

Metabolic syndrome: Are we at risk?

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ABSTRACT

The metabolic syndrome also called syndrome X, is a constellation of interrelated risk factors of metabolic origin - *metabolic risk factors* - that appear to share insulin resistance as a possible pathogenetic factor that directly promote the development of atherosclerotic cardiovascular diseases and increase the risk for developing type 2 diabetes mellitus. The recommended first step for treatment of metabolic syndrome is lifestyle modifications such as weight loss, aerobic exercise, smoking cessation, and improved diet which independently improve insulin resistance and slow progression to type 2 diabetes mellitus. Even though success achieved through lifestyle modification is limited, the significance of it cannot be overemphasized. Specific dietary changes that are appropriate for addressing different aspects of the syndrome include reducing saturated fat intake to lower insulin resistance, reducing sodium intake to lower blood pressure, and reducing high-glycemic-index carbohydrate intake to lower triglyceride levels. Furthermore, drugs able to reduce insulin resistance, such as metformin and thiazolidinediones, already in the therapeutic armamentarium of type 2 diabetes, could be used in subjects with the metabolic syndrome as a preventive measure.

Keywords: metabolic syndrome; insulin resistance; lifestyle modification; metformin

INTRODUCTION

Differences in body-fat distribution (i.e., gynecoid versus android) associated with an altered metabolic profile were documented in the medical literature 50 years ago. Given the name *Syndrome X* in 1988¹ each component of the syndrome has been associated with an increased risk of cardiovascular disease.² After several name changes over the past two decades, including the term diabetes, insulin resistance syndrome used in lay publications, the name became metabolic syndrome. Since cardiovascular disease (CVD) is one of the leading cause of death for adults in both developed and developing countries, many medical studies focus on treating or preventing heart disease and stroke.

The metabolic syndrome is a constellation of interrelated risk factors of metabolic origin - *metabolic risk factors*- that appear to directly promote the development of CVD and increase the risk for developing type 2 diabetes mellitus. The most widely recognized of the metabolic risk factors are atherogenic dyslipidemia, elevated blood pressure, and elevated plasma glucose. Indeed due to life style habits of increased caloric intake and reduced or absent physical activity, the prevalence of the metabolic syndrome will continue to rise as well as obesity, diabetes type 2 and CVD.³ The rate of its occurrence is growing exponentially, especially in children and young adults.⁴ People with metabolic syndrome are twice likely to die from and three times as likely to have a CVD or strokes compared with people without the syndrome. Soon, metabolic syndrome will overtake cigarette smoking as the number one risk factor for heart disease among the U.S. population.⁵ Aggressive lifestyle modification and possible use of medications to treat the conditions that make up the metabolic syndrome may reduce a person's chances of developing CVD, Diabetes, or stroke.⁶⁻¹¹

Definition: Metabolic syndrome is characterized by the presence of a cluster of metabolic abnormalities (disturbance in glucose metabolism; obesity - mainly abdominal; hypertension; atherogenic dyslipidemia; microalbuminuria; prothrombotic and pro-inflammatory states) sharing insulin resistance as a possible pathogenetic factor is of great clinical relevance for drawing attention to the concurrence of several risk factors for CVD. Several definitions of the metabolic syndrome proposed by health organizations and scientific societies have emphasized one or the other of the different components of the syndrome, however there is much overlap among the criteria utilized for diagnosis. Table-1 describes the 3 sets of criteria commonly used to define the presence of metabolic syndrome. The most recent of these, released by the International Diabetes Foundation (IDF), includes sex and ethnic group-specific elevated waist circumference as a major criterion in its definition of metabolic syndrome. According to the IDF, the waist circumference cutoffs for obesity are listed in Table-2.

A report of the Adult Treatment Panel (ATP III) of the National Cholesterol Education Program has proposed a simple working diagnosis of the syndrome using criteria based on the values of variables such as: fasting blood glucose, triglycerides, HDL cholesterol, blood pressure and waist circumference.¹² Although this proposed definition might have a low sensitivity in detecting subjects with insulin resistance¹³ it has the potential to be used in epidemic studies and to easily identify and manage individuals with the syndrome.

Metabolic syndrome is associated with a proinflammatory / prothrombotic state that may include elevated levels of C-reactive protein, endothelial dysfunction, hyperfibrinogenemia, increased platelet aggregation, increased levels of plasminogen activator inhibitor 1, elevated uric acid levels, microalbuminuria, and a shift toward small, dense particles of low-density lipoprotein (LDL) cholesterol. Insulin resistance also has been implicated in polycystic ovary syndrome and nonalcoholic fatty liver disease (NAFLD).¹⁴ We are now aware that the natural history of borderline increase of serum transaminases might not be so benign as it was supposed to be.¹⁵ The coexistence of these conditions of metabolic syndrome in the same patient is related to an increased incidence of CVD and DM as well as their consequences.

Prevalence: Limited information is available about the prevalence of the metabolic syndrome. The prevalence of metabolic syndrome is estimated to be around 20.0-25.0% of the population.¹⁶ An estimated 47 million US adults have metabolic syndrome. Some experts predict that at least half of persons over age 60 would meet the criteria for this syndrome. From 1999 to 2000, 64.0% of US adults aged 20 to 74 were overweight or obese, according to data from the Department of Health and Human Services.⁶ A more recent survey analysis found that as many as 4.2% of US adolescents aged 12 to 19 years have the disorder. Prevalence rates of metabolic syndrome differ across ethnic groups. The highest overall prevalence has been found in Mexican Americans, who make up a rapidly growing segment of the US population.

WHO = World Health Organization; ATP = Adult Treatment Panel; BMI = body mass index; HDL = high-density lipoprotein; WC = Waist circumference, TG = Triglyceride, IGT= Impaired glucose tolerance, IFG= impaired fasting glucose

*—Insulin resistance is identified by impaired glucose intolerance (IGT), type 2 diabetes mellitus or IFG or hyperinsulinemia (upper quartile of fasting insulin in nondiabetic population).

§ — As determined by sex- and ethnic group-specific elevated WC, Table-2.

†—The 2001 definition identified fasting plasma glucose ≥ 110 mg/dL (6.1 mmol/L) as elevated. This was modified in 2004 to be ≥ 100 mg/dL (5.6 mmol/L), in accordance with American Diabetes Association's updated definition of IFG.

Based on published studies, in various developing countries prevalence of the metabolic syndrome varies from 13.0% in China to 30.0% in Iran. In a survey in Singapore, the prevalence of the syndrome varied between the three major ethnic groups – from the Chinese at 15.0% and Malays at 19.0%, to the Indians at 20.0%.¹⁷ All these studies have used either WHO or ATP III criteria for defining the metabolic syndrome. In a large cross-sectional survey on urban Asian Indians, the Chennai Urban Rural Epidemiology Study, the prevalence of the metabolic syndrome was found to be 23.0%, 18.0% and 26.0% using the WHO, ATP III and IDF definitions respectively.¹⁸

In the SHARE study, one third of South Asian volunteers had either glucose intolerance or overt diabetes as diagnosed by fasting glucose and a 2-hour glucose tolerance test, a prevalence much higher than in other populations.¹⁹ Similar findings have been observed among urban adults in India.²⁰ When Adult Treatment Panel III criteria and modified waist circumference cutoffs were used, the metabolic syndrome was present in 41.1% of urban Indian adults and in 27.9% of subjects with normal plasma glucose levels. In those with elevated fasting plasma glucose, the prevalence of metabolic syndrome was 70.0%. Data regarding prevalence of metabolic syndrome in Nepal are not available.

Pathophysiology: While the pathogenesis of the metabolic syndrome and each of its components is complex and not well understood, central obesity and insulin resistance are acknowledged as important causative factors. However, it may be related to dyslipidemia, and hypertension, all of which stem from dietary excess, a sedentary lifestyle, and genetic predisposition.²¹ Further research is required to pinpoint the exact etiology of this syndrome. Inflammation in the vasculature might be an important pathogenic link between CVD and the metabolic syndrome. C- reactive protein (CRP) has been shown to be a strong independent predictor of vascular events. The development of a simple, stable, noninvasive test to measure high-sensitivity CRP has provided a clinical tool that may have an important role in the identification and assessment of individuals likely to develop CVD or metabolic disease.²²

Clinical Implication: The metabolic syndrome is an important risk factor for subsequent development of type 2 diabetes and/or CVD. Thus, the key clinical implication of a diagnosis of metabolic syndrome is identification of a patient needing aggressive lifestyle modification focused on weight reduction and increased physical activity.

Risk of CVD: Since the release of the NCEP guidelines for metabolic syndrome in 2001, numerous published clinical studies have established that people with metabolic syndrome are twice as likely to develop CVD and are at an overall increased risk of mortality.^{23-28, 5} The most recent of these studies, which involved a large community-based sample of middle-aged men, demonstrated that, after taking established cardiac risk factors into account, people with metabolic syndrome were at a 40.0-60.0% increased risk for total and cardiovascular mortality.²⁹ The increased risk of coronary and cardiovascular mortality was found across all age groups, including young adults, adolescents and elderly adults.³⁰⁻³¹ Another interesting observation obtained from a recently published study is that metabolic syndrome confers a higher long-term risk of death in patients with preexisting coronary heart disease (CHD).³² Dysglycemia appears to be responsible for most of the associated risk.

Risk of Diabetes: Prospective observational studies demonstrate a strong association between the metabolic syndrome and the risk for subsequent development of type 2 diabetes.³³⁻³⁶ In an analysis of 890 nondiabetic Pima Indians, 144 developed diabetes over four years of follow-up.³³ The metabolic syndrome increased the relative risk for incident diabetes by 2.1-fold with the ATP III definition and 3.6-fold using the WHO definition. This difference highlights the importance of insulin resistance (a required characteristic of the WHO definition) in the pathogenesis of type 2 diabetes.

The metabolic syndrome seems to have an even more powerful effect on the risk for diabetes in Caucasians. Among 4423 non-diabetic subjects in the Beaver Dam Study who were followed over five years, the metabolic syndrome (using a definition similar to WHO criteria) increased risk of incident diabetes by 9 to 34-fold.³⁵ Similar findings were noted among 5974 non-diabetic men followed for five years in the primary prevention West of Scotland Coronary Prevention Study (WOSCOPS).³⁶ The metabolic syndrome (defined by ATP III criteria, but with obesity defined by an elevated BMI rather than waist circumference) increased the risk for incident diabetes by 7 to 24-fold.

Prospective data from a Framingham Heart Study cohort, also predominantly Caucasian, showed that the population attributable risk for the development of type 2 diabetes associated with the metabolic syndrome (revised ATP III criteria, excluding baseline diabetes) was about 60 percent in men and 45 percent in women.³⁷

Other associations: The metabolic syndrome has also been associated with several obesity-related disorders including: 1. Nonalcoholic fatty liver disease with steatosis, fibrosis, and cirrhosis ;³⁸⁻³⁹ 2. Chronic kidney disease (CKD) and microalbuminuria;⁴⁰ 3. Polycystic ovary syndrome;⁴¹ 4. Sleep-disordered breathing, including obstructive sleep apnea.⁴²⁻⁴³ Several components of the metabolic syndrome, including hyperlipidemia, hypertension, and diabetes have been associated with an increased risk of cognitive decline and dementia.⁴⁴

Controversy: Whether metabolic syndrome criteria enhance prediction of CVD events beyond the Framingham Heart Study prediction score is still controversial. As metabolic syndrome criteria do not include major, well-established cardiovascular risk factors such as age, smoking, and LDL cholesterol levels, metabolic syndrome criteria are considered inferior to the Framingham score in predicting CVD events.⁴⁵⁻⁴⁶ However, among individuals with the same Framingham score, those with metabolic syndrome are at higher risk of CVD than are those without metabolic syndrome. Also, a clear gradation in the risk of CVD outcome is evident with each additional component of metabolic syndrome; men with 3 or more components and women with 2 or more components are at statistically elevated risk.⁴⁶ The Framingham Heart Study prediction score can be used for short-term (<10 y) prediction of CHD events, whereas metabolic syndrome criteria can be used to predict events in the long term.⁴⁷ However, the utility of metabolic syndrome criteria as predictive of CHD events is questionable and needs to be well defined.⁴⁸

Treatment: Debate continues about the best approach for management of metabolic syndrome. Many experts believe that the initial approach is to direct therapy to the syndrome, and if implementing that strategy isn't successful, to target treatment to the individual components. Therapy should be tailored to a patient's specific risk factors and comorbid conditions, and decisions about what is most appropriate should be made within the context of a close working relationship between patient and physician. The recommended first step for treatment of metabolic syndrome is lifestyle modifications such as weight loss, aerobic exercise, smoking cessation, and improved diet which independently improve insulin resistance and slow progression to type 2 diabetes mellitus. Even though success achieved through lifestyle modification is limited, the significance of it cannot be overemphasized (Table 3).

Pharmacotherapy involves the aggressive management of well-established risk factors (eg, hypertension, obesity, dyslipidemia) and possible use of insulin sensitizers.

Lifestyle Changes

Weight loss: Although some persons with metabolic syndrome are of normal weight, many are overweight or obese, and weight loss through long-term behavior modification and a reduced-calorie diet is the goal. Obesity experts recommend as an initial goal a weight loss of 10.0% of baseline over a 6-month period. For persons who need to therapeutically lose weight but struggle long and hard to slim down, weight-loss medications can be an adjunct to diet and exercise. For some obese persons, diet, exercise, and even medication are unsuccessful. If they are extremely obese (BMI, >40 kg/m²) or have a BMI between 35 and 40 kg/m² and one or more serious comorbid conditions, bariatric surgery (eg, gastroplasty, Roux-en-Y gastric bypass) may be appropriate.

Physical activity: The physical activity needed for improved health seems on the surface to be manageable for almost anyone: 30 minutes of moderate exercise 5 days a week. The activity can be broken up during the day as fits the person's schedule. Exercise generally improves circulation, increases high-density lipoprotein cholesterol (HDL-C) levels, and burns calories. Muscles are the primary disposal and storage site of glucose, and as exercise leads to more muscle and less fat, blood glucose tends to stabilize at a normal level. Encouragement and advice from their primary care physician can be crucial and can give the support and provide the information and skills that many people need to better manage metabolic syndrome.

Pharmacotherapy

If efforts at weight control and exercise do not succeed, medications can be effective in reducing risk in metabolic syndrome.

Hypertension: Weight loss, exercise, and a diet low in sodium offer a sound first approach for antihypertensive therapy. However, if these steps do not reduce blood pressure to an acceptable level, medication may be necessary. The exact blood pressure target for patients with metabolic syndrome is still debated, but a goal matching that recommended for patients with diabetes <130/80 mm Hg is appropriate. Recommendations of the seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure also apply to management of metabolic syndrome.⁴⁹

As an initial approach, a thiazide diuretic should be used in most cases of uncomplicated hypertension. Diuretic therapy can be used alone or in combination with a drug in the other classes of antihypertensives (eg, angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, B-blocker, calcium channel blocker). Findings in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) showed that therapy using a diuretic and a B-blocker was the best choice to lower blood pressure effectively. Among the patients in ALLHAT, about 25% met the criteria for metabolic syndrome.⁵⁰

Triglycerides, HDL-C: Strategies to decrease triglycerides and increase HDL-C incorporate (1) increased physical activity, (2) limited fat and alcohol intake, (3) limited dietary sugar and carbohydrates, and (4) smoking cessation. These lifestyle changes may need to be complemented by medications that can better control risk factors. Agents include 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors ("statins"), fibric acid derivatives, and niacin. A conclusion that all patients with metabolic syndrome need a statin is premature.

Glucose intolerance: Persons with impaired glucose tolerance (IGT, fasting blood glucose, 110 to 126 mg/dL) are at risk for diabetes, CVD, and metabolic syndrome. Annually, IGT carries a 1.0% to 10.0% rate of progression to diabetes. Medication to treat insulin resistance before diabetes occurs is controversial, but it is an area of high interest and active investigation. The Diabetes Prevention Program showed that metformin hydrochloride reduced diabetes risk by 31% in patients with IGT. Beyond metformin, thiazolidinediones can modify insulin levels as well as other parameters, most specifically triglyceride levels.⁵¹

Waist circumference: Weight loss and exercise are key to reducing visceral adiposity. However, according to the National Heart, Lung, and Blood Institute, a weight-loss medication may be appropriate for patients with a BMI of 27 to 29.9 kg/m² who have comorbid diseases or for those who have a BMI greater than 30 kg/m². Such medication should be used only as part of a comprehensive weight-reduction plan. The primary classes of weight loss drugs are appetite suppressants and nutrient absorption inhibitors. Sibutramine and orlistat, typically prescribed as single agents, are approved by the US Food and Drug Administration for long-term use. Before prescribing weight-loss agents, physicians

need to determine the risk-benefit status for the individual and decide if such a drug is appropriate. Once medication is started, the patient should be monitored carefully.

Prothrombotic state: Low dose aspirin (ie, 81 mg) taken daily is effective in lowering thrombotic risk.

Insulin sensitizers: Inflammation in vasculature can be reduced by a variety of approaches including diet, exercise, cardiovascular drugs, and insulin sensitizers. Statins and thiazolidinediones are being investigated for their potential role in the prevention and treatment of the inflammatory processes involved in the metabolic syndrome and CVD. Importantly, these different measures improve vascular function and reduce inflammation by distinct mechanisms. Therefore, combination therapy including lifestyle modifications and multiple drugs from separate classes might produce additive beneficial outcomes.⁵³

The definition of metabolic syndrome must be refined to better predict the occurrence of future cardiovascular events. The definitions provided by the WHO, NCEP-ATPIII, and IDF combine traditional risk factors and components of metabolic syndrome. A better understanding of the complex mechanism behind the metabolic syndrome will perhaps lead to better therapeutic strategies for its prevention and control. Drugs able to reduce insulin resistance, such as metformin and thiazolidinediones, already in the therapeutic armamentarium of type 2 diabetes, could be used in subjects with the metabolic syndrome as a preventive measure. To date, however, a first level management of the syndrome should consider life style changes such as increased physical activity, optimal weight maintenance and diet composition.

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Table-1: Diagnostic criteria for metabolic syndrome according to the WHO and the ATP III and IDF

Component	WHO (1998) diagnostic criteria (insulin resistance* plus two of the following)	ATP III(2001) diagnostic criteria (three of the following)	IDF (2005) diagnostic criteria (increased WC § plus any two of the following)
Abdominal/central obesity	Waist to hip ratio: > 0.90 (men), > 0.85 (women), or BMI > 30 kg per m ² ,	WC > 102 cm in men, > 88 cm in women	Table 2
Hypertriglyceridemia	≥150 mg/dL	≥150 mg/dL	≥150 mg/dL or on TG Rx
Low HDL cholesterol	< 35 mg/dL for men, < 39 mg/dL for women	< 40 mg/dL for men, < 50 mg/dL for women	< 40 mg/dL for men, < 50 mg/dL for women or on HDL-C Rx
High blood pressure	≥140/90 mm Hg or on hypertensive Rx	≥130/85 mm Hg on hypertensive Rx	≥130mmHg systolic or ≥85mm Hg diastolic or on hypertensive Rx
High fasting glucose	IGT, IFG, insulin resistance, or diabetes	≥110 mg/dL (includes diabetes) †	≥100 mg/dL
Microalbuminuria	Urinary albumin to creatinine ratio: 30 mg/g, or albumin excretion rate: 20 mcg/min		

Table-2: Ethnic specific values for waist circumference

Country/ Ethnic group	Waist Circumference*
European descent †	Male ≥94 cm Female ≥80 cm
South Asian (Chinese, Japanese and Asian- Indian) descent	Male >90 Female >80
South and Central American descent	Use South Asian cutoffs until more specific data are available
Eastern Mediterranean, Middle Eastern descent	Use European cutoffs until more specific data are available
Sub-Saharan African descent	Use European cutoffs until more specific data are available

*— Waist circumference measurement technique: Place measuring tape, holding it parallel to the floor, around abdomen at the level of the iliac crest. Hold tape snug but do not compress the skin. Measure circumference at end of normal expiration.

†— In the USA, the ATP III values (102 cm male and 88 cm females) are likely to continue to be used for clinical purposes

Table-3: Practical Advice for Lifestyle Interventions in Patients with Metabolic Syndrome ⁵²

Abnormality	Diet and physical activity interventions	Practical advice
Abdominal obesity	Reduce weight. Increase physical activity.	Reduce portion sizes to lower calorie intake. 30 minutes of moderate-intensity exercise daily.
Hypertriglyceridemia	Reduce weight Increase physical activity. Increase intake of low-glycemic-index	Reduce portion sizes to lower calorie intake. 30 minutes of moderate-intensity exercise daily. Replace refined carbohydrates (white bread, potatoes, foods. pasta) with legumes, whole grains, and monounsaturated fats (nuts, avocado, canola oil, olive oil).
	Reduce total carbohydrate intake. Increase omega-3 fatty acids. Limit alcohol consumption	Replace soda and juices with water, seltzer, and diet beverages. Eat fish at least once per week. Limit alcohol to no more than two drinks/day for men, or one drink per day for women.
Low HDL cholesterol level	Reduce weight Increase physical activity. Increase consumption of monounsaturated fats.	Reduce portion sizes to lower calorie intake. 30 minutes of moderate-intensity exercise daily. Eat fish, nuts, and avocados. Use olive or canola oils in salad dressing and for cooking.
High blood pressure	Stop smoking. Reduce weight Increase physical activity. Reduce saturated fat intake	Join a smoking cessation program. Reduce portion sizes to lower calorie intake. 30 minutes of moderate-intensity exercise daily Choose low-fat dairy products and reduce consumption of red meat, butter, and full-fat dairy products.
	Reduce sodium intake	Reduce sodium intake to no more than 2.4 g per day or 6 g per day of salt by using more herbs in cooking; read labels for sodium content; skip the salt shaker.
	Increase consumption of fruits and vegetables Increase low-fat dairy products.	Consume more than five servings of fruits and vegetables every day. Consume three servings of low-fat dairy products daily.
	Limit alcohol consumption	Limit alcohol to no more than two drinks/day for men and one drink per day for women.
High fasting glucose level	Reduce weight Increase physical activity. Reduce total carbohydrate intake; replace carbohydrates with monounsaturated fat.	Reduce portion sizes to lower calorie intake. 30 minutes of moderate-intensity exercise daily Replace refined grains with whole grains (oatmeal, brown rice, corn, and whole wheat) and monounsaturated fats(nuts, avocados, canola oil, olive oil).
	Increase dietary fiber (more than30 g per day).	Add legumes and fruit for soluble fiber.