Personalized Postprandial Glucose Response–Targeting Diet Versus Mediterranean Diet for Glycemic Control in Prediabetes

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OBJECTIVE

To compare the clinical effects of a personalized postprandial-targeting (PPT) diet versus a Mediterranean (MED) diet on glycemic control and metabolic health in prediabetes.

RESEARCH DESIGN AND METHODS

We randomly assigned adults with prediabetes ($n = 225$) to follow a MED diet or a PPT diet for a 6-month dietary intervention and additional 6-month follow-up. The PPT diet relies on a machine learning algorithm that integrates clinical and microbiome features to predict personal postprandial glucose responses. During the intervention, all participants were connected to continuous glucose monitoring (CGM) and self-reported dietary intake using a smartphone application.

RESULTS

Among 225 participants randomized (58.7% women, mean ± SD age 50 ± 7 years, BMI 31.3 ± 5.8 kg/m^2, HbA_{1c}, 5.9 ± 0.2% [41 ± 2.4 mmol/mol], fasting plasma glucose 114 ± 12 mg/dL [6.33 ± 0.67 mmol/L]), 200 (89%) completed the 6-month intervention. A total of 177 participants also contributed 12-month follow-up data. Both interventions reduced the daily time with glucose levels >140 mg/dL (7.8 mmol/L) and HbA_{1c} levels, but reductions were significantly greater in PPT compared with MED. The mean 6-month change in "time above 140" was −0.3 ± 0.8 h/day and −1.3 ± 1.5 h/day for MED and PPT, respectively (95% CI between-group difference −1.29 to −0.66, $P <$ 0.001). The mean 6-month change in HbA_{1c} was −0.08 ± 0.19% (−0.9 ± 2.1 mmol/mol) and −0.16 ± 0.24% (−1.7 ± 2.6 mmol/mol) for MED and PPT, respectively (95% CI between-group difference −0.14 to −0.02, $P = 0.007$). The significant between-group differences were maintained at 12-month follow-up. No significant differences were noted between the groups in a CGM-measured oral glucose tolerance test.

CONCLUSIONS

In this clinical trial in prediabetes, a PPT diet improved glycemic control significantly more than a MED diet as measured by daily time of glucose levels >140 mg/dL (7.8 mmol/L) and HbA_{1c}. These findings may have implications for dietary advice in clinical practice.

Prediabetes is a leading risk factor for the development of type 2 diabetes and other metabolic abnormalities, such as cardiovascular and kidney disease (1,2). The prevalence of prediabetes in the adult population has increased dramatically in

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the past 20 years, affecting more than one-third of the adult population in developed countries, such as the U.S. (3). Traditionally, the first line of treatment for prediabetes includes lifestyle modifications consisting of calorie-restricted dietary regimens and increased physical activity aimed for weight loss. Interventions, such as the Diabetes Prevention Program (DPP) (4) and the Finnish Diabetes Prevention Study (DPS) (5), are established as the primary care strategy for prevention of type 2 diabetes (6). However, in clinical practice, calorie-restricted dietary regimens often fail to achieve long-term weight control. This has been explained by poor long-term compliance and metabolic resistance to weight loss under circumstances of energy deficit (7,8).

Alternative approaches, such as dietary interventions that directly target blood glucose levels rather than weight loss for prevention of type 2 diabetes, are not well established and have been much less studied. In particular, postprandial (postmeal) glucose responses (PPGRs) are increasingly considered a major determinant of glycemic control, yet methods for predicting PPGRs to food remain elusive and of limited efficacy (9). In the absence of data-driven approaches to target postprandial glucose surges, current practice focuses on the meal carbohydrate content (6,10), even though it is insufficiently predictive of the meal response (11–13). Indeed, in type 2 diabetes management, for example, there is no consensus on the ideal amount of dietary carbohydrates, and low-carbohydrate diets are not proven superior to high-carbohydrate diets in their capacity to have an impact on long-term glycemic control or weight management (14,15). Other methods aimed at estimating PPGRs are the glycemic index and the derived glycemic load (16). However, these methods quantify PPGR to consumption of a single tested food type or meal and thus have limited applicability in assessing the PPGR to real-life meals (17). Indeed, studies examining the effect of diets with a low glycemic index on type 2 diabetes risk, weight loss, and cardiovascular risk factors have yielded mixed results, indicating that low-glycemic-index diets are not conclusively proven as effective for long-term glycemic control and cardiometabolic health (18–20). Critically, several studies have shown that the PPGRs of different people to the same food are highly variable and that this variability can be the key for personalization in dietary advice (12,13,21,22).

We previously recruited a population-based cohort of 900 people in which we continuously tracked blood glucose and obtained clinical and microbiota measurements that were used to devise a machine learning algorithm for predicting personalized PPGRs to any food combination (13). Here, we sought to evaluate the long-term clinical efficacy of a dietary intervention based on our algorithm in prediabetes, where PPGRs are known to be high (23), and to test whether a dietary treatment strategy that targets meal PPGR can lead to long-term improvements in glycemic control and other metabolic outcomes. As expected, dietary carbohydrates constitute a major factor of PPGR prediction in our algorithm. However, meal carbohydrate content explains only ∼15% of the variability in glycemic response, and adding clinical and gut microbiome features to the algorithm increases the variability explained to ∼50% (13). Thus, we expected that an algorithm-based dietary intervention would result in a relatively low average carbohydrate content but would complement this feature with other personalized parameters, such as carbohydrate content of the meal and specific foods and food combinations that fit to each person individually, and would collectively enable a more efficacious individualized set of recommendations. As a control diet to which to compare our approach, we chose the Mediterranean (MED) diet because it is commonly recommended in national guidelines of different countries and in clinical practice because of its multiple, well-established effects on glycemic control and other metabolic health factors (24,25). We opted against a low-carbohydrate control diet because such approaches are not well established. Importantly, caloric content and physical activity were closely monitored throughout the study, but caloric restriction and enhanced physical activity were not advised; thus, participants were given a weight maintenance caloric target and asked to maintain their habitual physical activity in order to primarily focus on the differential effects of the dietary regimens. As such, in this randomized clinical trial, we intentionally compared two dietary approaches that differ in macronutrient composition for their effect on glycemic control and other metabolic outcomes in prediabetes, independent of weight loss.

RESEARCH DESIGN AND METHODS

Trial Design

The study was a biphasic, randomized, controlled, single-blind dietary intervention. Phase one included a 6-month intervention that compared two diets targeting glycemic control, while phase two included a 6-month follow-up period. The two dietary interventions included *1*) a MED diet and *2*) an algorithm-based personalized PPT diet aimed at lowering PPGRs with real-time feedback through a smartphone application (app). The trial protocol was designed solely by the main investigators and approved by the institutional review board of the Weizmann Institute of Science (protocol #398-1). A sponsor-appointed data and safety monitoring board also approved the protocol. All enrolled participants provided written informed consent.

The data were collected by the trial personnel at the Weizmann Institute of Science and stored in a secure electronic data capture database. Trial personnel included research coordinators, certified dietitians, physicians, programmers, and laboratory technicians. All authors vouch for the accuracy and completeness of the data and all analyses.

Participant Recruitment

Enrollment and recruitment occurred between January 2017 and January 2019. The date of final follow-up was in March 2020. Recruitment, randomization, and follow-up numbers are summarized in the flowchart in Fig. 1*A*. Trial registration with ClinicalTrials.gov occurred 5 months after recruitment started because of technical and administrative reasons, but only 17 of the 225 participants were recruited during this period. The other 208 patients were recruited after trial registration. Importantly, the study design and protocol were set, finalized, and approved by the institutional review board committee and the

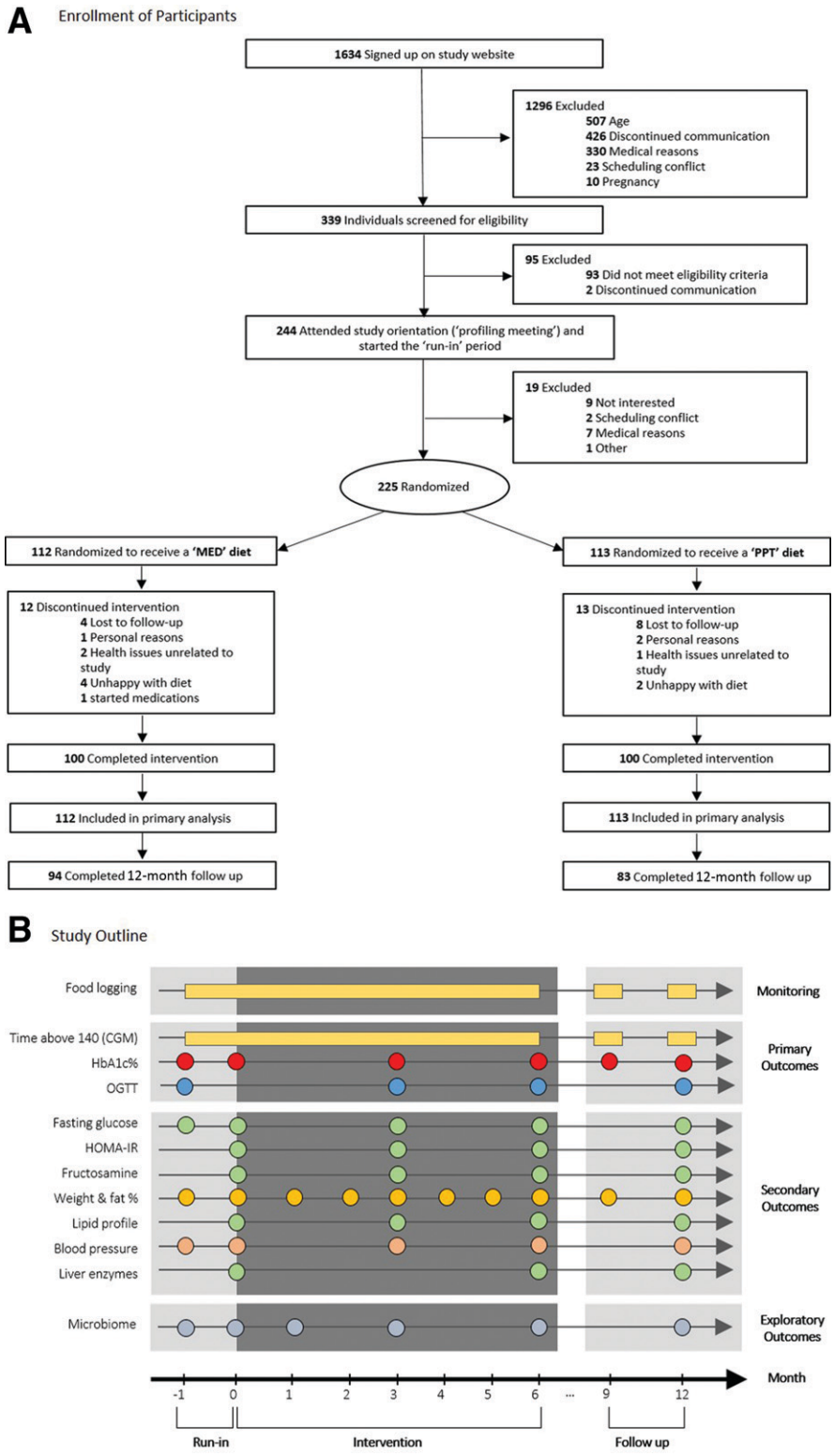

Figure 1—Trial flow and study outline. *A*: Diagram of trial flow. *B*: Scheme of study outline.

sponsor-appointed data and safety monitoring board before the trial start and before the first participant was enrolled. All participants signed the informed consent of this protocol.

Participants included in the study met two glycemic criteria for prediabetes as defined by the 2010 American Diabetes Association guidelines: *1*) fasting plasma glucose (FPG) levels between 100 and 125 mg/dL (5.6 and 6.9 mmol/L) and *2*) HbA_{1c} level between 5.7 and 6.5% (39 and 48 mmol/mol). Other inclusion criteria were age of 18–65 years and capability to work with a smartphone app on

a daily basis (for dietary intake logging). Key exclusion criteria were any use of diabetes or weight loss medications, use of antibiotics in the 3 months before enrollment, diagnosed chronic diseases, or chronic use of medications that affect glucose/energy metabolism or HbA_{1c} (for detailed exclusion criteria, see Supplementary Table 1).

The recruitment process relied primarily on self-assignment of volunteers from Israel who self-reportedly declared themselves as having prediabetes on the trial website. Registrants were screened for the above eligibility criteria based on a questionnaire and, if qualified, underwent a screening visit to determine final eligibility according to measured FPG and HbA_{1c} at the trial's central laboratory. Eligible participants were then invited for a "profiling" visit at the trial's site (Weizmann Institute of Science) during which they were informed in detail of all study procedures and requirements, provided a stool sample for baseline microbiome analysis (required for algorithm predictions), and were connected to continuous glucose monitoring (CGM) sensors (FreeStyle Libre, Abbott Laboratories) for a run-in period of 2–4 weeks before the start of the intervention. The CGM measures from this run-in period served as a baseline measure of glycemic state before the intervention started.

Interventions and Procedures

The trial outline is summarized in Fig. 1*B*. After completion of the run-in stage, participants were randomly assigned 1:1 to a MED or a PPT diet. Covariate adaptive randomization with minimization (26) was performed to ensure minimal differences between the groups in six prognostic baseline characteristics: sex, age, weight, BMI, HbA_{1c}, and FPG (Table 1). Randomization was computed by one programmer from the trial personnel who had no contact with participants. Participants and measurers were blinded to arm assignment, while the investigators and dietitians were not. Each dietitian was assigned a similar number of participants from each study arm. At the end of intervention, dietary assignment was revealed, and participants were asked to continue following their respective diets for 6 additional months.

Participants in both diet groups continuously received dietary advice by certified dietitians. Individual dietary follow-up meetings (each 30 min long) with a dietitian occurred monthly on site during the 6-month intervention period and at 9 and 12 months during the follow-up period. Between the in-person visits, interim contact with the dietitian (telephone or e-mail) was equally available at any time for all participants in both study arms. Participants were also asked to fill out electronic monthly follow-up questionnaires during the intervention and once at the 12-month follow-up time point. All visits, contacts, and questionnaires were designed to promote retention, encourage adherence to the trial regimen, and assess for occurrence of adverse events.

Table 1—Baseline characteristics of participants

	MED diet (*n* = 112)	PPT diet (*n* = 113)	*P* value	All
Age, years	50 (7)	50 (7)	0.51	50 (7)
Sex				
Female	63 (56)	69 (61)		132 (59)
Male	49 (44)	44 (39)		93 (41)
Highest level of education achieved				
Less than high school	1 (0.9)	3 (2.6)		4 (1.8)
High school	9 (8)	18 (15.9)		27 (12)
Professional	24 (21.4)	16 (14.2)		40 (17.8)
Graduate degree	31 (27.7)	32 (28.3)		63 (28)
Postgraduate degree	47 (42)	44 (39)		91 (40.4)
HbA_{1c}, %	5.9 ± 0.2	5.9 ± 0.2	0.13	5.9 ± 0.2
FPG, mmol/L	6.33 ± 0.61	6.33 ± 0.78	0.9	6.33 ± 0.67
Weight, kg	88.9 ± 17.4	87.4 ± 17	0.5	88.2 ± 17.2
BMI, kg/m^2	31.4 ± 6.2	31.2 ± 5.4	0.78	31.3 ± 5.8
Waist circumference, cm	102.3 ± 13.0	102.2 ± 12.9	0.92	102.3 ± 12.9
Total cholesterol, mmol/L	5.38 ± 1.11	5.51 ± 0.91	0.31	5.46 ± 1.01
HDL cholesterol, mmol/L	1.34 ± 0.34	1.37 ± 0.31	0.55	1.34 ± 0.34
LDL cholesterol, mmol/L	3.28 ± 0.96	3.36 ± 0.80	0.48	3.34 ± 0.88
Triglycerides, mmol/L	1.66 ± 0.76	1.72 ± 0.88	0.55	1.69 ± 0.82
Systolic blood pressure, mmHg	125.8 ± 17.9	125.4 ± 16.4	0.87	125.6 ± 17.1
Diastolic blood pressure, mmHg	83.6 ± 9.7	83.3 ± 10.1	0.81	83.4 ± 9.9
FLI	65.7 ± 28.1	66.2 ± 26.5	0.9	66.0 ± 27.2

Data are *n* (%) or mean ± SD. To convert HbA_{1c} from DCCT units (%) to International Federation of Clinical Chemistry units (mmol/mol), subtract 2.15 and then multiply the result by 10.929. To convert FPG values from International System of Units (SI) (mmol/L) to conventional units (mg/dL), divide by 0.05551. To convert HDL, LDL, and total cholesterol values from SI units (mmol/L) to conventional units (mg/dL), divide by 0.02586. To convert triglyceride values from SI units (mmol/L) to conventional units (mg/dL), divide by 0.01129.

To obtain the most informative view of glucose levels possible, participants in both arms were continuously connected to CGM sensors throughout the entire intervention period, with sensors replaced every 2 weeks (15,727 ± 4,430 glucose measurements per person). The CGM measures interstitial glucose concentrations every 15 min, and participants were blinded to glucose tracings. In addition, participants in both arms were asked to record their full dietary intake in real time every day for the full study period using a designated smartphone app (Personalized Nutrition Project). Each food item within every meal was logged along with its weight or portion units by selecting it from a database of >7,000 foods with full nutritional values based on the Israeli Ministry of Health database that we further improved and expanded with additional items from certified sources. The extensive meal logging by the study participants allowed us to continuously assess level of adherence to the diet regimen. Additional 2-week CGM connections (one sensor) accompanied by dietary intake records occurred at the postintervention follow-up period and the 9- and 12-month checkpoints.

Diets

Dietary recommendations for both groups were administered as menus, with meals selected from a meal bank generated for this study. The selection of meals for the menus relied on the diet principles in each group, as described hereafter and in Supplementary Fig. 1 and Supplementary Material, page 7. Menus were designed with a variety of foods and meal options to allow for diversity, to guarantee a balanced diet, and to suit the participant's personal tastes and preferences. Meals were selfprepared by participants at home. Upon inquiring, participants also received recommendations or discouragement to consume any other desired food or meal outside their menus, depending on the principles of the diet arm to which they were assigned (for PPT, based on the algorithm; for MED, based on dietitian judgment) (Supplementary Fig. 2*E* and Supplementary Material, page 8).

Since the primary goal of this trial was to test the effect of diet comp osition on glycemic control, independent of weight loss, no total calorie restriction was advised, and no physical activity was promoted. Menus were designed with a daily caloric target that was personally set to each participant to match their estimated energy expenditure (Supplementary Material, page 7). Participants were asked to follow their daily caloric target as they logged their meals on the app.

MED Diet

The dietary recommendations in this arm were based on the standard of care as advised by certified dietitians in Israel, according to the Israeli Ministry of Health, that refer to a MED diet as the strategy of choice for reducing the risk of developing type 2 diabetes and other metabolic disorders (27). Recommended foods on the MED diet included whole-wheat bread and grains, legumes, low-fat dairy products, fish, poultry, olive oil, fruits, and vegetables. Discouraged foods included commercial bakery goods, sweets and pastries, fried foods and snacks, fatty and processed meat, and high-fat dairy products. Menus in this diet arm were designed with the following diet composition: 45–65% of energy intake from carbohydrates, 15–20% from protein, and <35% from fat, with <10% from saturated fat. Meal selection for menus in this arm was based on meal scorings of our meal bank performed by four external dietitians (not part of the study team), with attention to personal dietary preferences as reported by participants on a food preferences questionnaire (see Supplementary Fig. 1 and Supplementary Material, page 7).

Personalized PPT Diet

Dietary recommendations in this arm were tailored to participants based on their personal predicted glucose responses according to a previously published algorithm that integrates clinical and gut microbiome features to predict PPGR to meals (13). Meal selection for menus was based on a scoring system that we developed for this study and applied to our meal bank such that meals were personally scored for each participant based on PPGR prediction rather than on uniform scoring as done in the MED arm (see Supplementary Fig. 1 and Supplementary Material, page 7).

Adherence

Adherence to the prescribed diets was evaluated during the intervention by the self-recorded dietary intake in the logging app and the monthly follow-up questionnaires. During the intervention period, semiautomatic feedback reports were sent via e-mail to participants in both diet groups every 2 weeks to encourage dietary adherence and self-monitoring. The feedback reports were based on self-recorded dietary intake and included composite grades (on a scale of 0–100) for calorie intake and diet composition according to the diet principles in each arm (see Supplementary Material, page 8, for details about feedback report grades). Participants were informed that accurate logging is crucial for receiving accurate grades in the feedback reports. Dietitians communicated to participants the message from these feedback reports during the monthly individual dietary follow-up meetings or, in the interim (between the in-person visits), through virtual contact (telephone or e-mail) as needed.

Outcomes

The primary outcomes in this trial were the 6-month changes in *1*) total daily time of CGM glucose levels >140 mg/dL (7.8 mmol/L) (hereafter "time above 140"), *2*) HbA_{1c}, and *3*) oral glucose tolerance test (OGTT). Time above 140 was used as a measure of glycemic control based on the glycemic goals for clinical management of postmeal hyperglycemia according to International Diabetes Federation guidelines (9). It was calculated from all CGM measurements of the entire intervention phase. An OGTT consisting of 75 g of glucose was provided to participants, who performed the test at home. Participants were asked to perform the test after an overnight fast (minimum of 8 h) and to log the time when they ingested the glucose on the app. The glucose values of OGTTs were calculated from CGM data as the 2-h change (Δ) in CGM glucose levels after the glucose was consumed.

Secondary outcomes included FPG, HOMA of insulin resistance (HOMA-IR), fructosamine, mean glucose (CGM based), 5-h PPGR excursions, lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides), fatty

liver (proxied by ALT and AST activity, by hepatic ultrasound, and by a fatty liver index [FLI]), blood pressure, body weight, and body composition (using a BC-418MA Segmental Body Composition Analyzer; Tanita). Fructosamine (a measure that reflects relatively recent, 2–3-week changes in blood glucose) (28), mean glucose obtained from CGM, and 5-h PPGR excursions were not included originally in the trial protocol but were added as independent measures in validating glycemic control. The FLI was also added post hoc as an additional measure for evaluating changes in liver fat content.

During intervention, participants were unaware of their blood test results. These were reviewed by a physician from the trial team, who delivered to participants (through dietitians) a notification letter for their primary care physician in the case of any abnormal results that required medical assessment. At the end of the 6-month intervention, participants received a summary report with all their personal measurements tested during the intervention. At follow-up, time above 140 and HbA_{1c} were measured at the 9-month checkpoint, and all outcomes were remeasured at the final 12-month checkpoint.

Laboratory Testing

Blood draws were done at the trial site (Weizmann Institute of Science) or at the central medical laboratory of the trial (AMC Medical Center Laboratory, Ltd.). All blood specimens were processed and laboratory tests performed by one technician at the central laboratory, which was not aware of arm assignment or any other characteristics of participants. HbA_{1c} determination was based on the turbidimetric inhibition immunoassay for hemolyzed whole blood, standardized according to the International Federation of Clinical Chemistry transferable to Diabetes Control and Complications Trial (DCCT)/NGSP (Tina-quant HbA_{1c} Gen. 3 assay, cobas; Roche) (29). Plasma glucose was measured with the use of a hexokinase method (GLUC2 assay, cobas; Roche). Fructosamine was measured with the use of a colorimetric test by reaction with nitroblue tetrazolium (filter retardation assay, cobas; Roche) (30). Insulin was measured with the use of a chemiluminescent microparticle immunoassay (ARCHITECT insulin assay; Abbott Laboratories). Total cholesterol, HDL, and triglycerides were measured with the use of an enzymatic colorimetric method (CHOL2, HDLC4, and TRIGL tests, respectively, cobas; Roche). LDL cholesterol levels were calculated at the medical laboratory of the trial as part of a standard lipid profile test based on the Friedewald equation (31). The HOMA-IR measure was calculated using the measured values of FPG and fasting insulin based on a published equation (32). The 5-h PPGR excursions were calculated from CGM data, using the incremental area under the curve (only the area above baseline was considered) of every 21 consecutive glucose measurements, demonstrating the glucose fluctuations during the day with no specific attention to meal loggings. The FLI was calculated using the measured values of BMI, waist circumference, blood triglycerides, and γ-glutamyl transferase, based on a published equation (33). The hepatic ultrasound outcome was calculated as a score from 0 to 3 based on categorical fatty liver degrees as interpreted by one radiologist (independent of the study team) who reviewed the ultrasound tests of all participants.

Stool samples for microbiome analysis (required for algorithm predictions) were collected by participants at home using an OMNIgene GUT (OMR-200; DNA Genotek) stool collection kit. These samples were used to extract bacterial DNA. Illumina libraries were prepared using Nextera DNA Library Prep Kit (Illumina #15028211) by Tecan Freedom Evo 200 robotic platform. IDT for Illumina Nextera DNA Dual Indexes were used for library preparation. Library concentration was measured using iQuant dsDNA HS Assay Kit (Cat# AP-N011; ABP Biosciences), and library size was a quantified by automated electrophoresis nucleic acid quality control-TapeStation system. Libraries were sequenced to a minimum depth of 10 million reads by a NextSeq 500 machine with NextSeq 500/550 High Output v2 75-cycle kit (Cat# FC-404-2005; Illumina). Metagenomic reads containing Illumina adapters and low-quality reads were filtered out, and low-quality read edges were trimmed. The host DNA was detected by mapping with Genome Multitool (34) to the human genome with inclusive parameters, and these reads were removed. The relative abundance (RA) of bacterial species was obtained from metagenomics sequencing via MetaPhlAn2 (35) with default parameters. Length-normalized RA of genes were assigned and obtained by similar mapping with Genome Multitool to the reference catalog of Li et al. (36) and to Kyoto Encyclopedia of Genes and Genomes Orthology entries (37), and these were then normalized to a sum of 1. RA of Kyoto Encyclopedia of Genes and Genomes modules and pathways were calculated by summation.

Statistical Analysis

The trial was designed with a target sample size of 234 participants assigned equally to PPT and MED groups on the basis of hypothesized difference of at least 0.1% (1.1 mmol/mol) in the reduction of HbA_{1c} levels (at 6 months) between the two diet groups, an estimated SD of 0.26 in HbA_{1c} reduction (38), two-sided α of 0.05, a power of 0.80, and an estimated withdrawal rate of 10%. Given three coprimary outcomes, statistical significance was defined by Bonferroni correction as $P < 0.05 / 3 = 0.0167$. This was done post hoc, after the data lock, upon the advice of a statistical advisory board. Analyses of 6-month changes in primary and secondary outcomes were conducted based on intention-to-treat principle, with the missing data assumed to be missing at random. Missing values were imputed using multiple imputation with chained equations (39). Imputation was based on all collected measurements (at 0, 3, and 6 months), and participant-specific characteristics, including sex, age, and baseline BMI. The treatment arm was not taken into account when doing imputations. For 12-month follow-up, we conducted a per-protocol analysis using the data collected from 177 participants who returned for follow-up.

CIs for change differences between treatments in primary and secondary outcomes (6-month changes) were assessed by using two-sample Welsh (unequal variance) *t* test, where the outcome distribution was assumed to be normal. For the ratio of total cholesterol to HDL cholesterol and HOMA-IR, which did not distribute normally, we used the Mann-Whitney nonparametric test. The comparison between treatments

in continuous variables over time (in multiple time points) was done using repeated-measures (mixed) ANOVA test to evaluate the interaction between time (within-subject factor) and diet treatment (between-subject factor), with the Greenhouse-Geisser correction used. The simple main effects of differences between the two diet groups at each time point were assessed using *t* test. Additionally, sensitivity analyses on primary outcomes were performed by using different appropriate imputation methods, and subgroup analyses by sex, age ($\leq$50 or $>$50 years), BMI ($\leq$25, 25 $<$ BMI $\leq$ 30, 30 $<$ BMI $\leq$ 35; $>$35 kg/m^2), and compliance (top 80% by diet scoring) were done post hoc, after the data lock. The "statsmodels" library v.0.10.1 of Python was used to assess CIs and *P* values of 6-month changes in primary and secondary outcomes, and "pingouin" library v.0.3.8 was used to perform the repeated-measures ANOVA test. SPSS software was used to perform multiple imputations.

RESULTS

Participants

Among 1,634 candidates screened, 339 were determined to be potentially qualified and invited to a further in-person screening visit to determine final eligibility according to measured FPG and HbA_{1c} at the trial's central laboratory. A total of 244 candidates were eligible according to the screening results and were invited to a profiling visit, which served as the start point of a run-in period of 2–4 weeks before the start of intervention (Fig. 1*B*). A total of 225 participants completed the run-in period and were randomly assigned to the MED or PPT diet arm. These participants were included in the intention-to-treat population and in the primary analysis. During the intervention, 25 participants (12 in MED and 13 in PPT) withdrew from the study for various reasons as detailed in Fig. 1*A*. In total, 88.9% of the cohort (100 participants in each arm) completed the 6-month intervention. A total of 177 participants (88.5% of those who completed the 6-month intervention; 94 from MED and 83 from PPT) also contributed follow-up data at 12 months. Notably, the difference in loss rates between groups at 12 months (6 participants in MED vs. 17 in PPT) might be related to a higher motivation of MED participants to attend the 12-month follow-up in order to get their personal predictions by the algorithm, as guaranteed at the time of enrollment, while PPT participants had no special incentive at that time point to attend the last follow-up meeting.

Baseline characteristics of the cohort are described in Table 1. In total, 58.7% of the participants were women, with mean ± SD age of 50 ± 7 years, BMI of 31.3 ± 5.8 kg/m^2 (range 19.7–54.4 kg/m^2), HbA_{1c} of 5.9 ± 0.2% (41 ± 2.4 mmol/mol), and FPG of 114 ± 12 mg/dL (6.33 ± 0.67 mmol/L). No significant differences were noted between the groups (Table 1).

Adherence

Self-reported adherence to the diet regimens was high and similar in both groups as assessed by dietary records and electronic follow-up questionnaires (Supplementary Fig. 2). Throughout the entire intervention period, participants logged a mean ± SD of 747 ± 299 meals (range 26–1,618 meals) and 242,000 ± 97,000 kcal (range 12,084–521,330 kcal) per person, with no significant difference noted between the groups (P = 0.85 and P = 0.62, respectively). In accordance with the trial aims of imposing no calorie restriction, participants in both groups had only a mild mean ± SD reduction in energy intake compared with baseline (−227 ± 307 kcal/day in MED and −263 ± 387 kcal/day in PPT), with no significant difference noted between the groups (P = 0.47) (Supplementary Fig. 2*F*). In terms of diet composition, the 6-month mean carbohydrate intake per day was 42.4% of energy in MED and 20.4% in PPT (P $<$ 0.001), protein intake per day was 20.0% of energy in MED and 21.7% in PPT (P = 0.001), fat intake per day was 34.8% of energy in MED and 55.8% in PPT (P $<$ 0.001), and saturated fat intake per day was 9.3% of energy in MED and 15.7% in PPT (P $<$ 0.001). The mean ± SD intake of dietary fiber per day was 15.8 ± 4.0 g/1,000 kcal in MED and 9.6 ± 3.3 g/1,000 kcal in PPT (P $<$ 0.001) (Supplementary Table 2). Overall, these dietary intakes represent a decrease in fat intake (mainly saturated fat) versus an increase in carbohydrates (including dietary fiber) and protein in the MED group compared with baseline. In the PPT group, there was an overall decrease in carbohydrate intake (including dietary fiber) and an increase in protein and fat intake (including saturated fat) compared with baseline (Supplementary Table 2). In accordance with the recommended foods on the MED diet, the most common foods consumed by MED participants included whole-wheat bread, rice, tahini, hummus, vegetables, and plain yogurt. Commonly consumed foods by PPT participants included tahini, eggs, nuts, high-fat cheese, vegetables, chicken, beef, and fish (Supplementary Fig. 2*A* and *B*, respectively).

As expected, the PPT diet resulted in a relatively low average carbohydrate content since dietary carbohydrates are considered a major factor of PPGR prediction. However, in these subjects with prediabetes, meal carbohydrate content explained only ~25% of the variability in glycemic response, while the PPT algorithm, which also included clinical and microbiome features, increased the variability explained to ~50% (Supplementary Figure 3*A* and *B*, respectively). Furthermore, for each person, meals with a similar amount of carbohydrates but different food components yielded different PPGR predictions and thus promoted different recommendations, such that two meals with the same amount of carbohydrates could generate different scores and result in distinct actual PPGR in the same participant (Supplementary Fig. 3*C*). Consistent with this notion, changes in dietary carbohydrate intake during the intervention only modestly correlated with changes in primary outcomes (Supplementary Fig. 3*D*–*F*). For example, for HbA_{1c}, the Pearson correlation was r = 0.274, and participants from both arms featured major variations in HbA_{1c} change (spread over a range of ~1.2% [13.1 mmol/mol] differences), even when grouped into similar narrow ranges of overall carbohydrate intake (Supplementary Fig. 3*F*).

Diet adherence assessed by scores from the feedback reports was also high, with a weekly average score per person of $>$80 (on a 0–100 scale) in both diet groups throughout the entire intervention period (Supplementary Fig. 2*G* and *H*). In monthly follow-up questionnaires, 62% of participants in the MED group and 81% in the

PPT group estimated their adherence to the diet regimen to be high or very high (scores 4 and 5, respectively, on a 1–5 scale) (Supplementary Fig. 2*C* and *D*). In terms of overall satisfaction from the dietary treatment (diet regimen and dietary follow-up) during the intervention, 75% of MED participants and 81% of PPT participants reported their satisfaction level to be high or very high (scores 4 and 5, respectively, on a 1–5 scale). As designed, there was no significant difference in physical activity level between the groups (mean ± SD 1.11 ± 1.70 and 1.15 ± 1.67 h/week of physical activity per participant logged on the app in the MED and PPT groups, respectively; $P = 0.51$).

Primary Outcomes

Among the 225 participants included in the primary analysis, there was a significant decrease in both time above 140 and HbA_{1c} at the end of the intervention. This difference was significantly greater in the PPT group than in the MED group (for time above 140: 95% CI between-group difference −1.29 to −0.66 h/day, $P < 0.001$; for HbA_{1c}: 95% CI between-group difference −0.14 to −0.02% [−1.5 to −0.2 mmol/mol], $P = 0.007$) (Fig. 2*A*). For OGTT, there was no significant difference between the groups in the 2-h change of CGM glucose levels (95% CI between-group difference −12.78 to 9.87 mg/dL [−0.71 to 0.55 mmol/L], $P = 0.8$) (Fig. 2*A*). In a sensitivity analysis of six imputation methods, the results remained statistically significant for time above 140 and HbA_{1c} (Supplementary Fig. 4). We also performed post hoc subgroup analyses for the difference between treatments in subgroups by age, BMI, sex, and compliance. Although the study was underpowered for assessing significant differences among subgroups, the results were mostly consistent with the findings of the main analysis and remained statistically significant in all subgroups for time above 140 and in subgroups of age >50 years, 25 < BMI ≤ 30 kg/m^2, women, and top 80% by compliance for HbA_{1c} (Supplementary Fig. 5).

The changes in primary outcomes over time are shown in Fig. 3*A*. Both time above 140 and HbA_{1c} decreased during the intervention period in both groups, with a greater reduction in the PPT group compared with the MED group ($P < 0.001$ for time above 140 and $P = 0.004$ for HbA_{1c}, for the interaction between diet group and time). For OGTT, there was no significant difference between groups ($P = 0.3$ for the interaction between diet group and time). At 6 months, the mean ± SD of time above 140 changed by −0.3 ± 0.8 h/day and −1.3 ± 1.5 h/day ($P < 0.001$ for the difference between groups), the mean ± SD of HbA_{1c} changed by −0.08 ± 0.19% (−0.9 ± 2.1 mmol/mol) and

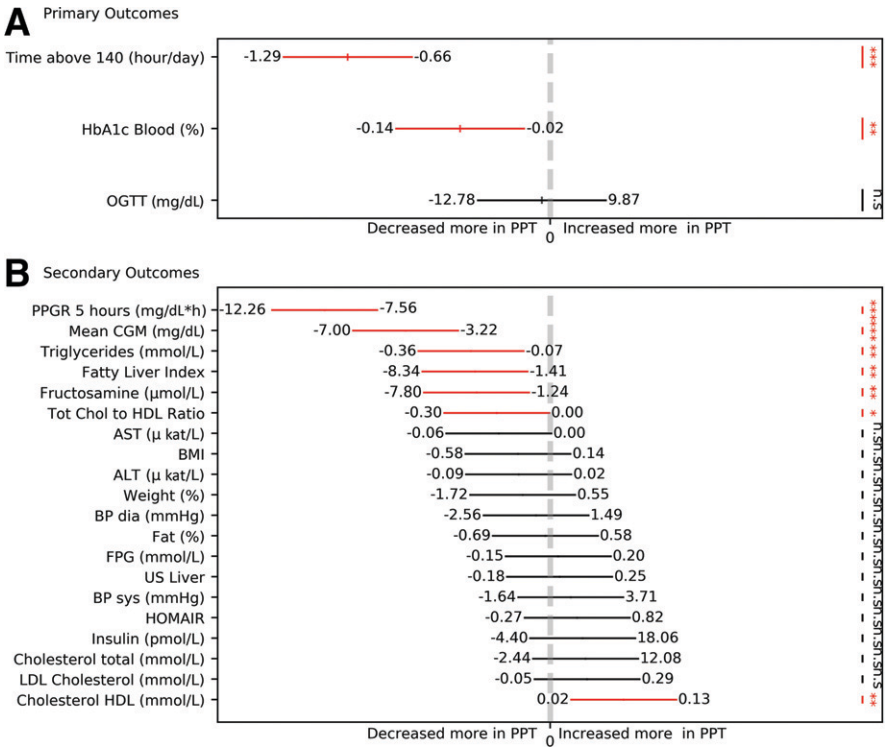

Figure 2—CIs for between-group change difference in primary and secondary outcomes. *A*: Primary outcomes. The 95% CI for between-group change difference in primary outcomes was calculated using *t* test. *B*: Secondary outcomes. The 95% CI for between-group change difference in secondary outcomes was calculated using *t* test in all measures except total cholesterol-to-HDL cholesterol ratio (tot chol to HDL ratio) and for HOMA-IR for which a Mann-Whitney nonparametric test was used. To convert OGTT and mean CGM glucose values from conventional units (mg/dL) to International System of Units (SI) (mmol/L), multiply by 0.05551. To convert FPG values from SI units (mmol/L) to conventional units (mg/dL), divide by 0.05551. To convert HDL, LDL, and total cholesterol values from SI units (mmol/L) to conventional units (mg/dL), divide by 0.02586. To convert triglyceride values from SI units (mmol/L) to conventional units (mg/dL), divide by 0.01129. To convert insulin values from SI units (pmol/L) to conventional units (µU/mL), divide by 6.945. To convert liver enzymes ALT and AST from SI units (µkat/L) to conventional units (U/L), divide by 0.017. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. BP dia, diastolic blood pressure; BP sys, systolic blood pressure; US, ultrasound.

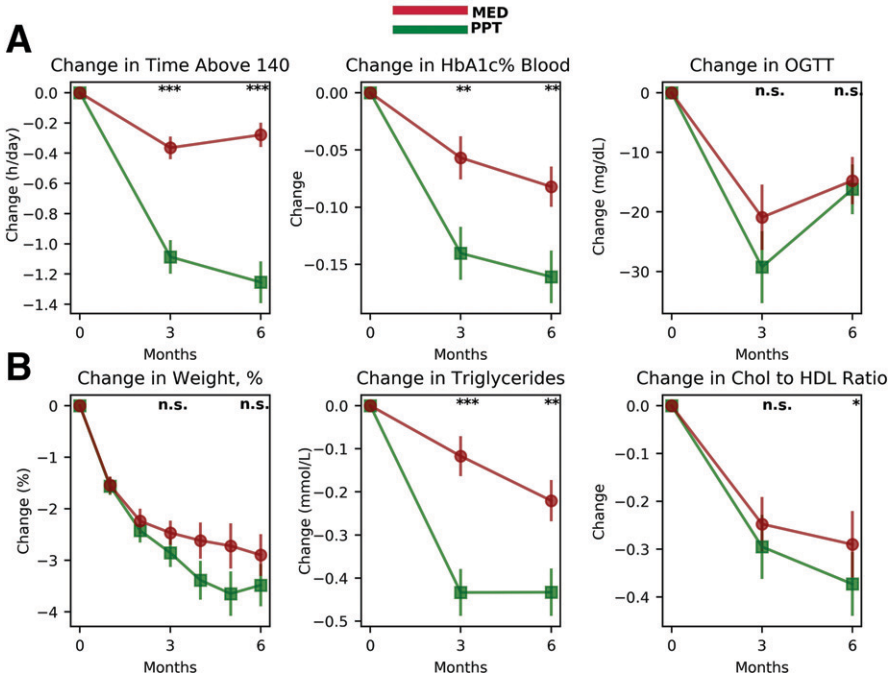

Figure 3—Changes in primary and selected secondary outcomes during the intervention phase. *A*: Changes in primary outcomes over time in the MED diet and PPT diet. Analysis was done based on intention-to-treat principle. To statistically evaluate the changes in outcomes over time, the repeated-measures ANOVA test was used, and the difference between groups at each time point was assessed by *t* test. For the interaction between diet group and time, $P < 0.001$ for time above 140, $P = 0.004$ for HbA_{1c}, and $P = 0.3$ for OGTT. *B*: Changes in three selected secondary outcomes over time in the MED diet and PPT diet. For the interaction between diet group and time, $P = 0.43$ for weight, $P < 0.001$ for triglycerides, and $P = 0.62$ for total cholesterol-to-HDL cholesterol ratio. To evaluate the differences between groups at each time point, a *t* test was used for weight and triglycerides, and a Mann-Whitney nonparametric test was used for total cholesterol-to-HDL cholesterol ratio. To convert OGTT CGM glucose values from conventional units (mg/dL) to International System of Units (SI) (mmol/L), multiply by 0.05551. To convert triglycerides values from SI units (mmol/L) to conventional units (mg/dL), divide by 0.01129. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$. Chol, cholesterol.

−0.16 ± 0.24% (−1.7 ± 2.6 mmol/mol) ($P = 0.007$ for the difference between groups), and the mean ± SD 2-h OGTT glucose levels changed by −14.8 ± 41.0 mg/dL (−0.82 ± 2.28 mmol/L) and −16.2 ± 44.0 mg/dL (−0.90 ± 2.44 mmol/L) ($P = 0.8$ for the difference between groups) in MED and PPT, respectively.

At the 12-month follow-up, the significant differences between the groups in time above 140 and HbA_{1c} were maintained (both $P < 0.001$ for the interaction between diet group and time). For OGTT, there was no significant difference between groups ($P = 0.3$ for the interaction between diet group and time). In the MED and PPT groups, the mean ± SD 12-month change in time above 140 was −0.2 ± 1.2 h/day and −1.4 ± 1.3 h/day ($P < 0.001$ for the difference between groups), and the mean ± SD 12-month change in HbA_{1c} was 0.04 ± 0.3% (0.4 ± 3.3 mmol/mol) and −0.11 ± 0.3% (−1.2 ± 3.3 mmol/mol) ($P = 0.008$ for the difference between groups), respectively (per-protocol analysis) (Supplementary Fig. 6).

Secondary Outcomes

Changes in secondary outcomes at the end of the intervention (6 months) are shown in Figs. 2*B* and 3*B* and Supplementary Figs 7 and 8. Glycemic outcomes of 6-month change in 5-h PPGR excursions, mean glucose levels (obtained from CGM), and fructosamine levels (blood test) decreased significantly more in PPT than in MED (for 5-h PPGR excursions: 95% CI between-group difference −12.3 to −7.6 mg/dL × h, mean ± SD change −3.4 ± 6.8 and −13.3 ± 10.0 mg/dL × h in MED and PPT, respectively, $P < 0.001$; for mean CGM glucose: 95% CI between-group difference −7.0 to −3.22 mg/dL [−0.39 to −0.18 mmol/L], mean ± SD change −3 ± 8 mg/dL [−0.17 ± 0.44 mmol/L] and −8 ± 9 mg/dL [−0.44 ± 0.50 mmol/L] in MED and PPT, respectively, $P < 0.001$; for fructosamine: 95% CI between-group difference −7.80 to −1.24 μmol/L, mean ± SD change −8.42 ± 11.97 and −12.94 ± 12.99 μmol/L in MED and PPT, respectively, $P = 0.007$). For other glycemic measurements, including FPG, insulin, and HOMA-IR, no significant differences were noted between the groups (Fig. 2*B*).

In serum lipid profile, triglycerides, HDL cholesterol, and total cholesterol-to-HDL cholesterol ratio improved significantly more in PPT than in MED at the end of intervention (for triglycerides: 95% CI between-group difference −0.36 to −0.07 mmol/L [−31.51 to −6.11 mg/dL], mean ± SD change −0.22 ± 0.51 and −0.43 ± 0.58 mmol/L [−19 ± 45 and −38 ± 51 mg/dL] in MED and PPT, respectively, $P = 0.003$; for HDL cholesterol: 95% CI between-group difference 0.02–0.13 mmol/L [0.77–4.9 mg/dL], mean ± SD change 0.02 ± 0.18 and 0.09 ± 0.22 mmol/L [0.8 ± 6.7 and 3.6 ± 8.5 mg/dL] in MED and PPT, respectively, $P = 0.003$; for total cholesterol-to-HDL cholesterol ratio: 95% CI between-group difference −0.3 to −0.00, mean ± SD change −0.29 ± 0.73 and −0.37 ± 0.71 in MED and PPT, respectively, $P = 0.025$) (Figs. 2*B* and 3*B*). For LDL cholesterol, there was no

significant difference between groups (95% CI between-group difference −0.05 to 0.29 mmol/L [−2.99 to 11.27 mg/dL], mean ± SD change −0.20 ± −0.66 and −0.08 ± 0.66 mmol/L [−7.7 ± 25.5 and −3.6 ± 25.5 mg/dL] in MED and PPT, respectively, $P = 0.2$). In FLI, there was a significant greater improvement in PPT than in MED (95% CI between-group difference −8.34 to −1.41; mean ± SD change of −7.4 ± 13.7 and −13.1 ± 14.3 in MED and PPT, respectively, $P = 0.005$) (Fig. 2*B* and Supplementary Figs. 7 and 8).

Additional secondary outcomes, including total cholesterol, blood pressure, liver enzymes (ALT, AST), hepatic ultrasound, and anthropometric measurements (weight, BMI, fat percentage) demonstrated significant reductions in each group compared with its own baseline, but these did not reach significant differences between groups (Fig. 2*B* and Supplementary Fig. 7). Average body weight was consistently lower in both diet groups every month throughout the intervention period but with no significant difference between the groups ($P = 0.43$ for the interaction between diet group and time). At the end of the intervention, the average weight loss observed was 2.9% and 3.5% of baseline weight in MED and PPT, respectively ($P = 0.31$) (Fig. 3*B*).

The changes in all secondary outcomes over time are shown in Fig. 3*B* and Supplementary Fig. 8. Overall, triglycerides and HDL cholesterol improved during the intervention period in both groups, with a greater improvement in the PPT group compared with the MED group ($P < 0.001$ for triglycerides and $P = 0.01$ for HDL cholesterol for the interaction between diet group and time). For other secondary outcomes, there was no significant interaction between diet group and time.

At 12-month follow-up, the significant difference between groups in mean CGM glucose and fructosamine were maintained ($P < 0.001$ for mean CGM glucose and $P = 0.007$ for fructosamine, for the interaction between diet group and time). For mean CGM glucose, the mean ± SD 12-month change was −2 ± 10 and −9 ± 7 mg/dL (0.11 ± 0.55 and 0.50 ± 0.39 mmol/L, $P < 0.001$); for fructosamine, the change was −4.0 ± 20.0 and −11.5 ± 19 μmol/L ($P = 0.02$) in MED and PPT, respectively. In other secondary outcomes, there was no significant difference between the groups at 12 months (Supplementary Fig. 6).

Adverse Events

Dietary Related

During the monthly individual dietary follow-up meetings, dietitians asked participants about tolerance and side effects related to the diet, including bloating, fullness, indigestion, or any other diet-related symptoms. Only temporary complaints were reported, and these were solved satisfactorily by standard dietary advice on eating patterns. In the monthly follow-up questionnaires, overall in 14% and 16% of questionnaires, temporary inconveniences or changes in defecation habits (including constipation or diarrhea) were reported by MED and PPT participants, respectively.

CGM Related

A small proportion of participants (∼5%) developed CGM-related skin symptoms, including allergy, itching, rash, or erythema. In some cases, the symptoms were resolved by the use of barrier products (e.g., Cavilon wipes) or drug therapy (e.g., Fenistil gel or hydrocortisone cream) as prescribed or simply by relocating the device to another area of the skin such that the effects were maintained at a tolerable, background level. In other cases, although the adverse events were generally mild or moderate, the longevity of the symptoms, despite use of treatment, contributed to participants' decision to stop the connections to CGM sensors. In these cases, we used the CGM data collected up to that time point and continued to collect other trial measures as usual, including dietary records, blood tests, and all other measurements.

CONCLUSIONS

In this randomized clinical trial of a 6-month dietary intervention in adults with prediabetes, advice to follow a diet aimed at lowering PPGR based on personalized predictions (PPT diet) resulted in greater improvements of glycemic control, as measured by primary outcomes of total daily time of glucose levels >140 mg/dL (7.8 mmol/L) and HbA_{1c}, compared with a MED diet. Other glycemic and metabolic measures also improved significantly more with the PPT diet, including 5-h PPGR excursions, mean CGM glucose, blood fructosamine, FLI, blood triglycerides, HDL cholesterol, and total cholesterol-to-HDL cholesterol ratio, demonstrating another potential benefit of the PPT approach in reducing cardiometabolic risks in prediabetes (1). These findings suggest that a dietary strategy focused on PPGR reductions is safe and effective for helping to improve glycemic control in prediabetes. At 12-month follow-up, the significant difference in glycemic control between the groups was maintained, suggesting that personalized PPGR-targeting diets may have long-term efficacy in improving blood glucose levels.

Our findings support the general importance and beneficial effects of lifestyle modifications for diabetes prevention in prediabetes, as previously demonstrated in the DPP (4). The DPP study, which used intensive behavioral modification strategies focused on calorie reduction, increased physical activity, and weight loss, reported a per-protocol 6-month reduction in HbA_{1c} of ∼0.1% (1.1 mmol/mol) in the lifestyle intervention arm compared with our only slightly smaller reduction of 0.08% (0.9 mmol/mol) in the MED group and larger reduction of 0.18% (2 mmol/mol) in the PPT group (per-protocol analysis as in DPP). The significant improvements achieved in glycemic control in the present trial, despite a modest weight loss in both diet groups (−2.5 kg in MED and –3.3 kg in PPT) compared with DPP (−5.6 kg in the lifestyle intervention arm), suggest that noncalorie-restricted interventions directly targeting reductions in PPGRs may be an effective treatment for improving glycemia in prediabetes, especially among those who find it difficult to follow a calorie-restricted regimen with additional physical activity and weight loss requirements.

While glycemia improved as measured by both time above 140 and HbA_{1c}, the results of a single OGTT at 6 months were not significantly different between the groups. This may be due to significant variability in the postprandial response to a single standard carbohydrate challenge compared with multiple other real-world meals over time. Alternatively, other biological mechanisms or study methodological aspects may explain this result, which

requires further investigation in future studies.

Advantages of this trial design include the use of CGM throughout the entire intervention period, which allowed us to directly measure the effects of every meal on glucose levels while evaluating the importance of long-term reductions in PPGRs to metabolic health. As such, and in contrast to blood tests, which provide a single point-of-care measure that may be sensitive to test errors, long-term CGM data may provide a more accurate reflection of the glycemic state. Indeed, the use of CGM in the research setting and clinical practice for diabetes management is becoming more common (40). Additionally, full dietary records logged by the study participants using a designated smartphone app allowed us to closely monitor compliance and diet adherence by participants in both arms while de facto assessing the distinction between the two dietary treatments. The fact that the two groups had a similar number of calories reported on average during the intervention, along with similar modest weight loss rates observed in both groups, suggests that the dietary records were indeed reliable. We find that this approach enables a major advantage. Typical dietary intake assessment in clinical trials is done by using food frequency questionnaires or occasional 24-h recalls and food diaries, which inaccurately assess actual dietary consumption throughout the intervention period, thereby limiting the ability to draw precise conclusions about health outcomes of different dietary approaches. Finally, the single-blind feature of this study is also unique to dietary interventions and might have contributed to participants' overall compliance. Since participants were blinded, the fact that more people in the PPT group (81%) estimated their adherence to the diet regimen to be high compared with the MED group (62%), suggests a potential benefit of the PPT diet as a feasible treatment compared with standard, one-size-fits-all recommendations.

Our study also has several limitations. We compared only two dietary approaches: a MED diet and our algorithm-based PPT diet. Since carbohydrate content of the meal constitutes an important component in the PPGR prediction algorithm, the PPT diet resulted in lower carbohydrate content on average compared with the MED diet. Thus, it is possible that the beneficial effects observed in the PPT diet are mainly driven by the lower carbohydrate content. However, we speculate that this is not the case because the change in dietary carbohydrate intake during the intervention was not highly correlated with primary clinical outcomes (e.g., for HbA_{1c} change, Pearson correlation $r = 0.274$), and participants in both arms had marked differences in HbA_{1c} change (spread over a range of $\sim$1.2% [13.1 mmol/mol] differences), even when grouped based on a similar narrow range of dietary carbohydrate change (Supplementary Fig. 3*F*). Furthermore, other studies demonstrated that low-carbohydrate diets are not superior to high-carbohydrate diets in terms of long-term glycemic control or weight management (14,15). In a systematic review and meta-analysis of dietary carbohydrate restriction in patients with type 2 diabetes, Snorgaard et al. (15) demonstrated that low-carbohydrate diets had a similar long-term ($\geq$1-year) effect on HbA_{1c} levels as high-carbohydrate diets. Gardner et al. (14) showed in their 1-year dietary intervention in overweight adults that a low-fat versus low-carbohydrate diet resulted in no significant difference in weight loss or other metabolic measures. Finally, beyond the overall macronutrient composition of the diet, the PPT diet enabled an individualized set of recommendations at the level of meals, regardless of their carbohydrate content, such that identical meals yielded different recommendation levels for different people (Supplementary Fig. 2*E*), and meals with the same amount of carbohydrates, but different food components, yielded different recommendation levels within the same person (Supplementary Fig. 3*C*). Nevertheless, differences between our algorithm-based PPT diet and other low-carbohydrate diets should be further explored. Other methodological limitations include the home use of OGTT, which is not standardized and, therefore, may yield inaccurate and "noisy" results; self-enrollment of participants through a website, which may have created a potential selection bias to the most adherent patients compared with enrollment through general clinic visits; and imbalance between the groups in terms of incentives to attend the final 12-month follow-up, which may have contributed to the higher attrition rate in the PPT group compared with the MED group at that time point.

These limitations notwithstanding, in this randomized clinical trial in prediabetes, a personalized PPT diet improved glycemic control significantly more than a MED diet. These findings may have implications for prediabetes dietary advice in clinical practice and potentially for other metabolic disorders, including type 2 diabetes, metabolic syndrome, and nonalcoholic fatty liver disease, pending rigorous clinical testing to generate evidence of benefit in these clinical conditions.

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No pharmaceutical manufacturers or other companies from the industry, including the sponsors mentioned above, contributed to the planning, design, or conduct of the trial. The analyses presented here were performed by Weizmann scientists independent of the sponsors. The scientists have the right to publish regardless of the outcome.

Author Contributions. O.B.-Y. was the clinical trial lead, oversaw the conduct of the study, and wrote the manuscript. O.B.-Y. and A.G. designed and directed the project and data collection and analyses, interpreted the results, and contributed equally to the study.

O.B.-Y., A.G., M.R., and A.W. conceived the study and designed the intervention. O.B.-Y., M.R., N.Kor., N.C.D., T.T.S., and K.S. provided dietary recommendations and personal dietetic support throughout the intervention to all study participants. A.G. directed all computational aspects of the study, with support from D.K. S.S. was the medical lead of the study with support from N.Z. B.C.W. and N.Kos. coordinated participant recruitment and management throughout the intervention and follow-up. A.W., with support from M.L.P., developed protocols and directed and performed microbiome sample sequencing. E.E. and E.S. conceived and directed the project and analyses, designed the analyses, interpreted the results, and wrote the manuscript. All authors reviewed and approved the manuscript and vouch for the accuracy and completeness of the data. E.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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