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Factors Contributing in Incidence and Diagnosis of Metabolic Syndrome: Updated Mini Review

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Authors' contribution

This review was written in collaboration among all authors. Authors AMKAM, AAA and SNA update literature review, collect data and write draft. Authors KOA, MAZ, TAK, QM, AMN and SSY revised and discussed the data and authors SSM, TAK and KOA commented and published. All authors read and approved the final manuscript.

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ABSTRACT

It has been well-established that obesity is the major contributing factor forthe development of metabolic syndrome (MetS), diabetes, cardiovascular disease and certain types of cancer. According to WHO, 44% increase of diabetes, 23% increase of ischaemic heart disease, and between 7% and 41% increase of certain cancer are due to obesity. The Middle East region is reported to have the highest prevalence of diabetes in adults in the world. In Saudi Arabia, over 35% of the population are obese, and it is estimated that 24% of adult has diabetes including undiagnosed diabetes cases. Obesity and chronic metabolic disease associated obesity impose the heavy financial burden on national healthcare in the Gulf countries as they do in most countries worldwide. Biochemical markers for MetS included changes in trace elements, vitamin D,hormonal (adipokines, leptin, adiponectin, ghrelin), inflammatory mediators (IL-6, TNF-α, IL-10), biochemical markers (Ox-LDL, uric acid) and prothrombic factors (PAI-1). Plasminogen Activator Inhibitor-1 (PAI-1) is the primary of four serine peptidase inhibitors that functions to modulate extracellular matrix remodeling and fibrinolysis. The link between PAI-1 and MetS has been established. This review screening major factors and the association between PAI-1, trace elemnts, vitamin D, obesity hormone and expression of obesity genes for early prediction of MetS for control and management to prevent late complications.

Keywords: Metabolic syndrome; insulin; plasminogen factor; trace elements.

1. BACKGROUND

In Gulf countries, it was reported that non-communicable diseases (NCDs) as obesity will cost $68 billion in 2030. The medical healthcare expenditures that are increased ten times higher ($3,686 vs. $380) [1]. These reports underline the urgent needs for a strategy to reduce the occurrence of these diseases and health care burden derived from it not only in the Middle East but also globally [2].The obesity rate has increased dramatically worldwide and emerged as a major global challenge. Obesity is a serious health concern because it is a risk factor for other diseases including diabetes, coronary heart disease, hypertension and certain types of cancer. In the Middle East, the prevalence of obesity has arisen as a substantial issue with 35% of obese rate in adult, and in accordance, the highest diabetes rate in the world [3]. A recent report has shown that 35.2% of Saudi Arabian population is obese, the second highest in the world. Current therapeutic approaches to treat obesity using drugs are unsatisfactory due to numerous side effects [4].

Diet-induced metabolic syndromes are widely spread nutritional disorders around the world and have arisen as a growing global challenge. Among them, obesity is a significant risk factor for other diseases including diabetes, coronary heart disease, hypertension, atherosclerosis and certain forms of cancer. Obesity is defined by a body mass index ≥ 30 according to the World Health Organization (WHO) [5]. Obesity arises from energy imbalance due to excessive energy intake from food consumption and insufficient energy expenditure which includes basal metabolism, physical activity and adaptive thermogenesis. In the Middle East, the prevalence of obesity has increased dramatically and become a serious health concern in the recent decades [6]. There is a notable increase in the incidence of obesity in Arabic-speaking countries with a prevalence of 2 to 55% in females and 1 to 30% in males. Increased consumption of fats, sugars, and carbohydrates in these countries is associated with change of dietary habits by Westernization, which can increase the risk for obesity. It is now known that obesity is the major cause of metabolic diseases such as type 2 diabetes and cardiovascular diseases (CVDs), yet mechanistic understanding of this pathology and current therapeutics are unsatisfactory [7].

The identificatiobn of genes that increase incidence for development of obesity hasbecome intersted. One of these genes is the GNB. Its name derived from the G-protein (GNB3) gene, which formed from 12 exons, present on chromosome 12p13 and produce β3 unit of G proteins. The polymorphism of this gene leads to a truncated splice variant. The *GNB3* 825T allele product has been associated with obesity, hypertension, and atherosclerosis [8].

The burgeoning rate of obesity is not only indicated in adult population, but also in children and adolescents [9]. This high prevalence of obesity has paralleled the rise of diabetes and hypertension. Poor eating habits and physical

inactivity due to their greasy and high calorie diet and sedentary lifestyle, respectively, are known to be the major contributors of obesity in the Middle Eastern population .The changes in diet of the Arab World includes increased calorie intake and substitution of the traditional diet with refined and processed foods and diets high in fat and salt. Recent studies have reported that natural compounds found in cruciferous vegetables such as broccoli, cabbage and radish have numerous beneficial effects on various diseases such as cancer, cardiovascular disease, and inflammation [10]. Adipogenesis and lipogenesis through cell cycle arrest and activation of AMP-activated protein kinase (AMPK) [11], but also promoting lipolysis mediated by activation of hormone-sensitive lipase (HSL), a lipase in adipocyte . Moreover, the exact mechanism of action of them in various organs which are closely related to obesity and insulin resistance have not been clearly understood. Therefore, it is important to prevent overweight or obesity to reduce the risk factor threatening our healthy lives. Regardless of which criteria are used, the primary concern is early detection of potential CVD complications and early intervention [12]. The prevalence of MetS in Saudi subjects was reported by Al-Nozha et al. to be 39.3% [13].

The aim of current survey for monitoring major factors that contribute for metabolic syndrome like plasma vitamin B_{12}, trace elements, prothrombic factors (PAI-1), lipid profile, hormonal changes (insulin, leptin and Ghrelin) as a predictive biomarkers for metabolic syndrome.

2. PREVALENCE OF MetS ESTIMATES BY COAGULATION FACTORS

Plasminogen Activator Inhibitor-1 (PAI-1) is a serine protease inhibitor that play a role in modulation of fibrinolysis. Its level is regarded as a index of an abnormal fibrinolysis and thrombosis. The correlation between PAI-1 and MetS was reported to be elevated and strongly association such MetS [14-17]. In efforts to treat obesity and its related metabolic diseases, numerous synthetic drugs and therapeutic approaches have been developing [18]. However, currently there are no effective drugs for obesity without side effects [19]. For examples, several drugs such as sibutramine andreductil are withdrawn from the pharmaceutical market due to their severe side effects [13]. Moreover, even though many synthetic drugs undergo developmental process, they failed during clinical phase trials due to their ineffectiveness or side effects.

3. PREVALENCE OF MetS ESTIMATES BY AGE

The risk of MetS is correlated to age, It was found that, less than 10% of subjects at age 20s and 40% at age 60s were affected. On the other hand, other reports revealed that in school children other factors may contribute as fast foods and soft drinks. There was correlation between childhood MetS and adult incidence of CHD [20]. It has been suggested that SES influences nutrition and sedentary habits, which are highly related to MetS components. Lower levels of education are associated with higher prevalence of MetS [21].

4. PREVALENCE OF MetS CAUSED BY OXIDATIVE STRESS

Another factor contributing to the development of the MetS is excessive ROS formation which can alter the mitochondrial function and endoplasmic reticulum which again will lead to defective insulin secretion and DMT2. Increased oxidative stress in accumulated fat, via increased nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and decreased antioxidant enzymes [15].

5. PREVALENCE OF MetS AFFECTED BY INSULIN ACTION

Insulin resistance with hyperinsulinemia seems to be a central factor in the pathogenesis of the MetS. An insulin-resistant state interferes with the hormonal actions taking place in the liver. Insulin produced in the β-cells of the pancreas travels quickly to the liver via the portal vein, and in the presence of the MetS, insulin has a selective dysfunction so that it does not diminish the hepatic glucose output, but rather increases it, and still, like in the normal state, increases the de novo lipogenesis, thereby releasing triglycerides to the circulation, causing dyslipidemia [22]. Further, insulin resistance causes increased renal sodium reabsorption and stimulate the sympathetic nervous system which can result in hypertension [23].

6. PREVALENCE OF MetS BY BIOCHEMICAL MARKERS

Metabolomics is a new research trend used to measure different metabolites for screening diagnosis and prognosis of some diseases. Some vitamins as A, D were implicated in MetS.

The obesity is considered as a type of inflammation due to oxidative stress and elevated free radicals. This is indicated by release of inflammatory mediators as(IL-6, TNF-α, IL-10). Trace elements are important for activation of some enzymes, synthetic pathway, and biomolecules. Their levels are changes and taken as markers for different diseases. Some of it were implicated in MetS as Zn, Cu, Fe and Se. In addition, hormonal changes as (adipokines, leptin, adiponectin, ghrelin) and biochemical markers (Ox-LDL, PON-1, uric acid) are important biochemical markers for MetS.

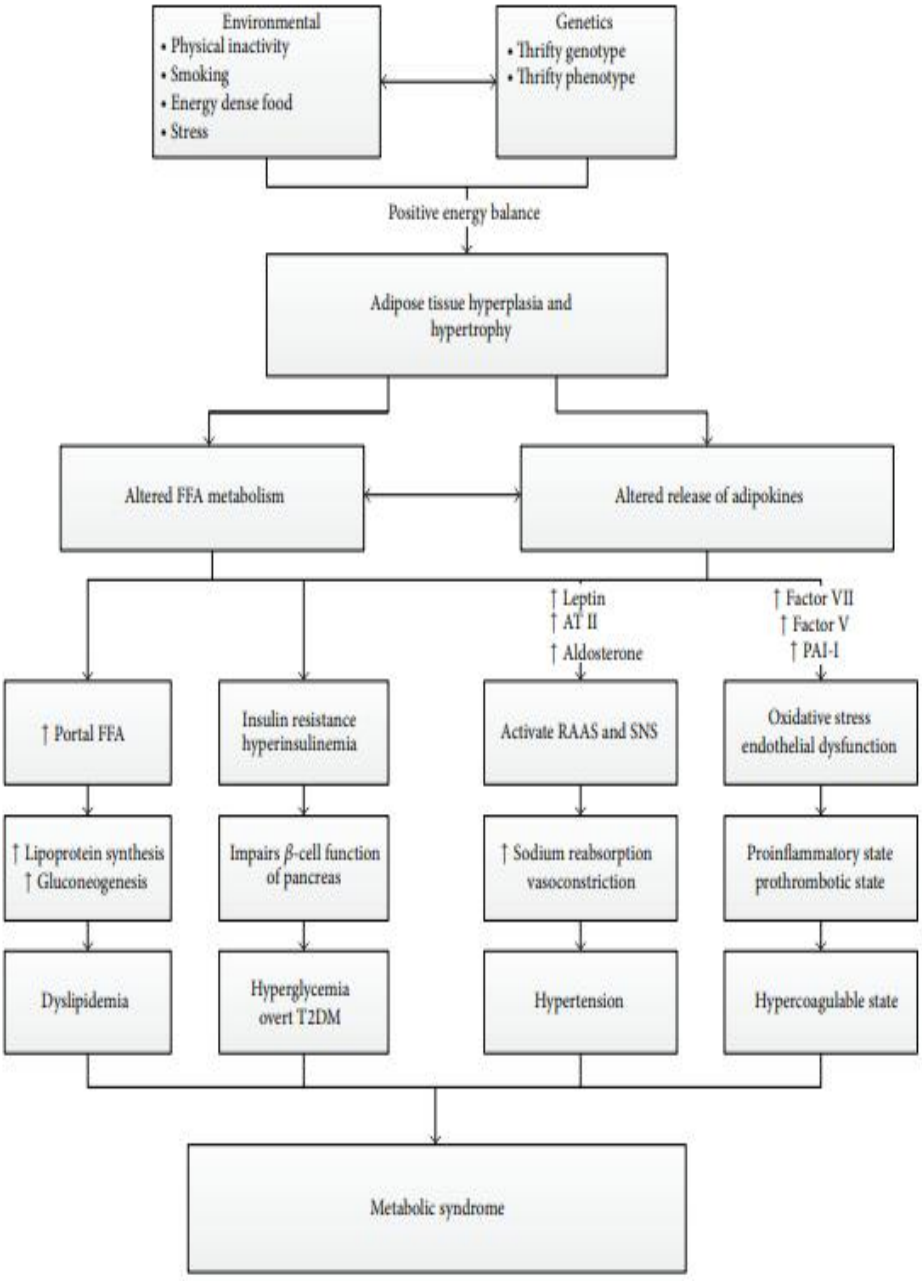

Fig. 1. Factors associated with MetS. (FFA: Free fatty acid, ATII: Angiotensin II, PAI-1: Plasminogen activator inhibitor-1, RAAS: Renin angiotensin aldosterone system, SNS: Sympathetic nervous system [21]

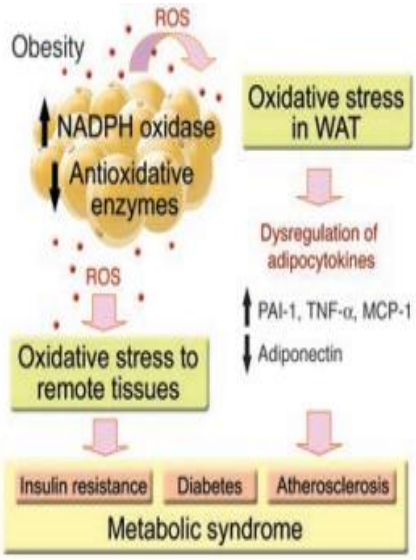

Fig. 2. Impact of ROS production in accumulated fat contributes to metabolic syndrome [15]

7. PREVALENCE OF MetS BY TRACE ELEMENTS

Trace elements has an important role in metabolism, growth, immunological, and neurological functions Copper (Cu), one of these elements, is mainly found in shellfish, organ meats, nuts, seeds, vegetables, and grains [24]. Throughout the years it has been shown that Cu abnormalities are linked to CVD [25] and cancer [20]. In fact, its deficiency may lead to arterial diseases and myocardial disease, besides pigmentation loss and neurological effects. Cu has an important role in the defense against free radical damage as an antioxidant [26]. Previous study found that Cu levels were significantly higher in subjects with MetS than in subjects without MetS, however, they did not analyze these values according to weight, since they also found that serum Cu levels were significantly higher in obese than in normal subjects and it is known that increasing weight increases the risk for developing MetS. The causal relationship between obesity and concentration of iron in the teenagers was already established [27].Further to that, a causal association between low blood Fe concentrations and adiposity in people has been noted [28].

8. CONCLUSIONS

Metabolic syndrome knowledge is essential for diagnosis and management for development of protocol for fast management for MetS. This will help to prevent and control risk diabetes, hypertension, Cardiovascular diseases and carcinogenic.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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