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Are cognitive disorders more common in geriatric diabetic patients? What factors contribute to cognitive decline?

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1. RECOMMENDATIONS

A. Cognitive screening is recommended for all geriatric DM patients. Suggested validated screening tests are the Short Portable Mental Status Questionnaire and the clock drawing test. Screening should be repeated on a twice-yearly basis in those who are borderline and annually in those who are negative. In the case of positive screening, a specialist clinical diagnostic assessment is recommended.
B. In patients with mild cognitive impairment and dementia, evaluating and treating possible modifiable risk factors is recommended, such as sensory and physical functional disorders, obstructive sleep apnea syndrome, etc.
C. Simplification of antidiabetic drug treatment is also recommended in these patients.

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2. STRENGTH OF THE RECOMMENDATIONS

The quality of the evidence is moderate. Recommendations are supported by published evidence and best practice (supported by expert opinion).

3. SUPPORTING EVIDENCE

See appendix.

4. AREAS OF UNCERTAINTY AND FUTURE PERSPECTIVES

Despite great efforts to clarify the specific mechanisms through which diabetes-related vascular and metabolic dysfunctions can influence cognitive function, many issues are still unclear. The impact of sensory deficits, which are commonly found in DM patients and can further increase the risk of cognitive disorders, is of particular interest. In this regard, the synergic effect of multiple sensory deficits affecting cognition needs to be investigated specifically in geriatric DM populations. In addition, future perspectives should focus on establishing the role that the development of muscle dysfunction and sarcopenia may have on the cognitive health of geriatric DM patients. Finally, the strong association of DM, sensory

deficits, and sarcopenia with the frailty syndrome, supports the need for new studies exploring how these conditions can interact each other and ultimately impact cognitive performance.

APPENDIX

The impact of DM on cognitive function, especially in old age, has been widely demonstrated in recent decades. A recent systematic review and meta-analysis of 144 studies published until June 2019 showed that DM is associated with an increased risk of developing cognitive deficits and dementia by 25-91% [1]. The same review showed that prediabetes and changes in glucose metabolism could also significantly increase the incidence of cognitive disorders. The negative effects of DM on cognition are mediated by various mechanisms. Among these, vascular and metabolic dysfunction are the two main pathways through which DM can cause neuronal damage. In the vascular pathway, DM is associated with microvascular and macrovascular complications that can lead to central and peripheral neuropathy and may increase the risk of atherosclerosis and stroke [2,3]. In the metabolic pathway, hyperglycemia/hypoglycemia, insulin-resistance, and the accumulation of advanced glycation end-products can increase both oxidative stress and inflammation, interact with Aβ aggregation, and cause further direct and indirect neuronal damage [4-6]. Furthermore, the negative impact of DM on cognitive function can be mediated by common comorbidities, such as obstructive sleep apnea syndrome (OSAS), which should be included among the possible factors contributing to neurodegenerative disorders in geriatric DM patients [7,8].
Despite great efforts to clarify the specific mechanisms through which vascular and metabolic dysfunction can influence cognitive performance, many issues are still unclear. For instance, the impact of common complications of diabetes, such as sensory deficits and muscular dysfunction, which can further increase the risk of cognitive disorders, is also of particular interest.
Several authors have highlighted that sensory deficits are significantly associated with an increased risk of cognitive impairment and dementia [9]. This effect seems to be particularly exacerbated for combined sensory deficits, suggesting a synergic effect of multiple sensory deficits affecting cognition [10-12]. Although this issue has been examined in home-dwelling and institutionalized older persons, there is little data on DM patients. However, within the DM population, vascular and metabolic dysfunction can increase the risk of having multiple sensory deficits [13-15], further exacerbating cognitive decline.
Regarding muscle dysfunction, several studies have shown a close link between DM and loss of muscle quality, quantity and strength, which are the main features of sarcopenia [16-18]. As underlined in chapter 3, sarcopenia is not an uncommon condition in DM patients [17,19] and may progressively lead to reduced physical functioning and self-sufficiency [20,21]. The strong relationship between physical and cognitive functioning [22] and the associations between sarcopenia and cognitive deficits [23] therefore raises the assumption that sarcopenia could be an additional factor that mediates the negative impact of DM on cognitive health.
Finally, another factor to consider in the relationship between DM and cognitive deficits is frailty. Frailty is a condition characterized by reduced resilience to external stressors, which is associated with adverse health outcomes such as disability, institutionalization, and mortality. DM [24,25], sensory deficits [26], and sarcopenia [27,28] are strongly associated with frailty. In turn, frailty can substantially accelerate other age-related degenerative processes, such as cognitive decline [29].

Ethical consideration
None.

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Conflict of interest
The Authors declare no conflict of interest.

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This statement is:	**Quality of the evidence** (in the case of recommendation):
☒ **Recommendation** (supported by published evidence) ☒ **Best practice** (supported by expert opinion)	☐ Low ☒ **Moderate** ☐ High