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COGNITIVE DYSFUNCTIONS IN TYPE 1 DIABETES

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Context: The review summarizes key studies assessing epidemiology, mechanisms, and consequences of cognitive dysfunction (CD) in type 1 diabetes (DM1).
Evidence Synthesis: In a number of studies, the severity of CD in DM1 was affected by the age of onset and diabetes duration, the presence of proliferative retinopathy and autonomic neuropathy. Diabetes-related CD has been observed not only in adults but also in children and adolescents. Most neuroimaging studies in DM1 did not show any differences in whole brain volumes, however, they did reveal selective deficits in grey matter volume or density within the frontal, posterior and temporal cortex, subcortical grey matter. Studies of middle-aged adults with long-standing DM1 using diffusion tensor imaging have demonstrated partial lesions of white matter and decreased fractional anisotropy in posterior brain regions. The mechanisms underlying diabetes-related CD are very complex and include factors related to diabetes per se and to diabetes-related cardiovascular disease and microvascular dysfunction: chronic hyperglycemia, hypoglycemia, macro- and microvascular disease, increased expression of inflammatory cytokines. The above mechanisms may contribute to the development and progression of both vascular dementia and Alzheimer disease.
Conclusions: Higher rates of CD and its faster progression in DM1 can be explained by both the direct effects of altered glucose metabolism on the brain and diabetes-related cardiovascular disease. Since the presence and progression of CD significantly worsens the quality of life of diabetic patients, further multidisciplinary studies based on the recent progress in both neuroimaging and type 1 diabetes management are warranted to tackle this problem.

The review summarizes key studies assessing epidemiology, mechanisms, and consequences of cognitive dysfunction in type 1 diabetes.

(1) Introduction

Diabetes, affecting approximately 350 million adults worldwide [1], has become one of the key medical and social challenges. Its better prevention and treatment are listed among the top priorities of national healthcare systems [2]. Continuous progress in both management of diabetes and associated risk factors have reduced the number of middle-age macro- and microvascular events, and substantially increased life expectancy in patients with glucose

intolerance [3, 4]. There is growing evidence that diabetes mellitus might contribute to early development and acceleration of age-related progression of various forms of cognitive impairment [5–8]. Recent research efforts have shifted from the traditional focus on diabetic neuropathy, (including alterations of the autonomic nervous system) to assessment of cognitive function as the main factor determining patient quality of life. The vast majority of studies investigated patients with type 2 diabetes [9–13], but much less is known about the relationship between cognitive dysfunction and type 1 diabetes. It is becoming clearer that this relationship is much more complex than initially thought.

The aim of our narrative review is to comprehensively summarize the relationship between type 1 diabetes and cognitive dysfunction. We have incorporated evidence from both animal and human studies assessing epidemiology, clinical characteristic and pathomechanisms underlying this link. We put special emphasis on neuroimaging as this fast-developing field offers a unique opportunity to advance our knowledge on cognitive dysfunction. Furthermore, we discuss evidence gaps and potential areas for further research.

Better prevention of type 1 diabetes – related cognitive impairment requires a close interdisciplinary collaboration. We hope that our review will serve as a catalyst to initiate large scale cognition-specific studies based on the recent progress in both neuroimaging and type 1 diabetes management.

We searched PubMed using the terms: „type 1 diabetes" AND „brain" AND („cognition" OR „dysfunction" OR „impairment"). Our initial search yielded 893 articles (of which 435 were published in the last 10 years), which we narrowed to … by excluding articles not published in the English language, duplicates and articles not discriminating type 1 and type 2 diabetes. We further selected studies based on the strength of design and publication date (preferring most recent articles). Nevertheless, we included older publications (preferring high-ranking journals) in case of seminal studies or when few studies were available for a specific topic. Of the articles retained, we included 97 that were most specific to cognitive dysfunctions in type 1 diabetes.

(2) Clinical characteristic of cognitive dysfunctions in type 1 diabetes

Compared to non-diabetic controls, patients with type 1 diabetes typically have reduced effectiveness in the following cognitive areas: intelligence, psychomotor efficiency, information processing speed, visual and constant attention, cognitive flexibility, and visual perception Interestingly, in some patients with type 1 diabetes, cognitive dysfunction was characterized by a slowing of mental speed and flexibility, while learning and memory were spared [14].

The severity of cognitive deficits in patients with type 1 diabetes is affected by age of onset and diabetes duration [14–16]. Cross-sectional data indicate that diabetic patients by 30-40 years of age already have cognitive impairments in areas such as general intelligence (general ability), psychomotor efficiency and cognitive flexibility [17]. In a prospective study by Ryan et al. [18], patients with type 1 diabetes (34-years of age at entry) showed a significant reduction in their psychomotor efficiency as compared to non-diabetic subjects, with no differences in memory, learning or problem-solving tasks, at 7-year follow-up. Severity of cognitive dysfunction has been linked to the presence of proliferative retinopathy and autonomic neuropathy [19]. Compared to healthy subjects, the adults with type 1 diabetes who developed chronic complications, performed significantly worse on tasks requiring constant attention, rapid analysis of visual-spatial details and eye coordination. Furthermore, there were no evident differences in test results when uncomplicated diabetics were compared with controls [19].

Importantly, diabetes-related cognitive alterations have been observed not only in adults but also in children and adolescents. In a nationwide study from Sweden, school scores in

children with diabetes were significantly lower [20] as compared to non-diabetic adolescents. Children with diabetes were 30–50% more likely to fail mathematics, English, Swedish and physical education classes. The effect was more pronounced with an earlier onset of diabetes [21]. These results are consistent with the findings of Ryan C.M. and colleagues [18], indicating that adults who developed type 1 diabetes in childhood or adolescence, had worse cognitive test results than age- and education-matched non-diabetic controls. Mental slowing is considered the primary cognitive deficit associated with type 1 diabetes in both younger and older patients [22]. However, learning and memory appear to be unaffected, even in patients with a long history of poor glycemic control. However, this representation of cognitive dysfunction might be affected by several other factors and co-morbidities. Therefore, the existence of a specific cognitive pattern in type 1 diabetes is still disputable.

(3) Neuroimaging findings

Several methods, including electroencephalography, structural and functional magnetic resonance imaging (fMRI), and diffusion tensor imaging (DTI) have been used to explore the link between changes in brain function/structure and cognitive deficiency [23–25].

Electroencephalographic studies have shown decreases in fast brainwave activity (α, β and γ), especially in temporal and occipital regions, with an increase in slow wave activity (δ and θ) in frontal regions, compared to non-diabetic controls [26, 27]. In a single-photon emission tomography-based study performed in patients with type 1 diabetes, significant regional variations in cerebral perfusion in many regions were documented (most noticeably in the cerebellum, frontal lobe, and fronto-temporal region) [28, 29]. These changes were associated with poor glycemic control and microvascular complications (such as retinopathy) [30]. Structural cerebral changes localized in grey and white matter were largely analyzed using different methods – visual and automated assessment.

One precise technique analyzing the stages of brain atrophy is the automated segmentation method. This can measure whole brain volumes, delineate anatomical regions and analyze changes in brain structure [31, 32]. Using voxel-based morphometric techniques, Musen G. and colleagues [31] documented a reduction of grey matter density in several brain regions in type 1 diabetic patients. They noticed lower grey matter density in the left hemisphere including posterior cingulate, hippocampus, and superior temporal gyrus, as well as right parahippocampal gyrus. These specific cortical regions are responsible for language processing, memory and attention. The reported alterations were correlated with averaged lifetime HbA1c values and severe hypoglycemic events [33, 34]. Brain changes during hyperacute hypoglycemic episodes cannot be seen in MRI studies using morphological sequences or diffusion-weighted imaging [35].

A similar observation concerning local brain atrophy was presented by Biessels G.J. and Reijmer Y.D. [23], who analyzed a number of cross-sectional studies in adults with type 1 diabetes. Although most studies did not show differences in whole brain volumes, they revealed selective deficits in grey matter volume or density within the frontal, posterior and temporal cortex, as well as in subcortical grey matter [23, 31, 32, 34]. Interestingly, the reduction in grey matter density was unrelated to cognitive test scores [30].

Contrary to other researchers, Van Duinkerken and colleagues [34] did not observe the cortical reduction associated with type 1 diabetes, possibly suggesting that the disease spares the cortex. Nevertheless, in the same study, they documented volume loss affecting the putamen bilaterally, and the right thalamus, in adults with a minimum of 10 years diabetes duration. They also found volume decrease affecting the nucleus accumbens bilaterally, in patients with proliferative retinopathy. However, this was not observed in healthy subjects, or in type 1 diabetic subjects without associated microangiopathy. Volume loss of the left nucleus accumbens (part of the ventral striatum within the basal ganglia) was independently

associated with type 1 diabetes–related cognitive dysfunction, while subcortical volume loss was connected to longer diabetes duration (and independently proliferative retinopathy).

In the study of Gallardo-Moreno Geisa B. et al. conducted on 16 patients with type 1 diabetes and 16 practically healthy subjects (using fMRI), it was possible to establish that in the absence of significant statistical difference in behavioral performance between the groups, related to the task, type 1 diabetic patients showed greater activation in the prefrontal inferior cortex, basal ganglia, posterior cerebellum, and substantia nigra (as compared to control subjects). Authors suggest that it can be a compensatory response to maintain behavioral effectiveness [36].

DTI is an MRI technique which can assess white matter microstructure and detect white matter lesions not visible on conventional MRI studies. DTI method characterizes white matter integrity by observing the movement of water molecules. Myelin and axonal membranes cause the anisotropic movement of diffusing water. Diffusion parameters like fractional anisotropy (FA), mean diffusivity (MD) or more characterize the displacement of water molecules in nerve fibers environment, their integrity and can tell more about myelin damage and axonal injuries [37, 38].

Studies of middle-aged adults with long-standing type 1 diabetes using DTI have demonstrated partial lesions of white matter (in particular, posterior coronary rays and optical radiations), which correlated with increased duration of diabetes, increased HbA1c levels and poor results in cognitive tasks [30, 36]. Results of DTI studies of middle-aged people with type 1 diabetes showed decreased fractional anisotropy (which reflect fiber density, axonal diameter, and myelination in white matter) in posterior brain regions (as compared to control subjects), which was associated with longer diabetes duration, decreased information processing speed and executive functioning [23, 39, 40].

Similarly, in children with type 1 diabetes changes in fractional anisotropy and apparent diffusion coefficient values (which may be features of axonal and myelinated fiber damage) significantly correlated with the severity of cognitive dysfunction [41]. In the future, DTI could be an effective quantitative method in predicting and monitoring progression of cognitive decline; which can result in dementia, given that DTI parameters are influenced by different biological (e.g. ageing) and methodological (e.g. data acquisition) factors.

Issues relating to attentional problems, slower information processing and poorer executive function were observed by Wessels A. et al. in people with type 1 diabetes and reduction of white matter volume [42]. However, recent studies concerning the presence of white matter lesions (WML) in patients with type 1 diabetes have shown inconclusive results. Some did not report any differences in the stages of leucoaraiosis between type 1 diabetic patients and healthy subjects [43], while others presented an increase in the number of WMLs connected to small vessels diseases and type 1 diabetes [44]. Marked changes (Fazekas scores 2 and 3 of leucoaraiosis) were noted in adults with childhood-onset type 1 diabetes, compared with Fazekas score 1 in the control group [45]. Higher volumes of WMLs were associated with slower information processing and other cognitive problems. The number of WMLs was significantly increased with age, disease duration, neuropathies, and smoking. In this group of patients, lacunar infarcts, strokes and the brain complications caused by type 1 diabetes were also noted.

It should be noted, that the effect of type 1 diabetes on cerebral white matter is not limited to white matter abnormalities and infarcts alone; microbleeds, usually rated on a visual assessment scale, may also be implicated. For example, in healthy, and type 1 diabetic subjects without complications, no difference in the occurrence of microbleeds was observed, however, more lesions were found in patients with proliferative diabetic retinopathy [46].

In summary, there is a close relationship between type 1 diabetes and cognitive impairment, including psychomotor speed and learning. The vast progression of cognitive

impairment in adults with type 1 diabetes may originate from the period of intensive brain development in childhood between the ages of five and seven. Even though magnetic resonance imaging with advanced techniques such as DTI, spectroscopy and functional imaging is available, there is still a lack of precise methodology for the early detection and assessment of risk factors for progressive brain volume loss in adulthood, and for protection of long-term cognitive decline.

(4) Pathogenesis of cognitive impairment in diabetes

Mechanisms underlying diabetes-related cognitive dysfunction are very complex and include factors related to diabetes per se (direct effects of altered glucose metabolism on the brain) and to diabetes-related cardiovascular disease and microvascular dysfunction. It should be noted that the nature of cognitive impairment in type 1 and type 2 diabetes differs due to differences in the pathophysiology of these two types of diabetes. In type 2 diabetes, cognitive dysfunction can be explained by a cascade of metabolic, hormonal and rheological disorders because of hyperinsulinemia and insulin resistance [47, 48]. At the same time in type 1 diabetes, in conditions of insulin deficiency, other mechanisms become triggers of cognitive impairment.

Role of hyperglycemia and hypoglycemia

Chronic hyperglycemia may trigger mechanisms that promote neuronal damage and endothelial dysfunction, which together may result in the development of cognitive dysfunction over time [49–52]. In the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cognitive follow-up study, 1144 participants were followed for 18 years. High long-term HbA1c levels, in addition to advanced age, lower number of years of education, and two clinically microvascular complications (proliferative diabetic retinopathy and renal complications) are associated with estimated cognitive decline [30, 53].

The negative effect of hyperglycemia on cognitive dysfunction was confirmed in a study with zebrafish in which type 1 diabetes was modeled by streptozocin (STZ) injection. In this study, it was shown that the exposure of zebrafish to glucose diluted in water during 14 days caused prolonged memory impairment associated with an increase in acetylcholinesterase activity, whereas galantamine treatment reversed the effect caused by hyperglycemia on memory. The findings showed that cognitive impairment in type 1 diabetes mellitus is directly related to acetylcholinesterase activity [54].

The study of Glaser N et al. was undertaken to determine whether cognitive deficits (decreased memory) could be detected after a single episode of diabetic ketoacidosis in an animal model (STZ-induced type 1 diabetes in juvenile rats). Data from this study showed that even a single episode of ketoacidosis leads to measurable deficits in learning in diabetic rats [55].

There is growing evidence that hypoglycemia increases cardiovascular risk. However, the relationship between hypoglycemia and cognitive decline is more controversial than initially thought [56–58]. In cross-sectional studies by Wredling R. et al. [59], and Langan S.J. et al. [60], recurring episodes of severe hypoglycemia were associated with poorer cognitive test results. Yaffe K. et al. described a bidirectional relationship between hypoglycemia risk and dementia. The presence of hypoglycemic episodes was associated with a two-fold higher risk of developing dementia. Conversely, the presence of dementia was associated with a three-fold higher risk of subsequent hypoglycemic episodes [50]. However, several other prospective studies were not able to document an independent relationship between hypoglycemia and cognitive decline. The DCCT/EDIC trial did not show more pronounced cognitive dysfunction (estimated with different cognitive tests) in those individuals who had

experienced one or more episodes of severe hypoglycemia [30, 53]. The DCCT sub-analysis [61], including only participants who were 13–19 years old at the time of entry into the study, did not show any association between cognitive decline and severe hypoglycemia. Similarly, in the Stockholm Diabetes Study (SDIS) cognitive function during the 10-year follow-up period was not associated with the number of severe hypoglycemic episodes and did not differ in treatment groups (with intensified conventional treatment and standard treatment) [19, 62]. The relationship between hypoglycemia and cognitive dysfunction might become overt in elderly patients. Although severe hypoglycemia [63] was not associated with long-term decline in cognitive ability in young patients with type 1 diabetes (DCCT follow-up study), recent studies of elderly patients (> 60 years old) with type 1 diabetes showed a higher prevalence of cognitive dysfunction [50].

Considering the controversial evidence of the effects of hypoglycemia on cognitive impairment, a study was conducted that tested the hypothesis that in diabetic mice, hypoglycemia (twice-weekly, insulin injections over 4 weeks) leads to cognitive dysfunction via a pathological response to oxidative stress. Interesting data were obtained, according to which hypoglycemia induces an nuclear factor E2-related factor 2 nuclear factor E2-related factor 2 (Nrf2)-dependent antioxidant response in the hippocampus, which counteracts oxidative damage; however, at the same time in diabetic mice, this neuroprotective mechanism is insufficient to prevent neuronal oxidative damage, resulting in chronic deficits in working and long-term memory [64].

Cerebrovascular diseases and microvascular dysfunction

Diabetes mellitus is a major risk factor for cerebrovascular disease. It has been associated with a multiple-fold increased risk of stroke, with a stroke relative-risk increase of 115% for every 1% rise in HbA1c [30, 65].

Stroke is the most common cause of dementia, while vascular dementia (caused by cerebral damage from cerebrovascular or cardiovascular diseases) which accounts for almost 20% of all cases, is the second most common cause of dementia [1]. The high prevalence of cognitive dysfunction in patients with type 1 diabetes could reflect both subclinical and overt cerebrovascular disease [66]. This relationship might be potentiated by hypertension and a high body mass index: factors identified as significant predictors of cognition problems in adult patients with type 1 diabetes. At the same time, the level of systolic blood pressure can be used to predict the decline in psychomotor speed in diabetic patients [67].

Dysfunction of small vessels might be another link between chronic hyperglycemia and cognitive dysfunction [67]. Chronic hyperglycemia dramatically increases the risk of microvascular disease typically attributed to diabetes (retinopathy, nephropathy and neuropathy). Priyam Mukherjee and colleagues [68] found a significant positive correlation between nephropathy, retinopathy and cognitive dysfunction. In adult diabetic patients, retinopathy was associated with poor cognitive performance relating to intelligence, attention/concentration ability and information processing [69]. Microvascular disease may also occur in the brain, which in turn may directly lead to cognitive dysfunction [70].

Both macro- and microvascular disease might predispose diabetic patients to depression, which per se is associated with a greater decline in cognitive function in diabetes and a negative impact on motivation for self-care [50]. The presence of cognitive dysfunction adversely affects the ability of patients to monitor glucose levels and adjust insulin doses [71].

The effect of diabetes on cerebrovascular lesions can also be explained by increased expression of inflammatory cytokines (such as IL-6 and TNFα) and subsequent chronic inflammation, which exacerbates cognitive dysfunction [72]. In spite of the small number of studies, it is justified to hypothesize that a certain role in the interrelation between diabetes, cognitive impairment and dementia may be further modified by genetic propensities. Studies

with APOE ε4 allele (a documented risk factors for cardiovascular disease and late Alzheimer's disease (AD) in the general population) have shown that ApoE ε4-negative diabetic participants were more likely to develop AD (compared to ApoE ε4-positive diabetic patients), yet patients included in these studies were predominantly diagnosed with type 2 diabetes [73, 74].

Other possible mechanisms (in animal studies)

The role of oxidative stress in the development of cognitive dysfunction was studied in the STZ-induced model of diabetic rats. This study was aimed at determining effect of troxerutin on the development of cognitive dysfunction and the expression level of Nrf2 (the main transcription factor of antioxidant stress) in the hippocampus of diabetic rats, when used in the early prophylactic stage. It was found that in diabetic troxerutin (60 mg/kg) intervention group, learning and memory levels were significantly improved as compared to the diabetic control group. Besides, in STZ diabetic rats treated with troxerutin, the expression level of Nrf2 in the hippocampus was increased; activity of superoxide dismutase was elevated, and malondialdehyde content was decreased [75].

Considering the fact that oxidative stress is one of the mechanisms for the development of cognitive impairment, another animal study focused on the effects of resistance training (climbing the ladder for a period of 5days/week for 10 consecutive weeks) and natural antioxidants (100mg/kg per day for a period of 10 weeks) on learning and memory in type 1 diabetic rats. It was established that exercise training and natural antioxidants synergistically ameliorated learning and memory deficits in type 1 diabetic rats by reducing oxidative stress and increasing antioxidant activity [76].

The positive effect of physical exercise on cognitive deficit was also found in the animal study with fifty-seven Wistar rats. It was found that physical exercise (5 weeks of physical training) prevents and/or reverts the cognitive deficits and astroglial alterations induced by type 1 diabetes [77].

Abnormal expression of estrogen receptor α (ERα) in hippocampus is considered as one of the mechanisms of development of cognitive impairment in type 1diabetes. In the study with alloxan-induced model of diabetic male Kunming mice, the spatial cognitive ability of the model mice was compared with control mice through Morris water maze test. It was found that abnormal expression of ER-α36 and related signal molecules may be important factors for diabetes-induced spatial cognitive impairment [78].

(5) Aging and development of dementia and other cognitive disorders in type 1 diabetes

Cognition includes a cluster of mental functions such as attention, learning, concentration, memory, reasoning, verbal feedback, problem-solving and decision making [1]. Cognitive function, especially memory, decreases with age [72]. Mild cognitive impairment not affecting daily independent function can be considered as a risk factor for the development of dementia at a later age [1]. Ten percent of the general population over 65 years has dementia, which is further increased to more than 50% in octogenarians [73]. It is generally accepted that the preservation of cognitive function and the prevention of cognitive decline is a key determinant of healthy aging [67].

Patients with diabetes are more likely to experience an accelerated age-related rate of cognitive decline or cognitive dysfunction, and are also more likely to develop dementia [65, 74–78]. In a large retrospective cohort study of 343,062 hospitalized patients with type 1 diabetes mellitus [17], the association between diabetes and dementia was particularly strong in younger diabetics (the relative risk for dementia in patients aged 30–39 years old was 7.10, 4.40 in patients aged 40–49, and 1.16 in elders of 80 years or older). The association between type 1 diabetes and vascular dementia was much stronger than with Alzheimer's disease (AD)

(rate ratio was 2.12 and 1.40, respectively) [17]. However, in the Rotterdam study, diabetes almost doubled the risk of dementia and AD. This finding is in line with results of from the Hisayama study which indicated that even glucose intolerance increases the incidence of AD two to four- fold. A meta-analysis of 14 studies also confirmed that diabetes increases the risk of AD [69].

In most cases, AD and vascular dementia co-exist and evolve on a background of age-related changes in the brain. However, the interrelation between these dementia subtypes and diabetes is still discussed [21, 79–81]. Two major neuropathologies associated with AD are extracellular plaques containing β-amyloid and intracellular neurofibrillary tangles composed of the microtubule-associated protein tau [79]. These two neuropathologies lead to progressive synaptic failure and neuronal loss, and as a consequence, memory loss and cognitive impairment. There are two main forms of AD: a familial form (linked to specific mutations in amyloid precursor protein or presenilin, leading to accumulation of toxic β-amyloid species in the brain by mid-life) and much more common, a sporadic one (manifesting later in life, with less clear triggers are less clear) [79].

Several mechanisms might contribute to the development and progression of both vascular dementia and AD including: (a) high glucose concentration, which has toxic effects on cerebral neurons through osmotic insults and oxidative stress; (b) the enhanced formation of end-products with potentially toxic effects on neurons; (c) increased release of inflammatory cytokines that can be neurotoxic. In experimental studies by Jolivalt C.G. and colleagues [82, 83], mice with systemic insulin deficiency were characterized by reduced insulin-signaling pathway activity in the brain. This phenomenon was associated with biochemical and behavioral features of AD (where amyloid-β (Aβ) protein and Tau phosphorylation levels were related to learning deficits). It was also established that the presence of type 1 diabetes was associated with increase in the progression of AD in mice model. In their later study [81], the authors showed that in amyloid precursor protein (APP) transgenic and insulin-deficient diabetic mice, similar manifestations of peripheral neuropathy and potentially convergent neurotoxic mechanisms were observed. The authors attributed these disorders to changes in the level of glucose and insulin in the blood in diabetes and/or with Aβ accumulation in the APP transgenic mice.

Morales-Corraliza et al. [84] examined brain tissue from STZ-treated type 1 diabetic adult male vervet monkeys which received twice-daily exogenous insulin injections over 8–20 weeks. The study found multiple biochemical changes in the brain (dysregulation of the insulin-signaling pathways, changes in tau phosphorylation, a decrease in neprilysin expression in the hippocampus coupled with a localized Aβ increase) associated with the development of AD.

In 2014, Ouwens D. Margriet and collegues [85] conducted the first human study, which examined the levels of cerebrospinal fluid (CSF) biomarkers (the change of which is associated with the transition from mild cognitive impairment to AD) in type 1 diabetic adults. It was found that patients with type 1 diabetes had elevated levels of CSF phosphorylated Tau (pTau), Aβ42 and low-density lipoprotein receptor-related protein 1 (sLRP1), as well as a tendency to increased CSF Tau levels (as compared to the control group). In patients with type 1 diabetes, increasing Tau levels were associated with a deterioration of white matter integrity in the right inferior fronto-occipital tract (which was decreased in type 1 diabetic patients and was associated with cognitive function) [85].

One of the mechanisms of AD development in diabetes can be the carriage of APOE ε4 allele (ApoE4 regulates lipid homeostasis by mediating lipid transport from one tissue or cell type to another) [86]. APOE ε4 is an established risk factor for both late AD and for cerebral amyloid angiopathy. In addition, APOE e4 increases the risk of hypertension, which is a well-known risk factor for cognitive decline [87].

The APOE ε4 allele is considered as a genetic risk factor of the development of late-onset AD in several populations. In the case-control study of Montufar S., et al., conducted on 56 people with clinically diagnosed AD (≥65 years of age) and 58 unrelated healthy subjects (≥65 years of age), it was established a high-risk association between APOE ε4 allele carriers and late-onset AD [88].

Association of *APOE*-ε4 with Alzheimer's disease risk was also found in the study of 533 healthy middle-aged individuals (among them there were 207 heterozygotes and 65 homozygotes of substantial representation of ε4-carriers). Authors established that *APOE-ε4* has additive effects on gray matter volumes in regions relevant for AD pathophysiology already in healthy individuals. These results also indicate dose-dependent disease vulnerability on the brain structure level in ε4-carriers [89].

In the same time, there are data about differential effects on memory performance depending on age in ε4-carriers were shown [90–92]. In these studies young adults and children (ε4-carriers) had better cognitive performance as compared to noncarriers, whereas with ageing, this carriage adversely affects cognitive ability [93].

Till now, there is no unified understanding of the cellular and molecular pathogenetic links of diabetes and AD. Recent studies that have established general pathophysiological changes and signaling pathways (PI3K-GSK3β signaling, neural stress signaling and inflammatory pathways) between AD and type 2 diabetes, called ‘type 3 diabetes’, cannot yet clearly explain how stimulators of signaling insulin act for the purposes of neuroprotection in AD brain [94].

(6) Treatment strategy

Given the advances in medicine over the past few decades, the number of aging patients with type 1 diabetes, facing new problems, is steadily increasing. In this case, patients with type 1 diabetes (unlike type 2 diabetic patients) are usually compliant, and therefore, cognitive dysfunction creates a sense of "lack of control" over their illness for the first time in their lives [50].

According to long-term prospective studies (DCCT and EDIC), good glycemic control is associated with slower cognitive decline in patients with type 1 diabetes. DCCT and EDIC studies also demonstrated a significant reduction in common vascular events with improved glycemic control and a decrease in the progression of intima-media thickness in the carotid artery, suggesting that this approach would be useful as would reduce the progression of cerebrovascular risk [30].

However, it should be noted that in the presence of cognitive impairments in diabetes mellitus it is difficult to achieve individualized glycemic goals, control blood pressure and blood lipid spectrum, adherence to an adequate diet. The presence of cognitive dysfunction adversely affects the ability of patients to monitor glucose levels and adjust insulin doses [68]. At the same time, new advances in technology (insulin pumps, the careful use of continuous glucose monitoring and Bluetooth-enabled insulin pens) help patients with type 1 diabetes manage their disease safely [50].

Several organizations have released neuropsychological assessment tools (among others the Mini-Mental State Examination and the Montreal Cognitive Assessment) to identify risk groups for the development of cognitive dysfunction [68, 95–97]. There are ongoing studies assessing the possibility of preventing or slowing the onset of diabetes to maintain cognitive function in the elderly [68].

According to Recommendations of American Diabetes Association 2017 [68], to prevent and slow the progression of cognitive impairment in diabetes mellitus recommended the following: to determine the goals and therapeutic approaches for diabetes management, it is necessary to evaluate the medical, mental, functional and social geriatric domains in older

adults; in older adults experiencing limitations in their basic and instrumental activities of daily living, the improvement of the quality of life requires the screening of geriatric syndromes; adults 65 years of age or older need an annual screening of cognitive impairment; older adults (>65 years) with diabetes should be considered as a high priority for depression screening and treatment; elderly people with diabetes should avoid both hypoglycemia and hyperglycemia, by regulating glycemic targets and pharmacological interventions; treatment of diabetes with goals similar to those for younger adults, applies to older people who are cognitively and functionally intact and have a significant life expectancy [68].

(7) Knowledge gaps and recommendations for future research

Firstly, as many of the previous studies have included older patients, who have survived for many years on insulin treatment (to reach an age range when dementia is becoming more common) it should be taken into account that such a long time period, from early childhood decades ago until today, covers very different treatment options. In the early days, insulin therapy was primitive as compared to modern treatment. This means that historical cohort effects could play a role, and that modern patients diagnosed and treated in the post-DCCT era might be much better off regarding risk of cognitive decline and dementia. Thus, newer treatment strategies might be associated with delayed onset and reduced degree of cognitive impairment, but this concept has to be verified in future studies.

Secondly, there is a clear need to assess the impact of other cardiovascular risk factors including hypertension, dyslipidaemia and arterial stiffness.

Thirdly, previous neuroimaging studies were cross-sectional. We need more prospective studies, especially focused on diabetes-related brain functional reorganization.

Fourthly, little is known about the relationship between cognitive dysfunction and altered autonomic cardiovascular regulation, and their relative contribution to cardiovascular morbidity and mortality.

Finally, it remains to be elucidated whether development and application of diabetes-specific neuropsychological assessment tools in clinical practice can improve patient outcome.

(8) Conclusions

Progress in medical technologies has led to a marked improvement in life expectancy in patients with type 1 diabetes. Unfortunately, a natural consequence of longer life is an increased risk for the development of long-term diabetes complications. Therefore, there is growing interest in clinical assessment of cognitive function and quality of life in all patients with diabetes. The results of numerous studies have clearly shown higher rates of cognitive dysfunction and its faster progression in type 1 diabetes. Concurrently, an emphasis is put on studying the mechanisms responsible for the development and progression of various forms of cognitive impairments in diabetic patients. Although the mechanisms underlying this link are not completely understood, several lines of evidence suggest that both the direct effects of altered glucose metabolism on the brain and diabetes-related cardiovascular disease might be implicated. Since the presence and progression of cognitive dysfunction significantly worsens the quality of life of diabetic patients, further studies based on novel neuroimaging methods and biomarkers are warranted to tackle this problem.

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