

A Systematic Review on Diabetic Encephalopathy, Its Type & Biomarkers

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Abstract

Diabetes and its complications become a major reason of morbidity and mortality associated with the changes of life style. Diabetic Encephalopathy is one of the complication of Diabetes Mellitus. The aim of this paper is to review the information on Diabetic Encephalopathy with emphasis on its etiology, pathogenesis and its treatment. Diabetic encephalopathy is the condition in which impairment of brain function occur. Diabetic encephalopathy is the complication of type 1 diabetes mellitus and type 2 diabetes mellitus that lead to cognitive decline. It include two type that are Primary Diabetic Encephalopathy and Secondary Diabetic Encephalopathy. It is caused by combination of metabolic factor, vascular disease factor, endocrine factor and CNS factor. The pathogenesis of autophagy in diabetic encephalopathy is not clearly marked in this review article. But increase level of oxidative stress, neuroinflammation that make CNS inflammation worsen, neuronal apoptotic mechanism that involve insulin signaling defect and C-peptide deficiency, and role of hyperglycemia maybe seen. Treatment with oral hypoglycemic agent and combination of antidiabetic medication for the prevention of diasese should also be studied. Non pharmacological therapy that is exercise also very helpful.

Keywords: Diabetes mellitus, Diabetic Encephalopathy, Cognitive decline, Oxidative stress, Hyperglycemia

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INTRODUCTION

Hyperglycemia, an excessive rise in blood glucose levels, is the primary symptom of diabetes mellitus (DM) a complicated and varied metabolic disease. This happens when either there is a resistance to the activities of insulin or pancreatic β -cells are unable to release enough insulin to maintain normoglycemia [1]. A condition that can arise from either type 1 or type 2 diabetes is known as "diabetic encephalopathy". There are significant secondary problems linked to both forms of diabetes that impact the kidney, retina, peripheral nerves, and vasculature [2]. Recently central nervous system issues have been identified more frequently that are known as Diabetic Encephalopathy [3]. A chronic consequence of diabetes mellitus is Diabetic Encephalopathy (DE) affects the central nervous system (CNS) and is characterized by motor dysfunctions and cognitive impairment that can compromise postural balance [4]. The clinical research revealed that even in those patients without diabetes mellitus, elevated glucose levels may be a risk factor for cognitive

impairment [5]. R. de Jong coined the term "diabetic encephalopathy" (DE) in 1950 [6]. It is a chronic condition that impairs both motor and cognitive function. Individuals diagnosed with DE have distinctive alterations in the brain, which include blood vessel angiopathy, cranial nerve demyelination, and neural alterations that result in a reduction in cognition [7]. DE impact learning, memory, problem solving, informative proposal, mental and motor speed. Compared to their healthy counterparts, patients with diabetes experience a markedly higher incidence of introversive symptoms, particularly physical complaints, insomnia, compulsive behaviors, and melancholy moods [8]. Hyperglycemia, hypertension, hypercholesterolemia, and hyperinsulinemia, as well as their commonly associated characteristics like obesity, are directly linked to the increased morbidity and mortality of encephalopathy in patients with type 2 diabetes [9] (Figure 1).

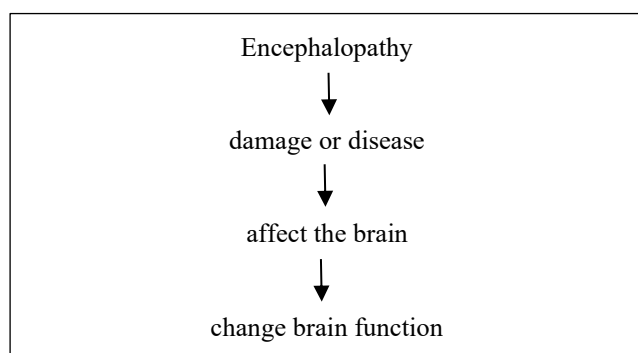


Figure 1. Diabetic Encephalopathy.

TYPES

Two varieties of diabetic encephalopathy are suggested that Primary Diabetic Encephalopathy and Secondary Diabetic Encephalopathy. Hyperglycemia and decreased insulin sensitivity, especially in type 1 diabetes, are the main causes of primary diabetic encephalopathy. This type is connected with a duration-related pattern of apoptotic neuronal death and cognitive impairment. The cause of secondary diabetic encephalopathy appears to be hypoxicischemic encephalopathy brought on by underlying microvascular illness or hypoglycaemia [10]. Serious persistent hypoglycemia episodes can result in seizures, a prolonged coma, and a wide range of other localized and global neurologic impairments, some of which can be misdiagnosed as stroke or other acute neurological conditions. Furthermore, unlike hypoxia encephalopathy, the clinical syndrome of hypoglycemia encephalopathy is not clearly described in the literature (Figure 2).

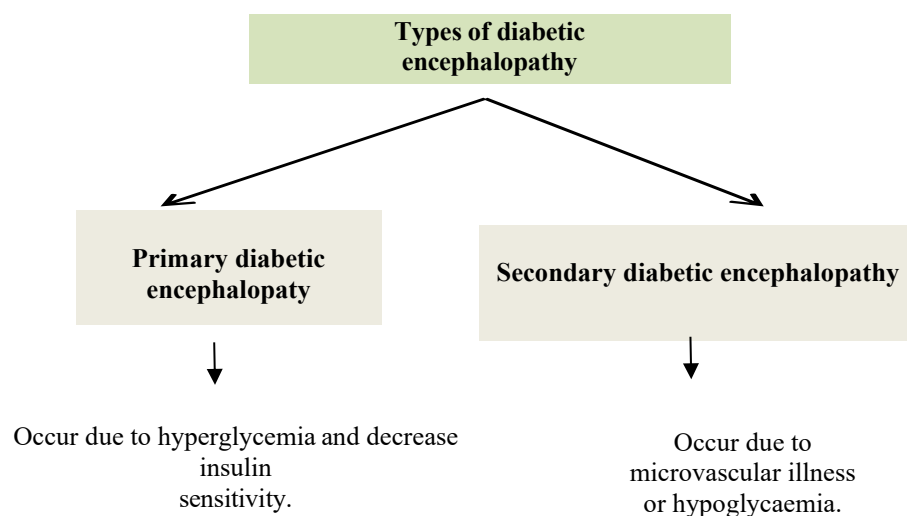


Figure 2. Types of Diabetic Encephalopathy.

Symptoms

There are wide range of symptoms that involve in Diabetic Encpohalopathy are as follow [11] (Figure 3).

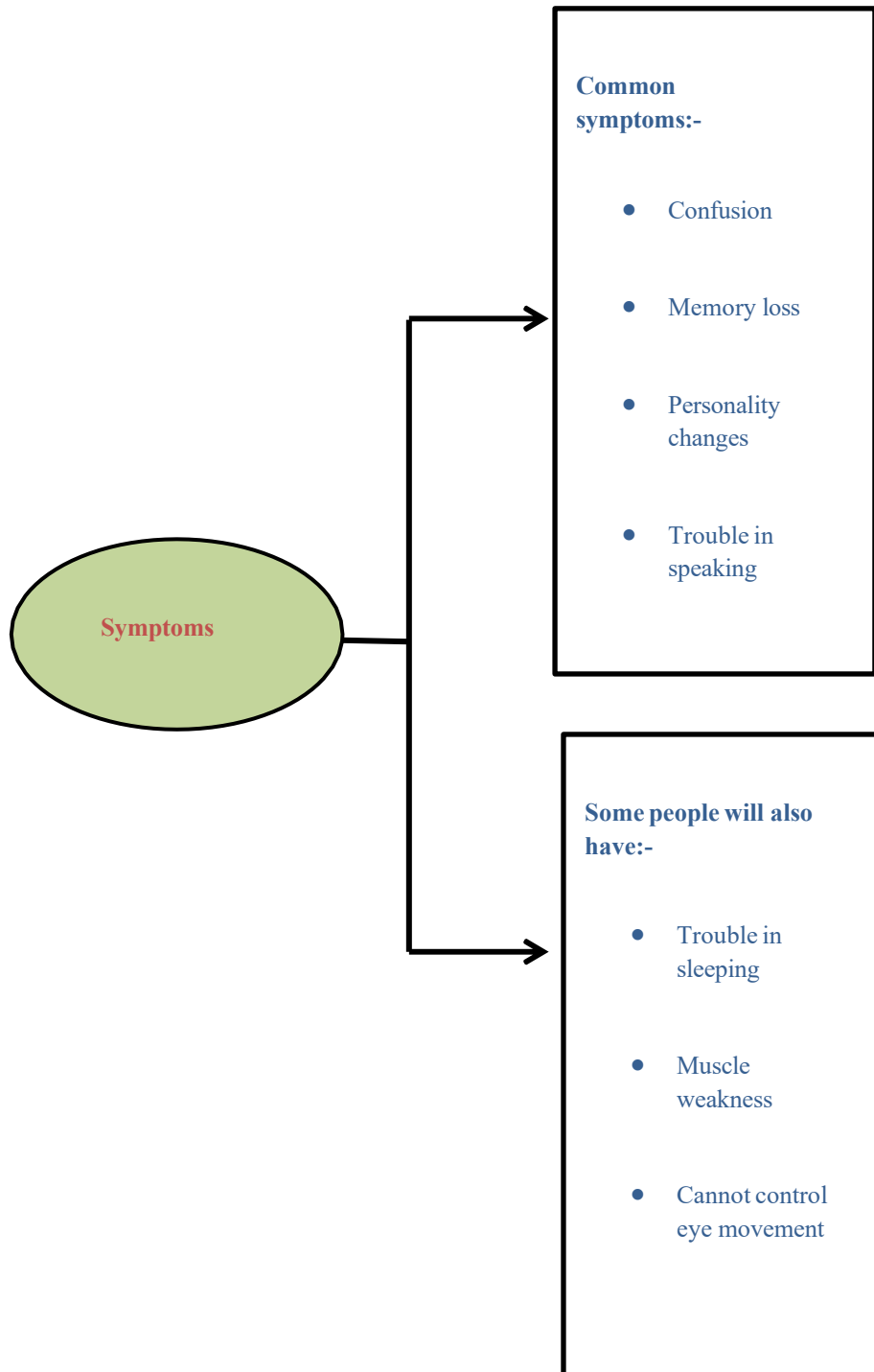


Figure 3. Symptoms appear during diabetic encephalopathy.

Pathogenesis

The causes of DE are currently not well understood, and the relationship between DM and the CNS is probably complex and multifaceted process [12]. It is expected that the etiology of DE has a

complex mechanism that includes the harmful impacts of chronic hyperglycemia and metabolic modulation, providing an in-depth analysis of the brain impact. Hyperglycemia and impaired insulin signaling in neurons increase apoptosis in type 2 diabetic encephalopathy, which is a major cause of inflammation, oxidative stress, and neurodegenerative illnesses [13]. The brain is affected structurally, neurophysiologically, and neuropsychologically by diabetes over the long term. A number of pathogenic factors, including hypoglycemic episodes, cerebrovascular changes, the function of insulin in the brain, and the mechanisms of hyperglycemia-induced damage, appear to be involved in the pathogenesis of the cerebral dysfunctioning in diabetes. Also, it is now believed that many of the symptoms of diabetes are actually better understood as accelerated brain aging [14] (Figure 4).

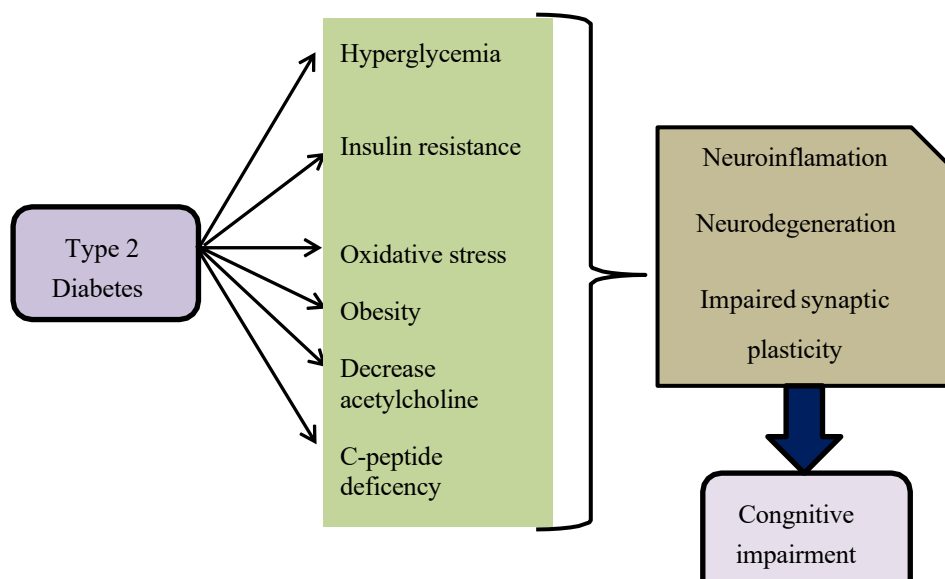


Figure 4. How Type 2 Diabetes can cause cognitive impairment [15].

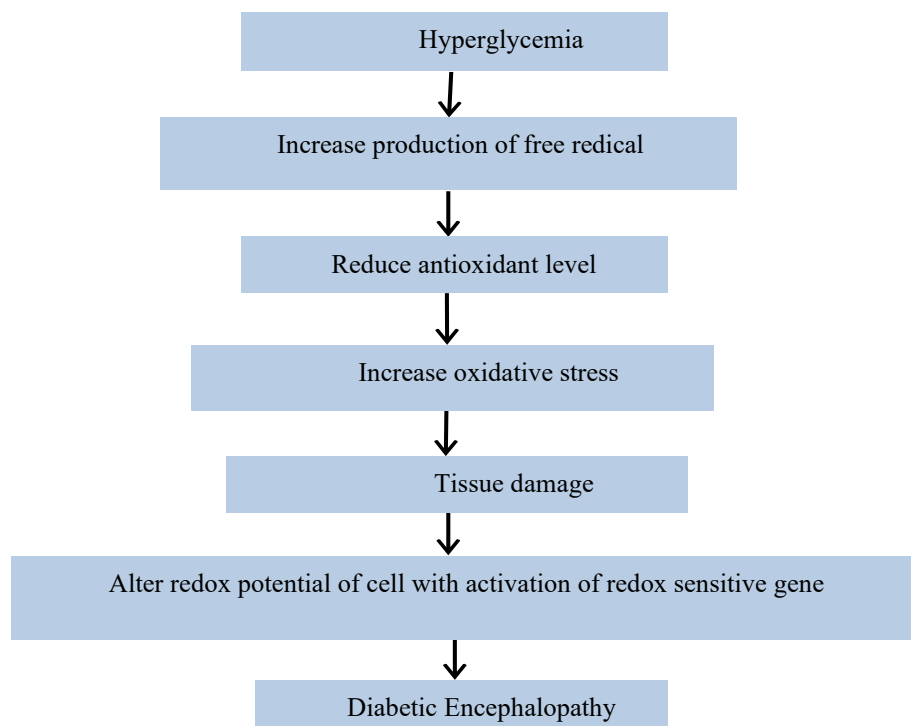


Figure 5. Role of oxidative stress in DE.

Role of Oxidative Stress In DE

One common hypothesis linking oxidative stress mediated by free radicals to cell death is the pathophysiology of brain impairment in Diabetic Encephalopathy and aging. Because of its rapid rate of oxygen consumption, high lipid content, and relative lack of antioxidant enzymes in comparison to other tissues, the brain is particularly susceptible to oxidative damage. Since neurons are especially sensitive to oxidative stressors, reactive oxygen species play a role in a number of cognitive conditions, including Diabetic Encephalopathy. Previous research and a wealth of data demonstrate that peroxidative damage to proteins and lipids happens with age, and the byproducts of these processes build up in the brain [16].

Hyperglycemia or free fatty acid are the major cause of oxidative stress that lead to insulin resistanc, pancreatic beta cell destruction and cognitive impairment (Figure 5, 6).

Similarly,

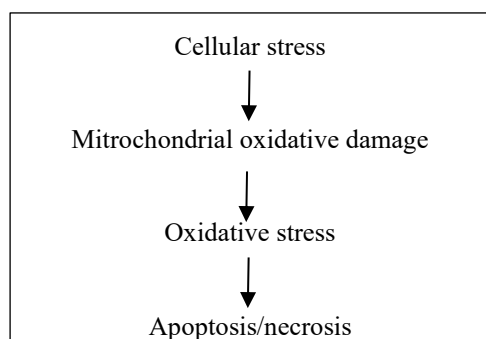


Figure 6. Oxidative stress also regulated by cellular stress.

Neuroinflammation in Type 2 Diabetes Mellitus

It has been shown that oxidative stress-induced chronic low-grade inflammation contributes to the onset and progression of type 2 diabetes. Moreover, it has been demonstrated that people with insulin resistance and diabetes have increased levels of the proinflammatory cytokines interleukin-6 (IL-6), C-reactive protein, and tumor necrosis factor alpha (TNF- α) [17] (Figure 7).

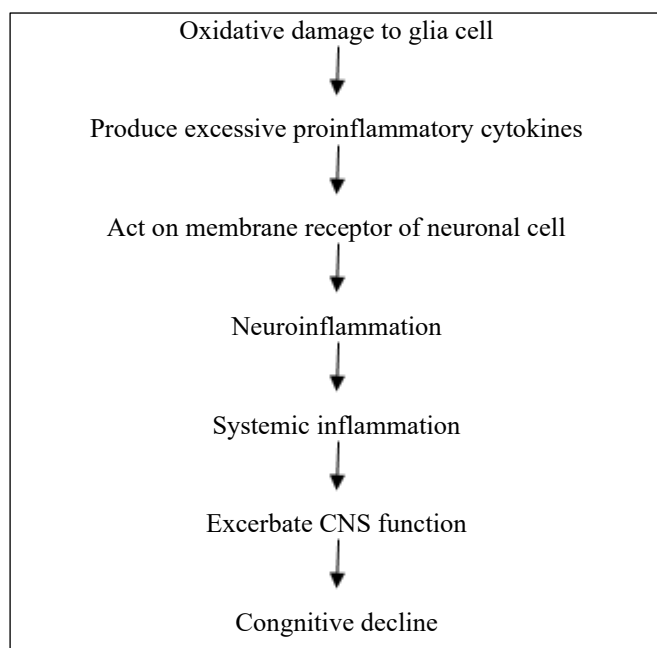


Figure 7. Cognitve decline occur due to neuroinflammation.

Autophagy

The conserved mechanism for diabetic encephalopathy is autophagy. The increasing amount of research on diabetic encephalopathy indicates that autophagy is a key factor in the condition [18]. Numerous recent investigations have revealed that autophagy is also compromised in the state of diabetes mellitus (DM), namely in the hippocampus and hypothalamus. These autophagic abnormalities are considered to have a role in the development of DE [19]. The Greek words "autophagos" and "kytos" are the origin of the word "autophagy," wherein "kytos" means "hollow" and "autophagos" means "self devouring". A conserved self-degradation mechanism called autophagy is essential for preserving cellular homeostasis under stressful circumstances. Initiation, nucleation, maturation, and degradation are the four essential phases in the autophagic process [20]. Autophagy is a catabolic process that uses lysosomal digestion to eliminate damaged organelles and protein aggregates from cells. Macro-autophagy, micro-autophagy, and chaperone-mediated autophagy (CMA) are the three main forms of autophagy. Although macro-autophagy is thought to be a non-selective cellular process, it really uses selective execution to control the quality of cellular contents [21].

Autophagy Dysregulation

Autophagy is dysregulated in the context of diabetes mellitus, according to several lines of evidence. The autophagosome formation process was shown to be compromised in T2DM C57B/L mice, as evidenced by the decrease in autophagosomal markers (ATG5 and ATG7) [22]. Numerous studies back up the claim that autophagy is compromised in DE, and that on the basis of this, decreasing autophagy can worsen cognitive impairment while increasing autophagy would improve symptoms in DE animal models. Undoubtedly, autophagy malfunction is a major factor in the development of DE; therefore, we need to investigate the possible pathways that connect autophagy to DE in more detail.

Neuronal Apoptotic Mechanism

It is unclear what causes neuronal apoptosis and central nervous system malfunction. We think that hyperglycemia, insulin insufficiency with concurrent C-peptide shortage, and even aging itself are important factors [23].

Insulin Signalling Defect

Insulin is a peptidergic hormone that is primarily made by the pancreatic beta cells. Initially, it was believed that insulin regulated blood glucose concentrations simply by attaching to its receptor and encouraging glucose uptake into peripheral cells [24]. Insulin receptors are widely distributed throughout the brain, with a particularly high density in neurons in the hippocampus, cortex, hypothalamus, olfactory bulb, and pituitary. Due to local synthesis, insulin in the brain can reach local concentrations one order of magnitude higher than in plasma. Insulin acts through both insulin receptors and the widely dispersed insulin-like growth factor 1 (IGF-1) receptors [25]. Complex signaling cascades triggered by insulin and IGF-1 are activated, regulating a variety of cellular functions such as growth, differentiation, and metabolism. Due to the broad spectrum of functions, IR signaling impairment is seen in a correspondingly varied group of psychiatric illnesses [26].

Impaired insulin regulates synaptic plasticity and cognitive functions, cellular proliferation and antiapoptotic mechanisms, neurotransmission, and antioxidant defense further in the central nervous system. Thus, abnormalities in the brain's insulin signaling pathways lead to change [27]. Pancreatic β -cell secretion is the main source of brain insulin, which is then mediated via an insulin receptor and saturable transport mechanism to cross the blood-brain barrier (BBB) [28]. For instance, mutations or abnormal posttranslational changes in the molecular building blocks of the insulin signaling pathway may lead to impaired insulin signalling [29]. Cells capacity to maintain energy homeostasis is seriously compromised by insulin resistance. The phosphorylation of IRS-1 at serine residues (IRS-1pSer) by the stress kinase c-Jun NH2-terminal kinase (JNK) in type 2 diabetes (T2D) prevents downstream insulin signaling and results in peripheral insulin resistance [30] (Figures 8, 9).

In Normal Condition

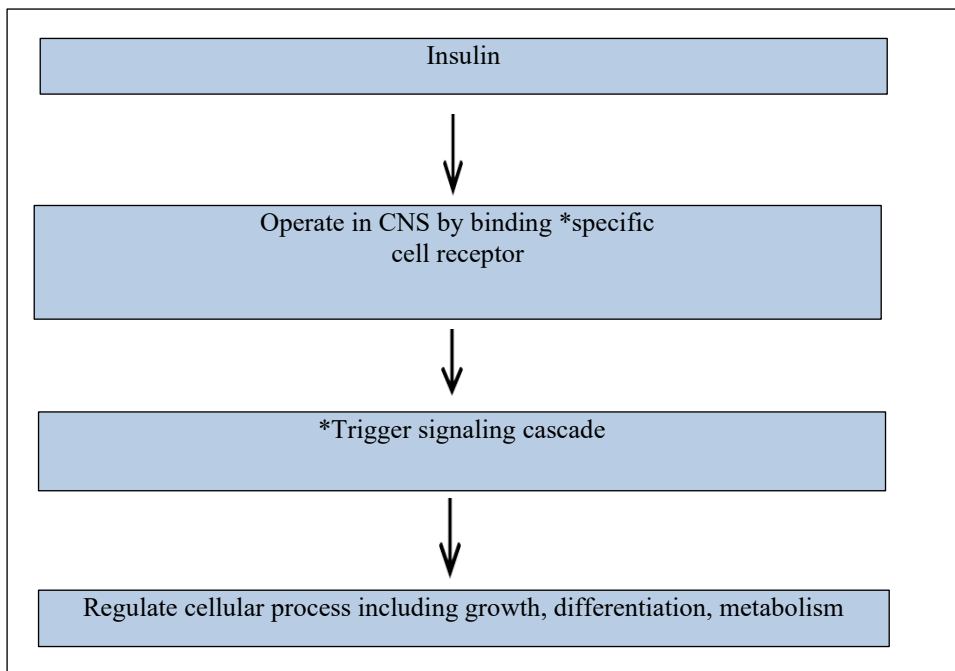


Figure 8. Function of insulin in normal condition.

In Disease Condition

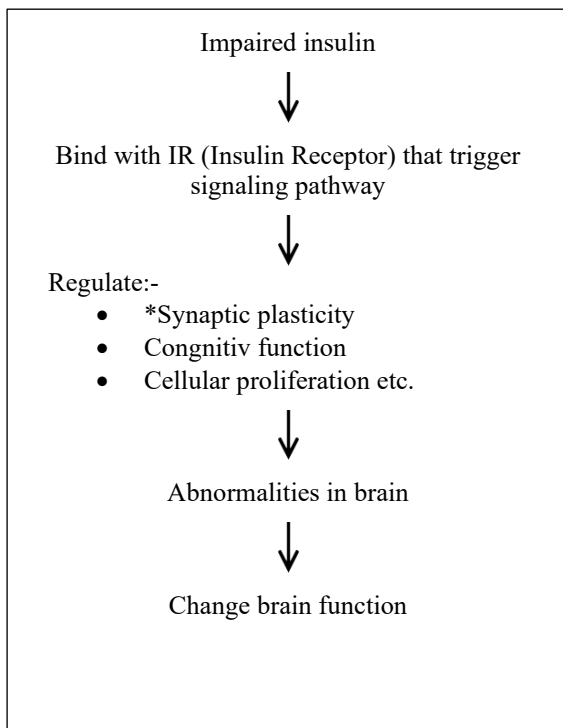


Figure 9. Impaired insulin alter brain function.

Signaling cascade

- i. Series of chemical reaction.
- ii. Occur inside the cell in response to stimuli.

Specific cell receptor

- i. Insulin and insulin growth factor 1 receptor:-
- ii. By activation perform specific different function
- iii. Control brain development and plasticity.
- iv. Circulating IGF-1 has impacts on cognition in addition to its neurotrophic effects.
- v. People who have lower serum IGF-1 levels and related cognitive impairment [31].
- vi. Insulin and insulin growth factor 2 receptor:-
 - a. Doesnot have signalling capabilities.
 - b. Memory enhancement [32].

Synaptic plasticity

- i. Neurons ability to change the strength of connection , synapse blw neurons.

C-peptide and C-peptide deficiency

- a. C-peptide, which is involved in the complex manufacturing and folding of insulin, was thought to have an insulin-like effect on glucose levels after it was discovered in the 1960s by Steiner [33].
- b. A 31-amino acid peptide called c-peptide is produced when proinsulin is broken down during the production of insulin. Bind to cell surface with high affinity [34].
- c. No specific C-peptide receptor found. Donot compete with insulin for receptor binding C-peptide give signal Through insulin signalling pathway [35, 36] (Figure 10- Figure 11).

In Normal Condition

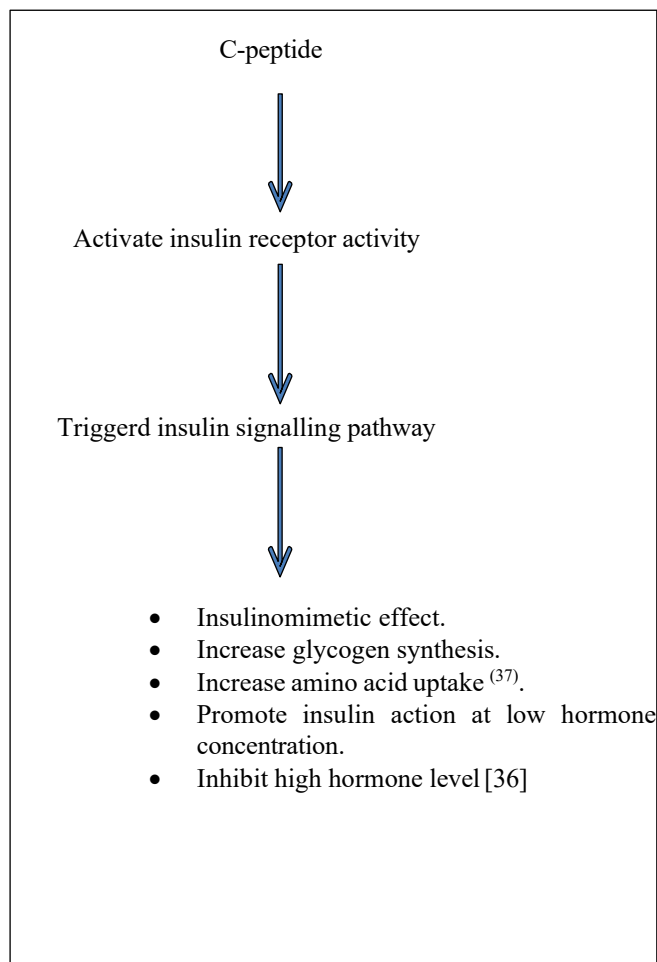


Figure 10. Role of C-peptide.

In Disease Condition

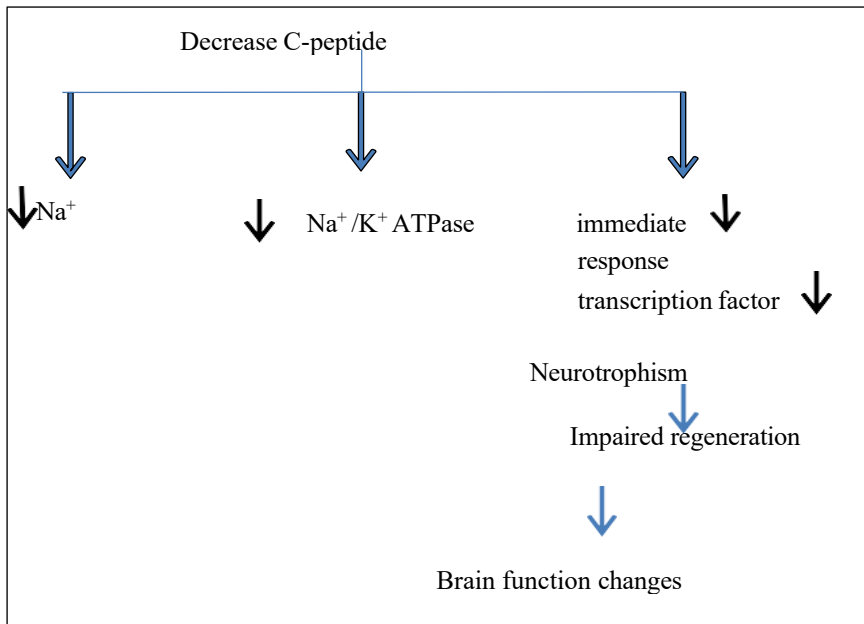


Figure 11. Deficiency of C-peptide can cause DE [37, 38].

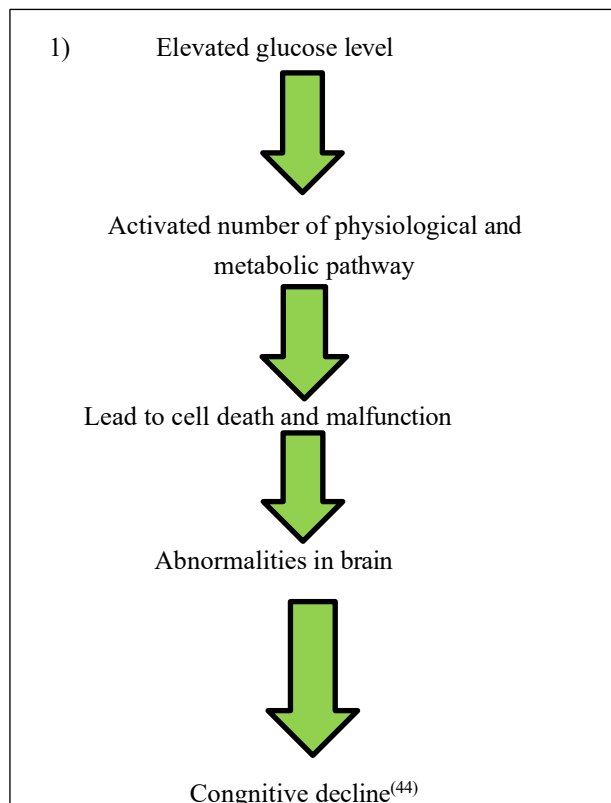


Figure 12. Cognitive decline due to elevated glucose level.

Hyperglycemia

More awareness of the potentially harmful impacts of long-term hyperglycemia on brain function has recently grown [39]. All of the variations in neurological complications between type 1 and type 2 diabetes, however, cannot be fully explained by hyperglycemia. It is now widely acknowledged that a

number of factors excluding hyperglycemia can act additively or synergistically to reduce neuronal homeostasis and increase neuronal vulnerability, which in turn can lead to cognitive decline. What is still unclear, though, is how these factors interact with one another to cause CNS complications [40]. The availability of glucose in the central nervous system (CNS) is essential for neuronal function, and the brain's glucose levels control both local neuronal activity and the body's energy consumption [41]. GLUT-1 is one of the membrane transport proteins that is recognized to be an important transporter of glucose over the blood-brain barrier and into the brain, helping to maintain glucose homeostasis in the central nervous system [42] (Figure 12).

The complicated process of glucose transport into the brain involves glial cells, including astrocytes, neurons, and endothelial cells of tiny blood arteries. The BBB-mediated transport of glucose is mediated by GLUT-1, which is highly expressed in the endothelial cells that make up the brain's microvasculature. Astrocytes are involved in the transfer of glucose to neurons [43].

An observational study found that middle-aged men with diabetes who had both high and low fasting blood glucose concentrations had worse cognitive functioning [45]. In the pathophysiology of diabetes's microvascular problems, the mechanisms of hyperglycemia toxicity have been thoroughly studied [46]. Perhaps as a result of the various ages of the research populations, the results of cross-sectional analyses regarding the relationship between HbA1c along with cognitive function and cognitive decline in individuals with type 2 diabetes have been inconsistent [47]. Overall, if adequate glycemic control is maintained, the relationship between type 2 diabetes and increased cognitive impairment seems to be rather weak before the age of 70. Cognitive impairment associated with persistent hyperglycemia is only evident in older individuals [48]. Changes in blood glucose levels brought on by exercise were linked to improvements in cognitive function in one of several intervention studies [49] (Figure 13-Figure 17).

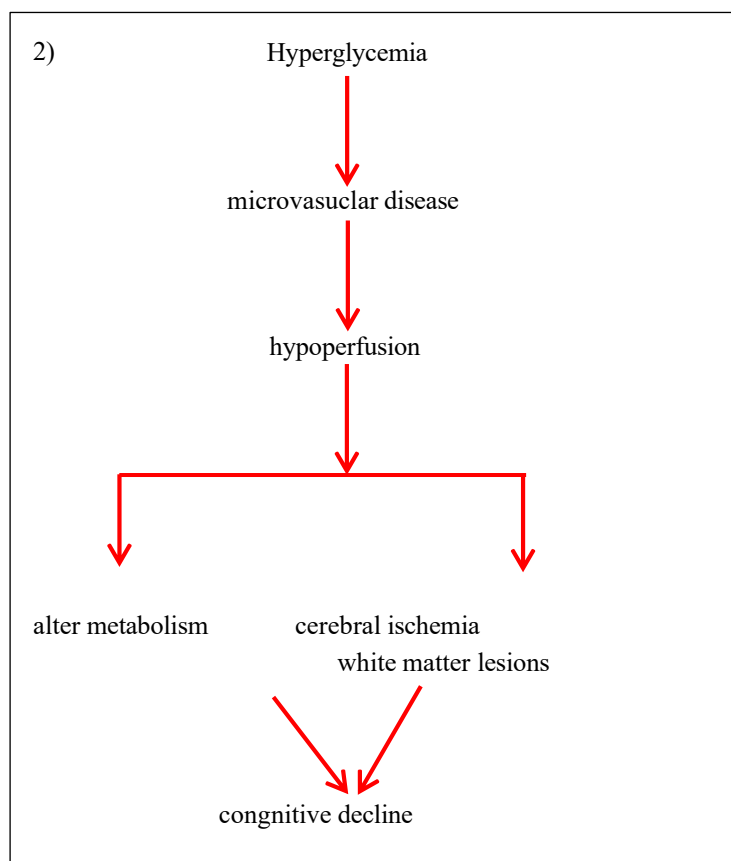


Figure 13. Possible pathogenesis that involve in cognitive decline in Type1 Diabetes [50].

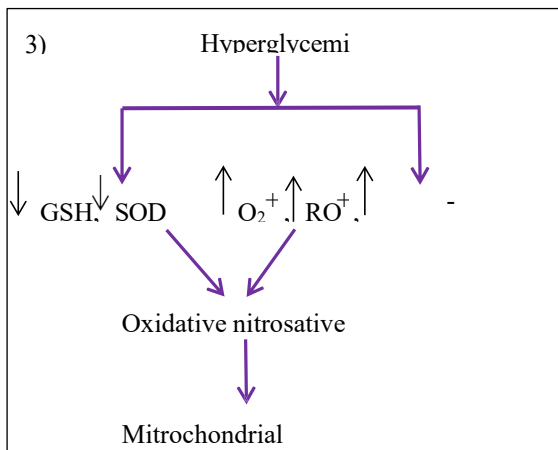


Figure 14. Molecular & biochemical pathogenesis of Diabetic Encephalopathy [51].

Factor Contributing in Development of Diabetic Encephalopathy

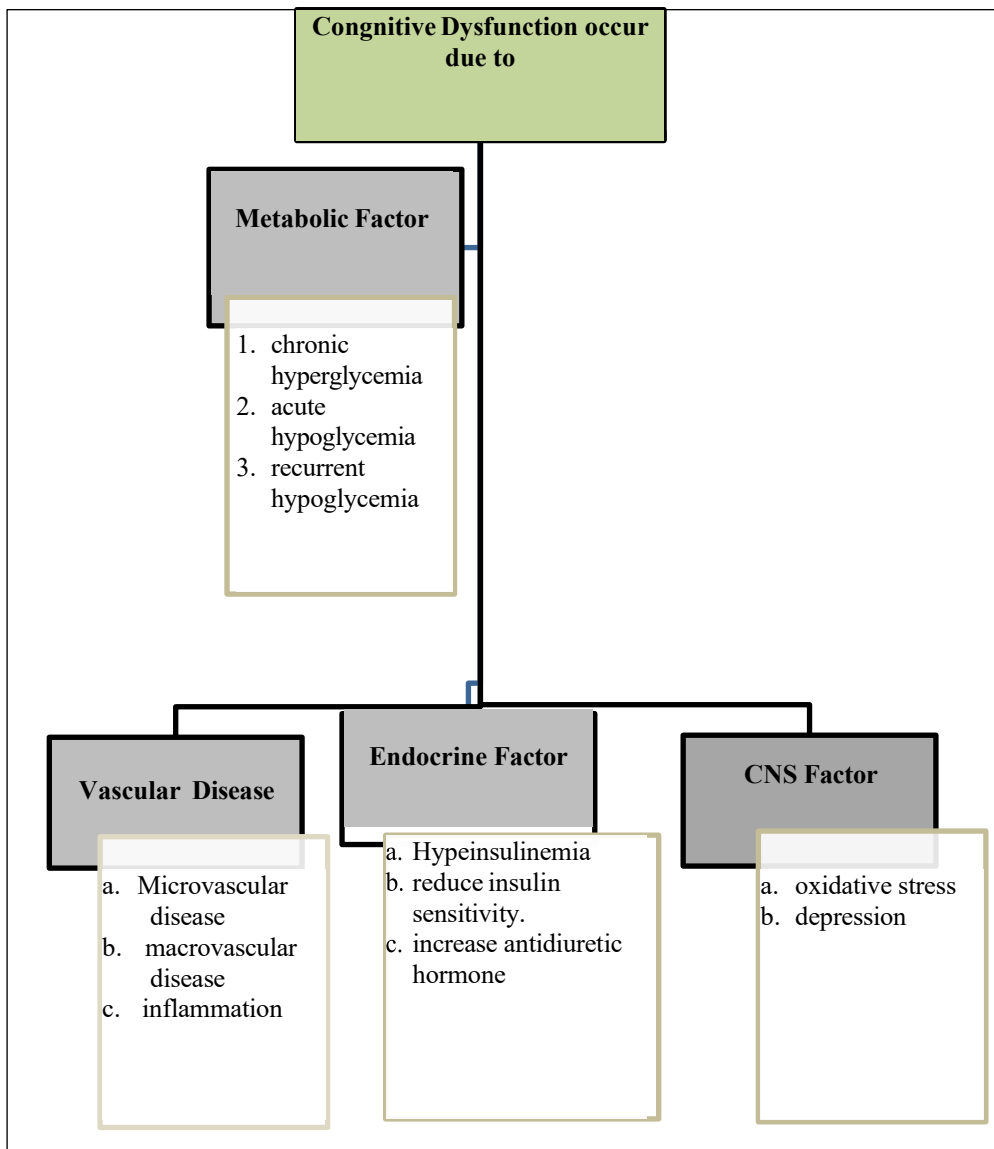


Figure 15. Factors affecting DE [52].

Complication

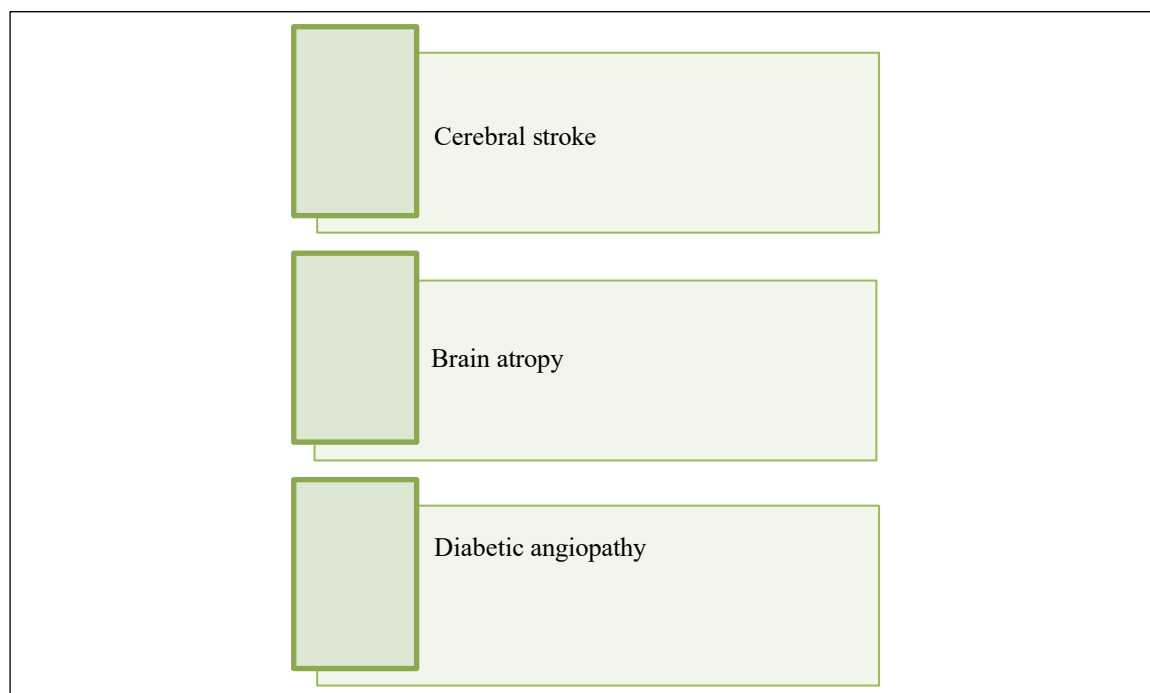


Figure 16 DE cause some serious complication [53].

Management Of Diabetic Encephalopathy

A short-term improvement in cognitive performance has been observed by numerous prior investigations using hypoglycemic medications [54]. Also improvements in C-peptide level and glycemic control may help lower the risk of diabetic brain damage, according to some research [55]. Another study discovered that multimodal medication therapy was superior over monotherapy in improving cognitive function and that oral hypoglycemic medicines were more beneficial when the disease has been present for a longer period of time [56]. Several investigations have shown that diabetic medications can, in fact, penetrate the brain after systemic delivery and mediate a physiological response, e.g. metformin, sulfonylurea, thiazolidine [57–60].

Drugs Used in Diabetic Encephalopathy

a. Oral Hypoglycemic Drug

Biguanide

Metformin

Sulfonylurea

Glipizide

Glyburide

Thiazolidinedione

Rosiglitazone

Pioglitazone

a. Oral Hypoglycemic Drug

BIGUANIDE

i. Metformin

Table 1. Mechanism of biguanide.

Drug	Class	Mechanism of action	Side effect
Metformin	Biguanide	Reduce neuroinflammation and decrease the loss of neuron in the hippocampus ↓ Improve spatial memory [61] <ul style="list-style-type: none"> • Play neuroprotective role. • Induce apoptotic cell death [62] • Normaliz the reduction of cell proliferation and neuroblast differentiation in rat model [63]. • In addition of antihyperglycemic role metformin help to reduce neuronal injury occur due to diabetes, 	Long term use can cause risk of Alzheimer ⁽⁶⁴⁾

The treatment of metformin to diabetic individuals may also raise their risk of cognitive impairment, according to another epidemiological study [65]. But since the authors did not assess the severity and duration of the diabetes, the length of the treatment, or the use of other hypoglycemic medications, the evidence from this study was insufficient to prove that metformin causes cognitive deficiency in diabetic individuals [66] (Table 1-Table 4).

Sulfonylurea

- i. Glipizide
- ii. Glyburide

Table 2. Mechanism of sulfonylurea drug.

Drug	Class	Mechanism
Glipizide	Sulfonylurea	Drug ↓ Interact with ATP – sensitivity potassium channel ↓ (K _{ATP}) in the pancreatic beta cell membrane ↓ Close the K _{ATP} channel ↓ Stimulate insulin secretion [67]
Glyburide	sulfonylurea	Drug ↓ Inhibit inflammasomes ↓ Prevent inflammation in brain ↓ Prevent cognitive impairment ↓ Prevent diabetic encephalopathy [68].

Thiazolidinedione

- i. Rosiglitazone
- ii. Pioglitazone

Table 3. MOA of thiazolidinedione.

Drug	Class	Mechanism of action
	Thiazolidinediones	Stimulate peroxisome proliferator activate receptor gamma (PPARs) ↓ Reduce neurodegradation ↓ Improve sensitivity of skeletal muscle and adipose tissue tom insulin [69].
Rosiglitazone	Thiazolidinediones	Reduce oxidative stress [70]. ↓ Inhibit production of proinflammatory cytokines or free redical.

Combination Therapies

The choice and combining of antidiabetic medications is another treatment-related concern to cognitive dysfunction [71].

Table 4. MOA of drug used in combination [72].

S.N.	Drug In Combination	Mechanism Of Action
1	Rosiglitazone + Metformin	Improve fasting blood glucose and working of memory.
2	Sulfonylurea + Metformin	Also improve blood glucose and working of memory.

Other Therapies

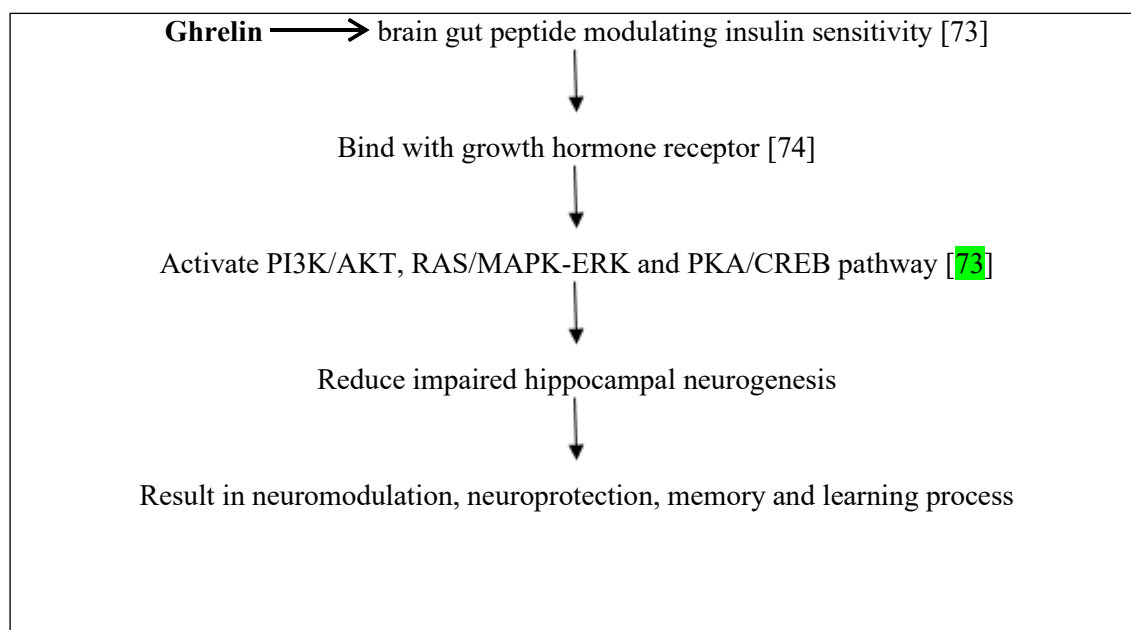


Figure 17. Ghrelin help to treat DE.

Exercise

Numerous studies show that exercise affects multiple aspects of brain function and has a wide range of impacts on the health of the brain overall. Its primary goals appear to be memory and learning enhancement, neurodegeneration prevention, and depression relief, especially in older adults. Physical activity may have a positive impact on health because it reduces inflammation by influencing growth factors. BDNF, IGF-1, and vascular endothelial growth factor are, in fact, the main growth factors that are known to influence the effects of exercise on the brain [76]. Thus, it is extremely important because experimental research has shown that physical exercise alters the neurobiology of the same brain systems that are involved in cognitive performance [77]. Additionally, it has been demonstrated that exercise raises the hippocampal levels of small heat shock proteins (sHSP), as well as the pre- and postsynaptic proteins synaptophysin and synapsin. These proteins are known to be involved in synaptic plasticity [78, 79].

Biomarker of Diabetic Encephalopathy

Inflammatory Marker

It is believed that elevated levels of long-term subclinical inflammatory markers, such as C-reactive protein (CRP) and interleukin-6 (IL-6), contribute to the formation of insulin resistance and disruption of insulin production in type 2 diabetes [80–82]. It has been documented that there is a connection between diabetes patients' rapid decrease in cognitive function and inflammation [83]. On the other hand, a cross-sectional investigation showed that poor cognitive performance is significantly correlated with higher plasma IL-6 and TNF- α , but not CRP [84].

Oxidative Stress Marker

The vast and diverse class of chemicals known as advanced glycation end products (AGEs) is created when physiologically reduced carbohydrates modify tissue proteins without the use of enzymes [85]. AGEs naturally build up with age, and oxidative stress and hyperglycemia, which are present in T2DM patients, accelerate their deposition. AGE accumulation has been associated with diabetes [86]. According to immunohistochemistry labeling, the post-mortem brains of individuals with diabetes have more AGE receptors and greater AGE levels than the brains of those with AD alone, indicating that AGEs promote an oxidative stress mechanism [87]. Furthermore, a cross-sectional investigation of 167 diabetes participants revealed that serum AGE levels were raised in MCI subjects, and this rise was inversely connected with global cognitive performance and associated with a 72% increase in MCI risk in T2DM patients; however, serum soluble RAGE concentration decreased in diabetes patients with MCI, and an increase in the RAGE level was associated with a 54% reduction in disease risk [88]. This finding proposes that RAGE protects against cognitive impairment in diabetes patients, partly by blocking AGEs–RAGE interaction [89].

Neurotrophic Factors- BDNF

In order to sustain learning and memory functions, the brain-derived neurotrophic factor (BDNF), a crucial member of the neurotrophin family of growth factors, controls cell survival, synaptic plasticity, and proliferation while lowering neuroinflammation in the central nervous system [90]. Diabetes-induced chronic hyperglycemia and AGE buildup were the main causes of the marked decrease in BDNF blood levels in diabetic patients compared to healthy controls [91, 92]. Additionally, in individuals with type 2 diabetes, a marked decline in blood BDNF levels was linked to both delayed memory and attention as well as poor cognitive function [93].

Adipokines

Leptin, TNF- α , IL-6, adiponectin, adipisin, heparin-binding epidermal growth factor (HB-EGF), and vascular endothelial growth factor (VEGF) are examples of adipokines, which are mediators released from adipose tissue. Many diseases have their pathophysiology linked to them. Increased energy consumption has been connected to abnormalities in brain structure and function as well as cognitive problems [94, 95]. Insulin-mediated cognitive impairment was linked to the adipocytokines, leptin, and adiponectin [96]. Older males with type 2 diabetes who had elevated serum leptin levels performed worse cognitively, primarily in the areas of control and mental flexibility, but not women [97]. Serum levels of adiponectin were found to be significantly lower and those of leptin and IL-1 β

to be significantly higher in T2DM patients with MCI. This suggests that lower levels of adiponectin and higher levels of leptin and IL-1 β could be diagnostic biomarkers of MCI risk in older diabetic patients [98].

Low levels of circulating adiponectin were also linked to reduced cerebral glucose metabolism in the parietotemporal areas of T2DM patients, as well as decreased hippocampal and grey matter volumes [99, 100].

CONCLUSION

Here, I have come to the end of this project on the topic “*A Systemic Review on Diabetic Encephalopathy, Its Type & Biomarkers*”. It was wonderful and learning experience for me while working on this project. From the above study it is concluded that Diabetic Encephalopathy is a chronic condition that affect the central nervous system and may lead to death if left untreated. From several study it was found that the exact pathogenesis of diabetic encephalopathy is not clearly known but studies show that there are various factor that involve in the pathogenesis of Diabetic Encephalopathy. If the person suffering from Diabetic Encephalopathy don't take treatment that this condition lead serious complication like brain atrophy etc. But this condition can better with proper medication recommended by registered physician, doing some physical activity like exercise and by food management. These result underscore the need for continues review or research on this condition as well as organizing the program to provide awareness regarding this disease. So at the end I want to say that there is need to develop epidemiology improved diagnostic facilities, effective risk communication and rapid response to control this disease.

REFERENCES

1. Rossetti L, Giaccari A, DeFronzo RA. Glucose toxicity. *Diabetes Care*. 1990;13:610–30.
2. Sima AAF. Encephalopathies: The emerging diabetic complications. *Acta Diabetol*. 2010;47(4):279–93.
3. Biessels GJ, Luchsinger JA (eds) *Diabetes and the brain*. Humana Press, New York. 2009.
4. Díaz-Gerevini GT, Daín A, Pasqualini ME, López CB, Eynard AR, Repossi G. Diabetic encephalopathy: beneficial effects of supplementation with fatty acids ω 3 and nordihydroguaiaretic acid in a spontaneous diabetes rat model. *Lipids Health Dis*. 2019;18(1):1–10.
5. Zhang S, Xue R, Hu R. The neuroprotective effect and action mechanism of polyphenols in diabetes mellitus-related cognitive dysfunction. *J Diabetes Res*. 2019;2019:1–10.
6. Belenichev I, Aliyeva O, Popazova O, Bukhtiyarova N. Molecular and biochemical mechanisms of diabetic encephalopathy. *Ukr Biochem J*. 2023;70(4):1–10.
7. Cheon SY, Song J. The association between hepatic encephalopathy and diabetic encephalopathy: The brain-liver axis. *Int J Mol Sci*. 2021;22(1):463.
8. Cai X, Xu H, Lu Y. C-peptide and diabetic encephalopathy. *Chin Med Sci J*. 2011;26(2):119–25.
9. Liu J, Wang S, Feng L, Ma D, Fu D, Song Y, et al. Hypoglycemic and antioxidant activities of paeonol and its beneficial effect on diabetic encephalopathy in streptozotocin-induced diabetic rats. *Molecules*. 2013;16(7):577–86.
10. Fazeli SA. Neuroprotection in diabetic encephalopathy. *Basic Clin Neurosci*. 2010;6:213–8.
11. Malmö K. What is encephalopathy? *Med Rev*. 2023;1(1):1–4.
12. Witsch J, Neugebauer H, Flechsenhar J, Jüttler E. Hypoglycemic encephalopathy: A case series and literature review on outcome determination. *J Neurol*. 2012;259(11):2172–81.
13. Cheng LZ, Li W, Chen YX, Lin JY, Miao Y. Autophagy and diabetic encephalopathy: mechanistic insights and potential therapeutic implications. *Neurochem Res*. 2022;13(2):447–57.
14. Nagayach A, Bhaskar R, Ghos S, Kumar Singh K, Han SS, Sinha JK. Advancing the understanding of diabetic encephalopathy through unravelling pathogenesis and exploring future treatment perspectives. *J Diabetes Metab Disord*. 2024;[Epub ahead of print].
15. Dutta JB, Singh S, Seksaria S, Das Gupta G, Singh A. Inside the diabetic brain: insulin resistance and molecular mechanisms associated with cognitive impairment and its possible therapeutic strategies. *Neuropharmacology*. 2022;[Epub ahead of print].

16. Biessels GJ, Van der Heide LP, Kamna A, Bleys RL, Gispen WH. Ageing and diabetes: implications for brain function. *Eur J Pharmacol.* 2002;441(1–2):1–14.
17. Schenk S, Horowitz JF. Acute exercise increases triglyceride synthesis in skeletal muscle and prevents fatty acid-induced insulin resistance. *J Clin Invest.* 2007;117:1690–8.
18. Muriach M, Bellver MF, Romero FJ, Barcia JM. Diabetes and the brain: Oxidative stress, inflammation, and autophagy. *Curr Pharm Des.* 2014;20(14):1–9.
19. Xia Q, Huang X, Huang J, Zheng Y, March ME, Li J, et al. The role of autophagy in skeletal muscle diseases. *Front Physiol.* 2021;12:1–20.
20. Onorati A, Dyczynski M, Pjha R, Amaravadi RK. Targeting autophagy in cancer. *Cancer Res.* 2018;124(16):3307–18.
21. Cheng LZ, Li W, Chen YX, Lin JY, Miao Y. Autophagy and diabetic encephalopathy: mechanistic insights and potential therapeutic implications. *Neurochem Res.* 2022;13(2):447–57.
22. Cui Y, Yang M, Wang Y, Ren J, Lin P, Cui C, et al. Melatonin prevents diabetes-associated cognitive dysfunction from microglia-mediated neuroinflammation by activating autophagy via TLR4/Akt/mTOR pathway. *FASEB J.* 2021;35:1–18.
23. Sima AAF, Kamiya H, Li ZG. Insulin, C-peptide, hyperglycemia, and central nervous system complications in diabetes. *J Neurol Sci.* 2004;490:187–96.
24. Gruber J, Hanseen R, Qubad M, Bouzouina A, Schack V, Sochor H, et al. Impact of insulin and insulin resistance on brain dopamine signalling and reward processing: An underexplored mechanism in the pathophysiology of depression? *Neuropsychopharmacology.* 2023;[Epub ahead of print].
25. Candeias E, Duarte AI, Carvalho C, Correia SC, Cardoso S, Santos RX, et al. The impairment of insulin signaling in Alzheimer’s disease. *J Alzheimers Dis.* 2012;64(12):951–7.
26. Lanzillotta C, Tramutola A, Di Giacomo G, Marini F, Butterfield DA, Di Domenico F, et al. Insulin resistance, oxidative stress and mitochondrial defects in Ts65dn mice brain: A harmful synergistic path in Down syndrome. *Free Radic Biol Med.* 2021;165:152–70.
27. Wada A, Yokoo H, Yanagita T, Kobayashi H. New twist on neuronal insulin receptor signaling in health, disease, and therapeutics. *J Pharmacol Sci.* 2005;99:128–43.
28. Soares E, Nunes S, Reis F, Pereira CF. Diabetic encephalopathy: The role of oxidative stress and inflammation in type 2 diabetes. *J Diabetes Metab.* 2012;4:78–85.
29. De Felice FG. Inflammation, defective insulin signaling, and mitochondrial dysfunction as common molecular denominators connecting type 2 diabetes to Alzheimer disease. *Diabetes.* 2014;63(7):2262–72.
30. Mielke JG, Wang YT. Insulin, synaptic function, and opportunities for neuroprotection. *Prog Mol Biol Transl Sci.* 2011;98:133–86.
31. Carro E, Nunez A, Busiguina S, Torres-Aleman I. Circulating insulin-like growth factor I mediates effects of exercise on the brain. *Nat Neurosci.* 2000;3(3):2926–33.
32. Alberini CM, Chen DY. Memory enhancement: Consolidation, reconsolidation and insulin-like growth factor 2. *Trends Neurosci.* 2012;35(5):274–83.
33. Fernqvist-Forbes E, Johansson BL, Eriksson MJ. Effects of C-peptide on forearm blood flow and brachial artery dilatation in patients with type 1 diabetes mellitus. *Acta Physiol Scand.* 2001;172(3):159–65.
34. Rigler R, Pramanik A, Jonasson P, Kratz P, Jansson O, Nygren PA, et al. Specific binding of proinsulin C-peptide to human cell membranes. *Proc Natl Acad Sci U S A.* 1999;96:13318–23.
35. Zierath JR, Galuska D, Johansson BL, Wallberg-Henriksson H. Effect of human C-peptide on glucose transport in in vitro incubated human skeletal muscle. *Diabetologia.* 1991;34:899–902.
36. Li ZG, Qiang X, Sima AAF, Grunberger G. C-peptide attenuates protein tyrosine phosphatase activity and enhances glycogen synthesis in L6 myoblasts. *Biochem Biophys Res Commun.* 2001;280:615–9.
37. Grunberger G, Qiang X, Li ZG, Mathews ST, Sbriessa D, Shiskeva A, et al. Molecular basis for the insulinomimetic effects of C-peptide. *Diabetologia.* 2001;44:1247–57.
38. Sima AAF. Acetyl-L-carnitine in diabetic polyneuropathy: Experimental and clinical data. *CNS Drugs.* 2007;21 Suppl 1:13–23.

39. Cox DJ, Kovatchev BP, Gonder-Frederick LA, Summers KH, McCall A, Grimm KJ, et al. Relationships between hyperglycemia and cognitive performance among adults with type 1 and type 2 diabetes. *Diabetes Care*. 2005;28:71–7.
40. Gaspar JM, Baptista FI, Macedo MP, Ambrósio AF. Inside the diabetic brain: role of different players involved in cognitive decline. *ACS Chem Neurosci*. 2015;7(2):131–42.
41. Shawahna R, Uchida Y, Decleves X, Ohtsuki S, Yousif S, Dauchy S, et al. Transcriptomic and quantitative proteomic analysis of transporters and drug metabolizing enzymes in freshly isolated human brain microvessels. *Mol Pharm*. 2011;8(4):1332–41.
42. Uchida Y, Ohtsuki S, Katsukura T, Ikeda C, Suzuki T, Kamiie J, et al. Quantitative targeted absolute proteomics of human blood-brain barrier transporters and receptors. *J Neurochem*. 2011;117(2):333–45.
43. Forsyth R, Fray A, Boutelle M, Fillenz M, Middleditch C, Burchell A. A role for astrocytes in glucose delivery to neurons? *Dev Neurosci*. 1996;18(5–6):360–70.
44. Wrihten SA, Piroli GG, Grillo CA, Reagan LP. A look inside the diabetic brain: Contributors to diabetes-induced brain aging. *Biochim Biophys Acta Mol Basis Dis*. 2009;1792:444–53.
45. Gallacher JE, Pickering J, Elwood PC, Bayer AJ, Yarnell JW, Ben-Shlomo Y. Glucoregulation has greater impact on cognitive performance than macro-vascular disease in men with type 2 diabetes: data from the Caerphilly study. *Eur J Epidemiol*. 2005;20:761–8.
46. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature*. 2001;414:813–20.
47. Feinkohl I, Price JF, Strachan MWJ, Frier BM. The impact of diabetes on cognitive decline: Potential vascular, metabolic, and psychosocial risk factors. *Alzheimers Res Ther*. 2015;7(1):1–13.
48. Messier C. Impact of impaired glucose tolerance and type 2 diabetes on cognitive aging. *Neurobiol Aging*. 2005;26 Suppl 1:26–30.
49. Yanagawa M, Umegaki H, Uno T, Oyun K, Kawano N, Maeno H, et al. Association between improvements in insulin resistance and changes in cognitive function in elderly diabetic patients with normal cognitive function. *Geriatr Gerontol Int*. 2011;11:341–7.
50. Wessels AM, Scheltens P, Barkhof F, Heine RJ. Hyperglycaemia as a determinant of cognitive decline in patients with type 1 diabetes. *Eur J Pharmacol*. 2008;585(1):88–96.
51. Kükürt A, Gelen V, Başer Ö, Devenci H, Karapehlivan M. Thiols: Role in oxidative stress-related disorders. In: *IntechOpen*; 2021.
52. McCrimmon RJ, Ryan MC, Frier BM. Diabetes and cognitive dysfunction. *Lancet*. 2012;379:2291–9.
53. Powell HC, Mizisin AP. Diabetic neuropathy. In: *Encyclopedia of Neuroscience*. 2009:511–6.
54. Strachan MWJ. The brain as a target organ in type 2 diabetes: exploring the links with cognitive impairment and dementia. *Diabet Med*. 2011;28:141–7.
55. Stettler C, Allemann S, Jüni P, et al. Glycemic control and macrovascular disease in types 1 and 2 diabetes mellitus: meta-analysis of randomized trials. *Am Heart J*. 2006;152:27–38.
56. Wu JH, Haan MN, Liang J, et al. Impact of antidiabetic medications on physical and cognitive functioning of older Mexican Americans with diabetes mellitus: A population-based cohort study. *Ann Epidemiol*. 2003;13:369–76.
57. Poupon-Bejuit L, Rocha-Ferreira E, Thornton C, Hagberg H, Rahim AA. Neuroprotective effects of diabetes drugs for the treatment of neonatal hypoxia-ischemia encephalopathy. *Front Cell Neurosci*. 2020;14.
58. Lv WS, Wen JP, Li L, Sun RX, Wang J, Xian YX, et al. The effect of metformin on food intake and its potential role in hypothalamic regulation in obese diabetic rats. *Brain Res*. 2012;1444:11–9.
59. Simard JM, Woo SK, Schwartzbauer GT, Gerzanich V. Sulfonylurea receptor 1 in central nervous system injury: a focused review. *J Cereb Blood Flow Metab*. 2012;32:1699–717.
60. Grommes C, Karlo JC, Caprariello A, Blankenship D, Dechant A, Landreth GE. The PPAR γ agonist pioglitazone crosses the blood-brain barrier and reduces tumor growth in a human xenograft model. *Cancer Chemother Pharmacol*. 2013;71:929–36.
61. Oliveira WH, Nunes AK, França MER, Santos LA, Lós DB, Rocha SW, et al. Effects of metformin on inflammation and short-term memory in streptozotocin-induced diabetic mice. *Brain Res*. 2016;1644:149–60.

62. El-Mir MY, Detaille D, R-Villanueva G, Delgado-Esteban M, Guigas B, Attia S, et al. Neuroprotective role of antidiabetic drug metformin against apoptotic cell death in primary cortical neurons. *J Mol Neurosci.* 2008;34(1):77–87.
63. Hwang IK, Kim IY, Joo EJ, Shin JH, Choi JW, Won MH, et al. Metformin normalizes type 2 diabetes-induced decrease in cell proliferation and neuroblast differentiation in the rat dentate gyrus. *Neurochem Res.* 2010;35(4):645–50.
64. Imfeld P, Bodmer M, Jick SS, Meier CR. Metformin, other antidiabetic drugs, and risk of Alzheimer's disease: A population-based case-control study. *J Am Geriatr Soc.* 2012;60:916–21.
65. Moore EM, Mander AG, Ames D, Kotowicz MA, Carne RP, Brodaty H, et al. Increased risk of cognitive impairment in patients with diabetes is associated with metformin. *Diabetes Care.* 2013;36:2981–7.
66. Goodarzi MO. Comment on Moore et al. Increased risk of cognitive impairment in patients with diabetes is associated with metformin. *Diabetes Care.* 2014;36:2981–7.
67. Abdelmoneim AS, Hasenbank SE, Seubert JM, Brocks DR, Light PE, Simpson SH. Variations in tissue selectivity amongst insulin secretagogues: A systematic review. *Diabetes Obes Metab.* 2012;14(2):130–8.
68. Lamkanfi M, Mueller JL, Vitari AC, Misaghi S, Fedorova A, Deshayes K, et al. Glyburide inhibits the Cryopyrin/Nalp3 inflammasome. *J Cell Biol.* 2009;187(1):61–70.
69. Heneka MT, Landreth GE, Feinstein DL. Role for peroxisome proliferator-activated receptor-gamma in Alzheimer's disease. *Ann Neurol.* 2001;49(2):276.
70. Pathan AR, Viswanad B, Sonkusare SK, Ramarao P. Chronic administration of pioglitazone attenuates intracerebroventricular streptozotocin-induced memory impairment in rats. *Life Sci.* 2006;79(23):2209–16.
71. Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: the Rotterdam Study. *Neurology.* 1999;58:1937–41.
72. Ryan CM, Fried MI, Rood JA, et al. Improving metabolic control leads to better working memory in adults with type 2 diabetes. *Diabetes Care.* 2006;29:345–51.
73. Barazzoni R, Zanetti M, Stulle M, Mucci PM, Pirulli A, Dore F, et al. Higher total ghrelin levels are associated with higher insulin-mediated glucose disposal in non-diabetic maintenance hemodialysis patients. *Clin Nutr.* 2008;27:142–9.
74. Korbonsits M. Ghrelin – a hormone with multiple functions. *Front Neuroendocrinol.* 2004;25(1):27–68.
75. Moon M, Kim S, Hwang L, Park S. Ghrelin regulates hippocampal neurogenesis in adult mice. *Endocr J.* 2009;56:525–31.
76. Cotman CW, Berchtold NC, Christie LA. Exercise builds brain health: Key roles of growth factor cascades and inflammation. *Trends Neurosci.* 2007;30:464–72.
77. Brito GN. Exercise and cognitive function: A hypothesis for the association of type II diabetes mellitus and Alzheimer's disease from an evolutionary perspective. *Diabetol Metab Syndr.* 2009;1(1):7.
78. Hu S, Ying Z, Gomez-Pinilla F, Frautschy SA. Exercise can increase small heat shock proteins (sHSP) and pre- and postsynaptic proteins in the hippocampus. *Brain Res.* 2009;1249:191–201.
79. Vaynman SS, Ying Z, Yin D, Gomez-Pinilla F. Exercise differentially regulates synaptic proteins associated with the function of BDNF. *Brain Res.* 2006;1070:124–30.
80. Dandona P, Aljada A, Bandyopadhyay A. Inflammation: the link between insulin resistance, obesity and diabetes. *Trends Immunol.* 2004;25:4–7.
81. Festa A, D'Agostino R, Tracy RP, Haffner SM. Elevated levels of acute-phase proteins and plasminogen activator inhibitor-1 predict the development of type 2 diabetes. *Diabetes.* 2002;51:1131–7.
82. Duncan BB, Schmidt MI, Pankow JS, Ballantyne CM, Couper D, Vigo A, et al. Low-grade systemic inflammation and the development of type 2 diabetes. *Diabetes.* 2003;52:1799–805.
83. Strachan MWJ, Deary IJ, Ewing FM, Frier BM. Is type II diabetes associated with an increased risk of cognitive dysfunction? A critical review of published studies. *Diabetes Care.* 1997;20:438–45.

84. Marioni RE, Strachan MW, Reynolds RM, Lowe GD, Mitchell RJ, Fowkes FGR, et al. Association between raised inflammatory markers and cognitive decline in elderly people with type 2 diabetes. *Diabetes*. 2009;59:710–3.
85. Biessels GJ, Nobili F, Teunissen CE, Simó R, Scheltens P. Understanding multifactorial brain changes in type 2 diabetes: a biomarker perspective. *Lancet Neurol*. 2020;19:699–710.
86. Brownlee MM. Advanced protein glycosylation in diabetes and aging. *Annu Rev Med*. 1995;46:223–34.
87. Valente T, Gella A, Fernández-Busquets X, Unzeta M, Durany N. Immunohistochemical analysis of human brain suggests pathological synergism of Alzheimer’s disease and diabetes mellitus. *Neurobiol Dis*. 2010;37:67–76.
88. Schalkwijk CG, Brouwers O, Stehouwer CDA. Modulation of insulin action by advanced glycation endproducts: a new player in the field. *Horm Metab Res*. 2008;40:614–9.
89. Wang P, Huang R, Lu S, Xia W, Cai R, Sun H, et al. RAGE and AGEs in mild cognitive impairment of diabetic patients: a cross-sectional study. *PLoS One*. 2016;11:e0145521.
90. Egoriska-Ciebiada M, Esaryusz-Wolska M, Borkowska A, Ciebiada M, Łoba J. C-reactive protein, advanced glycation end products, and their receptor in type 2 diabetic elderly patients with mild cognitive impairment. *Front Aging Neurosci*. 2015;7:209.
91. Kim OY, Song J. The importance of BDNF and RAGE in diabetes-induced dementia. *Pharmacol Res*. 2020;160:105083.
92. Zhen YF, Zhang J, Liu XY, Fang H, Tian LB, Zhou DH, et al. Low BDNF is associated with cognitive deficits in patients with type 2 diabetes. *Psychopharmacology (Berl)*. 2012;227:93–100.
93. Navaratna D, Guo SZ, Hayakawa K, Wang X, Gerhardinger C, Lo EH. Decreased cerebrovascular brain-derived neurotrophic factor-mediated neuroprotection in the diabetic brain. *Diabetes*. 2011;60:1789–96.
94. Ortiz BM, Emiliano JR, Ramos-Rodríguez E, Martínez-Garza S, Macías-Cervantes H, Solorio-Meza S, et al. Brain-derived neurotrophic factor plasma levels and premature cognitive impairment/dementia in type 2 diabetes. *World J Diabetes*. 2016;7:615–20.
95. Arnoldussen IA, Kiliaan AJ, Gustafson DR. Obesity and dementia: Adipokines interact with the brain. *Eur Neuropsychopharmacol*. 2014;24:1982–99.
96. Businaro R, Ippoliti F, Ricci S, Canitano N, Fusco A. Alzheimer’s disease promotion by obesity: Induced mechanisms—molecular links and perspectives. *Curr Gerontol Geriatr Res*. 2012;2012:1–13.
97. Davis C, Mudd J, Hawkins M. Neuroprotective effects of leptin in the context of obesity and metabolic disorders. *Neurobiol Dis*. 2014;72:61–71.
98. Labad J, Price JF, Strachan MW, Deary IJ, Seckl JR, Sattar N, et al. Serum leptin and cognitive function in people with type 2 diabetes. *Neurobiol Aging*. 2012;33:2938–42.e2.
99. Masaki T, Anan F, Shimomura T, Fujiki M, Saikawa T, Yoshimatsu H. Association between hippocampal volume and serum adiponectin in patients with type 2 diabetes mellitus. *Metabolism*. 2012;61:1197–200.
100. García-Casares N, García-Arnés JA, Rioja J, Ariza MJ, Gutiérrez A, Alfaro F, et al. Alzheimer’s-like brain changes correlate with low adiponectin plasma levels in type 2 diabetic patients. *J Diabetes Complications*. 2015;30:281–6.