Prevention and management of cognitive impairment in people with type 2 diabetes: An evidence-based guide for primary care

Calum Moulton

Type 2 diabetes is an established risk factor for cognitive impairment, cognitive decline and dementia. The clinical presentation of cognitive impairment in type 2 diabetes is broad and includes dementia, mild cognitive impairment and more subtle cognitive deficits that may be specific to type 2 diabetes. Several risk factors have been identified for cognitive impairment and dementia in type 2 diabetes, including vascular risk factors, depression and inflammation. Other than cardiovascular disease prevention, however, there is inadequate evidence to guide the specific treatment of any risk factor in preventing or slowing down cognitive decline. In parallel, there is very good evidence that cognitive impairment in type 2 diabetes predicts adverse diabetes outcomes, including increased risk of hypoglycaemia, and this should be considered by primary care practitioners when managing individuals with comorbid type 2 diabetes and cognitive impairment. Future interventional studies aiming to reduce cognitive decline in type 2 diabetes – in particular those addressing novel risk factors – in primary care are awaited.

Type 2 diabetes is an established risk factor for both cognitive decline and dementia. In addition to a 2.5-fold increased risk of vascular dementia, type 2 diabetes is associated with a 1.5-fold increased risk of Alzheimer's disease (Cheng et al, 2012). Importantly, type 2 diabetes is thought to exert cerebral effects independently of its association with other vascular risk factors (Biessels et al, 2006), and brain changes seen in type 2 diabetes have shown striking similarities with those seen in Alzheimer's disease (Moulton et al, 2015a). Moreover, the relationship seems to be bidirectional: whilst type 2 diabetes contributes to cognitive decline, cognitive decline itself is associated with adverse diabetes outcomes (Munshi et al, 2006). This paper reviews the current literature on cognitive decline in type 2 diabetes, including risk factors, clinical presentations and potential treatments. The review then summarises in detail the implications of the evidence for primary care practitioners, including the prevention, diagnosis and management of cognitive impairment in type 2 diabetes.

Clinical presentations of cognitive impairment in type 2 diabetes

There is increasing evidence that cognitive impairment is a spectrum that can be observed in people with type 2 diabetes, potentially with varying specificity to type 2 diabetes. Mild cognitive impairment (MCI) has been well characterised in diabetes cohorts and the general population. Briefly, MCI is a term used to describe cognitive impairment beyond that expected based on the age and education of the individual but not significant enough to interfere with daily activities (Petersen et al, 1999). People with diabetes are 1.5–3 times more likely to develop from MCI to dementia compared to people without diabetes, a progression that may be delayed by treatment of vascular risk factors (Li et al, 2011). However, even in individuals with diabetes, MCI and dementia are rare in people under the age of 65, though their prevalence doubles every 5 years thereafter (Biessels et al, 2006).

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Article points

1. The clinical presentation of cognitive impairment in type 2 diabetes is broad and includes dementia, mild cognitive impairment and more subtle cognitive deficits or decrements that may be specific to type 2 diabetes.
2. Practical steps are provided to diagnose and manage cognitive impairment in primary care.
3. Future interventional studies aiming to reduce cognitive decline – in particular those addressing novel risk factors such as depression – in the primary care setting are keenly awaited.

Key words

- Cognitive impairment
- Dementia
- Evidence-based guide

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Page points

1. The term diabetes-associated cognitive decrements has been developed to describe subtle subjective cognitive deficits that are seen in type 2 diabetes.
2. There has been considerable interest in identifying potentially modifiable factors that may underlie the relationship between type 2 diabetes and cognitive impairment and decline.
3. Potential risk factors for cognitive impairment include vascular factors, previous cardiovascular disease, hypoglycaemia, depression and inflammation.

Diabetes-associated cognitive decrements

In addition to MCI and dementia, there is evidence that more subtle cognitive decrements are identifiable in people with type 2 diabetes, which may be associated with diabetes. The term diabetes-associated cognitive decrements has been developed to describe subtle subjective cognitive deficits that are seen in type 1 or type 2 diabetes. These decrements often present with increased mental effort on daily tasks; however, daily life activities and diabetes self-management are unaffected. Diabetes-associated cognitive decrements can affect people of all ages, and are associated with symptoms that are less severe than cognitive deficits seen in MCI.

Diabetes-associated cognitive decrements have been observed in one or several areas (e.g. general intelligence, psychomotor speed and mental flexibility) among people with diabetes. Scores for these tests are typically 0.3–0.5 standard deviations (SDs) lower than in people without diabetes (Koekkoek et al, 2015). People with MCI, who have worse cognitive impairment, tend to typically score 1–1.5 SDs below those without diabetes on the tests (Koekkoek et al, 2015). For individuals with subtle cognitive decrements, the results from basic cognitive tests such as the Mini Mental State Examination (MMSE) tend to be normal.

In contrast to dementia and MCI, such subtle decrements are thought to progress slowly, if at all (Biessels et al, 2006). However, the risk factors for these decrements remain unknown and their specificity to diabetes is not certain (Akbaraly et al, 2010).

Risk factors for cognitive impairment in type 2 diabetes

There has been considerable interest in identifying potentially modifiable factors that may underlie the relationship between type 2 diabetes and cognitive impairment and cognitive decline.

Vascular risk factors

In cross-sectional studies, hypertension (Chen et al, 2012), hyperglycaemia (Moulton et al, 2015b) and hyperlipdaemia (Chen et al, 2011) have all been associations with cognitive impairment. However, prospective studies examining these risk factors have been far fewer in number and there have been frequent negative findings (Bruce et al, 2008a; 2008b). Compared to the large amount of observational research in this area, clinical trials modifying potential risk factors to improve cognitive outcomes have been few and generally disappointing. In the ACCORD–MIND (Action to Control Cardiovascular Risk in Diabetes–Memory in Diabetes) study, intensive glycaemic control (HbA_{1c} <42 mmol/mol [6.0%] versus 53–63 mmol/mol [7.0–7.9%]) was not associated with any difference in cognitive decline after 40-months' of follow-up (Launer et al, 2011). Similarly, disappointing findings were observed for treatment of both hypertension and hyperlipidaemia in the same cohort (Williamson et al, 2014). However, these studies were limited by a relatively short follow-up, and a long duration of type 2 diabetes (9 years in the ACCORD–MIND study) among the individuals may also have limited the level of cognitive improvement. Studies examining the effects of vascular risk factor management both in individuals with early-stage type 2 diabetes and over longer-term follow-up are awaited.

A history of cardiovascular disease (CVD)

In contrast to the mixed findings regarding individual vascular risk factors with cognitive decline in type 2 diabetes, a history of CVD, such as stroke, myocardial infarction or peripheral vascular disease, has demonstrated a consistent association with cognitive decline and dementia in type 2 diabetes (Bruce et al 2008a; Haroon et al, 2015). The reasons for this mismatch between individual vascular risk factors and established CVD are not clear. However, established CVD could represent a marker of higher overall vascular risk, and it has been suggested that the effect of vascular risk factors on cognitive decline may be greatest in middle-age, rather than late-life (Koekkoek et al, 2015).

Hypoglycaemia

There is mixed evidence supporting an association between prior episodes of hypoglycaemia and either cognitive impairment or incident dementia in type 2 diabetes. Some studies have found a positive association (Feinkohl et al, 2014), whilst

others have not (Bruce et al, 2008b). However, the evidence for the role of cognitive impairment on hypoglycaemia is more consistent (see the section below on the effects of cognitive impairment on diabetes management). An association in either direction between cognitive impairment and hypoglycaemia could have potentially important implications for glycaemic control targets.

Depression

In two high-quality cohort studies, depression has been shown to predict subsequent dementia and cognitive decline in people with type 2 diabetes (Katon et al, 2012; Sullivan et al, 2013). The reasons for the association are not known and occur independently of lifestyle factors and other potential confounders. However, these studies were not able to completely exclude the possibility that depression could be a precursor to dementia in some individuals. No clinical trial to date has attempted to modify depression in order to slow down or prevent cognitive decline in type 2 diabetes.

Inflammation

Chronic low-grade inflammation is a characteristic feature of both diabetes and Alzheimer's disease (Pickup and Crook, 1998; Glass et al, 2010). Higher levels of circulating inflammatory mediators, such as tumour necrosis factor-alpha, have demonstrated a significant association with subsequent cognitive decline in type 2 diabetes (Keller et al, 2012), suggesting an interaction between diabetes, inflammation and cognitive decline. However, modifying the inflammatory pathways in the prevention or treatment of cognitive decline has not yet been tested in human studies.

Effects of cognitive impairment on diabetes management

There is mounting evidence that the relationship between cognitive impairment and diabetes outcomes may be bidirectional. Specifically, cognitive impairment is associated with poorer glycaemic control (Munshi et al, 2006), increased occurrence of severe hypoglycaemia (Punthakee et al, 2012), increased risk of CVD and premature mortality (de Galan et al, 2009). This has potentially important implications for diabetes management in people with both type 2 diabetes and cognitive impairment.

Implications for primary care practice

Diagnosing cognitive impairment in type 2 diabetes

Some people will perceive they have poor memory or experience cognitive difficulty, but there will be no deficit after formal testing, while some people with dementia will not complain of symptoms (Koekkoek et al, 2015). The following steps may help in establishing a diagnosis of cognitive impairment, defining its severity and excluding important differential diagnoses (see *Box 1* for quick guide):

1. Obtain a detailed social history in order to measure the impact of subjective cognitive impairment on day-to-day functioning. Getting a history from a family member is advisable if possible.
2. Exclude other conditions that can also present with cognitive dysfunction, such as depression, and reassess cognition after appropriate treatment.
3. Exclude organic causes of cognitive impairment, such as hypothyroidism, vitamin B12 deficiency, folate deficiency, anaemia, hepatic dysfunction, renal dysfunction and hypercalcaemia.
4. Consider the age of the patient: dementia is rare under the age of 65 years so should prompt thorough evaluation for underlying causes in this age group.
5. Perform a brief cognitive assessment that covers a range of cognitive domains. The MMSE is suitable for this purpose, though several alternatives are now available, such as the General Practitioner Assessment of Cognition (GPAC; Brodaty et al, 2002) and the 7-minute screen (Solomon et al, 1998). The Mini-Cog test (Sinclair et al, 2013) is another brief cognitive assessment tool that is becoming more widely used and has been tested in primary care. Interpretation of scores should take into account educational background and prior level of functioning, as well as any difficulty in hearing, writing or language.

Page points

1. In two high-quality cohort studies, depression has been shown to predict subsequent dementia and cognitive decline in people with type 2 diabetes.
2. There is mounting evidence that the relationship between cognitive impairment and diabetes outcomes may be bidirectional.
3. Assess cognitive function using a tool such as the Mini Mental State Examination (MMSE), General Practitioner Assessment of Cognition (GPAC), 7-minute screen or Mini-Cog test.

Page points

1. The importance of optimising cardiovascular risk factors to prevent cognitive decline should be stressed, and this could also be presented in the clinic as an opportunity to improve or motivate optimum diabetes management.
2. Specific consideration should be given to the management of diabetes itself in people with comorbid type 2 diabetes and dementia because of the increased risk of diabetes mismanagement.
3. Managing people with type 2 diabetes and subjective cognitive deficits is a potentially controversial area.

6. If MCI or dementia is suspected, follow local protocols. NICE guidelines recommend that specialist memory assessment services should be the single point of referral for all people with a possible diagnosis of dementia (NICE, 2006). For MCI, NICE guidelines recommend considering referral to a memory clinic to aid early identification of dementia, as more than 50% of people with MCI later develop dementia (NICE, 2006). In considering such a referral, practitioners should take into account the more frequent progression to dementia seen in people with diabetes.
7. Follow-up is recommended, with repeat cognitive assessment if appropriate.

Preventing cognitive decline in type 2 diabetes

Robust clinical advice on dementia prevention in type 2 diabetes is hampered by the low numbers of clinical trials in this area. Nevertheless, individuals can be advised that CVD, such as stroke, is a robust risk factor for dementia, so prevention should be a priority. In addition, there is some evidence that treatment of vascular risk factors may delay progression from MCI to dementia. Therefore, the importance of optimising cardiovascular risk factors should be stressed, and indeed this could also be presented as an opportunity to improve or motivate optimum diabetes management. A lack of interventional studies means that treatment of depression or reduction in inflammation cannot yet be advocated as an effective means of preventing or delaying cognitive decline.

Box 1. Diagnosis quick-guide for cognitive impairment among people with diabetes.

1. Obtain social history.
2. Exclude other psychiatric diagnoses, such as depression.
3. Exclude organic causes of cognitive impairment, such as biochemical disturbances and vitamin deficiencies.
4. Take into account the age of the individual.
5. Perform a brief cognitive assessment using a validated tool.
6. Follow local protocols and NICE guidelines if mild cognitive impairment or dementia is diagnosed.
7. Follow-up.

Managing people with dementia and type 2 diabetes

If dementia is diagnosed, primary care should working alongside specialist memory services. Specific consideration should be given to the management of diabetes itself because of the increased risk of diabetes mismanagement in people with comorbid type 2 diabetes and dementia. Although there is a lack of specific evidence to guide appropriate adjustment of diabetes treatment in this setting, it seems sensible to reassess the patient's capacities for self-management and treatment adherence, particularly as there is some evidence that safe withdrawal of selected anti-diabetes medications may be feasible among older patient groups (Sjöblom et al, 2008). The International Diabetes Federation (2013) guideline on diabetes in older people includes guidance on target setting in people with dementia and minimising the risk of hypoglycaemia and hypotension. Consider assessing whether intensive treatment goals are still appropriate, although any de-intensification in glycaemic control should be weighed up against the well-established benefits of good glycaemic control, such as in the prevention of microvascular complications. In addition, consider using anti-diabetes medicines that have a lower risk of hypoglycaemia and consider introducing appropriate practical support, such as the use of medication aids, help from carers and regular reminders of appointments. Further practical guidance has been produced by TREND-UK and the Institute for Diabetes in Older People (2013). Sinclair et al (2014) have produced a best clinical practice statement.

Managing people with type 2 diabetes and subjective cognitive deficits

Managing people with type 2 diabetes and subjective cognitive deficits or decrements is a potentially controversial area. Although there is increasing evidence that diabetes is associated with specific, yet subtle, cognitive decrements that are not seen in the non-diabetes population, the evidence for this is not definitive. Some authors advocate using the term diabetes-associated cognitive decrements, as individuals may respond well to the acknowledgement of their subjective cognitive complaints (Koekkoek et al, 2015). However, there

is the potential for psychological distress to be caused as individuals may feel that cognitive decrements are both an inevitable result of diabetes and unlikely to improve. In any case, repeat assessment is important if MCI or dementia is later suspected.

Conclusion

Type 2 diabetes is an established risk factor for both cognitive decline and dementia. Although a lack of high-quality interventional studies prevent specific clinical guidance in many areas, the prevention of CVD is likely to make an important contribution for the prevention of dementia in type 2 diabetes. There is also evidence that cognitive impairment in type 2 diabetes is associated with adverse diabetes outcomes such as poorer glycaemic control, increased episodes of severe hypoglycaemia, increased risk of CVD and premature mortality. This should be considered by primary care practitioners when managing individuals with comorbid type 2 diabetes and dementia. Future interventional studies aiming to reduce cognitive decline – in particular those addressing novel risk factors such as depression – in the primary care setting are keenly awaited. ■

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"There is very good evidence that cognitive impairment in type 2 diabetes is associated with adverse diabetes outcomes, and this should be considered by primary care practitioners when managing individuals with comorbid type 2 diabetes and dementia."