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Review

Mediterranean diet and the metabolic syndrome

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The metabolic syndrome (also referred to as syndrome X or the insulin resistance syndrome) has emerged as an important cluster of risk factors for atherosclerotic disease. Patients with the syndrome also are at increased risk for developing type 2 diabetes mellitus. Common features are central (abdominal) obesity, insulin resistance, hypertension, and dyslipidemia. Weight reduction deserves first priority in individuals with abdominal obesity and the metabolic syndrome. Both weight reduction and maintenance of a lower weight are best achieved by a combination of reduced caloric intake and increased physical activity. Dietary patterns close to the Mediterranean diet and rich in fruit and vegetables, and high in monounsaturated fats are negatively associated with features of the metabolic syndrome. Some recent studies dealing specifically with the effect of interventions on the resolution of the metabolic syndrome have demonstrated a 25% net reduction in the prevalence of the syndrome following lifestyle changes mainly based on nutritional recommendations. Similar rates of resolution have been obtained with drugs, such as rosiglitazone and rimonabant. The favourable benefit/hazard ratio makes Mediterranean-style diets particularly promising to reduce the cardiovascular burden associated with the metabolic syndrome.

Keywords: Cardiovascular disease / Lifestyle / Mediterranean diet / Metabolic syndrome / Type 2 diabetes

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1 Introduction

Modern society has brought with its profound changes in lifestyle and an increased incidence of atherosclerotic vascular disease. Body weights are on the rise, diets are becoming less healthy, and people are becoming increasingly sedentary, resulting in elevations of blood pressure and metabolic alterations that increase atherothrombotic risk. In fact, obesity, insulin resistance and diabetes are becoming a public health problem of epidemic proportions. The metabolic syndrome (also referred to as syndrome X or the insulin resistance syndrome) has emerged as an important cluster of risk factors for atherosclerotic disease [1]. Patients with the metabolic syndrome also are at increased risk for developing type 2 diabetes mellitus. Common features are central (abdominal) obesity, insulin resistance, hypertension, and dyslipidemia. Atherogenic dyslipidemia consists of an aggregation of lipoprotein abnormalities including elevated serum triglyceride and apolipoprotein B, increased small LDL particles, and a reduced level of HDL cholesterol. Insulin resistance is thought to be a key feature, as there are interesting parallels between the metabolic syndrome and type 2 diabetes mellitus. Abdominal obesity is associated with insulin resistance and hypertension; hypertension is frequently associated with insulin resistance and other features of the metabolic syndrome.

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Abbreviations: ATP III, adult treatment panel III; **CRP,** C-reactive protein; **CVD,** cardiovascular disease; **IDF**, International Diabetes Federation; **IL-6/-7/-18,** interleuken 6/7/18

2 Risk factors for the metabolic syndrome

The predominant underlying risk factors for the syndrome appear to be abdominal obesity [2] and insulin resistance [3]; other associated conditions can be physical inactivity [4], aging [5] and hormonal imbalance [6]. A diet rich in saturated fat and cholesterol can enhance risk for developing cardiovascular disease (CVD) in people with the syndrome, although this diet is not listed specifically as an underlying risk factor for the condition [7]. One theory holds that insulin resistance is the essential cause of the metabolic syndrome [8]. Although insulin-resistant individuals need not be clinically obese, they nevertheless com-

monly have an abnormal fat distribution that is characterised by predominant upper body fat. Upper-body obesity correlates strongly with insulin resistance. Excess upper body fat can accumulate either intraperitoneally (visceral fat) or subcutaneously. Regardless of the relative contributions of visceral fat and abdominal subcutaneous fat to insulin resistance, a pattern of abdominal (or upper-body) obesity correlates more strongly with insulin resistance and the metabolic syndrome than does lower-body obesity [9]. An interesting feature of upper-body obesity is an unusually high release of nonesterified fatty acids from adipose tissue; this contributes to accumulation of lipid in sites other than adipose tissue. Ectopic lipid accumulation in muscle and liver seemingly predisposes to insulin resistance [10] and dyslipidemia [11].

According to many experts, the increasing burden of obesity in the United States is the driving force behind the rising prevalence of the metabolic syndrome [12]. Adipose tissue in obese people is insulin resistant, which raises nonesterified fatty acid levels, worsening insulin resistance in muscle and altering hepatic metabolism; in addition, the adipose tissue of obesity exhibits abnormalities in the production of several adipokines that may separately affect insulin resistance and/or modify risk for CVD [13]. These include increased production of inflammatory cytokines [14, 15], and plasminogen activator inhibitor-1 [16]; at the same time the potentially protective adipokine, adiponectin, is reduced [17]. All of these changes have been implicated as causes of metabolic risk factors.

3 The metabobic syndrome and inflammation

Recently, this syndrome has been noted to be associated with a state of chronic, low-grade inflammation [18]. Some researchers speculate that inflammation of this type underlies or exacerbates the syndrome. For example, inflammatory cytokines reportedly induce insulin resistance in both adipose tissue and muscle [19]. In the presence of obesity, adipose tissue indeed produces cytokines in excess, whereas output of adiponectin is diminished; these responses appear to heighten the connection between obesity and inflammation. Interestingly, insulin-resistant people manifest evidence of low-grade inflammation even without an increase of total body fat.

All the parameters included in the diagnosis of the metabolic syndrome are associated with a low-grade inflammation state. Elevated levels of C-reactive protein (CRP), an easily measured inflammatory biomarker, has been proven to be a strong, independent predictor of both incident diabetes and incident CVD [20]. Obesity, insulin resistance, and diabetes are associated with a proinflammatory state [21], which in turn is associated with increased cardiovascular risk. In the apparently healthy women who participated in the Women's Health Study [22], those with the metabolic syndrome had significantly worse cardiovascular event-free survival than did those without the metabolic syndrome. Moreover, at all levels of severity of the metabolic syndrome, CRP added important and independent prognostic information in terms of future cardiovascular risk. An association of elevated levels of interleukin-6 (IL-6) and CRP with the metabolic syndrome has also been found among working men aged 45 to 63 years in the Whitehall II cohort [23].

4 Diagnosis of metabolic syndrome

In 2001, the National Cholesterol Education Program Adult Treatment Panel III (ATP III) introduced clinical criteria for defining the metabolic syndrome [24]. The purpose of ATP III was to identify people at higher long-term risk for CVD who deserved clinical lifestyle intervention to reduce risk. The ATP III criteria thus required no single factor for diagnosis, but instead made the presence of three of five factors the basis for establishing the diagnosis; these were abdominal obesity (also highly correlated with insulin resistance), elevated triglycerides, reduced HDL cholesterol, elevated blood pressure, and elevated fasting glucose (impaired fasting glucose or type 2 diabetes mellitus).

In particular, the cut-off values are the following: waist circumference >102 cm in men and >88 cm in women; triglycerides >150 mg/dL; HDL-cholesterol <40 mg/dL in men and <50 mg/dL in women; blood pressure >130/85 mm Hg; fasting glucose >110 mg/dL. Applying these criteria to the database of the Third National Health and Nutrition Examination Survey, it has been estimated that one out of four adults living in the United States merits the diagnosis [5].

Although ATP III did not make any single risk factor (*e.g.*, abdominal obesity) a requirement for diagnosis, it nonetheless espoused the position that abdominal obesity is an important underlying risk factor for the syndrome. Its cutpoints for abdominal obesity came from the definition in the 1998 National Institutes of Health obesity clinical guidelines [25]; they were a waist circumference of ≥102 cm (≥40 in) for men and ≥88 cm (≥35 in) for women. These cutpoints identify approximately the upper quartile of the US population.

The recent International Diabetes Federation (IDF) definition of metabolic syndrome is similar in practice to the modified ATP III definition adopted in the present statement. Obvious differences are 2-fold: IDF requires abdominal obesity as 1 factor and sets lower thresholds for abdominal obesity than used in the United States. Even so, most subjects with waist circumference ≥94 cm in men or ≥80 cm in women plus two other risk factors (IDF definition) will in fact have three risk factors (ATP III definition).

5 Weight reduction

Weight reduction deserves first priority in individuals with abdominal obesity and the metabolic syndrome [25, 26]. Both weight reduction and maintenance of a lower weight are best achieved by a combination of reduced caloric intake and increased physical activity and the use of principles of behaviour change. The first aim of weight loss is to achieve a decline of about 7 to 10% from baseline total body weight during a period of 6 to 12 months. This will require decreasing caloric intake by 500 to 1000 calories per day. Greater physical activity helps to enhance caloric deficit. Achieving the recommended amount of weight loss will reduce the severity of most or all of the metabolic risk factors. Maintenance of a lower weight is just as important; this requires long-term follow-up and monitoring. Currently available weight-loss drugs possess limited utility in the management of obesity. Nevertheless, in some patients they may be helpful.

6 Physical activity

Current recommendations for the public call for accumulation of ≥30 min of moderate-intensity exercise, such as brisk walking, on most, and preferably all, days of the week [27]; even more exercise adds more benefit. Thus, going beyond current recommendations will be particularly beneficial for people with the metabolic syndrome. Sixty minutes or more of continuous or intermittent aerobic activity, preferably done every day, will promote weight loss or weight-loss maintenance. Preference is given to 60 min of moderate-intensity brisk walking to be supplemented by other activities. The latter include multiple short (10 to 15 min) bouts of activity (walking breaks at work, gardening, or household work), using simple exercise equipment (*e. g.*, treadmills), jogging, swimming, biking, golfing, team sports, and engaging in resistance training; avoiding common sedentary activities in leisure time (television watching and computer games) is also advised. Self-monitoring of physical activity can help to achieve adherence to an activity program.

7 Atherogenic diets

Epidemiological studies have documented that nutritional factors may affect the prevalence of the metabolic syndrome. Williams *et al.* [28] showed that dietary patterns close to the Mediterranean diet and rich in fruit and vegetables, and high in monounsaturated fats were negatively associated with features of the metabolic syndrome. More recently, a reduced prevalence of the metabolic syndrome (38% lower) was observed among subjects of the Framingham Offspring Study consuming the highest intake of cereal fiber, as compared to the lowest intake [29]. In the ATTICA Study [30], 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.

So, beyond weight control and reduction of total calories, the diet should be low in saturated fats, *trans* fats, cholesterol, sodium, and simple sugars [31]. In addition, there should be ample intakes of fruits, vegetables, whole grains, and monounsaturated fat; fish intake should be encouraged. Interestingly enough, these features are very reminiscent of the nutritional principles currently used to define the Mediterranean-style diet [32]. Both high-carbohydrate diets and low-fat diets can exacerbate the dyslipidemia of the metabolic syndrome. To avoid any worsening of atherogenic dyslipidemia in patients with the metabolic syndrome, some investigators favour fat intakes in the range of 30 to 35%; others, however, are concerned about possible weight gain resulting from long-term ingestion of higher fat intakes and thus prefer intakes in the range of 25% to 30%. If the fat content exceeds 35%, it is difficult to sustain the low intakes of saturated fat required to maintain a low LDL cholesterol, at least in population not very familiar with vegetable fats.

One recent, long-term, ample size interventional study demonstrated that a dietary intervention low in fat and high in vegetables and fruits did not reduce the risk of CVD events in postmenopausal women [33]. Moreover, very recent data from the Nurses' Health Study [34] suggest that diets lower in carbohydrate and higher in protein and fat are not associated with increased risk of coronary heart disease (CHD); when vegetable sources of fat and protein are chosen, these diets may moderately reduce the risk of CHD. Lastly, restriction of refined carbohydrates in the context of a Mediterranean-style can be beneficial in reducing the risk of CVD in women with the metabolic syndrome [35].

8 Interventional studies to decrease the prevalence of the metabolic syndrome

To date, chronic diseases represent a huge proportion of human illness, as CDVs, various forms of cancer, and diabetes combine to make up nearly 70% of all deaths in the US [36]. Lifestyle changes, such as unhealthy diets and a lack of physical activity, have contributed to a worldwide increase in the prevalence of obesity and the metabolic syndrome [37]. Accordingly, low consumption of fruit and vegetables, together with physical inactivity, are now among the top ten causes of mortality in developed countries [38].

Lifestyle interventions are the initial therapies recommended for treatment of visceral obesity and the metabolic syndrome [39]. This recommendation, however, seems to have been built up exclusively on the assumption that, being

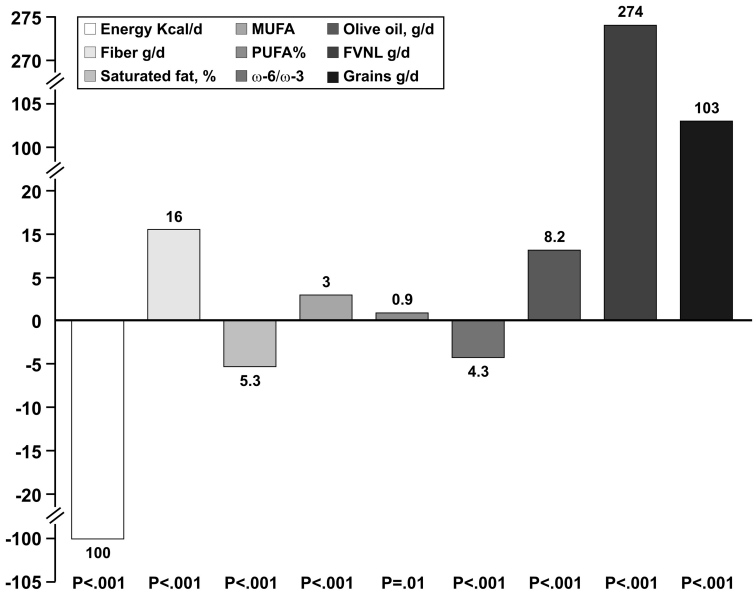

Figure 1. Nutrient indices after two years of a Mediterranean-style diet in subjects with the metabolic syndrome (n = 90). The results are expressed as net changes from the baseline corrected for the changes obtained in a control group (n =9 0) of subjects with the metabolic syndrome following a prudent-cardiac diet. Numbers from 1 to 9 indicate the 9 columns starting from the left. g/d = grams/day; FVNL = fruit, vegetable, nut, legumes. Changes in MUFA and PUFA are expressed in %. Adapted from ref. [40].

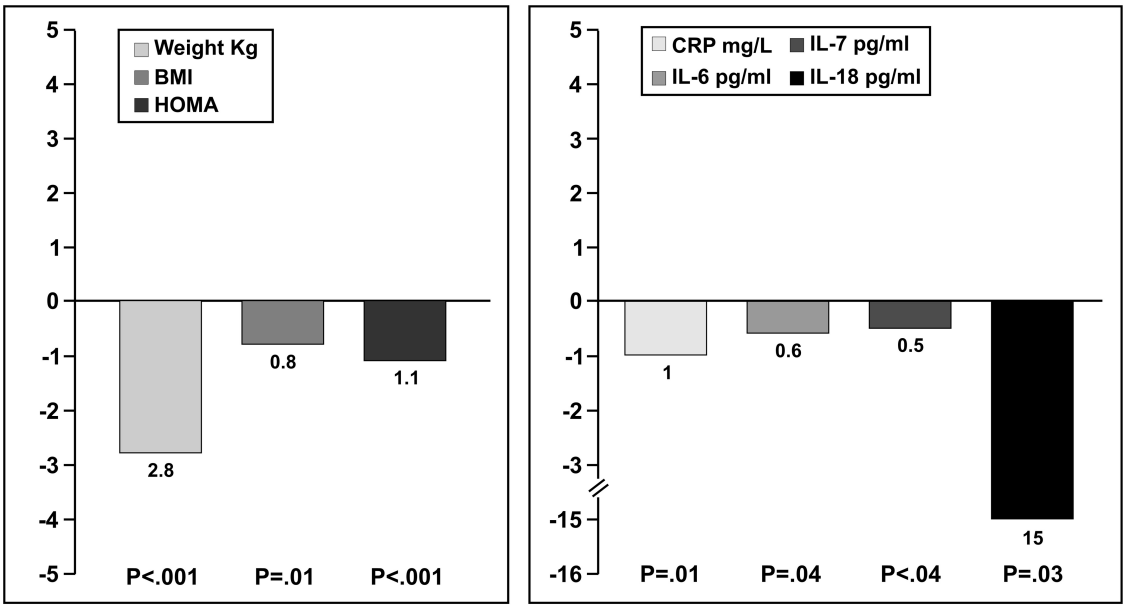

Figure 2. Effect of a Mediterranean-style diet on body weight, BMI (kg/m^2), and HOMA (Homeostatic Model Assessment, a surrogate index of insulin resistance), and on CRP, and IL-6, IL-7, and IL-18 circulating levels in subjects with the metabolic syndrome. See also legend to Fig. 1.

key elements in the treatment of all components of the syndrome when they occur in isolation, lifestyle interventions hold the premise to be also an effective treatment for the metabolic syndrome as a whole.

There are some recent studies dealing specifically with the effect of interventions on the resolution of the metabolic syndrome. These studies [40–46] were randomised controlled trials with a placebo/control group, a follow-up longer than six months, and absence of frank diabetes in participants. Three studies [40–42] were based on lifestyle interventions and five studies [41, 43–46] on drugs, with a total of 4351 subjects, 1399 on lifestyle changes and 2952 on drugs. The first study was published in 2004. Esposito *et al.* [40] explored possible mechanisms underlying a dietary intervention and randomised 180 patients (99 men, 81 women) with the metabolic syndrome to a Mediterranean-style diet (instructions about increasing daily consumption of whole grains, vegetables, fruits, nuts, and olive oil) *vs* a cardiac-prudent diet with fat intake less than 30% (Fig. 1). After two years, body weight decreased more in the inter-

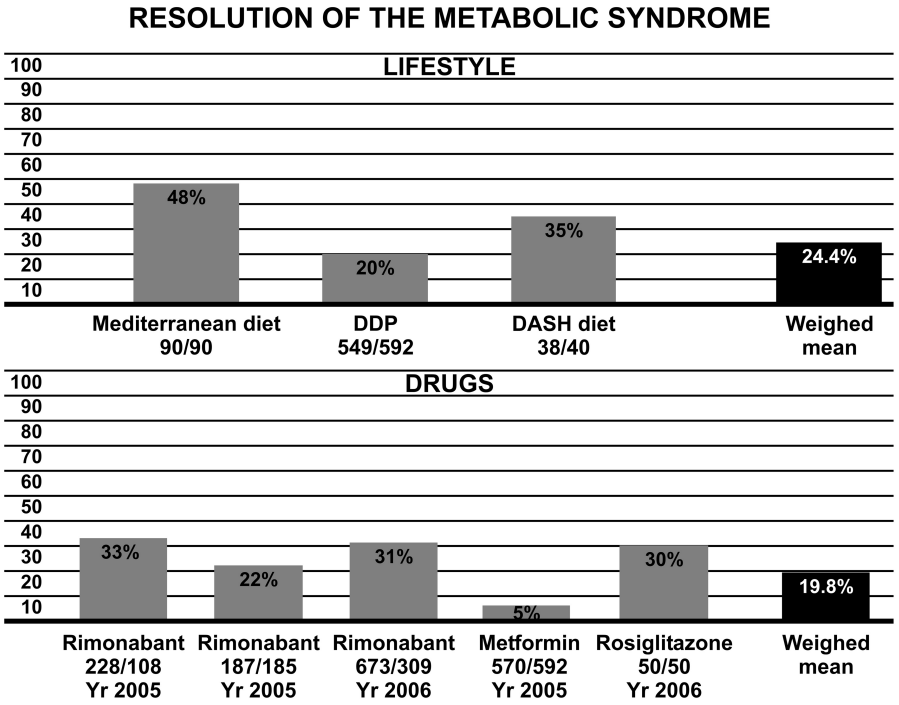

Figure 3. Effects of lifestyle changes or drugs on the resolution of the metabolic syndrome in placebo-controlled clinical trials. The numbers under the column heading indicate the size of interventional or placebo groups. The year is the year of publication of the study. DPP = Diabetes Prevention Program.

vention group than in the control group, but even after controlling for weight loss, inflammatory markers, such as IL-6, IL-7, IL-18, and CRP, and insulin resistance declined more in the intervention than in the control group, while endothelial function improved (Fig. 2). Only 40 patients in the intervention group still had metabolic syndrome after two years compared with 78 patients on the control diet; thus, there was a 48% net reduction in the prevalence of the syndrome. In the participants in the Diabetes Prevention Program [41] who had impaired glucose tolerance at baseline, 18% of the placebo group and 38% of the lifestyle group no longer had the syndrome at three years. The Dietary Approach to Stop Hypertension diet used in the Iranian study [42] is quite similar to a Mediterranean-style diet. Rimonabant is a cannabinoid-1 receptor blocker which has been shown promising in reducing body weight in obesity [43–45]. Besides reducing insulin resistance, rosiglitazone improves inflammation and endothelial dysfunction [46]. The weighed mean resolution of the syndrome was 24.4% for lifestyle changes and 14.5% for drugs (Fig. 3). In most studies, resolution of the syndrome was dependent on reduction in waist circumference and weight loss.

To date, intensive lifestyle interventions seem to work better than drugs in reducing the prevalence of the metabolic syndrome. The role of overall dietary patterns in predicting long-term risk of coronary heart disease has recently been demonstrated [47]. In practical terms, a prudent dietary pattern is characterised by the choice of foods that satisfy all the strategies for reducing CHD risk, that is, a higher intake of fruits, vegetables, legumes, whole grains, poultry, and fish. Needless to say, this pattern is associated with lower risk of CHD, as opposed to a Western dietary pattern (higher intakes of red and processed meat, sweets and desserts, potatoes and French fries, and refined grains) which is associated with an increased risk. As modern eating patterns of Western societies generate an almost endless postprandial phase through the day, a chronic activation of the innate immune system could exist during most parts of the day.

Although the whole diet approach cannot allow determining whether the benefit is due to an added nutrient, a removed nutrient, or a combination of both, the evidence suggests that numerous dietary changes contribute to the reduction in chronic disease risk, including CVD and diabetes [48].

9 Conclusions

The clustering atherogenic and diabetogenic abnormalities of the metabolic syndrome are highly prevalent in our affluent, sedentary populations. The shift towards energy-dense, refined diet that has been adopted by an increasing proportion of people may have led to the development of a positive energy balance, weight gain, and obesity. Adipose tissue excess, particularly in the visceral compartment, is widely

acknowledged as an endocrine organ secreting an increasing number of mediators, including proinflammatory cytokines. As visceral obesity is a key promoter of low-grade systemic inflammation [49 – 51] and is characterised by the most severe metabolic abnormalities [52, 53], it is possible that persons with abdominal adiposity are particularly prone to the proinflammatory effects of unhealthy diets. Although this evidence is still lacking, the Quebec Family Study has shown that a decrease in the consumption of fat-foods or an increase in consumption of whole fruits predicted a lower increase in body weight and adiposity indicators over a six year follow-up in [54]. However, no specific dietary recommendations have been advocated by health agencies for treatment of insulin resistance or the metabolic syndrome. Given that the metabolic syndrome is an identifiable and potentially modifiable risk state for both type 2 diabetes and CDV, adopting a Mediterranean-style dietary pattern, as that used in the study of Esposito *et al.* [40], may reduce the potential risk of these diseases. As a similar decrease in the prevalence of the metabolic syndrome has been obtained with rimonabant, a cannabinoid receptor blocker, in a group of obese patients after one year treatment, with a 30% rate of discontinuation for side effects [55], a whole diet approach, such as that of Mediterranean-style diets, seems particularly intriguing and promising to reduce the cardiovascular burden associated with the metabolic syndrome.

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