Corresponding risk factors between cognitive impairment and type 1 diabetes mellitus: A narrative review

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HIGHLIGHTS
- Corresponding risk factors between cognitive impairment and type 1 diabetes mellitus.
- Duration and age; Education and gender and Glycemic states.
- Diabetic ketoacidosis; Microvascular complications and Glycemic control–HbA1c.
- Neuropsychology and emotion; Intestinal flora; Dyslipidemia and Sleep Quality.

ABSTRACT
Type 1 diabetes mellitus (T1DM) is a type of diabetes caused by the destruction of pancreatic β cells and the absolute lack of insulin secretion. T1DM usually starts in adolescence or develops directly as a severe disease state of ketoacidosis. T1DM and its complications make many people suffer and have psychological problems, which make us have to pay more attention to the prevention and early control of T1DM. Cognitive impairment (CI) is one of the major complications of T1DM. It can further develop into Alzheimer's disease, which can seriously affect the quality of life of the elderly. Furthermore, the relationship between T1DM and CI is unclear. Hence, we conducted a narrative review of the existing literature through a PubMed search. We summarized some risk factors that may be associated with the cognitive changes in T1DM patients, including onset age and duration, education and gender, glycemic states, microvascular complications, glycemic control, neuropsychology and emotion, intestinal flora, dyslipidemia, and sleep quality. We aimed to provide some content related to CI in T1DM, and hoped that it could play a role in early prediction and treatment to reduce the prevalence.

1. Introduction
Cognition is the intelligence processing process by which the body recognizes and acquires knowledge. The mechanisms underlying cognitive impairment (CI) are thought to include insulin resistance, inflammation, oxidative stress, and neurovascular dysfunction [1]. CI is increasingly recognized as a major complication of diabetes and is associated with complications related to the treatment of diabetes.

Diabetes is a group of metabolic diseases characterized by high blood sugar. In particular, the onset of type 1 diabetes mellitus (T1DM) is relatively rapid, insulin is insufficient absolutely in the body, and ketoacidosis is prone to occur. Long-term complications, in particular microvascular complications (including proliferative retinopathy and other dysfunction in various tissues, including the eyes and kidneys), develop as a consequence of prolonged hyperglycemia [2].

It is well known that diabetes is associated with lower levels of cognitive function and may be a risk factor for the development of CI and even dementia. At the same time, mild cognitive impairment (MCI) is also a complication in children and adults with T1DM. Subjects clinically defined as MCI are heterogeneous; however, approximately 10%–15%...
develop Alzheimer's disease per year [3]. It is necessary to identify the factors that contribute to CI in T1DM patients. We previously examined type 2 diabetes mellitus (T2DM) and CI, although there are similarities between type 1 and type 2 in CI, differences still exist [4]. In this article, we reviewed some existing studies on the corresponding risk factors between T1DM and CI, including diabetic complications, comorbidities, and blood glucose control.

2. Methods

To summarize the factors associated with T1DM in the pathogenesis of CI, a PubMed database search was performed for published articles from 2005 to 2021. The search used the terms: (‘T1DM’ OR ‘diabetes’) AND (‘cognitive impairment’ OR ‘cognitive dysfunction’) OR (‘diabetic ketoacidosis’ OR ‘DKA’) OR ‘HbA1c’ OR ‘microangiopathy’ OR ‘dyslipidemia’ OR ‘intestinal flora’ OR ‘sleep quality’. Articles not related to type 1 diabetic dementia and risk factors would be excluded. After these exclusion criteria, the research yielded 127 articles. In this review, qualitative and quantitative studies included clinical animal studies and systematic reviews were also taken into account. We reviewed the effects of different risk factors on cognitive function (Table 1). These studies were more valuable than animal studies or review articles because they directly reported the association of a specific risk factor with CI in T1DM populations, including case-control studies, prospective cohort studies, cross-sectional studies, randomized controlled trials, etc. In addition, we made a figure to show the relationship between each risk factor and CI (Figure 1).

3. Results

3.1. Duration and age

3.1.1. Duration

Lower cognitive performance was associated with long-standing T1DM. Researchers found an association between long-term T1DM without complications and cognitive functioning, which suggested that long-term T1DM might affect cognition, even when there were no other diabetes-related complications [5]. In addition, greater risks were also associated with longer disease duration and younger age of onset, and a study found that middle-aged patients with childhood onset T1DM had more obvious clinically related CI [6]. In addition, T1DM was mostly seen in teenagers, who were often in the stage of MCI. However, with the prolongation of the disease course, diabetes would aggravate the progression of MCI to CI or even dementia [7]. Consequently, diabetes duration probably had an impact on cognitive function along the continuum from normal cognition to MCI to dementia [8]. These results showed that age and duration of diabetes were the causes of T1DM-associated cognitive decline, and it could be considered that CI was related to the course of diabetes [9].

3.1.2. Children and adolescents

T1DM mainly occurred in childhood, and if not diagnosed and treated in time, it would cause serious complications, prolong the course of the disease, and aggravate the CI in future adulthood. Poor glycemic control was often associated with CI in children with T1DM due to predisposing factors and immature mental and physical functioning during childhood.
Since most children with T1DM needed insulin injection for treatment, the degree of children’s cooperation in treatment and their adherence were also an important factor that affecting the curative effect [12, 13]. Children with T1DM have persistent and mild attention problems, and this was closely related to the age and duration of T1DM [14]. A study examining children aged 6–11 with T1DM found that structural changes in the brains of children with T1DM were associated with CI and that they tend to have poor glycemic control compared with controls [10]. In newly diagnosed children with T1DM, the researchers found reduced cerebral blood perfusion in the visual and sensorimotor areas of the cerebral cortex [15]. Moreover, compared with non-diabetic children, T1DM children exhibited significantly lower performance on the full IQ and motor speed tests. Compared with adults, adolescents with T1DM also demonstrated severely impaired vascular health and cognitive decline [16]. Therefore, in the group of children with T1DM, their pathogenic factors were diverse, which required early diagnosis and treatment, especially good control of blood glucose, so as to avoid adverse cognitive results in adulthood.

3.1.3. Adults and elders

T1DM is becoming more and more common in adults as children with T1DM grow up. Studies found that in Chinese adults with T1DM, their memory/language, executive function, attention, abstraction ability, visuospatial ability performance were worse [17]. As we know, diabetic peripheral neuropathy was a non-negligible complication of diabetes. A study found a positive association between diabetic peripheral neuropathy and CI in Chinese adults with T1DM [17]. What’s more, there was extensive damage of white matter microstructures in the frontal temporal lobe brain regions associated with emotional and cognitive functions, which was considered to be a neurological pathological change associated with cognitive dysfunction in adults with T1DM [18]. In a cross-sectional study, HbA1c and the course of diabetes were significantly associated with CI in patients from aged 45–59 years [19]. Therefore, the occurrence of cognitive dysfunction in adults with T1DM was also a combination of multiple factors.

3.2. Education and gender

Educational attainment in T1DM is associated with CI. A crucial reason was that the higher level of education, the higher compliance with treatment of the patients, the better control of blood sugar [8, 20]. Studies suggested that increasing age, female gender and family history were unchangeable risk factors for cognitive dysfunction and even Alzheimer’s disease. The higher prevalence in women may be linked to low estrogen levels after menopause and structural differences in the brain. What’s more, ending a marriage or losing a spouse could lead to loneliness and reduced communication, which may be factors affecting women more than men. Finally, the level of education had a great influence on cognition, which strongly supported the perspective that better education could increase the brain’s knowledge reserve and prevent cognitive decline [20].

3.3. Glycemic states

Some studies suggested that impaired cognitive performance in patients with T1DM may be due to exposure to glycemic extremes, including hyperglycemia and hypoglycemia [8, 21]. Based on a large number of studies that focused on the effects of hyper- and hypoglycemia on CI, some conclusions have been reached. Here, we divide glycemic states into hyperglycemia, hypoglycemia, and severe hypoglycemia (SH).

3.3.1. Hyperglycemia

Hyperglycemia that lead to CI has many reasons, including inflammatory factors, oxidative stress, endothelial cell damage, mitochondrial...
A study of zebra-fish injected with STZ for simulating T1DM found the negative effects of hyperglycemia on CI [24]. The elderly who maintained hyperglycemia for a long time would eventually develop cognitive decline or even AD [8]. A study showed that long-term exposure to hyperglycemia and the presence of microvascular disease could induce CI in T1DM [25]. Another study also found that long-term exposure to hyperglycemia could damage the blood-brain barrier and induce the production of a variety of inflammatory mediators in the brain that damage surrounding cells, leading to cognitive dysfunction [26].

Hyperglycemia was a major clinical symptom of diabetes and was associated with CI, which involved inflammatory changes in the hippocampus that have been widely studied [27, 28]. The hippocampus regulated emotions and was involved in memory formation and cognitive function, which played a vital role in CI [29, 30]. Many studies found that inflammatory factors appeared in the hippocampus of T1DM patients and were likely to cause damage to the hippocampus that subsequently led to CI [31, 32]. A number of factors have been studied, such as IL-1β, IL-6, IL-18, TNF-α, NOD-like receptor protein 3 (NLRP3) and high mobility group box-1 protein (HMGB1) [33, 34, 35, 36, 37]. Caspase-1 was shown to be an important substance that promoted the development of inflammation and ischemalike damage formation [35]. Vitro studies suggested that hyperglycemia caused HMGB1 to activate toll-like receptor (TLR)-4, which in turn stimulated NLRP3- and caspase-1-mediated inflammatory pathways, leading to the inflammatory effects of inflammatory factors, such as IL-1β, IL-6 [30, 35]. Ultimately, HMGB1 led to the development of central nervous system diseases and the formation of CI. Of course, this was only one of the mechanisms by which hyperglycemia promotes CI, and there were still many mechanisms that remained unclear, which need to be further studied. But it was clear that high blood glucose leads to CI, which required our attention and prevention, especially to control blood glucose well and reduce complications.

3.3.2. Hypoglycemia

Hypoglycemia was a common condition in T1DM patients, and its relationships with cognitive changes have been studied widely. As the main and efficient treatment method for T1DM, insulin therapy was also shown to increase the occurrence of hypoglycemia, which was a serious complication [38]. A study suggested that there seemed to be a bidirectional relationship between CI (even dementia) and hypoglycemia in elderly patients with diabetes. Hypoglycemia would impair cognitive ability, and CI would reduce patients’ ability to control blood glucose and increase the prevalence of hypoglycemia [39]. Early visual information processing and contrast sensitivity were impaired during hypoglycemia in T1DM adult patients, and reaction time and psychomotor speed were significantly reduced in school-age children during hypoglycemic episodes [40]. One study found that neonatal hypoglycemia was associated with a combination of poor executive function and visual motor function at 4.5 years of age [41]. Further, another study found that recurrent, non-severe hypoglycemia affected the integrity and function of neurons, and thus affect cognitive function [42]. Animal studies have found that that recurrent moderate hypoglycemia damaged the CA1 dendrite region of the hippocampus, resulting oxidative damage to hippocampus [43]. Interestingly, we also found that some studies did not conclude that hypoglycemia was associated with CI. In the Diabetes Control and Complications Trial (DCCT), SH or intensive therapy with insulin was not associated with cognitive decline in participants aged 13–19 years [44]. A prospective trial with the 30-year follow-up of the Diabetes Intervention Study mentioned similar results to the DCCT, suggesting that the number of episodes of SH was not associated with CI [45]. A randomized controlled trial suggested that non-severe hypoglycemia and SH had no effect on cognitive function, and conversely, the non-severe hypoglycemia might reduce the occurrence of CI [46]. However, Shalimova thought that although the association between hypoglycemia and CI was controversial in young patients (according to the patients’ age in DCCT), the association became more pronounced in older patients [24]. This may be related to inability of brain to adapt to counter-regulation after the elderly experience chronic hypoglycemia.

Glucose was the main source of energy for the brain. When hyperglycemia occurred, abnormal changes in glucose transporters (GLUTs) in the brain were usually. The GLUTs in the brain played a crucial role in the development of CI in T1DM, and GLUT 1, 3 and 4 have been studied [47]. Animal studies showed the changes in glucose transporters in the brains of rats with hypoglycemia. Under hypoglycemic conditions, their small vessels of brain increased the number of glucose transporters in the brain to increase the use of glucose inbrain [47]. GLUT3 and GLUT4 mediated changes in glucose uptake by hippocampus and cerebellum neurons in the brain of mice induced by diabetes may be associated with cognitive dysfunction [47]. In addition, other studies found that in insulin-induced recurrent hypoglycemia rats, hypoglycemia could lead to impaired neurotransmission of cholinergic activity in the cerebellum, which was precisely caused by the disorder of glucose transporters in the cerebellum, in which GLUT3 expression was elevated [48].

On the one hand, in adults with T1DM, their cognitive dysfunction may be related to chronic, recurrent hypoglycemia. Although patients exposed to chronic/recurrent hypoglycemia become significantly tolerant to this state, this was insufficient to prevent SH with neuroglycopenic decompensation, probably because symptomatic and counter-regulatory responses adapt even more [21]. We speculated that long-term exposure to hypoglycemia may increase the number of glucose transporters in the brain that maintained transient energy expenditure, but patients with recurrent hypoglycemia may experience irreversible changes in the brain due to decompensated responses and loss of brain cell energy. On the other hand, an animal study found that in mice with moderate recurrent hypoglycemia, their hippocampus and other vulnerable brain regions produced pathological oxidative stress response, which could induce cognitive dysfunction. They also found that hypoglycemia induced nuclear factor E2-related factor 2 (Nrf2)-dependent antioxidant responses in the hippocampus of mice to counteract oxidative damage. Unfortunately, this neuroprotective mechanism was not sufficient to combat oxidative damage in the hippocampus caused by repeated chronic hypoglycemia [43]. Therefore, long-term repeated hypoglycemia may have a certain impact on cognitive dysfunction. Of course, the specific mechanism needed further research and exploration.

Acute hypoglycemia affected the energy production of brain cells and led to irreversible functional changes and neuronal death [49, 50]. When acute hypoglycemic adverse events occurred early in childhood in the context of T1DM, cognitive dysfunction became apparent in adulthood [51]. Thus, hypoglycemia was a very important factor in both adults and children, not matter it was acute or chronic.

3.3.3. SH

As the most serious side effect of insulin therapy, SH affected 30–40% of T1DM patients [40]. The association between cognitive dysfunction and SH reflected the effects of a severe neuroglycopenic event on the aging brain [52]. A study suggested that a history of SH or low fasting glucose was associated with sustained attention deficits in adolescents [14]. A cohort study showed that SH affected both recent and lifelong cognitive function in elderly patients with T1DM, and active prevention of SH slowed the onset of dementia [53]. Patients, who previously exposed to moderate recurrent hypoglycemia, new episodes of SH lead to severe CI, were associated with the death of neurons in the hippocampus and frontal parietal lobes [49]. Furthermore, it reported that the damage of neurons in the hippocampus after SH was associated with reduced cognitive function, at the same time, impaired hippocampal synaptic function may be one cause of cognitive dysfunction caused by moderate recurrent hypoglycemia [54]. But these conclusions were contrary to the results of the DCCT and the Stockholm Diabetes Intervention Study mentioned earlier. They did not find a relation between SH and CI. We considered that there was a lack of long-term follow-up in the older study subjects. These results appeared that the effect of SH on cognitive dysfunction was uncertain and this deserved our attention and
prevention. However, frequent self-monitoring of blood glucose could promote early recognition and treatment of hypoglycemia, suggesting that SH risk could be minimized [55].

3.4. Diabetic ketoacidosis (DKA)

As a serious and special complication of T1DM, DKA would cause serious physical and psychological damage to patients, including cognitive decline. Therefore, DKA was discussed separately. DKA was a typical and exceedingly serious complication of severe hyperglycemia in T1DM that could lead to coma or death [56]. Meanwhile, exposure to both hyperglycemia and DKA may also affect cognitive performance [57]. DKA was a high-risk factor for CI in patients with T1DM [40]. A research reported that cognitive dysfunction was not only associated with chronic hyperglycemia, but also with acute metabolic brain damage, such as brain damage caused by DKA [58]. A single episode of DKA in T1DM children was associated with a slight memory decline shortly thereafter, and IQ decline can be detected [59]. In addition, a study of Saudi Arabian children with T1DM showed that those with DKA often had poor blood glucose control and poor lifestyle habits [60]. Recurrent DKA negatively affected the brain of elderly patients with T1DM, affecting their overall cognitive function [61]. In the original study by Glaser of rat models, DKA caused acute systemic inflammation, including neuroinflammation. Importantly, the neuroinflammatory response induced by DKA was long-lasting, suggesting that DKA may contribute to long-term cognitive decline in patients with diabetes [62]. Although the underlying mechanisms remained to be elucidated, as a serious complication of hyperglycemia, it was suggested that DKA played an important role in diabetes-related cognitive decline.

It suggested that DKA and a history of chronic hyperglycemia appeared to be more harmful than SH in the cognitive effects of patients with T1DM [12], and the relationship between hypoglycemia and CI remained to be further studied.

3.5. Microvascular complications

Microangiopathy, one of the main complications of diabetes, affects the tiny blood vessels of the brain, retina, kidney and so on [63, 64, 65]. For middle-aged and older adults with long-duration T1DM, poorer cognition was associated not only with an episode of severe hyper- and hypoglycemia but also with the abnormal presence of micro- and/or macrovascular conditions [52].

Angiopathy in T1DM patients could manifest as either micro/mac- roangiopathy or both [40]. Nephropathy and retinopathy were two forms of diabetic microangiopathy and were suggested to have relationships with CI in T1DM [66]. Both albuminuria and kidney dysfunction were associated with CI [67]. Advanced chronic kidney disease was independently associated with cognitive dysfunction [68]. Studies of adults with T1DM demonstrated that the development of microvascular complications such as retinopathy/nephropathy may adversely affect mental efficiency [52]. Narrower retinal arteriolar diameters were associated with mental slowing in middle-aged adults with T1DM, and damage to the retinal microvasculature may play a role in the transition from MCI to AD [69]. Diabetic retinopathy and long-term arterial retinal changes were associated with CI [70, 71]. At the same time, damages to retinal microvessels have been observed commonly in children with diabetes [66]. Early detection and prevention should be carried out in children with diabetes to prevent the progression of cognitive dysfunction to dementia in middle and old age [71, 72].

On the other hand, long-term hyperglycemia could lead to the accumulation of damage, including damage to the parenchyma and vasculature of the brain [64]. The retinal microvasculature reflected small-vessel disease in the brain. Examination of the retinal microvasculature, a biomarker of small-vessel disease in the brain, may potentially contribute additional information on the etiology of CI [73]. Moreover, narrower retinal arterioles, wider venules that related to brain atrophy (primarily white matter atrophy) and cerebral microbleeds were all associated with poorer mental efficiency and executive function [52, 74]. Some studies confirmed these results and suggested that retinal microvascular signs reflected microvascular pathology in the brain, which contributed to the diagnosis of CI and dementia [73]. Autopsy studies suggested that cerebral amyloid angiopathy was a cerebrovascular disorder and associated with a high risk of CI and dementia [75, 76]. White matter ischemic lesions may underlie some of the impaired processing speed associated with cerebral amyloid angiopathy [52]. Patients with T1DM had impaired cerebral microvascular system, declined glucose metabolism, and white matter hyperperfusion caused by microbleeds or infarcts which led to damage and atrophy of white matter and ultimately led to cognitive dysfunction [77]. In T1DM patients, smaller white matter volumes were significantly associated with microvascular complications [9]. It was well known that neuropsychological performance was related to whole-brain gray and white matter volume; therefore, measures of brain atrophy were well correlated with and predictive of CI [9]. In sum, microangiopathy was an important complication of diabetes mellitus and was closely related to CI.

3.6. Glycemic control–HbA1c

The association between CI and HbA1c was complicated. Measures of hyperglycemia have been studied in relation to CI and HbA1c, and levels of HbA1c were used in clinical practice to monitor glycemic control [78]. Moreover, some findings showed a linear correlation between cognitive decline and circulating HbA1c levels [8, 79]. For example, one study compared the differences in cognitive performance between Chinese children with T1DM and healthy controls to evaluate whether cognitive dysfunction was related to glycemic control. The results showed that Chinese juveniles with T1DM who did not have good glycemic control had deficits in IQ and attention [57]. A randomized controlled trial found that controlling blood glucose in diabetic patients, especially elderly patients, could alleviate their cognitive dysfunction to a certain extent [80]. A study reported that CI was observed in 61.3% of the patients without optimal glycemic control (HbA1c>7%), and CI was observed in 11.1% of patients with optimal glycemic control [40]. A study found that higher levels of HbA1c were associated with poorer information task performance in T1DM children [81]. The linear correlation of HbA1c levels with global cognitive decline was primarily driven by impairments in the domains of memory and executive function (functions dependent on the commissural tracts and corticospinal projections), which suggested that cognitive decline related to high circulating glucose levels could be specific to dysfunction in certain brain regions or subcortical pathways involved in memory and executive function [79, 82]. Therefore, controlling blood sugar was crucial for patients against CI in any glycemic states.

3.7. Neuropsychology and emotion

Neuropsychological factors were closely associated with glycemic control and CI in T1DM. T1DM not only affected cognition through neurobiological factors, but also caused psychological changes. Anxiety and even depression were common in patients with shorter T1DM duration [83]. In youth and adulthood, T1DM was also associated with MCI and mood disorders, such as depression and anxiety [84]. A review mentioned that patients with T1DM had a higher level of psychological distress, tending to have cognitive dysfunction [85]. Patients’ inner pain would also directly affect their own blood glucose monitoring and treatment compliance, especially in children [13]. Cognitive-behavioral therapy had potential benefits for patients with poor blood glucose control (high HbA1c), which may reduce fear of diabetes complications and change negative attitude towards diabetes, so as to cooperate with treatment and strengthen self-management actively [86]. For patients with T1DM, we should not only pay attention to their physical problems, but also their mental and psychological status, and actively carry out psychological intervention to prevent the decline of cognitive function.
3.8. Intestinal flora

The gut brain axis played an important role in diabetic encephalopathy. At the same time, the role of microorganisms in cognitive function in diabetes was extensively studied, and probiotics were also considered to be used to improve cognitive dysfunction [87]. A study found that T1DM mice had a specific serotype and hippocampal metabolic phenotype, characterized by reduced in tricarboxylic acid cycle and disrupted in glutamine cycle. They thought that this may be modulated by the gut microbiota in microbiota-host metabolic correlation analysis [88].

Another investigational therapeutic trial concluded that Yam gruel, a paste made by peeling, slicing and boiling Chinese yam, could improve cognitive function by increasing intestinal probiotics and reducing oxidative stress and inflammation in the gut and cerebral cortex caused by high blood sugar [89].

In addition, study revealed that chronic acetic acid deficiency due to depletion of acetate-producing bacteria may reduce synthaporphyrin in the hippocampus and worsen cognitive dysfunction in mice with T1DM [90]. Another animal experiment suggested that metformin reduced blood glucose, regulated the composition of intestinal flora in mice, so as to inhibited neuroinflammation in the brain of mice, which was used to intervene in cognitive dysfunction [91]. In conclusion, there was a definite correlation between intestinal flora and cognitive function, which provided us some new directions and suggestions for the clinical treatment of diabetic cognitive dysfunction.

3.9. Dyslipidemia

Dyslipidemia was one of the risk factors for CI. Poorer cognitive performance was associated with higher BMI in a linear manner [92]. The prevalence of CI with dyslipidemia (triglycerides>150 mg/dl) was 78.6%, and the mean triglyceride values were higher in patients with CI [93]. Diets consisting of an increased consumption of saturated and trans fats incurred an increased incidence of CI, while diets rich in healthy fats were protective [94]. Poor glycemic control and insulin resistance were associated with a worse lipoprotein profile, and furthermore, obesity and dyslipidemia (especially LDL particles) resulting from particular diets could also act on the brain through insulin resistance [95]. Hence, obesity and consequent metabolic dysfunction have been strongly linked to metabolic syndrome-associated CI and dementia [96].

Apo-E played an important role in mediating CI in T1DM patients, and Apo-E-ε4 carriers had lower levels of brain insulin than ε4 noncarriers [94, 97]. At the same time, hyperlipidemia may lead to atherosclerosis in cerebrovascular arteries, and lipid accumulation affected the hippocampus such that an inflammatory response was produced [22, 98]. One study found that Simvastatin improved cognitive function in mice with diabetes; nevertheless, the beneficial effects of statin therapy in patients with CI have not been firmly established [99, 100]. It reported that rFGF21 treatment significantly reduced elevations in serum total cholesterol and LDL/HDL ratio, it was also confirmed to have a potent and beneficial effect in modulating hyperlipidemia in obese mice fed a high-fat diet [96]. High plasma fibrinogen levels were associated with poor performance in attention tasks in patients with CI, regardless of Apo-E genotype or vascular risk factors [101]. At the same time, increased fibrinogen synthesis was associated with insulin deficiency, which perhaps as an acute-phase response that T1DM led to [102]. We speculated that dyslipidemia was one cause of CI in T1DM patients. However, the relationship between lipid metabolism and CI in T1DM patients remained to be further studied.

3.10. Sleep quality

Sleep duration and sleep quality related to the risk of insulin resistance, impaired glucose metabolism, and T2DM have been linked by considerable research [103, 104]. Experimental studies also found that T1DM patients have lower sleep quality and higher HbA1c, and Free Style Libre could be used to improve the sleep quality and diabetes distress [105, 106]. We would discuss the relationship between T1DM and sleep here.

Health-related quality of life, especially poor sleep, was a potential risk factor for CI and dementia [107]. The higher degree of sleep disturbance resulted the higher likelihood of CI [108]. This relationship seemed to be primarily driven by the association between poor sleep quality and executive function and the poor sleep quality was also associated with higher levels of cortisol and proinflammatory cytokines, both of which were associated with cognitive function or decline [109]. The results showed that in older Chinese individuals, lower habitual sleep efficiency was associated with a higher risk of memory impairment and poorer cognitive function [110]. A pilot study showed that an eight-week (four-session) ‘sleep well, think well’ group intervention was associated with significant and pronounced improvements in subjective sleep disturbance in those with CI [111]. Having good sleep quality was ideal for the prevention and treatment of cognitive disorders [112, 113]. A report suggested that hypoglycemia negative impacted diabetes management, sleep quality, and next day functioning [114, 115]. Therefore, the risk factors leading to CI interacted with each other along with T1DM-related risk factors, which needed us to pay more attention to sleep quality.

Another important risk factor for CI in sleep quality was obstructive sleep apnea (OSA) that was led by obesity [116]. Obesity was becoming more common in patients with T1DM [117, 118]. OSA was sleep apnea caused by the collapse of the airway and subsequent obstruction and low ventilation; with this disease, clinical manifestations include daytime sleepiness and symptoms such as memory loss [119]. Poor sleep quality and OSA prevalence had relationship with T1DM, which may be bidirectional [120]. Although there have been few clinical studies with T1DM patients with OSA, some researchers have gradually begun to study the relationship between T1DM and OSA [121, 122]. Obstructive sleep-disordered breathing was not only associated with adverse events of hypoglycemia at night, but also may be associated with HbA1c [118, 123]. In addition, studies showed that poor sleep quality in diabetic patients was associated with glycemic control [105, 124]. These relationships allow us to use sleep disorders as a bridge to study the associations between T1DM and CI.

4. Discussion

Among the risk factors mentioned above, microangiopathy and HbA1c were not only important risk factors for CI in T1DM patients, but also biological risk markers of CI. T1DM was known to damage blood vessels, including the tiny blood vessels and the small peripheral blood vessels. Changes in peripheral small vessels, such as narrowing of central retinal artery and widening of central vein, could predict the occurrence of intracerebral vascular lesions and CI. HbA1c was a marker of glycemic control and widely used in glycemic monitoring. According to the linear correlation between HbA1c and CI, we could combine HbA1c with retinal blood vessels to predict the occurrence of CI early.

In addition, membrane fluidity changes and membrane homeostasis were also associated with CNS disease. It was found that inhibition of phospholipase A2 could alter membrane fluidity in the hippocampus of mice, which may lead to CI even AD [125]. Another study suggested that the fluidity of the membrane of brain cells in houtonson's disease was also changed, which was also considered to be one of the biomarkers for neurological diseases [126]. Of course, changes in membrane fluidity occur not only in the brain, but also in red blood cells. Some studies found that blood glucose could be controlled by detecting the fluidity of erythrocyte membrane in T1DM patients, which was another mean of differing retinal blood vessels and HbA1c [127]. Changes in erythrocyte membrane fluidity may also be a marker of retinopathy in T1DM patients [128]. The measurement of erythrocyte membrane fluidity changes provided a more sensitive index of disease progression in T1DM patients than HbA1c. Combining imaging data with molecular information, such
as lipidomics and signal cascades, provided a multidisciplinary approach to the analysis of biofilms [129]. These detection methods would help us to conduct early diagnosis and treatment of T1DM patients in the future to prevent obvious CI patients.

Age and duration of diabetes were the primary factors affecting cognitive ability. The earlier the age of onset resulted the longer duration of diabetes and the more serious the CI of patients. Blood glucose status were also important factors affecting cognition, whether hyper- or hypo-, because both of them had adverse effects on the brain. At present, the main controversy was the relationship between hypoglycemia and CI. Some literature suggested that hypoglycemia could have definite cognitive effects. However, some experiments did not find such a relationship, and even some articles suggested that non-severe hypoglycemia was negatively associated with poorer cognitive performance. We should consider the relationship between them carefully. First, we knew that glucose was the only efficient energy source for the brain. If the brain did not properly metabolize glucose aerobically, the supplement of brain's energy would be affected [130]. So we believe that acute SH would have adverse effects on the brain of patients. If T1DM patients had poor blood glucose control, SH would have a huge impact on the brain and affect their cognitive function [131]. T1DM occurred frequently in children, SH may cause irreversible damage to the brain or nervous system of children with T1DM. Even though tests of intelligence or other cognitive tests in these children showed no significant abnormalities, these cognitive declines would become more pronounced when they grow up [132]. Secondly, some studies believed that hypoglycemia had little influence on children or young people, while its influence on the elderly was inevitable. We considered that patients who experienced hypoglycemic events at an early age would experience cognitive decline with age. Frequent hypoglycemia would aggravate the brain damage of patients, especially in elderly patients, though their brain would produce adaptive counter-regulation [21]. Mice may increase glucose uptake by increasing GLUTs in the brain, but it was unknown whether this regulation applied to humans. Another candidate was vascular endothelial growth factor, which was thought to be positive associated with cognitive performance in hypoglycemia by promoting glucose transport in the blood-brain barrier [21]. The sympathetic adrenal medulla system also released epinephrine to raise blood sugar in response to hypoglycemia. But in fact, repeated hypoglycemia triggered a habitual process that suppressed the production of adrenaline, lowering the blood sugar threshold that stimulated adrenaline secretion [133]. This may result in a diminished response to subsequent damage of SH. Some studies suggested that although the brain developed a tolerance to repeated hypoglycemia, it was insufficient to cope with subsequent SH with neuro-hypoglycemic symptoms decompensated [21, 133]. Finally, the effects of hypoglycemia on the brain and the mechanisms that the brain responded to hypoglycemia remained unclear, further studies were needed to explore. We always thought that low blood sugar could affect the brain adversely and even produce CI. Some studies believed that non-severe hypoglycemia was negative correlated with CI [46], which was contrary to general view. The study suggested that these patients' baseline cognitive abilities were better, which could control their blood sugar to the point [46]. These findings could also give us new ideas about non-severe hypoglycemia. Therefore, we could conclude that the level of cognitive function interacted with the level of glucose control. However, we noted that this study involves people with T2DM. As there was no intervention study on T1DM patients with the purpose of preventing cognitive decline, such research was necessary to increase the attention of T1DM patients on blood glucose control and CI, and provide clinical researchers a new idea for treatment or prevention.

Hypertension also affected cognitive function. A study found that from 1 to 20 years after onset, the incidence of hypertension and hyperlipidemia in children with T1DM was much higher than that in children without diabetes [134]. Hypertension could lead to peripheral neuropathy as well as central neuropathy [135, 136]. There were many reasons, including oxidative stress, vascular endothelial injury, inflammation and so on. These mechanisms could lead to pathological changes such as white matter lesions, blood brain barrier damage and neurovascular unit damage [136]. In addition, another study found that the reduction of intestinal flora, such as bifidobacteria, could lead to hypertension in children with T1DM [137]. Controlling blood pressure was helpful for reducing the incidence of CI in T1DM patients.

5. Conclusions

This paper summarized the risk factors for CI in T1DM patients. We believed that HbA1c was extremely important. Better blood glucose control was an important factor to reduce the occurrence of CI, especially for those middle-aged and elderly patients with childhood onset. The influence of hypoglycemia on cognitive ability needed further study. Insulin therapy was the main means to treat T1DM patients, so as the hypoglycemia was the most common complication of insulin therapy. Therefore, we needed to remind the harm of hypoglycemia for the patients. At the same time, we also summarized some other factors, such as blood lipids, sleep and intestinal flora. Metabolic factors and their complications were also beneficial to the prevention and treatment of CI. As an independent risk factor for CI, hypertension should also be highly valued by T1DM patients. At last, we should also pay attention to the bidirectional action of psychology and emotion in T1DM patients.

The treatment of cognitive dysfunction was becoming a multidisciplinary multi-field comprehensive treatment. In this article, we aimed to provide some content related to CI in T1DM, hoping that these information could play a role in early prediction and treatment to reduce the prevalence of CI in T1DM patients.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

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No data was used for the research described in the article.

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The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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