

# Metabolic Syndrome: A Growing Clinical Challenge

Syed Amin Tabish

Sher-i-Kashmir Institute of Medical Sciences, Srinagar

## ABSTRACT

Metabolic Syndrome (MetS) is a complex disorder and an emerging clinical challenge. Introduced as Syndrome X by Reaven in 1988 and also termed insulin resistance syndrome, metabolic syndrome is recognized clinically by the findings of abdominal obesity, elevated triglycerides, atherogenic dyslipidemia – ie, low levels of high-density lipoprotein cholesterol (HDL-C), elevated blood pressure, high blood glucose and/or insulin resistance. Metabolic syndrome affects approximately 24% of the US adult population; according to the Third National Health and Nutrition Examination Survey (NHANES III) criteria. Although prevalence of obesity as defined by the World Health Organization (WHO) is relatively low in Asia compared to western countries, metabolic syndrome is growing into a significant public health problem. Future randomized controlled trials should be conducted in large numbers of patients with metabolic syndrome to evaluate the comparative benefits of different treatment approaches on mortality, cardiovascular events, and conversion to type 2 diabetes, glycemic regulation, lipid levels, and circulating thrombotic and inflammatory markers. [IJEM 2008;12(5):11-14 ]

**Key words:** Metabolic Syndrome X, diabetes mellitus, cardiovascular disease, PCOS

## INTRODUCTION

Metabolic Syndrome (MetS) is a complex disorder and an emerging clinical challenge. Introduced as Syndrome X by Reaven in 1988 and also termed insulin resistance syndrome, metabolic syndrome is recognized clinically by the findings of abdominal obesity, elevated triglycerides, atherogenic dyslipidemia – ie, low levels of high-density lipoprotein cholesterol (HDL-C), elevated blood pressure, high blood glucose and/or insulin resistance. Metabolic syndrome is also characterized by a prothrombotic state and a proinflammatory state.

Weight gain predisposes individuals to pivotal components of metabolic syndrome: obesity and insulin resistance. Therefore, the high prevalence of metabolic syndrome is largely attributed to the alarmingly high and increasing prevalence of obesity across the world.

A person can be defined as having the MetS if he/she has central obesity plus any two of the following four factors:

1. Serum triglycerides 1.7 mmol/L, or specific treatment for this lipid abnormality;

2. Serum HDL-cholesterol < 1.03 mmol/L in males and < 1.29 mmol/L in females, or specific treatment for this lipid abnormality
3. Blood pressure 130 mmHg systolic or 85 mmHg diastolic, or treatment of previously diagnosed hypertension;
4. Fasting plasma glucose 5.6 mmol/L, or previously diagnosed type 2 diabetes.

Pre-diabetes and the Metabolic Syndrome are highly prevalent conditions, affecting between one in six and one in three adults in most developed countries, and a similar proportion in the urban areas of many developing countries. Both conditions have a big public health importance because they are associated with a markedly increased risk of diabetes and cardiovascular disease (CVD), thus contributing to the epidemic proportions of these diseases.

Diabetes is an important CVD risk factor. Impaired glucose metabolism among cardiac patients is extremely prevalent, and research on the impact of dysglycemia on patients with CHD is expanding.

## Epidemiology

Metabolic syndrome affects approximately 24% of the US adult population; according to the Third National Health and Nutrition Examination Survey (NHANES III) criteria, about 47 million people have metabolic syndrome, including

*Address for correspondence:*

Dr. Syed Amin Tabish, Additional Professor,  
Sher-i-Kashmir Institute of Medical Sciences, Srinagar - 190011  
E-mail: amintabish@hotmail.com

44% of those in the 50-year age group. Metabolic syndrome is present in 10% of women and 15% of men with normal glucose tolerance; 42% and 64% of those with impaired fasting glucose; and 78% and 84% of those with type 2 diabetes. Most patients (> 80%) with type 2 diabetes have metabolic syndrome, but the converse is not necessarily true.

Given the widespread availability of fast foods in modern industrialized societies, environmental factors are often cited as causes of the American obesity epidemic. On the other hand, environmental factors do not play equally causative roles in all racial and ethnic groups. Populations that are genetically or otherwise susceptible include South Asians (Indian subcontinent), Southeast Asians (eg, Polynesian, Japanese), African-Americans (particularly African-American women), Mexicans, and Native Americans (eg, Pima Indians).

Metabolic syndrome (without type 2 diabetes) significantly increases the risk of coronary heart disease (CHD). Risk increased strikingly when type 2 diabetes developed. Notably, the presence of metabolic syndrome increased the risk of major coronary events irrespective of 10-year absolute coronary risk above or below 20%, the ATP-III threshold for initiating treatment to reduce low-density lipoprotein cholesterol (LDL-C) to levels of 100 mg/dL or below.

### MetS in Asia

Although prevalence of obesity as defined by the World Health Organization (WHO) is relatively low in Asia compared to western countries, metabolic syndrome is growing into a significant public health problem. Comparative studies indicate that metabolic responses to obesity may be greater in South and East Asians than their western counterparts at given Body Mass Indexes (BMIs). Higher percentage body fat in Asians at given BMIs and over-responsiveness to obesity may in part explain the phenomenon for which the underlying causes are not clear. Macronutrient composition and the quality of the diet are associated with the risk of metabolic syndrome. More research is needed to relate diet and metabolic syndrome in Asians.

Most prevalence data in literature used either the 2001 or the 2005 version of the NCEP-ATP III definition. According to the 2005 version; China, Taiwan, Hong Kong, and Thailand had similar prevalence rates ranging between 10-15%. India had strikingly high prevalence rates compared to the rest of Asia, approaching that of US population. Metabolic syndrome prevalence in Turkey and Iran was comparable to that of the US with a large excess in females. Considering the relatively low mean BMI and the low prevalence of obesity (BMI > 30) in east and south Asians, the magnitude of the metabolic syndrome prevalence is unusually high.

A series of comparative data pointed out that under fixed BMI or fatness, metabolic risk was much greater in South

Asians compared to Caucasians in terms of diabetes mellitus, insulin resistance and hypertriglyceridemia.

Metabolic syndrome is associated with increased risk of all cause mortality and cardiovascular events. Ford et al conducted a meta-analysis on 12 prospective studies primarily for Caucasian populations and demonstrated a 74% increase in cardiovascular risk.

It is accepted that the Mediterranean diet with fish, vegetable, fruit, red wine, and olive oil may protect against the development of metabolic syndrome. But up to this point, only a dozen of cross-sectional studies and a relatively small number of prospective studies have tried to determine the association between diet and the metabolic syndrome and comprised of primarily Caucasian studies (Framingham, WHS, NHANES, Boston, ATTICA-greece), one Japanese-Brazilian, and a few Iranian study.

Increased consumption of whole grains, dairy products, vegetables, fruits, calcium, magnesium, fiber from cereals, linoleic acid, and the maintenance of a healthy dietary pattern (high in fruits, tomatoes, poultry, legumes, cruciferous and green leafy vegetables, other vegetables, tea, fruit juices, and whole grains) have shown to be protective.

A low carbohydrate diet may be associated with a reduced risk of hypertriglyceridemia, low-HDL-C, but an elevated risk of hypercholesterolemia compared to the American Heart Diet.

### Pathogenesis

Complex, mutually reinforcing interactions between obesity and insulin resistance largely account for the pathogenesis of metabolic syndrome. Central pathophysiologic features of metabolic syndrome include:

- Insulin resistance, which may be linked to CHD;
- Atherogenic dyslipidemia, chiefly manifested as a triad of low HDL-C together with increases in triglycerides and small, dense LDL (sdLDL) particles — Fasting and postprandial chylomicrons and glycated LDL particles prone to oxidation are also frequently increased;
- Hypertension, which occurs frequently in persons with insulin resistance;
- A proinflammatory state, with increases in acute-phase reactants (eg, C-reactive protein [CRP]); and
- A prothrombotic state, with increases in plasminogen activator inhibitor (PAI-1) and fibrinogen.

Both the proinflammatory and prothrombotic states of metabolic syndrome derive largely from the secretory activity of adipose tissue, particularly intra-abdominal or visceral fat. Cytokines and other inflammatory markers or signaling molecules released by adipocytes — termed “adipokines”— include leptin, tumor necrosis factor alpha (TNF-alpha), interleukin-6, resistin, and adiponectin. Adiponectin levels are inversely related to fasting plasma insulin and glucose levels.

Both the proinflammatory and prothrombotic states

resulting from obesity may increase the risk of coronary events. CRP is a pivotal acute-phase reactant that is considered an index of inflammation and is associated with cardiovascular risk, particularly the risk of acute coronary syndrome.

Insulin resistance refers to a reduced ability to utilize insulin to control glycaemia. In insulin-sensitive individuals, insulin promotes glucose uptake in target tissues and inhibits glucose production by the liver. Insulin resistance is associated with abnormalities in glucose and lipid metabolisms, as well as with higher arterial blood pressure. These abnormalities are associated with an increased risk of cardiovascular disease (CVD) and are often present before the onset of overt type 2 diabetes.

In a meta-analysis of seven European population-based studies it was observed that in subjects with the MetS, 91% of men and 90% of women had hypertension; the proportions for hyperglycemia were 73% and 64%; for elevated triglyceride and/or low-HDL 77% and 77%, respectively. The overall prevalence of the MetS was 38% in men and 36% in women. The age-specific prevalence increased up to the age of 60 years and leveled off thereafter in men, while in women it increased up to the oldest age group.

Recent advances in the understanding of the molecular basis of genetic lipodystrophies have helped understanding of how adipose tissues disorders can cause MetS and its complications. This holds promise for elucidating pathways and mechanisms by which common disorders of obesity cause metabolic complications.

### Cormorbidity

There is a higher prevalence of metabolic syndrome than among the general population for people with:

- Obesity (eg. prevalence in children < 85th BMI percentile 0.1% & 29% BMI > 95th percentile)
- Diabetes (63-92% of people with T2DM)
- Cardiovascular disease (40-69%)
- Mental illness (42-63%)

Prevalence of MS increases with BMI in both men and women in blacks, Hispanic and whites (NHANES III and ATP-III criteria).

### Consequences/ associations

- Cancer
- Diabetes
- Cardiovascular disease
- Renal disease
- PCOS
- Fatty liver
- COPD

### Management

The key to management lies in prevention. Lifestyle choices must be inculcated at an early age. It is imperative to recognize that insulin resistance becomes apparent in

infancy, probably because of IUGR in pregnancy and catch-up growth in early infancy result in metabolic programming leading to higher risk of various components on MetS in adult life. Increasing evidence links maternal malnutrition, low birth weight and nutritional programming in early life, with the development of a constellation of metabolic (NAFLD) and cardiovascular diseases in adult life, with the common denominator of insulin resistance. Therefore, a balanced nutrition during pregnancy coupled with healthy lifestyle choices during childhood is essential.

### Looking ahead

Metabolic syndrome has emerged as a growing health problem and a major clinical challenge. Multidisciplinary treatment combining therapeutic lifestyle counseling with lipid-altering pharmacotherapy is recommended to prevent or delay the development of CHD and/or type 2 diabetes in patients with metabolic syndrome. Future randomized controlled trials should be conducted in large numbers of patients with metabolic syndrome to evaluate the comparative benefits of different treatment approaches on mortality, cardiovascular events, and conversion to type 2 diabetes, glycemic regulation, lipid levels, and circulating thrombotic and inflammatory markers.

### REFERENCES

1. Einhorn D, Reaven GM, Cobin RH, et al. American College of Endocrinology position statement on the insulin resistance syndrome. *Endocr Pract.* 2003;9:237-252.
2. Alexander CM, Landsman PB, Teutsch SM, Haffner SM. NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. *Diabetes.* 2003;52:1210-1214.
3. Expert Panel (ATP III). 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;285:2486-2497.
4. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). 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) final report. *Circulation.* 2002;106:3143-3421.
5. 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.
6. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome—a new worldwide definition. *Lancet.* 2005;366:1059-62.
7. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, Jr., Spertus JA, Costa F. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation.* 2005;112:2735-52.
8. Gu D, Reynolds K, Wu X, Chen J, Duan X, Reynolds RF, Whelton PK, He J. Prevalence of the metabolic syndrome and overweight among adults in China. *Lancet.* 2005;365:1398-405.
9. Kim HM, Kim DJ, Jung IH, Park C, Park J. Prevalence of the metabolic syndrome among Korean adults using the new International Diabetes Federation definition and the new abdominal obesity criteria for the Korean people. *Diabetes Res Clin Pract.* 2007;77:99-106.

10. Gupta R, Deedwania PC, Gupta A, Rastogi S, Panwar RB, Kothari K. Prevalence of metabolic syndrome in an Indian urban population. *Int J Cardiol.* 2004;97:257-61.
11. Ford ES. Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the U.S. *Diabetes care.* 2005;28:2745-9.
12. Chen HJ, Bai CH, Yeh WT, Chiu HC, Pan WH. Influence of metabolic syndrome and general obesity on the risk of ischemic stroke. *Stroke.* 2006;37:1060-4.
13. Ninomiya T, Kubo M, Doi Y, Yonemoto K, Tanizaki Y, Rahman M, Arima H, Tsuruyaya K, Iida M, Kiyohara Y. Impact of metabolic syndrome on the development of cardiovascular disease in a general Japanese population: the Hisayama study. *Stroke.* 2007;38:2063-9.
14. Iso H, Sato S, Kitamura A, Imano H, Kiyama M, Yamagishi K, Cui R, Tanigawa T, Shimamoto T. Metabolic syndrome and the risk of ischemic heart disease and stroke among Japanese men and women. *Stroke.* 2007;38:1744-51.
15. Chien KL, Hsu HC, Sung FC, Su TC, Chen MF, Lee YT. Metabolic syndrome as a risk factor for coronary heart disease and stroke: An 11-year prospective cohort in Taiwan community. *Atherosclerosis.* 2007;194:214-221.
16. Patel A, Barzi F, Woodard M, Ni Mhurchu C, Ohkubo T, Lam TH, Welborn T. An evaluation of metabolic risks for coronary death in the Asia Pacific region. *Diabetes Res Clin Pract.* 2006;74:274-81.
17. Dhingra R, Sullivan L, Jacques PF, Wang TJ, Fox CS, Meigs JB, D'Agostino RB, Gaziano JM, Vasan RS. Soft drink consumption and risk of developing cardio-metabolic risk factors and the metabolic syndrome in middle-aged adults in the community. *Circulation.* 2007;116:480-8.