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 C18:1*trans*. 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^{-4} $min^{-1} \cdot \mu U^{-1} \cdot ml^{-1}$, 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 monounsaturate, 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.

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Abbreviations: AIR_g, acute insulin response to glucose; IRAS, Insulin Resistance Atherosclerosis Study; M diet, monounsaturated fat diet; RMR, resting metabolic rate; S diet, saturated fat diet; S_G, glucose effectiveness; S_I, insulin sensitivity index; T diet, *trans* fatty acid diet.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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

Nutrient	Target	Biochemical analysis		
		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
C18:1*cis* (% of total fatty acid)	—	54.9 ± 1.1	33.6 ± 0.5	29.4 ± 0.4
C18:1*trans* (% 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 C18:1*cis* 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 C18:1*cis*; 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 (C18:1*cis*; M diet). The other diets targeted 9% of energy as palmitic acid (C16:0; saturated fat [S] diet) or elaidic acid (C18:1*trans*; T diet). To achieve an isolated exchange of 9% of energy of the C18:1*cis* for the test fatty acid, specially formulated fat blends were developed for each experimental diet using various vegetable oils and decholesterolized 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 isotopically labeled glucose ([6,6,$^2H_2$]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 4°C, and the serum was stored at −20°C until analysis for glucose and insulin. The ^2H enrichment of glucose was measured by positive chemical ionization mass spectrometry (Finnigan TSQ7000 quadrupole GC/MS; Finnigan, San Jose, CA). Glucose and insulin data were used for calculation of the insulin sensitivity index (S_I), glucose effectiveness (S_G), and acute insulin response to glucose (AIR_g). S_I reflects the effect of an incremental change in plasma insulin to increase fractional glucose clearance independent of glycemia. S_G is the fractional glucose disappearance rate at basal insulin. The disposition index was calculated as the product of S_I and AIR_g. The minimal model analysis was done using the MINMOD-PC program and kinetic analysis for the stable isotope by applying the minimal model for glucose disappearance, modified for tracer data (14,15).

Insulin pulsatile secretion. Insulin pulsatility was evaluated as described by Peiris et al. (16). After an overnight fast, an intravenous cannula was inserted into the antecubital vein. A heating pad was used to obtain arterialized venous samples. Beginning at 0700, blood samples (3 ml) were drawn every 2 min for 90 min for determination of peripheral serum insulin concentration. Deconvolution analysis was used to determine frequency amplitude, pulse area, interpulse interval, and short-term insulin oscillatory peaks, as previously validated (17).

Metabolic rate and substrate oxidation. Metabolic rate and substrate oxidation were assessed using indirect calorimetry. RMR was measured in overnight-fasted subjects for 30 min, after a 30-min rest period, to determine energy needs. Fat and carbohydrate oxidation were calculated as described by Jequier et al. (18). Protein oxidation was calculated using the urinary nitrogen measures. Deltatrac 2 portable metabolic carts (Datex, Helsinki, Finland) were used to measure RMR and substrate oxidation. The precision of these instruments is 3% in our laboratory.

Serum fatty acid composition. From each serum 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-ditricosanoyl-sn-glycero-3-phosphocholine,triheptadecenoin, cholesteryl heptadecanoate. Lipid class separation was performed using Baker Bond solid-phase extraction aminopropylsilane bonded silica gel columns (JT Baker, Phillipsburg, NJ) (20). All lipids were transmethylated using a 14% wt/vol solution of boron trifloride 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 Synchron 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% drop in S_I on the S diet and an 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_G, 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
$S_I \times 10^{-4}$ ($min^{-1} \cdot \mu U^{-1} \cdot ml^{-1}$)	3.44 ± 0.26	3.20 ± 0.26	3.40 ± 0.26
S_G (min^{-1})	1.95 ± 0.11	1.76 ± 0.11	1.90 ± 0.11
AIR_g ($\mu U \cdot ml^{-1} \cdot min^{-1}$)	440.4 ± 45.1	418.9 ± 45.3	399.3 ± 45.1
Disposition index	1,362.3 ± 140.0	1,291.3 ± 141.1	1,273.1 ± 140.0
$S_I^* \times 10^{-4}$ ($min^{-1} \cdot \mu U^{-1} \cdot ml^{-1}$)	3.52 ± 0.25	3.67 ± 0.26	3.40 ± 0.26
S_G^* (min^{-1})	2.56 ± 0.36	2.77 ± 0.37	2.72 ± 0.37
Basal insulin secretion ($\mu U \cdot ml^{-1} \cdot min^{-1}$)	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
LDL cholesterol (mmol/l)	2.15 ± 0.09	2.20 ± 0.09	2.24 ± 0.09
HDL cholesterol (mmol/l)	1.23 ± 0.04†	1.28 ± 0.04	1.23 ± 0.04†
Triglycerides (mmol/l)	0.88 ± 0.10	0.88 ± 0.10	0.94 ± 0.10

Data are means ± SE, adjusted for time and reflect measures made at the end of each 4-week diet period. S_I^* and S_G^* are parameters from stable-label minimal model. Lipid data are also adjusted for sex. †Significantly different from palmitic acid diet ($P < 0.05$).

than for the second or third diet periods (2.74 ± 1.1 vs. 3.41 ± 1.1 and 3.33 ± 1.1 $\times 10^{-4}$ $min^{-1} \cdot \mu U^{-1} \cdot ml^{-1}$, respectively; $P = 0.003$). Similarly, S_G for period 1 was significantly lower than that for period 3 (1.64 vs. 2.08 min^{-1}; $P = 0.004$).

There were significant main effects of diet on serum lipids (Table 2). Both total and HDL cholesterol were significantly higher on the S diet, as expected. Triglycerides and LDL cholesterol did not differ significantly among the three diets.

Significant main effects of diet were also observed for fat oxidation measured by indirect calorimetry. Subjects oxidized the least fat over 8 h on the M diet (26.0 ± 1.5 g/day) and the most fat on the T diet (31.4 ± 1.5) ($P = 0.02$, adjusted for sex and diet order). Fat oxidation on the S diet was intermediate (29.0 ± 1.5 g/day) and not significantly different from either the M or T diets. There was no significant effect of diet on carbohydrate oxidation, although the trend was opposite to that of fat oxidation, as expected. The respiratory quotient on the M, S, and T diets was 0.83 ± 0.02, 0.82 ± 0.02, and 0.78 ± 0.2, respectively (NS).

Significantly higher serum concentrations of C18:1*cis* were observed on the M diet, significantly higher levels of C16:0 on the S diet, and significantly higher levels of C18:1*trans* on the T diet (data not shown). Thus, subjects were apparently compliant with the diets, and 4 weeks was a sufficiently long feeding period to produce significant changes in the appropriate fatty acids. Associations between serum fatty acids and S_I were analyzed on the three different experimental diets after adjustment for BMI (Table 3). The relationships between serum fatty acids and insulin sensitivity differed depending on the background diet being consumed. Neither serum C16:0 nor *trans* fatty acids were significantly inversely associated with S_I as hypothesized. There were no significant relationships using the conservative *P* value of 0.01, although S_I tended to be inversely correlated with C14:0 and positive related to C18:3 n-6, C22:1, and C22:5 n-3 on at least one of the diets.

CONCLUSIONS — Feeding studies in animals have consistently shown an adverse effect of saturated fat on insulin action (5). Human studies have tended to support these observations, although the majority of clinical studies have been correlational in nature (7,9,10). In contrast, the present randomized controlled feeding trial suggests that there is no effect of high saturated or *trans* fatty acids on insulin action in healthy lean adults. Similarly, Brynes et al. (22) recently performed a controlled feeding trial comparing high monounsaturated fat diets with high polyunsaturated fat diets in individuals with type 2 diabetes and observed no changes in insulin sensitivity despite significant changes in plasma fatty acid composition. Thus, the results of these two controlled feeding trials do not support significant effects of individual fatty acids on insulin action in humans.

A methodological issue in interpreting the results of both these feeding trials, however, is the total amount of fat in the diet. Total dietary fat impacts insulin sensitivity such that high-fat diets (≥40% fat) worsen insulin resistance, whereas low-fat diets (typically 20% fat) improve it (1–4). The total fat in our study diets was measured to be 28%, slightly less than the targeted 30%. It is therefore possible that in the context of <30% total dietary fat, a relative enrichment of saturated or *trans* fatty acids does not significantly alter insulin sensitivity. On the other hand, in the study of Brynes et al. (22), the diets were relatively high fat (~40%), and a favorable impact of monounsaturated fatty acids may not be seen in that context. This suggestion is supported by recent data from the KANWU study in which a beneficial effect of monounsaturated fat enrichment on insulin sensitivity was seen only in individuals consuming diets <37% total fat (23).

Luan et al. (24) have recently shown a gene-diet interaction between the dietary polyunsaturated/saturated fat ratio and a polymorphism in peroxisome proliferator–activated receptor γ2. Because of the relatively small number of subjects in our

Table 3—*Correlations between serum fatty acid composition and S_I on three experimental diets in 25 healthy men and women*

Fatty acid	M diet	S diet	T diet
C12:0	−0.54 (n = 5)	0.23 (n = 12)	−0.77 (n = 5)
C14:0	−0.39	−0.03	−0.004
C16:0	−0.35	−0.36	−0.04
C16:1	−0.12	−0.19	−0.18
C18:0	0.36	0.12	0.36
C18:1*cis*	−0.07	0.12	−0.15
C18:1*trans*	0.03	0.002	0.08
C18:2 n-6	−0.13	−0.10	−0.09
C18:3 n-6	0.44	0.11	0.14
C18:3 n-3	−0.23	0.12	−0.04
C20:3 n-6	0.13	−0.33	−0.12
C20:4 n-6	0.33	−0.24	0.06
C22:1	0.47	0.08	0.32
C20:5 n-3	0.31	0.09	0.24
C22:5 n-3	0.37	0.15	0.43
C22:3 n-3	0.02	−0.003	−0.06

Data are Pearson correlation coefficients. S_I data were log-transformed and adjusted for BMI prior to analysis.

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/m^2) 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 [^{13}C]-labeled fatty acids, C18:1*trans* was more highly oxidized than C18:1*cis* 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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