

Comparison of low- and high-carbohydrate diets for type 2 diabetes management: a randomized trial^{1–4}

Jeannie Tay,^{5,6,10} Natalie D Luscombe-Marsh,^{5,6} Campbell H Thompson,⁶ Manny Noakes,⁵ Jonathan D Buckley,⁷ Gary A Wittert,⁶ William S Yancy Jr,^{8,9} and Grant D Brinkworth^{5*}

⁵Commonwealth Scientific and Industrial Research Organisation–Food and Nutrition Flagship, Adelaide, Australia; ⁶Centre for Nutritional and Gastrointestinal Diseases, Discipline of Medicine, University of Adelaide, Adelaide, Australia; ⁷Alliance for Research in Exercise, Nutrition and Activity, Sansom Institute for Health Research, University of South Australia, Adelaide, Australia; ⁸Division of General Internal Medicine, Department of Medicine, Duke University Medical Center, Durham, NC; ⁹Center for Health Services Research in Primary Care, Veterans Affairs Medical Center, Durham, NC; and ¹⁰Agency for Science, Technology and Research, Singapore

ABSTRACT

Background: Few well-controlled studies have comprehensively examined the effects of very-low-carbohydrate diets on type 2 diabetes (T2D).

Objective: We compared the effects of a very-low-carbohydrate, high-unsaturated fat, low-saturated fat (LC) diet with a high-carbohydrate, low-fat (HC) diet on glycemic control and cardiovascular disease risk factors in T2D after 52 wk.

Design: In this randomized controlled trial that was conducted in an outpatient research clinic, 115 obese adults with T2D [mean ± SD age: 58 ± 7 y; body mass index (in kg/m²): 34.6 ± 4.3; glycated hemoglobin (HbA1c): 7.3 ± 1.1%; duration of diabetes: 8 ± 6 y] were randomly assigned to consume either a hypocaloric LC diet [14% of energy as carbohydrate (carbohydrate <50 g/d), 28% of energy as protein, and 58% of energy as fat (<10% saturated fat)] or an energy-matched HC diet [53% of energy as carbohydrate, 17% of energy as protein, and 30% of energy as fat (<10% saturated fat)] combined with supervised aerobic and resistance exercise (60 min; 3 d/wk). Outcomes were glycemic control assessed with use of measurements of HbA1c, fasting blood glucose, glycemic variability assessed with use of 48-h continuous glucose monitoring, diabetes medication, weight, blood pressure, and lipids assessed at baseline, 24, and 52 wk.

Results: Both groups achieved similar completion rates (LC diet: 71%; HC diet: 65%) and mean (95% CI) reductions in weight [LC diet: −9.8 kg (−11.7, −7.9 kg); HC diet: −10.1 kg (−12.0, −8.2 kg)], blood pressure [LC diet: −7.1 (−10.6, −3.7)/−6.2 (−8.2, −4.1) mm Hg; HC diet: −5.8 (−9.4, −2.2)/−6.4 (−8.4, −4.3) mm Hg], HbA1c [LC diet: −1.0% (−1.2, −0.7%); HC diet: −1.0% (−1.3, −0.8%)], fasting glucose [LC diet: −0.7 mmol/L (−1.3, −0.1 mmol/L); HC diet: −1.5 mmol/L (−2.1, −0.8 mmol/L)], and LDL cholesterol [LC diet: −0.1 mmol/L (−0.3, 0.1 mmol/L); HC diet: −0.2 mmol/L (−0.4, 0.03 mmol/L)] (*P*-diet effect ≥ 0.10). Compared with the HC-diet group, the LC-diet group achieved greater mean (95% CI) reductions in the diabetes medication score [LC diet: −0.5 arbitrary units (−0.7, −0.4 arbitrary units); HC diet: −0.2 arbitrary units (−0.4, −0.06 arbitrary units); *P* = 0.02], glycemic variability assessed by measuring the continuous overall net glycemic action-1 [LC diet: −0.5 mmol/L (−0.6, −0.3 mmol/L); HC diet: −0.05 mmol/L (−0.2, −0.1 mmol/L); *P* = 0.003], and triglycerides [LC diet: −0.4 mmol/L (−0.5, −0.2 mmol/L); HC diet:

−0.01 mmol/L (−0.2, 0.2 mmol/L); *P* = 0.001] and greater mean (95% CI) increases in HDL cholesterol [LC diet: 0.1 mmol/L (0.1, 0.2 mmol/L); HC diet: 0.06 mmol/L (−0.01, 0.1 mmol/L); *P* = 0.002].

Conclusions: Both diets achieved substantial weight loss and reduced HbA1c and fasting glucose. The LC diet, which was high in unsaturated fat and low in saturated fat, achieved greater improvements in the lipid profile, blood glucose stability, and reductions in diabetes medication requirements, suggesting an effective strategy for the optimization of T2D management. This trial was registered at www.anzctr.org.au as ACTRN12612000369820. *Am J Clin Nutr* doi: 10.3945/ajcn.115.112581.

Keywords: diabetes, diet, macronutrient composition, obesity, weight loss

INTRODUCTION

Effective strategies are urgently needed to combat the global diabetes epidemic. A dietary intervention is a cornerstone of diabetes management with guidelines indicating dietary patterns

¹ Some outcome data were presented at Obesity Week 2014: the combined annual meeting of The Obesity Society (TOS) and the American Society for Metabolic & Bariatric Surgery (ASMBS), Boston, MA, 2–7 November 2014; the International Diabetes Federation–Western Pacific Region (IDF-WPR) Congress 2014, Singapore, 21–24 November 2014; Nutrition Society of Australia (NSA) Annual Scientific Meeting, Hobart, Australia, 26–28 November 2014.

² Supported by the National Health and Medical Research Council of Australia (project grant 103415) and the Agency for Science, Technology and Research, Singapore (postgraduate research scholarship to JT).

³ Funding sponsors had no role in the design, conduct, or reporting of the study or the decision to submit the manuscript for publication.

⁴ Supplemental Tables 1 and 2 are available from the “Supplemental data” link in the online posting of the article and from the same link in the online table of contents at <http://ajcn.nutrition.org>.

*To whom correspondence should be addressed. E-mail: grant.brinkworth@csiro.au.

Received April 7, 2015. Accepted for publication July 2, 2015.

doi: 10.3945/ajcn.115.112581.

varying in macronutrient composition may offer individualized approaches for treatment (1). However, the efficacy of various diets is an important consideration in guiding clinical practice. Specifically, very-low-carbohydrate, high-fat diets have become popular but few well-controlled studies have comprehensively examined their long-term effects on glycemic control and cardiovascular disease (CVD)¹¹ risk in type 2 diabetes (T2D). This lack of research has precluded health authorities from making conclusive recommendations regarding the use of very-low-carbohydrate diets for T2D management (1).

Very-low-carbohydrate diets that typically replace carbohydrate with fat are often criticized for increasing saturated fat, which elevates LDL cholesterol, which is a primary CVD risk target (2, 3). Meta-analyses of previous trials have suggested that very-low-carbohydrate diets promote less-favorable LDL cholesterol responses than do traditional high-carbohydrate, low-fat (HC) diets (4, 5). Previous studies have also limited the assessment of glycemic control to glycated hemoglobin (HbA1c) (6–11); frequently without an objective quantification of diabetes medication changes or the assessment of glycemic variability (GV), which is an emerging independent risk factor for diabetes-related complications (12, 13). Moreover, very-low-carbohydrate diets have typically been assessed without the inclusion or control of physical activity as part of a comprehensive lifestyle-modification program (6–9, 11). Previous studies have also examined the effects of very-low-carbohydrate diets by using ad libitum approaches (6–11). Consequently, differences in energy intake and weight loss between comparison diets limit the understanding of the metabolic efficacy of different dietary approaches.

We recently reported, in obese adults with T2D, that a lifestyle-modification program that incorporated a very-low-carbohydrate, high-unsaturated fat/low-saturated fat (LC) diet achieved greater reductions in HbA1c, GV, diabetes medication requirements, and improvements in the blood lipid profile (greater reductions in triglycerides and increases in HDL cholesterol without any detrimental effect on LDL cholesterol) than did an energy-matched HC diet after 24 wk (14). In the current study, we report the findings over a more clinically pertinent time frame after 1 y to provide information about the longer-term sustainability of any diet-related effects.

METHODS

Design overview

Participants, the study design, and dietary interventions of this single-center, randomized controlled study were previously described (14). The Commonwealth Scientific Industrial Research Organization Human Research Ethics Committee approved the study, and all participants provided written informed consent.

¹¹ Abbreviations used: CONGA-1, continuous overall net glycemic action of observations 1 h apart; CONGA-4, continuous overall net glycemic action of observations 4 h apart; CRP, C-reactive protein; CVD, cardiovascular disease; FFM, fat-free mass; GV, glycemic variability; HbA1c, glycated hemoglobin; HC, high carbohydrate, low fat; HOMA2-IR, homeostasis model assessment of insulin resistance index 2 to assess insulin resistance; HOMA2-%B, homeostasis model assessment index 2 to assess β cell function; LC, very low carbohydrate, high unsaturated fat, low saturated fat; MAGE, mean amplitude of glycemic excursion; MES, medication effect score; SD_{Glucose}, SD of blood glucose; T2D, type 2 diabetes.

Setting and participants

The study was conducted at the Commonwealth Scientific and Industrial Research Organisation Clinical Research Unit (Adelaide, Australia) between May 2012 and September 2013. Overweight and obese adults [BMI (in kg/m²): 26–45; age: 35–68 y] with T2D (HbA1c \geq 7.0% or taking a diabetes medication) were recruited via a public advertisement. Exclusion criteria were as follows: type 1 diabetes; impaired renal function, proteinuria, or abnormal liver function assessed at screening; any overt endocrinopathy (other than stable treated thyroid disease); history of malignancy; respiratory disease, gastrointestinal disease, or CVD; pregnancy or lactation; and a history of an eating disorder or smoking or having a current eating disorder or current smoking.

Random assignment and interventions

In a parallel design, participants were block-matched for age, sex, BMI, HbA1c, and diabetes medication by using random varying block sizes before a random computer-generated assignment to either an LC or an HC diet in a 1:1 ratio (**Figure 1**). Randomization procedures (sequence generation and allocation concealment) were performed by research associates not involved in outcome assessments and the intervention delivery.

At baseline, diet plans were individualized and matched for energy with moderate (~30%) restriction to facilitate weight loss (500–1000-kcal/d deficit; 1357–2143-kcal/d energy prescription) (15). Energy-content prescriptions remained constant throughout the study to maintain the isocaloric control between diets. The planned macronutrient compositions were, for the LC diet, 14% of total energy from carbohydrate (<50 g/d), 28% of energy as protein, and 58% of energy as total fat (35% mono-unsaturated fat and 13% polyunsaturated fat) and, for the HC diet, 53% of energy as carbohydrate (emphasis on low-glycemic index foods), 17% of energy as protein, and <30% of energy as total fat (15% monounsaturated fat and 9% polyunsaturated fat) to reflect conventional dietary guidelines (16). Both diets limited saturated fat to <10% of energy. Diets were structured to include specific foods to achieve the targeted macronutrient profile (**Supplemental Table 1**), which were listed in a quantitative food record that participants completed daily. Participants met individually with a dietitian (every 2 wk for 12 wk and monthly thereafter), and key foods (~30% of total energy) that were representative of assigned diet profiles were provided for 12 wk. Thereafter, key foods or vouchers worth 50 Australian dollars were provided on alternate months. Participants undertook, free of charge, 60-min professionally supervised exercise classes in a circuit training format on 3 nonconsecutive days per week that incorporated moderate intensity aerobic and resistance exercise that was consistent with diabetes management guidelines (17). Attendance records were kept, and participants were encouraged to make up missed sessions. To maximize adherence to study visits, participants were provided with an appointment schedule at the commencement of the study and received appointment reminders (phone calls or text messages) before visits.

Outcomes and follow-up

The primary outcome was the change in HbA1c (Institute of Medical and Veterinary Science Pathology). Secondary outcomes

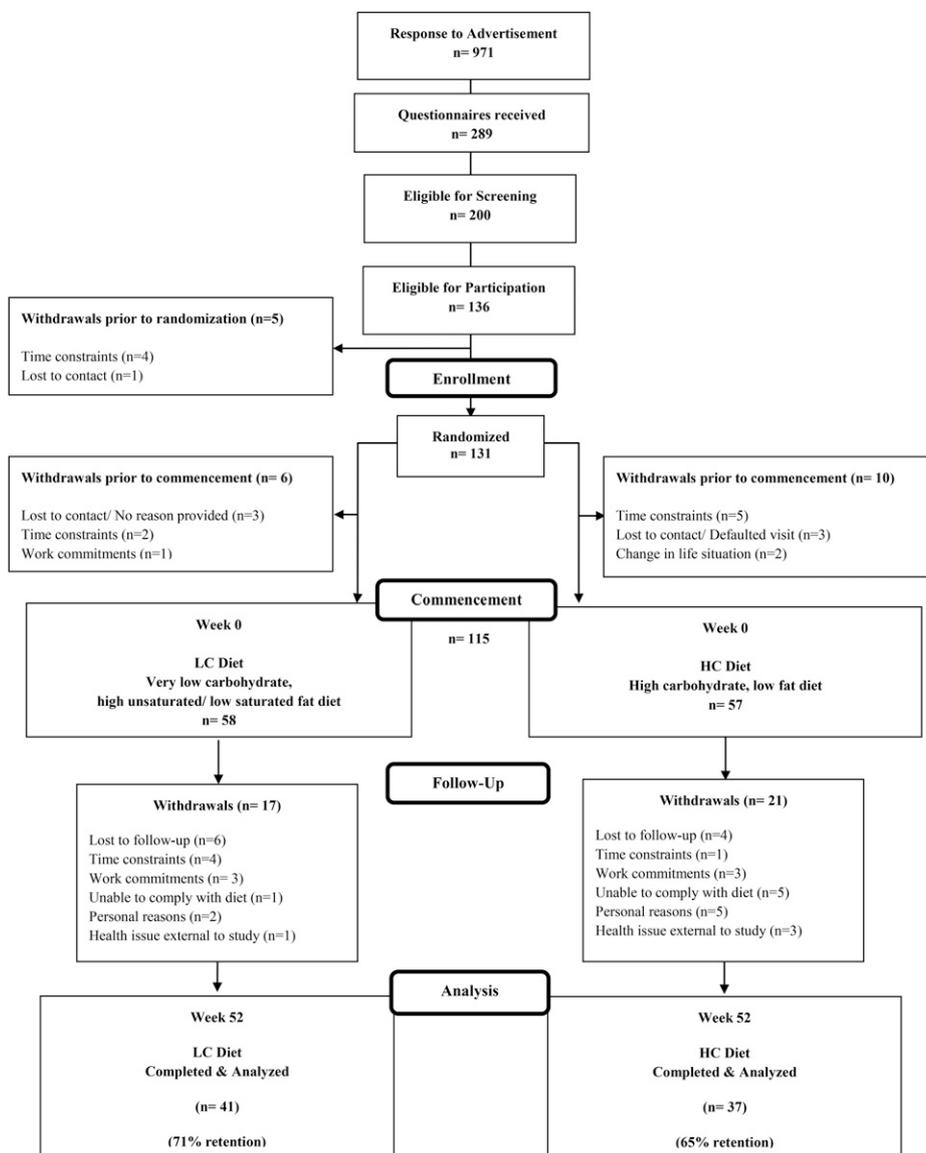


FIGURE 1 Study flow diagram.

were changes in GV, fasting blood glucose, diabetes medication, weight, blood lipids, and blood pressure. Weight was assessed monthly; all other outcomes were assessed at weeks 0, 24, and 52. Although the diet assignment was discernible by participants and diet interventionists, blinding was maintained for researchers involved in the outcome assessment and data analysis until study completion.

Height was measured with use of a stadiometer (SECA), body mass was measured with use of calibrated electronic scales (Mercury AMZ1), and waist circumference was measured by using a tape measure positioned 3 cm above the iliac crest. Fat mass and fat-free mass (FFM) were determined by using whole-body dual-energy X-ray absorptiometry (Lunar Prodigy; General Electric Corp.). Seated blood pressure was measured by using automated sphygmomanometry (SureSigns VS3; Phillips). Plasma glucose, serum total cholesterol, HDL cholesterol, triglycerides, and C-reactive protein (CRP) were measured with a Roche Hitachi 902 auto-analyzer (Hitachi Science Systems Ltd.) with use of standard enzymatic kits (Roche Diagnostics). LDL cholesterol was calculated by using Friedewald's equation (18). Plasma insulin concentrations were

determined with use of a commercial enzyme immunoassay kit (Mercodia AB). We used the homeostasis model assessment index 2 to assess β cell function (HOMA2-%B) and the homeostasis model assessment of insulin resistance index 2 to assess insulin resistance (HOMA2-IR) (19).

Diurnal glucose profiles (48 h, consisting of interstitial glucose readings every 5 min) were collected with use of continuous blood glucose monitoring (iPro 2; Medtronic). GV measures computed from continuous glucose monitoring data were as follows: the minimum, maximum, and mean blood glucose; intraday SD of blood glucose ($SD_{Glucose}$); mean amplitude of glycemic excursions (MAGEs) (average of blood glucose excursions >1 SD of the mean blood glucose value) (20); continuous overall net glycemic action of observations 1 h apart (CONGA-1) and continuous overall net glycemic action of observations 4 h apart (CONGA-4) (SD of differences between observations) (21); and glucose range. The MAGEs and continuous overall net glycemic action were computed by using an automated algorithm (22). The proportion of total time spent in

the hypoglycemic range (<3.9 mmol/L), euglycemic range (3.9–10 mmol/L), or hyperglycemic range (>10 mmol/L), as defined by American Diabetes Association glycemic control targets (23), were calculated.

Medications (including doses and schedules) at baseline and changes throughout the study were documented. Changes in diabetes medication requirements were quantified by the anti-glycemic medication effect score (MES), which was computed on the basis of the potency and dosage of diabetes medications including insulin (6). A higher MES corresponded to a higher diabetes medication requirement.

Dietary intake was assessed randomly from 7 consecutive days of daily weighed food records for every 14-d period. Data were analyzed with Foodworks Professional Edition Version 7 software (2012; Xyris Software) to calculate the average quarterly nutrient intake over 52 wk. The ratio of 24-h urinary urea to creatinine (Institute of Medical and Veterinary Science) was assessed as a marker of protein intake (24). Plasma β -hydroxybutyrate concentrations were assessed monthly as a marker of reduced carbohydrate intake (RANBUT D-3 Hydroxybutyrate kit; Antrim). Physical activity levels were assessed with 7 consecutive days of triaxial accelerometry (GT3X+model; ActiGraph) by using pre-defined validity cutoffs (25) and exercise-session attendance.

Statistical analysis

Data were examined for normality, and the following skewed variables were transformed before analyses: HbA1c (reciprocal transformation); FFM, accelerometry data, insulin, HOMA2-IR, and HOMA2-%B (square-root transformation); and fasting glucose, $SD_{Glucose}$, the glucose range, MAGEs, CRP, the MES, and β -hydroxybutyrate (logarithmic transformation). Group differences in baseline characteristics and exercise attendance were compared by using independent *t* tests and chi-square tests for continuous and categorical variables, respectively. The primary analysis was performed by using a random-coefficient analysis with data assumed to be missing at random. The restricted maximum-likelihood, mixed-effects model permitted a variable number of observations for participants, and an unstructured covariance accounted for the correlation between repeated measures over time by allowing the intercept for individuals to vary randomly. The model included all available data from the 115 participants who commenced the study, and changes from weeks 0 to 52 are reported. The model contained the following fixed effects: the main effect for each time-point, diet group assignment, and diet group-by-time point interaction. The proportion of total time spent in the hypoglycemic, hyperglycemic, or euglycemic range was analyzed by using mixed β regression with generalized estimating equations via the GLIMMIX procedure (SAS software, version 9.2; SAS Institute Inc.) (26). A repeated-measures ANOVA with diet as the between-subject factor and time as the within-subject factor was used to assess changes in dietary intake, β -hydroxybutyrate concentrations, and the urinary urea: creatinine excretion ratio between groups. The trial was designed to have 80% power to detect a previously reported 0.7% absolute difference in HbA1c (primary outcome) between diets (6, 7, 27). Results are presented as estimated marginal means and 95% CIs by using a linear mixed-effects model analysis and were performed with SPSS 20.0 for Windows software (SPSS Inc.), unless otherwise stated. Statistical tests were 2 tailed with significance set at $P < 0.05$.

RESULTS

Participants

A total of 115 participants (LC-diet group: $n = 57$; HC-diet group: $n = 58$) commenced the study. Baseline characteristics did not differ between groups (Table 1). Sixteen participants withdrew before the commencement and assignment disclosure (Figure 1). After 52 wk, 68% of participants (LC-diet group: $n = 41$; HC-diet group: $n = 37$) completed the study (Table 2). Attrition rates were comparable between diets ($P = 0.51$).

Glycemic control and variability

HbA1c and fasting blood glucose were similarly reduced in both groups ($P \geq 0.10$; Table 2). Compared with the HC diet, the LC diet produced at least ~ 2 -fold greater mean (95% CI) decreases in GV indexes including MAGEs [LC diet: -1.7 mmol/L (-2.3 , -1.1 mmol/L); HC diet: -0.8 mmol/L (-1.4 , -0.2 mmol/L); $P = 0.09$], $SD_{Glucose}$ [LC diet: -0.7 mmol/L (-0.9 , -0.5 mmol/L); HC diet: -0.4 mmol/L (-0.6 , -0.2 mmol/L); $P = 0.07$], CONGA-1 [LC diet: -0.5 mmol/L (-0.6 , -0.3 mmol/L); HC diet: -0.05 mmol/L (-0.2 , 0.1 mmol/L); $P = 0.003$], and CONGA-4 [LC diet: -1.1 mmol/L (-1.4 , -0.8 mmol/L); HC diet: -0.5 mmol/L (-0.8 , -0.2 mmol/L); $P = 0.02$] (Figure 2), which indicated a greater diurnal blood glucose stability.

Compared with participants who consumed the HC diet, subjects who consumed the LC diet were more likely to spend a lower proportion of time in the hyperglycemic range (P -time \times diet = 0.049) with a trend for a greater proportion of time in the euglycemic range ($P = 0.07$). Both diet groups spent a comparable proportion of time in the hypoglycemic range ($P = 0.33$).

Medication changes

The LC diet achieved a greater reduction in the antiglycemic MES than did the HC diet ($P = 0.02$). A greater proportion of LC-diet participants (52%) compared with HC-diet participants (21%) experienced a $\geq 20\%$ reduction in the antiglycemic MES ($P < 0.01$; Table 2). For each individual who completed the study, changes in diabetes medication and the total daily dose at baseline and after 52 wk of the dietary interventions are presented in Supplemental Table 2. Ten participants reduced (LC-diet group: $n = 4$; HC-diet group: $n = 6$) and 4 participants increased (LC-diet group: $n = 3$; HC-diet group: $n = 1$) their lipid-lowering medications. Twenty-one participants reduced (LC-diet group: $n = 13$; HC-diet group: $n = 8$) and 3 participants increased (LC-diet group: $n = 2$; HC-diet group: $n = 1$) their antihypertensive medications.

Body weight and composition

Overall, a 9.1% weight loss was achieved (Figure 3) with comparable changes in fat mass, FFM, and waist circumference in both groups ($P \geq 0.09$; Table 2).

Blood pressure, lipids, and other CVD risk markers

Compared with the HC diet, the LC diet resulted in greater reductions in triglyceride and increases in HDL cholesterol. Both groups experienced similar reductions in total cholesterol, LDL

TABLE 1
Baseline participant characteristics¹

	LC diet (n = 58)	HC diet (n = 57)
Age, y	58 ± 7 ²	58 ± 7
Sex, n (%)		
F	21 (36)	28 (49)
M	37 (64)	29 (51)
Duration of diabetes, y	7 ± 5	9 ± 7
Body weight and composition		
Body weight, kg	101.7 ± 14.4	101.6 ± 15.8
BMI, kg/m ²	34.2 ± 4.5	35.1 ± 4.1
Waist circumference, cm	112.4 ± 10.6	112.5 ± 10.6
Total FFM, kg	62.0 ± 10.5	60.1 ± 11.3
Total FM, kg	39.8 ± 10.5	41.5 ± 9.9
FM:FFM ratio	0.7 ± 0.2	0.7 ± 0.2
Glycemic control		
HbA1c, %	7.3 ± 1.1	7.4 ± 1.1
Fasting glucose, mmol/L	7.8 ± 2.1	8.4 ± 2.1
Mean glucose, ³ mmol/L	8.4 ± 2.1	8.7 ± 1.7
Minimum glucose, ³ mmol/L	4.8 ± 1.5	4.8 ± 1.4
Maximum glucose, ³ mmol/L	14.0 ± 3.6	14.3 ± 3.2
Glucose range, ³ mmol/L	9.1 ± 3.5	9.5 ± 2.9
SD _{glucose} , ³ mmol/L	2.0 ± 0.8	2.1 ± 0.7
MAGE, ³ mmol/L	5.2 ± 2.1	5.2 ± 1.9
CONGA- 1, ³ mmol/L	1.7 ± 0.6	1.7 ± 0.5
CONGA- 4, ³ mmol/L	3.0 ± 1.3	2.9 ± 1.0
CVD risk markers		
SBP, mm Hg	130.4 ± 13.1	132.6 ± 13.2
DBP, mm Hg	80.0 ± 8.9	80.8 ± 10.1
Fasting insulin, ⁴ mU/L	16.3 ± 8.3	15.9 ± 7.6
HOMA2-IR ⁴	2.3 ± 1.1	2.2 ± 1.0
HOMA2-%B ⁴	75.5 ± 38.7	67.7 ± 33.4
Total cholesterol, mmol/L	4.5 ± 1.0	4.3 ± 1.0
LDL cholesterol, mmol/L	2.5 ± 0.9	2.4 ± 0.9
HDL cholesterol, mmol/L	1.2 ± 0.2	1.3 ± 0.3
TGs, mmol/L	1.6 ± 0.7	1.4 ± 0.6
CRP, ⁵ mg/L	2.8 ± 2.3	2.7 ± 2.2
Medication		
Diabetes medications		
Antiglycemic MES	1.3 ± 1.0	1.1 ± 1.1
Insulin, n (%)	6 (10)	6 (11)
Metformin, n (%)	46 (79)	41 (72)
Sulfonylureas, n (%)	20 (34)	16 (28)
Thiazolidinediones, n (%)	3 (5)	3 (5)
GLP-1 agonists, n (%)	1 (2)	1 (2)
DPP-4 inhibitors, n (%)	1 (2)	2 (4)
Lipid-lowering medication, n (%)	35 (60)	36 (63)
Antihypertensive medication, n (%)	41 (71)	35 (61)
Physical activity ⁶		
Activity count, counts/min	188.9 ± 65.9	182.7 ± 67.7
MVPA, min/d	46.4 ± 19.2	44.0 ± 19.4
MVPA, % of total wear time	3.5 ± 1.4	3.4 ± 1.5

¹Total analyzed: n = 115 (LC-diet group: n = 58; HC-diet group: n = 57) for all data unless otherwise stated. To convert mM/L to mg per deciliter, multiply by 18 (for glucose), 38.7 (for cholesterol), and 88.6 (for TGs). All baseline characteristics were not significantly different between diet groups (P > 0.05) by using the independent samples t test (for continuous variables) or the chi-square test (for categorical variables). CONGA-1, continuous overall net glycemic action of observations 1 h apart; CONGA-4, continuous overall net glycemic action of observations 4 h apart; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; DPP-4, dipeptidyl-peptidase-4; FFM, fat-free mass; FM, fat mass; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; HC, high carbohydrate, low fat; HOMA2-IR, homeostasis model assessment of insulin resistance index 2 to assess insulin resistance; HOMA2-%B, homeostasis model assessment index 2 to assess β cell function; LC, very low carbohydrate, high unsaturated fat, low saturated fat; MAGE, mean amplitude of glycemic excursion; MES, medication effect score; MVPA, moderate to vigorous intensity physical activity SBP, systolic blood pressure; SD_{glucose}, SD of blood glucose; TG, triglyceride.

²Mean ± SD (all such values).

³Computed from continuous glucose monitoring data.

⁴Total analyzed: n = 103 (LC-diet group: n = 52; HC-diet group: n = 51) for insulin, HOMA2-IR, and HOMA2-%B data; 12 participants who were taking insulin medication at baseline were excluded from these analyses.

⁵Total analyzed n = 105 (LC-diet group: n = 54; HC-diet group: n = 51) for CRP data; 10 participants with CRP concentrations >10 mg/L at baseline were excluded from these analyses.

⁶Computed from accelerometry data.

TABLE 2

Estimated marginal changes in body composition, glycemic control, and cardiovascular disease risk markers after 52 wk of consumption of an LC or an HC diet¹

Variable	LC diet	HC diet	Difference in change between groups	<i>P</i>
Body composition				
BMI, kg/m ²	-3.2 (-3.9, -2.6) ²	-3.5 (-4.2, -2.9)	0.3 (-0.6, 1.2)	0.31
Waist circumference, cm	-9.8 (11.9, -7.7)	-9.1 (-11.2, -7.0)	-0.7 (-3.7, 2.3)	0.36
Total FFM, kg	-1.8 (-2.3, -1.2)	-1.6 (-2.2, -1.0)	-0.2 (-1.0, 0.6)	0.67
Total FM, kg	-7.9 (-9.7, -6.0)	-8.6 (-10.5, -6.8)	0.8 (-1.8, 3.4)	0.09
FM:FFM ratio	-0.1 (-0.1, -0.08)	-0.1 (-0.2, -0.1)	0.01 (-0.03, 0.1)	0.15
Glycemic control				
HbA1c, %	-1.0 (-1.2, -0.7)	-1.0 (-1.3, -0.8)	0.1 (-0.3, 0.5)	0.65
Fasting glucose, mmol/L	-0.7 (-1.3, -0.1)	-1.5 (-2.1, -0.8)	0.8 (-0.1, 1.6)	0.10
Glucose, ³ mmol/L	-1.3 (-1.9, -0.8)	-1.5 (-2.1, -1.0)	0.2 (-0.6, 1.0)	0.09
Minimum glucose, ³ mmol/L	-0.3 (-0.7, 0.2)	-0.6 (-1.0, -0.1)	0.3 (-0.4, 1.0)	0.42
Maximum glucose, ³ mmol/L	-2.6 (-3.7, -1.6)	-2.0 (-3.1, -0.9)	-0.6 (-2.2, 0.9)	0.17
Glucose range, ³ mmol/L	-2.4 (-3.4, -1.3)	-1.4 (-2.5, -0.4)	-0.9 (-2.4, 0.5)	0.31
CVD risk markers				
SBP, mm Hg	-7.1 (-10.6, -3.7)	-5.8 (-9.4, -2.2)	-1.3 (-6.3, 3.7)	0.81
DBP, mm Hg	-6.2 (-8.2, -4.1)	-6.4 (-8.4, -4.3)	0.2 (-2.7, 3.1)	0.38
Total cholesterol, mmol/L	-0.1 (-0.3, 0.1)	-0.1 (-0.3, 0.1)	-0.02 (-0.3, 0.3)	0.97
LDL cholesterol, mmol/L	-0.1 (-0.3, 0.1)	-0.2 (-0.4, 0.03)	0.1 (-0.2, 0.4)	0.76
HDL cholesterol, mmol/L	0.1 (0.1, 0.2)	0.06 (-0.01, 0.1)	0.1 (-0.03, 0.2)	0.002
TG, mmol/L	-0.4 (-0.5, -0.2)	-0.01 (-0.2, 0.2)	-0.4 (-0.6, -0.1)	0.001
Fasting insulin, ⁴ mU/L	-5.8 (-7.6, -4.0)	-4.9 (-6.8, -3.1)	-0.9 (-3.5, 1.7)	0.49
HOMA2-IR ⁴	-0.7 (-0.9, -0.5)	-0.6 (-0.9, -0.4)	-0.08 (-0.4, 0.2)	0.69
HOMA2-%B ⁴	-8.4 (-13.8, -2.9)	-1.3 (-6.8, 4.2)	-7.1 (-14.8, 0.7)	0.15
CRP, ⁵ mg/L	-0.9 (-1.5, -0.2)	-1.2 (-1.9, -0.6)	0.4 (-0.5, 1.3)	0.65
Medication				
Antiglycemic MES	-0.5 (-0.7, -0.4)	-0.2 (-0.4, -0.06)	-0.3 (-0.6, -0.05)	0.02
MES reduction ≥20%, <i>n</i> (%)	30 (52)	12 (21)	—	0.001
MES reduction ≥50%, <i>n</i> (%)	17 (29)	10 (18)	—	0.14
Physical activity⁶				
Activity count, counts/min	16.9 (-2.0, 35.8)	41.3 (22.0, 60.6)	-24.3 (-51.4, 2.7)	0.24
MVPA, min/d	4.1 (-1.3, 9.5)	9.1 (3.6, 14.6)	-5.0 (-12.7, 2.7)	0.52
MVPA, % of total wear time	0.3 (-0.1, 0.7)	0.7 (0.3, 1.1)	-0.4 (-0.9, 0.2)	0.53

¹Total analyzed: *n* = 115 (LC-diet group: *n* = 58; HC-diet group: *n* = 57) for all data unless otherwise stated. To convert mM/L to mg per deciliter, multiply by 18 (for glucose), 38.7 (for cholesterol), and 88.6 (for TGs). Values were determined by using a linear mixed-effects model analysis. *P* values are for between-group differences over time (time × diet interaction). CONGA-1, continuous overall net glycemic action of observations 1 h apart; CONGA-4, continuous overall net glycemic action of observations 4 h apart; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; FFM, fat-free mass; FM, fat mass; HbA1c, glycated hemoglobin; HC, high carbohydrate, low fat; HOMA2-IR, homeostasis model assessment of insulin resistance index 2 to assess insulin resistance; HOMA2-%B, homeostasis model assessment index 2 to assess β cell function; LC, very low carbohydrate, high unsaturated fat, low saturated fat; MAGE, mean amplitude of glycemic excursion; MES, medication effect score; MVPA, moderate to vigorous intensity physical activity SBP, systolic blood pressure; TG, triglyceride.

²Mean; 95% CIs in parentheses (all such values).

³Total analyzed: *n* = 115 (LC-diet group: *n* = 58; HC-diet group: *n* = 57) for continuous glucose monitoring data; the continuous glucose monitoring device did not collect valid data for one LC-diet participant at 24 wk because of poor system connectivity.

⁴Total analyzed: *n* = 106 (LC-diet group: *n* = 55; HC-diet group: *n* = 51) for insulin, HOMA2-IR, and HOMA2-%B data; 9 participants who were taking an insulin medication at baseline, 24 wk, and 52 wk or who withdrew before these time points were excluded from these analyses.

⁵Total analyzed: *n* = 112 (LC-diet group: *n* = 56; HC-diet group: *n* = 56) for CRP data; 3 participants with CRP concentrations >10 mg/L at baseline, 24, wk, and 52 wk or who withdrew before these time points were excluded from these analyses.

⁶Total analyzed: *n* = 115 for accelerometry data; 2 participants (LC-diet group: *n* = 1; HC-diet group: *n* = 1) at 24 wk and 6 participants (LC-diet group: *n* = 4; HC-diet group: *n* = 2) at 52 wk who did not meet the validity criteria were excluded from these analyses.

cholesterol, blood pressure, CRP, insulin, HOMA2-IR, and HOMA2-%B (*P* ≥ 0.15; Table 2).

Diet and physical activity compliance

Reported dietary intakes were consistent with the planned diets; energy intakes did not differ between groups (Table 3). The LC-diet group had lower intakes of carbohydrate and

fiber and higher intakes of protein, total fat, saturated fat, monounsaturated fat, polyunsaturated fat, and cholesterol than the HC-diet group did (*P* < 0.001 for all). Plasma β-hydroxybutyrate concentrations increased more with the LC diet after 4 wk and remained higher over 52 wk than with the HC diet (*P*-time by diet < 0.001; data not shown). Similarly, the ratio of urinary urea:creatinine excretion increased with the LC diet and remained higher than with the HC diet over 52 wk

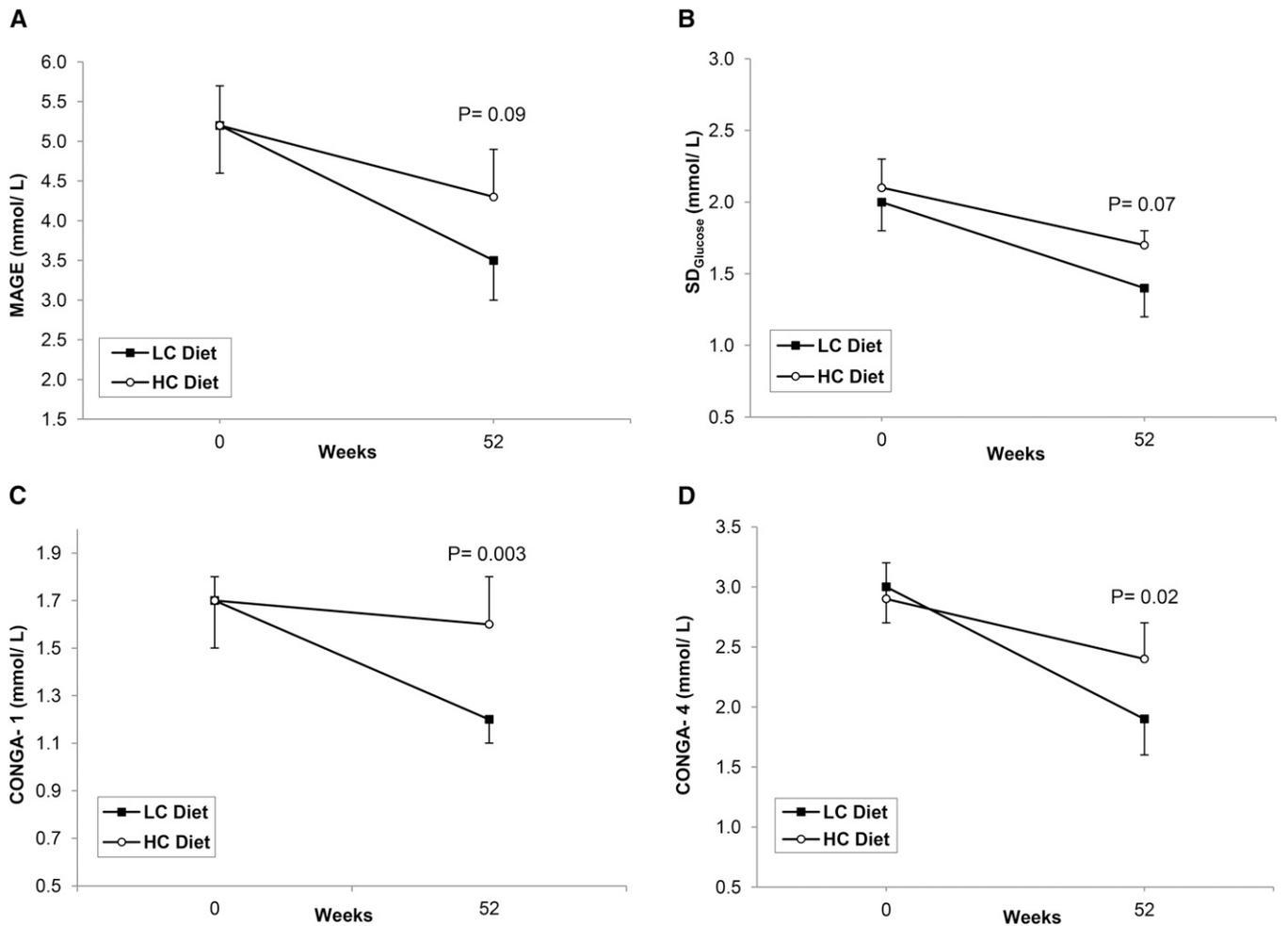


FIGURE 2 Estimated mean (95% CI) marginal changes in glycemic variability indexes [MAGE (A), SD_{Glucose} (B), CONGA-1 (C), and CONGA-4 (D)] after 52 wk of consumption of an LC or HC diet on the basis of a linear mixed-effects model ($n = 115$). P values are for-between group differences. CONGA-1, continuous overall net glycemic action of observations 1 h apart; CONGA-4, continuous overall net glycemic action of observations 4 h apart; HC, high carbohydrate, low fat; LC, very low carbohydrate, high unsaturated fat, low saturated fat; MAGE, mean amplitude of glycemic excursion; SD_{Glucose}, SD of blood glucose.

(P -time by diet < 0.01 ; data not shown), which indicated a lower carbohydrate and higher protein intake in LC-diet participants, respectively.

Mean \pm SD exercise-session attendance was similar between groups (LC diet: $81.2 \pm 18.0\%$; HC diet: $77.5 \pm 21.6\%$; $P = 0.47$). Both groups had similar increases in mean activity count and time spent in moderate to vigorous physical activity ($P \geq 0.24$; Table 2).

Adverse events

Twenty-one participants (LC-diet group: $n = 8$; HC-diet group: $n = 13$) reported musculoskeletal ailments. These ailments were associated with exercise training in 14 participants (LC-diet group: $n = 6$; HC-diet group: $n = 8$) that allowed program continuation after recovery. Three participants (LC-diet group: $n = 2$; HC-diet group: $n = 1$) reported gastrointestinal disorders (constipation and diverticulitis); one HC-diet participant reported esophageal ulcers with *Helicobacter pylori* infection; one LC-diet participant had a nonhospitalized hypoglycemia incident; one HC-diet participant was hospitalized for arrhythmia with suspected

heart failure; one LC-diet participant and one HC-diet participant were diagnosed with prostate cancer and melanoma, respectively. Other adverse events include nonstudy related workplace injuries

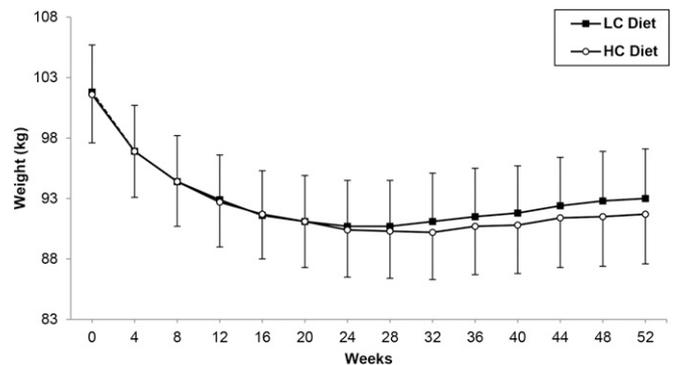


FIGURE 3 Estimated mean (95% CI) marginal changes in body weight after 52 wk of consumption of an LC or HC diet on the basis of a linear mixed-effects model ($n = 115$). For between-group differences, $P = 0.18$. HC, high carbohydrate, low fat; LC, very low carbohydrate, high unsaturated fat, low saturated fat.

TABLE 3
Energy intake and macronutrient composition of diets over 52 wk¹

Nutrient and diet group	0–12 wk	13–24 wk	25–36 wk	37–52 wk
Total energy, kcal				
LC	1552 ± 236	1599 ± 249	1705 ± 312	1700 ± 335
HC	1555 ± 171	1627 ± 183	1689 ± 239	1737 ± 309
Carbohydrate, ² g				
LC	54.0 ± 7.0	59.7 ± 11.0	70.7 ± 17.7	74.0 ± 18.1
HC	202.0 ± 25.2	207.5 ± 24.5	215.1 ± 32.0	217.6 ± 35.1
Carbohydrate, ² E%				
LC	13.4 ± 1.4	14.4 ± 2.3	15.9 ± 2.7	16.6 ± 2.5
HC	50.5 ± 2.4	49.9 ± 2.4	49.8 ± 3.6	49.0 ± 3.2
Protein ² , g				
LC	103.1 ± 15.8	102.9 ± 15.5	105.2 ± 18.4	106.1 ± 18.9
HC	72.1 ± 8.4	75.7 ± 9.8	76.4 ± 11.0	78.5 ± 14.8
Protein, ² E%				
LC	27.0 ± 1.5	26.3 ± 1.7	25.3 ± 2.1	25.6 ± 2.1
HC	18.9 ± 1.0	18.9 ± 1.2	18.4 ± 1.2	18.4 ± 1.4
Total fat, ² g				
LC	95.9 ± 17.3	98.3 ± 18.4	103.4 ± 21.6	101.5 ± 23.5
HC	42.4 ± 6.6	45.4 ± 6.9	48.8 ± 10.9	51.8 ± 14.1
Total fat, ² E%				
LC	54.4 ± 2.5	54.1 ± 3.2	53.5 ± 3.3	52.5 ± 3.0
HC	24.1 ± 2.7	24.6 ± 2.5	25.4 ± 3.5	26.1 ± 3.5
Saturated fat, ² g				
LC	17.2 ± 3.2	18.6 ± 3.4	21.0 ± 5.2	21.2 ± 5.5
HC	12.6 ± 2.2	14.4 ± 3.1	15.9 ± 4.4	16.8 ± 4.8
Saturated fat, ² E%				
LC	9.8 ± 0.9	10.3 ± 0.9	10.9 ± 1.4	11.0 ± 1.4
HC	7.2 ± 1.0	7.8 ± 1.4	8.3 ± 1.7	8.5 ± 1.5
Monounsaturated fat, ² E%				
LC	30.7 ± 1.7	30.3 ± 2.2	29.4 ± 2.3	28.8 ± 2.3
HC	11.4 ± 1.5	11.4 ± 1.2	11.5 ± 1.6	12.0 ± 1.9
Polyunsaturated fat, ² E%				
LC	12.4 ± 1.0	12.0 ± 1.3	11.6 ± 1.6	11.1 ± 1.4
HC	4.1 ± 0.6	4.0 ± 0.6	4.2 ± 0.9	4.2 ± 0.8
Total cholesterol, ² mg				
LC	238 ± 44	250 ± 50	260 ± 62	270 ± 67
HC	126 ± 21	150 ± 37	150 ± 39	151 ± 37
Dietary fiber, ² g				
LC	24.4 ± 3.6	24.7 ± 3.9	25.6 ± 4.7	25.7 ± 4.5
HC	31.6 ± 3.9	31.0 ± 3.6	31.2 ± 4.4	31.4 ± 5.7

¹All values are means ± SDs. Total number of diet records analyzed at each time point: $n = 78$ (LC-diet group: $n = 41$; HC-diet group: $n = 37$). E%, percentage of energy; HC, high carbohydrate, low fat; LC, very low carbohydrate, high unsaturated fat, low saturated fat.

²Between-group differences at each time point, $P < 0.001$ (repeated-measures ANOVA).

in 4 participants (LC-diet group: $n = 3$; HC-diet group: $n = 1$); one LC-diet participant was hospitalized for pneumonia; one LC-diet participant was diagnosed with malignant hyperthermia; one HC-diet participant developed an anaphylactic reaction to the influenza vaccine; and one HC-diet participant had a motor vehicle accident.

DISCUSSION

This study showed that hypocaloric, energy-matched LC and HC diets administered as part of a holistic lifestyle-modification program incorporating regular exercise achieved substantial weight loss, improved glycemic control, and reduced CVD risk factors in obese adults with T2D. In addition, compared with the HC diet, the LC diet achieved greater reductions in diabetes

medications and enhanced improvements in diurnal blood glucose stability and the lipid profile. These effects were sustained over 1 y, which indicated the durability of the findings over the long term.

Previous studies that compared ad libitum very-low-carbohydrate diets with calorie-restricted HC diets in T2D reported mixed results with some studies reporting greater weight loss after a very-low-carbohydrate diet (11, 28), and others reporting no differential effect (6–8, 10). In the current study, diets were isocalorically prescribed and achieved comparable weight loss, which suggested that the caloric deficit, independent of the macronutrient composition, is the primary determinant of weight loss. The overall 9.1% weight loss achieved was clinically relevant and associated with an expected 25% reduction in mortality risk (29), which was comparable with that of

pharmacotherapy (3–11 kg) (30) and superior to that achieved by many other lifestyle interventions in T2D (2–5 kg) (31, 32). This marked weight loss could be attributed to the intensity of the lifestyle intervention, which included a detailed diet and exercise prescription administered with regular professional support (33). Therefore, although the study's highly controlled clinical setting may have limited the generalizability of results to a community setting, the substantial weight loss achieved underscored the importance of comprehensive lifestyle-modification programs for long-term weight loss success.

The sustained weight loss achieved promoted substantial reductions in blood pressure, insulin resistance, and inflammation. The blood pressure reductions observed have been associated with clinically significant reductions in risks of diabetes-related complications, CVD, and mortality (34). Reboli et al. (35) reported risk of stroke decreases by 13% for each 5-mm Hg reduction in systolic blood pressure and by 11.5% for each 2-mm Hg reduction in diastolic blood pressure.

In contrast to previous studies that administered very-low-carbohydrate diets *ad libitum*, the current study compared isocaloric LC and HC diets that led to comparable weight loss and HbA1c reductions. These results are consistent with some previous studies (6, 8–10). However, other studies have shown greater HbA1c reductions with a very-low-carbohydrate diet (7, 27, 28) that could be explained by differences in energy intakes and weight loss between the very-low-carbohydrate and HC diets examined. The 1% HbA1c reduction achieved in the current study is comparable with the reductions observed in the Look AHEAD (Action for Health in Diabetes) study (from 7.3% to 6.6%) after an intensive lifestyle intervention in T2D (36). These HbA1c reductions are similar to those observed with monoglycemic and combination noninsulin hypoglycemic agents (37), and are expected to be associated with marked reductions in diabetes related mortality and complications (38). Although several randomized controlled trials that targeted HbA1c (<6%) with intensive medical therapy showed no benefit for reducing CVD events or mortality (39–41), it is possible this absence of a benefit observed may have been attributed to medication-related side effects, including hypoglycemia, which has been associated with increased mortality risk (42).

In the current study, although no apparent diet differences in HbA1c were evident, greater reductions in diabetes medications occurred with the LC diet. Compared with the HC diet, the LC diet achieved comparable HbA1c reductions with a significantly greater reduction in diabetes medication requirements, suggesting the achievement of better glycemic control. Because of the progressive nature of T2D, a reduced reliance on pharmacotherapy to achieve glycemic control presents important advantages for long-term diabetes management. These advantages include potential reductions in treatment costs and a reduced likelihood of drug-related side effects including hypoglycemia risk and weight gain with implications for long-term weight-loss maintenance. A health economics analysis was beyond the scope of this trial but should be undertaken in future studies to evaluate the cost effectiveness of the interventions examined. Nevertheless, the current results suggest that lowering HbA1c by a lifestyle modification (diet, exercise, and weight loss) may confer greater health benefits than by intensifying medications through concurrent improvements of other metabolic risk factors and the mitigation of pharmacotherapy-related side effects.

In addition to the diet-related difference in diabetes medications requirements, compared with the HC diet, the LC diet consistently induced at least ~2-fold greater reductions across several GV markers, although significance was not achieved for all markers, which was possibly due to the lack of statistical power. Specifically, the LC diet achieved significant, greater effectiveness at mitigating short-term GV assessed by using CONGA-1 and CONGA-4 to achieve a more physiologically stable blood glucose profile. GV (a measure of the amplitude, frequency, and duration of diurnal glucose fluctuations), including postprandial glucose excursions, is emerging as independent risk factors for diabetes complications (12, 13, 43–46). Collectively, these results suggest that an LC diet may have greater usefulness for optimizing glycemic control and preventing diabetes complications. However, individuals with uncontrolled diabetes at baseline (HbA1c >11.0%) were excluded from the study, and whether these results are generalizable to these patients requires confirmation.

Similar to previous studies, the LC diet achieved greater reductions in triglycerides and increases in HDL cholesterol than with the HC diet (4, 47). These results suggest that an LC diet is more effective at improving lipid abnormalities associated with insulin resistance and the metabolic syndrome, which increases CVD risk in T2D (48). Combined with the substantial weight loss achieved, these consistent blood lipid changes that reflected differences in carbohydrate intake between groups showed the strength of the study to achieve and maintain high dietary adherence throughout the intervention.

In contrast to meta-analyses of previous trials that reported improvements in LDL cholesterol favoring HC compared with very-low-carbohydrate diets (4, 5), the current study showed both diets achieved comparable LDL-cholesterol reductions. This result may have been attributed to the replacement of carbohydrate with unsaturated fats in the LC diet (49, 50) and was consistent with previous observations in carbohydrate-restricted diets that showed greater reductions in LDL cholesterol with lower compared with higher saturated fat intakes (51). These results highlight the clinical significance of the unique fatty acid profile of the LC diet used in the current study that was similarly low in saturated fat as in the HC diet, therefore distinguishing it from very-low-carbohydrate diets that have been investigated in previous studies that were typically high in saturated fat. Consequently, an LC diet that is high in unsaturated fat and low in saturated fat diet may provide the optimal combination for improving glycemic control and CVD risk reduction in T2D. Furthermore, a separate line of evidence has suggested a very-low-carbohydrate diet alters the LDL subclass profile by preferentially increasing large, buoyant LDL particles that, unlike small, dense LDL particles, are less atherogenic (51). This evidence suggests that CVD risk assessment should consider both the quantity and quality of LDL subfractions (52). Therefore, an additional evaluation of the effects on clinical endpoints such as CV events and diabetes complications will provide greater understanding of the therapeutic potential of LC diets.

In conclusion, both the LC and HC diets produced comparable weight loss and improvements in HbA1c and several CVD risk markers. The LC diet had more favorable effects on triglycerides, HDL cholesterol, and glycemic control as shown by lower diabetes medication requirements and greater attenuation of diurnal blood glucose fluctuation. These results suggest that LC diets

with high-unsaturated and low-saturated fat contents may be advantageous for T2D management over the long term.

We thank the following individuals of the Clinical Research Team at the Commonwealth Scientific and Industrial Research Organisation–Animal, Food and Health Sciences, Adelaide, South Australia (SA) for their work: Ann McGuffin, Julia Weaver, and Vanessa Courage for coordinating the trial; Pennie Taylor, Janna Lutze, Paul Foster, Gemma Williams, Hannah Gilbert, and Fiona Barr for assisting in designing and implementing dietary intervention; Lindy Lawson and Theresa Mckinnon for nursing expertise; Vanessa Russell, Cathryn Pape, Candita Dang, Andre Nikolic, and Sylvia Usher for performing biochemical assays; Thomas Wycherley for conducting dual-energy X-ray absorptiometry scans; Julie Syrette for assisting with the data management; Kylie Lange and Mary Barnes for assisting with statistical analyses; Luke Johnston, and Annie Hastwell (Fit for Success, SA), Kelly French, Jason Delfos, Kristi Lacey-Powell, Marilyn Woods, John Perrin, Simon Pane, and Annette Beckett (SA Aquatic Centre & Leisure Centre), and Angie Mondello and Josh Gniadek (Boot Camp Plus, SA) for conducting exercise sessions.

The authors' responsibilities were as follows—GDB: was the guarantor of this work and, as such, had full access to all data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis; JT and GDB: drafting of the manuscript; NDL-M, CHT, MN, JDB, GAW, and WSY: critical revision of the manuscript for intellectual content; GDB, MN, JDB, NLD-M, and CHT: obtainment of funding; GDB, NDL-M, CHT, MN, and JDB: study supervision; and all authors: study concept and design, analysis and interpretation data, and reading and approval of the final manuscript. None of the authors reported a conflict of interest related to the study.

REFERENCES

- Evert AB, Boucher JL, Cypress M, Dunbar SA, Franz MJ, Mayer-Davis EJ, Neumiller JJ, Nwankwo R, Verdi CL, Urbanski P, et al. Nutrition therapy recommendations for the management of adults with diabetes. *Diabetes Care* 2013;36:3821–42.
- Sacks FM, Katan M. Randomized clinical trials on the effects of dietary fat and carbohydrate on plasma lipoproteins and cardiovascular disease. *Am J Med* 2002;113(Suppl 9B):13S–24S.
- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486–97.
- Nordmann AJ, Nordmann A, Briel M, Keller U, Yancy WS Jr., Brehm BJ, Bucher HC. Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2006;166:285–93.
- Bueno NB, de Melo IS, de Oliveira SL, da Rocha Ataide T. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials. *Br J Nutr* 2013;110:1178–87.
- Mayer SB, Jeffreys AS, Olsen MK, McDuffie JR, Feinglos MN, Yancy WS Jr. Two diets with different haemoglobin A1c and antiglycaemic medication effects despite similar weight loss in type 2 diabetes. *Diabetes Obes Metab* 2014;16:90–3.
- Stern L, Iqbal N, Seshadri P, Chicano KL, Daily DA, McGrory J, Williams M, Gracely EJ, Samaha FF. The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. *Ann Intern Med* 2004;140:778–85.
- Davis NJ, Tomuta N, Schechter C, Isasi CR, Segal-Isaacson CJ, Stein D, Zonszein J, Wylie-Rosett J. Comparative study of the effects of a 1-year dietary intervention of a low-carbohydrate diet versus a low-fat diet on weight and glycaemic control in type 2 diabetes. *Diabetes Care* 2009;32:1147–52.
- Guldbrand H, Dizdar B, Bunjaku B, Lindstrom T, Bachrach-Lindstrom M, Fredrikson M, Ostgren CJ, Nystrom FH. In type 2 diabetes, randomisation to advice to follow a low-carbohydrate diet transiently improves glycaemic control compared with advice to follow a low-fat diet producing a similar weight loss. *Diabetologia* 2012;55:2118–27.
- Yancy WS Jr., Westman EC, McDuffie JR, Grambow SC, Jeffreys AS, Bolton J, Chalecki A, Oddone EZ. A randomized trial of a low-carbohydrate diet vs orlistat plus a low-fat diet for weight loss. *Arch Intern Med* 2010;170:136–45.
- Shai I, Schwarzfuchs D, Henkin Y, Shahar DR, Witkov S, Greenberg I, Golan R, Fraser D, Bolotin A, Vardi H, et al. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *N Engl J Med* 2008;359:229–41.
- Tay J, Thompson CH, Brinkworth GD. Glycemic variability- assessing glycemia differently and the implications for dietary management of diabetes. *Annu Rev Nutr* 2015 May 6 (Epub ahead of print; DOI: 10.1146/annurev-nutr-121214-104422).
- Brownlee M, Hirsch IB. Glycemic variability: a hemoglobin A1c-independent risk factor for diabetic complications. *JAMA* 2006;295:1707–8.
- Tay J, Luscombe-Marsh ND, Thompson CH, Noakes M, Buckley JD, Wittert GA, Yancy WS Jr., Brinkworth GD. A very low-carbohydrate, low-saturated fat diet for type 2 diabetes management: a randomized trial. *Diabetes Care* 2014;37:2909–18.
- Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. *Hum Nutr Clin Nutr* 1985;39(Suppl 1):5–41.
- Rodbard HW, Blonde L, Braithwaite SS, Brett EM, Cobin RH, Handelsman Y, Hellman R, Jellinger PS, Jovanovic LG, Levy P, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. *Endocr Pract* 2007;13(Suppl 1):1–68. Erratum in: *Endocr Pract* 2008;14:802–3.
- Colberg SR, Albright AL, Blissmer BJ, Braun B, Chasan-Taber L, Fornhall B, Regensteiner JG, Rubin RR, Sigal RJ, American College of Sports M, et al. Exercise and type 2 diabetes: American College of Sports Medicine and the American Diabetes Association: joint position statement. Exercise and type 2 diabetes. *Med Sci Sports Exerc* 2010;42:2282–303.
- Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972;18:499–502.
- Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care* 2004;27:1487–95.
- Service FJ, Molnar GD, Rosevear JW, Ackerman E, Gatewood LC, Taylor WF. Mean amplitude of glycemic excursions, a measure of diabetic instability. *Diabetes* 1970;19:644–55.
- McDonnell CM, Donath SM, Vidmar SI, Werther GA, Cameron FJ. A novel approach to continuous glucose analysis utilizing glycemic variation. *Diabetes Technol Ther* 2005;7:253–63.
- Baghurst PA. Calculating the mean amplitude of glycemic excursion from continuous glucose monitoring data: an automated algorithm. *Diabetes Technol Ther* 2011;13:296–302.
- American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care* 2014;37(Suppl 1):S14–80.
- Simmons WK. Urinary urea nitrogen-creatinine ratio as indicator of recent protein intake in field studies. *Am J Clin Nutr* 1972;25:539–42.
- Tudor-Locke C, Camhi SM, Troiano RP. A catalog of rules, variables, and definitions applied to accelerometer data in the National Health and Nutrition Examination Survey, 2003–2006. *Prev Chronic Dis* 2012;9:E113.
- Hunger M, Doring A, Holle R. Longitudinal beta regression models for analyzing health-related quality of life scores over time. *BMC Med Res Methodol* 2012;12:144.
- Westman EC, Yancy WS Jr., Mavropoulos JC, Marquart M, McDuffie JR. The effect of a low-carbohydrate, ketogenic diet versus a low-glycemic index diet on glycaemic control in type 2 diabetes mellitus. *Nutr Metab (Lond)* 2008;5:36.
- Rock CL, Flatt SW, Pakiz B, Taylor KS, Leone AF, Brelje K, Heath DD, Quintana EL, Sherwood NE. Weight loss, glycemic control, and cardiovascular disease risk factors in response to differential diet composition in a weight loss program in type 2 diabetes: a randomized controlled trial. *Diabetes Care* 2014; 37:1573–80.
- Aucott L, Poobalan A, Smith WC, Avenell A, Jung R, Broom J, Grant AM. Weight loss in obese diabetic and non-diabetic individuals and long-term diabetes outcomes—a systematic review. *Diabetes Obes Metab* 2004;6:85–94.
- Rueda-Clausen CF, Padwal RS. Pharmacotherapy for weight loss. *BMJ* 2014;348:g3526.
- Terranova CO, Brakenridge CL, Lawler SP, Eakin EG, Reeves MM. Effectiveness of lifestyle-based weight loss interventions for adults with type 2 diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab* 2015;17:371–8.

32. Norris SL, Zhang X, Avenell A, Gregg E, Bowman B, Serdula M, Brown TJ, Schmid CH, Lau J. Long-term effectiveness of lifestyle and behavioral weight loss interventions in adults with type 2 diabetes: a meta-analysis. *Am J Med* 2004;117:762–74.
33. Dombrowski SU, Knittle K, Avenell A, Araujo-Soares V, Snichotta FF. Long term maintenance of weight loss with non-surgical interventions in obese adults: systematic review and meta-analyses of randomised controlled trials. *BMJ* 2014;348:g2646.
34. Arauz-Pacheco C, Parrott MA, Raskin P, American Diabetes Association. Treatment of hypertension in adults with diabetes. *Diabetes Care* 2003;26(Suppl 1):S80–2.
35. Reboldi G, Gentile G, Angeli F, Ambrosio G, Mancina G, Verdecchia P. Effects of intensive blood pressure reduction on myocardial infarction and stroke in diabetes: a meta-analysis in 73,913 patients. *J Hypertens* 2011;29:1253–69.
36. Look AHEAD Research Group, Pi-Sunyer X, Blackburn G, Brancati FL, Bray GA, Bright R, Clark JM, Curtis JM, Espeland MA, Foreyt JP, et al. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the Look AHEAD trial. *Diabetes Care* 2007;30:1374–83.
37. Bennett WL, Maruthur NM, Singh S, Segal JB, Wilson LM, Chatterjee R, Marinopoulos SS, Puhan MA, Ranasinghe P, Block L, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. *Ann Intern Med* 2011;154:602–13.
38. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000;321:405–12.
39. Duckworth W, Abaira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009;360:129–39.
40. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr., Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358:2545–59.
41. Advance Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560–72.
42. Bonds DE, Miller ME, Bergenstal RM, Buse JB, Byington RP, Cutler JA, Dudl RJ, Ismail-Beigi F, Kimel AR, Hoogwerf B, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. *BMJ* 2010;340:b4909.
43. Di Flaviani A, Picconi F, Di Stefano P, Giordani I, Malandrucchio I, Maggio P, Palazzo P, Sgreccia F, Peraldo C, Farina F, et al. Impact of glycemic and blood pressure variability on surrogate measures of cardiovascular outcomes in type 2 diabetic patients. *Diabetes Care* 2011;34:1605–9.
44. Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol JP, Colette C. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA* 2006;295:1681–7.
45. Buscemi S, Re A, Batis JA, Arnone M, Mattina A, Cerasola G, Verga S. Glycaemic variability using continuous glucose monitoring and endothelial function in the metabolic syndrome and in Type 2 diabetes. *Diabet Med* 2010;27:872–8.
46. Ceriello A, Esposito K, Piconi L, Ihnat MA, Thorpe JE, Testa R, Boemi M, Giugliano D. Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. *Diabetes* 2008;57:1349–54.
47. Brinkworth GD, Noakes M, Buckley JD, Keogh JB, Clifton PM. Long-term effects of a very-low-carbohydrate weight loss diet compared with an isocaloric low-fat diet after 12 mo. *Am J Clin Nutr* 2009;90:23–32.
48. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, Taskinen MR, Groop L. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001;24:683–9.
49. Clarke R, Frost C, Collins R, Appleby P, Peto R. Dietary lipids and blood cholesterol: quantitative meta-analysis of metabolic ward studies. *BMJ* 1997;314:112–7.
50. Garg A. High-monounsaturated-fat diets for patients with diabetes mellitus: a meta-analysis. *Am J Clin Nutr* 1998;67:577S–82S.
51. Krauss RM, Blanche PJ, Rawlings RS, Fernstrom HS, Williams PT. Separate effects of reduced carbohydrate intake and weight loss on atherogenic dyslipidemia. *Am J Clin Nutr* 2006;83:1025–31.
52. Krauss RM. Atherogenic lipoprotein phenotype and diet-gene interactions. *J Nutr* 2001;131:340S–35S.

Online Supplemental Material

Online Supplemental Table 1. Food profile of diet interventions

LC Diet, 1429kcal	HC Diet, 1429kcal
<ul style="list-style-type: none">• 30g high fibre, low GI cereal*• 1 crispbread (e.g. Ryvita)*• 250g lean chicken, pork, fish, red meat (3-4 times/ week)*• 40g almonds & 20g pecans*• 3 cups low starch vegetables• (exclude potato/ sweet potato/ corn)• 200ml skim (<1% fat) milk• 100g diet yoghurt• 20g (1 slice) regular cheese• 30g (6 tsp) margarine/oil of monounsaturated variety (e.g. canola oil/ margarine)	<ul style="list-style-type: none">• 40g high fibre, low GI cereal*• 5 crispbread (e.g. Ryvita)*• ½ cup cooked pasta/rice/ potato*• 2 slices wholegrain bread (70g)• 80g lean chicken, pork, red meat (4 times/ week)*• 80g fish (2 times/ week)*• 80g legumes (1 time/ week)*• 3 cups vegetables• 400g fruit• 250mL reduced (1- 2%) fat milk• 150g reduced fat yoghurt• 20g (1 slice) regular cheese• 25g (5 tsp) margarine/oil of monounsaturated variety (e.g. canola oil/ margarine)

* Key foods supplied, representing ~30% of total energy intake

LC diet = Very low carbohydrate, high unsaturated/ low saturated fat diet, HC diet = High carbohydrate, low fat diet, GI= Glycemic Index

Online Supplementary Table 2. Diabetes medication and total daily dose at baseline and after 52 weeks of the dietary interventions ¹

Participant	Diet Group	Diabetes medication	Total daily dose at baseline	Total daily dose after 52 weeks
1	LC	Diabex	2000 mg	ceased
2	LC	Insulin Metformin	30 units 3000 mg	ceased 2000 mg
3	LC	Diabex	1000 mg	ceased
4	LC	Diaformin	1000 mg	ceased
5	LC	Actos Diabex XR Glucovance	45 mg 1000 mg 1000/ 10 mg	45 mg 1000 mg ceased
6	LC	Metformin	2550 mg	500 mg
7	LC	Diamicron MR Metformin	60 mg 2000 mg	ceased 2000 mg
8	LC	Metformin Gliclazide MR Actos	2000 mg 120 mg 30 mg	2000 mg ceased ceased
9	LC	Metformin	2000 mg	ceased
10	LC	Diabex Gliclazide MR	1700 mg 30 mg	1700 mg ceased
11	LC	Metformin	2000 mg	1000 mg

12	LC	Diamicon MR	60 mg	ceased
		Diaformin	1000 mg	ceased
13	LC	Metformin	2000 mg	1000 mg
		Novomix 30	66 units	ceased
14	LC	Byetta	20 µg	20 µg
		Glyade	160 mg	ceased
15	LC	Diamicon MR	120 mg	120 mg
		Diaformin	425 mg	1000 mg
16	LC	Diamicon MR	60 mg	ceased
17	LC	Diabex	3000 mg	2000 mg
		Diamicon MR	120 mg	ceased
18	LC	Diaformin	2000 mg	ceased
		Glyade MR	30 mg	ceased
19	LC	Metformin	1000 mg	1000 mg
20	LC	Metformin	1000 mg	ceased
21	LC	Diabex	2000 mg	ceased
		Diamicon MR	30 mg	ceased
22	LC	Metformin	500 mg	1000 mg
		Diamicon MR	60 mg	ceased
		Daonil	-	2.5 mg
23	LC	Diaformin	3000 mg	2000 mg
		Lantus	50 units	36 units
24	LC	Diamicon MR	60 mg	30 mg
		Metformin	1700 mg	1700 mg

25	LC	Metformin	2000 mg	2000 mg
		Januvia	-	100 mg
26	LC	Metformin	1500 mg	2500 mg
27	LC	Metformin	2000 mg	2000 mg
		Gliclazide	160 mg	ceased
28	LC	Diaformin	3000 mg	3000 mg
		Glimel	15 mg	ceased
29	LC	Metformin	2000 mg	2000 mg
30	LC	Metformin XR	2000 mg	2000 mg
		Lantus	40 units	24 units
31	LC	Metex XR	1000 mg	ceased
		Metformin	-	1000 mg
32	LC	Galvumet	100/ 2000 mg	100/ 2000 mg
33	LC	Metformin	1000 mg	1000 mg
34	LC	Metformin XR	2000 mg	ceased
		Gliclazide MR	120 mg	ceased
		Pioglitazone	15 mg	ceased
		Janumet	-	100/ 2000 mg
35	LC	Metformin	2000 mg	1000 mg
36	LC	Metformin	3000 mg	2000 mg
37	LC	Metformin	2000 mg	2000 mg
		Lantus	40 units	ceased
38	LC	Metformin	3000 mg	3000 mg
		Glyade MR	120 mg	120 mg

39	HC	Metformin	2000 mg	250 mg
40	HC	Diamicron MR	60 mg	ceased
41	HC	Diabex XR	1000 mg	1000 mg
42	HC	Metformin XR	2000 mg	2000 mg
		Glimepiride	4 mg	ceased
		Actos	30 mg	ceased
		Januvia	-	100 mg
43	HC	Diaformin	3000 mg	2000 mg
		Dimirel	4 mg	ceased
		Lantus	16 units	6 units
44	HC	Metformin	500 mg	500 mg
45	HC	Diaformin	1500 mg	1500 mg
46	HC	Glucovance	1000/ 10 mg	1000/ 5 mg
		Metformin	500 mg	500 mg
47	HC	Metformin	1000 mg	ceased
48	HC	Diabex XR	1000 mg	1000 mg
		Diamicron MR	30 mg	30 mg
		Actos	30 mg	ceased
		Trajenta	-	5 mg
49	HC	Diaformin	2550 mg	2550 mg
50	HC	Metformin	500 mg	500 mg
51	HC	Diabex XR	2000 mg	2000 mg
52	HC	Diabex XR	2000 mg	2000 mg
		Diamicron MR	120 mg	120 mg

		Protophane	52 units	ceased
		Novomix 30	-	50 units
		Byetta	-	20 µg
53	HC	Metformin	2000 mg	2000 mg
54	HC	Diabex XR	2000 mg	2000 mg
55	HC	Diaformin	2000 mg	2000 mg
		Diamicron MR	60 mg	60 mg
56	HC	Formet	1000 mg	1700 mg
		Diamicron MR	120 mg	ceased
57	HC	Metformin	1000 mg	1000 mg
58	HC	Diamicron MR	60 mg	30 mg
59	HC	Metformin	2000 mg	2000 mg
		Diamicron MR	90 mg	60 mg
60	HC	Diabex	500 mg	500 mg
61	HC	Diamicron MR	60 mg	30 mg
		Metformin	3000 mg	1500 mg
62	HC	Metex XR	1000 mg	Ceased
63	HC	Avandamet	8/ 2000 mg	8/ 2000 mg
		Trajenta	5 mg	ceased
		Diamicron MR	-	120 mg
64	HC	Diaformin	1000 mg	1000 mg
65	HC	Novomix 30	18 units	8 units
66	HC	Diabex XR	1000 mg	ceased
67	HC	Diabex	2000 mg	2000 mg

		Januvia	-	100 mg
--	--	---------	---	--------

¹Data reported for 67 participants who were on diabetes medications at baseline and completed 52 weeks of the dietary interventions.

LC diet - Very low carbohydrate, high unsaturated/ low saturated fat diet; HC diet - High carbohydrate, low fat diet