



A Very Low-Carbohydrate, Low-Saturated Fat Diet for Type 2 Diabetes Management: A Randomized Trial

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OBJECTIVE

To comprehensively compare the effects of a very low-carbohydrate, high-unsaturated/low-saturated fat diet (LC) with those of a high-unrefined carbohydrate, low-fat diet (HC) on glycemic control and cardiovascular disease (CVD) risk factors in type 2 diabetes (T2DM).

RESEARCH DESIGN AND METHODS

Obese adults ($n = 115$, BMI 34.4 ± 4.2 kg/m², age 58 ± 7 years) with T2DM were randomized to a hypocaloric LC diet (14% carbohydrate [<50 g/day], 28% protein, and 58% fat [$<10\%$ saturated fat]) or an energy-matched HC diet (53% carbohydrate, 17% protein, and 30% fat [$<10\%$ saturated fat]) combined with structured exercise for 24 weeks. The outcomes measured were as follows: glycosylated hemoglobin (HbA_{1c}), glycemic variability (GV; assessed by 48-h continuous glucose monitoring), antiglycemic medication changes (antiglycemic medication effects score [MES]), and blood lipids and pressure.

RESULTS

A total of 93 participants completed 24 weeks. Both groups achieved similar completion rates (LC 79%, HC 82%) and weight loss (LC -12.0 ± 6.3 kg, HC -11.5 ± 5.5 kg); $P \geq 0.50$. Blood pressure ($-9.8/-7.3 \pm 11.6/6.8$ mmHg), fasting blood glucose (-1.4 ± 2.3 mmol/L), and LDL cholesterol (-0.3 ± 0.6 mmol/L) decreased, with no diet effect ($P \geq 0.10$). LC achieved greater reductions in triglycerides (-0.5 ± 0.5 vs. -0.1 ± 0.5 mmol/L), MES (-0.5 ± 0.5 vs. -0.2 ± 0.5), and GV indices; $P \leq 0.03$. LC induced greater HbA_{1c} reductions ($-2.6 \pm 1.0\%$ [-28.4 ± 10.9 mmol/mol] vs. $-1.9 \pm 1.2\%$ [-20.8 ± 13.1 mmol/mol]; $P = 0.002$) and HDL cholesterol (HDL-C) increases (0.2 ± 0.3 vs. 0.05 ± 0.2 mmol/L; $P = 0.007$) in participants with the respective baseline values HbA_{1c} $>7.8\%$ (62 mmol/mol) and HDL-C <1.29 mmol/L.

CONCLUSIONS

Both diets achieved substantial improvements for several clinical glycemic control and CVD risk markers. These improvements and reductions in GV and antiglycemic medication requirements were greatest with the LC compared with HC. This suggests an LC diet with low saturated fat may be an effective dietary approach for T2DM management if effects are sustained beyond 24 weeks.

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An energy-reduced, high-carbohydrate, low-protein, low-fat (HC) diet is the traditional dietary approach for type 2 diabetes (T2DM) management (1). However, evidence shows dietary carbohydrate elicits greater postprandial glucose (PPG) responses compared with fat or protein, which independently suppress this response (2–4). This has increased interest in and the use of very low-carbohydrate diets (LC; 20–70 g carbohydrates/day) that are also high in protein and fat for diabetes management (5).

Previous studies in T2DM show that, compared with an HC diet, an LC diet achieves at least comparable reductions in body weight, blood pressure, and insulin concentrations (6–8), with greater improvements in glycemic control (6,8–10). However, these studies are limited by poor dietary compliance and the absence and/or control of physical activity, an integral component of lifestyle modification for weight and diabetes management (11). Energy intake and weight loss differences between comparison diets secondary to their ad libitum designs, particularly for the LC diet, may also confound the metabolic outcomes reported. Prior studies also limit glycemic control assessment to glycosylated hemoglobin (HbA_{1c}) and fasting glucose (6–8,10). However, glycemic variability (GV; amplitude, frequency, and duration of diurnal glucose fluctuations) and PPG excursions are also considered independent risk factors for diabetes complications, including cardiovascular disease (CVD) risk (12,13), yet no study has systematically evaluated the effects of LC diets on these outcomes. These limitations preclude clear conclusions, highlighting the necessity for well-controlled studies that comprehensively examine effects of LC diets on glycemic control in T2DM.

Previous studies also show that compared with an HC diet, whereas an LC diet favorably lowers triglycerides (TGs) and elevates HDL cholesterol (HDL-C), greater increases in LDL cholesterol (LDL-C), a primary therapeutic target and CVD risk marker (14), are observed (6,8,15–17). LC diets used in previous studies, in addition to increasing total fat intake, concomitantly increased saturated fat intake, which elevates LDL-C (18). Furthermore, a prospective cohort study suggests a vegetable-based LC diet is associated with lower all-cause and CVD mortality risk (19).

These data suggest the health effects of LC diets may be influenced by fat quality, and an LC diet with high-unsaturated and low-saturated fat content may promote greater improvements in glycemic control in T2DM without detrimental effects on LDL-C. However, this hypothesis and the combined effects of these dietary components have not been tested in a well-controlled intervention trial. This study compared the effects of a hypocaloric LC, high-unsaturated/low-saturated fat diet with those of an energy-matched HC diet, as part of a holistic lifestyle modification program, on glycemic control, including GV and CVD risk factors in T2DM.

RESEARCH DESIGN AND METHODS

Study Population

Overweight/obese adults ($n = 115$, BMI 26–45 kg/m², age 35–68 years) with T2DM (previously diagnosed with HbA_{1c} $\geq 7.0\%$ [53 mmol/mol] and/or taking antiglycemic medication), recruited via public advertisement, participated in this single-center, randomized, controlled study, conducted between May 2012 and February 2013 at the Commonwealth Scientific and Industrial Research Organization (CSIRO) Clinical Research Unit in Adelaide, Australia (Fig. 1). Exclusion criteria were type 1 diabetes; proteinuria (urinary albumin-to-creatinine ratio ≥ 30 mg/mmol); impaired renal function (eGFR < 60 mL/min); abnormal liver function (alanine aminotransferase [ALT], aspartate aminotransferase [AST], or γ -glutamyl transferase [GGT] ≥ 2.5 times the normal upper limit) assessed at screening; any significant endocrinopathy (other than stable treated thyroid disease); history of malignancy (other than nonmelanoma); liver, respiratory, gastrointestinal, or cardiovascular disease; pregnancy or lactation; clinical depression; history of/or current eating disorder; or smoking. Participants provided written, informed consent to the study protocol approved by the CSIRO Human Ethics Committee.

Study Design and Intervention

In a parallel design, participants were block matched for age, sex, BMI, HbA_{1c}, and antiglycemic medication using random varying block sizes before random computer-generated assignment to either an LC or HC diet in a 1:1 ratio. Randomization procedures (sequence generation and allocation concealment)

were performed by research associates independent of outcome assessments and intervention delivery. Planned macronutrient profiles of the diet interventions were as follows: LC diet, 14% of total energy as carbohydrate (objective to restrict intake to < 50 g/day), 28% protein, and 58% total fat (35% mono-unsaturated fat and 13% polyunsaturated fat); HC diet, 53% carbohydrate with emphasis on low-glycemic index foods, 17% protein, and $< 30\%$ total fat (15% monounsaturated fat and 9% polyunsaturated fat). Saturated fat was limited to $< 10\%$ in both diets. Planned nutrient composition of the HC diet comparison group was based on conventional recommendations of current guidelines (1). Diet plans were individualized and matched for energy levels with moderate restriction (500–1,000 kcal/day) (20). Diets were structured to include specific foods (Table 1), listed in a quantitative food record that participants completed daily. To facilitate compliance, participants met individually with a dietitian biweekly for 12 weeks and monthly thereafter. Dietitians provided dietary advice and instruction on the eating plan and reporting requirements. Participants were supplied key foods ($\sim 30\%$ total energy) representative of their allocated diet profile for 12 weeks and key foods or AU \$50 food voucher on alternate months thereafter.

Under supervision of exercise professionals, participants undertook, free of charge, 60-min structured exercise classes on 3 nonconsecutive days per week, incorporating moderate-intensity aerobic/resistance exercises, consistent with diabetes management guidelines (11). Attendance records were kept and participants were encouraged to make up any missed sessions. Apart from the planned exercise program, participants were instructed to maintain habitual physical activity levels.

Outcomes

Primary outcome was HbA_{1c} (IMVS, Adelaide, Australia). Secondary outcomes included GV, antiglycemic medication changes, and blood lipids and pressure. Outcomes were assessed at weeks 0 and 24. Although diet assignment was discernible by participants and interventionists, blinding was maintained for outcome assessment and data analysis.

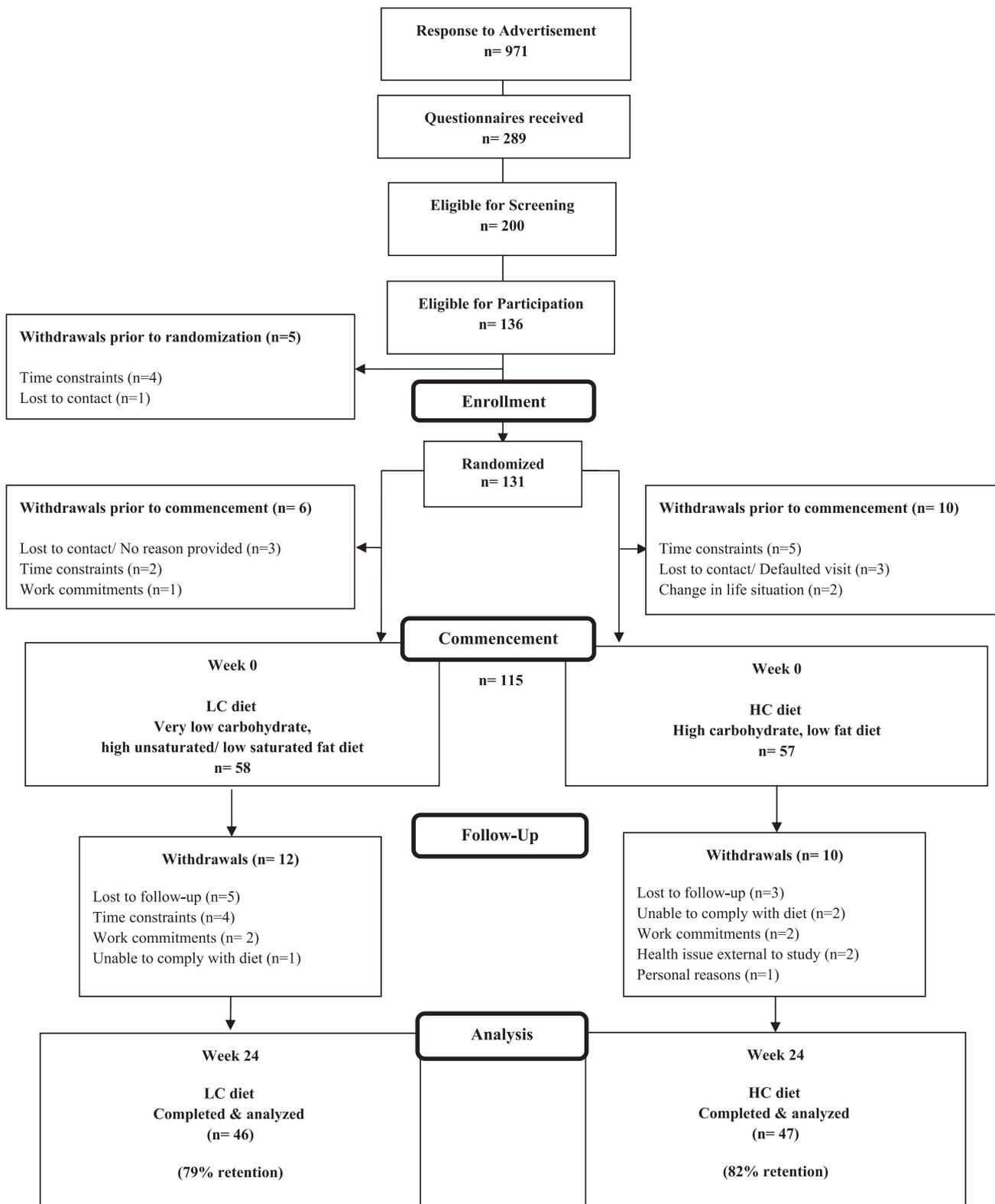


Figure 1—Participant flow.

Anthropometric Measurements and Blood Pressure

Height was measured using a stadiometer. Body mass was measured using calibrated electronic scales (Mercury

AMZ1, Tokyo, Japan) and waist circumference by tape measure positioned 3 cm above the iliac crest. Body composition was determined by whole-body DEXA (Lunar Prodigy; General Electric

Corporation, Madison, WI) to assess total fat (FM) and fat-free mass (FFM). Seated blood pressure was measured by automated sphygmomanometry (SureSigns VS3; Philips, Andover, MA).

Table 1—Food profile of diet interventions

LC diet, 1,429 kcal	HC diet, 1,429 kcal
• 30 g high-fiber, low-GI cereal*	• 40 g high-fiber, low-GI cereal*
• 1 crispbread (e.g., Ryvita)*	• 5 crispbread (e.g., Ryvita)*
• 250 g lean chicken, pork, fish, red meat (3-4 times/week)	• 1/2 cup cooked pasta/rice/potato*
• 40 g almonds and 20 g pecans*	• 2 slices wholegrain bread (70 g)
• 3 cups low-starch vegetables (exclude potato/sweet potato/corn)	• 80 g lean chicken, pork, red meat (4 times/week)*
• 200 mL skim (<1% fat) milk	• 80 g fish (2 times/week)*
• 100 g diet yogurt	• 80 g legumes (1 time/week)*
• 20 g (1 slice) regular cheese	• 3 cups vegetables
• 30 g (6 tsp) margarine/oil of monounsaturated variety (e.g., canola oil/margarine)	• 400 g fruit
	• 250 mL reduced-fat (1–2%) milk
	• 150 g reduced-fat yogurt
	• 20 g (1 slice) regular cheese
	• 25 g (5 tsp) margarine/oil of monounsaturated variety (e.g., canola oil/margarine)

GI, glycemic index. *Key foods supplied, representing ~30% of total energy intake.

Glycemic Control and Variability and CVD Factors

Plasma glucose, serum total cholesterol, HDL-C, TG, and C-reactive protein (CRP) were measured on a Roche Hitachi 902 auto-analyzer (Hitachi Science Systems Ltd., Ibaraki, Japan) using standard enzymatic kits (Roche Diagnostics, Indianapolis, IN). LDL-C levels were calculated by the Friedewald equation (21). Plasma insulin concentrations were determined using a commercial enzyme immunoassay kit (Mercodia AB, Uppsala, Sweden). HOMA index 2 assessed β -cell function (HOMA2-%B) and insulin resistance (HOMA2-IR) (22).

Diurnal glucose profiles (48 h; consisting of interstitial glucose level readings every 5 min) were collected using continuous blood glucose monitoring (CGM-iPro 2 device; Medtronic, North Ryde, Australia). GV measures subsequently computed include total area under the curve standardized by valid wear time ($AUC_{total\ per\ min}$); minimum, maximum, and mean blood glucose; intraday standard deviation ($SD_{intraday}$); mean amplitude of glycemic excursions (MAGE; average of blood glucose excursions exceeding 1 SD of the mean blood glucose value) (23); continuous overall net glycemic action (CONGA-1 and CONGA-4, SD of differences between observations 1 or 4 h apart, respectively) (24); glucose range; interday SD of glucose readings between successive 24-h periods ($SD_{interday}$); and mean of daily blood glucose differences (MODD; difference between paired blood glucose values during successive

24-h periods) (25). MAGE, CONGA, and MODD were computed by automated algorithm (26). Percentage of total time spent in the hypoglycemic (<3.9 mmol/L), euglycemic (3.9–10 mmol/L), or hyperglycemic range (>10.0 mmol/L), defined by American Diabetes Association glycemic control targets (27), was calculated.

Medication Changes

Medications at baseline and changes throughout the study were documented. Medication effects score (MES) (10) based on potency and dosage of antiglycemic agents and insulin usage was used to quantify antiglycemic medication levels. Higher MES corresponds to higher antiglycemic medication usage.

Dietary Intake and Adherence

Dietary intake and adherence was assessed from 7 consecutive days (including 2 weekend days) of daily weighed food records for every 14-day period. These data were analyzed using Foodworks Professional Edition Version 7 (Xyris Software 2012, Highgate Hill, Australia) to calculate the average nutrient intake over the entire 24 weeks. Urine samples (24 h) were collected to assess urea-to-creatinine ratio (IMVS), as an objective marker of protein intake (28). Plasma β -hydroxybutyrate levels were assessed monthly as a marker of reduced carbohydrate intake (RANBUT D-3 Hydroxybutyrate kit; Randox, Antrim, U.K.).

Physical Activity

Physical activity levels were assessed with 7 consecutive days of triaxial

accelerometry (GT3X+ model; ActiGraph, Pensacola, FL), using previously defined validity cutoffs (29).

Statistical Analysis

Data were examined for normality; non-normally distributed variables (HbA_{1c} , glucose range, MAGE, CONGA-1, CRP, HOMA2-%B, and β -hydroxybutyrate) were logarithmically transformed. Baseline characteristics, dietary data, and exercise session attendance between groups were assessed by independent Student *t* tests and χ^2 tests for continuous and categorical variables, respectively. This study used a randomized groups, pretest-posttest design, and data were analyzed using ANCOVA to test between-group differences at posttest assessments (week 24), with baseline and sex as covariates. ANCOVA confers greater statistical power, correcting for regression to the mean (30). Comparisons of regression slopes (test of the interaction between the pretest data and the grouping variable) were conducted to determine whether the ANCOVA assumption of homogeneity of regression slopes was met. For variables that did not meet this assumption (HDL, HbA_{1c} , $AUC_{total\ per\ min}$, and mean and maximum glucose), the Johnson-Neyman (J-N) procedure (31) was appropriately used to identify regions of significance along the observed range of the pretest measure that indicated where group (diet) differences on the posttest measures occurred (i.e., where the diet groups differed). For these variables, group means above and below

the identified critical points on the pretest measures are presented. Percentage of total time spent in the hypo-, hyper-, or euglycemic range was analyzed by β -regression using mean and precision parameterization, which is efficient for characterizing percentages (SAS software, version 9.2; SAS Institute Inc., Cary, NC) (32). Repeated-measures ANOVA with diet and sex set as between-subject factors and time as a within-subject factor was used to assess changes in β -hydroxybutyrate between groups. No sex effects were observed for any outcome. The trial was designed to have 80% power to detect a 0.7% (7.7 mmol/mol) absolute difference in HbA_{1c} (primary outcome) between the diets that has been previously reported (6,8,10) and considered clinically significant (33). Data are presented as means \pm SD, unless otherwise stated. Statistical tests were two-tailed with statistical significance at $P < 0.05$ and performed using SPSS 20.0 for Windows (SPSS Inc., Chicago, IL) unless otherwise stated.

RESULTS

Participants

A total of 115 participants commenced the study. Baseline characteristics were similar between groups (mean \pm SD; LC and HC): age 58 ± 7 and 58 ± 7 years, weight 101.7 ± 14.4 and 101.6 ± 15.8 kg, and BMI 34.2 ± 4.5 and 35.1 ± 4.1 kg/m²; sex distribution (males/females) 37/21 and 29/28; HbA_{1c} 7.3 ± 1.1 and $7.4 \pm 1.1\%$ (56 ± 12 and 57 ± 12 mmol/mol) (Supplementary Table 1). A total of 16 participants withdrew prior to commencement and diet assignment disclosure (Fig. 1). A total of 93 (81% retention) participants completed the study and were included in the primary analysis (Table 2). Attrition rates were comparable between diets ($P = 0.50$), with no difference in baseline characteristics between participants who completed/withdrew ($P \geq 0.25$).

Diet and Physical Activity Compliance

Reported dietary intakes were consistent with diet prescriptions (Supplementary Table 2). Energy intake did not differ between groups (LC $1,563 \pm 225$ kcal, HC $1,587 \pm 171$ kcal; $P = 0.56$). Relative to the HC diet group, the LC diet group consumed less carbohydrate (LC 56.7 ± 8.0 vs. HC 204.9 ± 22.8 g;

14 ± 2 vs. $50 \pm 2\%$ total energy) and dietary fiber (24.7 ± 3.5 vs. 31.1 ± 3.2 g), more protein (102.8 ± 14.7 vs. 73.6 ± 8.3 g; 27 ± 1 vs. $19 \pm 1\%$ total energy), total fat (96.5 ± 16.5 vs. 44.3 ± 7.4 g; 54 ± 3 vs. $25 \pm 3\%$ total energy), saturated fat (10.0 ± 0.9 vs. $7.5 \pm 1.1\%$ total energy), monounsaturated fat (30.4 ± 1.8 vs. $11.5 \pm 1.3\%$ total energy), polyunsaturated fat (12.2 ± 1.1 vs. $4.1 \pm 0.6\%$ total energy), and cholesterol (243 ± 42 vs. 138 ± 25 mg); $P < 0.001$ for all. Plasma β -hydroxybutyrate concentrations showed a time-by-diet interaction ($P < 0.001$); levels increased threefold more on the LC compared with the HC diet after the initial 4 weeks and remained higher throughout the study, indicating a relatively lower carbohydrate intake. There was a significant diet effect for urinary urea-to-creatinine excretion ratio ($P < 0.001$), which decreased with the HC diet (-2.2 ± 6.2) and increased with the LC diet (4.2 ± 8.7), indicating a higher protein intake in the LC diet group.

Exercise session attendance was similar between groups (LC $76.7 \pm 14.8\%$, HC $78.5 \pm 18.5\%$; $P = 0.59$). Mean activity count and time spent in moderate to vigorous physical activity from accelerometry increased similarly in both groups ($P \geq 0.51$) (Table 2).

Body Weight, Composition, and CVD Risk Markers

At week 24, body weight, BMI, waist circumference, FM, FFM, FM-to-FFM ratio, blood pressure, insulin, HOMA2-IR, HOMA2-%B, total cholesterol, LDL-C, and CRP were similar between groups ($P \geq 0.10$) (Table 2). Diet composition significantly affected TG ($P = 0.001$) with fivefold greater reductions with the LC diet. For HDL-C, due to the heterogeneity of regression slopes, indicating the diet effects depended on baseline levels for this parameter (significant group \times baseline interaction), the J-N method was used to explore the intervention effect to identify the range on the baseline measure where differences between groups were statistically significant. This revealed that for the range of available baseline values, greater increases in HDL-C occurred with the LC diet ($P = 0.007$) for participants with a baseline HDL-C < 1.3 mmol/L, with no difference between groups for participants with baseline HDL-C ≥ 1.3 mmol/L.

Glycemic Control and Variability

Due to the significant interaction of group and baseline HbA_{1c} ($P = 0.02$), indicating the diet effects depended on initial HbA_{1c} levels, the J-N method was used to explore the intervention effect on HbA_{1c} and identify the range of the baseline measure where differences between groups were statistically significant (Fig. 2). The result showed the LC diet reduced HbA_{1c} to a greater extent among participants with baseline HbA_{1c} $> 7.8\%$ (62 mmol/mol), with no diet effect in participants with baseline HbA_{1c} $\leq 7.8\%$. Percentage weight loss was not different between the groups for participants with baseline HbA_{1c} $> 7.8\%$ (LC $-11.9 \pm 5.6\%$, HC $-11.2 \pm 5.4\%$; $P = 0.77$).

No significant diet effect on fasting blood glucose, minimum blood glucose, and glucose SD_{interdays} occurred ($P \geq 0.06$). Compared with HC, the LC diet had greater reductions in blood glucose range, SD_{intraday}, MAGE, CONGA-1, CONGA-4, and MODD ($P \leq 0.049$). Due to heterogeneity of regression slopes indicated by the significant interaction of group and baseline mean blood glucose, maximum blood glucose, and blood glucose AUC_{total per min} ($P \leq 0.04$), the J-N method was used to explore the intervention effect in these parameters. This showed the LC diet produced greater reductions ($P \leq 0.04$) among participants with a baseline mean glucose > 8.6 mmol/L, maximum blood glucose > 13.2 mmol/L, and AUC_{total per min} > 18.0 mmol/L, for these parameters respectively (Table 2).

β -Regression analyses demonstrated that participants on the LC diet were 85% more likely and 56% less likely to spend higher proportions of time in the euglycemic and hyperglycemic ranges, respectively, compared with their HC diet counterparts ($P \leq 0.03$). The LC diet group was also 16% less likely compared with HC diet group to spend more time in the hypoglycemic range, but the residual plots suggested model misfit ($P = 0.42$).

Medication Changes

At baseline, medication usage and the antiglycemic MES were similar in both groups ($P \geq 0.29$ for all) (Supplementary Table 1). After 24 weeks, the LC diet group experienced twofold greater reductions in the antiglycemic MES, with more participants experiencing a reduction

Table 2—Body weight and composition, glycemic control, and cardiovascular risk markers after 24 weeks on an LC diet or an energy-matched HC diet*

	LC diet (n = 46)		HC diet (n = 47)		P value†
	Week 24	Change	Week 24	Change	
Body weight and composition					
Body weight (kg)	88.1 (13.7)	−12.0 (6.3)	89.9 (14.9)	−11.5 (5.5)	0.57
BMI (kg/m ²)	30.0 (4.4)	−4.0 (2.0)	30.9 (4.2)	−4.0 (1.8)	0.74
Waist circumference (cm)	100.5 (10.9)	−10.6 (7.1)	103.2 (11.9)	−9.1 (6.4)	0.25
Total FFM (kg)‡	58.8 (10.0)	−1.7 (2.0)	57.7 (10.6)	−1.9 (1.7)	0.66
Total FM (kg)‡	29.1 (11.8)	−10.2 (5.7)	32.2 (11.3)	−9.6 (5.2)	0.64
FM-to-FFM ratio (kg/kg)‡	0.5 (0.2)	−0.2 (0.1)	0.6 (0.2)	−0.1 (0.1)	0.76
Glycemic control					
Fasting glucose (mmol/L)	6.8 (1.5)	−1.1 (2.2)	6.7 (1.6)	−1.6 (2.5)	0.67
Mean glucose (mmol/L)§					
Baseline >8.6	6.9 (1.2)	−3.4 (2.2)	7.6 (1.8)	−2.5 (1.6)	0.01††
Baseline ≤8.6	6.2 (0.8)	−0.9 (1.2)	6.6 (1.1)	−0.8 (1.0)	
Minimum glucose (mmol/L)§	4.2 (0.9)	−1.9 (2.0)	4.3 (1.1)	−1.6 (1.6)	0.81
Maximum glucose (mmol/L)§					
Baseline >13.2	10.1 (2.3)	−6.3 (2.6)	12.7 (3.7)	−3.6 (4.0)	0.04‡‡
Baseline ≤13.2	9.3 (1.7)	−1.4 (2.3)	9.3 (1.8)	−2.1 (2.1)	
Glucose range (mmol/L)§	5.5 (2.0)	−3.6 (3.1)	7.1 (3.5)	−2.5 (3.8)	0.049
SD _{intraday} (mmol/L)§	1.1 (0.5)	−0.9 (0.7)	1.5 (0.7)	−0.6 (0.8)	0.004
SD _{interday} (mmol/L)	0.3 (0.2)	−0.2 (0.5)	0.4 (0.3)	−0.1 (0.5)	0.06
MAGE (mmol/L)§	2.9 (1.4)	−2.3 (2.0)	3.9 (2.1)	−1.4 (2.3)	0.03
CONGA-1 (mmol/L)§	1.0 (0.4)	−0.6 (0.5)	1.4 (0.6)	−0.3 (0.6)	0.002
CONGA-4 (mmol/L)§	1.6 (0.8)	−1.4 (1.1)	2.1 (1.1)	−0.8 (1.2)	0.005
MODD (mmol/L)	1.1 (0.5)	−0.8 (0.7)	1.5 (0.7)	−0.5 (0.9)	0.002
AUC _{total per min} (mmol/L)§					
Baseline >18.0	13.3 (2.7)	−7.9 (5.0)	15.4 (4.0)	−5.4 (3.7)	0.005§§
Baseline ≤18.0	12.5 (1.7)	−1.6 (3.5)	12.5 (2.8)	−2.5 (3.6)	
CVD risk markers					
SBP (mmHg)	120.1 (11.4)	−11.0 (10.6)	122.9 (14.2)	−8.7 (12.5)	0.26
DBP (mmHg)	72.4 (6.3)	−8.2 (5.6)	74.3 (7.5)	−6.4 (7.8)	0.10
Insulin (mU/L)¶	8.7 (4.7)	−7.7 (6.2)	9.5 (4.7)	−6.5 (5.7)	0.22
HOMA2-IR¶	1.2 (0.6)	−1.1 (0.9)	1.3 (0.7)	−1.0 (0.8)	0.23
HOMA2-%B¶	62.3 (30.8)	−8.8 (19.9)	64.2 (25.1)	−4.7 (22.9)	0.12
Total cholesterol (mmol/L)	4.0 (0.9)	−0.3 (0.70)	4.0 (0.9)	−0.3 (0.9)	0.89
LDL-C (mmol/L)	2.1 (0.8)	−0.3 (0.5)	2.1 (0.8)	−0.3 (0.7)	0.81
HDL-C (mmol/L)					
Baseline <1.3	1.3 (0.2)	0.2 (0.3)	1.1 (0.2)	0.05 (0.2)	0.007
Baseline ≥1.3	1.5 (0.2)	0.03 (0.2)	1.6 (0.2)	−0.06 (0.2)	
TG (mmol/L)	1.1 (0.5)	−0.5 (0.5)	1.3 (0.5)	−0.1 (0.5)	0.001
CRP (mg/L)#	2.1 (2.1)	−0.6 (1.7)	1.6 (1.5)	−0.6 (1.7)	0.62
Medications					
Antiglycemic MES	0.8 (0.7)	−0.5 (0.5)	1.0 (1.1)	−0.2 (0.5)	0.003
Proportion of cohort that achieved decrease in MES					
≥20% decrease, n (%)	31 (67.4)		13 (27.7)		<0.005
≥50% decrease, n (%)	16 (34.8)		8 (17.0)		0.05
Physical activity**					
Mean activity count (counts/min)	232.7 (88.5)	44.3 (57.9)	232.5 (78)	51.7 (45.3)	0.51
MVPA (min/day)	58.0 (25.9)	11.8 (17.0)	55.7 (21.6)	12.6 (13.0)	0.83
MVPA (% of total wear time)	4.3 (1.9)	0.8 (1.2)	4.1 (1.6)	0.9 (1.0)	0.81

Data are means (SD), unless otherwise stated. DBP, diastolic blood pressure; MVPA, moderate- to vigorous-intensity physical activity; SBP, systolic blood pressure. To convert mmol/L to mg/dL, multiply by 18 (for glucose), 38.7 (for cholesterol), and 88.6 (for TGs). *Total analyzed n = 93 (LC 46 and HC 47) for all data unless otherwise stated. †P value refers to between-group differences over time (diet effect) by ANCOVA and J-N procedure where appropriate. ‡Total analyzed n = 92 (LC 45 and HC 47) for body composition data; DEXA scan was not performed at baseline for one participant in LC diet group. §Total analyzed n = 91 (LC 46 and HC 45) for CGM data; CGM device did not collect valid data for two participants in the HC diet group at 24 weeks due to poor system connectivity. ||Total analyzed n = 83 (LC 42 and HC 41) that met requirement of 48-h valid CGM data collection to calculate comparisons between 2 successive days. ¶Total analyzed n = 82 (LC 41 and HC 41) for insulin and HOMA2 data; 11 participants on insulin medication were excluded from these analyses. #Total analyzed n = 84 (LC 43 and HC 41) for CRP data; nine participants with CRP >10 mg/L were excluded from these analyses. **Total analyzed n = 91 (LC 45 and HC 46); two participants with accelerometry data that did not meet the validity criteria were excluded. ††Significant group × baseline interaction, with significant group effect for baseline mean glucose >8.6 mmol/L (LC 18 and HC 22). ‡‡Significant group × baseline interaction, with significant group effect for baseline maximum glucose >13.2 mmol/L (LC 26 and HC 28). §§Significant group × baseline interaction, with significant group effect for baseline AUC_{total per min} >18.0 mmol/L (LC 14 and HC 17). |||Significant group × baseline interaction, with significant group effect for baseline HDL-C <1.3 mmol/L (LC 33 and HC 28).

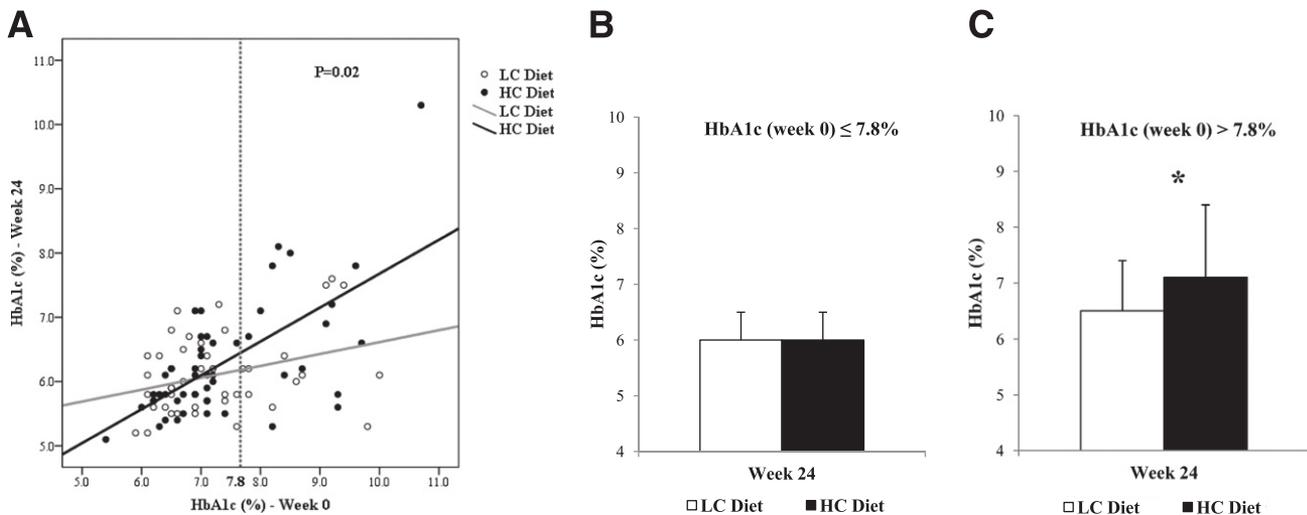


Figure 2—Effect of dietary interventions on HbA_{1c}. A: Scatterplot and regression lines of HbA_{1c} (%) at week 24 against week 0 for the LC diet ($n = 46$) and HC diet ($n = 47$). Perforated line represents the critical point for the region of significance on the covariate HbA_{1c} (week 0) > 7.8% (62 mmol/mol), LC significantly lower than HC diet; $P = 0.02$. HbA_{1c} after 24 weeks on an LC or energy-matched HC diet for participants with HbA_{1c} (week 0) ≤ 7.8% (LC 37 and HC 33) (B) or HbA_{1c} (week 0) > 7.8% (62 mmol/mol) (LC 9 and HC 14) (C). Values are means ± SD. White bars and white circles, LC diet; black bars and black circles, HC diet. * $P < 0.05$ significantly different between diets at 24 weeks.

of >20% compared with HC diet group ($P < 0.005$) (Table 2). Six participants reduced (LC 4 and HC 2) and five increased (LC 3 and HC 2) lipid-lowering medication. Eleven participants reduced (LC 10 and HC 1) and six increased (LC 3 and HC 3) antihypertensive medication.

Adverse Events

Eleven participants (LC 5 and HC 6) reported musculoskeletal ailments with exercise training that allowed program continuation following recovery. Two LC diet participants reported gastrointestinal disorders (constipation and diverticulitis); one HC diet participant reported esophageal ulcers with *Helicobacter pylori* infection; one LC diet participant was diagnosed with prostate cancer; three HC participants had elective surgical procedures performed; four participants (LC 3 and HC 1) experienced non-study-related workplace injuries; one HC diet participant had a motor vehicle accident.

CONCLUSIONS

This study demonstrates that both energy-reduced LC and HC diets with low-saturated fat content produce substantial improvements in glycemic control and several cardiometabolic risk markers in obese adults with T2DM. However, the LC diet induced greater improvements in glycemic control, blood glucose profiles, and reductions in diabetes medication requirements compared with the HC diet. The LC diet also promoted

a more favorable CVD risk profile by elevating HDL-C and reducing TG levels, with comparable reductions in LDL-C compared with the HC diet. These effects were most evident in participants with greater metabolic derangements, suggesting that an LC diet with high-unsaturated/low-saturated fat content can improve primary clinical diabetes management targets beyond conventional lifestyle management strategies and weight loss.

One study strength was the energy-matched prescription of diets that achieved comparable weight loss between groups, which removed this potential confounder and enabled metabolic differences between groups to be attributed to differences in the macronutrient profiles. Both groups achieved substantial reductions in HbA_{1c}, although importantly, a further greater reduction of 0.7% (7.7 mmol/mol) (absolute) occurred with the LC diet. This effect size is consistent with previous very low-carbohydrate ad libitum studies (6,8,10) and is comparable to those associated with antiglycemic agents (34). A 1% (10.9 mmol/mol) HbA_{1c} reduction is estimated to reduce the risk of diabetes-related death by 21%, myocardial infarction by 14%, and microvascular complications by 37% (33). Therefore, the additional 0.7% HbA_{1c} reduction achieved by the LC diet could translate to significant further reductions in diabetes complications risk.

In contrast to previous studies (6,8,10), a diet by baseline score interaction was present for HbA_{1c}, indicating that diet effects were dependent on initial levels and that the greater HbA_{1c} reductions with the LC diet were only evident in participants with a baseline HbA_{1c} > 7.8% (62 mmol/mol). This difference between studies could be attributed to differences in the statistical approaches used. The current study used ANCOVA combined with the J-N procedure, enabling effects of the covariate (baseline values) on the posttest outcomes to be revealed and regions of significance for any diet (group) differences to be determined. It is therefore possible that the relatively lower mean baseline HbA_{1c} levels of participants in the present compared with previous studies (7.3 vs. 7.4–8.8%; 56 vs. 57–73 mmol/mol) (6,8,10) may have facilitated this response. This suggests greater HbA_{1c}-lowering effects of an LC diet are most evident in those with higher baseline levels. However, given the relatively small subgroup of participants, this result should be interpreted with some caution.

Importantly, the LC diet group also experienced twofold greater reductions in antiglycemic MES, an effect that occurred across the entire study sample. It is therefore possible that the greater reductions in diabetes medication usage with the LC diet tempered the magnitude of HbA_{1c} reductions observed in

these participants and masked any differential HbA_{1c} changes between the diets in individuals with lower HbA_{1c} levels. These substantial greater reductions in antihyperglycemic medication requirements with the LC diet per se represent marked improvements in glycemic control of clinical importance and would represent significant cost savings. In the U.S., 30% of the estimated \$245 billion diabetes-related costs are attributed to medication costs (35). Further studies should quantify cost effectiveness of the medication reductions observed that was beyond the scope of the current investigation.

This trial extends previous studies with the inclusion of GV measures that assess glycemic control beyond conventional markers. Growing evidence suggests GV and glucose oscillations are crucial in the pathogenesis of diabetes complications via pathways that increase oxidative stress and endothelial dysfunction, independent of hemoglobin glycation (36,37). PPG excursions represent a component of GV that has shown to be an independent CVD risk factor (38). MAGE, CONGA, MODD, SD, AUC, maximum glucose, and range assess different aspects of GV associated with important surrogate measures of CVD outcomes (39,40). This study showed that an LC diet had greater efficacy in improving GV and reducing major and minor blood glucose excursions. This is evident from the greater attenuation of both within- and between-day(s) blood glucose fluctuations and reductions in several GV measures identified above. Moreover, the 2.3 mmol/L reduction in MAGE observed with the LC diet is substantially greater than the 1.59 mmol/L reduction observed with DPP-4 inhibitor therapy, which was associated with reductions in oxidative stress and systemic inflammatory markers implicated in atherosclerosis (41). This suggests an LC diet may be advantageous for achieving a more physiological diurnal blood glucose profile, which lowers CVD risk. The HEART2D study showed that GV improvements by insulin treatment targeting PPG did not alter macrovascular complications compared with a basal insulin strategy (42). However, posttreatment GV remained higher compared with the current study after 24 weeks on the LC diet (MAGE 3.1 ± 1.4 vs. 2.9 ± 1.1

mmol/L). Whether these GV improvements persist beyond 24 weeks and improve clinical end points requires further investigation.

Compared with the HC diet, participants on the LC diet were less and more likely to spend time in the hyperglycemic and euglycemic ranges, respectively. The LC diet group was also less likely to spend time in the hypoglycemic range, suggesting overall improvements in glycemic regulation. This is consistent with other studies demonstrating that lower GV (SD) is associated with reduced hypoglycemic risk (43). However, β -regression model residual plots analyzing time spent in the hypoglycemic range suggested a model misfit. Hence these data should be interpreted with caution and larger studies conducted to confirm these results.

Consistent with previous ad libitum studies comparing LC and HC diets, greater reductions in TG and increases in HDL-C occurred with the LC diet (15–17). In contrast, previous studies have observed higher LDL-C levels following an LC compared with an HC diet (6,8,15–17), albeit not reaching statistical significance in all cases. In the current study, LDL-C reduced similarly with both diets. The exact reason for this discrepancy is unclear. Unlike previous studies evaluating LC diets that were high in saturated fat content, the LC diet used in this study was low in saturated fat. Dietary saturated fat has been shown to elevate LDL-C (18), suggesting the lower-saturated fat content of the LC diet could explain the lack of differential LDL-C responses between the diets in this study. Additionally, the LC diet also comprised higher relative intakes of both mono- and polyunsaturated fats compared with the HC diet, which have been shown to improve both glycemic and lipoprotein profiles without adversely affecting LDL-C in diabetes (44,45). Collectively this evidence suggests that compared with an HC diet, an LC diet high in unsaturated fat and low in saturated fat does not adversely affect LDL-C and may promote greater CVD risk reduction.

The effectiveness of nutritional therapy in diabetes management to reduce complication risk necessitates long-term adherence to a dietary strategy. This is notoriously difficult. The intensity

of the intervention delivered with high levels of professional support and subsidized food provisions that facilitated high compliance were strengths of this study to deliver its purpose of establishing the efficacy of the diets evaluated. Moreover, inclusion of a closely monitored and professionally supervised physical activity program may have also contributed significantly to the successful weight and cardiometabolic improvements observed in both groups. It is possible this delivery approach may potentially limit success for widescale community adoption. Future initiatives need to integrate these lifestyle program components within cost-effective community-based delivery models. Whether the observed effects are sustained beyond 24 weeks also requires further investigation.

This study shows that both LC and HC diets incorporated as part of a lifestyle modification weight loss program achieve significant improvements in glycemic control and cardiovascular risk markers in overweight and obese adults with T2DM. However, the greatest improvements were achieved following the LC diet. This suggests an LC diet with high unsaturated and low saturated fat may confer advantageous therapeutic potential for T2DM management. Further research is required to establish the longer-term effects.

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References

- Rodbard HW, Blonde L, Braithwaite SS, et al.; AACE Diabetes Mellitus Clinical Practice Guidelines Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus [published correction appears in *Endocr Pract* 2008;14:802–803]. *Endocr Pract* 2007;13(Suppl. 1):1–68
- Sheard NF, Clark NG, Brand-Miller JC, et al. Dietary carbohydrate (amount and type) in the prevention and management of diabetes: a statement by the American Diabetes Association. *Diabetes Care* 2004;27:2266–2271
- Gannon MC, Nuttall JA, Damberg G, Gupta V, Nuttall FQ. Effect of protein ingestion on the glucose appearance rate in people with type 2 diabetes. *J Clin Endocrinol Metab* 2001;86:1040–1047
- Gentilcore D, Chaikomin R, Jones KL, et al. Effects of fat on gastric emptying of and the glycemic, insulin, and incretin responses to a carbohydrate meal in type 2 diabetes. *J Clin Endocrinol Metab* 2006;91:2062–2067
- Evert AB, Boucher JL, Cypress M, et al.; American Diabetes Association. Nutrition therapy recommendations for the management of adults with diabetes. *Diabetes Care* 2013;36:3821–3842
- 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 glycemic control in type 2 diabetes mellitus. *Nutr Metab (Lond)* 2008;5:36
- Davis NJ, Tomuta N, Schechter C, et al. Comparative study of the effects of a 1-year dietary intervention of a low-carbohydrate diet versus a low-fat diet on weight and glycemic control in type 2 diabetes. *Diabetes Care* 2009;32:1147–1152
- Stern L, Iqbal N, Seshadri P, et al. 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;140:778–785
- Ajala O, English P, Pinkney J. Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes. *Am J Clin Nutr* 2013;97:505–516
- Mayer SB, Jeffreys AS, Olsen MK, et al. Two diets with different haemoglobin A1c and anti-glycaemic medication effects despite similar weight loss in type 2 diabetes. *Diabetes Obes Metab* 2014;16:90–93
- Colberg SR, Albrigh AL, Blissmer BJ, et al.; American College of Sports Medicine; American Diabetes Association. 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;42:2282–2303
- Nalysnyk L, Hernandez-Medina M, Krishnarajah G. Glycaemic variability and complications in patients with diabetes mellitus: evidence from a systematic review of the literature. *Diabetes Obes Metab* 2010;12:288–298
- Brownlee M, Hirsch IB. Glycemic variability: a hemoglobin A1c-independent risk factor for diabetic complications. *JAMA* 2006;295:1707–1708
- 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;285:2486–2497
- 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
- Nordmann AJ, Nordmann A, Briel M, et al. 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;166:285–293
- Foster GD, Wyatt HR, Hill JO, et al. Weight and metabolic outcomes after 2 years on a low-carbohydrate versus low-fat diet: a randomized trial. *Ann Intern Med* 2010;153:147–157
- 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
- Fung TT, van Dam RM, Hankinson SE, Stampfer M, Willett WC, Hu FB. Low-carbohydrate diets and all-cause and cause-specific mortality: two cohort studies. *Ann Intern Med* 2010;153:289–298
- Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. *Hum Nutr Clin Nutr* 1985;39(Suppl. 1):5–41
- 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;27:1487–1495
- Service FJ, Molnar GD, Rosevear JW, Ackerman E, Gatewood LC, Taylor WF. Mean amplitude of glycemic excursions, a measure of diabetic instability. *Diabetes* 1970;19:644–655
- McDonnell CM, Donath SM, Vidmar SI, Werther GA, Cameron FJ. A novel approach to continuous glucose analysis utilizing glycemic variation. *Diabetes Technol Ther* 2005;7:253–263
- Molnar GD, Taylor WF, Ho MM. Day-to-day variation of continuously monitored glycaemia: a further measure of diabetic instability. *Diabetologia* 1972;8:342–348
- 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—2013. *Diabetes Care* 2013;36(Suppl. 1):S11–S66
- Simmons WK. Urinary urea nitrogen-creatinine ratio as indicator of recent protein intake in field studies. *Am J Clin Nutr* 1972;25:539–542
- 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
- Vickers AJ, Altman DG. Statistics notes: analysing controlled trials with baseline and follow up measurements. *BMJ* 2001;323:1123–1124
- Preacher KJ, Curran PJ, Bauer DJ. Computational tools for probing interactions in multiple linear regression, multilevel modeling, and latent curve analysis. *J Educ Behav Stat* 2006;31:437–448
- Swearingen CJ, Melguizo Castro MS, Bursasc Z. Modeling percentage outcomes: the %beta_regression macro. In *Proceedings of the SAS Global Forum, Las Vegas, NV, 2011*, paper 335:1–12
- Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000;321:405–412
- Nathan DM, Buse JB, Davidson MB, et al.; American Diabetes Association; European Association for Study of Diabetes. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2009;32:193–203
- American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. *Diabetes Care* 2013;36:1033–1046
- Ceriello A, Ichnat MA. ‘Glycaemic variability’: a new therapeutic challenge in diabetes and the critical care setting. *Diabet Med* 2010;27:862–867
- Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes* 2005;54:1615–1625

38. Cavalot F, Pagliarino A, Valle M, et al. Postprandial blood glucose predicts cardiovascular events and all-cause mortality in type 2 diabetes in a 14-year follow-up: lessons from the San Luigi Gonzaga Diabetes Study. *Diabetes Care* 2011;34:2237–2243
39. Di Flaviani A, Picconi F, Di Stefano P, et al. Impact of glycemic and blood pressure variability on surrogate measures of cardiovascular outcomes in type 2 diabetic patients. *Diabetes Care* 2011;34:1605–1609
40. Monnier L, Mas E, Ginet C, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA* 2006;295:1681–1687
41. Rizzo MR, Barbieri M, Marfella R, Paolisso G. Reduction of oxidative stress and inflammation by blunting daily acute glucose fluctuations in patients with type 2 diabetes: role of dipeptidyl peptidase-IV inhibition. *Diabetes Care* 2012;35:2076–2082
42. Siegelaar SE, Kerr L, Jacober SJ, Devries JH. A decrease in glucose variability does not reduce cardiovascular event rates in type 2 diabetic patients after acute myocardial infarction: a reanalysis of the HEART2D study. *Diabetes Care* 2011;34:855–857
43. Kilpatrick ES, Rigby AS, Goode K, Atkin SL. Relating mean blood glucose and glucose variability to the risk of multiple episodes of hypoglycaemia in type 1 diabetes. *Diabetologia* 2007;50:2553–2561
44. Garg A. High-monounsaturated-fat diets for patients with diabetes mellitus: a meta-analysis. *Am J Clin Nutr* 1998;67(Suppl.):577S–582S
45. McEwen B, Morel-Kopp M-C, Tofler G, Ward C. Effect of omega-3 fish oil on cardiovascular risk in diabetes. *Diabetes Educ* 2010;36:565–584