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The Impact of Diabetes on Hippocampus

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Abstract

Maternal Diabetes is one of the most common metabolic disorders resulting an increased risk of abnormalities in the developing fetus and offspring. It is estimated that the prevalence of diabetes during pregnancy among women in developing countries is approximately 4.5 percent and this range varies between 1 to 14 percent in different societies. According to earlier studies, diabetes during pregnancy is associated with an increased risk of maternal and child mortality and morbidity as well as major congenital anomalies including central nervous system (CNS) in their offspring. Multiple lines of evidence have suggested that infants of diabetic women are at risk of having neurodevelopmental sequelae. Previous studies reveal that the offspring of diabetic mothers exhibit disturbances in behavioral and intellectual functioning. In the examination of cognitive functioning, a poorer performance was observed in the children born to diabetic mothers when compared with the children of non-diabetic mothers. Therefore, it is important to study the possible effects of maternal diabetes on the hippocampus of these infants.

Keywords: Maternal diabetes, Central nervous system, Hippocampus, Hyperglycemia

1. Introduction

1.1 Hippocampus

The hippocampus in humans is a part of the cortical region that is connected to the limbic system and consists of two cortical structures: the hippocampal formation and the parahippocampal region. Hippocampal formation refers to a group of structures with a unique cellular structure and arrangement that accompany the hippocampus and include: dentate gyrus, hippocampus, subiculum, presubiculum, and parasubiculum [1, 2]. The main difference between these two structures is the number of cortical layers and their general connections. The hippocampus in the coronal sections is a C-shaped structure located into the lower horn of the lateral ventricle. Its general shape is similar to a seahorse (**Figure 1A**) [3].

The most common classification for the hippocampus in non-human primates and other laboratory animals is, the hippocampus is divided into 4 subfields, CA1-CA4. In humans, most parts of the hippocampal formation are located on the floor of the temporal horn of the lateral ventricle (**Figure 1B**). The part of the
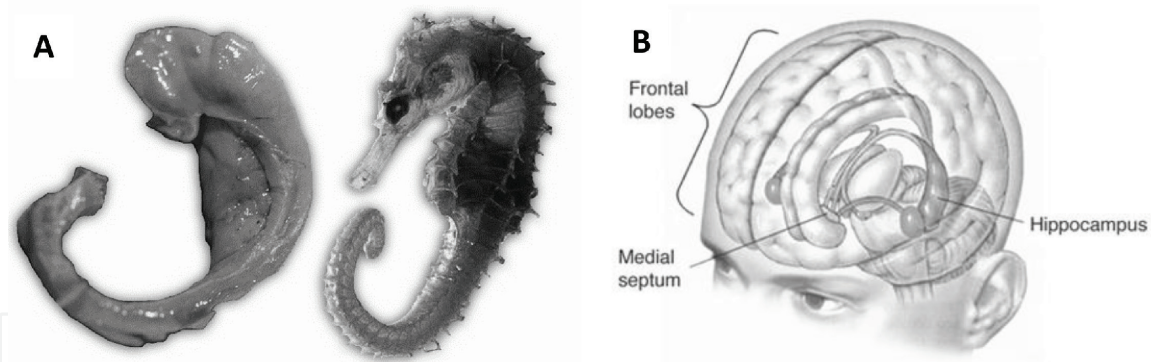
Figure 1.
Isolated hippocampus of human which is similar to seahorse (A). The shape and location of the hippocampus in humans (B).

hippocampus that is located in the floor of the lateral ventricular temporal horn (most parts of CA1 and CA2 and the distal part of CA3) is about 4 cm long [1].

1.1.1 Evolution of hippocampal formation in humans

By the ninth week of pregnancy, the primary hippocampus develops within the cerebral hemispheres but does not resemble an adult hippocampus. At the middle of the third trimester of pregnancy (weeks 19–15), immature dentate gyrus, the subiculum, and different areas of the hippocampus can be identified. The hippocampal groove deepens and different areas of the hippocampus appear to be more developed, at the end of the 25th week of pregnancy. Although cell layers are more pronounced in CA1 and CA2-CA3; But the boundary between CA1 and subiculum is not clear. By the last trimester of pregnancy (34 weeks), the hippocampal groove is narrower and the boundary between CA1 and subiculum is distinguishable; CA1, CA2, and CA3 are recognizable and seem the dentate gyrus has a mature appearance.

It should be noted that a decrease in hippocampal cell density is observed in the postnatal period, which is probably due to the apoptosis and the growth of neurons and filaments. No significant morphological changes are seen until puberty and, and the only myelination is gradually completed [4, 5].

1.1.2 Hippocampal functions

The first theory suggested that the hippocampus has a key role in olfactory functions. But this theory was not accepted because Studies in later years showed that the hippocampus did not receive any nerve fibers directly from the olfactory bulb; However, the further study indicated that the hippocampus may be involved in olfactory responses, and in particular in olfactory memory [6]. In addition, Jeffrey Gray suggested that the hippocampus might play a role in anxiety [7].

Years later, three main ideas for hippocampal function were explained: response inhibition, learning and memory, and spatial cognition [8]. The majority of psychologists and neuroanatomists believe that the hippocampus plays a principal role in the formation of new memories about experienced events (episodic or autobiographical memory), which is part of the role of the hippocampus in its activity in discovering new events, places, and stimuli [9, 10]. Some researchers believe that the hippocampus is responsible for declarative memory in addition to episodic memory [11, 12]. Severe damage to the hippocampus can cause problems with the formation of new memory, as well as impairment of earlier formed memory.

However, the memory from years before the hippocampal injury may remain intact, which appears to be due to the transfer of memory from the hippocampus to other parts of the brain over the years [8].

Interestingly, damage to the hippocampus does not affect some types of memory, such as motor memory and the ability to learn new motor and cognitive skills, such as playing a musical instrument and solving a variety of tables. This implies that these abilities depend on other types of memory called working memory, which involve different areas of the brain [13]. Several researchers distinguish between conscious recollection and familiarity which depends on the hippocampus and portions of the medial temporal lobe, respectively [14]. The hippocampus and related areas are necessary for the systematic formation and organization of memory, their retrieval, and the repetition of learned experiences. Hippocampal neurons encode a large amount of information received in the form of senses and experiences and are implicitly organized [9].

The hippocampal/internal temporal lobe (HC/MTL) complex seems to be necessary for the formation of spatial memory. This memory requires the interpretation and processing of sensory information received from the environment. In mammals in general, the proper functioning of the hippocampus, especially CA1, is essential for the formation and processing of space-related memory. Evidence suggests that the right hippocampus in humans plays a key role in spatial memory, and in rodents, the amount and accuracy of spatial memory are directly related to the number of hippocampal mossy fibers [15–17].

1.2 Diabetes

According to the World Health Organization (WHO), the term diabetes mellitus refers to a metabolic disorder with a variety of causes, including chronic hypoglycemia and impaired metabolism of carbohydrates, fats, and proteins due to impaired insulin secretion, insulin function, or both. Diabetes mellitus can have long-term effects and involve a variety of organs, including the central and peripheral nervous system, cardiovascular system, kidneys, and muscles. According to the World Health Organization, approximately 347 million people worldwide suffer from diabetes. However, 80% of these patients live in developing countries, and this number is increasing day by day [18, 19]. In addition, the number of people suffering from this metabolic disease in 2000 was 171 million, which will increase to 366 million in 2030 if proper prevention and treatment strategies are not implemented [20]. It is also estimated that by 2050 the incidence of diabetes in the world will increase by 198%, which will have a significant impact on increasing health care costs [20, 21]. As well as, global estimates suggest that by 2030, most people with diabetes will be 45 to 64 years old. The prevalence of type 2 diabetes is much faster than type 1, due to the increasing prevalence of obesity and reduced physical activity, which is one of the consequences of the industrialization of countries [22].

1.2.1 Diabetes can be divided into three general categories

1.2.1.1 Type 1 diabetes (T1D)

Type 1 diabetes, or insulin-dependent diabetes, is caused by the destruction of pancreatic beta cells as a result of insufficient insulin release. This type of diabetes is most common in adolescence and young adulthood and accounts for 10% of all diabetes cases [23].

1.2.1.2 Type 2 diabetes (T2D)

Type 2 or non-insulin-dependent diabetes, which is more common than type 1 diabetes, occurs due to insensitivity and resistance to insulin in the body along with insufficient insulin release. This type of diabetes is more common in the elderly, especially women [22].

1.2.1.3 Gestational diabetes mellitus (GDM)

Gestational diabetes mellitus is another type of diabetes that can be diagnosed during pregnancy and is defined as any amount of glucose intolerance that develops or is first diagnosed during pregnancy. However, in most cases, it is type 2 diabetes, which obviously leads to type 2 diabetes in 30 to 50 percent and in some cases has a similar course to type 1 diabetes [24]. According to this issue, diabetics and pregnant people can be divided into two groups: a group of people with diabetes who had diabetes before pregnancy (pre-existing diabetes) and may have one type of diabetes (T1D or T2D); The second group of people in whom gestational diabetes is diagnosed for the first time during pregnancy [25, 26].

1.2.2 Diabetes during pregnancy

Diabetes mellitus is the most common and important metabolic complication in pregnancy that can affect maternal and fetal health [27]. According to studies, diabetes is seen in around 7% of pregnancies and its prevalence depends on the study population and diagnostic tests from 1 Up to 14% have also been reported [24, 28]. Gestational diabetes is one of the leading causes of mortality in pregnant women which can be elevating the risk for spontaneous abortion, stillbirth, congenital malformations, and perinatal morbidity and mortality [29]. It is well documented that maternal glycemic control during pregnancy can markedly decrease congenital malformation outcomes in the fetus. Studies have shown that infants born to diabetic mothers have a higher risk of congenital disorders in the nervous, cardiovascular, kidney, and gastrointestinal tracts [26, 30–32].

1.2.2.1 Pathophysiology of gestational diabetes on embryonic development

In healthy mothers and under normal conditions, pregnancy causes hyperplasia of pancreatic beta cells and increases insulin levels in the mother's bloodstream [33]. On the other hand, at the beginning of pregnancy, insulin sensitivity is observed in pregnant women, which turns into insulin resistance as the pregnancy progresses. Maternal insulin resistance appears to occur due to the production of placental diabetogenic hormones such as growth hormone, placental lactogen, corticotropin-releasing hormone, and progesterone [33, 34]. This insulin resistance decreases after the placenta leaves the mother's body and increases the risk of hyperglycemia in mothers 7 to 15 weeks after delivery [35, 36].

Previous studies have illustrated that increase in the level of maternal blood glucose and a decrease in insulin is the main reason for diabetes during pregnancy [37]. In the above conditions, glucose can easily pass through the placenta into the fetal bloodstream, leading to fetal hyperglycemia. During the first few weeks of pregnancy, fetal islet cells (beta cells) cannot release enough insulin in response to hyperglycemia, which is the main cause of fetal hyperglycemia. In response to this condition, after week 20, the fetal pancreas is stimulated and the pancreatic beta cells begin to hypertrophy and hyperplasia, which eventually leads to increased fetal insulin levels. In addition to impairing the development of various organs, this

complication can be followed by hypoglycemia and hyperinsulinemia in the first few days after birth [30, 37–39].

Results from previous experiments have shown that insulin can influence carbohydrate, fats, and protein metabolism, membrane transport of glucose, amino acids, and ion exchange in cells as well as protein and DNA synthesis. In addition, insulin can stimulate or inhibit the activity of certain enzymes and regulate gene expression [40]. On the other hand, alters and reduction of ions transfer can lead to the reduction level of some vital ions such as zinc. Thereby, this process has a negative effect on the migration of marginal layer cells in the fetus of diabetic mothers which increases defects in the central nervous system [41]. In this regard, some studies indicate that high concentrations of beta-hydroxybutyric acid, which occurs in diabetes mothers, can delay the development of the central nervous system of the fetus [42–44].

Although hyperglycemia is believed to be the most important teratogenic element in diabetic pregnancy; Some researchers suggest that changes in maternal metabolic status (i.e., triglyceride and β-hydroxybutyrate levels and branched-chain amino acids) lead to disrupted fetal metabolism of inositol, sorbitol, prostaglandins, and arachidonic acid could have a teratological effect and therefore be important for the incidence of fetal disorders. An excess of fetal reactive oxygen species (ROS) has also been linked to the etiology of congenital malformations induced by diabetes. These free radicals may cause increasing neuronal death by oxidizing proteins, damaging DNA, and inducing the lipoperoxidation of cellular membranes. In vitro and in vivo studies have shown that the disturbed development of embryos in a diabetic milieu can be normalized by treatment with different antioxidant factors [27, 45–47].

1.2.3 The effects of gestational diabetes on fetal development and infant health

It is well documented that fetuses of mothers with diabetes during pregnancy are in a completely different environment than a healthy mother. Glucose, alanine, and free fatty acids are transported in large quantities from the mother's blood to the fetus. As a result, the concentration of insulin in the amniotic fluid increased, which indicates a compensatory response of the fetus to an increase in these factors [48]. Hyperglycemia in the first trimester of pregnancy increases significantly the risk of congenital malformations and stillbirth [49].

Several studies have shown that maternal hyperglycemia during pregnancy causes fetal hyperglycemia and neonatal hypoglycemia; Because circulating glucose simply crosses the placenta by facilitating diffusion, resulting in fetal hyperglycemia [35, 37]. In contrast, to compensate for this event, the fetal pancreas is stimulated and the pancreatic beta cells begin to hypertrophy, which causes increased fetal insulin levels. Due to the inability of the growing beta cells in the pancreas to secrete enough insulin, this condition soon leads to fetal hypoinsulinemia [37, 50]. Although this complication is temporary; However, studies show that fetuses from mothers with diabetes develop hyperinsulinemia in the last trimester of pregnancy. This condition in the fetus, in addition to affecting various organs, puts infants at risk for hypoglycemia in the few first days after birth, which is one of the most important causes of infant mortality in diabetic mothers [51, 52]. Previous studies report that gestational diabetes can increase the risk of impaired fetal and neonatal development, mortality, and also problems in infancy, childhood, and adulthood [31, 32]. Abundant human studies have identified type 1 diabetes during pregnancy as an important factor in the development of fetal and neonatal complications such as stillbirth, fetal macrosomia, respiratory distress syndrome, diabetes, jaundice, asphyxia, hypertension, neonatal hyperglycemia, hypocalcemia and hypomagnesemia, cardiac abnormalities, hypoxia, and neonatal polycythemia [53–55].

Studies have also shown that diabetes can have teratogenic effects and also negative effects on embryogenesis, organogenesis, and fetal growth [56]. The frequency of the mentioned problems is the same for both types of diabetes and the incidence of these complications depends directly on the severity of maternal diabetes [57]. Studies have shown that in gestational diabetes, there is a linear relationship between maternal glucose levels in early pregnancy and the incidence of birth defects [58].

1.2.3.1 Fetal and infant mortality

In past years, the rate of infant mortality from diabetic mothers has been significantly high. But nowadays, due to advances in medical and obstetrical management in the pregnancy period, this rate has decreased significantly. But despite these advances, the mortality rate in these infants is still reported to be 3 to 10 times higher than in infants under normal pregnancy conditions, as well as the prevalence of congenital malformations is 4 to 10 times higher than that of healthy mothers [29, 33]. Studies show that fetal malformations are the reason 30 to 40 percent of infant deaths in diabetic mothers. However, it has been clearly shown that precise control of blood glucose during pregnancy reduces maternal and neonatal mortality [59, 60].

1.2.3.2 Neonatal hypoglycemia

A sharp drop in plasma glucose concentration after delivery is a characteristic feature of newborns born to poorly controlled diabetic mothers. This event occurs due to chronic maternal hyperglycemia resulting in fetal pancreatic cell hyperplasia. Subsequently, this hyperplasia causes stimulation of fetal pancreatic beta cells to release a high level of insulin. In addition to stimulating somatic growth, hyperinsulinemia is also one of the main causes of hypoglycemia in the first few minutes after birth [24, 49].

1.2.3.3 Congenital malformations

Fetal malformations, which usually occur between 7 and 10 weeks, account for 30 to 40 percent of prenatal deaths. Studies show that the rate of severe malformations in children of healthy mothers is 7.8%, but 15% in children of diabetic mothers. These malformations usually affect the central nervous system, heart, kidneys, and urinary system [27, 33].

1.2.3.4 Macrosomia

It is more common in infants of mothers with diabetes and increases the risk of death at birth. Diabetes during pregnancy can double the incidence of macrosomia and other neonatal anthropometric indexes in diabetic mothers compared to babies born to non-diabetic mothers. Previous studies have clearly established that maternal diabetes can induce macrosomia in most fetal organs except the brain. These events are closely related to fetal hyperinsulinemia and maternal hyperglycemia [24, 61].

1.2.3.5 Neuropsychological effects of gestational diabetes on infants

Previous studies have shown that infants of diabetic mothers have a significant decrease in brain weight and size compared to healthy mothers [37]. Moreover,

multiple lines of evidence indicated that offspring of diabetic mothers exhibit disturbances in behavioral and intellectual functioning. In this way, other studies have shown a link between brain size and intelligence. These children also show poorer cognitive function than children of healthy mothers, which is related to the effects of maternal metabolic changes on the development of the fetal central nervous system (CNS) [62–64]. Long-term studies of offspring born to diabetic mothers have shown that diabetes during pregnancy reduces IQ in these children [65].

Researchers believe that gestational diabetes is a teratogen for the development of the central nervous system [66]. Since the brain is one of the major organs using up glucose in the body, any defect in the process of supplying glucose to the brain, even for a short time, can cause brain disorders [67]. In humans, the differentiation and maturation of the cerebral cortex occur at the end of the second trimester of pregnancy, and therefore at this time, any change in blood glucose levels can have irreversible effects [65, 67, 68]. It is believed that hypoglycemia due to hyperinsulinemia in infants born to mothers causes neuronal damage in the internal temporal region and also memory-related areas [69].

Smoak and Sadler examined the role of glucose in brain development in mouse embryos. The researchers showed that a 50 percent reduction in blood glucose levels for 2 hours in mice at the stage of neural tube formation causes developmental disorders in the nervous system [70]. Habituation is a sign of proper functioning of the central nervous system. Studies have shown that fetuses of diabetic mothers have poorer habituation than fetuses of healthy mothers. This reduction is indicative of the effect of gestational diabetes on suitable central nervous system function [62, 71].

1.2.3.6 Attention deficit disorder and hyperactivity

Neural damage in infants of mothers with diabetes during pregnancy is not only limited to a negative effect on their intelligence but also can reduce their concentration [65]. Studies have indicated a higher incidence of developmental delay and behavioral problems including short attention span, over-activity, and attention-seeking in children born to mothers with diabetes [58]. Moreover, growth motor skills and speech and language delay were the main development areas of concern that could link between maternal diabetes and development in children aged 1–6 years [72]. Other studies demonstrated that school-age children younger than 9 years, born to diabetic mothers, had a higher rate of attention deficit, lower cognitive scores, and lower gross and fine motor achievements than matched control children did. as well as the period might affect the later cognitive and behavioral function of progeny by influencing developing brain cells in utero [73, 74].

In general, it can be said that diabetes during pregnancy disrupts the development, function, and maturity of the CNS in the children of diabetic mothers, which manifests itself in the form of intelligence, educational and behavioral problems. It should be noted that both increase and decrease in blood sugar during brain development can lead to a decrease in various cognitive functions [64, 65, 75].

1.2.3.7 Intelligence and memory disorders

Children born to diabetic mothers suffer from neuropsychiatric disorders, including decreased intelligence and memory disorders. In 1997, Rizzo and colleagues followed 139 women with gestational diabetes and reported that their children's intelligence was directly related to maternal glucose metabolism in the second and third trimesters of pregnancy [76]. In animal studies, the hippocampus, which is particularly involved in memory, has been identified as the most susceptible area

to the negative effects of hypoglycemia, which can occur in the fetus or immediately after birth. Overall, the results of various studies indicate the negative impact of maternal diabetes on cognitive functions, which can cause memory and intelligence deficits [75, 77, 78].

1.3 Effects diabetes during pregnancy on hippocampus

As mentioned before, the hippocampus is an important brain structure crucial for spatial learning and memory. In diseases that cause memory loss and other intellectual functions, such as Alzheimer's disease, hippocampus cells are among the first cells to undergo degenerative changes. it is well documented that the hippocampus provides a stimulus that converts short-term memory to long-term memory, and whatever its mechanism, it would not have happened without the hippocampus [3].

Studies have shown hippocampus is very sensitive to changes in glucose concentration during development. in this regard, there is a bulk of studies that show children born to diabetic mothers are more likely to have neurodevelopmental abnormalities including impairments in memory, learning ability, activity level, attention span, and motor functioning. These infants also show lower IQ scores compared to infants born to healthy mothers [37, 58].

When pregestational and gestational diabetes-exposed children were grouped together in the study of DeBoer et al., it was demonstrated a negative link between maternal diabetes and development of memory, circuitry, and behavioral mnemonic performance in children at 1-year of age. Moreover, they showed that the metabolic abnormalities due to diabetes during pregnancy alters prenatal development, which can influence memory performance on a delay recall task. It is well documented that metabolic abnormalities which occur in diabetes during pregnancy can impair fetal CNS development, which leads to structural and functional defects, especially in the hippocampus [79].

Experimental models of diabetes during pregnancy in animals have shown a decrease in the numerical density of neurons in some parts of the fetal CNS, particularly in the hippocampus, which is reflected in decreased memory and learning and impaired memory storage and recall of information [37].

In the study by Sadeghi et al., stereological change in the hippocampus of rat offspring due to diabetes in pregnancy was evaluated. In that study, the authors found a significant reduction in total volumes of the hippocampus in offspring born to diabetic mothers when compared to the control group. In addition, their results have been shown the hippocampal subfields volumes, especially the CA1, DG, and subiculum, were significantly decreased. Moreover, they reported a significant decrease in the number of hippocampal cells in infants born to diabetic mothers [80].

A study by Tehranipour and Khakzad examines the effect of maternal diabetes on neural density in the hippocampus of newborn rats immediately after birth. Their results showed that diabetes during pregnancy can decrease the number of neurons in the hippocampus, especially in the CA3 area [81].

Synaptogenesis is one of the key events which happen throughout the development of the central nervous system. The chemical synapses in the central nervous system contain the presynaptic apparatus, the synaptic cleft, and the postsynaptic region. During synaptic transmission, In the presynaptic part, neurotransmitters stored in the synaptic vesicle through the exocytosis process, release into the synaptic cleft and then fuse with their receptors in the postsynaptic membrane. This process is highly regulated in CNS. The bulk of studies were performed to recognize and specify the components of the synaptic vesicle membrane. These

studies have been found several proteins, including synaptophysin, synaptobrevin, and synaptogamin that functions as the regulators of exocytosis. In recent studies, synaptophysin has been utilized as a valid marker for synaptic density and synaptogenesis [66, 82, 83].

In a study by Vafaei-Nezhad et al., researchers revealed that the SYP expression levels were significantly reduced in hippocampus sub-regions of pups born to diabetic animals, especially at P7 and P14, compared with the control group [66]. SYP as a major protein of the synaptic vesicle membrane may play an important role in transmitter release. Thus, the early decrease in SYP expression may reflect a down-regulation of synaptic functions and may be related to the release of the neurotransmitters. Since SYP and other synaptic vesicle proteins have been implicated in the mechanisms of cellular plasticity underlying learning, a decrease in the expression of this protein might disrupt memory formation [84–86]. SYP is also a reliable indicator of synaptic plasticity, and has previously been demonstrated to correlate well with the loss of cognitive function in animal models with neurodegeneration and in humans with Alzheimer's disease [87]. Earlier study also demonstrated a correlation between aging-related deficits in cognitive functions and disturbances in SYP expression in the hippocampus. There are also documents showing that upregulation of SYP expression may contribute to the mechanisms that underlie learning and memory [85, 86].

In another investigation by Sadeghi et al., the effects of maternal diabetes on neurogenesis in the developing hippocampus were examined. in the study, researchers probe NeuN and DCX markers changes. They found a significant higher mean number of DCX-positive cells and an up-regulation in mRNA expression of DCX in neonates born to diabetic mothers. Moreover, they demonstrated a significant reduction in the mean number of NeuN-positive cells and down-regulation in NeuN expression in the newborns to diabetic animals [88].

This author in another study also revealed that maternal diabetes could result in developmentally induced increase in the hippocampal GFAP expression and numerical density of GFAP positive cells in the DG hippocampal subfield of the offspring born to diabetic mothers compared to healthy mothers [89].

In experimental animals, it is reported that diabetes during pregnancy can increase apoptosis in the central nervous system in neonates. In this context, research by Lotfi et al. revealed that maternal diabetes in newborns of diabetic mothers leads to a marked increase in the number of apoptotic cells in the CA3 subregion of the hippocampus. They also suggested that hyperglycemia during pregnancy could cause a developmental change in the density of neuronal cells in the offspring's hippocampus [90]. In consist with this study, in another research has been reported that diabetes during pregnancy leads to up-regulate in Bax and down-regulated in Bcl-2 gene expression (apoptosis-regulatory genes) in the hippocampus of rat neonates born to mothers with diabetes [91].

Nowadays, neurotrophic factor such as brain-derived neurotrophic factor (BDNF) is considered for its role in regulating the development of the fetal nervous system. In the experiment by Sardar et al., they assessed the effects of maternal diabetes on gene expression and distribution pattern of BDNF in the hippocampus of neonatal rats. The results of the present study showed that diabetes during pregnancy causes marked BDNF downregulation and numerical density of BDNF⁺ cells reduction in both sides' hippocampi of the male/female diabetic group [92].

In another study by Hami et al., the effects of diabetes in pregnancy on gene expression and protein concentration of IGF1R and IR in the developing rat hippocampus at postnatal days 0, 7, and 14 were evaluated. In that study, the authors found a markedly upregulation of both IR and IGF1R expression in the hippocampus of diabetic group newborns at first postnatal day. At the same time point, they

showed only slight changes in their hippocampal protein transcripts. In 7-day, old rats, there was a significant decreased in IGF-1R gene expression and protein levels in the newborns born to diabetic dams. Moreover, they found a down regulation in hippocampal IGF1R transcripts in 14-day old diabetic group offspring. Two weeks after birth, the IR gene expression was significantly declined in the hippocampus of diabetic newborns [18].

1.4 Effects diabetes on the hippocampus in adults

A bulk of studies have been demonstrated that all types of diabetes have adverse effects on the central nervous system such as disruption in hypothalamic and hippocampal neuropeptides gene expression, a change in hippocampal function and decreased hippocampal synaptic plasticity, glutamate neurotransmission abnormalities, and neurotoxicity [93, 94]. Studies have shown that people with diabetes have a higher risk of developing memory and learning disorders and also Alzheimer's disease, depression, stroke, and dementia compared to healthy people [95]. A previous study showed that diabetes induction in animal models can elevate corticosterone levels and defects hippocampal synaptic plasticity, learning, and long-term potentiation in the CA1-field [96, 97]. Recent studies showed that STZ-induced diabetes notably decreased the number of proliferating cells in the dentate gyrus of rats by changing the hippocampal synaptic plasticity [98].

There is some evidence that diabetes can decrease hippocampal cell proliferation and survival, while some researchers suggest that diabetes also has adverse effects on neuronal differentiation. Several preclinical studies revealed the bulk of evidence that diabetes has adverse effects morphological integrity of the hippocampus and that it reduced hippocampal neurogenesis. These hippocampal dysfunctions may cause cognitive and mood disorders in diabetic's people [99].

In the study by Revsin et al., Neuronal and astroglial alterations in the hippocampus of a mouse model for type 1 diabetes have been evaluated. Their results showed that diabetic condition in mice can cause a significant increase in the number of astrocytes positive for apolipoprotein-E (Apo-E), a marker of ongoing neuronal dysfunction, abnormal expression of Jun + neurons in CA1 and CA3 layers and dentate gyrus, and Fos-expressing neurons in CA3 layer, and augmented activity of NADPH-diaphorase which is linked to oxidative stress, in CA3 region. They state that these changes could be one of the reasons for the negative effects of diabetes on the hippocampus [94]. Similar to the results of this study Stereological studies have shown that there is no significant change in the total neuron number values and the volume of the hippocampus in diabetic animals compared to healthy animals [94, 100].

It is well known that type 2 diabetes mellitus can lead to cognitive deficits in patients. In this regard, a study by Liu et al., has been revealed that diabetes could alter effective connectivity (EC) between hippocampus and default mode network (DMN), which is interpreted to be related to cognitive disorders in patients with T2DM especially affecting learning and memory [101].

In experimental animals by Kamal et al., they assessed Synaptic transmission changes in diabetic rat s' hippocampus. Their data illustrated that intracellular recording from the pyramidal hippocampal cells of the AMPA summation responses in the diabetic animals was markedly lower than control animals. Hence, they suggest that diabetes can change pre and postsynaptic cells functions which may play a key role in in the synaptic plasticity disorder observed in diabetic animals [93].

Defects in glucose metabolism in the nervous system are not only important for neural cells function but also normal astrocyte activity is related to it. Astrocytes

have many important roles in central nervous system such as glucose uptake. Astrocyte dysfunction in the hippocampus have been seen in pathological conditions such as aging, stress, autoimmune diseases, neurodegenerative diseases, and diabetes. In the hippocampus of the animal diabetic model has been reported a significant increase in GFAP immunoreactivity, glial fibrillary acidic protein (GFAP), an astrocyte intermediate filament cytoskeletal protein which is considered the main indicator of astroglial activation caused by CNS injury [102]. In line with this study, a study by Lebed et al. showed that diabetes can alter GFAP and S100B levels in the hippocampus. These findings propose that the reaction of astroglial cells can be the first reaction to impaired glucose metabolism, which is likely to play a crucial role in the mechanisms underlying diabetes-related disorders of CNS function. [103].

In a study by Pamidi et al., the Effect of streptozotocin-induced diabetes on rat hippocampus was assessed. They used Cresyl violet staining for evaluating the number of surviving neurons in the subfield of the hippocampus. Their findings revealed that the number of survived neurons in the subfield of the hippocampus (CA1, CA2, CA3, dentate hilus, dentate gyrus) in diabetic animals was significantly reduced compared to controls. Hence, researchers suggested that uncontrolled and long-term diabetes could cause intense hippocampal neurodegeneration [104].

In another study, researchers examined the effects of STZ-induced diabetes on NCAM protein expression in various parts of the nervous system, including the hippocampus. The results of this study have been demonstrated that diabetic animals developed remarkable defects in learning and memory behaviors which were evaluated by passive avoidance and water maze tests. Their results also indicate that streptozotocin-induced diabetes disrupts cognitive functions and causes an imbalance in NCAM expression in some parts of the brain, particularly the hippocampus, which is involved in memory and learning. Based on the results of their study, the researchers concluded that changes in the expression of NCAM in the hippocampus of diabetic people could be one of the main causes of memory and learning disorders [105].

Axonal transport has a critical role in normal CNS function and disruption of this process has been linked to various neurodegenerative diseases and could also play a role in diabetes-related diseases that affect the nervous system. Given the importance of this process, Baptista et al. assessed the impact of diabetes on axonal transport in the hippocampus. in this regard, they evaluated KIF1A, KIF5B, and dynein in the hippocampus. Their results showed a significant increase in KIF1A and KIF5B mRNA and protein levels, in CA1, CA3, and DG hippocampal subregion, in the diabetic animals. Nevertheless, no changes in dynein protein were observed [106].

The animal experiment has been revealed that diabetes can cause a reduction of nuclear and perikaryon diameters as well as neuronal density in the sub-region of the hippocampus (CA1, CA2, CA3, and dentate gyrus) [107]. In addition, it has been reported that levels of Caspase-3, Bax, and Bcl-2 in the hippocampus increase after diabetes [108].

1.5 Effects of diabetes during pregnancy on the other parts of CNS

The source of the mammalian neural tube is the ectoderm layer in the embryo. During the first few months of pregnancy which is called the embryonic period, part of the ectoderm becomes a neural plate. Then, this plate is folded, raised, and connected in the midline, which becomes the neural tube [109, 110]. The mentioned procedure is mediated by several signaling molecules and transcription elements [111, 112]. There is strong evidence that diabetes during pregnancy causes

abnormalities in the development of the nervous system, including the neural tube, which itself can cause neural tube defects (NTD) [113, 114]. Neural tube formation during the embryogenesis period is tightly regulated by several cellular mechanisms such as proliferation, migration, differentiation, and apoptosis of neural progenitor cells. Previous studies have shown that pregnancy-related hyperglycemia can disrupt cell migration and proliferation, as well as induce programmed cell death during embryogenesis. Studies have revealed that any changes in the mentioned processes can cause NTDs [95, 115].

Spina bifida, which is one of the common NTD, results from failure of neural tube fusion in the spinal area. This abnormality is a common congenital defect that occurs in infants of diabetic mothers [116]. The exact mechanism underlying the teratogenic effects of diabetes during pregnancy is not entirely understood, but it is suggested that the incidence and intensity of congenital malformations in infants born to diabetic mothers are correlated with the degree of maternal metabolic control [37].

Diabetes during pregnancy causes biological changes in the mother that can affect the development of the fetal nervous system. These biological changes can affect nervous system development and neurological abnormalities in the fetus by affecting neurotransmitters, synaptic membranes, and the expression of growth factors that are involved in nervous system development. Studies have shown that increased oxidative stress plays an important role in fetal development and indirectly can cause some of the nervous system developmental disorders that occur in fetuses from diabetic mothers [22]. Free radicals can also alter the biological activity of proteins and peptides, increase neuronal death, and cause DNA damage [37, 117, 118]. Experimental research showed that maternal hyperglycemia can lead to a significant decrease in the volume of gray and white matter, and also can reduce the number of neurons in the gray matter of the CNS in this offspring [119].

Evaluations of cognitive functioning and the behavior of the children born to diabetic mothers provide the chance to functionally assess the CNS development. Hence, behavioral and cognitive assessments in neonates of diabetic mothers can shed light on the effects of maternal diabetes on CNS development [64, 65, 72, 73].

Animal models of diabetes during pregnancy indicate a decrease in the numerical density of neurons in some parts of the fetal central nervous system, particularly in the brain, hippocampus, and cerebellum, due to diabetes during pregnancy, which may be followed by decreased memory and learning ability, and memory defects and information retrieval [37, 58, 80, 120]. Studies by Khaksar on gestational diabetes have shown that gestational diabetes can affect the infant CNS and reduce the number of cells and the thickness of the white and gray matter of the infant cerebrum, cerebellum and spinal cord [119]. Earlier research on the neurologic development in infants of diabetic mothers illustrated fundamental CNS deficits even when there were no structural abnormalities. These alterations were markedly less serious when maternal diabetes was controlled and treated, but some alterations in cognitive function may continue all over childhood [37].

The study by Hami et al. showed that diabetes during pregnancy in infants born to diabetic mothers can lead to a significant decrease in cerebellar volume, the thickness of cerebellar cortical layers, and also decreases in the numerical densities of cerebellar Purkinje and granular cells. They suggested that this event may delay the normal development of the cerebellum and may be a cause of the motor, behavioral, structural, and cognitive disorders seen in the offspring of diabetic mothers [120].

It is well documented that diabetes during pregnancy has structural and functional effects the on central nervous system in both human and animal studies. Despite much research in the field, the exact mechanism by which diabetes affects

the development of the nervous system during pregnancy is not yet clearly understood. Some studies have suggested that diabetes itself may have teratogenic effects that can increase the risk of abnormal fetal development in the fetal organs [37].

Some studies suggested that hyperglycemia conditions during pregnancy can induce programmed cell death and impair cell proliferation in mouse embryo neural tubes. Recent experiments suggest that tumor necrosis factor (TNF) plays an important role in neurodevelopmental disorders in babies born to diabetic mothers. TNF could cross the placenta and enter the embryo's bloodstream, which has neurotoxic effects on fetal brain development and can also lead to white matter damage and cerebral palsy [35, 121].

Other investigations implicated that infants born to diabetic mothers have iron metabolism abnormalities. This deficiency can lead to neurodevelopmental and neurobehavioral disorders. Experimental studies in animal models have shown that iron impairment during pregnancy and after childbirth has negative effects on myelination, the metabolism of neurotransmitters in the brain, and the regulation of brain energy. The perinatal iron disorder can elevate the vulnerability of the neonatal brain, especially the hippocampus, to the hypoxic–ischemic insult which leads to abnormal cognitive processing in the newborn period [122, 123].

Kinney *et al*. found that the only female offspring born to diabetic dams showed deficits in long-term memory and learning. These results have suggested that the *in utero* diabetic condition has gender-specific effects on CNS development [78]. In a study by Plagemann *et al*., alterations in catecholamines levels in the hypothalamic nuclei of newborns born to diabetic animals were evaluated. They reported an increased hypothalamic dopamine (DA) and norepinephrine (NE) concentrations in the offspring born to diabetic rats at birth. Twenty-one day- old pups born to diabetic mothers, NE levels were strikingly increased in the ventromedial hypothalamic nucleus and the lateral hypothalamic area (LHA), while DA levels were significantly elevated in the paraventricular hypothalamic nucleus and the LHA. The authors concluded that there are strikingly differences in hypothalamic catecholaminergic systems during early development in the rat newborns born to diabetic animals [124].

Studies have shown that brain weight in infants born to diabetic mothers is significantly lower than in infants born to healthy mothers [66]. Interestingly, Xiang et al. explained a close correlation between diabetes during pregnancy with an elevated risk of autism spectrum disorder (ASD) in infants [125]. Animal models of diabetes during pregnancy indicate a decrease in the numerical density of neurons in some parts of the fetal central nervous system, particularly in the brain, hippocampus, and cerebellum, due to diabetes during pregnancy, which may be followed by decreased memory and learning ability, and memory defects and information retrieval [37, 58].

Much research has shown that fetal hyperglycemia during pregnancy can alter gene expression that is involved in the proliferation and differentiation of nerve cells. These changes can be the basis of the neurocognitive and neurodevelopmental disorders seen in babies of diabetic mothers [37, 58].

Previous studies have shown that insulin and insulin receptor (InsR), and insulin-like growth factor-1 (IGF-I) and IGF-1 receptor (IGF-1R) play key roles in regulating the growth and development of the CNS. It is well documented that insulin and IGF-1 stimulate the proliferation of neuronal progenitor cells, increases the survival of neurons and oligodendrocytes, elevate synaptogenesis and neurotic outgrowth, inhibit neural cell apoptosis, and induces differentiation of neurons. With this in mind, the researchers examined the effects of maternal diabetes on the expression of this factor in the nervous system. Their results have been revealed that maternal diabetes can strongly influence the regulation of these factors at the level of mRNA and protein in neonates' central nervous system [18, 37, 58, 126, 127].

Synaptic transmission and information transfer are highly regulated processes in the nervous system. Information transfer occurs when neurotransmitters stored in synaptic vesicles release into the synaptic cleft and attach to their receptors in the postsynaptic cell membrane. Synaptic vesicles are responsible for collecting neurotransmitters and releasing them into the synaptic cleft through exocytosis. The exocytosis process during the release of neurotransmitters has been extensively studied [82, 83]. Several families of proteins that are present in the membranes of synaptic vesicles which involved in the regulation of this process have been identified [82]. One of these proteins is synaptophysin. This protein is widely found in the membranes of vesicles containing neurotransmitters in neurons.

Synaptophysin is a protein involved in the construction of synaptic vesicles that researchers use as a suitable marker of synaptic density, synaptogenesis [128]. Studies have also shown that synaptophysin may be involved in the exocytosis of synaptic vesicles [129]. It is well documented that synaptophysin levels also change in pathological brain conditions such as Alzheimer's, Parkinson's, schizophrenia, and bipolar disorder [87, 130–132]. Previous studies illustrated that diabetes during pregnancy can reduce significantly downregulate synaptophysin gene expression in different layers of the neonate cerebellum which is born to diabetic mothers [74].

2. Conclusions

As the prevalence of diabetes increases in various societies, particularly in developing countries, the total number of fetuses born to diabetic mothers will continue to increase in the coming decades. The metabolic changes caused by maternal diabetes disrupt glucose homeostasis in the fetus and cause numerous problems for the fetus. Nowadays, these metabolic disorders are discussed in various studies. Previous studies have clearly shown an association between maternal blood sugar levels and an increased risk of birth defects. Researchers have found that maternal hyperglycemia can have teratogenic effects on fetuses. However, the exact mechanism of the cause of the malformations in the fetuses of diabetic mothers is not yet known. It is well documented that diabetes during pregnancy has significant effects on fetal central nervous system development, particularly the hippocampus, which can lead to disorders in learning, memory, and attention in newborns and adults. In this regard, it is suggested that suitable management of hyperglycemia and dissecting out the mechanisms responsible for diabetes-related changes in the functions of the hippocampus, could help to prevent impaired cognitive and memory functions in offspring and adults.

Conflict of interest

The authors declare no conflict of interest.

Acronyms and Abbreviations

CNS	Central nervous system
WHO	World Health Organization
T1D	Type 1 diabetes
T2D	Type 2 diabetes
GDM	Gestational diabetes mellitus
ROS	Reactive oxygen species

NTD	Neural tube defects
TNF	Tumor necrosis factor
DA	Dopamine
NE	Norepinephrine
LHA	Lateral hypothalamic area
ASD	Autism spectrum disorder
InsR	Insulin receptor
IGFI	Insulin-like growth factor-1
IGF-1R	IGF-1 receptor
HC/MTL	Hippocampal/internal temporal lobe
Apo-E	Effective connectivity (EC)
DMN	default mode network

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