INTRODUCTION

The prevalence of metabolic syndrome (MS) is very high in coronary heart disease (CHD) patients. MS confers a higher risk of long-term major adverse cardiac and cerebral events ***(Hu et al., 2006).***

World Health Organization (WHO) clinical critical criteria for MS insulin resistance (IR) identified by one of following:

- Type II diabetes.
- Impaired fasting glucose.
- Impaired glucose tolerance.

Plus any 2 of the following:

- Antihypertensive medication and/or high blood pressure 140mmHg systolic and/or 90mmHg diastolic.
- Plasma triglycerides >150mg/dL.
- High density lipoproteins (HDL) < 35mg/dL in men and < 39mg/dL in women.
- Waist hip ratio > 0.9 in men and > 0.85 in women albumin: creatinine ratio 30mg/g.

(Alberti et al., 2005)

The National Cholesterol Education Program (NCEP) adult treatment panel III (ATP III) guidelines recommend that patient with at least 3 of the following clinical variables be designated as

having MS: abdominal obesity as reflected in increased waist circumference; a law high-density lipoprotein cholesterol (HDL-C) level < 35mg/dL in men and < 39mg/dL in women, an elevated triglyceride level > 150mg/dL, elevated blood pressure >140/190 or treatment with antihypertensive medication and/or elevated fasting plasma glucose > 100mg/dL or treatment with antidiabetic medication. Unless patients with MS change their lifestyle, existing cardiovascular and metabolic risk factors will be worsen or new risk factors will develop. This helps explain why these patients are at increased risk for type II diabetes mellitus (DM) and CHD ***(Stone et al., 2006)***.

The new ***International Diabetes Federation (IDF)*** definition for MS ***(2005):***

Central obesity, defined as waist equal to or more than 94 cm for males and 80 cm for females together with any two of the following:

1- Raised triglycerides: > 150 mg/dL (1.695 mmol/L) or on specific treatment for this lipid abnormally.

2- Low HDL-cholestcrol: < 40 mg/dL (1.0 mmol/L) in males and < 50 mg/dL (1.3 mmol/L) in females or on specific treatment for this lipid abnormality.

3- Raised blood pressure: systolic BP > 130 or diastolic > 85 huypertension.

4- Fasting blood glucose > 100mg/dL (6.1 mmol/L) or previous diagnosis of diabetes or impaired glucose

tolerance (The IDF consensus new world definition of the metabolic syndrome) ***(Grundy et al., 2005).***

CHD represents the leading cause of death in adult in the western world. Myocardial infarction (MI) is a lethal manifestation of CHD and can present as sudden death. Although MI mainly occurs in patients older than 45, young men or women can suffer MI, although with a lower incidence. However the disease carries significant morbidity, psychological effect, and financial constraint for the person and the family when it occurs at a young age. The protection offered by young age has been slowly taken away by the increased prevalence of risk factor for CHD in adolescent such as smoking, obesity and lack of physical activity. Better prognosis among young adults is achieved when the appropriate investigation and treatment are offered. The cut off age of 45 has been used in most studies to define young patients with CHD or MI ***(Strike et al., 2003).***

MS Associated with a host of traditional and emerging pro inflammatory and pro thrombotic cardiovascular (CV) risk factor. This result in a 2-4 fold increase in CV event when subject with diabetes are excluded form analysis ***(Alexander et al., 2003).***

MS is common among subject with diabetes and is a very common risk factor of macrovascular complications however its contribution to the microvascular complication has not been assessed ***(Nawaf et al., 2006).***

AIM OF THE WORK

The aim of the study is to assess the relation between metabolic syndrome and acute coronary syndrome in the intensive cane unit and how can this relation affect the management.

METABOLIC SYNDROME

The MS (also known as metabolic syndrome X) is a grouping of cardiac risk factors that result from IR (when the body's tissues do not respond normally to insulin). A person with metabolic syndrome has a greatly increased risk of cardiovascular disease (CVD) and premature death.

The MS has received increased attention in the past few years. It consists of multiple, interrelated risk factors of metabolic origin that appear to directly promote the development of atherosclerotic cardiovascular disease (ASCVD) ***(Grundy et al., 2005).***

The terms "metabolic syndrome", "insulin resistance syndrome", and "syndrome X" are now used specifically to define constellation of abnormalities that is associated with increased risk for the development of type 2 diabetes and ASCVD (e.g. heart disease and stroke) ***(Grundy et al., 2005).***

The pathogenesis of the syndrome has multiple origins. However, obesity and sedentary lifestyle coupled with diet and still largely unknown genetic factors clearly interact to produce the syndrome (Figure 1) ***(Steinberger et al., 2009).***

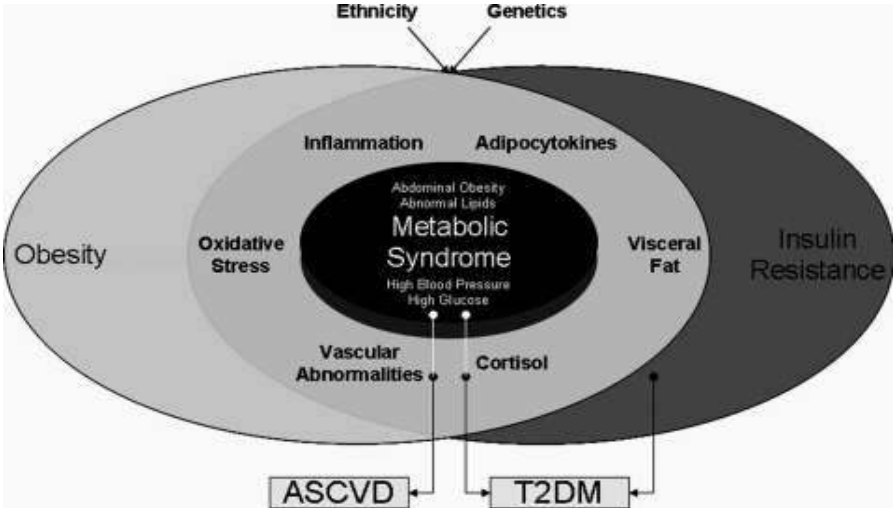

Figure (1): Schematic of components of the MS
(Steinberger et al., 2009).

Epidemiology of metabolic syndrome:

The prevalence of MS has increased significantly over the past decade among both adults and adolescents. Based on United State (US) population-weighted estimates, >47 million adults and >2 million adolescents currently have the MS phenotype. The trend for increasing MS prevalence is evident in both sexes and in most ethnic groups. Older age, postmenopausal state, higher body/mass index (BMI) (especially, visceral fat), high carbohydrate intake, and physical inactivity are associated with an increased risk of developing the MS with concomitant increase in diabetes and CHD ***(Kolovo et al., 2007).***

According to data in the Journal of American Medical Association, it is estimated that 47 million have MS with the

incidence of the syndrome arising progressively as individuals begin to age, reaching a peak between the ages of 60–69, with the prevalence increasing from 10% in the 30–39 year age group to 45% in the 60–69 year age group ***(Ford and Giles, 2002).***

The frequency of the syndrome is lower in black than in white men. Nevertheless, black adults are susceptible to hypertension (HTN) and carry a greater risk for diabetes than whites ***(Mainous et al., 2004).***

Definition of metabolic syndrome:

There have been several definitions of MS, but the most recent definitions are from the IDF (table 1), ***(IDF, 2006; Alberti et al., 2005)*** and from the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) ***(table 2) (Grundy et al., 2005a; Grundy et al., 2005b).***

Table (1): The IDF criteria for definition of metabolic syndrome ***(Alshehri, 2010).***

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

Central obesity (defined as waist circumference ≥ 94cm for Europid men and ≥ 80cm for Europid women, with ethnicity specific values for other groups)

Plus any two of the following four factors:

- **Raised TG level:** ≥ 150 mg/dL (1.7 mmol/L), or **specific treatment for this lipid abnormality**
- **Reduced HDL-C**: < 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**
- **Raised blood pressure(BP)*:*** systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg, **or treatment of previously diagnosed hypertension**
- **Raised fasting plasma glucose** (FPG) ≥ 100 mg/dL (5.6 mmol/L), **or previously diagnosed type 2 diabetes mellitus(type2DM)**

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

TG; Triglyceride; HDL-C: High density lipoprotein-cholesterol;
OGGT: Oral glucose tolerance test

Table (2): AHA/NHLBI criteria for diagnosis of metabolic syndrome ***(Alshehri, 2010).***

Measure (any 3 of 5 constitute diagnosis of metabolic syndrome)	Categorical cut-off points
Elevated waist circumference	≥102 cm (≥40 inches) in men ≥88 cm (≥35 inches) in women
Elevated triglycerides	150 mg/dL (1.7 mmol/L) or on drug treatment for elevated triglycerides
Reduced HDL-C	≥ 40 mg/dL (≥1.03 mmol/L) in men ≥ 50 mg/dL (≥1.3 mmol/L) in women or on drug treatment for reduced HDL-C
Elevated blood pressure	≥130 mm Hg systolic blood pressure or ≥ 85 mm Hg diastolic blood pressure or on antihypertensive drug treatment in a patient with a history of hypertension
Elevated fasting glucose	≥100 mg/dL Or on drug treatment for elevated glucose

Pathophysiology of Metabolic Syndrome:

The pathophysiology of MS is extremely complex, and has been only partially explained. Most patients are old and obese with a sedentary lifestyle and a variable degree of IR. Stress can also be contributing factor. This phenomenon is frequent in people with visceral adiposity, HTN, hyperglycemia and dyslipidemia. IR in fat cells results in elevated hydrolysis of stored TG which increases the mobilization of free fatty acids (FFA) into the plasma. IR reduces glucose uptake in skeletal muscle, and in hepatocytes it impairs glycogen synthesis and storage, suppressing glucose production and release into the blood ***(Eckel et al., 2005).***

In the presence of IR, the visceral adipose cells in particular produce significant amounts of pro-inflammatory cytokines, such as tumour necrosis factor(TNF),interleukin – 1(IL-1) and interleukin-6(IL-6). In experimental models, these pro-inflammatory cytokines disrupt normal insulin action in fat and muscle cells, and this may be the major factor in causing the whole-body insulin resistance observed in patients with visceral adiposity. Further, visceral adiposity is related to an accumulation of fat in the liver, a condition known as nonalcoholic fatty liver disease (NAFLD). The result of NAFLD is an excessive release of free fatty acids into the bloodstream, and an increase in hepatic glucose production, both of which have the effect of exacerbating peripheral IR and increasing the likelihood of Type 2 diabetes ***(Liu et al., 2010).***

Table (3): Metabolic syndrome: proposed components and associated findings ***(Phillippa, 2005).***

1. Insulin Resistance*(IR)
2. Hyperinsulinemia*
3. Obesity: visceral (central), but also generalized obesity*
4. Dyslipidemia: high TG, low HDL, small dense LDL#
5. Adipocyte dysfunction
6. Impaired glucose tolerance (IGT) or type 2 diabetes mellitus (type2DM)*
7. Fatty liver (nonalcoholic steatohepatosis, steatohepatitis)
8. Essential hypertension: increased systolic and diastolic blood pressure*
9. Endothelial dysfunction (ED).
10. Renal dysfunction: micro- or macroalbuminuria
11. Polycystic ovary syndrome (PCO).
12. Inflammation: increased C-reactive protein (CRP) and other inflammatory markers
13. Hypercoagulability: increased fibrinogen and plasminogen activator inhibitor type 1(PAI-1)
14. Atherosclerosis leading to increased cardiovascular morbidity and mortality*

*Most widely incorporated into the definition and pathogenesis of MS.
LDL: low density lipoprotein.

The MS 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 MS. Among hemostasis disturbances, the strong rise in PAI-1 plasma level is the most documented abnormality implicating the participation of the oxidative stress and inflammatory state developed during the MS. ED 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 MS may predispose not only to atherosclerosis but also to venous thrombosis ***(Alessi et al., 2008).***

Obesity represents a major component of the MS and has a significant association with IR. Clearly most individuals with MS are overweight or frankly obese and indeed most people with IR have truncal obesity, and for these patients weight reduction must be the top priority. It is this truncal, central, visceral, or predominately upper body distribution of body fat that has a stronger association for CVD than just being overweight or possessing an increased BMI. Clearly, the greater the weight, the greater are the medical risks (table4), ***(Codario, 2010).***

Table (4): Classification of overweight and obesity risk for diabetes, CVD, HTN ***(Codario, 2010***).

			Risk of diabetes CVD and HTN	
			WC	WC
			Men<40	Men>40
	BMI	CLASS	Women<35	Women>35
Underweight	<18.5	-	-	-
Normal	18.5-24.5	-	-	-
Overweight	25.0-29.9	-	Increased	High
Obesity	30.0-34.9	I	High	Very high
Obesity	35.0-39.9	II	Very high	Very high
Extreme obesity	>39.9	III	Extremely high	

WC=waist circumference in inches

1- Role of Adipocyte in MS (adipocyte dysfunction):

The adipocyte is an active endocrine secretory cell releasing FFA and producing several cytokines including TNF, IL6, leptin, and adiponectin ***(Berg et al., 2005).***

Adiponectin, cardioprotective hormone is the most abundant adipokine secreted by adipose cells that may couple regulation of insulin sensitivity with energy metabolism. Adiponectin is a 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, 2002).***

Weight reduction increases plasma adiponectin levels. Among Pima Indian, individuals with high adiponectin concentrations were less likely to develop type 2 DM than those with low concentrations.In gestational DM, a condition that is biochemically and epidemiologically similar to type 2DM, adiponectin concentrations were significantly lower in women with gestational diabetes than in controls ***(Williams et al., 2004).***

2- Inflammation and Atherosclerosis:

Chronic inflammation is a pathogenic feature of atherosclerosis. Initiation of vascular inflammation is multifactorial. Direct injury to the vessel wall causes endothelial and smooth muscle cells of large arteries to become transcriptionally active and synthesize proinflammatory proteins, including chemokines, cell adhesion molecules (CAMs), and cytokines as well as growth factors and pro thrombogenic substances. Cytokine-activated macrophages and smooth muscle cells secrete matrix metalloproteinases, which, when activated, digest connective tissue elements within the vessel wall and then the fibrous cap overlying vulnerable plaques. This increases the potential for plaque rupture with exposure of thrombogenic plaque contents ***(Kwang et al., 2005)***.

Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a pre-dominantly macrophage-synthesized lipase that hydrolyzes oxidatively modified phosphatidylcholine on LDL and yields a more highly oxidized LDL particle (LDL-P) and the two biologically active inflammatory mediators lyso phosphatidyl choline (lyso-PC) and oxidized non-esterified fatty acids (ox-NEFA). These mediators are soluble within atherosclerotic lesions and elicit pro -atherogenic effects in endothelial cells, monocytes/macrophages, T-cells, neutrophils, and smooth muscle cells. For example, they increase the expression of adhesion molecules and chemokines, induce activation of

inflammatory cytokines, and activate proteolytic enzymes that impair the structural integrity of the fibrous plaque (Figure 2) ***(Robert, 2008).***

Noto et al. (2006) have shown that Lp-PLA2 concentrations are higher among patients with the MS and increased levels of Lp-PLA2 are associated with incremental components of the MS in insulin-treated patients with type 2DM.

In the cross-sectional analysis, hypertriglyceridemia, which is highly and inversely correlated with LDL size, was the only multivariate-adjusted MS component associated with Lp-PLA2 mass ***(Robert, 2008)***.

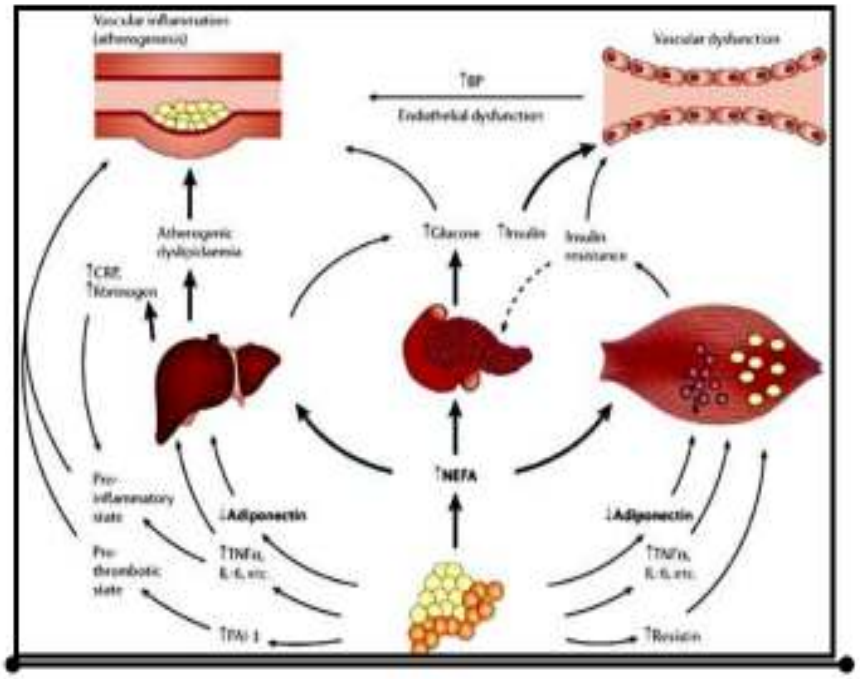

Figure (2): Pathophysiology of the MS ***(Robert, 2008)***