The chicken or the egg? Does glycaemic control predict cognitive function or the other way around?

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Abstract

The association between type 2 diabetes and cognitive dysfunction is well established. Prevention of the development of type 2 diabetes and its complications, as well as cognitive dysfunction and dementia, are leading goals in these fields. Deciphering the causality direction of the interplay between type 2 diabetes and cognitive dysfunction, and understanding the timeline of disease progression, are crucial for developing efficient prevention strategies. The prevailing perception is that type 2 diabetes leads to cognitive dysfunction and dementia. There is substantial evidence showing that accelerated cognitive decline in type 2 diabetes starts in midlife (mean age 40–60 years) and that it may even begin at the prediabetes stage. However, in this issue of *Diabetologia*, Altschul et al (doi: <https://doi.org/10.1007/s00125-018-4645-8>) show evidence for the reverse causality hypothesis, i.e. that lower cognitive function precedes poor glycaemic control. They found that cognitive function at early adolescence (age 11 years) predicts both HbA_{1c} levels and cognitive function at age 70 years. Moreover, they found that lower cognitive function at age 70 is associated with an increase in HbA_{1c} from age 70 to 79 years. Based on these findings, future studies should explore whether developing prevention strategies that target young adolescents with lower cognitive function will result in prevention of type 2 diabetes, breaking the vicious cycle of type 2 diabetes and cognitive dysfunction.

Keywords Adolescence · Cognitive decline · Cognitive function · Dementia · Diabetes · HbA_{1c} · Prevention · Type 2 diabetes

Abbreviations

LBC1936 Lothian Birth Cohort of 1936
MCI Mild cognitive impairment

Introduction

Type 2 diabetes is one of the modern era epidemics [1] and preventing its development and complications are two of the most important goals in the field. Cognitive dysfunction in old

age [2], which is associated with type 2 diabetes [3, 4], might result in another modern era epidemic, dementia. Development of both type 2 diabetes and dementia is partially attributed to modifiable risk factors, including glycaemic control [5, 6]. When developing prevention strategies, several factors must be well defined, including the intervention target, the most susceptible population, and the age range at which the intervention may have the highest preventive potential. In this issue of *Diabetologia*, the study by Altschul et al, which used the Lothian Birth Cohort of 1936 (LBC1936) [7], presents tantalising findings related to the interplay between glycaemic control and cognitive dysfunction. This study examined the association of cognitive function at early life (age 11 years) and late life (age 70 years), and of cognitive decline from age 70 to 79 years, with HbA_{1c} at age 70 and its change from age 70 to 79. The cognitive domains tested were memory, processing speed, visuospatial ability and crystallised ability, which were combined to create a global cognition measure. The authors found that cognitive function at age 11 predicts both HbA_{1c} levels and cognitive function at age 70. They also showed that lower cognitive function at age 70 is associated with an increase in HbA_{1c} from age 70 to 79.

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HbA_{1c} level at age 70 was not consistently associated with cognitive function at age 70 or with the decline of cognitive function from age 70 to 79 [7] (summarised in Fig. 1).

HbA_{1c} is the gold standard measure of glycaemic control and a surrogate for analysis of complications associated with type 2 diabetes [8]. Moreover, HbA_{1c} predicts type 2 diabetes and is useful for identifying individuals with elevated type 2 diabetes risk [9]. Hence, Altschul et al's findings shed light on two important aspects relevant to the development of prevention strategies for both type 2 diabetes and cognitive dysfunction: the direction of causality and the timeline in the interplay of type 2 of diabetes with cognitive dysfunction. Disentangling the direction of causality may help to elucidate the mechanisms of cognitive dysfunction and type 2 diabetes, in order to develop relevant intervention tools. Identifying periods in life when cognitive dysfunction and type 2 diabetes affect each other may point to the most effective window of opportunity for intervention. In this commentary, we elaborate on both of these aspects.

The chicken or the egg: which comes first, poor glycaemic control or cognitive dysfunction?

Type 2 diabetes is associated with elevated risks for cognitive dysfunction, accelerated cognitive decline, mild cognitive impairment (MCI) and dementia [4]. Importantly, type 2 diabetes in midlife (when cognitive dysfunction due to a neurodegenerative process is very rare) has been strongly associated with late-life dementia. This suggests that type 2 diabetes may predict dementia [10]. However, some evidence suggests otherwise, as discussed below.

Fig. 1 A simplified schematic showing the main findings from the study by Altschul [7]. This study examined whether cognitive function at early life (age 11 years) and late life (age 70 years), and cognitive decline from age 70 to 79 years, were associated with HbA_{1c} at age 70 and its change (HbA_{1c} slope) from age 70 to 79. Rectangles represent cognitive function/decline; ovals represent HbA_{1c} level/slope. Arrows indicate associations tested: blue arrows, statistically significant; red arrows, not statistically significant

Type 2 diabetes precedes cognitive dysfunction

The prevailing perception is that type 2 diabetes leads to cognitive dysfunction and dementia. We have recently published a comprehensive summary of 119 studies, comparing cognitive function between individuals without diabetes with that of those with type 2 diabetes in different stages of the disease (prediabetes, newly diagnosed type 2 diabetes, and prevalent type 2 diabetes at midlife, old age and very old age) [3]. There were two main findings from this summary; first, cross-sectionally, elderly individuals (mean age 60–80) with prevalent type 2 diabetes (i.e. who were not newly diagnosed) performed worse in both global cognitive function, as well as the cognitive subdomains tested (memory, attention, executive function, language and perceptual-motor), except for the subdomain of semantic memory. In contrast, other participant subgroups (individuals with prediabetes, newly diagnosed type 2 diabetes, and prevalent type 2 diabetes at midlife or very old age) had similar cognitive function to individuals without diabetes in most cognitive subdomains. Second, longitudinally, the accelerated cognitive decline over time in type 2 diabetes in most cognitive subdomains is most evident in midlife [3] and might even begin at the prediabetes stage [11], suggesting that the deleterious effects of type 2 diabetes on the brain may begin early in the type 2 diabetes process.

Additionally, characteristics related to type 2 diabetes, including higher blood glucose levels, higher serum fasting insulin and insulin resistance [12–14], have been linked to cognitive dysfunction, accelerated cognitive decline and dementia in elderly individuals, even in those without diabetes [14, 15]. Moreover, in addition to blood glucose and HbA_{1c} levels, poor long-term HbA_{1c} trajectories [16] and glucose peaks [17] have been shown to be associated with cognitive function.

Although it may seem surprising that Altschul et al [7] did not find an association of HbA_{1c} level at the age of 70 with cognitive function at the same age, or with cognitive decline at age 70–79, a few possible explanations are proposed. As noted above, individuals with prevalent type 2 diabetes have poorer cognitive function than those without diabetes. The main analyses by Altschul et al were not stratified by type 2 diabetes diagnosis [7], possibly masking the association of HbA_{1c} with cognition, which is stronger among individuals with type 2 diabetes [18]. This is particularly relevant in the LBC1936 cohort, where the prevalence of type 2 diabetes is relatively low (7–12% depending on the year of assessment). The prevalence of type 2 diabetes in the Lothian region for individuals aged over 65 years is 15% [19], and in the United States it is 20% [20]. This interpretation is reinforced by the results of the secondary analyses which excluded participants with type 2 diabetes patients, as effect sizes were slightly reduced, suggesting that even the very small number of individuals with type 2 diabetes had a substantial impact on the results. Also, the use of medication for type 2 diabetes, which

was not specified in the study, might have normalised or improved glycaemic control in those taking it, further masking potential associations between HbA_{1c} and cognition.

The lack of an association between HbA_{1c} and cognitive decline at age 70–79, may be additionally explained by the cognitive domains assessed in the study, which included memory, processing speed, visuospatial ability and crystallised ability. In previous studies, type 2 diabetes status has not been associated with decline in these domains in participants within the same age range [21–24]. In contrast, other studies found greater decline in other cognitive domains, such as attention, executive functions, motor and perceptual abilities, when compared with individuals without diabetes [24–27]. This reflects the complexity of the relationship between type 2 diabetes and cognition, suggesting that type 2 diabetes may affect specific brain regions that underlie particular cognitive functions [28].

Lower cognitive dysfunction precedes type 2 diabetes

Contrary to the predominant perception, Altschul et al's findings [7] present evidence for an alternative hypothesis of reverse causality: lower cognitive function leads to poor glycaemic control. This is consistent with previous studies by the same research group, where cognitive function at age 11 has been shown to be associated with type 2 diabetes status and HbA_{1c} levels at the age of 70 [29, 30]. In line with this, lower cognitive function at late adolescence (age 17 years) has been associated with elevated risk for impaired fasting glucose and future type 2 diabetes [31, 32]. Furthermore, Altschul et al [7] showed that poorer cognitive function at the age of 70 is associated with increasing HbA_{1c} levels over the following decade.

The reverse causality hypothesis has several possible explanations. Poor cognitive function may lay the foundation for 'health illiteracy' and poor health management skills, such as physical inactivity, that increase the risk of type 2 diabetes and its risk factors (e.g. obesity) [33]. The attenuation of the association between cognitive function at age 11 and type 2 diabetes at the age of 70 after adjusting for BMI and cholesterol level support this explanation [30]. An alternative explanation for the reverse causality hypothesis is that there is a third common driver for both cognitive dysfunction and type 2 diabetes, such as a pleiotropic gene, similar to the pleiotropic genes that lead to both type 2 diabetes and obesity independently [34].

A 'vicious cycle' of type 2 diabetes and cognitive dysfunction

The two hypotheses described above may not be mutually exclusive. For example, early-life lower cognitive function might lead to type 2 diabetes, which then might lead to worse cognitive function, eliciting a 'vicious cycle'. Difficulties in performing self-care tasks, such as glucose monitoring and

adhering to diet and medication (including adjustment of insulin dose), possibly contributes to this vicious cycle [35]. These difficulties might result in higher prevalence of hyperglycaemic and hypoglycaemic states, both of which may aggravate type 2 diabetes complications, including deterioration of cognitive function [36, 37]. Since hypoglycaemia is the main limiting factor in glucose-lowering therapy, with possibly fatal outcomes, the ADA recommends relaxed glycaemic goals for patients with even MCI; the recommended target HbA_{1c} is <64–69 mmol/mol (<8.0–8.5%) for these individuals, whilst for patients with type 2 diabetes with few coexisting chronic illnesses and intact cognitive function, it is 58 mmol/mol (7.5%) [35].

Timeline of the interplay between type 2 diabetes with cognitive dysfunction

Both type 2 diabetes and dementia are often perceived diseases of older age. However, the preclinical incipient period (i.e. when insulin resistance and beta cells dysfunction develop in diabetes or dementia-related neuropathology aggregation commences) begins years, if not decades before clinical symptoms are manifested [38, 39]. Thus, prevention of these diseases must begin at early stages, although the precise time point for intervention is unknown and may depend on individual variability. The association between cognitive function in early adolescence (age 11) and type 2 diabetes risk in older age (age 70) [7, 29, 30] suggests that targeting individuals with lower cognitive function at a young age may improve life-long health. Promoting health education and awareness, and encouraging healthy behaviours may help to prevent type 2 diabetes or ameliorate its effects, possibly 'breaking' the vicious cycle. However, further studies are required before it is clear at what ages such interventions would be effective.

Perspective

In this commentary, we have presented some of the findings related to the interplay of type 2 diabetes with cognitive dysfunction. These findings provide additional evidence in favour of the development of strategies for prevention of both conditions. Since accelerated cognitive decline in type 2 diabetes begins in the first few years following type 2 diabetes diagnosis [3], and possibly even in the prediabetic stage [11], efforts to prevent diabetes and, thus, cognitive decline (as well as other complications of type 2 diabetes), should start then. This does not detract from late-life efforts to prevent type 2 diabetes complications, which include cognitive dysfunction. Even among elderly individuals with type 2 diabetes, good trajectories of glycaemic control are associated with better cognitive function [16]. However, long-term damage from the interplay between

hyperglycaemia and cognitive dysfunction may limit effectiveness of preventive interventions in old age.

In addition, the findings by Altschul et al [7], along with others [29–32], support the concept that early-life cognitive function is associated with the risk for developing type 2 diabetes (or related characteristics, such as poor glycaemic control) in late life. This underlies the hypothesis that early adolescents with lower cognitive function may be at risk for developing type 2 diabetes later in life, and that there may be value in targeting preventive intervention strategies at this age group. Of course, decreasing type 2 diabetes risk in late life (and possibly dementia risk) by improving early-life health literacy and other relevant modifiable lifestyle factors, is an enormous endeavour that must be examined empirically.

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