INTRODUCTION

The metabolic syndrome is a clustering of metabolic abnormalities that have been associated with an increased risk of coronary heart disease, stroke and cardiovascular mortality compared to the presence of an individual component ***(Mazza, 2008).***

The prevalence of metabolic syndrome manifestations is rapidly increasing worldwide, and is becoming an important health problem. Actually, metabolic syndrome includes a combination of clinical complications such as obesity (central adiposity), insulin resistance, glucose intolerance, dyslipidemia, non-alcoholic fatty liver disease and hypertension. All these alterations predispose individuals to type 2 diabetes and cardiovascular disease inducing earlier mortality rates among people ***(Martínez et al., 2011).***

Metabolic syndrome identifies clinical symptoms and lab results, including abdominal obesity, insulin resistance, hyperglycemia, hyperlipidemia, and hypertension, that lead to an increased risk of cardiovascular disease (CVD). Obesity typically results in insulin and leptin resistance and a shift from expansion of subcutaneous fat to deposition of abdominal and ectopic fat. These conditions cause metabolic deregulations ***(Gade et al., 2010).***

Increased body weight plays the most important role in metabolic syndrome, it was shown recently that each 11 cm increase in waist circumference is associated with an adjusted 80% increased risk for developing the syndrome within 5 years ***(Palaniappan et al., 2004).***

There are striking similarities between Cushing's syndrome and the metabolic syndrome as both are characterized by central obesity, hypertension, insulin resistance and glucose intolerance, several lines of evidence from different studies consistently support the view that subclinical Cushing's syndrome (autonomous cortisol secretion) may be associated with the clinical phenotype of the insulin resistance syndrome that fosters several unwanted metabolic and vascular manifestations ***(Alberti et al., 2009).***

High glucocorticoid levels lead to muscle, liver and adipocyte insulin resistance. Almost all patients with Cushing's syndrome are obese or overweight and have abdominal visceral adiposity ***(Newell et al., 2002).***

Metabolic syndrome therefore may be a clue to the presence of Cushing syndrome, however relatively high prevalence of occult CS was found in some studies up to 26 % ***(Bo, 2007).***

AIM OF THE WORK

The aim of the present study is to evaluate role of HPA (Hypothalamic Pituitary Adrenal axis) activity in relation to obesity in metabolic syndrome patients by using the overnight 1 mg dexamethasone suppression test.

METABOLIC SYNDROME

I- Epidemiology of metabolic syndrome:

Metabolic syndrome is a common condition that goes by many names (dysmetabolic syndrome, syndrome X, insulin resistance syndrome, obesity syndrome and Reaven`s syndrome). The National Heart Lung and Blood institute (NHLBI) estimates that in the U.S. about 47 million adults have metabolic syndrome. It can affect anyone at any age, but it is most frequently seen in those who are significantly overweight with most of their excess fat in the abdominal area and inactive ***(Rizzi, 2006).***

The metabolic syndrome 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). At present, it is not clear whether the metabolic syndrome has a single cause, and it appears that it can be precipitated by multiple underlying risk factors. The most important of these underlying risk factors are abdominal obesity and insulin resistance. Other associated conditions include physical inactivity aging, hormonal imbalance and genetic or ethnic predisposition ***(American Heart Association Science, 2005).***

A quarter of the world's adults have metabolic syndrome. People with metabolic syndrome are twice as likely to die from cardiovascular diseases and three times as likely to have a heart attack or stroke compared with people without the syndrome. People with metabolic syndrome have a fivefold greater risk of developing type 2 diabetes. Up to 80% of the 200 million people with diabetes globally will die because of cardiovascular disease ***(American Heart Association Science, 2005).***

- ***Prevalence:***

The prevalence of insulin resistance in the general population is growing at a rate that is commonly referred to epidemic in proportions, caused largely by the rise of obesity and by lifestyle changes. Twenty million individuals have diabetes and an additional 26% of the population in the United States has impaired fasting glucose levels. The core element of insulin resistance, however, is the hyperglycemic development of diabetes that increases with advancing age. Therefore, as the aging population continues to grow and the average life expectancy increases, so the appearance of glucose deregulation and resulting diabetes also increases. Currently about 20% of patients over 65 years of age suffer from diabetes ***(Mazza, 2008).***

It is estimated that around 20 - 25 % 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 heart attack

or stroke compared with people without the syndrome. In addition, people with metabolic syndrome have a fivefold greater risk of developing type 2 diabetes ***(Alberti et al., 2009).***

Prevalence of metabolic syndrome varies markedly from country to country. This seems to be caused by two factors:

1) Variations of lifestyle (especially, diet, smoking and level of physical exercise) between countries.

2) Variations in ethnicity. In all settings and all population, the prevalence of metabolic syndrome increase with age ***(Bo et al., 2007).***

A Survey involved 286 obese, 568 overweight, 320 underweight, and 3076 non obese adolescents from 7 governorates representing Egypt, about the prevalence and magnitude of childhood obesity and it's relation to the metabolic syndrome, showed an overall prevalence of the metabolic syndrome of 7.4% with no sex or area of residence predilection ***(Nebal et al., 2010).***

- ***Age and Race:***

Frequencies vary among ethnic groups, in the United States, metabolic syndrome is present in 70% of European American diabetes, 65% of African American diabetes, and 62% of Mexican American diabetes. Hispanics, Caucasians, Afro-Americans, Mexican-Americans, Asians, Chinese, Australian,

Aboriginals, Polynesians and Micronesians seem to be at greater risk for metabolic syndrome than other races are, as well, metabolic syndrome is more common in older ages ***(Hwang et al., 2007).***

- ***Gender:***

Frequency of metabolic syndrome was significantly high in males; the majority of patients has obesity and high fasting blood sugar levels. Males demonstrated higher levels of triglycerides and lower levels of HDL (high density lipoprotein) compared to females while blood pressure readings was observed to be the same in the both males and females ***(Jahan et al., 2007)***.

- ***Mortality / Morbidity:***

The clustering of cardiovascular disease (CVD) risk factors that characterize the metabolic syndrome is now considered to be the driving force for a new CVD epidemic. This puts the metabolic syndrome and diabetes way ahead of AIDS in the morbidity and mortality terms yet the problem not well recognized ***(Stern et al., 2004).***

The metabolic syndrome is associated with increased risk of a variety of disease outcomes including diabetes, CVD, fatty liver and non - alcoholic steatohepatosis. It is also associated with polycystic ovary syndrome, gall stones, asthma, sleep apnea and some malignant diseases. The biggest impact the

metabolic syndrome has on health is the increased incidence of atheromatous vascular disease. Thus, incidence of mortality is increased by 20 - 80 % in individuals with the metabolic syndrome, with 60 % mortality from CVD, 70% death from coronary heart disease, and 24 % developed peripheral arterial disease ***(Wild et al., 2004).***

II- Risk factors for metabolic syndrome mortality & morbidity:

Each risk factor of the metabolic syndrome is subject to its own regulation through metabolic, hormonal, genetic and lifestyle interactions which are very complex leading to variability in expression of risk factors ***(Orho-Melander, 2006).***

A) Central obesity:

Increased body weight plays the most important role in the metabolic syndrome. The observed prevalence of metabolic syndrome in Third National Health and Nutrition Examination Survey was 5% among the subjects of normal weight, 22% among the overweight and 60% among the obese. It was shown recently that each 11 cm increase in waist circumference is associated with an adjusted 80% increased risk for developing the syndrome within 5 years ***(Palaniappan et al., 2004).***

Central obesity is a clinical marker of insulin resistance and reflects the increased amount of visceral fat. In clinical practice, central obesity is assessed by calculating the waist:hip

ratio, but simple measurement of waist circumference is considered to be even more useful and is much simpler to perform. These two measurements are of more use in assessing risk than the body mass index (BMI), which gives no indication of fat distribution and therefore cardiovascular risk factors (CVD) risk ***(Després et al., 2001).***

Obesity has been known to be positively related to insulin resistance. Increased secretion of free fatty acids, inflammatory cytokines and decreased secretion of adiponectin are molecules mediating obesity and insulin resistance, visceral obesity is closely linked to insulin resistance, and is currently regarded as a principle component of the metabolic syndrome. It is well documented that insulin resistance is predictive of the risk of type 2 diabetes and cardiovascular disease ***(Fareed et al., 2011).***

An Egyptian study demonstrated a strong linear relationship between waist circumference and metabolic syndrome in Egyptian population. The increase was evident even in subjects with the average size of waist, i.e., 80-127 cm. It was also found that 115 cm in male and 105 cm in female of waist circumference were an optimal cutoff for predicting metabolic syndrome ***(Fareed et al., 2011).***

B) Insulin resistance:

Most people with categorical obesity (BMI of 30kg/m2) have postprandial hyperinsulinemia and relatively low insulin

sensitivity, but variation in insulin sensitivities exists even within the obese population ***(Abbasi et al., 2002).***

Overweight persons (BMI 25 to 29.9kg/m2) likewise exhibit a spectrum of insulin sensitivities, suggesting an inherited component to insulin resistance. For example, South Asians and others who manifest insulin resistance with only mild to moderate overweight can be said to have primary insulin resistance. Thus, dissociation of obesity and primary insulin resistance in patients with metabolic syndrome is difficult ***(Grundy et al., 2004).***

Once hyperinsulinemia and insulin resistance are present, a cascade of metabolic changes occurs leading to dyslipidemia, hypertension, hyperglycemia and eventually type 2 diabetes and coronary heart disease (CHD). Individuals who develop insulin resistance, due to either their genetic make-up or increased obesity, also develop specific abnormalities of vascular reactivity, inflammatory responses and coagulation defects. In addition, these people are more prone to other specific clinical disorders, such as polycystic ovarian syndrome, non-alcoholic fatty liver disease, hyperuricemia and gout ***(Reaven et al., 2004).***

C) Atherogenic dyslipidemia:

Atherogenic dyslipidemia manifests in routine lipoprotein analysis by raised triglycerides and low

concentration of high density lipoprotein cholesterol. A more detailed analysis usually reveals other lipoprotein abnormalities such as increased remnant lipoproteins, elevated apolipoprotein B, small LDL particles and small HDL particles ***(Grundy et al., 2004).***

In addition TG/HDL ratio positively correlates with insulin resistance and is used as a surrogate measure. This means that if in an individual with essential hypertension, the TG/HDL-C concentration ratio is low; he does not have insulin resistance and so, is not at increased risk of (CHD) ***(Reaven, 2004).***

The TG/HDL ratio indicates the relative size of the LDL particles and their atherogenic particles whereas high TG/HDL ratio (above 2) indicates a greater population of small dense, pro-atherogenic LDL particles with which prospective studies indicate that TG/HDL ratio highly correlates with reduction in developing CVD ***(Bimenya et al., 2006).***

D) Hypertension:

Elevated blood pressure is strongly associated with obesity and commonly occurs in insulin -resistant persons. Hypertension is thus commonly listed among metabolic risk factors ***(Grundy et al., 2004).***

- **Proposed mechanisms of hypertension in metabolic syndrome:**

There are several possible mechanisms for development of hypertension in metabolic syndrome:

1) Endothelial dysfunction:

Firstly, impairment of direct insulin-mediated vascular effects especially in obese diabetic patients causing endothelial dysfunction as it normally mediates vasodilatation. Also, the blunting of biological effect of nitric oxide (a potent endothelium -derived vasodilator and increased production of vasoconstrictors such as angiotensin II, endothelin -I and cyclooxygenase and lipooxygenase products of arachidonic acid metabolism contribute to endothelial dysfunction. In addition, increasing intracellular sodium and calcium in the vascular smooth muscle (which enhance contractility) causes hypertrophy and hyperactivity of vascular smooth muscle ***(Taylor, 2001).***

2) Sodium retention:

Secondly, hyperinsulinemia causes sodium retention. This is especially reported in obese patients with resistance to insulin metabolic effects ***(Hansson et al., 2004).***

3) Increased sympathetic tone:

Thirdly, hyperinsulinemia stimulates sympathetic nervous system (SNS) activity. Increased SNS activity has been documented in association with obesity ***(Ward et al., 2003)***.

4) Hormonal imbalance:

The renin-angiotensin system is clearly present in adipose tissue. In addition, secretory products from adipocyte have been shown to stimulate mineralocorticoid secretion from adrenal cells. This suggests a novel pathway that could account for the relative increase in aldosterone that is often seen in obese patient. Also Leptin secreted by adipose tissue may play a role through increasing blood pressure by causing sympathetic activation ***(Bloomgarden, 2002).***

D) Aproinflammatory and prothrombotic state:

A proinflammatory state which is recognized clinically by elevation of C-reactive protein (CRP) is commonly present in persons with metabolic syndrome.

Multiple mechanisms seems to underlie elevations of CRP. Excess adipose tissue releases inflammatory cytokines that may elicit higher CRP levels. Recently, a pro-inflammatory state has been implicated directly to cause insulin resistance as well as atherogenesis ***(Grundy et al., 2004).***

Hyperglycemia has been associated with inflammation in general. A connection has been established among diabetes, inflammation and disability in older persons. Uncertainty exists to whether inflammation and obesity cause a decline in functional status or if disability is a result of diabetes itself. A recent study of the inflammatory markers C-reactive protein and interleukin-6 in adults suggested that increased inflammation correlated negatively with persistent functional limitation ***(Mazza, 2008).*** A prothrombotic state, characterized by increased plasma plasminogen activator, inhibitor-1 and fibrinogen, is also associated with metabolic syndrome. Increased levels of fibrinogen are associated with both chronic inflammation and insulin resistance. Low grade chronic inflammation has been associated with increased release of soluble tissue factor and factor VII ***(Ford, 2003).***

Furthermore, factor VII activity correlates with body mass index and triglycerides levels. The simultaneous increase in both soluble tissue factor and factor VII clearly enhances the risk of activation of the coagulation cascade. Insulin resistance and chronic inflammation contribute to the increase in PAI-1 especially in patients with characteristics of metabolic syndrome ***(Godsland et al., 2004).***

Finally platelets from obese insulin resistant subjects have reduced sensitivity to the anti-aggregatory effects of insulin. Moreover, very low density lipoprotein and triglycerides have been shown to increase platelet

aggregability, whereas this effect is reversed by HDL cholesterol ***(Doggen et al., 2004).***

F) Microalbuminuria:

Microalbuminuria is often used in diabetic patients as a marker of impending renal disease. It is also a marker of diffuse endothelial dysfunction, which is an inherent part of metabolic syndrome and contributes to its co-morbidity and cardiovascular mortality, there is a strong association between microalbuminuria and cardiovascular disease, even in non - diabetics which may be due to the fact that it reflects the abnormal vascular, coagulation and inflammatory state in the kidney ***(Pi-Sunyer, 2004).***

G) Hyperhomocysteinaemia:

Hyperhomocysteinaemia (HH) has also been linked to metabolic syndrome. It is one of the causes of the hypercoagulable state, Hyperhomocysteinaemia has been documented in up to 40% of type 2 DM with macro vascular disease due to resistance to the suppressive effect of insulin on homocystein levels. HH is associated with premature vascular disease and endothelial dysfunction, causing patchy endothelial cell loss together with increased platelet adhesion and aggregation ***(Gideon, 2007).***