Metabolic Syndrome: An Emerging Threat
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Abstract
Metabolic syndrome (MetS) is a multifaceted syndrome, which occurs frequently in the general population. It represents a cluster of metabolic abnormalities that include hypertension, central obesity, insulin resistance, and atherogenic dyslipidemia, and is strongly associated with an increased risk for developing diabetes and atherosclerotic and nonatherosclerotic cardiovascular disease (CVD). The pathogenesis of MetS involves both genetic and acquired factors that contribute to the final pathway of inflammation that leads to CVD. MetS has gained significant importance recently due to the exponential increase in obesity worldwide. Early diagnosis is important in order to employ lifestyle and risk factor modification. Here, we review the epidemiology, diagnostic criteria, pathogenesis and disease associations of MetS, and summarize existing management modalities.

Key-words: Metabolic syndrome, CVD, Insulin resistance, obesity, Dyslipidemia, Hypertension.

Introduction
The Metabolic Syndrome (MetS), also known as ‘insulin resistance syndrome’, ‘syndrome X’, ‘hypertriglyceridemic waist’, and ‘the deadly quartet’ is a constellation of an interconnected physiological, biochemical, clinical, and metabolic factors that directly increases the risk of atherosclerotic cardiovascular disease (ASCVD), Type 2 Diabetes Mellitus (T2DM)2,3. The diabetes consultation group of the World Health Organization (WHO)4 created the first internationally recognized definition of MetS in 1998. They defined MetS as the presence of insulin resistance (impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes mellitus) in addition to two of the following risk factors: obesity (waist-hip ratio or body mass index), hyperlipidemia (hypertriglyceridemia, low high-density lipoprotein [HDL] cholesterol), hypertension or microalbuminuria5.

Worldwide prevalence of MetS ranges from <10% to as much as 84%, depending on the region, urban or rural environment, composition (sex, age, race, and ethnicity) of the population studied, and the definition of the syndrome used5,6. In general, the International Diabetes Federation (IDF) estimates that one-quarter of the world’s adult population has the MetS7. Higher socioeconomic status, sedentary lifestyle, and high body mass index (BMI) were significantly associated with MetS. According to National Cholesterol Education Programme Adult Treatment Panel III (NCEP-ATP III) criteria, 2001 the prevalence of MetS varied from 8% to 43% in men and from 7% to 56% in women around the world8. Ponholzer et al. reported that there is high prevalence of MetS among postmenopausal women, which varies from 32.6% to 41.5%9. A Framingham Heart Study report indicated that a weight increase of ≥2.25 kg over a period of 16 year was associated with up to 45% increased risk of developing the MetS10, and it has been shown by Palaniappan et al. that each 11 cm increase in waist circumference (WC) is associated with an adjusted 80% increased risk of developing the syndrome within 5 years11.

MetS confers a 5-fold increase in the risk of type 2 diabetes mellitus (T2DM) and 2-fold the risk of developing cardiovascular disease (CVD) over the next 5 to 10 years12. Further, patients with the MetS are at 2- to 4-fold increased risk of stroke, 3- to 4-fold increased risk of myocardial infarction (MI), and 2-fold the risk of dying from such an event compared with those without the syndrome13 regardless of a previous history of cardiovascular events14.

Diagnostic Criteria
Since the initial description of MetS, several iterations of this definition have been proposed1 (Table-I). The most commonly used criteria for definition at present are from the WHO15, the European Group for the study of Insulin Resistance (EGIR)16, the NCEP ATP III17, and the AACE18. The MetS diagnostic criteria proposed for the MetS

| Table-I: Diagnostic criteria proposed for the MetS |
| --- |
| **Clinical measures** | WHO (1998)15 | EGIR (1999)16 | ATP III (2001)17 | AACE (2003)18 | IDF (2005)19 |
| **Insulin resistance** | IGT, IFG, or lower insulin Sensitivity* plus any 2 of the following | Plasma insulin >75th percentile plus any 2 of the following | None, but any 4 of the following or any 5 features | IGT or IFG plus any of the following based on the clinical judgment | None, but any 4 of the following or any 5 features |
| **Body weight** | Waist-hip ratio: Men: >0.90 & Women: >0.85 & BMI >30 kg/m2 | Waist circumference: Men: ≥94 cm & Women: ≥80 cm | Waist circumference: Men: ≥102 cm & Women: ≥88 cm | BMI ≥ 25 kg/m2 | Increased WC (population specific) plus any 2 of the following |
| **Lipids** | TGs ≥150 mg/dL & HDL-C <40 mg/dL or men or women | TGs ≥150 mg/dL & HDL-C <40 mg/dL in men or women | TGs ≥150 mg/dL & HDL-C <40 mg/dL in men or women | None, but any 4 of the following or any 5 features or on HDL-C Rx. HDL-C <40 mg/dL in women or <50 mg/dL in men or <50 mg/dL in women or on HDL-C Rx. | None, but any 4 of the following or any 5 features or on HDL-C Rx. HDL-C <40 mg/dL in women or <50 mg/dL in men or <50 mg/dL in women or on HDL-C Rx. |
| **Blood pressure** | ≥140/90 mm Hg | ≥140/90 mm Hg & on hypertension Rx | ≥130/85 mm Hg | ≥130/85 mm Hg | ≥130/85 mm Hg & on hypertension Rx |
| **Glucose** | IGT, IFG, or T2DM | IGT or IFG (but not diabetes) & for diabetes | ≤110 mg/dL (includes diabetes) | IGT or IFG (but not diabetes) | ≤100 mg/dL (includes diabetes) |
| **Other** | Microalbuminuria, urinary creatinine ratio of >5 mg in men or albumin:creatinine ratio of ≥3 mg/m | Other features of insulin resistance | Other features of insulin resistance** |

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Insulin Resistance is defined as a proinflammatory state is a hallmark of MetS. The discovery of endocrine, autocrine, and paracrine signals to mediate the multiple processes including insulin sensitivity measured under hyperinsulinemic euglycemic conditions, glucose uptake below lowest quartile for background population under investigation.

** In 2003, the American Diabetes Association (ADA) changed the criteria for IFG tolerance from >110 mg/dl to >100 mg/dl [10].

*** Includes family history of type 2 diabetes mellitus, polycystic ovary syndrome, sedentary lifestyle, advancing age, and ethnic groups susceptible to type 2 diabetes mellitus.

**Pathophysiology**

There is a wide variation in geographic distribution of MetS. Recent ‘catch up’ in the developing world emphasize the importance of environmental and lifestyle factors such as the consumption of excess calories and lack of physical activity as being major contributors. Visceral adiposity has been demonstrated to be a primary trigger for most of the pathways involved in MetS, thus stressing the importance of a high caloric intake as a major causative factor. Of all the proposed mechanisms, insulin resistance, neurohormonal activation and chronic inflammation appear to be the main players in the initiation, progression and transition of MetS to CVD (Figure-1). Insulin resistance-mediated increase in circulating free fatty acids (FFAs) is believed to play a pivotal role in the pathogenesis of MetS. The discovery of endocrine and immune properties of adipocytes has provided further mechanistic insights into the development of MetS. Adipokines released from visceral adipose tissue have been shown to be associated with MetS and CVD. Activation of various proatherogenic pathways in MetS culminates in a final common pathway of inflammation that eventually leads to clinical manifestations of MetS.

![Figure-1: Pathophysiologcal Mechanisms in Metabolic Syndrome](image)

**Associations of Metabolic Syndrome**

**Abdominal Obesity:** The “obesity epidemic” is principally driven by an increased consumption of cheap, calorie-dense food and reduced physical activity. With obesity and progressive adipocytes enlargement, the blood supply to adipocytes may be reduced with consequent hypoxia. Hypoxia has been proposed to be an inciting etiology of necrosis and macrophage infiltration into adipose tissue that leads to an overproduction of biologically active metabolites known as adipocytokines. Adipocytokines integrate the endocrine, autocrine, and paracrine signals to mediate the multiple processes including insulin sensitivity, oxidant stress, energy metabolism, blood coagulation, and inflammatory responses which are thought to accelerate atherosclerosis, plaque rupture, and atherothrombosis.

**Insulin Resistance:** Insulin Resistance is defined as a pathophysiological condition in which a normal insulin concentration does not adequately produce a normal insulin response in the peripheral target tissues such as adipose, muscle, and liver. Under this condition, pancreatic beta cell secretes more insulin (i.e., hyperinsulinemia) to overcome the hyperglycemia among insulin-resistant individuals. Although hyperinsulinemia may compensate for insulin resistance to some biological actions of insulin, that is, maintenance of normoglycemia, however, it may cause an overexpression of insulin activity in some normally sensitive tissues. This accentuation of some insulin actions coupled with a resistance to other actions of insulin results in the clinical manifestations of MetS. An inability of the pancreatic beta cells over time to produce sufficient insulin to correct the worsening tissue insulin resistance leads to hyperglycemia and overt T2DM.

**Dyslipidemia:** This dyslipidemia is characterised by a spectrum of qualitative lipid abnormalities reflecting perturbations in the structure, metabolism, and biological activities of both atherogenic lipoproteins and antiatherogenic HDL-C which includes an elevation of lipoproteins containing apolipoprotein B (apoB), elevated TGs, increased levels of small particles of LDL, and low levels of HDL-C. Insulin resistance leads to an atherogenic dyslipidemia in several ways. These anomalies are closely associated with an increased oxidative stress and an endothelial dysfunction, thereby reinforcing the proinflammatory nature of macrovascular atherosclerotic disease.

**Hypertension:** Essential hypertension is frequently associated with the several metabolic abnormalities, of which obesity, glucose intolerance, and dyslipidemia are the most common.

**Hypercoagulable State:** A proinflammatory state is characterized by elevated circulating cytokines and acute-phase reactants (e.g., CRP). Further, a prothrombotic state signifies anomalies in the procoagulant factors, that is, an increase in fibrinogen, factor VII and factor VIII as well as the antifibrinolytic factor (PAI-1), platelet abrasions, and endothelial dysfunctions.
Systemic Effects of Metabolic Syndrome

The key sign of metabolic syndrome is central obesity, also known as visceral, male-pattern or apple-shaped adiposity. It is characterized by adipose tissue accumulation predominantly around the waist and trunk. Other signs of metabolic syndrome include high blood pressure, decreased fasting serum HDL cholesterol, elevated fasting serum triglyceride level, impaired fasting glucose, insulin resistance, or prediabetes. Associated conditions include hyperuricemia; fatty liver (especially in concurrent obesity) progressing to nonalcoholic fatty liver disease; polycystic ovarian syndrome in women and erectile dysfunction in men; and acanthosis nigricans (Table II). MetS is also closely related to several diseases such as IHD, CVD/Stroke, Obstructive Sleep Apnea, Obesity Hyperventilation Syndrome, Gout, Psoriasis, Subfertility, Depression and various cancers (Figure-2).

Table-II: Systemic effects of MetS.

| Renal          | Microalbuminuria, hypofiltration, hyperfiltration, glomerulonegaly, focal segmental glomerulosclerosis, and chronic kidney disease |
|--------------|---------------------------------------------------------------------------------------------------------------------------|
| Hepatic       | Increased serum transaminase, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), hepatic fibrosis and cirrhosis |
| Skin          | Acanthosis nigricans, lichen planus, systemic lupus erythematosus, burn-induced insulin resistance, psoriasis, androgenetic alopecia, skin tags, skin cancer and acne inversa |
| Ocular        | Nondiabetic retinopathy, age related cataract-nuclear, cortical, posterior subcapsular; central retinal artery occlusion, primary open angle glaucoma, oculomotor nerve palsy and lower lid entropion |
| Sleep         | Obstructive sleep apnea (OSA) |
| Reproductive  | Hypogonadism, polycystic ovarian syndrome (PCOS) and erectile dysfunction |
| Cardiovascular| Coronary heart disease (CHD), myocardial infarction (MI) and stroke |
| Cancers       | Breast, pancreas and prostrate |

Management

MetS is a state of chronic low-grade inflammation with profound systemic effects. Clinical identification and management of patients with MetS are important to begin efforts to adequately implement the treatments to reduce their risk of subsequent diseases. Effective preventive approaches include lifestyle changes, primarily weight loss, diet, and exercise, and the treatment comprises the appropriate use of pharmacological agents to reduce the specific risk factors. Pharmacological treatment should be considered for those whose risk factors are not adequately reduced with the preventive measures and lifestyle changes. Most physicians treat each component of MetS separately, laying a particular emphasis on those components that are easily amenable to the drug treatment. The goals of therapy are to reduce both a short-term and lifetime risk. The presence of the MetS per se indicates a higher lifetime risk. Lifestyle modification treatment should be delivered by a multidisciplinary approach and a team composed of physicians and nonphysician health professionals, such as dieticians or professionals with a master degree in exercise physiology, behavioural psychology, or health education.

Weight Reduction: Four therapies can be used for weight reduction: calorie restriction (e.g., 500 kcal/d deficit), increased physical activity, behavioural modification, and, in appropriate patients, FDA-approved weight-reducing drugs. The effective and healthful methods for the long-term weight loss are reduced-energy diets, consisting of a modest 500 to 1000 calories/day reduction. Current physical activity guidelines recommend practical, regular, and moderate regimes for exercise. The standard exercise recommendation is a daily minimum of 30 minutes of moderate-intensity physical activity. However, a preference is given to 60 minutes of moderate-intensity brisk walking to be supplemented by other activities. The emphasis in behavioural change should include the benefit of social support, stress management, the value of a regular exercise regimen, and an improvement in eating habits. The National Institutes of Health guidelines for the treatment of obesity recommend a consideration of pharmaceutical therapy for weight loss for the individuals with a BMI of at least 30 kg/m² or for those with a BMI of at least 27 kg/m² and comorbidities associated with their excess weight. Pharmacological approaches to weight loss include two main classes: appetite suppressants and inhibitors of nutrient absorption. A single agent is generally recommended and an average weight loss ranges greatly from 5% to 10% of initial weight. Appetite suppressants include phenetermine derivatives and sibutramine. Orlistat (an inhibitor of gastrointestinal lipase) is the only nutrient absorption inhibitor currently available. It prevents absorption of up to 30% of the fat consumed and must be taken at the time of consumption. Surgery is recommended for the individuals who do not respond to weight loss diet or medications, are extremely obese (BMI > 40 kg/m²), or if they have a BMI > 35 to 40 kg/m² and one or more

Figure-2: Metabolic Syndrome with its associated risk factors and diseases
comorbid conditions\textsuperscript{45}. Improvements in the metabolic profile have been documented presumably due to the redistribution of adiposity\textsuperscript{46}. Bariatric surgery techniques using laparoscopic adjustable banding of stomach along with Roux-en-Y and other forms of gastric bypass are now favoured for the severe and morbid obesity\textsuperscript{47}.

**Dyslipidemia:** The guidelines recommend that the LDL-C goals be set at less than 130 mg/dL with the option of targeting less than 100 mg/dL in the moderately high-risk individuals. Target goals should be set at an LDL-C less than 100 mg/dL in the high-risk patients with the option of aiming for less than 70 mg/dL in the "very high-risk" patient\textsuperscript{48}. The goal for the non-HDL-C is 30 mg/dL greater than LDL-C. Statins are considered to be the most effective class of drugs for reducing the LDL-C concentrations due to their minimal drug-drug interactions and side effects\textsuperscript{49}. Niacin has favourable effects on essentially all of the abnormalities of the metabolic dyslipidemia. It is considered the most effective agent for raising HDL-C (15 to 35%) and increasing HDL particle size\textsuperscript{50}. Niacin significantly lowers TGs (20 to 50%) and LDL-C (5–25%)\textsuperscript{49}. The two fibrates currently used clinically are gemfibrozil and fenofibrate, both of which can lower TGs by 25% to 30% with the greater reductions in individuals that are hypertriglyceridemic. Fibrates further increases HDL-C by 5–15% and reduces LDL-C by 0–30\%\textsuperscript{51}.

**Hypertension:** It has been proposed that angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) should be the first-line classes of agents in the MetS, especially in the setting of diabetes or CKD\textsuperscript{52}.

**Insulin Resistance and Hyperglycemia:** In MetS, patients with IFG (or IGT if assessed), weight reduction, increased physical activity, or both will delay (or prevent) the onset of T2DM\textsuperscript{53}. In addition, metformin\textsuperscript{53}, thiazolidinediones\textsuperscript{54}, and acarbose\textsuperscript{55} will lower the risk of T2DM in people with IFG or IGT.

**Hypercoagulable State:** Measurement of CRP is the most practical way to assess the presence of an inflammatory state. An elevated CRP (≥3 mg/L) is an emerging risk factor for CVD\textsuperscript{56}. Several drugs used to treat the other metabolic risk factors have been reported to reduce the CRP levels (e.g., statins, nicotinic acid, fibrates, ACE inhibitors, and thiazolidinediones)\textsuperscript{56}.

**Nutraceuticals in the management of MetS:** Dietary supplements that provide health benefits in addition to basic nutritional value are termed nutraceuticals. Various natural compounds derived from plant extracts, spices, herbs and essential oils (Turmeric, Garlic, Cinnamon, Neem, Cumin, Ginger, Grapes, Onions etc) have demonstrable benefit in the management of patients with MetS\textsuperscript{1}.

**Conclusion**
MetS is a global epidemic and an established risk factor for atherosclerotic and nonatherosclerotic CVD. Significant variations exist in the diagnostic criteria and definition of MetS, which represent a temporal change in the understanding of this disease. Various stimuli culminating in a state of chronic inflammation seem to be the main pathophysiological drivers for MetS. Existing therapies to tackle various components of MetS are limited by various factors. Firstly, the existence of only a handful of medications that have been shown to have a convincing effect on long-term outcomes makes the choice of therapy challenging. Secondly, the chronic nature of the components of MetS warrant prolonged and often indefinite use of various medications such as statins, leading to an increased burden of drug-related adverse effects and patient noncompliance. In this context, the development of nutraceuticals that are readily available and with minimal side effects may represent an area of promise in the development of novel therapies.

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