Hypotensive Effect of Low-Fat, High-Carbohydrate Diet Can Be Independent of Changes in Plasma Insulin Concentrations

Nora E. Straznicky, Christopher J. O’Callaghan, Vicki E. Barrington, William J. Louis

Abstract—To examine the relationship between diet, blood pressure, and plasma insulin concentrations, we studied 14 healthy males who were prescribed low-fat and high-fat diets. The low-fat diet contained 25% (of energy intake) fat and 54% carbohydrate; the high-fat diet was 45% fat (predominantly saturated fat) and 36% carbohydrate. The diets were consumed over consecutive 2-week periods in random sequence, separated by a 2-week washout period. Resting supine systolic and diastolic blood pressures decreased significantly by 7 and 3 mm Hg, respectively, and plasma total cholesterol, LDL cholesterol, and HDL cholesterol concentrations all fell (by 21.6%, 25.7%, and 18.0%, respectively; all P<0.001) on the low-fat compared with the high-fat diet. Fasting glucose and the glucose area under the curve during the frequently sampled intravenous glucose tolerance test (300 mg/kg glucose load with blood sampling for 180 minutes) were significantly lower, and the glucose disappearance rate tended to be faster after the low-fat diet. In contrast, fasting insulin concentrations and the insulin response (insulin area under the curve) to glucose challenge were unchanged. Insulin sensitivity (defined as the rate of glucose disappearance per unit of insulin increase during the period 0 to 40 minutes after the glucose load) was significantly higher on the low-fat diet. These results suggest that the hypotensive effects of a low-fat, high-carbohydrate diet, although associated with an improvement in insulin sensitivity, are not mediated by changes in plasma insulin concentration. (Hypertension. 1999;34:580-585.)

Key Words: blood pressure ■ diet ■ glucose tolerance test ■ lipoproteins ■ fatty acids

Major cardiovascular risk factors such as hypertension, hyperglycemia, hyperinsulinemia, insulin resistance, and dyslipidemia often cluster in the same individual, and it has been proposed that these risk factors are linked by a common metabolic disorder.1–2 Reaven et al1 postulated that insulin resistance plays a central role, mediated by compensatory hyperinsulinemia, which in turn directly increases blood pressure and alters lipid metabolism.

Diet is considered an important environmental factor influencing lipid metabolism, blood pressure, and insulin-mediated glucose uptake. Although high-fat feeding consistently produces insulin resistance in experimental animals,3 this has not always been the case in clinical studies.4 Dietary fats may also influence blood pressure independently of changes in plasma insulin concentrations. For example, we have previously reported5,6 that the reduction in 24-hour ambulatory blood pressure produced by changing from a high-fat Western diet to a low-fat, high-carbohydrate diet is accompanied by specific alterations in cardiac β-adrenergic reactivity.

In the present study, we have used the same 2 experimental diets and simultaneously measured their effects on blood pressure, insulin levels, and lipid and carbohydrate metabolism to determine whether changes in plasma insulin levels contribute to the hemodynamic effects observed on these diets. In accordance with Reaven et al,1 we hypothesized that fasting and stimulated plasma insulin levels and blood pressure would all be decreased on the low-fat relative to the high-fat diet.

Methods

Subjects
The study population consisted of 14 nondiabetic men. Their mean (±SD) age was 26±4 years, body mass index (in kg/m²) 25.9±3.4, fasting plasma glucose 5.0±0.4 mmol/L, plasma total cholesterol 5.0±0.6 mmol/L, and triglyceride level 1.1±0.4 mmol/L. Resting supine blood pressure averaged 131±11/73±5 mm Hg at entry. All subjects were apparently healthy as assessed by physical examination, routine biochemical and hematologic tests, and an ECG, and they were not taking any medication known to affect carbohydrate or lipid metabolism. One subject smoked. Approval for the study had been given by the Ethics Committee of the Austin Hospital. All subjects gave written informed consent to participate in the study.

Study Design
The study used a randomized crossover design. Each dietary period lasted 2 weeks, and there was a 2-week washout period between the

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Experimental diets. Body weight, plasma lipoprotein and triglyceride levels, and fatty acid composition were measured in the morning after a 12-hour fast at the end of each dietary period. A frequently sampled intravenous glucose tolerance test (IVGTT) was then performed.

**Experimental Diets**

The diets were designed to provide (as percent energy) either 43% fat (3% as polyunsaturated, 15% as monounsaturated, and 25% as saturated fatty acids) and 40% carbohydrate or 25% fat (with 8% as each fatty acid group) and 56% carbohydrate. Daily energy intake was calculated at 10.5 MJ (2500 kcal) for both diets and was adjusted when necessary to keep body weight constant. Food was prepared by volunteers in their own home. Main fat sources were sunflower oil and polyunsaturated margarine on the low-fat diet and butter and cream on the high-fat diet. Carbohydrate sources were fruit, whole-grain bread, brown rice, white pasta, and potato. The ratio of sugars to starch was identical (0.44:0.56) in the 2 diets. Diets were balanced for sodium and potassium content. During both diets, subjects kept a 14-day prospective record of all food intake. Compliance with the diets was assessed by home visits, by computerized analysis of food records (XYRIS Diet 1 Nutrient Analysis Program, Highgate Hill), and by measurement of plasma fatty acids.

**Measurement of Blood Pressure**

Blood pressure was measured supine from the left upper arm after a 5-minute rest by use of a Dinamap 845XT monitor (Critikon Inc). Five consecutive readings were averaged and defined as resting clinic blood pressure.

**Frequently Sampled IVGTT**

Indwelling catheters were inserted into an antecubital vein for blood sampling and into a contralateral vein for infusion of the intravenous glucose load (50% solution at a dose of 0.3 g/kg, given over 1 minute). Glucose was administered after 30 minutes’ recumbency and immediately flushed through with 10 mL of normal saline. Blood samples (4 mL) for glucose and insulin determinations were collected at −20, −10, −1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 19, 22, 25, 27, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 140, 160, and 180 minutes after the glucose load.

**Laboratory Methods**

Blood samples were collected into lithium heparin tubes and placed immediately on ice. They were centrifuged within 20 minutes of collection, and plasma was stored at −20°C until assay. Plasma glucose was measured in duplicate by the hexokinase enzymatic method (Glukose HK, Sigma Diagnostics). Intra-assay and interassay coefficients of variation (CVs) were 3% and 4.7%, respectively.

Plasma insulin levels were determined in duplicate by radioimmunoassay (Phadeseph Insulin RIA, Kabi Pharmacia Diagnostics). Plasma samples for each subject during the 2 dietary phases were analyzed together in the same assay. Intra-assay CVs were 4.5% and 8.4% for concentrations above and below 10 mU/L, respectively.

Fatty acid composition was determined by gas chromatography as previously described.6 Plasma total cholesterol and triglyceride levels were measured by enzymatic methods; HDL cholesterol was measured in the same manner after isolation with propylene glycol 6000.6 The Friedewald approximation was used to calculate plasma LDL cholesterol concentration.

**Data Analysis and Statistics**

Fasting plasma glucose and insulin concentrations were defined as the average of values measured at −20, −10 and −1 minute. Glucose tolerance was defined as the area under the plasma concentration (AUC) versus time curve calculated with the trapezoidal rule.

To determine insulin release and insulin sensitivity, we used the simplified method of Galvin et al.7 This is a modification of the minimal-model method, and it permits quantification of the first phase of insulin secretion during the IVGTT. First-phase insulin secretion (defined as the change in plasma insulin concentration during the first 10 minutes after glucose injection) has the form of an instant secretory pulse that is proportional to the peak increment in plasma glucose concentrations. In contrast, second-phase insulin secretion represents continuous secretion, which is assumed to relate to the time-dependent changes in plasma glucose concentration.7,8 Thus, the rise in plasma insulin concentrations during the first phase of insulin secretion, when expressed with respect to the rise in plasma glucose concentrations, provides a convenient and simple method of comparing insulin secretion between experiments, ie,

\[
\frac{\Delta \text{insulin area above basal}(0\text{-}40\text{ min})}{\Delta \text{glucose peak above basal}(0\text{-}10\text{ min})}
\]

According to the method of Galvin et al, insulin sensitivity is estimated by expressing the rate of change in glucose concentration with respect to the quantity of insulin secreted. After intravenous glucose injection, the initial rate of change in plasma glucose concentration is determined by both glucose distribution and insulin-mediated glucose uptake. However, after ~10 minutes, glucose distribution is complete, and the reduction of glucose concentration is largely dependent on insulin-mediated glucose uptake.7,9 Therefore, insulin sensitivity is calculated from the formula

\[
\text{Insulin sensitivity (min}^{-1}\text{per }\mu\text{U}\text{ per mmol L}^{-1}) = \frac{K_r}{\Delta \text{insulin area above basal}(0\text{-}40\text{ min})}
\]

where \(K_r\) = slope of the ln (glucose concentration, mmol/L) between 10 and 40 minutes after glucose injection.

Using this method, Galvin et al10 demonstrated a close correlation between simple IVGTT and minimal-model IVGTT estimations for first-phase insulin release and insulin sensitivity in individuals with normal to moderately impaired glucose tolerance.

Data were analyzed with the Minitab (version 12.1 for Windows, Minitab Inc) statistics program. Comparisons between the 2 diets were made by Student paired \(t\) test (2-tailed). The normal distribution of variables was checked with the Anderson-Darling test, and when appropriate, logarithmic transformations were performed before statistical analysis. The order of the diets did not affect the results of the study. Two-way ANOVA was used to test for interactions between treatment and period effects, which were excluded for all parameters. Associations between variables were determined by Pearson correlation coefficients. All data are expressed as mean±SD.

**Results**

**Subjects and Dietary Compliance**

There was no significant difference in the weight of subjects at the end of each diet (80.1±9.8 kg, low-fat diet; 80.6±10.1 kg, high-fat diet; 95% CI of mean difference −0.2 and 1.3 kg). Table 1 gives the average composition of the 2 experimental diets based on individual food records. Mean energy intake was significantly higher (by 1880 kJ) on the high-fat diet, which is best explained by the higher than prescribed fat intake by subjects. The low-fat diet provided less saturated (by 19.1% of energy) and monounsaturated (by 8.3% of energy) fatty acids and more polyunsaturated fatty acids (by 6% of energy) than did the high-fat diet. It also contained less total fat (by 21.8% of energy) and cholesterol (by 240 mg/d) and greater quantities of carbohydrate (by 18% of energy) and fiber (by 11/g). Alcohol intake averaged 1.0% (of energy) on the low-fat and 1.8% on the high-fat diet (\(P=\text{NS}\)). Sodium intake was on average 15±15 mmol/d greater on the high-fat diet (\(P<0.001\)), whereas magnesium intake was 96±47 mmol/d greater on the low-fat diet (\(P<0.001\)). Urinary sodium excretion over 24 hours averaged 126±43 and 145±39 mmol/d on the low- and high-fat diets, respectively,
whereas the values for magnesium were 5.9 ± 2.2 and 6.2 ± 2.6 mmol/d, respectively (both \( P = \text{NS} \)).

A good level of dietary compliance was confirmed by the observed changes in plasma fatty acid composition (Table 2). Saturated fatty acids (palmitic and stearic) increased significantly by 8.1% and 29.1%, respectively, whereas polyunsaturated linoleic acid decreased significantly by 12.3% on changing from the low- to the high-fat diet.

### Intravenous Glucose Tolerance Test

Table 3 and the Figure show glucose and insulin data from the IVGTT. Fasting plasma glucose concentration and the AUC for glucose were both significantly reduced on the low-fat compared with the high-fat diet, by 6% \( (P = 0.03) \) and 7.7% \( (P = 0.003) \), respectively. This improvement in glucose tolerance was observed in 12 of the 14 subjects. Glucose concentrations were significantly greater on the high-fat diet at all

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**TABLE 1.** Average Daily Nutrient Intake During Each 14-Day Dietary Period

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low-Fat Diet</th>
<th>High-Fat Diet</th>
<th>95% CI of Mean Difference</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy, kJ</td>
<td>9150±880</td>
<td>11030±870</td>
<td>1340, 2410</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Energy, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat</td>
<td>24.7±1.2</td>
<td>46.5±2.8</td>
<td>20.2, 23.3</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Palmitic (16:0)</td>
<td>1.9±0.7</td>
<td>1.5±0.5</td>
<td>-0.7, -0.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Palmitoleic (16:1)</td>
<td>11.7±4.1</td>
<td>15.1±5.2</td>
<td>1.4, 5.4</td>
<td>0.003</td>
</tr>
<tr>
<td>Oleic (18:1)</td>
<td>19.3±2.8</td>
<td>18.2±3.5</td>
<td>-2.7, 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Linoleic (18:2)</td>
<td>33.2±4.8</td>
<td>29.1±5.0</td>
<td>-7.4, -0.9</td>
<td>0.02</td>
</tr>
<tr>
<td>Arachidonic (20:4)</td>
<td>9.2±1.7</td>
<td>9.3±1.5</td>
<td>-0.7, 0.9</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean±SD; \( n = 14 \). Food records were analyzed with Australian food-composition tables.

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**TABLE 2.** Plasma Lipid, Lipoprotein, and Fatty Acid Concentrations at End of Each Dietary Period

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Low-Fat Diet</th>
<th>High-Fat Diet</th>
<th>95% CI Mean Change</th>
<th>( P ) (Between Diets)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipids and lipoproteins, mmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglyceride</td>
<td>1.1±0.4†</td>
<td>0.8±0.3</td>
<td>0.8±0.3</td>
<td>-0.3, 0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>5.0±0.6*</td>
<td>4.0±0.6</td>
<td>5.1±0.8</td>
<td>0.8, 1.4</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>3.3±0.6*</td>
<td>2.6±0.5</td>
<td>3.5±0.8</td>
<td>0.5, 1.2</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>1.21±0.26*</td>
<td>1.05±0.19</td>
<td>1.28±0.23</td>
<td>0.16, 0.29</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Ratio of LDL to HDL cholesterol</td>
<td>2.8±0.8</td>
<td>2.6±0.9</td>
<td>2.9±1.0</td>
<td>-0.0, 0.6</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean±SD.

*\( P < 0.01 \) vs low-fat diet; †\( P < 0.01 \) vs low-fat and high-fat diets.
time points between 4 and 70 minutes and at 140 minutes after the glucose bolus. Although the glucose disappearance rate ($K_g$) was faster on the low-fat diet, the difference between diets did not reach statistical significance ($P=0.12$). No significant correlations were found between the changes in plasma fatty acid composition and glucose tolerance.

In contrast to the significant changes in glucose concentration, neither fasting plasma insulin concentration or the insulin response to glucose challenge was affected by the diets. Insulin concentrations did not differ between diets at any of the sampling times during the IVGTT. However, insulin sensitivity, calculated by the simplified IVGTT method, was significantly improved on the low-fat diet, as indicated by a faster glucose disappearance rate per unit increase in insulin concentration.

**Blood Pressure**

Resting supine systolic and diastolic blood pressures were both significantly reduced on the low-fat diet (122±11/65±6 mm Hg) compared with the high-fat diet (129±13/68±7 mm Hg; both $P<0.01$). Blood pressure did not correlate with fasting insulin levels or with the insulin AUC (0 to 180 minutes). A significant inverse relationship was found to exist between change in diastolic blood pressure and change in insulin sensitivity ($r=-0.697$, $P=0.008$), which indicates that subjects with the largest increase in insulin sensitivity on the low-fat diet also experienced the largest fall in diastolic blood pressure.

**Lipids**

Compared with the high-fat diet, all lipoprotein cholesterol fractions were significantly reduced on the low-fat diet: total cholesterol by 21.6%, LDL cholesterol by 25.7%, and HDL cholesterol by 18.0% (all $P<0.001$). No differences were found in the LDL cholesterol–to–HDL cholesterol ratio or in triglyceride levels between diets.

**Discussion**

Diet, exercise, and weight reduction are all treatments that are known to have beneficial effects on plasma lipids and blood pressure. Each of these interventions affects insulin sensitivity, and it has been hypothesized that the subsequent changes in plasma insulin concentrations could account for the changes in blood pressure and lipids. To examine the relationship between dietary fat intake, blood pressure, and plasma insulin concentrations, we compared 2 dietary ex-
tremes. The low-fat diet, which was high in carbohydrate and moderately high in fiber and contained equal amounts of each fatty acid group, is similar to current recommendations for the general population, as well as for the management of diabetic patients. The high-fat diet, which was high in saturated fat and low in polyunsaturates and carbohydrate, was extreme according to average Australian intakes (35% total fat, polyunsaturated to saturated fat [P/S] ratio 0.48) and represented the highest quintile of fat consumption in Australia.

The major findings of the present study are that short-term consumption of a low-fat, high P/S diet is accompanied by beneficial changes not only in blood pressure and plasma lipid concentrations but also in glucose tolerance. Resting systolic and diastolic blood pressures decreased by 7 and 3 mm Hg, respectively; total cholesterol and LDL cholesterol levels were lowered by >20%; and both fasting glucose and glucose tolerance were improved, as was insulin sensitivity (measured by the method of Galvin et al7), on the low-fat diet compared with the high-fat diet. In contrast, neither fasting nor stimulated plasma insulin concentrations were altered by dietary change. Thus, the present study has demonstrated that short-term dietary intervention can influence blood pressure and lipids even in the absence of an obvious change in plasma insulin levels.

These results do not necessarily mean that the hypothesis of Reaven et al1 is inoperative. The reasons for the absence of a fall in insulin levels in association with improved insulin sensitivity on the low-fat diet are unclear. It may be that our period of dietary intervention was too short to demonstrate this fall. Alternatively, it may be that any effect of improvement in insulin sensitivity on insulin levels was insufficient to compensate for the effect of the increased carbohydrate load in the low-fat diet. In any event, blood pressure fell, which indicates that an improvement in insulin sensitivity and/or the associated metabolic effects of the low-fat diet can have beneficial effects on blood pressure, even if insulin levels remain unchanged.

Our findings are consistent with a number of reports that indicate that insulin resistance may be more important than hyperinsulinemia as a determinant of blood pressure. Insulin-resistant states are associated with attenuated insulin-mediated vasodilation, which may tip the balance between pressor and depressor actions of insulin in favor of the former and ultimately result in hypertension. In support of this hypothesis, biguanides and thiazolidinediones both have been reported to improve insulin sensitivity and lower blood pressure.

Because dietary fats have several different hemodynamic effects, it is possible that the alteration in fat intake contributed to the change in blood pressure. Diminished inotropic and chronotropic cardiac responses to β-adrenergic drugs have been demonstrated in rodents and humans after a high linoleic acid diet and may be due to alterations in adenylate cyclase activity and cAMP formation, secondary to decreased density of β-adrenergic receptors. Dietary fatty acids can also modulate the production of vasodilatory or natriuretic prostanoids and of nitric oxide by endothelial cells.

Dietary records showed that daily sodium intake was on average 38 mmol greater on the high-fat diet. It is possible, although unlikely, that such small differences would have contributed to the observed differences in blood pressure. In normotensive populations, sodium intake varying between 50 and 200 mmol/d had no effect on blood pressure in subjects younger than 50 years of age. Similarly, it is unlikely that the small differences in magnesium intake on the diets (96 mg, or 3.9 mmol/d) affected blood pressure, because it has been proposed that a supplement of 40 mmol/d may be required to lower blood pressure.

A further benefit of the low-fat diet in the present study was an improvement in glucose tolerance and fasting glucose levels. Remarkably few clinical studies to date have compared the effects of high-fat, low-carbohydrate and lower-fat, high-carbohydrate diets on glucose tolerance and insulin action, and available data are contradictory. In general, those studies that used more extreme carbohydrate (>70%) intakes and contained a higher dietary P/S ratio have shown beneficial effects on glucose tolerance and insulin sensitivity. It is likely that the 10-fold change in P/S ratio (from 0.12 to 1.25) in the present study contributed to the improved glucose tolerance on the low-fat diet. Clinical studies show a positive relationship between an increased P/S ratio in serum phospholipids and increased metabolic clearance rates of glucose. Although the difference in fiber content between our 2 diets was modest (averaging 11 g/d), this may also have contributed to the improvement in glucose tolerance.

In summary, short-term consumption of a high-carbohydrate, low-fat diet resulted in lower blood pressure and fasting glucose levels and a slightly improved glucose tolerance but no change in fasting or stimulated insulin levels. We conclude that the hypotensive effect of the low-fat diet used in this study was not mediated by changes in plasma insulin concentrations but may reflect at least in part the change in insulin sensitivity. A limitation of the present study is that it does not distinguish between the effects of total fat intake versus the effects of individual fatty acid groups in mediating the observed cardiovascular and metabolic effects. Findings from animal and cross-sectional studies suggest that fatty acids play a pivotal role in mediating these effects. This is further supported by recent prospective epidemiological investigations that show that replacing saturated fat with monounsaturated and polyunsaturated fats is more effective in preventing coronary heart disease than reducing overall fat intake. Thus, additional studies are needed to clarify the effects of fat quality independent of changes in total fat intake on insulin sensitivity.

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References


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