# 50 *Metabolic Syndrome: Assessing Cardiometabolic Risk*

*YP Munjal, Anurag Saxena*

**Abstract:** The metabolic syndrome refers to a constellation of coronary heart disease risk factors, including obesity and abdominal fat distribution, disorders of glucose and lipid metabolism, and hypertension. Among the traditional risk factors, diabetes, hypertension, and abdominal obesity together account for approximately half of the risk of a first myocardial infarction, esp. in the Asian Indian population. 'Cardiometabolic risk' is a new entity that goes beyond metabolic syndrome to encompass a cluster of risk factors that may predispose individuals to CVD and type 2 diabetes mellitus. These risk factors, some of which are currently undermanaged in clinical practice, involve multiple pathways and physiological systems, and point to a need for a comprehensive management approach. Cardiometabolic risk factors tend to cluster. Assessment of the full spectrum of cardiometabolic risk must be done in every patient who has even one or two clinically evident risk factors. The latest trials show that tackling insulin resistance with thiozoladinediones is showing promise in patients with metabolic syndrome. Successful management of cardiometabolic risks depends on the physician's ability to identify all appropriate risk factors, as well as on the development of more comprehensive management options.

## INTRODUCTION

During the 20th century, public health policies promoting risk factor reduction, including exercise and smoking cessation programs, contributed to the decline in cardiovascular disease (CVD) death rates. Currently, however, high energy diet and a lack of physical activity appear to be fuelling the ongoing and expanding obesity and metabolic syndrome epidemics. As a result, both incident and prevalent CVD will likely continue to increase in the next decades with significant socioeconomic consequences. CVD patients with metabolic syndrome must be identified and managed aggressively to reduce both morbidity and mortality for what is in large part a preventable condition. The worldwide prevalence of the Metabolic Syndrome (MetS) has reached epidemic proportions and there is no evidence that this rapid growth will "plateau" in the coming years. ***Changes in human behavior and life-style observed over the last century, which have promoted a positive energy balance, weight gain, obesity and the progressive development of a dysmetabolic state, have resulted in a dramatic increase in the prevalence of the MetS worldwide.***

## DEFINITION AND CONSTITUENTS OF METABOLIC SYNDROME

The contemporary definition of the Metabolic Syndrome "refers to a cluster of metabolic abnormalities related to a state of insulin resistance which is often associated with a high-risk overweight/obesity phenotype. The major characteristics of metabolic syndrome include insulin resistance, abdominal obesity, elevated blood pressure, and lipid abnormalities (i.e., elevated

levels of triglycerides and low levels of high-density lipoprotein [HDL] cholesterol). 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 inhibitor1(PAI 1), elevated uric acid levels, microalbuminuria, and a shift toward small, dense particles of low-density lipoprotein (LDL) cholesterol."

The concept of the MetS viewed as precursor to the development of both type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) has progressively emerged with a formal recognition by the World Health Organization (WHO) in 1998 and the National Cholesterol Education Program Adult Treatment Panel III in 2001 (NCEP ATP III), which have recently proposed a formal definition of the MetS. The NCEP-ATP III identified six key components of the Metabolic Syndrome that are most closely related to cardiovascular diseases: abdominal obesity, atherogenic dyslipidaemia, hypertension, glucose intolerance/insulin resistance, proinflammatory state and prothrombotic state.[1]

According to the ATP III, patients with three or more of the clinical criteria (Table 50.1) have metabolic syndrome.[1] Recently, the ADA recommended that the glucose cutpoint that defines impaired fasting glucose should be lowered from = 110 mg/dL to = 100 mg/dL.[2] A subsequent consensus conference on the definition of metabolic syndrome suggested that this new cutoff should be used for metabolic syndrome as well.

Contrasting this the changes proposed with reference to ethnicity and consensus as postulated by IDF 2006 are given in Table 50.2.

**Table 50.2:** The 2006 International Diabetes Federation (IDF) definition of the metabolic syndrome

| |
|---|
| **According to the new IDF definition, for a person to be defined as having the metabolic syndrome, they must have:** |
| ***Central obesity*** (defined as waist circumference >/= 94 cm for Europid men and >/= 80 cm for Europid women, with ethnicity specific values for other groups) |
| **plus any 2 of the following 4 factors:** |
| • Raised TG level: >/= 150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality |
| • Reduced HDL-cholesterol: < 40 mg/dL (1.03 mmol/L) in men and < 50 mg/dL (1.29 mmol/L) in women, or specific treatment for these lipid abnormalities |
| • Raised BP: systolic BP >/= 130 or diastolic BP >/= 85 mm Hg, or treatment of previously diagnosed hypertension |
| • Raised fasting plasma glucose: FPG >/= 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes |
| If above 5.6 mmol/L or 100 mg/dL, an OGTT is strongly recommended, but is not necessary to define the presence of the syndrome. |

*TG = triglycerides; HDL = high-density lipoprotein; FPG = fasting plasma glucose; OGTT = oral glucose tolerance test*

## Cardiometabolic Risk

The term 'cardiometabolic risk' evolved from an enhanced understanding of established and emerging risk factors associated with a predisposition to cardiovascular and metabolic diseases. Cardiometabolic risk is defined as a cluster of modifiable risk factors and markers that identify individuals at increased risk for CVD (myocardial infarction, stroke, peripheral artery disease) and T2DM.[3] This cluster of risk factors includes those associated with the ATP III definition of metabolic syndrome, as well as other risk factors also identified in ATP III as significantly contributing to cardiometabolic morbidity[1] (Table 50.3).

**Table 50.3:** Cardiometabolic risk factors

| |
|---|
| **Cardiometabolic risk factors** |
| • Elevated blood pressure |
| • Abdominal Adiposity |
| • Low HDL-C |
| • Elevated triglycerides |

- Elevated blood glucose
- Smoking
- Elevated LDL-C
- Inflammatory markers
- Insulin resistance

---

The presence of the MetS is associated with an increased risk of coronary heart disease, myocardial infarction, and stroke in both sexes.[4] Malik, et al, determined that in subjects with more than three risk factors (which constitute metabolic syndrome in ATP III), the hazard ratio was 2.71 compared to subjects with no risk factors ($p < 0.0001$)[5] [Fig. 50.1]. This substantial increased risk of cardiovascular morbidity and mortality associated with the presence of the MetS appeared as independent of other important and potentially confounding factors, such as smoking, plasma LDL-cholesterol levels, and alcohol consumption.[6] In terms of pathophysiology, the association of metabolic abnormalities represents a highly atherogenic state promoting the formation and growth of atheroma plaques in arteries. It has been recognized that insulin-resistance/hyperinsulinaemia and the underlying consequences related to defects in insulin metabolism are associated with the presence of cardiovascular risk factors such as hypertriglyceridaemia, low HDL-cholesterol, hypertension, abdominal obesity, impaired fibrinolytic system capacity even in the absence of diabetes.

These findings underscore the need to consider the cardiovascular risk of individuals beyond the presence of diabetes, or intolerance to glucose with a specific attention to the presence of the features of the MetS. The risk of cardiovascular events conferred by the presence of the MetS was greater than the risk associated with any of the individual components, emphasizing the predictive value of this clinical entity in terms of cardiovascular complications.[7]

Abdominal obesity is considered to be more highly associated with metabolic risk factors than overall (subcutaneous) obesity.[8] The presence of intra-abdominal fat is also an independent predictor of coronary artery disease. Elevated waist and fasting plasma triglycerides concentration identify subjects at high risk of coronary artery disease and T2DM. Visceral fat is recognized as a source of inflammatory cytokines such as TNFα and interleukin-6 that have been associated with both insulin-resistance and increased risk of cardiovascular events.

Cardiometabolic risk not only involves multiple risk factors but also multiple physiologic systems. The endocrine system is a major piece of the cardiometabolic risk paradigm. Adipose tissue, previously believed to be an inert storage depot, is now recognized as an endocrine organ.[9] It secretes adipokines with endocrine functions and expresses receptors that enable it to respond to afferent signals from numerous hormones. Within the endocrine system, the renin-angiotensin system (RAS) is a network of hormones that regulates blood pressure. RAS is known to be present in human adipose tissue, thereby offering a potential link between obesity and hypertension, as well as the prothrombotic properties of CVD.[10] The immune system plays an integral role in terms of mediating inflammatory cytokines.[8] Adipose tissue secretes signaling molecules, like TNFα, IL6 and C-reactive protein (CRP). Conditions including obesity, diabetes, hypertension and atherosclerosis, accompanied by increase in these inflammatory markers and cytokines, have been shown to be predictive of both CVD and T2DM. Dyslipidemia represents the circulatory component of cardiometabolic risk. The newly identified endocannabinoid system plays a role in regulating satiety signals and food intake, thereby influencing body weight and abdominal adiposity.[11]

INTERHEART was the first major study looking at the relationship between risk factors and myocardial infarction according to age, gender, ethnic background, or geographic region. The INTERHEART study looked at more than 29,000 individuals in 52 countries worldwide (15,152 cases and 14,820 controls, age and sex matched). The study found that nine potentially independent risk factors, such as smoking, history of hypertension and diabetes, alcohol consumption, psychosocial factors, waist/hip ratio, dietary habits, physical activity,

apolipoproteins, and alcohol consumption, were all related to myocardial infarction. Taken together, these nine risk factors accounted for 90% of the population attributable risk in men and 94% in women. Interestingly, the association between the nine risk factors and myocardial infarction were observed irrespective of gender, age or ethnic/region of the world.[12]

Among original contributions of the INTERHEART study, the measurement of an anthropometric index of abdominal fat distribution, the waist/hip ratio, has been studied. Although the conventional measure of overall adiposity, the body mass index, has been found to be modestly associated with myocardial infarction, the risk was eliminated once the variation in abdominal obesity has been taken into account. These results emphasize the fact that we need to go beyond total obesity in the clinical evaluation of the risk associated with obesity and that, rather, we need to pay attention to where the adipose tissue is located. Moreover, the ratio of apolipoprotein B/apolipoprotein AI, which globally represents the proportion of atherogenic on cardioprotective particles, was found to be one the most powerful variables associated with myocardial infarction in multivariate analyses. This large case-control study has clearly demonstrated that some features of the metabolic syndrome such as elevated apolipoprotein B concentrations and abdominal obesity are independently associated with an increased risk of myocardial infarction.

Although results from this landmark study are very important, INTERHEART leaves us with very useful clinical lessons that could apply for everyone and everywhere in the world. It is now time to implement simple intervention strategies to change these potentially modifiable risk factors and, therefore, reduce the risk of myocardial infarction. Thus, an adequate examination and interpretation of these simple potentially modifiable risk factors, easily obtained in clinical practice, should translate a huge amount of relevant information related to heart disease.

### Assessment of Metabolic Syndrome

NCEP-ATP III has proposed simple clinical variables to identify individuals at risk of having the MeS. Among the five parameters (waist circumference, triglycerides, HDL-cholesterol, fasting glycaemia, blood pressure) that used to identify carriers of the MetS, the introduction of waist circumference rather than the body mass index has been a major conceptual leap, recognizing the greater role of abdominal rather than overall obesity as the most prevalent cause of the MetS in our phenotypical, sedentary population.[13] Furthermore, these new guidelines recognize the importance of elevated triglycerides and of reduced HDL-cholesterol concentrations as useful lipid markers of the presence of the atherogenic "dysmetabolic" milieu of MetS.

### Clinical Evaluation

The routine medical and family history helps to identify patients at risk for cardiovascular disease or diabetes mellitus. Questions about recent or past weight changes, and a brief diet and physical activity history, including occupational and leisure-time physical activity, are important. The patient should be asked to estimate how many hours a day he or she is sedentary. Questions about typical food intake and efforts to reduce dietary fat or other specific dietary changes allow the physician to estimate the patient's readiness to change life-styles habits.

The patient's height, weight, and blood pressure should be measured. Body mass index (BMI) should be determined by calculating weight (kg)/height ($m^2$), and waist circumference should be measured at the high point of the iliac crest at minimal respiration. Waist circumference appears to be a better predictor of cardiovascular risk than waist-to-hip ratio.[13] Patients suspected of having MetS should have a fasting glucose level and a fasting lipid profile level obtained. A euglycemic clamp or homeostasis model assessment is used in research studies to accurately assess insulin resistance, but is impractical for use in the clinical setting.

Fasting insulin levels and glucose challenge tests are indicators of insulin resistance but do not need to be measured in most situations because a fasting glucose level alone suffices for the definition of metabolic syndrome. If LDL cholesterol is normal, measuring levels of

apolipoprotein B is not necessary. New tests that measure LDL particle size are expensive and unnecessary, because low HDL cholesterol levels and high triglyceride levels predict small, dense LDL particles.

## Management of Metabolic Syndrome with CVD Risk

### *Treatment Strategies*

Given the critical role of insulin resistance in the development of both diabetes and CVD, the targeted treatment of insulin resistance continues to generate significant clinical and research interest. Recent evidence suggests that improving insulin sensitivity by means of life-style changes (including weight loss and increased physical activity) or by the use of the various pharmacological agents can reduce the risk of developing T2DM. In addition, there is increasing evidence that treating insulin resistance may also significantly limit CVD risk – both by directly improving insulin sensitivity and by improving many of the associated CVD risk factors that occur in those with insulin resistance.[14]

Currently, no randomized controlled trials specifically examining the treatment of metabolic syndrome have been published. Based on clinical trials, aggressive management of the individual components of the syndrome should make it possible to prevent or delay the onset of diabetes mellitus, hypertension, and cardiovascular disease.[15]

Both clinical and epidemiologic data support a strong association between insulin resistance and a 2- to 3-fold increase in CVD risk.[16] Targeting insulin resistance has been suggested not only for improving insulin action itself, but also for its potential impact on the associated components of the insulin resistance syndrome that likely contribute to CVD risk—including hypertension, dyslipidemia, glucose intolerance, and vascular, hemodynamic, and hemostatic abnormalities. Treating insulin resistance has been shown to have beneficial effects on several of the components of CVD risk that occur in those with insulin resistance, the metabolic syndrome, and/or diabetes. All patients diagnosed with metabolic syndrome should be encouraged to change their diet and exercise habits as primary therapy. Weight loss improves all aspects of the metabolic syndrome, as well as reduces all-cause and cardiovascular mortality. While many patients find weight loss difficult to achieve, exercise and dietary changes that can lower blood pressure and improve lipid levels will improve insulin resistance, even in the absence of weight loss. Weight loss and physical activity target not only glucose intolerance, but can also lower blood pressure, reduce levels of LDL cholesterol, and raise levels of HDL cholesterol. For patients whose risk factors are not reduced adequately by lifestyle changes, pharmacologic interventions to control their blood pressure and lipid levels are indicated. Use of aspirin and statins lowers C-reactive protein levels, but so does weight loss. Aggressive pharmacologic management of risk factors has been shown to be more effective than routine care in preventing cardiovascular disease in patients with T2DM.

Similarly, the insulin-sensitizing thiazolidinediones (TZD) improve glycemic control, have been reported to improve the characteristic dyslipidemia of diabetes, and may have favorable effects on other vascular and procoagulant abnormalities seen in insulin-resistant individuals.[17] TZD therapy may reduce markers of vascular inflammation, improve endothelial function, and limit thrombotic risk.

## Insulin Sensitizers in Metabolic Syndrome

Numerous reports during the last two years have focused on the potential impact of insulin-sensitizing therapies on CVD risk. Data from long-term studies with both pioglitazone and rosiglitazone reported improvements in dyslipidemia. Alfonso Perez, MD, and colleagues reported pooled data from clinical trials of pioglitazone that demonstrated reductions in triglycerides and increased HDL-cholesterol concentrations with therapy.[18] These investigators also reported improvement in the composition of lipid sub fractions—with reduced

concentrations of small dense LDL particles with pioglitazone therapy. Similar increases in LDL particle size were reported in African-American subjects treated with rosiglitazone.[19]

Studies of the impact of thiazolidinedione therapy on the increased thrombotic risk in diabetes were also reported. In vitro studies reported by Manish Khanolkar, et al, were the first to demonstrate a direct antiplatelet aggregatory effect with rosiglitazone therapy.[20] Simone Pampanelli discussed improved markers of coagulation and thrombosis in patients treated with pioglitazone, noting that these improvements appeared to be independent of improvements in glycemic control and suggesting a direct effect of insulin-sensitizing therapy.[21]

Several studies also reported the impact of insulin-sensitizing therapy on vascular behavior. Both pioglitazone and rosiglitazone appear to improve vascular reactivity, an effect likely mediated through endothelial cell signals. How these agents exert this beneficial effect is not currently known.[22] Despite the ever-larger base of evidence supporting a role for insulin-sensitizing therapy in managing CVD risk, no clinical outcome trial has been completed that specifically assesses TZD therapy or other treatments. Currently, several large clinical outcome trials have been done, including the PROactive trial, assessing the impact of TZD therapy. The PROactive trial has shown that pioglitazone significantly reduces the combined risk of heart attacks, strokes and death by 16 percent ($P = 0.027$).[23]

### Cardiometabolic Risk and Insulin Resistance—Where Are We Now?

Given the increasing evidence outlining the important role of insulin resistance on CVD risk and the even greater evidence of a direct benefit from therapy for insulin resistance, the impact of specific therapy on CVD risk remains uncertain. With the preponderance of evidence supporting a favorable effect, practitioners should consider early use of agents that target insulin resistance – particularly in patients with diabetes and the MetS at highest risk for CVD. In particular, use of these agents should be considered in any patient with clinical evidence of MetS, and may be of particular benefit in patients with lipid disorders (particularly low HDL levels), established CVD, or evidence of vascular inflammation suggesting the presence of unstable atherosclerotic plaque.

The clinical community awaits the results of long-term intervention trials designed to determine the full clinical benefit of therapy with agents such as TZDs. In the absence of these data, it is still clear that the treatment of insulin resistance offers significant potential and will likely emerge as an important component of treatment for the management of both CVD risk and glucose intolerance.

## REFERENCES


1. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285: 2486-97.
2. American Diabetes Association. Frequently Asked Questions About Pre-Diabetes. Available at http:/www.diabetes.org/pre-diabetes/faq.jsp
3. Sowers JR. Update on the cardiometabolic syndrome. Clin Cornerstone 2001;4:17-23.
4. Kendall DM, Sobel BE, Coulston AM, et al, for the PAIR Advisory Panel. The insulin resistance syndrome and coronary artery disease. Coron Artery Dis 2003;14:335-48.
5. Malik S, Wong ND, Franklin SS, et al. Impact of the metabolic syndrome on mortalitycoronary heart disease, cardiovascular disease and all causes in United States adults. Circulation 2004;110:1245-50.
6. Haffner SM, Valdez RA, Hazuda HP, Mitchell BD, Morales PA, Stern MP. Prospective analysis of the insulin resistance syndrome (syndrome X). Diabetes 1992;41:715-22.
7. Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 2001;24:683-9.
8. Lee YH, Pratley RE. The evolving role of inflammation in obesity and the metabolic syndrome. Curr Diabetes Rep 2005;5:70-5.
9. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. J Clin Endocrinol Metab 2004;89:2548-56.
10. Harte A, McTernan P, Chetty R, et al. Insulin-mediated up regulation of the rennin angiotensin system in human subcutaneous adipocyte is reduced by rosiglitazone. Circulation 2005;111: 1954-61.
11. Cota D, Marsicano G, Tschop M, et al. The endogenous cannabinoid systemeffects energy balance via central orexigenic drive and peripheral lipogenesis. J Clin Invest 2003;112:423-31.

12. Yusuf S, Hawken S, Ounpuu S, on behalf of the INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004;364:937-52.
13. Misra A, Wasir JS, Vikram NK. Waist circumference criteria for the diagnosis of abdominal obesity are not applicable uniformly to all populations and ethnic groups. Nutrition 2005;21:969-76.
14. Ford ES. Risk for all-cause mortality, cardiovascular disease and obesity associated with the metabolic syndrome: a summary of the evidence. Diabetes Care 2005;28:1769-78.
15. Reilley MP, Rader DJ. The metabolic syndrome: more than the sum of its parts? Circulation 2003;108:1546-51.
16. Lakka H-M, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total cardiovascular disease mortality in middle-aged men. JAMA 2002;288:2709-16.
17. Parulkar AA, Pendergrass ML, Granda-Ayala R, Lee TR, Fonseca VA. Nonhypoglycemic effects of thiazolidinediones. Ann Intern Med 2001;134:61-71.
18. Perez A, Khan M, Johnson T, Kurunaratne M. Effects of pioglitazone on lipid subspecies and subparticle profiles: Results from a double-blind, randomized study of pioglitazone HCl vs placebo in reducing or eliminating insulin requirement in subjects with type 2 diabetes. Program and abstracts of the 64th Scientific Sessions of the American Diabetes Association; June 4-8, 2004; Orlando, Florida. Abstract 593-P.
19. Banerji MA, Lebovitz HE, Dahong Y, Porter LE, Murdoch SJ, Brunzell JD. Rosiglitazone improves postprandial glycemia, insulin resistance and LDL buoyancy in African American subjects with impaired glucose tolerance. Program and abstracts of the 64th Scientific Sessions of the American Diabetes Association; June 4-8, 2004; Orlando, Florida. Abstract 501-P.
20. Khanolkar M, Thomas A, Singh N, Morris K, Evans LM. Effects of rosiglitazone on platelet aggregation. Program and abstracts of the 64th Scientific Sessions of the American Diabetes Association; June 4-8, 2004; Orlando, Florida. Abstract 556-P.
21. Pampanelli S, Rinaldi T, Perriello G, Brunetti P. Effects of pioglitazone on coagulation and thrombosis in comparison to gliclazide in patients wtih type 2 diabetes. Program and abstracts of the 64th Scientific Sessions of the American Diabetes Association; June 4-8, 2004; Orlando, Florida. Abstract 589-P.
22. Annaswamy R, Gehard Herman MD, Knauft W, Warren ML, Judy PF, Simonson DC. Effect of pioglitazone on insulin sensitivity, vascular reactivity and cardiovascular risk factors in Asian Indians. Program and abstracts of the 64th Scientific Sessions of the American Diabetes Association; June 4-8, 2004; Orlando, Florida. Abstract 1463-P.
23. New Results from the Landmark PROactive Trial: www.takeda.com/press/06061301.htm