Effect of a high-carbohydrate vs a high–cis-monounsaturated fat diet on lipid and lipoproteins in individuals with and without type 2 diabetes

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Abstract

It is not known whether the extent of the improvement in lipids and lipoproteins on a high–cis-monounsaturated (high-mono) diet compared with a high-carbohydrate (high-carb) diet is different in patients with type 2 diabetes mellitus (T2DM) and nondiabetic subjects. The aim of this study is to compare the effect of a high-mono and a high-carb diet on lipids and lipoproteins in patients with T2DM and nondiabetic subjects.

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Ten healthy nondiabetic men, 8 men with T2DM on dietary therapy alone, and 10 men with T2DM requiring insulin therapy were fed an isoenergetic high-carb diet (60% energy as carbohydrate and 25% as fat) and a high-mono diet (50% energy as fat and 35% as carbohydrate) for 2 to 4 weeks in a randomized, crossover fashion. Dietary fiber, simple carbohydrates, and cholesterol were held constant across diets. The lipid and lipoprotein responses to these diets were compared in nondiabetic and T2DM subjects by repeated measures analysis of variance model. Patients with T2DM had 2.2 to 2.3 times greater reductions in plasma triacylglycerol, very low-density lipoprotein (VLDL) cholesterol, and total cholesterol/high-density lipoprotein cholesterol ratio (TC/HDLC) on the high-mono diet compared with the high-carb diet than the nondiabetic subjects ($P = .02-.04$). The reductions in triacylglycerol and VLDL cholesterol were 2.7 times greater ($P = .009-.02$) in T2DM subjects with high plasma triacylglycerol concentrations ($\geq 2.26$ mmol/L) but only 1.4 to 2.0 times greater ($P = .16-.52$) in T2DM patients with low triacylglycerol concentrations ($<2.26$ mmol/L) compared with nondiabetic subjects who all had low triacylglycerol concentrations ($<2.26$ mmol/L). Patients with T2DM experienced greater decreases in plasma triacylglycerol, VLDL cholesterol, and TC/HDLC on a high-mono diet compared with a high-carb diet than nondiabetic subjects. The extents of the improvements were likely related to plasma triacylglycerol concentrations in patients with T2DM.

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1. Introduction

According to a meta-analysis [1], a number of studies have reported that replacing high-carbohydrate (high-carb) diets with diets high in cis-monounsaturated fatty acids (high-mono) improves lipid and lipoprotein profile in patients with type 2 diabetes mellitus (T2DM). The high-mono diets reduce plasma triacylglycerol and very low-density lipoprotein (VLDL) cholesterol concentrations and modestly increase high-density lipoprotein (HDL) cholesterol concentrations without adversely affecting low-density lipoprotein (LDL) cholesterol concentrations in these patients.

The beneficial effects of replacing high-carb diets with high-mono diets on lipid and lipoprotein profile have also been observed among nondiabetic subjects in several studies [2-6]. However, it is not clear whether the nondiabetic individuals experience the beneficial effects of the high-mono diets on lipid and lipoproteins to the same extent as individuals with T2DM. This is an interesting question because T2DM patients have many unique metabolic derangements such as hyperglycemia, increased VLDL secretion, impaired clearance of VLDL particles, and increased catabolism of apolipoprotein A-I [7-10], which may influence their responses to nutritional interventions. The question is not easy to address from the available literature because different studies have used diets with varying levels of fat, carbohydrate, and cholesterol content [1-6]. In addition, the fiber and simple carbohydrate content of the diets, when reported, has been different [1-6]. These dietary differences make it difficult to compare the 2 groups because individual nutrients are well known to affect lipid and lipoproteins values [11,12].

The purpose of this study, therefore, was to compare the effect of a high-carb and a high-mono diet on lipid and lipoproteins in nondiabetic individuals with those in patients with
2. Methods and materials

2.1. Subjects

Ten healthy nondiabetic men, 8 men with T2DM on dietary therapy alone, and 10 men with T2DM requiring insulin therapy were studied at the General Clinical Research Center (GCRC) of University of Texas Southwestern Medical Center at Dallas. The nondiabetic subjects were recruited through advertisements posted on bulletin boards at University of Texas Southwestern Medical Center and the diabetic subjects were recruited from the diabetes and lipid clinics at the Department of Veterans Affairs Medical Center at Dallas. The protocols were approved by the Institutional Review Board, and each participant gave informed consent. The data on men with T2DM have been published elsewhere [13,14] and the data on nondiabetic men have not been published before.

The nondiabetic men were 25 ± 4 years (mean ± SD) and their body weight and body mass index were 79.9 ± 24.9 kg and 25.3 ± 6.5 kg/m², respectively. The respective figures for men with T2DM on diet therapy were 63 ± 2 years, 89.0 ± 4.5 kg, and 30.0 ± 1.0 kg/m²; for men with T2DM on insulin therapy, 56 ± 2 years, 88.4 ± 4.0 kg, and 29.0 ± 3.0 kg/m².

None of the men with T2DM had a history of ketosis. All had an insidious onset of diabetes with minimal symptoms, mostly after the age of 40 years. In those on diet therapy, diagnosis of T2DM was confirmed by a standard oral glucose tolerance test [15]. None of the individuals had thyroid, renal, or hepatic disease and none were taking any lipid lowering therapy.

2.2. Experimental design

All 3 protocols were randomized crossover studies, and all subjects consumed 2 isoenergetic diets, one high-mono and the other high-carb. The protocols were implemented over the same period, and the high-mono diet and the high-carb diet were the same in the 3 studies. Each diet was consumed for 2 to 3 weeks by the nondiabetic subjects, 3 weeks by the subjects with T2DM on diet therapy, and 4 weeks by the subjects with T2DM on insulin therapy. All the subjects were instructed to maintain a constant level of physical activity throughout the study.

2.3. Diets

Daily energy intake of the nondiabetic subjects was estimated from the 3-day food record kept by the subjects before the study. The subjects with T2DM were observed for 5 to 7 days before initiation of the study diets (baseline period), during which time they received an isoenergetic diet as recommended by the American Diabetes Association [16]. The diet was used to establish requirements for total energy and insulin dosage (in patients requiring insulin).

Both diets consisted of solid foods. All meals were cooked at the metabolic kitchen at the GCRC, and the food selections and menus used were the same in the 3 protocols. The nutrient compositions of the study diets are shown in Table 1. The high-carb diet provided 25% of
total energy as fat (8% saturated, 12% cis-monounsaturated, and 5% polyunsaturated fatty acids) and 60% as carbohydrates (11% simple, 49% complex). The high-mono diet provided 50% of total energy as fat (11% saturated, 32% cis-monounsaturated, 7% polyunsaturated fatty acids) and 35% as carbohydrates (10% simple, 25% complex). All diets provided 15% of energy from protein, 200 mg of cholesterol, and 30 g of dietary fiber per day. Olive oil was the main source of fat in the high-mono diet, whereas a mixture of 30% corn oil and 70% palm oil was used for fat in the high-carb diet. Patients were allowed to consume plain coffee or tea in restricted amounts. Energy intake was adjusted to maintain a constant body weight during the study.

2.4. Procedures

Fasting blood was obtained for lipid and lipoprotein analysis at baseline and for 3 to 5 days at the end of each diet period in nondiabetic subjects and in patients with T2DM. Fasting plasma samples were analyzed for total cholesterol (TC), triacylglycerol, and lipoprotein cholesterol according to the Lipid Research Clinic procedures [18], except that cholesterol and triacylglycerol were measured enzymatically. VLDL (density \(<1.006\) kg/L) were removed by preparative ultracentrifugation, and cholesterol was measured in the VLDL subfraction and the infranatant. Plasma HDL cholesterol was measured enzymatically after lipoproteins containing apolipoprotein B had been precipitated with heparin-manganese. Cholesterol in the LDL fraction was taken as the difference between the cholesterol content of the 1.006 kg/L infranatant and cholesterol in the HDL fraction.

2.5. Statistical analysis

The diet by group interaction effect was analyzed by repeated measures analysis of variance (ANOVA) models. Because no interaction effect was observed in the 2 groups of patients with T2DM and nondiabetic subjects, we pooled the data on the T2DM subjects and compared it with the data on the nondiabetic subjects. All nondiabetic subjects had normal fasting plasma triacylglycerol concentrations (\(<2.26\) mmol/L), but fasting plasma triacylglycerol concentrations in patients with T2DM varied from 0.87 to 4.36 mmol/L. Therefore, to assess the possible confounding effects of differences in fasting plasma triacylglycerol

<table>
<thead>
<tr>
<th>Component</th>
<th>Percentage of energy intake per day</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>High-carb diet</td>
</tr>
<tr>
<td>Protein</td>
<td>15</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>60</td>
</tr>
<tr>
<td>Simple</td>
<td>11</td>
</tr>
<tr>
<td>Complex</td>
<td>49</td>
</tr>
<tr>
<td>Fat</td>
<td>25</td>
</tr>
<tr>
<td>Saturated</td>
<td>8</td>
</tr>
<tr>
<td>Monounsaturated</td>
<td>12</td>
</tr>
<tr>
<td>Polyunsaturated</td>
<td>5</td>
</tr>
</tbody>
</table>

Calculations are based on the US Department of Agriculture’s handbook (no. 8-15) [17].
Table 2
Plasma lipid and lipoprotein levels during the studies

<table>
<thead>
<tr>
<th></th>
<th>Nondiabetic subjects</th>
<th>T2DM patients</th>
<th>P ANOVA interaction: nondiabetic vs combined T2DM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2-3 weeks (n = 10)</td>
<td>3 Weeks (n = 8)</td>
<td>Combined, 3-4 weeks (n = 18)</td>
</tr>
<tr>
<td></td>
<td>High-carb</td>
<td>High-mono</td>
<td>High-carb</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>4.57 ± 0.48</td>
<td>4.47 ± 0.55</td>
<td>5.12 ± 0.80</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.28 ± 0.38</td>
<td>0.98 ± 0.48*</td>
<td>3.25 ± 0.79</td>
</tr>
<tr>
<td>VLDL cholesterol (mmol/L)</td>
<td>0.53 ± 0.23</td>
<td>0.38 ± 0.27*</td>
<td>1.44 ± 0.39</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>2.95 ± 0.53</td>
<td>2.90 ± 0.62</td>
<td>3.01 ± 1.06</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.09 ± 0.21</td>
<td>1.23 ± 0.26**</td>
<td>0.68 ± 0.12</td>
</tr>
<tr>
<td>TC/HDL ratio</td>
<td>4.30 ± 0.90</td>
<td>3.80 ± 0.90*</td>
<td>7.65 ± 1.07</td>
</tr>
</tbody>
</table>

Values are mean ± SD. * P < .05, ** P < .001, and *** P < .01, between the high-mono and high-carb diet within each group. To convert millimoles per liter to milligrams per decileter, multiply by 38.674 for cholesterol and 88.57 for triglycerides.
concentrations, we also categorized the T2DM patients by fasting plasma triacylglycerol concentrations (low triacylglycerol concentration < 2.26 mmol/L; high triacylglycerol concentration > 2.26 mmol/L) and compared their data with that observed in nondiabetic subjects. The difference in response to the 2 diets between groups was assessed using the diet by group interaction factor. Contrasts from the ANOVA models were used to analyze the differences within groups. Data are presented as mean and SD unless otherwise noted. Confidence intervals (CIs) are also reported to aid in interpretation of nonsignificant results. Statistical analysis was performed using SAS release 8.2 (SAS Institute, Cary, NC).

3. Results

3.1. Within-group effects of diet

Mean plasma lipid and lipoprotein concentrations on the high-carb and high-mono diets are presented in Table 2. Compared with the high-carb diet, the high-mono diet resulted in a significant reduction of 21.5% to 25.2% in serum triacylglycerol ($P = .0001-.03$), 21.5% to 33.9% in VLDL cholesterol ($P = .0001-.05$), and 11.6% to 15.1% in TC to HDL cholesterol ratio (TC/HDLC, $P = .0001-.04$), and a significant increase of 11.8% to 12.8% in HDL cholesterol ($P = .0001-.02$) in nondiabetic subjects and T2DM patients on either diet or insulin therapy. The study diets did not affect LDLC or TC in any group except in the combined group of patients with T2DM in which the high-mono diet resulted in a significant reduction of 4.4% in TC ($P = .02$) compared with the high-carb diet.
3.2. Diet by group interaction effects

Comparing the lipid and lipoproteins responses of the 2 groups of patients with T2DM with those in nondiabetic subjects revealed no significant diet by group interaction for any of the lipid and lipoprotein values. However, for plasma triacylglycerol and VLDL cholesterol, the ANOVA $P$ value approached statistical significance (.09 and .06, respectively). Because the lipid and lipoprotein responses of the 2 groups of patients with T2DM were very similar, we pooled their data together for subsequent analysis.

When the data on the 2 groups of T2DM patients were pooled, a significant diet by group interaction was observed for plasma triacylglycerol ($P = .03$; 95% CI, 0.04-0.69), VLDL cholesterol ($P = .02$; 95% CI, 0.03-0.38), and TC/HDL ratio ($P = .04$; 95% CI, 0.04-1.18) (Table 1). Compared with the high-carb diet, the high-mono diet resulted in a 2.2 times greater decrease in plasma triacylglycerol, 2.3 times greater decrease in VLDL cholesterol, and 2.2 times greater decrease in TC/HDL ratio in the combined T2DM patients than in the nondiabetic subjects (Fig. 1). No significant diet by group interaction was seen for TC ($P = .40$; 95% CI, −0.18-0.43), LDL cholesterol ($P = .54$; 95% CI, −0.39-0.21), and HDL cholesterol ($P = .29$; 95% CI, −0.03-0.11).

Grouping the T2DM patients by plasma triacylglycerol concentrations (low or high) resulted in a significant diet by group interaction for triacylglycerol ($P = .01$) and VLDL
cholesterol \((P = .04)\), but not for TC \((P = .24)\), LDL cholesterol \((P = .09)\), HDL cholesterol \((P = .49)\), and TC/HDLC ratio \((P = .12)\). The T2DM patients with high triacylglycerol concentrations had 2.7 times greater reduction in plasma triacylglycerol \((P = .009; 95\% \text{ CI}, 0.14-0.85)\) and VLDL cholesterol \((P = .017; 95\% \text{ CI}, 0.05-0.45)\) with the high-mono diet compared with the nondiabetic subjects (Fig. 2). In comparison, T2DM patients with low triacylglycerol concentrations had 1.4 to 1.9 times greater reduction in plasma triacylglycerol and VLDL cholesterol with the high-mono diet compared with the nondiabetic subjects, but the differences did not reach statistical significance (plasma triacylglycerol: \(P = .52; 95\% \text{ CI}, -0.23-0.44\); VLDL cholesterol: \(P = .16; 95\% \text{ CI}, -0.06-0.3\)).

4. Discussion

As expected, the nondiabetic subjects, just like the T2DM patients, showed a significant improvement in their plasma triacylglycerol, VLDL cholesterol, and HDL cholesterol concentrations and TC/HDLC ratio in response to the high-mono diet compared with the high-carb diet. These results are corroborated by other similar studies in T2DM patients [1] and nondiabetic subjects [2-6].

Whether the desirable changes in these variables in response to the high-mono diet occur to the same extent in nondiabetic subjects compared with T2DM patients has not been assessed previously. Comparison using the available literature is difficult because of varying macronutrient contents [1-6] between studies. In our studies where the cholesterol, fiber, and simple carbohydrate content were held constant, and the high-carb and high-mono diets were the same across all 3 studies, we found that the improvement in plasma triacylglycerol, VLDL cholesterol, and TC/HDLC ratio in response to the high-mono diet compared with the high-carb diet was 2.1 to 2.5 times greater in the T2DM patients on either diet therapy or insulin therapy than in the nondiabetic subjects. These differences, however, did not reach statistical significance possibly because of the small sample sizes. When the data on the 2 groups of T2DM patients were combined, the diet by group interaction was statistically significant for plasma triacylglycerol, VLDL cholesterol, and TC/HDLC. These variables decreased 2.2 to 2.3 times more in the combined T2DM patients than in the nondiabetic subjects in response to the high-mono diet compared with the high-carb diet.

A possible limitation is that the nondiabetic subjects consumed the diets for 2- to 3-week period each, whereas the T2DM patients consumed them for 3 to 4 weeks each. This, however, should not affect the results because maximum response to these diets is achieved in 2 weeks [13].

Another possible limitation of this study is that patients with T2DM, both those on diet therapy and insulin therapy, compared with the nondiabetic subjects, had higher triacylglycerol \((0.87-4.36 \text{ vs } 0.57-2.22 \text{ mmol/L, respectively})\) and VLDL cholesterol concentrations \((0.24-2.04 \text{ vs } 0.15-1.09 \text{ mmol/L, respectively})\) and TC/HDLC ratio \((4.25-11.74 \text{ vs } 2.57-6.41, \text{ respectively})\) and lower HDL cholesterol concentrations \((0.51-1.19 \text{ vs } 0.78-1.59 \text{ mmol/L, respectively})\) and thus could have had a greater regression to the mean effect. The regression to the mean, however, is unlikely because all 3 studies were randomized crossover designs with the same diets. Nevertheless, we further addressed this issue by grouping the T2DM patients by their triacylglycerol concentrations (low triacylglycerol <2.26 mmol/L; high
triacylglycerol > 2.26 mmol/L) and compared these groups to the nondiabetic subjects who all had triacylglycerol concentrations less than 2.26 mmol/L. The diet by group interaction was significant for triacylglycerol and VLDL cholesterol concentrations. Both these variables were reduced by nearly 3 times more in the T2DM patients with high triacylglycerol than in nondiabetic subjects and by about 1.5 to 2.0 times more in T2DM patients with low triacylglycerol than in nondiabetic subjects in response to the high-mono diet compared with the high-carb diet. The difference, however, was significant only between the T2DM group with high triacylglycerol concentrations and the nondiabetic subjects. A possible explanation for the lack of statistical significance in the difference between the T2DM with low triacylglycerol concentrations and the nondiabetic subjects may be because only 6 of 18 T2DM patients had triacylglycerol concentrations lower than 2.26 mmol/L. Nevertheless, these results show that T2DM patients with high triacylglycerol concentrations have a greater response to a high-mono diet than T2DM patients with low triacylglycerol concentrations or nondiabetic subjects. It would be interesting to study the lipid and lipoprotein response of nondiabetic, hypertriglyceridemic patients to a high-mono diet in comparison with patients with T2DM with similar baseline levels of plasma triacylglycerol concentrations.

The higher body mass index (BMI) of the T2DM subjects compared with the nondiabetic subjects may be a potential limitation. We addressed this issue by conducting a subset analysis including only the subjects with a BMI of 23 to 27 kg/m². In the subset of nondiabetic subjects, the mean BMI was 24.0 ± 0.3 kg/m², and in the subset of T2DM subjects, the mean BMI was 25.9 ± 0.2 kg/m². The decreases in triacylglycerol, VLDL cholesterol, and TC/HDLC ratio were about 2.1 to 2.8 times higher in the subset of T2DM patients than in the subset of nondiabetic subjects on the high-mono diet compared with the high-carb diet. In addition, the point estimates or mean changes were very similar in the subset analysis compared with the respective estimates in the analysis in which all the subjects were included. For example, in the T2DM subjects, the decreases in triacylglycerol, VLDL cholesterol, and TC/HDLC ratio on the high-mono diet compared with the high-carb diet were 0.57 mmol/L, 0.36 mmol/L, and 1.12, respectively, in the subset analysis and 0.66 mmol/L, 0.35 mmol/L, and 1.12, respectively, in the analysis that contained all the subjects. In the nondiabetic subjects, the respective figures were 0.20 mmol/L, 0.15 mmol/L, and 0.55 in the subset analysis and 0.29 mmol/L, 0.14 mmol/L, and 0.50 in the analysis including all the subjects. The diet by group interaction, however, was not significant, possibly because we had only 4 subjects in each subset.

One possible mechanism that explains the increase in plasma triacylglycerol and VLDL cholesterol concentrations in T2DM patients on a high-carb diet includes increased hepatic secretion of VLDL triacylglycerol [7,9,19], presumably because of increased synthesis of hepatic triacylglycerol, which are incorporated in VLDL particles [20]. A similar study in normal healthy men concluded that the increase in plasma triacylglycerol and VLDL triacylglycerol secretion on a high-carb diet is probably because of increased hepatic fatty acid availability resulting from reduced hepatic fatty acid oxidation and presumably channeled toward triacylglycerol synthesis [6]. Another study in normoinsulinemic and hyperinsulinemic subjects concluded that hepatic de novo lipogenesis might be one mechanism by which low-fat, high-carb diets induce hypertriacylglycerolemia in human subjects [21].
A second possible mechanism is reduced lipolysis of triacylglycerol-rich lipoproteins. Blades and Garg [19], however, found no change in postheparin lipoprotein lipase (LPL) activity in T2DM patients on a high-carb diet for 6 weeks. Jackson and colleagues [22], who studied the effect of a high-carb diet in healthy men, however, found lower LPL activity within a week of starting the diet but it gradually increased over time, and by day 28 of the diet, it was not different from that during the high-fat diet. Another study in nondiabetic men reported a reduction in skeletal muscle LPL activity after short-term feeding of high-carb diets [23]. Other studies in nondiabetic subjects, however, found no decrease in VLDL triacylglycerol clearance [6] or LPL concentrations [5] after a high-carb diet.

In conclusion, both the nondiabetic and T2DM subjects responded favorably to the high-mono diet compared with the high-carb diet with respect to their lipid and lipoprotein concentrations including triacylglycerol, VLDL cholesterol, and TC/HDL cholesterol ratio. The extent of these improvements were significantly higher in the T2DM patients than in the nondiabetic subjects, particularly in those with hypertriglyceridemia.

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