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THE METABOLIC SYNDROME – AN ONGOING STORY

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The metabolic syndrome refers to the clustering of cardiovascular risk factors that include diabetes, obesity, dyslipidaemia and hypertension. Due to various definitions and unexplained pathophysiology it is still a source of medical controversy. Insulin resistance and visceral obesity have been recognized as the most important pathogenic factors. Insulin resistance could be defined as the inability of insulin to produce its numerous actions, in spite of the unimpaired secretion from the beta cells. Metabolic abnormalities result from the interaction between the effects of insulin resistance located primarily in the muscle and adipose tissue and the adverse impact of the compensatory hyperinsulinaemia on tissues that remain normally insulin-sensitive. The clinical heterogeneity of the syndrome can be explained by its significant impact on glucose, fat and protein metabolism, cellular growth and differentiation, and endothelial function. Visceral fat represents a metabolically active organ, strongly related to insulin sensitivity. Moderating the secretion of adipocytokines like leptin, adiponectin, plasminogen activator inhibitor 1 (PAI-1), tumor necrosis factor alfa (TNF-alfa), interleukin-6 (IL-6) and resistin, it is associated with the processes of inflammation, endothelial dysfunction, hypertension and atherogenesis. In 2005, the International Diabetes Federation (IDF) has proposed a new definition, based on clinical criteria and designed for global application in clinical practice. Visceral obesity measured by waist circumference is an essential requirement for diagnosis; other variables include increased triglyceride and decreased HDL levels, hypertension and glucose impairment. Whatever the uncertainties of definition and etiology, metabolic syndrome represents a useful and simple clinical concept which allows earlier detection of type 2 diabetes and cardiovascular disease.

Key words: *metabolic syndrome, insulin resistance, visceral obesity, type 2 diabetes, cardiovascular disease*

INTRODUCTION

The metabolic syndrome refers to the clustering of cardiovascular risk factors that include diabetes, obesity, dyslipidaemia and hypertension (1, 2). This clustering of risk factors, which is not thought to be grouped by chance alone, is frequently seen in everyday clinical practice. Approximately 1 adult in 4 or 5, depending on the country, has metabolic syndrome. Incidence increases with age; it has been estimated that in the category over 50 years of age, metabolic syndrome affects more than 40% of the population in the United States and nearly 30% in Europe (2, 3).

Metabolic syndrome has been widely accepted as a simple clinical tool for earlier detection of type 2 diabetes and cardiovascular disease (4, 5). It has been estimated that people with the metabolic syndrome are at twice the risk of developing cardiovascular disease compared with those without the syndrome, and experience a five-fold increased risk of type 2 diabetes (1, 4).

However, due to unclear underlying pathophysiologic processes leading to its development, and confusion between the conceptual definitions, metabolic syndrome continues to be a source of medical controversy.

Recently, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have advised refocusing on the individual components of the syndrome without regarding the syndrome as an identifiable target. This statement was not accepted by the International Diabetes Federation (IDF), which emphasized that regardless of the uncertainties of definition and aetiology, it is advisable to regard the metabolic syndrome as a whole (5, 6).

PATHOPHYSIOLOGY

The association of obesity and metabolic abnormalities with poor cerebrovascular outcome had been recognized long before the concept of the metabolic syndrome became popular. However, it was in 1988 when Dr Gerald Reaven postulated "the syndrome X", which we now call the metabolic syndrome (7). Reaven noticed that there were many people who at the same time had glucose intolerance, hyperinsulinaemia, high triglycerides (TG), low high-density lipoprotein (HDL) cholesterol, and hypertension, all being factors leading to the development of cardiovascular disease. He proposed insulin resistance as the driving force of the syndrome, which has enabled more insight into the condition (7, 8).

Over the past decades many other abnormalities, in particular chronic pro-inflammatory and pro-thrombotic states,

were added to the syndrome, rendering the definition more complex. The issue of abdominal obesity as the core of the syndrome has gained more attention (9-11). It has been recognised that metabolic abnormalities linked to insulin resistance are usually found in patients with abdominal obesity (12, 13). Although endocrine research had identified insulin resistance and visceral obesity as important players in its pathogenesis, they failed to present a unifying hypothesis (*Fig. 1*). From a practical point of view, it seems that there is no need to dissociate the two conditions. Insulin resistance is considered to be at the core of the syndrome, while central obesity is its most prevalent clinical manifestation (14).

INSULIN RESISTANCE

Insulin resistance can be defined as the inability of insulin to produce its numerous actions, in spite of the unimpaired secretion from the beta cells (15-17). Insulin is the most potent anabolic hormone in our body, which has a significant role in glucose, fat and protein metabolism, but also influences cellular growth and differentiation, as well as the endothelial function. These numerous actions explain the clinical heterogeneity of the metabolic syndrome (7).

Insulin elicits its various biological responses by binding to a specific receptor (15, 16). The ability of insulin receptor to autophosphorylate and phosphorylate intracellular substrates is crucial for complex cellular responses to insulin (15-17). Insulin binding to the alfa subunit of insulin receptor results in conformational changes in the receptor, stimulation of the tyrosine kinase activity intrinsic to the β subunit which in turn triggers the signalling cascades (*Fig. 2*).

Insulin receptor transphosphorylation of several substrates including insulin receptor substrate (IRS) proteins 1-4 leads to the activation of downstream signalling pathways which mediate insulin actions. The four IRS proteins show tissue-specific differences in mediating insulin action, with IRS-1 playing a prominent role in the skeletal muscle and IRS-2 in the liver. Two major signalling pathways activated by insulin binding to its receptor are the phosphatidylinositol-3'-kinase (PI3K) pathway and mitogenic, or mitogen-activated protein kinase (MAPK) pathway.

PI3K pathway plays a crucial role in the metabolic actions of insulin, glycogen, lipid and protein synthesis, vasodilatation and

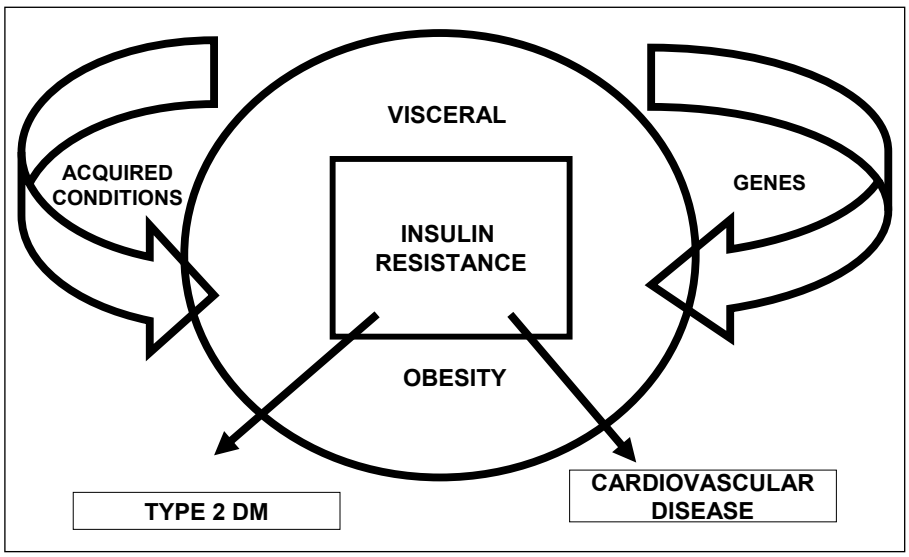


Figure 1. Pathophysiology of the metabolic syndrome

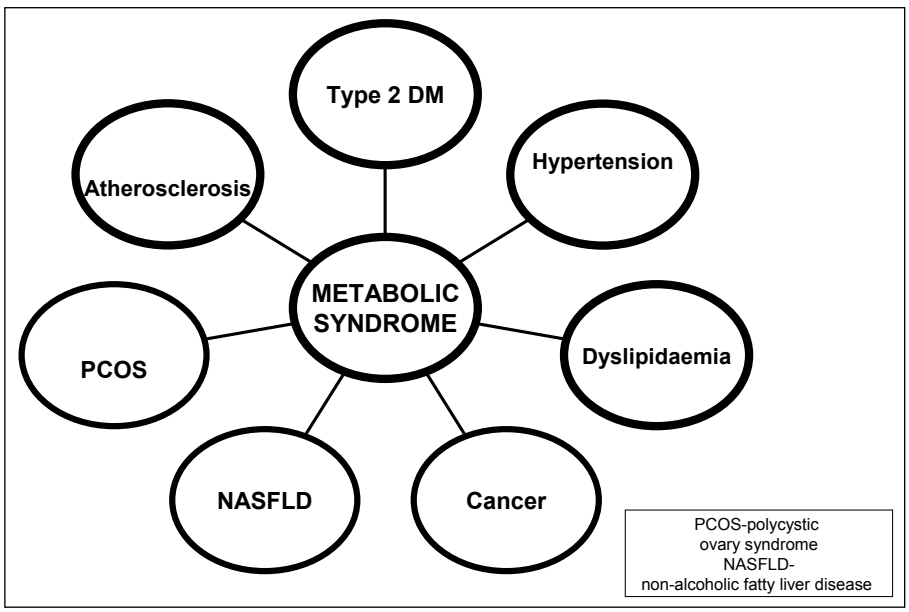
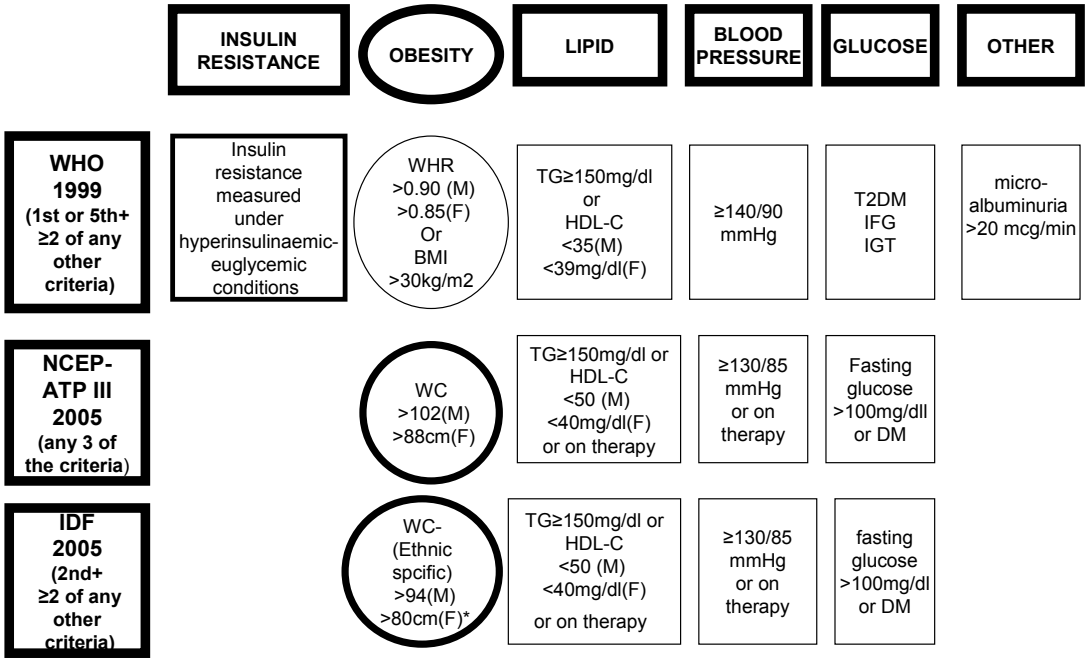


Figure 2. Conditions associated with the metabolic syndrome

Table 1. Definitions of the Metabolic Syndrome



WHR-waist-To-Hip ratio; WC-waist Circumference;TG-triglyceride; BMI-body mass index

anti-inflammatory effects. This pathway has been demonstrated to be upstream of glucose transporters (GLUT) 4 translocation, by which insulin promotes glucose uptake by muscle and adipose tissue. The activation of MAPK pathway is associated with cell growth and proliferation, decrease in nitric oxide production and procoagulant effects (17, 18).

Insulin resistance could be caused by various genetic and acquired conditions. Except in a few rare cases involving antibodies against insulin receptor or mutations in the insulin receptor gene, insulin resistance of the metabolic syndrome results from impairments in cellular events distal to the interaction between insulin and its surface receptor (7, 8). Metabolic abnormalities result from the interaction between the effects of insulin resistance located primarily in the muscle and adipose tissue and the adverse impact of the compensatory hyperinsulinaemia on tissues that remain normally insulin sensitive (15, 16).

VISCERAL ADIPOSITY

Although adiposity has been traditionally defined as an increase in total body mass, visceral fat accumulation has been found to correlate with a cluster of metabolic abnormalities observed among the metabolic syndrome patients (19).

Waist circumference is accepted as an easily obtainable indicator of visceral adiposity. The standard calls for measurement at the high point of the iliac crest in the supine position (19-22).

Visceral fat, in comparison with the subcutaneous tissue, represents a metabolically active organ, strongly related to insulin sensitivity (23). Adipocytes from visceral fat have a very different histology and biology from subcutaneous fat. Subcutaneous fat tissue, characterised by small, insulin-sensitive adipocytes, is a storage fat depot, without vascular stroma and cellular infiltration. Fat taken from visceral compartments and composed of large, insulin resistant adipocytes, has a well-developed vasculature with the infiltration of inflammatory cells. Increased lypolisis in large insulin resistant adipocytes leads to increased synthesis of very-low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) in the liver, driving some of typical changes in the lipoprotein profile.

Inflammatory cells regulate adipocyte behaviour as a source of hormones and cytokines, called adipokines, with proinflammatory and proatherogenic effects. Circulating levels of cytokines including resistin, leptin, TNFα, interleukin -6 (IL-6), C-reactive protein, fibrinogen and plasminogen activator inhibitor 1 (PAI-1) are generally increased in obese subjects and in patients with diabetes (23-26). On the contrary, visceral adiposity is a state with a relative deficiency of adiponectin, a tissue-specific circulating hormone with insulin-sensitising and anti-atherogenic properties. Adiponectin stimulates glucose use and fatty acid oxidation in the muscle, enhances insulin sensitivity in the liver, increases free fatty acid (FFA) oxidation, reduces hepatic glucose output and inhibits monocyte adhesion and macrophage transformation to foam cells within the vascular wall (24-26).

DEFINITIONS

Throughout the years several classifications for the metabolic syndrome have been proposed, emphasising insulin resistance or visceral obesity. However, there are 3 main ones: The World Health Organization (WHO) definition, the Adult Treatment Panel III (ATPIII) Report and the International Diabetes Federation (IDF) consensus on the metabolic syndrome (*Table 1*).

According to the WHO definition from 1999, the syndrome is present in a person with diabetes, impaired fasting glucose, impaired glucose tolerance or insulin resistance harbouring at least two of the following criteria: waist-to-hip ratio >0.90 in men or >0.85 cm in women, serum triglyceride ≥150mg/dl or HDL-C<35mg/dl in men and <39mg/dl in women, urinary albumin excretion rate >20 mcg/min and blood pressure ≥140/90 mmHg (27).

In 2001, the National Cholesterol Education Program - Adult Treatment Panel (NCEP–ATPIII) defined the metabolic syndrome as having at least three of the following abnormalities: waist circumference >102 cm in men and >88 cm in women, serum triglyceride ≥150mg/dl, HDL-C 40mg/dl in men and <50mg/dl in women, BP≥130/85 mmHg and serum glucose ≥110mg/dl (28). This definition was slightly modified in 2005 (2, 14). That same year, the International Diabetes Federation (IDF) proposed a new definition based on clinical criteria and designed for global application in clinical practice. This definition represents modifications of the WHO and ATP III definitions and places greater emphasis on visceral obesity as the core feature of the syndrome. Visceral obesity measured by waist circumference is an essential requirement for the diagnosis, while other variables employed by ATP III are slightly (*Table 1*). IDF defined visceral obesity for different ethnic populations based on waist circumference measurements obtained from epidemiologic data of various ethnic populations (14).

CONDITIONS ASSOCIATED WITH THE METABOLIC SYNDROME

Type 2 Diabetes

In insulin resistant state primary effects of insulin blood glucose, *i.e.* decreased glucose hepatic production and increased peripheral glucose uptake in the muscle, are abolished. As long as the pancreatic beta cells are able to secrete large amounts of insulin needed to prevent increases in plasma glucose, normal glucose tolerance is maintained. In individuals with abnormal beta cells due to both genetic and acquired conditions, frank hyperglycaemia with relative insulin deficiency will develop (8, 11, 16, 17). Although approximately 25% of insulin resistant patients have normal glucose tolerance test, this condition significantly increases the risk of developing type 2 diabetes (16).

Dyslipidaemia

Insulin resistant state is characterised by resistance to insulin-inhibited lipolysis in the adipose tissue, leading to overproduction of FFAs in the plasma and increased FFA uptake by the liver.

FFA leads to increased liver concentrations of TG and cholesterol esters (CE). High blood TG concentrations in the form of VLDL induce cholesterol ester transfer protein (CETP) activity, which promotes transfer of TG from VLDL to HDL and a subsequent increase in HDL clearance and decreased HDL concentrations. It also promotes the transfer of TG into LDL in exchange for LDL cholesterol ester. The triglyceride-rich LDL can undergo hydrolysis by hepatic lipase or lipoprotein lipase, which leads to a small, dense, cholesterol-depleted LDL particle (SD-LDL).

All three components of atherogenic dyslipidaemia are individually associated with a cardiovascular risk (29, 39).

Hypertension

Insulin resistance and subsequent hyperinsulinaemia induce blood pressure elevation by activating sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS) resulting in sodium retention and volume expansion, and endothelial and renal dysfunction (12, 16, 18). Hyperinsulinaemia stimulates the activation of RAAS in blood vessels and the heart, generating the production of angiotensin II and its pro-atherogenic effects. At the same time, hyperinsulinaemia in insulin resistant subjects stimulates the MAPK pathway, which promotes vascular and cardiac injury (15, 16). The local RAAS in the visceral adipose tissue exerts more powerful systemic effects compared with the subcutaneous adipose tissue. Angiotensin II acts through angiotensin 1 receptors, inhibiting vasodilatatory effects of insulin on blood vessels and glucose uptake into the skeletal muscle cells by blocking insulin action on phosphatydilinositol-3 kinase and protein kinase beta through free oxygen production (16, 18, 31). This leads to a decrease in nitric oxide (NO) production in endothelial cells, vasoconstriction in smooth muscle cells, and GLUT 4 inhibition in the skeletal muscles. The second mechanism by which insulin resistance contributes to hypertension includes angiotensin 1 receptor overactivity, which further leads to vasoconstriction and volume expansion (12, 17, 18).

Polycystic ovary syndrome (PCOS)

PCOS is the most common endocrine abnormality in premenopausal women, characterised by oligo/anovulation, clinical and/or biochemical hyperandrogenism and polycystic ovarian morphology. Although the pathophysiology is not completely understood, there is evidence that insulin resistance and compensatory hyperinsulinaemia play a key role (8, 16, 32, 33). Hyperinsulinaemia acting on normally insulin sensitive tissues augments androgen production. It has been proposed that insulin acts directly and indirectly through the pituitary.

Insulin increases LH activity, stimulates ovarian receptors of insulin and IgF, enhances the amplitude of serum LH pulses, stimulates adrenal androgen production and suppresses hepatic production of sex-hormone-binding globulin (SHBG), resulting in increased testosterone (16, 17, 32-34).

Many studies have proven that women with PCOS are at an increased risk for the development of type 2 diabetes, dyslipidaemia, hypertension and cardiovascular disease (33-35). The prevalence of the metabolic syndrome was found to be nearly 2-fold higher in women with PCOS than in general population, matched for age and BMI (34).

Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) represents a spectrum of several non-alcoholic-related steatotic liver diseases, ranging from benign fatty liver to non-alcoholic steatohepatitis (NASH), associated with cirrhosis and hepatocellular carcinoma. Increased prevalence of obesity, diabetes, hyperlipidaemia, and insulin resistance in patients with NAFLD implicate a close link with the metabolic syndrome (35, 36). Insulin resistance, present in 98% of patients with NAFLD, leads to increased lipolysis and circulating FFAs, decrease in insulin-mediated glucose disposal, inhibition of glucose utilization and promotion of gluconeogenesis (7, 8, 16). Elevated plasma glucose and insulin concentrations promote de novo fatty acid synthesis (lipogenesis) and impair β-oxidation, thereby contributing to the development of hepatic steatosis. Decreased adiponectin hinders FFAs oxidation contributing to fat accumulation in the liver (8, 11, 17). However, the reason some patients with benign disease develop the more aggressive form of NASH is unclear. It seems reasonable that the development of NASH requires additional pathophysiologic abnormalities. In the context of multiple-hit hypothesis oxidative stress and various cytokines like TNF-α have been implicated in the progression of fatty liver to NASH. TNF-α, synthesised by hepatocytes and Kupffer, cells cause hepatocyte injury and inflammation, leading to the activation of stellate cells and fibrosis (36, 37). Various cytokines secreted by adipose tissue contribute to

insulin resistance in the muscle and liver (32-38). Recently it has been postulated that the liver could be the primary source of systemic insulin resistance. Insulin resistance caused by hepatic activation of NF-κB promoting systemic inflammation and insulin resistance in the skeletal muscle was documented in a mice model (37, 38). Although there is no doubt that insulin resistance, visceral obesity and fatty liver are strongly interrelated, it seems that the old question concerning the metabolic syndrome is raised again: what comes first?

THERAPEUTIC APPROACH TO PATIENTS WITH THE METABOLIC SYNDROME

The lack of specific algorithm makes the therapeutic approach to patients with the metabolic syndrome difficult and heterogeneous. Weight reduction by means of dietary changes and promotion of physical activity are widely accepted as the main approaches. Both patients and physicians agree that unhealthy lifestyle aggravates the underlying pathology (39-41). However, in clinical practice lifestyle modifications are usually not sufficient to obtain the target value of individual risk factors. This fact underlines the therapeutic importance of pharmacological interventions capable of reducing blood pressure, dyslipidaemia, glucose metabolism impairment and other abnormalities related to the metabolic syndrome.

Although a clinical diagnosis of the metabolic syndrome is not sufficient to assess global risk for cardiovascular disease, this syndrome involves three or more risk factors, often organ damage and diabetes (1, 2, 8, 14). For this reason the primary goal in the treatment of patients with the metabolic syndrome should be the prevention of major vascular events. To achieve this goal, physicians should pay attention to the choice of drug in order to avoid aggravation of metabolic abnormalities.

Drugs that improve insulin sensitivity such as metformin and glitazones are indicated in the treatment of type 2 diabetes. They have also shown efficacy in the prevention of diabetes and treatment of PCOS and NASH (42-44). To control atherogenic dyslipidaemia, a combination therapy of statin and fibrates is usually required (45). In the treatment of hypertension a particular emphasis should be placed on ACE inhibitors and angiotensin II receptor blockers, as these drugs have shown efficacy in the prevention of diabetes. Central sympatholytic agents like moxonidine exert additional beneficial effects of increasing insulin sensitivity (46). If type 2 diabetes is present, in 2/3 of the patients target blood pressure values can be achieved only with two or more antihypertensive drugs (12, 13, 46).

Increased understanding of the mechanisms contributing to the vicious cycle of the metabolic syndrome, as well as critical analysis of the results of ongoing trials are important for developing a logical, evidence-based treatment strategy.

CONCLUSION

Whether or not one accepts this condition as a distinct entity, and in spite of the controversies surrounding its pathophysiology, the concept of the metabolic syndrome continues to gain attention. The prevalence of the metabolic syndrome is increasing at a disturbing rate and within the context of a proven association with cardiovascular disease, the leading cause of mortality in the modern world.

In spite of a recent debate, the metabolic syndrome remains important in the clinical practice, as it integrates the most common abnormalities representing major cardiovascular risk factors. The arguments for and against the significance of the metabolic syndrome will continue to be a matter for debate. On the other hand, many other conditions will be added in the future, creating a vicious cycle of “the ongoing story of the metabolic syndrome”.

Conflict of interests: None declared.

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