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Metabolic Syndrome: Practice Essentials, Background, Pathophysiology

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Abstract

Metabolic syndrome (MetS) is a *cluster of metabolic disorders* and diagnosed with increased blood pressure, raised blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels. These metabolic disorders collectively or independently, increases the risk of an individual for developing cardiovascular disease (CVD), diabetes mellitus, and vascular or neurological complications.

Multiple definition of MetS has been proposed by the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III), the International Diabetes Federation (IDF), and the World Health Organization (WHO). All international agencies focus on *majorly five medical conditions,* which are also used as *diagnosis guidelines* by health practitioner, viz.abdominal obesity/ waist circumference, high blood pressure, abnormal high fasting plasma glucose, elevated serum triglycerides and low HDL.

Major risk factor for MetS - are obesity, physical inactivity, atherogenic diet; smoking, hypertension, elevated LDL/low HDL cholesterol, family history of premature coronary heart disease, insulin resistance, glucose intolerance, stress and pro-inflammatory state. The existence of MetS confers an additional risk for CVD. The more components of risk factors cause high CVD risk and mortality.

According to National Heart, Lung, and Blood Institute, "a person with metabolic syndrome is twice as likely to develop heart disease and five times as likely to develop diabetes as someone without metabolic syndrome. Lifestyle change and weight loss are considered as primary target of intervention for MetS; followed by secondary intervention which includes medication to treat existing risk factors like blood pressure, lipids, and blood glucose levels.

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Introduction

Metabolic syndrome (MetS), also known as Syndrome X, Deadly quartet, Reaven's syndrome. It is a disorder of energy use and storage and finding suggest that approximately 20-25% of the world population are suffering from MetS. Individuals with metabolic syndrome are at higher risk to develop cardiovascular disease, stroke and disease related to fat deposition in artery walls. Finding suggest that, people with MetS has double the chance to develop heart disease or/and five times as likely to develop diabetes with people without the syndrome or/and three times as likely to have a heart attack or stroke [1-4].

The prevalence of MetS increases with age, region, population and varies widely depending on the definition used for treatment strategy (given by NCEP AATP III/IDF/WHO). According to National Health and Nutrition Examination Survey (NHANES), prevalence of MetS in the US adults aged 18 years or older, rose by more than 35% from 1988-1994 to 2007-2012, increasing from 25.3% to 34.2%. Approximately 7% of this population includes teens, of which nearly 7% were overweight and 29% were obese adolescents. Also nearly 40% of people over age 60 meet the criteria of having MetS [5-8]. The primary reason for developing MetS includes; overweight/ obesity, ethnicity, physical inactivity, genetic factors and aging [2,9].Clinically MetS syndrome is diagnosed on the following criteria and if the individualis positive for three or more of the following measurements, is treated as positive syndrome patients [1,10-12]:

- Abdominal obesity/waist circumference (≥94-102 cm in men or ≥80-88 cm in women)
- High Blood pressure (≥130/85 mm Hg)
- Abnormal fasting glucose (≥100 mg/dL)
- Elevated Triglycerides (≥150 mg/dL)

- Low HDL (Males <40 mg/dL; Females<50 mg/dL)

Multiple attempts have been made to craft a clinical definition or diagnostic criteria for the syndrome, yet no standardization exists. The first classification was given by World Health Organization (WHO) in 1998 (Table1) [13]. According to WHO, essential criteria for MetS were: impaired glucose tolerance, diabetes mellitus, and insulin resistance and PLUS any of these two: Draw backs in the WHO Definition: BMI is not a reliable measure to obesity (does not show the difference between excess fat and muscle) and microalbuminuria is very rarely found in absence of diabetes. Later on in 2001-02, NCEP (National Cholesterol Education Program-Table 2) ATP (Adult Treatment Panel) III drafted new guidelines as mentioned in Table 2 [14] and patients must meet three of five criteria for metabolic syndrome to be recognized: Surprisingly, NCEP didn't take an account for ethnic consideration in the cut-off points which play vital role in diagnostic criteria.

In 2005-06, the International Diabetes Foundation (IDF) defines the MetS, according to which central obesity (defined by waist circumference) and ethnicity is an essential component for diagnosis of the syndrome along with any two of the following factors (Table 3) [15]: The IDF definition is universally accepted and simple to use clinically with clear cut off points, and considering different ethnic groups.

Risk Factors for Metabolic Syndrome

National Cholesterol Education Program ATP III guidelines (2005) suggest that, there are multiple factors that increase the likelihood of acquiring MetS. These factors were classified into *underlying, major, and emerging risk factors*. *Underlying riskfactors* for CVD are obesity (especially abdominal obesity), physical inactivity, and atherogenic diet; the *major riskfactors* are cigarette smoking, hypertension, elevated LDL cholesterol, low HDL cholesterol, family history of premature coronary heart disease (CHD), and aging; and the *emerging risk factors* include elevated triglycerides, small LDL particles, insulin resistance, glucose intolerance, pro-inflammatory state, and pro-thrombotic state [12,16-18].

The above-mentioned risk factors can be also classified on the basis of - Non-modifiable, behavioral and physiological risk factors:

- **Non-modifiable risk factors** include age, sex, race, and family history of CVD, which can identify high-risk populations
- **Behavioral risk factors** include sedentary lifestyle, unhealthful diet, heavy alcohol or cigarette consumption.
- **Physiological risk factors** include hypertension, obesity, lipid problems, and diabetes, which may be a consequence of behavioral risk factors.

Markers of Metabolic Syndrome

Based on the risk factors multiple biological markers are suggested for diagnosis of MetS such as those related to adipose tissue (percentage of abdominal fat using digital tomography, blood levels of leptin, adiponectin), other markers of dyslipidemia (apolipoprotein B or LDL/HDL), insulin resistance (oral glucose tolerance test) endothelial dysfunction (measured by the vasodilatory response in the humeral artery), inflammation markers (C-reactive protein, TNF-a, IL-6, IL-8) or thrombosis markers (high fibrinogen or plasminogen activator inhibitor-1) [19,20].

Component	Measurement technique
Abnormal body fat	Central fat distribution (CT/MRI) General Body fat distribution (DEXA) Adipose tissue marker: adiponectin and leptin Liver fat content
Atherogenic dyslipidemia	Lipid Profile: triglycerides, HDL ApoB and Small LDL particles
Hyperglycemia/Insulin resistance	Oral Glucose Tolerance Test (OGTT) Fasting insulin/proinsulin levels
Vascular or endothelial dysfunction	Blood pressure Microalbuminuria
Pro-inflammatory Marker	C reactive proteins Inflammatory cytokines (TNF alpha and IL-6)

Assessment of Risk Factor/Components of Metabolic Syndrome

Upper-body obesity

Most persons with the MetS are categorically obese. Obesity commonly assessed by a single measure, the Body Mass Index (BMI), which uses a mathematical formula based on a person's height and weight. Persons with a BMI ranging from 25 to 29.9 are considered overweight and greater than of 30 and above are considered obese. Individual's with predominant upper-body obesity are most prone to MetS and fat deposition can be either in the intraperitoneal (visceral) or subcutaneous region of the body. Both type of fat depositions are associated with MetS, however upper body sub-cutaneous fat deposition is more risky for developing syndromes. Contrary to upper body fat deposition, lower body fat deposition is observed in the lower side of body, it is also known as gluteo-femoral obesity or lower body obesity. This type of obesity is predominant in women, however can be found in men too and can be also a contributing factor for MetS [15,21,22].

Elevated blood pressure

Elevated blood pressure is another important component of the MetS. Quite a few mechanism have been proposed to explain the co-relation between elevated blood pressure and obesity (and caloric excess). Insulin resistance and reduced blood flow to different

Table 1: WHO Proposed Diagnostic Criteria for Metabolic Syndrome.

Diagnostic Criteria (any 3 below)	Defining Points
Hypertension	BP >140/90 mmHg
Dyslipidemia	High plasma TGs (>1.7mmol/L)
	Low HDL cholesterol (men <0.9, women <1.0 mmol/L)
Central or General obesity	Waist to hip ratio >0.9 in men, >0.85 in women
	And/or BMI >30
Microalbuminuria	Urinary albumin excretion rate ≥ 20ug/min or
	albumin: creatinine ratio ≥ 30mg/g

Table 2: NCEP ATP III Proposed Diagnostic Criteria for Metabolic Syndrome.

Diagnostic Criteria (any 3 below)	Defining Points
Elevated waist circumference	Men >102 cm (>40 in)
	Women >88 cm (>35 in)
Elevated Triglycerides	>150 mg/dL
Reduced HDL cholesterol	Men <40 mg/dL
	Women <50 mg/dL
Elevated Blood pressure	130/ 85 mm Hg (systolic/diastolic)
Elevated fasting glucose	>100 mg/dL

Table 3: Proposed Diagnostic Criteria for Metabolic Syndrome.

Diagnostic Criteria (any 3 below)	Defining Points
Obesity	Waist circumference BMI ≥ 30kg/m^2 Ethnic/Race
Raised Triglycerides	>150 mg/dL
Low HDL cholesterol	Men <40 mg/dL Women <50 mg/dL
Elevated Blood pressure	130/ 85 mm Hg (systolic/diastolic)
Impaired fasting glucose	>100 mg/dL

parts of body due thickening of the arterial wall, plaque formation (since heart has apply more pressure/force to pump blood to reach different parts of the body), along with this there is an enhanced renal re-absorption of sodium, high intra-vascular volume, and activates renin–angiotensin system. These factors act in conjunction and leads to increase in blood pressure [17].

Elevated Glucose levels/Hyperglycemia

Patients with metabolic syndrome have slightly elevated plasma glucose, characterized by fasting glucose in pre-diabetic individuals with range of 100–125 mg/dL or post-prandial level of 140–199 mg/dLor fasting glucose ≥126 mg/dL or a postprandial level ≥200 mg/dL in diabetic patient. The primary cause of hyperglycemia in patients with MetS is insulin resistance (when cells of the liver, adipose/fat tissue become less sensitive and eventually resistant to insulin) or beta-cell dysfunction (pancreatic cell - glucose intolerance). Hyperglycemia typically is not the first indication of MetS, but develops as a later sequelae [4,23].

Atherogenic Dyslipidemia

Most individuals with MetS also exhibit atherogenic dyslipidemia and is characterized by elevated triglyceride levels (>185 mg/dL) and reduced HDL cholesterol levels (men, <40 mg/dL; women, <50 mg/dL) which is due to impaired insulin signaling. Additionally, due to impaired signaling, lipid/fat start deposition within the artery and leads to plaque formation, which is usually has a cholesterol-rich core. Once this plaque is dislodged/rupture, individual suffers from acute cardiovascular events like myocardial infarction or stroke [9,24].

Metabolic Syndrome and Cardiovascular Disease

Individuals or patients with MetS are significantly at higher risk of getting CVD. A vigilant observation of initial symptoms/markers for metabolic disorder or risk factor analysis can also predict the population who are prone to CVD or having a chance to develop CVD. In a study, Framingham investigators analyzed whether the MetS conveys an incremental risk beyond the usual risk factor and finding suggest that, age adjusted cardiovascular events like cardiac ischemia, stroke, arrhythmia etc. are linearly co-related to hypertension and the risk is even higher or situation get worse in individuals who also have impaired glucose tolerance. Further, analysis suggest that MetS alone can predicted 25% of all new onset of CVD patients. Various investigators and agencies have develop algorithm for evaluation of individual risk factor as well as by adding new or multiple–risk factor in algorithm. Some of the models are: (1) the standard Framingham algorithm, (2) NCEP ATP III metabolic syndrome risk factors alone, (3) metabolic syndrome risk factors: age, (4) usual Framingham risk factors: unique metabolic syndrome risk factors (obesity, triglycerides, glucose), and (5) usual Framingham risk factors: metabolic syndrome as a single variable. Analysis of these models suggest that, majority of the risk factor for MetS are captured by age, obesity, diabetes, blood pressure, total cholesterol, and HDL cholesterol [17,24,25].

Kuopio Ischemic Heart Disease Risk Factor Study- KIHD, a population based prospective cohort of 1209 Finnish men, aged between 42–60years at baseline (from period of 1984-1989), who were initially free from CVD, cancer and diabetes. These individuals were followed-up to 11.4 years and finding suggest that, men with MetS as defined by NCEP were have a higher risk of 2.5 time more likely to die of CHD. Similar finding were reported in another study done 4400 patients aged range 35-70 years from Finland and Sweden using WHO criteria. Outcome of the study suggest that, risk of getting CHD or stroke was increased by three fold in individuals with MetS. Above finding suggest that, MetS can serve as initial marker for onset or can be used as diagnosed criteria for CVD [26].

Managing Metabolic Syndrome

Different approaches have been projected to prevent the development of MetS. For rapid and fast management of MetS primary intervention focus on lifestyle changes, weight reduction, BMI < 25, a healthy reduced calorie diet and increased aerobic/physical activity. Secondary intervention includes pharmacological therapy focusing to treat existing risk factors like management of blood pressure (anti-hypertensive drugs - Angiotensin converting enzyme inhibitors), abnormal lipid levels (statins, fibrates), blood glucose (metformin, thiazolidinediones) etc. Along with primary and secondary interventions following steps can be taken in account for improve adherence with individual suffering from MetS:

a) Focus on patient: Make simpler medication regimens, encourage for increase in physical activity and aerobics, and include good counseling technique with reinforce and reward adherence. Provide easy, explicit instruction to the patient with patient involvement through self-monitoring.

b) Focus on physician/trainer/family: Planning or structured training to given physician/trainer/family members for standardize treatment plan or in case individual requirement is needed, with feedback from the past performance to show change and implement new plans for future care.

Focus on Health delivery system: All plans during the course of treatment focus on lipid management, weight loss and increase physical activity which can be managed by lipid clinics, aerobics sessions by trainers/ nurses. Utilize individual case management by nurses

Conclusions

In summary, the central features of the metabolic syndrome are obesity, insulin resistance, visceral adiposity, atherogenic dyslipidemia and endothelial dysfunction. These conditions are interrelated and share common mediators, pathways and pathophysiological mechanisms. MetS have adverse social-economic impact on individual as well as to care givers. MetS lead to the poor quality life and impairs day to day functioning. Despite the enduring controversy about whether the notion of metabolic syndrome is useful, it distinctly defines specific pathophysiological mechanisms that connect the central features. Consideration of metabolic syndrome as a specific

entity allows for research on the genetic basis for susceptibility to this syndrome, a better understanding of its underlying pathophysiology and the development of treatment approach.

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