Effects of moderate variations in the macronutrient content of the diet on cardiovascular disease risk factors in obese patients with the metabolic syndrome$^1$$^3$

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ABSTRACT

Background: The metabolic syndrome is a cluster of abnormalities that is accompanied by a 2-fold increase in the risk of cardiovascular disease. Even if there is full agreement that lifestyle changes to induce weight loss are the first-line approach, the ideal diet for the treatment of the metabolic syndrome remains uncertain. The objective was to compare the effects of 2 diets on cardiovascular disease risk factors in obese patients with the metabolic syndrome.

Design: The study was carried out in 100 patients randomly assigned to either a diet relatively rich in carbohydrate [65% of energy as carbohydrate, 13% as protein, and 22% as fat (17% as unsaturated fat)] or a diet that was low in carbohydrate and high in protein and in monounsaturated fat [48% of energy as carbohydrate, 19% as protein, and 33% as fat (24% as unsaturated fat)].

Results: All 100 patients completed the 5-mo study. At the end of the study, all the components of the metabolic syndrome (except HDL cholesterol concentrations) were observed. Although the extent of the resolution of the metabolic syndrome was not different between groups, the low-carbohydrate diet was associated with a greater decrease in the prevalence of hypertension ($P < 0.05$) and of hypertriacylglycerolemia ($P < 0.001$).

Conclusion: Tailoring diet interventions to the specific presentation of the metabolic syndrome may be the best way of reducing the risk factors for cardiovascular disease. Am J Clin Nutr 2007;86: 946–51.

KEY WORDS Metabolic syndrome, diet treatment, cardiovascular disease risk factors, high-protein diets, low-carbohydrate diets, high-lipid diets, insulin resistance, blood pressure

INTRODUCTION

The prevalence of obesity is rapidly increasing in Western populations, causing a parallel rise in the prevalence of the metabolic syndrome (1), a cluster of lipid and nonlipid risk factors of metabolic origin possibly linked to insulin resistance (2). There is full agreement that lifestyle changes focused primarily on weight reduction are the first-line approach to patients with the metabolic syndrome (2, 3). Nevertheless, the optimal diet for the treatment of the metabolic syndrome remains uncertain. The current recommendations support a diet containing 25–35% of energy as fat, 50–60% as carbohydrate, and ≈15% as protein (3). It is possible that the patients with the metabolic syndrome who have one set of qualifying risk factors may respond better to a particular dietary approach than will those patients with a different set of risk factors. Furthermore, tailoring the dietary treatment not on the basis of the presence of the metabolic syndrome per se but on the specific elements of the syndrome in each patient may be the more successful approach to the resolution of the risk factors.

Decreasing the dietary intake of carbohydrate has been repeatedly confirmed to lower fasting plasma triacylglycerol concentrations in patients with or without type 2 diabetes (4, 5). Low-carbohydrate diets high in protein (6) or in monounsaturated fat (7) or both (8) have been reported to increase insulin sensitivity, although not consistently (9–11). Epidemiologic evidence (12–14) and intervention studies (11, 15–17) suggest that the partial substitution of carbohydrate with protein (increasing the latter to ≈25% of energy) lowers blood pressure, although this may not be the case in obese hyperinsulinemic patients (9, 10). The substitution of carbohydrate with a monounsaturated fat has also been effective in lowering blood pressure (15, 18). Because lifestyle therapies in the metabolic syndrome focus primarily on weight reduction, a high-protein diet may be of value in preserving lean mass during calorie restriction (19). Notwithstanding the potential benefits of the partial substitution of carbohydrate with protein or monounsaturated fat, concerns regarding these diets have been raised. High-protein diets may exacerbate kidney damage in patients with a compromised renal function, and increased phosphorus loads can cause acidosis and worsen insulin resistance (20). Furthermore, protein foods from animal sources (with the exception of fish and low-fat dairy products) are often

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higher in saturated fat and in cholesterol, and animal protein is the most expensive source of calories in the food budget. High-fat diets tend to be higher in saturated fat, which may increase LDL cholesterol. In addition, such diets are commonly deficient in fruit, vegetables, and whole grains (2, 21). The present study was conducted to explore the hypothesis that hypocaloric diets of differing macronutrient composition have differential effects on specific risk factors, depending on the particular presentation of the metabolic syndrome.

SUBJECTS AND METHODS

Participants

The present study was carried out in 100 obese patients with the metabolic syndrome as diagnosed according to the criteria of the National Cholesterol Education Program Adult Treatment Panel III (2). Between July 2005 and September 2006, 112 patients were invited to participate in the present study. Twelve patients were randomly invited because they felt that the study would be too time consuming, which left 100 patients in the study. The inclusion criteria were as follows: age of >18 years, a body mass index (BMI; in kg/m²) > 30, and a willingness to adhere to the prescribed diet. The exclusion criteria were as follows: a history of thyroid disease or diabetes mellitus, current pregnancy, an unstable medical condition, or the current use of medications known to affect weight, appetite, or blood lipids. The local ethics committee reviewed and approved the study. Each eligible participant gave written informed consent.

Study design

This single-center study was conducted at the G Salvini Hospital (Garbagnate Milanese, Milan, Italy) on an outpatient basis for 5 mo. The eligible patients were randomly allocated to consume either a diet consisting of 65% of energy as carbohydrate, 13% as protein, and 22% as fat (high-carbohydrate diet) or a diet consisting of 48% of energy as carbohydrate, 19% as protein, and 33% as fat (low-carbohydrate diet). Both diets provided a deficit of -500 kcal/d on the basis of each patient’s estimated daily energy expenditure according to the current dietary recommendations for the treatment of the metabolic syndrome (2, 3). The mean composition of the prescribed diets is reported in Table 1. In addition, the patients were encouraged to increase their physical activity, preferably by aerobic activities (22). After the initial visit, the patients met in monthly group sessions lasting 2 h with the staff of the nutrition unit, for 5 mo. Each group session included only those patients receiving the same diet. The adherence to the diet was assessed at the last visit by administering to each patient a 20-item questionnaire designed to measure a participant’s food intake during the study. At that time, the patients were asked additional questions related to the items of the questionnaire to better categorize their knowledge of the prescribed diet and their adherence to the diet. Concordance between the weight-loss goal of -5% of initial body weight and the observed weight loss was assessed to further evaluate adherence to the diet. During the visit, the patients were also asked about their physical activity.

Measurements

Body weight was measured while the subjects were wearing light clothing and no shoes. Height without shoes was measured by using a stadiometer, and BMI was calculated. Waist girth was measured as the narrowest circumference between the bottom of the rib cage and the iliac crest by using an unstretched tape measure. Blood pressure was measured twice at each visit with the use of a standard mercury sphygmomanometer after the patients had been sitting for 15 min. The mean of the 2 measurements was recorded. The patients receiving antihypertensive therapy (n = 28, high-carbohydrate diet; n = 21, low-carbohydrate diet) were maintained on a stable medical regimen, and the timing of the antihypertensive medication in relation to the measurement of blood pressure was kept unchanged throughout the study. The staff involved in the measurement of blood pressure were unaware of the group assignments.

Serum chemistry values were determined in the hospital laboratory. Blood samples were collected and immediately centrifuged (at 2000 × g for 10 min at 5 °C) in the morning after the patients had fasted 12 h. Total cholesterol was measured by using the CHOD-PAP method (Roche Diagnostics, Mannheim, Germany), serum triacylglycerol concentrations were measured by...
using the GPO-PAP method (Roche Diagnostics), and HDL-cholesterol concentrations were measured with the use of the HCL-C Olympus System (Olympus Diagnostica, O’Callaghan’s Mills, Ireland). Serum lipid and HDL-cholesterol concentrations were measured with the use of an Olympus AU 560 autoanalyzer (Olympus Optical Co, Sizuoka, Japan). The accuracy of the lipid measurements was assessed according to the intra- and interlaboratory quality control program UNITY (version 1.3; Bio-Rad Laboratories, Segrato, Italy). LDL cholesterol was calculated according to Friedewald et al (23). Insulin was determined by using a radioimmunoassay kit (Insulin RIA; Adaltis, Casalecchio sul Reno, Italy). Homeostasis model assessment was used as a surrogate measure of insulin sensitivity and was calculated according to Matthews et al (24).

Statistical analysis

Data are presented as means ± SDs. Potential within-group treatment effects on body weight, blood pressure, and metabolic characteristics and metabolic profile (Table 2 and Table 3), and no differences were observed in the mean values or in the prevalence of the diagnostic criteria of the metabolic syndrome.

At the end of the present study, the patients showed a satisfactory knowledge of the prescribed diet. At the end of the study period, body weight, BMI, waist girth, systolic and diastolic blood pressures, total cholesterol, serum triacylglycerol, blood glucose, insulin, and the homeostasis model assessment of insulin resistance decreased significantly in both dietary groups, whereas HDL cholesterol did not change significantly from baseline (Figure 1). The mean percentage changes from baseline of body weight, BMI, waist girth, diastolic blood pressure, total cholesterol, blood glucose, insulin, and the homeostasis model assessment of insulin resistance were similar in both dietary groups (Figure 1). No relation was found between the baseline body weight and the change in body weight at the end of the study (low-carbohydrate group: r = 0.12, NS; high-carbohydrate group: r = 0.11, NS).

<table>
<thead>
<tr>
<th>Variable</th>
<th>High-carbohydrate diet</th>
<th>Low-carbohydrate diet</th>
<th>p²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13</td>
<td>14</td>
<td>NS</td>
</tr>
<tr>
<td>Female</td>
<td>37</td>
<td>36</td>
<td>NS</td>
</tr>
<tr>
<td>Age (y)</td>
<td>52.1 ± 16.7</td>
<td>52.7 ± 16.3</td>
<td>NS</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>93.2 ± 13.2</td>
<td>95.7 ± 16.1</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>37.1 ± 5.1</td>
<td>37.3 ± 6.7</td>
<td>NS</td>
</tr>
<tr>
<td>Waist girth (cm)</td>
<td>110.8 ± 8.9</td>
<td>111.1 ± 12.4</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>140.9 ± 16.6</td>
<td>142.2 ± 14.6</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>82.0 ± 11.5</td>
<td>84.9 ± 8.8</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>75.9 ± 12.3</td>
<td>77.7 ± 12.6</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>212.6 ± 35.8</td>
<td>210.8 ± 36.2</td>
<td>NS</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>132.0 ± 31.6</td>
<td>126.8 ± 31.9</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>47.7 ± 11.0</td>
<td>49.6 ± 12.9</td>
<td>NS</td>
</tr>
<tr>
<td>Serum triacylglycerols (mg/dL)</td>
<td>164.0 ± 65.6</td>
<td>171.7 ± 60.3</td>
<td>NS</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>107.9 ± 24.9</td>
<td>105.1 ± 19.9</td>
<td>NS</td>
</tr>
<tr>
<td>Insulin (µU/mL)</td>
<td>24.2 ± 21.4</td>
<td>17.9 ± 8.1</td>
<td>NS</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>6.9 ± 7.4</td>
<td>4.5 ± 2.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

1 Patients were randomly allocated to consume a high-carbohydrate diet (n = 50) or a low-carbohydrate diet (n = 50). HOMA-IR, homeostasis model assessment of insulin resistance.

2 Student’s t test for unpaired data.

3 x ± SD (all such values).

<table>
<thead>
<tr>
<th>Variable</th>
<th>High-carbohydrate diet</th>
<th>Low-carbohydrate diet</th>
<th>p²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low HDL cholesterol (%)</td>
<td>54</td>
<td>56</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertriglyceridemia (%)</td>
<td>56</td>
<td>64</td>
<td>NS</td>
</tr>
<tr>
<td>Hypglycemia (%)</td>
<td>64</td>
<td>56</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>96</td>
<td>88</td>
<td>NS</td>
</tr>
<tr>
<td>Central obesity (%)</td>
<td>100</td>
<td>100</td>
<td>NS</td>
</tr>
<tr>
<td>3 Components</td>
<td>46</td>
<td>48</td>
<td>NS</td>
</tr>
<tr>
<td>4 Components</td>
<td>36</td>
<td>40</td>
<td>NS</td>
</tr>
<tr>
<td>5 Components</td>
<td>18</td>
<td>12</td>
<td>NS</td>
</tr>
</tbody>
</table>

1 Patients were randomly allocated to consume a high-carbohydrate diet or a low-carbohydrate diet.

2 Chi-square test.

3 Defined as HDL-cholesterol concentration <40 mg/dL in men and <50 mg/dL in women.

4 Defined as serum triacylglycerol concentration ≥150 mg/dL.

5 Defined as fasting blood sugar concentration ≥100 mg/dL.

6 Defined as systolic blood pressure >130 mm Hg and diastolic blood pressure >85 mm Hg or as the use of hypotensive therapy.

7 Defined as waist girth >82 cm in women and >102 cm in men.
The low-carbohydrate diet was associated with a greater decrease in systolic blood pressure and in serum triacylglycerol concentrations than was the high-carbohydrate diet. Heart rate decreased only with the former, and LDL cholesterol decreased only with the latter (Figure 1).

An analysis of variance failed to show group-by-time interactions. Multiple backward stepwise regression analyses showed that the protein content of the diet was the only variable significantly associated with the percentage changes in systolic blood pressure ($\beta = -0.0018, P < 0.05$) and that the carbohydrate content of the diet ($\beta = -0.049, P < 0.05$) and weight loss ($\beta = 1.86, P < 0.01$) were independently predictive of the percentage changes in serum triacylglycerol concentrations. The prevalence of central obesity significantly decreased in both dietary groups, and that of hypertension and hypertriacylglycerolemia significantly decreased in both dietary groups. Systolic blood pressure and serum TG decreased more in the low-carbohydrate diet than was the high-carbohydrate diet. HDL cholesterol did not change significantly.‡#Significantly different from baseline:‡

<table>
<thead>
<tr>
<th>Percentage change from entry (%)</th>
<th>High-carbohydrate diet ($n = 50$)</th>
<th>Low-carbohydrate diet ($n = 50$)</th>
<th>$P^{2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central obesity (%)$^{f}$</td>
<td>26$^{d}$</td>
<td>28$^{d}$</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperglycemia (%)$^{f}$</td>
<td>44</td>
<td>36</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension (%)$^{b}$</td>
<td>12</td>
<td>27$^{7}$</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hypertriacylglycerolemia (%)$^{b}$</td>
<td>36</td>
<td>81$^{4}$</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low HDL cholesterol (%)$^{f}$</td>
<td>15</td>
<td>29</td>
<td>NS</td>
</tr>
<tr>
<td>Metabolic syndrome (%)</td>
<td>40$^{d}$</td>
<td>54$^{d}$</td>
<td>NS</td>
</tr>
</tbody>
</table>

$^{f}$ Patients were randomly allocated to consume a high-carbohydrate diet or a low-carbohydrate diet. The prevalence of central obesity decreased in both dietary groups, and that of hypertension and hypertriacylglycerolemia decreased in patients with the low-carbohydrate diet. The extent of recovery from the metabolic syndrome was not significantly different between the 2 dietary groups.

$^{d}$ Chi-square test.

$^{b}$ Defined as waist girth > 82 cm in women and > 102 cm in men.

$^{7}$ Significantly different from baseline (chi-square test): $^{b} P < 0.001$.

$^{4}$ As expected, in both groups, body weight loss was associated with favorable effects on blood pressure and metabolic abnormalities and with reductions of total cholesterol, serum triacylglycerol, blood glucose, plasma insulin, and insulin resistance.

The low-carbohydrate diet was more effective than was the high-carbohydrate diet in reducing systolic blood pressure and heart rate. The latter was more effective at lowering LDL cholesterol. Therefore, the macronutrient composition of the diet had specific effects on lipid and nonlipid abnormalities of the metabolic syndrome in addition to those effects determined by weight loss alone.

The greater decrease in serum triacylglycerol concentrations with the low-carbohydrate diet was not unexpected on the basis of previous studies that reported the same effect (4–8, 11, 15–18). In the present study’s series of nondiabetic obese patients with the metabolic syndrome, both diets produced a similar decrease in body weight (10%). Recent meta-analyses showed that low-carbohydrate diets were associated with a greater loss of body mass than were low-fat diets; however, in those studies (19, 25), the carbohydrate content was much lower than that in the present study’s low-carbohydrate diet. As expected, in both groups, body weight loss was associated with favorable effects on blood pressure and metabolic abnormalities and with reductions of total cholesterol, serum triacylglycerol, blood glucose, plasma insulin, and insulin resistance.

**DISCUSSION**

The present study was designed to compare 2 dietary approaches to treating the metabolic syndrome, both of which fell within the relatively broad macronutrient ranges recommended by the National Cholesterol Education Program Adult Treatment Panel III (3). The 2 diets were different in several aspects: the high-carbohydrate diet was low in fat, relatively poor in protein, and rich in carbohydrate, whereas the low-carbohydrate diet was relatively rich in protein and in monounsaturated fat and poor in carbohydrate. Evidence of the benefits of both of these dietary patterns was published (4–8, 11, 15–18).

In the present study’s series of nondiabetic obese patients with the metabolic syndrome, both diets produced a similar decrease in body weight (10%). Recent meta-analyses showed that low-carbohydrate diets were associated with a greater loss of body mass than were low-fat diets; however, in those studies (19, 25), the carbohydrate content was much lower than that in the present study’s low-carbohydrate diet. As expected, in both groups, body weight loss was associated with favorable effects on blood pressure and metabolic abnormalities and with reductions of total cholesterol, serum triacylglycerol, blood glucose, plasma insulin, and insulin resistance.

The low-carbohydrate diet was more effective than was the high-carbohydrate diet in reducing systolic blood pressure and heart rate. The latter was more effective at lowering LDL cholesterol. Therefore, the macronutrient composition of the diet had specific effects on lipid and nonlipid abnormalities of the metabolic syndrome in addition to those effects determined by weight loss alone.

The greater decrease in serum triacylglycerol concentrations with the low-carbohydrate diet was not unexpected on the basis of previous studies that reported the same effect (4, 5, 25). Indeed, multiple backward regression analysis confirmed that the carbohydrate content of the diet was independently predictive of triacylglycerol concentrations. Likewise, a decrease in LDL cholesterol was expected only with the high-carbohydrate diet because it is well-known that diets low in saturated fat and cholesterol are associated with a decrease of LDL cholesterol (25, 26). Importantly, these changes in the lipid profile were obtained with...
minor differences in the macronutrient balance, within the limits of a healthy diet (2, 3, 27).

In the present study, the low-carbohydrate diet lowered systolic blood pressure by \( \leq 6\% \) more than did the high-carbohydrate diet. As suggested by multiple backward regression analysis, the greater reduction in blood pressure during the low-carbohydrate diet was mainly due to its higher protein, not higher fat, content. Previous interventional studies that evaluated the effects of the substitution of protein for carbohydrate on blood pressure showed that this substitution was effective in reducing blood pressure in most situations (11, 15–17, 28, 29), but not in obese hyperinsulinemic patients (9, 10). However, in most of the studies in which the results were positive, the protein content of the diet was rather high (\( \approx 25\% \) of energy). In the present study, we obtained an effect on blood pressure with lower protein amounts (ie, 19% of energy), mainly of animal origin.

In another study in which protein amounts (ie, 19% of energy), mainly of animal origin. In the present study, we obtained an effect on blood pressure with lower protein amounts (ie, 19% of energy), mainly of animal origin. This result is in agreement with a recently published interventional study specifically designed to test the efficacy of animal protein in reducing blood pressure (17) and with the results of another study in which >50% of the protein intake in a high-protein diet was of animal origin (15). Nevertheless, plant protein is also effective in lowering blood pressure (16, 29), and the relative efficacy of the 2 kinds of protein remains to be established. Epidemiologic studies that evaluated this topic gave conflicting results (14, 30–33).

The 8-mm Hg difference in the mean reduction of systolic blood pressure between the 2 dietary groups in the present study was greater than that observed in previous trials with different study populations (15–17) or with shorter intervention periods (11). Also, the patients did not lose weight in those studies. The data in the present study show that even a moderate and long-term sustainable increase in the protein content of the diet (from 13% to 19% of energy) can improve hypertension in patients with the metabolic syndrome, at least when such diets are accompanied by an increase in fat intake and a decrease in carbohydrate intake.

Several possible explanations have been proposed for the effects of the substitution of protein for carbohydrate on blood pressure, including improvements in endothelial function with vasodilation (34, 35) and in diuresis (36), but the underlying mechanisms remain unclear (17, 37). A further possibility is the decrease in sympathetic tone that may be suggested by the significant reduction in the heart rate in the patients on the low-carbohydrate diet in the present study. The effects on heart rate resulting from the replacement of carbohydrate with protein was previously evaluated in only 2 studies, 1 of which found an effect (29) and 1 that did not (17). The substitution of monounsaturated fat for carbohydrate also reduces heart rate (18), which raises the possibility that the underlying mechanism relates to carbohydrate rather than to protein or fat.

In conclusion, the present study showed that a moderate and generally sustainable low-calorie diet relatively rich in protein and in monounsaturated fat and poor in carbohydrate can improve blood pressure and fasting triacylglycerol concentrations, which gives an additional benefit to the expected reduction of cardiovascular disease risk factors determined by weight loss. This evidence suggests that tailoring the diet to the specific metabolic and physical profiles of each metabolic syndrome patient may be a fruitful approach. Carbohydrate could substitute for fat in those patients with high LDL-cholesterol concentrations, but a diet lower in carbohydrate, higher in protein, and higher in fat may be optimal for patients with high blood pressure or high triacylglycerol concentrations or both. Future studies should prospectively test the hypotheses generated in the present study by specifically matching each dysmetabolic profile with a dietary pattern most likely to resolve the metabolic syndrome.

The authors’ responsibilities were as follows—FM and LM: designed the experiment, collected and analyzed the data, and wrote the manuscript; WSH: wrote the manuscript and provided significant advice and consultation; DS: analyzed the data and wrote the manuscript; and AB: analyzed the data and provided significant advice and consultation. None of the authors had any conflict of interest to declare.

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