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Diabetic Retinopathy: Current Understanding, Mechanisms and Treatment Strategies

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ABSTRACT

Researchers have been assuming about the possible connection between the eye and the central nervous system (CNS) for a considerable amount of time. This is primarily due to the fact that the eye is considered to be an extension of the brain, which is a reasonable assumption. The neural tube is the beginning of both structures, and neurons are the building blocks of both structures. Retinal ganglionic cells, also known as RGCs, are a specific type of cell that are found in the retina. These cells are responsible for receiving light signals from the environment around them and then transmitting them to photoreceptors, which are involved in the process of vision. The retina, which is found inside the eye, is responsible for converting light into electrical impulses, which are then sent to the brain through the optic nerve. Glaucoma, age-related macular degeneration (AMD), and diabetic retinopathy are only few of the eye illnesses that can be caused by chronic progressive neurodegeneration of the retina, which is more prevalent in older people. It is the elderly who are most likely to be affected by these eye disorders; nevertheless, younger people are also susceptible to them and may experience permanent vision loss or a reduction in their eyesight. In most cases, neurodegenerative disorders that are characteristic of CSN are characterised by common symptoms and a cause that is only partially understood. Although certain risk factors have been identified, they do not account for all instances. On the other hand, according to a number of studies, several illnesses of the central nervous system (CNS), such as Alzheimer's disease (AD) and Parkinson's disease (PD), which are responsible for a significant amount of mortality and morbidity on a global scale, display distinctive alterations at the ocular level. It is helpful to be aware of potential linkages in order to have a better understanding of the mechanics on which onset occurs. In addition, experts have not yet reached a consensus regarding the factors that are responsible for these various disorders. In this overview, the symptoms of ocular illnesses are discussed in detail, with a particular focus on the interaction between the brain and the eye. At some point in the future, a more in-depth understanding could be of assistance in the development of innovative treatments that could help reduce or prevent blindness and improve quality of life.

Keywords: CNS, Diabetic, eye disease, retinal disorder.

I. INTRODUCTION

It is generally accepted that hyperglycemia is the primary factor that leads to diabetic retinopathy. There is a considerable reduction in the incidence of diabetes in people when blood glucose levels are strictly regulated [1,2]. Retinopathy may be recreated in animal models of long-term systemic galactosemia, which demonstrates

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that hexose plays a direct role in the pathogenesis of the disease [3,4]. One of the most significant cellular effects of hyperglycemia is an increase in oxidative stress [5]. Hyperglycemia is characterised by the upregulation of many pathogenic pathways. As a consequence of this, a great number of research have been conducted to examine the ways in which oxidative stress plays a role in the development of diabetic retinopathy and other complications associated with diabetes, as well as the ways in which treatments might be developed that precisely target the systems that directly cause increased oxidative stress. Despite the fact that we have made significant progress, there are still a great deal of things that we do not know. For example, we do not know how exactly diabetic retinal reactive oxygen species (ROS) arise in cells, nor do we know what processes link oxidative stress to a variety of diseases.

Among the various compounds and radicals, the reactive oxygen atom is responsible for their beginnings, reactions, and impacts. Some examples of these radicals and compounds are superoxide, hydrogen peroxide, and the hydroxyl radical. This is the reason why the term "reactive oxygen species" is used to describe these compounds and radicals [6]. As a result of the fact that certain experimental procedures and studies do not differentiate between the ROS that are seen, this review makes use of the general term ROS in situations where it is applicable and specifies the species where information is available. The situation known as oxidative stress is responsible for the damage that is produced to macromolecules, cells, and tissues. This damage is generated by an increased production of reactive oxygen species (ROS).

It has been established that superoxide is one of the reactive species that is associated with the beginning of oxidative stress in diabetic patients. In addition to superoxide, other reactive oxygen species (ROS) and the products of their reactions are also involved in the pathogenic processes [7]. An increased amount of superoxide is produced by the retinas of diabetic mice in comparison to the retinas of control mice [8,9].

According to [10], this is also the case in rats. Among the many pressures that can cause an increase in superoxide generation, hyperglycemia, hypoxia, and cytokines are among the triggering factors. When diabetes is present, oxidative stress can arise in a number of different types of retinal cells or it can have its effects felt by other types of retinal cells too. There are a number of retinal illnesses that involve oxidative stress in their aetiology [11,12,13]. Some of these diseases include retinitis pigmentosa, age-related macular degeneration, retinopathy of prematurity, and diabetic retinopathy. The mechanisms that cause oxidative stress and the cell types that are most impacted by these illnesses, however, are different from one another. In the case of diabetic retinopathy, for instance, hyperglycemia is thought to be the major source of oxidative stress, whereas other potential sources of oxidative stress include age, heredity, and oxygen dyshomeostasis. The molecular underpinnings of reactive oxygen species (ROS) formation and endogenous defensive systems are comparable, which means that treatments that target oxidative stress may have effects that are transferable to other situations.

A clinical description of diabetic retinopathy is presented in this article before the authors delve into the pathogenic mechanisms that mediate the damage that is caused by the generation of reactive oxygen species (ROS). Following that, it discusses the cellular and molecular origins of reactive oxygen species (ROS). A discussion of protective mechanisms and potential therapy approaches is included in the conclusion of this investigation. Pathophysiology of diabetic retinopathy: a pathological.

The retina is especially susceptible to reactive oxygen species (ROS) and free radicals due to the fact that it requires a significant amount of energy. A number of different components are involved in the pathophysiology. In addition to oxidative stress (OS), hyperglycemia can cause either ischemia or hyperosmotic damage, both of which can lead to changes in the structures of the nervous system and the blood vessels. Inflammation, mitochondrial failure, cell death (by pyroptosis, apoptosis, or autophagia), and neurodegeneration are all results of oxidative stress, which in turn causes damage to the nervous system, blood vessels, and retina. Inflammation is due to the fact that oxidative stress causes mitochondria to fail. New research demonstrates that neurodegeneration is the first impairment to develop, followed by microvascular dysfunction, clinical characteristics, and symptoms[14].

This order of manifestation is consistent with the particular order in which these impairments manifest. The findings of the study reject the notion that these processes occur sequentially and in isolation. Instead, they present evidence that numerous biomechanisms are at work simultaneously and have an effect on one another. According to Figure 1, the retina is made up of numerous layers of distinct cells, beginning on the inner side of the eye with the endothelium layer and finishing on the outer side, at the choroidal surface, with the retinal pigmented cell layer. These layers are arranged in a hierarchical structure[15]. It is possible for many biomechanisms, such as neurodegeneration, pyroptosis, and inflammation, to appear simultaneously at various layers, and the interaction between these biomechanisms and elevated levels of reactive oxygen species and oxidative stress is a complicated process.

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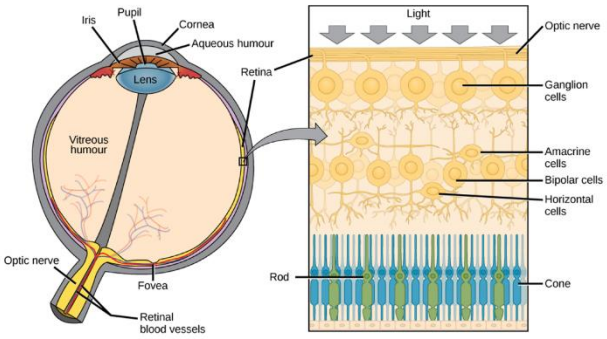

Fig: 1 Eye and retinal anatomy explained. These are the various components and structures of the eye, together with a detailed representation of the retina's makeup, which may be found in the right panel.

There are two principal routes that are responsible for the primary formation of reactive oxygen species (ROS) [16]. These processes largely include mitochondrial oxidative phosphorylation and the nicotinamide adenine dinucleotide phosphate- (NADPH) oxidase (Nox) system.

As shown in Figure 1, the bulk of the reactive oxygen species (ROS) that are formed by the body are naturally produced in mitochondria. This is because the electron transport chain (ETC) in mitochondria is responsible for consuming oxygen from the cell and producing ATP [17].

On the inner membrane of mitochondria, the majority of the electron transport chain (ETC) is composed of complexes I, II, III, and IV. NADH and FADH2 are the electron donors that these complexes use, and they are responsible for reducing oxygen to water. For the purpose of establishing a voltage across the inner mitochondrial membrane, the protons are injected into the intermembrane gap. To put it simply, this is the answer. This proton gradient is said to be the source of the energy that drives ATP synthase to create ATP, as stated in references [18], and [19], Within the context of this process, it is worth noting that only a limited quantity of oxygen molecules undergo the transformation into reactive oxygen species (ROS), comprising O2−. In diabetic cells, on the other hand, the breakdown of glucose in the tricarboxylic acid cycle (TCA cycle) requires an excess of glucose. This, in turn, induces a proton gradient across the inner membrane, which causes the inner membrane to reach its maximum threshold. This, in turn, forces more NADH or FADH2 into the mitochondrial electron transport chain. As a result of the obstruction in electron transfer, molecular oxygen is able to generate superoxide with the assistance of coenzyme Q, which ultimately results in an excessive amount of reactive oxygen species (ROS) [20]. The dissociation of the relationship between reactive oxygen species (ROS) and hyperglycemia can be accomplished by uncoupling mitochondrial electron transport, which can be accomplished by overexpressing uncoupling protein (UCP) to collapse voltage gradient [21].

DR has been shown to be connected with increased retinal superoxide generation; this has been established by a substantial body of studies conducted on animals [22]. One of the most important sources of superoxide in diabetic retinopathy is photosensitizers, which also have a greater number of mitochondria than other retinal cells [23]. The presence of hyperglycemia in streptozotocin-induced diabetic mice for a period of two months led to an increase in superoxide, which was caused by a faulty mitochondrial electron transport chain (ETC) in diabetic eye photoreceptor cells. The administration of methylene blue, which is an alternate electron transporter, could, on the other hand, reduce the severity of this increase [23].

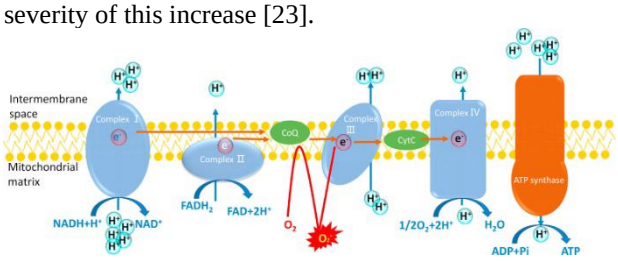

Fig: 2 The mitochondrial electron transport pathway and reactive oxygen species production. Electrons are transferred to Complex I from NADH and to Complex II from FADH2. The third complex involves the transfer of electrons to cytochrome C (Cyt C) from coenzyme Q (CoQ). Lastly, in order to create H2O, complex IV gives electrons to O2. As part of this mechanism, each complex expels proton from the mitochondrial matrix, creating a proton gradient between the intermembrane space and the mitochondrial matrix. In order to produce ATP, ATP synthase is driven by the energy of the proton gradient. When blood sugar levels are too high, the electron transport chain becomes clogged, and oxygen gas undergoes a transformation into reactive oxygen species by accepting the electrons.

II. REGULATION OF OXIDATIVE STRESS BY NON-CODING RNA

Among adults and the elderly, diabetic retinopathy is high as a cause of blindness. Diabetic retinopathy develops in almost all people with type I diabetes and in over 60% of people with type II diabetes [24]. Both non-proliferative and proliferative diabetic retinopathies are recognised in the medical community. Vascular closure, followed by an increase in vascular permeability, is a hallmark of non-proliferative diabetic retinopathy. As proliferative diabetic retinopathy develops, macular edoema can occur as a result of blood leaking into the vitreous, which is caused by the retina's abnormally growing blood vessels in reaction to the ischemia [25]. Evidence suggests that lncRNA H19

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controls inflammation in diabetic retinopathy [26] and prevents endothelial-mesenchymal transition [27] in retinal endothelial cells. H19 can alter X-box binding protein 1 (XBP1) and sponge miR-93, as demonstrated by Luo et al., allowing for the downregulation of pro-inflammatory cytokines [29]. Alternatively, anti-oxidant enzyme supplements may slow diabetes retinal development [30] and prevent redox-sensitive nuclear transcriptional factor activation [31], according to a number of investigations. What follows is a synopsis of the roles played by lncRNAs in the control of diabetic abnormalities of retinal metabolism.

HOTAIR

There is evidence that patients with diabetic retinopathy have elevated serum HOTAIR levels, which can be utilised to distinguish between diabetic retinopathy and non-diabetic retinopathy [32]. In support of this conclusion, one in vitro study shown that human retinal endothelial cells produce HOTAIR at significantly higher levels in response to high glucose, leading to an increase in oxidative damage, endothelial cell junction disruptions, and mitochondrial abnormalities [33]. A different research showed that HOTAIR can directly bind to LSD1 with the use of retinal endothelial cells [34]. High hyperglycemia increases Sp1 and LSD1 binding to SOD2 (MnSOD), and siRNA suppression of LSD1 improves SOD2-induced H3K4 demethylation, leading to increased SOD2 gene expression [35]. Based on these results, HOTAIR may influence the epigenetic remodelling of SOD2 to control antioxidant capacity in diabetic retinopathy development.

MALAT1

Researchers have found that diabetic retinas from STZ-induced type I DM mice [36] and db/db type 2 DM mice [37] had an abnormal overexpression of MALAT1. Nrf2 and antioxidant genes, such as Nqo1 and Cat, are increased in MALAT1 null mice, while reactive oxygen species (ROS) and protein carbonylation caused by ROS are downregulated in hepatocytes and islets. Through modulating JNK activity and Akt phosphorylation, MALAT1 modulates insulin resistance through its interaction with Nrf2, as shown by Chen et al. [38]. An further important role for MALAT1 in diabetic retinopathy is its control of the antioxidant defence mechanism including Keap1 and Nrf2. The binding of the Sp1 transcription factor to the MALAT1 promoter is enhanced in response to elevated glucose, which in turn increases MALAT1 expression. In addition, an increase in MALAT1 promotes the transcription of Keap1 by recruiting additional Sp1 to the Keap1 promoter [39]. The transcription of antioxidant response enzymes, like HO1 and SOD2, is also reduced because Keap1 reduces Nrf2's transcriptional activity [80].

A different research found that MALAT1 promotes neovascularization in diabetic retinopathy by binding competitively to miR-125b, which inhibits vascular endothelial-cadherin [40]. Reports indicate that, under high-glucose conditions, transfection with the miR-125b-5p mimic significantly increases ROS generation in neuronal PC12 cells, however there is no clear evidence that the MALAT1/miR-125b axis impacts oxidative stress [41]. It is worthwhile to investigate if the interaction between MALAT1 and miR-125b influences the redox homeostasis in diabetic retinopathy. Retinal function and retinal vascular dysfunction are both improved in diabetic rats when MALAT1 is knocked down. Retinal endothelial cells also show improvements in cell viability, migration, tube formation, inflammation, and oxidative stress. Liu et al. found that inhibiting MALAT1 activity through p38 mitogen-activated protein kinase (MAPK) signalling stops retinal endothelial cells from hyper-proliferating [42]. Diabetic cataracts have a comparable finding. The abnormal expression of MALAT1 in the anterior lens capsule tissues of diabetic cataract patients and human lens epithelial cells treated with high glucose has been recently discovered [43]. Also, via the p38MAPK pathway, MALAT1 knockdown reverses high glucose-induced oxidative stress, which is characterised by elevated levels of the oxidative stress indicator malondialdehyde and decreased levels of the antioxidants glutathione peroxidase (GSH-PX) and superoxide dismutase (SOD) [44]. All things considered, MALAT1 appears to regulate ROS through the p38MAPK route and the Keap1-Nrf2 axis.

MEG3

Research has demonstrated that MEG3 expression is significantly reduced in diabetic fibrovascular membranes, retinas of STZ-induced diabetic mice, and Müller cells, the primary glial cells in the retina, when treated with high glucose [45]. Research has demonstrated that MEG3 can reverse the inhibition of SIRT1 by miR-204 by acting as a ceRNA for this miRNA [46]. Deacetylation of SIRT1 target genes, namely forkhead box o1 (FOXO1) and nuclear factor kappa B (NF-κB) component p65, as shown in later research by Tu et al., reduces inflammation and oxidative stress in Müller cells treated with high glucose [47]. Research has shown that MEG3 enhances Nrf2 in human retinal pigment epithelial cells by removing miR-93, a protein that inhibits inflammation and apoptosis caused by high glucose [48]. In a similar vein, MEG3 can reduce inflammation and apoptosis linked to high hyperglycemia by blocking the connection between miR-34a and SIRT1 in retinal cells, which in turn inhibits NF-κB signalling [88]. Based on these findings, MEG3 has the potential to alleviate diabetic retinopathy symptoms by reducing inflammation and oxidative stress[49].

SNHG16

According to multiple research, SNHG16 worsens diabetic retinopathy. Research has shown that SNHG16 is significantly overexpressed in hRMECs treated with H2O2, high glucose, or AGE [89,90]. According to Cai et al., SNHG16 enhances cell proliferation, migration, and angiogenesis in high

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glucose-stimulated hRMECs, which in turn promotes proliferative diabetic retinopathy. This is achieved by modulating the miR-146a-5p/interleukin-1 receptor-associated kinase 1 (IRAK1) and miR-7-5p/insulin receptor substrate 1 (IRS1) signalling pathways, which activate the NF-κB and PI3K/AKT signalling pathways, respectively. According to another study, SNHG16 enhances hRMEC apoptosis by regulating E2F transcription factor-1 (E2F1) expression through sponging miR-20a-5p [50]. The direct effects of excessive glucose on retinal neurons, glial cells, and blood vessels [51] are mediated by E2F1, and E2F1 regulates oxidative metabolism [52]. More than that, by influencing the miR-195/mitofusin 2 (mfn2) axis, SNHG16 heightens oxidative stress-induced pathological angiogenesis in hMRECs. The diabetic retina shows downregulation of Mfn2, a protein that is involved in controlling mitochondrial membrane fusion [53]. Recent research has shown that mfn2 overexpression reduces the buildup of mitochondrial ROS caused by glucose [54]. The data indicate that the SNHG16, which is suppressed by high glucose levels, could potentially contribute to the increased oxidative stress in DR through the miR-20a-5p/E2F1 or miR-195/mfn2 pathways.

CNS & Eye Neurodegeneration

Neurodegenerative central nervous system illnesses are characterised by morphologic changes and the progressive loss of neuronal function, leading to the degeneration and eventual death of nerve cells; these diseases are both disabling and mostly incurable. This category encompasses both disorders of movement (also known as ataxias) and disorders of mental function (sometimes known as dementias). In illnesses of the central nervous system (CNS), not only do neurons deteriorate over time, but glial cells and the blood vessels are also involved. In the beginning, there is contact between the cells; later, the whole cellular structure is damaged till death. The etiopathogenesis of certain diseases is also influenced by genetic variables; for example, the risk of acquiring neurodegenerative diseases is increased due to genetic influences [46,47].

The figure is from Figure 3. Worldwide, more than 30 million people suffer from Alzheimer's disease and 5 million from Parkinson's disease, making them the most well-known and prevalent diseases among the elderly [48,49]. Anterograde (affected postsynaptic neurons) and retrograde (affected presynaptic neurons) trans-synaptic neurodegeneration, triggered by the death of retinal ganglion cells, is the primary mechanism implicated in neurodegenerative processes, according to some evidence [50]. When neurons and their axons sustain damage to the cells they communicate with, a loss of synaptic transmission and subsequent atrophic changes occur in the nervous system [51].

Thus, damage propagates from the original site to neural projections in trans-synaptic degeneration. Retrograde trans-synaptic degeneration in the human visual system, specifically in relation to glaucoma, has only been brought to light in the last few decades, while it has long been established in the motor system and cerebellar pathways [52,53,54]. It exacerbates the vision problems seen in people with a wide range of disorders, including MS [55]. Additionally, optic nerve and retinal ganglion cell damage, as well as direct degeneration of the visual pathways [56], are common causes of ocular symptoms in central nervous system (CNS) diseases [57]. Numerous similarities in the epidemiology and histology of the pathogenesis of the age-related eye disorders glaucoma and Alzheimer's disease have been identified [58]. The neuroinflammatory response is a key etiological element in age-related central nervous system (CNS) illnesses; this inflammatory response can happen in the retina because it is an extension of the brain. In spite of this, microglial cells—the CNS's immunocompetent cells—play an important role in these neurodegenerative diseases by their morphological alterations, proliferation, migration, and inflammatory cytokine release in response to damage and degeneration [59]. Microglia are a common feature of many inflammatory and degenerative diseases of the retina, and they can quickly multiply in pathological conditions like inflammation and neuroinflammation. As a result, they play a role in the development and progression of a number of neurological disorders [60].

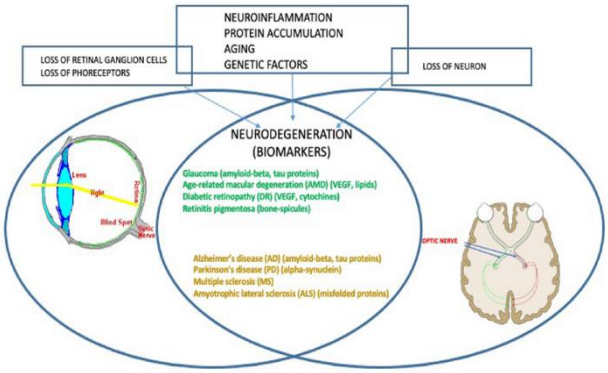

Fig. 3: Central nervous system and ocular neuropathologies. The CNS and the eye share the same factors in the etiophatology of disease. Neurodegeneration is common, as are some biomarkers, reported in parentheses for each pathology.

III. CONCLUSION

Oxidative stress is implicated in the development of diabetic retinopathy, according to a large body of research. Hyperglycemia, hypoxia, and cytokines are among the many stimuli that can cause oxidative stress in the cells of the retina. It is not yet entirely apparent which stresses affect different cell types the most in vivo. Hyperglycemia may cause oxidative stress in all cell types directly. On the other hand, hypoxia-induced oxidative

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stress could be caused by hypermetabolic photoreceptors that cause an oxygen deficit in the inner retinal layers. When oxidative stress occurs, it disrupts metabolism and leads to the buildup of harmful byproducts like AGEs. Crucially, it alters signalling pathways that regulate ROS generation, damages DNA in the nucleus and mitochondria, and produces epigenetic modifications, all of which have long-lasting effects. Once this damage has progressed far enough, oxidative stress is probably able to sustain itself. The clinical hallmarks of diabetic retinopathy, which include neurodegeneration, vascular leakage, and vessel degeneration, are thought to be caused by cell death and dysfunction as a result of these mechanisms. The retina's high metabolic activity makes it more susceptible to oxidative stress than other tissues. Antioxidant mechanisms including mitochondrial uncoupling and the NRF2 transcription factor have a high basal activity, reflecting this. Oxidative stress is allowed to occur in diabetes due to the downregulation or bypass of mechanisms that normally protect against it. Although oxidative stress-targeting therapeutics show promise as a diabetic retinopathy treatment, they are not currently available to the public. Early use of scavenging-type antioxidants may be necessary to prevent long-term harm from occurring over the course of a disease. The development of medicines that target the processes of persistent harm or that cure such damage, as well as antioxidants that enhance the body's inherent ROS defence mechanisms, are potential routes for advancement.

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