DIABETIC ENCEPHALOPATHY A MINI-REVIEW

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ABSTRACT:
Type 2 diabetes mellitus (T2DM) is a complex metabolic condition linked to an increased risk of central nervous system complications. Diabetic encephalopathy is a relatively unknown diabetic consequence marked by electrophysiological, structural, neurochemical, and degenerative neuronal alterations that result in cognitive impairment. Apart from persistent hyperglycemia and dyslipidemia, diabetic encephalopathy is the most important risk factor for cognitive impairment, dementia, and, ultimately, Alzheimer's disease (AD), often known as "Type 3 diabetes". T2DM, cognitive decline, and neurodegenerative diseases, including Alzheimer's disease, are all linked to oxidative stress and inflammation. As a result, we examined Diabetic Encephalopathy in this review.

Keywords: *Dyslipidemia, Diabetic encephalopathy, Cognitive Impairment, Metabolic Disorder.*

INTRODUCTION:

Diabetes mellitus (DM) is a multifaceted metabolic condition marked by an excessive rise in blood glucose levels (hyperglycemia)[1]. This happens when pancreatic cells fail to produce sufficient quantities of insulin to sustain normoglycemia and/or insulin's activities are resistant[2]. The prevalence of diabetes mellitus (DM) has grown dramatically in recent years (International Diabetes Federation [IDF])[3], making it one of the most prevalent diseases in the world: it currently affects around 285 million people and is expected to climb by 50% by 2030. Insulin resistance (IR) is a pathophysiological condition in which insulin fails or becomes ineffective in promoting glucose absorption and/or utilization by target tissues[4]. This causes an increase in insulin release, followed by insufficient insulin secretion[5]. Elevated fasting glucose levels as a result of IR can lead to type 2 diabetes mellitus (T2DM), which is characterized by -cell dysfunction, increased hepatic glucose production, and increased IR, primarily in skeletal muscle[6]. The majority of persons with T2DM have several risk factors that occur together, forming what is now recognized as metabolic syndrome. Diabetes, elevated fasting plasma glucose, abdominal obesity, high cholesterol, and high blood pressure are all examples, according to the IDF. Furthermore, patients with metabolic syndrome are five times as likely to acquire T2DM[7].

T2DM is linked to several problems, which are classified as macrovascular (like coronary artery disease, peripheral arterial disease, and stroke) or microvascular (such as diabetic nephropathy, neuropathy, and retinopathy)[8]. There is mounting evidence that the brain is a significant source of T2DM damage, partly independent of atherosclerosis. Diabetic encephalopathy refers to abnormalities of the central nervous system (CNS) in T2DM patients[9],[10]. Diabetic encephalopathy, persistent hyperglycemia, and dyslipidemia are the most important risk factors for cognitive impairment in this largely unknown DM consequence, which is characterized by electrical and structural CNS alterations [11],[12]. Indeed, multiple studies have found a link between T2DM and cognitive impairments, including an increased risk of dementia [13]. In diabetic encephalopathy, an emerging and pressing type 2 diabetic complication, oxidative stress and inflammation, which underpin multiple cellular pathways that can ultimately lead to the onset and progression of subsequent complications of T2DM, are being envisioned as two key players[14]. In addition, there was a clear link between hyperglycemia, poor insulin signaling, free fatty acids (FFAs), oxidative stress, and inflammation, all of which are characteristics of T2DM.[15]–[18]

HISTORY:

Diabetes is linked to the development of well-known microvascular complications such as retinopathy, nephropathy, and peripheral neuropathy. For more than 80 years, the idea of central neuropathy has been a source of debate. Diabetes can cause cognitive impairment, which has been known since 1922 [19]. The prevalence of cognitive impairment is difficult to calculate since it is very dependent on how it is measured. The reported prevalence is around 40 percent in long-standing or poorly managed diabetes [20]. Diabetes causes cognitive impairment, which manifests itself in a variety of ways, the most notable of which is a slowdown of mental speed and a loss of flexibility [21]. Although the severity of these cognitive deficiencies appears to be modest to moderate, they can severely impede everyday

functioning and have a negative impact on quality of life [22]. Although there is no evidence to support this theory, cognitive deterioration in diabetes individuals treated with insulin has been generally attributed to recurring bouts of hypoglycemia rather than hyperglycemia [23], [24]. In 1950, the term "diabetic encephalopathy" was used to indicate cognitive impairment in diabetics as a medical consequence [25]. In the brains of 16 long-term juvenile diabetic patients who died from diabetes-related vascular problems, certain pathological alterations were discovered [26] Pseudocalcinosis, severe angiopathy of the cerebral vasculature, atrophy of the dentate nucleus, demyelination of cranial nerves, and leptomeninges fibrosis are all symptoms of generalized degenerative abnormalities. This histological pattern, according to the authors, "justifies the name "diabetic encephalopathy" because it is distinct from that found in any other clinical illness." However, the word 'encephalopathy' is not generally used for a variety of reasons. To begin with, the term has strong negative connotations and does not appear to correspond to the minor cognitive issues reported in (non-demented) diabetic individuals. Second, and most critically, there are no clear diagnostic criteria for diabetic encephalopathy, making it difficult to determine. Historically, diabetic encephalopathy has only been used to describe type 1 diabetes individuals. Functional cerebral impairment and central neuropathy are two more terminologies used in the literature to characterize cognitive problems in diabetics.

PHYSIOPATHOLOGY

Diabetic encephalopathy (DE) is a long-term consequence of diabetes mellitus that affects the central nervous system (CNS) and causes cognitive and motor dysfunctions, as well as postural balance problems. DE's physiopathology may be traced back to long-term hyperglycemia, high blood pressure, hyperinsulinemia, frequent and severe hypoglycemia episodes, and dyslipidemia.

MECHANISMS:

Low-grade chronic inflammation (LGCI) has been linked to type 2 diabetes mellitus (DM2) [27], [28]. As a result, we investigated a putative link between DE [29], neurocognitive changes, and glicolipotoxicity in a murine model of spontaneous DM2, the Stillman-Salgado (eSS) rats [30]. The combined, adverse effects of raised glucose, triglycerides (TG), greater calorie consumption, and free fatty acid levels (FFA) on pancreatic beta-cell function and survival are referred to as glucolipotoxicity. Reduced insulin production, reduced insulin gene expression, and beta-cell death by apoptosis result from high levels of circulating FFA and glucose [31]. The extracellular-regulated kinase (ERK1/2) pathway, the metabolic sensor Per-Arnt-Sim kinase, and the ATF6 branch of the unfolded protein response have all been implicated in fatty-acid suppression of insulin gene expression. Increased lipid storage in non-adipose tissues can occur when plasma FFA or triglycerides (TG) levels are high, which can contribute to "lipotoxicity." Lipotoxicity may occur in DM2, neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease (AD), amyotrophic lateral sclerosis, and heart failure, according to studies conducted in experimental animals and humans [32]. Lipid accumulation in the heart, skeletal muscle, pancreatic, and liver tissues might have a role in the etiology of these disorders [33]. Obese people and people with metabolic syndrome have higher FFA levels in their blood. Due to oxidative stress, these high FFA and non-esterified FFA

levels can cause lipotoxicity, which can affect insulin signaling and glucose sensitivity in pancreatic -cells. Saturated fatty acids (SFAs), such as palmitic acid (PA), found in red meat, appear to be important in inhibiting the insulin signaling pathway and inducing endoplasmic reticulum (ER) stress in a variety of tissues, including hypothalamic neurons, according to experimental and clinical evidence. ER stress in hypothalamic neurons is expected to cause pathogenic abnormalities in primary cortical neurons that are similar to those seen in Alzheimer's disease. When astrocytes experience increased oxidative stress and FFA metabolism, their apoptotic cell death, PC12 cells, and brain progenitor cells may all rise. In the long term, these persistent metabolic insults to the central nervous system (CNS) in DM2 may cause cognitive impairment and motor dysfunction, leading to the onset of DE. Epidemiological, clinical, and experimental data demonstrated that mild type DM2 might cause subtle and gradual metabolic abnormalities as well as a delayed but evident beginning of cognitive impairment, particularly when PUFAs from families 6 and 3 (6/3) is imbalanced [34].

TREATMENT STRATEGIES:

Anti-inflammatory and antioxidant therapies have the potential to help diabetic encephalopathy patients. Agonists for the PPAR gene the peroxisome proliferator-activated receptor (PPAR) is a nuclear receptor that coordinates the expression of genes involved in lipid absorption, adipogenesis, and inflammation to control fatty acid storage and glucose metabolism. [35] Thiazolidinediones, which are PPAR agonists, appear to be a potential therapeutic for improving insulin sensitivity and lowering inflammatory markers, suggesting that they might be used as a potential anti-inflammatory approach[36]. GLP-1 The incretin hormone glucagon-like peptide-1 (GLP-1) not only promotes glucose-dependent insulin production and maintains glucose homeostasis, but it also slows food absorption. GLP-1, interestingly, has qualities similar to insulin growth factor and is neuroprotective.

Insulin is a supposed antioxidant. Insulin has been considered as a neuroprotective drug in the treatment of neurodegenerative illnesses in which oxidative stress is a prominent factor [37]. Bélanger and colleagues, for example, hypothesized that the lack of cognitive and electrophysiological dysfunctions in ZDF rats (a T2DM model) may be attributable to hyperinsulinemia's protective effect [38].

EXERCISE:

Several studies show that exercise affects various elements of brain function and has a wide range of benefits on overall brain health. Learning and memory, neurodegeneration prevention, and depression relief appear to be its key goals, especially in senior people. Exercise's positive effects may be due to its anti-inflammatory qualities, which are mediated by growth factors. In reality, the main growth factors known to mediate the effects of exercise on the brain are BDNF, IGF-1, and vascular endothelial growth factors. Exercise may also reduce the burden of A, which has proinflammatory effects, lowering the levels of proinflammatory cytokine in the AD brain.

CONCLUSION:

Diabetic encephalopathy is a serious diabetes-related condition of the central nervous system (CNS) marked by neurochemical and anatomical alterations that cause cognitive dysfunction.

Its cellular and molecular causes are still unknown, and potential therapeutics are missing in clinical trials. In this work, we looked at how distinct hippocampal neurons changed during diabetic encephalopathy in mice models of diabetes by evaluating the activity and synaptic transmission of glutamatergic and GABAergic neurons in brain slices at the same time. Diabetic encephalopathy irreversibly decreases the excitability of GABAergic neurons and synaptic transmission mediated by aminobutyric acid, as compared to findings from a control group (GABA). Glutamatergic neurons, on the other hand, appear to be more stimulated. Our findings emphasize the importance of GABAergic and glutamatergic neuron dysfunction in the hippocampus during diabetes encephalopathy in terms of neurological damage, as well as a method for preventing the progression of diabetic encephalopathy by preserving central neurons.

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