International Journal of Physiology, Nutrition and Physical Education

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Metabolic syndrome: The bane of Indian population

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Abstract
Metabolic syndrome (MetS) is a cluster of risk factors for the occurrence of type 2 diabetes mellitus and cardiovascular diseases. It involves following interrelated biological components: abdominal obesity, dyslipidemia, hypertension and type 2 diabetes mellitus. Indians may be susceptible to the syndrome due to foetal malnutrition and rapid post independence urbanization. This review attempts to explain the prevalence, risk factors and management for prevention of MetS, which may help the health authorities and policy planners to realize the current status of MetS in Indian population.

Keywords: Metabolic syndrome, type 2 diabetes mellitus, abdominal obesity, hypertension, dyslipidemia

1. Introduction
The rapid growth of non-communicable diseases (NCDs) is threatening the health of the people. India, being a developing country, is still struggling to fight infectious diseases have another challenge i.e., to control the rise in NCDs that broadly includes diabetes mellitus, cardiovascular diseases, cancer, chronic respiratory diseases, hypertension, obesity and mental illness. Urbanization in India has modified people's lifestyle and dietary habits, resulting in increase in rate of obesity. Metabolic syndrome started as a concept rather than a diagnosis, is a public health issue requiring immediate attention [1-3].

"A cluster of risk factors for cardiovascular diseases and type 2 diabetes mellitus occurring together lead to a condition called metabolic syndrome" [4]. It represents a constellation of interrelated biological factors including abdominal obesity, dyslipedemia, hypertension and type 2 diabetes mellitus [5]. Several definitions have been given to describe metabolic syndrome. Generally, it is agreed that a combination of three or more characteristics must be present [6]. The definition given by IDF (International Diabetes Federation) states that "a person is identified to have metabolic syndrome when he/she must have central obesity specific to ethnicity values plus any of the two factors including raised triglycerides, reduced HDL cholesterol, raised blood pressure, and raised fasting blood glucose" [7]. In 2009, Joint Interim Statement stated that "presence of any three of the following five conditions is essential, to be diagnosed with MetS i.e., increased waist circumference, low HDL cholesterol, elevated blood pressure, and elevated blood sugar" [4, 6].

Barker *et al.* (1998) reported increased susceptibility to metabolic syndrome could be a result of maternal nutritional deprivation leading to Intrauterine Growth Retardation (IUGR). Programming of IUGR foetal tissues during critical periods of developments have lifelong effects, which with affluences and urbanization manifest adult obesity and chronic degenerative diseases [8, 9]. According to 2011 report, nearly 20% of new born have low birth weight [10]; showing a wide prevalence of Intrauterine Growth Retardation in India. Hence, under nutrition at one age spectrum may bring those populations at risk of developing metabolic syndrome in adult life [8, 9]. So, Indians seem to be more prone to development of MetS (metabolic syndrome); as this population has a history of foetal malnutrition and greater incidence of low birth weight babies, who at present are adults, may be possible sufferers of MetS.

Patients having metabolic syndrome have a 2-fold and 5-fold increased risk of developing cardiovascular diseases and type 2 diabetes mellitus respectively over the next 5 to 10 years [1]. Furthermore it is seen around 20-25% world's adult population suffer from MetS and it confers 2- to 4- fold increased risk of stroke, a 3- to 4-fold increased risk of myocardial

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infarction and 2- fold risk of dying compared to people without syndrome [1, 7]. Age, heredity, lifestyle factors and socioeconomic status have a major impact on its pathogenesis [7]. Prevalence of MetS worldwide ranges from <10% to as much as 84%, depending on various demographic factors: region, urban/rural environment, composition (sex, age, race, and ethnicity) of the patient, and the definition used. While in India the prevalence of MetS has been documented to be from 11% to 41% across the country with socio-cultural variations [11]. Surveys in large cities of India show that one-third of the urban population suffers from MetS while prevalence in rural population is comparatively low.

Determining and controlling various components of MetS at population level is complex and requires multi-sectoral policy approach focused on delivering balanced nutrition, lifestyle modification and environment to improve physical activity [12].

2. Historical Background
The concept of MetS dates back to as early as 250 years ago, Morgagni identified association between abdominal obesity, arterial hypertension, atherosclerosis, high level of uric acid in the blood and frequent respiratory disorders during sleep (the obstructive sleep apnea) [13]. In 1923, Kylin demonstrated association of hypertension, hyperglycemia and gout as a syndrome. While in 1940s, Vague stated that abdominal obesity was commonly linked with metabolic abnormalities found in cardiovascular diseases and diabetes. Later on, at European Association for the study of Diabetes in an annual meeting held in 1965, Avogaro and Crepaldi presented an abstract describing a syndrome including obesity, hypertension and hyperglycemia [14, 1]. The term 'metabolic syndrome' was first time coined in 1981, Hanefield and Leonhardt gave first definition of metabolic syndrome, describing it as "simultaneous occurrence of hyper-dyslipoproteinemia, hyperglycemia, hypertension, gout and obesity in combination with an increased risk of cardiovascular diseases, fatty liver and cholelithiasis in overfed, physically inactive and genetically predisposed people" [15]. Further in 1988, the phrase 'Syndrome X' was first time used by Reavan to describe metabolic syndrome as a constellation of risk factors for diabetes and cardiovascular diseases creating clinical significance though excluding obesity. He introduced the concept of insulin resistance but missed out very important feature of obesity from the definition later added as a crucial abnormality [14, 1]. Kaplan in 1989, renamed metabolic syndrome as 'The Deadly Quartet' and described syndrome as presence of obesity, hypertension, hypertriglyceridemia and glucose intolerance as commonly coexisting components [16]. While in 1991, Defronzo and Ferrannini represented syndrome X as 'Insulin Resistance Syndrome11. Several agencies have described diagnostic criteria for MetS. WHO (World Health Organization) diabetes group made first attempt in 1998 to define MetS, later was modified by European Group for the study of Insulin Resistance (EGIR) in 1999. National Cholesterol Education Programme Adult Treatment Panel (NCEP/ATP) also released definition of MetS in 2001. In 2003 American Association of Clinical Endocrinologists also expressed its views regarding the syndrome. Understanding the need of unified definition IDF gave a worldwide definition of MetS in April 2005¹. In 2009, harmonized definition was given by IDF and the American Heart Association/ National Heart, Lung and Blood Institute (AHA/NHLBI) with an agreement that "the measure for central obesity there should not be an obligatory component, but that waist measurement would continue to be a useful preliminary screening tool" [17].

3. Materials & Methods
A literature review was done to obtain relevant information, searching the online databases PubMed, Medline, Google scholar and NCBI and related books. Research articles such as cross-sectional, prospective and longitudinal studies and reviews were identified. Following keywords: 'Non-communicable diseases', 'Metabolic syndrome', 'History', 'Definitions', 'Pathophysiology', 'Risk factors', 'Cardiovascular diseases', Type2 Diabetes', 'Prevalence', 'In utero malnutrition', 'Chronic Degenerative Disease', 'Diet' and 'Exercise' were used in search strategy. This review highlights prevalence, components and consequences of metabolic syndrome in Indians, with an attempt made to retrieve relevant concepts and studies on Indian population.

4. Definitions
Many expert groups from international organizations like WHO, EGIR, NCEP ATP III, AHA/NHLBI and IDF have come up with definitions to describe MetS [18]. However, obesity, insulin resistance, dyslipidemia and hypertension have been the main components of MetS in all of the definitions [14]. However, a harmonized definition was given in 2009, as improvement in previous definitions stating that "presence of any three of the following five conditions is essential, to be diagnosed with MetS i.e., increased waist circumference (males: ≥90 cm and for females: ≥80 cm), hypertrig1yceredimia ≥150 mg/dl (1.7 mmol/l), low HDL (Males <40 mg/dl (1 mmol/l) and for females <50 mg/dl (1.3 mmol/l), elevated blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg or drug treatment for hypertension), and elevated blood sugar (fasting blood sugar ≥100 mg/ dl (5.6 mmol/l) or drug treatment for diabetes mellitus)".

5. Components
Studies reveal association between obesity and insulin resistance underlying pathophysiology of MetS. It becomes difficult to understand which one causes pathogenesis and progression of MetS [13]. Several other risk factors constitute the syndrome including: age, ethnicity/race, diet, physical inactivity, genetic susceptibility, dyslipidemia, elevated blood pressure, imbalances in hormone levels, drugs and chronic stress making it very complex [14, 1].

5.1 Abdominal Obesity
High consumption of cheap, calorie dense foods along with sedentary lifestyle has lead to increased incidence of obesity globally [1]. Studies estimate that about 50% of adults worldwide are expected to be obese by 2030. Obesity may be defined by BMI (Body Mass Index) being 30 or above, but central obesity may not always occur with an elevated BMI. Presence of excess visceral fat deposits on abdomen is a major risk factor for systematic inflammation, hyperlipidemia, insulin resistance and cardiovascular disease. Abdominal obesity may be measured by taking anthropometric measurements such as waist circumference or waist: hip ratio [19]. Abdominal obesity is defined by large waist circumference according to the ethnicity specific values. For Asian Indians, waist circumference for males≥90cm and female≥80cm is considered to have abdominal obesity [4].

5.2 Dyslipidemia
Dyslipidemia is characterized by high plasma triglycerides and free fatty acid levels due to alterations in atherogenic and antiatherogenic lipoproteins due to abnormal lipid metabolism. The condition may be due to increased levels of atherogenic lipoproteins or increased production of very low-density lipoproteins (VLDL) and low-density lipoproteins (LDL) and decreased levels of high-density lipoproteins (HDL). It may also result from decreased clearance of triglyceride-rich-lipoprotein due to deficiency of enzyme insulin-sensitive lipoprotein lipase. This condition is important feature of MetS which increases risk of type2 diabetes and cardiovascular diseases [20]. According to harmonized definition, raised triglycerides ≥150mg/dl and reduced HDL cholesterol <40mg/dl in males and <50mg/dl in females lead to atherogenic dyslipidemia [4].

5.3 Hypertension
Hypertension also becomes associated with insulin resistance, obesity and dyslipidemia being common risk factors. Recent data show conditions like hyperglycemia and hyperinsulinemia activate renin angiotensin pathway causing increased expression of angiotensinogen, Angiotensinogen II, AT1 receptors. All these processes lead to elevated blood pressure in patients with insulin resistance. Symathetic nervous system is activated when there is a persistent elevated level of glucose and insulin in blood which causes increased sodium reabsorption by the kidneys, increased cardiac output and then, hypertension. Recent studies show that adipocytes produce aldosterone in response to Angiotensin II causing sodium retention and raised blood pressure. According to recent guidelines, systolic BP≥130mmHg or diastolic BP≥85mmHg is diagnosed with hypertension [4, 21].

5.4 Type 2 Diabetes Mellitus
Insulin resistance is a condition in which cells of various organs become insensitive and resistant to insulin hormone and glucose cannot be absorbed by the body causing rise in blood glucose, eventually type 2 diabetes [7]. This may become a potential risk factor for MetS as seen in majority of subjects diagnosed with MetS in studies. Diabetic patients have increased risk of developing hypertension, dyslipidemia, cardiovascular diseases and obesity [22]. According to the harmonization definition raised fasting plasma glucose of ≥100mg/dl is a characteristic feature of MetS [4].

6. Prevalence in India
Recent data show MetS is a major contributing risk factor for various diseases. A cross-sectional study was conducted in Kerala, South India with around 5000 subjects revealed prevalence of MetS to be 33% and is associated with the presence of coronary artery disease and increased cardiovascular mortality in the state [23]. Another study of North India in rural districts of Haryana with 1700 subjects, prevalence of MetS was 26.6% and showed increased risk for progression of type2 diabetes and heart diseases [23]. Processes of MetS may begin at a very early age of life during childhood to young adulthood and reach to 50% prevalence in obese youngsters. In a study of Gujarati asymptomatic young population on 1500 subjects, prevalence was found to be 16%. It also showed increased incidence of diabetes, hypertension, dyslipidemia and atherosclerosis in subjects with advance in age [25]. Another study in Central India, in the area of Chambal in Madhya Pradesh on 700 type 2 diabetic patients showed prevalence of MetS to be 57.7% stated increased risk of long term cardiovascular complications along with long term diabetic complications [26].

Studies also reveal that MetS has a strong association with renal and chronic kidney disease. Incidence of other health problems like osteoarthritis, gout, and renal stones with addition of MetS traits also increases. Further it may also be associated with various cancers. Major factors of MetS like obesity, diabetes and dyslipidemia increases the risk of breast, colon/colorectal, liver, pancreatic, bladder and endometrial cancers. In addition to this; it has also been linked to cognitive and psychiatric issues leading to sleep apnea, vascular and Alzheimer's dementia [27].

7. Prevention and Management
The most effective treatment of MetS has not been established. However long-term life style modification may be possible treatment in controlling and preventing major components of MetS. Long term dietary alterations may help in weight reduction, managing blood glucose, blood pressure and cholesterol levels. Studies show improvements in MetS criteria by following various types of diet like low-fat, mediterranean, ketogenic, high-protein, DASH (Dietary Approaches to Stop Hypertension) and Nordic diet. Apart from diet, improved physical activity level can also prove to be beneficial for patients with MetS. Exercise and increased physical activity level may reduce abdominal fat, risk of cardiovascular diseases and diabetes [28, 19].

People with metabolic syndrome have an increased risk of developing diabetes, myocardial infarction, cardiovascular diseases and dying from heart stroke[1]. Following healthy dietary patterns and lifestyle modification can improve status of MetS. The protective effect of energy-restricted diets seems to be beneficial as it may help to make small changes in the individual components rather than a large effect on any single component of MetS. Thus treatment for MetS should be focused on weight-loss and increased physical activity in order to achieve significant improvements for the betterment of the people [28, 19].

8. Conclusion
This review article intends to clarify, how MetS may become a possible threat on Indian population. Looking back at its history, organizations and researchers have described the syndrome as interlinked biological factors such as obesity, raised blood pressure, blood glucose, triglycerides and cholesterol levels. These factors may give rise to various health problems like cardiovascular diseases, type 2 diabetes, kidney diseases, cholelithiasis, and fatty liver diseases. These consequences of MetS have been reported in various studies in India.

Health education programs should be planned to control MetS to help reduce its burden. Multi-sectoral approach to control MetS in Indian population may help to control its unsavoury repercussions.

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