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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/m². Patients were initially screened for the study based on the study's inclusion and exclusion criteria[36]. 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[36]. We also recruited and followed a cohort of patients with T2D (n=87) who were categorized as UC[36]. 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[36]. 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[36].

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].

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

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

TABLES

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

	BMI (kg/m²) at baseline				P value
	25-	30-	35-	>40	
	29.9	34.9	35.9	N=120	
	N=22	N=50	N=70		
					0.121†
<5%, n (%)	6 (33)	14 (29)	16 (17)	18 (18)	
5-10%, n (%)	5 (24)	14 (27)	17 (29)	30 (33)	
≥10%, n (%)	11 (43)	22 (43)	37 (54)	72 (59)	

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

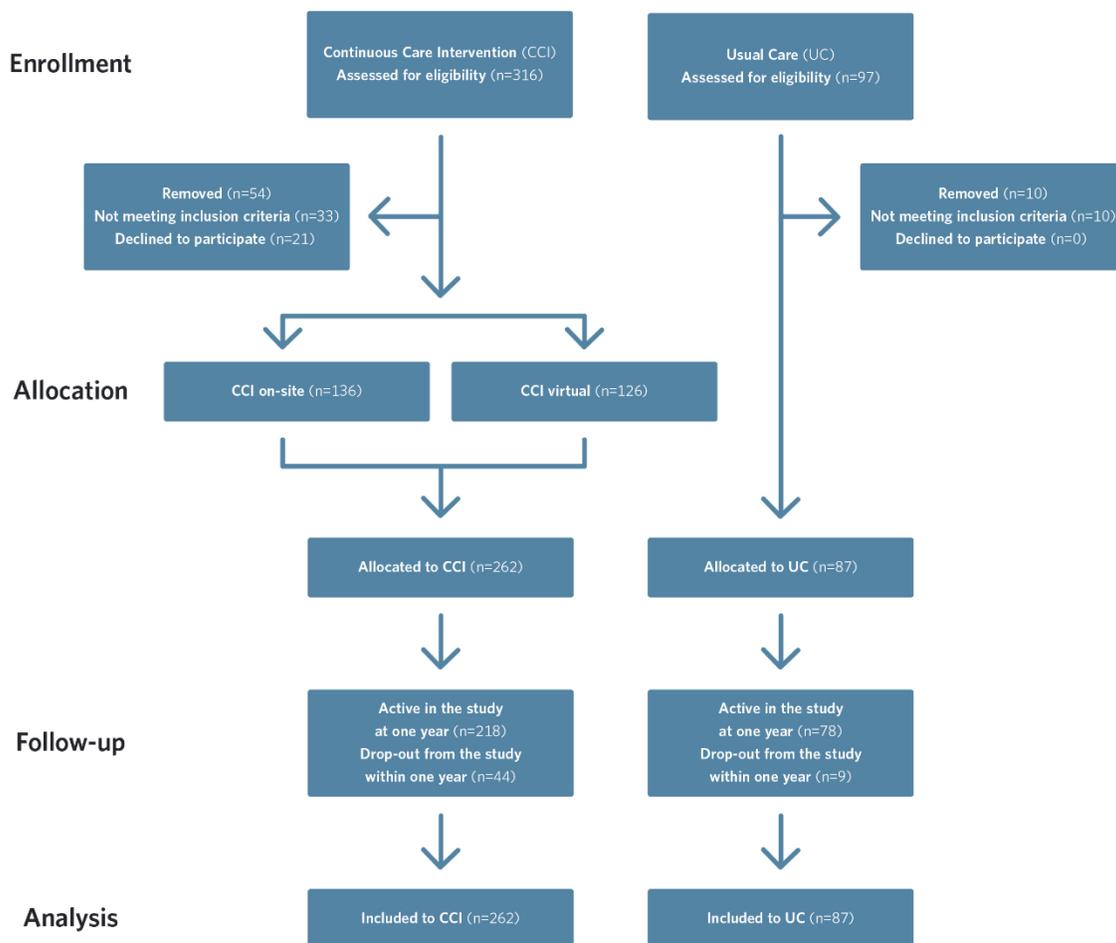
The +/- sign means SEs.

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 based on ITT analysis

Supplemental Figure 1

Supplemental Figure 2

P<0.001

