Effects of Diets Enriched in Saturated (Palmitic), Monounsaturated (Oleic), or trans (Elaidic) Fatty Acids on Insulin Sensitivity and Substrate Oxidation in Healthy Adults

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OBJECTIVE — Diets high in total and saturated fat are associated with insulin resistance. This study examined the effects of feeding monounsaturated, saturated, and trans fatty acids on insulin action in healthy adults.

RESEARCH DESIGN AND METHODS — A randomized, double-blind, crossover study was conducted comparing three controlled 4-week diets (57% carbohydrate, 28% fat, and 15% protein) enriched with different fatty acids in 25 healthy men and women. The monounsaturated fat diet (M) had 9% of energy as C18:1 cis (oleic acid). The saturated fat diet (S) had 9% of energy as palmitic acid, and the trans fatty acid diet (T) had 9% as C18:1trans. Body weight was kept constant throughout the study. After each diet period, insulin pulsatile secretion, insulin sensitivity index (S_I) by the minimal model method, serum lipids, and fat oxidation by indirect calorimetry were measured.

RESULTS — Mean S_I for the M, S, and T diets was 3.44 ± 0.26, 3.20 ± 0.26, and 3.40 ± 0.26 × 10^{-1} μU^{-1}·ml^{-1}, respectively (NS). S_I decreased by 24% on the S versus M diet in overweight subjects but was unchanged in lean subjects (NS). Insulin secretion was unaffected by diet, whereas total and HDL cholesterol increased significantly on the S diet. Subjects oxidized the least fat on the M diet (26.0 ± 1.5 g/day) and the most fat on the T diet (31.4 ± 1.5 g/day) (P = 0.02).

CONCLUSIONS — Dietary fatty acid composition significantly influenced fat oxidation but did not impact insulin sensitivity or secretion in lean individuals. Overweight individuals were more susceptible to developing insulin resistance on high-saturated fat diets.

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High-fat diets have been shown to produce insulin resistance relative to high-carbohydrate diets (1–4), and certain fatty acids may have a more deleterious effect on insulin action than others. In animal models, Storlien et al. (5,6) found that high intake of saturated and polyunsaturated fats induce severe insulin resistance, whereas monounsaturated fats and ω-3 fatty acids are less detrimental. In humans, saturated fatty acid intake is a significant independent predictor of fasting and postprandial insulin in middle-aged men (7) and young men and women (8).

The composition of lipids in serum or muscle (markers of dietary fatty acid intake) also correlates with insulin resistance. In a cross-sectional population study of >4,000 healthy individuals, fasting insulin concentration was positively associated with the percentage of saturated fat and inversely associated with the percentage of monounsaturated fat in plasma phospholipids (9). We have previously reported inverse associations between insulin sensitivity and serum concentrations of myristic acid (C14:0), palmitoleic acid (C16:1), and dihomo-γ-linolenic acid (C20:3 n-6) (10). Similarly, an association between increased C16:1 and C20:3 n-6 in serum cholesterol esters and risk of developing type 2 diabetes has also been reported (11).

Insulin secretion is also differentially effected by various fatty acids in vitro. Longer-chain fatty acids and those with greater degree of saturation increase insulin secretion from perfused rat pancreas (12). In mouse islet cells, trans fatty acids potentiate insulin secretion relative to cis isomers of the same chain length (13). cis Isomers also decreased glucose oxidation during hyperglycemia, whereas trans isomers had no effect.

The present study compared the effects of diets enriched in saturated or trans fatty acids with a reference diet enriched in a monounsaturated, oleic acid. We hypothesized that the saturated fat diet would reduce insulin sensitivity relative to the reference diet and that trans fatty acids, which alter insulin secretion in vitro, would alter whole-body insulin sensitivity and/or secretion.
Dietary fatty acid effects on insulin sensitivity

Table 1—Target and actual nutrient composition of the experimental diets and fat blends

| Nutrient                        | Target | M diet | S diet | T diet |
|---------------------------------|--------|--------|--------|--------|
| Carbohydrate (% energy)         | 54     | 57.2 ± 0.4 | 58.0 ± 0.4 | 57.8 ± 0.5 |
| Protein (% energy)              | 16     | 14.8 ± 0.2  | 15.3 ± 0.5  | 15.2 ± 0.7  |
| Total fat (% energy)            | 30     | 27.8 ± 0.4  | 27.0 ± 0.6  | 26.8 ± 0.2  |
| Saturated fat (% energy)        | 5      | 5.8 ± 0.6   | 2.9 ± 0.1   | 7.3 ± 0.1   |
| Monounsaturated fat (% energy)  | 10     | 15.2 ± 0.6* | 9.3 ± 0.3   | 8.4 ± 0.1   |
| Polyunsaturated fat (% energy)  | 6      | 6.3 ± 0.1   | 6.4 ± 0.2   | 4.0 ± 0.1   |
| Test fatty acid (% Energy)      | 9      | *          | 8.4 ± 0.1   | 7.3 ± 0.2   |
| C12:0 (% of total fatty acid)   | —      | 1.0 ± 0.1   | 1.7 ± 0.1   | —          |
| C14:0 (% of total fatty acid)   | —      | 1.2 ± 0.1   | 1.8 ± 0.1   | 3.6 ± 0.2   |
| C16:0 (% of total fatty acid)   | —      | 12.9 ± 0.3  | 31.4 ± 0.4  | 12.5 ± 0.1  |
| C16:1 (% of total fatty acid)   | —      | 0.3 ± 0.1   | 0.4 ± 0.1   | —          |
| C18:0 (% of total fatty acid)   | —      | 6.1 ± 0.6   | 6.2 ± 0.6   | 10.8 ± 0.1  |
| C18:1cis (% of total fatty acid)| —      | 54.9 ± 1.1  | 33.6 ± 0.5  | 29.4 ± 0.4  |
| C18:1trans (% of total fatty acid)| —    | —        | —        | 27.0 ± 0.4  |
| C18:2 (% of total fatty acid)   | —      | 22.7 ± 0.2  | 23.6 ± 0.3  | 14.9 ± 0.2  |
| C20:1 (% of total fatty acid)   | —      | 1.0 ± 0.1   | 1.0 ± 0.1   | 0.9 ± 0.02  |
| Fatty acid content of fat blends (database values) | | | |
| Saturated fat (%)               | —      | 16.9       | 61.4      | 21.6       |
| Monounsaturated fat (%)         | —      | 71.7       | 28.3      | 22.1       |
| Polyunsaturated fat (%)         | —      | 10.1       | 9.6       | 10.3       |
| Test fatty acid (%)             | —      | 71.7       | 50.1      | 22.1       |

Data are means ± SE, unless otherwise indicated. *Since C18:1cis is the predominant monounsaturated fatty acid in the diet, it made up most of the monounsaturated fatty acids in all diets. To achieve comparability between diets, we did not attempt to reach 10% of kcal from monounsaturated fatty acids other than C18:1cis; therefore, the test fatty acid for the M diet is part of the total monounsaturated fatty acid category.

RESEARCH DESIGN AND METHODS

Subjects. Subjects were recruited from the Baton Rouge area using flyers and advertisements in local newspapers. To be eligible to participate, volunteers had to be healthy nonobese men or premenopausal women. Exclusion criteria were the presence of any chronic disease, use of prescription medication (except oral contraceptives), smoking, and LDL cholesterol or triglycerides <5th or >95th percentile for age. All subjects signed an informed consent form before participation. Pennington Biomedical Research Center’s Institutional Review Board approved the protocol, consent form, and advertisements.

Experimental design. After a standard screening procedure, eligible subjects were enrolled in the study. The study design was a randomized, crossover, double-blind, controlled-feeding trial. Each of the three experimental diets was fed for 4 weeks with a minimum 2-week washout between diets. This length of feeding significantly elevated the fatty acid of interest in serum for each diet (see RESULTS). There was no evidence of carry-forward effects from previous diets in the serum fatty acid profiles, indicating that the washout period was of adequate length. All subjects completed each of the diets in random order. At the end of each 4-week diet period, subjects returned to the clinic for measurement of insulin sensitivity, insulin secretion, resting metabolic rate (RMR), and substrate oxidation. Investigators and personnel collecting outcomes data were blinded to treatment order.

Experimental diets. The target nutrient composition for all three diets was 55% carbohydrate, 30% fat, 15% protein, 275 mg/day cholesterol, and 7.5 g/1,000 kcal dietary fiber. On the reference monounsaturated fat diet (M diet), the target was to have a minimum of 9% of energy as oleic acid (C18:1cis; M diet). The other diets targeted 9% of energy as palmitic acid (C16:0; saturated fat [S] diet) or elaidic acid (C18:1trans; T diet). To achieve an isolated exchange of 9% of energy of the C18:1cis for the test fatty acid, specially formulated fat blends were developed for each experimental diet using various vegetable oils and decholesterol- ized butter fat. These fat blends provided ~50% of the day’s fat calories (i.e., 15% of kcal as fat) and were formulated to wholly contain the planned changes in fatty acid composition. Thus, when added to the common base diet, the individual fat blends provided final diets containing identical amounts of total fat but differing by 9% of energy in the fatty acid of interest. The foods on each diet were identical except for the fat blend added to baked goods or other menu items. The composition of the experimental diets and fat blends is shown in Table 1.

All diets were prepared in a metabolic kitchen with precise control of both nutrient and caloric content. Calories were adjusted as needed to maintain subject body weight throughout the study such that whenever a subject experienced a change in weight of 2 kg in a week, unit portions of food (100 kcal each) would be added or subtracted as necessary until baseline weight was achieved. Subjects ate breakfast and dinner during the week at the Pennington Center, with lunch and weekend meals boxed for takeout. Subjects were required to eat all the food provided, and a daily compliance log was completed. A 5-day menu cycle was used throughout the study to provide variety.
Alcohol was prohibited during the 4-week diets, but subjects could consume alcohol with their habitual diets during the washout periods.

**Insulin sensitivity.** The minimal model method was used to assess insulin sensitivity. A frequently sampled intravenous glucose tolerance test using stable isotope-labeled glucose (16,6,2H$_2$)glucose was performed after an overnight fast (14,15). Subjects refrained from vigorous exercise for 48 h before the test. Baseline blood samples from the antecubital vein for determination of glucose and insulin were obtained at −15, −10, and 5 min. Through another antecubital catheter, 300 mg/kg glucose (as 50% dextrose) was injected over 45 s. Time 0 was marked at the end of glucose administration, and collection of blood samples (4 ml) at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 19 min followed. At 20 min, a bolus injection of insulin (0.03 units/kg Humulin; Eli Lilly, Indianapolis, IN) was given, and frequent sampling resumed at 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, and 180 min. Each blood sample was kept chilled on ice, centrifuged at 160, and 180 min. Each blood sample resumed at 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, and 180 min. From each sample, 200 µl were extracted using the method of Bleigh and Dyer (19) for total lipids after the addition of 20 µg of the internal standard tricosanoic acid and an internal standard mixture that contained 1,2-ditricosanol-sn-glycero-3-phosphocholine, triheptadecenoin, cholesteryl heptadecanoate. Lipid class separation was performed using Baker Bond solid-phase extraction aminopropylsiline bonded silica gel columns (JT Baker, Phillipsburg, NJ) (20). All lipids were transmethlylated using a 14% wt/vol solution of boron trifluoride in methanol (21). The resulting fatty acid methyl esters were analyzed using a Hewlett-Packard 5890 gas chromatograph with a 10:1 split-injection ratio on a capillary column using flame ionization detection. Data were expressed as a percent of total fatty acid weight (% by wt).

**Laboratory measures.** Serum glucose, triglycerides, cholesterol, and HDL cholesterol were assayed on an autoanalyzer (Beckman Synchrone CX7 or CX5; Beckman, Brea, CA). The dextran sulfate precipitation method was used for the HDL measurement. LDL was calculated using the Friedewald equation, assuming triglycerides within normal limits. Insulin concentrations were determined using a microparticle enzyme immunoassay on an Abbott IMx analyzer (Abbott Laboratories, Abbott Park, IL). This assay has <1% cross-reactivity with proinsulin.

**Statistical analyses.** All statistical analyses were performed using SAS-PC (SAS, Cary, NC). A priori power analysis indicated that 22 subjects would provide >85% power to detect a difference in S$_I$ of 0.45 units between diets. A change of this magnitude in S$_I$ would be expected to be clinically meaningful in subjects with average insulin sensitivity. Descriptive data were obtained on all variables using the univariate procedure with an option allowing for assessment of the normality of the distribution. Variables that were not normally distributed were log-transformed before analysis. Repeated measures of ANOVA were used to compare differences in outcome variables among the three diets. The analysis was adjusted for covariates, including diet order and sex, as needed. P < 0.05 was considered statistically significant, except for correlations where a P value of 0.01 was used due to multiple comparisons.

**RESULTS** — A total of 31 subjects were enrolled, and 12 men and 13 women (23 Caucasian and 2 Asian) completed the study. For those who completed the study, mean age at randomization (±SE) was 28.0 ± 2.0 years and BMI was 23.5 ± 0.5 kg/m$^2$. Of the subjects, 18 were lean (BMI < 25 kg/m$^2$) and 7 were overweight (BMI 25–30 kg/m$^2$). Two women and four men dropped out before completion. The dropouts were similar in age, race, and body weight to those who completed the entire study (data not shown). Subject weight remained constant throughout the study (68.0 ± 2.4, 67.9 ± 2.4, and 67.9 ± 2.4 kg at the end of the M, S, and T diets, respectively; NS).

The effects of the three controlled diets on parameters of insulin sensitivity and secretion are shown in Table 2. There were no main effects of diet on any of the insulin parameters, regardless of whether standard or stable-label minimal modeling was used. When subjects were divided into lean and overweight groups based on BMI, overweight subjects had a larger decrease in S$_I$ on the S and T diets than the lean subjects. Overweight subjects experienced a 24% decrease in S$_I$ on the S diet and a 11% decrease on the T diet relative to the M diet (not statistically significant). Lean subjects, on the other hand, did not exhibit any change in S$_I$ across the diets.

Significant effects of time were observed for S$_I$, S$_c$, and disposition index, although there were no diet-by-time interactions for these variables. Least squares mean estimates for S$_I$, averaged across all three experimental diets, were significantly lower for the first diet period.
Table 2—Effects of diet on insulin sensitivity and secretion and serum lipids in 25 healthy adults

|                          | M diet     | S diet     | T diet     |
|--------------------------|------------|------------|------------|
| Fasting glucose (mmol/l) | 4.9 ± 0.1  | 4.8 ± 0.1  | 4.7 ± 0.1  |
| Fasting insulin (pmol/l) | 26.2 ± 1.8 | 24.0 ± 1.8 | 25.2 ± 1.8 |
| S <sub>1</sub> × 10<sup>-4</sup> (min<sup>-1</sup> • μU<sup>-1</sup> • ml<sup>-1</sup>) | 3.44 ± 0.26 | 3.20 ± 0.26 | 3.40 ± 0.26 |
| S<sub>0</sub> (min<sup>-1</sup>) | 1.95 ± 0.11 | 1.76 ± 0.11 | 1.90 ± 0.11 |
| AIR<sub>0</sub> (μU • ml<sup>-1</sup> • min<sup>-1</sup>) | 440.4 ± 45.1 | 418.9 ± 45.3 | 393.9 ± 45.1 |
| Disposition index        | 1,362.3 ± 140.0 | 1,291.3 ± 141.1 | 1,273.1 ± 140.0 |
| S<sub>1</sub>* × 10<sup>-4</sup> (min<sup>-1</sup> • μU<sup>-1</sup> • ml<sup>-1</sup>) | 3.52 ± 0.25 | 3.67 ± 0.26 | 3.40 ± 0.26 |
| S<sub>0</sub>* (min<sup>-1</sup>) | 2.56 ± 0.36 | 2.77 ± 0.37 | 2.72 ± 0.37 |
| Basal insulin secretion (μU • ml<sup>-1</sup> • min<sup>-1</sup>) | 0.52 ± 0.04 | 0.54 ± 0.4  | 0.57 ± 0.04 |
| No. insulin bursts per 90 min | 7.95 ± 0.26 | 7.91 ± 0.26 | 8.27 ± 0.26 |
| Total insulin secretion (pmol/l) | 473.4 ± 29.4 | 461.4 ± 29.4 | 437.4 ± 29.4 |
| Mean insulin concentration (pmol/l) | 26.4 ± 1.6  | 25.2 ± 1.6  | 27.6 ± 1.6  |
| Insulin production rate (pmol/l) | 185.4 ± 25.8 | 163.2 ± 25.2 | 183.6 ± 25.2 |
| Total cholesterol (mmol/l) | 3.78 ± 0.11† | 3.93 ± 0.11 | 3.90 ± 0.11 |
| HDL cholesterol (mmol/l) | 2.15 ± 0.09  | 2.20 ± 0.09  | 2.24 ± 0.09  |
| Triglycerides (mmol/l)    | 1.23 ± 0.04† | 1.28 ± 0.04 | 1.23 ± 0.04† |

Data are means ± SE, adjusted for time and reflect measures made at the end of each 4-week diet period. S<sub>1</sub>* and S<sub>0</sub>* are parameters from stable-label minimal model. Lipid data are also adjusted for sex. †Significantly different from palmitic acid diet (P < 0.05).
study, we were unable to test the hypothesis that gene polymorphisms influence the response to dietary fatty acids; however, further research may show genetic background to be key in such responses.

We observed a greater decrease in $S_I$ on the S diet in overweight individuals (BMI 25–30 kg/m²) relative to lean individuals. Although the 24% decrease in $S_I$ in overweight subjects on the S diet relative to the M diet was not statistically significant because of the small numbers in this group, such a substantial drop could certainly be of clinical relevance. Similar results were reported in the Insulin Resistance Atherosclerosis Study (IRAS), in which higher dietary fat intakes were associated with insulin resistance in obese but not lean individuals (4). One explanation for the different response in overweight individuals may be that their relative baseline insulin resistance produces a diminished ability to respond to environmental challenges to glucose-insulin homeostasis. A second possibility is that genes related to obesity may influence response to dietary fatty acids.

Trans fatty acids did not have any effect on insulin sensitivity or secretion in the present study. A previous study in individuals with type 2 diabetes showed that a diet high in trans fatty acids produced hyperinsulinemia during an oral glucose tolerance test compared with a diet high in cis fatty acids (25). Because insulin sensitivity was not directly measured in that study, it is not clear whether the observed effect was due to changes in insulin sensitivity, secretion, or clearance. Furthermore, because we observed differences in dietary response between lean and obese subjects, it is possible that individuals with diabetes (who also tend to be obese) may respond differently than those without diabetes.

During the high trans diet, subjects oxidized significantly more fat than during the high oleic acid diet. To our knowledge, differences in whole-body fat oxidation between long-term cis and trans fatty acid diets have not been reported. However, we have previously reported acute differences in the rate of oxidation of cis and trans fatty acids in humans. Specifically, in lean men fed [13C]-labeled fatty acids, C18:1trans was more highly oxidized than C18:1cis over a 9-h period (26). These results may suggest that a high oleic acid diet could promote weight and/or fat gain, although further research is clearly needed. Consistent with this suggestion, however, are preliminary data from Lefevre et al. (27) suggesting that free-living subjects were not as effective in reducing caloric intake or body weight on a high monounsaturated fat diet compared with a low-fat high-carbohydrate diet.

Several studies have examined the effects of dietary fat on insulin secretion. In the IRAS, dietary fat intake was positively related to insulin secretion, measured by the minimal model, in subjects with normal glucose tolerance but not in those with impaired glucose tolerance (28). In contrast, a study by Larsson et al. (29) did not find any correlation between intake of specific dietary fatty acids and insulin secretory response to arginine in postmenopausal women. Similarly, our data in younger men and women did not show an effect of fat type on insulin secretion.

We observed an unexpected significant effect of time on both $S_I$ and $S_G$. Because diet order was randomized, one possible reason for this observation is that seasonal changes in $S_I$ affected the results. A seasonal variation in plasma glucose and insulin in humans has been reported, with both being higher in fall than spring (30), and the incidence of type 2 diabetes is twice as high in winter versus summer months (31). On the other hand, Gravholt et al. (32) did not find a seasonal variation in $S_I$ or $S_G$, measured by the minimal model, in healthy young men. In the present study, both $S_I$ and $S_G$ were lower in diet period 1, which occurred during the fall, than in diet periods 2 and 3, which ran from January to March. Another explanation for the time effect is that there were carry-forward effects from previous diets. This is unlikely, however, since analysis of serum did not indicate enrichment in fatty acids from the previous diet.

In summary, the present study demonstrates that healthy lean subjects do not exhibit any change in insulin sensitivity or secretion in response to controlled high-saturated or trans fatty acid diets. Further studies of obese individuals or healthy subjects eating diets higher in total fat are warranted.

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