Journal of Diabetes & Clinical Practice

Bereda, J Diabetes Clin Prac 2022, 5:2

Review Article Open Access

Risk Factors, Classifications and Pathogenesis of Diabetic Retinopathy

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Abstract

Diabetic retinopathy, a microangiopathy affecting all of the small retinal vessels, such as arterioles, capillaries and venules, is characterized by increased vascular permeability, ocular haemorrhages, lipid exudate, by vascular closure mediated by the development of new vessels on the retina and the posterior vitreous surface. The most relevant risk factors for the development of diabetic retinopathy are the duration of the disease, poor glycemic control (high glycosylated hemoglobin levels) and the presence of hypertension. However, the impact of blood-glucose control in the development of diabetic retinopathy is stronger that the impact of blood-pressure control. Proliferative diabetic retinopathy is characterized by the hallmark feature of pathologic preretinal neovascularization. Inflammation is a nonspecific response to injury that includes a variety of functional and molecular mediators, including recruitment and activation of leukocytes. Inflammation typically has beneficial effects on an acute basis, but can have undesirable effects if persisting chronically. The increased expression of many inflammatory proteins is regulated at the level of gene transcription through the activation of proinflammatory transcription factors, including nuclear factor kappa B.

Keywords: Classifications; Diabetic retinopathy; Pathogenesis; Risk factors

Introduction

Diabetic retinopathy, which results from chronic high blood glucose levels and almost occurs in medium and late stage of type 1 and type 2 diabetes is one of the most serious microvascular complications of diabetes mellitus. Diabetic retinopathy can result in severe visual impairment, vitreous hemorrhage, and even blindness [1-3]. Epidemiological studies have shown that the global prevalence of diabetic retinopathy was 27% from 2015 to 2019. With the increase of diabetic retinopathy patients, the visual impairment caused by diabetic retinopathy has become severe [4-6]. Diabetic retinopathy affects 34.6% of patients with diabetes and is the leading cause of blindness worldwide [7-10]. The diabetic retinopathy is a complication of diabetes, causing abnormalities in the retina, and in the worst case, blindness. Typically there are no salient symptoms in the early stages of diabetes, but the number and severity predominantly increase during the time. The diabetic retinopathy typically begins as small changes in the retinal capillary. The first detectable abnormalities are mircroaneyrysms which are local distensions of the retinal capillary and which cause intra-retinal haemorrhage when ruptured. In time, the retinal edema and hard exudates are followed by the increased permeability of the capillary walls. The hard exudates are lipid formations leaking from these weakened blood vessels. This state of the retinopathy is called non-proliferative diabetic retinopathy [11, 12].

Risk factors of diabetic retinopathy

The most relevant risk factors for the development of diabetic retinopathy are the duration of the disease, poor glycemic control (high glycosylated hemoglobin levels) and the presence of hypertension. However, the impact of blood-glucose control in the development of diabetic retinopathy is stronger that the impact of blood-pressure control [13-15]. Other risk factors for diabetic retinopathy include dyslipidemia, a higher body mass index, puberty, pregnancy, and cataract surgery. Despite the importance of glycemic control in diminishing the progression of diabetic retinopathy, intensive glycemic control appeared to increase mortality among participants in the Action to Control Cardiovascular Risk in Diabetes trial, which raises concerns over the care of persons with type-2 diabetes who are at high risk of cardiovascular events, and highlights the need for close collaboration between diabetologists and ophthalmologists [13, 16-20].

Classifications diabetic retinopathy

Diabetic retinopathy falls into two broad categories such as the earlier stage of nonproliferative diabetic retinopathy and the advanced stage of proliferative diabetic retinopathy. Classification of nonproliferative diabetic retinopathy is based on clinical findings manifested by visible features, including microaneurysms, retinal hemorrhages, intraretinal microvascular abnormalities, and venous caliber changes and (1) mild nonproliferative diabetic retinopathy: There are a few microaneurysms; (2) moderate nonproliferative diabetic retinopathy: In this form, there are less than 20 microaneurysms. Hard yellow exudates, cotton wool spots, and venous beading are present also in only one quadrant; (3) severe nonproliferative diabetic retinopathy: It is identified as any of following clinic features; microaneurysms in all 4 quadrants; Venous beading in 2 or more quadrants; intraretinal microvascular abnormalities in 1 or more quadrant; and (4) very severe nonproliferative diabetic retinopathy: This form includes 2 or more of the criteria for severe nonproliferative diabetic retinopathy, while proliferative diabetic retinopathy is characterized by the hallmark feature of pathologic preretinal neovascularization and as a response to ischemia, neovascularization grows at the optic nerve and elsewhere in the retina except the optic disc. In general, neovascularization grows at the border zone of perfused and non-perfused retina. These new vessels are permeable, and the leakage of plasma contents probably causes a structural change in the adjacent vitreous. Also, neovascularization

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Received: 26-Feb-2022, Manuscript No: jdce-22-55635; **Editor assigned:** 28-Feb-2022, PreQC No. jdce-22-55635(PQ); **Reviewed:** 11-Mar-2022, QC No. jdce-22-55635; **Revised:** 11-Mar-2022, Manuscript No. jdce-22-55635(R); **Published:** 18-Mar-2022, DOI: 10.4172/jdce.1000149

Citation: Bereda G (2022) Risk Factors, Classifications and Pathogenesis of Diabetic Retinopathy. J Diabetes Clin Prac 5: 149.

may cause preretinal and subhyaloid vitreous hemorrhages and can become membrane formations on the posterior hyaloid surface [21-25].

Pathogenesis of diabetic retinopathy

Hyperglycemia and retinal microvasculopathy: Histologically, vascular lesions in the early stages of diabetic retinopathy are characterized by the presence of saccular capillary microaneurysms, pericyte deficient capillaries, and obliterated and degenerate capillaries. These degenerate capillaries are not perfused, and so increases in their frequency represent reductions in retinal perfusion. Capillary occlusion and degeneration initially occurs in single, isolated capillaries, and has no clinical importance when only few capillaries have become nonperfused. As more and more capillaries become occluded, however, retinal perfusion likely decreases, at least locally. Hyperglycemia is considered to play an important role in the pathogenesis of retinal microvascular damage. Multiple metabolic pathways have been implicated in hyperglycemia-induced vascular damage including the polyol pathway, advanced glycation end products accumulation, the protein kinase C pathway and the hexosamine pathway. The earliest responses of the retinal blood vessels to hyperglycemia are dilatation of blood vessels and blood flow changes [26-31].

Inflammation: Inflammation is a nonspecific response to injury that includes a variety of functional and molecular mediators, including recruitment and activation of leukocytes. Inflammation typically has beneficial effects on an acute basis, but can have undesirable effects if persisting chronically. The increased expression of many inflammatory proteins is regulated at the level of gene transcription through the activation of proinflammatory transcription factors, including nuclear factor kappa B. These proinflammatory transcription factors are activated and play a critical role in amplifying and perpetuating the inflammatory process. Transcription factors associated with production of proinflammatory mediators include nuclear factor kappa B, activator protein 1, specificity protein 1, peroxisome proliferator-activated receptors and other members of the nuclear receptor superfamily. Proinflammatory proteins (including Cyclooxegenase-2, interleukin-1, tumor necrosis factor alpha) can contribute to cell damage and death in tissues including brain and retina, at least in part via activation of nuclear factor kappa B [32-34].

Oxidative stress and diabetic retinopathy: The retina has high content of polyunsaturated fatty acids and has the highest oxygen uptake and glucose oxidation relative to any other tissue. This phenomenon renders retina more susceptible to oxidative stress. It has been suggested that the correlation between hyperglycemia, changes in the redox homeostasis, and oxidative stress are the key events in the pathogenesis of diabetic retinopathy [35-37].

Retinal neurodegeneration: Retinal neurodegeneration is an early event during the progression of diabetic retinopathy. Apoptosis of retinal neurons can be observed in diabetic rats as early as one month after induction of diabetes [34]. Upregulation of pro-apoptotic molecules such as cleaved caspase-3, Bax and Fas has been detected in retinal neurons in diabetic animals and subjects [35–37]. Mitochondrial dysfunction has been implicated in retinal degeneration in diabetic retinopathy. In donor eyes of diabetic subjects, retinal expression of pro-apoptotic mitochondrial proteins such as cytochrome c and apoptosis-inducing factor were found to be significantly increased [38-40].

Changes in retinal blood flow: The earliest functional changes in nonproliferative diabetic retinopathy which cannot be visualized photographically include alterations in the rate of retinal blood flow and loss of autoregulatory mechanisms for adjusting retinal capillary perfusion to local metabolic demand. The retinal vasculature lacks autonomic innervation and modulation of blood flow through the neuropile is dependent on local signalling mechanisms [41].

Vascular endothelial growth factor: Vascular endothelial growth factor is a crucial mediator in microvascular complications of diabetes mellitus. Normally, numerous retinal cells such as, retinal pigment epithelial cells, Mueller cells, and pericytes, produce vascular endothelial growth factor. When a hypoxia occurs vascular endothelial growth factor is secreted much more than normal production by hypoxic retinal tissues. Vascular endothelial growth factor levels were prominently increased in patients with proliferative diabetic retinopathy. Additionally, vascular endothelial growth factor has a crucial role in the pathogenesis of diabetic macular edema by increasing vascular permeability [42].

Conclusion

Diabetic retinopathy is the leading cause of visual impairment among people of working age and has social consequences beyond sight loss. The most relevant risk factors for the development of diabetic retinopathy are the duration of the disease, poor glycemic control (high glycosylated hemoglobin levels) and the presence of hypertension. However, the impact of blood-glucose control in the development of diabetic retinopathy is stronger that the impact of blood-pressure control. Histologically, vascular lesions in the early stages of diabetic retinopathy in man and animals are characterized by the presence of saccular capillary microaneurysms, pericyte deficient capillaries, and obliterated and degenerate capillaries. These degenerate capillaries are not perfused, and so increases in their frequency represent reductions in retinal perfusion.

Acknowledgments

The author would be grateful to anonymous reviewers by the comments that increase the quality of this manuscript. **Data Sources:** Sources searched include Google Scholar, Research Gate, PubMed, NCBI, NDSS, PMID, PMCID, Scopus database, Scielo and Cochrane database. Search terms included: risk factors, classifications and pathogenesis of diabetic retinopathy

Funding

None

Availability of data and materials

The datasets generated during the current study are available with correspondent author.

Competing interests

The author has no financial or proprietary interest in any of material discussed in this article.

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