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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Keywords: Diabetes; Elderly patient; Cognitive impairment; Dementia; Hypoglycaemia

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
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 glycemic control

Many studies have demonstrated a link between poor glucose control and deteriorated cognitive function in diabetes. Higher haemoglobin HbA1c 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 HbA1c 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 ≥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 diabetic 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
indicated that, in patients with lower baseline cognitive status, cognitive decline [as defined by a lower score on the Digit Symbol Substitution Test (DSST)] increased the risk of subsequent severe hypoglycaemia to a greater extent [26]. The risk of presenting with severe hypoglycaemia is also significantly higher for diabetic patients diagnosed with dementia [27,28]. The greater risk of hypoglycaemia in those with impaired cognitive function may at least be partly explained by behavioural limitations: cognitive impairment may interfere with the ability to manage medication; it may lower food intake as dementia progresses; and older age and polypharmacy may be additional factors leading to hypoglycaemia. Strategies to reduce the risk of hypoglycaemia (such as reinforced supervision and increased blood monitoring) are no doubt necessary for this group of patients.

4.3. Different processes may promote cognitive impairment and dementia in T2D

Cognitive impairment ranges from subtle cognitive deficits to its most severe clinical form, dementia. Dementia refers to a variety of diseases with different pathological mechanisms. AD accounts for about two-thirds of dementia cases, with pathological hallmarks including extraneuronal plaques (β-amyloid peptide) and axonal neurofibrillary tangles (phosphorylated tau protein), while vascular dementia, the second most common form of dementia, is characterized by single or multiple cortical/subcortical infarcts and/or white-matter abnormalities. The exact mechanisms behind the association between T2D and dementia are certainly multifactorial, reflecting the metabolic complexity of T2D and the wide diversity of dementias [29].

4.3.1. Cerebrovascular mechanisms

As diabetes is strongly associated with atherosclerosis and microvascular disease, stroke and vascular comorbidity are likely to be important determinants of the risk of dementia, of whatever type, in patients with diabetes [30]. In imaging studies, those with T2D had significantly greater chances of having cerebrovascular disease (infarcts and white-matter hyperintensities) and markers of AD (structural atrophy and reduced cerebral glucose metabolic rate in brain regions predictive of AD). An increased risk for brain cortical/subcortical infarction and changes in cerebral microvasculature has been confirmed in autopsy studies, but no clear association has been found with AD pathological hallmarks, suggesting that the predominant vascular pathology in diabetes may be lowering the threshold at which AD pathology becomes manifest (see Luchsinger for a review) [31].

4.3.2. Glucose toxicity

The toxic effects of high glucose concentrations are mediated through the polyol and hexosamine pathways, an imbalance in generation of oxygen species (oxidative stress), and generation of advanced glycation end products (AGEs). These processes directly affect brain tissue and are implicated in the ageing process of the brain [14]. AGEs are of particular interest. Clinical findings suggest that high peripheral AGE levels are associated with greater cognitive decline in older adults [32]. AGEs are also related to the classical microvascular complications of T2D, and may be implicated in accelerated β-amyloid deposition and senile plaque formation [14,32].

4.3.3. Impact of insulin resistance

Insulin resistance is another possible mechanism linking T2D with neurodegenerative brain lesions (see Craft for a review) [33]. Under normal conditions, insulin modulates cognitive function: insulin receptors are found in brain structures (including the medial temporal cortex and hippocampus) involved in cognition and memory that are known to be affected early in AD. In insulin resistance, chronic peripheral hyperinsulinaemia has been associated with a pattern in which brain concentrations of insulin are decreased, a condition that, in turn, may result in the down-regulated expression of an enzyme (insulin-degrading enzyme, or IDE) that mediates clearance of β-amyloid protein. In addition, low concentrations of insulin in the brain may increase phosphorylation of tau protein. These findings suggest that hyperinsulinaemia, independently of cerebrovascular disease, may be a possible risk factor for AD and its pathological hallmarks.

4.3.4. Impact of hypoglycaemia on brain function

Brain structures are highly sensitive to hypoglycaemia as they rely exclusively on glucose for their metabolism. A major concern in diabetes patients is that repeated episodes of hypoglycaemia may result in neuronal loss because of an impaired fuel supply [34]. The role of repeated hypoglycaemic episodes in the development of cognitive impairment has been explored in several clinical studies (as detailed above). In animal models, exposure to acute hypoglycaemia exacerbates neuronal damage in brain structures related to cognitive processes, whereas the impact of repeated hypoglycaemia on cell loss is less clear. Nevertheless, it is most likely that severe recurrent hypoglycaemia has deleterious effects on the brain in elderly patients with T2D who are also exposed to a number of comorbidities.

5. Cognitive impairment contributes to negative health outcomes

Cognitive deficits, in addition to other complications of late-life diabetes, can compromise patients’ daily activities and become potential barriers to self-care in diabetic patients. Cognitive fragility may also have social and economic consequences for such patients, and may contribute to significantly altered quality of life in this population.

5.1. Autonomy and affective status are altered

Diabetes and its complications are associated with multiple functional impairments (such as difficulty in walking, shopping and preparing meals), and increase the risk of falls and fractures [35]. Clearly, older diabetic adults who exhibit cognitive impairment especially in their executive functions (planning, coordinating, sequencing and monitoring of cognitive operations) are likely to experience further functional impairment and
reduced autonomy [36]. Cognitive impairment along with physical disabilities in diabetics are also associated with an increase in depressive symptoms [37] which, in turn, reduce social interactions, and affect quality of life and treatment adherence.

5.2. Diabetes therapy is poorly managed

Cognitive impairment is potentially a barrier to self-care in diabetes patients. Optimal management of the disease requires the patient’s active participation in self-monitoring blood glucose, and adjusting medication and diet to avoid hypoglycaemia. Good cognitive function is therefore crucial for safely managing diabetes. In patients aged >70 years attending geriatric diabetes clinics, one-third of them reported depressive symptoms and one-third had cognitive impairment, and the presence of cognitive dysfunction was inversely correlated to diabetes control and HbA1c levels [38].

5.3. Prognosis and life expectancy are compromised

Cognitive deficits are associated with a poor prognosis in diabetes. In the second US Longitudinal Study of Aging, patients with low-to-normal levels of cognitive function were 20% more likely to die during a 2-year follow-up compared with patients with normal cognition [36]. In the ADVANCE trial, diabetic patients with mildly impaired cognitive function (as assessed by MMSE scores) were at significantly greater risk of both cardiovascular events and death during a follow-up period of 5 years, while patients with more severe cognitive dysfunction were at even greater risk [25]. The contribution of impaired cognition to the development of functional disability and its prognosis is currently being explored in the French GERODIAB cohort of T2D patients aged ≥70 years. Although only autonomous patients were included in the study, 26% of the 987 participants had an impaired MMSE score at baseline (<25/30). Patients will be prospectively followed for up to 5 years to evaluate the link between glycaemic control and morbidity/mortality [3].

6. Specific treatment strategies are required

As they advance in age, diabetic patients are more likely to develop comorbidities and functional impairment; they also usually have a higher prevalence of depression, and an increased risk of cognitive decline and dementia. For these reasons, a patient-centred approach that takes into account the presence of associated diseases and geriatric conditions, and the patient’s needs and preferences, is a core principle underlying healthcare for elderly patients. This approach has been systematically proposed by all of the recent guidelines for older patients with diabetes (Table 1) [39–43].

Older patients with T2D living either in the community or in care homes should undergo regular assessment of their functional status, including the three major domains: physical; affective; and cognitive. Diabetes complications, cardiovascular diseases and all other somatic comorbid conditions need to be identified, the vulnerability to hypoglycaemia should be evaluated, and all factors, including the risk of drug interactions due to polytherapy, need to be considered. Detecting impaired cognition can indicate whether the patient needs further neurological investigations to identify the cause of the decline, and whether the ability to self-manage can be maintained or whether supervision is needed for managing treatment [39]. The French version of the MMSE can be used by the endocrinologist to detect cognitive deficits during the diabetes consultation or at the patient’s bedside [44], and should help in deciding whether to refer the patient for comprehensive geriatric assessment. Finally, whether the patient can self-manage or needs assistance must be considered before proposing any specific therapy adapted to the given patient’s needs.

Non-pharmacological treatment, including physical activity for maintaining muscle mass/function and dietary measures to maintain appropriate nutritional status, is essential for the prevention of functional impairment. The main aim of drug therapy in elderly diabetic patients is to control blood pressure, plasma lipids and blood glucose. In vulnerable patients, the target for glucose control should be less ambitious than in younger healthy individuals and should be weighed against the risk of hypoglycaemia [40]. Lower targets for glycaemic control should be considered [41,43]: HbA1c levels <9% have been suggested as reasonable targets to avoid metabolic decompensation and minimize the risk of hypoglycaemia (Table 2) [42].

Treatment of hyperglycaemia relies on the same agents as in younger patients, but with age-related considerations (Table 2). Metformin should be preferred as the first-line therapy if there are no contraindications [40,42]. A dipeptidyl peptidase (DPP)-4 inhibitor combined with metformin may be preferred as the second-line treatment in cases of failure to achieve glucose targets. Sulphonylureas should be used [42] with considerable caution and close monitoring due to the increased risk of hypoglycaemia in the elderly with their use. If oral agents cannot be

| Table 1 |
| Management strategy for older patients with type 2 diabetes (T2D). |
| **Key points** |
| Older patients have a higher cardiovascular disease burden, reduced renal function and more comorbidity |
| They are more likely to present with depression and cognitive impairment |
| Many are at risk of adverse events due to polypharmacy |
| Older patients are more likely to be compromised by hypoglycaemia |
| Life expectancy is reduced |
| **Management strategy** |
| Diet, exercise and education remain the cornerstones of T2D treatments |
| Cardiovascular risk reduction is a major focus of therapy |
| Glycaemic targets should be less ambitious than those for younger healthy people |
| Choice of antidiabetic agent should focus on drug safety, and especially preventing heart failure, renal disease and drug interactions |
| Therapy should be adjusted to minimize the risk of hypoglycaemia |


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Table 2
Treatment strategy recommended for type 2 diabetes (T2D) patients aged 75 years and over.

<table>
<thead>
<tr>
<th>Key points in T2D patients aged ≥ 75 years</th>
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<tbody>
<tr>
<td>Reduced renal function</td>
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<tr>
<td>Polypharmacy</td>
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<tr>
<td>Marked risk of hypoglycaemia with deleterious outcome</td>
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<tr>
<td>Risk of malnourishment</td>
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Glycaemic targets adapted to patient’s health status

HbA1c ≤ 7%: healthy patient; longer life expectancy
HbA1c ≤ 8%: vulnerable patient; limited functional and cognitive abilities; reduced adaptive skills
HbA1c <9% and/or fasting glucose 1–2 g/L: frail patient; poor health status with multiple chronic diseases; dependency and social isolation

Treatment strategy

Metformin, barring contraindications
(± sulphonylurea (SU), with careful monitoring)

- Failure to achieve glucose target
- OR
- SU cannot be used:
  - Moderate-to-high risk of hypoglycaemia

Metformin + DPP-4 inhibitor

- Oral antidiabetics cannot be used
  - (dehydration, functional renal insufficiency, etc.)
  - OR
  - Risk of glucose imbalance (acute infection, etc.)

Insulin ± caregiver assistance

GLP-1 agonists should not be used in older patients because of their limited clinical experience

Source: French National Authority for Health (HAS), 2013 [42].

DPP-4: dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1.

* Including renal/hepatic dysfunction, respiratory/heart failure, anorexia, gastrointestinal disease.

* Associated with increased risk of hypoglycaemia in older patients.

taken or there is a risk of glucose imbalance, then insulin may be given [42], preferably administered by a nurse or caregiver in cases of cognitive impairment to enhance diabetes management. Acetylcholinesterase inhibitors and the N-methyl-D-aspartate receptor inhibitor memantine are two pharmacological classes indicated and prescribed for symptomatic treatment of AD. Although there is no evidence of either pharmacokinetic or pharmacodynamic interactions between these two drug classes and the antidiabetic drugs used in elderly diabetics [43], the risk of adverse events due to polytherapy should always be borne in mind in this high-risk population.

Educational measures also need to be in line with the cognitive and functional status of the given diabetic patient and his/her ability to manage medication, including insulin therapy. Diabetes education for older people should be adapted [46] with a focus on individual therapeutic goals and maintenance of autonomy. All functionally independent patients should receive educational advice on how to achieve metabolic targets and minimize hypoglycaemia. In patients with significantly altered cognitive capacity, it is important to identify carers—family and other non-professional caregivers—and provide them with support and education to help keep the patient at home and avoid hospital admission.

7. Conclusion

People with diabetes have an increased risk of cognitive dysfunction and dementia. Some researchers have even suggested that cognitive impairment and dementia be included in the list of late complications of diabetes. Diabetic patients with cognitive deficits are also at greater risk of presenting with severe hypoglycaemia. Because cognitive impairment in elderly diabetic patients can have a considerable impact on their daily life activities, functional autonomy and ability to manage medication, detecting early cognitive deficits is especially important in diabetic patients aged > 70 years, in those with a long history of diabetes or diabetic complications and in those with poor glycaemic control. For the most vulnerable patients, including those with significant cognitive decline, the treatment goals, type of drug therapy and educational measures need to be adjusted to avoid hypoglycaemic events as far as possible. Also, early preventative strategies to reduce the risk of cognitive impairment are essential.

Disclosure of interest

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Appendix A. Supplementary data

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References


