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Diabetic Retinopathy: Review Article

Namir Mahmoud Mohammed Abouelwafa
Department of Ophthalmology, Ahmed Maher Teaching Hospital, Egypt
Corresponding author: Namir Mahmoud Mohammed, **Mobile:** (+20) 01001706423, **E-mail:** nabouelwafa@gmail.com

ABSTRACT

Background: One out of every three people with DM will develop diabetic retinopathy (DR), a particular microvascular complication of the disease. DR, often known as diabetic eye disease, is a vascular microvascular illness that is brought on by microangiopathy and results in blindness and gradual retinal degeneration. DR occurs when blood sugar or glycemic levels are out of control.

Objective: This article aimed to study DR and other diabetic complications since DR is a major contributor to blindness.

Methods: A thorough search for studies on diabetic retinopathy using the following keywords: Diabetic retinopathy, diabetes mellitus and diabetic macula oedema. It was done in PubMed, Google Scholar, and Science Direct. Only the most recent or thorough investigations, which ran from May 2011 to November 2022 were taken into account. Additionally, the author evaluated citations from relevant publications. Because there are insufficient resources for translation, documents written in languages other than English have been ignored. Papers that were not regarded as significant scientific research included dissertations, oral presentations, conference abstracts, and unpublished manuscripts.

Conclusion: The longer an individual has diabetes, the greater their chance of getting ocular complications. DR is the most frequent microvascular/blinding consequence of diabetes, and it is associated with a sedentary lifestyle, a longer life expectancy, and changes in dietary habits that resulted in obesity. PDR and macular edema are the most serious DR consequences that impair vision. As a result, diabetic people require regular retinal examinations.

Keyowrds: DM, DR, DME, PDR.

INTRODUCTION

DR is the primary cause of blindness and visual loss in those of working age and a serious consequence of diabetes. Slow and gradual destruction to the retinal microvasculature is the characteristic of DR, which affects persons with type I or type II diabetes. The length of diabetes, hypertension, and hyperglycemia are the main risk factors for DR. Elevations in circulating apolipoproteins A and B are more potent risk factors for DR than total cholesterol and triglyceride levels, suggesting that dyslipidemia may possibly be a risk factor. Obesity, puberty, pregnancy, and the degree of diabetic nephropathy are additional risk factors for DR [(1)].

About one-third of DR patients will develop proliferative DR (PDR) and diabetic macula oedema (DME), two vision-threatening types of the illness. With a projected 191 million individuals with DR and 56.3 million with vision-threatening DR (VTDR) by 2030, the incidence of DR is on the rise worldwide. Given that various types of VTDR can have a sneaky beginning and can subsequently negatively affect education, career, and daily living, this increase in DR is concerning [(2)].

Without effective management, DR moves from NPDR to PDR in a systematic manner. A comprehensive evaluation found that the annual progression from moderate NPDR to PDR varied from 0% to 3.3%. The vision-related functional impact of mild or moderate NPDR is similar to that of diabetic patients without DR in terms of visual function, but it is much higher for those with severe NPDR and PDR. Compared to NPDR, PDR, which is characterized by neovascularization and has a 1.4% worldwide incidence, is linked to a noticeably increased risk of visual loss. Nearly 50% of PDR-affected eyes may eventually have significant visual loss [(3)].

ETIOLOGY

People who have DM, whether diagnosed or not, are susceptible to DR. The likelihood of developing DR is closely correlated with the patient's age, the length of their diabetes, poor glycemic management, and blood pressure fluctuations [(4)].

Risk factors for DR may be categorized into four categories [(4)]:

1-Non-modifiable: [Pregnancy and puberty].
2- Modifiable: [obesity, poor glycemic control, dyslipidemia, hypertension, and nephropathy].
3-Newer risk factors: [apolipoprotein, hormonal effect (leptin and adiponectin), inflammation, vitamin D, oxidative stress, and genetic variables].

EPIDEMIOLOGY

Previously thought to be a problem of wealthy countries, diabetes is now becoming a major public health issue in developing countries due to a number of factors, including urbanization, sedentary lifestyles, population aging, and obesity. In 2010, about 285 million people, or 6.4% of the world's population, had DM; by 2015, that number had risen to 415 million. The International Diabetes Federation has projected that by 2030, there will be 552 million people with diabetes, or a prevalence of 7.7%. In the foreseeable future, low- and middle-income nations will account for 80% of the world's diabetic population, with 60% of those countries

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being in Asia. In Asia, diabetes patients are often young to middle-aged people, whereas the majority of diabetic patients in the West are old. Many young people are at risk for DR due to the rising trend of childhood obesity [(5)].

With a frequency of 5–10% in the 1990s, DM is a significant new clinical and public health issue in Egypt. Nearly 9 million Egyptians, or more than 13% of the population over 20, are predicted to develop DM by 2025. The reported incidence of DM (3.4–29%) and its consequences, particularly DR (7.6–60%), vary significantly, even within the same country, according to epidemiological studies of DM and DR conducted in Middle Eastern nations, including Egypt [(6)].

DR is more common in people with type 1 diabetes, which is caused by an autoimmune attack on the pancreatic beta cells that produce insulin, than in people with type 2 diabetes (a metabolic disease marked by high blood glucose, insulin resistance, and relative insulin deficiency). Type 1 diabetes also has a 2.5-fold higher prevalence of sight-threatening retinopathy. This result is unaffected by how long a person had diabetes. After controlling for other established risk factors, the META-EYE study's aggregated data from 35 research revealed that type 1 diabetics with more than 20 years of illness had a 2.7-fold higher chance of developing any DR than those with type 2 diabetes for ten years. Blood pressure, cholesterol, HbA1c, and the length of diabetes all increase the prevalence of DR [(7)].

Early pathophysiology of DR

Thickness of the capillary BM (basement membrane) is among the first histological alterations seen in diabetes people and diabetic mice. Increased production of collagen IV, fibronectin, and laminin, as well as decreased catabolic enzyme breakdown of the BM, are assumed to be the causes of thickening. Although, it is still unclear if BM thickening plays a primary or secondary role in the development of DR, it has been hypothesized that these matrix modifications could be linked to abnormal cell interaction with constituent BM proteins, defects in capillary autoregulation, or impaired endothelial-pericyte communication [(8)].

When exposed to high glucose settings, retinal pericyte mitochondria show signs of fragmentation, metabolic inefficiency, and decreased extracellular acidification. This might be the cause of the early apoptotic death of smooth muscle cells and pericytes in DM. In diabetic individuals, the pericyte-to-endothelial cell ratio drops from 1:1 to 1:4. At the same time, vascular endothelial cells malfunction, yet they can temporarily make up for the cellular deficit that is growing. Long-term exposure to the biochemical environment caused by diabetes eventually seriously impairs the endothelial cells' capacity to replicate [(9)].

The vascular endothelium has been suggested to be the main cellular abnormality in DR, and retinopathy may be classified as an endotheliopathy. The endothelium is essential to the proper operation of other capillary complex cells. Although, the exact cause of endothelial, pericyte, and smooth muscle dysfunction in the diabetic retinal microvasculature is still unknown, it is most likely related to a variety of cumulative biochemical insults combined with the cells' decreased capacity for self-repair and self-renewal. Important growth/survival factors are necessary for retinal pericytes and smooth muscle cells, including PDGF (platelet-derived growth factor)-B, which is preferentially reduced in diabetics and is intimately linked to the development of acellular capillary casts [(10)].

Macular edema

Two separate circulations provide nourishment to the retina: The choriocapillaris supplies nutrition to the outer third of the retina and the two vascular layers of the retinal capillary circulation (The deep plexus in the inner nuclear layer and the superficial plexus in the axon and ganglion cell layers). There are two different kinds of diabetic maculopathy, however they frequently coexist: Macular edema is caused by the breakdown of the blood-retinal barrier (BRB) in the retinal capillaries and/or RPE, whereas ischemic maculopathy is caused by capillary dropout. Because both extracellular and intracellular sites have been implicated in prior research, it is unclear whether macular edema occurs in one or both of these locations. Histologic examinations of enucleated eyes with DR have revealed extracellular cystic areas as well as Müller, bipolar, ganglion, and photoreceptor cell enlargement and degeneration. Macular edema and angiographic ischemia may coexist, although they seem to have separate effects on visual acuity. Arend concluded that inner retinal ischemia is not the cause of macular edema since he could not find a connection between blood flow and the condition. Although ischemia did not correlate with macular thickening, retinal thickening seemed to be associated with BRB breakdown, indicating that extracellular expansion was the primary source of retinal thickening. The main cause of macular edema is extracellular fluid buildup, while ischemia may cause some intracellular swelling. Diabetes has the ability to alter retinal blood flow even before visible retinopathy appears. However, retinal blood flow often rises after retinopathy has established. Both arterioles and venules are observed to widen and elongate, and the autoregulatory function of retinal blood vessels is abolished. As a result, pressure is lost across the arteriole's length and arteriole resistance is reduced [(11)].

As the retinal capillaries' effective intraluminal pressure rises, more fluid moves into the extracellular area in accordance with Starling's law. Through a number of processes, the BRB is broken down by the concurrent release of vasoactive cytokines (including VEGF) from endothelial cells, neuroglia, and activated leukocytes, which causes albumin to migrate into the interstitium. Patients with diabetes see a reduction in

total flow through the choroidal circulation. While, indocyanine green angiography reveals discrete regions of choroidal non-perfusion in eyes with diabetic pigment epitheliopathy, bulk flow to the choroid remains mostly unaltered in diabetics [12].

There are instances when eyes with only mild retinopathy have significant leaking across the pigment epithelium. Compared to people without diabetes, diabetics are more likely to have blockage of the choriocapillaris and neovascularization inside the choroidal. These processes most likely stem from the same triggering events that cause DR, namely angiogenesis and basement membrane degradation [13].

- **Blood-retinal barrier**

There are two different BRBs that protect the retina: The outer BRB is made up of the retinal pigment epithelium and its tight junctions, while the inner BRB is made up of the retinal capillary endothelial cells and their tight connections. The bilayer cell membranes of endothelial and epithelial cells include hydrophilic glycerols that bind hydrophobic long-chain fatty acid moieties [14].

The cell membranes provide an impassable barrier to ions and larger uncharged polar molecules under physiological circumstances, but they let water, tiny hydrophobic molecules, and small uncharged polar molecules to get through. Occludin, claudin (23 isoforms), 7H6, cingulin, zonula occludens (ZO)-1,2,3, junction adhesion molecule (JAM), membrane-associated guanylate kinases with inverted domain structures (MAGI)-1,2,3, partition defective genes (PAR)3/6, and multi-pdz protein-1 (MUPP1) are among the intercellular proteins that make up the tight junctions that connect adjacent retinal vascular endothelial cells and retinal pigment epithelial cells. A large portion of the barrier function is controlled by occludin and the claudins, two of the proteins that have been well investigated and well described. When diabetic rats lose occludin, a substance unique to vascular endothelial cells, their blood-retinal permeability to albumin (molecular weight of 66 kD) but not rhodamine-dextran (molecular weight of 10 kD) increases. This might be because of changes in hydrophobicity rather than pore size. Claudin-5 inhibits the flow of tiny molecules (less than 0.8 kD) across the blood-brain barrier and likely has a similar function in the retina. ZO-1 is thought to control the intracellular assembly of the junctional complex in retinal capillary endothelial cell tight junctions and is a good measure of the overall function of tight junctions. The JAM aids in the formation of tight junctions and promotes communication between leukocytes and endothelial cells. Since intracellular circumferential actin bundles gather at occludin-positive cell contact locations but not at occludin-negative sites, junctional proteins may aid in cellular structure. Ion and molecular transport across the BRB can occur either transcellularly or paracellularly [15].

While paracellular passage happens when the integrity of the tight connections is lost, transcellular passage happens when the barrier status or pumping ability of endothelial cells changes. Increased fluorescein levels in the vitreous can be identified by vitreous fluorophotometry in human and rat models of diabetes before fluorescein angiograms reveal signs of DR. According to these findings, the creation of retinal edema requires the transit of bigger proteins like albumin, but not smaller ones like fluorescein, which are made possible by early BRB breakdown [14].

- **Biochemical abnormalities responsible for DR**

The part inflammation plays in the pathogenesis of DR has received a lot of attention in recent years (Table 1). Pro-inflammatory cytokine expression is elevated in the neural retina, and the following are upregulated:

Table (1): Enumerates a number of the cytokines (growth factors) and chemokines (pro-inflammatory chemicals) linked to the onset of DR [12].

Chemokines
Chemokine (C-C) motif ligand 2 (CCL2)
Endothelin-1
Intercellular adhesion molecule-1 (ICAM-1)
Interleukin 1α (IL-1α)
Interleukin 1β (IL-1β)
Interleukin 6 (IL-6)
Interleukin 8 (IL-8)
CXCL 10/Interferon induced protein 10 (IP-10)
Monocyte chemotactic protein 1 (MCP-1)
P-selectin
Vascular cell adhesion molecule-1 (VCAM-1)
Cytokines
Angiopoietin – 2 (Ang 2)
Platelet-derived growth factor AA (PDGF-AA)
Transforming growth factor β (TGF-β)
Tumor necrosis factor-α (TNF-α)
Vascular endothelial growth factor (VEGF)

Both the development of acellular capillaries and neurovascular dysfunction have been connected to vascular adhesion molecules that support leukostasis. Leukocytes have been shown to actively harm the retinal vascular endothelium. Global mRNA expression analysis has identified changes in proinflammatory cytokine expression in both the neuroglia and the retinal vasculature [10].

A complex environment of dysregulated pro-inflammatory factors, such as TNF-α, IL-1β, IL-6, and IL-1α, forms inside the diabetic retina. Despite being essential to inflammatory-mediated disease of the central nervous system, the function of microglia and

infiltrating monocytes in DR is much less clear. Numerous in vitro and in vivo analyses of human postmortem specimens and animal models suggest that by regulating cytokine expression and other pathologic responses, retinal microglia activation may have a significant regulatory role in diabetes-mediated retinal inflammation [(16)].

Microglia and monocytes are crucial for maintaining retinal homeostasis, but they are also at the heart of neuroinflammation, which has been demonstrated to rise in diabetes in both human and animal models. Animals with experimental diabetes show physiological alterations and a range of molecules are elevated in their retinas very quickly after the disease starts. In animal models of DR, retinal oxygen tensions drop prior to retinal capillary loss. Within the first week of experimental diabetes in mice, retinal VEGF mRNA increases, and some writers have argued that oxidative stress is the reason of this upregulation [(17)].

Upregulation of VEGF is associated with increased expression of intercellular adhesion molecules (ICAM-1), leukostasis, and BRB breakdown. Upregulation of pro-inflammatory cytokines including TNF-α and complement factors leads to activation of the kallikrein-kinin and renin-angiotensin systems. Each of these modifications has been linked to the pathophysiology of DR, and because some of these pathways are not VEGF-dependent, they give more evidence that inflammation and hypoxia may be separate causes of DR [(15)]. Patients with PDR or DME have greater levels of pro-inflammatory cytokines (TNF-α, IL-8, IL-6, VEGF), chemokines (monocyte chemotactic protein-1, or MCP-1), and other proteins (endothelin-1, sE-selectin, ICAM-1, and CXCL10/IP-10) in their vitreous fluid than do controls. The finding that alpha-lipoic acid reduces leukocyte adherence provides evidence that oxidative stress and other downstream mediators are linked to leukostasis [(12)].

Hemodynamic changes that accompany leukostasis are caused by mechanisms associated with PKC pathways. By binding to certain membrane receptors, advanced glycation end products increase vascular cell adhesion molecule-1 (VCAM-1), which supports leukostasis and may hasten the development of diabetic vasculopathy. Human retinal RNA enters the systemic circulation more readily after a few hours of hypoxia, and levels return to normal within 24 hours after oxygen tensions return to normal. The production of hypoxia-regulated vasoproliferative factors, including VEGF, is stimulated by hypoxia; nevertheless, VEGF has been seen to be elevated in diabetic animal retinas prior to capillary closure, suggesting that it is upregulated early in the course of diabetes by other causes [(18)].

It has been demonstrated that VEGF disrupts the BRB by causing tight junction damage as well as encouraging molecular migration between cells. Rat and frog endothelial cells, but not monkey cells, exhibit membrane fenestrations in response to VEGF injections. Transcellular gaps are more common and result in higher hydraulic conductivity. Vesiculovacuolar organelles form a continuous, transcellular chain, with just fenestrations separating them, within 24 hours of vascular endothelial cells being perfused with VEGF [(18)]. Three alterations in the tight junctions have been noted when exogenous VEGF is given to diabetic eyes: (1) phosphorylation of tight junction proteins; (2) reorganization of existing junctions; and (3) reduction in junctional protein levels [(15)].

- **Mechanism of BRB breakdown**

The precise process via which the BRB breaks down is not entirely understood. According to available data, it might be caused by alterations in the membrane state or pumping ability of the cells or by damage to the junctional complexes between capillary endothelial cells and RPE cells. The formation of fenestrations across the cytoplasm of endothelial cells, enhanced transcellular transport through vesicles, and greater RPE infolding that facilitates choroidal to subretinal space transudation have all been proposed as causes of leakage [(19)].

It has been demonstrated that high glucose concentrations cause insulin-mediated BRB breakdown and lower the electrical resistance of cultured capillary endothelial cells. Attention has been drawn to tight junctions with the discovery of vascular endothelial growth factor (VEGF) and other inflammatory cytokines, which have a significant impact on junctional and interstitial proteins. ZO-1 production and intercellular barrier function are both increased concurrently by cultured astrocytes, indicating a close connection between the two mechanisms. Junctional and matrix protein concentrations are altered by diabetes. Diabetic rats' retinas have lower amounts of occludin, while VEGF-treated cultured brain endothelial cells have lower levels of occludin and ZO-1 [(20)].

Animals with diabetes had higher levels of MMP-2, MMP-9, and MMP-14 mRNA in their retinas. Through increased transepithelial electrical resistance and occludin degradation, cells treated with MMP-2 and MMP-9 undergo altered gap junction development. VEGF has been the subject of much investigation, despite the fact that the exact molecular route that causes the BRB to break down is unclear. Since its discovery in 1989, VEGF has been the subject of much research, and a better knowledge of its effects has been essential to the development of treatments for clinically relevant DR [(21)].

The majority of VEGF's effects on the eyes are caused by VEGF-A isoforms attaching to the transmembrane receptor VEGFR2. Vascular permeability is increased and angiogenic and mitogenic alterations in vascular endothelial cells are stimulated by VEGF-mediated dimerization and phosphorylation

of VEGFR-2. Vascular permeability is increased by VEGF via a number of methods. First, it causes intracellular calcium to be released by stimulating inositol triphosphate (IP3). Elevated calcium levels relax vascular smooth muscle and raise cyclic GMP and nitrous oxide levels [(22)].

Blood flow, angiogenesis, vessel diameter, and vascular permeability are all correlated with nitrous oxide synthetase levels. Second, VEGF promotes the synthesis of DAG, which directly raises cellular permeability via DAG-sensitive Ca2+ channels. Thirdly, PKC is activated by increased DAG production. Exogenous VEGF-trap treatment reduces neovascularization by 66% in mice models of experimental neovascularization, while VEGFR-1 gene transfer reduces neovascularization by 53–86% [(12)].

These findings imply that VEGF plays a crucial role in the neovascularization process. Animal studies have demonstrated that VEGF is enough to induce leaking from healthy blood vessels after intravitreal injections or the implantation of continuous VEGF-release devices. Few in vitro studies have been conducted on the impact of VEGF on vascular permeability, despite the fact that hundreds of publications have been published on the subject [(21)].

VEGF has been found to enhance hydraulic conductivity and diffusive permeability to albumin. However, it has no effect on the oncotic reflection coefficient, which measures the likelihood that a molecule would bounce off a pore instead of passing through it. Permeability and angiogenesis may be encouraged or inhibited independently, as evidenced by the fact that compliance, the inverse of stiffness, and hydraulic conductivity, a measure of how easily fluid flows through a lumen, may be stimulated independently [(20)].

VEGF not only affects the retinal vasculature but also acts as a survival factor for endothelial cells in vitro and in vivo, preventing apoptosis. via inhibiting the phosphatidylinositol 3-kinase/V-akt murine thymoma viral oncogene homolog (PI3 kinase/Akt) pathway, VEGF stops starvation-induced endothelial apoptosis. This may be accomplished via triggering the antiapoptotic proteins Bcl-2, A1, XIAP, and survivin. By increasing the creation of ICAM-1 (intercellular adhesion molecule), VEGF promotes inflammation by making leukocytes adhere to arterial walls. By synthesizing VEGF, these activated leukocytes increase the synthesis of VEGF [(23)].

The BRB is compromised, localized retinal ischemia is made worse, and VEGF production is further increased by adherent leukocytes, which also constrict capillary lumens and reduce downstream perfusion. Since eyes with PDR often have greater intravitreal VEGF concentrations and eyes with BDR have lower amounts, there is a correlation between the two and the severity of DR. Aqueous VEGF levels had a strong correlation with the severity of DME, even within the subgroup of individuals with DME [(19)].

Numerous growth factors, such as TNF-α, TGF-β, epidermal growth factor, insulin-like growth factor-1, fibroblastic growth factor, platelet-derived growth factor, and inflammatory cytokines including IL-1α and IL-8, all increase VEGF. Low tissue O2 tension is one of the main factors that stimulates the production of VEGF mRNA. There are parallels between erythropoietin and VEGF's hypoxia regulation. The human VEGF gene's promoter has a 28-base region that has been found to have binding properties comparable to those of hypoxia-inducible factor (HIF)-1α, a crucial modulator of hypoxic responses [(24)].

Since HIF is the primary transcriptional regulator of the hypoxic response. It has been referred to as the "cell's oxygen sensor." Prolyl hydroxylase hydroxylates free HIF-1α when oxygen is present. After hydroxylated HIF-1α attaches itself to the von Hippel-Lindau factor (pVHL), intracellular proteasomes break down the pVHL/HIF-1α complex. Low tissue oxygen tension permits HIF-1α to dimerize with HIF-1β and inhibits its hydroxylation [(25)]. After stabilizing, the dimer travels to the nucleus, where it attaches itself to the VEGF gene's promoter region and initiates transcription. Because hypoxia stabilizes the protein and permits the accumulation of HIF-1α mRNA, it raises the levels of HIF-1α subunits. Reactive oxygen species (ROS) are produced by an intact mitochondrial electron transport chain, which is necessary for HIF-1α stability during hypoxia. The concentration of ROS may serve as the cell's oxygen sensor [(25)]. High amounts of ROS can indicate low intracellular oxygen tension and impair a cell's capacity to hydroxylate HIF-1α. HIF-1α stability is affected by many molecules, including ROS, IGF-1 and 2, and AGEs. Tight glucose management may aggravate retinopathy since insulin stabilizes HIF-1α and upregulates VEGF [(12)]. HIF-1α can be modulated through a variety of biochemical approaches, including phosphatidylinositol 3-kinase inhibitors, mitogen-activated protein kinase inhibitors (MAPK), prolyl-4-hydroxylase domain activators, microtubule disrupting agents, cyclooxygenase-2 (COX-2), heat shock protein inhibitors, and antisense therapy. Breakthroughs in treating ischemic retinal disease may be followed by novel cancer medicines such as topotecan and camptothecin analogues [(25)].

When diacylglycerol is present, the protein kinase C pathway is activated. By activating serine/threonine phosphatases or deactivating kinases, which both dephosphorylate the tight junction proteins occludin and claudins, and by causing endothelial cell contraction through phosphorylation of the cytoskeletal proteins vimentin and caldesmon, activated PKC increases vascular permeability. By preventing NO generation, protein kinase C raises matrix protein deposition, a defining feature of DR, which in turn raises TGF-β1, fibronectin, and type IV collagen. Numerous investigations have demonstrated the potential role of activated PKC in BRB degradation. In

rats without diabetes, protein kinase C inhibitors prevent VEGF-mediated BRB degradation [26].

In non-diabetics, BRB breakdown can be induced by intravitreal PKC injection. In advanced DR, PKC can modulate the activity of VEGF, so generating a reinforcing loop. Protein kinase C inhibitors also stop hyperglycemia-induced VEGF synthesis. Hyperglycemia can exacerbate pre-existing retinopathy by upregulating p42/p44 MAPK and activating PKC. Stabilization of HIF-1α is necessary for both of these mechanisms. A perfect balance between angiogenic factors (like VEGF) and inhibitors (such angiostatin and pigment epithelium-derived factor, or PEDF) is necessary to maintain the normal retinal vasculature [25].

PEDF possesses anti-inflammatory and antipermeability qualities and is released by Müller and endothelial cells. Eyes with BDR have low vitreous PEDF levels, which return to normal following pan-retinal photocoagulation for PDR. PEDF inhibits the vasculopathic effects of VEGF by competitively interacting with VEGF for VEGFR-2 and lowering HIF-1α levels through MAPK-mediated activation, which increases endogenous PEDF synthesis [12].

It has been hypothesized that anti-inflammatory drugs used by rheumatoid arthritis patients counteract the effects of vasoactive cytokines since these patients seem to have less severe DR. These medications do not lower VEGF levels, but they may counteract VEGF's effects. By reducing the expression of nitrous oxide synthetase, aspirin and TNF-α inhibitors lower ICAM-1 levels and leukocyte adhesion. Integrins that bind to ICAM-1 are expressed less often when aspirin is taken [LFA-1 (CD11a/CD18) and Mac-1 (CD11b/CD18)] [27].

Development of PDR

Acellular capillaries, hypoxia from retinal non-perfusion, and PDR with enough activation of cellular growth hormones are the outcomes of apoptosis of retinal vascular endothelial cells and the development of pericyte ghosts. TNF-α is one of numerous cytotoxic factors that are upregulated, which causes the vascular cells to die. TNF-α upregulates the forkhead transcription factor FOXO1, which therefore controls cell death. In type 1 and type 2 diabetic rats, RNA interference (RNAi) inhibiting FOXO1 decreases microvascular cell death and cell apoptosis both in vitro and in vivo [28]. Genes that control the activity of endothelial cells, such as those involved in vascular remodeling and angiogenesis, are markedly activated by these stimuli. The inner two-thirds of the retina experience hypoxia due to patchy non-perfusion caused by occlusion of retinal capillaries. The stabilization of HIF-1α brought on by hypoxia increases the production of VEGF, which is correlated with the onset of neovascularization over time [12].

The pathophysiology of PDR involves not just VEGF but also pro-inflammatory cytokines, angiopoietins, hepatocyte growth factor (HGF), insulin-like growth factor-1, PDGF, and basic fibroblast growth factor (b-FGF). Anti-angiogenic factors such PEDF, TGF-β, thrombospondin (TSP), and somatostatin are also present in the retina and vitreous. It is well accepted that an imbalance between angiogenic and anti-angiogenic agents causes neovascularization [25].

Symptoms

Maculopathy and DR have always been asymptomatic. Thus, even in the absence of visual impairment and consistent ophthalmological control intervals need to be maintained**.** Warning indicators of retinal complications include sudden changes in visual acuity and uncorrectable visual degradation. If the macula is affected, symptoms may include reading difficulties, color sense disorders, blurred vision, and "floaters" in front of the eye caused by vitreous hemorrhages. Persistent vitreous hemorrhages or tractive retinal detachment can lead to practical blindness [29].

Early detection of DR

Numerous research have been conducted on the identification of people with DR in a variety of potential methods. A classification system based on several retinal image processing algorithms, such as the diameter of the optic disk, was proposed by **Bhatia *et al.*** [30] in 2016. The approach used altered decision trees, adaBoost, Naïve Bayes, and SVM to predict the existence of DR. **Chen *et al.*** [31] came next, using streamlined machine learning methods to accurately forecast the occurrence of chronic illness outbreaks in places where the condition is common. They used both organized and unstructured data gathered from several institutions to create a multimodal illness risk prediction system based on convolutional neural networks. In the years to come, more research will be done, and from all the data that is already accessible as well as additional research situations, useful answers and conclusions will be reached. A computer-aided diagnostic approach based on retinal fundus pictures was developed by **Asiri *et al.*** [32] in 2019. This technique is effective and efficient for diagnosing DR and includes several steps, such as the detection, segmentation, and categorization of lesions in fundus images. An integrated summary of the state of knowledge on new methods of artificial intelligence integration in national screening programs worldwide was given by **Bellemo *et al.*** [33] in their work. The DR dataset was normalized by **Gadekallu *et al.*** [34] using the conventional scalar approach. The most important characteristics were then extracted from the pictures using Principal Component Analysis. Additionally, the Firefly method is used to reduce dimensionality. Additionally, several other studies have been carried out to support the use of all available learning and classification algorithms in the analysis and diagnosis of DR.

Treatment of associated risk factors

- Systemic hypertension: Effective blood pressure management is essential for the advancement of DR. It has been demonstrated that managing systemic hypertension lowers the chance of developing new DR and slows the course of pre-existing DR.
- Glucose control: Both the UK Prospective Diabetes Study and the Diabetes Control and Complications Trial (DCCT) have demonstrated the significance of appropriate blood glucose management in the development of DR [(4)].
- Blood lipids: The role that appropriate blood lipid management plays in the development of diabetic maculopathy.
- Smoking: Smoking may increase the chance of developing DR in people with type 1 diabetes. However, the data regarding type 2 illness is debatable [(4)].

New medical interventions for treatment

Results from randomized controlled clinical trials have demonstrated the effectiveness of therapies other than hypoglycemic medications to prevent or slow the progression of diabetic retinal problems since the publication of the most recent edition of Diabetes in America. Some studies (such as the RASS, EUCLID, and UKPDS) have demonstrated that angiotensin-converting enzyme inhibitors that target the renin-angiotensin system and lower uncontrolled blood pressure can minimize the risk of DR development [(35)].

By lowering triglycerides, fenofibrates have also been demonstrated to slow the onset and development of DR. However, aldose reductase, protein kinase C and metalloproteinase inhibitors have not been found to be effective in halting the onset and development of DR in individuals with diabetes in randomized controlled clinical studies. Steroids and VEGF inhibitors given intravitreally have been shown to be effective in treating DME and PDR in controlled clinical studies elsewhere [(20)].

CONCLUSION

The longer an individual has diabetes, the greater their chance of getting ocular complications. DR is the most frequent microvascular/blinding consequence of diabetes, and it is associated with a sedentary lifestyle, a longer life expectancy, and changes in dietary habits that resulted in obesity. PDR and macular edema are the most serious DR consequences that impair vision. As a result, diabetic peoples require regular retinal examinations.

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