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A REVIEW ON METABOLIC SYNDROME: A NEW ENEMY OF PUBLIC HEALTH

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ABSTRACT

Metabolic Syndrome is a cluster of several cardiovascular risk factors that include glucose intolerance, central obesity, dyslipidemia, and hypertension. The public health impact of this syndrome is weighty; given it is a primary risk factor for cardiovascular diseases, obstructive sleep apnea, and type II diabetes. This current plight is further underscored by recently emerging evidence that Metabolic Syndrome is also associated with albuminuria and increasing incidence of chronic kidney disease, Moreover, this relationship persists even after exclusion of individuals with diabetes. Thus, Metabolic Syndrome is an independent risk factor for the development of chronic kidney disease, in the absence of diabetes, and independent of hypertension.

INTRODUCTION: During the past two decades, we have witnessed a global epidemic in Metabolic Syndrome [1] (MetS). It is estimated that one fourth of the adult population has the syndrome and the increasing prevalence is largely attributed to a parallel rise in the prevalence of obesity [2]. Emerging evidence suggests that increased dietary consumption of fructose in Western society may be a potentially important factor in the growing rates of obesity and the MetS.

Data from the recent National Health and Nutrition Examination Survey (NHANES) show the prevalence of obesity (body mass index ≥30) was 33.3% among adult men and 35.3% among adult women in 2005 through 2006. The global figures are predicted to rise 46% from 150 million cases in 2000 to 221 million in 2010 [3]. MetS and obesity are also increasing at an alarming rate among children and adolescents [4], which of course are a cause of serious concern because obese children invariably grow into obese adults. The National Cholesterol Education Program's Adult Treatment Panel III report (ATP III) identified the MetS as a multiplex risk factor for cardiovascular diseases (CVD) that deserves more clinical attention. The cardiovascular community has responded with heightened awareness and interest. Most individuals who develop CVD have multiple risk factors. In 1988, Reaven [5] noted that several risk factors (eg, dyslipidemia, hypertension, and hyperglycemia) commonly cluster together. This clustering he called *Syndrome X*, and he recognized it as a multiplex risk factor for CVD.

Reaven and subsequently others postulated that insulin resistance underlies Syndrome X (hence the commonly used term insulin resistance syndrome), is a collection of common pathologies, including central obesity, glucose intolerance, impaired fasting glycemia, insulin resistance, hyperinsulinemia, dyslipidemia, and hypertension [6]. It is well-established that MetS is associated with endothelial-dysfunction, oxidative stress [7], and also elevation of the serum uric acid level [8]. Elevated serum uric acid predicts the development of obesity and hypertension [9].

Metabolic Syndrome as a marker for long-term risk: Some researchers have envisioned the MetS as a risk assessment tool to predict absolute, short-term risk for (atherosclerotic cardiovascular disease) ASCVD [10]. But because it is only one of several risk factors and does not incorporate all other risk factors, it is not an adequate global risk assessment tool. Persons with MetS nonetheless can be considered to be at a higher lifetime risk for ASCVD [11]. Persons with MetS are candidates for more advanced short-term (10-yr) risk assessment for ASCVD, such as Framingham scoring, or when diabetes is present, with the UK Prospective Diabetes study (UKPDS) risk engine [12].

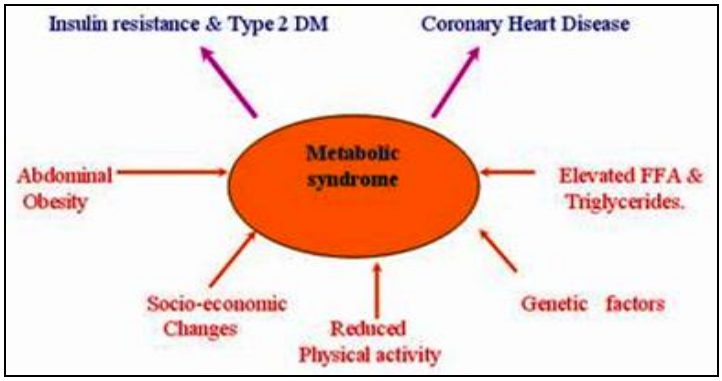

FIGURE 1: PROPOSED SCHEMES FOR PATHOGENESIS OF METS AS A CARDIOVASCULAR RISK FACTOR AND INSULIN RESISTANCE CONDITION

Metabolic Syndrome: A - Global burden: Each year, 3.2 million people around the world die from complications associated with MetS. These cardiovascular complications of MetS, which is also a leading cause of blindness, amputation and kidney failure, account for much of the social and financial burden of the disease [13]. The prediction that MetS incidence will double by 2025 heralds a parallel rise in cardiovascular-related illness and death, with an inevitable and profound impact on global healthcare systems. The metabolic syndrome is a cluster of the most dangerous heart attack risk factors: diabetes and prediabetes, abdominal obesity, high cholesterol and high BP. It is estimated that around a quarter of the world's adult population have MetS [14] and they are twice as likely to die from and three times as likely to have a heart attack or stroke compared with people without the syndrome [15].

In addition, people with MetS have a fivefold greater risk of developing type-2 diabetes [16]. The clustering of CVD risk factors that typifies the metabolic syndrome is now considered to be the driving force for a CVD epidemic. With a rise in comorbid disease on this scale, the burden on healthcare systems and budgets is almost incalculable. The annual direct healthcare cost of MetS worldwide for this age group is calculated to be as much as 286 billion, or even more. If diabetes prevalence continues to rise as anticipated, it is possible that this figure will increase to 396 billion. This will mean a spend of up to 13 per cent of the world's healthcare budget on MetS care in 2025, with high prevalence countries spending up to 40 per cent of their budget [13].

TABLE 1: ESTIMATED PREVALENCE OF THE METABOLIC SYNDROME USING THE ADULT TREATMENT PANEL III DEFINITION AMONG NORMAL WEIGHT, OVERWEIGHT, AND OBESE MEN AND WOMEN IN THE NHANES-III REPORT [17]

Category	BMI, kg/m^2	MetS Prevalence (%)	
		Men	Women
Normal weight	<25.0	4.6%	6.2%
Overweight	25.0–29.9	22.4%	28.1%
Obese	>30	59.6%	50.0%

BMI, body mass index

Clinical Diagnosis of the Metabolic Syndrome:

TABLE 2: CLINICAL CRITERIA FOR METABOLIC SYNDROME BY- WHO, NCEP ATP III AND IDF GUIDELINES [18]

WHO	NCEP ATP III	IDF
Insulin resistance identified by type 2 diabetes or impaired fasting glucose or impaired glucose tolerance or insulin resistance (by insulin clamp) plus two or more of the following:	MetS is defined by three or more of the following risk factors:	Central obesity (waist circumference, ethnicity specific) plus two or more of the following:
BMI >30 kg/m^2 and/or waist: hip ratio >0.9 (male) and >0.85 (female)	Waist circumference; >88 cm (women) and >102 cm (men)	
Triglycerides ≥150 mg/dl	Triglycerides ≥150 mg/dl	Triglycerides ≥150 mg/dl or treatment for this abnormality
BP ≥ 140/90 mm Hg and/or antihypertensive drugs	BP ≥130/85 mm Hg	BP ≥130/85 mg/dl or Pharmacologic treatment
HDL cholesterol <35 (male) and <39 (female)	HDL cholesterol <40 (male) and <50 (female)	HDL cholesterol <40 (male) and <50 (female) or specific treatment
Microalbuminuria (albumin excretion rate ≥20 µg/min) or albumin: creatinine ratio ≥30 mg/g	Fasting glucose level ≥110 mg/dl	

IDF, International Diabetes Federation; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; WHO, World Health Organization

Pathogenesis of Metabolic Syndrome: Much of the debate about the MetS centers on its pathogenesis. The metabolic interactions leading to a clustering of metabolic risk factors are not completely understood. The underlying an etiology of the MetS is still debated and many factors seem to be involved:

A. Insulin resistance: and its consequent hyperinsulinemia is recognized as an important or even essential factor in the MetS:

- Reaven proposed that insulin resistance is central to the syndrome's etiology and is the unifying pathological feature [19].
- Insulin resistance itself seems to be due to a combination of genetic factors, physical activity and obesity [20].
- Hypertension and insulin resistance are closely linked [19].
- Sphingolipids, such as ceramide, may play a role in the regulation of insulin sensitivity [21].

B. Lifestyle factors:

i. **Obesity:** Body mass index, abdominal obesity and upper body obesity are all linked to the MetS; some experts suggest that abdominal obesity or upper body obesity are closer linked than BMI. Adipose tissue in obese people is insulin resistant, and adversely affects lipids, inflammatory mediators and other mediators which influence insulin resistance and CVD [22]. Obesity has been found to be an independent risk factor for CKD [23], and treating obesity might stabilize renal function or reverse early hemodynamic abnormalities and glomerular dysfunction. Obesity has been associated with a type of focal segmental glomerulosclerosis (FSGS) called "obesity-related glomerulopathy" [24].

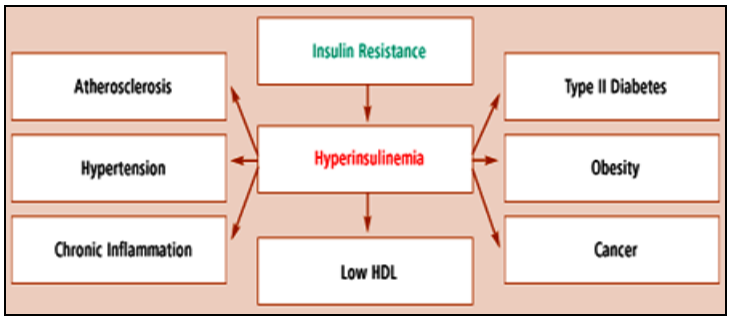

FIGURE 2: PROPOSED SCHEME FOR HYPERTENSION AND OTHER METABOLIC DEFECT BY INSULIN RESISTANCE

- **Physical inactivity:** Increased physical activity helps control body weight and blood pressure, improves lipid profiles and reduces cardiovascular risk and the risk of diabetes [25].

- **Atherogenic diet:** Modern Western diets are very different in composition from traditional human diets. Notably, they are high in refined carbohydrates and refined vegetable oils; and low in omega-3 fatty acids, fresh fruit and vegetables. All these have a role in obesity, adverse lipid profiles and the MetS [26].

ii. **A pro-inflammatory state:** Obesity, inflammation and cardiovascular risk seem to be connected. C-reactive protein (CRP) levels and white cell counts both seem to increase with obesity or the MetS, and there is some evidence linking them to CVD risk. The mechanism may again be related to the behavior of adipose tissue which, in the presence of obesity, produces excess (proinflammatory) cytokines and less of the protective adiponectin [22].

iii. **A pro-thrombotic state:** There is evidence for high circulating levels of prothrombotic factors in the MetS, which could contribute to CVD, characterized by increased plasma plasminogen activator inhibitor (PAI)-1 and fibrinogen, also associates with the MetS. Fibrinogen, an acute-phase reactant like CRP, rises in response to a high-cytokine state. Thus, prothrombotic and proinflammatory states may be metabolically interconnected [27].

iv. **Atherogenic dyslipidemia:** The MetS and insulin resistance are linked to an atherogenic lipid profile, which includes; Raised triglycerides (TG), including the atherogenic remnant lipoproteins, increased low density lipoprotein (LDL) and small LDL particles, increased apoB- containing lipoproteins and reduced high density lipoprotein (HDL) particles [27].

Clinical management of Metabolic Syndrome: The management of the MetS is not specific to the syndrome, but consists of management of the underlying risk factors for CVD and diabetes, and treatment of any established disease such as hypertension, heart disease or diabetes.

Recommendations are that clinicians should evaluate and treat all CVD risk factors without regard to whether a patient meets the criteria for diagnosis of MetS [28].

i. **Lifestyle advice for the Metabolic Syndrome:** This is the cornerstone of treatment for the MetS. This advice concord with the general recommendations for lifestyle changes to reduce cardiovascular risk (JBS guidelines, 2005). Scottish intercollegiate guidelines network (SIGN) advises that those with should have professional help regarding diet, exercise and weight [29].

ii. **Drug treatment:** The manifestations and complications of MetS should be treated according to established guidelines for the treatment of hyperlipidaemia, CVD, hypertension and diabetes [28, 19].

- Statins to raise HDL and reduce triglyceride and LDL cholesterol levels.
- Diuretics and ACE inhibitors to reduce blood pressure below 130/80 (mm Hg).
- Anti-diabetic agents to reduce glucose levels.
- Drugs to assist with weight loss.
- The aim of prescribing cholesterol lowering agents is to primarily to reduce the LDL cholesterol, but lower TG and higher HDL cholesterol are expected benefits as well.
- ACE inhibitors have also been shown to reduce the levels of insulin resistance and actually deter the development of type 2 diabetes.
- Metformin, glitazones and acarbose have been suggested as either improving the syndrome or delaying progression to type-2 diabetes [29], though recent safety concerns do not favor glitazones.
- The Gliptins are new once daily, competitive and fully reversible inhibitors of Dipeptides peptidase-4 (DPP-4), the enzyme that is responsible for the rapid degradation of the incretin hormone glucagon-like peptide-1 (GLP1). Clinical studies to date indicate that DPP-4 inhibitors effectively stimulate insulin secretion, suppress glucagon release and improve glycaemic control by reducing both fasting and postprandial glucose concentrations.
- Rimonabant, a selective blocker of the endocannabinoid receptor CB1, has been shown to decrease appetite and food intake, hence reducing weight and improving CVD risk factors in obese patients with the MetS or multiple CVD risk factors.

iii. **The role of vitamin D:** Vitamin D normally helps maintain adequate insulin levels. It also reduces cell proliferation (particularly in the skin) and has immunosuppressive effects. Vitamin D deficiency is common in obese individuals and in those with MetS. This is because fat retains vitamin D and because obese patients tend to have less sun exposure. In these patients, vitamin D supplements may be helpful [30].

iv. **Follow-up:**

- People identified with the MetS should have regular follow up to monitor their progress in reducing cardiovascular risk [29].
- Arguably, a glucose tolerance test should be performed for people with the MetS who have normal fasting glucose, as this may identify some with occult diabetes [22].

CONCLUSION: Global urbanization and sedentary life habits are producing a sharp increase in obesity and its concomitant metabolic risk; the latter combined into a multiplex risk factor for ASCVD goes by the name of MetS. The syndrome is not a discrete entity known to be caused by a single factor. Moreover, it shows considerable variation in the components among different individuals. This variation is even greater among different racial and ethnic groups. The metabolic syndrome is a secondary target for reducing cardiovascular events. Smoking cessation, lowering the levels of LDL-C, and blood pressure management are primary targets for risk reduction. Lifestyle interventions are the initial therapies recommended for treatment of the metabolic syndrome.

If lifestyle change is not sufficient, then drug therapies for abnormalities in the individual risk factors may be indicated. To date, there is insufficient evidence for primary use of drugs that target the underlying causes of the metabolic syndrome. Considerable additional research is needed to better refine the most appropriate therapies for individuals with the metabolic syndrome.

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