Habitual dietary intake and insulin sensitivity in lean and obese adults\textsuperscript{1-3}

Jennifer Lovejoy and Mario DiGirolamo

ABSTRACT  Studies in rodents have shown that short-term increases in dietary fat result in fat cell enlargement and insulin resistance. In humans, although high-fat diets have been associated with obesity, little is known about the specific metabolic effects of these diets. In this study we explored possible associations between habitual dietary composition and insulin sensitivity. Twenty-two lean and 23 obese subjects were characterized by dietary history (food frequency questionnaire), anthropometrics, oral glucose tolerance, and insulin sensitivity ($S_h$ from the minimal model). As shown previously, body mass index was positively correlated with percent of energy intake as fat ($r = 0.47, P = 0.001$). Increasing fat intake was also associated with diminished $S_h$ ($r = -0.41, P = 0.01$). In contrast, $S_h$ was positively correlated with fiber intake ($r = 0.43, P = 0.007$). Multivariate analysis confirmed the importance of dietary fiber for $S_h$. We conclude that habitually low dietary fiber intake, along with elevated dietary fat, correlates with diminished $S_h$ in otherwise healthy lean and obese subjects. *Am J Clin Nutr* 1992;55:1174–9.

KEY WORDS  Dietary fat, dietary fiber, insulin sensitivity, obesity, minimal-model method

Introduction

Previous studies in both animals (1–3) and humans (4–6) have demonstrated an association between dietary fat intake and obesity. In animals, high-fat diets (particularly those high in saturated, ω-9, or ω-6 fatty acids) also produce insulin resistance (7, 8). In humans the relationship of dietary fat to insulin resistance is less clear. Several studies have suggested that low-fat, high-carbohydrate diets exert a positive effect on insulin sensitivity in humans. Fukagawa et al (9) demonstrated that high-carbohydrate, high-fiber diets improve glucose disposal rates in young individuals, although less of an effect was seen in older individuals. A stronger effect in elderly subjects was seen by Chen et al (10), who found significantly improved whole-body insulin sensitivity and glucose tolerance after only 3–5 d of an 85% carbohydrate diet.

In contrast, Borkman et al (11) could not show an effect of a high-fat vs a high-carbohydrate diet on insulin sensitivity, assessed as whole-body glucose uptake during a glucose clamp. Similarly, Nestel et al (12) found that consumption of a low-fat, high-fiber diet for 10 d had no effect on peripheral glucose uptake in normal subjects. In a recent study, nondiabetic Pima Indians and Caucasians were fed a “traditional” Pima diet (high-carbohydrate) or a “modern” (high-fat) diet for 14 d (13). There were no statistically significant changes in insulin sensitivity with the high-fat diet, although 14 of 24 subjects had lower insulin sensitivity after this diet. The dietary changes did cause some metabolic alterations, however, since both noninsulin-mediated glucose disposal (glucose effectiveness) and β-cell sensitivity to glucose were significantly impaired by the high-fat diet.

Most previous experimental studies of dietary effects on wholebody insulin action have used relatively acute dietary manipulations (ranging from 3 d to 4 wk), where subjects’ usual patterns of food consumption are changed (9–13). Although epidemiologic studies of diet and metabolic risk factors have suggested that high-fat diets result in obesity and metabolic abnormalities (4, 5), these studies typically do not measure insulin sensitivity directly because of the difficulties of using available methods with large subject numbers. The purpose of the present study was to understand the effects of an individual’s habitual dietary pattern on insulin sensitivity, assessed using precise, quantitative methods.

Methods

Subjects

Forty-five lean and obese volunteers (34 women, 11 men) were studied. Obesity was defined as a body mass index (BMI; in kg/m\textsuperscript{2}) > 27 in both males and females. Height, weight, and the waist-hip ratio (WHR; smallest waist to largest hip circumference) were measured in all subjects after an overnight fast. Informed consent was obtained from all subjects before participation in the studies. All procedures were approved by the Emory University Institutional Review Board for Human Subjects.

Metabolic measures

Subjects underwent a 75-g, 5-h oral glucose-tolerance test (OGTT) to assess glucose tolerance. All subjects included in the

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analyses had normal glucose tolerance by the criteria of the National Diabetes Data Group (14).

Insulin sensitivity was assessed 2-14 d after the OGTT by using a modified frequently sampled intravenous glucose tolerance test (FSIGT) as previously described (15). Briefly, 300 mg glucose/kg body wt (50% dextrose injection; Abbott Hospital Products, Chicago) was given as a bolus over 1 min. Blood samples (5 ml) were collected at 1, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, and 19 min postglucose. Twenty minutes after the glucose injection, 0.03 U/kg (in lean subjects) or 0.05 U/kg (in obese subjects) regular human insulin (Novolin, Squibb-Novo, Wilton, CT) was administered. Sample collection continued at 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, and 180 min postglucose.

All blood samples were assayed for glucose (hexokinase method) and insulin (ICN Micromedic Systems, Inc, Horsham, PA). The insulin sensitivity index (SI) was calculated from the glucose and insulin data by using the minimal-model method of Bergman et al (16). The SI reflects the increase in fractional glucose disappearance for a given increase in plasma insulin. Higher SI values indicate greater sensitivity to insulin. In addition to insulin sensitivity, the Bergman method also allows calculation of glucose effectiveness (SE), or glucose disposal at basal insulin.

Nutrition assessment

Dietary intake was determined by using the Health Habits and History Questionnaire (long form) developed by the National Cancer Institute (NCI) (17). This instrument is a food frequency questionnaire that inquires about habitual intake over the past year. Although limited by the difficulties of retrospective interpretation, this questionnaire has been extensively validated in comparison with 24-h diet records and other diet-history methods (17, 18). Subject responses on the questionnaire were coded and entered into a personal computer for analysis and summary. Variables analyzed included total energy intake; carbohydrate, fat, and protein intakes as a percentage of total energy; the ratio of polyunsaturated to saturated fatty acids (P:S); dietary fiber intake, and alcohol intake (as a percent of energy).

Data analysis

Simple and multiple linear regression were used to relate anthropometric and metabolic variables to dietary intake. A Student’s t test was used for group comparisons. Because the SI was not linearly related to other variables, a log transformation of all SI data was performed before correlation analysis. All dietary variables were normally distributed, except for total energy, percent energy as alcohol, and fiber intake. A log transformation was performed on these three variables before analysis. Statistical analyses were performed on a VAX mainframe computer, using the Statistical Analysis System (SAS Institute, Inc, Cary, NC).

Results

Subject characteristics are shown in Table 1. Obese subjects (n = 23) had significantly higher fasting glucose and insulin concentrations than did lean subjects. The obese individuals also had an elevated sum of glucose during OGTT (although all subjects were within normal limits) and a diminished SI, indicating insulin resistance. Obese subjects were slightly but significantly older than lean subjects.

Actual dietary-intake values for the lean and obese subjects are shown in Table 2. Obese individuals consumed significantly less fiber and carbohydrate and significantly more fat (as a percent of total energy) in this analysis. There were no differences between lean and obese subjects in total energy consumed, percent of energy as protein or ethanol, or in the P:S.

Table 3 shows a correlation matrix between dietary variables, SI, and BMI. Obesity (as BMI) was positively correlated with percent of total energy as fat (Fig 1), and inversely correlated with percent of energy from carbohydrate. BMI was not significantly related to total energy consumed; protein, alcohol, or fiber intakes; or P:S.

SI was inversely correlated with percent of energy from fat (Fig 2), suggesting that as individuals increase the proportion of fat in their diet, relative insulin resistance results. SI was also significantly, but positively, associated with absolute dietary fiber intake (in g) (Fig 3). Interestingly, the magnitude of the correlation between SI and fiber was maintained when lean subjects were examined separately from obese subjects (r = 0.37, P = 0.13), although the smaller subject number resulted in a lack of statistical significance.

### Table 1

<table>
<thead>
<tr>
<th>Characteristics of the study subjects*</th>
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<tbody>
<tr>
<td>Lean (7 M, 15 F)</td>
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<tr>
<td><strong>Age (y)</strong></td>
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<tr>
<td><strong>Body mass index‡</strong></td>
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<tr>
<td><strong>Basal glucose (mmol/L)</strong></td>
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<td><strong>Basal insulin (pmol/L)</strong></td>
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<tr>
<td><strong>Sum of glucose (mmol/L)</strong></td>
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<tr>
<td><strong>Sensitivity index (×10⁻³)</strong>**</td>
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</table>

* x ± SE.
†‡§ Significantly different from lean subjects: †P < 0.05, §P = 0.0001.
† In kg/m².
‡ 0 + 1 + 2 + 3-h glucose concentrations during 75 g oral glucose tolerance test.
** In min⁻¹·pmol⁻¹·L⁻¹. To convert to min⁻¹·μU⁻¹·mL⁻¹, multiply by 0.6.

### Table 2

<table>
<thead>
<tr>
<th>Comparison of nutrient intakes from food frequency questionnaires in lean and obese subjects*</th>
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<tbody>
<tr>
<td>Lean</td>
</tr>
<tr>
<td>Total daily energy intake (kJ)</td>
</tr>
<tr>
<td>Fat (%)</td>
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<tr>
<td>Carbohydrate (%)</td>
</tr>
<tr>
<td>Protein (%)</td>
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<tr>
<td>Ethanol (%)</td>
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<tr>
<td>Fiber (g)</td>
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<td>P:S</td>
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</tbody>
</table>

* x ± SE.
†‡§ Significantly different from lean subjects: †P = 0.001, ‡P = 0.007, §P = 0.006.
| Ratio of polyunsaturated to saturated fatty acids. |
of statistical significance. No association was seen between $S_i$ and total energy consumed or protein or alcohol intakes. In addition, despite previous suggestions that saturated fatty acids produce greater insulin resistance than do unsaturated fatty acids, there was no relationship between $S_i$ and P:S.

Several other relationships among metabolic and dietary variables were of particular interest. Basal glucose concentrations were significantly and inversely associated with fiber intake ($r = -0.32, P = 0.03$). Sum of glucose, as a measure of oral glucose tolerance, was positively associated with percent energy from fat ($r = 0.38, P = 0.01$). Finally, the WHR, an index of central obesity, was directly related to both percent of energy from fat and total fat intake in the population as a whole ($r = 0.39, P = 0.01$ and $r = 0.31, P = 0.04$, respectively). When men and women were examined separately, there were significant relationships between WHR and percent of energy as fat ($r = 0.39, P = 0.02$) and total fat ($r = 0.38, P = 0.03$) in women, whereas no relationship between WHR and either variable was seen in the men ($r = 0.02$ and $r = 0.04$ for percent fat and total fat, respectively). Note, however, that the number of men in the study was small ($n = 11$), although the range of WHRs was reasonably large (0.83–0.98).

Because there were many interrelationships among dietary variables, a stepwise multiple-regression analysis was performed

### Table 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>BMI</th>
<th>$S_i$</th>
<th>Total energy</th>
<th>% Fat</th>
<th>% Carbohydrate</th>
<th>% Protein</th>
<th>% Ethanol</th>
<th>P:S</th>
<th>Fiber</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td></td>
<td>-0.80†</td>
<td>0.09</td>
<td>0.47‡</td>
<td>-0.40§</td>
<td>0.12</td>
<td>-0.15</td>
<td>-0.11</td>
<td>-0.21</td>
</tr>
<tr>
<td>$S_i$</td>
<td></td>
<td></td>
<td>0.08</td>
<td>-0.41§</td>
<td>0.31</td>
<td>0.01</td>
<td>0.10</td>
<td>-0.07</td>
<td>0.43§</td>
</tr>
<tr>
<td>So</td>
<td></td>
<td>-0.09</td>
<td>-0.19</td>
<td>0.15</td>
<td>-0.02</td>
<td>0.07</td>
<td>0.07</td>
<td>-0.25</td>
<td>-0.09</td>
</tr>
<tr>
<td>Total energy</td>
<td></td>
<td></td>
<td>-0.09</td>
<td>0.26</td>
<td>-0.09</td>
<td>-0.44§</td>
<td>-0.05</td>
<td>-0.14</td>
<td>0.51‡</td>
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<tr>
<td>% Fat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.77†</td>
<td>-0.14</td>
<td>-0.19</td>
<td>0.04</td>
<td>-0.39§</td>
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<tr>
<td>% Carbohydrate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.32‖</td>
<td>0.28</td>
<td>0.10</td>
<td>0.42‡</td>
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<tr>
<td>% Protein</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>0.08</td>
<td>-0.16</td>
<td>-0.10</td>
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<tr>
<td>% Ethanol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.13</td>
<td>-0.14</td>
<td></td>
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<tr>
<td>P:S</td>
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<td></td>
<td>0.16</td>
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</tbody>
</table>

* $n = 38$ for $S_i$ and $S_o$. BMI, body mass index; $S_i$, log insulin sensitivity index; % Fat, % Carbohydrate, % Protein, and % Ethanol, percent of total energy from fat, carbohydrate, protein, and ethanol, respectively; P:S, ratio of polyunsaturated to saturated fatty acids; Fiber, dietary fiber intake (in g).

† $P < 0.0001$.
‡ $P < 0.001$.
§ $P < 0.01$.
‖ $P < 0.05$.

![FIG 1. Relationship between body mass index (in kg/m²) and dietary fat intake as a percent of total energy in 45 lean and obese subjects.](https://academic.oup.com/ajcn/article-abstract/55/6/1174/4715410)

![FIG 2. Relationship between insulin sensitivity (expressed as log of the insulin sensitivity index) and dietary fat intake as a percent of total energy in 38 lean and obese subjects.](https://academic.oup.com/ajcn/article-abstract/55/6/1174/4715410)
to examine the effects of specific dietary components on obesity and insulin resistance. Independent variables included in the multiple-regression model were total energy intake, percent energy from fat and carbohydrate, and dietary fiber. Results of this analysis for BMI and S1 are shown in Table 4. For BMI, percent of energy from fat explained 23% of the variance in BMI, while total energy intake, percent energy from carbohydrate, and fiber were not significant. For insulin sensitivity, dietary fiber intake accounted for 18% of the variance in S1 whereas dietary fat intake independently accounted for 7% of the variance, which was of borderline significance.

In view of the strong correlation between BMI and S1, we also performed a multivariate analysis on insulin sensitivity after adjusting for BMI. When this was done, dietary fiber and fat were no longer statistically significant in the model (P > 0.05); however, their regression coefficients in the models with and without BMI did not change by more than one standard deviation. This suggests that, despite the lack of statistical significance (perhaps because of the small numbers and the strength of the relationship with BMI), dietary factors are still important predictor variables for S1.

Discussion

Results of the present study show that insulin sensitivity, assessed by the minimal-model method, is inversely related to habitual dietary fat intake but is positively related to intake of dietary fiber. Although some previous studies have reported an association between increased fat intake and decreased insulin sensitivity (9, 10), these studies have used dietary manipulations of relatively short duration. In addition, other investigators have not observed an effect of dietary manipulation on insulin sensitivity (11–13). One suggested explanation for the conflicting results of the studies in humans may be the fact that dietary interventions of different lengths were used (9).

To eliminate the confounding effects of dietary intervention, we chose to examine subjects’ habitual dietary intake, using a food frequency questionnaire. Using this approach, we were able to confirm those studies of dietary intervention that showed a negative effect of high-fat, low-carbohydrate, and low-fiber diets on insulin sensitivity. We recognize that our approach raises another set of difficulties, namely the problem of quantifying dietary intake on the basis of retrospective analysis. The NCI instrument we used, however, has been extensively validated, both in comparison with other assessment methods (24-h records and 4-d records collected three times per year) as well as with direct observation of dietary intake under controlled conditions (17, 18). In addition, the fact that some of our results confirm the findings of previous studies suggests that the instrument is valid in at least identifying stronger relationships with dietary intake.

There have been few epidemiologic studies of the effects of habitual dietary intake on insulin action, undoubtedly because the large subject numbers used prohibited the detailed measurements we were able to perform in our smaller population. One report from a large population of healthy individuals in Zutphen, The Netherlands (19), showed that saturated fatty acid intake is positively correlated with fasting glucose concentrations whereas fiber (pectin) intake is inversely correlated with glucose area under the curve during an OGTT. These findings, although not directly comparable, are congruent with our present observations that glucose tolerance (sum of glucose) is related to percent energy from fat, whereas basal glucose is inversely associated with fiber intake. Unfortunately, the Zutphen study had no insulin measures in their population and could not examine relationships between dietary variables and insulin resistance.

Another approach to examining the effect of dietary factors on insulin resistance and glucose tolerance has been to look at individuals with non-insulin-dependent diabetes mellitus (NIDDM). Unfortunately, NIDDM patients, results of the effects of dietary fat on circulating glucose and insulin concentrations are also conflicting and may depend on the amount and type of fat consumed in the diet. Studies can be found in which either high-carbohydrate diets (20) or high-fat diets (21) result in elevated glucose and insulin concentrations. It has been suggested that increasing monounsaturated fatty acids in the diet improves glycemic control and blood lipids in patients with NIDDM more than does a high-carbohydrate diet (22). Finally, a beneficial effect of dietary linoleic acid on insulin-mediated glucose disposal and blood lipid concentrations has been reported (23). Thus, as in normal subjects, the effect of dietary manipu-
lations on insulin resistance in diabetic patients is still somewhat controversial. This may, in part, result from the fact that diabetic patients have altered metabolic processes as a result of their disease, which may mask associations between diet and metabolism.

In the present study we also observed that $S_f$ was not significantly related to any dietary variable measured. This finding contrasts with previous results (13), which showed that high-fat diets fed to Pima Indian and Caucasian volunteers for 2 wk resulted in diminished $S_f$ without affecting $S_i$. The reasons for these conflicting results are not apparent although the two studies cannot be directly compared since Swinburn et al used a short-term dietary intervention. In addition, most of their subjects were obese and relatively insulin resistant whereas our subjects had a wider range of BMI and insulin sensitivity.

We observed a strong inverse relationship between degree of obesity and insulin sensitivity ($r = -0.80$), reflecting the well-known association of these variables. Furthermore, when we adjusted for BMI in the multivariate analysis with $S_i$, the dietary variables lost their statistical significance. It is possible, therefore, that the effects of dietary factors on $S_i$ may be mediated by obesity (ie, increased dietary fat and decreased fiber lead to obesity, which results in insulin resistance). On the other hand, the fact that the regression coefficients for fat and fiber in the two models (with and without BMI) remained within 1 SD, and the observation that dietary fiber intake correlates with $S_i$ in lean, insulin-sensitive subjects suggests that the associations between diet and $S_i$ are not completely mediated by obesity. Further study is needed to separate the effects of diet on these two closely related variables.

In addition to suggesting a relationship between habitual dietary intake and insulin sensitivity, our results confirm and expand previous reports showing that increased dietary fat intake (and, conversely, decreased carbohydrate intake) is associated with increased obesity. Although studies in animals have focused mainly on acute fat feeding as a way of inducing obesity and insulin resistance (1, 2), population-based studies in humans have demonstrated this phenomenon as well. Romieu et al (4) found a significant relationship between total fat intake (as g/d) and obesity in 141 middle-aged women. Fat intake was not calculated as a percent of total intake in this study; however, obesity was associated with somewhat decreased total intake in their population (not significant after adjusting for other confounding variables).

Similarly, in obese, middle-aged men, Dreon et al (5) found a positive relationship between total fat (in grams) and both BMI and percent body fat. Interestingly, both of these studies as well as an epidemiologic study by Feskens and Kromhout (19) report a significant relationship between obesity and saturated fatty acid intake (in grams), although we did not observe a significant relationship between obesity and P:S. This may reflect the fact that total grams of dietary fat (increased in obesity) include absolute increases in all types of fat, whereas our data only show the relative proportion of the two types of fatty acids. Alternatively, the methodological difficulties inherent in using a food frequency questionnaire to quantify intake may prevent our observing subtle differences in type of fat consumed.

In summary, these results suggest that decreased dietary fiber intake and increased dietary fat consumption are associated with increased insulin resistance in healthy, free-living individuals. Short-term data reported previously in humans have given inconclusive results on the effects of diet on insulin sensitivity (9–13). The discrepancy in these reports may result from the short duration of the diets used, or the variable experimental design used. On the other hand, epidemiologic data support the idea that dietary fat intake is related to obesity and glucose tolerance, but provide no direct data on insulin sensitivity. The lack of epidemiologic data on insulin sensitivity is probably due to the fact that methods for determining insulin action are not suitable for field research. In the present study we had the opportunity to study lean and obese subjects using detailed measurements of insulin sensitivity, combined with dietary measures that reflect habitual intake.

The clinical relevance of understanding factors that influence insulin sensitivity cannot be overemphasized since insulin resistance has been associated with a variety of abnormalities, including diabetes, hypertension, and heart disease (24). Although this study and others (9, 10) suggest an association between dietary components and insulin sensitivity, further research is required to establish whether long-term dietary modification can improve whole-body insulin action. The association between dietary fat intake and obesity seems to be more consistent than the dietary associations with insulin sensitivity, thus emphasizing even more the importance of early intervention to prevent development of these health risks.

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References