Metabolic Syndrome: from the Pathophysiology to the Treatment. A Comprehensive Review

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Preamble

The "metabolic syndrome" is an unifying definition to assess a clustering of specific cardiovascular risk factors that are associated with an increased risk of cardiovascular diseases (CVD).

The aim of the review is to assess the metabolic syndrome, its pathogenesis, its association with cardiovascular diseases and the evidence for the goals and impact of treatment.

Definition and classification

The clustering of obesity, type 2 diabetes (DM2), hyperlipidemia, and hypertension (1–3) was first described. Although insulin resistance was first described many years earlier (4), hyperinsulinemia is considered a key feature of type 2 diabetes (5, 6), as well as hyperlipidemia (7–9), obesity (10–13), and hypertension (12–14). In addition, a cluster of heart disease risk factors seemed clearly related to type 2 diabetes (15).

For this reason, investigators proposed the existence of a unique pathophysiological condition that called the "metabolic" (1–3) or "insulin resistance" (11) syndrome. This concept was introduced by Reaven's in 1988. The syndrome has also been given several other names, including the metabolic syndrome, the insulin resistant syndrome, the plurimetabolic syndrome, and the deadly quartet (16-20).

In 1998, the term "metabolic syndrome" has been defined and institutionalized by the World Health Organization (WHO) (21) and then by the Third Report of the National Cholesterol Education Program's Adult Treatment Panel (ATP III) (22, 23). In addition, other organizations have developed similar, but again not identical, definitions (24-28).

The convergence of ideas between the American Heart Association and the International Diabetes Federation (IDF) represents an improvement over previous definitions. In this new definition, the prerequisite of abdominal obesity has been reconsidered. Instead, this criterion is one of the five diagnostic parameters, as insulin resistance and metabolic syndrome can exist in the absence of traditional anthropomorphic measures of obesity. Three of the following five – elevated waist circumference, elevated triglycerides, low high-density lipoprotein (HDL), blood pressure of at least 130/85 mmHg, or fasting glucose of at least 100 mg/dl (5.6 mmol/l) – are required for making the diagnosis (29).

Then, in 2009, IDF and the American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) representatives held discussions to attempt to resolve the remaining differences between definitions of MetS. Both sides finally agreed that abdominal obesity should not be necessary for diagnosis, requiring any 3 of the 5 risk factor. Furthermore, it was stressed the importance of adopting different values for waist measurement in different ethnic groups, recognizing that the risk of CVD and DM2, associated with a particular waist measurement, will differ in various populations.

Pathophysiology

The current definition of metabolic syndrome include four central features: insulin resistance, visceral obesity, atherogenic dyslipidemia and endothelial dysfunction.

In patients with metabolic syndrome, weight loss can improve multiple features, so a certain degree of adiposity appears to be required to manifest the abnormal pathophysiology. Conversely, there are patients who are obese but who don't manifest any of the other components of metabolic syndrome, so both

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metabolic predisposition to insulin resistance and obesity appear to be necessary for expression of the metabolic syndrome phenotype.

Atherogenic dyslipidemia follows from insulin resistance and visceral obesity, and can be captured in the definition by including separate criteria for high serum triglycerides levels and low HDL levels. Endothelial dysfunction also follows from insulin resistance and from adipokines and free fatty acids (FFAs) that are released from visceral adipose tissue. Endothelial dysfunction is captured by the requirement for hypertension in the definition. Both atherogenic dyslipidemia and endothelial dysfunction contribute mechanistically to the development of atherosclerosis and CVD. (30)

Other findings such as systemic inflammation, hypercoagulability, microalbuminuria and hyperuricemia are important to the pathophysiology, they would not be necessary as part of the definition because these findings would not be required independently.

Insulin resistance

Insulin is made in the pancreas by β-cells in response to hyperglycemia and stimulates glucose use differently in various tissues. The tissues that remove glucose from the circulation are skeletal muscle, liver and adipose tissue. In skeletal muscle and adipose tissue, insulin promotes glucose uptake into the cells by activating a complex cascade of phosphorylation-dephosphorylation reactions. In the skeletal muscle and liver, insulin stimulates the synthesis of glycogen from glucose and inhibits glycogenolysis. In the liver, insulin also decreases hepatic gluconeogenesis. In adipose tissue, insulin inhibits lipolysis and stimulates glucose uptake. The final effect is the increase of glucose uptake, the decrease of circulating glucose levels and the increase the conversion of glucose into the storage molecules, glycogen or fat (31). In insulin resistance, a β-cell defect initiates the disturbance in glucose homeostasis and adipose, muscle and liver cells do not respond appropriately to insulin. Insulin resistance is a common metabolic disorder that predicts of T2D, metabolic syndrome and obesity, and hyperinsulinemia is a surrogate marker for insulin resistance. Thus, insulin signaling coordinately affects peripheral glucose use, vascular tone and blood flow. Common mechanisms that contribute to insulin resistance can, therefore, also affect vascular function, including hyperglycemia, advanced glycation products, toxicity from FFAs, obesity, dyslipidemia and other proinflammatory conditions.

Visceral adiposity

Many investigators demonstrated that the visceral adipose tissue mass and not the subcutaneous or total adipose tissue mass were significantly correlated in multivariate analyses with insulin resistance, type 2 diabetes, and cardiovascular events. (32-39)
Visceral obesity causes a decrease in insulin-mediated glucose uptake, and it causes insulin resistance. The mechanisms for this probably involve adipokines (40), tumor necrosis factor α (TNFα) and interleukin-6 (IL-6), which are proinflammatory and contribute to insulin resistance and vascular dysfunction.

Atherogenic dyslipidemia

The key features of atherogenic dyslipidemia are increased blood concentrations of small, dense low-density lipoprotein (LDL) particles, decreased high-density lipoprotein (HDL) particles, and increased triglycerides (TGs). Insulin resistance and visceral obesity are associated with atherogenic dyslipidemia (41). In atherogenic dyslipidemia, the pattern of lipoprotein abnormalities includes elevations of VLDL levels, increased small LDL particles, and low HDL-cholesterol. There is a causal role of small LDL particles in atherosclerotic disease, with evidence that small, dense, lipid-poor LDL particles may be more atherogenic than large LDL particles (42). Insulin resistance leads to atherogenic dyslipidemia in several ways. First, insulin normally suppresses lipolysis in adipocytes, so insulin resistance increases lipolysis resulting in increased FFA levels. In the liver, FFAs serve as a substrate for synthesis of TGs. FFAs also stabilize the production of ApoB, the major lipoprotein of very-low-density lipoprotein (VLDL) particles, resulting in more VLDL production. Second, insulin normally degrades ApoB so insulin resistance directly increases VLDL production. Third, insulin regulates the activity of lipoprotein lipase, the rate-limiting and major mediator of VLDL clearance. (42)

Endothelial dysfunction

Endothelial dysfunction is the final common pathway between many cardiovascular risk factors and the development of atherosclerosis (43) The endothelium senses and responds to physiological and pathological stimuli, and produces vasoactive substances, including NO, prostacyclin and Endothelins. The healthy endothelium is able to respond to physical and chemical signals by production of a wide range of factors that regulate vascular tone, cellular adhesion, thromboresistance, smooth muscle cell proliferation, and vessel wall inflammation.

Cardiovascular risk factors including smoking, aging, hypercholesterolemia, hypertension, hyperglycemia, and a family history of premature atherosclerotic disease are all associated with alteration in endothelial function (44-46)

Hyperuricemia

An elevated serum urate concentration is commonly associated with the metabolic syndrome [47]; while the increase in serum urate has often been considered to be secondary, recent evidences suggest that it may have an important contributory role (48). First of all, elevated serum urate levels commonly precede insulin resistance, DM2 (49,50), and obesity (51), which is consistent with hyperuricemia as a possible causal factor; moreover, studies in cell culture and animal models have suggested a causative role for urate in models of the MetS.

Two mechanisms are proposed (48,52,53): 1) the hyperuricemia-induced endothelial dysfunction, leading to reduced insulin-stimulated nitric oxide-induced vasodilatation in skeletal muscle and, as a consequence, reduced glucose uptake in the muscle itself; 2) the inflammatory and oxidative changes caused by intracellular urate levels in adipocytes.

For example, mice lacking xanthine oxidase (the enzyme that produces uric acid from xanthine) only have half the adipocyte mass of their wild-type littermates. Besides, a recent review [54] suggests a bidirectional and causal relationship between hyperuricemia and hyperinsulinemia, the former reducing nitric oxide bioavailability and the latter decreasing the renal excretion of urate, that has been found to be inversely related to insulin resistance (55), as confirmed by experimental studies in healthy volunteers and hypertensive patients (56,57).

Another evidence, supporting the role of urate in MetS, comes from a study in obese mice with the MetS (58). These mice were hyperuricemia and lowering urate levels with allopurinol improved their pro-inflammatory phenotype in adipose tissue, and decreased macrophage infiltration and insulin resistance.

However, due to the lack of studies on humans, a causal link between hyperuricemia and MetS still remain controversial. What is sure is that hyperuricemia is often present in MetS subjects, and thus, it could at least contribute to the determinism of systemic inflammation, hypertension, endothelial dysfunction and cardiovascular events in these patients (59).

Relationship between metabolic syndrome and CVD

Many studies have shown that patients with the metabolic syndrome have more prevalent and greater risk to develop CVD (59-65). In these studies, the increased CVD risk ranged from 30 to 400%; this wide variation is probably due to the population, the inclusion criteria, and the length of follow-up.

In our studies (63, 64), we studied a population of 529 asymptomatic patients (mean age 62 ± 12.8 years), performing at baseline the ultrasound examination of Carotid intima-media thickness. After a 20 years follow-up, we found that patients suffering from MetS showed reduced survival and a higher prevalence of all cerebro and cardiovascular events (144 vs. 98, p<0.0001), and of all non-fatal CV events (120 vs. 79, p<0.0001). We demonstrated also that patients with metabolic syndrome had higher mean values of carotid intima-media thickness compared to individuals without MetS, and the presence of the syndrome determined an increased risk of cardiovascular events in both patients with preclinical atherosclerosis and in patients without atherosclerotic lesions (64).

It is not known whether the substitution or addition of any other well-known, conventional CVD risk factor(s) would improve the predictive value of the syndrome. In studies demonstrating that metabolic syndrome was associated with higher CVD risk (59-67), this excess risk remained after adjustment for other conventional risk factors. This would suggest that if other risk factors are included in the definition, the predictive value of the syndrome may improve.
Markers of inflammation might be used to predict CVD events. C-reactive protein (CRP) has been studied in great detail, and has been found to be an independent CVD risk factor (68-72) and an independent marker of insulin resistance. Three large population studies examined the relationship between CRP, the metabolic syndrome, and incident cardiovascular events (72). In all three, CRP was a strong independent predictor of events, and its predictive value was equal to that of the metabolic syndrome. The discrepant results have not, however, deterred some investigators from advocating that CRP be included in the definition of the metabolic syndrome (73).

There is also an association between other markers of inflammation and insulin resistance/hyperinsulinemia (73-75), as well as inflammation and obesity, leading some investigators to conclude that inflammation is integrally related to the components of the metabolic syndrome. Several other molecules have also been found to be closely associated with insulin resistance, metabolic syndrome risk factors, and the risk of CVD

such as plasminogen activator inhibitor and fibrinogen.

Management

The initial management of metabolic syndrome involves lifestyle modifications, including changes in diet and exercise habits, losing weight, being physically active, following a heart healthy diet, and quitting smoking.

Lifestyle change, diet and exercise

Lifestyle change and weight loss are considered the most important initial steps in treating metabolic syndrome. The long-range target is to lower your body mass index (BMI) to less than 25. BMI measures your weight in relation to your height and gives an estimate of your total body fat. A BMI between 25 and 29.9 is considered overweight. A BMI of 30 or more is considered obese. A BMI of less than 25 is the goal for prevention and treatment of metabolic syndrome.

Diets rich in dairy, fish, and cereal grains may be associated with a lower risk of developing metabolic syndrome). Not surprisingly, Mediterranean-style diets appear to be associated with a much lower risk and possibly with resolution of metabolic syndrome in patients who have met diagnostic criteria, especially when coupled with adequate exercise regimens. (76) Exercise is thought to be an important intervention, and the current recommendation is for patients to perform regular moderate-intensity physical activity for at least 30 minutes continuously at least 5 days per week (ideally, 7 days per week). Maintaining long-term adherence, however, remains a challenge. (77-79)

Hypertension

Treatment of hypertension had been based on the recommendations of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines, to achieve a goal blood pressure of less than 140/90 mm Hg or, in patients meeting diagnostic criteria for diabetes mellitus, less than 130/80 mm Hg. However, the 2014 report of the Eight Joint National Committee (JNC-8) has led to less stringent recommendations for drug therapy (140/90 mm Hg for most populations, 150/90 mm Hg for patients aged 60 or older), (80) with continued emphasis on the importance of promoting healthy diet and exercise behaviors, as addressed by 2013 guidelines from the American College of Cardiology. (81, 82)

Obstructive sleep apnea

Treatment of associated obstructive sleep apnea may play a significant role in the management of metabolic syndrome. (83) In a 2011 study, Sharma SK et al showed that patients with at least moderate obstructive sleep apnea who used continuous positive airway pressure (CPAP) therapy for 3 months had significant improvements in their metabolic profile, including reductions in systolic and diastolic blood pressure, LDL-C, triglycerides, and glycated hemoglobin. Furthermore, reversal of metabolic syndrome occurred to a greater degree in the CPAP therapy group than in patients who underwent sham treatment (13% vs 1%, respectively). (84)

Dyslipidemia

When lifestyle modifications fail, medical therapy for elevated triglycerides may include niacin and fibrates, though a distinction should be made between gemfibrozil and fenofibrate/fenofibric acid due to their different dosing patterns and different propensities for drug interactions, particularly if combined with a statin. The addition of omega-3 fatty acids to treatment is also likely to help lower triglyceride levels. (85-88)

Elevated fasting glucose

Drug therapy for hyperglycemia in patients with metabolic syndrome typically begins with an insulin-sensitizing agent, such as metformin. Some literature suggests that metformin may help to reverse the pathophysiologic changes of metabolic syndrome. This includes when it is used in combination with lifestyle changes (89) or with peroxisome proliferator-activated receptor agonists, such as the fibrates (90) and thiazolidinedione, (91) each of which may produce favorable metabolic alterations as single agents in patients with metabolic syndrome. (92) Management of diabetes mellitus, including screening for end-organ complications, should proceed under current guidelines. (93)

Prothrombotic state

Aspirin therapy may be helpful in the primary prevention of cardiovascular complications, (94) particularly in patients with at least an intermediate risk of suffering a cardiovascular event (i.e., >6% 10 y risk). (95)
Patients with the metabolic syndrome have enhanced platelet aggregation, increased fibrinogen, increased clotting factors, and decreased fibrinolysis from increased levels of plasminogen activator inhibitor-1, all resulting in an increased risk of atherothrombosis. (96) We previously suggested that all patients in the augmented intermediate-risk category (calculated 10-

year Framingham risk 6–20%) and all high-risk patients with the metabolic syndrome should be treated with 75–81 mg/day of aspirin in the absence of contraindications.

Conclusion

In summary, the central features of the metabolic syndrome are insulin resistance, visceral adiposity, atherogenic dyslipidemia and endothelial dysfunction. These conditions are interrelated and share common mediators, pathways and pathophysiological mechanisms. A comprehensive definition of the metabolic syndrome, expressed as simply as possible, would contain only these features. The requirement of multiple criteria would ensure the exclusion of people with individual components (e.g. isolated hypertension or isolated hyperlipidemia), as opposed to the composite pathophysiology discussed above. Inclusion of both TG and HDL criteria increases the specificity for atherogenic dyslipidemia, and inclusion of the blood pressure criterion ensures that the physiologic derangements are severe enough to have resulted in endothelial dysfunction.

Of the various definitions for the metabolic syndrome, the NCEP ATP III definition is the easiest to apply clinically and epidemiologically, because it uses straightforward criteria that are measured readily. Despite the ongoing controversy about whether the concept of metabolic syndrome is useful, it clearly defines specific pathophysiological mechanisms that link the central features. Consideration of metabolic syndrome as a specific entity allows for research on the genetic basis for susceptibility to this syndrome, a better understanding of its underlying pathophysiology and the development of treatment approaches.

The initial management of metabolic syndrome involves lifestyle modifications, including changes in diet and exercise habits. Indeed, evidence exists to support the notion that the diet, exercise, and pharmacologic interventions may inhibit the progression of metabolic syndrome to diabetes mellitus. (97)

Treatment of hypertension had been based on the recommendations of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) guidelines, to achieve a goal blood pressure of less than 140/90 mm Hg or, in patients meeting diagnostic criteria for diabetes mellitus, less than 130/80 mm Hg. However, the 2014 report of the Eight Joint National Committee (JNC-8) has led to less stringent recommendations for drug therapy (140/90 mm Hg for most populations, 150/90 mm Hg for patients aged 60 or older), (80) with continued emphasis on the importance of promoting healthy

diet and exercise behaviors, as addressed by 2013 guidelines from the American College of Cardiology. (82)

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