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DIABETIC RETINOPATHY: AN OVERVIEW

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ABSTRACT: Diabetes mellitus is a merge of assorted disorders commonly arise with happening of hyperglycemia and glucose intolerance due to which there be a lack of insulin production will occur. The two major classes of diabetes mellitus are type 1 diabetes mellitus and type 2 diabetes mellitus. For the prevention and controlling the increase of glucose, medical science uses a large array of pharmaceutical interventions. The disease occurs due to diabetes is of two types, the one which occurs in the small vessel is the microvascular disease, and the injury which occurs in the large blood vessels of the body is the macrovascular disease. Diabetic retinopathy is the common microvascular complication of diabetes. The diabetic retinopathy and the microvascular complication of diabetes are depending on the duration of diabetes and the severity of the increased production of glucose in the body. Various types of DR have been reported like mild non-proliferative retinopathy, moderate non-proliferative retinopathy, severe non-proliferative retinopathy, and proliferative retinopathy. Some signaling mechanisms are implicated in the pathogenesis of diabetic retinopathy. Diabetes mellitus and the cognitive decline are comparing with the patient having proliferative diabetic retinopathy with the patient having non-proliferative diabetic retinopathy or no retinopathy. From this comparison, it was shown that the severity of the diabetic retinopathy is inversely proportional to the severity of cognitive impairment.

INTRODUCTION: Diabetes mellitus is a merge of assorted disorders that commonly arise with the happening of hyperglycemia and glucose intolerance. Due to which there be a lack of insulin production will occur [1]. Such problem arises due to derangements in the restrictive systems for entrepot and gathering of metabolic fuels, which include the anabolism and catabolism of lipids and proteins emerge from faulty insulin secretion, insulin action, or both [2].

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The two major classes of diabetes mellitus are type 1 diabetes mellitus and type 2 diabetes mellitus. Type 1 diabetes mellitus is also known as insulin-dependent diabetes or juvenile onset diabetes. Type 1 diabetes mellitus is the chronic condition in which our body pancreas does not produce insulin or produces very less quantity of insulin. Different factors like genetic and some viruses may lead to type 1 diabetes mellitus [3].

Type 1 diabetes mellitus usually appears in childhood, but in some cases, it may develop in adult also. As there be no cure for type 1 diabetes mellitus, we can control the blood sugar level by using medicine or by giving insulin by injection. Symptoms increase in thrust, increase urination or frequent urination, increase in hunger [4].

Type 2 diabetes mellitus is also known as noninsulin-dependent diabetes and maturity onset diabetes. It is the chronic condition in which our body cell does not produce sufficient insulin to maintain the normal glucose level of our body. This type was mainly found in adult and the obese patient [3]. There be no cure for type 2 diabetes mellitus, but we can manage the condition by doing exercise, control our diet, or by maintaining the weight. If the diet and exercise fail to maintain the glucose level than the medicine and the insulin are given to the patient to maintain the blood glucose level. Symptoms occur frequent urination, increase thrust, increase hunger [4].

Epidemiology: Diabetic retinopathy (DR) is a major cause of blindness among the working age group [5, 6, 7]. According to the World Health Organization, India will become one of the major hubs of the diabetic population during the next 2 decades; the number of cases of adult-onset diabetes mellitus will grow to nearly 80 million in 2030 from 18 million in 1995 [6]. In the Indian subcontinent, only limited data are available on the prevalence of DR in the general population.

The Chennai Urban Rural Epidemiology Study (CURES) reported the prevalence of DR in urban Chennai to be 17.6% in diabetic population [8], and the Aravind Comprehensive Eye Study reported the prevalence of DR (in self-reported subjects with diabetes) in rural South India to be 10.5% [9]. Because diabetes and its complications are a public health problem, data on the prevalence of DR will help in formulating primary and secondary prevention programs in India.

Pathophysiology:

Normal Glucose Homeostasis: Blood glucose levels in the healthy people are normally maintained in the range by the harmonization between absorption of the glucose, uptake, and metabolism by the tissue that is peripheral tissue and hepatic glucose production. For the regulation of the blood glucose level, insulin is the main hormone. The insulin is secreted by the pancreatic beta cells located in the pancreas. As the insulin maintain the blood glucose level in the body. It has a major biological effect by binding and activating a specific plasma membrane receptor at the target tissue in peripheral [10].

By the translocation the glucose transporter 4 from the site of the intracellular to the surface of the cell, the insulin stimulates imbibing in fat cells and muscle. After that, the insulin promotes glycolysis and stores the glucose and other substances restorative lipid glycolysis and protein synthesis. Insulin stimulates glycogen synthesis and lipid synthesis in hepatocytes. It also inhibits the production and the release of glucose by suppressing gluconeogenesis and glycogenolysis [11].

Insulin Resistance and *β*-cell Dysfunction: The alteration in the glucose level leads to diabetes, including insulin resistance, large or overproduction of the glucose in the liver and the abnormalities in the pancreatic beta cell function. This defect can occur due to the factor like environmental risk, obesity, or may be due to genetic also; sometimes the hyperglycemia itself can damage the beta cell [12].

Insulin Resistance: Insulin resistance is the condition in which our concentration of insulin fails to produce their effects. Skeletal muscles need more than 80% of insulin for the use of glucose, as by the insulin resistance there is a decreased glucose intake and impaired glucose level. In the liver, the insulin resistance leads to an overproduction of glucose [13]. In adipose tissue, the rate of production of fatty acids is not inhibited due to the impaired insulin production, as this further stimulates the other production and syntheses like triglyceride synthesis and glucose production in the liver. There might be some factors that affect insulin resistance [14].

Beta Cell Dysfunction: Beta-cell dysfunction is the decrease in the sensitivity of the beta cell due to the reduction of insulin production. The reduction of the insulin will occur due to the abnormalities in pulsatile insulin release and the qualitative abnormalities of insulin, beta cell loss and its progression [10]. Due to this the insulin response are delayed and reduced during an oral glucose tolerance test. The possible mechanism of progressive reduction in insulin is due to the genetic defect in the beta cell function [14, 15].

An overview of the multiple interacting pathways leading to the pathogenesis of diabetic retinopathy is shown in **Fig. 1** below.

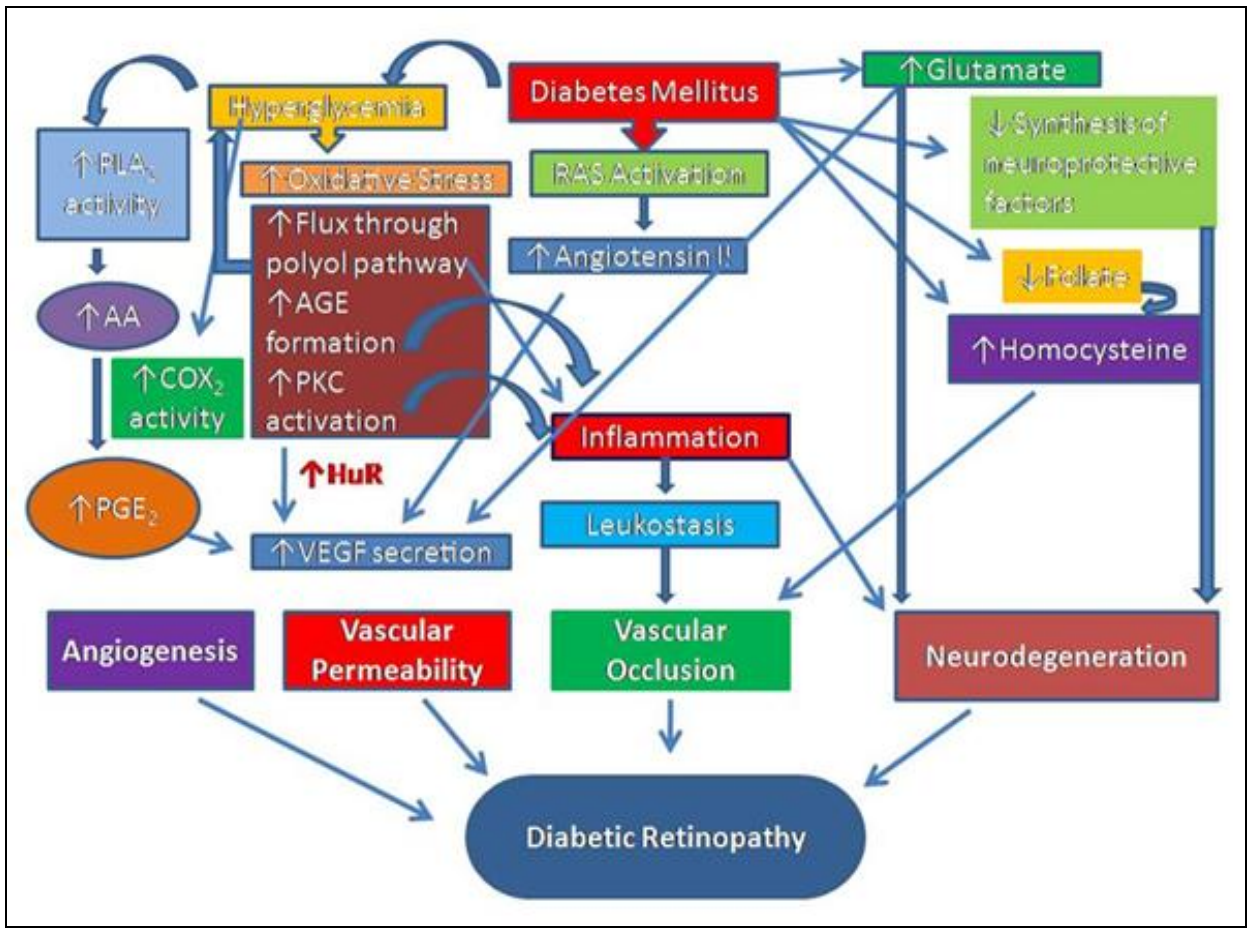

FIG. 1: AN OVERVIEW OF THE MULTIPLE INTERACTING PATHWAYS LEADING TO THE PATHOGENESIS OF DIABETIC RETINOPATHY. Abbreviations: PLA2, phospholipase A2; AA, arachidonic acid; COX2, cyclooxygenase 2; PGE2, prostaglandin E2; AGE, advanced glycation end-products; PKC, protein kinase C; VEGF, vascular endothelial growth factor; RAS, renin-angiotensin system.

Macrovascular and Microvascular Complication of Diabetes: Diabetes is the groups of the disease which occur due to the hyperglycemia as increase the glucose level in the body. Due to the increase in the glucose level in the body, they can harm our body in many ways. For the prevention and controlling the increase of glucose, medical science uses the large array of pharmaceutical interventions [16]. The disease occurs due to diabetes is of two types, the one which occurs in the small vessel is the microvascular disease, and the injury which occurs in the large blood vessels of the body is the macrovascular disease [17].

Macrovascular complications of diabetes: Macrovascular disease are the complication of diabetes, the macro means the large blood vessel which includes coronary artery, the aorta, and the arteries in the limbs and the brain. The macrovascular disease sometimes occurs due to the extended period of diabetes. Fats and the blood clot ore formed and deposited at the site of the large blood vessels. Three common macrovascular diseases are the coronary disease which is found in the heart, cerebrovascular disease which is found in the brain, and the peripheral vascular disease which is found in the limbs [18]. Macrovascular disease is the disease which arises due to the accelerated atherosclerosis. The mechanism between them is unknown as it is not fully yet understood. The macrovascular disease may lead to developing the coronary artery disease, peripheral vascular disease, stroke and increased risk of infection. People with type 2 diabetes mellitus may more have the macrovascular disease than the type 1 diabetic patient [19].

Microvascular Complication of Diabetes: Patient with diabetes may have the complication of the microvascular. Microvascular complications are appearing due to the high risk of increasing atherosclerosis which culminates in cardiovascular and cerebrovascular events. In a cardiovascular system, the microvessels are the basic functional

unit which is comprised of capillaries, venules and arterioles [20]. When there be any complication arises in this system due to diabetes than it is said to be the microvascular complication. The microvascular complications which are arising due to the diabetes are diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy. People with type 2 diabetes mellitus may more have the microvascular disease than the type 1 diabetic patient [21].

Diabetic Retinopathy: Diabetic retinopathy is the common microvascular complication of diabetes. The diabetic retinopathy and the microvascular complication of diabetes are depending on the duration of diabetes and the severity of the increased production of glucose in the body. It was found that the severity of hyperglycemia that increases production of glucose may lead to developing the diabetic retinopathy in the patient with diabetes [20].

Diabetic retinopathy and the diabetic complication may develop to the participation of the aldose reductase. In the intracellular polyol pathway, the aldose reductase is the initial enzyme.

In this pathway, the conversion of the glucose into the sorbitol (glucose alcohol) occurs [16]. Through the polyol pathway, the flux of the sugar molecules increases due to the increase in the glucose level in our body. The increase in the glucose level causes the sorbitol accumulation in cells [17, 22].

Classification of Diabetic Retinopathy (DR): Diabetic retinopathy is the disease of the retina which leads to the blindness. In diabetic retinopathy the microvasculature of the retina get damage, and the blood vessels get swells. Due to the swelling, the blood vessels leak the fluid and grow the new blood vessels which may lead to the detachment of the retina. We can clinically detect the diabetic retinopathy by check the presence of the visible ophthalmoscopic retinal microvascular lesion in the patient with diabetes. The diabetic retinopathy into the following four types:

1. Nonproliferative Retinopathy: Nonproliferative retinopathy is the type of diabetic retinopathy in which our retinal swells. The swelling mainly looks like a balloon. The nonproliferative retinopathy is recognized as the first stage or the early stage of the diabetic retinopathy [23, 24].

2. Moderate Nonproliferative Retinopathy: Moderate nonproliferative retinopathy is the second stage of the diabetic retinopathy. This stage is more severe than the nonproliferative retinopathy. In this stage, the blood vessels nourishing the retina and get blocked [23-25].

3. Severe Nonproliferative Retinopathy: This is the stage of the retinopathy in which the retinopathy spreads is the retinal area and the blood vessels get blocked in the several areas of the retina [23, 24].

4. Proliferative Retinopathy: This is the last stage of the retinopathy. This stage is severe than the other ones. In this stage, the retina sends the signals for the growth of the unwanted new blood vessels [24, 25].

Signaling Mechanisms Involved in Diabetic Retinopathy: Diabetic retinopathy has resulted from the biochemical alteration. These biochemical alterations are taking place in the vascular tissue of the retina [24]. Due to the increase in the level of the glucose, the glucose may accumulate in the retinal endothelial cell [23]. Due to the storage of the glucose, there is the activation of the various biochemical pathways. Some of these are described below [25].

I. Oxidative Stress: It is found that there will be the high content of polyunsaturated fatty acid and the high oxygen uptake; this may lead the retina to be more suspect of the oxidative stress. It is reported that the lipid membrane peroxidation and the damage to DNA by oxidative and the ROS induced injury are elevated in the retina in the diabetic patient that further play role of oxidative stress in diabetic retinopathy [26]. The activation of the enzyme that is antioxidant defense enzyme in diabetes are responsible for the forage of free radicals such as SOD, glutathione peroxide and the catalase are decreased in the retina [27].

II. Aldose Reductase and Polyol Pathway: The aldose reductase (AR) is the reductase which catalyzes the reductase of the glucose to sorbitol. Aldose reductase is an NADPH dependent oxidoreductase which is mainly known for the catalyzing. The polyol pathway first step is to metabolize glucose [27]. It is noticed that in the normal conditions the glucose is metabolized firstly

through the glycolytic pathway, but in the diabetic condition, there be access production of the glucose, due to this the excessive glucose is utilized or metabolized by the polyol pathway or the aldose-reductase enzyme. The increase in the aldose-reductase activity may develop diabetic complications. The glucose flux may lead to sorbitol gathering and accompanying cellular damage through polyol and aldose-reductase [28].

III. Advanced Glycation End Products: It has been noted that modification of the protein plays an important role in the diabetic complication. The glucose produces the advanced glycation end products (AGEs) participates in non-enzymatic glycation. The AGEs and the receptor of the AGEs are localized to the retinal vasculature and the vascular ECs. The protein function is altered by the AGEs which interfere with the extracellular matrix function and cause the advancement of cytokines [29, 30].

IV. Protein Kinase C Activation: Protein kinase plays an important role in the transduction of the adverse effects of high level or increased level of glucose in retinal vasculature. This was proved by the fact that the exposure of cultured ECs to the hyperglycemia or the high level of glucose leads to the rapid induction of the protein kinase family [31]. The protein kinase activates PKM in the framework of diabetes. Due to the activation of the PKM, the vascular effects leading to the progression of the diabetic retinopathy. PKM involved the various growth factors and regulated cellular activity [32].

V. Mitogen-Activated Protein Kinase Activation: It was shown that the MAPK (Mitogen-activated protein kinase) pathway play an important role in the progression and the development of a diabetic complication. MAPKKK, MAPKK, and MAPK are the sequence for the activation of the MAPK. By the activation of MAPK, the glucose-induced ECM protein synthesis in ECs is mediated [32]. There be the activation of the transcription factors like NF-κB and activation protein 1 (AP1) by MARK phosphorylation. It was noted that the inhibition of MAPK or PKC helps to normalize the effect of hyperglycemia. As the MAPK activates it may lead to the increasing level of the glucose and patient will suffer from diabetes and the diabetic retinopathy [33].

VI. Leukostasis and Platelets Activation: It was known that for the inflammatory processes the attraction and adhesion of leukocytes to the vascular wall are mediatory. There is the leukocyte stiffness due to the increasing level of the glucose that develops the capillary nonperfusion in retinal vessels [34]. Leukostasis has been suggested as the main factor in the death of the retinal endothelial cell in diabetes. A postulated cause of capillary nonperfusion involves platelet activation in diabetes [35].

VII. Nuclear Factor Kappa B: Nuclear factor kappa B is the transcriptional factor which is the important factor in the regulation of the many genes which involves mammalian inflammatory and immune responses, proliferation and apoptosis [29]. There is the inhibition of the protein which is regulated by NF-κB which further inhibits the diabetes-induced degeneration of retinal capillaries. The development of the retinopathy is inhibited by the inhibition of the NF-κB [28, 29].

Complication of Diabetic Retinopathy: In the diabetic retinopathy, there is an abnormal growth of the blood vessels at the site of the retina. This complication may lead to a serious problem. Vitreous hemorrhage is the first complication that occurs due to diabetic retinopathy. In this complication, the new blood vessels will bleed into a clear, a jelly-like substance that fills the center of the eyes. In several cases, the blood fills in the vitreous cavity, and the vision is completely blocked. As the bleeding does not cause the permanent blinding as the person will after the clear of the blood from the eye after the few weeks and month [36]. Retinal detachment is the second complication associated with diabetic retinopathy. In this complication, the stimulation of the scar tissue will occur due to the abnormal growth of the blood vessels.

Due to this, the retina will pull away from the back of the eye which ultimately causes the spots floating in the vision and the many other problems like severe vision loss. Glaucoma is the other complication of the diabetic retinopathy. In this, there will be leaking of the blood vessels occur and also have an abnormal growth of the new blood vessels in the retina which can lead the abnormal growth of blood vessels in iris that disturbs the

normal flow of fluid in the eyes that cause the pressure to build up. It ultimately leads to damage to the optical nerve and sometimes causes permanent damage to the vision [37-39].

Diabetic Retinopathy and Cognitive Impairment:

Memory and Cognition: Cognition is defined as the mental action and the process of understanding through thought, senses, and experience. Memory is the process of retrieving knowledge. The knowledge is gained by experience such things like remembering events, thing, places, and the name and another important thing would be considered as memory [40]. The memory can be categorized into two parts that are the declarative memory and non-declarative memory. Learning new thing, new facts, events, and material come under the declaration memory. While the reflective or incidental memories come under the nondeclarative memory.

The "brain working memory" is defined as the ability of the brain to recall the information immediately when it needed or for the subsequent thought. A wide range of cognitive impairment will occur when the working memory is damage. Due to this damage, the person will not be able to think properly in a different situation, and sometimes he or she will not recognize their family member also [40]. Our knowledge is the mechanisms of remembering and thinking of things. Our every thought will arise for the different area of the brain such as the cerebral cortex, thalamus, limbic system and the reticular formation of the brain stem. The memory is the result of some events in the synaptic transmission by changing its basic sensitivity. The temporal memory trace can create short-term memory. When there may be temporary chemical and physical changes which can last for the few minutes and few weeks makes an intermediate long-term memory. There be the structural changes or alteration will occur which are last for weeks to year are the long-term memory loss. Which thought are important which are saved into the memory are decided by the thalamus part of our brain. There is a neuropsychological evaluation that measures the cognitive abilities of the patient. As the sensitivity, reliability, and specificity are the important aspects that should be considered [41].

Cognitive Impairment and Diabetic Retinopathy: It is known that there will be a relation between cognitive impairment and diabetic retinopathy. Some of the studies show that diabetic complication such as retinopathy is more probable to have a cognitive impairment or decline. In the systemic review, it is shown that the patient with diabetic retinopathy has increased the risk of cognitive decline.

However, the relation between diabetic retinopathy and the cognitive decline are unknown [42]. As only one study shows that men are more prone to have cognitive impairment than women. Diabetes mellitus and the cognitive decline are comparing with the patient having proliferative diabetic retinopathy with the patient having nonproliferative diabetic retinopathy or no retinopathy.

From this comparison, it was shown that the severity of the diabetic retinopathy is inversely proportional to the severity of cognitive impairment. The person who has no or mild diabetic retinopathy have no change in their language, attention, memory, and other activities. While the person who is suffering the advanced stages of the diabetic retinopathy may have changed in their language, attention, memory, and other activities as we can be called that they have the cognitive decline due to the retinopathy. As from the above, it was shown that cognitive impairment is more prominent in the people having retinopathy [42, 43].

CONCLUSION: Diabetes is a metabolic disorder characterized by hyperglycemia, polyuria, polydipsia, and polyphagia. Diabetic retinopathy has been considered to be the major complication of diabetes that may lead to permanent damage to eyes. Various studies have already been reported to overcome the damage caused by Diabetic retinopathy.

However, these studies are not sufficient to have permanent prevention from the damaging effects of Diabetic retinopathy. The severity of diabetic retinopathy is inversely proportional to the severity of cognitive impairment. The person who has no or mild diabetic retinopathy have no change in their language, attention, memory, and other activities. While the person who is suffering the advanced

stages of the diabetic retinopathy may have changed in their language, attention, memory and other activities as we can be called that they have the cognitive decline due to the retinopathy. Hence, further studies are needed to overcome the mortality and morbidity caused by diabetes and its complications.

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