Review Article

In Shortly about Retinopathy

Sinisa Franjic*

*Corresponding Author: Sinisa Franjic, Independent Researcher.

Received Date: April 5, 2021

Publication Date: April 13, 2021

Abstract

Diabetic retinopathy is the most common eye disease in people who have diabetes for a long time - it becomes very dangerous if left untreated and increases the risk of blindness. The risk of blindness is 10-20 times higher in diabetics than in people who do not have diabetes. This metabolic disorder affects all parts of the eye, but most of all the retina, which is rich in a network of tiny blood vessels that are most susceptible to damage. The disease itself occurs due to higher blood sugar levels. Sugar damages small blood vessels in many organs, including the eye, and they rupture and lose blood flow to some parts of the retina.

Keywords: *Eye, Diabetes, Diabetic Retinopathy, Health.*

Introduction

Diabetic retinopathy is due to microangiopathy affecting the retinal precapillary arterioles, capillaries, and venules **[**1**]**. Damage is caused by both microvascular leakages due to breakdown of the inner blood-retinal barrier and microvascular occlusion. These two pathological mechanisms can be distinguished from each other by fluorescein angiography, which is the "gold standard" for assessing diabetic retinopathy.

It is generally accepted that microvascular disease, such as retinopathy, neuropathy, and nephropathy, is a function of the degree and duration of hyperglycemia **[**2**]**. Changes of diabetic retinopathy were reported in 7.9% of the impaired glucose group and in 12.6% of the group that developed diabetes on follow-up. Although the subjects who developed retinal changes were not significantly different from

those without these changes in the impaired glucose group, they tend to have a higher baseline prevalence of hypertension, lower HDL, higher triglycerides, and a history of gestational diabetes. The rates of retinopathy and nephropathy were higher in individuals with impaired fasting glucose in comparison to those with impaired glucose tolerance on 10 years of follow-up of a group of Pima Indians, also supporting the previous evidence that IFG might denote a metabolically advanced state. As opposed to these results, the incidence of diabetic retinopathy was reported to be very low at 28–31/10,000 person-years of follow-up in a large Japanese cohort of atomic bomb survivors with impaired glycemia. A steep rise in the incidence and prevalence of fundus changes were noted only when the fasting plasma glucose was >125 mg/dl and the 2–hour post-challenge glucose >198 mg/dl. A clear threshold effect was not evident for microalbuminuria and the relation to rising in glucose was more gradual. Collectively, although there is evidence for increased prevalence and incidence of microvascular changes before the onset of diabetes, these changes predominantly occur with higher levels of glycemia.

Approximately 20% of patients with type 2 diabetes show signs of retinopathy at the time of diagnosis **[**3**]**. Progression is orderly from mild abnormalities (small retinal hemorrhages) to proliferative retinopathy with the growth of new vessels on the retina and into the vitreous culminating in vision loss. The risk of retinopathy increases with increasing A1c and duration of the disease, but African Americans develop retinopathy at lower levels of A1c. In the ACCORD trial, intensive therapy lowered retinopathy but not ultimate vision loss. Patients with type 1 diabetes may begin yearly ophthalmology visits 5 years after diagnosis, but patients with type 2 should begin yearly office visits with diagnosis. Laser photocoagulation therapy is the only treatment option once the disease progresses.

Risk Factors

Diabetic retinopathy first affects blood vessels in the retina **[**4**]**. The retina has a fine structure of capillary vessels to meet the high demand of oxygen and glucose to change the light into the electric signal of nerves. However, with the increase of the duration of diabetes, retinal capillaries are obstructed, and severe ischemia is induced in the retina. This ischemic change induces the expression of VEGF (vascular endothelial growth factor) and induces neovascular vessel formation in the retina. The neovascular vessels bleed easily, and the proliferation of the vessels is uncontrolled, which causes the eyeball to fill with blood.

The most important risk factor for diabetic retinopathy is the duration of diabetes. Diabetic retinopathy is seen in roughly 20% of patients with a 5-year duration of diabetes, which increases to 60% in a 20-year duration. Poor glycemic control, increased blood pressure, smoking, and alcohol are also risk factors for diabetic retinopathy. The Maillard reaction is known to be involved in the development of

diabetic retinopathy. In diabetic patients, the blood sugar level is increased, and the proteins in the body are constantly exposed to this high glucose level. The proteins in the body and the blood sugar react to form a Schiff base and initiate the Maillard reaction. An example of glycated proteins is glycated hemoglobin in the blood. Hemoglobin A1c is now clinically used as a reference for the average blood sugar level of diabetic patients. Increased blood sugar levels also induce the glycation of proteins in the retina. Increased accumulation of the Maillard reaction products and advanced glycation end products are seen in experimental animals, as well as diabetic patients. Increased interaction of advanced glycation end products and RAGE (Receptor for AGEs) expressed in vascular endothelial cells and pericytes is speculated to play an important role in the development of diabetic retinopathy.

Characteristics

Diabetic retinopathy (DR) is characterized by microvascular changes in the retina, increasing vascular permeability and capillary degeneration with resulting microaneurysms, exudates, and neovascularization **[**5**]**. The main clinical risk factors for DR are the duration of diabetes, chronic hyperglycemia, hypertension, and lipids.

The prevalence of DR is double for patients with microalbuminuria and a sixfold increase in patients with macroalbuminuria compared to patients with no signs of renal dysfunction suggesting both common and unique mechanisms. Clinical data support at least two, potentially distinct, pathological processes for DR, resulting in proliferative retinopathy and macular edema, respectively.
The heritability of DR has been estimated to 18–57%, which is consistent with a substantial genetic component but might also reflect challenges in defining the phenotype consistently.

Classification

The classification of diabetic retinopathy is based on visible/ophthalmoscopic features, but unseen changes occurring before these helps explain the clinical findings **[**6**]**. Amongst the first is thickening of the capillary basement membrane and loss of the pericytes embedded in it.

As the basement membrane thickens, it loses its negative charge and becomes 'leakier'. In normal retinal capillaries, there is a 1:1 relationship between endothelial cells and pericytes, which is the highest ratio for any capillary network in the body. Pericytes may control endothelial cell proliferation, maintain the structural integrity of capillaries and regulate blood flow. This along with increased blood viscosity, abnormal fibrinolytic activity and reduced red cell deformity may lead to capillary occlusion, tissue hypoxia and the stimulus for new vessel formation.

While the toxicity of glucose/hyperglycemia is accepted, exactly how locally produced growth factors, altered protein kinase C activity, alterations in oxidative stress responses and alterations in the autoregulation of retinal blood flow combine to cause this remains unclear, but is avidly debated.
The natural progression is from background to pre-proliferative/pre-maculopathy then to proliferative retinopathy/maculopathy and ultimately sight-threatening disease.

Causes

Diabetic retinopathy is one of the leading causes of blindness in the USA and in the developed world **[**7**]**. With the increase in the survival of the aging population and the increase in the prevalence of diabetes, the number of individuals affected with diabetic retinopathy will increase as a major public health disease. Any preventive measure may lessen the impact on the potential toll this disease may take in terms of health care cost, personal loss in productivity, and societal cost and burden.

The two main causes of vision loss associated with diabetic retinopathy are diabetic macular edema and proliferative diabetic retinopathy. The risk factors known to be associated with the development and progression of sight-threatening diabetic retinopathy are varied and numerous. However, some of these factors are not yet proven conclusively to be associated with the development and progression of retinopathy because there are either inconsistent findings across various studies or the nature of the supportive data is only observational.

Complication

One common complication of diabetes is retinopathy, a disease of the retina, the light-sensing region of the inner eye **[**8**]**. The retina acts like a miniature “movie screen” in the back of your eye, on which the images you see are projected. Retinopathy is caused by damage to the blood vessels that supply blood to the retina.

Retinopathy is more common among people with type 1 diabetes, but people who have had type 2 diabetes can also develop it. There are two major forms of retinopathy. In one type, called nonproliferative (or background) retinopathy, blood vessels can close off or weaken. When this happens, they leak blood, fluid, and fat into the eye. Although this can lead to blurry vision, it does not cause blindness, unless there is leakage in the macula, the area of the retina near the optic nerve that is responsible for most of our vision.

Nonproliferative retinopathy can progress to a more serious, although a less common, form of an eye disease called proliferative retinopathy. This occurs when new blood vessels sprout or proliferate, in the

retina. This may seem like a good thing, but the new vessels don't grow in the way they should. Instead, they grow out of control. They are fragile and rupture easily during exercise or even while sleeping, especially if you have high blood pressure. When this happens, blood can leak into the fluid-filled portion of the eye in front of the retina. This can block the light coming into the eye and impair vision. In addition, scar tissue can form on the retina. The scar tissue often shrinks, and when that happens, it can tear the layers of the retina apart. This damages your eyesight. Glaucoma, or high pressure within the eye, and cataracts occur more often in people with diabetes. If found early, glaucoma can be treated. Retinopathy can also cause swelling of the macula of the eye. Because the macula is that central portion of the retina that allows you to see fine detail, when it swells, vision can be impaired and blindness can result. This condition is known as macular edema.

Exercise

The confluence of diabetes and retinopathy poses an additional layer of concern for risks of exercise to the patient **[**9**]**. The concern is that exercise may also exacerbate several diabetes-related complications. One of the most potentially serious among those is proliferative retinopathy, which predisposes to vitreous hemorrhage and traction retinal detachment. Exercises that increase blood pressure, particularly high-intensity resistance exercise that involves Valsalva maneuvers, as well as jarring head motions, can precipitate these devastating complications. Patients with proliferative retinopathy have significant restrictions on the type and intensity of activity that they can safely engage in due to this risk of severe ocular damage.

The underlying mechanisms hypothesized to incite these devastating events include increasing systolic blood pressure causing vessel rupture and retinal hemorrhage, trauma causing retinal detachment, or hemorrhage. It was found that patients with diabetic retinopathy had a higher resting heart rate, while those without diabetic retinopathy showed a higher heart rate increase during exercise. It was also observed that there were differences in the increase of heart rate during exercise and in the recovery phase after exercise. Such increases in systolic BP could precipitate retinal or vitreous hemorrhage. Activities that include rapid head motion may also precipitate retinal detachment or vitreous hemorrhage, which helps to explain why moderate weight training may be a safer activity than most high-intensity aerobic exercises. There is no such concern in nonproliferative retinal disease or macular edema.

Eating Disorders

Body image and weight management concerns in adolescent females, as well as males with diabetes, are of particular concern **[**10**]**. Eating disorders and disordered eating behaviors are significant health

problems for many children and adolescents. Controversy exists regarding whether there is an increased prevalence of diagnosable eating disorders and disordered eating behaviors in patients with type 1 diabetes compared with people without diabetes, with some studies showing a higher rate in type 1 diabetes patients and others finding the same or lower rates. Estimates of diagnosable eating disorders and disordered eating behaviors in adolescent and young adult females with type 1 diabetes range from 3.8 to 27.5% for patients classified as bulimic or having binge eating disorder. When insulin omission is considered purging the estimate goes as high as 38–40%. The presence of diagnosable eating disorders and behavior categorized as subclinical disordered eating behaviors has been associated with increases in retinopathy, neuropathy, transient lipid abnormalities, hospitalizations for diabetic ketoacidosis, and poor short-term metabolic control. Adolescents with diabetes should be screened regularly for insulin omission and eating disorders to prevent the serious medical consequences of very poor glycemic control. Warning signs that may be indicative of an eating disorder in adolescents include lack of adequate weight gain or growth, significant weight loss without illness, suboptimal overall glycemic control, and recurrent diabetic ketoacidosis.

Other issues of concern in adolescents with diabetes include the potential use of alcohol. Adolescents must be instructed on the potential hypoglycemic effects of alcohol and on responsible drinking, should they choose to use alcohol. Adolescents who drive should be instructed on blood glucose monitoring before driving and carrying a source of carbohydrate with them at all times should hypoglycemia occur. Finally, adolescents with diabetes may experiment with alternative eating patterns, such as a vegetarian diet, or they may choose to use nutritional supplements. Practical information on these topics will enable adolescents to make wise choices for their health.

Mirror

The most specific diabetes-related complication is diabetic retinopathy **[**11**]**. It is considered a mirror of hyperglycemic damage. The onset and severity of retinopathy directly correlate with duration and degree of hyperglycemia, as opposed to other microvascular complications like neuropathy and nephropathy, which are also influenced by non-glycemic factors. The incidence of diabetic retinopathy progressively increases from an HbA1c of 7 to 10% and plateau thereafter.

Ophthalmoscopic fundus examination with the dilated pupil is the simplest and inexpensive initial workup. Fundus photography may be used for documentation and monitoring of diabetic retinopathy. Fluorescein angiography is indicated in patients with macular ischemia, painless loss of vision and for guiding treatment of clinically significant macular edema. Optical coherence tomography (OCT) is to be performed in those who have a suspicion of macular edema.

The severity of diabetic retinopathy is classified by Early Treatment Diabetic Retinopathy Study scale (ETDRS)/International Classification of Diabetic Retinopathy and Diabetic Macular Edema, after a detailed fundus examination with a dilated pupil. The presence of microaneurysm, soft exudates, intraretinal microvascular abnormalities, and venous beading constitutes non-proliferative diabetic retinopathy (NPDR). Proliferative diabetic retinopathy (PDR) is characterized by neovascularization (at the disk or elsewhere), vitreous hemorrhage, and retinal detachment. Clinically significant macular edema (CSME) is characterized by retinal thickening and/or hard exudates within 500 µm from the center of the macula. CSME can occur with any stage of NPDR or PDR.

Control

Microaneurysms, intraretinal hemorrhages, cotton wool spots, and lipid deposits due to vascular leakage are the retinal changes seen in early diabetic retinopathy **[**12**]**. Later stages include retinal ischemia and neovascularization with subsequent vitreous hemorrhage often associated with traction or rhegmatogenous retinal detachment. Diabetic retinopathy may be asymptomatic until vision decreases, usually from macular edema or vitreous hemorrhage. The presence of renal microvascular disease correlates well with the presence of diabetic retinopathy.

Careful control of blood sugar and blood pressure appears to reduce the incidence and severity of diabetic retinopathy. Epidemiologic studies show that many diabetics fail to have recommended yearly eye examinations. If patients are followed closely and early retinopathy is detected and treated according to the guidelines of the early treatment diabetic retinopathy study (ETDRS), the risk of severe visual loss is less than 5%. Treatment consists of photocoagulation, either of the maculae to reduce edema or of the retinal periphery to reduce ischemic neovascular changes. Adjunctive intravitreal injection of triamcinolone with laser treatment has been suggested for macular edema and proliferative retinopathy. Intravitreal injections of agents that neutralize vascular endothelial growth factor (VEGF) now play a central role in the treatment of diabetic macular edema. These anti-VEGF agents may also be useful for the treatment of proliferative disease. Rare complications from these injections include endophthalmitis and steroid-induced glaucoma.

Conclusion

Diabetic retinopathy is most often detected during a detailed examination of the eye, which includes measurement of visual acuity, measurement of intraocular pressure, examination of the anterior segment of the eye on a biomicroscope and examination of the fundus, ie after dilation of the pupils. Diabetic retinopathy is caused by a long-term rise in blood sugar levels. Over time, high blood sugar levels can weaken and damage small blood vessels inside the retina, causing bleeding, fluid leakage from

the vessels, or even swelling of the retina. Diabetic retinopathy is a major cause of blindness and is particularly severe in type 1 diabetes. The degree of retinopathy is strongly associated with the duration of diabetes and poor blood glucose control. Nonproliferative retinopathy first develops. Proliferative retinopathy is more severe and can lead to vitreous hemorrhage and retinal detachment.

References

1.Watkins, P. J. (2003.): „ABC of Diabetes, Fifth Edition“, BMJ Publishing Group Ltd, London, UK, pp. 47.

2.Muthusamy, K.; Vella, A. (2011.): „Is prediabetes a risk factor or is it a disease?“ in Vella, A.; Rizza, R. A. (eds): „Clinical Dilemmas in Diabetes“, John Wiley & Sons Ltd, Chichester, UK, pp. 4. – 5.

3.Vail, B. (2015.): „Diabetes Mellitus“ in South-Paul, J. E.; Matheny, S. C.; Lewis, E. L. (eds): „CURRENT Diagnosis & Treatment in Family Medicine, Fourth Edition“, McGraw-Hill Education, New York, USA, pp. 384.

4.Kaji, Y. (2018.): „Diabetic Eye Disease“ in Yamagishi, S. (ed): „Diabetes and Aging-related Complications“, Springer Nature Singapore Pte Ltd., Singapore, Singapore, pp. 24. – 25.

5.Prasad, R. B.; Ahlqvist, E.; Groop, L. (2018.): „Genetics of Diabetes and Diabetic Complications“ in Diabetes“ in Bonora, E.; DeFronzo, R. A. (eds): „Diabetes - Epidemiology, Genetics, Pathogenesis, Diagnosis, Prevention, and Treatment“, Springer International Publishing AG, Cham, Switzerland, pp. 124.

6.Shotliff, K.; Duncan, G. (2005.): „Diabetes and the Eye“ in Shaw, K. M.; Cummings, M. H. (eds): „Diabetes - Chronic Complications, Second Edition“, John Wiley & Sons Ltd, Chichester, UK, pp. 6. – 7.

7.Chew, E. Y. (2008.): „Diabetic Retinopathy - Can it be Prevented?“ in LeRoith, D.; Vinik, A. I. (eds): „Controversies in Treating Diabetes - Clinical and Research Aspects“, Humana Press, Totowa, USA, pp. 96.

8.(2005.): „American Diabetes Association Complete Guide to Diabetes, Fourth Edition, Completely Revised“, American Diabetes Association, Inc., Alexandria, USA, pp. 317. – 318.

9.Mar, J.; Botein, S. H.; Hamdy, O. (2018.): „Conditions That May Interfere with Exercise“ in Reusch, J. E. B.; Regensteiner, J. G.; Stewart, K. J.; Veves, A. (eds): „Diabetes and Exercise - From Pathophysiology to Clinical Implementation, Second Edition“, Springer International Publishing AG, Cham, Switzerland, pp. 248. – 249.

10.Franz, M. J.; Evert, A. B. (eds) (2012.): „American Diabetes Association Guide to Nutrition Therapy for Diabetes, Second Edition“, American Diabetes Association, Inc., Alexandria, USA, pp. 160. – 161.

11.Bhansali, A.; Gogate, Y. (2015.): „Clinical Rounds in Endocrinology, Volume I - Adult Endocrinology“, Springer India, New Delhi, India, pp. 420. – 421.

12.Tsai, L. M.; Pitha, I.; Kamenetzky, S. A. (2015.): „The Eye & Ocular Adnexa“ in Doherty, G. M. (ed): „Current Diagnosis and Treatment - Surgery, 14th Edition“, McGraw-Hill Education, New York, USA, pp. 947.

Volume 2 Issue 4 April 2021