

REVIEW ARTICLE

Diabetic retinopathy causes, symptoms, and complications: a review

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ABSTRACT

Diabetic retinopathy (DR) is commonly known among diabetic patients, which causes blindness. Proliferative diabetic retinopathy (PDR) and macular edema are the most common complications of DR that adversely impact the vision. Therefore, the current review aimed to investigate the causes, symptoms, complications, risk factors, and treatments of DR. Scientific articles linked to the present topic were obtained using an online searching process. The searching process included several scientific websites such as Google Scholar and PubMed. We obtained 17 articles that matched with the current subject and were written in English. Of those 17 articles, six were excluded as they were published before 2000, or did not focus on the current topic, or were written in a language other than English; therefore, only 11 papers were included, and they were published till 2020. Articles were selected according to the inclusion criteria, and the discussion of the subject was carried out under the main titles. DR is the most common microvascular/blinding complication of diabetes. PDR and macular edema are the most common complications of DR that adversely impact the vision of diabetic patients. Therefore, regular retinal investigations are crucial among diabetic patients. Laser photocoagulation is effective for treatment and prevention strategies. New therapeutic options should be implemented to improve the ophthalmic care of diabetic patients. Also, to reduce the ophthalmic complications' risks, blood pressure and other metabolic functioning should be controlled.

Keywords: Diabetic retinopathy, diabetic macular edema, proliferative diabetic retinopathy, laser photocoagulation, ophthalmic complications.

Introduction

Diabetic retinopathy (DR) is a retinal microangiopathy that is considered to be the most common microvascular/blinding complication of diabetes. Almost all diabetic patients suffer from DR [1,2]. DR is a public health problem worldwide, affecting almost hundreds of individuals globally and affecting 3%-4% of the European population. Visual blindness/impairment caused by DR increased by 27% in 2010. By 2030, its effect will increase by 69% worldwide and by 20% in most industrialized countries and might affect almost 24 million African individuals, according to epidemiological studies [3-5]. Diabetic patients with type 1 diabetes mellitus (T1DM) are more likely to experience DR than those with type 2 diabetes mellitus (T2DM) [6]. Due to an increase in the prevalence of sedentary lifestyles, life expectancy, and alteration of eating habits that resulted in obesity, the incidence of the complications of diabetic mellitus has increased in the last years [7].

Ocular complications due to DR ranged from impaired visual acuity to blindness [7]. Retinal complications' probability increased by increasing the disease duration

(changes of vision-threatening retinal developed over time) among patients with T1DM (50%), compared to patients with T2DM (30%). Although the retinal change in the early stages (before adolescence) cannot be observed in patients with T1DM, almost one-third exhibited DR signs at the initial time of diagnosis [2,8]. Recently, it was reported that progression of DR among patients with T1DM increased the nephropathy development and vice versa, which means the incidence risk of one of them increases the incidence risk of another one [9]. Additionally, another study reported that an increased incidence rate of DR is associated with increased

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cardiovascular events and the overall mortality rate in T1DM and T2DM [10]. DR is a degenerative vascular disease that results from poorly controlled diabetes. DR has two most severe complications threatening the vision of patients: proliferative diabetic retinopathy (PDR) and diabetic macular edema [2,11]. Patients with T1DM are more experienced to have PDR risks (such as; neovascular glaucoma, tractional retinal detachment, and vitreous hemorrhage) than patients with T2DM, while diabetic macular edema is commonly found among T2DM [12].

Materials and Methods

Scientific articles linked to the present topic were obtained by using an online searching process. The searching process included different scientific websites such as Google Scholar and PubMed, using several keywords such as diabetic retinopathy, diabetic macular edema, proliferative diabetic retinopathy, laser photocoagulation, and ophthalmic complications. We obtained 17 articles that matched with the current subject and which were written in English. Of the 17 articles, six were excluded as they were published before 2000, or did not focus on the present topic, or were written in a language other than English; therefore, only 11 papers were included, and they were published till 2020.

Discussion

DR pathogenesis/causes

DR is a retinal microangiopathy (because of hyperglycemia in diabetic patients) which occurs due to the changes in both rheological properties of the blood and the vascular wall. It leads to angiographic and retinal ischemia leakage (vascular leakage), resulting in capillary occlusion and diabetic macular edema [2,13]. Erythrocytes diminished deformability, basilar membrane thickening, elevated platelet aggregation, loss of endothelial cells, loss of pericytes, reduced serum albumin concentration, elevated concentration of fibrinogen, and α_2 -globulin, and microaneurysms are considered to be the most histopathological changes that occurred in the rheological properties of the blood and the vascular wall that resulted in capillary occlusion and diabetic macular edema [2,13]. Retinal ischemia and the increasing level of vascular endothelial growth factor due to capillary occlusion led to neovascularization development and DR proliferative stage [2]. There are several new pathways regarding DR pathogenesis, such as epigenetics, nerve growth factor autophagy, and inflammation [2].

Biochemical signal pathways/alterations included advanced glycation end-product formation (AGE) due to activation of protein glycosylation and protein kinase C activation that caused neo-vascularization in the anterior and posterior segments of the eye. This might have occurred due to cell interactions, including vascular endothelial growth factor, so the vascular

permeability increased that led to inner blood-retina barrier collapse and leakage [12]. Additionally, there are other biochemical changes, such as oxidative stress, increasing the vascular permeability by kinin B1 and B2, leukocytes inflammation, and infiltrations, particularly kinin B1, which is upregulated in the diabetic patients' retina. Changes of inflammatory vessel wall and vasoconstriction (diabetics' complications) could be mediated by AGE, which is taken exogenously in food as well as formed in greater amounts endogenously due to hypoglycemia. These changes resulted in atheromatous plaque formation, and endothelial cells and macrophages' functioning are influenced. In addition, pigment epithelium, transforming growth factor β , and insulin-related growth factor I and II are also involved among the factors playing a pivotal role in the DR pathogenesis [14,15].

In the last years, it was reported that DR could be deteriorated during pregnancy and adolescence hormonal changes [16]. Also, diabetic mellitus impaired the whole retinal neurovascular system which resulted in neurodegeneration, neurovascular coupling, and neuroinflammation, which could be detected early before vascular damage [17]. Furthermore, diabetic patients are more likely to exhibit impaired color, visual field defects, dark adaption reduction, and contrast vision [2].

DR classification

DR is a silent disease that can be managed and controlled through early intervention and detection [18]. Diabetic maculopathy and proliferative diabetic retinopathy (PDR) are the most common complications for loss of vision.

Non-PDR

Neovascular glaucoma, tractional retinal detachment, and vitreous hemorrhage are examples of PDR complications [2]. In the early stages, there are several alterations which occur in the non-PDR (early DR), such as retinal hemorrhages, exudates, and aneurysms, which are temporarily observed in the central area of the macula that might arise from the loss of pericytes and deranged vascular integrity [2]. After that, in the later stage of the disease, dilated intraretinal microvascular anomalies might have developed, which is considered a possible risk of PDR and neovascularization [2]. An increased level of intraocular vascular endothelial growth factor as a result of capillary occlusion retinal ischemia leads to PDR [2].

Proliferative DR

At the optic disk or in the retina, neovascularization grows (proliferation), which leaks on fluorescein angiography, causing vitreous hemorrhage and resulting in tractional retinal detachment. A neurosensory retina is separated from the retinal and causes loss of visual acuity and scotoma among those with macular involvement [12].

DR symptoms and complications

There are several complications related to PDR, such as combined tractional-rhegmatogenous retinal detachment, tractional retinal detachment, severe fibrovascular proliferation, such as dragging, which comprises vitreous hemorrhage, media opacity due to fibrovascular tissue, tractional macular edema, and macular distortion [19]. The occurrence of DR is influenced by the type of diabetes. Among patients with T1DM, proliferative retinopathy might have arisen after passing 10 years of diagnosis. On the contrary, patients with T2DM are more likely to exhibit macular edema risks than T1DM patients. It was reported that after 5 years of proliferation among persons with T2DM, proliferation was observed among only three eyes [7]. Additionally, patients' gender is also related to blindness risks; females are more likely to be diabetic than males. As reported earlier by the Marburg University Department of Ophthalmology, 446 diabetic females versus 233 diabetic males were blind or severely visually impaired [7]. The duration of diabetes is a risk for developing DR; patients who were diagnosed before the age of 30 and exhibited it for less than 5 years were less likely to have DR than those who had diabetes for more than 15 years (17% and 90%, respectively) [20]. Additionally, the quality of glycemic control was found to be related to the development of DR. Previous results reported that diabetic patients who had diabetes for more than 6 years and the use of insulin therapy or pump for those with T1DM decreased the incidence of DR and its progression by 76% and 54%, respectively, as reported by the Diabetes Control and Complications Trial. Additionally, severe non-PDR or the frequency of PDR was reduced by 47%, compared to a rigid insulin schedule [21].

DR prevention and treatments

Diabetic macular edema

Focal and grid laser photocoagulation are clinically diabetic macular edema and diffuse diabetic macular edema. Focal laser photocoagulation of microaneurysms and leakage decreased the risk of loss of vision by 50% [22]. Focal laser photocoagulation enhances oxygen diffusion from choroidal vessels, so it boosts the retinal oxygenation. Also, focal laser photocoagulation stimulates the pigment of retinal capillaries and endothelial cells [2]. Grid laser photocoagulation should be replaced by intravitreal Anti-vascular endothelial growth factor (anti-VEGF) therapy due to its reduced functional prognosis [23].

Vascular endothelial growth factor caused retinal edema and leakage due to its relationship with the blood-retinal barrier breakdown [24]. Anti-VEGF medications intravitreal application enables a low systematic exposure, which is necessary to be repeated, especially among patients with center-involving diabetic macular edema. Intravitreal anti-VEGF therapy is safe, and the

average number of injections should not exceed by seven times in the first year and four times in the second year of injection [25].

Proliferative diabetic retinopathy

Pan-retinal laser photocoagulation could effectively reduce the risks of visual loss, while those with more advanced PDR need surgery [26]. The ophthalmologists could early detect the proliferation of laser treatment by screening intervals of diabetic patients [2]. To prevent PDR complications, such as tractional retinal detachment and/or vitreous hemorrhage, pan-retinal laser photocoagulation should be carried out during fundoscopy or via fluorescein angiography [26]. The pan-retinal laser reduces intravitreal VEGF levels and ischemia, as well as stimulates proliferation by eliminating non-perfused retinal parts [26]. However, there are some side effects related to pan-retinal laser treatments, such as loss of rod function, so it reduces dark adaption and visual fields constriction and might interfere with the ability of the patient to drive [2,27]. In patients who had both diabetic macular edema and PDR, firstly, macular edema should be treated to prevent worsening of the situation.

Conclusion

DR is the most common microvascular/blinding complication of diabetes related to the prevalence of a sedentary lifestyle, life expectancy, and alteration of eating habits that resulted in obesity. PDR and macular edema are the most severe DR complications that adversely impact the vision. Therefore, regular retinal investigations are crucial among diabetic patients. Laser photocoagulation is an effective treatment and prevention strategy. New therapeutic options should be implemented to improve the ophthalmic care of diabetic patients. Additionally, to reduce the ophthalmic complications' risks, blood pressure and other metabolic functioning should be controlled.

List of Abbreviations

DR	Diabetic retinopathy
PDR	Proliferative diabetic retinopathy
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
VEGF	vascular endothelial growth factor

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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