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DIABETES AND CARDIOVASCULAR INJURY – AN INEXORABLE CONSEQUENCE

DIABETES E LESÃO CARDIOVASCULAR - UMA CONSEQUÊNCIA INEXORÁVEL

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ABSTRACT

The cardiovascular disease in diabetics has multiple mechanisms. The clinical manifestations are diverse, with macro and microvascular disease, heart failure and chronic kidney failure being particularly prevalent. The mechanisms appear gradually and are diverse in form, depending on the degree of glycemic control and other associated risk factors. Autonomic dysfunction, glucose and lipid metabolic abnormalities, renin angiotensin system activation, endothelial dysfunction, energetic impairment, arterial hypertension, obesity and increased inflammatory and prothrombotic activity have been described and appear to be related to the clinical phenotype of the disease. When complications such as coronary heart disease, heart failure or kidney failure are diagnosed, the prognosis of the disease becomes more critical, in spite of notable therapeutic advances.

Keywords: Dyslipidemia; Arterial hypertension; Autonomic dysfunction; Macro- and microvascular disease; Heart failure.

RESUMO

A doença cardiovascular do paciente com diabetes possui múltiplos mecanismos. As manifestações clínicas são variadas, sendo particularmente prevalentes a doença macro e microvascular, a insuficiência cardíaca e a insuficiência renal crônica. Os mecanismos manifestam-se de maneira gradual e diversificada, dependendo do grau de controle glicêmico e de outros fatores de risco associados. A disfunção autonômica, alterações metabólicas glicêmicas e lipídicas, ativação do sistema renina angiotensina aldosterona, disfunção endotelial, comprometimento energético, hipertensão arterial, obesidade e aumento da atividade inflamatória e pró-trombótica têm sido descritos e parecem relacionados ao fenótipo clínico da doença. Uma vez que complicações como doença coronariana, insuficiência cardíaca e renal sejam diagnosticadas, o prognóstico da doença torna-se mais crítico, apesar do notável avanço terapêutico.

Descritores: *Dislipidemia; Hipertensão arterial; Disfunção autonômica; Doença macro e microvascular; Insuficiência cardíaca.*

INTRODUCTION

According to the World Health Organization, approximately 1 in 10 individuals worldwide have diabetes, which contributes to the high rate of premature complications of cardiovascular disease.[1]

In developed countries such as the US, it is estimated that treatment of patients with diabetes-related complications accounts for 20% of total health spending.[2] For developing countries, at least 5% of total health spending is associated with the treatment of patients with diabetes.[3] These expenditures are mainly due to macrovascular complications, such as coronary, peripheral vascular, and cerebrovascular diseases.[4,5] Heart failure, whether or not is associated with these macrovascular complications, is yet another manifestation of the highly prevalent cardiovascular disease in these patients.[6,7]

The mechanisms of cardiovascular disease are numerous and do not all occur due to high blood sugar, making the control of cardiovascular disease a major challenge, in view of the variability of metabolic alterations and stages of the disease.

THE PHYSIOPATHOLOGICAL BASIS OF CARDIOVASCULAR DISEASE

It has been recognized that defects associated with high glycemic levels are present even before the diagnosis of diabetes including lower insulin sensitivity and progressive pancreatic beta cell failure.[8] Most recently, other defects have been described, such as decreased *glucagon-like* peptide 1 (GLP-1), increased hepatic glucose production, increased secretion of glucagon by the alpha-cells, increased lipolysis, pancreatic impairment of neurotransmitters, increased renal reabsorption of glucose, and reduced levels of adiponectin.[9-11]

Furthermore, elevated blood pressure, obesity, increased inflammatory markers and thrombosis, endothelial dysfunction, dyslipidemia, autonomic neuropathy, cardiac energetic impairment, and changes in vascular and myocardial compliance are present in many patients and are associated with atherosclerotic coronary disease and extra-coronary artery disease, renal failure, and heart failure (Figure 1).[5,6,12,13]

Arterial Hypertension

There are multiple mechanisms linked to increased blood pressure in patients with diabetes that are often associated with the progressive impairment of renal functioning. They include the inappropriate activation of the kidney angiotensin aldosterone, increased sympathetic tone, increased volume expansion based on increased renal reabsorption of sodium, peripheral vasoconstriction in connection with an increase in circulating levels of endothelin-1 and reactive oxygen species, and an increase in inflammatory markers and glycation end products, all of which are related to endothelial dysfunction and decreased vascular compliance.[14-17]

Obesity and Dyslipidemia

Lipid abnormalities are present in 85% of patients with diabetes and seem to be significantly associated with obesity, hyperinsulinemia, and reduced peripheral insulin sensitivity.[18,19] LDL-C levels in patients with diabetes are similar to those of the non-diabetic population. However, this cholesterol is usually distributed as greater numbers of LDL particles, the so-called small and higher density LDL, which are linked to increased cardiovascular risk.[20]

Increased triglycerides constitute another important characteristic of patients with diabetes. Interestingly, genetics-based studies have shown that polymorphisms associated with high triglycerides are independently associated with cardiovascular risk, possibly because of the remaining excess particles that are rich in triglycerides.[21-23]

Low levels of HDL-C are another notable lipid alteration in these patients. Although they are epidemiologically related to increased cardiovascular risk, studies of genetic polymorphisms associated with higher values of HDL-C and interventions designed to increase HDL-C levels have not yielded the anticipated benefits, suggesting that decreased HDL-C may be associated with other cardiovascular risk mechanisms that are not eliminated merely by increasing the levels of cholesterol *per se* in this lipoprotein.[24]

Heart Failure and Chronic Kidney Disease

Heart failure is a more frequent cause of hospital admission in patients with diabetes, particularly among those taking insulin and those with chronic nephropathy, than stroke or coronary disease.[6,25] Once present, heart failure is associated with a 10 times higher mortality than that observed in patients with diabetes without this condition, with reduced survival for 5 years.[26-28]

The presence of chronic kidney disease adds other factors that contribute to worsening heart failure, such as anemia, proteinuria, volume overload, disorders of mineral metabolism, oxidative stress, and increased inflammation.[29,30] Ventricular dysfunction is strongly associated with chronic kidney disease. Approximately 3/4 of patients in a state of advanced renal disease undergoing dialytic treatment have left-ventricular hypertrophy, 1/3 have cardiomegaly, and 1/6 have ventricular dysfunction.[31]

In chronic kidney disease, vascular and valvar calcification are highly prevalent. They are predictors of cardiovascular mortality. This vascular calcification is established both in the intima and middle layers of the vessels and is related to an increase in the calcium-phosphate (Ca x P) product caused by hypercalcemia and/or hyperphosphatemia.[32-34]

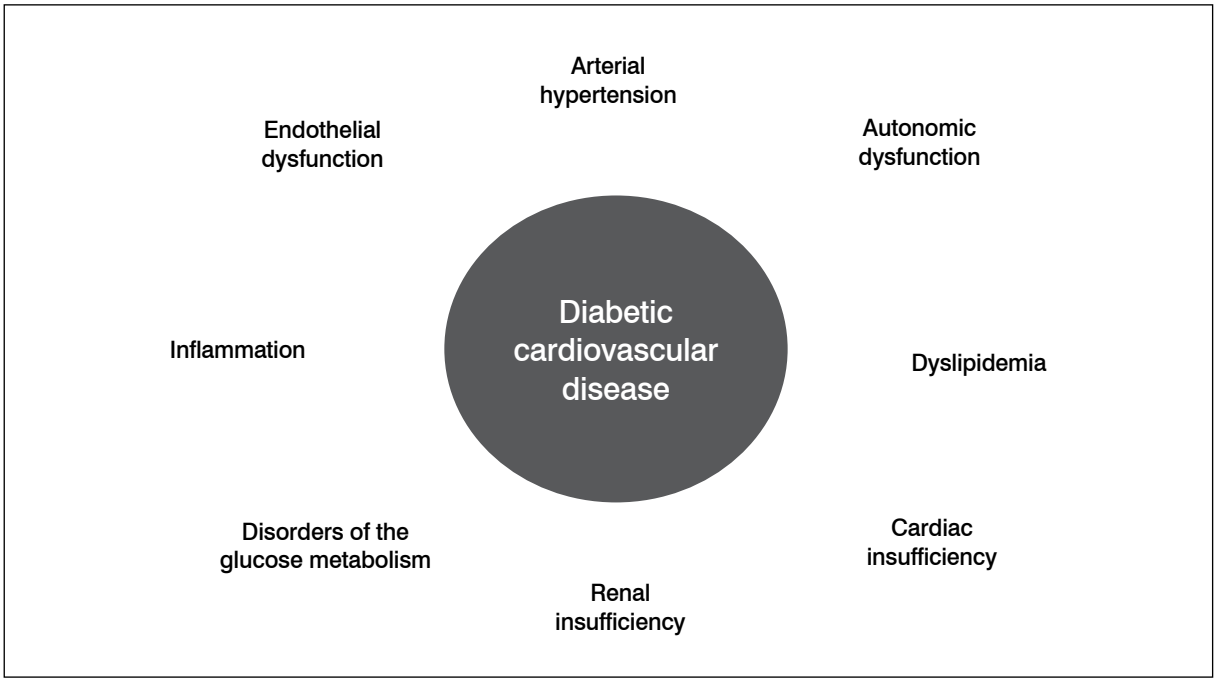

Figure 1. Principal manifestations of cardiovascular disease in patients with diabetes and related mechanisms.

Microangiopathy and Cardiomyopathy

Classically, microangiopathy refers to microvascular retinal disease, nephropathy, and neuropathy. However, more recently, the concept of microvascular disease has been expanded to include coronary microangiopathy. Diabetic microangiopathy is characterized by the abnormal growth and rupture of the endothelial barrier, resulting in functional alterations and edema of the small vessels and inducing independent perfusional complications in atherosclerotic macrovascular disease. The presence of advanced glycation end products causes increased oxidative stress and elevated expression of local *Toll-like* receptors and inflammatory markers due to the effects of hyperglycemia on lipids, lipoproteins, and amino acids, and thereby contributes to the functional impairment of microcirculation in the heart.[35,36]

The impairment of insulin-mediated cell signaling (due to both its deficiency and its lower cellular sensitivity) results in complications in the production of nitric oxide, reducing capillary recruitment and leading to decreased glucose capture. In addition, activation of the renin angiotensin system contributes to cardiac thickening and progressive ventricular dysfunction.[37]

Cardiac Autonomic Neuropathy

In addition to affecting the genitourinary, gastrointestinal, and ocular systems, autonomic neuropathy manifests itself in cardiovascular disease. Therefore, besides gastroparesis, constipation or diarrhea, erectile dysfunction, and urinary retention or incontinence, sympathetic and parasympathetic dysfunction also induces tachycardia, hypotension, and postural and exercise intolerance.[38] Autonomic cardiac dysfunction affects about one in three individuals with type 2 diabetes and seems to be related to immune-related inflammatory changes.[39,40] The first alteration stems from parasympathetic impairment (vagus nerve), inducing greater sympathetic tonus and increased concentrations of norepinephrine and prompting increased heart rate, greater energy expenditure, baroreflex complications, and reduced heart rate variability. Over time, complications of the sympathetic nervous system also occur. All these changes seem to be associated with the duration of diabetes, glycemic control (including hypoglycemia), and associated risk factors. In addition to tachycardia and postural hypotension, autonomic dysfunction is associated with higher rates of operative complications and mortality, as well as silent myocardial infarction.[41-44] The toxicity of increased sympathetic tone and greater exposure to catecholamines affects ventricular remodeling, promotes hypertrophy, and contributes to diabetic cardiomyopathy.

CONCLUSIONS

Diabetes is associated with cardiovascular disease via multiple mechanisms, posing a significant challenge in selection of optimal therapies. Cardiovascular disease is progressive, but its mechanisms change over time, and the treatment should be individualized, according to the presence of complications such as heart failure, kidney failure, and micro- and macrovascular disease. Associated inflammation and autonomic dysfunction, along with glucose, lipid, or metabolic changes or those caused by hypertension, indicate greater complexity and often require management by a multidisciplinary team.

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest in this work.

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