revisão

An Update on Cardiovascular Risk of Metabolic Syndrome

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ABSTRACT

Efforts are being made to identify cardiovascular (CV) risk factors (RF) and intervene in high-risk subjects aiming to reduce CV mortality. Disorders grouped under the metabolic syndrome (MS), linked by insulin resistance (IR), confer high CV risk due to the cluster of glucose intolerance, hypertension, elevated triglycerides and low HDL-cholesterol levels in addition to several recently described RF. Hyperinsulinemia is considered an independent RF; central obesity is associated with major RF independently of BMI. High visceral fat lipolytic activity results in overproduction of free fatty acids and metabolic consequences, characterizing the IR state. Association of microalbuminuria with hypertension, triglyceride and fibrinogen levels suggested a role in predicting CV disease. It should be considered a marker of generalized endothelial dysfunction. Hypofibrinolysis due to fibrinogen and PAI-1 elevations, induced by the IR state, facilitates atherothrombosis in patients with MS. The thrombin activator fibrinolysis inhibitor is also independently associated with markers of obesity, glycated hemoglobin and IR. Hyper-homocystinemia is associated with deleterious vessel effects and seems to be result from endothelial damage, chronic inflammatory status and kidney impairment. C-reactive protein and adiponectin - sensitive markers of inflammation - are also associated with IR. Endothelin-1 can lead to MS disorders and increased production might reflect endothelial damage caused by IR. In summary, patients with MS are at the highest risk of dying from CV events. Interventional trials directed to components of MS and also to increase insulin sensitivity are needed to establish the prognostic impact in CV morbidity and mortality. **(Arq Bras Endocrinol Metab 2003;47/3:220-227)**

Keywords: Metabolic syndrome; Cardiovascular risk factors; Glucose intolerance; Hypertension; Dyslipidemia.

RESUMO

Uma Atualização em Risco Cardiovascular da Síndrome Metabólica.
Esforços são feitos para identificar fatores de risco (FR) cardiovascular (CV) e intervir em indivíduos com alto risco, visando reduzir a mortalidade CV. Os distúrbios agrupados como síndrome metabólica (SM), ligados pela resistência à insulina (RI), conferem um alto risco CV devido à combinação de intolerância à glicose, hipertensão, triglicérides elevados e HDL baixo, em adição a outros FR recentemente descritos. A hiperinsulinemia é um FR independente e a obesidade central é um FR maior, independente do IMC. A elevada atividade lipolítica da gordura visceral resulta em hiperprodução de ácidos graxos livres e suas consequências metabólicas, caracterizando o estado de RI. A associação de microalbuminúria com hipertensão, triglicerídeos e fibrinogênio, sugerem um papel na predição da doença CV e deve ser considerada um marcador de disfunção endotelial generalizada. Hipofibrinólise, devida a elevações do fibrinogênio e do PAI-1, induzidas pelo estado de RI, facilita a aterotrombose em pacientes com SM. O inibidor do ativador da trombina é, também, associado independentemente com marcadores de obesidade, hemoglobina glicada e RI. Hiper-homocistinemia está associ-

ada com efeitos deletérios nos vasos e parece resultar de dano endotelial, estado inflamatório crônico e comprometimento renal. A proteína C-reativa e a adiponectina - marcadores sensíveis de inflamação - também estão associados com RI. A endotelina-1 pode levar a distúrbios da SM e sua produção aumentada refletir dano endotelial causado pela RI. Em resumo, pacientes com SM têm o mais elevado risco de morte por eventos CV. Estudos clínicos intervencionistas, dirigidos aos componentes da SM e também para aumentar a sensibilidade à insulina, são necessários pra estabelecer o impacto prognóstico sobre a morbidade e mortalidade CV. **(Arq Bras Endocrinol Metab 2003;47/3:220-227)**

Descritores: Síndrome metabólica; Fatores de risco cardiovascular; Intolerância à glicose; Hipertensão; Dislipidemia.

CARDIOVASCULAR (CV) DISEASE is the main cause of populational death and two thirds of these events are attributed to coronary artery disease (1). In Brazil, coronary heart disease (CHD) was responsible for almost one third of deaths in 1999 according to DATASUS (2). Mortality rates due to CV diseases have been declining worldwide; in US, a downtrend was detected in the late 60's, Europe mid 70's and Brazil mid 80's. Considering the progress in the diagnosis and treatment of CV disease, substantial reductions in morbidity and mortality would be expected. As atherosclerosis is present for many years prior to clinical onset, early identification of risk factors is essential to prevent CV events. The deleterious effects of smoking, hypertension, dyslipidemia and diabetes mellitus (DM) on the circulatory system are consistently reported in several prospective epidemiological studies (1), as has been the efficacy of intervention programs to reduce the incidence of CV events (3-5). In addition to the major CV risk factors, others have been described during recent decades, although their association with atherosclerotic disease may not necessarily indicate a cause-effect relationship.

Three of the major CV risk factors – DM, hypertension and dyslipidemia – present a common denominator: insulin resistance. Among other clinical abnormalities, such diseases comprise a syndrome presently known as metabolic syndrome (MS). More recently, inflammation has also been associated with insulin resistance. This paper discusses the relationship between insulin resistance and a cluster of disorders whose endpoint is CV disease.

CONCEPT OF METABOLIC SYNDROME

When Reaven described the original "syndrome X" in 1988 (6), such patients presented with glucose intolerance, systemic hypertension, dyslipidemia and CV disease, all linked by insulin resistance, defined as a genetic or acquired condition characterized by reduced tissue uptake of glucose in response to insulin stimulation. Due to insulin resistance, a compensatory increase in beta cell secretion may occur, resulting in elevation of circulating insulin levels. The "gold standard" to assess insulin sensitivity is the euglycemic hyperinsulinemic clamp (7), a complex, costly and time-consuming method. Because of these limitations, the clamp has not been used in clinical settings. Even for research purposes, a variety of alternative methods have been proposed in an attempt to quantify insulin resistance (8,9).

As a number of metabolic abnormalities were further associated with those initially described by Reaven's syndrome X, the concept of the syndrome was expanded (10), and its denomination changed to metabolic syndrome (MS). In spite of the nonexistence of an internationally accepted definition, some entities have tried to characterize it. Besides glucose intolerance, hypertension and dyslipidemia (hypertriglyceridemia and low HDL-cholesterol), also central obesity, postprandial hyperlipemia, microalbuminuria, hyperuricemia, hypofibrinolysis and hyperandrogenism are also described as part of MS. The World Health Organization (11) has suggested that this diagnosis should be established when, in addition to disturbance of glucose metabolism (insulin resistance and/or glucose intolerance), the patient shows at least two of the following components: (a) blood pressure ≥140/90 mmHg, (b) hypertriglyceridemia (≥150 mg/dl) and/or low levels of HDL-cholesterol (<35 mg/dl for men and <40 mg/dl for women); (c) central obesity (waist-to-hip ratio >0.90 for men and >0.85 for women) and/or body mass index >30 kg/m^2 and (d) microalbuminuria (urinary albumin excretion ≥20 μg/min or albumin-to-creatinine ratio ≥30 mg/g). It is underscored that such subjects who are at the highest CV risk represent one of the major diagnostic and therapeutic challenges. The National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATPIII) (12) has proposed a similar criteria based on the presence of three or more components, but with different cutoff values: (a) waist circumference ≥102 cm for men and ≥88 cm for women, (b) triglyceride ≥150 mg/dl c) HDL-cholesterol <40 mg/dl for men and <50 mg/dl for women, (d) blood pressure ≥135/80 mmHg and (e) fasting plasma glucose ≥110 mg/dl.

Due to hemodynamic (angiotensin II and elevated blood pressure) and metabolic effects (high levels of plasma glucose and small dense LDL particles) on vasculature of subjects predisposed to MS, there is an increase in oxidative stress, which provokes endothelial cell injury and reduction in nitric oxide levels – a potent vasodilator (13). As a consequence, deficient vasodilation and fibrinolysis will occur which have a negative prognostic impact on CV risk.

CENTRAL OBESITY AND METABOLIC SYNDROME

Based on marked differences in association with diseases and their risk factors between obesity located in the abdominal as opposed to the gluteal-femoral region, "central obesity" was included in the spectrum of MS. The association of abdominal adiposity with CV risk has been widely recognized (14). Such adipose tissue distribution is mainly dependent on the accumulation of visceral fat, which has been implicated in the pathogenesis of insulin resistance. Increased waist circumference or waist-to-hip ratio has been recognized as intra-abdominal fat deposition, although these parameters are somehow influenced by the subcutaneous fat in this area. In prospective studies where the predictive power of central or generalized adiposity was analyzed, a low body mass index in combination with a high waist-to-hip ratio was the strongest risk factor combination (15). This is in agreement with our findings in non-obese Japanese migrants in Brazil who proved to be highly susceptible to MS (16). It is known that genetic and environmental factors contribute to this obesity pattern. Bjorntorp (17) proposed the involvement of the hypothalamic-pituitary-adrenal axis in the genesis of visceral adiposity. Stress-dependent hyperactivity of the hypothalamus would be a determinant of visceral fat deposition, causing a central obesity pattern similar to that seen in patients with hypercortisolism such as Cushing's disease. Visceral adipose tissue is characterized by intense lipolytic activity (receptors with high affinity for catecholamines and cortisol) and less effective antilipolytic activity (less insulin receptor binding), which results in free fatty acids production. A plausible trigger for the effects of visceral fat might be an exaggerated release of free fatty acids into general and portal circulation. A number of metabolic consequences of the excess of circulating fat acids, mainly in the liver, pancreas and skeletal muscle, have been described, such as elevate plasma triglyceride concentration through increased hepatic secretion of VLDL. It has long been known that increased fatty acid oxidation in liver promotes the pathway of gluconeogenesis and promotes hyperglicemia, which in turn stimulates beta cell secretion, favoring hyperinsulinemia. Also fatty acids oxidation in muscle determined decreased glucose transport and insulin effectiveness (18), long-term hyperinsulinemia provokes down-regulation of muscle insulin receptors, characterizing the insulin resistance state. A sustained lipotoxic effect on the pancreas may deteriorate insulin production progressively precipitating the occurrence of hyperglycemia.

In addition to central obesity predisposing to glucose metabolism disturbance via insulin resistance, it is also a strong risk factor for dyslipidemia, hypertension, fibrinolysis abnormalities and premature CV disease (19,20). The high CV risk of the patient with MS is attributable not only to the cluster of these diseases, but to obesity *per se*, recognized as an independent risk factor (21). Despite the fact that CV benefits from even a slight weight reduction (5 to 10%), it is also known that such an objective represents one of the hardest goals to be achieved when treating patients with MS.

GLUCOSE METABOLISM DISTURBANCES

According to the pathophysiological sequence proposed, it is agreed that the glucose tolerance status in patients with MS may vary from near-normal plasma glucose level to overt DM. A compensatory beta cell overproduction of insulin, together with its decreased hepatic clearance, favors the condition of hyperinsulinemia. However, when beta cells become unable to increase insulin secretion to overcome tissue resistance and promote glucose uptake, a range of increased glucose levels will manifest. Considering that impaired fasting glycemia, impaired glucose tolerance and DM are parts of the natural history of the same disease, several investigators have included any degree of glucose intolerance in the concept of MS. However, when fasting plasma glucose levels are within the normal range, a parameter reflecting the insulin resistance state is required for diagnosis. The finding of fasting hyperinsulinemia may be indicative of insulin sensitivity deterioration, but nevertheless confirmation is still recommended through more accurate methods such as the homeostasis model assessment (HOMA) and tests of glucose load with concomitant plasma glucose and insulin determinations (8,9).

The hypothesis that insulin levels *per se* might elevate CV risk has been investigated. The Quebec

Cardiovascular Study, conducted in approximately 4,500 men, detected an association of hyperinsulinemia and coronary artery disease, independent of classical risk factors (22). The Paris Prospective Study investigated whether circulating insulin levels were the direct cause of vascular complications (23). Speculation on the mechanisms involved in the association of insulin resistance and/or hyperinsulinemia with coronary artery disease has been based on metabolic, hemostatic, trophic and hemodynamic effects of insulin. It has been proposed that hyperinsulinemia might increase CV risk by inducing a pro-thrombotic state, dependent on PAI-1 activation (24). In addition to its own action originated in insulin growth factors (IGFs), insulin may determine structural changes in LDL-cholesterol particles and stimulate muscle cells proliferation from the vascular walls favoring atherogenesis (25).

Disturbances of glucose metabolism are important targets of the MS treatment. However, epidemiological studies on the type 2 DM treatment enable the affirmation that when the goal is the improvement of their CV risk the therapeutic approach for patients with MS should be broader reaching and not only directed to the glucose metabolism disturbance. In UKPDS, CV disease – main cause of mortality among type 2 diabetic patients – cannot be prevented by exclusive control of hyperglycemia (26). Only those patients in whom blood pressure levels were strictly controlled achieved CV benefits with intervention attempts (27). This and other evidence allowed the affirmation that hyperglycemia is only one abnormality among a number of other hemodynamic and metabolic disturbances present in patients with MS who require concomitant treatment in order to effectively reduce morbidity and mortality.

SYSTEMIC HYPERTENSION AND LIPOPROTEIN METABOLISM DISTURBANCES

Both clinical trials and epidemiological studies have shown increased prevalence of hypertension among individuals with DM and both conditions are accompanied by obesity and lipid profile disturbances (28). Although there is no consensus regarding the role of insulin resistance and/or hyperinsulinemia in the genesis of hypertension, it is reasonable to suppose that exaggerated physiologic actions of this hormone, such as renal sodium reabsorption, sympathetic activity and trophic effects on the smooth muscle tissue, could contribute to blood pressure elevation (29-31). Even in the lack of hyperinsulinemia, it was demonstrated that insulin resistance at vascular level reduces the production of important endothelium vasodilator factor, the nitric oxide, favoring the elevation of blood pressure levels (13). This endothelial dysfunction probably occurs widely and participates in the micro and macrovascular lesions of MS.

Even considering that other mechanisms could be involved in the hypertensive process frequently found in subjects with obesity and type 2 DM, it is known that insulin resistance is a common metabolic abnormality among these diseases and should be treated by non-pharmacological and pharmacological interventions. Potential deleterious side effects on glucose and lipoprotein metabolisms should be taken into consideration when choosing the anti-hypertensive therapeutic scheme (32).

Hypertriglyceridemia and low levels of HDL-cholesterol are the most characteristic lipid profile changes found in the insulin resistance state. Free fatty acids originated from visceral adipose tissue induce increased hepatic production of VLDL particles, which are the substrate for gluconeogenesis. As a result, hypertriglyceridemia and hyperglycemia are typical manifestations of MS. Triglyceride synthesis is stimulated even further by hyperinsulinemia. The role of hypertriglyceridemia as a marker of cardiovascular risk is still a matter of discussion, since the association with myocardial infarction or angina was detected in some (33,34) but not all studies (35). The classic low HDL-cholesterol concentration in MS has been attributed to activation of the cholesterol ester transferase protein (CETP), which increases cholesterol esters transfer from the chylomicron to the HDL-cholesterol. Small dense particles of LDL-cholesterol are also characteristics of MS, which are highly atherogenic. Such particles are able to pass through the endothelium and, in the intima, trigger the formation of foam cells, the initial step in the atherogenic process. Epidemiological studies in which diabetic and non-diabetic patients were treated by statins have demonstrated the efficacy of these drugs in improving their CV prognosis (3,5).

OTHER DISTURBANCES OF METABOLIC SYNDROME

Patients with any degree of glucose intolerance, present up to a three-fold risk of developing coronary artery disease when compared to non-diabetic population (36). However, excessive mortality in the diabetic population due to CV causes cannot be explained solely by the presence of the classic risk factors. The similarity

between diabetic individuals and those with MS must combine a number of other non-classical factors, the sum of which results in high CV risk. Some of these factors have been included in the spectrum of MS.

Microalbuminuria

In the 1980's, microalbuminuria (urinary albumin excretion ranging between 20 and 200 μg/min) was seen as a predictive factor for the development of nephropathy in diabetic patients, particularly in those with type 1 DM (37). Further studies, conducted in diabetic and non-diabetic individuals, found an association between microalbuminuria and other CV risk factors, such as increased blood pressure, triglyceride and fibrinogen levels, suggesting it also has a role in the prediction of CV disease (38,39). Nowadays, microalbuminuria is part of the expanded MS and there is evidence that it constitutes an independent risk factor for CV events (40). This abnormality has been interpreted as indicative of endothelial dysfunction at glomerular level. The determination of urinary albumin excretion in the assessment of CV risk and planning therapeutic strategies has been recommended.

Hemodynamic and metabolic mechanisms participate in the increased albuminuria of DM. Hyperglycemia-dependent glomerular hyperfiltration, together with elevated blood pressure, increase intracapillary glomerular pressure, basement membrane permeability disturbance and glomerular capillar injury. The chronic hyperglycemic state also provokes glycosilation of structural proteins, advanced glycosilation end products (AGEs) accumulation and loss of the glomerular basement membrane negative potential, which aggravates its permeability to plasma macromolecules. Increased production of cytokines such as TGFβ, which induces mesangial expansion, also has been involved in the microalbuminuria determinants of diabetic patients (41).

High insulin and proinsulin concentrations have been reported in microalbuminuric non-diabetic subjects (42). However, these findings did not imply a role of insulin resistance for glomerular dysfunction. Yudkin (43) attributed endothelial dysfunction a key role in explaining the increased frequency of microalbuminuria among patients with MS. Endothelial injury in micro and macrovascular territories could be the primary change that would explain the presence of both, microalbuminuria and insulin resistance. Thus, the origin of deficient insulin action would be at the endothelial level, which would lead to abnormalities in the lipoprotein metabolism and fibrinolysis and atherogenesis. It is known that the vasodilator effect of insulin is mediated by the endothelium and that hormonal tissue action is largely dependent on the blood flow (13). Therefore, in the presence of endothelial dysfunction and inadequate tissue perfusion, insulin sensitivity deteriorates and a resistance state is established. It is possible that genetic factors predispose the endothelial damage. Maternal malnutrition may be partially responsible for endothelial dysfunction in adulthood. Considering that skeletal muscle is a main site of insulin action, a less dense capillarization or endothelial dysfunction during pregnancy might contribute to the occurrence of microalbuminuria and insulin resistance in adulthood with increased CV mortality as a consequence (43).

In conclusion, the presence of microalbuminuria in MS should be considered not only as an expression of endothelial damage at the glomerular microvasculature level, but mainly as a marker of generalized endothelial dysfunction.

Abnormalities of Blood Coagulation - Fibrinolytic System

An additional explanation for the increased risk of formation of atheromatous lesion, thrombosis and CV events found in patients with MS is a defect in coagulation-fibrinolysis system, which could be responsible for the onset and late complications of atherothrombosis. Consistent data have shown that changes in blood coagulability, such as activation of factor VIII and Von Willebrand factor, elevation of fibrinogen and plasminogen activator inhibitor 1 (PAI-1), which facilitate thrombus formation, are consequences of the insulin resistance state (44,45). Fibrin deposit contributes to atherosclerotic plaque growth by stimulation of cell proliferation and the accumulation of low-density lipoprotein. Decreased removal of fibrin deposit - involved in the development of atherothrombosis - may be consequent to an increase in PAI-1 found in hyperinsulinemic conditions (24,46). Other evidence has indicated that PAI-1 synthesized by endothelial cells may be due to hypertriglyceridemia. The ability of VLDL particles, obtained from hypertriglyceridemic patients, in stimulating PAI-1 production has been demonstrated *in vitro* (47). Experimental studies suggested that an overproduction of PAI-1 in adipocytes might contribute to hypofibrinolysis found in animal obesity (48). Recently, another potent fibrinolysis inhibitor has been isolated from human plasma, the thrombin activable fibrinolysis inhibitor (TAF-1). Higher levels of TAF-1 were observed in obese diabetic patients as compared to healthy subjects (49). TAF-1 has shown to be independently associat-

ed with markers of obesity, glycated hemoglobin levels and insulin resistance.

Epidemiological and intervention studies are need to evaluate the impact of treating insulin resistance on abnormalities of the coagulation-fibrinolytic system and minimizing CV risk among patients with MS.

Hyperuricemia

Hyperuricemia has also been found to be associated with obesity, DM, hypertension and dyslipidemia. From two to 50% of patients with glucose intolerance are described to have elevated uric acid levels (50). A major study conducted in the general population from Israel reported a significant association between insulin and uric acid concentrations, adjusted for confounders such as body mass index, glucose intolerance, blood pressure and triglyceride levels (51). A fall in renal excretion of uric acid was verified following insulin administration and chronic hyperinsulinemia induced progressive expansion of uric acid pool. These findings are in agreement with the observation of insulin resistance and hyperinsulinemia in hyperuricemic subjects (52). The mechanisms underlying the elevation of CV risk seen in hyperuricemic subjects might include increased platelet aggregation, blood viscosity and coagulability and also due to the association with dyslipidemia and hypertension (53).

Homocysteine

Elevated homocysteine levels – an intermediate aminoacid in the conversion of methionine to cysteine – have been described in association with atherogenesis. Although its role as an independent risk factor for CV disease is a matter of great discussion, hyperhomocystinemia was found to be related to a number of deleterious effects in vessels. It seems to induce endothelial cytotoxicity, lipid peroxidation, increases in the platelet aggregation process, activation of coagulation and proliferation of smooth muscle cells. Diabetic patients with micro- or macrovascular disease, hypertension or microalbuminuria have shown high homocysteine concentrations when compared to those without long-term complications (54). However, homocystinemia did not seem to be directly related to insulin sensitivity, but to be a consequence of other processes such as endothelial lesion, chronic inflammatory status and renal dysfunction (55).

Markers of Inflammation

The Insulin Resistance Atherosclerosis Study recently suggested that chronic subclinical inflammation is part of the insulin resistance syndrome (56). C-reactive protein and adiponectin, an adipose-specific protein, have been indicated as sensitive markers of inflammation, which were associated with insulin resistance. Adiponectin seems to play a protective role in experimental models of vascular injury, perhaps because it suppresses the attachment of monocytes to endothelial cells, which is a fundamental step in experimental vascular damage as well as an early event in the atherosclerotic process (57). Physiologic concentrations of this substance exhibit inhibitory effects on TNF-α-induced monocyte adhesion and adhesion molecule expression, and it seems to act as an endogenous regulator of endothelial cells in response to inflammatory stimuli. Low adiponectin levels have been found in subjects with conditions that integrate the MS, such as obesity, type 2 DM (58) and CV disease (57).

Endothelin-1

Recent studies have shown that endothelin-1 – a peptide with potent and characteristically sustained vasoconstrictor action – can determine several disorders included in MS (59). Since it is also implicated in the proliferation of vascular smooth muscle cells (60), endothelin-1 could cause hypertension and atherosclerotic CV disease. Higher levels of endothelin-1 have been reported in patients with MS when compared to normal subjects (61). An increased production of this endothelial factor might be reflecting endothelial damage caused by the insulin resistance syndrome. In multiple regression analysis, triglyceride was shown to be a strong predictor of endothelin-1, independent of HDL or total cholesterol levels. However, prospective studies are necessary to investigate the cause-effect relationship between endothelin-1 and components of MS. It is not known whether improvement in insulin resistance, lipid profile and the reduction of endothelium-derived factors secretion could offer benefits in reducing CV risk among patients with MS.

Considering the data as a whole, we concluded that patients with MS are at the highest risk of dying from CV events. Large trials, which include several therapeutic strategies against different components of MS and also to increase insulin sensitivity, are needed to establish their prognostic impact for CV morbidity and mortality.

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