Cognition in Adults and Older Adults With Type 1 Diabetes: Chicken or Egg?

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IN BRIEF Cognitive impairment and cognitive decline are common in adults with type 1 diabetes. Although several diabetes-related variables have been associated with cognitive functioning in both cross-sectional and longitudinal studies, inconsistencies remain. This is particularly true in older adults. Cognitive impairment appears to be both a consequence of and a risk factor for poor diabetes self-management and associated glycemic outcomes. Interventions such as cognitive compensatory strategies, assistive technology, and simplified treatment regimens may limit the impact of cognitive impairment on self-management in adults and older adults with type 1 diabetes.

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As described by Cato and Hershey in this issue (p. 197), it is well established that children and adolescents with type 1 diabetes have small but significant cognitive impairments relative to control subjects, with greater impairment in those with certain diabetes-related risk factors. However, questions remain about the course of cognitive change into adulthood and old age in those with type 1 diabetes.

Cognitive Impairment in Adults

As in the literature regarding children and adolescents, there is general consensus from cross-sectional studies that type 1 diabetes is associated with cognitive deficits in adults compared to normal control subjects (1–3). In a meta-analysis of 33 studies of cognition in adults with type 1 diabetes, Brands et al. (1) reported poorer performance compared to control subjects in the domains of intelligence, information processing speed, psychomotor efficiency, attention, cognitive flexibility, and visual perception (d = 0.3–0.7). However, in adults with childhood-onset type 1 diabetes, these differences could represent stable cognitive impairments since childhood, with some authors speculating that there is no further cognitive decline in adults apart from the cognitive effects of diabetes complications (4). In an attempt to address this issue, a meta-analysis of 55 studies (32 in adults and 23 in children) found cognitive differences in more cognitive domains and larger effect sizes in adult compared to child samples (5). This could indicate that the brain continues to be vulnerable to damage associated with type 1 diabetes in adulthood. In support of this hypothesis, Nunley et al. (6) reported more pronounced cognitive impairment in middle-aged adults with type 1 diabetes (28% impaired; mean age 49 years) and twice the rate of clinically significant cognitive impairment compared to that reported in child samples (6).

Cognitive Decline in Adulthood

The Diabetes Control and Complications Trial (DCCT) and its subsequent follow-up study measured cognitive functioning from early adulthood to middle age (7). This large and comprehensive study found no evidence of marked cognitive decline over 18 years in the overall cohort. This study has been regarded by some as definitively determining that cognition does not change over time in adults with type 1 diabetes.

Although it is certainly an important study and has contributed much to our understanding of the value of intensive glycemic control with regard to complications, there are several limitations that need to be considered when interpreting the DCCT cognitive data. First, this sample does not appear to be representative of the broader adult population with type 1 diabetes. The majority of participants were diagnosed as adults (mean age 27 years at enrollment with average duration of 6 years), and, more importantly, the average IQ at enrollment was 114 (high average). Furthermore, cognitive performances were at or above the performance of normal control participants on nearly all cognitive tests, and the majority of participants were employed in professional or technical occupations. Given the protective effect of higher cognitive functioning or "cognitive reserve" on cognitive decline (8), a sample with less impressive cognitive skills at baseline may be more vulnerable to brain dysfunction over time. Additionally, the investigators used an average of individual test z scores to calculate cognitive domain scores. Although this reduces the risk for type 1 error associated with multiple comparisons, it can result in above-average test scores canceling out below-average or impaired scores within domains, which would reduce the likelihood of detecting meaningful cognitive impairment if only some tests within a domain were sensitive to type 1 diabetes–related cognitive decline.

In contrast to the DCCT findings, Ryan et al. (9) reported that 39% of their middle-aged sample (average age 40 years) had a cognitive decline of at least 0.5 SD in processing speed over 7 years.

Cognitive Decline and Dementia in Older Adults

As a result of advances in medical treatment, the life expectancy of people with type 1 diabetes has increased, resulting in a growing population of older adults with the disease (10). There is a paucity of research on the cognitive status of this population, however.

Although there are strong associations between type 2 diabetes and cognitive decline and dementia in older adults (11–18), the nature, severity and risk factors for, and trajectory of cognitive impairment in older adults with type 1 diabetes are less clear. No longitudinal studies have reported the incidence of dementia in type 1 diabetes or risk factors for conversion from mild cognitive impairment (MCI) to dementia. However, recent evidence from a national retrospective cohort study from England (19) suggests that type 1 diabetes is associated with increased vascular dementia risk. In contrast, there is also speculation that type 1 diabetes may protect older adults from Alzheimer's disease due to the protective effects of exogenous insulin in the brain (20).

The only longitudinal study in older adults (average age 60 years) with type 1 diabetes (21) reported mild information processing speed deficits compared to matched control subjects at baseline but no significant cognitive decline over 4 years. Incident severe hypoglycemic events and cardiovascular events were associated with declines in information processing speed, however. Of note, this was a small sample (n = 36), so the study may have been underpowered to detect other variables associated with cognitive decline. Given the absence of robust longitudinal data on cognition in those >60 years of age, it is not known how the preexisting cognitive weaknesses associated with type 1 diabetes are affected by the aging process.

Risk Factors

It is clear that not all adults with type 1 diabetes have cognitive impairment. It is important to identify cognitive risk factors for several reasons: *1*) to understand mechanisms underlying cognitive impairment in type 1 diabetes, *2*) to potentially modify risk, and *3*) to appropriately refer at-risk patients for detailed evaluation and recommendations regarding the potential impact of cognitive impairment on self-management and other aspects of daily living. It is important to note that, although adults with type 1 diabetes diagnosed in childhood retain the same risk factors for cognitive impairment present in that age-group (see Cato and Hershey in this issue, p. 197), those diagnosed as adults may have a different set of risk factors for cognitive decline. For example, diabetic ketoacidosis, a risk factor for cognitive impairment in children, may not be a risk factor for cognitive impairment in those diagnosed as adults, given evidence that the developing brain may be at greater risk for adverse effects of glycemic extremes (4).

Age of Onset and Duration of Diabetes

Age of onset and duration of type 1 diabetes have been linked to cognitive ability in adult samples (5,22–24). Ferguson et al. (24) found that adults with early-onset diabetes (n = 26) had lower current intellectual ability (Wechsler Adult Intelligence Scale–Revised performance IQ, P = 0.03) and information processing ability (Choice Reaction Time, P = 0.006) than those with later-onset diabetes (n = 45). Furthermore, lateral ventricular volumes were 37% greater (P = 0.002), and ventricular atrophy was more prevalent (61 vs. 20%, P = 0.01) in the early-onset group. In addition, in a sample of 150 adults with type 1 diabetes, Brismar et al. (22) reported that age of onset and duration of diabetes were the strongest predictors of neuropsychological performance, with long diabetes duration and young age of onset predicting low scores in psychomotor speed, memory, processing speed, attention, working memory, verbal ability, general intelligence, executive functions, and global score.

Diabetes Complications

Micro- and macrovascular complications of diabetes, including retinopathy and neuropathy, have been consistently linked to greater cognitive impairment in adult samples (9,25–27). Using meta-analysis, Brands et al. (1) reported that cognitive deficits in adults with type 1 diabetes were associated with microvascular complications. Retinopathy and polyneuropathy measured 5 years before cognitive testing were predictive of poorer cognitive functioning in middle-aged adults (6). In addition, brain white matter disease occurred earlier and was associated with neuropathy and slowed cognition (28). In a longitudinal study of middle-aged adults with type 1 diabetes (9), the development of proliferative retinopathy and autonomic neuropathy predicted decline in psychomotor speed (P <0.01), as did incident macrovascular complications (P <0.05).

Glycemic Extremes

The relationship between glycemic extremes (i.e., hypoglycemia and hyperglycemia) and cognitive functioning remains controversial. In the DCCT, there was no evidence of greater cognitive decline associated with incident severe hypoglycemic episodes, and other studies have also failed to find an association between a history of severe hypoglycemic events and cognitive functioning (1). However, there is an apparent link between hypoglycemia and cognitive impairment in older adults with type 2 diabetes (29–31), and a recent case-control study found that older adults with type 1 diabetes who had recent severe hypoglycemic events had poorer cognitive functioning than those who had not had an event in the past 3 years (32). Thus, the neurological effects of severe hypoglycemia may be greatest during early development and during age-associated neurodegeneration (4).

As described by Cholerton et al. in this issue (p. 210), chronic hyperglycemia has been linked to cognitive decline and dementia risk in type 2 diabetes (18,33). This also appears to be the case in type 1 diabetes. DCCT investigators reported declines in motor speed and psychomotor efficiency (but not in other cognitive domains) in those with the highest A1C (>8.8%) over 18 years in their now middle-aged sample (7). Likewise, average A1C over the previous 14 years was associated with cognition in midlife (6). However, Brands et al. (1) did not find a relationship between cognition and A1C in their meta-analysis.

Implications for Self-Management

Researchers studying the relationship between cognitive functioning and chronic disease typically have assumed that chronic disease causes cognitive impairment. However, cognition also may be a risk factor for outcomes in chronic conditions with high self-management demands. For example, there is evidence that lower cognitive ability precedes obesity (34) in children who later become obese. This concept of "reverse causality" provides a rationale for a novel approach to behavioral intervention based on individual cognitive risk factors and using cognitive compensatory strategies, prompts, and environmental modifications to improve patients' adherence to self-management behaviors despite cognitive barriers.

Fluid Cognition Declines With Age and Is Related to Medical Self-Management

Fluid cognition is a broad descriptor of a diverse set of discrete cognitive skills, including executive functioning, working memory, prospective memory, episodic memory, mental flexibility, attention, and complex processing speed and is highly sensitive to the effects of normal aging (35). Many of these cognitive skills also have been linked to medication self-management among diverse populations, including those with HIV (36,37), MCI and dementia (38), and Parkinson's disease (39).

Executive functioning is the most consistently cited cognitive domain in research focused on predicting instrumental activities of daily living in older adults (40) and neurological populations (41). Of note, longitudinal decline in executive functioning and memory is associated with concomittant decline in instrumental activities of daily living in older adults both with and without MCI (38). Typically, when evaluating cognition in older adults, researchers control for the effects of normal age-related cognitive decline. Although this is appropriate when diagnosing a pathological disease state, it may not be appropriate when determining risk for medical mismanagement. It is possible that *even normal age-related decline, coupled with the high demands of managing type 1 diabetes, could result in self-management problems*. It is therefore crucial to identify the level of absolute cognitive performance that increases risk for self-management problems, even within the normal range.

Cognitive Impairment Is a Risk Factor for Poor Diabetes Self-Management

Although data in adults with type 1 diabetes are scarce, cognitive performance in older adults is associated with performance on simulated cognitively demanding diabetes self-management tasks (42). There is also evidence that cognition predicts self-management ability in children with type 1 diabetes and adults with type 2 diabetes. McNally et al. (43) used structural equation modeling to demonstrate that treatment adherence mediated the relationship between executive functioning and glycemic control in their sample of youth with type 1 diabetes. The alternative model (that adherence led to glycemic control, which in turn led to executive dysfunction) was not supported by the data. There are also increasing data suggesting that cognitive performance predicts type 2 diabetes self-management (44–46). Most studies have focused on the important role of executive functioning (i.e., planning, problem-solving, and mental flexibility) in managing diabetes.

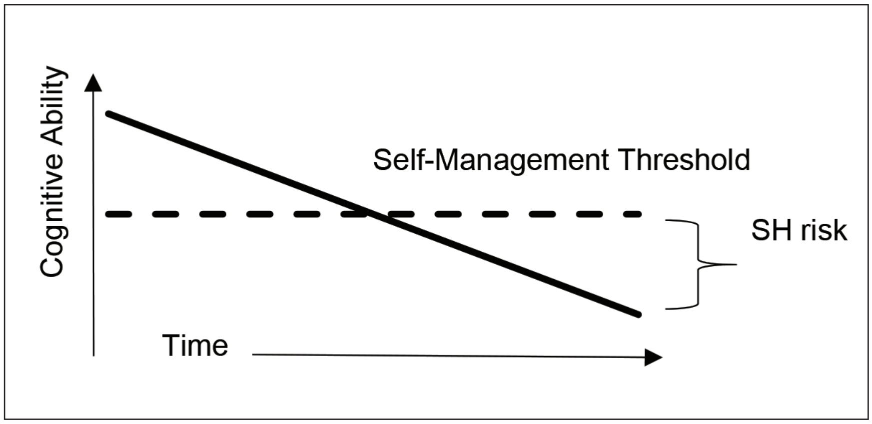

FIGURE 1. Hypothesized model linking cognitive decline, self-management, and severe hypoglycemia (SH) risk.

Prevention of hypoglycemic events is a key self-management task that may be affected by cognitive function. The ACCORD-MIND trial (47) in patients with type 2 diabetes found that cognitive performance at baseline predicted hypoglycemic episodes at the 20-month follow-up in those with no baseline hypoglycemia. In addition, this trial found that cognitive decline from baseline to 20 months was predictive of hypoglycemic episodes at 20 months for those patients who began the trial with average or lower cognitive ability. These data indicate that cognitive ability must cross a functional threshold to begin to affect self-management and hypoglycemia risk (Figure 1). In another longitudinal study in type 2 diabetes, lower cognition at baseline was associated with a twofold higher risk of incident severe hypoglycemia over the next 4 years, and previous hypoglycemia also was associated with steeper cognitive decline (30). Executive functioning, processing speed, and memory (i.e., fluid cognition) had the strongest associations with hypoglycemia. It is possible that those with declining cognition are less able to prevent, recognize, and treat hypoglycemia.

Psychosocial and Demographic Factors

Of course, psychosocial variables such as depression (48,49), diabetes distress (50,51), self-efficacy (52), social support (53), and hypoglycemia fear (54) are associated with type 1 diabetes self-management. Demographic factors, including age, sex, and socioeconomic status (i.e., education, income, and insurance status), also have been linked to self-management behaviors (55,56). It is therefore important to account for these factors in addition to cognitive impairment.

Future Directions

It is evident from this summary of the literature on cognitive functioning in adults with type 1 diabetes that many questions remain unanswered. Overall, as a group, adults with type 1 diabetes have poorer cognitive performance than those without. Younger age of onset, longer diabetes duration, presence of diabetes complications, and chronic hyperglycemia are associated with poorer performance and greater decline. Cognitive problems in adults with type 1 diabetes appear to be primarily in fluid cognition (i.e., processing speed, executive functioning, and memory), although other domains also can be affected. More research is needed to better understand the course and magnitude of cognitive change over time, particularly in older adults, and the implications of cognitive change on diabetes self-management. With this knowledge, cognitive rehabilitation approaches could be developed to compensate for changing cognition and lessen its impact on diabetes self-management and quality of life. Elsewhere in this issue (p. 224), Hopkins et al. provide an excellent summary of practical strategies that may be beneficial in this regard.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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