Contemporary Clinical Trials 79 (2019) 80–88

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

The rationale and design of the personal diet study, a randomized clinical trial evaluating a personalized approach to weight loss in individuals with pre-diabetes and early-stage type 2 diabetes

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A B S T R A C T

Weight loss reduces the risk of type 2 diabetes mellitus (T2D) in overweight and obese individuals. Although the physiological response to food varies among individuals, standard dietary interventions use a "one-size-fits-all" approach. The Personal Diet Study aims to evaluate two dietary interventions targeting weight loss in people with prediabetes and T2D: (1) a low-fat diet, and (2) a personalized diet using a machine-learning algorithm that predicts glycemic response to meals. Changes in body weight, body composition, and resting energy expenditure will be compared over a 6-month intervention period and a subsequent 6-month observation period intended to assess maintenance effects. The behavioral intervention is delivered via mobile health technology using the Social Cognitive Theory. Here, we describe the design, interventions, and methods used.

1. Introduction and background

The cause of obesity is under considerable debate [1,2]. The conventional theory suggests obesity is the result of energy imbalance where energy intake exceeds energy expenditure. In contrast, the Carbohydrate-Insulin Model of obesity proposes diets resulting in a high postprandial glycemic response (PPGR) have been shown to promote weight gain, stimulate hyperinsulinemia, suppress fat mobilization (trapping fat) and delay hypoglycemia [3]. This cascade of events leads to subsequent stimulation of hunger, overconsumption of calorie-dense foods and a reduction in energy expenditure [4]. Proponents of this model assert that a diet designed to minimize PPGRs is a valuable adjuvant to weight loss interventions [1].

Carbohydrates primarily drive PPGR, but PPGR also varies considerably depending on the type of carbohydrate consumed. Glycemic Index (GI) and glycemic load (GL) are often used to describe PPGR in response to specific foods. Several reports suggest that a reduction in the consumption of high-GI and high-GL foods enhances weight loss due to the reduction in PPGR and insulin secretion [5–8]. Furthermore, minimizing PPGR may attenuate the decline in resting energy expenditure (REE) observed with weight loss [9].

The results of human intervention studies manipulating carbohydrates, GI, and/or GL for weight loss are often no more efficacious than other diets [10–12]. Indeed, recent obesity management guidelines developed by the American Heart Association and American College of Cardiologists, and affirmed by the Academy of Nutrition and Dietetics, concluded that in comparison to higher carbohydrate/lower protein or lower fat diets, carbohydrate-restricted diets do not result in greater weight losses [13]. Furthermore, there was insufficient evidence to comment on weight loss interventions involving complex versus simple carbohydrates, GL dietary approaches, or other dietary pattern approaches [13].

Standard dietary interventions based on GI/GL may fail to consistently produce weight loss because individuals vary in their glycemic response to the same foods [14]. Consequently, patients may experience postprandial hyperglycemia despite consuming low-GI/GL meals. The disconnection between lifestyle efforts (e.g., following a low-GI/GL diet) and outcome (e.g., weight loss or blood glucose control), may be a disincentive for self-management efforts.

A potential factor that may explain the between-subject variability to diets differing in GI/GL may lie within the gut microbiota. Animal studies demonstrate that the obese microbiome has an increased

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https://doi.org/10.1016/j.cct.2019.03.001
Received 2 October 2018; Received in revised form 20 February 2019; Accepted 1 March 2019
Available online 04 March 2019
1551-7144/

capacity to harvest energy from the diet [15,16]. There is a strong association between the gut microbiota and glucose intolerance, insulin resistance, and T2D [17–20]. In humans, the transfer of intestinal microbiota from lean humans to those with metabolic syndrome increased insulin sensitivity [21]. In 2015, with the Personalized Nutrition Project (PNP), Segal et al. developed a novel machine-learning algorithm that predicts individuals' PPGR to pre-consumed or unseen meals [22]. They demonstrated that participants had high between-subject variability in PPGR to the same foods, suggesting that universal dietary recommendations are of limited utility for controlling elevated postprandial glucose. In a subsequent validation study, Segal et al. demonstrated that a personally tailored intervention based on the predicted response significantly improved PPGR to meals [22]. Until now, no study has attempted to apply personalized nutrition in the context of a behavioral weight loss intervention in pre-diabetics and T2D.

A potential mediator of weight loss and weight regain may stem from production of advanced glycation end products (AGEs), as they accumulate at an accelerated rate in the presence of hyperglycemia, including acute glycemic variability (GV) [23]. AGEs appear to exert their pathological effects at least in part through their binding to the receptor for advanced glycation end products (RAGE), which results in the generation of oxidative stress and inflammation [24,25]. The AGE-RAGE axis is associated with diabetes and obesity, and RAGE may serve as a “brake” to weight loss and predispose participants to weight regain via metabolic adaptation [26]. The presence of hyperglycemia also triggers neutrophil and monocyte release of a protein complex, S100A8/A9, a ligand of RAGE [27]. Furthermore, soluble RAGEs (sRAGE) serve as endogenous RAGE ligand-sequestering molecules, interfering with the ability of the RAGE ligands to activate the cell surface receptor – blocking the ability of RAGE to brake energy expenditure, thereby facilitating weight loss. Little is known regarding the relationship between GV and AGEs, sRAGE, RAGE activation (i.e., increased levels of proinflammatory RAGE ligands), and circulating mediators of inflammation as they relate to weight loss.

1.1. Objectives

The purpose of the Personal Diet Study is to compare two weight loss interventions: (1) a low-fat diet (LFD) versus (2) a diet that is personalized (PD) using the PNP algorithm to predict PPGR. Interventions will be compared regarding their effects on body weight, body composition, and energy expenditure (e.g., metabolic adaptation). In addition, we will examine the mediating effects of self-efficacy, and glycemic variability and, in a subset of participants, the AGE/RAGE/S100A8/A9 pathway on these outcomes.

1.1.1. Design

The study is a two-arm, parallel-group, randomized clinical trial in overweight and obese adults with pre-diabetes and early-stage T2D. The trial involves two 6-month phases: an active intervention phase (phase 1) followed by a maintenance/observation phase (phase 2) (Fig. 1). Participants are randomized with equal allocation to either LFD or PD. Measurements occur at baseline 3, 6, and 12 months. All measurement visits and data are collected at the Clinical Research Center (CRC) of the NYU Langone Health (NYULH) Clinical and Translational Science Institute (CTSI) in New York City. Microbiome analysis and data processing for the purpose of the PNP prediction algorithm are completed at the Weizmann Institute of Science in Rehovot, Israel.

1.1.2. Eligibility and sample requirements

To be eligible for this study, patients must be between 18 and 80 years of age, have a body mass index (BMI) between 27 and 50 kg/m^2, and have a hemoglobin A1c (HbA1c) between 5.7 and 8.0% (Table 1). Patients treated with medications other than metformin or who have evidence of kidney disease, assessed with estimated glomerular filtration rate (< 60 ml/min/1.73 m^2) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, are excluded to avoid recruiting patients with advanced T2D [28]. Furthermore, patients with conditions or treatments that affect glycemia (e.g., corticosteroids), impact weight loss efforts (e.g., bariatric surgery, weight loss medications), or affect the gut microbiome (e.g., inflammatory bowel disease) are excluded. Because the PNP application is currently only available in English and Hebrew, non-English literate participants are also excluded. Eligible participants with the recent use of antibiotics or antifungal medications are postponed 3 months prior to randomization because of the impact on the gut microbiota. Those who fail to log an average of 2 meals per day during the run-in period are excluded (see section 3.3).

1.1.3. Recruitment, screening, and enrollment procedures

The first study cohort was recruited in January 2018 and recruitment is expected to conclude in December 2019. The primary recruitment method involves an electronic medical record (EMR) system to identify potentially eligible patients who receive care at NYULH-affiliated practices. Patients meeting the search criteria are sent a message describing the study in their patient portal, or via email. Patients self-refer by clicking on a link that notifies study staff of their interest in participating. Secondary recruitment includes self-referrals from ClinicalTrials.gov and CenterWatch.com.

Screening for eligibility is completed by telephone. Individuals who meet screening criteria are scheduled for an in-person screening visit at the CRC-CTSI. At this visit, signed informed consent is obtained, and height and weight are measured (see section 2.4.1). A non-fasting blood sample is collected by a certified phlebotomist to assess HbA1c and serum creatinine (i.e., eGFR). In addition, participants are provided with a self-administered questionnaire to complete and bring to their baseline visit. Participants without their own smartphones are provided loaner phones and no-cost service plans to use for the duration of the study. Each participant is provided the PNP smartphone app to use to self-monitor their diet, physical activity, and body weight. This app is integrated with the USDA Food Composition Database (Release 28.1), allowing participants to select from thousands of food and beverage items. Participants are trained on how to enter meals, snacks, and physical activity, and on how to search for foods and beverages, enter serving sizes, create a “favorite” food-item, and create a “saved meal” into the PNP app. Participants with a BMI under 27 or > 50 kg/m^2, HbA1c ≥8.0%, or an estimated glomerular filtration rate based on serum creatinine < 60 ml/min/1.73 m^2 are excused from further participation. Table 2 provides a timeline of measurement visits.

1.2. Measurements

Study visits are conducted at the CRC-CTSI at baseline, 3, 6, and 12 months. Table 3 outlines the study variables obtained at each assessment time point and are described in more detail below.

1.2.1. Primary and secondary outcomes

1.2.1.1. Anthropometric data. BMI is calculated from height and weight. Height is measured to the nearest 1 cm using a portable stadiometer (SECA 213, Seca GmbH & Co. KG, Hamburg, Germany), and body weight is measured in light clothing without shoes to the nearest 0.1 kg using a Stow-A-Weigh scale (Scale-Tronix, Welch Allyn, Skaneateles, NY, USA). Waist, hip, and neck circumferences are measured in duplicate using a Gulick tape (McKesson Medical-Surgical, Fairfield, NJ, USA) to the nearest 1 cm using techniques detailed elsewhere [29]. Body fat percentage, fat-free mass (FFM, in kg) and fat mass (FM, in kg) are measured using bioelectrical impedance analysis (BIA; InBody 270, InBody, Inc. Cerritos, CA, USA).

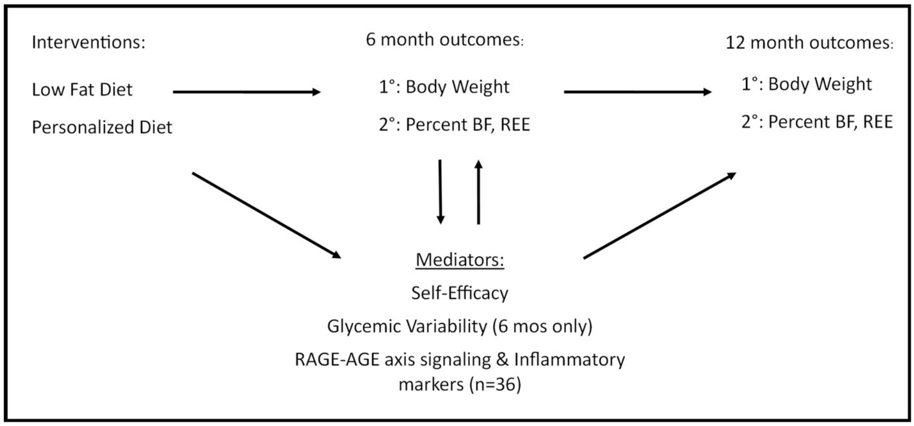

Fig. 1. Study phases.
AGE, advanced glycation end-products; BF, body fat; REE, resting energy expenditure; RAGE, receptor for advanced glycation end-products.

Table 1
Inclusion and exclusion criteria.

Inclusion criteria
18–80 yrs. old
BMI ≥27 kg/m^2
Pre-diabetic (HbA1c 5.7–6.4%)
T2D (HbA1C ≤8%)
eGFR > 60 ml/min/1.73 m^2
Exclusion criteria
BMI < 27 kg/m^2 or > 50 kg/m^2
HbA1c > 8%
eGFR < 60 ml/min/1.73 m^2
± 5% body weight change within 1 month of screening
Non-English-speaking
Unable or unwilling to: provide informed consent, participate meaningfully in an intervention, accept randomization assignment
Women who are pregnant, or plan to become pregnant in the next 13 months, or who become pregnant during the study
Institutionalized (e.g., nursing home)
Bariatric surgery or are unwilling to delay bariatric surgery for the next 12 months Unable to walk without a walker or cane for 2 city blocks
Diagnosed with heart disease without physicians clearance to participate
Diagnosed with kidney disease, or retinopathy (to rule-out those with long-standing T2D)
Chronically active inflammatory or neoplastic disease in the past 3 years
Diagnosed with a chronic gastrointestinal disorder (e.g. inflammatory bowel disease)
Antibiotics within 3 months or prescribed antibiotics during the study
Taking aspirin unless prescribed by a physician
Use of chronic immunosuppressive medications or within 3 months prior to participation
Managing glycemia with insulin, GLP-1 agonists (exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide), insulin secretagogues (Glimepiride, Glipizide, Glyburide, Repaglinide, Nateglinide), or SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, empagliflozin/metformin, dapagliflozin/metformin)
Prescribed medications expected to result in weight loss such as Orlistat, Naltrexone, Bupropion, Lorcaserin, Phentermine, Topiramate, or Liraglutide
Taking other medications that could interfere with weight loss including steroids and anti-psychotics

BMI, body mass index; eGFR, estimated glomerular filtration rate HbA1c; glycated hemoglobin; T2D, type 2 diabetes; GLP-1, glucagon-like peptide 1; SGLT2, sodium-glucose cotransport 2.
Individuals who are taking antibiotics during screening or are prescribed antibiotics during the course of the study will be allowed to continue but will be delayed until the next cohort begins.
Aspirin affects the accuracy of the continuous glucose monitoring.

1.2.1.2. Resting Energy Expenditure (REE). REE is assessed via open-circuit indirect calorimetry (Quark RMR, COSMED USA Inc., Chicago, IL, USA) using a ventilated hood system after a 12-h overnight fast. Participants are directed to lay supine for 10 min during which the metabolic cart is calibrated per the manufacturer's instructions. Oxygen and carbon dioxide production are measured for 20–25 min following a 5-min run-in period, with participants in a relaxed, awake state. Room temperature and humidity are maintained at a constant level, and ambient noise and lighting are minimized as best as possible. REE is calculated from the Weir equation [30].

1.2.1.3. Blood samples, resting heart rate and blood pressure. Resting heart rate (RHR) and systolic and diastolic blood pressure (BP) are measured following a 5-min, seated resting period using an automated blood pressure machine (Welch Allyn PROPAQcs, Welch Allyn, Inc., Skaneateles Falls, NY, USA). In both the PD and LFD groups, fasting blood samples are collected by a certified phlebotomist to measure glucose and insulin at baseline, 3 and 6 months. A complete blood count (CBC) is collected at baseline only in the PD group for the purposes of the predictive algorithm.

1.2.2. Mediators

1.2.2.1. Self-efficacy. Self-efficacy for weight loss is assessed using the validated, 20-item Weight Efficacy Lifestyle Questionnaire [31]. Participants are asked to rate their self-efficacy for each item on a 10-point Visual Numeric Scale ranging from 0 (not confident) to 9 (very confident). Items assess self-efficacy for resisting eating under various circumstances such as negative emotions, availability, social pressure, physical discomfort, and positive activities [31]. An overall score and subscale scores will be computed by summing relevant questionnaire items. These scores will be used to evaluate the mediating effect of self-efficacy on the relationship between weight loss and randomization group.

1.2.2.2. Glycemic exposure. HbA1c is obtained using high-pressure liquid chromatography (HPLC; Variant II) Turbo analyzer, Bio-Rad Laboratories, Inc., Hercules, CA, USA). In addition, GV is examined for up to 14 days with a continuous glucose monitor (CGM; Abbott Freestyle Libre Pro, Abbott Park, IL, USA), which measures interstitial glucose concentrations every 15 min. The skin surface is prepared with Skin Tac (TORBOT Group, Inc., Cranston, RI, USA) to help prevent detachment of the CGM device and, once inserted, covered with a Simpatch adhesive patch. Participants are blinded to glucose tracings [32]. CGM data will be used to calculate standard measures of GV, including mean amplitude of glycemic excursion (MAGE), which is a value of variation about the mean by summing the absolute rises or falls of glucose levels encountered daily, ignoring excursions of < 1 standard deviation (SD) [33]. CGM data will be used to generate other indices of GV including (1) SD, (2) continuous overall net glycemic action, (3) mean postprandial area under the curve, and (4) incidence and time spent outside the normal glycemic range (< 70 and > 180 mg/dl), and extremely out of range (< 50 and > 300 mg/

Table 2
Description of measurement visits.

Phase 1: active intervention	
Screening visit (−35 days)	- Informed consent - Review medical history - Questionnaires (personal habits, medical history, sociodemographics, self-efficacy) - Non-fasting HbA1c and serum creatinine (eGFR) - Height and weight (determine BMI) - Load Personalized Nutrition Program (PNP) app onto phone
Baseline measurement visit (−28 to −21 days)	- Review PNP entries (< 2 meals per day/week, retrain as needed) - REE - BIA - WC, HC, NC - SBP, DBP, RHR - Insert CGM - Activity monitor (Fitbit) - Fasting glucose, insulin - CBC (PD only[a]) - Fecal collection kit (PD only) - BMI ≥35 kg/m^2 (n = 36): RAGE, AGE, S100A8/A9 and inflammatory markers
Device visit (−14 to −7 days)	- Remove CGMs - Collect Fitbits - Load Webex® app - Profiling week (PD only): - Fecal samples collected - Insert CGM - Provide re-charged Fitbit - Test meals provided - Participants wear CGM and Fitbit for a maximum of 14 days
3-month (91 +/− 21 days) and 6-month measurement visit (183 +/− 21 days)	Fasting glucose, HbA1c,insulin - REE - BIA - WC, HC, NC - SBP, DBP, RHR - Self-efficacy questionnaire - Insert CGM - Activity monitor (Fitbit) - BMI ≥35 kg/m^2 (n = 36): RAGE, AGE, S100A8/A9 and inflammatory markers
Phase 2: observation	
12-month measurement visit (365 +/− 21 days)	- REE - BIA - WC, HC, NC - SBP, DBP, RHR - Self-efficacy questionnaire - BMI ≥35 kg/m^2 (n = 36): RAGE, AGE, S100A8/A9 and inflammatory markers

AGE, advanced glycation end-products; BIA, bioelectrical impedance analysis; BMI, body mass index; CBC, complete blood count; CGM, continuous glucose monitor; DBP, diastolic blood pressure;
eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HC, hip circumference;
LFD, low-fat diet arm; NC, neck circumference; PD, personalized diet arm; RAGE, receptor for advanced glycation end-products; REE, resting energy expenditure; RHR, resting heart rate; S100A8/A9, ligand of RAGE; SBP, systolic blood pressure; WC, waist circumference.

[a] Unbind randomization assignment to determine testing glycemic profiling labs.

dl) [34]. All GV indices will be calculated using EasyGV 8.6 software [35]. Fasting serum insulin and plasma glucose concentrations are used to calculate insulin resistance (HOMA-IR) and β-cell function (HOMA-β). The HOMA2 model will be used for this purpose [36].

1.2.2.3. Advanced Glycation End products (AGEs) and inflammation. The first 36 participants randomized to the study (18 in each group) having

Table 3
Study outcomes, mediators and covariates.

	-1 mos	0 mos	3 mos	6 mos	12mos
Primary aim 1					
% Body weight	x	x	x	x	x
Secondary aims					
FFM, FM, TBW		x	x	x	x
REE, metabolic adaptation		x	x	x	x
Weight regain					x
Mediators					
Self-efficacy		x	x	x	x
Glycemic Variability		x	x	x	
RAGE/AGE/S100A8/A9, Inflammatory markers (TNF-α,IL-1-β, IL-4, IL-10, IL-17)		x	x	x	x
Covariates					
Age	x				
Race	x				
Gender	x				
Comorbid conditions	x				
Living arrangements	x				
Education level	x				
Income	x				
Medication regimen	x	x	x	x	
Health events	x	x	x	x	
Antibiotic use	x	x	x	x	
Physical activity (FitBit)		x	x	x	
Blood biomarkers					
HbA1c	x		x	x	
Insulin		x	x	x	
Glucose		x	x	x	

AGE, advanced glycation end-products; CBC, complete blood count; FM, fat mass; FFM, fat-free mass; HbA1c, glycated hemoglobin; IL1-beta, interleukin-1-beta; IL-4, interleukin-4; IL-10, internleukin-10; IL-17, interleukin-17; LFD, low fat diet arm; PD, personalized diet arm; RAGE, receptor for advanced glycation end products; REE, resting energy expenditure; TBW, total body water; TNF-alpha, tumor necrosis factor-alpha.

BMI ≥35 kg/m^2 are assessed for the RAGE/AGE/S100A8/A9 pathway with additional serum and plasma measurements. AGEs are detected using Fluorescence Microplate reader (BioTek Synergy HI microplate reader, BioTeck Instruments, Inc., Winooski, VT, USA). RAGE, sRAGE and S100A8/A9 are determined using enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems Quantikine Immunoassay, Minneapolis, MN, USA). In addition, inflammatory markers (e.g., TNF-alpha, IL1-beta, IL4, IL10, and IL-17) are also assessed via commercially-available ELISA kits.

1.2.3. Covariates

1.2.3.1. Sociodemographic and clinical variables. At baseline, the following sociodemographic variables are collected using self-administered questionnaires: age, race, gender, living arrangement, education, employment status, income, family countries of origin, comorbidities, weight history, hunger, sleep quality, smoking status, bowel habits and function, birth history, and in females only, menstrual cycle. At each assessment time point, we will inquire about new health events and changes in medications and treatments during the prior interval.

1.2.3.2. Physical activity. Physical activity is measured using the Fitbit Alta HR (Fitbit, Inc., San Francisco, CA, USA). Participants are instructed to wear the device for up to 14 days. Participants in the LFD and PD group wear the device at baseline, 3 and 6 months. The screen on the device provides the participants with daily feedback on heart rate, caloric expenditure and steps per day, but weekly accumulated data are not shared with the participant. Those in the PD group wear the device again during the profiling week. Participants in the PD group are instructed to carry out their habitual exercise routine during the profiling, and are not provided with any additional feedback regarding physical activity levels.

1.3. Pre-intervention

1.3.1. Pre-intervention training (both groups)

Participants in both the LFD and PD group attend a pre-intervention training visit one or two weeks before the start of the intervention. Here the WebEx application is downloaded on their phones or the study loaner phones, and participants are trained in its use and how to join group-based counseling sessions. WebEx is a communications application on the NYULH Cisco Server, which is a HIPAA-compliant conferencing program. WebEx allows users to sign-in securely and join meetings from mobile devices. During this time, the interventionist provides further training on the PNP app, which includes troubleshooting and PNP app clarification. Participants randomized to PD undergo additional procedures described below.

1.3.2. Pre-intervention glycemic profiling (PD group only)

Participants in the PD group undergo one week of glycemic profiling immediately after the pre-intervention visit to generate personalized feedback regarding the predicted PPGR from the PNP algorithm. At the baseline visit, participants were provided with an Omnigene stool collection kit (DNA Genotek, Inc., Ottawa, ON, Canada) used for gut microbiota profiling. Stool samples are collected during the pre-intervention visit and shipped to the Weizmann Institute for microbiome analysis. A new CGM device is then inserted and worn for 7 days. Participants are instructed to follow their normal daily routine and dietary habits, except for the first meal of every day (hereafter "test meal"), and to refrain from eating for 2 h after the test meal is consumed. Six test meals are provided to the participants, including two of each of the following: (1) 110 g white bread, (2) 110 g white bread and 30 g of butter, and (3) 50 g glucose. Test meals are labeled with the day that they are to be consumed. Participants enter meals (test and other meals) and snacks, the timing of meals and snacks, physical activity, sleep, and hunger over the next 7 days into the PNP app. Participants are instructed to consume food with a minimum of 2 h in-between meals and snacks in order to permit meals and snacks to be linked to their glycemic tracings. During the profiling week, study staff monitor participants' PNP dashboards daily, and contact participants as necessary to ensure that meals are logged and reported as accurately as possible. At the conclusion of the profiling week, participants remove the CGM sensor, place it into a sharps-proof container, and return it to the investigators by mail. Time-stamped CGM and PNP data are uploaded to a HIPPA-compliant NYULH server, with baseline laboratory and physical assessment data.

1.3.3. Development of PNP algorithms

Data collected during the screening and baseline visits are shared, using the NYULH server, with the Weizmann Institute where data processing occurs. Anthropometric data, a blood chemistry panel, microbiota profiling (metagenome sequencing), up to one full week of interstitial glucose measurements using a CGM device, and a one-week log of date- and time-stamped meals and snacks from participants are integrated with the PNP database at the Weizmann Institute using gradient boosting regression to develop personalized PNP algorithms for predicting PPGR.

The predictive model was originally trained off an Israeli adult cohort [22]. The model has also been shown to be predictive of PPGRs ($R = 0.62$) in a U.S. cohort of adults without T2D consuming a Western-style diet [37]. The original PNP dataset (unpublished data) included participants with prediabetes ($n = 127$), T2D ($n = 27$, HbA1c > 6.5%), and participants prescribed metformin ($n = 8$). The Pearson Correlation predictor performances for these subgroups were 0.56, 0.61, and 0.71, respectively. In other words, compared to the overall predictive performance of the model (R = 0.6), the model performed better in those with diagnosed diabetes, and best in those under treatment with metformin.

A meal database was created consisting of Western-style meals ($n = 135$) and snacks ($n = 68$) varying in GL to generate feedback on the PPGR to pre-consumed meals. Using the participants' PNP algorithm, personalized PPGRs are calculated for every meal and snack in the database based on their nutrient composition, and calorie-adjusted quintile cutoffs of PPGR are used to create meal ratings of "excellent," "good," "medium," "bad," and "very bad."

1.4. Interventions

1.4.1. Phase 1 – both groups

The 6-month active intervention phase targets a weight loss of 7% through caloric restriction in both groups. Participants are also instructed to participate in 150 min/wk. of moderate-to-vigorous physical activity (MVPA) and engage in resistance training 2–3 times per week [38]. Participants in both arms attend group behavioral counseling sessions that are guided by study dietitian. Group sessions ($n = 14$) are limited to 10 participants, and are held weekly during the first month, and then every other week in months 2–6.

Group behavioral counseling is based on the SCT, with an emphasis on enhancing self-efficacy (confidence) in their ability to engage in healthy behaviors leading to weight loss [39,40]. Group sessions are conducted via WebEx (Cisco Systems Inc., San Jose, CA, USA) using a smartphone to minimize participant burden of attending face-to-face group sessions. The duration of each group session is approximately one hour. Each session is anchored by two brief videos (~5–7 min each) to enhance intervention fidelity; one that provides educational content, and one that focuses on behavior change. Periodically, the interventionist pauses the videos and introduces scripted open-ended questions designed to elicit discussion. At the conclusion of the session, the videos are posted on the study website for participants to review as desired, and all participants are e-mailed a link to the videos presented. All videos posted on the study website are integrated into BrainShark (Brainshark Inc., Waltham, MA, USA), a software program that allows the investigators to document exposure to content independent of intervention sessions.

As outlined in Table 4, the behavioral component is identical between the LFD and PD groups. The only between-group differences occur with the educational content delivered with sessions 5 and 14, during which time participants are instructed in dietary behaviors relevant to their randomization assignment. The full sessions, including participant discussions, are recorded, retained, and 10% are reviewed by a trained rater to assess fidelity of the interventionist to the behavioral counseling techniques used in the session. The rater provides feedback to the interventionist to ensure consistent counseling delivery based on the proposed behavioral theories supporting the intervention. These recorded sessions are not posted or shared with participants.

For the duration of the intervention, participants are directed to self-report into the PNP app everything that they eat or drink, their physical activity, and their body weight (weekly). The PNP app is pre-programmed with a: (1) weight loss target (−7% body weight); (2) hypocaloric energy target (−500 kcal/day, based on REE measurements from indirect calorimetry and a physical activity factor of 1.4 (lightly active)); and (3) physical activity target of 30-min per day. Participants are counseled to use the PNP app to monitor, in real-time, their behaviors concerning the study targets. Example screenshots of nutritional details, meal totals, and physical activities are shown in Figs. 2 and 3.

1.4.2. Phase 1 – low-fat diet arm only

The LFD arm is counseled to follow a low-fat (< 25% dietary fat) diet containing < 7% energy intake from saturated fat. They are instructed to review the PNP meal entries, in real time, to ensure they keep their daily intake below their total calorie target, as well as the

Table 4
Intervention content.

	Education materials (video)	Social cognitive theory (coaching)
1	Welcome to the Personal Diet Program: Overview of obesity risks and benefits of weight loss	Setting personal health goals for life
2	Self-monitoring for success: Self-monitoring diet and physical activity	Where am I? Finding a path to behavior change
3	Being a Calorie Detective: Identifying healthy portion sizes and “empty calories”	Setting goals for weight loss success
4	Introducing physical activity into your life: Finding time for fitness and exercise safety	Self-Reward: Turning goals into habits
5	Being a fat detective: Identifying healthy and unhealthy fats as part of total calorie intake (LFD group only)	Social support: Developing and working your social support network
	Getting to Green: Using personalized meal feedback to meet your goals (PD group only)	
6	Maintaining muscle with strength training: Techniques for incorporating strength training into your routine	Introduction to the problem-solving model
7	The role of sleep and stress in weight gain and loss: Role of lifestyle choices to support weight loss	Problem solving: Stress management
8	Weight loss plateaus: Strategies to mitigate plateaus in weight loss	Problem solving: Behavioral triggers and stimulus control
9	Adding color and fiber to your diet: How to incorporate important nutrients for weight loss	Problem solving: Anticipating high-risk situations
10	Breakfast and meal frequency for weight loss success: Meal timing and frequency to meet weight loss goals	Problem solving: Eliminating negative self-talk
11	Snacking and sugar-sweetened beverages: Reducing intake of “empty calories” in your diet	Problem solving: Food cravings, addictions, and habitual over-eating
12	Eating on Special Occasions: Changing seasons, life events, and eating a restaurants	Problem solving: Emotional eating
13	Achieving positive body image: Working toward body acceptance and confidence	Problem solving: Lapses and relapses
14	Putting it all together: Review of diet and lifestyle recommendations for weight control	Problem solving: Coping with lapses

The title of session 14 is the same for both the LFD and PD groups, but the video scripts are different.

25% total fat and 7% saturated fat targets.

1.4.3. Phase 1 – personal diet arm only

The PD arm subjects are instructed to review their PNP meal entries daily in the smartphone app concerning targets for total calories. PD participants receive personalized feedback regarding the nature of their personalized predicted PPGR for foods entered into the PNP app prior to consumption (See Fig. 2). The feedback is color-coded consistent with a traffic light as green (foods with a “good” or “excellent” PPGR), yellow (“medium” PPGR), and red (a “bad” or “very bad” PPGR). Participants are advised to maintain PPGR in the “good” or “excellent” range and, when they receive yellow or red scores, to make different choices/food substitutions. Initial guidance is provided regarding low- and high-GL foods, as well as the addition of healthy fats to the meal. However, participants are informed that because their glycemic response is specific to them, experimentation will be required to determine which meals and snacks are most suitable for them.

1.4.4. Phase 2

Phase 2 is a 6-month observation period. During this time, participants are encouraged to continue monitoring diet, physical activity, and body weight, and enter the data into the PNP app, however, no further contact is made by the interventionist or study dietitian. Four newsletters are mailed to all study participants discussing general health-

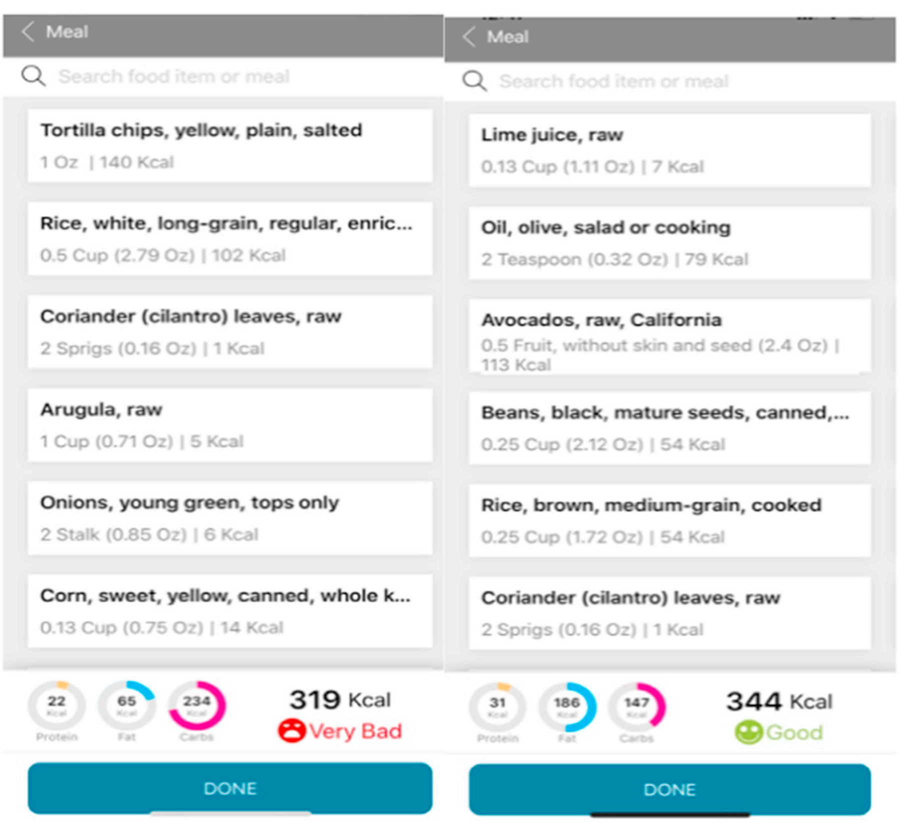

Fig. 2. Screenshots of PNP app for meal scores.
The Personalized Nutrition Program (PNP) smartphone app allows participants to log foods and hunger level in real-time. Those in the PD group will receive feedback regarding the meal score. In this example, the screenshot on the left shows a “very bad” score for this individual. Modifying the meal changes the score to “good” (right).

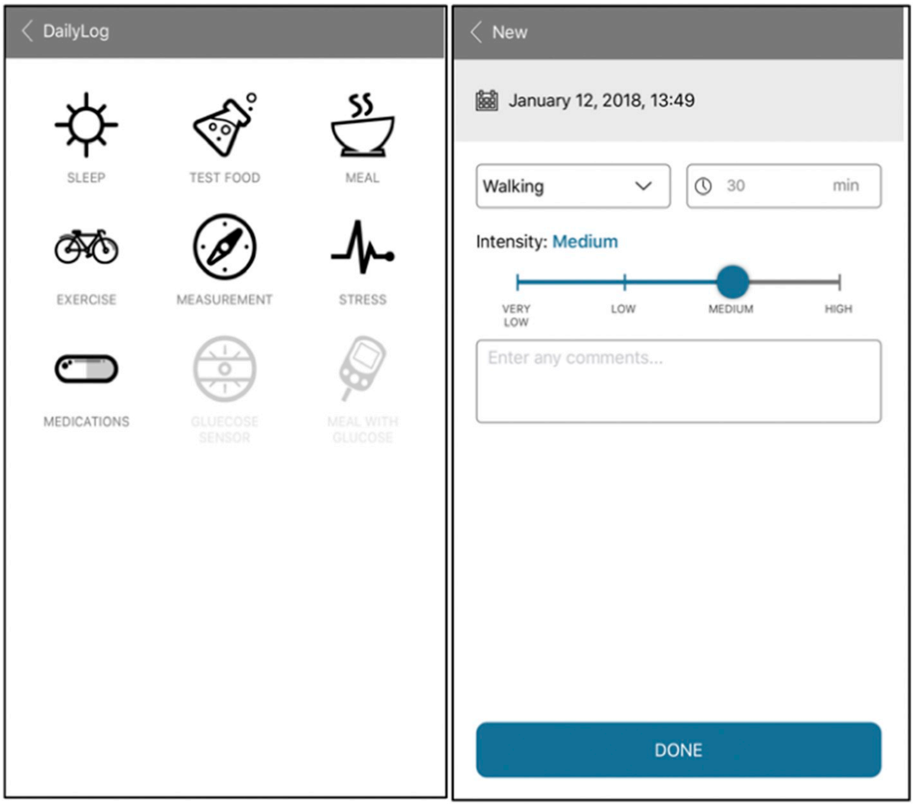

Fig. 3. Screenshots of PNP app for physical activity logging.
The Personalized Nutrition Program (PNP) smartphone app allows participants to log physical activity duration and intensity in real-time. Participants in both groups are recommended to log their daily physical activity levels. Feedback regarding their physical activity is not provided to either group.

related topics to maintain communication and engagement.

1.5. General approach

A descriptive analysis of all data collected will be performed using appropriate graphical and numerical exploratory data techniques. The information obtained from this preliminary investigation of the data will be used to: (1) assess data quality and completeness; (2) describe univariate and bivariate distributions at baseline, 3, 6 and 12 months; and (3) identify univariate associations between variables. We will identify features of the data that may necessitate special methods (e.g., excess zeros, missing data, and departures from distributional assumptions). During preliminary analysis, we will examine: (1) comparability of treatment arms at baseline (based on Chi-squared statistics or *t*-tests, as appropriate), (2) relationships between the response variables and potential covariates, and (3) predictors of missing data/drop-out.

A linear mixed model will be used to model the baseline, 3, 6 and 12 months outcome variables. In the model, presence/absence of T2D, time, and intervention will be included as fixed effects, and the participant will be the random effect. The intervention effect of interest is the treatment*time interaction in this model. Identified predictors of missing data will be included as covariates in this random effect framework, to provide unbiased estimates of the intervention effect under an assumption of missing at random (i.e., missingness depends on observed covariates but not on unobserved covariates). Other demographic and clinical covariates will be included as necessary in adjusted analyses. Model assessment will be conducted using appropriate regression diagnostics. The primary and secondary analyses will be done using SAS (SAS 9.4, Cary, NC, USA).

1.5.1. Sample size

The goal for both groups is 7% weight loss at 6 months. This goal is based on similar lifestyle interventions using behavioral modification, low-calorie diets and 150-min/wk. physical activity targets (Diabetes Prevention Program and Look AHEAD trials) [41,42]. The project is powered to test the hypothesis that, at 6 months, weight losses in the PD group will be greater than weight losses in the LFD group. The sample size calculations are based on the assumption that a clinically significant, minimum weight loss of 5% will achieved by the LFD group, which is consistent with our pilot work in a similar population (mean weight loss of 5.94%, SD = 4.54%, unpublished data). With a sample of 164 (82 per group), type I error $\alpha = 0.05$ and a power of 80%, we can detect a between- group difference in weight loss as small as 2%. To account for an expected loss of about 20% of participants to drop-out, we will recruit 200 participants.

1.5.2. Analysis of primary outcomes

For hypotheses pertaining to weight loss, the primary outcome of interest is the percent of baseline body weight lost at 6 months and whether or not these losses will be sustained at 12 months. A random effects linear regression model will be used to test time-specific differences attributable to the intervention. We also will use the “lincom” command to estimate differences in time-specific changes from baseline. In additional analyses, we will adjust for other covariates (e.g., insulin secretion, insulin sensitivity, glycemic control, habits and history that could influence weight loss, and sociodemographic, and medication regimen) unbalanced between the treatment arms at baseline at $p = .10$. A splined linear mixed model with repeated measures will be used to compare changing trends in different periods: early intervention (0–3 months) and late intervention (3–6 months). In this analysis, adjustments will be made for the covariates noted above.

1.5.3. Analysis of secondary outcomes

For hypotheses related to body fat distribution and metabolic adaptation at 6 and 12 months, and weight regain at 12 months, the random effects linear regression model will be used to test time-specific differences attributable to the intervention using a similar approach to that of analyses for the primary aim of weight loss. Mediation analysis will be performed to assess whether, and by how much, self-efficacy mediates and the intervention effect on weight loss. Covariates (such as age, gender, race, and baseline T2D status) will be included in the model and we will explore the possibility of multiple mediators.

Similar mediation analyses including self-efficacy and glycemic exposure will be performed to examine the underlying biologic mechanisms that influence weight loss/regain metabolic adaptation and fat distribution at 6 and 12 months.

1.5.4. Adherence

Adherence to the study intervention will be assessed based on attendance to measurement visits and WebEx intervention meetings and on viewing of the Brainshark videos. In addition, adherence to self-monitoring will be evaluated based on the frequency of using the PNP app to record diet, physical activity, and body weight, and the proportion of days meeting > 50% of calorie target. Adherence to the dietary interventions will be analyzed based on the proportion of meals and days in which dietary fat is < 25% calories (LFD arm), and the proportion of meals logged as "good" or "excellent" (PD arm). Adherence to physical activity recommendations will be examined using the proportion of weeks in which participants record > 150 min/wk. of MVPA.

1.5.5. Safety

During the study, participants' weights and HbA1c are monitored. Each participant's percent weight change is assessed at each measurement visit. Participants are counseled by study dietitians to slow their rate of weight loss if their percent weight change is severe, defined as > 7.5% in 3 months, > 10% in 6 months, and > 20% in one year. Participants are reminded to continue to see their primary care physician and that study procedures are not provided in lieu of standard medical care. Participants are instructed to focus on a slow progressive increase in physical activity until reaching a goal of 150 min/wk. These guidelines are in line with the 2008 physical activity guidelines advisory committee report recommendations for sedentary individuals [38].

1.5.6. Limitations

Although this study will provide valuable data on personalized nutrition and the Carbohydrate-Insulin Model of obesity, there are several limitations to consider. Use of a 7-day run-in to assure that participants are willing and able to self-monitor diet may limit generalizability. Due to the nature of behavioral interventions, participants and dietitians are unblinded to treatment allocation. The PNP algorithm requires the PD arm to undergo metabolic profiling at baseline. However, collection of profiling data and the 7 days of additional attention this entails are unlikely affect weight loss success. Participants who have experienced weight loss failures may harbor unrealistic "magic bullet" expectations about a personalized weight loss program. Participants randomized to the LFD may be disappointed and less invested in their randomization assignment than the PD group. This, in turn, could influence weight loss success. Differences in intervention engagement will be accounted for by considering protocol adherence in the analysis (e.g., adherence to self-monitoring, attendance at counseling sessions). We also intend to explore predictors of drop-out as potential behavioral determinants of intervention efficacy.

The PNP application also has inherent limitations. The application is currently available in English and Hebrew, which restricted our target population. Importantly, English is common among people from diverse racial/ethnic backgrounds in New York City, and if efficacious, the PD intervention can be adapted, and tested in non-English speaking individuals. In addition, as in many food diary applications, PNP was developed using the USDA Nutrient Database for Standard Reference (Rel 28.1). While this ensures that the nutrient composition data is of high quality, many foods, in particular processed foods, are not included in the database. As a result, certain participants may have difficulty finding foods, or appropriate substitutions, which could impact adherence to self-monitoring.

2. Discussion

Body weight differences in response to weight-loss diets are substantial [43]. Standard dietary interventions targeting weight loss follow a "one-size-fits-all" approach in which uniform dietary recommendations are provided. However, evidence regarding the efficacy of these interventions for long-term weight loss is mixed. This paper describes the rationale for and methods being used in our study, currently underway, comparing PD to standard LFD recommendations in a novel technology-supported behavioral intervention that utilizes real-time feedback from a machine-learning algorithm targeting PPGR to meals in order to facilitate weight loss. The interventions are implemented using mobile health technologies that permit remote delivery of counseling and self-monitoring in a manner that is convenient for patients and has great potential for dissemination. Arming participants with food-specific recommendations tailored to their unique physiological response to meals may increase their adherence to lifestyle changes and enhance their weight loss success.

Funding

This work was supported by Grant 17SFRN33590133 from the American Heart Association.

ClinicalTrials.gov Identifier: NCT03336411

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