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Vascular Impairment in the Brain of Diabetic Patients as Revealed by Neuroimaging

Comprometimento Vascular Cerebral na Diabetes Tipo 2 Revelado pela Neuroimagem

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Abstract

The nature of vascular impairments in diabetes and their impact on cognition remain widely debated. Regarding end-stage markers of small vessel disease burden, the extent into which it mediates the link between diabetes and cognitive decline remains to be determined. A mediation role may be present early on, when endothelial function and neurovascular coupling become impaired. Studies at earlier phases of the natural history of the disease, focusing on the functional and structural integrity of the components of the neurovascular unit, will probably shed light on the relative role of neural and vascular factors on the pathophysiology of neurobehavioral deficits in diabetes.

Keywords: neural and vascular factors; neurobehavioral deficits; diabetes *mellitus*; neuroimaging

Resumo

A natureza das alterações vasculares na diabetes e o seu impacto sobre a cognição continuam a ser amplamente debatidos. No que diz respeito aos marcadores do impacto de doenças de pequenos vasos no estádio terminal, ainda não foi determinado até que ponto estabelecem a ligação entre a diabetes e o declínio cognitivo. Um papel de mediação poderá estar presente precocemente, quando a função endotelial e o acoplamento neurovascular ficam comprometidos. Estudos em fases iniciais da história natural da doença, focados na integridade funcional e estrutural dos componentes da unidade neurovascular irão, provavelmente, clarificar o papel relativo dos fatores neuronais e vasculares na fisiopatologia dos défices neurocomportamentais na diabetes.

Palavras-chave: fatores neurais e vasculares; défices neurocomportamentais; diabetes *mellitus*; neuroimagem

Diabetes *mellitus* is characterized by chronic hyperglycemic toxicity and chronic microinflammation. [1] This metabolically adverse environment underlies the development of classical chronic microvascular (retinopathy, nephropathy and autonomic or sensorimotor peripheral neuropathy) and macrovascular (ischemic coronary artery disease, cerebrovascular disease and peripheral artery disease) complications as well as emerging complications (cognitive disability and affective disorders, liver disease, periodontal disease, bone disease, skin disorders, cancer and infection) that are equally important and contribute to the disease burden. [2] From a pathophysiological point of view, there are several hyperglycemia-induced cellular pathways that contribute to the disruption of the vascular system by the continuous free

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radical formation that modify proteins through enzymatic and nonenzymatic reactions, leading to the transcription of a broad range of genes that regulate angiogenesis and fibrosis. [3]

Hyperglycemia increases the activity of essential enzymes in the polyol pathway, leading to intracellular sorbitol accumulation that rises cellular osmotic injury and exacerbates oxidative stress. [4] Furthermore, the protein kinase-C pathway is stimulated under the influence of aldose reductase, via diacylglycerol production. [5] The normal glycolytic pathway shifts to the hexosamine pathway, increasing the burden of oxidative stress via the production of excess uridine diphosphate-N-acetyl glucosamine (UDP-GlcNAc), resulting in an increase in the expression of transforming growth factor-1 (TGF-1) and plasminogen activator inhibitor-1 (PAI-1) that leads to stimulation of vascular atherosclerosis, fibrosis and reduction of mesangial cell differentiation. [6] The accumulation of advanced glycation end-products (AGEs) in cells, disrupts their normal metabolic activities and alters gene expression. In addition, increased dispersion of AGEs to the extracellular matrix can impair cellular signaling, and may stimulate receptor-binding of AGEs. [5]

These disruptive mechanisms affect several cells, with the highest impact on those without intracellular glucose regulating systems, such as endothelial cells, mesangial cells, neurons and neuroglia cells. [7] The structural and functional diabetes-induced brain damage is a good example of an outcome from a multi-tissue dysfunction, as neurodegeneration results from a complex interplay of cerebral small vessel disease and direct neuronal injury. [8] Several disruptive mechanisms precede cognitive dysfunction, such as brain insulin resistance, [9] accumulation of advanced glycation end-products [10] and neuroinflammation. [11] Structural abnormalities such as altered blood-brain barrier permeability, [12] impaired capillary flow patterns [13] and aberrant neurovascular coupling [14] result in perfusion deficits and hypoxia triggering inflammation and angiogenesis mechanisms. [15] Last but not least, an adverse vascular risk factor profile, which develops in a prediabetic stage, might be a contributor to the small vessel disease burden. [16]

Several imaging techniques can be used to assess signs of microvascular brain dysfunction, and direct or indirect brain injury. MRI structural features of cerebral small vessel disease include white matter hyperintensities and lacune of presumed vascular origin, cerebral microbleeds, perivascular spaces, total brain atrophy and microinfarcts. [17] These features are indirect and represent end-stage markers of small vessel abnormalities because they reflect brain parenchymal damage potentially related to several functional and structural small vessel changes. [12] White matter hyperintensities are regions of high signal intensity on T2-weighted MRI images including fluid attenuated inversion recovery (FLAIR), and materialize in imaging as bright areas. They most often occur bilaterally, often symmetrical, and can vary in size. White matter hyperintensities are strongly associated with vascular disease and vascular risk factors, but their exact pathogenesis is not well understood and might be multifactorial. [12] A meta-analysis of 25 studies comparing the occurrence of white matter hyperintensities in patients with type 2 diabetes with a reference population revealed no consistent association between type 2 diabetes and white matter hyperintensities across different study populations. [18] In a systematic review ten studies that reported the association between measures of glycemic control and white matter hyperintensities in people with type 2 diabetes were analyzed and surprisingly HbA1c levels were not associated with the presence or progression of white matter hyperintensities. Two of six cross-sectional studies showed a significant but week association between high fasting glucose concentration and white matter hyperintensities, however the associations reported were in opposite directions. Two studies reported the correlation of higher HOMA-IR with the presence of white matter hyperintensities, but fasting insulin concentrations were not associated with the progression of white matter hyperintensities. [19] The links between diabetes and white matter hyperintensities remain unclear. The reasons for this uncertainty may be related to the different cohorts (vascular risk factor burden and comorbid conditions in different samples) or differences in scales used to rate white matter hyperintensities.

Cerebral infarcts on MRI can be categorized as small subcortical or large-vessel infarcts. Although type 2 diabetes is often associated with a higher prevalence of MRI infarcts, in a large cross-sectional study, this excess prevalence did not appear to mediate the association between diabetes and cognitive function. [20] Similarly, in a Japanese study of 153 neurologically preserved individuals, the association between diabetes and lower executive function was independent of silent brain infarcts. [21] A recent systematic review has shown global negative results amongst studies that explore the association between glycemic control indexes and cerebral infarcts in type 2 diabetes patients. Three cross-sectional studies showed HbA1c, fasting glucose and HOMA-IR were not correlated with the presence of cerebral infarcts. [19] Also, in a longitudinal study, the progression of recent small subcortical infarcts was not associated with HbA1c, fasting blood glucose or fasting insulin concentrations. [22]

Regarding MRI markers of small vessel disease, some studies observe that diabetes-associated cognitive decline is independent of small vessel disease burden, [23] whereas others report slight or evident mediation of small vessel disease (infarcts, white matter hyperintensities, but not microbleeds) in the association of diabetes with memory, processing speed, and executive functioning. [24] In summary, type 2 diabetes is associated with an increased burden of cerebral microvascular disease, but the relation between microvascular brain disease MRI markers and cognitive dysfunction is, however, not specific to diabetes, and the extent to which microvascular disease mediates the link between diabetes and cognitive decline remains to be determined. Further studies using 7T MRI may help to explore the potential contribution of microinfarcts to diabetes-related brain impact regarding cognitive performance.

With the advent of MRI techniques that study the cerebrovascular physiology (perfusion) and the integrity of the neurovascular unit, more information begins to emerge that can add to structural features of cerebrovascular disease and contribute to its understanding. The blood-brain barrier is formed by a tightly linked layer of endothelial cells, together with a basement membrane, mural cells, and astrocyte endfeet. The blood-brain barrier protects neurons from factors present in the systemic circulation and maintains the highly controlled CNS internal milieu. [12] Increased blood-brain barrier permeability leads to leakage of plasma constituents into perivascular space, which might directly damage neurons and trigger inflammatory responses. [25] Some small studies have used dynamic contrast enhancing MRI to show postcontrast enhancement of brain parenchyma in type 2 diabetes, which is presumed to suggest increased blood-brain permeability. Additionally, blood-brain barrier permeability worsens with proximity to the white matter hyperintensities and it is linked to the development of new white matter hyperintensities over time. [15] In a preliminary study, type 2 diabetes was associated with lower regional brain volumes, perfusion and vasoreactivity in frontal and temporal cortex. In a larger cohort, abnormalities in cerebral perfusion and vasoreactivity were strongest in those with insulin resistance and intermediate in type 2 diabetes patients compared with controls, suggesting a protective effect of type 2 diabetes treatment and adequate glycemic control. [26]

Neurovascular coupling is the cerebrovascular reactivity to neuronal demand, defined by a rapid change in the blood flow in response to increased neuronal activity. This response reflects the ability of the brain microvasculature to dilate in response to increased neuronal metabolic needs, and is endothelium dependent. [27] In task-based functional MRI studies, patients with type 2 diabetes have shown impaired neurovascular coupling, and this impairment was related to an altered microvascular hemodynamic response. [14] Two more recent studies showed that this impaired neurovascular coupling is reflected in a distinct hemodynamic response curve in diabetic patients. [28,29] This curve shows lower amplitude, larger latency and often an initially increased negative dip, suggesting that vascular autoregulation phenomena are impaired in diabetes. These impairments can be detected using deep learning artificial intelligence tools. [29] However, one should not disregard the possibility that direct neural impairment may occur even prior to early vascular and endothelial damage. We have shown that this may be the case, by demonstrating neurophysiological impairments even before the barrier is disrupted in diabetic patients. [30]

Neuroimaging has contributed significantly to our understanding of the brain impact of diabetes. Taken together, data gathered over the last decade seem to support the possibility of neurovascular coupling mechanisms modulated by central insulin signaling pathways linking type 2 diabetes, neuronal health, and cognition. However it is difficult to explore whether cerebral perfusion changes occur before or after cerebral metabolic changes, as measures of vascular status and measures of cerebral metabolism correlate strongly with neurodegeneration and with each other. More data are required to complete this understanding, specially on the relationship with cognitive impairment. The contribution of cerebrovascular factors and neurodegeneration, their interactions and their underlying mechanisms require more elucidation. The link between neuropathology and clinical phenotype will provide the possibility to understand the influence of anti-hyperglycemic therapy on diabetes-associated associated dementia risk.

Awareness of the cognitive complications of diabetes is increasing worldwide, but does not yet constitute a priority in diabetes management nor a treatment goal, since neither a prevention strategy nor a specific treatment are available for these conditions. Multimodal neuroimaging studies, including analysis of neurovascular coupling, can contribute to explore the causal nature of the association between diabetes and cognitive decline, specially using data of large cohort longitudinal studies with advanced computational analysis, that can help to guide the development of individualized therapeutic interventions. <

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