FEATURE ARTICLE

Effect of a Dietary Intervention on Insulin Requirements and Glycemic Control in Type 1 Diabetes: A 12-Week Randomized Clinical Trial

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This study compared the effects of a low-fat vegan diet to those of a portion-controlled diet in people with type 1 diabetes. Over 12 weeks, the average total daily dose of insulin decreased significantly and insulin sensitivity increased significantly in the vegan group, while no significant changes were observed in the group receiving the portion-controlled diet. Total and LDL cholesterol decreased in the vegan group, as did the ratio of blood urea nitrogen to creatinine. A1C decreased in both groups. These findings suggest that a low-fat vegan diet may yield improvements in insulin sensitivity, insulin requirements, glycemic control, and markers of cardiovascular and renal health compared with a portion-controlled diet in people with type 1 diabetes.

Type 1 diabetes is a chronic disease characterized by hyperglycemia resulting from the destruction of insulin-producing pancreatic β-cells. The prevalence of type 1 diabetes is 0.5% among adults in the United States (1), with ∼40,000 new cases diagnosed each year (2). Type 1 diabetes affects individuals of all ages; 18% are <20 years of age at diagnosis, 64% are between 20 and 59 years of age, and 19% are ≥60 years of age (3). Two recent analyses projected a 60–107% increase in the prevalence of type 1 diabetes by 2040 (3,4), which suggests an environmental component in the development of the disease.

The mean annual cost of type 1 diabetes care increased by >50% from 2012 and 2016, primarily because of rising costs of insulin and diabetes monitoring equipment (5). The development of novel treatments for type 1 diabetes is urgently needed for both health and financial reasons.

In theory, dietary interventions are inexpensive and can be implemented at home, but the most effective approaches are still to be identified. Dietary recommendations for people with type 1 diabetes typically emphasize carbohydrate counting, limited consumption of processed and sugar-sweetened foods and drinks, and increased intake of whole grains, fruits, vegetables, and legumes (6) because these fiber-rich foods reduce postprandial blood glucose levels (7).

Individuals with type 1 or type 2 diabetes are at increased risk for cardiovascular disease and premature mortality. A plant-based diet has been shown to improve glycemic control and insulin resistance in people with type 2 diabetes (8,9) and to improve β-cell function in overweight adults (10). A plant-based diet also improves body weight, plasma lipids, and blood pressure, all of which are cardiovascular risk factors. Two case studies of individuals with type 1 diabetes suggested increased insulin sensitivity, reduced insulin dose, and improved cardiovascular risk factors after adopting a plant-based diet (11). However, no randomized clinical trial has tested the efficacy of this diet in people with type 1 diabetes.

This 12-week randomized clinical trial compared the effects of a conventional portion-controlled, carbohydrate-controlled diet to those of a low-fat vegan diet without restrictions on carbohydrates or portions on insulin requirements, insulin sensitivity, glycemic control, plasma

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lipid levels, and indices of renal health in people with type 1 diabetes.

Research Design and Methods

Study Design and Eligibility

The study was conducted between August 2021 and November 2022 in Washington, DC, using a single-center, randomized, open parallel study design. Men and women with diagnosed type 1 diabetes who were ≥18 years of age and had a stable insulin regimen for the previous 3 months were enrolled. Individuals with type 2 or gestational diabetes; a BMI ≥40 kg/m^2; an A1C ≥12.0%; smoking, alcohol, or drug abuse; a current pregnancy or lactation; or evidence of an eating disorder were excluded. The study protocol was approved by the Chesapeake Institutional Review Board on 3 February 2021 (protocol number Pro00048903). All participants gave written informed consent.

Randomization and Study Groups

Participants were randomly assigned in a 1:1 ratio to the vegan group (n = 29), which was asked to follow a low-fat vegan diet, or the portion-controlled group (n = 29), which was asked to follow a portion-controlled diet. The low-fat vegan diet (∼75% of energy from carbohydrates, 15% from protein, and 10% from fat) consisted of vegetables, grains, legumes, and fruits, with no limits on calories or carbohydrates. Participants were instructed to avoid animal products and added fats and to favor foods with a low glycemic index. No meals were provided. The portion-controlled diet included individualized diet plans that reduced daily energy intake by 500–1,000 kcal/day for overweight participants (BMI >25 kg/m^2) and kept carbohydrate intake stable over time. This diet derived 60–70% of energy from carbohydrate and monounsaturated fats, 15–20% from protein, and <7% from saturated fat and contained ≤200 mg/day of cholesterol. Both groups received weekly online nutrition education classes and support from registered dietitians. The content of all meals was recorded using the Cronometer mobile application (Cronometer, Inc., Revelstoke, British Columbia, Canada).

Participants in both groups took a vitamin B_{12} supplement (100 μg/day). For both groups, alcoholic beverages were limited to one per day for women or two per day for men. All study participants were asked not to alter their exercise habits and to continue their preexisting medication regimens for the duration of the study except as modified by their personal physicians. Insulin doses were reduced in cases of repeated hypoglycemia. Participants recorded their carbohydrate intake and insulin dose for each meal and calculated the carbohydrate-to-insulin ratio for each meal. In cases of repeated hypo- or hyperglycemia, insulin doses were adjusted based on the actual carbohydrate-to-insulin ratio.

Outcomes

All measurements were performed at baseline and 12 weeks on an outpatient basis.

The primary clinical outcomes were insulin requirements (total daily dose [TDD] of insulin), insulin sensitivity, and glycemic control (A1C). TDD was calculated as a sum of basal and bolus insulin units injected per day. Insulin sensitivity was assessed by the carbohydrate-to-insulin ratio, which was calculated as the number of total grams of dietary carbohydrate to total units of insulin administered. For these variables, an average from three consecutive days (two weekdays and one weekend day) was used. Dietary intake data were collected and analyzed by a staff member certified in Nutrition Data System for Research, v. 2021-22, developed by the Nutrition Coordinating Center of the University of Minnesota in Minneapolis (12). Physical activity was assessed by the International Physical Activity Questionnaire (13).

Food acceptability was assessed using a validated Food Acceptability Questionnaire, which consists of 12 questions related to the foods eaten during the preceding 2 weeks, using 7-point response scales (14).

Height at baseline was self-reported. Weight was measured using self-calibrating digital scales (Renpho Model ES-CS20M, Anaheim, CA), which were accurate to 0.05 kg. Continuous glucose monitoring (CGM) was performed throughout the study using a Dexcom G6 CGM system (Dexcom, San Diego, CA).

All laboratory assessments were made after fasting 10–12 hours overnight with only water allowed ad libitum. A1C was measured by turbidimetric inhibition immunoassay. Lipid concentrations were measured by enzymatic colorimetric methods. All test kits were made by Roche (Basel, Switzerland). Blood urea nitrogen (BUN) and creatinine were measured by an enzymatic rate method and Jaffe kinetic method, respectively.

Statistical Analysis

The sample size was estimated using a power analysis with an α value of 0.05 to test for group differences.

Fifteen participants per group were deemed necessary to yield 80% power to demonstrate a significant difference for an effect size of 0.61 units/day. To account for an estimated attrition rate of 20%, 19 participants were required for each group, for a total of 38 participants.

For baseline characteristics, between-group *t* tests were performed for continuous variables and χ^2 or Fisher exact tests were performed for categorical variables. The analysis included all participants with complete data at baseline and week 12. A repeated-measure ANOVA model was used with between-subject and within-subject factors and interactions. Factor group, subject, and time were included in the model. Interaction between group and time was calculated for each variable. Within each group, paired comparison *t* tests were calculated to test whether the changes from baseline to 12 weeks were statistically significant. Pearson correlations were used to test the association between changes in insulin dose and insulin sensitivity and changes in body weight. A standard linear regression model was fit using change in body weight as a single predictor of changes in TDD and insulin sensitivity in both groups combined. The statistician was blinded to the interventions. All results are presented as mean with 95% CIs.

Results

Participant Characteristics

Of 377 people who completed an initial screening, 58 met participation criteria and were randomly assigned to the vegan ($n = 29$) or portion-controlled ($n = 29$) groups, and 35 participants completed the whole study (18 participants in the vegan group and 17 in the portion-controlled group) (Figure 1). Dropout rates were comparable in both groups and were mostly related to the use of CGM and challenges in recording meal intake and insulin dosing for each meal throughout the study.

Demographic characteristics of the study completers are shown in Table 1, and those of study dropouts are provided in Supplementary Table S1. Among study completers, there were no differences between the study groups in any characteristics. All of the dropouts from the portion-controlled group were White and non-Hispanic, whereas the racial and ethnic distribution of the dropouts from the vegan group was more diverse. Dietary intake, physical activity, anthropometric and laboratory variables, insulin use and insulin sensitivity, as well as the CGM data in response to 12 weeks of each diet are shown in Supplementary Table S2.

Dietary Intake and Physical Activity

There was no significant change in energy intake or physical activity in either group. Carbohydrate consumption increased in the vegan group by an average of 111 g/day ($P = 0.004$) compared with no significant change in the portion-controlled group (−38 g/day, $P = 0.17$; treatment effect +149 g/day, 95% CI +61 to +238 g/day, $P = 0.002$). Fat intake decreased in the vegan group (treatment effect −25.0 g/day, 95% CI −48.4 to −1.5, g/day, $P = 0.04$), and fiber consumption increased in the vegan group (treatment effect +18.8 g/day, 95% CI +10.4 to +27.3 g/day, $P = 0.04$).

Food Acceptability

Both diets were rated as acceptable and were comparable in ratings for ease of purchase and dining out. The participants liked the vegan diet better ($P < 0.001$) and gave it higher scores in taste ($P < 0.001$), appeal ($P < 0.001$), ease of preparation ($P = 0.02$), effort ($P = 0.03$), satisfaction after the meals ($P < 0.001$), satisfaction with the diet ($P < 0.001$), and food costs ($P < 0.001$), and they found it less boring ($P < 0.001$).

Body Weight and BMI

Body weight decreased by 5.2 kg in the vegan group ($P < 0.001$) compared with a nonsignificant change in body weight in the portion-controlled group (treatment effect −4.3 kg, 95% CI −6.1 to −2.4 kg, $P < 0.001$). Correspondingly, BMI decreased by 1.9 kg/m^2 in the vegan group ($P < 0.001$) compared with a nonsignificant change in body weight in the portion-controlled group (treatment effect −1.6 kg/m^2, 95% CI −2.2 to −0.9 kg/m^2, $P < 0.001$).

Insulin Use, Insulin Sensitivity, and Glycemic Control

Insulin TDD decreased by 12.1 units/day in the vegan group ($P = 0.007$) compared with no significant change in the portion-controlled group (−1.4 units/day, $P = 0.66$; treatment effect −10.7, 95% CI −21.3 to −0.2, $P = 0.046$) (Figure 2*A*). Total insulin dose per kg of body weight decreased by 24% (−0.15 units/kg in the vegan group, $P = 0.047$), whereas there was no significant change in the portion-controlled group (−0.01 units/kg, $P = 0.81$; treatment effect −0.14, 95% CI −0.27 to −0.01, $P = 0.03$). Basal insulin doses decreased in both groups (vegan group −7.7 units/day, $P = 0.009$, and portion-controlled group −4.5 units/day, $P = 0.03$; treatment effect −3.2, 95% CI −9.9 to +3.5,

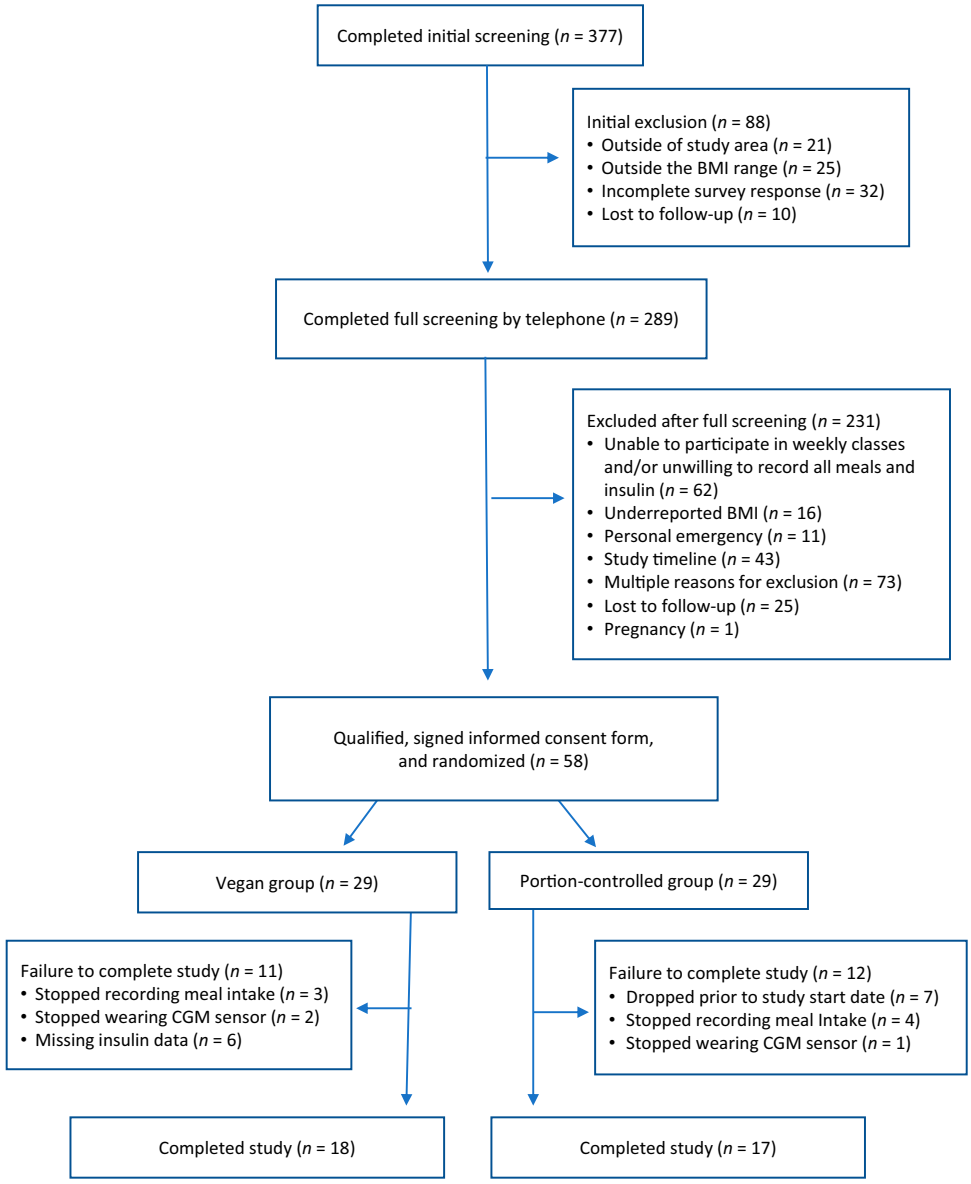

FIGURE 1 Trial participant flowchart.

$P = 0.3$). Bolus insulin doses did not change significantly in either group. Insulin sensitivity, assessed by the carbohydrate-to-insulin ratio, increased in the vegan group by 6.6 g of carbohydrate per unit of insulin on average ($P = 0.002$) compared with no significant change in the portion-controlled group (−1.6, $P = 0.26$; treatment effect +8.2, 95% CI +3.6 to +12.8, $P = 0.001$) (Figure 2*B*).

Changes in insulin TDD and insulin sensitivity correlated with changes in body weight ($r = +0.45$, $P = 0.008$ and $r = -0.44$, $P = 0.009$, respectively), and these associations remained significant after adjusting for baseline BMI ($r = +0.44$, $P = 0.01$ and $r = -0.48$, $P = 0.005$, respectively). A 1-kg weight loss was associated with a 2.16-unit decrease in insulin TDD and with a 0.9-unit increase in insulin sensitivity.

Changes in insulin sensitivity correlated with changes in carbohydrate and fiber intake ($r = +0.82$, $P < 0.001$ and $r = +0.83$, $P < 0.001$, respectively), even after adjusting for changes in body weight ($r = +0.81$, $P < 0.001$ and $r = +0.81$, $P < 0.001$, respectively). Every 10-g increase in carbohydrate and fiber consumption was associated with an increase in insulin sensitivity by 0.43 and 4.23 g of carbohydrate per unit of insulin, respectively, and, after adjusting for changes in body weight, by 0.42 and 4.29, respectively.

A1C decreased by 0.8 absolute percentage points in the vegan group ($P < 0.001$) and by 0.6 absolute percentage points in the portion-controlled group ($P = 0.002$; treatment effect −0.2, 95% CI −0.7 to +0.2, $P = 0.34$). There were no differences between the groups in mean

TABLE 1 Baseline Demographics of the Study Completers

Variable	Vegan Group (n = 18)	Portion-Controlled Group (n = 17)	P
Age, years	51.4 ± 14.4	47.5 ± 15.5	0.45
Age range, years	19–79	21–72	
Sex			0.69
Male	3 (17)	4 (24)	
Female	15 (83)	13 (76)	
Race/ethnicity			0.56
Black, non-Hispanic	2 (11)	0 (0)	
Asian, Pacific Islander	2 (11)	2 (12)	
Native American, non-Hispanic	1 (6)	0 (0)	
White, non-Hispanic	13 (72)	14 (82)	
White, Hispanic	0 (0)	1 (6)	
Marital status			0.13
Not married	5 (28)	9 (53)	
Married	13 (72)	8 (47)	
Education			0.17
High school, partial or graduate	2 (11)	0 (0)	
College, partial or graduate	9 (50)	7 (41)	
Graduate degree	7 (39)	10 (59)	
BMI, kg/m^2	25.3 ± 3.0	27.0 ± 5.9	0.31

Data are mean ± SD or n (%) unless otherwise noted.

glucose, coefficient of variability, time in range, or mean amplitude of glycemic excursion.

Indices of Cardiovascular and Renal Health

At baseline, plasma lipid concentrations were generally in the normal range in both groups. Nonetheless, total cholesterol decreased by 32.3 mg/dL in the vegan group (P <0.001) and by 10.9 mg/dL in the portion-controlled group (P = 0.03; treatment effect −21.4 mg/dL, 95% CI −35.6 to −7.2, P = 0.004). LDL cholesterol decreased by 18.6 mg/dL in the vegan group (P <0.001) and did not change significantly in the portion-controlled group, with no significant difference between the groups (treatment effect −9.1 mg/dL, 95% CI −22.6 to +4.5, P = 0.18). HDL cholesterol decreased by 12.4 mg/dL in the vegan group compared with no change in the portion-controlled group (treatment effect −9.0 mg/dL, 95% CI −14.5 to −3.4, P = 0.003). Triglycerides did not change significantly in either group.

BUN decreased by 6.0 mg/dL in the vegan group (P <0.001) and did not change significantly in the portion-controlled group (treatment effect −5.2 mg/dL, 95% CI −7.9 to −2.5 mg/dL, P <0.001). The BUN-to-creatinine ratio decreased by 5.1 mg/dL in the vegan group (P <0.001) and did not change significantly in the portion-controlled group (treatment effect −6.7, 95% CI −10.7 to −2.6, P = 0.002).

Discussion

In this study, a low-fat vegan diet with no limits on caloric or carbohydrate intake reduced insulin requirements by 28%, increased insulin sensitivity by 127%, and improved glycemic control in people with type 1 diabetes compared with a portion-controlled diet. These results are in line with previous studies in type 2 diabetes, which showed that plant-based diets increased insulin sensitivity, reduced the need for diabetes medications, and improved glycemic control (8,9). Significant improvements were also noted in plasma lipids and indices of renal function.

The primary defect in type 1 diabetes is the absence of pancreatic insulin secretion. However, individuals with type 1 diabetes may also have significant insulin resistance, just as people with type 2 diabetes and many otherwise healthy individuals do. Insulin resistance is strongly influenced by diet, and particularly dietary fat. A crucial point in the physiology of glycemic control is that dietary fat increases hepatocellular and

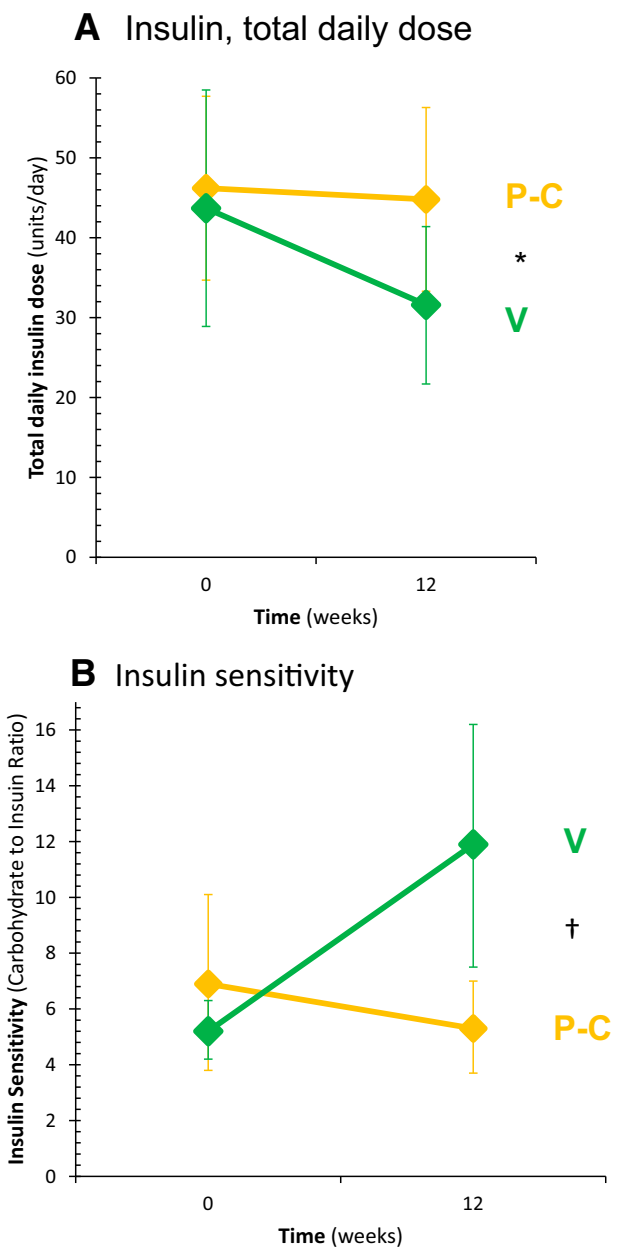

FIGURE 2 Changes in insulin total daily dose (*A*) and insulin sensitivity (*B*) in the vegan (V) and portion-controlled (P-C) groups. *P <0.05. †P <0.01.

intramyocellular lipids, which in turn increase insulin resistance, with both acute and chronic effects on glycemic control. The effect of dietary fat on insulin resistance is central to type 2 diabetes, but it also plays an important, if under-appreciated, role in type 1 diabetes.

The improvements in glycemic control were strongly associated with weight loss, even after adjusting for baseline BMI. A low-fat vegan diet has been shown to reduce body weight and hepatocellular and intramyocellular lipids in overweight people (15).

However, insulin dose units per kg of body weight decreased by 24% on the low-fat vegan diet, so weight loss is apparently not an adequate explanation for these effects. In addition, the low fat content of the vegan diet is likely to play a significant role at each mealtime because dietary fat has been shown to have a major impact on insulin sensitivity and insulin requirements in people with type 1 diabetes. A crossover study in people with type 1 diabetes demonstrated that a single high-fat meal (60 g fat) resulted in hyperglycemia and significantly higher insulin requirements over the subsequent 18 hours compared with a low-fat meal (10 g fat) with the same carbohydrate and protein content (16). Another randomized within-subject trial tested the effects of dietary fat quantity and quality on postprandial glycemia and insulin dose. Adults with type 1 diabetes consumed meals containing 45 g carbohydrate with 0, 20, 40, or 60 g fat (either saturated, monounsaturated, or polyunsaturated). The addition of fat to the meals resulted in significant late-postprandial hyperglycemia and increased insulin requirements 2–5 hours after meal ingestion regardless of the type of fat consumed (17). This result is consistent with previous findings that free fatty acids induce insulin resistance in humans by inhibition of glucose transport and phosphorylation, which is then followed by an reduction of ∼50% in the rate of muscle glycogen synthesis and glucose oxidation (18).

Furthermore, a systematic review has demonstrated that both dietary fat and dietary protein have late-postprandial glucose-raising effects in people with type 1 diabetes (19). The addition of 30 g of fat to 30 g of carbohydrate increased postprandial glycemia by 1.8 mmol/L in the subsequent 5 hours. Similarly, the addition of 40 g protein to 30 g carbohydrate increased late-postprandial glycemia by 2.4 mmol/L. When both 30 g fat and 40 g protein were added to the meal with 30 g carbohydrate, postprandial glycemia increased by 5.4 mmol/L, suggesting that the effects of fat and protein are additive (20). High protein intake in people with type 1 diabetes has been shown to reduce branched chain amino acid uptake in the muscle and increase the uptake of glucogenic amino acids in the liver, thereby increasing endogenous glucose production and exacerbating hyperglycemia (21,22).

Although increased protein intake promotes late-postprandial hyperglycemia, reduced protein intake has been shown to decrease postprandial glucose levels and reduce insulin requirements in people with type 1 diabetes. A 10-day protein-restricted diet resulted in a 30%

decrease in average blood glucose concentrations and a concurrent 25% decrease in both basal and bolus insulin doses. This effect appears to be mediated in part by decreased hepatic gluconeogenesis (23).

In addition to glycemic control, people with type 1 diabetes benefit from maintaining a healthy body weight to prevent the development of diabetes complications. In a T1D Exchange clinic registry study, about half of adults with type 1 diabetes had excess weight. More specifically, 29% were overweight and 20% had obesity (24). These findings highlight the importance of weight management in people with type 1 diabetes. In this context, the weight loss of 7.8% body weight in the vegan group observed in this study, which brought the average BMI of the vegan group from the overweight to the healthy range, is clinically significant. Because plant-based diets have been proven beneficial for weight management (25), their therapeutic value is increased for people with type 1 diabetes.

Geisinger Health System data from 2004–2018 showed that, after adjusting for age differences, people with type 1 diabetes were almost twice as likely to develop chronic kidney disease than those with type 2 diabetes, and obesity significantly increased the odds in type 1 diabetes (26). Interestingly, in the present trial, BUN levels and the ratio of BUN to creatinine, although in the normal range for most participants, significantly decreased for those on the vegan diet, suggesting improved kidney function.

Type 1 diabetes is associated with an increased risk of cardiovascular morbidity and mortality (27). During 30 years of follow-up in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (28), higher insulin doses were significantly associated with a less favorable cardiometabolic risk profile in people with type 1 diabetes (i.e., higher BMI, pulse rate, and triglycerides and lower HDL cholesterol). An increase of 0.1 unit/kg/day in insulin dose was associated with a 6% increased risk of any cardiovascular disease.

In light of this information, the lower insulin requirements and improved cardiometabolic outcomes, including body weight, A1C, and blood lipids, that were observed on the low-fat vegan diet in the current study represent a significant step toward improving cardiometabolic health in people with type 1 diabetes and are consistent with the beneficial effects of plant-based diets on cardiometabolic health in people with type 2 diabetes (29). The insulin daily dose per kg of body weight was reduced by 0.15 units/kg on the vegan diet, which corresponds to a 9% reduction in cardiovascular risk. In addition, the decrease in A1C by 0.8 absolute percentage points corresponds to reduced risks of myocardial infarction by 12% and of cardiovascular disease by 8.8–12% (30–32). The 20% reduction in LDL cholesterol indicates a reduction in the risk for a major cardiac event, including heart attack and stroke, by ∼20% (33).

A low-fat vegan diet has been shown to lead to angiographic improvements in atherosclerotic heart disease (34,35), with reductions in total, LDL, and HDL cholesterol. The decrease in HDL cholesterol in these studies, and observed in the present investigation, is a response to a more pronounced reduction in LDL cholesterol, which signals a lower demand for reverse cholesterol transport by HDL cholesterol.

Strengths and Limitations

The strengths of this study include the randomized parallel design, in which all participants started simultaneously, allowing investigators to rule out possible effects of seasonal fluctuations in the diet. The study duration was reasonably long, providing sufficient time for adaptation to the diet. We used a physiological measure of insulin sensitivity, which is clinically relevant, and all the meals were tracked using the Cronometer mobile application. The use of a CGM system helped participants minimize risks of repeated hypoglycemia and extended hyperglycemia. Given that the participants were living at home and preparing their own meals or eating at restaurants, our results are applicable outside of the research setting, in free-living conditions. Both diets were well accepted, and the participants on the vegan diet gave it higher ratings overall and reported being more satisfied with it responses from those on the portion-controlled diet, indicating the potential for wide use of the vegan diet.

The study also has important limitations. Dietary intake was calculated based on self-reported diet records, which have well-known limitations (36). Furthermore, the study requirements included careful meal and blood glucose monitoring, which contributed to a higher attrition rate. These burdens did not reflect difficulties in following the diet, but rather, reflected the burden of data-gathering for research purposes that would not be required when the diet is used in a routine clinical setting; the diet itself was viewed as reasonably easy to follow. Although most of the study participants had normal renal function at baseline, the improvements in renal parameters on the vegan diet in a relatively short

period of 12 weeks are encouraging. Finally, our participants were health conscious and willing to make substantial changes to their diet. In this regard, they may not be representative of the general population but may be representative of a clinical population seeking help for type 1 diabetes management.

In addition to the current dietary recommendations that emphasize carbohydrate counting, limited consumption of processed and sugar-sweetened foods and drinks, and increased intake of whole grains, fruits, vegetables, and legumes, this study provides substantial support for a low-fat vegan diet that is high in fiber and carbohydrates, low in fat, and moderate in protein.

Conclusion

This study demonstrated that a low-fat vegan diet without limits on caloric or carbohydrate intake, significantly reduces insulin requirements, increases insulin sensitivity, and improves glycemic control and favorably influences indices of cardiovascular and renal health in people with type 1 diabetes compared with a portion-controlled diet. The study suggests the potential therapeutic use of a low-fat vegan diet in type 1 diabetes management. Larger trials are needed to confirm these findings.

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DUALITY OF INTEREST

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AUTHOR CONTRIBUTIONS

H.K. and N.D.B. designed and conducted the study and wrote the manuscript. T.Z.-M., K.S., M.S., and D.N.H. administered the intervention, collected the data, and reviewed the manuscript. C.K. and R.B. administered the intervention and reviewed the manuscript. M.S. and D.P. helped with patient recruitment and reviewed the manuscript. R.H. performed the statistical analysis and reviewed the manuscript. H.K. 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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