Comparison of monounsaturated fat with carbohydrates as a replacement for saturated fat in subjects with a high metabolic risk profile: studies in the fasting and postprandial states

Lars Berglund, Michael Lefevre, Henry N Ginsberg, Penny M Kris-Etherton, Patricia J Elmer, Paul W Stewart, Abby Ershow, Thomas A Pearson, Barbara H Dennis, Paul S Roheim, Rajasekhar Ramakrishnan, Roberta Reed, Kent Stewart, and Katherine M Phillips for the DELTA Investigators

ABSTRACT
Background: In subjects with a high prevalence of metabolic risk abnormalities, the preferred replacement for saturated fat is unresolved.

Objective: The objective was to study whether carbohydrate or monounsaturated fat is a preferred replacement for saturated fat.

Design: Fifty-two men and 33 women, selected to have any combination of HDL cholesterol ≤30th percentile, triacylglycerol ≥70th percentile, or insulin ≥70th percentile, were enrolled in a 3-period, 7-wk randomized crossover study. The subjects consumed an average American diet (AAD; 36% of energy from fat) and 2 additional diets in which 7% of energy from saturated fat was replaced with either carbohydrate (CHO diet) or monounsaturated fatty acids (MUFA diet).

Results: Relative to the AAD, LDL cholesterol was lower with both the CHO (−7.0%) and MUFA (−6.3%) diets, whereas the difference in HDL cholesterol was smaller during the MUFA diet (−4.3%) than during the CHO diet (−7.2%). Plasma triacylglycerols tended to be lower with the MUFA diet, but were significantly higher with the CHO diet. Although dietary lipid responses varied on the basis of baseline lipid profiles, the response to diet did not differ between subjects with or without the metabolic syndrome or with or without insulin resistance. Postprandial triacylglycerol concentrations did not differ significantly between the diets. Lipoprotein(a) concentrations increased with both the CHO (20%) and MUFA (11%) diets relative to the AAD.

Conclusions: In the study population, who were at increased risk of coronary artery disease, MUFA provided a greater reduction in risk as a replacement for saturated fat than did carbohydrate. Am J Clin Nutr 2007;86:1611–20.

KEY WORDS Diet, nutrition, fatty acids, lipids, lipoproteins

INTRODUCTION
Metabolic factors are important predictors of cardiovascular disease (1). Beyond LDL cholesterol, the presence of dyslipidemia with low blood concentrations of HDL cholesterol, high triacylglycerol concentrations, or both; obesity; impaired glucose tolerance; and hypertension have been shown to be associated with cardiovascular disease risk (1–3). Clusters of these factors have been identified as the metabolic syndrome and syndrome X and as indicators of insulin resistance (1, 4–6). The constellation of these factors has been suggested to provide a high-risk metabolic milieu in which the cardiovascular disease risk exceeds that predicted by LDL cholesterol. Furthermore, individuals at increased risk of coronary artery disease (CAD) with low HDL cholesterol, high triacylglycerol, or both together make up a greater fraction of individuals with premature CAD than those with isolated elevated LDL cholesterol (7). In addition, hyperinsulinemia—either directly, or more likely as a surrogate for insulin resistance—may independently contribute to the development of CAD (8).

Lifestyle modifications are recommended as first line interventions to improve metabolic risk factors. Current dietary recommendations by the National Cholesterol Education Program (NCEP) (9) and the American Heart Association (10) to reduce

1 From the Department of Medicine, Columbia University College of Physicians and Surgeons, New York, NY (LB, HNG, and RR); the Division of Nutrition and Chronic Disease, Pennington Biomedical Research Center, Baton Rouge, LA (ML); the Nutrition Department, Pennsylvania State University, University Park, PA (PMK-E); the Division of Epidemiology, University of Minnesota School of Public Health, Minneapolis, MN (PJE); the Department of Biostatistics, Collaborative Studies Coordinating Center (PWS) and the Department of Nutrition, School of Public Health and School of Medicine (BHD), The University of North Carolina at Chapel Hill, Chapel Hill, NC; the Division of Cardiovascular Diseases, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD (AE); the Research Institute, Mary Imogene Bassett Hospital, Cooperstown, NY (TAP and RR); the Department of Physiology, Louisiana State University Medical School, New Orleans, LA (PSR); and the Department of Biochemistry, Virginia Polytechnic Institute and State University, Blacksburg, VA (KS and KMP).

2 Supported by NIH grants (5-U01-HL 049644, HL 049648, HL 049649, HL 049651, and HL 049659) and M01-NCTRL 00645. The following companies made in-kind contributions of products: AARHUS, Bertoli USA, Best Foods, Campbell Soup Company, Del Monte Foods, General Mills, Hershey Foods Corporation, Institute of Edible Oils and Shortenings, Kraft General Foods, Land O’Lakes, McCormick Incorporated, Nabisco Foods Group, Neomonde Baking Company, Palm Oil Research Institute, Park Corporation, Procter and Gamble, Quaker Oats, Ross Laboratories, Swift-Armour and Eckrich, Van Den Bergh Foods, Cholestech, and Lifelines Technology Incorporated.

3 Reprints not available. Address correspondence to L Berglund, Department of Medicine, University of California, Davis, UCD Medical Center, CRISP, 2921 Stockton Boulevard, Suite 1400, Sacramento, CA 95817. E-mail: lars.berglund@ucdmc.ucdavis.edu. Received January 8, 2007. Accepted for publication July 26, 2007.
the intake of total fat, saturated fatty acids (SFAs), and cholesterol target primarily elevated LDL-cholesterol concentrations. Although the efficacy of these diets with regard to LDL cholesterol has been shown (11–17), there is concern over their potential to lower HDL cholesterol, raise triacylglycerol, and cause unfavorable postprandial lipid changes (17–20). Although carbohydrates have been advocated as a replacement for saturated fats, there has been less focus on the specific carbohydrate composition of such replacement diets, which may modulate the extent of diet-induced hypertriglyceridemia (21, 22). These concerns, coupled with concerns about increases in the risk of type 2 diabetes, have prompted alternative dietary approaches, some with higher fat intakes (23, 24). Studies in healthy subjects have shown benefits with regard to cardiovascular risk by substituting either a protein-rich diet or a diet rich in unsaturated fat for a carbohydrate-rich diet (25). However, the question remains whether individuals at risk of premature CAD because of metabolic risk factors such as low HDL cholesterol, high triacylglycerol, high fasting insulin, or a combination thereof would achieve a more favorable overall risk factor profile through replacement of saturated fat by carbohydrates or by alternative dietary approaches.

The DELTA Program (Dietary Effects on Lipoproteins and Thrombogenic Activity) comprised 2 multicenter controlled diet studies that examined the effect of changes in dietary fat on CAD risk factors. In the first study, we showed that replacement of dietary saturated fat with carbohydrate reduced total and LDL-cholesterol concentrations across sex and ethnicity (17). In the present study we sought to determine whether the replacement of dietary saturated fat with monounsaturated fat, as opposed to carbohydrate, would result in a better overall risk factor profile in nondiabetic individuals with one or more of the following: low HDL-cholesterol, high triacylglycerol, or high insulin concentrations. To be able to reflect the postabsorptive physiologic state as well as to assess diet response to a standardized metabolic fat load challenge, we also evaluated 2 separate postprandial conditions in our study. We further explored whether the diet response would differ depending on baseline lipid concentrations or the presence of the metabolic syndrome and insulin resistance.

SUBJECTS AND METHODS

Study population

Four research centers (Columbia University, Pennington Biomedical Research Center, Pennsylvania State University, and the University of Minnesota) each enrolled 20–30 participants between the ages of 21 and 65 y. Recruitment goals focused on enrolling participants who were likely to be at risk of the potential negative effects of low-fat diets. Thus, subjects were eligible if the average of 2 screening measurements met any of the following requirements based on criteria of the third National Health and Nutrition Examination Survey specific for age, sex, and race: 1) HDL cholesterol ≤30th percentile, 2) triacylglycerol ≥70th percentile, and 3) insulin ≥70th percentile. Subjects were ineligible if their 1) average screening total cholesterol was <25th percentile or >90th percentile, 2) LDL cholesterol was >4.91 mmol/L, 3) fasting triacylglycerol concentrations were <30th percentile or >5.65 mmol/L, or 4) HDL cholesterol was >70th percentile. Additionally, subjects had to be in good health, free of chronic disease (including documented heart disease and diabetes) and taking no medications known to affect lipids or thrombotic factors. Subjects were classified as having the metabolic syndrome if any 3 of the 5 defined characteristics of the syndrome were present at baseline (4). Subjects with a baseline homeostasis model assessment index >3 were classified as having insulin resistance. All participants provided written informed consent. The experimental protocol was approved by the Institutional Review Board at each respective site.

For subgroup analyses based on eligibility criteria, we recategorized participants using eligibility criteria obtained while participants were consuming an average American diet (AAD) to estimate underlying response differences without the confounding effect of habitual dietary intake. We examined lipid responsiveness to the diets by each eligibility criterion individually, ie, participants with low HDL compared with those with normal HDL, participants with high triacylglycerol compared with those with normal triacylglycerol, and participants with high insulin compared with those with normal insulin.

Study protocol

Three diets were fed in a randomized, double-blind, 3-way crossover design with each diet period lasting 7 wk. There were “rest periods” of 4 to 6 wk duration between each diet period. Twelve-hour fasting blood samples were obtained from each subject for endpoint determinations once weekly during weeks 5, 6, and 7. With the exception of a self-selected Saturday evening meal, all foods consumed by subjects were provided by the research centers. Subjects were counseled to eat the Saturday evening meal based on the NCEP Adult Treatment Panel Step I guidelines (9). Subjects were weighed twice weekly; if necessary, adjustments were made in energy intake to maintain stable body weight. Compliance with the protocol was assessed each week through a review of daily questionnaires.

Diets

The AAD was designed to reflect typical consumption patterns of the US population (Table 1). The carbohydrate-replacement diet (CHO diet) was designed to meet nutrient specifications of the NCEP Step I diet, whereas the monounsaturated fat–replacement diet (MUFA diet) was designed to not only match the saturated and polyunsaturated fat content of the CHO diet, but to also match the total fat content of the AAD. Thus, 7% of energy from SFAs was replaced with either carbohydrate (primarily as complex carbohydrates) on the CHO diet or with monounsaturated fat on the MUFA diet. In keeping with current guidelines, the CHO diet was designed to contain more fiber than the AAD. All 3 diets were designed to provide the same amount of cholesterol (300 mg/d). The target nutrient intakes for the 3 diets are summarized in Table 1. The methods used for menu development, validation, preparation, and delivery were described previously (26).

A diet-monitoring protocol was established to confirm the uniformity of diet composition over time and between the 4 research center kitchens. Daily menus were sampled and shipped frozen to the Food Analysis Laboratory and Control Center at Virginia Polytechnic Institute and State University, where 8-d menu cycle composites were prepared and assayed as described previously for total fat, total carbohydrates, protein, fatty acids, cholesterol, and energy (26). Glucose, fructose, maltose, sucrose, and lactose contents were measured by HPLC (27, 28) and...
reported as total sugars, the amount of starch was assayed enzymatically (29), and total dietary fiber was assayed by an enzymatic-gravimetric procedure (30). Measured concentrations of the key components in each experimental diet are summarized in Table 1. As seen in the table, the data demonstrate that the composition of the diets as fed to the participants was close to design targets and very precise over time and feeding sites.

### Postprandial studies

During week 7 of each diet period, 2 d-long studies were performed as part of the DELTA 2 protocol. The studies were designed to test the effect of the consumption of natural food and of a high-fat load. In the first study, blood samples were drawn from 68 participants (43 men and 25 women) during fasting conditions, prelunch, and predinner (fasting and 4 and 8 h) for each of the 3 different diets. The second day-long study was on the last day of each diet period, separated by 2 d from the premeal study. After a fasting blood draw, a standardized high-fat meal was administered; patients remained in a fasting state during the day, and repeated blood samples were drawn at 4 and 8 h. In both postprandial studies, insulin, glucose, and triacylglycerol concentrations were measured at those time points, and comparisons between studies were based on the area under the curve for each analyte (16). The high-fat meal, prepared within 24 h before administration, included 190.0 g heavy cream (Tuscan heavy cream, grade A; Nestle, Glendale, CA), 90.0 g ice cream (Breyers, Green Bay, WI) 22.0 g safflower oil (Hain Food Group, Melville, NY), 25.0 g of a powered whey protein (Promod; Ross Laboratories, Columbus, OH), 30.0 g syrup (Nestle Quik, Glendale, CA), and 0.2 g Lactaid (McNeil Nutritional, Ft Washington, PA) as a precaution against lactose intolerance in any of the participants. The nutrient composition of the meal, based on a body surface area of 2 m², included 105 g fat (7% of total calories; 52 g saturated fat), 48 g carbohydrate (15% of total calories), 32 g protein (10% of total calories), 300 mg cholesterol, and 1237 calories. The body surface area of the subjects was calculated by using the Dubois equation to gauge the appropriate weight of the meal for each subject. The subjects consumed the meal within a 15-min period. The meal containers were rinsed with chilled distilled water to ensure that the entire content was consumed.

### Laboratory analyses

Standardized blood sampling and processing procedures were validated and used at all 4 research centers. Plasma and serum samples were collected, processed, and enzymatically assayed for total cholesterol, LDL cholesterol, HDL cholesterol, triacylglycerol, glucose, and uric acid at each research center (17). A special lipid standardization protocol administered by the Centers for Disease Control showed that the precision and accuracy of each research center’s laboratory were adequate for the assayed values to be combined. Apolipoprotein (apo) A-I and apo B concentrations were assayed by rate immunonephelometry as previously described (Beckman, Fullerton, CA) (31), lipoprotein(a) [Lp(a)] concentrations were measured by enzyme-linked immunosorbent assay (Terumo, Elkton, MD), and insulin concentrations were evaluated by radioimmunoassay. All these assays were performed centrally. Insulin resistance was estimated by using the homeostasis model assessment of insulin resistance (HOMA-IR) index: fasting plasma glucose concentration (mmol/L) × fasting plasma insulin concentration (μU/mL)/22.5. A HOMA index > 3.0 was defined as insulin resistance.

### Statistical analyses

The effects of changing diet composition were evaluated in terms of 10 response variables: total cholesterol, LDL cholesterol, HDL cholesterol, triacylglycerol (natural log scale), apo B, apo A-I, Lp(a) (square root scale), glucose, insulin, and uric acid. The linear statistical model, the set of primary hypotheses, the strategy for controlling type I error, and the estimation procedures were all specified a priori. The model assumed 3 components of variance: subject, subject-by-diet, and residual. The means of the conditional distribution of assay values were assumed to be a linear function of 5 categorical factors (number of levels shown in brackets): diet [3], sex-age group [4], race [2], research center [4], feeding period [3], and interaction of diet with research center. Statistical computations for estimation and testing were performed via established methods (32) by using the

---

### Table 1

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Goal</th>
<th>Assay2</th>
<th>Goal</th>
<th>Assay2</th>
<th>Goal</th>
<th>Assay2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein (% of energy)</td>
<td>16</td>
<td>15.3 ± 0.2</td>
<td>16</td>
<td>15.5 ± 0.1</td>
<td>16</td>
<td>16.1 ± 0.2</td>
</tr>
<tr>
<td>Carbohydrate (% of energy)</td>
<td>47</td>
<td>49.0 ± 0.2</td>
<td>47</td>
<td>48.8 ± 0.3</td>
<td>54</td>
<td>54.9 ± 0.2</td>
</tr>
<tr>
<td>Sugar (% of energy)</td>
<td>18.5 ± 0.5</td>
<td>18.1 ± 0.4</td>
<td>26.7 ± 0.6</td>
<td>29.2 ± 0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Starch (% of energy)</td>
<td>26.2 ± 0.3</td>
<td>26.7 ± 0.6</td>
<td>19.4 ± 0.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat (% of energy)</td>
<td>37</td>
<td>35.8 ± 0.2</td>
<td>37</td>
<td>35.7 ± 0.3</td>
<td>30</td>
<td>29.0 ± 0.2</td>
</tr>
<tr>
<td>SFA (% of energy)</td>
<td>16</td>
<td>15.6 ± 0.1</td>
<td>8</td>
<td>8.7 ± 0.2</td>
<td>8</td>
<td>8.0 ± 0.1</td>
</tr>
<tr>
<td>MUFA (% of energy)</td>
<td>14</td>
<td>14.4 ± 0.1</td>
<td>22</td>
<td>20.8 ± 0.2</td>
<td>15</td>
<td>15.5 ± 0.2</td>
</tr>
<tr>
<td>PUFA (% of energy)</td>
<td>7</td>
<td>5.8 ± 0.1</td>
<td>7</td>
<td>6.2 ± 0.1</td>
<td>7</td>
<td>5.5 ± 0.1</td>
</tr>
<tr>
<td>Cholesterol (mg/d)</td>
<td>300</td>
<td>302 ± 8</td>
<td>300</td>
<td>293 ± 8</td>
<td>300</td>
<td>292 ± 6</td>
</tr>
<tr>
<td>Fiber (g/1000 kcal)</td>
<td>7.5</td>
<td>10.6 ± 1.3</td>
<td>7.5</td>
<td>11.0 ± 1.3</td>
<td>15.0</td>
<td>17.0 ± 2.0</td>
</tr>
</tbody>
</table>

1 AAD, average American diet; MUFA diet, 7% of energy from saturated fatty acids (SFA) replaced with monounsaturated fatty acids; CHO diet, 7% of energy from SFAs replaced with carbohydrates.

2 ± SEM of 8 menu cycles (8 d/menu cycle) for each diet.

3 More than 50% of the increase in carbohydrates in the CHO diet was in the form of complex carbohydrates.
mixed-model procedure of the SAS software system, version 9.1.3 (33). Fasting concentrations in weeks 5, 6, and 7 were tested for any time trends. No time trends were seen, which indicated stability in the final 3 wk of each diet period. The 3 values were averaged before further analysis. For each outcome variable, factors whose interactions were nonsignificant (meaning that diet effects were not affected by the level of that factor) were removed from the model one by one; the final model for each outcome variable included, besides the diets, only those factors with a significant interaction. The model also included diet period to allow for seasonal variation in outcome variables. HDL cholesterol was found to be higher in the third period by 0.024 mmol/L (P = 0.002) and triacylglycerol higher in the second period by 0.4% (P = 0.01). For the a priori analysis, a P < 0.01 was chosen as statistically significant. Auxiliary analyses were used to evaluate the sensitivity of the main results to perturbations of the modeling assumptions and to address secondary research questions. Results are presented with the values corrected for the seasonal changes. The results of the statistical analyses were unaffected if no seasonal correction is made.

RESULTS

Of the 110 participants randomly assigned, 85 completed all 3 diet periods. The final study population ranged in age from 21 to 61 y and included 33 women and 10 African Americans (Table 2). In accordance with the recruitment strategy, our study population was characterized by having, at screening, low HDL cholesterol, moderately elevated triacylglycerol and insulin, and near normal LDL cholesterol. When characterized by specific eligibility criteria, 82% of the subjects had HDL cholesterol ≤ 30th percentile, 58% of the subjects had triacylglycerol ≥ 70th percentile, and 22% had insulin values ≥ 70th percentile. Thirty-eight percent of the subjects qualified in 2 eligibility categories: low HDL cholesterol with high triacylglycerol was the most common combination (29%). Eighteen percent qualified in all 3 categories. Total cholesterol and LDL cholesterol were, on average, 5.5% and 7.0% lower, respectively, when subjects consumed the CHO diet, respectively (Table 3). Comparable differences in total cholesterol and LDL cholesterol were observed between the AAD and the MUFA diet (−6.0% and −6.3%, respectively), and

### Table 2
Subject characteristics during the reference average American diet

<table>
<thead>
<tr>
<th></th>
<th>Men (n = 52)</th>
<th>Women (n = 33)</th>
<th>Total (n = 85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American</td>
<td>4</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Age (y)</td>
<td>33.3 ± 8.6 2</td>
<td>39.0 ± 9.7 2</td>
<td>35.5 ± 9.4</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.4 ± 4.2</td>
<td>27.9 ± 4.6</td>
<td>27.6 ± 4.4</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.16 ± 0.9</td>
<td>5.15 ± 0.8</td>
<td>5.16 ± 0.8</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>3.33 ± 0.6</td>
<td>3.29 ± 0.7</td>
<td>3.32 ± 0.6</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.01 ± 0.2</td>
<td>1.18 ± 0.3 3</td>
<td>1.08 ± 0.2</td>
</tr>
<tr>
<td>Triacylglycerols (mmol/L)</td>
<td>1.38 (1.06–2.07) 4</td>
<td>1.35 (0.90–1.81)</td>
<td>1.38 (1.02–2.03)</td>
</tr>
<tr>
<td>Apolipoprotein A-I (mg/dL)</td>
<td>122.7 ± 11.5</td>
<td>136.9 ± 17.1 4</td>
<td>128.2 ± 15.5</td>
</tr>
<tr>
<td>Apolipoprotein B (mg/dL)</td>
<td>109.9 ± 21.2</td>
<td>111.2 ± 25.1</td>
<td>110.4 ± 22.7</td>
</tr>
<tr>
<td>Lipoprotein(a) (mg/dL)</td>
<td>5.2 (2.3–14.7)</td>
<td>13.3 2 (4.7–28)</td>
<td>9.0 (2.7–18.7)</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.18 ± 0.7</td>
<td>5.13 ± 0.6</td>
<td>5.16 ± 0.7</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>6.44 ± 1.2</td>
<td>4.53 ± 1.2 2</td>
<td>5.70 ± 1.5</td>
</tr>
<tr>
<td>Insulin (μU/mL)</td>
<td>11.7 (8.4–14.9)</td>
<td>9.9 (7.9–14.4)</td>
<td>11.3 (8.2–14.8)</td>
</tr>
</tbody>
</table>

1 x ± SD (all such values).
2 Significantly different from men, P < 0.01.
3 Median; interquartile range in parentheses (all such values).

### Table 3
Effect of the 3 diets on the primary study endpoints

<table>
<thead>
<tr>
<th></th>
<th>AAD</th>
<th>MUFA diet</th>
<th>CHO diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.17 ± 0.08</td>
<td>4.86 ± 0.08 2</td>
<td>4.89 ± 0.08 2</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>3.31 ± 0.08</td>
<td>3.10 ± 0.08 2</td>
<td>3.08 ± 0.08 2</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.08 ± 0.03</td>
<td>1.03 ± 0.03 2</td>
<td>1.00 ± 0.02 2, 4</td>
</tr>
<tr>
<td>Triacylglycerols (mmol/L)</td>
<td>1.48 ± 0.08</td>
<td>1.42 ± 0.07</td>
<td>1.59 ± 0.08 2, 4</td>
</tr>
<tr>
<td>Apolipoprotein A-I (mg/dL)</td>
<td>128 ± 2</td>
<td>125 ± 2 2</td>
<td>122 ± 2 2</td>
</tr>
<tr>
<td>Apolipoprotein B (mg/dL)</td>
<td>110 ± 3</td>
<td>106 ± 2 2</td>
<td>107 ± 2 2</td>
</tr>
<tr>
<td>Lipoprotein(a) (mg/dL)</td>
<td>9.9 ± 1.4</td>
<td>11.0 ± 1.5 2</td>
<td>11.9 ± 1.6 2</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.1 ± 0.1</td>
<td>5.1 ± 0.1</td>
<td>5.1 ± 0.1</td>
</tr>
<tr>
<td>Insulin (μU/mL)</td>
<td>12.2 ± 0.6</td>
<td>12.3 ± 0.6</td>
<td>12.1 ± 0.7</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>5.7 ± 0.2</td>
<td>5.7 ± 0.2</td>
<td>5.6 ± 0.2</td>
</tr>
</tbody>
</table>

1 All values are x ± SEM, except for triacylglycerols and Lp(a), which are medians ± SEM. AAD, average American diet; MUFA diet, 7% of energy from saturated fatty acids replaced with monounsaturated fatty acids; CHO diet, 7% of energy from saturated fatty acids replaced with carbohydrates.
2 Significantly different from AAD on the basis of adjusted values from the a priori linear regression model, P < 0.01.
3 Significantly different from the MUFA diet on the basis of adjusted values from the a priori linear regression model, P < 0.01.
LDL-cholesterol concentrations with the MUFA and CHO diets did not differ. In contrast, the CHO and MUFA diets differed significantly with respect to their effects on both HDL cholesterol and triacylglycerol concentrations. Although HDL-cholesterol concentrations were lower with both the MUFA and CHO diets than with the AAD (P < 0.01 for each comparison), the difference with the MUFA diet (−4.3%) was less than the difference observed with the CHO diet (−7.2%). Furthermore, as seen in Table 3, HDL-cholesterol concentrations with the CHO and the MUFA diets differed significantly (P < 0.01). In addition, whereas plasma triacylglycerol concentrations tended to be lower with the MUFA diet than with the AAD (−4.9%; P < 0.03), triacylglycerol concentrations were significantly higher with the CHO diet than with either the AAD (6.5%) or the MUFA (11.4%) diet (P < 0.01 for each comparison). Changes in apo A-I and apo B paralleled changes in HDL cholesterol and LDL cholesterol, respectively.

As seen in Table 3, average median Lp(a) concentrations were significantly higher during both the CHO and MUFA diets (11% and 20%, respectively) than during the AAD, and Lp(a) concentrations with the 2 latter diets were not significantly different from each other. Finally, although our study population was chosen for a potential predisposition to insulin resistance, the fasting concentrations of glucose, insulin, and uric acid were not affected by changes in diet.

We next examined whether the lipid responses differed between subgroups, representing individuals having either low HDL cholesterol, high triacylglycerol, or high insulin on AAD. Relative to the normal-HDL group (n = 40), individuals with low HDL cholesterol (n = 45) had smaller reductions in HDL cholesterol in response to either the MUFA or CHO diet (P = 0.02) (Figure 1). For the CHO diet, the decrease in HDL cholesterol in the low-HDL group was half that observed in the normal-HDL group. When comparing the MUFA and CHO diets, significant differences in HDL-cholesterol concentrations were seen only in the normal-HDL group. In contrast, reductions in LDL cholesterol with either the CHO or MUFA diet tended to be greater in the low-HDL group, whereas changes in triacylglycerol concentrations with either the MUFA or the CHO diets were similar in both HDL groups.

The high (n = 39) and normal (n = 46) triacylglycerol groups experienced similar changes in HDL and LDL cholesterol, but differed significantly in their triacylglycerol response to the 2 diets (P = 0.007) (Figure 1). In individuals with high triacylglycerol concentrations, triacylglycerol concentrations were not different when the amount of total dietary fat was decreased from 37% to 30% (2.13 mmol/L with the AAD and 2.18 mmol/L with the CHO diet), whereas triacylglycerol concentrations were significantly lower with the MUFA diet (2.13 mmol/L with the AAD and 1.90 mmol/L with the MUFA diet; P = 0.0005).

HDL cholesterol, LDL cholesterol, and triacylglycerol responses to the CHO and MUFA diets did not differ in individuals categorized as having either normal (n = 54) or high (n = 31) fasting insulin concentrations (data not shown).

We next examined whether the fasting lipid responses differed by the presence of the metabolic syndrome or insulin resistance. As seen in Table 4, triacylglycerol concentrations with the AAD diet were significantly higher in subjects with the metabolic syndrome (n = 20; 12 men and 8 women) or with insulin resistance (n = 28; 18 men and 10 women) than in subjects who did not fulfill these criteria. Baseline HDL and LDL cholesterol did not differ across insulin resistance strata, whereas HDL-cholesterol concentrations were lower and LDL-cholesterol concentrations were higher in subjects with the metabolic syndrome. As seen in Figure 2, the triacylglycerol and HDL cholesterol responses to the MUFA and the CHO diets, compared with the AAD, did not differ significantly for subjects with or without the metabolic syndrome or insulin resistance. Similar results were seen for total and LDL cholesterol (data not shown).

The postprandial responses of triacylglycerol, insulin, and glucose are shown in Figure 3. As outlined above, 2 different postprandial protocols were carried out, a daylong meal study and a standardized metabolic challenge fat-load study. As seen in Figure 3, the triacylglycerol response was not different for the 3 diets during the daylong study, whereas glucose concentrations were lower in the postlunch phase of the daylong study for the CHO diet (Figure 3). Insulin concentrations were highest with the AAD diet during the daylong study (Figure 3). No differences were observed between the 3 diets during the fat-load study (data not shown). We then analyzed the postprandial responses in subjects with and without the metabolic syndrome or insulin resistance. Daylong and post-fat-load triacylglycerol or insulin concentrations did not differ between the diets in these subgroups (data not shown). Although no between-diet difference was seen in glucose concentrations during the daylong study, somewhat more pronounced differences were observed during the standardized fat load in subjects with the metabolic syndrome, although the differences were not significant (Figure 4).

**DISCUSSION**

Diet modification is universally adopted as an important and early intervention approach to modifying risk factors for CAD. It is well documented that dietary SFA is associated with an increased prevalence of CAD and that the intake of polyunsaturated fatty acids (PUFAs) reduces cardiovascular morbidity (34, 35). Meta analyses and reviews of numerous dietary trials have concluded that as a replacement for SFA, either MUFA or carbohydrates lower LDL cholesterol with equal effectiveness (36–38). Whether a reduction in SFA intake, particularly via its replacement with MUFAs or carbohydrates, results in a reduction in cardiovascular morbidity or mortality has not been conclusively established. The choice of replacement for SFA might also affect the potential for weight reduction.

With an increasing frequency of a clustering of metabolic abnormalities that accentuate cardiovascular risk (1–6, 39), examination of the preferred replacement for SFA in the diet needs to focus not only on lowering LDL cholesterol but also on the effects of replacement nutrients on other metabolic risk factors. This issue is of particular importance to the large segment of the population who are at risk of CAD because of an unfavorable and complex metabolic milieu that includes low HDL-cholesterol concentrations, high triacylglycerol concentrations, or insulin concentrations. In the present randomized, double-blind, controlled feeding study, we directly compared the ability of 2 approaches for reducing SFA to favorably affect plasma lipids, lipoproteins, and indexes of glucose metabolism in a study population with a high prevalence of one or more metabolic abnormalities. The present study confirms the primary importance of reducing dietary SFAs, independent of changes in total dietary fat, to...
achieve reductions in LDL cholesterol concentrations. Replacement of 7% of energy from SFAs in the AAD with either carbohydrate or MUFA produced an equivalent 6–7% reduction in LDL cholesterol, consistent with previous observations (16, 40).

This level of LDL cholesterol lowering would, by itself, be predicted to reduce CAD risk by $\frac{50514}{50512}10\%$ (41). In the recent Women’s

![FIGURE 1. Mean (±SD) differences in LDL-cholesterol, HDL-cholesterol, and log triacylglycerol (TG) concentrations between diet groups in participants classified by HDL-cholesterol or TG concentrations. Participants were either classified as those with low HDL (HDL cholesterol ≤30th percentile; $n = 45$) or normal HDL (HDL cholesterol >30th percentile; $n = 40$) based on average values obtained while consuming the average American diet (AAD) or as those with high TG (≥70th percentile; $n = 39$) or normal TG (<70th percentile; $n = 46$) based on average values obtained while consuming the AAD. MUFA diet, 7% of energy from saturated fatty acids replaced with monounsaturated fatty acids; CHO diet, 7% of energy from saturated fatty acids replaced with carbohydrates. Significant diet effects within each HDL or TG group: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$.](image)

TABLE 4
Classification of subjects as having the metabolic syndrome or insulin resistance on the basis of lipid concentrations during the average American diet$^1$

<table>
<thead>
<tr>
<th>Metabolic syndrome</th>
<th>HOMA &gt; 3</th>
<th>HOMA ≤ 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>$5.76 \pm 0.78$</td>
<td>$4.96 \pm 0.75$</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>$3.64 \pm 0.52$</td>
<td>$3.23 \pm 0.65$</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>$0.98 \pm 0.18$</td>
<td>$1.11 \pm 0.23$</td>
</tr>
<tr>
<td>Triacylglycerols (mmol/L)</td>
<td>$2.28 \pm 0.55%$</td>
<td>$1.29 \pm 0.38%$</td>
</tr>
</tbody>
</table>

$^1$ All values are $\bar{x} \pm SD$. HOMA, homeostasis model assessment. Subjects were classified as having the metabolic syndrome if any 3 of the 5 defined characteristics of the syndrome were present at baseline. Subjects with baseline HOMA > 3 were classified as having insulin resistance.
were found (42). However, women with the lowest SFA intake changes in triacylglycerol or HDL-cholesterol concentrations, participants with AAD HDL cholesterol concentration and the difference in HDL-cholesterol concentrations fell when SFAs were replaced by either carbohydrates or MUFAs. Second, the difference in average HDL-cholesterol concentrations between the CHO and the MUFA diets was only 0.03 mmol/L. Earlier studies that showed beneficial effects of MUFA diets on HDL-cholesterol concentrations examined greater contrasts in total fat levels (38–50% compared with 20–25% of energy as fat) (43–47). However, when diets high in MUFAs have been compared against diets with total fat levels consistent with AHA Step 1 recommendations, differences in HDL-cholesterol concentrations have been typically <0.05 mmol/L, similar to our findings (16, 48, 49). Furthermore, our results are very similar to the findings in the OmniHeart study (25).

We found a negative correlation between the AAD HDL-cholesterol concentration and the difference in HDL-cholesterol concentrations between the AAD diet and the CHO diet. Furthermore, compared with participants with normal HDL-cholesterol concentrations, participants with AAD HDL cholesterol < 30th percentile had smaller reductions in HDL-cholesterol with both the CHO and MUFA diet. Thus, although there was a clear advantage of an MUFA diet in maintaining HDL-cholesterol concentrations in participants with normal HDL-cholesterol concentrations, this advantage was substantially diminished in participants with low HDL cholesterol.

In addition, there are potentially unfavorable effects of dietary changes on plasma triacylglycerol concentrations. We observed moderate differences between the replacement diets in the present study: relative to the AAD, triacylglycerol concentrations were higher with the CHO diet and lower with the MUFA diet. This finding is in agreement with the results for healthy subjects by Appel et al (25). Notably, essentially all of the reductions in triacylglycerol associated with the MUFA diet could be attributed to the response of those participants with AAD triacylglycerol concentrations ≥ 70th percentile, where triacylglycerol concentrations were 10% lower. In this group, no difference in triacylglycerol concentrations was seen between the AAD and CHO diets. This suggests that, in some individuals, SFAs are both hypercholesterolemic and hypertriacylglycerolemic (50, 51).

We also investigated the responses to the 3 diets between subgroups of subjects with or without the metabolic syndrome and with or without insulin resistance. The differences in the lipid responses to replacement of SFAs with CHO or MUFA were similar to those observed for the overall study group. These results reinforce the conclusion that diet modulation for subjects with a more broadly identified metabolic risk milieu is of importance in the prevention of CAD.

In addition to fasting lipid concentrations, postprandial lipemia is an emerging indicator of cardiovascular risk (20, 52). We did not observe any significant difference between the diets in response to either daylong meals or a high-fat load.
risk factors, the overall emphasis on LDL-cholesterol concentrations as the target of therapy suggests that reductions in LDL-cholesterol should be a primary focus. Our study indicates that reductions in HDL cholesterol associated with a reduced saturated fat intake were variable and significantly less during the MUFA diet than during the CHO diet.

We recognize that our study had some limitations. We maintained the weights of our subjects during the study and could not, therefore, address the issue of dietary effects on lipid concentrations under "free-living conditions." Reductions in body weight and body fat are associated with favorable changes in coronary heart disease risk factors, and, in outpatient studies, weight loss with low-fat diets is often observed (11, 57, 58). However the extent of weight loss that can be achieved with a CHO diet in a free-living population may be modest (42, 59) and insufficient to reverse the potential adverse changes in HDL cholesterol and triacylglycerol. Overall, our results suggest that, in individuals considered at increased risk of CAD because of an unfavorable metabolic setting, the replacement of dietary SFA with MUFA rather than CHO is preferred because of associated smaller reductions in HDL cholesterol and a trend toward a reduction in fasting triacylglycerol concentrations. Diets lower in SFAs and higher in MUFAs may be particularly beneficial in individuals with normal HDL-cholesterol concentrations or with higher triacylglycerol concentrations. Our study further suggests that rather than relying on a single dietary recommendation for everyone at risk of CAD, individualized dietary recommendations...
based on underlying risk factors may be a more effective approach for CAD prevention.

DELTA Research Investigators: Columbia University (Henry N Ginsberg, Principal Investigator; Rajasekhar Ramakrishnan; Wahida Karmally; Lars Berglund; Malina Siddiqui; Nien-Tzu Chen; Steve Holleran; Colleen Johnson; Roberta Holeman; Karen Chirgwin; Kellye Stennett; Lency Ganga; Tajudeen T Towalawi; Minnie Myers; Colleen Ngi; Nelson Fon-tanez; Jeff Jones; Carmen Rodriguez; and Norma Useehe), Pennington Bio-
medical Research Center (Michael Lefevre and Paul S Roheim), Co-Principal Investigators; Donna H Ryan; Marlene M Most; Catherine M Champagne; Donald Williamson; Richard Tullely; Ricky Brock; Deonne Bodin; Betty Kennedy; Michelle Barkate; and Elizabeth Foust), Pennsylvania State Un-
iversity (Penny Kris-Etherton, Principal Investigator; Satya S Jonnalagadda; Janice Derr; Abr Farhat-Wood; Vikkie A Mustad; Kate Meaker; Edward Mills; Mary-Ang Tilley; Helen Smicklakas-Wright; Madeleine Sigman-Grant; Jean-Xavier Guinard; Pamela Sechevich; Ch Channa Reddy; Andrea M Mastro; and Allen D Cooper), University of Minnesota (Patricia Elmer, Principal Investigator; Aaron Folsom; Nancy Van Heel; Christine Wold; Kay Fritz; Joanne Slavin; and David Jacobs), University of North Carolina at Chapel Hill, Coordinating Center (Barbara H Dennis, Principal Investigator; Paul Stewart; CE Davis; James Hosking; Nancy Anderson; Susan Blackwell; Lynn Martin; Hope Bryan; W Brian Stewart; Jeffrey Abolafia; Malachy Foley; Conroy Zien; Szu-Yun Leu; Marston Youngblood; Thomas Goodwin; Monica Miles; and Jennifer Wehbe), Mary Imogene Bassett Research In-
itute (Thomas A Pearson and Roberta Reed), University of Vermont (Rus-
fell Tracy and Elaine Cornell), Virginia Polytechnic and State University (Kent K Stewart and Katherine M Phillips), Southern University (Bernestine B McGee and Brenda Williams), Beltsville Agricultural Research Center (Gary R Beecher, Joanne M Holden, and Carol S Davis), and the National Heart, Lung, and Blood Institute (Abby G Ershow, David J Gordon, Michael Prosch, and Basil M Rifkind).

All authors contributed to the planning of the studies, the recruitment and study visits, the laboratory and statistical analyses, and the drafting of the manuscript. None of the authors had a conflict of interest.

REFERENCES

11. Bae CY, Keenan JM, Wenz J, McCaffrey DJ. A clinical trial of the American Heart Association step one diet for treatment of hyperchole-
19. Grundy SM, Denke MA. Dietary influences on serum lipids and lipopro-
20. Hyson D, Rutledge JC, Berglund L. Postprandial lipemia and cardio-
21. Parks E, Hellerstein MK. Carbohydrate-induced hypertriglyceride-
22. Howard BV, Wylie-Rosett J. Sugar and cardiovascular disease. Circu-
drate intake on blood pressure and serum lipids. Results of the Omni-
Heart Randomized Trial. JAMA 2005;294:2545–64.
29. Thivend P, Mercier C, Guilbot A. Determination of starch with gly-
30. Cranker KJ, Phillips KM, Stewart KK. Fine tuning a bile-enzymatic-
31. Tuck CH, Holleran S, Berglund L. Postprandial lipemia and cardio-
32. Muller KE, Stewart PW. Linear model theory: univariate, multivariate,
34. Kris-Etherton PM, Hecker KD, Binkoski AE. Polyunsaturated fatty ac-
35. Wang C, Harris WS, Chung M, et al. Fatty acids from fish or fish-oil
supplements, but not
36. Derr J, Kris-Etherton PM, Pearson TA, Seligson FH. The role of fatty acid saturation on plasma lipids, lipoproteins, and apolipoproteins: II.


