

# Mild cognitive decline in type 2 diabetes mellitus patients – risk factors and pathogenesis: role of DPP4 activity and future possible therapeutic targets

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## Dear editor

We read with great interest, the recently published article “Risk factors for developing dementia in type 2 diabetes mellitus patients with mild cognitive impairment” by Albai et al.<sup>1</sup> The article provided a great insight into evaluating the prevalence of mild cognitive impairment (MCI) in patients with type 2 diabetes (T2DM) and highlighted the risk factors for conversion of MCI to dementia. We would like to add some knowledge of the mechanisms and pathogenesis of the development of MCI in T2DM patients and a guide to possible future therapeutic developments.

The study included a total of 207 patients with T2DM aging between 33 and 81 years. Scoring with the Mini-Mental State Examination test was mainly used for the diagnosis of dementia; however, imaging modalities (computed tomography and magnetic resonance imaging) and some other neuropsychiatric testing also provided support to the study. According to the study, MCI was found to be more prevalent among old aged patients and factors such as duration of diabetes and body fat amounts were notably associated with increased risk of MCI. Factors such as increased glucose and serum low-density lipoprotein levels, previous stroke history, and presence of cardiovascular disease were also found to be associated with conversion of MCI to full blown dementia.<sup>1</sup>

Several factors such as the role of chronic hyperglycemia in endorsing the development of cerebral microvascular disease, inflammation and oxidation stress have been implicated in brain injury leading to cognitive decline. T2DM patients are especially at risk because of high levels of glucose and inflammatory markers such as IL-6 and CRP. Moreover, an increased level of dipeptidyl peptidase (DPP4) in T2DM was found for the first time to be associated independently with MCI in elderly patients according to one study. The exact mechanism was thought to be the linkage between high DPP4 levels and the development of inflammation and oxidative stress. The study concluded by imparting a great concern to DPP4 activity both as a biological marker and a future therapeutic target.<sup>2</sup> Another study evaluated the role of increased DPP4 and decreased brain-derived neurotrophic factor (BDNF) levels with MCI development and found higher odds ratio for MCI in elderly T2DM patients with high DBR (ratio of DPP4 to BDNF).<sup>3</sup>

DPP4 inhibitors have now been used commonly in the treatment of T2DM due to their role in countering peripheral insulin resistance and safety profile; however, no study on humans has yet depicted the role of DPP4 inhibitors in managing cognitive

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impairment in T2DM.<sup>2</sup> A study conducted in 2013 on high-fat diet-induced insulin-resistant mice showed the positive impact of DPP4 inhibitors in decreasing brain oxidative stress, reducing hippocampal mitochondrial dysfunction, and improving learning behaviors.<sup>4</sup> In 2015, another study on type 2 diabetic mice demonstrated the effect of DPP4 inhibition in alleviating oxidative stress and ameliorating cognitive dysfunction.<sup>5</sup>

Although enough knowledge has been attained in terms of risk factors and pathogenesis of MCI development in T2DM, the lack of enough studies regarding the drug modalities to counter this cognitive decline is an issue that needs to be addressed. As trials on mice have given us some positive results, we call for studies on humans to assess and clarify the role of these therapeutic targets in future.

## Disclosure

The authors report no conflicts of interest in this communication.

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