Are there specific treatments for the metabolic syndrome?[1–3]

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ABSTRACT

The concept of the metabolic syndrome, although controversial, continues to gain acceptance. Whereas each risk factor of the metabolic syndrome (visceral obesity, atherogenetic dyslipidemia, elevated blood pressure, and dysglycemia) can be dealt with individually, the recommended initial therapeutic approach is to focus on reversing its root causes of atherogenetic diet, sedentary lifestyle, and overweight or obesity. No single diet is currently recommended for patients with the metabolic syndrome, although epidemiologic evidence suggests a lower prevalence of the metabolic syndrome associated with dietary patterns rich in fruit, vegetables, whole grains, dairy products, and unsaturated fats. We conducted a literature search to identify clinical trials specifically dealing with the resolution of the metabolic syndrome by lifestyle, drugs, or obesity surgery. Criteria used for study selection were English language, randomized trials with a placebo or control group (except for surgery), a follow-up lasting ≥6 mo, and a time frame of 5 y. We identified 3 studies based on lifestyle interventions, 5 studies based on drug therapy, and 3 studies based on laparoscopic weight-reduction surgery The striking resolution of the metabolic syndrome with weight-reduction surgery (93%) as compared with lifestyle (25%) and drugs (19%) strongly suggests that obesity is the driving force for the occurrence of this condition. Although there is no "all-inclusive" diet yet, it seems plausible that a Mediterranean-style diet has most of the desired attributes, including a lower content of refined carbohydrates, a high content of fiber, a moderate content of fat (mostly unsaturated), and a moderate-to-high content of vegetable proteins. *Am J Clin Nutr* 2008;87:8–11.

KEY WORDS Metabolic syndrome, obesity, clinical trials, literature search

INTRODUCTION

The metabolic syndrome constitutes a growing problem worldwide, although reference to it as a full-blown epidemic may appear to be somewhat of a cliché. Whether or not one accepts this condition as a byproduct of our modern lifestyle, the concept of metabolic syndrome, although controversial (1), continues to gain acceptance (2) because it places a growing burden on finite healthcare resources. Despite the complexity of its origins, there is general agreement that its rising prevalence is largely due to the increasing incidence of obesity. Perhaps one major merit of the syndrome is to have brought increasing attention on the concept of "cardiometabolic risk"—a neologism used to indicate the strict link between metabolic alterations and cardiovascular events. Ironically, the cardiologist community seems more enthusiastic about the metabolic syndrome than does the diabetologist community from which the syndrome originated (1). Irrespective of the ideologic field, the metabolic syndrome is currently a focus of much research and clinical interest.

CURRENT TREATMENT STRATEGIES

A report from the National Cholesterol Education Program Adult Treatment Panel III identified the metabolic syndrome as a constellation of clinical characteristics associated with an increase in the risk of developing both type 2 diabetes and atherosclerotic cardiovascular disease (3). The report also considered the metabolic syndrome an indication for intensive lifestyle modification. The current epidemic of the metabolic syndrome has been seen as the unwanted result of the dietary low-fat crusade of the second half of the past century. Because dietary fat consumption has decreased since 1976 while obesity in the United States has increased by ≈33%, this divergence has been advocated as proof of the apparent lack of utility in low-fat diets for weight loss (4). However, this view may be too simplistic. The recent Women's Health Initiative Dietary Modification Trial, involving 48 835 women aged 50–79 y (5), showed that, in the absence of a specific indication to cut daily calories, there was a weight loss of ≈2.2 kg in the first year and an average weight loss of 1.3 kg (NS) in the intervention group by the end of intervention. The effect of a Mediterranean-style diet on body weight was evaluated in 190 overweight women who were followed for up to 2 y (6). The 115 women who had a dietary intake of carbohydrate that exceeded 50% of energy were compared with the 75 who had a carbohydrate intake ≤50%. Women who consumed a low-carbohydrate diet lost more weight than did those who consumed a high-carbohydrate diet (**Figure 1**). In a randomized trial of 73 obese young adults, a low-glycemic-load (40% carbohydrate and

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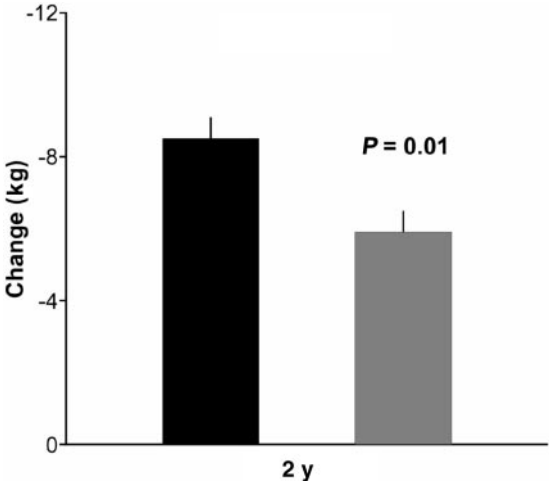

FIGURE 1. Mean (±SD) changes in body weight at the 2 y follow-up in the 115 women who consumed a high-carbohydrate, Mediterranean-style diet (58 ± 3.1% carbohydrate; black column) and in the 75 women who consumed a low-carbohydrate, Mediterranean-style diet (45 ± 3.3% carbohydrate; gray column).

35% fat) diet was compared with a low-fat (55% carbohydrate and 20% fat) diet (7). Changes in body weight and percentage body fat did not differ significantly between the diet groups overall, although the low-glycemic-load diet produced a greater decrease in weight (−5.8 compared with −1.2 kg; $P = 0.004$) in individuals with high insulin secretion than did the low-fat diet at 18 mo. As suggested by Howard (8), the results of diet trials underscore that nutrition information is complex and cannot always be delivered as simple sound messages.

Whereas each risk factor of the metabolic syndrome (visceral obesity, atherogenetic dyslipidemia, elevated blood pressure, and dysglycemia) can be dealt with individually, the initial therapeutic approach to the metabolic syndrome should focus on reversing its root causes, ie, an atherogenetic diet, a sedentary lifestyle, and overweight or obesity. Whether there is general agreement about increasing physical activity and reducing body weight, no single diet is currently recommended for patients with the metabolic syndrome. A series of recent scientific statements recommend the modification of atherogenetic diets as a major lifestyle intervention to reduce metabolic risk factors (9). The recommendations include a saturated fat intake of <7% of total calories, a reduction in the *trans* fatty acid intake <1% of total calories, dietary cholesterol <200 mg/dL, and a range of 25–35% of total calories from fat with an emphasis on unsaturated fat. In the very recent American Heart Association scientific statement on diet and lifestyle recommendation 2006, consumption of moderate fat intake for patients with the metabolic syndrome is reinforced (10).

The message of predominantly fat-centered dietary recommendations for patients with the metabolic syndrome leaves carbohydrates oscillating from 50% to 60% of total calories, assuming a fixed 15% protein intake. It seems ironic that popular diets seem more interested in proving their innocence than their merit. In the Women's Health Initiative Dietary Modification Trial (5), a low-fat eating pattern is said to result in no weight gain in postmenopausal women during a mean follow-up of 7.5 y; the more recent data of the Nurses' Health Study (11) suggest that diets lower in carbohydrate and higher in fat were not associated with an increased risk of coronary heart disease in women during a 20 y of follow-up.

Low-fat diets tend to be high in carbohydrates; there is ample evidence that such diets may increase triacylglycerols and further reduce HDL cholesterol. Needless to say, elevated concentrations of triacylglycerols and low concentrations of HDL cholesterol are 2 criteria for the diagnosis of metabolic syndrome. This did not escape the attention of the 2006 American Heart Association statement: "very-low-fat diets should be avoided if elevated triacylglycerol or depressed HDL-cholesterol concentrations are present (in patients with the metabolic syndrome)" (10).

EPIDEMIOLOGIC EVIDENCE LINKING DIETARY PATTERNS WITH THE METABOLIC SYNDROME

Epidemiologic studies have documented that dietary factors may affect the prevalence of the metabolic syndrome. Williams et al (12) showed that, in 802 subjects aged 40–65 y, dietary patterns with a frequent intake of raw and salad vegetables, fruit in both summer and winter, fish, pasta, and rice and a low intake of fried foods, sausages, fried fish, and potatoes was negatively correlated with many components of the metabolic syndrome, including central obesity, fasting plasma glucose, and triacylglycerols and were positively correlated with HDL cholesterol. The Coronary Artery Risk Development in Young Adults Study (13) showed that consumption of dairy products was associated with a significantly reduced risk of the metabolic syndrome; the adjusted odds of developing the metabolic syndrome were 72% lower among overweight individuals in the highest (≥35 times/wk, $n = 24/102$ individuals) compared with the lowest (<10 times/wk, $n = 85/190$ individuals) category of dairy consumption.

In the third National Health and Nutrition Examination Survey (NHANES III), participants with the metabolic syndrome were found to have significantly lower concentrations of several antioxidants, such as retinyl esters, vitamin C, and carotenoids, except lycopene, and to consume fewer fruit and vegetables than those without the metabolic syndrome (14). Other data from NHANES III were used to measure the risk of having the metabolic syndrome in healthy adult Americans following certain lifestyle behaviors. Low physical activity level, high carbohydrate intake, and current smoking habits were all significantly associated with an increased risk of having the metabolic syndrome, even after adjustment for other related covariates (15).

In a cross-sectional analysis of 2834 participants of the Framingham Offspring Study, whole grain and cereal fiber intakes were associated with a reduced risk of the metabolic syndrome (38% lower); cereal fiber accounted for most of the whole-grain effect (16). In the ATTICA Study (17), adherence to a Mediterranean-style dietary pattern was associated with a 20% lower risk of having the metabolic syndrome, irrespective of many confounding variables, including age, sex, physical activity, lipids, and blood pressure.

The epidemiologic evidence suggests a lower prevalence of the metabolic syndrome associated with dietary patterns rich in fruit, vegetables, whole grains, dairy products, and unsaturated fats. No individual component seems to be wholly responsible for the association of diet with metabolic syndrome and its components. Rather, it is likely that the interaction between many components of the diet or the overall diet quality offers protection against the metabolic syndrome (18). This view seems to be consistent with the results of recent epidemiologic studies indicating the importance of dietary patterns as risk factors for the

occurrence of the metabolic syndrome in women (19–21). The 12-y prospective analysis of 300 healthy women in the Framingham Offspring-Spouse study who were free of risk factors for the metabolic syndrome at baseline showed that participants with a higher nutritional risk profile consumed more dietary lipids and alcohol and less fiber and micronutrients. Compared with women with the lowest nutritional risk, those in the highest tertile had a 2- to 3-fold risk of developing the metabolic syndrome (20).

INTERVENTIONAL EVIDENCE

Lifestyle interventions are the initial therapies recommended for treatment of the metabolic syndrome (9). This recommendation, however, seems to have been built up exclusively on the assumption that, being key elements in the treatment of all components of the syndrome when they occur in isolation, lifestyle interventions promise to be an effective treatment for the metabolic syndrome as a whole. The ideal therapy for the metabolic syndrome should be the one leading to its resolution: to use an old adage, no disease, no risk! We wondered whether there are treatments specific to the syndrome itself rather than to its clustered and associated cardiovascular disease risk factors. We conducted a literature search to identify clinical trials specifically dealing with the resolution of the metabolic syndrome by lifestyle, drugs, or obesity surgery. Criteria used for study selection were as follows: English language, randomized trials with a placebo or control group (except for surgery), a follow-up lasting ≥6 mo, and a time frame of 5 y (from January 2002 to December 2006).

Lifestyle

We identified 3 studies based on lifestyle interventions (22–26). The first study (22) explored possible mechanisms underlying a dietary intervention and randomly assigned 180 patients (n = 99 men and 81 women) with the metabolic syndrome to either a Mediterranean-style diet (an increase in daily consumption of whole grains, vegetables, fruit, nuts, and olive oil) or a cardiac-prudent diet with a fat intake of <30% of total calories. (**Figure 2**). Only 40 patients in the intervention group still had metabolic syndrome after 2 y compared with 78 patients who consumed the control diet; thus, there was a 48% net reduction in the prevalence of the metabolic syndrome. Of the participants in the Diabetes Prevention Program (23) who had the metabolic syndrome at baseline and were randomly assigned to intensive lifestyle intervention (n = 549), metformin therapy (n = 570), or placebo (n = 592), 38% of the lifestyle group and 18% of the placebo group no longer had the syndrome after a mean follow-up of 3.2 y. The Dietary Approach to Stop Hypertension (DASH) diet used in the Iranian study (24) is similar to a Mediterranean-style diet. This was a randomized controlled outpatient trial conducted in 116 patients with the metabolic syndrome. The prevalence of the metabolic syndrome decreased by 35% in the DASH diet group (n = 38) compared with the control diet (n = 40).

Drugs

We identified 5 studies based on drug therapy, 3 with rimonabant (25–27), 1 with metformin (23), and 1 with rosiglitazone (28). All rimonabant studies (25–27) lasted 1 y and used a fixed 20-mg daily dose. The number of patients with the metabolic syndrome assigned to rimonabant or placebo in the 3 studies was 228 and 108, 187 and 177, and 419 and 192, respectively. The percentage resolution of the metabolic syndrome was similar across the 3 studies: 33%, 30%, and 30%, respectively. The metformin study represented one arm of the Diabetes Prevention Program trial (23): 570 patients took metformin (850 mg twice daily) and 592 patients took placebo. The resolution of the syndrome was not significant (5%). In the rosiglitazone trial (28), 50 patients with the syndrome took 4 mg rosiglitazone/d and 50 patients took placebo; after 1 y, 30 subjects receiving rosiglitazone still had features of the syndrome compared with 45 subjects receiving placebo.

Surgery

We identified 3 studies based on laparoscopic weight- reduction surgery. In the first study (29), 337 morbidly obese patients with the metabolic syndrome were reassessed 1 y after vertical banded gastroplasty or gastric bypass; the resolution rate was 96%. The syndrome resolved after a mean follow-up of 15 mo in 80% of 49 severely obese patients (30) with the syndrome who underwent gastric bypass. Finally, of 32 obese patients with the syndrome at baseline, only 1 still had features of the syndrome 6 mo after gastric bypass (31).

CONCLUSIONS

The striking resolution of the metabolic syndrome after weight-reduction surgery strongly suggests that obesity is the driving force for the occurrence of this condition. Obviously, surgery has precise indications and is not to be considered a routine treatment for the metabolic syndrome. Moreover, there is agreement that full expression of the syndrome depends on a complex interaction between genetic determinants (still largely unknown) and acquired factors related mainly to lifestyle habits. The problem is complicated by the likelihood that several gene products, each making a relatively small contribution, interact to make up the genetic component associated with the syndrome. In

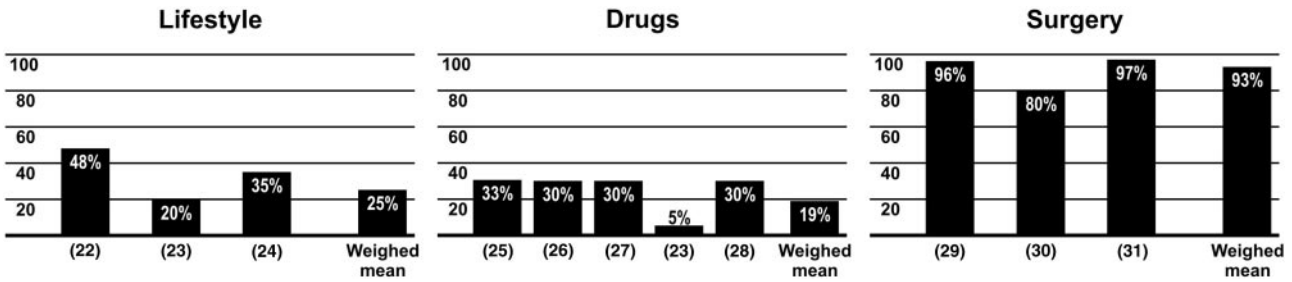

FIGURE 2. Resolution of the metabolic syndrome according to treatment. The numbers within or above the columns represent the percentage resolution after treatment; the numbers below the columns in parentheses indicate the number of studies in the reference list.

this context, it is hoped that large studies based on multicenter collections and done with standardized methods may help successful localization of several genes for this complex disease. Moreover, treatment may be different depending on the prevalence of different components of the metabolic syndrome.

To date, both intensive lifestyle interventions and some drugs (rimonabant and rosiglitazone) may reduce the prevalence of the metabolic syndrome in ≈25–33% of patients. However, the achievement of modifications in lifestyle has proven to be difficult, and weight-reduction drugs have not been particularly effective for treatment of obesity. In the meantime, lifestyle modifications may be a good companion to drugs for reducing the metabolic and cardiovascular burden of the syndrome.

In theory, the ideal diet should target many, if not all, the dietary components thought to influence the cardiometabolic risk, including all types of fat (saturated, polyunsaturated, monounsaturated, and *trans* fats), fiber, fish, carbohydrates, and proteins. Although there is no such "all-inclusive" diet yet, it seems plausible that a Mediterranean-style diet has most of the desired attributes, including a lower content of refined carbohydrates, a high content of fiber, a moderate content of fat (mostly unsaturated), and a moderate-to-high content of vegetable proteins. There is evidence that dietary patterns similar to those of the Mediterranean-style diet exert positive effects on almost all components of the metabolic syndrome and other conditions associated with, including inflammation, insulin resistance, and endothelial dysfunction (32, 33). Although only suggestive, the data presented in this review need to be confirmed and extended. Future research should focus on the long-term efficacy and safety of Mediterranean-style diets in populations at risk of the metabolic syndrome and type 2 diabetes, such as those who are overweight or obese.

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