Neuronal Changes in Diabetics: A Continuous Debate

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Abstract

Diabetes mellitus (DM) is a metabolic disease marked by poor blood glucose control, primarily a chronic state of hyperglycemia, as well as frequent episodes of hypoglycemia due to various pathogenic processes. The disease is primarily classified as type 1 and type 2, but there are other specific types that can be attributed to endocrinopathies, drugs, infections, immunologic, genetic, and pancreatic causes. These metabolic dysregulations are the primary cause of death and can result in a number of problems that affect the heart, kidneys, blood vessels, eyes, and neurological system. Our aim of work was to outline the neuronal changes in diabetics and their various pathomechanisms. The clinical impact of diabetes and diabetes-related comorbidities is steadily increasing, with risk factors such as obesity on the rise worldwide. However, progress has been made in the therapeutic field, with a plethora of new medications being produced to treat the disease. Better treatment procedures, new medicines, and recombinant insulin all contribute to better glycemic control, thereby preventing and delaying the advancement of neuronal alterations in DM. However, more study is needed in this area, particularly on medications that stop and reverse the neurological consequences of diabetes.

Key Words: Diabetes; Neurological; Neuropathy.

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Introduction:

Diabetes mellitus (DM) is a metabolic disease marked by poor blood glucose control, primarily a chronic state of hyperglycemia, as well as frequent episodes of hypoglycemia due to various pathogenic processes [1]. The disease is primarily classified as type 1 and type 2, but there are other specific types that can be attributed to endocrinopathies, drugs, infections, immunologic, genetic, and pancreatic causes. These metabolic dysregulations are the primary cause of death and can result in a number of problems that affect the heart, kidneys, blood vessels, eyes, and neurological system [2]. The hypothalamus integrates with several hormones to regulate food intake, energy expenditure, insulin secretion, hepatic glucose production, and glucose/fatty acid metabolism in adipose tissue and skeletal muscle. The brain makes up 2% of our body weight, consumes 25% of oxygen, and uses about 20% of the body's glucose [3].

Even so, the brain depends on glucose to give it the energy it needs for everything from cellular upkeep to the production of neurotransmitters [4]. Glucose plays a key role in the regulation of oxidative stress, cell death, and pathways whose mechanisms are implicated in disrupted hypothalamic circuits and sensing of glucose and insulin, which furthermore contribute to the pathophysiology of neurological disorders. Therefore, glucose regulation is critical [5]. Axonopathies, neurodegenerative diseases, neurovascular diseases, and general cognitive impairment are among the nervous system complications of diabetes mellitus (DM). In addition, nearly all DM patients have multiple vascular, metabolic, and other comorbidities that, when combined with uncontrolled glucose levels, accelerate neurological complications [2, 6]. While these effects are well known, the cellular mechanisms, such as increased advanced glycation end (AGE) products, enhanced polyol pathway, neuromodulatory, neurotrophic, and microvascular, are among other molecular changes that remain unclear [7].

Aim of work

To outline the neuronal changes in diabetics and their various pathomechanisms.

Glucose metabolism: a secret soldier

Almost every bodily system exhibits the harmful consequences of abnormal glucose metabolism. Neuronal bodies are all significantly altered. But not everyone with diabetes mellitus experiences issues [8]. For example, people who receive no treatment or care are more likely to develop diabetic nephropathy. Therefore, inadequate diabetes management leads to glucotoxicity, which ultimately causes patients to experience issues with several organ systems. Therefore, those with poorly controlled diabetes are often at a higher risk because the development of complications is governed by the control of serum glucose levels [4]. Furthermore, a higher risk of neurologic complications,

particularly polyneuropathy, is linked to age, height, obesity, diastolic blood pressure, smoking status, chronic kidney disease, vascular disease, low HDL cholesterol, high triglyceride, and glycosylated hemoglobin (HbA1c) levels in DM patients [5, 9].

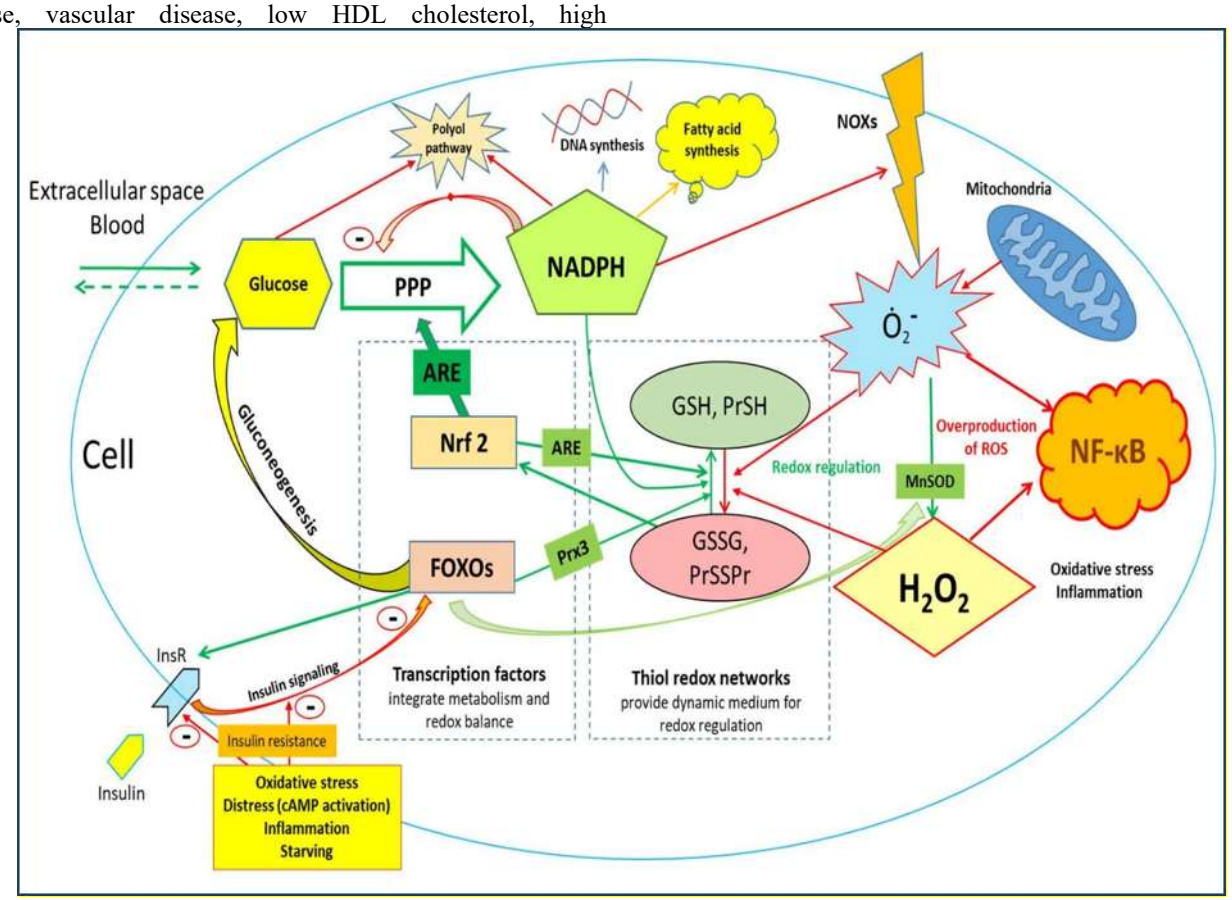

Figure (1): Glucose metabolism in diabetes [2].

Pathomechanisms of neuronal changes in diabetics

Understanding the key factors in pathogenesis allows one to intervene easily and reduce the risk of developing the disease [10].

- Molecular factors damaging neurons

Neuronal alterations brought on by hyperglycemia are known to be caused by oxidative stress. Major metabolic processes also involve a number of other molecular components [4]. The polyol pathway, advanced glycation end (AGE) products pathway, protein kinase C signaling, poly adenosine phosphate ribose polymerase (PARP) pathway, hexosamine pathway, mitogen-activated protein kinase (MAPK) pathway, nuclear factor-κB (NF-kB) signaling, cyclooxygenase pathway, and the function of tumor necrosis factor-α (TNF-α) are a few examples [11].

- Polyol Pathway

Sorbitol dehydrogenase and aldose reductase (AR) are important players in the polyol pathway's glucose metabolism. In general, AR's affinity for glucose is weaker. A hyperglycemic state in diabetes mellitus leads to the polyol pathway being used to metabolize extra glucose [12]. The mechanism begins with aldose reductase using nicotinamide adenine dinucleotide phosphate (NADPH) to reduce glucose to sorbitol. This is followed by sorbitol dehydrogenase using nicotinamide adenine dinucleotide (NAD+) to oxidize sorbitol to fructose. NADPH stores are depleted and sorbitol concentration rises as a result of the reduction process [13]. Reduced glutathione (GSH) cannot be produced without NADPH. When NADPH levels drop, GSH is downregulated, which damages endothelial cells and reduces nitric oxide-mediated vasodilation, which has a detrimental effect on the neuronal vasculature [14].

- Hexosamine Pathway

Due to hyperglycemia, there is an increased concentration of fructose-6-phosphate which proceeds to the hexosamine pathway where it is converted into glucosamine-6-phosphate followed by the production of uridine diphosphate N-acetyl glucosamine (UDPGlcNAc) by glucosamine-6-phosphate amidotransferase [15]. N-acetyl glucosamine (GlcNAc) induces oxidative stress leading to pancreatic beta (β)-cell functional deficit. Overexpression of glutamine fructose-6 phosphate aminotransferase results in inhibition of glucose transporter 2 (GLUT2), insulin leading to hyperglycemia, and increased hydrogen peroxide levels leading to oxidative stress affecting the neuronal environment [16]. Sp1 controls the gene expression of plasminogen activator inhibitor-1 (PAI-1) and

transforming growth factor β 1 (TGF-β 1). Hyperglycemia increases GlcNAc and activation of gene transcription factor Sp1. Up-regulation of PAI-1 increases vascular smooth muscle cell division which is responsible for atherosclerosis [2, 17].

- Advanced Glycation End-Products Pathway

AGE products are produced through the non-enzymatic interaction of glucose, aldehydes, and other saccharides with nucleotides, proteins, and lipids. Fructose-lysine and AGE concentrations have been observed to be elevated in the peripheral nerves of streptozotocin-treated diabetic rats. In diabetic rats' sciatic nerves, quantities of N(epsilon)-[carboxymethyl]-lysine, an advanced glycation end product, are increasing compared to controls [18]. Schwann cells in peripheral nerves contained advanced glycation end product receptors (RAGE), and their quantity increased in diabetic neuropathy. Advanced glycation end products may cause inflammation and apoptosis through their interaction with RAGE and it also up-regulates NF-κB. RAGE increases the expression of the p65 subunit of NF-κB in diabetic neuropathy. AGE products from glyceraldehyde and glycolaldehyde can cause irreversible death of Schwann cells, decrease in cell replication and viability, up-regulation of NF-κB, mitochondrial membrane potential decrease, and increase in inflammatory cytokines like TNF-α and interleukin-1 β in diabetic rats [6].

- Oxidative Stress

Oxidative stress arises when there is an imbalance between free radical scavengers and free radical species (reactive nitrogen, oxygen species), and it plays an important role in diabetic neuropathy [3]. Reactive free radical species can damage the lipids of myelinated nerve structures, resulting in damage to the nervous system's microvasculature. Neuropathic pain is caused by oxidative stress on peripheral nerves, which causes hyperexcitability in central neurons and afferent nociceptors, resulting in spontaneous impulses in axons and dorsal nerve ganglia. Nitrosative stress plays a significant role in diabetic neuropathy [12]. The difference in the GSSG/GSH ratio causes an increase in lipid peroxidation, a decrease in the following enzymes that play important roles in antioxidant cell response, such as superoxide dismutase, ascorbate, and catalase, and oxidative stress in the peripheral nerves. Furthermore, diabetes-induced oxidative stress might disrupt the mitochondrial membrane potential, resulting in edema and increased permeability [1, 7, 10].

- Protein Kinase C Pathway

Protein kinase C belongs to the family of serine/threonine-related protein kinases. They influence signal transduction pathways that control cell differentiation, proliferation, and death. Conventional isoforms (α, β I, β II, and γ) require diacylglycerol, calcium, and phosphatidylserine to activate, while new isoforms (η, δ, θ, and ε) require diacylglycerol and atypical isoforms (ι/λ, M ζ) do not [5, 17]. Each of the aforementioned isoforms has distinct action, distribution, and expression in diabetes. Immunochemical examination of nerves reveals the presence of protein kinase C isoforms α, β I, β II, γ, ε, and δ. Diabetic transgenic mice overexpressing aldose reductase showed activation of protein kinase C-II beta isoform. This protein kinase C increases TGF-β1, vascular endothelial growth factor (VEGF), PAI-1, and NF-κB, leading to various diabetes problems. In diabetic neuropathy, protein kinase C inhibitors restored normal sciatic nerve blood flow and conduction velocity. Insulin resistance has been demonstrated in various investigations including activation of protein kinase C in diabetic individuals [8, 18].

- Poly Adenosine Phosphate Ribose Polymerase Pathway

Normally, PARP is involved in DNA repair and apoptosis. Overexpression of PARP in diabetics has been linked to tissue damage [3]. It has previously been observed that diabetes-induced hyperglycemia causes the generation of reactive free radicals, followed by single-strand DNA breaks and PARP activation; however, more recent studies show that both single-strand DNA breakage and oxidative-nitrosative stress are not required for PARP activation; rather, it occurs due to phosphorylation by extracellular regulated kinase. Hyperglycemia and nonesterified fatty acids may activate PARP leading to damage of neurilemma through oxidative stress and retinal pericytes [19].

- Mitogen-Activated Protein Kinase Pathway

MAPKs are made up of three families of protein kinases: c-Jun N-terminal kinase (JNK), extracellular signal-related kinase (ERK), and p38. They are responsible for signal transduction in response to a variety of stimuli. ERK 1/2 regulates neuronal survival. It may also play a role in the development of neuropathic pain. JNK and p38 are implicated in neuronal apoptosis. Streptozotocin-treated diabetic rats' spinal ganglia neurons revealed increased levels of p38, JNK, and ERK. JNK and p38 levels were found to be elevated in the sural nerves of type 1 and type 2 diabetics [9, 15].

- Nuclear Factor-kB Pathway

Nuclear factor-kB (NF-kB) is a transcriptional factor that regulates inflammation, immunity, and apoptosis. In diabetic transgenic mice, NF-kB activity was found to be higher in the dorsal root ganglia, sciatic and sural nerves than in normal control animals. In addition, endoneurium, epineural vasculature, and perineurium in sural nerve samples from diabetic patients showed active NF-kB [7, 11, 20].

- Tumor Necrosis Factor-α

TNF-α is a key regulator of immune cells. It is up-regulated by a variety of mediators, including lymphocytes (CD4+), activated macrophages, eosinophils, and natural killer cells. In a study on the role of TNF-α in diabetic neuropathy, diabetic mice with TNF-α (-/-) showed reduced sensory and motor nerve conduction velocity compared to control mice. Diabetic patients with elevated TNF-α or inducible nitric oxide synthase levels are more likely to develop diabetic neuropathy [7, 9].

- Cyclo-Oxygenase Pathway

Cyclo-oxygenase (COX) enzymes play a crucial role in prostaglandin synthesis and arachidonic acid metabolism. They are classified into two types: cyclo-oxygenase 1 (COX-1), which maintains cellular homeostasis, and cyclo-oxygenase 2 (COX-2), which is activated by oxidative stress, protein kinase C, inflammatory cytokines, tumor promoters, and growth factors. It has been observed that streptozotocin-induced diabetic rats' neurons express more COX-2 [2, 3, 7]. COX-deficient animals have shown immunity to diabetes-induced neuronal conduction loss and decreased blood flow

surrounding the myelin sheath when compared to wild-type COX-2 (+/+) diabetic mice. This suggests that COX-2 plays an important role in nerve function. Other chemicals and processes that play important roles include nerve growth factor, the lipoxygenase pathway, autophagy, the wingless/integrated (Wnt) route, the hedgehog pathway, and interleukins [19].

Measures to prevent and treat neuronal changes in diabetes

Given all of the aforementioned characteristics, it is critical to assess patients with diabetes for neurologic problems and prevent and treat them. The goal is to keep serum glucose levels under careful control to avoid neurological changes [5, 11]. There is a distinction between T1DM and T2DM; in the former, there are details that increase glycemic index to avoid the development of neuronal changes at an early stage of the disease, whereas there is no evidence that this can be beneficial in T2DM [5, 17].

A greater understanding of diabetes and its pathophysiology is essential for patient management and preventing future complications, resulting in better medication adherence. Education on exercise and dietary management improves glucose control. Switching to a low carbohydrate, low-fat, and high fiber diet can help regulate glucose levels. As a result, the disease would advance at a slower rate [20]. According to several research, eating patterns such as the Mediterranean diet may influence glycemic levels and cardiovascular outcomes. The ketogenic diet (KD) and calorie restriction (CR) also influence oxidative stress, autophagy, and signaling pathways, resulting in elevated insulin levels, fat oxidation, decreased adipose tissue, reduced inflammation, and improved various molecular pathways. Both diets have been shown to be beneficial in the treatment of epilepsy, Alzheimer's disease, cancer, autism spectrum disorder, metabolic syndrome, vascular diseases, and other neurodegenerative disorders such as Parkinson's disease [4, 11]. The KD delivers ketone bodies as a brain energy source instead of glucose, stabilizing synapses and boosting brain energy reserve, resulting in improved neuronal performance. The CR likewise reduces glucose sensitivity, but does not produce ketone bodies. The KD should be recommended with caution; more evidence is needed to support this type of therapy; there is concern in patients with T1DM because of the lipid profile provided by the diet; and in patients with T2DM due to increased cardiovascular risk; thus, each diet should be tailored for each patient [21].

In addition to glycemic control, certain risk factors, such as high low-density lipoprotein (LDL) and cholesterol, obesity, and hypertension, that contribute to the development of neurological changes must be managed. Once the neuronal changes begin, the therapy differ depending on the stage of the disease. Therapies can either target the underlying condition or focus on treating the symptoms. Nonetheless, some research indicates that treatments that target the underlying pathways have greater results [17, 20]. Cognitive dysfunction caused by diabetes should be treated using a multidisciplinary approach that takes into account characteristics such as the severity of memory impairment, age, and previous medication. Each regimen should be personalized to each individual. Screening for cognitive impairment should normally begin at age 65. Management comprises educating the patient and caregiver, as well as providing pharmaceutical treatment. It is important not to employ any intense treatment for glucose control, as this might result in severe hypoglycemia and other consequences [5, 8].

Diabetic peripheral neuropathy is the most prevalent neurologic consequence observed in long-term patients with poor glucose control. Symptomatic DPN patients may present with foot ulcers, diabetic foot, and, in some cases, amputation. Nowadays, DPN is mostly treated with anticonvulsants, such as gabapentin, with or without opioids, to improve pain modulation [3, 9]. The European Federation of Neurological Sciences (EFNS) considers lamotrigine and sodium valproate useless. Tricyclic antidepressants (particularly amitriptyline) and tetracyclic antidepressants are commonly used to treat neuropathic pain. Topical treatments, such as capsaicin (0.075%), a capsicum pepper extract, serve to reduce mean pain intensity. Some prospective medicines target glucose metabolic pathways, such as sorbinil, an aldolase reductase inhibitor that works in the polyol route but is not currently being used due to side effects [10, 14]. As previously stated, oxidative stress contributes to peripheral neuropathy in uncontrolled diabetes patients. Nutraceutical therapies, such as vitamin E, as well as dietary goods like cruciferous vegetables and red grapes, can assist to reduce oxidative stress levels. However, not all pain management techniques rely on medicines; for example, percutaneous and transcutaneous electrical nerve stimulation (PENS, TENS), as well as acupuncture, have a substantial effect on boosting arterial circulation in T2DM patients [20, 22].

Diabetic autonomic neuropathy (DAN) affects practically all major organ systems; treatment remains primarily focused on rigorous glycemic control, but it differs depending on the system involved. In the instance of cardiovascular autonomic neuropathy (CAN), alpha-lipoic acid demonstrated some promising symptom relief. Orthostatic hypertension is managed with fluid and salt monitoring, physical activity, and, if necessary, pharmacological treatment with midodrine and droxidopa [3, 8, 11]. Loperamide is used to decrease excessive bowel movements in diabetic diarrhea, while tetracyclines aid to inhibit unwanted bacterial growth. There are no pharmaceuticals that can relieve symptoms of bladder disruption, but some medications, such as oxybutynin, an antimuscarinic drug for detrusor hyperreflexia, and interventions, such as intermittent self-catheterization, can aid. Statins, 5-phosphodiesterase inhibitors, and transurethral prostaglandins can be used to treat mild erectile dysfunction, although penile implants are preferable for severe instances [2, 9].

There are several particular treatments for T1DM, including as islet transplantation, which has demonstrated considerable improvements in neurological symptoms; however, studies have indicated that this is useful for DPN but not for DAN. Although the presentation of symptomatic neural alterations in T1DM is not always clear, identifying subclinical impairment may offer us an advantage in preventing disease development [5, 22].

Conclusion and recommendations:

The clinical impact of diabetes and diabetes-related comorbidities is steadily increasing, with risk factors such as obesity on the rise worldwide. However, progress has been made in the therapeutic field, with a plethora of new medications being produced to treat the disease. Better treatment procedures, new medicines, and recombinant insulin all contribute to better glycemic control, thereby preventing and delaying the advancement of neuronal alterations in DM. However, more study is needed in this area, particularly on medications that stop and reverse the neurological consequences of diabetes.

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