Introduction

Metabolic syndrome (MS) is represented by a cluster of risk factors associated with insulin resistance syndrome. The literature reports important variations in prevalence of metabolic syndrome, depending on diagnostic criteria. At the present time there are more than five definitions for metabolic syndrome. The definition most frequently accepted in clinical practice was first described in 2001 and updated in 2005 by the National Cholesterol Education Program, Adult Panel III (NCEP APIII). This definition establishes that three or more of the following criteria should be met to diagnose metabolic syndrome: fasting blood glucose (FBG) ≥100 mg/dl, triglycerides (TG) ≥150 mg/dl, low high-density lipoprotein cholesterol (HDL-c) (<40 mg/dl in males, <50 mg/dl in females), hypertension ≥130/85 mmHg or under hypertension treatment, and abdominal obesity detected using waist circumference (WC) (>102 cm for males and >88 cm for females) ***(Miller et al., 2010).***

The metabolic syndrome is associated with a 2-fold increase in cardiovascular outcomes and 1.5-fold increase in all-cause mortality ***(Babic et al., 2011).***

The prevalence of MS in patient with acute myocardial infarction (AMI) is high as shown by many studies (between 40%-50%) ***(Clavijo et al, 2006; Zeller et al, 2005 & Solymoss et al, 2004).*** Risk factors of metabolic syndrome: hypertension, dyslipidemia, and obesity are thought to be the factors responsible for the increased morbidity in this group of patients.

Increased blood glucose level was also thought to affect the prognosis as increased morbidity and mortality in patients with diabetes following AMI is well-described ***(Levantesi et al., 2005; Abraham et al., 2003 & Abbud et al., 1995).*** Long term survival can be improved via intensive insulin treatment among diabetics with elevated glucose on presentation ***(Malmberg et al., 1999).***

In long-term follow-up, high blood glucose was associated with increased rates of death, recurrent myocardial infarction (MI), heart failure, decreased ejection fraction, and increased infarct size ***(Stranders et al., 2004).***

Among patients who have a history of AMI, metabolic syndrome was recently shown to be associated with a higher rate of all-cause death and the composite of cardiovascular death, nonfatal stroke, and nonfatal MI. Metabolic syndrome has also been shown to be associated with a higher incidence of severe heart failure following AMI ***(Zeller et al., 2005).***

Abdominal obesity, insulin resistance, atherogenic dyslipidemia, elevated blood pressure, prothrombotic and proinflammatory states are the principal factors of this multifaceted syndrome. The prevalence of cardiovascular disease and cardiovascular disease related morbidity and mortality has been reported to be significantly higher in patients with MS. Moreover, metabolic syndrome has been shown to be associated with poor in-hospital outcome in patients with AMI.

Aim of the Study

Is to discuss the correlation between metabolic syndrome and myocardial dysfunction and also to discuss the Management of underlying risk factors.

Chapter (1): Metabolic Syndrome and its Components

Metabolic syndrome (MetS) is a multiplex risk factor that arises from insulin resistance accompanying abnormal adipose deposition and function. It is a risk factor for coronary heart disease, as well as for diabetes, fatty liver, and several cancers.

* Historical Background

The term "metabolic syndrome" dates back to at least the late 1950s, but came into common usage in the late 1970s to describe various associations of risk factors with diabetes that had been noted as early as the 1920s ***(Joslin, 1921 and Kylin, 1923)*.**

- The Marseilles physician Dr. Jean Vague, in 1947, observed that upper body obesity appeared to predispose to diabetes, atherosclerosis, gout, and calculi ***(Vague, 1947).***
- Avogadro, Crepaldi and coworkers described six moderately obese patients with diabetes, hypercholesterolemia, and marked hypertriglyceridemia, all of which improved when the patients were put on a hypocaloric, low-carbohydrate diet ***(Avogadro et al., 1967).***
- In 1977, Haller used the term "metabolic syndrome" for associations of obesity, diabetes mellitus, hyper-lipoproteinemia, hyperuricemia, and hepatic steatosis when describing the additive effects of risk factors on atherosclerosis ***(Haller, 1977).***

- The same year, Singer used the term for associations of obesity, gout, diabetes mellitus, and hypertension with hyperlipoproteinemia ***(Singer, 1977).***
- In 1977 and 1978, Gerald B. Phillips developed the concept that risk factors for myocardial infarction concur to form a "constellation of abnormalities" (i.e., glucose intolerance, hyperinsulinemia, hyper-cholesterolemia, hypertriglyceridemia, and hypertension) associated not only with heart disease, but also with aging, obesity and other clinical states. He suggested there must be an underlying linking factor, the identification of which could lead to the prevention of cardiovascular disease; he hypothesized that this factor was sex hormones ***(Phillips, 1978).***
- In 1988, in his Banting lecture, Gerald M. Reaven proposed insulin resistance as the underlying factor and named the constellation of abnormalities syndrome X. Reaven did not include abdominal obesity, which has also been hypothesized as the underlying factor, as part of the condition ***(Reaven, 1988).***

The terms "metabolic syndrome," "insulin resistance syndrome," and "syndrome X" are now used specifically to define a constellation of abnormalities associated with increased risk for the development of type 2 diabetes and atherosclerotic vascular disease (e.g., heart disease and stroke) ***(Reaven, 1988).***

* Pathophysiology

The metabolic syndrome, a concurrence of abdominal fat, disturbed glucose and insulin metabolism, dyslipidemia, and hypertension has been strongly associated not only with subsequent development of type II diabetes (T2D) but also with athero-thrombosis. The physiopathology of this association is complex. The metabolic syndrome affects the thrombogenicity of circulating blood. Apart from its effect on platelets, a procoagulant and hypofibrinolytic state has been identified; mainly the result of the inflammatory state, dyslipidemia, and liver fat accumulation that accompany the metabolic syndrome. Among haemostasis disturbances, the strong rise in the inhibitor of plasminogen activator type I plasma level is the most documented abnormality implicating the participation of the oxidative stress and inflammatory state developed during the metabolic syndrome. Endothelial dysfunction is also a central feature. Moreover, secretion products of fat tissues (adipokines) are now thought to have direct modulating effects on the vascular and the circulating cells. In support of these data, the metabolic syndrome may predispose not only to atherosclerosis but also to venous thrombosis ***(Alessi et al., 2008)***.

- ***Role of Adipocyte:***

The adipocyte is an active endocrine secretory cell releasing free fatty acids and producing several cytokines including tumor necrosis factor (TNF), interleukins (ILs), leptin, and adiponectin ***(Berg et al., 2002)***.

Adiponectin is the most abundant adipokine secreted by adipose cells that may couple regulation of insulin sensitivity with energy metabolism. Adiponectin is a 30-kDa protein that consists of an N-terminal collagenous domain and a C-terminal globular domain. Under normal conditions, the adiponectin gene (AMP1) located on chromosome 3q27 is expressed exclusively in adipose tissue, and recent genome-wide scans have mapped a diabetes susceptibility locus to this chromosome ***(Stumvoll et al., 2002).***

Women have about 40% higher circulating levels of adiponectin than men ***(Han et al., 2007).***

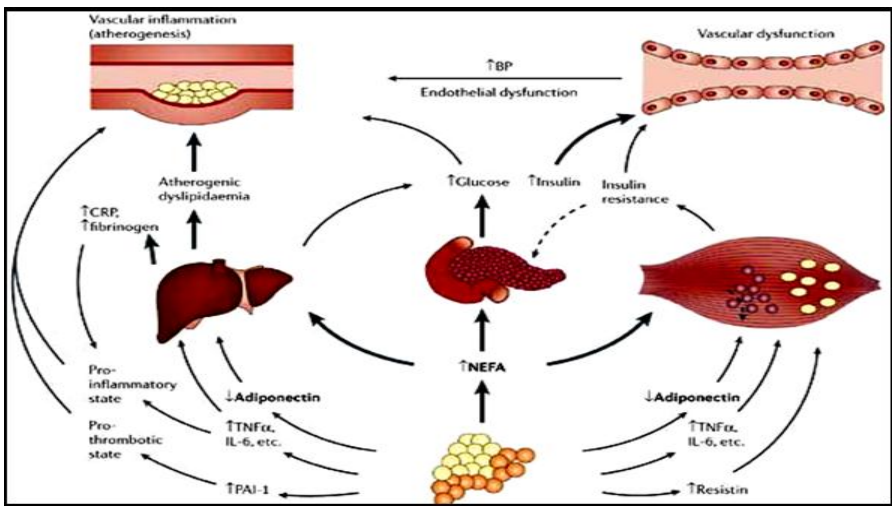

Fig. (1): Pathophysiology of the metabolic syndrome ***(Rosenson et al., 2008)***

- ***Microalbuminuria:***

Microalbuminuria is a risk factor for coronary artery disease and progressive renal disease in patients with diabetes mellitus. Some correlations have been shown between microalbuminuria and indicators of cardiovascular risk in nondiabetic patients as well, but conflicting data have also been reported. These studies may be summarized by saying that insulin resistance is common among people with microalbuminuria, but that microalbuminuria is rare among all subjects with insulin resistance. Available data for nondiabetic normotensive patients do not support microalbuminuria as a risk factor for coronary artery disease or as a significant component of metabolic syndrome ***(Miranda et al., 2005).***

- ***Hypertension:***

Among patients with hypertension, approximately half are insulin resistant. Insulin resistance might also increase blood pressure via reduced nitric oxide-mediated vasodilation, increased salt sensitivity, or plasma volume expansion. These mechanisms might also underlie the decreased response to antihypertensive therapy seen in insulin-resistant individuals. Hypertension is a therapeutic target for angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. The role of these agents may extend to metabolic syndrome ***(Miranda et al., 2005).***

- ***Sleep-related breathing disorder:***

Investigation into other causes or exacerbating factors should be considered. For example, sleep-related breathing disorders, such as obstructive sleep apnea, are becoming increasingly relevant and novel risk factors for metabolic syndrome ***(Tasali et al., 2008)***.

The difficulty in clarifying the associations between obstructive sleep apnea and metabolic syndrome lie in part with the confounding effect of obesity ***(Lam et al., 2007).***

* Etiology

Risk factors for metabolic syndrome include family history, poor diet, and inadequate exercise.

Metabolic syndrome is thought to be caused by adipose tissue dysfunction and insulin resistance. Dysfunctional adipose tissue also plays an important role in the pathogenesis of obesity-related insulin resistance ***(Goossens, 2008).*** Both adipose cell enlargement and infiltration of macrophages into adipose tissue result in the release of proinflammatory cytokines and promote insulin resistance ***(Gustafson et al., 2007).***

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 ***(Lann et al., 2007).***

Additional contributors to insulin resistance include abnormalities in insulin secretion and insulin receptor signaling, impaired glucose disposal, and proinflammatory cytokines. These abnormalities, in turn, may result from obesity with related increases in free fatty acid levels and changes in insulin distribution (insulin accumulates in fat) ***(Lewis et al., 2002).***

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 ***(Després et al., 2008).***

Abdominal fat is known to produce potentially harmful levels of cytokines, such as tumor necrosis factor, adiponectin, leptin, resistin, and plasminogen activator inhibitor ***(Türkoglu et al., 2003).***

Psychological characteristics, including anger, depression, and hostility, may be linked to increased risk for metabolic syndrome ***(Goldbacher et al., 2007).*** However, psychological disorders, especially anxiety, may represent comorbidity or a complication of metabolic syndrome ***(Sardinha et al., 2013)***.

* Epidemiology

• International occurrence

Metabolic syndrome is an increasing global problem. Approximately one fourth of the adult European population is estimated to have metabolic syndrome, with a similar prevalence in Latin America ***(Grundy, 2008).*** It is also considered an emerging epidemic in developing East Asian countries, including China, Japan, and Korea. The prevalence of metabolic syndrome in East Asia may range from 8-13% in men and from 2-18% in women, depending on the population and definitions used ***(Nestel et al., 2007).***

In Japan, the Ministry of Health, Labor, and Welfare has instituted a screening and interventional program ***(Kohro, 2008).*** Metabolic syndrome has been recognized as a highly prevalent problem in many other countries *worldwide* ***(Kolovou et al, 2007; Mahadik et al, 2007 and Malik et al, 2008).***

• Occurrence in the United States

Metabolic syndrome is increasing in prevalence, paralleling an increasing epidemic of obesity. In the United States, where almost two thirds of the population is overweight or obese, more than one fourth of the population meets diagnostic criteria for metabolic syndrome ***(Grundy, 2008).*** In the United States, data from a 1999-2000 survey showed that the age-adjusted prevalence of metabolic syndrome among adults aged 20 years or older had risen from 27% (data from 1988-1994) to 32% ***(Ford et al., 2004).***

- ***Race-related demographics***

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. The original metabolic syndrome criteria were derived in mostly Caucasian populations, and some have argued for modification of individual criteria for specific ethnic subgroups, as has been done with waist circumference for patients of Asian origin ***(Banerjee et al., 2007)***.

In the United States, metabolic syndrome has a high prevalence in African Americans, particularly African American women, and this has been attributed to the higher prevalence of obesity, hypertension, and diabetes in this population ***(Clark et al., 2007).*** However, the highest age-adjusted prevalence of metabolic syndrome in the United States is found in Mexican Americans, approximately 31.9% of whom had the condition (compared with 27% of the general population) in a 1988-1994 survey ***(Ford et al., 2002).***

A study by Ukegbu et al, found that African immigrants have a worse metabolic profile than do African Americans but that they have a similar prevalence of metabolic syndrome. This may mean that metabolic syndrome may underpredict metabolic risk in Africans ***(Ukegbu et al., 2011)***.

- ***Sex-related demographics***

Metabolic syndrome is similarly prevalent in men (24%) and women (23%), after adjusting for age. However, several considerations are unique to women with metabolic syndrome, including pregnancy, use of oral contraceptives, and polycystic ovarian syndrome ***(Bentley-Lewis et al., 2007).*** Metabolic syndrome and polycystic ovarian syndrome share the common feature of insulin resistance; they therefore share treatment implications as well ***(Essah et al., 2007).*** Cardiometabolic risk is thought to be elevated in both groups ***(Cussons et al., 2007).***

In addition, a modest association is apparent between metabolic syndrome and breast cancer, especially in postmenopausal women ***(Xue et al., 2007).*** Overall, the prevalence of metabolic syndrome in women appears to be increasing, particularly in those of childbearing age ***(Ramos et al., 2008).***

Bhasin et al, as part of the Framingham Heart Study, found that sex hormone-binding globulin is independently associated with the risk of metabolic syndrome, whereas testosterone is not. Age, body mass index (BMI), and insulin sensitivity independently affect sex hormone-binding globulin and testosterone levels ***(Bhasin et al., 2011).*** More recent studies have raised the possibility of an association between testosterone deficiency and metabolic syndrome ***(Tsujimura et al., 2013).***

- ***Age-related demographics***

The prevalence of metabolic syndrome increases with age, with about 40% of people older than 60 years meeting the criteria ***(Ford et al., 2004).*** However, metabolic syndrome can no longer be considered a disease of only adult populations. Alarmingly, metabolic syndrome and diabetes mellitus are increasingly prevalent in the pediatric population, again in parallel with a rise in obesity ***(De Ferranti et al., 2007).***

In the United States, children are becoming obese at triple the rate compared with the 1960s, making the study and treatment of this problem paramount. The epidemic of metabolic syndrome in children and adolescents is an international phenomenon, leading the International Diabetes Foundation to publish an updated consensus statement to guide diagnosis and further study of the condition ***(Morrison et al., 2008).***

* Diagnosis

- ***History***

As with other diseases, careful history taking is important in metabolic syndrome. Even though the condition is diagnosed based on physical and laboratory features, it may be suspected if symptoms of any of the component disorders are present, such as the increased hunger, thirst, or urination that may accompany hyperglycemia ***(Olufadi et al., 2008)***.

Patients reporting a history of hypertension, dyslipidemia, or hyperglycemia warrant screening for metabolic syndrome. Symptoms suggesting the rise of cardiovascular and other complications, such as chest pain or shortness of breath, must be investigated carefully. As lifestyle changes can ameliorate the condition, attention should be paid to the patient's dietary habits and exercise routines so that areas for improvement can be identified ***(Olufadi et al., 2008)***.

The patient's social history is important for identifying additional risks, such as **tobacco** use, which may exacerbate the increased cardiovascular complications associated with metabolic syndrome ***(Olufadi et al., 2008).***

A family history should be obtained because genetics may play an important role in metabolic syndrome. This feature of the disease is under active investigation; however, no gene or group of genes has yet been implicated consistently, suggesting that environment exerts substantial influence ***(Joy et al., 2008).***

Finally, a thorough review of systems may help to identify related problems, such as menstrual irregularities that can be seen in polycystic ovarian syndrome.

- ***Signs and symptoms:*** ***(Olufadi et al., 2008)***

Clinical manifestations of metabolic syndrome include the following:

- Hypertension
- Hyperglycemia