

Metabolic Syndrome-An Update

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Summary

Metabolic Syndrome (MetS) is a complex of risk factors for the development of cardiovascular complications and type 2 diabetes mellitus. The conventional components of the syndrome are four in number: dyslipidaemia, hypertension, hyperglycaemia and abdominal obesity. This particular constellation of risk factors puts the patient at a much higher cardiovascular risk, when compared with the general population. The syndrome has a multifactorial aetiology and pathogenesis. Various modalities of treatment such as non-pharmacological, pharmacological and surgical are available for the management of MetS. The angiotensin converting enzyme inhibitors or angiotensin receptor blockers are the preferred drugs for the management of hypertensive component of MetS. Recent studies have shown that they also have antioxidant, anti-inflammatory, vasoprotective and insulin sensitizing action. Hence, they may be better choice in controlling the various components of MetS.

Introduction

The World Health Organization (WHO) proposed the first definition of Metabolic Syndrome (MetS) in 1998. Since then, there have been several evolutionary changes in the definition and in the diagnostic criteria, which only reflect the profound prevalence of the syndrome itself. Although there exist several criteria for diagnosing and defining MetS, most specialists recommend the use of National Cholesterol Education Program and Adult Treatment Panel III (NCEP: ATP III) 2001 and Harmonizing definition criteria for the same [1]. The NCEP: ATP III 2001 criteria (revised in 2005) are one of the most widely used diagnostic aids. The criteria for diagnosing MetS are a) Central obesity: waist circumference > 102 cm (males) and > 88 cm (females), b) Hypertriglyceridemia: triglyceride level \geq 150 mg/dL or on specific medication, c) Decreased High Density Lipoprotein (HDL) cholesterol: < 40 mg/dL (males) and < 50 mg/dL (females) or on specific medication, d) Hypertension: blood pressure \geq 130 mmHg (systolic) or \geq 85 mmHg (diastolic) or on specific medication, e) Hyperglycemia: fasting plasma glucose level \geq 100 mg/dL or on specific medication or previously diagnosed type 2 diabetes mellitus are as follows [1,2]. Presence of three or more of the above criteria entitles the physician to diagnose a patient of MetS [1].

MetS is a complex of various risk factors for the development of type 2 Diabetes Mellitus (DM) and cardiovascular diseases. It is considered to be an epidemic due to its widespread prevalence. The chief constituents of MetS are dyslipidaemia, hypertension, hyperglycaemia and abdominal obesity. By convention, these factors play a key role in the diagnosis of MetS. However, recently, other risk factors like chronic inflammation, prothrombotic conditions, fatty hepatic disease (non-alcoholic), and sleep apnoea are also being considered under the single roof of MetS. Although each of these constituents is a risk factor for development of cardiovascular diseases by itself, the constellation of these factors enhances the inherent risk [3].

Epidemiology

The prevalence of MetS varies across the globe. Among US adults aged 18 years or older, the prevalence of metabolic syndrome was found to be 34.2% [4]. Based on several studies, the highest prevalence has been found in the Native American population, and it has been found to be more prevalent in female Native Americans (60% versus 45% in males). Also, the prevalence of MetS increases with increasing age [1]. In recent study, it was reported that nearly 35 percent of all U.S. adults and 50 percent

of those 60 years of age or older were estimated to have the metabolic syndrome in 2011-2012 [5]. The prevalence of MetS in India, China, Turkey, Finland, Saudi Arabia and Oman varies from 10-38%. However, recent data pertaining to these countries are not available.

Risk Factors: The risk factors for MetS are obesity, sedentary lifestyle, aging, diabetes mellitus, cardiovascular disease, lipodystrophy and drugs like a typical antipsychotics [1].

Pathophysiology

Insulin resistance

The aetiology of MetS is believed to be multifactorial, and its pathophysiology is poorly understood. However, the most widely accepted hypothesis is that of insulin resistance [1,2]. The reason for this insulin resistance is again unknown. It may be due to the presence of abundant free fatty acids released from adipose tissues. Insulin normally inhibits lipolysis in the adipose tissue. Due to the development of insulin resistance, lipolysis is no longer inhibited. A vicious cycle follows, which decreases the insulin sensitivity, which in turn releases freer fatty acids from adipose tissue. The increased levels of free fatty acids in the blood incite hepatic gluconeogenesis and triglyceride accumulation. This results in hyperglycaemia and insulin resistance [1,6]. Also, an increase in the release of Interleukin-6 (IL-6) and Tumour Necrosis Factor α (TNF- α) results in aggravation of insulin resistance. IL-6 also increases hepatic gluconeogenesis and may also enhance the hypertensive component [1].

By definition, insulin resistance is said to have set in, if the following are seen [7].

- a. A high steady state plasma glucose along with prevailing plasma insulin level.
- b. A high plasma insulin level, as compared to normal range.

Leptin resistance

Another hypothesis that has been put forward to explain MetS is the leptin resistance hypothesis. Leptin is responsible for control of appetite, expenditure of energy and enhancement of insulin sensitivity. In the presence of obesity, there is a resultant hyperleptinaemia, which ultimately leads to leptin resistance at the tissue level. This causes insulin resistance, hyperlipidaemia and a range of cardiovascular events, as leptin is also known to regulate cardiac and vascular functions [6-8].

Increase in waist circumference

All the diagnostic criteria give importance to the waist circumference, especially the IDF criteria (wherein increased waist circumference is an essential component to diagnose MetS). An increase in waist circumference may be due to increased subcutaneous deposition or visceral deposition. Visceral deposition of

fats leads to an increased hepatic generation of glucose and lipid products [9,10].

Dyslipidemia

Since there is an increase in the trafficking of free fatty acids to the hepatic tissues, there is an increase in the release of Very Low-Density Lipoproteins (VLDLs) which are rich in triglycerides. Also, patients of MetS have been found to have raised levels of ApoCIII, which plays an inhibitory role to lipoprotein lipase. Hence, this further contributes to hypertriglyceridaemia [1,11]. Also, reduction in HDL levels may be due to increased clearance of the same [1].

Oxidative stress

Ageing is a physiological process, which induces oxidative stress in any individual. A similar situation is seen in patients with type 2 DM, obesity and in off springs of these populations. This may be due to a defect in the mitochondrial oxidative phosphorylation [2]. This oxidative stress has been implicated in the development of insulin resistance, type 2 DM and various complications of DM [12].

Glucose intolerance

Insulin resistance leads to increased production of glucose in the liver, and decreased utilization of glucose in the peripheries, resulting in hyperglycaemia, which is initially corrected by compensatory mechanisms, but ultimately results in glucose intolerance and/or DM [1,6].

Hypertension

Insulin physiologically plays a role as a vasodilator with additional action on sodium reabsorption in the kidneys. Once there is insulin resistance, the vasodilatory action is lost, whereas the sodium absorbing capacity is maintained. This could be one of the causes for the onset of hypertension in the setting of insulin resistance [1,13]. Hyperuricaemia secondary to the development of insulin resistance may also play a role in the origin of hypertension [1,13].

Adiponectin

Adiponectin levels have been found to be decreased in MetS. Adiponectin is a cytokine that is released by adipose tissue. It is believed to play an anti-inflammatory role. Also, adiponectin increases the sensitivity of tissue to the action of insulin [1,14].

Resistin

Resistin, a protein secreted by the adipose tissue, has been found to be present in high quantities in patients with MetS. However, the clinical significance is still debated upon [15].

Pro-inflammatory mediators

Pro-inflammatory mediators like IL-1, IL-6, IL-18, TNF- α and C-Reactive Protein (CRP) are found in excess in MetS. The explanation that can support this process is that there is hyperpro-

duction by the adipose tissue. However, the exact significance in the pathogenesis is unclear [1].

Prothrombotic state

Patients with MetS are known to have increased levels of plasma Plasminogen Activator Inhibitor-1 (PAI-1), which leads to prothrombotic states. This increase could be secondary to the increase in pro-inflammatory mediators. Also seen are increase in the levels of fibrinogen, clotting factor VII and clotting factor VIII [16].

Chronic stress

Overproduction of the stress hormones (like cortisol) may enhance the hepatic gluconeogenesis, fatty acid synthesis, visceral fat deposition and development of hypertension [16].

High dietary fat intake

High dietary fat intake is associated with increase in the oxidative stress, and also an increase in the nuclear factor kappa-B, which is a pro-inflammatory transcription factor [16,17].

Genetics

Although a genetic role is believed to be involved in the development of MetS, the exact type of involvement has not been proven. It is clear that children of type 2 DM are more prone to MetS [18]. Also, two hypotheses, “Thrifty Genotype” and “Thrifty Phenotype” have been proposed. According to these hypotheses, when an individual who is chronically “Thrifty” (malnourished) suddenly consumes excess of energy, he is more likely to develop MetS [16].

Clinical Presentation

MetS may not present with clinically significant symptoms of its own. Most often, on examination of the patient, an increased waist circumference or an elevated blood pressure will be present. Rarely, acanthosis nigricans (blackish discolouration of the back of the neck) or lipoatrophy may be detected. Evidence of any of these findings should instigate the physician to look for other features of MetS [1]. Patients of MetS may also present primarily with the commonly associated conditions like non-alcoholic fatty liver, hyperuricaemia, polycystic ovarian disease, obstructive sleep apnoea, prothrombotic states, etc.

Diagnosis of Mets

Diagnosis of MetS involves fulfillment of the various criteria that are used universally. To satisfy these criteria, proper history-taking (including family history), clinical examination and laboratory tests have to be done [1].

Treatment

Treatment of MetS requires a multimodal approach, which includes lifestyle changes (non-pharmacological) and manage-

ment of the individual components and their complications. If a drug was the precipitating factor for the onset of MetS, then the drug has to be discontinued. Most commonly, atypical antipsychotics (clozapine, olanzapine, etc.) are the drugs responsible for development of MetS [19].

Non-pharmacological management

Reduction of weight is one of the key approaches to ideal management of MetS. Once the patient’s weight is within normal limits, there might be a reversal of insulin resistance, which in turn affects the other components of MetS in a positive manner. Dietary modification (restriction of calories and salt), aerobic physical exercise, smoking cessation (if applicable) and behavioral changes are to be strictly enforced [1,18].

Pharmacological management

Pharmacological management involves the usage of multiple therapeutic options. Each component of MetS is managed with separate drugs. Drugs for weight loss include drugs that suppress appetite and those that inhibit absorption from the gut. Phentermine, topiramate and lorcaserin are drugs that can be used to suppress the patient’s appetite, while orlistat is a drug that inhibits the absorption of fats from the gut [1,18]. For management of hypertriglyceridaemia, fibrates (gemfibrozil and fenofibrate) are the drugs of choice. Fibrates have also been shown to lower cardiovascular risk in patients with type 2 DM [1]. Other drugs that may be used are statins, nicotinic acid and high dose omega-3 fatty acids. Statins also help by significantly reducing LDL cholesterol and minimizing cardiovascular complications. In addition, statins have cholesterol-independent effects like their anti-inflammatory, anticoagulant and antioxidant actions, improvement in endothelial function, etc. Nicotinic acid can additionally raise the levels of HDL cholesterol. However, several trials have shown that nicotinic acid may not have any influence on the cardiovascular risk [1,18]. Recommended cut-offs (based on NCEP ATP III guidelines) for lipid levels are [3]: LDL cholesterol < 100 mg/dL, HDL cholesterol > 40 mg/dL and triglycerides < 150 mg/dL.

Currently, ACEIs and ARBs are the preferred drugs for managing the hypertensive component of MetS [18,20]. However, these drugs may also be used for other components in the syndrome. While captopril was the earliest synthesized ACEI, newer drugs like enalapril, ramipril, lisinopril and moexipril are more commonly prescribed in modern practice. Enalapril, a pro-drug (that gets converted to its active form, enalaprilat), is the most commonly used ACEI. It has an oral bioavailability of about 60% with a half-life of 1.3 hours (11 hours for the active form) [21]. Although beta blockers are known to be potent antihypertensives and to also reduce the incidence of sudden cardiac deaths, their adverse profile on glycaemic control excludes these agents in the management of MetS [18]. If there is impairment of fasting glucose, metformin can be initiated. However, several trials have shown that metformin is inferior to lifestyle modifications

in terms of prophylactic efficacy [1]. Insulin resistance, which is said to be the hallmark of MetS, can be managed using biguanides (e.g., metformin) or thiazolidinediones (e.g., pioglitazone). While both these classes of drugs can enhance the action of insulin in the liver, the latter can significantly enhance peripheral utilization of glucose as well [1]. More recently, statins have been shown to improve insulin resistance, probably by enhancing the sensitivity to insulin signaling [3].

In addition, low dose aspirin has been recommended by experts for its pleiotropic effects. Aspirin has significant anti-inflammatory and antioxidant, and also reduces the incidence of adverse cardiovascular events [18].

Surgical management

Surgery is chiefly indicated for immediate weight loss (metabolic or bariatric surgery), especially in the following categories of patients with MetS [2]: Body mass index (BMI) > 40 kg/sq.m, BMI > 35 kg/sq.m. with comorbidities and BMI > 30 kg/sq.m. with DM.

As evident from the above-mentioned description, ideal management of MetS needs a handful of drugs, in addition to lifestyle changes (and surgery, if required). In the clinical setup, most often, there is improper management, due to non-compliance of the patient or due to improper initiation of drug therapy. One solution for this issue could be the introduction of one single "Polypill", which will contain all the required drugs in one package, so as to improve the patient compliance. Another approach could be to target the underlying pathogenesis, and not the individual components. Drugs that are likely to modify the underlying pathogenesis are statins and drugs that inhibit the renin-angiotensin-aldosterone system (ACEIs and ARBs) [18].

Conclusion

Due to multifactorial risk factors MetS is often resistant to drug treatment. However, ACEIs have multiple actions that target the underlying pathogenesis of MetS and have shown some hopes in the management of MetS. Other modalities of management namely non-pharmacological and surgical approach combined with pharmacological treatment may be able to combat this problem.

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