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Metabolic Syndrome: Pathophysiology and Treatment

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ABSTRACT

Background: Metabolic syndrome is a group of abnormal laboratory and physical findings, such as dyslipidemia, hypertension, glucose intolerance, proinflammatory state, and prothrombotic state that results in a patient having significantly higher risk for atherosclerosis, cardiovascular disease, and overall mortality. There are slight differences between institutions in defining metabolic syndrome across the world. To achieve adequate management and treatment and decrease the risk of subsequent diseases, proper identification of symptomatic patients with metabolic syndrome is necessary.

Aim: In this review, we aimed to study the pathophysiology behind the development of metabolic syndrome, and also to explore the approach to its management.

Materials and Methods: We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 2001, through February 2017. The following search terms were used: metabolic syndrome, pro-thrombotic state, pro-inflammatory state, diabetes mellitus, insulin resistance, obesity and cardiovascular mortality. **Results:** The major aspects of treatment include weight reduction by diet, medication, as well as bariatric surgery (in some cases), and managing hyperglycemia and insulin resistance with diet and medication. **Conclusion:** The most important intervention in managing patients with metabolic syndrome is lifestyle modification with improved diet and exercise. To achieve adequate treatment and decrease the risk of adverse outcomes, proper identification of symptomatic patients with metabolic syndrome is necessary.

Keywords: metabolic syndrome, diabetes mellitus, insulin resistance, obesity, cardiovascular mortality, pro-thrombotic state, pro-inflammatory state.

INTRODUCTION

Metabolic syndrome (MetS) consists of a collection of abnormal physical and laboratory findings that occur due to the integration between biochemical, clinical, physiological, and metabolic factors, resulting in a significant increase in atherosclerosis, cardiovascular disease, and overall mortality. These abnormal findings include dyslipidemia, hypertension, glucose intolerance, pro-inflammatory state, and pro-thrombotic state. This definition of MetS is considered the most recent and is based on the World Health Organization (WHO), the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), American Association of Clinical Endocrinologists (AACE), the European Group for the study of Insulin Resistance (EGIR), and the International Diabetes Federation (IDF) [1].

There are minimal differences between the definitions of MetS by each organization, which can make a single definition harder. The definitions suggested by AACE, WHO, and EGIR depend mainly on insulin resistance. So, the diagnosis will be done with an oral glucose tolerance test, and/or hyperinsulinemic-euglycemic clamp (which is not used in clinical settings). On the other hand, the ATPIII use other more reliable measures for diagnosis, making this easier to clinicians. However, the most concerning limitation of the ATPIII definition is its inaccuracy when applied to different ethnicities, especially when dealing with obese patients. For example, the prevalence of obesity is higher in Europe than Asia, which will directly affect the risk of type 2 diabetes mellitus. Therefore, it has been difficult to create a unified definition for MetS with unified criteria with specific cut-offs that can be applied to different racial and ethnic groups. This made IDF propose their new criteria that takes varying populations, races, ethnicities, and nationalities into consideration when evaluating body weight and waist circumference. These criteria also consider the differences between groups regarding the association between these values, and cardiovascular diseases risk [2].

METHODOLOGY

• Data Sources and Search terms

We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 2001, through February 2017. The following

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search terms were used: metabolic syndrome, pro-thrombotic state, pro-inflammatory state, diabetes mellitus, insulin resistance, obesity and cardiovascular mortality. **The study was done after approval of ethical board of King Abdulaziz university**.

• Data Extraction

Two reviewers have independently reviewed the studies, abstracted data, and disagreements were resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.

Pathophysiology

As we previously mentioned, MetS is caused by the continuous presence of low-grade inflammation due to the integration between environmental and genetic factors. This inflammation is influenced by abdominal obesity, endothelial dysfunction, hypertension, dyslipidemia, insulin resistance, hypercoagulability, and/or chronic stress [3].

Abdominal Obesity

The increased use of cheap, calorie-dense fast food has caused a dramatic decline in physical activity, causing an 'obesity epidemic'. Adipose tissue consists of adipocytes, stroma, immune cells, and endothelium. Adipose tissue is easily affected by changes in diet, and excess nutrients, leading to hyperplasia and hypertrophy.

Consequently, the blood supply will become insufficient for the demands of this progressively enlarging adipose tissue, leading to hypoxia and necrosis with macrophages infiltration. This process will cause the release of adipocytokines; biologically active metabolites that include proinflammatory mediators, glycerol, and free fatty acids (FFA). These adipocytokines will induce inflammation that starts in the adipose tissue and progresses to the body, causing comorbidities associated with obesities. This will influence insulin sensitivity, oxidative stress, energy metabolism, coagulation, and systemic inflammatory response, and will subsequently cause atherosclerosis, plaque rupture, and atherothrombosis [4].

Insulin Resistance

Insulin sensitivity is associated with normal weight, moderate activity, consumption of low-fat diet, and absence of abdominal or visceral obesity. Insulin resistance is known as the inadequate response of peripheral tissues to normal insulin concentrations. These tissues include adipose, muscle and liver. Consequently, more insulin will be released by beta cells in response to hyperglycemia, causing hyperinsulinemia. This hyperinsulinemia will partially compensate for the abnormalities, and will try to maintain normoglycemia. However, overexpression of insulin receptors will take place, causing the clinical complications of MetS. These include features of glucose metabolism dysfunction such as abnormal glucose challenge response, high fasting glucose levels, decreased insulin activity (which can be confirmed with the euglycemic clamp technique), and/or overt hyperglycemia. Type II diabetes will eventually develop due to the inadequate pancreatic cells compensation over time [5].

Normally, insulin acts by binding to its receptor with a ligand-activated tyrosine kinase, which will result in a downstream phosphorylation of substrates, with activation of two pathways: the phosphoinositide 3-kinase (PI3K) pathway and the mitogen activated protein (MAP) kinase pathway. In cases of insulin resistance, the MAP pathway maintains its functions, but the PI3K does not, leading to alternation in these pathways balance. This abnormal activity of PI3K pathway causes a decline in NO production from endothelial cells, leading to a decrease in translocation of GLUT4. This will inhibit glucose uptake by skeletal muscles. The MAP will continue working unaffected, causing continuous production of endothelin-1 (ET-1), with increased adhesion molecules expression, and smooth muscle cells stimulation. The results of these complex mechanisms will include atherosclerosis due to resulting vascular abnormalities. Individuals with insulin resistance are not necessarily obese, but they will have abnormal adipose tissue distribution especially in upper body.

Generally, abdominal (upper body) obesity is strongly associated with insulin resistance, in contrast to lower body obesity [6].

Dyslipidemia

In MetS, dyslipidemia can be attributed to several abnormalities resulting from dysfunctional structure, metabolism, and biology of atherogenic and antiatherogenic lipoproteins. This will cause increased levels of apolipoprotein B(apo B), TGs, LDL, with decreased levels of HCL [7].

Normally, insulin inhibits lipolysis, thus in MetS, insulin resistance causes increased lipolysis activity and increased free fatty acids levels, which will move the liver and participate in the synthesis of TGs. Free fatty acids will also stimulate and increase apo B production, causing an increase in VLDL levels. Insulin also participates in apo B degradation, so in this case, insulin resistance will directly cause increased VLDL levels. The regulation of lipoprotein lipase activity is also controlled by insulin, and when

there is insulin resistance, VLDL clearance will be impaired causing the accumulation of lipoproteins promoting the formation of atheromas [8].
HDL receives TGs from VLDL with the activity of the cholesterol ester transport protein (CETP). This interaction will result in VLDL rich in cholesteryl ester, and HDL particles rich in TGs, which can be rapidly cleared by hepatic lipase. In cases of insulin resistance, the liver will have high levels of free fatty acids, high rates of TGs synthesis, and increased fat storage. Consequently, this will directly cause increased liver secretion of VLDL. Increased oxidative stress, endothelial dysfunction, and the continuous inflammatory state, are all strongly associated with these mechanisms and will contribute to the macro-vascular atherosclerosis [7].

Hypertension

Many abnormal metabolic status are associated with primary hypertension like obesity, dyslipidemia, and diabetes. Hyperinsulinemia and hyperglycemia are thought to increase angiotensin, angiotensin II (AT II), and the AT1 receptor expression causing stimulation of the renin angiotensin system. This activation of the renin angiotensin system will promote hypertension in insulin-resistant patients [9].
Hyperinsulinemia also plays a role in the activation of sympathetic nervous system causing increased reabsorption of sodium in the kidneys, increased cardiac output, and increased vasoconstriction of arteries, which will all lead to hypertension. Moreover, adipocytes response to ATII causes aldosterone production making adipocytes a mini renin angiotensin aldosterone system [10].

Genetics

Although many individuals have similar environmental factors and risk profiles, MetS shows wide variations in susceptibility and clinical picture. This observation led to the suggestion of the interaction between environmental and genetic factors in the development of the disease. For example, some patients with MetS and insulin resistance may even not be obese. These variations are most obvious among individuals with one or two diabetic parents, or patients with a second-degree relative with diabetes. It is also clearly seen in South Asian populations. To explain this, it was assumed that each risk factor is influenced by different genes, which affect the individual's response to different kinds of exposure. An example of this, is the worsening dyslipidemia in obese individuals which is caused by different polymorphic genes that target lipoprotein metabolism [11].

Another example is the exacerbated raise of plasma glucose levels, among genetically predisposed patients with both insulin resistance and defective insulin secretion. Inadequate intrauterine nutrition causes babies to adapt to poor nutrition and reduce their energy expenditure. Later in life, when these individuals are poorly nourished, this adaptation will be beneficial for them. However, this adaptation will increase their life time risk of MetS if they increase their food intake. The well-documented association between insulin resistance and a history of low birth weight supported this hypothesis in several populations [12].

Chronic Stress and Glucocorticoid (GC) Action

Cortisol and other stress mediators in genetically predisposed individuals can cause accumulation of fat in the viscera. Glucocorticoids increase lipoproteins secretion, and stimulate the activities of fatty acid synthesis enzymes. They also enhance gluconeogenesis in the lever, differentiation of adipocytes, inhibition of amino acid uptake by adipocytes, and oxidation of lipids. It was observed that plasma corticosteroids levels positively correlates with clinical feature of MetS, including hypertension and fasting glucose levels. In conclusion, abnormalities in these hormones levels will cause increased secretion of insulin, increased upper body obesity, sarcopenia, dyslipidemia, hypertension, and diabetes [13].

Treatment

The main underlying mechanism of MetS is the chronic proinflammatory state that causes systemic manifestations. To achieve adequate management and treatment and decrease the risk of subsequent diseases, proper identification of symptomatic patients with MetS is important. Life style changes affecting diet, weight, and exercise are considered the cornerstone of treatment. Pharmacological agents aim to reduce certain risk factors, and is considered when life style modifications alone are not sufficient. No recognized protocol is present to improve or prevent the whole syndrome, making clinical management challenging. Most practitioners treat MetS symptomatically according to the clinical presentation and present features. Actually, sometimes anti-hypertensive, anti-hyperglycemic, or anti-lipids drugs are usually easier by patients that lifestyle modifications like changes in diet and exercise are difficult to modify. Physicians should use the National Cholesterol Education Program (NCEP), the seventh Joint National Commission (JNC-VII), the American Diabetes Association (ADA), the American Heart Association (AHA), and the National Institute of Health and Obesity Initiative

guidelines to treat and reduce risk factors like high blood pressure and glucose levels [14].

Weight Reduction

Four modalities of treatment are popular for weight reduction: restriction of calories to less than 500 kcal/d, modifications to behaviors, high levels of physical activity, and/or the use of weight-reducing drugs that were approved by FDA. A goal of 10% reduction within the first year is recommended by most experts. Following this, modifications should continue until achieving a BMI lower than 25. Although all patients struggle with weight loss, achieving this will improve hypertension, lipid levels, and insulin resistance [15]. TGs levels can significantly decrease with 5-10% of weight loss. Moreover, a modest weight loss will improve blood pressure levels. Weight loss will also contribute towards improvement of fasting blood glucose, insulin, and hemoglobin A1c levels. Exercise without weight loss is also beneficial and causes significant loss in abdominal adipose tissue and prevention of weight gain. A 5-10% of weight loss over six months is expected from a regular combined schedule of exercise, calorie restriction, and behavioral modifications. Although patients may perceive this loss as small, it will lead to significant improvements in obesity related comorbidities and MetS manifestations. The Finnish Diabetes Prevention Study and the US Diabetes Prevention Program (DPP) proved that exercise and diet significantly decreased the risk of diabetes development [16, 17].

Pharmacological Approach

Obesity treatment guidelines published by the National Institute of Health recommend pharmacotherapy in individuals whose BMI is more than 30 kg/m^2, or with patients with BMI more than 27 kg/m^2 associated with other comorbidities. Otherwise, only lifestyle modifications are recommended. Two main classes of drugs are used: absorption inhibitors and appetite suppressants. Usually, only one agent is used, and will subsequently lower weight from 5-10% [18]. Phentermine derivatives and sibutramine are examples of appetite suppressants, and are usually administrated in the morning to cause reduced appetite in the afternoon and evening. More than weight loss, sibutramines were associated with improvement of MetS manifestations and risk factors. They cause a reduction of abdominal adipose tissue, lipid levels, hemoglobin A1c, and uric acid levels. The only approved agent for nutrient absorption inhibition is orlistat, which acts as an inhibitor of lipase in the gastrointestinal tract. It can prevent the absorption of about 30% of consumed fat, and to achieve this, it needs to be taken with food consumption. However, it is associated with several limiting adverse events like flatulence and oil leakage in the stool. A published clinical trial showed that obese patients who used orlistat had improved glucose levels, and better weight reduction of 6% versus 4% in patients who used placebo. Another meta-analysis found that drugs were associated with about 4 kgs loss more than placebo, and that all drugs had similar effects. The only limitation of these drugs is the high incidence of adverse events causing poor patients compliance on the long term basis [19].

Bariatric Surgery

Individuals who do not respond to lifestyle modifications and weight loss drugs are recommended to undergo surgery. Surgery is also recommended for extremely obese patients with BMI more than 40 kg/m^2, or BMI more than 35 kg/m^2 with other comorbidities. Laparoscopic banding of stomach with Roux-en-Y are used in bariatric surgery and favored over other techniques. These techniques will result in about 25-30% weight loss, with fast improvement in glucose and blood pressure levels. About 95% of patients will become asymptomatic within a year of undergoing surgery. Hypertension, diabetes, cardiovascular disease, arthritis, polycystic ovarian syndrome, dyslipidemia, hyperuricemia, infertility, as well as other several diseases have been associated with improved prognosis after surgery. However, we still do not have sufficient data about the long-term effects of surgery, and some reports have recorded significant morbidity and mortality especially in the elderly [20].

Insulin Resistance and Hyperglycemia Management

The onset of diabetes can be delayed in patients with MetS by several modalities including IFG, weight reduction, and/or increased exercise. Oral hypoglycemics like metformin, thiazolidinediones, and/or acarbose will also play a role in reducing diabetes risk. Metformin works by inhibiting gluconeogenesis, causing lower glucose levels. It has been shown to decrease the risk of diabetes by about 31%. However, intensive lifestyle modifications have been associated with higher rates of prevention up to 58%. Metformin did not improve cardiovascular risk factors. These results conclude that metformin is less important than life style modifications in terms of MetS treatment. Another study on acarbose, also found it to decrease the risk of diabetes in patients with MetS. It works by inhibiting carbohydrates absorption, and is approved

for diabetes treatment. The main limitation of this drug is its poor compliance by patients due to adverse events. Another class of drugs is pioglitazone that were proved to improve blood pressure, blood glucose, and TGs with other manifestations of MetS. Pioglitazone also reduce the urinary albumin/creatinine ratio, and decrease the risk of cardiovascular complications in high risk populations [5].

CONCLUSION

The integration of physiological, biochemical, clinical, and metabolic pathologies cause MetS, leading to atherosclerosis, cardiovascular disease, type 2 diabetes, and higher overall mortality. Factors that impact the manifestations of MetS include visceral adiposity, insulin resistance, atherogenic dyslipidemia, endothelial dysfunction, visceral adiposity, hypertension, genetic susceptibility, hypercoagulability, and chronic stress. The most important intervention in MetS patients is lifestyle modification with improved diet and exercise. Patients with higher risk, or who do not respond to lifestyle modifications are recommended to use weight lowering agents.

The ideal target for overweight patients is 7-10% reduction over 6-12 months. A minimum of 30-minute-moderate exercise is also recommended. Improved diet habits include consuming food with low fat levels, simple sugars, and/or high glycemic food, with increased levels of vegetables, fruits, and grains. To achieve sufficient levels of LDL reduction, statins can be administrated with fenofibrates or niacin. Most patients with MetS with hypertension, will require several agents to achieve proper control with ACEIs/ARBs, beta blockers, CCBs, and other antihypertensives. MetS patients with diabetes are recommended to use oral hypoglycemic like metformin, thiazolidinediones, and/or acarbose to control their glucose blood levels.

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