

## Introduction

Metabolic syndrome (MetS) is a complex disorder that is considered a worldwide epidemic. MetS is defined by a cluster of interconnected factors that directly increase the risk of coronary heart disease (CHD), other forms of cardiovascular atherosclerotic diseases (CVD), and diabetes mellitus type 2 (DMT2). Its main components are dyslipidemia (elevated triglycerides and apolipoprotein B (apoB)-containing lipoproteins, and low high-density lipoproteins (HDL)), elevation of arterial blood pressure (BP) and dysregulated glucose homeostasis, while abdominal obesity and/or insulin resistance (IR) have gained increasing attention as the core manifestations of the syndrome.<sup>(1-3)</sup>

A number of expert groups have developed clinical criteria for the metabolic syndrome. All groups agreed on the core components of the metabolic syndrome: obesity, insulin resistance, dyslipidaemia and hypertension.<sup>(4, 5)</sup>

The three components of atherogenic dyslipidemia (increased low-density lipoprotein (LDL), decreased HDL and high blood triglyceride concentrations) are individually associated with a cardiovascular risk can contribute to the buildup of plaques in arteries. These plaques can cause arteries to narrow and harden, which can lead to a heart attack or stroke.<sup>(6)</sup>

MetS has been associated with atherosclerosis in some epidemiological studies. It is important to investigate the prevalence of MetS and its components, and study the association of the MetS with subclinical atherosclerosis. The presence and extent of coronary artery calcium (CAC) are strongly correlated with the magnitude of coronary atherosclerosis plaque burden and subsequent coronary events.<sup>(7)</sup>

Coronary artery disease is one of the leading causes of death. Quantifying the amount of coronary artery calcium with unenhanced CT calcium score has been shown to be a reliable noninvasive technique for screening risk of future cardiac events<sup>(8,9)</sup> and can be quantified by using the Agatston score<sup>(10)</sup> or scores such as the volume score<sup>(11)</sup> or calcium mass<sup>(12)</sup>. Large patient studies have shown that the amount of coronary artery calcium based on the Agatston score is a strong predictor for risk of myocardial infarction and sudden cardiac death, independently of conventional coronary risk factors<sup>(13-15)</sup>.

## Aim of the Work

The purpose of this study is to assess the presence and extent of coronary calcium in patients with metabolic syndrome by MSCT.

## Chapter one

# The Metabolic Syndrome

Over the past two decades, a striking increase in the number of people with metabolic syndrome (MetS) has taken place, it is considered one of the important public health challenges in the world. MetS includes hypertriglyceridemia, abdominal obesity, insulin resistance, glucose intolerance and hypertension, representing a clustering of cardiovascular risk factors.<sup>(16)</sup> MetS and its components are all associated with increased atherosclerotic burden, and therefore, increased risk of cardiovascular disease.<sup>(17)</sup>

Its main components are dyslipidemia (elevated triglycerides and apolipoprotein B (apoB)-containing lipoproteins, and low high-density lipoproteins (HDL), elevation of arterial blood pressure (BP) and dysregulated glucose homeostasis, while abdominal obesity and/or insulin resistance (IR) have gained increasing attention as the core manifestations of the syndrome. Recently, other abnormalities such as chronic proinflammatory and prothrombotic states, non-alcoholic fatty liver disease and sleep apnea have been added to the entity of the syndrome, making its definition even more complex.<sup>(2, 3)</sup>

A main evolving aspect of MetS is its increasing prevalence in both childhood and young adulthood and the future implications to the global health burden this may confer.<sup>(18)</sup>

It is estimated that around 20-25 percent of the world's adult population have the metabolic syndrome 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. In addition, people with metabolic syndrome have a five fold greater risk of developing type 2 diabetes.<sup>(19)</sup>

MetS appears to have a component of heritability, which suggests a genetic basis <sup>(20)</sup>.

### **General Prevalence of the MetS:**

Clearly, the prevalence of MetS varies and depends on the criteria used in different definitions, as well as the composition (sex, age, race and ethnicity) of the population studied <sup>(21)</sup>. No matter which criteria are used, the prevalence of MetS is high and rising in all western societies, probably as a result of the obesity epidemic <sup>(22-24)</sup>.

Similarly to western societies, the prevalence of MetS is rapidly increasing in developing countries, ranging from 9.8% in male urban North Indians to 42% in female urban Iranians. This increase is observed regardless of the criteria used and reflects the transition from a traditional to a Western-like lifestyle.<sup>(25)</sup>

**Special prevalence:***Age-related demographics*

The prevalence of metabolic syndrome increases with age, with about 40% of people older than 60 years meeting the criteria <sup>(26)</sup> However, metabolic syndrome can no longer be considered a disease of only adult populations. Alarming, metabolic syndrome and diabetes mellitus are increasingly prevalent in the pediatric population, again in parallel with a rise in obesity.<sup>(27)</sup>

*Sex-related demographics*

Metabolic syndrome is similarly prevalent in men and women after adjusting for age. However, several considerations are unique to women with metabolic syndrome, including pregnancy, use of oral contraceptives, and polycystic ovarian syndrome.<sup>(28)</sup> Metabolic syndrome and polycystic ovarian syndrome share the common feature of insulin resistance; they therefore share treatment implications as well.<sup>(29)</sup> Cardiometabolic risk is thought to be elevated in both groups<sup>(30)</sup> In addition, a modest association is apparent between metabolic syndrome and breast cancer, especially in postmenopausal women<sup>(31)</sup> Overall, the prevalence of metabolic syndrome in women appears to be increasing, particularly in those of childbearing age.<sup>(32)</sup>

***Race-related demographic:***

The fact that the diagnostic criteria for metabolic syndrome vary between ethnic populations is testimony to significant nuances in the manifestation of metabolic syndrome in these groups. In the United States, metabolic syndrome has a high prevalence in African Americans, particularly and this has been attributed to the higher prevalence of obesity, hypertension, and diabetes in this population.<sup>(33)</sup>

**Aetiology:**

The underlying aetiology of the metabolic syndrome is still debated. Various factors seem to be involved.<sup>(34, 35)</sup>

- Insulin resistance: Insulin resistance appears to be the primary mediator of metabolic syndrome. Insulin promotes glucose uptake in muscle, fat, and liver cells and can influence lipolysis and the production of glucose by hepatocytes.<sup>(36)</sup>
- Obesity: The distribution of adipose tissue appears to affect its role in metabolic syndrome. Fat that is visceral or intra-abdominal correlates with inflammation, whereas subcutaneous fat does not. There are a number of potential explanations for this, including experimental observations that omental fat is more resistant to insulin and may result in a higher concentration of toxic free fatty acids in the portal circulation.<sup>(37)</sup>
- Lack of physical activity.
- Atherogenic diet and atherogenic dyslipidaemia.
- Prothrombotic and proinflammatory states.<sup>(37)</sup>

**Other factors:**

In addition to age, race, and weight, other factors associated with an increased risk of metabolic syndrome in NHANES III included postmenopausal status, smoking, low household income, high carbohydrate diet, and physical inactivity.<sup>(38)</sup> In the Framingham Heart Study, soft drink consumption was also associated with an increased risk of developing adverse metabolic traits and the metabolic syndrome.<sup>(39)</sup> Use of atypical antipsychotic medications, especially clozapine, significantly increases risk for the metabolic syndrome.<sup>(40)</sup> A parental history of metabolic syndrome increases risk, and genetic factors may account for as much as 50 percent of the variation in levels of metabolic syndrome traits in the offspring.<sup>(41-44)</sup>

**Definitions:**

MS was firstly defined by World Health Organization (WHO) in 1998<sup>(45)</sup>, after that many international agencies and organizations purposed various definitions to screen it. Out of these the most widely used definitions are by the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP-III) proposed in 2001<sup>(46)</sup> and the International Diabetes Federation (IDF) proposed in 2005<sup>(47)</sup>. But all the groups agreed on the core components of MS that consist of obesity, insulin resistance, dyslipidemia and hypertension, however the specific factors and their cut off values used in the various definitions



were different to identify MS. According to a recent systematic review of studies published between 1998 and 2005, has shown the strong association between the MS and the risk of CVD<sup>(48)</sup> and diabetes.<sup>(49)</sup>

The last **International Diabetes Federation (IDF) Worldwide Definition of the Metabolic Syndrome** provides physicians with the tools to quickly identify those at risk and also to compare the impact across nations and ethnic groups. The new IDF worldwide definition addresses both clinical and research needs, providing an accessible, diagnostic tool suitable for worldwide use and establishing a comprehensive ‘platinum standard’ list of additional criteria that should be included in epidemiological studies and other research into the metabolic syndrome.<sup>(47)</sup>

***The new International Diabetes Federation (IDF) definition:***

According to the new IDF definition, for a person to be defined as having the metabolic syndrome he must have:

**Central obesity: (defined as waist circumference with ethnicity specific values)**

**Plus any two of the following four factors:**

- ***Raised TG level:  $\geq 150$  mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality***

- ***Reduced HDL cholesterol:*** < 40 mg/dL (1.03 mmol/L) in males and < 50mg/dL (1.29 mmol/L) in females, ***or specific treatment for this lipid abnormality.***
- ***Raised blood pressure:*** systolic BP  $\geq$  130 or diastolic BP  $\geq$  85 mm Hg, ***or treatment of previously diagnosed hypertension.***
- ***Raised fasting plasma glucose (FPG)  $\geq$  100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes.***

If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define presence of the syndrome.

***\* If BMI is  $>30\text{kg/m}^2$ , central obesity can be assumed and waist circumference does not need to be measured.*** <sup>(50)</sup>

While the pathogenesis of the metabolic syndrome and each of its components is complex and not well understood, **central obesity** and **insulin resistance** are acknowledged as important causative factors. <sup>(51-55)</sup>

**Table (1):** Ethnic specific values for waist circumference <sup>(47)</sup>

Central obesity is most easily measured by waist circumference using the guidelines in which are gender and ethnic-group (not country of residence) specific.

| Country/Ethnic group                                             | Waist circumference                                                                                                                                                   |
|------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Europids</b>                                                  | Male $\geq 94$ cm<br>Female $\geq 80$ cm<br><i>In the USA, the ATP III values (102 cm male; 88 cm female) are likely to continue to be used for clinical purposes</i> |
| <b>South Asians</b>                                              | Male $\geq 90$ cm <i>Based on a Chinese, Malay and Asian-Indian population</i><br>Female $\geq 80$ cm                                                                 |
| <b>Chinese</b>                                                   | Male $\geq 90$ cm<br>Female $\geq 80$ cm                                                                                                                              |
| <b>Japanese</b>                                                  | Male $\geq 90$ cm<br>Female $\geq 80$ cm                                                                                                                              |
| <b>Ethnic South and Central Americans</b>                        | <i>Use South Asian recommendations until more specific data are available</i>                                                                                         |
| <b>Eastern Mediterranean and Middle East (Arab) and Africans</b> | <i>Use European data until more specific data are available</i>                                                                                                       |

*(Source: International Diabetic Fedration, 2005)*

The IDF consensus group has highlighted a number of other parameters that appear to be related to the metabolic syndrome which should be included in research studies to help determine the predictive power of these extra criteria for CVD and/or diabetes. <sup>(47)</sup>

**Table (2):** Additional criteria of metabolic syndrome <sup>(47)</sup>

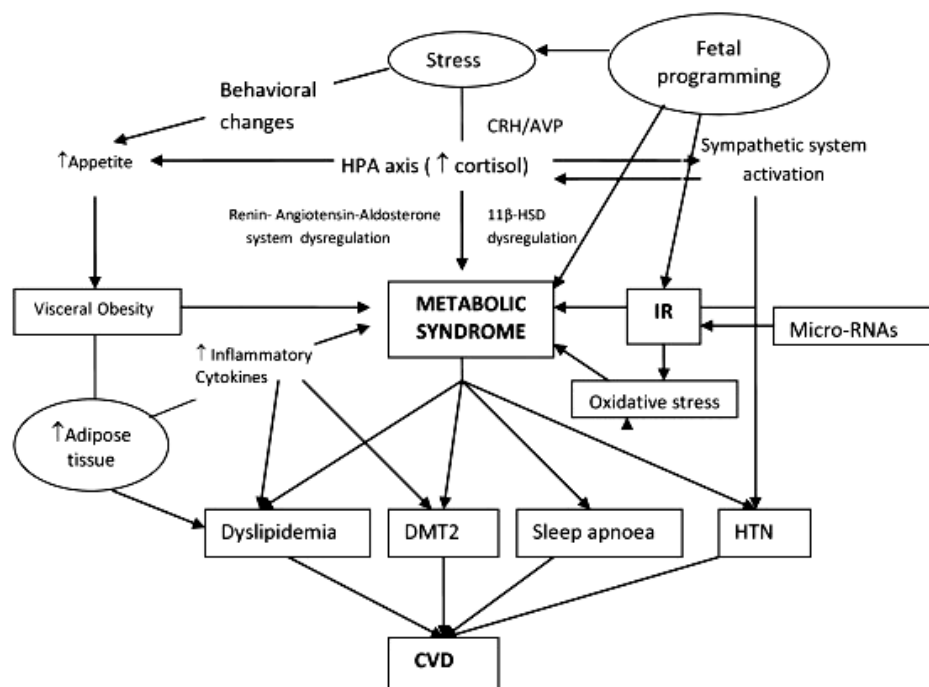
|                                                                                  |                                                                                                                                                                          |
|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>1-Abnormal body fat distribution</b>                                          | General body fat distribution (DEXA)<br>Central fat distribution (CT/MRI)<br>Adipose tissue biomarkers: leptin, adiponectin<br>Liver fat content (MRS)                   |
| <b>2-Atherogenic dyslipidaemia</b><br>(beyond elevated triglyceride and low HDL) | ApoB (or non-HDL-c)<br>Small LDL particles                                                                                                                               |
| <b>3-Dysglycaemia</b>                                                            | OGTT                                                                                                                                                                     |
| <b>4-Insulin resistance</b><br>(other than elevated fasting glucose)             | Fasting insulin/proinsulin levels<br>HOMA-IR<br>Insulin resistance by Bergman Minimal Model<br>Elevated free fatty acids (fasting and during OGTT)<br>M value from clamp |
| <b>5-Vascular dysregulation</b> (beyond elevated blood pressure)                 | Measurement of endothelial dysfunction<br>Micro albuminuria                                                                                                              |
| <b>6-Proinflammatory state</b>                                                   | Elevated high sensitivity C-reactive protein<br>Elevated inflammatory cytokines (e.g. TNFalpha, IL-6)<br>Decrease in adiponectin plasma levels                           |
| <b>7-Prothrombotic state</b>                                                     | Fibrinolytic factors (PAI-1, etc)<br>Clotting factors (fibrinogen, etc)                                                                                                  |
| <b>8-Hormonal factors</b>                                                        | Pituitary-adrenal axis                                                                                                                                                   |

*(Source: International Diabetic Fedration, 2005)*

Currently, the two most widely used definitions are those of the NCEP: ATP III and IDF focusing specifically on waist circumference, which is a surrogate measure of central obesity. In contrast, the WHO and the EGIR definitions are all largely focused on insulin resistance.<sup>(56)</sup>

## Pathophysiology of Metabolic Syndrome:

The insight into the pathophysiology of metabolic syndrome provide a practical tool to identify patients with an increased risk of cardiovascular disease (CVD) and diabetes mellitus type 2. Identification of metabolic syndrome is a public health strategy to define susceptible people, which may prompt early diagnosis of previously undetected components of metabolic syndrome.<sup>(57)</sup>



**Fig. (1):** A schematic image of the conditions implicated in the pathophysiology of the metabolic syndrome and their potential interactions. IR: Insulin Resistance; HTN: Hypertension; HPA axis: Hypothalamic-Pituitary-Adrenal Axis; DMT2: Diabetes Mellitus type 2; CVD: Cardiovascular disease; CRH: Corticotropin Releasing Hormone; AVP: Arginine Vasopressin (Source: Kassi et al. *Bio Med Central Medicine* 2011).

### **1- Central (abdominal) obesity:**

Obesity is an expanding public health problem worldwide, creating a global health epidemic. According to the World Health Organization, worldwide obesity has doubled since 1980 with 1.5 billion adults considered obese in 2008.<sup>(57, 58)</sup> Obesity has long been associated with an increased risk for coronary heart disease (CHD). In a meta-analysis of studies assessing the impact of body weight on CHD, there was a 29 percent increase in CHD for each five-unit increase in body mass index (BMI).<sup>(59)</sup> The risk of CHD in obese and overweight persons is compounded by the frequent coexistence of other CHD risk factors such as hypertension, dyslipidemia, and diabetes. Evidence does exist to suggest that obesity, particularly visceral adipose, among adolescents is associated with acceleration of atherosclerosis.<sup>(60-62)</sup>

The International Obesity Task Force (IOTF) reports that 1.7 billion of the world's population is already at a heightened risk of weight-related, non-communicable diseases such as type 2 diabetes.<sup>(63)</sup>

The mechanism by which excessive body fat causes insulin resistance and impairs glucose metabolism is not clearly defined but fat stores (particularly visceral adipose tissue) are an important cause of increased FFA and TG in the skeletal muscle, which impairs insulin secretion, raising blood glucose levels and the likelihood of developing diabetes. Excess adipose tissue (particularly the visceral fat tissue in the abdomen) also releases inflammatory cytokines that increase

insulin resistance in the body's skeletal muscles. Furthermore, central obesity is also associated with a decreased production of adiponectin, which is the adipose-specific, collagen-like molecule found to have antidiabetic, anti-atherosclerotic and anti-inflammatory functions.<sup>(64)</sup>

## ***2- Insulin resistance:***

Is present in the majority of people with the metabolic syndrome. It strongly associates with other metabolic risk factors and correlates univariately with CVD risk. These associations, combined with belief in its priority, account for the term insulin resistance syndrome. Patients with longstanding insulin resistance frequently manifest glucose intolerance, another emerging risk factor. When glucose intolerance evolves into diabetes-level hyperglycemia, elevated glucose constitutes a major, independent risk factor for CVD.<sup>(65)</sup>

The mechanisms responsible for insulin resistance syndromes include genetic or primary target cell defects, auto antibodies to insulin, and accelerated insulin degradation.<sup>(66)</sup> Given that glucose and lipid metabolism largely depend on mitochondria to generate energy in cells, mitochondrial dysfunction may play an important role in the development of insulin resistance and associated complications.<sup>(67)</sup>

Inflammation and adipocytokines probably play some role in the etiopathogenesis of metabolic syndrome.<sup>(68-70)</sup> Increased levels of the acute-phase inflammatory marker C-