

Changes in ectopic lipids, insulin sensitivity, and beta cell function after a low-fat vegan diet in adults with type 2 diabetes: a 16-week single-arm clinical trial

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ABSTRACT

Objective The aim of this study was to explore the effects of a low-fat plant-based diet on hepatocellular and intramyocellular lipids, advanced glycation end products (AGEs), insulin resistance, and beta-cell function in adults with type 2 diabetes.

Research design and methods Participants (n=25) were asked to follow a low-fat vegan diet for 16 weeks. Dual X-ray absorptiometry was used to measure body composition. Hepatocellular and intramyocellular lipids were quantified by ¹H magnetic resonance spectroscopy. Tissue accumulation of AGEs was measured using a skin fluorescence technique. Insulin resistance was assessed in a fasting state with the Homeostasis Model Assessment (HOMA-IR) index. Postprandial insulin sensitivity was assessed with the predicted insulin sensitivity index (PREDIM). Beta-cell function was calculated by a mathematical model after a standard meal, using C-peptide deconvolution.

Results Mean body weight decreased by 6.0 kg (95% CI −7.0 to −5.1; p<0.001), a 6.6% (95% CI −7.5 to −5.8) decrease relative to baseline. This was largely due to the reduction in fat mass (−4.2 kg, 95% CI −5.7 to −2.7; p<0.001). Visceral fat volume decreased by 290 cm³ (95% CI −467 to −114; p=0.003). Hepatocellular lipids decreased by 33.0% (95% CI −48.7 to −17.3; p<0.001). The AGE score decreased by 0.4 (95% CI −0.6 to −0.2; p=0.002). The HOMA-IR index, a measure of insulin resistance, fell (−2.5, 95% CI −4.1 to −0.9; p=0.004), whereas PREDIM, a measure of insulin sensitivity, increased on the vegan diet (+1.3 mg/min/kg, 95% CI +0.6 to +2.1; p=0.002). Several markers of beta-cell function improved on the vegan diet. Specifically, insulin secretion at 6 and 7 mmol/L glucose, beta-cell glucose sensitivity, rate sensitivity, and potentiation factor all increased.

Conclusions On an ad libitum low-fat plant-based (vegan) dietary intervention, the participants with type 2 diabetes experienced reductions in ectopic fat, particularly visceral and hepatocellular fat, improvements in insulin sensitivity, reductions in AGEs, and improvements in beta-cell function.

Trial registration number NCT06106035.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Ectopic lipid accumulation in the liver and skeletal muscle, together with advanced glycation end-products (AGEs), drives insulin resistance and progressive beta-cell dysfunction in type 2 diabetes.
- ⇒ Caloric-restriction diets reduce hepatocellular and intramyocellular lipid content and improve insulin sensitivity in type 2 diabetes but require active energy monitoring or portion control, which can limit long-term adherence.
- ⇒ A low-fat vegan diet reduces hepatocellular and intramyocellular lipids, lowers AGEs, and improves insulin sensitivity and beta-cell function in people without diabetes but had not previously been tested for these mechanistic endpoints, without a prescribed caloric target, in adults with type 2 diabetes.

INTRODUCTION

Ectopic lipid accumulation in the liver and skeletal muscle plays a central role in insulin resistance, ultimately leading to progressive beta-cell dysfunction and chronic hyperglycemia. Extra body weight is typically associated with elevations in circulating fatty acids and increases in hepatic lipid (HL) and intramyocellular lipid (IMCL) content, where specifically *sn*-1,2 diacylglycerols located in the plasma membrane cause activation of novel protein kinase C isoforms, which inhibit insulin signaling in the liver and muscle,^{1 2} causing tissue-specific insulin resistance. At the same time, chronic exposure to elevated plasma fatty acid concentrations induces oxidative stress and mitochondrial dysfunction in beta-cells, leading to diminished glucose-stimulated insulin secretion and progressive beta-cell dysfunction.³ Moreover,

WHAT THIS STUDY ADDS

- ⇒ In adults with type 2 diabetes, 16 weeks of an ad libitum low-fat vegan diet, with no prescribed caloric target, was associated with reductions in body weight (6.6%), visceral fat, and hepatocellular lipid content (33%) and with reduced tissue AGE accumulation.
- ⇒ Insulin resistance (Homeostasis Model Assessment) and insulin sensitivity (oral glucose insulin sensitivity and predicted insulin sensitivity index) improved, along with multiple markers of beta-cell function (glucose sensitivity, rate sensitivity, potentiation factor, and glucose-stimulated insulin secretion), without any requirement for calorie counting.
- ⇒ This is the first study to simultaneously quantify hepatocellular lipid, intramyocellular lipid, visceral fat, and tissue AGE accumulation within a single plant-based dietary intervention in type 2 diabetes, providing an integrated mechanistic picture.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ These findings suggest that a qualitative, food-based shift toward a low-fat, plant-based diet may be a feasible, ad libitum alternative to strict caloric restriction for addressing the mechanistic drivers of type 2 diabetes, without requiring patients to count calories or measure portions.
- ⇒ Because this was a single-arm study without a control group, the observed changes cannot be attributed to dietary composition independent of the accompanying reduction in energy intake and weight loss; randomized controlled trials with weight-matched or standard-care comparators are needed to determine their independent contributions.

sustained hyperglycemia accelerates the non-enzymatic formation of advanced glycation end-products (AGEs) that trigger proinflammatory and oxidative signaling pathways, which further contribute to insulin resistance and beta-cell dysfunction.⁴

Dietary interventions effectively address these underlying mechanisms. In people with type 2 diabetes, a 16-week period of caloric restriction resulted in weight reduction of ~10%, normalization of HL content (<2%), and an improvement in hepatic insulin resistance and glycemic control.⁵ Plant-based diets promote satiety without intentional energy restriction, largely through their high fiber and complex carbohydrate content, and have demonstrated efficacy in the treatment of type 2 diabetes, with better metabolic outcomes, compared with portion-controlled, carbohydrate-restricted dietary approaches.^{6,7} People following plant-based diets may also have lower IMCL concentrations, compared with omnivores.⁸ In individuals without diabetes, a low-fat, vegan diet reduces HL and IMCL content,⁹ reduces dietary AGEs,¹⁰ increases insulin sensitivity,^{9,11} and improves beta-cell function¹¹ but has not been tested for these endpoints in adults with type 2 diabetes.

Using a single-arm interventional design, adults with type 2 diabetes were asked to follow a low-fat vegan diet for 16 weeks. Before and after the intervention period, we measured IMCL and HL content using ¹H magnetic resonance spectroscopy (MRS), AGEs, insulin sensitivity, and

beta-cell function. We hypothesized the dietary intervention would result in reductions in IMCL and hepatocellular lipid content and AGEs, increased insulin sensitivity, and improvement in beta-cell function.

RESEARCH DESIGN AND METHODS**Study design and eligibility**

The study was conducted between January 2024 and November 2025 in Washington, DC, USA. Adults with type 2 diabetes, treated solely by diet and/or oral hypoglycemic agents other than sulfonylureas, with glycated hemoglobin (HbA1c) values between 6.5% and 10.5%, and body mass indices between 26 and 40 kg/m², were enrolled. Exclusion criteria were type 1 diabetes, treatment with insulin or sulfonylureas, smoking, use of weight-loss medications including incretin-based therapies, alcohol or drug abuse, pregnancy or lactation, metal implants, claustrophobia, and current use of a vegan diet.

Dietary intervention

The participants were asked to follow a low-fat vegan diet (~75% of energy from carbohydrates, 15% protein, and 10% fat), which consisted of vegetables, grains, legumes, and fruits. Participants were instructed to avoid animal products and added fats. No meals were provided. The participants received weekly group support and individual counseling from a registered dietitian who provided instruction on selecting and preparing low-fat, plant-based foods (eg, food group substitutions and strategies to reduce dietary fat and increase fiber intake) but did not prescribe a specific caloric target or energy deficit; consistent with the study's ad libitum design, participants were counseled to eat to satiety rather than to a defined energy goal. Vitamin B₁₂ was supplemented (500 µg/day). Alcoholic beverages were limited to one per day for women and two per day for men. The participants were asked not to alter their exercise habits and to continue their preexisting medication regimens, except as modified by their personal physicians.

Outcomes

All measurements were performed at baseline and 16 weeks on an outpatient basis. A 3-day dietary record was completed by each participant. Dietary intake data were collected and analyzed by a staff member certified in the Nutrition Data System for Research version 2024, developed by the Nutrition Coordinating Center, University of Minnesota, Minneapolis, Minnesota, USA.¹² Physical activity was assessed by the International Physical Activity Questionnaire.¹³ All laboratory assessments were made after fasting 10–12 hours overnight with only water allowed ad libitum. Height (baseline only) and weight were measured using a stadiometer and a periodically calibrated scale accurate to 0.1 kg, respectively.

Body composition

Body composition was measured by dual-energy X-ray absorptiometry (Lunar iDXA, GE Healthcare; Madison,

Wisconsin, USA) with Encore 2005 V.9.15.010 software and the CoreScan module (GE Healthcare), which also provides an estimate of visceral adipose tissue volume and mass. The iDXA unit was calibrated daily using the GE Lunar calibration phantom, and a trained operator performed all scans following standard protocol for participant positioning.

Hepatocellular lipid and IMCL

Liver, extramyocellular (EMCL), and IMCL contents were measured at the Magnetic Resonance Research Center at Yale School of Medicine, New Haven, Connecticut, USA, at 4Tesla (Bruker, Billerica, Massachusetts, USA).¹⁴ Hepatocellular lipid content was measured using a ¹H respiratory-gated Stimulated Echo Acquisition Mode spectroscopy technique in a 15×15×15 mm³ voxel. Acquisition was synchronized to the respiratory cycle and triggered at the end of expiration. A water-suppressed lipid spectrum and a lipid-suppressed water spectrum were acquired in three different locations of the liver to account for liver inhomogeneity, and the total HL content was calculated and averaged. In addition, HL content was corrected for transverse relaxation, using the transverse relaxation times of 22 ms for water and 44 ms for lipid. The EMCL and IMCL contents were measured in the soleus muscle using an 8.5-cm diameter circular ¹³C surface coil with twin, orthogonal circular 13-cm ¹H quadrature coils. Scout images of the lower leg were obtained to ensure correct positioning of the participant and to define an adequate volume for localized shimming using the Fast Automatic Shimming Technique by Mapping Along Projections procedure.¹⁵

Advanced glycation end products

AGEs were measured using the AGE reader (Diagnoptics, Groningen, Netherlands), which produces ultraviolet light to excite AGEs in human skin. The AGE Reader measures skin fluorescence to quantify the tissue accumulation of AGEs. This measurement is used to determine the corresponding level of AGEs in the blood vessel wall.

Thermic effect of food

Resting energy expenditure and postprandial metabolism were measured by indirect calorimetry (Cosmed Quark CPET, Chicago, Illinois, USA) utilizing a ventilated hood system. Measurements were taken in the fasting state and then 120 min after a liquid breakfast (Boost Plus, Nestlé, Vevey, Switzerland; 720 kcal, 34% of energy from fat, 16% protein, and 50% carbohydrate). Each measurement took 20 min.

Insulin secretion and beta-cell function

Insulin secretion was assessed after stimulation with the liquid breakfast. Serum concentrations of glucose, immunoreactive insulin, and C-peptide were measured at 0, 30, 60, 120, and 180 min. Serum glucose was analyzed using the hexokinase ultraviolet endpoint method (Roche, Basel, Switzerland). Immunoreactive insulin and C-peptide concentrations were determined using insulin and

C-peptide electrochemiluminescence immunoassay kits (Roche). HbA1c was measured by turbidimetric inhibition immunoassay (Roche). Lipid concentrations were measured by enzymatic colorimetric methods (Roche).

Beta-cell function was assessed by a mathematical model,^{16 17} as follows: insulin secretory rates were calculated from plasma C-peptide concentrations by deconvolution¹⁶ and expressed per square meter of estimated body surface area. The dependence of insulin secretory rates on glucose concentrations was modeled separately for each participant and each study day.

Insulin secretion consists of two components. The first represents the static dependence of insulin secretion on glucose concentration and is characterized by a dose-response function. Its parameters are the mean slope of the dose-response in the glucose range (named beta-cell glucose sensitivity) and the insulin secretion at prescribed glucose levels (especially: 5 mmol/L—typical fasting glucose level in nondiabetic individuals—as well as 6 and 7 mmol/L). The dose-response is modulated by a potentiation factor, quantified as the ratio between final and initial values. The second insulin secretion component represents a dynamic dependence of insulin secretion on the rate of change of glucose and is determined by the rate sensitivity.¹⁷ The model parameters (ie, the parameters of the dose-response, the potentiation factor, and the rate sensitivity) were estimated from glucose and C-peptide concentration by regularized least squares.^{16 17} Regularization involves the choice of smoothing factors that were selected to obtain glucose and C-peptide model residuals with SD close to the expected measurement error (~1% for glucose and ~5% for C-peptide). C-peptide has been used for the calculation of insulin secretion, as it is secreted with insulin in an equimolar fashion but does not undergo liver elimination. Therefore, plasma C-peptide provides a more accurate estimation of insulin secretion.

Insulin resistance and sensitivity

Plasma insulin has been used for the assessment of insulin resistance and sensitivity, both in fasting and postprandial conditions. Insulin resistance was calculated using the Homeostasis Model Assessment insulin resistance (HOMA-IR) index.¹⁸ The oral glucose insulin sensitivity (OGIS) index was calculated as a measure of dynamic postprandial insulin sensitivity.¹⁹ Predicted insulin sensitivity index (PREDIM), which has been validated against clamp-derived measures of insulin sensitivity,²⁰ was calculated as well as a measure of dynamic postprandial insulin sensitivity.

Power analysis

Based on two previous interventional clinical trials,^{9 21} assuming a reduction in IMCL of 0.26 percentage points with a SD of 0.3, to have 90% power to detect a difference of this magnitude would require 16 study completers. Assuming an attrition of 20%, the required sample size was 20 starters.

Statistical analysis

The completer (per-protocol) analysis was restricted to participants with data available at both time points for the outcome being analyzed. The data distribution was tested for normality. Paired comparison t-tests were calculated to test whether the changes from baseline to 16 weeks were statistically significant. Because of the exploratory nature of this single-arm pilot study and the number of secondary outcomes examined, p-values were not adjusted for multiple comparisons. The statistician was blinded to the dietary intervention. All results are presented as means with 95% CIs. Two-sided p-values less than 0.05 were deemed to be statistically significant.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

RESULTS

Characteristics of the participants

Of 1244 people screened by telephone, 108 completed in-person screening, 59 completed baseline testing, 26 met the participation criteria, and 25 started the dietary intervention. One participant dropped out, and 24/26 (92%) completed the study. A laboratory error led to lost glucose tolerance data for three participants, leaving 21 participants with complete glucose tolerance data (figure 1). Demographic characteristics are listed in table 1. Baseline physical activity, dietary intake, anthropometric and laboratory variables, parameters of insulin resistance/sensitivity, and beta-cell function, as well as their changes in response to 16 weeks of the diet, are shown in table 2.

Dietary intake, physical activity, and medication changes

Self-reported energy intake decreased on the vegan diet by a mean of 346 kcal/day (95% CI -641 to -50; $p=0.02$). The participants increased their intake of carbohydrate and fiber and reduced consumption of fat, protein, and cholesterol. Physical activity decreased slightly (-346 metabolic equivalent of task-min/week, 95% CI -570 to -122; $p=0.004$). Of the 17 participants taking metformin at baseline, one dropped out, nine remained on the same dose, five had their metformin dose reduced, and two discontinued metformin entirely. No participant initiated or increased a glucose-lowering medication during the study.

Body weight, body composition, hepatocellular lipid, and IMCL

Mean body weight decreased by 6.0 kg (95% CI -7.0 to -5.1; $p<0.001$), which represented a 6.6% (95% CI -7.5 to -5.8) decrease relative to baseline weight. This was primarily due to the reduction in fat mass (-4.2 kg, 95% CI -5.7 to -2.7; $p<0.001$) and a smaller reduction in lean mass (-2.4 kg, 95% CI -2.9 to -1.8; $p<0.001$). Visceral fat volume also fell on the vegan diet (-290 cm³, 95% CI -467 to -114; $p=0.003$).

Hepatocellular lipids decreased by 33.0% (95% CI -48.7 to -17.3; $p<0.001$). The reduction in IMCLs did not reach statistical significance (-13.1%; 95% CI -29.6 to +3.4; $p=0.11$). There was no significant change in extramucocellular lipids (-2.5%; 95% CI -19.9 to +14.8; $p=0.77$) or leg subcutaneous fat (-2.4%; 95% CI -15.2 to +10.4; $p=0.71$).

Fasting and postprandial metabolism

There was no significant change in the fasting or postprandial energy expenditure. The increase in thermic effect of food did not reach statistical significance.

Laboratory tests

There were significant reductions in total and low-density lipoprotein cholesterol (-32.3 mg/dL, 95% CI -47.4 to -17.1; $p<0.001$ and -22.0 mg/dL, 95% CI -35.1 to -9.0; $p=0.002$, respectively), as well as in fasting plasma glucose and insulin. HbA1c fell by 1.0% (95% CI -1.5 to -0.5; $p<0.001$). The AGE score decreased by 0.4 (95% CI -0.6 to -0.2; $p=0.002$).

Insulin resistance/sensitivity and beta-cell function

The HOMA-IR index, a measure of insulin resistance, fell (-2.5, 95% CI -4.1 to -0.9; $p=0.004$), and OGIS and PREDIM, measures of insulin sensitivity, increased on the vegan diet (+92.5 mL/min/m², 95% CI, +51.3 to +133.6; $p<0.001$ and +1.3 mg/min/kg, 95% CI +0.6 to +2.1; $p=0.002$, respectively).

Several markers of beta-cell function improved on the vegan diet. Specifically, insulin secretion at glucose levels 6 and 7 mmol/L increased by 48.1 pmol/min/m² (95% CI +6.6 to +89.7; $p=0.03$) and 101.6 pmol/min/m² (95% CI +37.9 to +165.3; $p=0.003$), respectively. Glucose sensitivity, rate sensitivity, and potentiation factor all increased by 56.0 pmol/min/m²/mM (+8.1 to +103.8; $p=0.02$); 1826 pmol/m²/mM (+242.3 to +3410; $p=0.03$) and 0.47 (+0.06 to +0.87; $p=0.03$), respectively.

DISCUSSION

Main findings

In this single-arm study, a low-fat vegan dietary intervention prescribed with no caloric target was associated with reductions in body weight, fat mass, visceral fat, HL content, AGEs, and insulin resistance, and with improvements in beta-cell function in adults with type 2 diabetes. Because there was no control group, these changes cannot be attributed specifically to dietary composition independent of the accompanying reduction in energy intake and weight loss.

The accumulation of HL and IMCL content is a key contributor to tissue-specific insulin resistance and the pathogenesis of type 2 diabetes.^{1 2} Excess ectopic lipid deposition in the liver and skeletal muscle interferes with insulin signaling through lipotoxic intermediates, such as plasma membrane-associated *sn*-1,2 diacylglycerols, impairing insulin receptor kinase->insulin receptor

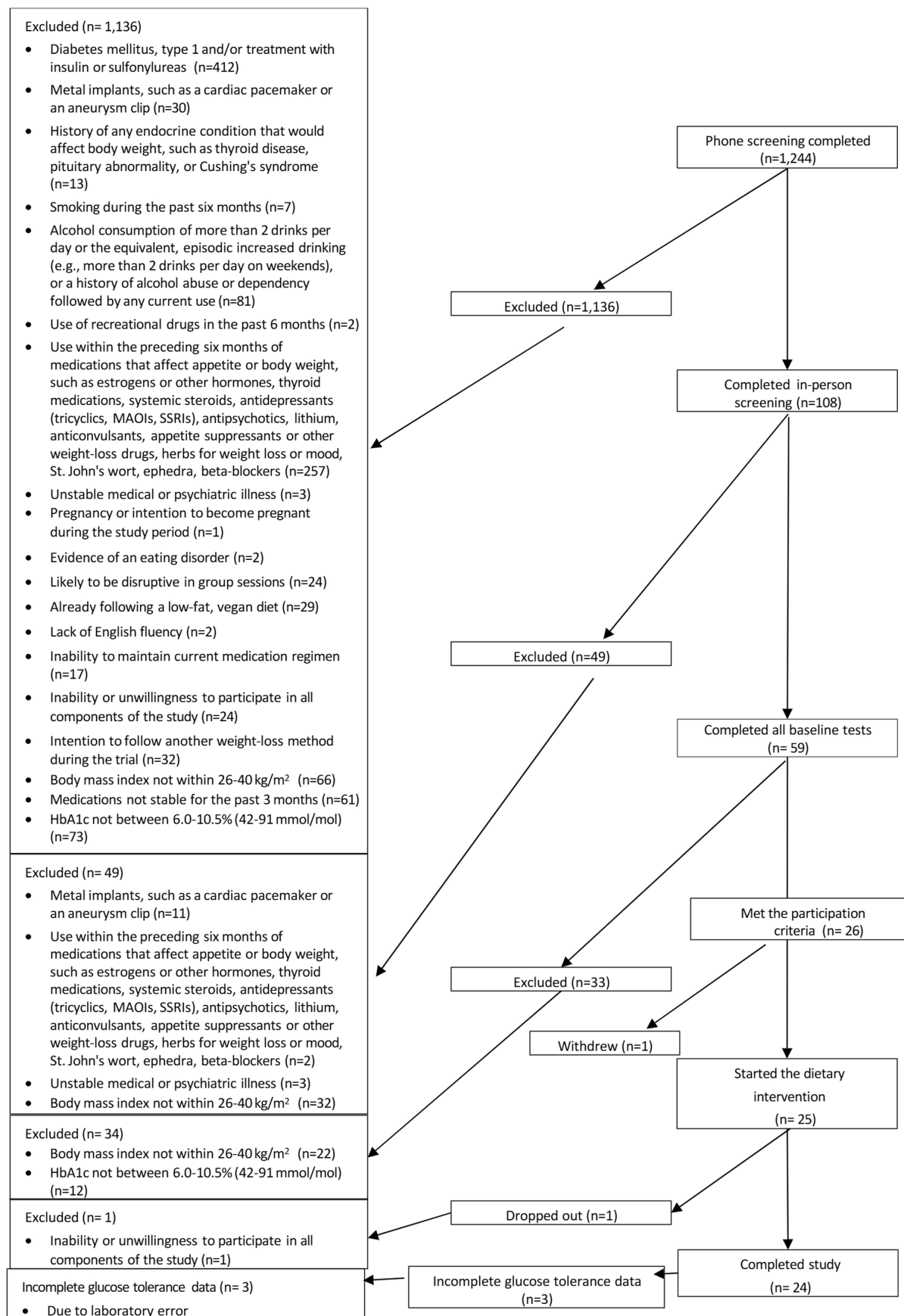


Figure 1 Participant flow chart. HbA1c, glycated hemoglobin; MAOIs, monoamine oxidase inhibitors; SSRIs, selective serotonin reuptake inhibitors.

Table 1 Baseline demographics

Variable	Study group (n=25)
Mean age, years (SD)	59.0 (7.6)
Age range	44–79
Race and ethnicity	
Black, non-Hispanic	13 (52%)
White, non-Hispanic	9 (36%)
Other	3 (12%)
Marital status	
Not married	11 (44%)
Married	14 (56%)
Education	
College, partial, or graduate	7 (28%)
Graduate degree	18 (72%)
Medication use	
Antidiabetic medications	17 (68%)
Metformin	17 (68%)
Antihypertensives	13 (52%)
Cholesterol-lowering medications	10 (40%)
Thyroid medications	0 (0%)
Body weight in kg, mean (SD)	90.6 (13.1)
Body mass index in kg/m ² , mean (SD)	31.4 (4.6)
Duration of diabetes (years), mean (SD)	6.6 (3.1)
Data are shown as means with a SD (SD).	

substrate 1->phosphoinositide 3-kinase->protein kinase B activation.^{1 22}

These negative metabolic consequences of ectopic lipid accumulation may be counteracted by interventions that reduce this accumulation. One of these is weight loss. Goodpaster *et al* showed that weight loss was associated with significant reductions in IMCLs and improvements in insulin-stimulated glucose uptake.²³ Similar findings have been demonstrated in insulin resistant but otherwise lean offspring of parents with type 2 diabetes after a hypocaloric dietary intervention.²⁴ These findings collectively support a causal role of IMCL accumulation in impaired skeletal muscle glucose uptake.

In parallel, HL accumulation has been shown to strongly predict hepatic insulin resistance. Caloric restriction in people with type 2 diabetes resulted in reductions in HL content and improved whole-body glucose metabolism.²⁵ Caloric restriction reliably reduces both IMCL and HL content, as demonstrated in several human metabolic studies. For example, Larson-Meyer *et al* reported that 6 months of moderate energy restriction decreased IMCLs by 28% and hepatocellular lipids by ~40%, with improvements in insulin sensitivity correlating with reductions in ectopic fat stores.²⁶ Likewise, Lim *et al* observed that severe dietary energy restriction in individuals with type 2 diabetes led to rapid reductions in

liver fat and normalization of hepatic insulin sensitivity within weeks.²⁵ Together, these data provide strong evidence that reductions in ectopic lipid stores are a key mechanism driving improvements in insulin action and glycemic control.

Dietary interventions that include caloric restriction have been consistently shown to reduce IMCL and intra-hepatic lipid content while improving insulin sensitivity in people with type 2 diabetes and/or insulin-resistant individuals.^{27–29} In insulin-resistant people with type 2 diabetes, a hypocaloric (~1200 kcal), low-fat (3%) diet led to weight loss of ~8 kg, an 81% reduction in hepatocellular lipid concentrations, and normoglycemia within 3–12 weeks.⁵ Similarly, a hypocaloric diet (~1200 kcal) in young, lean, insulin-resistant offspring of parents with type 2 diabetes, and in ~9 weeks, the diet resulted in an average weight loss of 4.1 kg and a 30% reduction of IMCLs and improved muscle insulin sensitivity.²⁷ These studies demonstrate that reductions in ectopic fat through energy restriction improve insulin sensitivity, supporting IMCL and HL stores as mechanistic drivers of insulin resistance and type 2 diabetes. It is noteworthy that the low-fat dietary intervention reduced HL, whereas the reduction in IMCL was smaller and did not reach statistical significance. This pattern is consistent with prior work showing that hepatic fat is highly labile and often declines early during dietary change, with rapid improvement in hepatic insulin resistance (and fasting glycemia) occurring before measurable changes in skeletal-muscle lipid stores.³⁰ These studies suggest that a longer duration of dietary intervention may be required for consistent IMCL reductions.

While caloric restriction has previously been shown to reduce ectopic lipid content and improve insulin sensitivity in people with type 2 diabetes,^{27–29} the novelty of the present study lies in demonstrating that comparable reductions in hepatocellular lipid and IMCL content, together with measurable improvements in beta-cell function and tissue AGE accumulation, can accompany a qualitative shift in dietary composition undertaken without a prescribed caloric target, even though the relative contributions of dietary composition versus the accompanying reduction in energy intake and weight loss cannot be separated in this design. Prior caloric-restriction trials have generally required active energy monitoring or portion control, whereas participants in the present study ate ad libitum. This distinction has practical relevance: dietary interventions that do not require deliberate calorie counting tend to show better long-term adherence and greater feasibility in free-living settings. In addition, to our knowledge, this is among the first studies to simultaneously quantify hepatocellular lipid, IMCL, visceral fat, and tissue AGE accumulation within a single plant-based dietary intervention in type 2 diabetes, offering a more integrated mechanistic picture than has previously been available from studies reporting single outcomes in isolation.

Table 2 Changes in dietary intake, anthropometric, clinical, and laboratory variables during the study

	Baseline	Week 16	Week 16–0	P value
Total physical activity (metabolic equivalent of tasks)	1148 (844.1–1451)	801.4 (522.6–1080)	–346.2 (–570.0 to –122.4)	0.004
Dietary intake				
Total weight (g/day)	1594 (1351–1836)	1839 (1574–2105)	+245.4 (–57.8 to +548.6)	0.11
Caloric intake (kcal/day)	1774 (1474–2074)	1428 (1201–1655)	–345.9 (–641.4 to –50.4)	0.02
Total fat (g/day)	76.7 (59.0–94.3)	24.6 (19.3–29.9)	–52.1 (–69.4 to –34.7)	<0.001
Saturated fatty acids (g/day)	21.3 (17.2–26.5)	4.5 (3.3–5.6)	–16.9 (–21.1 to –12.6)	<0.001
Monounsaturated fatty acids (g/day)	27.5 (20.1–34.8)	7.5 (5.5–9.5)	–20.0 (–27.7 to –12.3)	<0.001
Polyunsaturated fatty acids (g/day)	21.0 (15.2–26.9)	10.1 (7.6–12.6)	–10.9 (–16.5 to –5.4)	<0.001
Total carbohydrates (g/day)	197.7 (158.2–237.1)	259.3 (216.7–301.8)	+61.6 (+11.8 to +111.4)	0.02
Total protein (g/day)	79.4 (66.2–92.5)	59.2 (44.9–73.5)	–20.2 (–36.8 to –3.6)	0.02
Animal protein (g/day)	47.8 (35.4–60.2)	0.09 (–0.02–0.20)	–47.7 (–60.1 to –35.3)	<0.001
Vegetable protein (g/day)	31.6 (24.9–38.3)	59.1 (44.8–73.4)	+27.5 (+13.2 to +41.9)	<0.001
Alcohol (g/day)	1.7 (–0.01 to +3.4)	0.6 (–0.5 to +1.7)	–1.1 (–2.5 to +0.3)	0.11
Cholesterol (mg/day)	290.0 (195.7–384.2)	0.01 (0.0–0.03)	–289.9 (–384.2 to –195.7)	<0.001
Total dietary fiber (g/day)	24.0 (19.7–28.3)	41.4 (34.4–48.4)	+17.5 (+10.8 to +24.1)	<0.001
Soluble dietary fiber (g/day)	7.1 (5.7–8.5)	11.2 (9.3–13.2)	+4.2 (+2.2–+6.1)	<0.001
Insoluble dietary fiber (g/day)	16.8 (13.5–20.2)	30.0 (24.4–35.6)	+13.2 (+7.8 to 18.6)	<0.001
Glycemic index (glucose reference)	56.5 (53.9–59.1)	53.6 (51.2–56.0)	–2.9 (–5.3 to –0.55)	0.02
Anthropometric variables				
Body weight (kg)	90.4 (84.8–96.0)	84.4 (79.1–89.6)	–6.0 (–6.95 to –5.1)	<0.001
(% change)			–6.6% (–7.5 to –5.8)	
Body mass index (kg/m ²)	31.5 (29.5–33.5)	29.4 (27.5–31.3)	–2.1 (–2.4 to –1.8)	<0.001
Fat mass (kg)	36.7 (32.3–41.1)	32.5 (28.9–36.1)	–4.2 (–5.69 to –2.69)	<0.001
Lean mass (kg)	51.1 (47.5–54.8)	48.8 (45.3–52.3)	–2.4 (–2.9 to –1.8)	<0.001
Fat-free mass (kg)	54.0 (50.3–57.8)	51.3 (47.6–55.0)	–2.7 (–3.5 to –1.9)	<0.001
Visceral fat volume (cm ³)	2168 (1694–2643)	1878 (1473–2283)	–290.3 (–467.1 to –113.5)	0.003
Magnetic resonance spectroscopy				
Extramyocellular lipids (absolute change)	2.6 (1.7–3.6)	2.8 (1.4–4.2)	+0.2 (–0.5 to +0.8)	0.56
(% change)			–2.5% (–19.9 to +14.8)	0.77
Intramyocellular lipids (absolute change)	2.0 (1.5–2.4)	1.7 (1.2–2.3)	–0.2 (–0.5 to +0.03)	0.08
(% change)			–13.1% (–29.6 to +3.4)	0.11
Hepatocellular lipids (absolute change)	8.8 (6.0–11.7)	5.4 (3.7–7.1)	–3.5 (–5.6 to –1.4)	0.003
(% change)			–33.0% (–48.7 to –17.3)	<0.001
Subcutaneous fat (absolute change)	0.78 (0.64–0.93)	0.75 (0.61–0.89)	–0.04 (–0.10 to +0.03)	
(% change)			–2.4% (–15.2 to +10.4)	0.71
Laboratory variables				
Total cholesterol (mg/dL)	194 (176.7–211.2)	161.7 (149.8–173.7)	–32.3 (–47.4 to –17.1)	<0.001
High-density lipoprotein cholesterol (mg/dL)	55.4 (49.9–61)	47.4 (42.4–52.5)	–8.0 (–11.6 to –4.5)	<0.001
Low-density lipoprotein cholesterol (mg/dL)	107.7 (91.7–123.6)	85.6 (73.1–98.2)	–22 (–35.1 to –9.0)	0.002
Very low-density lipoprotein cholesterol (mg/dL)	30.8 (24.5–37.2)	28.6 (23.4–33.8)	–2.3 (–7.9 to +3.4)	0.42
Triglycerides (mg/dL)	154.3 (122.5–186.2)	140.5 (113.8–167.2)	–13.8 (–43.2 to +15.5)	0.34
Fasting plasma glucose (mg/dL)	155.1 (132.2–178.1)	115.5 (107.8–123.2)	–39.7 (–61.5 to –17.8)	0.001

Continued

Table 2 Continued

	Baseline	Week 16	Week 16–0	P value
Fasting plasma insulin ($\mu\text{U/mL}$)	13.5 (9.2–17.7)	8.8 (5.9–11.6)	–4.7 (–8.7 to –0.7)	0.02
Fasting C-peptide (ng/mL)	3.0 (2.4–3.6)	2.5 (2.0–3.0)	–0.43 (–0.99 to +0.12)	0.12
Glycated hemoglobin (diabetes control and complications trial, %)	7.6 (7.0–8.2)	6.6 (6.2–7.0)	–1.0 (–1.5 to –0.5)	<0.001
Advanced glycation end product score	3.1 (2.8–3.4)	2.7 (2.5–3.0)	–0.4 (–0.6 to –0.2)	0.002
Thermic effect of food				
Fasting metabolic rate (kcal/day)	1697 (1546–1848)	1631 (1499–1763)	–66.3 (–220.8 to +88.2)	0.38
Postprandial metabolic rate (kcal/day)	2051 (1868–2235)	2037 (1859–2214)	–14.4 (–211.5 to +182.8)	0.88
Thermic effect of food (kcal/day)	354 (243–465)	406 (282–530)	+52 (–132 to +235)	0.56
Insulin sensitivity/resistance				
Homeostatic Model Assessment	5.0 (3.4–6.7)	2.5 (1.6–3.4)	–2.5 (–4.1 to –0.9)	0.004
Oral glucose insulin sensitivity (mL/min/m^2)	254.9 (218–291.6)	347.3 (314.5–380.2)	+92.5 (+51.3 to +133.6)	<0.001
Predicted insulin sensitivity index (mg/min/kg)	3.1 (2.2–4.0)	4.4 (3.7–5.2)	+1.3 (+0.6 to +2.1)	0.002
Beta cell parameters				
Area under the curve glucose (mmol/L/min)	2096 (1751–2441)	1440 (1282–1598)	–656.4 (–959.9 to –352.8)	<0.001
Basal glucose (mmol/L)	8.6 (7.3–9.9)	6.4 (6.0–6.8)	–2.2 (–3.4 to –1.0)	0.001
Mean glucose (mmol/L)	11.7 (9.7–13.6)	8.0 (7.1–8.9)	–3.7 (–5.3 to –2.0)	<0.001
Basal insulin (pmol/L)	80.9 (55.5–106.3)	52.6 (35.4–69.8)	–28.2 (–52.2 to –4.2)	0.02
Mean insulin (pmol/L)	309.5 (186.3–432.7)	245.3 (172.8–317.9)	–64.1 (–173.0 to +44.8)	0.23
Basal insulin secretion (pmol/L)	122.4 (98.4–146.4)	106.9 (85.7–128.0)	–15.5 (–39.0 to +8.1)	0.19
Insulin secretion at 5 mmol/L glucose (pmol/min/m^2)	57.5 (32.6–82.3)	77.3 (51.0–103.5)	+19.8 (–18.1 to +57.7)	0.29
Insulin secretion at 6 mmol/L glucose (pmol/min/m^2)	94.9 (53.3–136.5)	143.0 (98.6–187.5)	+48.1 (+6.6 to +89.7)	0.03
Insulin secretion at 7 mmol/L glucose (pmol/min/m^2)	151.4 (75.8–227.0)	253.0 (165.3–340.7)	+101.6 (+37.9 to +165.3)	0.003
Glucose sensitivity ($\text{pmol/min/m}^2/\text{mM}$)	70.7 (27.6–113.8)	126.7 (67.4–186.0)	+56.0 (+8.1 to +103.8)	0.02
Rate sensitivity ($\text{pmol/m}^2/\text{mM}$)	849.8 (192.8–1507)	2676 (824.7–4528)	+1826 (+242.3 to +3410)	0.03
Potential factor ratio	1.2 (1.0–1.5)	1.7 (1.4–2.0)	+0.47 (+0.06 to +0.87)	0.03

Data are means with 95% CIs. Listed p values are for change from baseline to 16 weeks, assessed by paired comparison t-tests.

The present study differed from these prior investigations in that no prescribed caloric target or energy deficit was imposed. Rather, the low-fat vegan diet allowed participants to eat ad libitum, to satiety, markedly enhancing acceptability and sustainability. This does not mean that energy intake did not diminish. Rather, in the absence of any intentional energy restriction, self-reported energy intake decreased by a mean of 346 kcal/day , and body weight decreased by 6.6% over the intervention period. The qualitative dietary shift toward high-carbohydrate, high-fiber, low-fat foods, therefore, led to a spontaneous reduced energy intake, which is itself a plausible mediator of the observed metabolic changes; the effects of the vegan dietary pattern on ectopic lipid content, insulin sensitivity, and beta-cell function cannot be distinguished from those attributable to this reduced energy intake and the accompanying weight loss. In addition, lipid

intake diminished significantly, which may influence HL and IMCL accumulation apart from the effect of energy intake.

Another possible mechanism by which the intervention diet led to weight loss and reduced insulin resistance is the reduction in AGEs, a large heterogeneous group of compounds resulting from the spontaneous, non-enzymatic reaction of the carbonyl groups of sugars with free amino groups in protein.³¹ AGEs have been linked with inflammation, oxidative stress, insulin resistance, increased body weight, and increased risk of type 2 diabetes.^{31–32} Several studies have shown that a diet low in dietary AGEs is associated with reduced circulating AGE markers, weight loss, improved body composition, and other cardiometabolic outcomes.^{33–36} In overweight adults, a low-fat vegan diet was shown to reduce dietary AGEs by 79%, which was associated with weight loss

and improved body composition (ie, reduced fat mass and volume of visceral fat).¹⁰ The present study quantified tissue accumulation of AGEs in people with type 2 diabetes, using a skin fluorescence technique, and demonstrated that AGE tissue accumulation may be reduced on a low-fat vegan diet.

Apart from its effect on insulin sensitivity, an energy-restricted diet also improves beta-cell function in people with type 2 diabetes.^{37,38} The current study demonstrates that a qualitative change in macronutrient composition, with no limit on energy intake, elicits an improvement in insulin sensitivity and beta-cell function. The results are in accordance with previous findings showing that metabolic crosstalk of fatty liver with pancreatic islets may contribute to obesity-related impairment of beta-cell glucose sensitivity.³⁹ In the present study, a low-fat vegan diet reduced hepatic insulin resistance, which was accompanied by an improvement in beta-cell function. This is in line with the findings from the Finnish Diabetes Prevention Study, showing that reduced type 2 diabetes incidence after a lifestyle intervention is related to improvement in insulin sensitivity, which has beneficial effects on preservation of beta-cell function.^{40,41}

Beta-cell function is improved by therapies that reduce body fat (such as diet and exercise, glucagon-like peptide-1 agonists, or bariatric surgery) or change fat distribution (such as thiazolidinediones).^{42,43} Plant-based diets have been shown to be effective for weight loss and particularly for reduction in visceral and ectopic fat, and this may contribute to beta-cell function improvement.⁹ Additional possible mechanisms for improved beta-cell function observed with the dietary intervention involve the incretin hormones, which are released from the gastrointestinal tract in response to nutrient ingestion to enhance meal-dependent insulin secretion from the pancreas.⁴⁴ Indeed, compromised incretin action plays a role in the development of beta-cell dysfunction and type 2 diabetes.⁴⁵ We showed previously that a plant-based diet improved incretin secretion in people with type 2 diabetes.⁴⁶ Therefore, in the present study, it is plausible that the dietary intervention may have improved beta-cell function through enhanced incretin action. Other factors that have been hypothesized to be involved in improvement of beta-cell function include reduced lipotoxicity, glucotoxicity, oxidative stress, and inflammation.^{7,47}

The decrease in lean mass (−2.4 kg) accounted for about 40% of total weight loss, while the remaining 60% came from fat mass. This decline likely reflects the modest reductions in energy and protein intake alongside a small decrease in physical activity, though the latter would not be expected to account for the observed improvement in insulin sensitivity. Given the older population with type 2 diabetes, future studies should examine whether resistance exercise or attention to protein distribution can further preserve lean mass during plant-based dietary interventions, alongside broader assessment of body composition and bone health in longer-term trials.

More broadly, the physiological implications of plant-based dietary patterns may extend beyond weight and glycemic outcomes: recent evidence in young adult women has reported differences in bioelectrical impedance-derived measures of body composition and cellular health among vegetarians,⁴⁸ while quantitative ultrasound research has similarly identified associations between vegetarian diets and bone parameters.⁴⁹ Although these populations differ substantially from adults with type 2 diabetes and should not be directly extrapolated to the present findings, they underscore the value of multidimensional body composition and musculoskeletal assessment—including bone health—in future long-term plant-based dietary trials in this population.

Strengths and limitations

The strengths of this study include the comprehensive assessment of the main mechanisms involved in type 2 diabetes. The study duration was reasonably long, providing sufficient time for adaptation to the diet and the elaboration of physical changes. We used physiological stimulation by a standard mixed meal, enabling us to study insulin sensitivity and insulin secretion during a physiological perturbation. A unique feature of our study lies in the measurement of ectopic fat, including visceral fat, hepatocellular lipid, and IMCL. The intervention was acceptable and sustainable. Given that the participants were living at home and preparing their own meals or eating at restaurants, our results are applicable outside the research setting, in free-living conditions. The study also has important limitations. The participation criteria (eg, the exclusion of people treated with insulin) may limit the generalizability of the findings. Dietary intake was calculated based on self-reported diet records, which have well-known limitations.⁵⁰ However, it is reassuring that the reported changes in nutrient intake were paralleled by weight loss and improvements in cardiometabolic outcomes. The single-arm design precludes causal attribution to the dietary intervention and does not allow separation of effects of dietary composition from weight loss. In addition, 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 weight problems or type 2 diabetes.

CONCLUSION

In conclusion, this study demonstrated that an ad libitum low-fat plant-based (vegan) dietary intervention was associated with reductions in visceral and hepatocellular fat content and with improvements in insulin sensitivity, reductions in AGEs, and improvements in beta-cell function in adults with type 2 diabetes. These findings suggest potential metabolic benefits of a low-fat vegan dietary intervention in adults with type 2 diabetes; controlled trials are needed to determine the independent

contribution of dietary composition, energy intake, and weight loss.

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Contributors HK, KP, GIS, and NDB designed and performed the whole study. TZ-M, SD, HB, and CM performed all the tests. AT did the mathematical modeling to assess markers of insulin sensitivity and beta-cell function. RH performed the statistical analysis. HK 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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Competing interests HK, TZ-M, HB, CM, and RH received compensation from the Physicians Committee for Responsible Medicine for their work on this study. KP, GIS, SD, and AT report no conflict of interest. NDB is an adjunct professor of medicine at the George Washington University School of Medicine. He serves without compensation as president of the Physicians Committee for Responsible Medicine and NDB Medical Center in Washington, DC, USA, non-profit organizations providing educational, research, and medical services related to nutrition. He writes books and articles and gives lectures related to nutrition and health and has received royalties and honoraria from these sources.

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Ethics approval This study involves human participants. This study was approved by the Advarra Institutional Review Board on October 5, 2023 (Pro00074571). Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available upon reasonable request. Data will be made available upon request at hana.kahleova@gmail.com.

Author note The lead author (HK) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

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