Metabolic Syndrome (MS): Definition, Classification and Potential Associated Factors

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ABSTRACT

Many lifestyle-related risk factors for cardiovascular disease have been identified. The most powerful and consistent risk factors for cardiovascular disease (CVD) are dyslipidemia, hypertension, obesity (particularly central obesity) and diabetes mellitus, which are also known as metabolic syndrome. It is also commonly used term was insulin resistance syndrome (Syndrome X). At present, there is various accepted definition of the metabolic syndrome. When comparing to the defining level between The Adult Treatment Panel III (ATPIII) and World Health Organization (WHO), a higher blood pressure was required in WHO than in ATPIII. Instead of waist circumferences in ATPIII, body mass index (or increased waist: hip ratio) was used in WHO. The requirement of objective evidence of insulin resistance in WHO requirement should give more power to predict diabetes than does ATPIII, but like ATPIII, the presence of type 2 diabetes does not exclude a diagnosis of metabolic syndrome. The differences in diagnostic criteria for this syndrome are partially responsible for variations in the reported prevalence among different studies. Metabolic syndrome is correlated with different possible factors which may associate and predict its existence and intensity. Some of these factors are explained in this review.

Key words: Metabolic Syndrome (MS), Diabetes, Lipids Disorder, Blood Pressure (BP), Obesity & the Adult Treatment Panel III (ATP III).

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of mortality and a major cause of morbidity (Bello et al., 2004). In the United States, more than 32 million people have one or more form of CVD (American Heart Association, 2000). According to World Health Organization (WHO) (2001), cardiovascular disease is a group of disease comprising of ischaemic heart disease (which include angina and myocardial infarct), cerebrovascular disease, rheumatic heart disease, hypertensive heart disease, disease of pulmonary circulation and other forms of heart disease (dysrhythmias, heart failure, etc) and other disease of circulatory system.

Many lifestyle-related risk factors for cardiovascular disease have been identified. The most powerful and consistent risk factors for CVD are hypertension, obesity, abnormal blood lipid and diabetes mellitus, which are also known as metabolic syndrome (Wood et al., 1998; Ford et al., 2004).

Definition of MS

In general, the term “metabolic syndrome” is used to describe a constellation of risk factors that predispose people to cardiovascular disease (CVD) and its complications. Abdominal obesity,
Atherogenic dyslipidemia, high blood pressure, insulin resistance (with or without glucose intolerance), a pro-inflammatory state, and a prothrombotic state are generally considered to be key components (Park & Lindholm, 2009; Anne, 2004; Isomaa, 2003).

Several mechanisms have been suggested to explain the clustering of metabolic disturbances and cardiovascular risk factors described in connection with the metabolic syndrome (Isomaa, 2003; Reilly et al., 2003). The differences in diagnostic criteria for this syndrome are partially responsible for variations in the reported prevalence among different studies (Alberti et al., 1998). However, the metabolic syndrome is now thought to represent a number of strongly interrelated risk factors for cardiovascular disease. These include dyslipidemia, hypertension, obesity (particularly central obesity) and insulin resistance (Scott, 2003; Isomaa, 2003).

Lifestyle and behavioral changes over the preceding century, such as increasingly sedentary lifestyle, excessively dietary intake such as diet high in saturated fats, obesity and lack of physical exercise, have contributed to a dramatic increase in the occurrence of diabetes and metabolic syndrome (Zimmett et al., 2001). As the prevalence of obesity increases in developed and developing country, the prevalence of metabolic syndrome may be expected to increase markedly (Tuomilehto et al., 2005).

Furthermore, the individual components of the metabolic syndrome represent pre-nosologic or prodromal states for subsequent disease states (Marwick, 2006). Thus, dyslipidemia and hypertension lead to CVD; obesity and impaired glucose tolerance IGT (and impaired fasting glucose IFG) lead to type 2 diabetes, and also predict increased CVD risk. The prediabetes status at baseline conferred a doubling of the 10-year risk for CVD mortality, while the degree of glycemia (as assessed by glycosylated hemoglobin HbA1c emerged as an independent predictor of CVD mortality (Gallwitz, 2009). The relationship between HbA1c and CVD mortality was evident as a continuum of risk, beginning well before the glycemic threshold for the diagnosis of diabetes is reached (Nakanishi et al., 2005).

Classification of MS

Three major lines of evidence have been merged to identify the metabolic syndrome concept. It has been noted that obesity is strongly associated with multiple risk factors and undoubtedly contributes significantly to them. These include hypertension, hypercholesterolemia, hypertriglyceridemia, low levels of high-density lipoproteins, and hyperglycemia, plus any two of the following four factors: 1) raised TG level: ≥ 150 mg/dl (1.7 mmol/L), or specific treatment for this lipid abnormality; 2) reduced HDL cholesterol: < 40 mg/dl (1.03 mmol/L) in males and < 50 mg/dl (1.29 mmol/L) in females, or specific treatment for this lipid abnormality; 3) raised blood pressure: systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg, or treatment of previously diagnosed hypertension and 4) raised fasting plasma glucose (FPG) ≥ 100 mg/dl (5.6 mmol/L), or previously diagnosed type 2 diabetes (Anderson et al., 2001).

According to Fonseca (2008), the components and clinical identification of the metabolic syndrome are summarized in figure (1); where Individuals who exhibit at least three of these medical conditions are defined as having metabolic syndrome.

The new International Diabetes Federation (IDF) consensus definition of the metabolic syndrome in Asians uses as a measure of obesity a waist circumference of >90 cm for men and >80 cm for women (Zimmet et al., 2005). World Health Organization in 1999 identifies the metabolic syndrome a patient must present with glucose intolerance, impaired glucose tolerance (IGT) or diabetes and/or insulin resistance, together with two or more of the following components: 1) Raised arterial pressure ≥ 140/90 mm Hg; 2) Raised plasma triglycerides (≥ 1.7 mmol/L; 150 mg/dl) and/or low HDL cholesterol (< 0.9 mmol/L,
Central obesity (males: waist to hip ratio > 0.90; females: waist to hip ratio > 0.85) and/or BMI > 30 kg/m²; 4) Microalbuminuria (urinary albumin excretion rate ≥ 20 g/min or albumin: creatinine ratio ≥ 30 mg/g) (WHO, 1999).

On the other hand, The Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program NCEP in the United States is the third major line has its own identification for the metabolic syndrome concept. ATP III published a comprehensive report on treatment of high cholesterol in adults. Within this report they recognized the existence of the metabolic syndrome as a major contributor to cardiovascular risk (NCEP-ATP III, 2001). The simplicity of the Adult Treatment Panel III definition, however, was attractive to many researchers and clinicians and has sparked great interest. ATP III guidelines are summarized in Table (1).

### Table (1): ATP-III clinical identification of the metabolic syndrome (MS)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Defining level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central obesity</td>
<td>Waist circumference (WC)</td>
</tr>
<tr>
<td>• Men</td>
<td>&gt; 102 cm (&gt; 40 in)</td>
</tr>
<tr>
<td>• Women</td>
<td>&gt; 88 cm (&gt; 35 in)</td>
</tr>
<tr>
<td>Triglycerides (TG)</td>
<td>≥ 150 mg/dl (1.7 mmol/L)</td>
</tr>
<tr>
<td>HDL cholesterol (HDL-C)</td>
<td>≤ 40 mg/dl (1.03 mmol/L)</td>
</tr>
<tr>
<td>• Men</td>
<td>≤ 40 mg/dl (1.03 mmol/L)</td>
</tr>
<tr>
<td>• Women</td>
<td>≤ 50 mg/dl (1.29 mmol/L)</td>
</tr>
<tr>
<td>Blood pressure (BP)</td>
<td>≥ 130/80 mmHg</td>
</tr>
<tr>
<td>Fasting glucose (Gluc)</td>
<td>≥ 110 mg/dl (6.1 mmol/L)</td>
</tr>
</tbody>
</table>

### Diabetes

Diabetes mellitus is a group of metabolic disorders of carbohydrate metabolism in which glucose is underused, producing hyperglycemia. Type 2 diabetes develops over a long period of time in adults, most of whom initially present with impaired glucose tolerance (IGT) and/or an impaired fasting glucose (IFG). IGT is defined as a plasma glucose concentration of 140 to 199 mg per deciliter (7.8 to 11.0 mmol per liter) 2 hours after a 75 gram oral glucose load. IFG is defined as a plasma glucose concentration of 100 to 125 mg per deciliter (5.6 to 6.9 mmol per liter) in the fasting state. Prediabetes in adults may be defined as the presence of IFG and/or IGT in individuals with a BMI greater than or equal to 25 (NDDG, 1997).

### Lipids Disorder

The clinical significance of lipids is primarily associated with coronary heart disease CHD and various lipoprotein disorders. Coronary heart disease (CHD), the most common form of cardiovascular disease, usually involves atherosclerosis and hypertension (Whitney et al., 2016). Atherosclerosis is one of the most disease states that are known to be promoted by changes in plasma lipoprotein concentrations in individuals (Olson, 1998).

Dietsch, (1998) reported, from several publications, that there is a strong correlation between rates of CHD death and the plasma TC concentration even in...
populations that traditionally have very low values of both of these parameters. These data suggest that the incidence of CHD death would be essentially zero at plasma TC concentrations below ~140 mg/dl, but above this level would increase in a nearly linear relationship to the serum cholesterol concentration. Serum cholesterol levels are strongly related to coronary artery disease risk, because LDL have a central role in the pathogenesis of atherosclerosis, and that reductions in LDL levels are associated with reduced coronary disease risk (Anderson & Hanna, 1999; Krauss et al., 2001).

Cholesterol per se is not the agent of atherosclerosis because LDL, which contains cholesterol, is pro-atherogenic whereas HDL, which contains cholesterol, is anti-atherogenic. (Olson 1998). It is believed that HDL carry cholesterol away from the arteries and back to the liver. Although the reasons are unclear, high levels of HDL may protect against the development of plaque. Conversely, low HDL may favor the development of plaque (Whitney et al., 2016). To a lesser extent, elevated triglycerides are also linked to atherosclerosis. Elevated triglycerides often occur together with elevated LDL, low HDL, and other conditions that favor plaque development such as overweight and diabetes, so it is difficult to determine if elevated triglycerides alone are problematic (Whitney et al., 2016). Some studies have demonstrated that a reduction in LDL cholesterol is correlated with progression in the atherosclerotic lesion (Ravnskov, 2002).

**Blood Pressure (BP)**

High BP is a primary risk factor for stroke, congestive heart failure, renal failure and coronary heart disease, at all ages and in both genders. Since genetic factors contribute only about 30% to blood pressure variance, high BP is a proven modifiable risk factor and hypertension is a preventable and treatable disease. This could be accomplished with control of causal and risk factors associated with hypertension (Staessen et al., 2003).

Some investigators have been reluctant to link elevated BP with the metabolic syndrome because factor analysis has shown a weak relation between hypertension and other metabolic abnormalities that define the syndrome (Shen et al., 2003; Ford, 2003). On the other hand, the linkage of elevated BP with the metabolic syndrome is strong through the causative pathway of obesity, although only about half of those with hypertension or obesity have the metabolic syndrome (Rahmouni et al., 2005).

**Obesity (Abdominal Obesity)**

Obesity is a serious problem but its insidious nature perhaps hides its current and future impact on human health. Obesity and other related diseases are killing millions more people. Obesity is not only a primary risk factor for serious chronic disease in its own right, but also acts indirectly by adversely affecting other primary risk factors such as lipid profile, glycaemic control and blood pressure, among others (Johnson, 2007).

Body mass index (BMI) as an indicator for the obesity is calculated as a measure of weight relative to height (Table 2).

**Table (2): Classification of Body Mass Index (BMI)**

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 16.0</td>
<td>Chronic Energy Deficiency (CED)</td>
</tr>
<tr>
<td>16.0 - 16.9</td>
<td>CED grade 2</td>
</tr>
<tr>
<td>17.0 - 18.4</td>
<td>CED grade 1</td>
</tr>
<tr>
<td>18.5 - 24.9</td>
<td>Normal</td>
</tr>
<tr>
<td>25.0 - 29.9</td>
<td>Obesity grade 1</td>
</tr>
<tr>
<td>30.0 - 39.9</td>
<td>Obesity grade 2</td>
</tr>
<tr>
<td>40.0 and above</td>
<td>Obesity grade 3</td>
</tr>
</tbody>
</table>

(Source: WHO,1995)

Waist circumference is an indicator of total body fat and specifically visceral fat. Waist circumference is taken as the circumferences at the midway between the lowest rib and the iliac crest; while hip circumference is measured as the maximal protrusion of buttocks with the foot together. The averages of the duplicate measurements for hip and waist girth is used to calculate the waist to hip ratio (WHR). There is an increased risk where a female’s waist is greater than 88 cm and a male’s
waist is greater than 102 cm. Simple waist circumference measurement is as good a predictor of disease risk as waist-to-hip ratio, however, and so the latter is less commonly used (NIHCE, 2007).

**Potential Associated Factors of Metabolic Syndrome**

Metabolic syndrome is correlated with different possible factors which may associate and predict its existence and intensity. The subsequent sections explain some of them.

**Metabolic Syndrome (MS) and Physical Inactivity**

The problem currently facing the global community is that, faced with an abundance of calories and diminished requirements for physical activity, a significant portion of the population are unable to maintain energy balance, leading to increased fat mass. Excess consumption of calories, especially associated with high fat diets, is a significant factor causing obesity and insulin resistance (Collins et al., 2004). The latter is the defining feature of the insulin resistance syndrome, formerly called the metabolic syndrome (Reaven, 2005).

The epidemic of sedentary lifestyle and overweight has serious public health and economical consequences. Physical inactivity increases the incidence of coronary artery disease (CAD), stroke, hypertension, obesity, Type 2 diabetes, osteoporosis, cancers of the breast and colon, depression, and premature mortality. Overweight and obesity increase the risk of CAD, hypertension, Type 2 diabetes and premature mortality. Physical inactivity, unhealthy diet, and CAD have been estimated to account for about 54.8 per 100 000 inhabitants of Malaysia. If current trends continue, these modifiable risk factors will overtake smoking as the primary preventable cause of death (Noor, 2002).

The worldwide epidemic of excess weight is a consequence of positive energy balance due to both reduced energy expenditure and increased energy intake. The almost unlimited availability of highly palatable, energy-dense foods and drinks and increased portion sizes are undoubtedly contributing to the current epidemic of overweight and obesity (Formiguera & Canton, 2004).

**Metabolic Syndrome (MS), Gender and Age**

Young men with the metabolic syndrome are at 20% high CVDs risk level compared to women with MS (Wong et al., 2003). This situation changes drastically in middle age and beyond: there is a sex-related reversal whereby more women than men develop hypertension, primarily of the ISH phenotype (Franklin et al., 2001). Postmenopausal women who gain appreciable weight, regardless of the level of physical activity, have a high prevalence of the metabolic syndrome with ISH, an increased propensity for developing diabetes, and a greatly increased risk for CVD (Carr, 2003). In a large European study of postmenopausal women followed up for a mean of 8.5 years, cardiovascular mortality was strongly related to abdominal obesity and to all elements of the metabolic syndrome, especially elevated serum triglycerides (Tanko et al., 2005).

**Metabolic Syndrome (MS) and Ethnicity**

Populations vary in their susceptibility to the complications of obesity. South Asians, Chinese, and Japanese develop the metabolic syndrome in association with only moderate weight gain (Zimmet et al., 2005). In South Asians, the increased coronary artery disease (CAD) risk is twofold greater than can be explained by standard risk factors; insulin resistance is thought to be the emerging risk factor that predisposes to premature CAD and Type 2 diabetes (Miller et al., 1989). In contrast, Blacks of African origins are prone to early and severe development of hypertension when they gain weight (Lteif et al., 2005). Blacks are more resistant to developing low HDL-cholesterol and high serum triglycerides with the same degree of weight gain, suggesting that these atherogenic dyslipidemic factors are not reliable markers of insulin resistance (Sumner et al., 2005).
Obese Native Americans and Hispanics are more susceptible to the development of Type 2 diabetes and less so to hypertension (Gonzalez-Villalpando et al., 1999). This heterogeneity in body habitus and susceptibility to different elements of the metabolic syndrome could be due to the variation in genetic makeup as well as environmental influences.

It has been reported an increasing prevalence of metabolic syndrome diseases in Singapore, the overall prevalence rising 1.99% in 1975 to 4.7% in 1984 with a further increase to 8.6% in 1992. The rise in prevalence occurred in Chinese (4% in 1984 to 8% in 1992), Malays (7.6% in 1984 to 9.3% in 1992) and the most predominant change was among Indians who had a 44% rise, i.e. from 8.9% in 1984 to 12.8% in 1992. The changes were attributed to the rising affluence, change in lifestyle with increasing obesity, and the migration of rural people to urban areas. In Kuala Lumpur, migrant Indians had a prevalence of 4.2% in 1966, 6.1% in 1975 and 16% in 1988 (Lee et al., 2008).

Metabolic Syndrome (MS) and Urbanization

Urbanization in recent decades has resulted in a progressive reduction in the level of habitual physical activity associated with work and chores of daily living, as well as a growing amount of time spent in very sedentary activities such as watching TV, working on the computer, and playing video games (WHO, 2000). Indigenous cuisine and traditional food habits are being supplanted by a Westernized, energy dense diet with its unhealthy concentration on soft drinks and meat consumption. A sharp decline in the cost of vegetable oils and sugar has put them in direct competition with cereals as the least expensive food ingredients worldwide (Caballero & Popkin, 2002). This in turn has reduced the proportion of the diet derived from grain and grain products and greatly increased world average energy consumption of sugar and oil, although this increase is not evenly distributed throughout the world’s population. Taken together, this transition towards foods of animal origin, increased fats, and refined foods, along with the more sedentary lifestyle that accompanies urbanization, contribute to the current global epidemics of obesity, diabetes, and cardiovascular disease (Popkin, 2001).

The pace of change for both diet and physical activity has accelerated to varying degrees in different regions of the world. The shift of countries and large populations into the stage of development (as resulted from the urbanization) is characterized by high prevalence of metabolic syndrome which is part of nutrition-related non-communicable diseases NR–NCDs (Drewnowski, 2000).

Metabolic Syndrome (MS) and HFIS

Food insecurity is used to denote the limited, inadequate, or insecure access of individuals and households to sufficient, safe, nutritious, personally acceptable food both in quality and quantity to meet their dietary requirements for a healthy and productive life (Tarasuk, 2005). As resources become increasingly depleted, food insecurity is characterized by quantitative compromises in food intake and the attendant physical sensation of hunger. At its most severe stage, food insecurity is experienced as absolute food deprivation (i.e., not eating at all). Across this continuum of severity, food insecurity also has defined psychological and social manifestations (Tarasuk, 2001).

Household food insecurity occurs commonly among poor households, contributing to poor health, nutrition and functional outcomes among children, women and the elderly. These groups were found to have inadequate calorie and nutrient intakes, lower intake of fruits and vegetables, disordered eating behaviors, lower academic achievement and were more likely to have higher cholesterol and fat intakes and be overweight and obese (Kendall et al., 1995; Kendall et al., 1996; Rose & Oliveira, 1997; Vailas et al., 1998).

Poor households spent their expenditure on additional food without
modifying the composition of their food balance, acquiring most of their calories from carbohydrates and only a marginal amount from proteins (meat, fish, eggs, and legumes) and oils and fats (Thang and Popkin, 2004). On the other hand, rich households, tended to buy more expensive items like fish, beverages, oil, vegetables, and processed food as replacements for rice. In addition, Thang & Popkin (2004) found that rich households do not significantly increase the proportion of calories from proteins (only fish increases), while they increase that from lipids and from processed food, typically rich in saturated fats and refined sugar. This shift towards products that are generally associated with increased risk of obesity, diabetes and heart diseases, and certain types of cancer is of great concern if we take into consideration that it occurred only at the beginning of the economic boom faced by the country. In particular urban areas in the south East Asian countries the overweight population is steadily increasing (Cuong et al. 2006).

According to Tarasuk & Beaton (1999), lower energy and nutrient intakes observed among women in households with more severe food insecurity may put them at risk of nutrient deficiencies and potential nutritional problems. These inadequacies might impose detrimental long-term impact if the condition was not corrected. Many studies on the relationship between food security and obesity have been conducted. Both the food-secure and insecure groups are more likely to be obese. However although mild or moderate food insecurity is associated with a higher risk of obesity, severe food insecurity is associated with a lower risk. However, poverty and food insecurity were not associated with obesity in men (Burns, 2004). In a large European study of postmenopausal women followed up for a mean of 8.5 years, cardiovascular mortality was strongly related to abdominal obesity and to all elements of the metabolic syndrome, especially elevated serum triglycerides (Tanko et al., 2005).

**CONCLUSION**

The term “metabolic syndrome” is used to describe a constellation of risk factors that predispose people to cardiovascular disease (CVD) and its complications. There are two general approaches to the treatment of the metabolic syndrome. The first one is the strategy to modify root causes of MS, overweight, obesity, physical inactivity with its associated condition and insulin resistance. The second approach treats the metabolic risk factors. However, the greatest potential for management of the syndrome, as suggested by ATP III, lies in reversible its root causes. A possible explanation for this can be ascribed to the ways (ATP III, IDF and WHO) used to classify the metabolic syndrome, where each one has its own background of inclusion the clinical criteria, which will finally contribute to the formulation of metabolic syndrome. This review also focused on the relationship of the metabolic syndrome with its determinants and outcomes; socio-economic status, dietary, anthropometric and health measures. In addition, it will participate in solving and completing the metabolic syndrome status “puzzle” from health point of view.

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