Effect of Lowering the Glycemic Load With Canola Oil on Glycemic Control and Cardiovascular Risk Factors: A Randomized Controlled Trial

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OBJECTIVE

Despite their independent cardiovascular disease (CVD) advantages, effects of α-linolenic acid (ALA), monounsaturated fatty acid (MUFA), and low-glycemic-load (GL) diets have not been assessed in combination. We therefore determined the combined effect of ALA, MUFA, and low GL on glycemic control and CVD risk factors in type 2 diabetes.

RESEARCH DESIGN AND METHODS

The study was a parallel design, randomized trial wherein each 3-month treatment was conducted in a Canadian academic center between March 2011 and September 2012 and involved 141 participants with type 2 diabetes (HbA_{1c} 6.5%–8.5% [48–69 mmol/mol]) treated with oral antihyperglycemic agents. Participants were provided with dietary advice on either a low-GL diet with ALA and MUFA given as a canola oil–enriched bread supplement (31 g canola oil per 2,000 kcal) (test) or a whole-grain diet with a whole-wheat bread supplement (control). The primary outcome was HbA_{1c} change. Secondary outcomes included calculated Framingham CVD risk score and reactive hyperemia index (RHI) ratio.

RESULTS

Seventy-nine percent of the test group and 90% of the control group completed the trial. The test diet reduction in HbA_{1c} units of −0.47% (−5.15 mmol/mol) (95% CI −0.54% to −0.40% [−5.92 to −4.38 mmol/mol]) was greater than that for the control diet (−0.31% [−3.44 mmol/mol] [95% CI −0.38% to −0.25% (−4.17 to −2.71 mmol/mol)], $P = 0.002$), with the greatest benefit observed in those with higher systolic blood pressure (SBP). Greater reductions were seen in CVD risk score for the test diet, whereas the RHI ratio increased for the control diet.

CONCLUSIONS

A canola oil–enriched low-GL diet improved glycemic control in type 2 diabetes, particularly in participants with raised SBP, whereas whole grains improved vascular reactivity.

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New pharmacological treatments for diabetes are required to be tested for cardiovascular safety before licensing (1) due to concerns over possible increased cardiovascular disease (CVD) risk in some studies (2). Dietary strategies, although less effective in improving glycemic control, may have the advantage of actually reducing CVD risk (3,4).

Low-glycemic-load (GL) diets have been associated in cohort studies with a reduction in both diabetes incidence and CVD events (3–5), especially in overweight individuals (3), and have been recommended by many diabetes associations (6–8). Monounsaturated fatty acids (MUFAs) and short-chain-length n-3 fatty acids (α-linolenic acid [ALA]) reduced CVD risk in randomized controlled trials (9,10). Furthermore, high ALA and MUFA intake may also lower the GL of the diet. An increased proportion of vegetable oil calories in the meal would be expected to reduce postprandial glycemia both by decreasing the carbohydrate content of the meal and by delaying gastric emptying, whereas the increase in vegetable oil over the longer term would predict a reduction in serum lipids. This combined dietary approach may therefore benefit both glycemia and CVD risk in diabetes. Despite these possible advantages, the effects of ALA and MUFA as part of a low-GL diet have not been tested in type 2 diabetes.

To determine the possible advantages of this combination, we tested the effect of a commonly used oil, canola oil, containing both ALA (9.1%) and MUFA (63%) when used as part of a low–glycemic index (GI) diet. This dietary intervention was compared with a high-whole-grain–cereal diet. Such whole-grain diets have invariably been associated with a reduced risk of diabetes (11,12) and CVD in cohort studies (12–14), despite generally having no effect on conventional CVD risk factors (15).

RESEARCH DESIGN AND METHODS

Participants

Participants were recruited from newspaper, public transportation, and hospital clinic advertisements. One hundred and forty-one participants were eligible and randomized (Fig. 1). Recruitment took place from 28 March 2011 to 17 September 2012, with the last study visit on 4 December 2012. Eligible participants had at least a 6-month history of type 2 diabetes based on clinical criteria, were taking a stable dose of oral antihyperglycemic agents for at least the previous 2 months, and had HbA_{1c} values between 6.5% (48 mmol/mol) and 8.5% (69 mmol/mol) both at the initial screening and at the visit 1 week before randomization (Fig. 1). No participants had clinically significant cardiovascular, renal (creatinine $>$150 μmol/L), or liver (alanine aminotransferase level more than three times the upper limit of normal) disease or a history of cancer. None were smokers, and alcohol intake was two or fewer drinks a day for men and one or fewer drinks a day for women. Participation rate and reasons for exclusion are given in Fig. 1.

Protocol

The study followed a randomized, parallel design with two treatment arms of 3 months duration as follows: *1*) a low-GL diet with a canola oil–enriched bread provided as a supplement (test) or *2*) a high wheat-fiber diet emphasizing whole-wheat foods (control). After stratification by sex and HbA_{1c} $>$7.1% or $\leq$7.1% (54 mmol/mol) but without a predetermined block size, participants were randomized in a blinded fashion by a statistician who was geographically separate from the study center. The dietitians and participants could not be blinded, but equal emphasis was placed on the potential importance of both diets for health. The analytical technicians, statistician, and study investigators were blinded to treatment up to and including the analysis of the primary outcome.

Participants attended the Risk Factor Modification Centre of St. Michael's Hospital, a teaching hospital of the University of Toronto, for screening and weeks $-$1, 0, 2, 4, 8, 10, and 12 of the study. They were weighed at each visit; waist circumference was measured while standing at the level of the umbilicus, and fasting blood samples were taken at all visits except week 2. Seated blood pressure was measured in triplicate with an automatic sphygmomanometer (Omron HEM 907 XL; Omron Healthcare Inc., Burlington, ON, Canada) and the mean taken. Seven-day food records covering the week before each visit were discussed with the dietitian. No specific exercise advice was given, but participants were asked to keep exercise constant. Baseline exercise routine was recorded and any subsequent change noted. The study conformed to the same general principles as other studies of this duration run from the center (16).

The study was approved by the research ethics board of St. Michael's Hospital and the University of Toronto, and written consent was obtained from all participants. The study was registered with ClinicalTrials.gov (identifier: NCT01348568).

Dietary Interventions

The test diet included 4.5 slices of canola oil–enriched whole-wheat bread (500 kcal/day) provided as a supplement. The supplement delivered 31 g canola oil or 14% of total dietary calories of a 2,000-kcal diet (Supplementary Table 1). The control diet included 7.5 slices of whole-wheat bread without canola oil per day (500 kcal) (Supplementary Table 1). Dietary advice on the test diet emphasized low-GI foods, including legumes, barley, pasta, parboiled rice, and temperate-climate fruit, as outlined in previous studies (17). For the control diet, participants were instructed to avoid white-flour products and replace them with whole-wheat breakfast cereals, study breads, brown rice, and so forth.

Dietary Assessment

Participants provided 7-day food records covering the previous 7 days before clinic visits. These records were discussed with the dietitians for clarification for future formal dietary analyses and to indicate where further dietary advice was required. The different nature of the diets precluded blinding; however, the advantages of both diets were emphasized with reference to their benefits as recorded in the literature (11–14). Adherence to the diet was assessed from the 7-day food records; 106 participants provided complete dietary records for the 3-month study. Participants ranked their level of satiety on a scale of $-$4 (starved/feeling weak) to +4 (painfully full) and palatability of study breads and diets at each visit on a scale of 1–10 (1 = strongly dislike, 10 = like very much).

Biochemical and Dietary Analyses

HbA_{1c}, blood glucose, and serum lipids were measured in the hospital routine

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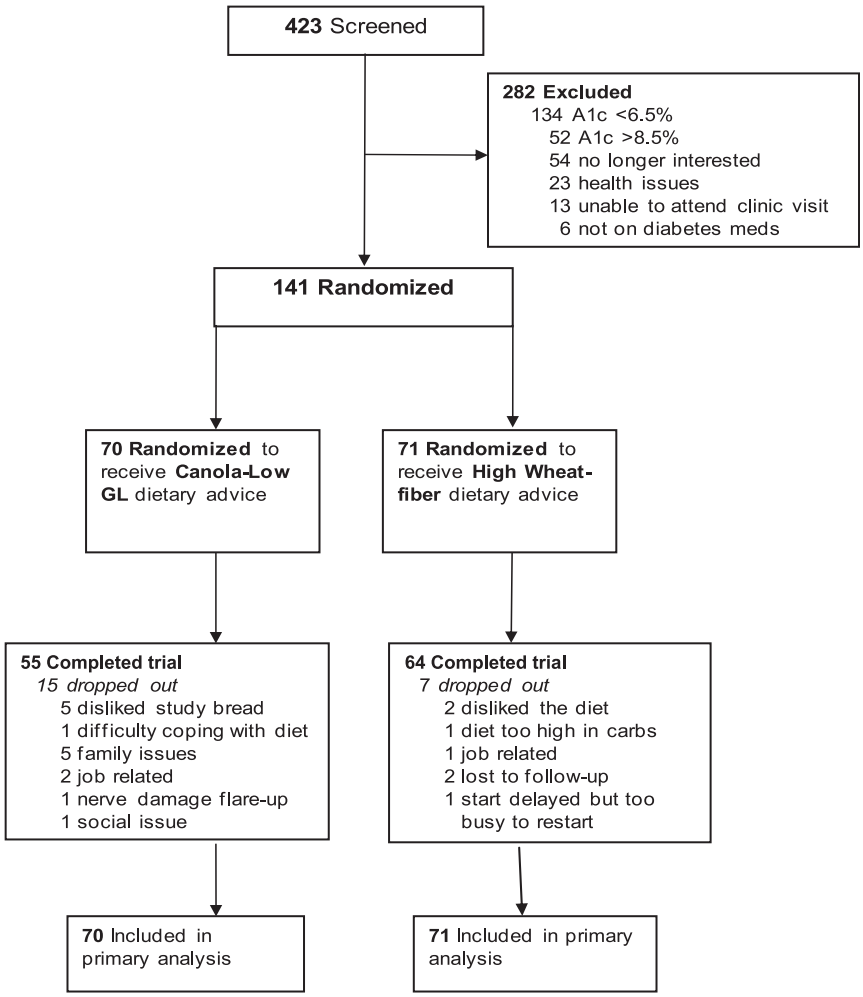

Figure 1—Flow of participants through the study.

analytical laboratory by techniques as previously described (17). The reactive hyperemia index, as a marker of flow-mediated vasodilatation, was measured with the EndoPAT system (Itamar Medical Ltd., Franklin, MA), which assesses the capillary blood refill to finger tips after a 5-min occlusion of the forearm with a cuff inflated to 50 mmHg above the participant's resting systolic blood pressure and expressed as a ratio of the blood flow in the opposite arm (18). Diet records were analyzed using a computer program (ESHA Food Processor SQL version 10.9; ESHA, Salem, OR) based on U.S. Department of Agriculture data (19) and international GI tables (20) using the bread scale (where bread = 100; for the glucose scale, bread scale values were multiplied by 0.71) (21) (Supplementary Table 1).

Statistical Analyses

Results are expressed as mean ± SEM or 95% CI. Both the absolute and the relative CVD risk score were calculated using the Framingham risk equation for total 10-year cardiovascular events (22), in which only systolic blood pressure and total and HDL cholesterol (HDL-C) changed during the study. All patients who met the inclusion criteria were included in the analysis (n = 141). Week 0 HbA_{1c} was taken as baseline, and weeks 8, 10, and 12 were selected as end of study to allow for stabilization of HbA_{1c} as the main outcome. Treatment differences in physical and biochemical measures were assessed from all available data. The analysis of treatment effect within a repeated-measures study design used the mixed (random-effects) linear model, with change from baseline over time as the response variable and diet (low-GL canola vs. wheat bran) and time (weeks 8, 10, and 12) as the main effects. Neither baseline nor other covariates were used in the primary analysis, which was performed with SAS 9.2 software (23). Within-treatment changes for all variables were estimated by the least squares means technique within the mixed model.

Changes in medication use were assessed either by two-tailed Fisher exact test in the case of 2 × 2 tables or by the Mantel-Haenszel test for larger contingency tables. For the values used in Fig. 2 and associated Supplementary Table 2, multiple imputation using five sets of randomly imputed values for missing data was generated by PROC MI and analyzed by PROC MIXED, and the five sets of results were pooled by PROC MIANALYZE in SAS 9.2 (23).

We also assessed the interactions between the effect of diet on HbA_{1c} and the baseline measures of components of the metabolic syndrome (waist circumference, systolic and diastolic blood pressure, HDL-C, fasting triglyceride level, and blood glucose level) together with the additional components of the

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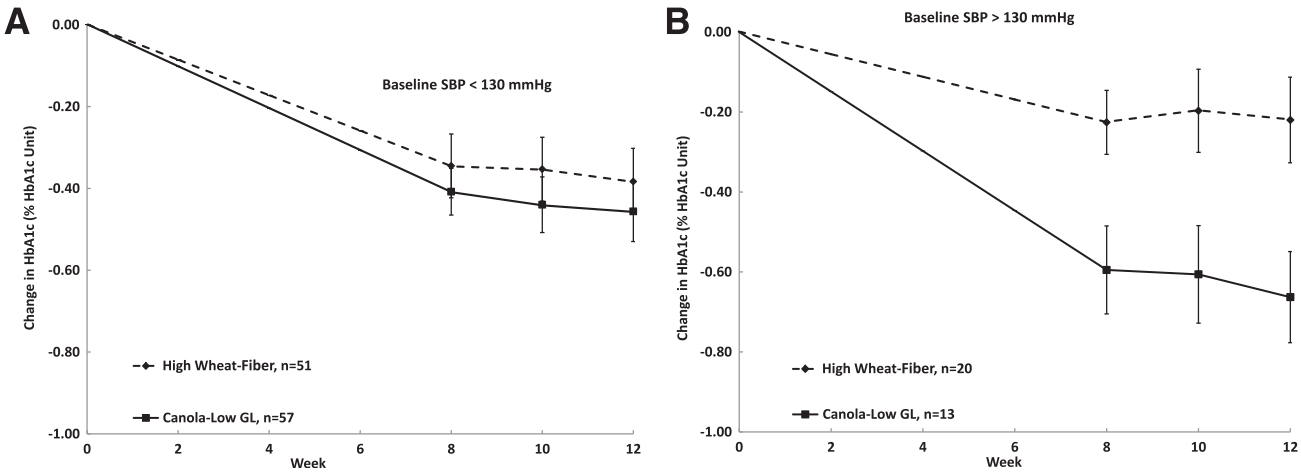

Figure 2—Changes from baseline in HbA_{1c} (percent absolute HbA_{1c} units) during canola low-GL (test) and high wheat-fiber (control) diets. Diet results in participants with lower (*A*) or higher baseline systolic blood pressure (SBP) (*B*) than the metabolic syndrome cut points. HbA_{1c} was reduced more for the test diet than for the control diet in those with higher baseline SBP ($P = 0.003$).

Framingham risk score (age, sex, total cholesterol:HDL-C) (Supplementary Table 2). HbA_{1c} response data were stratified according to whether the participants' baseline measures were above (or equal to) or below the cut point for metabolic syndrome components (24) or the median for CVD risk factor components of the Framingham risk score (22). The HbA_{1c} data for upper and lower systolic blood pressure cut points are also presented in graphic form (Fig. 2). The treatment differences between these subgroups and the significance of the interaction with baseline measures (Supplementary Table 2) were calculated for both raw and multiply imputed data. To determine whether any baseline measures affected the HbA_{1c} response by >10% and might thus be considered a modifier of the effect size, we undertook a bivariate regression analysis of HbA_{1c} change (repeated measures) involving baseline measures of predictors suggested by the metabolic syndrome diagnostic criteria (6) and Framingham CVD risk factors (3) by using one predictor at a time.

Initially, we planned to recruit 120 participants. However, because of a larger-than-expected dropout at the start and to capture smaller effect sizes seen in our more-recent studies, participant recruitment numbers were increased to 140 (16,25). On the basis of data from a 12-week study in type 2 diabetes (16) from an ANCOVA model, we would require 116 completers to detect a treatment difference in HbA_{1c} change of 0.15% with an SD of 0.48% [assuming $\alpha = 0.05$, $1 - \beta = 0.8$, using $r = 0.8$ to account for the high degree of correlation between successive measures (26)].

RESULTS

Fifty-five of 70 participants (79%) completed the test diet (i.e., provided at least one blood sample in the final month), compared with 64 of 71 (90%) on the control diet (Fig. 1). Of the 119 participants with data in the last month (completers), 3 on the test diet and 7 on the control diet were missing one or two of the three final values. The attrition rates were not significantly different between treatments (Fig. 1). No baseline differences were seen (Table 1) except for a higher baseline dietary GI in the test group compared with the control group (3 GI units [95% CI 1.1–4.9], $P = 0.003$) (Supplementary Table 3). The test bread was rated more palatable than the control bread, as was the overall test diet compared with the control diet (Supplementary Table 3).

By design, the test diet resulted in significantly greater increases in MUFA and ALA intake and corresponding lower carbohydrate intake, and hence GL, relative to the control diet (Supplementary Table 3). The relative GI and GL reductions for the test diet compared with the control diet were −19 GI units (95% CI −20 to −17, $P < 0.0001$) and −52 GL units (95% CI −59 to −45, $P < 0.0001$), respectively, and compliance with the test bread was 89% (95% CI 86%–93%) versus the control bread 77% (95% CI 74%–80%) ($P < 0.0001$).

Glycemic Control and Body Weight

Oral antihyperglycemic medication dosages increased in one and were reduced in five participants on the test diet. They decreased in four participants on the control diet, with no significant treatment differences.

The mean HbA_{1c} change was −0.47% (−5.15 mmol/mol) absolute HbA_{1c} units (95% CI −0.54% to −0.40% [−5.92 to −4.38 mmol/mol], $P < 0.001$) for the test diet and −0.31% (−3.44 mmol/mol) absolute HbA_{1c} units (95% CI −0.38% to −0.25% [−4.17 to −2.71 mmol/mol], $P < 0.001$) for the control diet. The relative HbA_{1c} reduction for the test diet was −0.16% (−1.71 mmol/mol) (95% CI −0.25% to −0.06% [−2.77 to −0.65 mmol/mol], $P = 0.002$) (Table 2) and remained statistically significant after adjustment for body weight change ($P = 0.010$). The body weight reductions were similar at −2.1 kg and −1.6 kg for both the test and the control diets, respectively (Table 2). There was no significant treatment difference in waist circumference, although, as with body weight, both treatments were associated with a reduction (waist circumference −1.8 vs. −2.4 cm for test and control diets, respectively) (Table 2).

Serum Lipids

Lipid-lowering medications were decreased in one participant on the test diet and three on the control diet, with no significant treatment difference in

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Table 1—Baseline (week 0) characteristics of study participants

Characteristic*	Participants	
	Control diet (n = 71)	Test diet (n = 70)
Age (years)	59 ± 10	59 ± 10
Sex		
Female	32 (45)	32 (46)
Male	39 (55)	38 (54)
Race/ethnicity		
African	2 (3)	4 (6)
East Indian	13 (18)	21 (30)
European	29 (41)	24 (34)
Far Eastern	8 (11)	4 (6)
Other white/Caucasian	13 (18)	9 (13)
Other	6 (8)	8 (11)
Weight (kg)	84 ± 19	85 ± 20
BMI (kg/m^2)	31 ± 6	30 ± 5
Waist (cm)	106 ± 14	104 ± 13
Current smokers	0	0
Duration of diabetes (years)	7.5 ± 5.4	7.6 ± 6.9
Glucose (mmol/L)	7.5 ± 1.6	7.7 ± 1.5
HbA_{1c} (%)	7.2 ± 0.6	7.4 ± 0.6
HbA_{1c} (mmol/mol)	55.7 ± 6.8	57.1 ± 6.9
Participants ≤7.1%	34 (48)	31 (44)
Participants >7.1%	37 (52)	39 (56)
Total cholesterol (mmol/L)	3.99 ± 1.00	4.15 ± 1.12
LDL-C (mmol/L)	2.13 ± 0.85	2.25 ± 0.90
HDL-C (mmol/L)	1.16 ± 0.28	1.20 ± 0.30
Triglycerides (mmol/L)	1.52 ± 0.80	1.54 ± 0.76
Systolic blood pressure (mmHg)	122 ± 11	121 ± 12
Diastolic blood pressure (mmHg)	72 ± 8	71 ± 8
Heart rate (bpm)	73 ± 10	73 ± 11
Absolute CVD risk score†	10.3 ± 5.1	9.6 ± 3.7
Relative CVD risk score	1.3 ± 0.7	1.3 ± 0.5
RHI ratio	1.73 ± 0.36	1.86 ± 0.50
Antihyperglycemic medications	71 (100)	70 (100)
Metformin	67 (94)	65 (93)
Sulfonylurea	18 (25)	22 (31)
Thiazolidinedione	4 (6)	8 (11)
Dipeptidyl peptidase-4 inhibitors	12 (17)	12 (17)
Meglitinides (nonsulfonylurea)	2 (3)	1 (1)
α-Glucosidase inhibitors	0 (0)	1 (1)
Injectable GLP-1 analog (Victoza)	0 (0)	1 (1)
Combination (Janumet)	2 (3)	2 (3)
Cholesterol-lowering medications	51 (72)	50 (71)
Blood pressure medications	43 (61)	39 (56)

Data are mean ± SD or n (%). RHI, reactive hyperemia index. *No significant differences in baseline (week 0) characteristics were seen between treatments. †CVD risk score was calculated by using the Framingham CVD predictive equation by Anderson et al. (22).

medication use (P = 0.620). The test produced significant falls within treatment in total cholesterol, LDL cholesterol (LDL-C), triglycerides, and the ratios of total cholesterol:HDL-C and LDL-C:HDL-C (Table 2). Relative to the control diet, the test diet resulted in significant reductions in total cholesterol (−0.34 mmol/L [95% CI −0.46 to −0.23], $P < 0.0001$), LDL-C (−0.25 mmol/L [95% CI −0.34 to −0.15], $P < 0.0001$), triglycerides (−0.14 mmol/L [95% CI −0.26 to −0.03], P = 0.018), and HDL-C (−0.03 mmol/L [95% CI −0.06 to 0.00], $P < 0.041$), albeit with still significant reductions in the ratios of total cholesterol:HDL-C (−0.21 [95% CI −0.32 to −0.11], $P < 0.0001$) and LDL-C:HDL-C (−0.16 [95% CI −0.24 to −0.07], P = 0.001) (Table 2).

Blood Pressure, Heart Rate, and Reactive Hyperemia Index

No significant treatment differences were seen in blood pressure or heart rate (Table 2). There was a nonsignificant reduction in vascular reactivity for the test diet but a nearly significant rise for the control diet, resulting in a relative increase in the reactive hyperemia index for the control diet (−0.24 [95% CI −0.42 to −0.06], P = 0.009) (Table 2).

CVD Risk

The Framingham risk score for CVD was reduced for both treatments but significantly more for the test diet (−0.6 [95% CI −1.1 to −0.2], P = 0.008) (Table 2).

Effect of Baseline Metabolic Syndrome Components and Framingham Risk Score Components on HbA_{1c} Response

To determine whether participants at higher risk benefited more or less from the intervention, we assessed the HbA_{1c} treatment effect for those with higher versus lower baseline measures for components of the metabolic syndrome and Framingham risk score. In general, the effect size and degree of significance was greatest in those whose baseline measures were elevated (Supplementary Table 2). However, by multiple imputation for missing data, only for those with higher systolic blood pressure (≥130 mmHg) was the treatment difference significantly different from those with lower systolic blood pressure (<130 mmHg). In participants with systolic blood pressure >130 mmHg, the test diet HbA_{1c} reduction was substantial at −0.62% (−6.79 mmol/mol) (95% CI −0.77% to −0.47% [−8.40 to −5.19 mmol/mol], $P < 0.001$) (Fig. 2 and Supplementary Table 2). The treatment difference in HbA_{1c} in those with systolic blood pressure >130 mmHg (−0.41% [−4.45 mmol/mol] [95% CI −0.62% to −0.19% (−6.80 to −2.09 mmol/mol)], P = 0.001) was more than five times the treatment difference (P = 0.003) seen in those with systolic blood pressure <130 mmHg (−0.07% [−0.81 mmol/mol] [95% CI −0.20% to 0.06% (−2.22 to 0.60 mmol/mol)], P = 0.253) (Supplementary Table 2).

To identify possible confounders, bivariate regression of HbA_{1c} change on baseline components of the metabolic syndrome and Framingham risk score indicated that only age was a significant

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Table 2—Changes from baseline in study measurements on the basis of raw data and significance of treatment differences for raw and multiple imputation

	Control diet			Test diet			Between diets		
	Week 0 (n = 71)[b]	Change[a] within diet		Week 0 (n = 70)[b]	Change[a] within diet		Change[a]	P value (raw)	P value (MI)
Weight (kg)	84.4 (79.9, 88.9)	−1.6 (−2.0, −1.3)	*	84.5 (79.7, 89.4)	−2.1 (−2.5, −1.7)	*	−0.5 (−1.0, 0.0)	0.070	0.458
Waist (cm)	106 (103, 110)	−2.4 (−2.9, −1.9)	*	104 (101, 108)	−1.8 (−2.4, −1.3)	*	0.6 (−0.2, 1.3)	0.143	0.065
HbA_{1c} (% HbA_{1c} unit)	7.2 (7.1, 7.4)	−0.31 (−0.38, −0.25)	*	7.4 (7.2, 7.5)	−0.47 (−0.54, −0.40)	*	−0.16 (−0.25, −0.06)	0.002	0.016
HbA_{1c} (mmol/mol)	55.7 (54.1, 57.3)	−3.44 (−4.17, −2.71)		57.1 (55.4, 58.8)	−5.15 (−5.92, −4.38)		−1.71 (−2.77, −0.65)		
Fasting glucose (mmol/L)	7.5 (7.1, 7.9)	−0.30 (−0.48, −0.12)	*	7.7 (7.3, 8.0)	−0.37 (−0.56, −0.18)	*	−0.07 (−0.33, 0.19)	0.591	0.491
Cholesterol (mmol/L)	4.0 (3.8, 4.2)	0.04 (−0.03, 0.12)		4.1 (3.9, 4.4)	−0.30 (−0.38, −0.22)	*	−0.34 (−0.46, −0.23)	0.000	0.000
LDL-C (mmol/L)	2.1 (1.9, 2.3)	0.04 (−0.02, 0.11)		2.2 (2.0, 2.5)	−0.20 (−0.27, −0.13)	*	−0.25 (−0.34, −0.15)	0.000	0.000
HDL-C (mmol/L)	1.2 (1.1, 1.2)	0.00 (−0.02, 0.02)		1.2 (1.1, 1.3)	−0.03 (−0.05, −0.01)	*	−0.03 (−0.06, 0.00)	0.041	0.164
Triglycerides (mmol/L)	1.5 (1.3, 1.7)	−0.01 (−0.09, 0.07)		1.5 (1.4, 1.7)	−0.15 (−0.24, −0.07)	*	−0.14 (−0.26, −0.03)	0.018	0.085
Total cholesterol/HDL-C	3.6 (3.3, 3.8)	0.02 (−0.05, 0.10)		3.6 (3.3, 3.8)	−0.19 (−0.27, −0.11)	*	−0.21 (−0.32, −0.11)	0.000	0.000
LDL-C/HDL-C	1.9 (1.7, 2.1)	0.03 (−0.03, 0.09)		1.9 (1.7, 2.1)	−0.13 (−0.19, −0.07)	*	−0.16 (−0.24, −0.07)	0.001	0.000
Systolic BP (mmHg)	122 (120, 125)	−5.1 (−6.7, −3.5)	*	121 (118, 124)	−4.7 (−6.4, −2.9)	*	0.4 (−1.9, 2.8)	0.718	0.892
Diastolic BP (mmHg)	72 (70, 74)	−3.3 (−4.2, −2.3)	*	71 (69, 73)	−3.0 (−4.1, −2.0)	*	0.2 (−1.2, 1.7)	0.740	0.763
Heart rate (bpm)	73 (71, 76)	−2.6 (−3.6, −1.6)	*	73 (70, 75)	−2.3 (−3.4, −1.3)	*	0.2 (−1.2, 1.7)	0.770	0.898
Absolute CVD risk[c] (10-year %)	10.3 (9.1, 11.5)	−0.53 (−0.84, −0.22)	*	9.6 (8.8, 10.5)	−1.16 (−1.49, −0.82)	*	−0.63 (−1.09, −0.17)	0.008	0.079
Relative CVD risk	1.3 (1.2, 1.5)	−0.07 (−0.12, −0.03)	*	1.3 (1.2, 1.4)	−0.16 (−0.20, −0.11)	*	−0.08 (−0.15, −0.02)	0.007	0.049
RHI ratio	1.7 (1.6, 1.8)	0.13 (0.00, 0.25)		1.9 (1.7, 2.0)	−0.12 (−0.24, 0.01)		−0.24 (−0.42, −0.06)	0.009	0.015

Data are mean (lower confidence limit, upper confidence limit). Physical and biochemical measures were obtained at week 0, representing baseline, and weeks 8, 10, and 12 — baseline, representing change from baseline. BP, blood pressure; MI, multiple imputation; RHI, reactive hyperemia index. *Significant difference from baseline ($P < 0.05$). [a]Mean, confidence limits, and P values determined using repeated-measures least squares means in PROC MIXED of SAS 9.2 with all available data. [b]Control: n = 71 at baseline and 64, 60, and 59 at weeks 8, 10, and 12, respectively. Test: n = 70 at baseline and 54 at weeks 8, 10, and 12. [c]CVD risk calculated using the Framingham CVD predictive equation by Anderson et al. (22).

independent predictor of HbA_{1c} change (P = 0.024), but the effect of the diet on HbA_{1c} remained significant after controlling for age. No baseline measures contributed >10% to the HbA_{1c} effect.

Adverse Events

There were no serious adverse events that required hospitalization. Five participants (three on the test diet and two on the control diet) were examined either by their family physician or at a local hospital emergency department for events unrelated to the diet. Five subjects had repeated HbA_{1c} values >8.5% (69 mmol/mol) (three on the control diet and two on the test diet). Five participants (three on the control diet and two on the test diet) reported experiencing hypoglycemic episodes.

CONCLUSIONS

Increased MUFA and ALA (canola oil) consumption as part of a canola low-GL diet modestly lowered HbA_{1c} but to a clinically significant extent in participants with raised blood pressure. Together with the reduction in Framingham risk score, these data support the use of canola oil in type 2 diabetes.

This study is the first to our knowledge to combine three dietary strategies (n-3 [ALA], MUFA, and low-GL diets) to manage diabetes that in the longer term have been associated with reduced CVD risk both in people with and without diabetes (3,4,9,10,27).

Previous meta-analyses of low-GI studies in type 2 diabetes have demonstrated a 0.43% reduction in HbA_{1c} (28), and large studies have reported 0.4%–0.5% (4.4–5.5 mmol/mol) HbA_{1c} reductions in their low-GI or -GL arm (25) similar to that seen in the current study. Recently, a major Spanish trial demonstrated a 30% CVD risk reduction after monounsaturated fat or nut (including n-3 [ALA]–rich walnuts) supplementation in high-risk trial participants, including those with type 2 diabetes (27). Furthermore, three meta-analyses of cohort studies indicated cardioprotective properties of low-GL diets in women without diabetes (4,29,30). In other studies, participants with increased BMI and insulin resistance but without diabetes demonstrated greater effects of low-GL diets on cardiovascular outcomes and weight loss, respectively (3,31). The current study also

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supports the concept of a greater effectiveness of low-GL diets in insulin-resistant states, including central adiposity, low HDL-C, and hypertension (24).

Despite the relatively low statin-treated LDL-C baseline concentrations of 2.17–2.22 mmol/L, canola oil consumption was associated with a significant additional reduction in LDL-C. According to statin dose-response studies, the observed LDL-C reduction could translate into an extra 7% reduction in CVD events or an additional 20 mg atorvastatin (32). Earlier studies demonstrated reduced triglyceride and VLDL cholesterol levels with increased MUFA intake in type 2 diabetes (33). To our knowledge, the current study is one of the first to assess the effect on serum lipids and glycemic control of an ALA-rich oil in type 2 diabetes. The effects of walnuts, as sources of ALA, have been studied in type 2 diabetes, and despite no effect on HbA_{1c}, they were shown to reduce LDL-C (34) and improve vascular reactivity (35). In nondiabetic study participants, walnut consumption has also been associated with a reduction in LDL-C (36).

Increased whole-grain intake has consistently been associated with reduced CVD events in cohort studies (12,13) without a clear mechanism for this benefit. Whole-wheat fiber is nonviscous, and unlike viscous fibers from oats, barley, and other sources, it does not lower serum cholesterol (15,37) or reduce postprandial glycemia (38). However, there is evidence that whole-wheat products may reduce insulin resistance (39). Thus, this finding together with the possible improvement in vascular reactivity seen here after wheat bran intake may be part of the explanation for the reduced CVD risk among whole-grain consumers (11–14,40).

A study limitation is the relatively small effect size of HbA_{1c}, the primary outcome, of 0.5% (5.1 mmol/mol) compared with the larger than previously seen reduction for the control diet of 0.3% (3.4 mmol/mol). However, in participants at increased risk for adverse outcomes, a clinically significant effect was observed, especially in those with hypertension, where the HbA_{1c} reduction for the test diet was 0.62% (6.79 mmol/mol) and the relative HbA_{1c} reduction was 0.41% (4.45 mmol/mol) and, therefore, in the range of 0.3%–0.4% and above that set by Food and Drug Administration guidelines for diabetes drug development (1). Furthermore, the study participants were already taking one or more oral antihyperglycemic agents, and 40% of the participants had HbA_{1c} levels at the clinical target of $\leq$7.0% (53 mmol/mol).

The strengths of this study include the participant numbers and frequency of blood sampling that allowed small treatment differences to be detected. Furthermore, because the baseline HbA_{1c} and blood lipid levels were close to target, it is likely that there may be greater reductions in participants with higher levels commonly seen in clinical practice.

The significance of differences have been provided for both the raw data, using repeated measures in the mixed model, and also where missing values have been derived by multiple imputation. Both approaches were similar in identifying significant differences. The raw data, however, also show significant treatment differences, favoring higher HDL-C, lower triglycerides, and lower absolute coronary heart disease risk for the test diet and indicate that older and more centrally obese (increased waist circumference) individuals responded better to the high-canola–low-GL diet. These data support the view that patients at greatest risk benefit most (3,24,31). The assessment using multiply imputed data failed to reach significance for these differences.

In conclusion, the reduction of GL by increasing the intake of MUFA and ALA (e.g., canola oil) to displace dietary carbohydrates and reduce the GL improved glycemic control, particularly in participants at high risk for diabetes complications, and reduced LDL-C, a feature not seen with similar low-GI diets (25). By contrast, whole-grain cereals appear to improve vascular reactivity, possibly helping to explain their benefit in CVD risk reduction.

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