

## SCIENTIFIC LETTER

## Are we underdiagnosing cognitive impairment in patients with type 2 diabetes mellitus?



### ¿Estamos infradiagnosticando el deterioro cognitivo en pacientes con diabetes mellitus tipo 2?

Demographic and lifestyle changes have positioned dementia (DE) and type 2 diabetes mellitus (T2DM) among the most significant challenges for health care systems. It is hypothesized that T2DM could be a precursor to cognitive decline.<sup>1</sup> People living with T2DM are 1.5 to 2.5 times more likely to develop cognitive impairment.<sup>2</sup> Cognitive impairment complicates self-care and increases the risk of hypoglycemia, thereby increasing comorbidity, hospital admissions, and T2DM-related costs.

Several authors suggest that glucotoxicity leads to an increase in neuronal insulin resistance, impaired insulin signaling, a pro-inflammatory state, mitochondrial dysfunction, and vascular damage, which result in the deposition of  $\beta$ -amyloid and tau proteins.<sup>3,4</sup>

In its 2023 consensus, the American Diabetes Association (ADA) recommends, with evidence level B, the early detection of mild cognitive impairment (MCI) or cognitive decline for adults older than 65 years during the initial visit, annually, and whenever the individual shows significant deterioration in their clinical condition due to increased difficulties with self-care activities, such as errors in calculating insulin doses, difficulties in carbohydrate counting, skipping meals, missing insulin doses, and problems recognizing, preventing, or treating hypoglycemia.<sup>5</sup> In this document, they advocate the use of 3 screening tools without preference for any (Mini-Mental State Examination, Mini-Cog, and Montreal Cognitive Assessment).

We conducted a prospective cross-sectional study in the context of a clinical trial, and recruited 219 consecutive patients with T2DM older than 60 years, 54.1% of whom were men, with long-standing T2DM (> 10 years) at Hospital Universitario Son Llàtzer (Balearic Islands, Spain) from March 2022 through January 2023. These patients were given a Montreal Cognitive Assessment (MoCA) questionnaire, and the cutoff points were adjusted by gender, race/ethnicity, and years of education, as suggested by Milani et al.,<sup>6</sup> to establish the diagnostic suspicions of unaffected cognitive function, MCI, and DE. Results are shown in Table 1.

**Table 1** Cognitive performance results n = 219.

No. (%)	
Unaffected	64 (29.69%)
Mild cognitive impairment	118 (53.88%)
Dementia	36 (16.43%)

We reported a higher-than-expected prevalence of MCI and DE. In their systematic review and meta-analysis, You et al.<sup>7</sup> showed, in a subgroup analysis, that the prevalence of MCI in patients older than 60 years was 44.3%. In Spain, a database selected patients with T2DM aged 60 years or older admitted to Spanish hospitals from 2011 through 2020 and found a prevalence of dementia of 8.31%.<sup>8</sup> In our study, we reported a prevalence of MCI of 53.88% and a prevalence of DE of 16.43%. Obviously, our sample is small, and it is a cross-sectional study from a single center; therefore, our findings should be interpreted with caution. However, if cognitive function screening were to become routine, it might reveal that we are underestimating cognitive impairment in people living with T2DM. In a study that included 442,428 individuals older than 65 years without dementia, Legdeur et al.<sup>9</sup> reported that vascular disorders no longer represent a risk factor for dementia in older adults (> 65 years).

Just as a fundus examination or a routine annual urine microalbumin/creatinine ratio is performed for people with diabetes, we should include an annual cognitive assessment for people older than 60 years living with diabetes, even though there are no specific and effective therapies for the treatment/prevention of cognitive impairment in people with T2DM. Therefore, we face the need for creating research lines that allow the identification of the clinical and epidemiological characteristics of patients with T2DM at high risk of DE, while simultaneously establishing and initiating future research lines to provide solutions for our patients.

### Ethical disclosures

The study that supports this letter was approved by the Clinical Research Ethics Committee of the Balearic Islands (CEI-IB) with No. "IB4719/21". The study was conducted in full compliance with Good Clinical Practice standards and the International Conference on Harmonization (ICH) Guidelines.

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## Declaration of competing interest

None declared.

## References

1. Mohamed-Mohamed H, García-Morales V, Sánchez Lara EM, González-Acedo A, Pardo-Moreno T, Tovar-Gálvez MI, et al. Physiological mechanisms inherent to diabetes involved in the development of dementia: Alzheimer's disease. *Neurol Int*. 2023;15:1253–72, <http://dx.doi.org/10.3390/neurolint15040079>.
2. Ninomiya T. Epidemiological evidence of the relationship between diabetes and dementia. *Adv Exp Med Biol*. 2019;1128:13–25, [http://dx.doi.org/10.1007/978-981-13-3540-2\\_2](http://dx.doi.org/10.1007/978-981-13-3540-2_2).
3. Bello-Chavolla OY, Antonio-Villa NE, Vargas-Vázquez A, Ávila-Funes JA, Aguilar-Salinas CA. Pathophysiological mechanisms linking type 2 diabetes and dementia: review of evidence from clinical, translational and epidemiological research. *Curr Diabetes Rev*. 2019;15:456–70, <http://dx.doi.org/10.2174/1573399815666190129155654>.
4. Bharadwaj P, Wijesekara N, Liyanapathirana M, Newsholme P, Ittner L, Fraser P, et al. The link between type 2 diabetes and neurodegeneration: roles for amyloid- $\beta$ , amylin, and tau proteins. *J Alzheimers Dis*. 2017;59:421–32, <http://dx.doi.org/10.3233/JAD-161192>.
5. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 13. Older adults: standards of care in diabetes-2023. *Diabetes Care*. 2023;46:S216–29, <http://dx.doi.org/10.2337/dc23-S013>.
6. Milani SA, Marsiske M, Cottler LB, Chen X, Striley CW. Optimal cutoffs for the Montreal cognitive assessment vary by race and ethnicity. *Alzheimers Dement (Amst)*. 2018;10:773–81, <http://dx.doi.org/10.1016/j.dadm.2018.09.003>.
7. You Y, Liu Z, Chen Y, Xu Y, Qin J, Guo S, et al. The prevalence of mild cognitive impairment in type 2 diabetes mellitus patients: a systematic review and meta-analysis. *Acta Diabetol*. 2021;58:671–85, <http://dx.doi.org/10.1007/s00592-020-01648-9>.
8. Lopez-de-Andres A, Jimenez-Garcia R, Zamorano-Leon JJ, Omaña-Palanco R, Carabantes-Alarcon D, Hernández-Barrera V, et al. Prevalence of dementia among patients hospitalized with type 2 diabetes mellitus in Spain, 2011-2020: sex-related disparities and impact of the COVID-19 pandemic. *Int J Environ Res Public Health*. 2023;20:4923, <http://dx.doi.org/10.3390/ijerph20064923>.
9. Legdeur N, van der Lee SJ, de Wilde M, van der Lei J, Muller M, Maier AB, et al. The association of vascular disorders with incident dementia in different age groups. *Alzheimers Res Ther*. 2019;11:47, <http://dx.doi.org/10.1186/s13195-019-0496-x>.

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