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Diabetes and cognitive dysfunction: a dangerous liaison

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Abstract

Cognitive dysfunction has been increasingly considered as a major comorbidity of diabetes mellitus, which can result in non-adherence to recommended therapies and higher risk of hypoglycemic events. Although the exact mechanisms underlying the relationship between markers of insulin homeostasis and cognitive decline in patients with diabetes are still not fully understood, several studies have recently showed that dietary and/or pharmacological interventions exert beneficial effects in terms of prevention and improvement of diabetes-related cognitive decline. Therefore, a better understanding of molecular mechanisms that account for the pathological loop between diabetes and neurological dysfunction would allow for better prevention strategies and more tailored therapies, especially in the elderly population.

Over the last years, cognitive dysfunction has been increasingly recognized as a major comorbidity of diabetes mellitus (DM)[1]. Apart from classical vascular risk factors (e.g. hypertension, dyslipidemia, microangiopathy, atherosclerosis and macroangiopathy), other factors have been involved in the pathogenesis of diabetes-related cognitive dysfunction, including hyperinsulinemia, insulin resistance, decreased beta-cell function, repeated hypoglycemic episodes, poor or tight glycemic control, and glycemic variability[2-7] (Figure 1). However, the mechanisms underlying the relationship between markers of insulin homeostasis and cognitive function in patients with DM are still not fully understood[5]. Magnetic resonance imaging (MRI) studies have suggested that both type 1 DM (T1DM) and type 2 DM (T2DM) are associated with brain atrophy, whereas increased white matter hyperintensities volume (WMHV) and greater occurrence of lacunes have been reported in patients with T2DM[8,9]. Nevertheless, these brain MRI lesions do not represent specific features of underlying aetiologies[10].

Clinical features and prognosis of diabetes-related cognitive dysfunction appear to depend on several factors, such as age and type, duration and severity of DM[11]. Mild cognitive impairment (MCI) and dementia - which represent more severe stages of cognitive dysfunction compared to mild diabetes-associated cognitive decrements[12] - primarily occur in older individuals (>65 years of age)[1,13]. However, even children with T1DM can exhibit mild changes in cognitive development, especially if they developed the disease early in life (<7 years of age)[14]. In addition, adult subjects with T1DM also show a significantly lowered cognitive performance on specific cognitive domains, such as psychomotor efficiency and cognitive flexibility[15]. Moreover, MCI has also been significantly associated with longer duration and greater severity of DM[16].

A number of studies have recently highlighted the importance of a prompt dietary and/or pharmacological intervention in modulating cognitive decline and risk of dementia among patients with DM. Of note, a recent longitudinal observational study (Boston Puerto Rican Health Study) showed that higher adherence to Mediterranean diet (as-

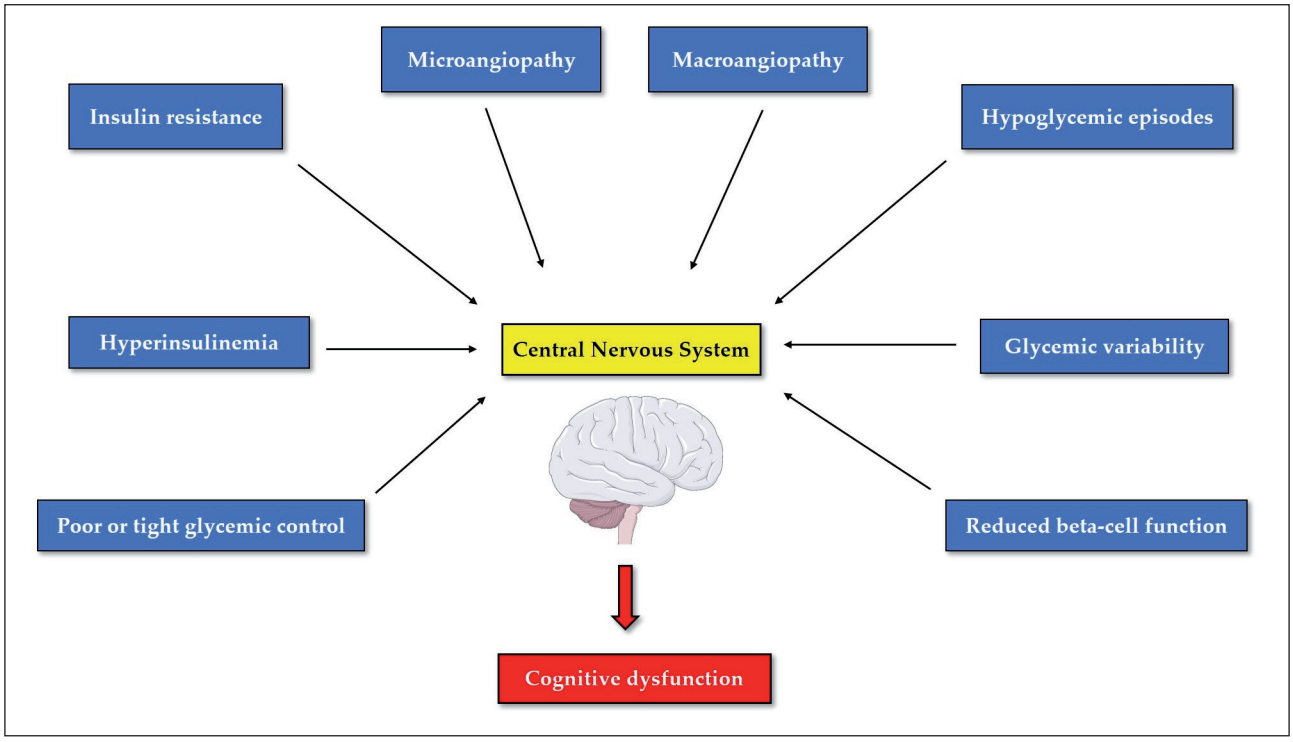

Figure 1. Potential mechanisms involved in diabetes-related cognitive dysfunction.

sessed by MeDS, Mediterranean diet score) was significantly associated with higher 2-year change in global cognitive function, Mini-Mental State Examination (MMSE), digit span forward, clock drawing test, and word recognition in patients with T2DM[17]. This association remained significant for T2DM patients under glycemic control at baseline or with stable/improved glycemic control over 2 years, but not for T2DM patients uncontrolled at baseline (defined as glycated hemoglobin, HbA1c ≥7%) or with poor/declined glycemic control at 2 years[17]. Therefore, these findings indicate that patients with T2DM adhering to a Mediterranean diet exhibit remarkable cognitive benefits, which are further sustained by optimal glycemic control.

With regard to pharmacological interventions, observational studies also documented that glucose-lowering agents may lead to cognitive improvement, with some compounds being associated with greater beneficial effects compared to others[18]. Hence, the beneficial effects on cognition of some antidiabetic drugs may go well beyond their antihyperglycemic effect and could be mediated by their effects on brain metabolism, neuroinflammation, and neuronal regeneration[18]. For instance, a large retrospective cohort study of US veterans with T2DM reported that metformin use was associated with a lower risk of subsequent dementia than sulfonylurea use in subjects <75 years of age[19]. These findings have been recently confirmed by Scherrer et al[20], who found that metformin *vs.* sulfonylurea initiation was associated with a significantly lower risk of dementia in African American veterans aged 50 to 74 years and in Caucasian veterans aged 65 to 74 years.

Reduced incretin activity - especially reduced levels of glucagon-like peptide 1 (GLP-1) - may represent a further potential pathophysiological link between T2DM and neurodegeneration and cognitive decline[21]. GLP-1 receptor (GLP-1R) is a G-protein-coupled receptor expressed not only in pancreatic islets, but also in several other tissues, including brain[22]. Indeed, the incretin-based medications GLP-1R agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors have been shown to play a protective effect on cognitive function. Experimental evidence suggests that GLP-1 receptor (GLP-1R) plays a neuroprotective role, controlling synaptic plasticity and memory formation[23]. Moreover, it has been shown that GLP-1R agonists improve hippocampal synaptic plasticity and prevent cognitive dysfunction in animal models of T2DM[24,25].

However, prospective studies are needed in order to assess whether GLP-1R agonists display similar effects in human subjects with DM. Furthermore, a 12-month randomized controlled trial has recently documented that SGLT2 (Sodium-glucose co-transporter 2)-inhibitors are not inferior to incretin-based therapy (GLP-1R agonists or DPP-4 inhibitors) in preventing cognitive decline in elderly patients with T2DM, although the small sample size (n=39) has certainly represented a limitation of the study[26]. Notably, Sa-Nguanmoo et al[27] previously demonstrated that the DPP-4 inhibitor vildagliptin and the SGLT2 inhibitor dapagliflozin were both able to improve brain function and prevent cognitive decline by potentially attenuating brain mitochondrial dysfunction, insulin resistance, apoptosis, and inflammation in high-fat diet-induced obese rats. Interestingly, evidence that intranasal insulin (IN-Ins) administration in patients with DM may acutely affect mood, behavior, and cognitive performance have suggested a further link between DM and cognitive dysfunction[28,29]. The results from the effects of IN-Ins use on cognitive diseases were so promising that in 2012, the U.S. National Institutes of Health allocated $7.9 million for a pilot trial called SNIFF (Study of Nasal Insulin in the Fight Against Forgetfulness; ClinicalTrials.gov Identifier: NCT01767909). SNIFF is a multicenter study aimed to examine the effects of IN-Ins on cognition, entorhinal cortex and hippocampal atrophy, and cerebrospinal fluid biomarkers in amnestic MCI or mild Alzheimer disease. The study has now been completed and we are waiting for publication of the results that look very promising. Reger et al[29], conducted a study on 25 participants that were randomly assigned to receive either placebo (n=12) or 20 IU BID IN-Ins (n=13) using an electronic atomizer. Cognitive measures and blood were obtained at baseline and after 21 days of treatment. The IN-Ins-treated group showed improvement in all tested cognitive performances, including attention and functional status. Moreover, IN-Ins treatment increased fasting plasma levels of the short form of the beta-amyloid peptide (A beta 40) without affecting the longer isoform (A beta 42)[29], thus suggesting a direct effect on the pathophysiology of Alzheimer disease that should be worthy to pursue.

The increasing occurrence of cognitive dysfunction in diabetic patients carries relevant clinical challenges. Since cognitive dysfunction is more prevalent and severe among older patients (>65 years), it can severely interfere with diabetes self-management, potentially resulting in non-adherence to recommended therapies and lifestyle behaviors, higher risk of hypoglycemic events, increased frequency of hospitalizations, and increased occurrence of major cardiovascular events and death[30-33]. In this regard, from the last years clinical diabetes guidelines started to take into account diabetes-related cognitive dysfunction and to suggest how cognitive dysfunction should affect diabetes management[34,35]. The Standards of Medical Care in Diabetes issued by the American Diabetes Association (ADA) in 2019 suggest to consider cognitive impairment screening in older adults (>65 years of age) with diabetes[36], and to avoid intensive glycemic control in patients with diabetes and cognitive dysfunction[37]. In particular, guidelines suggest a tailored glycemic therapy based on patient's characteristics and health status. For patients residing in long-term care facilities or affected by end-stage chronic illnesses, moderate to severe cognitive impairment or high dependency for activities of daily living, a value of HbA1c <8.5% is considered a reasonable treatment goal due to the lack of benefits of strict glycemic control in this population, along with the increased risk for hypoglycemia. On the other hand, guidelines recommend a tighter glycemic target (HbA1c <7.5%) for patients with intact cognitive and functional status and/or few coexisting chronic illnesses[37,38]. Moreover, Multidimensional Geriatric Assessment and several validated scales, which consider the complexity of older patients (e.g. comorbidities, polypharmacotherapy, and other domains of frailty), may further help to design tailored therapies in elderlies and to counteract cognitive diseases in patients with DM.

Conclusions

Prevention strategies and disease-modifying therapies able to improve long-term cognitive outcomes for patients with DM still represent unmet needs. However, a better understanding of the pathophysiological factors and molecular mechanisms underlying diabetes-related cognitive dysfunction will be critical for establishing effective prevention and intervention strategies. Finally, antidiabetic drugs should be investigated as disease-modifying agents for cognitive disorders in both subjects with and without diabetes.

Conflict of Interest:

The authors declare that they have no conflict of interest to disclose.

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