Metabolic syndrome

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ABSTRACT

Metabolic syndrome is a clustering of different risk factors that collectively increases the risk of developing cardiovascular disease and type 2 diabetes mellitus. The syndrome itself is associated with various metabolic abnormalities, including insulin resistance, non-alcoholic fatty liver disease, obstructive sleep apnoea, male hypogonadism and polycystic ovary syndrome. This review aims to discuss recent developments related to the syndrome, including the associated metabolic complications and goals for therapeutic strategies.

Keywords: cardiometabolic risk, cardiovascular risk, insulin resistance syndrome, metabolic syndrome

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INTRODUCTION

Metabolic syndrome (MetS) identifies patients at increased risk of developing cardiovascular disease (CVD) and type 2 diabetes mellitus. As it is a clustering of different risk factors, and with its pathogenesis not well understood, this has given rise to the development of multiple concurrent definitions. Central obesity and insulin resistance are acknowledged as important causative factors,[1-3] together with other associated conditions, including physical inactivity,[4] ageing[5] and hormonal imbalance[6,7] such as polycystic ovary syndrome (PCOS) or testosterone insufficiency.

The concept of clustering of risk factors was first described by Reaven[8] in 1988, when the term "insulin resistance syndrome" was conceived. However, as the mechanisms underlying the link to CVD risk factors remain uncertain and insulin resistance is not easily measurable in clinical practice, the more recent consensus, e.g. 2001 National Cholesterol Education Programme (NCEP) Adult Treatment Panel III (ATP III)[9] and the 2006 International Diabetes Federation (IDF) criteria,[10] favours focusing on other clinical parameters that are easier to measure. It is, therefore, imperative to bear in mind that as the newer criteria did not include insulin resistance as one of its diagnostic criteria, individuals diagnosed as having the syndrome using these criteria may not necessarily be insulin resistant. This is in contrast to the 1999 World Health Organization[11] and the 1999 European Group for the Study of Insulin Resistance[12] criteria, which emphasised insulin resistance. The IDF consensus, however, takes into account the importance of gender and ethnic differences in predicting early cardiovascular risk and may indeed be a better predictor for risk in women[13] and specific ethnic groups, e.g. South Asians (Indians), who appear to be more susceptible to the development of MetS at waist circumferences below that of the NCEP/ATP III cutpoints.[14] It is also worth noting that the NCEP/ATP III criteria were revised in 2004, with lowering of threshold for fasting glucose to ≥ 100 mg/dL (5.6 mmol/L) in concordance with American Diabetes Association criteria for impaired fasting glucose.[15] Hence, in view of the various diagnostic criteria used, care will need to be exercised when interpreting clinical studies related to MetS.

IMPORTANCE OF METS

MetS continues to be highly prevalent and contributes to a rapidly growing problem globally. About 40% of adults in the US population is estimated to have MetS by the time they reach the age of 60 years.[5,16] At least one-fourth of the adult European population may have MetS,[17-19] with a similar prevalence in Latin America.[20] MetS is also considered an emerging epidemic in developing Asian countries, including Singapore, China, Japan and Korea, with a prevalence of 8%–13% in men and 2%–18% in women, depending on the population and definitions used.[21-23]

PATHOPHYSIOLOGY

There had been several proposed hypotheses for the development of MetS. One such widely quoted hypothesis suggests that adipose tissue dysfunction is the underlying cause, resulting in abnormal metabolism of free fatty acids and the release of adipocytokines that are responsible for the inflammatory changes seen and insulin resistance.[24-26] Adipose tissue is in itself an endocrine organ[27-30] that is metabolically active, rather than purely an energy storage organ. Adiponectin is secreted exclusively by adipocytes in adipose tissue, and low levels in individuals had consistently predicted the presence of MetS and CVD risk.[31-35] In fact, adiponectin can be measured reliably in a clinical setting; its circulating values do not have diurnal fluctuation as much as other

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markers such as insulin, glucose or triglycerides, and only a small amount is required for its measurement, making this a potentially suitable biomarker for MetS.[36-38] Resistin[39-41] and visfatin[42-45] are the other adipocytokines implicated in the pathogenesis of MetS.

An alternative proposed aetiology suggests an underlying state of chronic, low-grade inflammation,[46-48] leading to endothelial dysfunction and the release of inflammatory cytokines, which induce insulin resistance in adipose tissue and muscle.[48,49] Indeed, insulin-resistant individuals manifest evidence of low-grade inflammation even without an increase in total body fat.[50]

METS AND ASSOCIATED CONDITIONS

Atherosclerosis

MetS is associated with the clustering of risk factors such as atherogenic dyslipidaemia, elevated blood pressure, endothelial dysfunction[51] and arterial stiffness.[52] Individuals with these characteristics commonly manifest pro-thrombotic and pro-inflammatory states, with a higher predictive probability of future development of CVD. However, the risk seen is above and beyond the magnitude contributed by the individual components of the syndrome.[53-63] The ability of MetS to predict the incidence of CVD may differ, depending on which definition is used. The NCEP/ATP III definition has been associated with a higher predictivity of CVD compared to others,[64-66] but the available studies are mainly within the context of Caucasian populations, and may possibly underestimate the risk of CVD in Asian populations.[67]

Type 2 diabetes mellitus

Type 2 diabetes mellitus has been described as a state of heightened cardiovascular morbidity and mortality. CVD is often already present at the time type 2 diabetes mellitus is diagnosed, and patients with diabetes mellitus are twice as likely to develop a cardiovascular event compared to one without the disease. Individuals with diabetes mellitus who have the other co-existing MetS factors have a higher risk for future cardiovascular events,[68] and its detection should thus alert clinicians to actively address the risk. In women with gestational diabetes mellitus, the presence of MetS significantly increases their risk of developing type 2 diabetes mellitus,[69,70] and therefore, these women should be actively counselled to lose weight through diet and lifestyle modification.

Insulin resistance

Insulin resistance is an important feature of MetS.[71] Although insulin-resistant individuals need not be clinically obese, they commonly have an abnormal fat distribution that is characterised by predominant upper body obesity (apple shape) rather than lower body obesity (pear shape) and by fat accumulated intra-peritoneally (visceral fat) rather than subcutaneously.[72] Upper-body obesity and insulin resistance are associated with a high release of non-esterified fatty acids from adipose tissue,[72,73] which results in impaired insulin-mediated hepatic glucose uptake and whole body glucose uptake,[74] and possibly, pancreatic beta-cell dysfunction.[75]

Non-alcoholic fatty liver disease

MetS is strongly linked to non-alcoholic fatty liver disease (NAFLD).[76-78] The prevalence of NAFLD is around 17%–33% of the general population in Western countries and increases to 57.5%–74.0% in obese individuals.[79,80] In the general population of China and Japan, the incidence of NAFLD is lower, at 15% and 14%, respectively.[81,82] However, this prevalence has been increasing in the recent years. Hepatic steatosis appears to have a close association with CVD, through the production of risk factors such as very low density lipoprotein, glucose, C-reactive protein, PAI-1 and fibrinogen.[83-86] Changes in enzyme gamma-glutamyltransferase and alanine-amino-transferase may also be related to cardiovascular risk.[87]

Obstructive sleep apnoea

Recent evidence suggests that sleep disturbances have strong association with weight gain, insulin resistance, dyslipidaemia, hypertension and CVD.[88-90] The association between obstructive sleep apnoea (OSA) with MetS remains significant even when controlled for body mass index,[91,92] suggesting that OSA is an independent risk factor for MetS. Elevated free fatty acids[93] and left ventricular diastolic dysfunction have also been seen in individuals with OSA.[94] Therefore, individuals found to have MetS should be asked (or their partners asked) about snoring and daytime somnolence, especially since the treatment of this condition with nasal continuous positive airway pressure therapy had been shown to successfully improve MetS.[95-97]

Renal disease

MetS is associated with renal adiposity and microvascular proliferation, leading to increased glomerular filtration and activation of oxidative stress and inflammation.[98] Individuals with MetS were found to have subclinical renal disease, and conversely those with chronic kidney disease who develop MetS present with a poorer prognosis.[99,100] It is therefore expected that treatment of the syndrome would improve the survival of patients with renal disease.

Reproductive: polycystic ovary syndrome and male hypogonadism

PCOS is a common disorder characterised by chronic anovulatory infertility and hyperandrogenism. Clinically, it presents as oligomenorrhoea, hirsutism and acne.[101] The prevalence of PCOS is 6%–7% among menstruating women,[102-105] but this may differ according to ethnic background; for example, women of South Asian (Indian) origin have a higher prevalence, present at a younger age and have more severe symptoms.[106,107] Many women with PCOS are obese and exhibit characteristics of MetS, as suggested by a higher reported incidence of hypertension, dyslipidaemia, visceral obesity, insulin resistance and hyperinsulinaemia.[108,109] They also have a higher prevalence of impaired glucose regulation and type 2 diabetes mellitus[110-113] as well as a strong association with sleep apnoea.[114,115] These women are more likely to fulfill the diagnosis of MetS, with an observed prevalence of 43%–47%.[6,109,116-118] Treatment for PCOS traditionally had targeted reproductive abnormalities, but it is also important to understand the potential long-term metabolic implications in order to offer a holistic approach to patient management.

In men, population-based studies have suggested the association of low testosterone with type 2 diabetes mellitus and MetS.[119-122] Those with MetS at baseline may also have increased odds of progression to hypogonadism.[123] Evidence for the use of testosterone replacement in hypogonadal men with type 2 diabetes mellitus and/or MetS is mixed, with some small studies showing favourable results,[124,125] whereas others showed no important cardiovascular effect.[126,127] Larger and adequately powered clinical trials are required to assess the benefits and risks of testosterone therapy in these men before any recommendations can be advocated for this purpose.

THERAPEUTIC STRATEGIES

All patients with MetS have a sufficiently high relative risk of CVD to justify for long-term intervention and monitoring in the clinical setting. The emerging epidemic of obesity significantly contributes to the rising prevalence of MetS, and thus burden of healthcare cost for CVD and other related chronic conditions. Intuitively, the first step in curbing this epidemic of MetS and subsequent risk of CVD would be to identify individuals at the early stage of the syndrome, so as to implement preventative measures for further development of the associated cardiometabolic complications. In this respect, there is a role within the public health domain to effectively promote lifestyle changes that are necessary to reduce the burden of the associated chronic diseases. Another utility for the diagnosis of MetS would be that in view of the "clustering" effect of risk factors, this should prompt clinicians to screen for other associated risks in individuals diagnosed with the syndrome.

The most important therapeutic intervention that has been proven effective in MetS is lifestyle modification through diet and exercise that aims for weight loss. Data from the Diabetes Prevention Programme has demonstrated the powerful effects of diet and exercise in treating patients with impaired glucose tolerance who are at high risk of developing diabetes mellitus. Lifestyle modification through exercise and diet resulted in a net loss of 7% body weight, leading to a 58% reduction in the progression to diabetes mellitus, while the metformin arm in the study showed reduction of only 21%.[128]

In the absence of clinical CVD or diabetes mellitus, the Framingham ten-year risk calculator[129] for coronary heart disease is a useful tool for estimation of absolute, short-term risk, and should ideally be performed in patients with MetS to guide therapeutic interventions. Individuals who already have diabetes mellitus are in the high-risk category and should be treated according to clinical practice guidelines for diabetes mellitus, and if the risk calculator is used, the UKPDS risk engine[130] may be more appropriate for this group of patients. The use of other emerging surrogate markers for CVD, e.g. carotid artery calcification and intima-media thickness, may be considered in certain individuals so as to further quantify their risk status after the ten-year risk score.

The goal for treatment of MetS as a whole is to reduce the lifetime risk for CVD as well as to enable earlier detection and treatment of risk factors. Once an individual has progressed to moderate or high risk of CVD over a ten-year period, drug therapies such as lipid-lowering medications and aspirin should be considered.

NEW DIRECTIONS IN THERAPY

Identification of a syndrome in clinical practice is a stimulus to other areas of medicine. Many publications have arisen, ranging from the epidemiology and prevalence of this syndrome in different populations and the different patterns of clustering in different ethnic groups to metabolic and genetic research on the underlying cause for this syndrome. The importance of the syndrome, as dictated by the "clustering" of the risk factors, is that there may be an underlying unifying pathology that defines the condition. Until the day when we manage to develop drugs that strike the core metabolic susceptibility of this syndrome, we currently continue to recommend medications that target individual risk factors.

CONCLUSION

The concept of MetS had been and continues to be useful to enhance awareness of risk factor clustering and to promote screening for individuals who present with CVD risk factors. It serves to highlight the risk associated with the increased prevalence of obesity globally and the potential implications in the years to come. Public health effort and healthcare systems have an important role to play in the promotion of weight control and physical activity as a preventative medicine for obesity and MetS.

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