9). Outcomes at two years and beyond indicate ~50% of patients can achieve ongoing diabetes remission(10,S37). The second Diabetes Surgery Summit recommended using bariatric surgery to treat T2D with support from worldwide medical and scientific societies(10), but both complications and cost limit its widespread use(11,S38). 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 carbohydrate (6,12,S39,S40).

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(13,S41); 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 versus 4.1% with a low-fat diet (14), and a small randomized trial utilizing a ketogenic diet demonstrated improved weight and diabetes control at one year (15). Systematic reviews also corroborate the effectiveness of a low-carbohydrate diet for T2D(16,S42) and it has recently become a consensus recommended dietary option(17). Nonetheless, sustained adherence is considered challenging(17), and an LDL-C increase is sometimes observed(18,S43,S44) with carbohydrate restriction. Given that total LDL-P, small LDL-P, and ApoB tend to improve or remain unchanged, the impact of an isolated 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(7). The CCI included telemedicine, health coaching, and guidance in nutritional ketosis using an individualized whole foods diet. Eighty-three percent of CCI participants remained enrolled 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(19). Here we report the results of this study at 2 years. The primary aims were to investigate the effect of the CCI on retention, glycemic control, 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; diabetes medication use, and disease outcomes (e.g. diabetes remission, metabolic syndrome); and (2) comparing 2-year outcomes between the CCI and UC groups.

Materials and methods

Study design and participants

The comprehensive study design has been published previously (7,25), and the results presented here are the follow-up 2-year results (*Clinical trials.gov identifier: NCT02519309*). This is an open-label, non-randomized, outpatient study and results presented here include data collected

between August, 2015 and May, 2018. Participants aged 21 to 65 years with a confirmed diagnosis of T2D and a body mass index (BMI) > 25 kg/m^2. Participants in the CCI accessed a remote care team consisting of a health coach and medical provider and reported routine biomarkers (weight, blood glucose and beta-hydroxybutyrate [BHB]) through a web-based application (app). Participants self-selected between two different CCI educational modes: on-site (n=136, CCI-onsite) or web-based (n=126, CCI-virtual). We also recruited another cohort of participants with T2D (n=87) who were categorized as usual care (UC). Exclusion criteria have been published previously (7,25). A brief description of the study participants and interventions (CCI and UC) are listed in the **supplementary data (Methods section).** All study participants provided written informed consent and the study was approved by the Franciscan Health Lafayette Institutional Review Board.

Outcomes

Primary Outcomes

The primary outcomes were retention, HbA1c, HOMA-IR-insulin and c-peptide derived (scores, equations in supplemental material A), 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 ratio), and lower extremities lean mss (LELM). Body composition was not assessed in UC participants. Cardiovascular-, liver-, kidney-, thyroid-related and inflammatory markers were analyzed (Table 1 and Supplementary Table 1). Changes in overall diabetes medication use, use by class, and insulin dose were tracked over the two years of the trial.

The prevalence of T2D (diabetes reversal, partial and complete remission), metabolic syndrome, suspected steatosis and absence of fibrosis were evaluated at 2 years in the CCI and UC groups using the criteria provided in Supplementary Table 2 (assignment references listed in the supplementary). Assignment of metabolic syndrome was based on the presence of three of the five defined criteria according to measured laboratory and anthropometric variables; pharmacological treatment for any of the conditions was not considered.

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

Laboratory and body composition measures

Clinical anthropometrics and laboratory blood analytes measurements were obtained at baseline, 1 year, and 2 years from the CCI and UC participants. Details of the methods were previously published(7,19). All blood analytes were measured at a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory. The CCI participants were also assessed for total body composition changes at baseline, 1 and 2 years using dual X-ray absorptiometry (DXA) (Lunar GE Prodigy, Madison, WI) and analyzed using GE Encore software(v11.10, Madison, WI). The details of the DXA procedure and analyses are listed in the **supplementary data (Methods section).**

Statistical analyses

All analyses were conducted using SPSS statistical software (Version 25.0, Armonk, NY). A detailed description of the statistical method is included in the **supplementary data (Methods section)**. Briefly, we conducted intent-to-treat analyses to assess study outcomes. For continuous study outcomes, linear mixed-effects (LMM) models were used to assess within-group changes from baseline to 2 years and between-group differences at 2 years. For dichotomous disease outcomes, generalized estimating equation models were used. Changes in diabetes medication use and insulin dosage from baseline to 2 years were assessed using McNemar's tests with continuity correction when appropriate and paired t-tests. Available data only was used to assess changes in medication use, which was routinely adjusted as part of the intervention protocol. Data from the two CCI educational groups were combined because no group differences were found, as in our prior time points(7,S45). Completers-only analyses were also conducted for all outcomes and results appear in the supplementary material. 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 significant differences between completers and dropouts on baseline characteristics for either group.

Retention and long-term dietary adherence

One hundred ninety four participants (of 262; 74%) remained enrolled in the CCI at 2 years (Figure 1), as did 78% of the UC group participants (68 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 0.3 ± 0.0 mmol L^{-1}, about 1.5 fold higher than the baseline value (0.2 ± 0.0 mmol L^{-1}). The mean laboratory BHB level was stable from 1 to 2 years, and 61.5% (n=161) of participants reported a blood BHB measurement ≥0.5mmol L^{-1} in the app at least once between 1 and 2 years.

All adjusted within and between group changes in study outcomes for the CCI and UC groups appear in Table 2.

Glycemic outcomes

From baseline to 2 years (Table 2), significant reductions in HbA1c (0.9% unit decrease, -12% relative to baseline, $P=1.8x10^{-17}$; Figure 2A), C-peptide (-27%, $P=2.2x10^{-16}$), fasting glucose (-18%, $P=6.8x10^{-9}$), fasting insulin (-42%, $P=2.2x10^{-18}$, Figure 2B), insulin-derived HOMA-IR excluding exogenous insulin users (-42%, $P=2.7x10^{-13}$), and C-peptide-derived HOMA-IR (-30%, $P=1.1x10^{-15}$) were observed in the CCI group, whereas no changes occurred in the UC group (Supplementary

Figures 1A and 1B) (Table 2). There were also significant between-group (CCI vs. UC) differences observed at 2 years in HbA1c, fasting glucose, fasting insulin, insulin-derived HOMA-IR excluding exogenous users, and C-peptide-derived HOMA-IR, with the CCI group having lower glycemic marker means (Table 2).

Metabolic and body composition outcomes

At 2 years, mean weight change from baseline was -10% ($P=8.8x10^{-28}$; Figure 2C) 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). Consistent with the weight loss observed, the CCI group had reductions in abdominal fat content, with decreases in CAF (-15%, $P=1.6x10^{-21}$, Figure 2D) and the A/G ratio (-6%, $P=4.7x10^{-8}$) from baseline to 2 years (Table 2). The CCI group's total spine BMD remained unchanged from baseline to 2 years after correction for multiple comparisons (Table 2). The changes in the average LELM in the CCI are included in the Table 2, and further elaborated in the **supplementary data** (**Discussion section**).

Cardiovascular risk factor outcomes

Decreases in systolic (-4%, $P= 2.4x10^{-6}$, Figure 2E) and diastolic (-4%, $P= 3.3x10^{-5}$, Figure 2F) blood pressures and triglycerides (-22%, $P=6.2x10^{-9}$) were observed in the CCI but not UC group at 2 years (Table 2, Supplementary Figures 3A and 3B). The CCI group's HDL-cholesterol (+19%, $P= 2.7x10^{-16}$) and LDL-cholesterol (+11%, $P=1.1x10^{-4}$) both increased from baseline to two 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 for systolic or diastolic blood pressure or total cholesterol (Table 2).

Liver-related outcomes

From baseline to 2 years, the CCI group's ALT (-21%, $P=4.0x10^{-10}$; Table 2, Figure 2G), AST (-12%, $P=5.1x10^{-5}$), ALP (-13%, $P=1.8x10^{-14}$), NLF (-78%, $P=2.9x10^{-25}$) and NFS (-60%, $P=2.3x10^{-9}$) were reduced, whereas no changes were observed in UC (e.g. ALT; Supplementary Figure 3C; Table 2). No bonferroni-corrected group differences were observed for bilirubin,ALT, nor AST at 2 years (Table 2).

Kidney, thyroid, and inflammation outcomes

The eGFR increased in the CCI (+3%, $P=1.6x10^{-4}$, Table 2) but not UC group at 2 years. The UC but not CCI group had increased anion gap and decreased uric acid (Table 2). 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 (-37%, $P=6.9x10^{-13}$, Table 2, Figure 2H) and white blood cell count (-7%, $P=4.3x10^{-5}$) 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).

Diabetes Medication

All within-group changes in diabetes medication use among study completers appear in eTable 3 (ns are listed in the table). The proportion of CCI completers taking any diabetes medication (excluding metformin) decreased from 55.7% at baseline to 26.8% at 2 years ($P=1.3x10^{-11}$, Figure 3A). Reductions in the use of diabetes medication classes included insulin (29.8% at baseline to 11.3% at 2 years, $P=9.1x10^{-9}$) and sulfonylureas (23.7% at baseline and 0% at 2 years, $P=4.2x10^{-12}$). At 2 years, no changes in the proportions of CCI completers taking SGLT-2 inhibitors (10.3% to 3.1%, P=0.01), DPP-4 (9.9% to 6.7%, P=0.42), GLP-1 agonists (13.4% to 10.8%, P=0.42), thiazolidinediones (1.5% to 2.6%, P=0.73), or metformin (71.4% to 63.9%, P=0.05) were observed after correction for multiple comparisons. No changes in use of any diabetes medication (excluding metformin) or individual diabetes medication classes were observed in the UC completers from baseline to 2 years. The mean

dose for insulin-using participants at baseline decreased among CCI participants by 81% (P= $2.6x10^{-12}$) at 2 years, but not in UC participants (+13%, P=0.45) (see Figure 3B). For participants who remained insulin-users at 2 years, the mean dose also decreased in the CCI group by 61% (P=$9.2x10^{-5}$) but not UC group (+19%, P=0.29). Among participants 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.

Disease Outcomes

All within-group changes and between-group differences in disease outcomes among the CCI and UC group participants appear in supplementary Table 4 (intent-to-treat analyses were conducted; all below n=262). The proportion of participants meeting the defined criteria for diabetes reversal at 2 years increased 41.4% (from 12.1% at baseline to 53.5% at 2 years, P<$0.0x10^{-36}$) in the CCI group, whereas no Bonferroni-corrected change was observed in the UC group (7.1% absolute decrease, P=0.04). In addition, 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.

At 2 years, 27.2% of CCI participants and 6.5% of UC patients showed resolution of metabolic syndrome. The proportion of participants with metabolic syndrome decreased from baseline to 2 years in the CCI (from 89.1% to 61.9%, P= $4.9x10^{-15}$) but not UC group. The two years improvements of suspected steatosis and fibrosis status are included in the supplementary Tables 4 and 5.

Safety and adverse events

In the CCI group, there were no reported serious adverse events between one and two years attributed to the intervention or that resulted in discontinuation, including no reported episodes of ketoacidosis or severe hypoglycemia requiring assistance. Adverse events occurring in the first year of intervention (n=6) were previously reported[10]. Details of the adverse events are included in the **supplementary data (Results section)**.

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(20,21,S46-S48). 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 insulin and all sulfonylureas that engender risks for weight gain and hypoglycemia(22,23). 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(24-26,S49-S51). 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 (25,26,S49,S51) with medication reduction. Two others studies reported no changes in HbA1c from baseline to 2 years, even though the low carbohydrate arm reduced HbA1c in the first 6 months(24,S50). This study observed a modest increase in HbA1c and weight between 1 and 2 years in CCI participants suggesting some reduction in long-term effectiveness. Interestingly, insulin-levels show no regression toward baseline from 1 to 2 years indicating long-term improvement in hyperinsulinemia, an important component of diabetes pathology(8,27).

Criticisms of low-carbohydrate diets relate to poor adherence and long-term sustainability(16,28). 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(S52). 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, 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 (eFigure 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 two years of the trial and an obtained laboratory value for HbA1c were 37.8% and 14.9%, respectively. CCI diabetes reversal exceeds remission as metformin prescriptions were usually continued given its role in preventing disease progression(7,29), preserving β-cell function(29) and in treatment of pre-diabetes per guidelines (28). Partial and complete remission rates of 2.4% and 0.2% per year, respectively, have been reported in 122,781 T2D patients receiving standard diabetes care(3).The two-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%)(4). Greater diabetes remission in the CCI versus Look AHEAD ILI could result from differences in the dietary intervention(14), patients' ability to self-select their lifestyle 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(3,4,6,S53). Despite a mean of 8.4 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 (-11.9kg) at 2 years. CCI weight loss was comparable to observed weight loss following surgical gastric banding (-10.7kg) at 2 years(29). Previous studies consistently report that weight loss increases the likelihood of T2D remission(3,4,6). CCI participants also improved blood pressure, triglycerides, and HDL-cholesterol. Total cholesterol

was unchanged and calculated LDL-cholesterol was increased at 2 years, but was not different from the LDL-cholesterol level observed at one year (+0.51, P=0.85). Despite the rise in LDL-cholesterol, the CCI cohort improved in 22 out of 26 CVD markers at one year(19). This includes a decrease in small LDL-particles and large VLDL-P and an increase in LDL-particle size with no changes in ApoB(19), a marker considered a better predictor of CVD risk than LDL-cholesterol(19,30,S54). Non-elevated LDL cholesterol values together with higher triglycerides and lower HDL-cholesterol are common in patients with abdominal obesity, T2D, and metabolic syndrome(31,S55,S56); these individuals often still have elevated atherogenic lipoproteins such as non-HDL(32,S57), small LDL particles(31,S58), and VLDL(31,S58). In the CCI group, non-HDL cholesterol did not change significantly from baseline to 2 years and several cardiovascular risk factors across various physiological systems improved, suggesting that the rise in LDL-cholesterol may not be associated with increased atherogenic risk(33).

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(18,24,34,35,S59). Anatomical distribution of fat around the abdominal area ("android" obesity) is associated with T2D(36,S60) and other comorbidities such as metabolic syndrome(37) and NAFLD(38,S61). The alleviation of visceral fat in the CCI group was concurrent with resolution of metabolic syndrome at 2 years, while sustaining one-year improvements of liver enzymes(7), steatosis and fibrosis (39 in press,S62-S67). While studies in animal models(40,S68,S69) and children treated with ketogenic diets(41,S70) have suggested retardation in skeletal development and reduction in BMD, in this study of T2D adults the CCI group had no change in total spine BMD over two years. Our results are consistent with other adult ketogenic dietary studies that reported no bone mass loss in short-term(34,S71) or long-term follow-up of 2(35,S72) and 5(S73) years. The differing findings of ketogenic diet on bone mass between adults and children could be due to differential effects on developed and mineralized versus developing bones(42).

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 LMMs to investigate intervention time and treatment effects. 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 a remote care team may have improved the patients' 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 limited racial diversity. Interpretation of DXA body composition was limited to subregion analyses due to to the scanner not accomodating the patients' complete body.

Conclusions

At 2 years, the CCI, including remote medical management with instruction in nutritional ketosis, led to improvements in blood glucose, insulin, HbA1c, weight, blood pressure, triglycerides, 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 higher prevalence of diabetes reversal and remission compared to the UC group following a standard diabetes care program. These results provide strong 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.

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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	26	53.8(8.4)	19	54.4(8.2)	68	51.9(8.7)	2.5±1.2
Usual Care	2	52.3(9.5)	4	51.4(9.4)	19	55.6(9.5)	-4.2±2.4
CCI-all vs. usual care	87	1.4±1.1	68	3.0±1.2		-3.6±2.4	
African American (%)							
CCI-all education	26	6.9±1.6	19	6.2±1.7	68	8.8±3.5	-2.6±3.6
Usual Care	2	0.0±0.0	4	0.0±0.0	19	0.0±0.0	—
CCI-all vs. usual care	87	6.9±1.6*	68	6.2±1.7*		8.8±3.5	
Body mass index (kg m^{-2})							
CCI-all education	25	40.42(8.81)	19	40.41(8.42)	67	40.46(9.90)	-0.05±1.25
Usual Care	7	36.72(7.26)	0	36.90(7.41)	19	36.11(6.89)	0.79±1.91
CCI-all vs. usual care	83	3.70±1.07*	64	3.51±1.18		4.34±2.43	
Female (%)							
CCI-all education	26	66.79±2.92	19	65.98±3.41	68	69.12±5.64	-3.14±6.66
Usual Care	2	58.62±5.31	4	60.29±5.98	19	52.63±11.77	7.66±12.90
CCI-all vs. usual care	87	8.17±6.06	68	5.69±6.76		16.49±12.35	

Waist circumference (in)							
CCI-all education	21	49.02(5.64)	15	49.04(6.40)	59	48.97(6.89)	0.06±1.00
Usual Care	8	46.41(5.64)	9	46.33(5.63)	19	46.67(5.82)	0.34±1.48
CCI-all vs. usual care	83	2.61±0.81	64	2.71±0.92		2.30±1.75	
Years since type 2 diabetes diagnosis	26	8.44(7.22)	19	8.15(7.02)	68	9.25(7.75)	-1.1±1.02
CCI-all education	1	7.85(7.32)	3	7.90(7.41)	8	7.38(7.05)	0.53±2.77
Usual Care	71	0.59±0.97	63	0.25±1.03		1.88±2.87	
CCI-all vs. usual care							
Glycemic							
Hemoglobin A1c (%)							
CCI-all education	26	7.6(1.5)	19	7.5(1.41)	68	7.9(1.7)	-0.4±0.2
Usual Care	2	7.6(1.8)	4	7.7(1.9)	19	7.41(1.4)	0.3±0.5
CCI-all vs. usual care	87	-0.0±0.2	68	-0.2(0.3)		0.45±0.43	
C-Peptide (nmol L^{-1})							
CCI-all education	24	4.36(2.15)	18	4.40(2.15)	63	4.25(2.17)	0.15±0.31
Usual Care	8	4.18(2.48)	5	3.86(2.22)	17	5.35(3.08)	-1.50±0.80
CCI-all vs. usual care	79	0.18±0.29	62	0.54±0.32		-1.10±0.80	
Fasting glucose (mg/dL)							
CCI-all education	25	160.77(61.37)	19	158.01(60.77)	67	168.64(62.86)	-10.63±8.81
Usual Care	8	156.20(72.60)	1	162.07(78.71)	19	135.47(39.85)	26.60±13.27
CCI-all vs. usual care	86	4.57±8.01	67	-4.06±10.57		33.17±15.25	
Fasting Insulin (pmol L^{-1})							
CCI-all education	24	28.56(23.88)	18	27.37(22.33)	63	32.06(27.86)	-4.70±3.87

Usual Care	8	29.11(24.85)	5	25.54(21.87)	17	42.12(30.95)	-16.58±6.58
CCI-all vs. usual care	79	-0.55±3.12	62	1.83±3.26		-10.05±7.79	
HOMA-IR (insulin derived), all							
CCI-all education	22	8.96(6.17)	16	8.92(6.19)	52	9.10(6.14)	-0.19±0.98
Usual Care	0	10.64(9.12)	8	9.56(8.35)	17	14.52(10.88)	-4.96±2.85
CCI-all vs. usual care	78	-1.68±1.11	61	-0.65±1.17		-5.41±2.77	
HOMA-IR (insulin derived), excluding exogenous users							
CCI-all education	15	8.80(5.64)	12	8.62(5.74)	36	9.41(5.31)	-0.78±1.07
Usual Care	7	9.41(8.35)	1	7.95(6.53)	10	14.09(11.77)	-6.15±2.90
CCI-all vs. usual care	42	-0.61±1.36	32	0.68±1.17		-4.68±3.82	
HOMA-IR (C-peptide derived), all							
CCI-all education	24	11.73(7.40)	18	11.52(6.55)	62	12.33(9.51)	-0.80±1.09
Usual Care	4	11.10(7.56)	2	10.63(7.64)	17	12.80(7.23)	-2.17±2.07
CCI-all vs. usual care	78	0.62±0.97	61	0.89±1.01		-0.47±2.49	
Metabolic and Body Composition							
Diabetes reversal (%)[a]							
CCI-all education	26	12.2±2.0	19	12.9±2.4	68	10.3±3.7	2.6±4.6
Usual Care	2	20.7±4.4	4	19.1±4.8	19	26.3±10.4	-7.2±10.6
CCI-all vs. usual care	87	-8.5±4.8	68	-6.2±5.4		-16.0±11.0	

Metabolic syndrome (%)							
CCI-all education	26	88.6±2.0	19	88.7±2.3	68	88.2±4.0	0.4±4.5
Usual Care	2	91.4±3.1	4	93.6±3.2	19	84.2±9.0	9.3±9.2
CCI-all vs. usual care	81	-2.8±4.0	62	-4.9±3.9		4.0±8.7	
Weight-clinic (kgs)							
CCI-all education	25	116.50(25.94)	19	115.97(24.94)	67	117.98(28.72)	-2.00±3.69
Usual Care	7	105.63(22.14)	0	105.32(21.81)	19	106.67(23.82)	-1.35±5.82
CCI-all vs. usual care	83	10.87±3.17*	64	10.65±3.50		11.32±7.21	
Spine bone mineral density (kg)							
CCI-all education	23 8	1.20(0.16)	17 8	1.20(0.15)	60	1.21(0.18)	-0.01±0.03
Central abdominal fat (kg)							
CCI-all education	23 7	5.77(1.69)	17 7	5.72(1.69)	60	5.94(1.72)	-0.22±0.25
Android: gynoid ratio							
CCI-all education	23 8	1.27(0.33)	17 8	1.26(0.33)	60	1.31(0.34)	-0.06±0.05
Lower extremities lean mass (kg)							
CCI-all education	23 8	18.45(4.05)	17 8	18.42(3.94)	60	18.53(4.40)	-0.11±0.61
Cardiovascular							

Systolic blood pressure (mmHg)							
CCI-all education	26	131.9(14.1)	19	132.2(14.2)	68	131.1(13.8)	1.2(2.0)
Usual Care	0	129.8(13.6)	2	129.0(13.6)	18	132.7(13.5)	-3.7(3.7)
CCI-all vs. usual care	79	2.1±1.8	61	3.3±2.1		-1.6±3.6	
Diastolic blood pressure (mmHg)							
CCI-all education	26	82.1(8.3)	19	81.7(8.0)	68	83.4(8.9)	-1.7±1.2
Usual Care	0	82.0(8.9)	2	82.1(8.8)	18	81.8(9.6)	0.3±2.4
CCI-all vs. usual care	79	0.1±1.1	61	-0.4±1.2		1.6±2.4	
Total cholesterol (mg/dL)							
CCI-all education	24	183.6(41.2)	18	181.9(40.3)	63	188.7(43.6)	-6.8±6.0
Usual Care	7	183.8(45.8)	4	186.5(49.3)	17	174.0(28.7)	12.5±12.5
CCI-all vs. usual care	79	-0.2±5.5	62	-4.6±6.3		14.7±11.2	
LDL-cholesterol (mg/dL							
CCI-all education	23	102.5(32.9)	17	101.1(33.0)	59	106.6(32.6)	-5.5±5.0
Usual Care	2	101.5(36.2)	3	103.8(38.3)	14	92.3(24.8)	11.5±10.8
CCI-all vs. usual care	70	1.0±4.6	56	-2.7±5.3		14.3±9.3	
HDL-cholesterol (mg/dL)							
CCI-all education	24	42.2(13.4)	18	42.5(13.7)	63	41.3(12.7)	1.1±2.0
Usual Care	7	37.6(11.2)	4	38.3(11.5)	17	35.2(10.1)	3.0±3.1
CCI-all vs. usual care	79	4.6±1.7	62	4.2±1.9		6.1±3.3	
Triglycerides (mg/dL)							
CCI-all education	24	197.2(143.4)	18	200.7(153.5)	63	187.1(109.0)	13.5±21.0
Usual Care	7	282.9(401.2)	4	283.7(443.6)	17	280.0(185.0)	3.7±110.5
CCI-all vs. usual care	79	-85.7±46.1	62	-83.0±57.5		-92.9±46.9	

Liver							
ALT (Units/L)							
CCI-all education	25	30.65(22.77)	19	31.65(24.54)	67	27.79(16.63)	3.86±3.23
Usual Care	7	27.74(19.81)	0	28.31(21.30)	19	25.74(13.59)	2.58±5.17
CCI-all vs. usual care	86	2.90±2.75	67	3.34±3.38		2.05±4.17	
AST (Units/L)							
CCI-all education	25	23.69(15.19)	19	24.37(16.79)	67	21.76(9.08)	2.61±2.16
Usual Care	7	23.90(19.39)	0	24.25(21.36)	19	22.63(10.02)	1.62±5.07
CCI-all vs. usual care	86	-0.20±2.04	67	0.12±2.57		-0.87±2.42	
ALP (Units/L)							
CCI-all education	25	74.11(22.14)	18	74.32(22.32)	67	73.54(21.79)	0.78±3.15
Usual Care	6	77.36(26.29)	9	78.25(27.67)	19	74.21(21.08)	4.04±6.86
CCI-all vs. usual care	86	-3.25±2.90	67	-3.94±3.39		-0.67±5.62	
Bilirubin (mg/dL)							
CCI-all education	25	0.54(0.21)	18	0.55(0.21)	67	0.49(0.18)	0.06±0.03
Usual Care	6	0.55(0.28)	9	0.54(0.27)	19	0.59(0.29)	-0.05±0.07
CCI-all vs. usual care	86	-0.02±0.03	67	0.01±0.04		-0.11±0.05	
NAFLD-Liver fat score							
CCI-all education	24	3.43(3.84)	18	3.26(3.62)	62	3.92(4.44)	-0.65±0.62
Usual Care	3	3.10(3.63)	1	2.49(3.00)	17	5.14(4.80)	-2.65±1.23
CCI-all vs. usual care	74	0.33±0.50	57	0.78±0.53		-1.23±1.24	
NAFLD-Fibrosis score							

CCI-all education	23	-0.23(1.36)	17	-0.25(1.37)	61	-0.18(1.35)	-0.07±0.20
Usual Care	8	-0.80(1.41)	7	-0.82(1.47)	17	-0.71(1.20)	-0.11±0.39
CCI-all vs. usual care	75	0.56±0.18	58	0.57±0.21		0.53±0.36	
Kidney							
Anion gap (mmol L^{-1})							
CCI-all education	25	6.83(1.67)	19	6.76(1.68)	67	7.03(1.62)	-0.27±0.24
Usual Care	7	6.93(1.82)	0	6.82(1.86)	19	7.32(1.67)	-0.50±0.47
CCI-all vs. usual care	86	-0.10±0.21	67	-0.06±0.25		-0.29±0.42	
BUN (mg/dL)							
CCI-all education	25	16.88(6.55)	19	17.17(6.05)	67	16.06(7.81)	1.11±0.93
Usual Care	8	16.05(6.25)	1	15.81(6.28)	19	16.89(6.24)	-1.09±1.63
CCI-all vs. usual care	86	0.84±-0.81	67	1.37±0.87		-0.84±1.95	
eGFR (mL s^{-1} m^{-2})							
CCI-all education	25	80.48(13.62)	19	80.36(13.53)	67	80.84(13.96)	-0.48±1.94
Usual Care	8	79.17(13.73)	1	79.39(13.72)	19	78.42(14.11)	0.97±3.59
CCI-all vs. usual care	86	1.31±1.70	67	0.97±1.93		2.42±3.64	
Serum creatinine (mg/dL)							
CCI-all education	25	0.88(0.24)	19	0.88(0.23)	67	0.90(0.26)	-0.02±0.03
Usual Care	8	0.91(0.25)	1	0.91(0.25)	19	0.90(0.22)	0.004±0.06
CCI-all vs. usual care	86	-0.02±0.03	67	-0.03±0.03		-0.01±0.07	
Uric acid (mg/dL)							
CCI-all education	26	5.85(1.46)	19	5.88(1.45)	68	5.77(1.48)	0.11±0.21
Usual Care	1	5.60(1.47)	3	5.58(1.34)	18	5.70(1.92)	0.12±0.39
CCI-all vs. usual care	85	0.25±0.18	67	0.30±0.20		0.07±0.42	

Thyroid							
TSH (mIU L^{-1})							
CCI-all education	25	2.32(1.74)	19	2.31(1.81)	67	2.36(1.52)	-0.05±0.25
Usual Care	9	3.80(17.07)	2	4.37(19.17)	18	1.65(1.05)	2.72±4.54
CCI-all vs. usual care	86	-1.48±1.84	68	-2.06±2.33		0.71±0.38	
Free T4 (ng/dL							
CCI-all education	26	0.92(0.17)	19	0.92(0.18)	67	0.91(0.17)	0.01±0.02
Usual Care	0	0.88(0.29)	3	0.87(0.31)	18	0.89(0.16)	-0.02±0.08
CCI-all vs. usual care	86	0.04±0.03	68	0.05±0.03		0.02±0.04	
Other							
Beta-hydroxybutyrate (mmol L^{-1})							
CCI-all education	24	0.17(0.15)	18	0.17(0.15)	63	0.19(0.16)	-0.03±0.02
Usual Care	8	0.15(0.13)	5	0.14(0.11)	17	0.20(0.18)	-0.06±0.04
CCI-all vs. usual care	79	0.02±0.20	62	0.03±0.18		-0.01(0.04)	
hsC-reactive protein (nmol L^{-1})							
CCI-all education	24	8.54(14.49)	18	8.92(16.35)	63	7.44(6.41)	1.48±2.12
Usual Care	9	8.89(8.62)	6	9.08(8.91)	18	8.18(7.64)	0.90±2.30
CCI-all vs. usual care	85	-0.34±1.67	67	-0.16±2.10		-0.74±1.79	
White blood cell (k/cumm)							
CCI-all education	26	7.24(1.89)	19	7.12(1.82)	67	7.57(2.08)	-0.45±0.27
Usual Care	0	8.14(2.39)	3	8.15(2.30)	19	8.08(2.73)	0.07±0.62
CCI-all vs. usual care	86	-0.90±0.28	67	-1.03±0.31*		-0.51±0.58	

Diabetes Medication							
Any diabetes medication, excluding metformin (%)							
CCI-all education	26	56.87±3.07	19	55.67±3.58	68	60.29±5.98	-4.62±7.00
Usual Care	2	66.67±5.08	4	66.18±5.78	19	68.42±10.96	-2.25±12.37
CCI-all vs. usual care	87	-9.80±5.94	68	-10.51±6.80		-8.13±12.71	
Sulfonylurea (%)							
CCI-all education	26	23.66±2.63	19	25.77±3.15	68	17.65±4.66	8.13±5.62
Usual Care	2	24.14±4.61	4	22.06±5.07	19	31.58±10.96	-9.52±11.19
CCI-all vs. usual care	87	-0.47±5.28	68	3.71±6.11		-13.93±11.91	
Insulin (%)							
CCI-all education	26	29.77±2.83	19	29.38±3.28	68	30.88±5.64	-1.50±6.47
Usual Care	2	45.98±5.37	4	48.53±6.11	19	36.84±11.37	11.69±12.91
CCI-all vs. usual care	87	-16.21±6.07	68	-19.15±6.93		-5.96±12.25	
Thiazolidinedione (%)							
CCI-all education	26	1.53±0.76	19	1.55±0.89	68	1.47±01.47	0.08±1.74
Usual Care	2	1.15±1.15	4	1.47±1.47	19	0.00±0.00	1.47±2.79
CCI-all vs. usual care	87	0.38±1.48	68	0.08±1.74		1.47±2.79	
SGLT-2 (%)							
CCI-all education	26	10.31±1.88	19	9.79±2.14	68	11.77±3.94	-1.97±4.30
Usual Care	2	14.94±3.84	4	14.71±4.33	19	15.79±8.59	-1.08±9.36
CCI-all vs. usual care	87	-4.64±4.28	68	-4.91±4.83		-4.03±8.71	
DPP-4 (%)							
CCI-all education	26	9.92±1.85	19	9.28±2.09	68	11.77±3.94	-2.49±4.23

Usual Care	2	8.05±2.93	4	5.88±2.87	19	15.79±8.59	-9.91±9.06
CCI-all vs. usual care	87	1.88±3.63	68	3.40±3.92		-4.03±8.71	
GLP-1 (%)							
CCI-all education	26	13.36±2.11	19	13.40±2.45	68	13.24±4.14	0.17±4.81
Usual Care	2	16.09±3.96	4	19.12±4.80	19	5.26±5.26	13.85±7.13
CCI-all vs. usual care	87	-2.73±4.31	68	-5.72±5.39		7.97±8.33	
Metformin (%)							
CCI-all education	26	71.37±2.80	19	71.65±3.24	68	70.59±05.57	1.06±6.39
Usual Care	2	60.92±5.26	4	60.29±5.98	19	63.16±11.37	-2.86±12.81
CCI-all vs. usual care	87	10.46±5.96	68	11.36±6.80		7.43±12.12	

Note. Abbreviations: 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.

[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.

Table 2. Adjusted mean changes over time

	Baseline		1 Year				2 Years			
	Mean ± SE	P	Mean ± SE	P	Change from baseline	P	Meas ± 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		-	**6.8×10^{-9}**
Usual Care	151.21±6.93		160.58±6.17		9.38±7.61	0.22	172.89±7.00		29.10±4.88	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}**	21.68±8.28	
Fasting Insulin (pmol 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		-	**2.2×10^{-18}**
Usual Care	27.57±2.29		26.47±2.06		-1.10±2.30	0.63	24.17±1.84		11.71±1.25	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}**	-3.40±2.22	

HOMA-IR (insulin derived), all[a]	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}**
CCI-all education	9.58±0.73		10.33±0.73		0.75±0.81	0.35	9.95±0.77		0.37±0.83	0.66
Usual Care	-0.49±0.85	0.57	-5.48±0.84	**2.9×10^{-10}**			-4.67±0.89	**3.4×10^{-7}**		
CCI-all vs. usual care										
HOMA-IR (insulin derived), excluding exogenous users[a]	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}**
CCI-all education	8.66±0.92		10.87±0.98		2.21±1.02	0.03	8.26±0.75		-0.40±0.94	0.68
Usual Care	0.43±1.03	0.68	-6.31±1.08	**2.2×10^{-8}**			-3.01±0.85	**5.4×10^{-4}**		
CCI-all vs. usual care										
HOMA-IR (C-peptide derived), all[a]	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}**
CCI-all education	11.04±0.67		11.81±0.71		0.77±0.72	0.28	10.62±0.64		-0.42±0.70	0.55
Usual Care	0.21±0.77	0.78	-3.75±0.81	**5.8×10^{-6}**			-2.74±0.74	**2.5×10^{-4}**		
CCI-all vs. usual care										
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		-	**8.8×10^{-28}**
Usual Care	111.07±1.09		111.71±1.47		0.64±1.17	0.58	112.35±1.90		11.94±0.96	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}**	1.28±1.63	
Spine bone mineral density (kg)	1.21±0.01	—	1.22±0.01	—	0.01±0.01	0.11	1.22±0.01	—	0.01±0.01	0.02
CCI-all education										
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)	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}**
CCI-all education										
Cardiovascular										
Systolic blood pressure (mmHg)	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}**
CCI-all education	130.3±1.6		129.5±1.6		-0.9±1.9	0.66	129.9±1.8		-0.5±2.1	0.83
Usual Care	1.4±1.8	0.43	-4.2±1.8	0.02			-3.9±2.1	0.06		
CCI-all vs. usual care										
Diastolic blood pressure (mmHg)	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}**
CCI-all education	82.1±1.0		81.3±1.0		-0.8±1.1	0.47	81.6±1.1		-0.6±1.3	0.65
Usual Care	-0.3±1.1	0.76	-3.2±1.1	0.41			-2.8±1.3	0.03		
CCI-all vs. usual care										
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	0.30	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}**		
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	0.10	-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	015
CCI-all vs. usual care	-0.01±0.03	0.64	-0.04±0.03	0.18			0.01±0.03	0.80		
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}**
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]	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
CCI-all education	0.90±0.02		0.87±0.02		-0.03±0.02	0.07	0.88±0.02		-0.01±0.02	0.39
Usual Care	-0.02±0.02	0.37	-0.04±0.02	0.12			-0.04±0.02	0.12		
CCI-all vs. usual care										
Uric acid (µmo L^{-1})										
CCI-all education	5.83±0.09		5.82±0.10		-0.01±0.08	0.90	5.72±0.10		-0.11±0.09	0.20
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]	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}**
CCI-all education	0.14±0.02		0.17±0.03		0.03±0.03	0.43	0.18±0.04		0.03±0.04	0.38
Usual Care	0.03±0.02	0.11	0.10±0.04	0.01			0.09±0.04	0.03		
CCI-all vs. usual care										

hsC-reactive protein (nmol L^{-1})[a]	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}**
CCI-all education	9.03±0.75		9.06±0.81		0.03±0.69	0.96	8.38±0.74		-0.65±0.65	0.32
Usual Care	-1.58±0.87	0.07	-4.05±0.94	**2.1×10^{-5}**			-3.69±0.86	**2.3×10^{-5}**		
CCI-all vs. usual care										
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}**
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}**		

Note. 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.

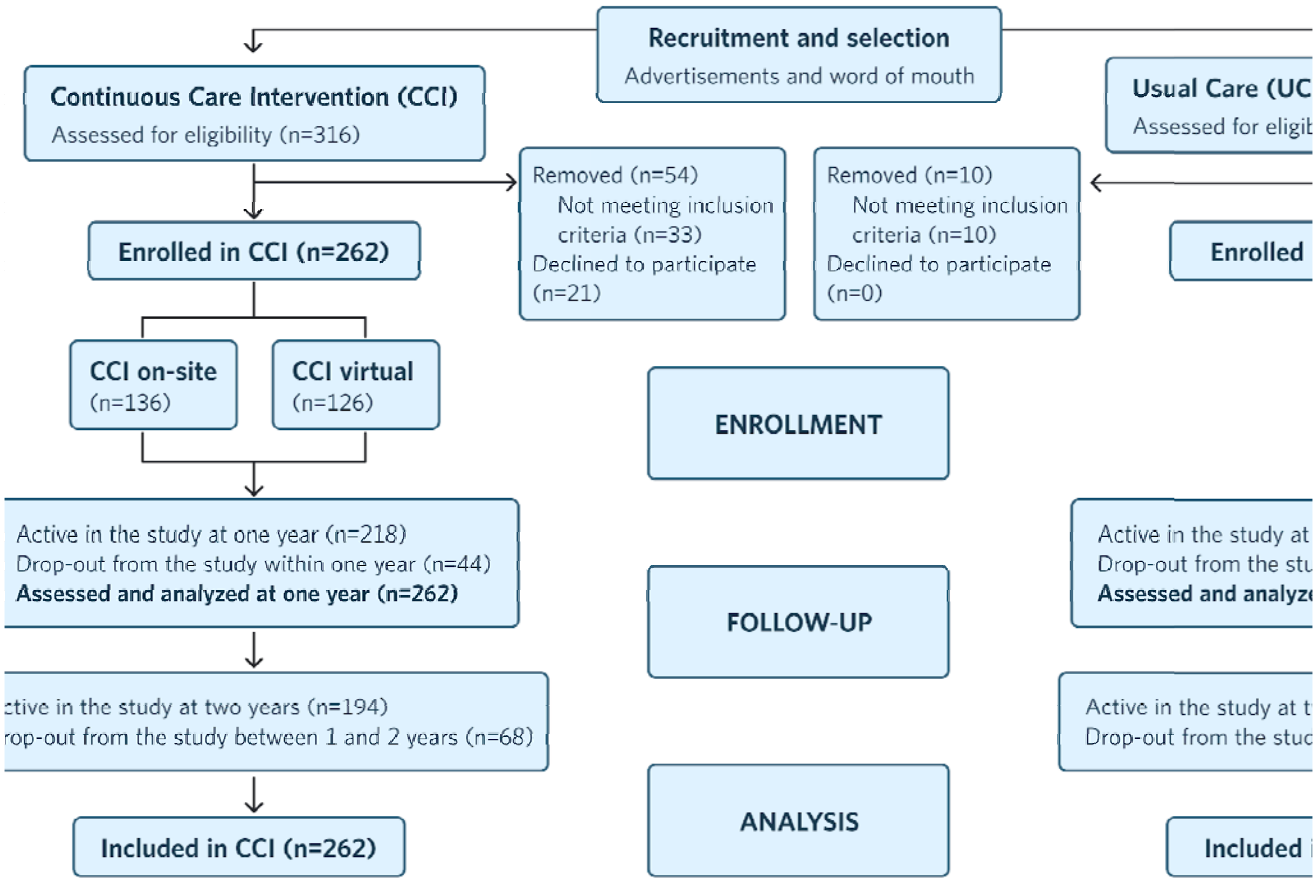
nds

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

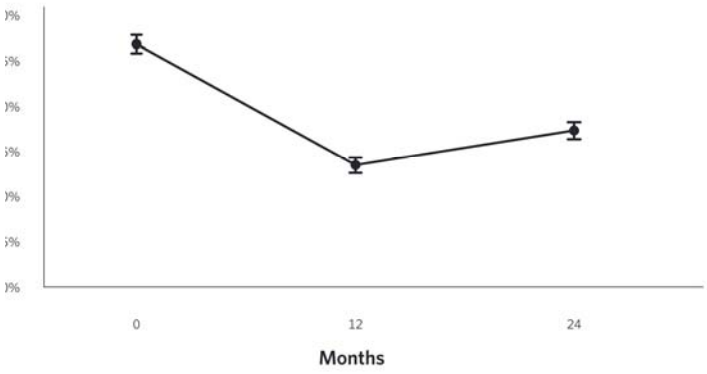
e 2. Adjusted mean changes from baseline to 2-years in the CCI group for (A) HbA1c, (B) Fasting insulin, (C) Weight, (D
al Abdominal Fat [CAF], (E) Systolic Blood Pressure, (F) Diastolic Blood Pressure (G) Alanine aminotransferase (ALT),
sensitive C-reactive protein (hsCRP).

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

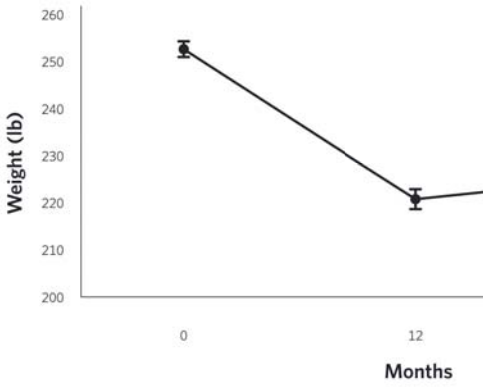
e 1

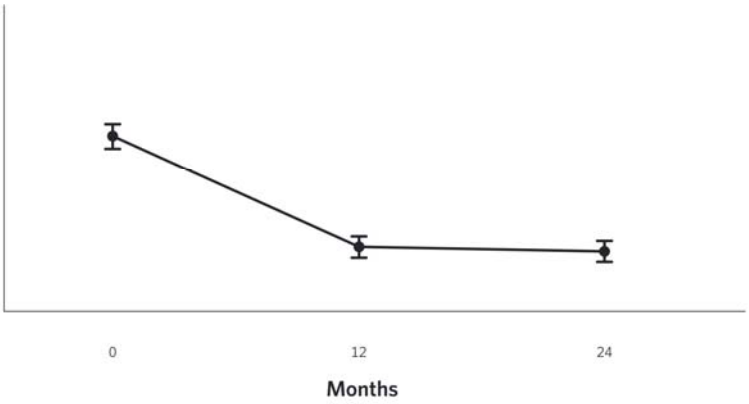

Recruitment and selection
Advertisements and word of mouth
Continuous Care Intervention (CCI)
Assessed for eligibility (n=316)
Usual Care (UC
Assessed for eligi
Removed (n=54)
Not meeting inclusion criteria (n=33)
Declined to participate (n=21)
Removed (n=10)
Not meeting inclusion criteria (n=10)
Declined to participate (n=0)
Enrolled in CCI (n=262)
Enrolled
CCI on-site (n=136)
CCI virtual (n=126)
ENROLLMENT
Active in the study at one year (n=218)
Drop-out from the study within one year (n=44)
Assessed and analyzed at one year (n=262)
Active in the study at
Drop-out from the stu
Assessed and analyz
FOLLOW-UP
ctive in the study at two years (n=194)
rop-out from the study between 1 and 2 years (n=68)
Active in the study at t
Drop-out from the stuc
ANALYSIS
Included in CCI (n=262)
Included

e 2

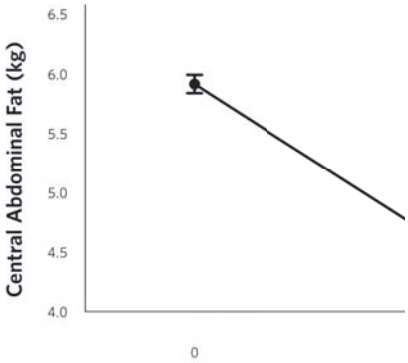

0
12
24
Months

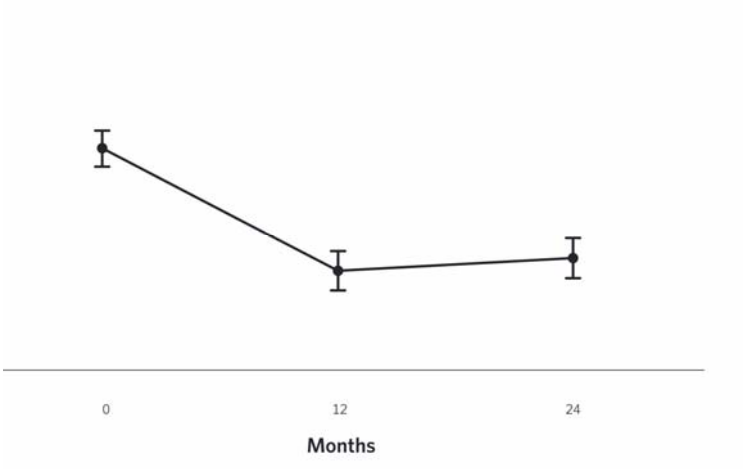
(c)


Weight (lb)
260
250
240
230
220
210
200
0
12
Months

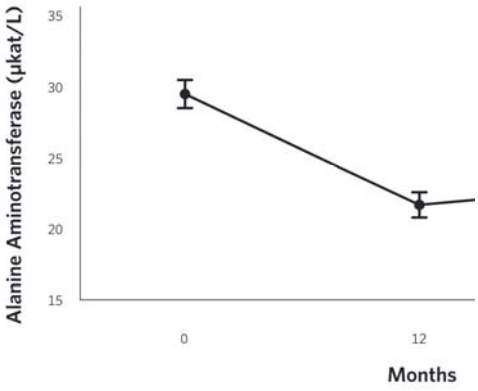

0
12
24
Months

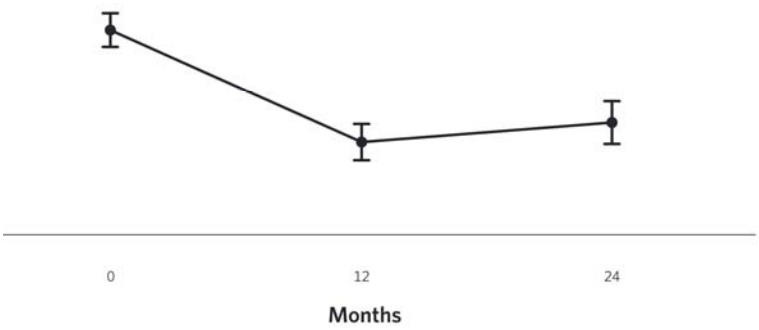
(d)


Central Abdominal Fat (kg)
6.5
6.0
5.5
5.0
4.5
4.0
0

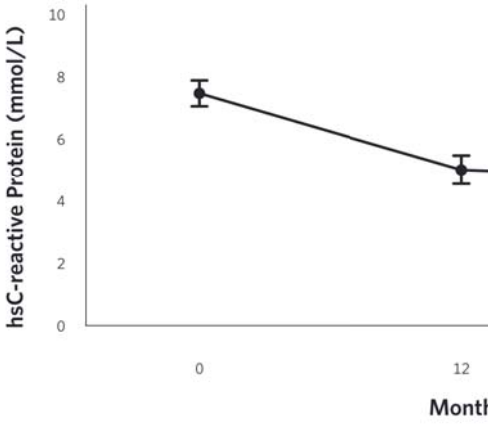

0
12
24
Months

(g)

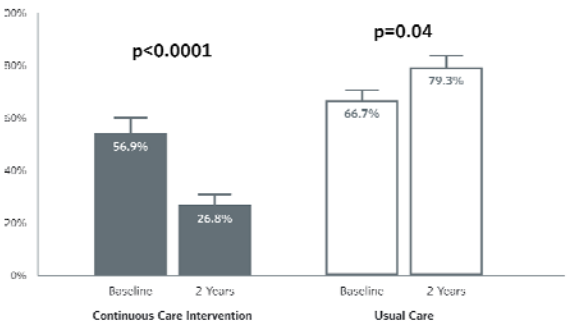

Alanine Aminotransferase (μkat/L)
35
30
25
20
15
0
12
Months


0
12
24
Months

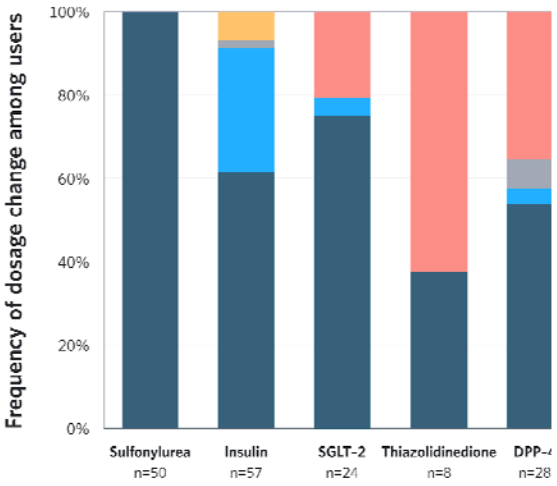
(h)


hsC-reactive Protein (mmol/L)
10
8
6
4
2
0
0
12
Montl

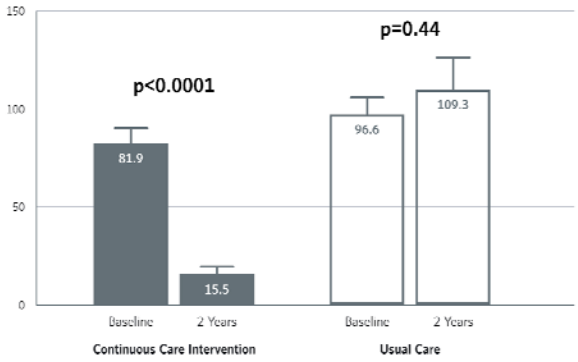
e 3

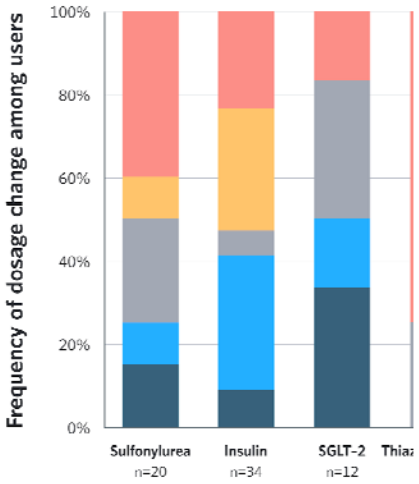

p<0.0001
p=0.04
56.9%
26.8%
66.7%
79.3%
Baseline
2 Years
Baseline
2 Years
Continuous Care Intervention
Usual Care

c


Frequency of dosage change among users
100%
80%
60%
40%
20%
0%
Sulfonylurea
n=50
Insulin
n=57
SGLT-2
n=24
Thiazolidinedione
n=8
n=28

b


150
100
50
0
p<0.0001
p=0.44
81.9
15.5
96.6
109.3
Baseline
2 Years
Baseline
2 Years
Continuous Care Intervention
Usual Care


Frequency of dosage change among users
100%
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20%
0%
Sulfonylurea
n=20
Insulin
n=34
SGLT-2
n=12