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Review

Type 1 Diabetes Mellitus and Cognitive Impairments: A Systematic Review

Wei Li[a,*], Edgar Huang[b] and Sujuan Gao[c]
[a]*Master of Physician Assistant Studies, School of Health and Rehabilitation Sciences, Indiana University-Purdue University Indianapolis, Indianapolis, IN, USA*
[b]*School of Informatics and Computing, Indiana University-Purdue University Indianapolis, Indianapolis, IN, USA*
[c]*Department of Biostatistics, School of Medicine, Indiana University, Indianapolis, IN, USA*

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Abstract. Type 1 diabetes mellitus (T1DM) is a major subtype of diabetes and is usually diagnosed at a young age with insulin deficiency. The life expectancy of T1DM patients has increased substantially in comparison with that three decades ago due to the availability of exogenous insulin, though it is still shorter than that of healthy people. However, the relation remains unclear between T1DM and dementia as an aging-related disease. We conducted a systematic review of existing literature on T1DM and cognition impairments by carrying out searches in electronic databases Medline, EMBASE, and Google Scholar. We restricted our review to studies involving only human subjects and excluded studies on type 2 diabetes mellitus or non-classified diabetes. A meta-analysis was first performed on the relationship between T1DM and cognitive changes in youths and adults respectively. Then the review focused on the cognitive complications of T1DM and their relation with the characteristics of T1DM, glycemic control, diabetic complications, comorbidities, and others. First, age at onset, disease duration, and glycemic dysregulation were delineated for their association with cognitive changes. Then diabetic ketoacidosis, angiopathy, and neuropathy were examined as diabetic complications for their involvement in cognitive impairments. Lastly, body mass index and blood pressure were discussed for their relations with the cognitive changes. Future studies are needed to elucidate the pathogenesis of T1DM-related cognitive impairments or dementia.

Keywords: Cognitive impairments, diabetic ketoacidosis, microangiopathy, severe hypoglycemia, type 1 diabetes mellitus

INTRODUCTION: T1DM AND THE RISK OF DEMENTIA

As a major subtype of diabetes, type 1 diabetes mellitus (T1DM) accounts for about 5% of all diabetic cases [1]. The main feature of T1DM is insulin deficiency, and patients with T1DM are treated with different types of exogenous insulin (rapid-, short-, intermediate-, and long-acting insulin). Thus, T1DM is also called insulin-dependent diabetes mellitus.

Although their life span expectancy is still shorter than that of healthy people, T1DM patients now live much longer than they did three decades ago due to the availability of exogenous insulin [2, 3]; the prolonged life span thus makes them at risk for the aging-related disease: dementia. In one retrospective study, the risk ratio for dementia in hospital-admitted T1DM patients is 1.65 times over the non-diabetic controls [4]. However, the study sample is not representative of the T1DM patient population as most T1DM patients are on an outpatient insulin treatment

*Correspondence to: Dr. Wei Li, Master of Physician Assistant Studies, School of Health & Rehabilitation Sciences, Indiana University Purdue University Indianapolis, 2039 N. Capitol Avenue, Indianapolis, IN 46202, USA. Tel.: +1 317 278 9575; Fax: +1 317 278 9555; E-mail: wl23@iu.edu.

plan. Therefore, how T1DM is related to dementia or cognitive impairments is an unanswered question for T1DM patients and healthcare providers.

We conducted a systemic review by searching the electronic databases Medline, EMBASE, and Google Scholar with the following keywords: type 1 diabetes, insulin-dependent diabetes mellitus, cognitive impairment, and dementia. After removing duplicates and review articles, the original search returned a total of 310 results. After the abstracts were examined, 215 studies were excluded from further analysis as they were either totally irrelevant ($n = 135$) or on type 2 diabetes mellitus ($n = 38$), animal models ($n = 13$), or non-classified diabetes ($n = 29$). The current review has focused on the 59 original reports published on or after the year of 1990 from the remaining studies ($n = 95$).

COGNITIVE CHANGES IN T1DM PATIENTS

Cognitive impairment refers to a continuum of severity from "mild," which might be noticed by the patient or healthcare providers, to "severe," such as dementia, which interferes with activities of daily life or disallows a patient to function without assistance. As age is an important factor for cognitive impairments, cognitive changes were reviewed separately in young or adult T1DM patients based on their age at the time of neuropsychological assessments. For young T1DM patients, the cognitive function or performance is presented in Table 1. Impaired executive functions [5] and motor speed task [6] are seen in young T1DM patients between 9 years old and 19 years old (Table 1). In another study, a worse performance on visual-spatial ability and memory is shown in pediatric T1DM patients than the control group [7]. In addition, lower verbal intelligence is observed in the young T1DM group than the non-diabetic control group [8, 9] (Table 1). However, the association between T1DM and impaired cognitive functions has not been observed in other studies. For example, no significant difference was found from a prospective study between young adults with early-onset T1DM and controls in general intellectual ability, memory, and emotional difficulties [10] (Table 1). Although students with T1DM had a significantly lower academic performance than their non-diabetic classmates [11] (Table 1), they and their unaffected siblings had no significant differences on measures of cognitive performance, academic achievement, or speech ability [12] (Table 1).

For adult T1DM patients, cognitive impairments were consistently reported from different studies [13–15] (Table 2). In one study, the incidence rate of cognitive impairments was 28% among adult patients with childhood-onset T1DM compared to 5% in those without diabetes, though the study had a relatively small sample size and only included T1DM cases with a childhood-onset [14]. Different types of cognitive functions are impaired in adult patients with T1DM. For example, the adult T1DM patients have a worse performance in memory than nondiabetic controls [16] (Table 2).

In addition, adult T1DM patients have significantly reduced psychomotor efficiency [16, 17], sustained

Table 1
Cognitive function changes were studied in children/young adults (≤22-years-old) with T1DM. Patient age, age at onset of T1DM, and disease duration are presented as mean ± standard deviation followed by range in years

Study Design	T1DM Patient Age (y)	Sample Size (n)	Cognitive Function Changes versus Controls	Age at Onset (y)	Disease Duration (y)	References
Case-control	(9–19)	70	Impaired executive functions: concept formation, cognitive flexibility, and anticipation	<6 ($n = 13$); ≥6 ($n = 55$)	0.9–13.7	[5]
Case-control	(9–18)	25	Impaired motor speed task			[6]
Case-control	(4–16)	119	Worse visual-spatial ability and memory		≥2	[7]
Cross-sectional	16.2 ± 3.1 (9–22)	61	Lower verbal intelligence	6.7 ± 2.9 (1–13)	9.4 ± 2.6 (5–17.7)	[8]
Case-control	12.1 ± 2.9	117	Lower verbal intelligence	6.8 ± 3.3	≥2	[9]
Prospective Cohort	19.3 ± 0.5	33	No significant changes	3.3 ± 0.3	16.0 ± 0.5	[10]
Cross-sectional	17.0 ± 0.5 (14.2–19.4)	36	Lower academic performance		6.1 ± 0.7	[11]
Case-control	12.4 ± 3.0 (6–20)	27	No significant difference in academic performance or cognitive functions	<5		[12]

Table 2
Cognitive function changes were studied in adult patients (>22 years old) with T1DM. Patient age, age at onset of T1DM, and disease duration are presented as mean ± standard deviation followed by range in years

Study Design	T1DM Patient Age (y)	Sample Size (n)	Cognitive Function Changes versus Controls	Age at onset (y)	Disease Duration (y)	References
Cross-sectional	43.3 ± 7.8	150	Cognitive impairment	17.2 ± 11.2	26.6 ± 11.4	[13]
Case-control	49.1 ± 6.6	97	Cognitive impairment	8.0 ± 4.2	41.0 ± 6.2	[14]
Case-control	39.2 ± 6.7	55	Cognitive impairment		(6–35)	[15]
Cross-sectional	32.3 ± 4.4	123	Lower performance in memory, executive function, and psychomotor speed	12.5 ± 5.2	19.9 ± 3.5	[16]
Case-control	40.4 ± 6.2	103	Decreased psychomotor efficiency	8.9 ± 3.9	31.5 ± 7.0	[17]
Case-control	43.4 ± 1.1	122	Impaired sustained attention	18.2 ± 1.0	25.4 ± 1.0	[18]
Case-control	60.9 ± 6.0	40	Slower information processing speed	≤18 (n = 14); >18 (n = 26)	34.0 ± 12.8	[19]

attention [18], and information processing speed [19] (Table 2). Lastly, adult patients with T1DM have impaired executive functions in concept formation, cognitive flexibility, and anticipation [16] (Table 2).

AGE AT ONSET, DISEASE DURATION, AND COGNITIVE IMPAIRMENTS

T1DM usually has an early age at onset (AAO) and is most often diagnosed in children and young adults; therefore, T1DM is also called juvenile diabetes. The developing brain might be more vulnerable to the effects of dysglycemia in young T1DM patients [20]. The AAO is an important characteristic of T1DM for influencing cognitive functions in patients with T1DM. A worse cognitive performance is usually associated with an earlier AAO. For example, learning and memory skills are more affected in pediatric T1DM patients with early onset than those with late onset [21]. Pathologically, more atrophic cerebral structural changes are found in early-onset than in late-onset young T1DM patients. Moreover, the medial prefrontal regions, insula, and cerebellum are the known rapidly developing brain regions in children, who are significantly affected by the early-onset T1DM [22]. These structural changes of decreased gray matter volume might have long-term effects on the cognitive functions.

Similarly, current intellectual ability and information processing ability are poorer in young adults with early-onset T1DM (<7 years old) than those with late-onset (7–17 years old) T1DM [23]. The fact that there is more prevalent central brain atrophy in the early onset T1DM group than in late-onset T1DM group suggests an organic contribution to different cognitive performance between the two groups. Further, the neurodevelopment in children may be affected by early-onset diabetes, which might have long-term consequential cognitive deteriorating effects [23].

Disease duration is another important characteristic of T1DM, which is inversely associated with cognitive performance. Together with AAO, disease duration has been reported to be strong predictors for impaired cognition functions in psychomotor speed, memory, processing speed, attention, working memory, verbal ability, general intelligence, and executive function in adult T1DM patients [13]. In addition, a delayed recall task performance is inversely related to the disease duration [24]. Further, disease duration could effectively predict the psychomotor speed decline in adult patients with T1DM [17]. However, the relationship between disease duration and cognitive changes has to be analyzed by taking into consideration the age factor. Not surprisingly, in one study, cognitive impairments in adolescent T1DM patients were reported to be independent of both glycemic control and disease duration, [5], and the finding suggested that T1DM might have direct pathological effects on cognitive functions.

GLYCEMIC CONTROL IN PATIENTS WITH T1DM

Although different types of exogenous insulin are available for optimizing glycemic control, T1DM patients could not regulate their glucose metabolism as effectively as a healthy person with the endogenous insulin can. Ironically, insulin therapy itself is associated with conditions of either hyperglycemia or hypoglycemia [25]. For example, insulin treatment is shown to be associated with the incidence rate of hypoglycemia in pediatric T1DM patients (9–15 years old) [26]. In addition, the glycemic control usually deteriorates along with the increasing duration

of T1DM [5]. Thus, either hyperglycemia or hypoglycemia or both are commonly seen in patients with T1DM.

HYPERGLYCEMIA AND COGNITIVE CHANGES

Hyperglycemia can be either chronic or induced acutely by using experimental technologies [27]. Chronic hyperglycemia is shown to be associated with low general cognitive abilities, slow fine motor speed, and low receptive language function among pediatric T1DM patients (<6 years old) [28]. Spelling performance is also reduced in the youth with T1DM and with increased exposure to chronic hyperglycemia in terms of disease duration and level of hyperglycemia [8]. In adult T1DM patients, poor performance on psychomotor tasks, slow mental subtraction speed, and increased subtraction errors are seen as the effects of acute hyperglycemia when the blood glucose is above15 mmol/L [29]. In addition, among middle-aged participants with T1DM, cognitive impairments are associated with chronic hyperglycemia [14]. Although most studies have shown that the chronic hyperglycemia is associated with the cognitive changes in T1DM patients, the same relationship is not observed on the long-term spatial memory performance in children with T1DM (6–18 years old) [30].

It is worthy to note that AAO may interact with hyperglycemia for influencing cognitive functions in T1DM patients. For instance, hyperglycemia is negatively correlated with visual-spatial ability in young T1DM patients, and the correlation is stronger in these patients with an early AAO than in those with late AAO [7]. The level of hyperglycemia is another important factor for influencing cognitive functions. For instance, the level of hyperglycemia is negatively associated with intelligence and information processing speed in pediatric T1DM patients [7]. In addition, a higher HbA1c at T1DM diagnosis in young patients (7–17 years old) is associated with a worse performance on the long-delay spatial delayed response task [31] as well as lower psychomotor and mental efficiency in adolescents (13–19 years old) [32]. Even an acute hyperglycemia achieved with a modified clamp technique is associated with impaired complex cognitive function in children with T1DM [27]. When blood glucose is in the 20– to 30–mmol/L range, the children's intelligence quotient is reduced by 9.5%. Also, HbA1c values are negatively associated with declines in motor speed and psychomotor efficiency, according to another study that involved a mixed age group of T1DM patients (13–39 years old [33]). Therefore, the effects of chronic hyperglycemia on cognitive performance are associated with the AAO of T1DM, T1DM duration, or both.

HYPOGLYCEMIA AND COGNITIVE FUNCTIONS

Hypoglycemia, another condition commonly seen in T1DM patients, has been studied for its relationship with cognitive changes as well. Attention flexibility [34], spatial ability [35], and speed of information processing [34] are impaired with hypoglycemia. Early visual information processing and contrast sensitivity are also impaired during hypoglycemia in adult T1DM patients [36]. In addition, psychomotor speed and reaction speed are significantly decreased during hypoglycemic episodes (based on home blood glucose readings) for school-aged children [37]. Besides the AAO, frequency of hypoglycemia seems to play an important role in the cognitive changes seen in T1DM patients. For instance, spatial intelligence and delayed recall are reduced only with repeated hypoglycemic episodes, particularly when those hypoglycemic episodes occur before the age of 5 [9]. However, the association between hypoglycemia and cognitive impairments has not been observed in other reports. For example, verbal intelligence is not lowered by increased exposure to hypoglycemia in young T1DM patients (5–17 years old) [9], and the number of prior hypoglycemic events is not associated with any changes in the cognitive functions in adult T1DM patients [13]. Moreover, sustained attention and intelligence are preserved during hypoglycemia induced with a hyperinsulineamic glucose clamp in adult T1DM patients [34].

SEVERE HYPOGLYCEMIA AND COGNITIVE FUNCTIONS

As the most serious side effect of insulin therapy, severe hypoglycemia (SH) affects 30–40% of T1DM patients [33, 38]. The risk of contracting SH increases with unawareness of hypoglycemia as well as increased glucose variability in adult patients with long-standing T1DM [39]. SH is defined as having low blood glucose level that requires the help of others for the treatment. In addition, patients with concurrent hypoglycemia (<70 mg/dL but

$\geq$ 40 mg/dL) and coma or seizure are also classified as having SH [10]. The association between SH and cognitive function changes has not been observed in young T1DM patients. For instance, a history of SH is not associated with the cognitive decrements in a T1DM patient group between 13 years old and 39 years old in a longitudinal study [40]. Moreover, SH is not associated with changes in either academic abilities [8, 21] or any other cognitive functions in children with T1DM [41]. Furthermore, it is still debatable how frequency of SH and AAO affect the cognitive functions in T1DM patients [33]. For example, children with an SH history have more neuropsychological impairments than those without it [42]. In addition, high frequency of and early exposure to SH in children with T1DM negatively affects spatial long-term memory performance [9, 30]. Nevertheless, one study reports that SH does not cause cognitive dysfunction in children even with severe hypoglycemia occurring during early childhood (<6 years old) [43]. By contrast, type 1 diabetic patients with recurrent SH are shown to have worse cognitive functions than those without a history of SH [44, 45].

DKA AND COGNITIVE FUNCTIONS

Diabetic ketoacidosis (DKA) is a very serious complication of T1DM that can lead to coma or death. This condition happens when the body does not have enough insulin for regulating glucose metabolism and when increased ketone production leads to metabolic acidosis. The prevalence rate of DKA varies from 20.9% to 75% in newly diagnosed T1DM patients, and the average rate is 38.8% [46–53]. The DKA is shown to be a risk factor for cognitive impairments in patients with T1DM. Pediatric patients with newly diagnosed T1DM and DKA show a definite trend for having worse cognitive functions than the age-matched T1DM patients without DKA [54]. For example, young T1DM patients with DKA at the time of diabetes diagnosis perform worse on the spatial delayed response task than their non-diabetic sibling controls [31]. A history of DKA is also correlated with lower verbal intelligence quotient in children with T1DM [55]. In addition, these patients perform poorly on measures of executive function when they have a positive history of both DKA and hyperglycemia [55]. So the glycemic control is probably interacting with DKA to worsen the cognitive performance. However, a history of DKA is not associated with either decreased academic abilities or an increased risk of learning problems in children or young T1DM patients in other studies [8, 21]. The effects of DKA, as well as its interaction with AAO, disease duration, and glycemic control, are yet to be investigated.

ANGIOPATHY AND COGNITIVE FUNCTIONS

Angiopathy in T1DM patients can be manifested as either microangiopathy or macroangiopathy or both. Retinopathy and nephropathy belong to microangiopathic complications of T1DM and are two common forms of diabetic microangiopathy, which has been suggested to be associated with cognitive impairments in patients with T1DM. Besides hyperglycemia, retinopathy [4, 14] and nephropathy [40, 56] are independently associated with decrements in psychomotor efficiency. In addition, diabetic retinopathy is associated with poor cognitive performance on intelligence, information processing, and attention/concentration ability in adult T1DM patients [57]. However, it is still inconclusive whether microangiopathic complications are associated with cognitive impairments in T1DM patients. For example, the presence of retinopathy is not a significant predictor of poor cognitive performance in adult patients with T1DM [13]. Furthermore, microvascular complication status is not a relevant factor for cognitive impairments though adult T1DM patients perform poorer on general cognitive ability, information processing speed, and motor speed than the controls [58].

On the other hand, macrovascular health is associated with cognitive impairments in adult T1DM patients [14]. For instance, a decline in psychomotor speed can be predicted by macrovascular complications, duration of diabetes, proliferative retinopathy, and autonomic neuropathy [17].

OTHER FACTORS

Polyneuropathy is shown as the best biomedical predictor of cognitive performance in adult T1DM patients [59]. High body mass index (BMI) [13, 14] and hypertension [13] are shown as significant predictors of poor cognition functions in adult patients with T1DM. Specifically, systolic blood pressure can be used to predict the decline in psychomotor speed [17]. On the other hand, neither hypertension nor BMI are implicated in cognitive impairments of T1DM

patients [40]. These studies are composed of T1DM patients who vary in age, age at onset of T1DM as well as disease duration. However, the discrepancy of these findings warrants further studies to examine hypertension's and BMI's roles in the cognitive changes of T1DM patients.

CONCLUSION

This review has focused on the cognitive impairments in young and adult T1DM patients. The cognitive changes have been examined from the following perspectives: AAO and duration of T1DM, glycemic dysregulation, DKA, and angiopathy. In addition, other factors such as blood pressure, BMI, and neuropathy are discussed for their relations with the cognitive changes in T1DM patients. In children with T1DM, impaired cognitive functions or poor cognitive performance were observed in most studies (Table 1). In contrast, the impaired cognitive functions were seen more consistently in studies with adult T1DM patients (Table 2). Very few studies have a follow-up long enough to show if the weakened cognitive performance and/or functions in childhood will last into adulthood. However, some evidence [22, 23] has shown early-onset T1DM is associated with brain structural changes, which might have long-lasting effects on cognitive functions. However, prospective studies with a long follow-up design will be useful for clarifying the long-term effects of early-onset T1DM on cognitive functions. In addition, future studies are needed to elucidate the underlying mechanism of T1DM-related cognitive impairments or dementia.

DISCLOSURE STATEMENT

Authors' disclosures are available online (http://j-alz.com/manuscript-disclosures/16-1250r1).

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