SUPPLEMENTARY APPENDIX

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METHODS

Study design and participants

Briefly, this was a non-randomized and open-label controlled longitudinal study, including patients between 21 to 65 years old with a diagnosis of T2D and a BMI > 25 kg/m^2. Patients were initially screened for the study based on the study's inclusion and exclusion criteria [35]. Major exclusion criteria included serious renal, or cardiovascular dysfunction, hepatic failure, infectious disease, uncontrolled psychiatric disorder, history of ketoacidosis, a intolerance to dietary fat, cancer with active treatment in the last five years, and pregnancy or planned pregnancy. Further, patients with high alcohol intake defined as average consumption of 3 or more alcohol-containing beverages daily or consumption of more than 14 standard drinks per week were excluded. Patients on 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-onsite) or via web-based educational contents (n=126, CCI-virtual). The CCI patients were routinely assessed for nutritional ketosis based on blood beta-hydroxybutyrate (BHB) concentrations. The on-site and virtual patients were grouped together for analyses since no significant differences were observed in biochemical markers between these two modes of educational delivery [35]. We also recruited and followed a cohort of patients with T2D (n=87) who were categorized as UC [35]. This group of patients received a standard diabetes

care treatment from their primary care physician or endocrinologist without modification. These patients were aware of the intervention cohort and could participate in that group if they chose.

Interventions

CCI including personalized nutrition

The CCI included support from a medical provider and health coach, education in nutrition and behavior change, peer support and individualized advice for maintaining nutritional ketosis during 1 year as described [35]. Briefly, all subjects were instructed to follow a ketogenic diet incorporating their personal preferences; health coaches monitored glycemic and ketosis status through patient reported daily blood glucose and blood BHB tests with a BHB target range of 0.5-3.0 mmol/L. Patients' dietary modifications included restricting total dietary carbohydrate to a target of less than 30 g daily. Daily protein intake was targeted to 1.5 g/kg of reference body weight. Patients were encouraged to consume dietary fat to satiety, by consuming adequate omega-3 and omega-6 polyunsaturated fatty acids with the remaining fats consumed coming from monounsaturated and saturated fatty acids. Patients were also counseled on adequate intake of minerals, fluids and non-starchy vegetables [35].

Usual care (UC)

Usual care for these participants was continued by their own primary care physician (PCP) or endocrinologist, and registered dietitians counseled UC participants on diabetes self-management, nutrition, and lifestyle based on the American Diabetes Association (ADA) recommendations [37].

Assessment and monitoring

CCI patients were requested to measure their daily biomarkers of weight, blood BHB and glucose and report them in the Virta Health web-based application (app). Clinical anthropometrics, laboratory blood analyte measurements and calculated estimated glomerular filtration rate (eGFR) were obtained at baseline, 70 days and 1 year for patients undergoing CCI, while patients under the UC arm had measurements assessed at baseline and 1 year [35]. Any adverse events encountered in the study were reported immediately to the Principal Investigator and reviewed by the Fransciscan Health Institutional Review Board.

Equations for calculating NAFLD liver fat score and NAFLD fibrosis score.

Score	**Equation**
NAFLD liver fat score (N-LFS)	-2.89 + 1.18 x **metabolic syndrome** (yes=1 or no=0) + 0.45 x **type 2 diabetes** (yes=2 or no=0)* + 0.15 x **fasting insulin** (mU/l) + 0.04 x **fasting serum AST** (U/L) – 0.94 x **AST/ALT**
NAFLD fibrosis score (NFS)	$-1.675 + 0.037 \times$ **Age** (yrs) + $0.094 \times$ **BMI** (kg/m^2) + $1.13 \times$ **IFG/diabetes** (yes = 1, no = 0) + $0.99 \times$ **AST/ALT ratio** $- 0.013 \times$ **Platelet** ($\times 10^9/L$) $-0.66 \times$ **Albumin** (g/dl)

* - As a conservative assumption, all patients were scored as 'yes' for type 2 diabetes status at one year despite improvements observed in intervention subjects relative to baseline

RESULTS

Baseline features of participants

At baseline, age was 53.4 ± 8.7 years. 226 (65%) participants were female. Type 2 diabetes had been diagnosed for a mean of 8.3 ± 7.2 years and 314 (90%) subjects were obese [35]. Two-hundred and ninety-three (84%) were on medication for diabetes and 118 (34%) were insulin users [35]. The proportion of patients with abnormal ALT was higher in CCI (60%) compared to the UC (44%). At baseline, 327 (96%) subjects had suspicion of NAFLD (N-LFS of > -0.640) and 91 (26%) subjects had high suspicion of advanced fibrosis (NFS > 0.675). Fewer patients (51 of 349 [15%]) had a NFS threshold of < -1.455 indicating low probability of advanced fibrosis. Compared to UC, mean baseline BMI and NFS levels were significantly higher in patients in the CCI. The remaining patient demographics and baseline features were generally not different between the two groups [35, 43]

Safety

Adverse events during this trial were previously reported [35]. Mean platelet count was significantly reduced in CCI (-18 ± 33) vs UC (-10 ± 31), P=0.03, however, the proportion of patients with a platelet count below 150 x 10^9 L was not different between both groups (CCI, 16 [6%] of 262 and UC, 4 [5%] of 87). There was no hepatic decompensation (variceal hemorrhage, ascites or hepatic encephalopathy) or ALT flare-up (>5 times the upper limit of normal) reported during the trial in either CCI or UC.

TABLES

Supplemental Table 1. Impact of CCI on weight loss based on BMI classes at baseline.

	BMI (kg/m^2) at baseline				
	25-29.9	**30-34.9**	**35-35.9**	**>40**	**P value**
	N=21	**N=51**	**N=72**	**N=118**	
Weight loss (%), mean ± SD	9.1 ± 7.6	8.9 ± 8.2	13.3 ± 9.1	12.8 ± 8.9	0.01*
					0.28†
<5%, n (%)	7 (33)	15 (29)	12 (17)	21 (18)	
5-10%, n (%)	5 (24)	14 (27)	21 (29)	27 (33)	
≥10%, n (%)	9 (43)	22 (43)	39 (54)	70 (59)	

* ANCOVA while adjusting by age and gender and with Bonferroni adjustments ($P<0.01$).

† Mantel-Haenszel chi-square test for overall trend.

Supplemental Table 2. Patients' baseline and 1-year characteristics. Sub-analysis in patients (n=91) with high risk of advanced fibrosis at baseline*. ITT analysis.

Variables	Continuous Care intervention, n=71				Usual Care, n=20				Between-groups P values†
	Baseline	**1 year**	**Change**	**P value†**	**Baseline**	**1 year**	**Change**	**P value†**	
BMI (Kg/m2)	47.8 ± 9.9	41.1 ± 9.6	-6.7 ± 5.3	<.01	41.5 ± 8.5	41.2 ± 9.3	-0.03 ± 2.7	.59	<.01
Weight loss (%)	-	13.9 ± 10.2	-	-	-	0.99 ± 6.7	-	-	<0.01
Metabolic parameters									
HbA1c (%)	7.84 ± 1.55	6.45 ± 1.12	-1.39 ± 1.44	<.01	7.73 ± 1.54	7.71 ± 1.7	-0.02 ± 1.2	.92	<.01
Fasting glucose (mg/dl)	167.5 ± 65.7	132.9 ± 47.8	-34.6 ± 7.3	<.01	144.6 ± 64.1	171.9 ± 123.5	27.3 ± 26.2	.32	<.01
Fasting insulin (m/Ul)	36.1 ± 29.7	26.9 ± 19.7	-9.2 ± 4.5	.02	28.5 ± 23.9	31.3 ± 26.2	2.8 ± 6.6	.61	<.01
HOMA-IR	15.4 ± 13.6	10.8 ± 9.7	-4.5 ± 1.8	<.01	12.5 ± 7.9	19.3 ± 15.6	6.8 ± 4.7	.18	<.01
Triglycerides (mg/dl)	196.9 ± 135.2	134.7 ± 77.7	-62 ± 14.2	<.01	179.5 ± 110.3	168.9 ± 92.6	10.6 ± 19.5	.59	<.01
Cholesterol (mg/dl)	173.6 ± 41.9	174 ± 42.8	0.4 ± 3.7	.90	181.2 ± 51.1	155.3 ± 42.9	-25.9 ± 11.5	.04	0.01
HDL cholesterol (mg/dl)	41.6 ± 12.7	46.5 ± 14.6	4.9 ± 0.91	<.01	39.1 ± 13.2	37.9 ± 15.3	-1.2 ± 1.6	.49	<.01
LDL cholesterol (mg/dl)	94.9 ± 33.5	100.6 ± 37.7	5.7 ± 3.6	.12	110.5 ± 43	86.8 ± 34.8	-23.7 ± 9.5	.02	<.01
Liver-related tests									
ALT (U/L)	32.6 ± 33.3	22.9 ± 15.4	-9.7 ± 12.4	.01	23.4 ± 10	21.6 ± 7.6	-1.2 ± 1.9	.38	<.01
AST (U/L)	27.5 ± 23.1	20.2 ± 8.7	-7.3 ± 2.7	<.01	21.5 ± 8.5	20.9 ± 6.6	-0.6 ± 1.6	.72	<.01

ALP (U/L)	74.2 ± 21.8	65.1 ± 21	-9.1 ± 1.7	<.01	78.8 ± 29	81.4 ± 32.8	2.6 ± 2.7	.34	<.01
Albumin (g/dl)	4.11 ± 0.26	4.15 ± 0.24	.04 ± 0.02	.06	4.20 ± 0.42	4.21 ± 0.29	.01 ± 0.06	.88	0.18
Platelet (x 10^9)	205 ± 47	196 ± 48	-9 ± 3	<.01	196 ± 54	201 ± 40	5 ± 6	.36	<.01
Non-invasive biomarkers									
NAFLD fibrosis score	1.549 ± 0.91	0.82 ± 0.75	-.725 ± 0.10	<.01	1.130 ± 0.50	1.088 ± 0.76	.041± 0.10	.70	<.01
> 0.675	71 (100%)	38 (54%)	-		20 (100%)	15 (75%)	-		0.05
Kidney function tests									
Creatinine (mg/dl)	0.92 ± 0.27	0.90 ± 0.27	-.02 ± 0.02	.12	0.99 ± 0.28	1.01 ± 0.36	.01 ± 0.02	.76	0.61
eGFR (CKD-EPI)	81.3 ± 19.4	83 ± 19.3	1.7 ± 11.1	.20	77.1 ± 19.1	77.3 ± 21.9	.30 ± 14.6	.93	0.56
Cut-offs				.77				.89	0.38
< 60 mL/min/1.73m2	11 (15%)	12 (17%)	-		4 (20%)	5 (25%)	-		
60-89 mL/min/1.73m2	30 (42%)	28 (39%)	-		8 (40%)	8 (40%)	-		
> 90 mL/min/1.73m2	30 (43%)	31 (44%)	-		8 (40%)	7 (35%)	-		
Other parameters									
CRP (mg/dl)	9.46 ± 8.1	6.72 ± 6.6	-2.74 ± 5.8	<.01	10.78 ± 10.7	9.23 ± 8.6	-1.55 ± 5.2	0.25	0.05
BOHB (mmol/l)	0.15 ± 0.10	0.30 ± 0.17	0.15 ± 0.34	<.01	0.13 ± 0.11	0.22 ± 0.13	0.09 ± 0.18	0.20	0.01

Abbreviations: ALT, alanine aminotransferase; **AST,** aspartate aminotransferase; **ALP**, alkaline phosphatase, **HbA1c,** Glycosylated hemoglobin; **HDL**, high density lipoprotein; **LDL**, low density lipoprotein; **eGFR**, estimated glomerular filtration rates; **CKD-EPI**, chronic kidney disease-epidemiological collaboration equation; **BHB**, beta-hydroxybutyrate; **NAFLD**, nonalcoholic fatty liver disease.

***** NAFLD fibrosis score > 0.675 corresponds with high probability of advanced fibrosis (PPV ≈ 85%).

† McNemar's or paired T test when appropriated. Chi-square or Wilcoxon signed-rank tests when appropriated.

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%).

* Mc Nemar's or paired T test when appropriated. Chi square or Wilcoxon signed-rank tests when appropriated.

FIGURE LEGENDS

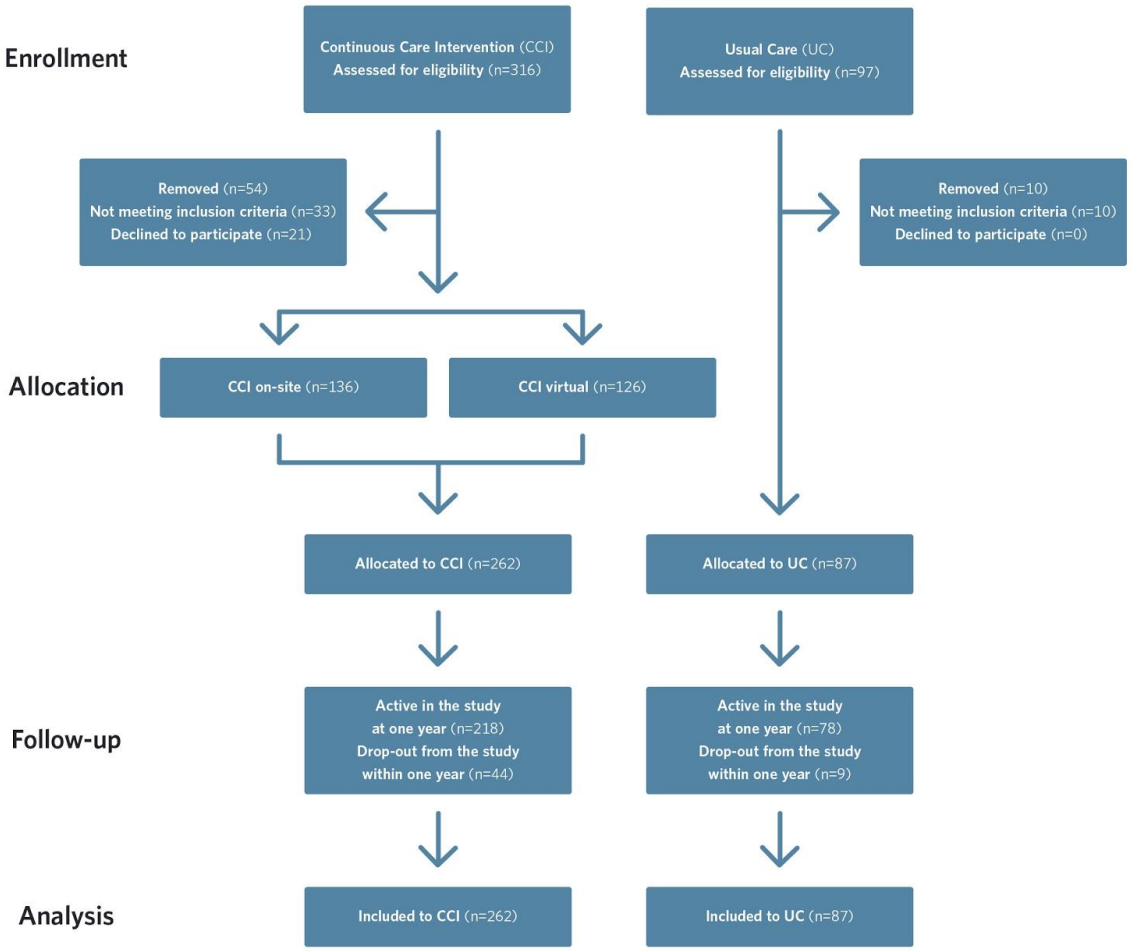
Supplemental Figure 1. Flow of patients through the study. Final analyses were performed on imputed data generated using a model of multiple imputation. Patients "Assessed for eligibility" are those patients who successfully screened for eligibility through phone conversation.

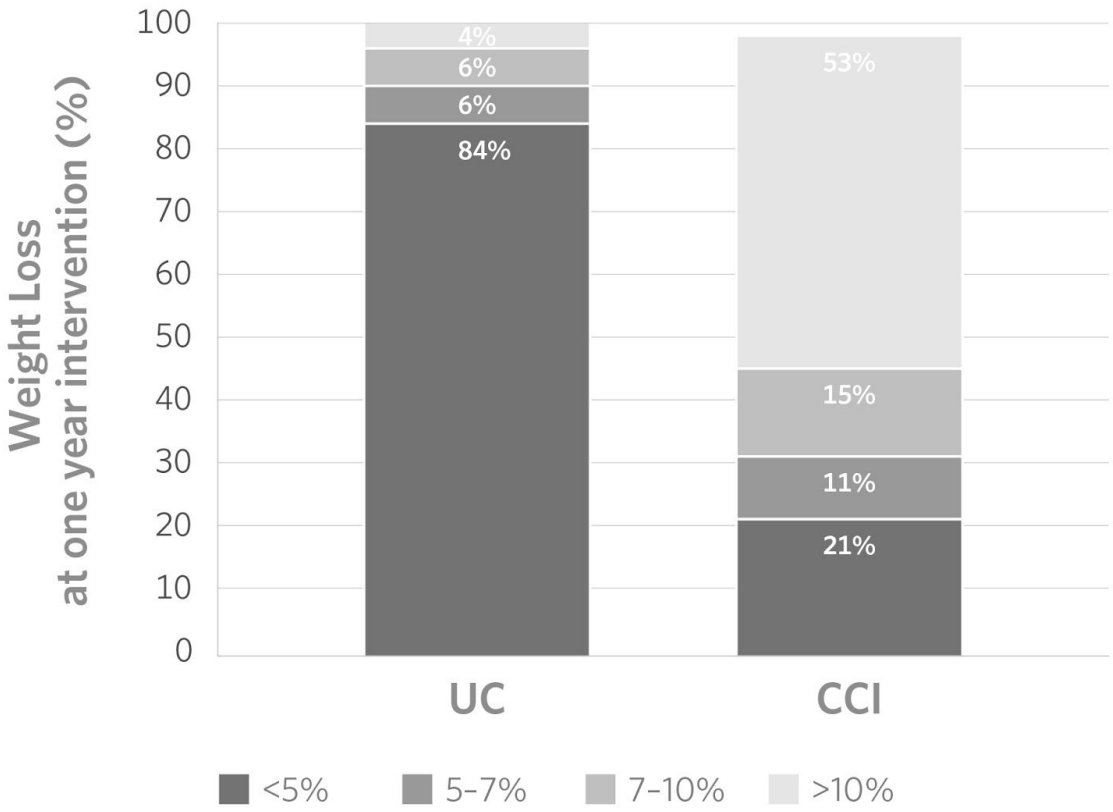
Supplemental Figure 2. Weight loss (%) at 1 year of intervention.

Weight loss (%) categories and stratification of patients in each category by treatment, UC and CCI.

* ALT levels < 19 in women and < 30 in men.

† Logistic regression adjusting by baseline levels of BMI, HbA1c, ALT and duration of diabetes, anti-diabetes medications and weight loss (%) at 1 year.


Enrollment
Continuous Care Intervention (CCI)
Assessed for eligibility (n=316)
Usual Care (UC)
Assessed for eligibility (n=97)
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)
Allocation
CCI on-site (n=136)
CCI virtual (n=126)
Allocated to CCI (n=262)
Allocated to UC (n=87)
Follow-up
Active in the study
at one year (n=218)
Drop-out from the study
within one year (n=44)
Active in the study
at one year (n=78)
Drop-out from the study
within one year (n=9)
Analysis
Included to CCI (n=262)
Included to UC (n=87)


Weight Loss
at one year intervention (%)
100
90
80
70
60
50
40
30
20
10
0
4%
6%
6%
84%
53%
15%
11%
21%
UC
CCI
<5%
5-7%
7-10%
>10%