

Review

# Update on cognitive decline and dementia in elderly patients with diabetes

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## Abstract

**Aim.** – This article is an update of the relationship between type 2 diabetes (T2D), cognitive dysfunction and dementia in older people.

**Methods and results.** – The number of older patients consulting for diabetes who also exhibit cognitive difficulties is consistently growing because of the increased longevity of the population as a whole and, according to a number of studies, the increased risk of cognitive impairment and dementia in older diabetic patients. Many studies have demonstrated a link between poor glucose control and deteriorated cognitive function in diabetic patients. A history of severe hypoglycaemic episodes has also been associated with a greater risk of late-in-life cognitive deficits and dementia in patients with T2D. Several processes are thought to promote cognitive decline and dementia in diabetics. Based on both clinical and non-clinical findings, the factors most likely to alter brain function and structure are cerebrovascular complications of diabetes, alterations in glucose and insulin, and recurrent hypoglycaemia. Together with other diabetes complications, cognitive deficits contribute to functional impairment, increased frequency of depression-related symptoms, greater incidence of recurrent hypoglycaemia, poorer adherence to treatment and, finally, poorer prognosis, as evidenced by recent longitudinal studies.

**Conclusion.** – Clinical guidelines have recently been devised for older diabetic patients, particularly those with cognitive deficits and a reduced capacity to self-manage. In the most vulnerable patients, specific treatment strategies have been proposed for glycaemic control to limit metabolic decompensation and avoid the risk of hypoglycaemia. Educational measures, provided mainly to maintain patient autonomy and avoid hospital admission, have also been adapted according to patients' cognitive and functional status.

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## 1. Introduction

In their everyday clinical practice, endocrinologists are facing a growing number of diabetic patients manifesting signs of cognitive decline and even full-blown dementia. The association is not surprising as these conditions share common features that are highly prevalent in the elderly population. In France, the prevalence of diagnosed diabetes increases with age to a maximum of 19.7% in men and 14.2% in women aged 75–79 years [1], while data from the PAQUID study suggest a 17.8% prevalence rate of dementia in people aged > 75 years [2]. The elevated frequency of cognitive dysfunction in elderly diabetics has been found in a majority of cross-sectional studies. Recently, 29% of the elderly patients with type 2 diabetes (T2D) included in the

French GERODIAB study had impaired cognition at baseline [3]. Thus, cognitive dysfunction is a frequent clinical problem that requires early identification and integration into the management of diabetes in the elderly.

The purpose of the present report is to provide an update of the most significant findings concerning cognitive deficits and dementia in elderly patients with T2D.

## 2. Diabetes increases the risk of cognitive decline and dementia

Diabetes itself has been recognized as an independent risk factor for the development of cognitive impairment in large prospective population-based studies with follow-up durations of up to 18 years [4–9]. In one extensive review [4], the annual rate of global cognitive decline, as measured by changes in Mini-Mental State Evaluation (MMSE) score [10], was found to be up to 1.5 times greater in diabetics than in non-diabetics. Some

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studies confirmed a greater risk of global cognitive decline in diabetics, whereas others identified a greater rate of decline only in certain cognitive functions (such as learning, mental speed and visuospatial processing). These variations, however, may simply reflect the different definitions used for cognitive decline, different age ranges of included subjects and/or failure to consider the duration or severity of diabetes on cognitive measures.

The relationship between diabetes and incidence of mild cognitive impairment (MCI) has also been addressed in longitudinal studies [11,12]. MCI represents the transitional phase from normal cognitive function to dementia, although not everyone with MCI goes on to develop dementia [13]. However, in elderly subjects who were either cognitively intact or diagnosed with MCI at baseline, diabetes increased the risk of dementia and also significantly accelerated the progression of MCI to dementia [12].

Longitudinal studies in which diabetes and dementia, including vascular dementia, Alzheimer's disease (AD) and mixed forms of dementia, were assessed in later life have demonstrated consistent results [5,12,14,15]. In a meta-analysis of eight prospective cohort studies, there was a 47% increased risk for diabetes patients to develop dementia and a 39% increased risk of AD, while the association of diabetes with dementia was independent of cardiovascular comorbidity [5]. Diabetes assessed in midlife also increased the risk of dementia in elderly patients [14]. In the Cardiovascular Health Cognition Study of more than 2500 participants, diabetes on its own or inheritance of the apolipoprotein E (ApoE) e4 allele alone increased the risk of developing AD [15]. Thus, diabetes is a proven risk factor for dementia in a number of studies. However, additional research is needed to examine the effects of age of diabetes onset (midlife vs late-life onset), comorbid conditions (such as vascular risk factors) and therapy on dementia risk to clarify the precise relationship between the two conditions.

### 3. Cognitive decline is related to poor glycaemic control

Many studies have demonstrated a link between poor glucose control and deteriorated cognitive function in diabetes. Higher haemoglobin HbA<sub>1c</sub> levels were consistently associated with lower scores on cognitive testing [16,17] and greater decline in cognition over time [18] in older adults with T2D. In contrast, cognitive benefits for working memory were achieved with improved glucose control in a short-term study of older diabetics [19]. More recently, dementia-free 55- to 80-year-old patients with T2D were included in the Action to Control Cardiovascular Risk in Diabetes–Memory in Diabetes (ACCORD–MIND) study to determine whether an intensive therapeutic strategy would reduce cognitive decline better than the standard therapeutic approaches. Although patients with higher HbA<sub>1c</sub> levels—in other words, poorer glucose control—had significantly lower scores on cognitive tests at baseline, there were no significant differences in severity of cognitive decline in patients receiving intensive therapy compared with those following a standard approach over a 40-month period [20,21]. It may be that the time interval was too short for observing any significant differences in decline intensity or that the intensive

strategy failed to improve the patients' outcomes targeted by the study.

To summarize, studies indicate that older patients with poor glycaemic control are more likely to have impaired cognitive function. Yet, although glucose control has been consistently proven, and is currently recommended, to prevent most diabetes-related complications, the effect of appropriate glucose control on preventing cognitive decline and delaying dementia has yet to be clearly demonstrated and confirmed in long-term studies.

### 4. Hypoglycaemia is important in diabetics with poor cognitive function

The incidence of hypoglycaemic episodes is important, but is probably underrecognized by diabetic patients as they advance in age: 33.6% of patients aged  $\geq 70$  years reported at least one hypoglycaemic episode; 3.3% have declared severe hypoglycaemia; and 0.6% have fallen into coma in the 6 months prior to inclusion in the GERODIAB study [3]. The link between the occurrence of hypoglycaemia and altered cognitive function has received much attention in older people with diabetes.

#### 4.1. Severe hypoglycaemia may be associated with late-life cognitive decline and dementia

The results of several clinical studies suggest that severe hypoglycaemic episodes are associated with an increased risk of cognitive decline and dementia in patients with T2D. In the cross-sectional Edinburgh study of more than 1000 patients, a self-reported history of severe hypoglycaemia was significantly associated with poorer later-life cognitive ability independent of prior/premorbid cognitive ability [22]. In a cohort of more than 16,000 older patients with T2D, the incidence of dementia was examined over a 4-year period: the accumulation of severe hypoglycaemic events over the preceding 20 years was significantly associated with a greater risk of dementia [23]. However, no such association was found in patients with type 1 diabetes (T1D): T1D patients followed for an average of 18 years in the Diabetes Control and Complications Trial (DCCT) showed high rates of recurrent severe hypoglycaemia, but no evidence of long-term decline in cognitive function [24]. Thus, the association of severe hypoglycaemia with accelerated cognitive decline in diabetes patients has yet to be clearly demonstrated in long-term prospective studies, although confirmation of such a relationship may have implications for the management of older patients for whom antidiabetic agents that induce hypoglycaemia may be contraindicated.

#### 4.2. Cognitive impairment is associated with increased incidence of hypoglycaemia

Patients with cognitive deficits have a significantly greater risk of presenting with severe hypoglycaemia. In the ADVANCE trial, this risk was increased more than two-fold in diabetic patients with severe cognitive dysfunction (MMSE score  $< 24/30$ ) compared with those with normal cognitive function [25]. Likewise, in the ACCORD trial, post-hoc analyses

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