https://doi.org/10.48047/AFJBS.6.2.2024.3828-3834

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Vitamin E and Cognition In Diabetes Mellitus

Mona Tarek Mohamed Ali Elsherif, Ahmed Bahaa Eldin Abdallah, Mohamed Abdelhamed Mohamed, Khaled Abdelfattah Abulfadle

Medical Physiology Department, Faculty of Medicine - Zagazig University, Egypt

Corresponding author: Mona Tarek Mohamed Ali Elsherif

Email: monytrk1992@gmail.com, MTElsharef@medicine.zu.edu.eg

Article History

Volume 6, Issue 2, Apr-Aug 2024

Received: 5 August 2024

Accepted: 15 August 2024

Published: 15 August 2024

doi: 10.48047/AFJBS.6.2.2024.3828-3834

Abstract: Previous studies indicate that diabetes mellitus might be accompanied by a certain erosion of brain function such as cognitive impairment. Vitamin E is an important antioxidant that primarily protects cells from damage associated with oxidative stress caused by free radicals. The brain is highly susceptible to oxidative stress, which increases during ageing and is considered a major contributor to neurodegeneration. High plasma vitamin E levels were repeatedly associated with better cognitive performance. There is evidence of a positive association between reduced levels of vitamin E and risk factors of type 2 diabetes mellitus (T2DM) including insulin resistance and hyperglycemia. It has been proposed that vitamin E inhibits glucose oxidation which is a necessary step for protein glycosylation and producing hemoglobin A1c (HbA1c). Additionally, a prior meta-analysis of prospective cohort studies showed that a higher intake of foods rich in vitamin E (nuts, seeds, liquid oil, and raisin) was associated with a reduced risk of hyperglycemia and diabetes. There is also further evidence indicating the beneficial effects of adherence to vitamin-E-rich diets on glycemic control in diabetic patients. Several clinical trials have examined the efficacy of Vitamin E supplementation in improving cognitive function in diabetic patients. Results have been mixed, with some studies showing beneficial effects while others reporting no significant improvements. This inconsistency may be attributed to variations in study design, participant characteristics (age, disease duration, severity), dosage of Vitamin E, and the duration of supplementation. Larger, well-designed clinical trials with standardized protocols are needed to clarify these findings.

Keywords: *Vitamin E, Cognition, Diabetes Mellitus*

Introduction.

Although the brain can use various metabolic substrates for energy production and utilization, it predominantly uses glucose as the substrate for intermediary metabolism under normal physiological conditions [1,2]. The neuronal functions such as motor commands, sensory perceptions, memory storage, and intellectual output are highly dependent on the basal and on-demand metabolic activity of brain tissue. A graphical representation of normal neuronal glucose utilization is shown in Figure (1) [3].

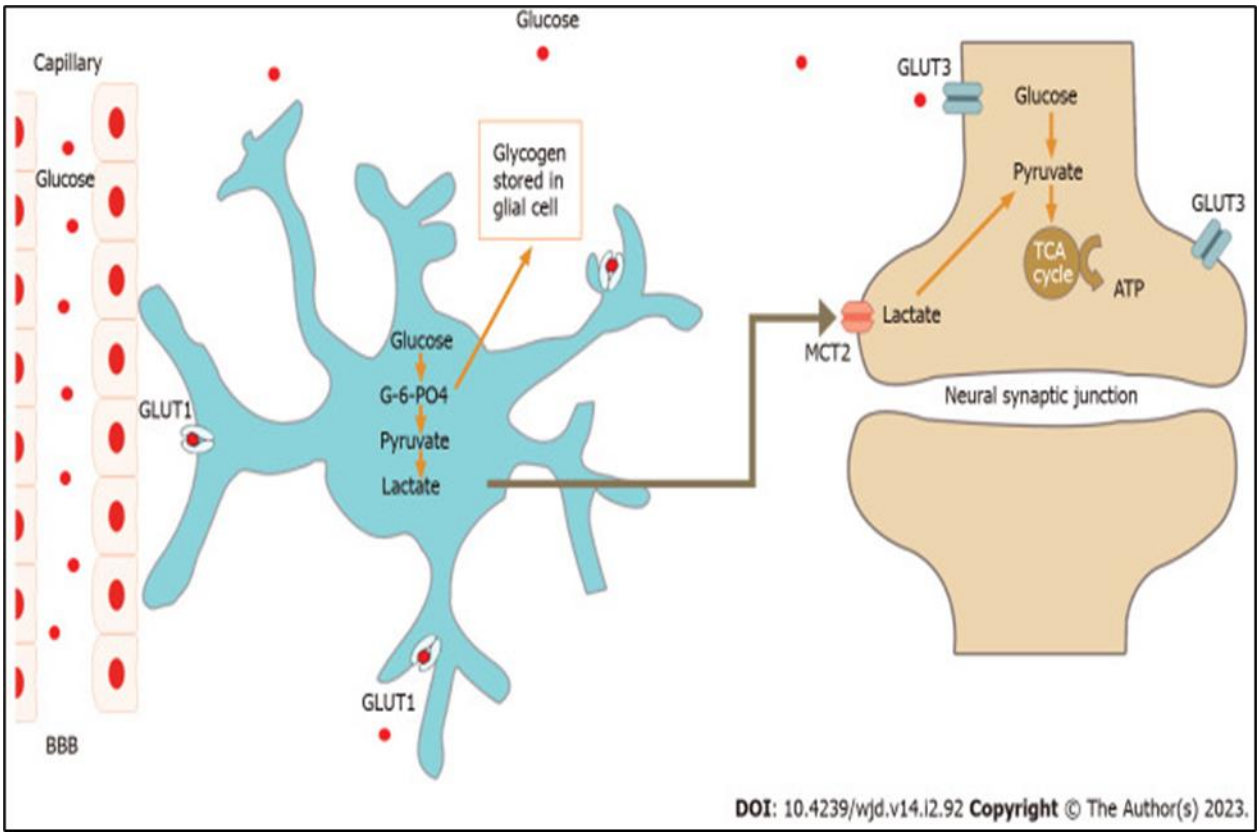

Figure (1): Neuronal utilization of glucose under normal resting condition. G-6-PO4: Glucose 6-phosphate; BBB: Blood brain barrier; TCA: Tricarboxylic acid; GLUT: Glucose transporter; MCT2: Monocarboxylate transporter [3].

The energy metabolism of the brain is highly variable in different areas depending on the neural functions and output of these regions. Most of the neural energy consumption is at the synaptic level for signal production and transmission along with the restoration of membrane potentials after depolarization [4]. To facilitate optimal function of brain areas depending on the degree of neuronal output, supply-according-to-demand mechanisms have evolved through neurovascular and neurometabolic coupling for efficient substrate supply to the brain for fueling intermediary metabolism. Neurovascular coupling involves an increase in blood flow and volume to improve glucose and oxygen supply to the areas of excess neuronal activity following stimulation, while neurometabolic coupling involves the changes in substrate utilization of astrocytes (predominantly by glycolysis) and neurons (predominantly by oxidative metabolism). These mechanisms are developed over centuries of genetic and metabolic adaptations in the evolution of the highly performing intellectual brain of modern man [3].

Brain metabolism and cognition

Intellectual capacities of the human brain such as memory, mathematical performance, cognition, language, and executive functions are highly dependent on the degree of cerebral metabolic activity [5]. Therefore, any gross alterations in the metabolic milieu of the brain are associated with marked changes in the neurocognitive balance in health and disease. Recent evidence suggests that there is a significant reduction in glucose metabolism and functional connectivity between the intrinsic connectivity networks of the brain with ageing, which would explain the age-related cognitive decline and decline in executive functions [5,6].

Pathophysiology of central nervous system disease in diabetes

DM can affect any organ system in the body, especially neural tissues and cerebrovascular structures causing various structural and functional disorders of the nervous system. Abnormalities in glucose metabolism including fasting and post-prandial hyperglycemia, prediabetic state and frank diabetes can result in neural dysfunction and various acute and chronic nervous system disorders including cognitive decline [7,8]. Cognitive dysfunction of chronic (and usually irreversible) nature that affects the usual intellectual performance of an individual is considered dementia [3].

Abnormalities in glucose homeostasis in diabetes are associated with marked changes in the structural and functional alterations in the brain. Several brain areas such as the hippocampus are very sensitive to local alternations in glucose metabolism inherent to diabetes which may result in neuronal synaptic reorganization, and augmented astrocyte proliferation. These in turn can result in cognitive decline of diabetes especially because glucose and insulin are instrumental regulators of cognitive function [3, 8].

Glucose hypometabolism manifests in animals with T2DM. Streptozotocin (STZ)-induced diabetic mice with cognitive impairment had a peculiar metabolic phenotype—decrease energy metabolism in the brain regions [9]. Like the human brain, brain region-specific metabolic disorders also exist in T2DM mice with cognitive impairment. Notably, metabolic patterns in the hippocampus were largely differentiated in T2DM mice with cognitive impairment relative to control mice [10]. Decreased glucose metabolism was found in diabetic mice's brains, while increasing glucose availability in specific brain areas can positively modulate the performance in cognitive tasks in T2DM mice [11].

An association between T1DM and cognitive impairment was reported. However, the mechanisms by which T1DM induces cognitive impairment are still unknown. Studies confirmed that T1DM mice induced by streptozotocin (STZ) injection had impaired working memory and spatial memory [12]. Long-term potentiation (LTP) induction defects and synaptic loss were observed in mice 20 weeks after STZ injection. Decreased levels of synaptic proteins, including the N-methyl-D-aspartic acid receptor (NMDAR) subunit NR2A, synaptophysin (SYP), and postsynaptic density 95 (PSD95), were found in the hippocampus and prefrontal cortex, revealing similarities in the alteration patterns of these synaptic proteins in aged Alzheimer's disease (AD) APP/PS1 mice and T1DM mice [12]. These findings expand the understanding of the mechanisms underlying T1DM-induced cognitive impairment.

Cognitive dysfunction and synaptic damage are highly associated with T1DM and Alzheimer's disease. Previous studies reported that synaptic plasticity, including LTP and long-term depression (LTD), is decreased in young adult-onset STZ rats, and APP/PS1 mice show LTP impairment as early as 3 months of age [13]. Studies assessed the levels of mRNA and protein expression of various synapse-associated proteins. NMDARs are necessary for inducing and maintaining LTP [13].

Abnormal NMDA receptor expression has been associated with the development of diabetic and AD neuropathy. Studies found two downregulated NMDA subunits, NR1 and NR2A, in STZ-induced mice [14]. However, additional results indicated that NMDAR gene expression was upregulated in the cerebellum and the dorsal horn of the lumbar spinal cord in insulin-induced hypoglycemic and STZ-induced diabetic rats [14].

One of the putative mechanisms for cognitive dysfunction in T2DM is insulin resistance (IR) in the brain [15]. Neuronal cells express insulin receptors for their normal functions such as synaptic density and plasticity of dendrites. Through various complex mechanisms, insulin receptor signaling improves synaptic and dendritic functions in the CNS to improve cognitive performance [16].

Abnormalities in insulin signaling and insulin receptor (IR) sensitivity in the neuron and dendritic processes in Alzheimer's disease have led to the hypothesis that metabolic dysfunction may be related to IR dysfunction. IRs are expressed in the neuronal soma and more importantly in synaptic terminals that have a key role in the preservation of memory in the hippocampus [17]. It is generally accepted that insulin signaling enhances memory and facilitates synaptic plasticity in the hippocampus, which has an important role in memory and learning [17].

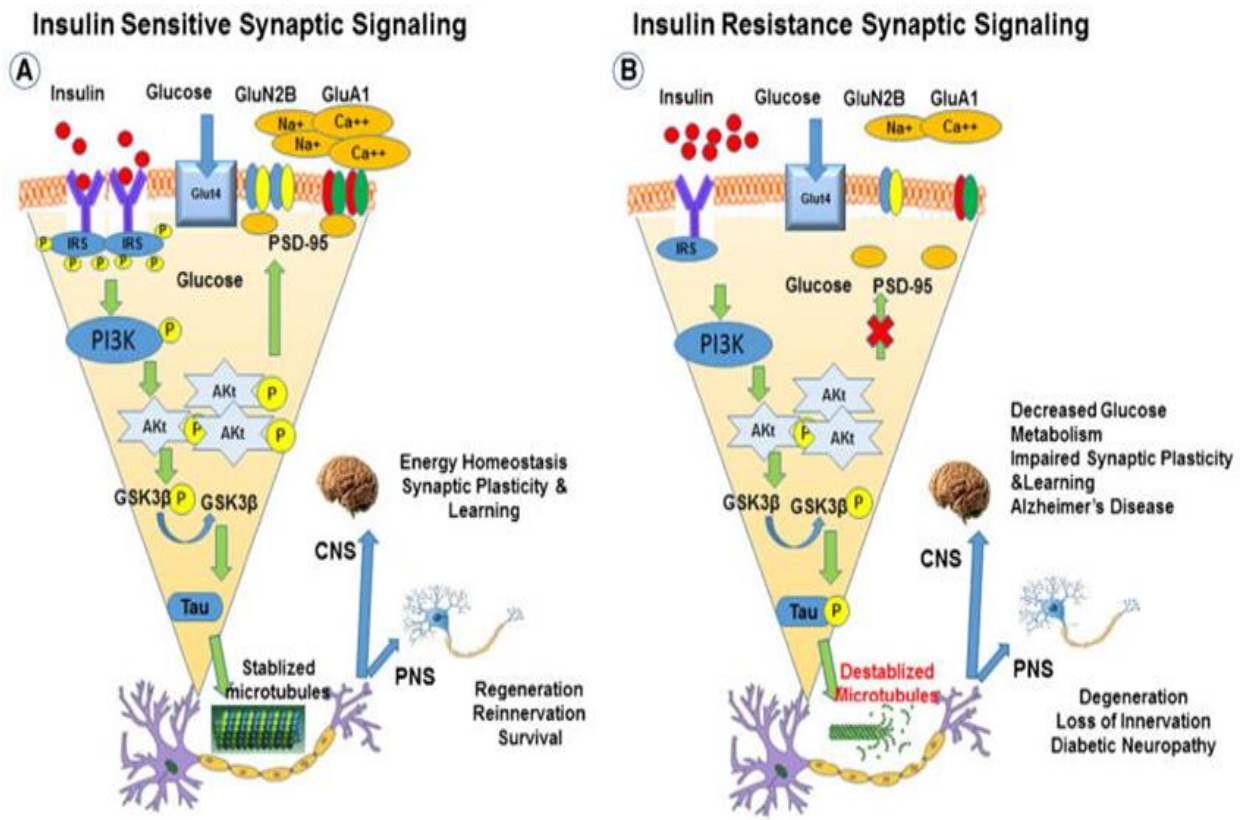

Figure 2: Neuronal insulin signaling in synaptic plasticity and memory in normal and diabetic brain. Schematic outline of neuronal insulin signaling in the normal brain (a) and in the diabetic brain (b). In physiological conditions, insulin binding to its receptor at the synapse triggers phosphorylation of insulin receptor substrate-1(IRS-1). This results in phosphoinositide 3-kinase (PI3K) activation, Akt phosphorylation, phosphorylation of GluA1, and increased presence of GluN2B at synapses. These events favor synapse formation and memory function. In the diabetic brain, insulin resistance decreases levels of insulin receptors and reduces insulin signaling. This leads to decreased levels of GluN2B and GluA1 phosphorylation at synapses, ultimately leading to impaired synaptic plasticity and memory. The reduction in brain insulin signaling increases GSK-3b activity which increases abnormal tau phosphorylation, [17]

Therefore, central IR in T2DM is often associated with impaired cognitive function. The balance between central insulin sensitivity and IR has also been implicated in feeding behavior, satiety, and the development of obesity in experimental models [18].

Overnutrition and obesity, which usually lead to T2DM, were found to be associated with disruption of the blood-brain barrier leading to a state of neuroinflammation which in turn results in cognitive dysfunction. It also results in morphological alterations in the hypothalamic neural circuitry that may augment overeating behavior as a vicious circle aggravating obesity-related pathobiological states. Alterations in the gut microbiome commonly observed as part of the adverse eating habits are also associated with CNS neural changes causing cognitive decline [19].

Diabetes-induced vasculopathy affects the CNS circulation altering the cerebral blood flow remarkably. Both micro- and macrovascular damage involving the cranial vascular bed from accelerated atherosclerotic processes inherent to diabetes are associated with neurocognitive decline and vascular dementia (VaD) [20, 21]. The occurrence of microinfarcts and full-blown strokes is characteristic of longstanding diabetes [20]. Diabetes is identified as one of the most important causes of VaD mandating early diagnosis and proper management to reduce this potential consequence of the disease. A graphical representation of cognitive dysfunction in diabetes is shown in Figure (3) [3].

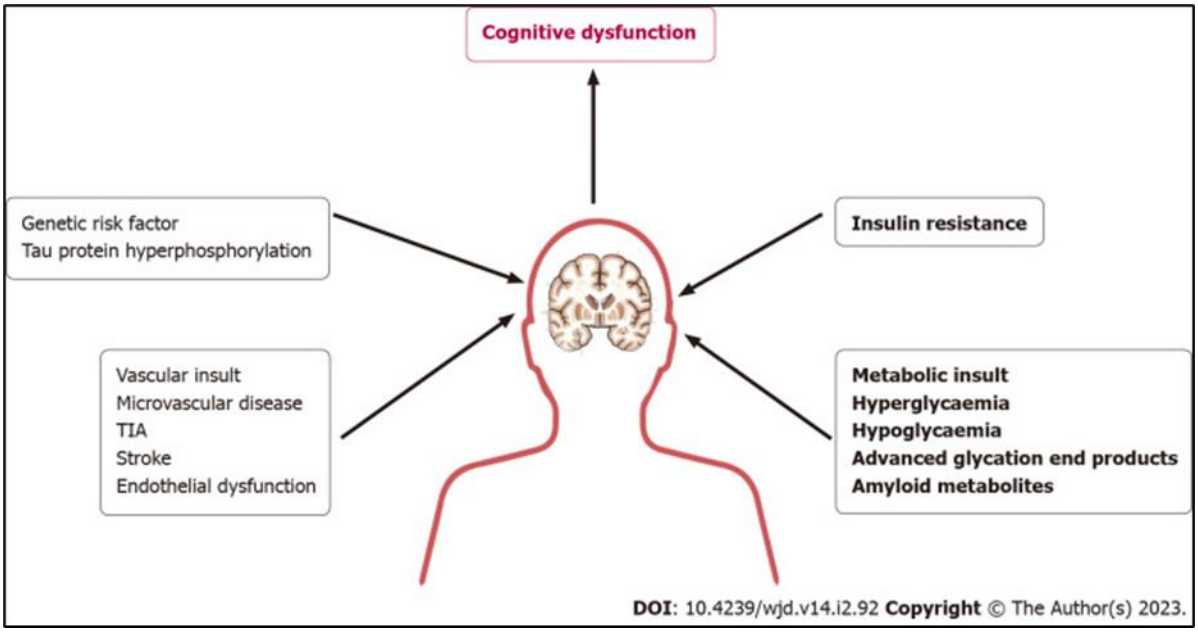

Figure (3): A graphical representation of the pathobiology of cognitive dysfunction in patients with diabetes. TIA: Transient ischemic attack. [3]

Diabetes Types and Dementia

Dementia may occur in patients with any form of diabetes regardless of the type. The degree of cognitive decline in such patients largely depends on the appropriateness of diabetes management. There is a growing interest in the effects of T1DM on brain development, cognition, and dementia, especially as the incidence and life expectancy of patients with diabetes increases. As neuronal conduction is ATP dependent, it remains unknown whether insulin deprivation has a detrimental effect on brain functional connectivity (FC) and cognitive performance in people with T1DM [22].

In adults with type 2 DM (T2DM), deficits in cognitive function can be divided into three stages according to severity: diabetes-associated cognitive decrements, mild cognitive impairment (MCI), and dementia [23].

There is some evidence to support that Alzheimer's disease (AD) may have an association with T2DM based on multiple epidemiological correlation studies [24]. Although the presumed genetic association between type 2 DM (T2DM) and AD (also known as type 3 diabetes) was recently refuted by a well-designed linkage analysis study [25], the two diseases appear to have a strong epidemiological link probably from a causal role of worsening AD in patients with diabetes. The metabolic dysregulation within the CNS may accelerate the progression of AD and would explain this association [26].

Although the pathobiological interlink is not very strong, in 2022, a study considered this association while planning management of patients with T2DM, especially because of the constraints imposed on glycemic care by the development of dementia [27]. Appropriate early administration of medications of the incretin mimetic class such as DPP-4i and GLP-1RA to optimize diabetes control and prevention of AD will help to some extent [27].

There is not much data on the incidence and prevalence of cognitive dysfunction in patients with other forms of diabetes such as diabetes in patients with chronic pancreatitis, monogenic diabetes, and syndromic type of diabetes. However, glycemic care can pose similar problems when cognitive decline becomes moderate to severe as in T1DM and T2DM. Nutritional imbalance from pancreatic diabetes and neurological problems in some patients with syndromic diabetes can pose problems in glycemic care [3].

Impact of dementia on diabetes care

Gradual decline in memory deficits over time is the usual long-term consequence of all forms of irreversible dementia. Worsening memory is expected to have a huge impact on diabetes care especially when patients self-

manage their diabetes. Medication compliance issues with inappropriate meal timings and improper administration of antidiabetic medications can adversely affect glycemic care with further decline in memory function. The resultant fluctuations in glycemia with uncontrolled hyperglycemia and recurrent hypoglycemic episodes will worsen diabetes-related complications and cause a rapid decline in neurocognitive functions [28]. On the other hand, many peptides have an important role in energy homeostasis and insulin resistance and are associated with long-term complications of DM [29, 30]. One of these peptides is Asprosin (ASP), a newly discovered fasting-induced glucogenic and orexigenic protein hormone. Therefore, findings showing that peptides secreted from various tissues regulate lipid, amino acid, and carbohydrate metabolism in the target tissues of insulin have been guiding in DM studies [31].

Vitamin E, particularly alpha-tocopherol, is a potent antioxidant that scavenges free radicals, thereby reducing oxidative stress. Preclinical studies in animal models of diabetes have demonstrated neuroprotective effects of Vitamin E, showing improvements in cognitive function and reduced neuronal damage. However, the translation of these findings to human populations has been inconsistent. (Further research needed to cite preclinical studies on Vitamin E and neuroprotection in diabetes models). [32].
Several clinical trials have examined the efficacy of Vitamin E supplementation in improving cognitive function in diabetic patients. Results have been mixed, with some studies showing beneficial effects while others reporting no significant improvements. This inconsistency may be attributed to variations in study design, participant characteristics (age, disease duration, severity), dosage of Vitamin E, and the duration of supplementation. Larger, well-designed clinical trials with standardized protocols are needed to clarify these findings. [32].
Future research should focus on large-scale, randomized controlled trials with rigorous methodologies to definitively assess the efficacy and optimal dosage of Vitamin E supplementation for improving cognitive function in diabetic patients. Further research is also needed to investigate potential interactions between Vitamin E and other medications or lifestyle factors that may influence cognitive outcomes in individuals with diabetes. A better understanding of the underlying mechanisms and the optimal timing of intervention is crucial for developing effective strategies to prevent or delay cognitive decline in this population.

References

[1] Nordström CH, Forsse A, Jakobsen RP, Mölström S, Nielsen TH, Toft P, Ungerstedt U. 2022: Bedside interpretation of cerebral energy metabolism utilizing microdialysis in neurosurgical and general intensive care. Front Neurol.; 13:968288.
[2] Baker LD, Cross DJ, Minoshima S, Belongia D, Watson GS, Craft S. Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. Arch Neurol. 2011;68(1):51-7.
[3] Sebastian MJ, Khan SK, Pappachan JM, Jeeyavudeen MS. Diabetes and cognitive function: An evidence-based current perspective. World J Diabetes. 2023;14(2):92-109.
[4] Harris JJ, Jolivet R, Attwell D. Synaptic energy use and supply. Neuron. 2012;75(4):762-77.
[5] Watts ME, Pocock R, Claudianos C. Brain Energy and Oxygen Metabolism: Emerging Role in Normal Function and Disease. Front Mol Neurosci. 2018;11:216.
[6] Xu K, Niu N, Li X, et al. The characteristics of glucose metabolism and functional connectivity in posterior default network during nondemented aging: relationship with executive function performance. Cereb Cortex. 2023;33(6):2901-2911.
[7] Barbiellini Amidei C, Fayosse A, Dumurgier J, et al. Association Between Age at Diabetes Onset and Subsequent Risk of Dementia. JAMA. 2021;325(15):1640-9.
[8] Wrighten SA, Piroli GG, Grillo CA, Reagan LP. A look inside the diabetic brain: Contributors to diabetes-induced brain aging. Biochim Biophys Acta. 2009;1792(4):444-53.
[9] Képes Z, Aranyi C, Forgács A, et al. Glucose-level dependent brain hypometabolism in type 2 diabetes mellitus and obesity. Eur J hybrid Imaging. 2021;5(1):3.
[10] Zheng H, Zheng Y, Zhao L, et al. Cognitive decline in type 2 diabetic db/db mice may be associated with brain region-specific metabolic disorders. Biochim Biophys Acta (BBA) - Mol Basis Dis. 2017;1863(3):266-73.

[11] Ruze R, Xu Q, Liu G, et al. Central GLP-1 contributes to improved cognitive function and brain glucose uptake after duodenum-jejunum bypass on obese and diabetic rats. Am J Physiol Endocrinol Metab. 2021;321(2):E392-E409.
[12] Wang Y, Yang Y, Liu Y, Guo A, Zhang Y. Cognitive impairments in type 1 diabetes mellitus model mice are associated with synaptic protein disorders. Neurosci Lett. 2022;777:136587
[13] Sasaki-Hamada S, Sacai H, Oka JI. Diabetes onset influences hippocampal synaptic plasticity in streptozotocin-treated rats. Neuroscience. 2012;227:293-304.
[14] Anu J, Peeyush Kumar T, Nandhu MS, Paulose CS. Enhanced NMDAR1, NMDA2B and mGlu5 receptors gene expression in the cerebellum of insulin induced hypoglycaemic and streptozotocin induced diabetic rats. Eur J Pharmacol. 2010;630(1-3):61-8.
[15] Kullmann S, Heni M, Hallschmid M, et al. Brain Insulin Resistance at the Crossroads of Metabolic and Cognitive Disorders in Humans. Physiol Rev. 2016;96(4):1169-209.
[16] Zhang Q, Jin K, Chen B, et al. Overnutrition Induced Cognitive Impairment: Insulin Resistance, Gut-Brain Axis, and Neuroinflammation. Front Neurosci. 2022;16:884579.
[17] Zilliox LA, Chadrasekaran K, Kwan JY, Russell JW. Diabetes and cognitive impairment. Curr Diabetes Rep. 2016;16(9):87.
[18] Clegg DJ, Gotoh K, Kemp C, et al. Consumption of a high-fat diet induces central insulin resistance independent of adiposity. Physiol Behav. 2011;103(1):10-6.
[19] Cope EC, LaMarca EA, Monari PK, et al. Microglia Play an Active Role in Obesity-Associated Cognitive Decline. J Neurosci. 2018;38(36):8889-904.
[20] Ehtewish H, Arredouani A, El-Agnaf O. Diagnostic, Prognostic, and Mechanistic Biomarkers of Diabetes Mellitus-Associated Cognitive Decline. Int J Mol Sci. 2022;23(11):6144.
[21] Biessels GJ, Despa F. Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. Nat Rev Endocrinol. 2018;14(10):591-604.
[22] Creo AL, Cortes TM, Jo HJ, et al. Brain functions and cognition on transient insulin deprivation in type 1 diabetes. JCI Insight. 2021;6(5):e144014.
[23] Koekkoek PS, Kappelle LJ, van den Berg E, et al. Cognitive function in patients with diabetes mellitus: guidance for daily care. Lancet Neurol. 2015;14(4):329-40.
[24] Kanthi A, Singh D, Manjunath NK, Nagarathna R. 2022 :Changes in Electrical Activities of the Brain Associated with Cognitive Functions in Type 2 Diabetes Mellitus: A Systematic Review. Clin EEG Neurosci. :15500594221089106.
[25] Hardy J, de Strooper B, Escott-Price V. Diabetes and Alzheimer's disease: shared genetic susceptibility? Lancet Neurol. 2022;21(10):962-4.
[26] Pedersen HE, Sandvik CH, Subhi Y, et al. Relationship between Diabetic Retinopathy and Systemic Neurodegenerative Diseases: A Systematic Review and Meta-analysis. Ophthalmol Retina. 2022;6(2):139-52.
[27] Yang X, Qiang Q, Li N, et al. Neuroprotective Mechanisms of Glucagon-Like Peptide-1-Based Therapies in Ischemic Stroke: An Update Based on Preclinical Research. Front Neurol. 2022;13:844697.
[28] Chen NC, Chen CL, Shen FC. The Risk Factors of Severe Hypoglycemia in Older Patients with Dementia and Type 2 Diabetes Mellitus. J Pers Med. 2022;12(12):1247.
[29] Yang, M., Zhang, Z., Wang, C., Li, K., Li, S., Boden, G., Li, L., Yang, G., (2012): Nesfatin-1action in the brain increases insulin sensitivity through Akt/AMPK/TORC2 pathway in diet-induced insulin resistanc. Diabetes 61, 1959–1968.
[30] Luo, K.R., Chao, C.C., Hsieh, P.C., Lue, J.H., Hsieh, S.T., (2012):Effect of glycemic control on sudomotor denervation in type 2 diabetes. Diabetes Care 35, 612–616.
[31] Duerrschmid C, He Y, Wang C, et al. Asprosin is a centrally acting orexigenic hormone. Nat Med. 2017;23(12):1444-53.
[32] La Torre ME, Villano I, Monda M, Messina A, Cibelli G, Valenzano A, Pisanelli D, Panaro MA, Tartaglia N, Ambrosi A, Carotenuto M,Monda V, Messina G, Porro C. 2021: Role of Vitamin E and the Orexin System in Neuroprotection. Brain Sci. 20;11(8):1098.