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DIABETES MELLITUS: THE ROOT OF THE PROBLEM

DIABETES MELLITUS: A RAIZ DO PROBLEMA

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ABSTRACT

Cardiovascular disease (CVD) of atherosclerotic origin is the main cause of morbidity and mortality in patients with diabetes mellitus (DM). Both the cardiovascular risk factors associated with insulin resistance (IR) in the context of visceral adiposity syndrome (VAS) and chronic hyperglycemia contribute to the risk of CVD in DM. Compensatory hyperinsulinemia established in IR stimulates the transcription factors SREBP1c and SREBP1a, which activate lipogenic genes, leading to high hepatic production of triglycerides. Hypertriglyceridemia triggers other lipid changes that contribute to the pro-atherogenic profile in IR, which is characterized by the predominance of small and dense LDL and reduction of HDL-cholesterol. Hyperinsulinemia is also closely linked to arterial hypertension, as it increases sympathetic tone and renal sodium reabsorption. IR is considered the best predictive factor for the occurrence of type 2 DM (DM2), and a concomitant defect in insulin secretion is required for hyperglycemia to be established. The harmful effects of hyperglycemia are due to activation of biochemical pathways that result in inflammation and cellular oxidative stress. Dyslipidemia and hypertension secondary to IR, as well as hyperglycemia, are important modulators of cardiovascular risk in VAS and DM2 and should be intensively and jointly addressed in the management and prevention of CVD.

Keywords: Insulin resistance; Hyperinsulinemia; Diabetes; Hypertension; Cardiovascular diseases.

RESUMO

A doença cardiovascular (DCV) de origem aterosclerótica é a principal causa da morbidade e mortalidade em pacientes com diabetes mellitus (DM). Tanto os fatores de risco cardiovascular associados à resistência à insulina (RI) no contexto da síndrome da adiposidade visceral (SAV) quanto a hiperglicemia crônica contribuem para o risco da DCV na DM. A hiperinsulinemia compensatória que se estabelece na RI estimula os fatores de transcrição SREBP1c e SREBP1 em que se ativam os genes lipogênicos, levando à grande produção hepática de triglicérides. A hipertrigliceridemia é o gatilho para as demais alterações lipídicas que contribuem para o perfil pró-aterogênico na RI, caracterizando-se pelo predomínio de LDL pequenas e densas e redução do colesterol HDL. A hiperinsulinemia, também, está intimamente ligada à hipertensão arterial, pois aumenta o tônus simpático e a reabsorção renal de sódio. A RI é considerada o melhor fator preditivo para a ocorrência de DM tipo 2 (DM2), sendo necessário um defeito concomitante na secreção de insulina para que a hiperglicemia se estabeleça. Os efeitos deletérios da hiperglicemia devem-se à ativação de vias bioquímicas que resultam em inflamação e estresse oxidativo celular. A dislipidemia e a hipertensão arterial secundárias à RI, assim como a hiperglicemia, são importantes moduladores do risco cardiovascular na SAV e na DM2 e devem ser intensiva e conjuntamente abordados no tratamento e prevenção da DCV.

Descritores: *Resistência à insulina; Hiperinsulinemia; Diabetes; Hipertensão; Doenças cardiovasculares.*

INTRODUCTION

Cardiovascular disease (CVD) of atherosclerotic origin, including coronary artery disease, cerebrovascular disease, and peripheral arterial disease, is the main cause of morbidity and mortality in patients with diabetes mellitus (DM).[1] Thus, DM is considered equivalent to coronary artery disease.[2]

Cardiovascular risk factors associated with insulin resistance (IR) in the context of visceral adiposity syndrome (VAS; also known as metabolic syndrome) and chronic hyperglycemia both contribute to the risk of CVD in DM and will be discussed below.

VAS

The association of visceral adiposity with arterial hypertension, hyperuricemia, and sleep apnea has long been known.[3] In recent decades, there has been much research on a group of cardiovascular risk factors that define VAS,

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including central (visceral) obesity, dyslipidemia (increased triglycerides and decreased high-density lipoprotein [HDL] cholesterol), and elevated blood sugar and blood pressure.[4] There is consensus on the importance of the involvement of visceral adipose tissue in the physiopathogenesis of this group of cardiovascular risk factors. IR has been considered the main mechanism in the association of visceral fat with other risk factors, including diabetes, hypertension, and dyslipidemia. However, autonomic modulation of visceral adipose tissue and increased sympathetic activity may play an important role in the development of VAS and contribute in different ways to IR.[5] The modulation of visceral adipose tissue by the sympathetic nervous system is associated with different adrenergic receptors. Adipocyte plasma membranes express beta-1 (β1), beta-2 (β2), beta-3 (β3), alpha-1 (α1), and alpha-2 (α2) adrenergic receptors.[6] The balance between alpha- and beta-adrenergic receptors is an important variable in the regulation of the number of adipocytes. Using a murine model with genetically modified alpha-2/beta-3 adrenoreceptors, Valet et al. demonstrated adipocyte hyperplasia.[7] In the context of autonomic modulation of visceral adiposity, it is also known that the fasting state is associated with adipolysis, which is modulated mainly by β3 adrenergic receptors. Conversely, adipogenesis is associated with activation of the parasympathetic system, but the receptor mediating adipogenesis is not well-defined.[8] Sympathetic/parasympathetic imbalance and α2 adrenergic/β3 receptor imbalance are associated with the storage of visceral adipose tissue and insulin sensitivity.

Etiopathogenesis of IR

IR is thought to decrease the metabolic (but not mitogenic) effects of insulin after binding to the tyrosine kinase receptor.[9] Visceral adiposity is the main determinant of IR, but genetic factors also predispose to its development.[10] Visceral white adipose tissue (WAT) differs from subcutaneous WAT in its metabolic activity, responding less to the antilipolytic effects of insulin and more to the lipolytic effects of catecholamines, which makes it more hazardous.[11]

It is believed that loss of WAT capacity to expand and store excess calories is a greater factor in the pathogenesis of VAS than the degree of obesity.[12] Excess chronic consumption of nutrients combined with insufficient energy expenditure exceeds the storage capacity of glycogen and triglycerides by "dedicated" metabolic tissues, namely, liver, muscle, and WAT. In this situation, other tissues are exposed to supraphysiologic concentrations of these nutrients.[13]

Fatty acid metabolites, such as ceramides and diacylglycerol, activate protein kinase C and modify the phosphorylation pattern of the insulin receptor and insulin receptor substrate, negatively affecting hormone signaling.[14] Furthermore, unsaturated fatty acids can bind to Toll-like receptors 2 and 4 that participate in the recognition of pathogens and innate immunity, particularly in adipocytes and macrophages. The result is negative interference in insulin receptor signaling and induction of nuclear transcription factor (NF-κB), resulting in the production of proinflammatory cytokines, such as tumor necrosis factor alpha (TNF alpha) and interleukin (IL) 6,[15] which also interfere with insulin receptor signaling.

The expansion of visceral WAT secondary to increased caloric intake leads to hypertrophic adipocyte necrosis/apoptosis and to the release of large fat droplets, which are toxic to surrounding cells and promote recruitment and a significant increase of macrophages from bone marrow. These macrophages are apparently stimulated by cellular debris to assume a classic M1 phenotype, characterized by the expression of proinflammatory cytokines (TNF alpha, IL1 and IL6) that worsen IR.[13] Inflammation associated with oxidative stress triggered by excess nutrients reduces the expression of adiponectin (and its receptors), a hormone produced by adipocytes that has anti-inflammatory effects and increases the uptake of fatty acids by muscles and glucose by muscles and WAT. Reduction in the concentration of this hormone also contributes to IR.[16]

IR develops in the target organs of insulin action and contributes to the VAS phenotype, as will be described below. In WAT, IR results in lipolysis and an increase of circulating free fatty acids, while in skeletal muscle, IR results in an increase in the tissue content of free fatty acids and triglycerides. Both conditions result in exacerbation of a deleterious hyperlipidemia-inflammation-IR cycle.[13,17] In the liver, IR results in increased hepatic glucose production, contributing to hyperglycemia.[13] Hepatic resistance also stimulates local synthesis of hepatocyte growth factor[18] and betatrophin.[19] These stimulate beta-cell hyperplasia, which together with free fatty acids and glucose contributes to compensatory hyperinsulinemia, which acerbates IR.[20] By involving the central nervous system, at least in animal models, IR leads to hyperphagia and increased fat mass.[21] In pancreatic alpha cells, IR results in decreased inhibition of glucagon secretion by insulin with consequent hyperglucagonemia. This increases hepatic glucose production and contributes to hyperglycemia.[22] In pancreatic beta cells, IR decreases insulin secretion in response to glucose exposure.[23]

IR and dyslipidemia

Compensatory hyperinsulinemia is generally considered a by-product of IR, but has repercussions, in that it overstimulates pathways of insulin action in some cell types.[24] In hepatocytes, chronic hyperinsulinemia stimulates expression of sterol regulatory element binding protein 1c and 1a, SREBP1c and SREBP1a, respectively, which activate lipogenic genes, leading to increased hepatic production of triglycerides.[25,26]

IR in the liver leads to greater activity of the microsomal triglyceride transfer protein, which transfers triglycerides to the nascent apolipoprotein B100 molecule. Increased activity of phospholipases and ARF ribosylation factor stimulates the synthesis of large particles of very low-density lipoprotein (VLDL). This process also occurs in enterocytes and results in the secretion of large chylomicron (CM) particles.[26]

In addition to being increased, VLDL and CM are metabolized less, since IR is associated with decreased production and lower lipoprotein lipase activity, resulting in postprandial

hyperlipidemia and accumulation of lipoproteins. These highly-atherogenic particles attach to the arterial wall and are captured by macrophages that have infiltrated the intima. Moreover, hypertriglyceridemia favors the formation of small and dense particles of low-density lipoprotein (LDL), which are less recognized by the LDL receptor in the liver and peripheral tissues and have greater access to the arterial intima, where they are more sensitive to oxidation and uptake by macrophages in the intima.[27]

Finally, during the hydrolysis of triglycerides associated with CM and VLDL, concomitant formation of HDL nascent particles occurs. As lipoprotein lipase activity is decreased in IR, there is less generation of new HDL particles. Reduction in HDL formation also results from increased generation of microRNA 33 by the intron of the gene encoding SREBP1. This microRNA promotes degradation of *ABCA1* mRNA in the liver. Translation into apolipoprotein A-I receptor is responsible for the export of excess cholesterol from hepatocytes, generating new HDL particles.[28] Thus, hypertriglyceridemia is the trigger for other lipid changes that contribute to a pro-atherogenic profile in IR, which is characterized by the predominance of small, dense LDL and decreased HDL cholesterol.[25,26]

IR and hypertension

Compensatory hyperinsulinemia is also closely linked to arterial hypertension, as it increases sympathetic tone and renal sodium reabsorption.[29,30] Moreover, the increase of circulating fatty acids secondary to IR increases sympathetic tone.[31]

One of the physiological effects of insulin is the phosphorylation of the enzyme endothelial nitric oxide synthase in vascular endothelium, resulting in generation of nitric oxide and vasodilation. Therefore, IR results in decreased flow-mediated vasodilation, which also participates in the genesis of hypertension.[32] The increase in circulating concentrations of components of the renin-angiotensin-aldosterone system has also been described as a participant in the genesis of hypertension associated with IR.[33]

IR, diabetes, and hyperglycemia

IR is considered the best predictor for the occurrence of type 2 DM (DM2),[34] and a concomitant defect in insulin secretion is required for hyperglycemia to be established. It is possible that IR is accentuated by aging and weight gain in genetically susceptible individuals. In those who also inherited a defect in pancreatic beta cells, reduced insulin secretion results in impairment of glucose tolerance and hyperglycemia, which can exert toxic effects on beta cells (glycotoxicity), exacerbating the secretory defect.[35] The increase in circulating free fatty acids resulting from IR also contributes to deficiency of insulin secretion (lipotoxicity).[36]

Epidemiological studies show a correlation between chronic hyperglycemia and CVD; in a meta-analysis of 13 prospective cohort studies, for each percentage point increase in HbA1c, the relative risk for any cardiovascular event was 1.18 (95% confidence interval 1.10-1.26).[37] Despite this, no randomized clinical studies have clearly demonstrated the beneficial effects of intensive glycemic control in patients with long-term DM2. However, follow-up results from patients who participated in the United Kingdom Prospective Diabetes Study suggest that intensive glycemic control (HbA1c $< 7.0\%$) reduces the risk of acute myocardial infarction, DM-related death, and overall mortality in patients with newly diagnosed DM2.[38] This apparent contradiction probably reflects the irreversible changes present in chronically poorly controlled patients who no longer benefit from intensive glycemic control, especially due to the high risk of hypoglycemia associated with this therapeutic modality.

The deleterious effects of hyperglycemia are due to the increased metabolism of glucose through the glycolytic pathway and the polyol, hexosamine, and protein kinase C pathways, as well as the formation of advanced glycation end-products (AGEs), resulting in inflammation and cellular oxidative stress.[39]

AGEs are formed from the covalent, non-enzymatic binding between glucose or other reducing sugars and lysine and arginine residues of proteins and the amino-terminal portion of lipids and nucleic acids.[40] Besides changing the structure of proteins, AGEs are recognized by numerous cell surface receptors such as the receptor for AGEs (RAGE) and scavenger receptors of the CD36 family. The interaction of AGEs with RAGE promotes the generation of reactive oxygen species and activation of NF-κB, which increases the expression of proinflammatory molecules and of RAGE itself, feeding a vicious cycle,[41] even in cells involved in atherosclerosis, such as macrophages, smooth muscle, and endothelial cells.[42]

Proteins and phospholipids present in lipoproteins may undergo glycation and contribute to the atherosclerotic process; glycated VLDL and CM are less susceptible to the action of lipoprotein lipase, which contributes to hypertriglyceridemia.[43] Glycated LDL is more susceptible to oxidation, making it more atherogenic,[44] whereas glycated HDL has a lower half-life, compromising reverse cholesterol transport.[45,46]

Glycated albumin, isolated from patients with poorly controlled DM, can also affect reverse cholesterol transport, in that it causes oxidative and inflammatory endoplasmic reticulum stress in macrophages. These events are associated with decreased HDL-receptor content, ABCA1, and ABCG1, thereby favoring the intracellular accumulation of cholesterol and cholesterol oxides, which perpetuate the proinflammatory and pro-apoptotic effect and contribute to atherosclerosis associated with hyperglycemia.[47-53]

CONCLUSION

Dyslipidemia and hypertension secondary to IR, as well as hyperglycemia, are important modulators of cardiovascular risk in VAS and DM2 and should be intensively and jointly addressed in the management and prevention of CVD.

CONFLITOS DE INTERESSE

Os autores declaram não possuir conflitos de interesse na realização deste trabalho.

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