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Cognitive Impairment in Diabetes Mellitus

Al-Zahraa Yosef[1], Nermin A. Hamdy[2], Nouran Hamza[3], Michael Atef Fawzy[1], Ahmed R. N. Ibrahim[4,1*]

[1]Department of Biochemistry, Faculty of Pharmacy, Minia University, Minia 61511, Egypt
[2]Department of Neurology and Psychiatry, Faculty of Medicine, Minia University
[3]Medical Agency for Research and Statistics (MARS), Giza, Egypt. PO, 12655
[4]Department of Clinical Pharmacy, College of Pharmacy, King Khalid University, Abha 62529, KSA

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Abstract

Cognitive function is a broad term that refers to mental processes involved in acquiring knowledge, manipulating information, and reasoning. Preserved cognitive functioning is integral to maintaining a healthy, active, and independent lifestyle. Both type 1 and type 2 diabetes mellitus have been linked with poor cognitive skills performance and proof of abnormalities in brain magnetic resonance imaging's structure and function. Cognitive impairment may happen at the earliest stages of diabetes and deteriorates over time, and significantly influences diabetes control and management. Cognitive impairment's pathophysiology is multifactorial. The pathophysiology might include hyperglycemia, deficiencies in insulin pathways, oxidative stress, neuroinflammation, and mitochondrial dysfunction. Determining the mechanism of impaired cognitive skills in diabetes is crucial for developing new approaches to therapy. This review article aims at revising our knowledge about the correlation between diabetes and cognitive impairment, emphasizing the putative underlying mechanisms.

Keywords

Cognitive impairment, Diabetes Mellitus, Inflammation

Introduction

Cognitive functions refer to mental processes involved in acquiring knowledge, manipulating information, and reasoning. Cognitive functions include the domains of perception, memory, learning, attention, decision-making, and language abilities. Preserved cognitive functioning is integral to maintaining a healthy, active, and independent lifestyle.

The number of people diagnosed with diabetes worldwide is approximately 537 million individuals. The prevalence of diabetes rises among older populations because diabetic patients' survival rate increases [1, 2]. The developed countries have registered a higher percentage of the elderly population during the last decades, which led to an increase in elderly diabetic patients [3]. Cognition deterioration is ordinary in older adults and can be resulted from several chronic diseases. It has been reported that diabetics had 63.8% cognitive impairment, compared to 10.8% in non-diabetics [4]. Cognitive dysfunction in individuals with diabetes can result from interactions between inherent metabolic abnormalities, such as hyperglycemia, hyperinsulinemia, and micro- and macrovascular complications, in addition to comorbid conditions as hypertension, dyslipidaemia, depression, and obesity.[1, 5-8].

Many studies have raised concerns about the long-term consequences of poor glycemic control on the impairment of cognitive functions [9]. On the other hand, cognitive impairment has a critical impact on diabetics. It significantly affects diabetes management [1, 10]. Cognitive impairment may affect the need for precise assessment of antidiabetic medications, compliance and adherence with these medications, and patient education provision [11].

Although diabetes is linked to an increased risk of cognitive impairment, awareness of the correlation between the two diseases is low, and limited recommendations are found to lead clinicians to address cognitive impairment in diabetics [12]. Clinical guidelines in diabetes have just started to emphasize the consequences of cognitive dysfunction in diabetics [11].

Here, we aim to synthesize knowledge about the correlation between diabetes and cognitive impairment, focusing on this correlation's possible mechanisms.

1. Impaired cognitive functions in Diabetic patients

The effects of Diabetes on the Peripheral Nervous System (PNS) are well established a long time ago. However, its impact on cognitive functions are often overlooked [13]. Cognitive impairment refers to a continuum of severity from “mild” (MCI) which is a cognitive deficits that do not significantly interfere with the autonomy or social behavior of the patient and appears in psychometric assessment, to “severe” such as dementia that interferes with activities of daily life [14].

Numerous studies indicate a relative memory impairment associated with aggressive therapy that is consistent with the effects of medial temporal dysfunction and severe hypoglycemia [15]. However, optimal therapy may cause improved cognitive function in young type 1 diabetic patients [16].

Several studies have found an association in elderly patients between T2D and mild cognitive impairment (MCI), Ma et al. showed that the presence of MCI in the T2D accelerated the median progression to dementia by 2.74 years [17, 18]. According to Berg et al., the association between diabetes and cognition differed among the domains; the processing speed was

**** Correspondence:*** *Ahmed R. N. Ibrahim*
Tel.: *+966554088979*
Email Addresses: *aribrahim@kku.edu.sa, a.ibrahim@minia.edu.eg*

significantly affected in 63% of the studies; attention, in 50%; memory in 44%; cognitive flexibility in 38%; and general intelligence in 31%. These functions are relevant as they involve behaviors such as problem-solving and judgement [19].
Other studied domains of cognitive functions in diabetic patients included:
- Impaired executive functions, concept formation, cognitive flexibility, and anticipation [20, 21].
-Impaired motor speed task [15].
-Impaired visual-spatial ability and memory [16].
-Decreased memory, language, and executive function (attention, concentration, and psychomotor speed) performance [22].

2. Putative mechanisms underlying cognitive impairment in diabetic patients

2.1. Hyperglycemia

Hyperglycemia is the main sign of type 1 diabetes mellitus (T1DM), T2DM, and GDM, resulting from a drop in insulin level to become inadequate for meeting the tissues' normal blood glucose demands. Hyperglycemia is found to be associated with cognitive decline in several reports [6, 7]. Several studies have shown an association between cognitive impairment and glycated hemoglobin (HbA1c) [6, 20, 23]. Zheng, et al. looked at the probable correlation between levels of HbA1c and long-term cognitive impairment and found that a 1 mmol/mol rising in HbA1c was significantly associated with deterioration in cognitive tests [24]. Moreover, Gupta et al. has confirmed this association, although the duration of their study was shorter [25]. One suggested mechanism of hyperglycemia-induced cognitive decline is the formation of advanced glycation end products (AGEs) [26]. A number of studies have shown the association between cognitive decline and AGEs, which suggested that AGEs are a biomarker of cognitive decline in diabetes patients. Spauwen et al. found a correlation between AGEs and poorer recall of delayed-word and worse overall cognitive skills [26]. Similarly, Wang et al. found that the measured levels of soluble receptors of AGEs and AGE-peptide T2DM patients were associated with mild cognitive impairment (MCI) [27]. The MCI group has been found to have an elevated level of AGE-P (3.55 vs. 2.71 U/mL) and a reduced level of its soluble receptor sRAGE (0.87 vs. 1.05 ng/mL) compared by the control group [27]. AGEs are products of non-enzymatic interactions between peptides and reduced sugars, mainly glucose [28]. These reactions occur in hyperglycemic and oxidative stress conditions, forming Schiff base. This Schiff base may undergo further non-enzymatic reactions to produce Amadori products, which is stable. They further transform into AGEs [29]. The glycation and cross-linking of proteins (e.g. amyloid and collagen) to generate AGEs can damage their structure and activity. Moreover, the AGEs buildup stimulates inflammatory, oxidative, and thrombosis reactions leading to cognitive decline [27].
Central nervous system (CNS)-related impairment and cognitive dysfunction have been correlated to the decline of cerebral blood flow [30, 31]. The hyperglycemic effect on the blood flow and vascular system has been well established. Hyperglycemic states induce unusual endothelial cell proliferation, narrowing the blood vessels, and dropping the organs' perfusion [30]. The blood-brain barrier (BBB) integrity and brain homeostasis have been affected by this process [30]. Brain vascular damage decreases amyloid-β (Aβ) protein clearance, deprives the brain of essential neurotransmitters, and allows oxidative and inflammatory molecules to infiltrate and damage the CNS [32, 33].

2.2. Insulin Resistance

Insulin resistance has a role in the phathophysiology of cognitive impairment. Several reports have demonstrated the correlation between insulin resistance and cognitive impairment [34-37]. Abnormalities in the insulin-signaling pathway may result in increased Aβ protein production, which is a product of β and γ secretase action on the amyloid precursor protein (APP). APP is typically cleaved by α-secretase, where soluble APP fragments (sAPP-α) are produced and participates in cell viability. Nevertheless, in diseases withimpaired cognition, β and γ secretases cleave most of APP, and release Aβ. Several reports showed that insulin therapy reduces Aβ level and increases sAPP-α production in the CNS, suggesting that sAPP-α secretion is mediated by insulin [38, 39], hence stimulating the insulin-signaling pathway [40, 41]. A cohort study has shown an association between Aβ plaques and cognitive impairment on one hand and serine-phosphorylated IRS-1 on the other hand [42]. A study compared 20 of the insulin-signaling pathway genes expression in cognitively impaired patients and healthy subjects and showed that eight of these genes are linked to cognitive skills [43].

2.3. Oxidative Stress

Diabetes mellitus is characterized by glucose oxidation impairment, lipid peroxidation, anti-oxidant-free radical imbalance, reactive oxygen species (ROS) production, and AGEs formation [44]. ROS affects the pathway of insulin signaling by decreasing insulin production and causing insulin resistance [45]. ROS activates insulin resistance in the peripheral tissues by disturbing the transduction of insulin receptors, leading to a down-regulation of cellular GLUT4 transporter expression [46]. Moreover, elevated ROS levels, superoxide dismutase, catalase, and anti-oxidant enzymes were shown to impair diabetic control [47, 48]. Superoxide dismutase regulates superoxides, which are by-products of glucose metabolism and cause cellular damage [44].The brain has a high lipid content, a high oxygen consumption rate, and low anti-oxidant enzymes. Thus, the brain is susceptible to oxidative stress [49]. Oxidative insults in the brain may enhance cellular apoptosis, leading to neuronal impairment and synapse loss [50]. Insulin resistance in the brain may also decrease anti-oxidant enzymes and increase free radical content, which chemically modifies the lipids, proteins, DNA, and RNA, affecting nerve cells' structural and functional [51]. It has been demonstrated that brain mitochondrial damage can lead to brain cell apoptosis, thus, cognitive dysfunction [52, 53]. Mitochondria convert energy into ATP; however, mitochondria also produce free radicals [50]. Mitochondrial quality control maintains the mitochondrial network. Diabetes causes uneven mitochondrial dynamics, impaired mitophagy, and proteostasis dysfunction. The mitochondrial quality control mechanism is a complex integrated hierarchical network of pathways, thus alterations in any mechanism can affect the quality control of mitochondria [2]. Insulin controls the function of mitochondria by stimulating the PI3K/AKT pathway and suppressing the FOXO1 pathway. Moreover, the electron transport proteins need heme for their functions. Heme depletion results in mitochondrial electron transport chain dysfunction, leading to mitochondria dysfunction [54]. Insulin resistance in brain cells may reduce anti-oxidant enzymes by elevating the p53 expression by inhibiting PI3K/AKT signaling [55]. Mitochondrial abnormalities are seen in cognitive dysfunctions. The activity of complex IV in the mitochondria, which performs an essential role in cell degeneration and necrosis, has been reduced in cognitive

impairment [56-59]. Correia et al. [57] noted that rodents given intracerebroventricular (icv) streptozotocin (STZ) injection encountered brain insulin resistance besides elevated free radical levels accompanied by mitochondrial deformities. As mentioned before, increased generation of brain free radicals might lead to apoptosis, neuronal cell death, and repress neurogenesis [60]. Increased expression of p53 activates nitric oxide synthase isoforms, essentially NADPH-oxidase (NOX) -1 and 3, and nitric oxide synthase (NOS) -1, 2, and 3, also represses anti-oxidant enzymes expression such as GPX, CAT, and SOD [61-63]. Moreover, hyperglycemia may decrease the levels of antioxidant enzymes, especially glutathione reductase [64].

2.4. Neuroinflammation

One of the features of diabetes is an altered inflammatory profile. Anderson et al. showed that the breakdown of immune tolerance in diabetic mice leads to the development of autoreactive T cells [65]. Moreover, CD8+ T cells can induce destructive inflammatory infiltration of peri-islet and diabetes [66, 67]. Interestingly, the CD20+ B cell profile also alters during diabetes progress. Studies observed That B cells closely align with the CD8+ T cells migration in islets infiltration [68, 69]. Macrophages are also important mediators of islet inflammation because of their capability to produce ROS and cytokines, such as Interleukin 1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) [68, 70]. The ALPHA particular pathway was suggested by Maedler et al., who noted that hyperglycemia might cause IL-1β production [71]. As stated earlier, adipose tissues produce adipocytokines such as TNF-α, IL-1β, and IL-6 that contribute to insulin resistance. They are pro-inflammatory cytokines, enhancing a chronic low-grade inflammatory state [72, 73]. Adipose tissues also release leptin and adipokines, where leptin enhances insulin sensitivity via elevating insulin production, glycogen synthesis, glucose utilization, and fat metabolism. Insulin resistance through inhibiting the PI3K/AKT signaling and hyperglycemia through the production of AGEs can also stimulate pro-inflammatory cytokine production. Elevated inflammatory mediators are a shared condition in impaired cognitive function and diabetes. Neuroinflammation may cause cognitive dysfunction, and many reports have reported brain inflammation in cognitive impairment [74-76]. Microglia activation also may lead to cognitive impairment [77, 78]. The primary CNS immune defense mechanism occurs via the activation of microglia proliferation in macrophages [79, 80]. IL-2, IL-6, and TNF-α activate microglia as they are neurotoxic cytokines [81]. Microglia activation may modify the gene expression of numerous pro-inflammatory cytokines such as IL-1β, TNFα, superoxide, nitric oxide, quinolinic acid, and eicosanoids [79, 80, 82]. This attracts leukocytes to the CNS, increasing the inflammatory processes and enhancing glial damage and neuron apoptosis [81, 83]. Aβ enhanced production by oxidative stress stimulates the NF-κβ, a crucial inflammatory cytokine that regulates numerous immune response genes [81]. NF-κβ activation leads to interleukins production (IL-2, IL-6, IL-8) and TNF-α [81]. The STZ-rats hippocampus region has shown elevated NF-κβ expression causing an increased pro-inflammatory cytokines production [84]. In elderly diabetic patients, TNF-α, CRP, and IL-6 have been found to correlate with MCI [75]. A higher level of these pro-inflammatory markers has been found in MCI groups than in control; however, there was no significant difference between the groups in IL-6 level [75]. Nevertheless, IL-1β and leptin serum levels were significantly elevated in the MCI group compared to the control [85]. Adiponectin has an anti-inflammatory property via depressing the phagocytosis of macrophages that releases TNF-α [86]. However, TNF-α and other inflammatory cytokines can also inhibit the formation of adiponectin. The inflammatory processes can also affect cerebral vasoregulation, enhancing cognitive deterioration in diabetic patients [74, 87]. Chung et al. showed that increased vascular adhesion molecules and hs-CRP levels were associated with depressed cerebral vasoreactivity and vasodilation [87]. Moreover, the decline in vasoreactivity has been associated with a decrease in cognitive functions in diabetic subjects. IL-6 is a pro-inflammatory cytokine classically associated with orchestrating an immune response to invading pathogens [88]. However, IL-6 can also directly or indirectly modify central nervous system function and alter higher-order functions, such as learning and the consolidation of memories [89]. Over-expression of IL-6 in mice promotes abnormal dendritic spine formation at both inhibitory and excitatory synapses and is associated with impaired cognitive abilities and learning deficits [89-91]. Prenatal exposure to IL-6 in rats leads to elevated hippocampal levels of IL-6, altered expression of NMDA and GABAA receptors, and deficits in spatial learning [92]. Furthermore, as previously mentioned, IL-6 can modify synaptic transmission and hippocampal synaptic network activity by modulating GABA-mediated signaling [93, 94]. Thus, IL-6 is a multifaceted neuroinflammatory molecule that can modify neural function by modulating synaptic transmission and synaptic plasticity, promoting neurite outgrowth, neurogenesis and/or neuronal survival [95-98].TNF-α is also involved in several processes relevant to cognition in the normal brain, including neuronal viability, neurotransmitter production [99], neuroendocrine responses [100], and modulation of neuronal and glial cell function [101]. In previous research, after activation of the immune system, elevated levels of TNF-α have been correlated to cognitive impairment in TNF over-expressing animal models [102-104] and clinical studies [105].

Conclusion

In T1DM and T2DM, degrees of cognitive impairment have been noticed in many domains. The underlying mechanism of diabetic cognitive dysfunction is complex but likely involves hyperglycemia, insulin resistance, increased oxidative stress, and inflammatory pathways. Determining the mechanism of impaired cognitive skills in diabetes is crucial for developing new approaches to therapy.

Conflict of interest

There are no conflicts of interest to declare.

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