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Metabolic Syndrome and its Impact on Cardiovascular Diseases

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Abstract

Over the past decade, metabolic syndrome has gained recognition as a significant contributor to cardiovascular mortality. Isolated metabolic syndrome, without diabetes mellitus, plays an increasingly essential role in the pathogenesis of Coronary Artery Disease (CAD). The risk factors for metabolic syndrome act synergistically to promote the development of Cardiovascular Disease (CVD); the more the risk factors, the higher the likelihood of developing CVD. Among these risk factors, obesity is the biggest culprit as it leads to an increase in the levels of free fatty acids (FFAs), thereby resulting in insulin resistance. This, in turn, causes impaired intracellular glucose metabolism and consequent production of free radicals that reduce nitrous oxide levels and cause endothelial dysfunction, leading to atherosclerosis. Also, visceral fat, being a source of C-reactive protein, indirectly promotes inflammation and atherosclerosis. However, in certain races, insulin resistance is fairly common, even in non-obese individuals. This implies the possibilities of multiple complex mechanisms at the microcellular level, causing insulin resistance over and above the aforementioned mechanisms occurring due to obesity. In spite of this fact, control of obesity still remains the first line of defense against metabolic syndrome and resulting cardiovascular mortality. Measures like proper diet and physical exercise, and medications such as statins, fibrates, niacin, and ACE inhibitors are the cornerstones of management of metabolic syndrome. Additionally, clinical trials using medications affecting peroxisome proliferator-activated receptors (PPARs) and intestinal enteropeptidases have shown promising results for treatment of metabolic syndrome. Moreover, current research is also focused on the role of adipokines, semicarbazide-sensitive amine oxidase/vascular adhesion protein-1 (SSAO/VAP-1), 5-HT2c receptors, and the LKB1/AMPK pathway in influencing the mechanisms of insulin resistance. In the near future, newly discovered mechanisms and highly potent novel drugs may reduce the prevalence of metabolic syndrome and subsequent cardiovascular mortality.

Keywords: Metabolic syndrome; Cardiovascular diseases; Cardiovascular mortality

Introduction

Metabolic syndrome is defined by a group of risk factors that have been known to independently and synergistically increase the risk of developing cardiovascular disease, including, but not limited to coronary artery disease (CAD) and heart failure. According to the National Cholesterol Education Program (NCEP)/Adult Treatment Panel (ATP III), metabolic syndrome is defined as the presence of any three of the following five traits [1]:

1. Abdominal obesity, defined as a waist circumference in men ≥102 cm (40 in) and in women ≥88 cm (35 in).

2. Serum triglycerides ≥150 mg/dL (1.7mmol/L) or drug treatment for elevated triglycerides.

3. Serum HDL cholesterol <40 mg/dL (1mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women or drug treatment for low HDL-C.

4. Blood pressure ≥130/85 mmHg or drug treatment for elevated blood pressure.

5. Fasting plasma glucose (FPG) ≥100 mg/dL (5.6 mmol/L) or drug treatment for elevated blood glucose.

Epidemiology

The prevalence of metabolic syndrome among US adults is close to 22% [2], which equates to about 47 million people. About 44% of those are above 50 years of age [3]. It is important to note that almost 64% of men and 42% of women with impaired glucose tolerance, and 84% of men and 78% of women with type 2 diabetes mellitus have metabolic syndrome [4]. In addition, increased body weight appears to be an important risk factor for metabolic syndrome. In NHANES III, metabolic syndrome was present in 5% of individuals with normal weight, 22% of those who were overweight and in 60% of those who were obese [5]. Obesity proves to be a major risk factor for metabolic syndrome in diabetics as well as non-diabetics.

Isolated metabolic syndrome, without diabetes mellitus, significantly increases the risk of developing cardiovascular disease. Multiple sub analyses, such as the Scandinavian Simvastatin Survival Study (4S) and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) showed that placebo controls

with isolated metabolic syndrome (without type 2 diabetes) were at ~1.5 time's higher risk of coronary events than those without metabolic syndrome [6]. According to the NHANES-III trial, among the participants with age 50 years or more, the prevalence of CAD was found to be the highest among patients with both metabolic syndrome and type 2 diabetes at 19.2%. Similarly, patients with isolated metabolic syndrome (without type 2 diabetes) had a prevalence of 13.2%.

Lastly, the risk of developing cardiovascular disease in metabolic syndrome increases synergistically with each risk factor, proving that the more the risk factors of metabolic syndrome, the higher the likelihood of developing CVD. As shown in the Prospective Cardiovascular Munster (PROCAM) study, the 4 year risk of having a myocardial infarction among men between ages 40 and 65 increased 2.5 times in the presence of either diabetes or hypertension, 8 times in the presence of both diabetes and hypertension, and 19 times in the presence of all 3 risk factors including hypertension, diabetes, and dyslipidemia. Hence, the risk factors associated with metabolic syndrome significantly contribute to the development of cardiovascular disease.

Pathogenesis

ATP III recognized six major components that account for the pathogenesis of metabolic syndrome.

1. Abdominal obesity

2. Insulin resistance [7]

3. Dyslipidemia [8]

4. Hypertension

5. Prothrombotic state, with elevated fibrinogen and plasminogen activator inhibitor (PAI-1)

6. Pro-inflammatory state, with an increase in acute phase reactants.

Abdominal obesity

ATP III considers abdominal obesity to be one of the prime culprits for the rising prevalence of metabolic syndrome. Contrary to the former concept of adipose tissue being inert, there is growing evidence that fat is implicit in the secretion of cytokines and other inflammatory markers like PAI-1 and adiponectin. The excess release of free fatty acids (FFA) by visceral fat or intra-abdominal fat leads to an adverse effect on insulin action and glucose metabolism in several tissues [9], in part by increasing the triglyceride reserves in the liver and muscle tissue, thereby depressing insulin action and increasing the output of VLDLs by the liver [10]. Weight loss in obese individuals has been associated with a marked reduction in visceral fat and in turn a reduction in FFA levels leading to improved insulin sensitivity [11,12].

The differences in distribution of fat in men and women may explain, in part, the higher prevalence of CAD in men than in women [13]. The abdominal distribution of fat seen in men, as opposed to the gluteofemoral distribution of fat in women, has a stronger predisposition for development of CAD [14]. Despite the above observation, it is important to note that patients of normal weight can also be insulin resistant. These have been labeled as metabolically obese, normal-weight individuals.

The impact of obesity on cardiovascular disease is well documented. In the Framingham Heart Study cohort, Wilson et al. showed that an increase in weight of 2.25 kg or more over 16 years was associated with a 21 to 45 percent increase in the risk for developing the syndrome [15]. A large waist circumference alone identifies up to 46% of individuals who could develop metabolic syndrome in the next five years [16]. The International Day of Evaluation of Abdominal Obesity [17], the largest study to assess the frequency of obesity in primary care patients, showed that abdominal obesity, measured by the waist circumference, showed a graded relationship with both CVD and diabetes at all levels of BMI. The Heart Outcomes Prevention Evaluation (HOPE) study concluded that abdominal adiposity worsens the prognosis of patients with CVD and that a weight reduction program should be integrated into the management of these patients [18]. There are a variety of alterations in the intrinsic structure and function of the heart which take place secondary to excess accumulation of adipose tissue. Cardiomyopathy of Obesity, also known as Adipositas Cordis is a phenomenon in which cardiac myocytes accumulate fat between them. This leads to pressure-induced atrophy from the intervening fat, resulting in myocyte degeneration and cardiac dysfunction. Those pathological processes related to obesity predispose the individual to an array of cardiovascular abnormalities such as Coronary Artery Disease (CAD), heart failure and sudden cardiac death. Hence, obesity plays a crucial role in the development of cardiovascular disease in metabolic syndrome, primarily via release of excessive FFAs.

Insulin resistance

It is the defect in insulin action that results in hyperinsulinemia, necessary to maintain euglycemia. A major culprit in the development of insulin resistance is the excessive FFAs released by the visceral fat. FFAs work by inhibiting insulin-mediated glucose uptake, thereby leading to reduced insulin sensitivity. Many investigators continue to argue that this is by far the most important component of metabolic syndrome, so much so that it was named Insulin Resistance Syndrome until recently [19]. It is difficult to assess the specific nature of insulin resistance individually given that it is linked to obesity. It is simplistic to note that increasing levels of body fat are associated with decreasing levels of insulin sensitivity [20] but what dilutes this concept is that there is a broad variation in sensitivities even within the obese population [21]. In certain racial populations like south Asians, insulin resistance is common even in individuals with BMI <25 kg/m^2. But even in these populations with a higher predisposition, the incidence of insulin resistance increases with increased visceral fat. Furthermore, insulin resistance, as identified by increased C-peptide levels, is significantly related to hazards of cardiovascular death in non-diabetic adults [22]. Multiple studies have demonstrated a strong association between metabolic syndrome and the risk of developing type 2 diabetes mellitus [23]. Meta-analysis of 16 multi-ethnic cohort studies by Ford et al. showed that the relative risk of developing diabetes in an individual with metabolic syndrome ranged from 3.53 to 5.17 based on the patient population [24]. Another interesting finding in this study was that the relative risk for incidence of diabetes was increased 2.1-fold if ATP III definition was used and a 3.6-fold if the WHO definition for metabolic syndrome was considered. This difference highlights the importance of insulin resistance, which is a required characteristic of the WHO definition, in the pathogenesis of type 2 diabetes.

Another growing school of thought with regards to the association of insulin resistance and cardiovascular disease is a theory that links endothelial dysfunction with insulin resistance. Endothelial dysfunction is a strong contributor in the pathophysiology of coronary

artery disease. Deficiency of endothelial derived Nitric Oxide (NO) is the primary defect that leads to inadequate vasodilation and paradoxical vasoconstriction in coronary vasculature. Nitric Oxide production and release is markedly reduced in the presence of high levels of free radicals like Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS), which are produced as a result of impaired intracellular glucose and lipid metabolism. Endothelial dysfunction, in turn, leads to impaired insulin action due to inadequate transcapillary passage of insulin to its target tissues, eventually culminating in a vicious cycle. Hence, it can be concluded that insulin resistance, secondary to excess FFAs as well as endothelial dysfunction, significantly increases the risk of cardiovascular disease in metabolic syndrome.

Prothrombotic and proinflammatory states

A fundamental concept is that atherogenesis represents a state of chronic inflammation characterized by lipid-induced insult that triggers a cascade of events including invasion of macrophages and proliferation of smooth muscle cells. Within the endothelium, the secretory nature of adipose tissue, particularly that of intra-abdominal and visceral fat, is in part responsible for the proinflammatory and prothrombotic states that almost always accompany obesity. How this translates into increased risk of atherosclerotic cardiovascular disease continues to remain a bone of contention. One hypothesis that has wider acceptance is endothelial dysfunction [25] leading to enhanced atherogenicity. An interesting study by Mauras et al. [26] in obese children with no other comorbidities that could put them at a risk for metabolic syndrome showed that these children had remarkably higher levels of proinflammatory and prothrombotic markers such as hsCRP, fibrinogen, IL-6 and PAI-1. CRP, which is an acute phase reactant and an index of inflammation, has been strongly associated with CAD and acute coronary syndrome due to its ability to destabilize an atherosclerotic plaque [27]. CRP plays an essential role in the development of cardiovascular disease, particularly in metabolic syndrome. The Insulin Resistance Atherosclerosis Study (IRAS) [28] showed that even in non-diabetic populations, CRP levels were directly proportional to the incidence of metabolic syndrome [28]. Previous studies have shown that polymorphisms of CRP gene that cause higher concentrations of CRP are associated with higher risk of CVD [30]. Ridker et al. concluded that giving statins to individuals with elevated levels of hsCRP but without dyslipidemia, was associated with a significant reduction in the incidence of coronary events [31]. The association between CRP, metabolic syndrome and CVD is suggestive, but it is not clear as to how the elevations of CRP in obese individuals could lead to major coronary events. A causal relationship between elevated CRP and metabolic syndrome could not be demonstrated in a study of phenotype patterns associated with metabolic syndrome and CRP levels [32]. It must be noted that this does not rule out a causative relationship.

Multiple studies including the original Framingham study have confirmed the fact that fibrinogen is as important a risk factor for CVD as is hypertension [33,34], hyperlipidemia and smoking. PAI-1 [35], which is also released by visceral fat [36], is the principal inhibitor of fibrinolysis. PAI-1 gene knockout mice studies showed that when these mice were fed high-calorie, high-fat diet they were able to prevent obesity and insulin resistance [37]. Newer markers such as Toll-like receptor activity are being studied for their association with metabolic syndrome. Jialal et al. [38] concluded in their study that there is an increase of expression and activity of TLR-2 and TLR-4 in the monocytes of patients with metabolic syndrome and this could contribute to increased risk for CVD and diabetes in these individuals.

Therapeutic Implications

According to ATP III, obesity is the biggest risk factor in developing cardiovascular disease in metabolic syndrome, and thus proves to be the primary target in the management of metabolic syndrome. Consequently, weight reduction and increased physical activity continue to remain the first line of therapy to effectively lower the cardiovascular risks in metabolic syndrome by reducing cholesterol levels, blood pressure, insulin resistance and increasing HDL levels. Second line therapy for management of metabolic syndrome is the use of medications, specifically targeted towards the major risk factors of metabolic syndrome such as dyslipidemia, hypertension, and insulin resistance.

Statins prove to be the most effective treatment for lowering LDL cholesterol as well as other forms of apolipoproteins. A large study involving 5 different centers using low-dose rosuvastatin in 580 patients for 12 weeks, showed significant improvement in the lipid panel from baseline. LDL and non-HDL/HDL cholesterol level ratio was reduced by 47%, non-HDL levels were down by 43%, triglyceride levels were down by 23%, and HDL levels were up by 10% [39]. However, more importantly, lipid-lowering benefits were of a similar scale in patients with metabolic syndrome in comparison to those without metabolic syndrome, proving statins to be an effective therapy for hyperlipidemia in metabolic syndrome.

Furthermore, fibrates greatly aid in lowering cardiovascular risks in metabolic syndrome, especially when used in combination with statins, by lowering pro-inflammatory markers such as CRP, fibrinogen and PAI-1 [40,41]. This is clearly demonstrated in VA-HIT trial as gemfibrozil significantly reduced the risk of developing major cardiovascular events in high-risk populations with diabetes and insulin resistance [42].

Additionally, in a recent 3-phase cross over trial [43], a patient population with metabolic syndrome diagnosed by ATPIII criteria as well as combined hyperlipidemia and hypertriglyceridemia were treated with placebo, simvastatin 10mg alone or simvastatin and fenofibrate combination. At the end of the three phases of the study, the simvastatin alone group showed a reduction of triglycerides by 23%, total cholesterol by 27%, non-HDL cholesterol by 30%, and VLDL by 36%, and an increase in HDL of 6%. Interestingly, the addition of fenofibrates had exponential effects in reducing the VLDL by an additional 36%, and increasing the HDL by another 16% as compared to the simvastatin group alone. Therefore, fibrates, especially when used in combination with statins, prove to be an effective treatment to reduce major risk factors associated with metabolic syndrome, thus reducing the incidence of cardiovascular disease in metabolic syndrome. A multicenter randomized controlled trial by Colhoun et al. [44] concluded that statin therapy is effective in reducing the risk of cardiovascular events in patients with type 2 diabetes even if the LDL levels were not elevated. Statins also have been shown to decrease inflammation by attenuating leukocyte-endothelial cell interactions [45], thereby amending ischemic injury in hypercholesterolemic mice independently of their lipid-lowering actions.

In addition to hyperlipidemia and hypertriglyceridemia, hypertension management remains an important entity to reduce cardiovascular risks associated with metabolic syndrome. Low-dose

aspirin has been proved to be an effective tool, targeting prothrombotic states in the primary and secondary prevention of CAD events in patients with metabolic syndrome. In patients with a Framingham risk score of >10% aspirin has been shown to have a favorable effect. Hence, targeting proinflammatory states has been the focus of recent research aimed at reducing the cardiovascular risks associated with metabolic syndrome.

Medicine has a famous saying by Ben Franklin, "An ounce of prevention is worth a pound of cure." In the case of metabolic syndrome, proper diet and exercise prove to be an effective tool for treatment as well as prevention. As shown in the Framingham Offspring Study, diet had a significant impact on insulin resistance. Specific food types such as total fiber, cereal fiber, fruit fiber, and whole grain intakes were associated with lower insulin resistance and thus significantly reduced the risk of metabolic syndrome [46]. Lastly, pharmacologic approaches can assist in controlling major risk factors such as dyslipidemia and hypertension using statins, fibrates, niacin as well as ace-inhibitors, and thus preventing the development of metabolic syndrome.

Future Perspectives

Diagnostic

ATP III has simple current guidelines for diagnosis of metabolic syndrome, encompassing five major criteria including abdominal obesity, serum triglycerides, serum HDL, and blood pressure and fasting plasma glucose, as mentioned earlier. However, due to significantly high risk of developing CHD and CAD associated with metabolic syndrome, early detection of the disease is crucial. In addition to currently established risk factors, few other tools have been proposed to diagnose metabolic syndrome.

Several new biomarkers continue to gain importance in early detection of metabolic syndrome correlating with CVD risk, such as high leptin, elevated fasting insulin and increased hs-CRP levels as well as high uric acid levels. In addition, C-peptide may prove to be of importance in early development of CVD in metabolic syndrome [47,48].

Therapeutic

There is a growing arm of research focusing on adipokines like adiponectins, leptins, resistins, and zinc alpha-2 glycoproteinsas [49] targets of therapy, particularly as more knowledge is being gathered on the roles of different depots of fat. Another field of interest is the inhibitors of semicarbazide-sensitive amine oxidase/vascular adhesion protein-1 (SSAO/VAP-1) [50]. They have shown to exert beneficial effects on insulin in adipocytes, proving to be potential targets for management of metabolic syndrome.

Additionally, 5-HT2c receptors have been studied for a while with regards to their role in obesity management. 5-HT2c agonists, which have been considered potential drugs for treatment of obesity, include Lorcaserin, which is the only one in its class approved by the FDA specifically for treatment of obesity [51].

Genetics experts have also been targeting a specific intestinal enteropeptidase, which is involved in the digestion of dietary proteins and lipids, thereby proving to be a potential therapy for managing the primary risk factor of obesity in metabolic syndrome [52]. The LKB1/AMPK pathway is another potential target for the treatment of metabolic syndrome [53]. This pathway involves serine/threonine kinases regulating anabolic and catabolic metabolic processes, representing attractive therapeutic targets for the treatment of obesity and type II diabetes, and thus reducing cardiovascular risks in metabolic syndrome.

Furthermore, reduction of endothelial-derived nitric oxide (eNOS) is the key mechanism of insulin resistance and visceral adiposity in metabolic syndrome [54]. Thus, future pharmacologic interventions targeting eNOS regulation and increasing insulin sensitivity may prove to be beneficial in treating metabolic syndrome. Laufs et al. [55] showed that inhibition of HMG CoA reductase results in upregulation of eNOS expression by posttranscriptional mechanisms in addition to lowering of cholesterol levels.

Dipeptidyl peptidase 4 (DPP-4) inhibitors (commonly referred to as gliptins) are a novel class of oral antihyperglycemic agents with demonstrated efficacy in the treatment of type 2 diabetes mellitus as noted by Andre J Scheen. [56] Studies have indicated a possible beneficial action on blood vessels and the heart, via glucagon-like peptide effects. DPP-4 inhibition increases the concentration of many peptides with potential vasoactive and cardioprotective effects. Clinically, DPP-4 inhibitors improve several risk factors in patients with T2DM. They improve blood glucose control (mainly by reducing postprandial glycaemia), are weight neutral (or even induce modest weight loss), lower blood pressure, improve postprandial lipemia, reduce inflammatory markers, diminish oxidative stress, and improve endothelial function. Some positive effects on the heart have also been described in patients with ischemic heart disease or congestive heart failure, as indicated by Marney et al. [57] in work describing the interactive hemodynamic effects of DPP-4 inhibition and Angiotensin-converting enzyme inhibition. The actual relationship between DPP-4 inhibition and cardiovascular outcomes remains to be proven. Major prospective clinical trials with predefined cardiovascular outcomes and involving various DPP-4 inhibitors are now underway in patients with T2DM and a high-risk cardiovascular profile.

Lastly, peroxisome proliferator-activated receptors (PPARs), which have three isoforms: PPAR-α, PPAR-γ, and PPAR-δ, play a key role in regulating adipogenesis, lipid and carbohydrate metabolism, as well as insulin resistance. A trial using troglitazone demonstrated potential for effective treatment of metabolic syndrome primarily by increasing nitric oxide production via PPARγ-dependent pathway, VEGF-KDR/Flk-1-Akt-mediated eNOS-Ser1179 phosphorylation, PPARγ-independent pathway, and eNOS-Ser116 dephosphorylation [58]. In addition, another potential therapy using bezafibrate can regulate eNOS expression via PPAR-α dependent pathway.

Conclusion

Cardiovascular disease is a primary outcome of metabolic syndrome, which is defined adequately by the ATP III criteria. Abdominal obesity and insulin resistance denote the greatest risk for developing cardiovascular events in the presence of metabolic syndrome, primarily via excessive release of FFAs and impairment of endothelium function. In addition, proinflammatory markers, such as adipokines, CRP and PAI-1 play a significant role in disrupting atherosclerotic plaques, thereby leading to cardiovascular complications in metabolic syndrome.

Regardless of the risk factors involved, conservative methods for treating obesity such as diet and exercise prove to be the primary mode

of treatment as well as prevention of cardiovascular disease in patients with metabolic syndrome. Pharmacologic therapy can be beneficial using statins, fibrates and aspirin to reduce the major risk factors involved in metabolic syndrome, thereby significantly lowering the risk of cardiovascular disease. Lastly, future research targeting proinflammatory markers as well as eNOS and PPARs may prove to impact the development of cardiovascular disease in metabolic syndrome.

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