Diabetes and cognitive impairment

A forgotten association?

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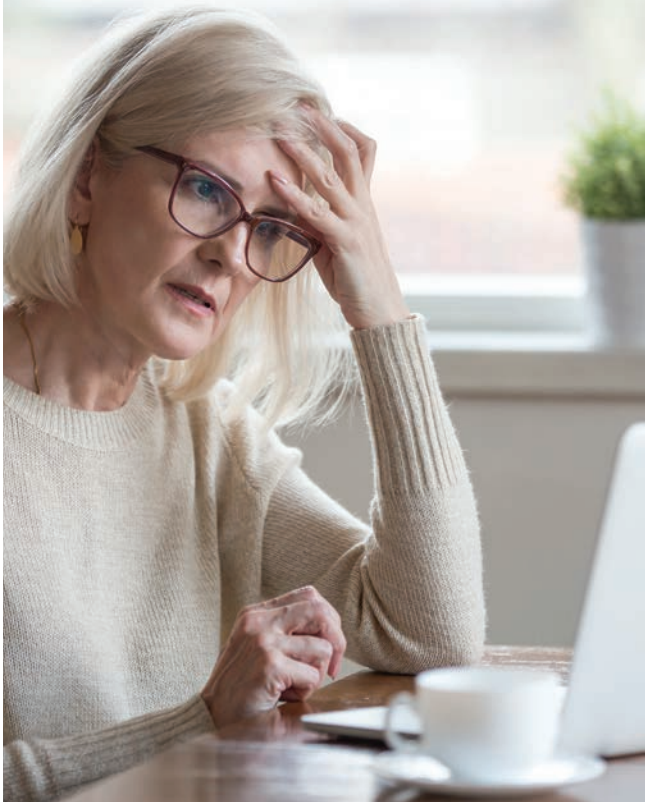
Cognitive impairment and dementia are common but insidious and under-recognised complications of diabetes. However, hypoglycaemia is also a risk factor for dementia, with implications for glycaemic control in patients with diabetes. It is important to remain alert to the possibility of cognitive decline in patients with diabetes and to take an individualised approach to glycaemic control.

Key points

- **Cognitive impairment is an under-recognised complication of diabetes.**
- **Recurrent hypoglycaemia is also associated with cognitive decline.**
- **Poor glycaemic control is a risk factor for impaired cognition.**
- **Cognitive impairment can interfere with self-management of diabetes, such as self-monitoring of blood glucose levels and medication frequency.**
- **Clinicians should remain aware of the impact of diabetes and recurrent hypoglycaemia on cognitive function, have a low threshold for further investigation into any cognitive deficits and refer patients to a geriatrician.**



Significant strides have been made in our understanding and management of diabetes, including in recognising, preventing and managing its micro- and macrovascular complications. However, cognitive impairment and dementia remain common yet under-recognised complications of diabetes, with awareness of these lagging considerably behind other well-established complications.

The prevalence of diabetes is rising, with projections estimating 693 million people living with the disease by 2045, including an increasing number of older people.[1] As such, a better understanding of the cognitive complications of diabetes is urgently needed. Cognitive impairment can detrimentally affect self-management of diabetes by interfering with the daily activities required for adequate management (e.g. self-monitoring of blood glucose levels and medication frequency).

Association between diabetes and cognitive impairment

Several longitudinal studies have shown that diabetes is a risk factor for dementia and cognitive decline.[2,3] In people with mild cognitive impairment, diabetes is associated with an accelerated risk of progression to dementia.[3] Poor glycaemic control, defined by increased glycated haemoglobin (HbA_{1c}) levels, has also been associated with impaired cognition.[4] Moreover, midlife obesity, which is often present before or comorbid with a diagnosis of diabetes, is a risk factor for

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cognitive impairment and dementia.[5] An 18-year longitudinal study found that an increase of one point in body mass index in 70-year-old women was associated with a 36% increase in the risk of Alzheimer's disease.[6] Metabolic syndrome has also been associated with an increased risk of cognitive dysfunction.[7]

Although poor glycaemic and metabolic control are risk factors for cognitive impairment, it is uncertain if tight glycaemic control could lead to improved cognitive function and delay dementia. In the Action to Control Cardiovascular Risk in Diabetes–Memory in Diabetes (ACCORD–MIND) study, intensive glycaemic control did not lead to less cognitive decline, although the follow-up period was limited to 40 months.[8] The patients recruited to this trial had a lengthy duration of diabetes (mean of nine years), which is itself a risk factor for cognitive impairment.

Both vascular dementia and Alzheimer's disease have been associated with diabetes. A meta-analysis found that diabetes was associated with a roughly 60% increased risk of dementia, with relative risks of 2.3 in women and 1.7 in men for vascular dementia, and 1.5 in both sexes for nonvascular dementia.[9] It has been suggested that Alzheimer's disease may result from cerebral insulin resistance and glucose dysregulation.[10] In a cohort study of 6370 people older than 55 years, 126 participants developed dementia during an average follow-up of 2.1 years, and 89 of these had Alzheimer's disease.[11] Diabetes doubled the risk of dementia, with participants who were receiving insulin being at four times the risk.[11] However, patients using insulin typically have a long duration of diabetes.

Association between hypoglycaemia and cognitive impairment

Recurrent hypoglycaemia, which can be associated with insulin or sulfonylurea therapy, has also been linked to cognitive impairment and is a risk factor for dementia.[12] Any cognitive deficit may then further increase the risk of hypoglycaemia and affect the patient's treatment adherence, mood and overall prognosis.

Similarly, it has been suggested that severe hypoglycaemic episodes (i.e. those that require the assistance of another person) are associated with cognitive impairment and increased risk of dementia in people with type 2 diabetes.[13] Studies in patients with type 1 diabetes have shown similar findings. In particular, the results of the Diabetes Control and Complications Trial (DCCT) and follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study indicated that the number of severe hypoglycaemic episodes was associated with significant cognitive decline during a 32-year follow up.[14] Cognitive decline was also associated with higher HbA_{1c} levels. Interestingly, this association was not seen in earlier DCCT or EDIC studies. At the 18-year follow up, hypoglycaemic events were not associated with cognitive decline, whereas poorly controlled diabetes, as defined by elevated HbA_{1c} levels, did show this association.[15] This suggests that severe hypoglycaemic episodes and poorly controlled diabetes are associated with cognitive decline later in life, or after a longer duration of diabetes or a greater number of severe hypoglycaemic episodes.

The association between recurrent nonsevere hypoglycaemic episodes (i.e. where the plasma glucose level is ≤3.9 mmol/L and the assistance of another person is not needed) and cognitive function is less clear.[16] As nonsevere hypoglycaemic episodes are typically self-managed and do not require hospitalisation or assistance, they often go unrecognised, leading to under-reporting. Retrospective recall of mild hypoglycaemic episodes is also poor, with estimates suggesting accurate recall of these events lasts no longer than a week. Other factors complicating accurate quantification of the effects of mild hypoglycaemic episodes include significant heterogeneity in the measurement and definition of cognitive impairment between studies and limited data regarding other comorbidities, the severity and duration of diabetes and the duration of hypoglycaemic events. Moreover, as nonsevere episodes do not cause acute cognitive impairment, it is not clear if they result in chronic cognitive effects. Further clinical studies are needed to elucidate the relationship between recurrent nonsevere hypoglycaemia and cognitive function. Every effort should nevertheless be made in clinical practice to minimise the risk of hypoglycaemia, as even nonsevere recurrent events are a risk factor for severe hypoglycaemic episodes.

In animal models, recurrent prolonged hypoglycaemia has been linked to worsening of cognitive function. Impairment in long-term recognition memory and spatial memory has been observed in behavioural tests, with mitochondrial dysfunction, neuronal injury, astrocyte overactivation, oxidative stress and impaired counter-regulatory response to oxidative damage thought to be involved in the underlying pathophysiology of cognitive impairment.[17-19] Dysfunction of transient receptor potential canonical channel 6 has been linked to Alzheimer's disease, and its expression was found to be repressed in diabetic mice with recurrent hypoglycaemia, leading to cognitive impairment, neuronal loss and neuronal activity.[20] In rodent models, glycaemic fluctuation and recurrent hypoglycaemia were observed to alter the expression of an NRG1-ErbB receptor signalling pathway, which is involved in neuronal regeneration.[21]

Implications for patients with diabetes

Patients with diabetes can have deficits in multiple cognitive domains, including verbal memory and processing speed.[22] Often, however, these deficits may not be apparent to the clinician, or even to the patient.

Cognitive impairment can substantially affect a patient's quality of life and autonomy. For people with diabetes, this can also mean a heightened risk of future hypoglycaemic episodes, as well as a detrimental effect on treatment adherence, which is crucial to diabetes management. Self-monitoring blood glucose levels at home, self-administering the appropriate amount of insulin and self-monitoring diet are all important aspects of diabetes management that can be negatively affected when a patient has cognitive impairment.

Mood may also be detrimentally affected, contributing to deteriorating treatment adherence, quality of life and autonomy.[23] Overall prognosis and life expectancy are reduced in patients with diabetes and cognitive impairment, compared with those with diabetes but without cognitive impairment.[24]

Management recommendations for GPs

Awareness of the cognitive complications associated with diabetes lags behind that for other established complications and needs to improve. Management priorities to minimise cognitive decline in patients with diabetes are summarised in the Box.

Avoidance of hypoglycaemia, especially severe episodes, should be a priority in the care of patients with diabetes. Where possible, medications that carry a low risk of hypoglycaemia should be used to achieve the appropriate individualised glycaemic target, although therapies such as insulin and sulfonylureas may be needed for some patients. Optimising glycaemic control is a priority, not only to reduce organ complications but potentially also to decrease cognitive impairment and dementia, although definitive studies are needed.

A position statement from the American Diabetes Association and European Association for the Study of Diabetes emphasises that a patient-centred approach should be used, weighing the benefits of improved glycaemic control with the risks of hypoglycaemia in the context of a patient's cognitive function, other comorbidities and functional status.[25] In particular, considering the risks of hypoglycaemia, intensive glycaemic control may not be recommended for older patients with diabetes.[26] It may be preferable to de-intensify therapy and create regimens that are less complex and minimise the risk of hypoglycaemia, to avoid patient-associated medication errors and potential deficits in self-care caused by cognitive impairment.

Avoidance of hypoglycaemia, especially severe episodes, should be a priority

Tight blood pressure control in patients with diabetes, but not overly tight (to avoid hypotension), may help prevent vascular dementia. Regular aerobic and resistance exercise may also reduce the risk of both vascular dementia and Alzheimer's disease. Dealing with other potential contributors to cognitive decline, such as lipid levels and smoking, should also be priorities in caring for patients with diabetes.

Clinicians should be aware of the potential for cognitive impairment in people with diabetes and carefully monitor for it, particularly in those with recurrent hypoglycaemic episodes. Cognitive impairment in patients with diabetes may present as forgetfulness about their appointments, medications and day-to-day management. A careful and comprehensive social history, with collaborative history from family members, may be helpful in further assessing the patient's level of functioning at home.

There are also established neuropsychological tests, such as the Mini-Mental State Examination and the Montreal Cognitive Assessment, that can be used to screen for the subtle decrements in cognition triggered by diabetes, as these may progress perniciously. Timely referral for psychogeriatric assessment of possible neurocognitive decline can be invaluable, as can targeted community support for patients with chronic cognitive decline living in nonresidential aged care. This can include programs such as the National Dementia Support Program, which aims to improve awareness of dementia and educate patients and their families on the support services available.

There is some interest in using metformin to prevent cognitive decline in patients with diabetes, although this remains unproven. As long-term metformin therapy can cause vitamin B12 deficiency, patients receiving ongoing metformin for diabetes should have routine (e.g. annual) blood level testing to exclude this. The glucagon-like peptide-1 receptor agonists are a more recent class of glucose-lowering therapy attracting considerable interest for treating people with type 2 diabetes. This medication class has shown potential benefits in animal models, with further research ongoing in humans.[27]

Management priorities to minimise cognitive decline in patients with diabetes

- Where possible, use diabetes medications with a low risk of hypoglycaemia
- Optimise glycaemic control
- Carefully control blood pressure and advise regular aerobic and resistance exercise
- Address other potential contributors to cognitive decline, such as lipid levels and smoking
- Monitor for cognitive impairment, particularly in patients with recurrent hypoglycaemic episodes
- Assess level of cognitive functioning at home through social history, with input from family members
- Use tests such as the Mini-Mental State Examination and the Montreal Cognitive Assessment to screen for cognitive impairment
- Consider referring patients for psychogeriatric assessment of neurocognitive decline

Conclusion

Diabetes is associated with subtle cognitive dysfunction that progresses insidiously. Timely detection of early cognitive decline in a person with diabetes can be difficult, often leading to delays in identification until deficits are frank and irreversible. Helping a patient with diabetes to maintain a physically active body and mind will minimise the risk of cognitive decline, as will managing their blood pressure, lipid levels, body weight and smoking. To sustain quality of life and safety, personalised approaches to glycaemic control are a cornerstone of care for people with diabetes who have evidence of cognitive decline. **ET**

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A list of references is included in the online version of this article (https://medicinetoday.com.au/mt/2025/may/supplements/focus-dementia-collection).

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