
Pathogenesis and treatment of diabetic retinopathy

Diyabetik retinopati patogenezi ve tedavisi

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ABSTRACT

Diabetic retinopathy (DR), one of the most important preventable and / or treatable causes of blindness worldwide, is one of the most important complications of diabetes. Compared to the general population, the risk of blindness is 25 times more. The prevalence of diabetic retinopathy is 77% in patients with type 1 diabetes and 25% in type 2 diabetes. According to the World Health Organization, DR is responsible for 4.8% of all blindness in the world. Although there have been many studies to understand the pathogenesis of diabetic retinopathy, it has not been fully elucidated. However, good blood glucose regulation and control of other systemic factors such as hypertension and hyperlipidemia are very important in stopping the progression of the disease. Despite all the advances in the treatment of diabetic retinopathy, there is no treatment yet that removes retinopathy and leads to sequel-free recovery. Nevertheless, current treatment modalities can prevent legal blindness and allow patients to continue their lives with a level of acceptable vision. It is important to compile up-to-date information, especially in ophthalmology, due to the current advances in the diagnosis and treatment methods of diseases. Therefore, the pathogenesis of diabetic retinopathy and current treatment methods were reviewed in this review.

Key Words: argon laser photocoagulation, diabetic retinopathy pathogenesis, diabetic retinopathy treatment, neovascularization, pars plana vitrectomy

ÖZET

Tüm dünyada önlenbilir ve / veya tedavi edilebilir en önemli körlük nedenlerinden biri olan diyabetik retinopati (DR), diabetin en önemli komplikasyonlarından biridir. Genel popülasyona göre körlük riski 25 kat daha fazladır. Diyabetik retinopati prevalansı tip 1 diyabetli hastalarda %77 iken, tip 2 diyabetik hastalarda ise % 25 civarındadır. Dünya Sağlık Örgütü verilerine göre dünya genelindeki tüm körlüklerin %4.8 den DR sorumludur. Diyabetik retinopati patogenezinin anlaşılmasına yönelik yapılan birçok çalışma olmasına rağmen, tam olarak aydınlatılamamıştır. Ancak iyi bir kan şekeri regülasyonu ve HT, hiperlipidemi gibi diğer sistemik faktörlerin kontrolü hastalığın progresyonunu durdurmada çok önemlidir. Diyabetik retinopati tedavisindeki tüm ilerlemelere rağmen henüz retinopatiyi ortadan kaldıran ve sekelsiz iyileşmeyi sağlayan bir tedavi yöntemi yoktur. Yine de, güncel tedavi yöntemleri, yasal körlüğün önüne geçebilmekte ve kabul edilebilir sınırlarda bir görme düzeyi ile hastaların hayatlarını sürdürmelerine olanak sağlamaktadır. Günümüzdeki hastalıkların, özellikle oftalmolojide, tanı ve tedavi yöntemlerindeki hızlı ilerlemeler nedeniyle güncel bilgilerin derlenmesi önem arz etmektedir. Bundan dolayı bu derlemede diyabetik retinopati patogenezi ve güncel tedavi yöntemleri incelenecektir.

Anahtar Kelimeler: Argon lazer fotokoagülasyon, diyabetik retinopati patogenezi, diyabetik retinopati tedavisi, neovaskülerizasyon, pars plana vitrektomi

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1. INTRODUCTION

Diabetic retinopathy (DR), one of the most important preventable and / or treatable causes of blindness worldwide, is one of the most important complications of DM.¹ According to data from the World Health Organization, it is estimated that the number of patients will increase from 171 million DM patients in 2000 to 366 million in 2030.² The World Health Organization study results also revealed that DR was accounted for 4.8% of all blindness worldwide.³ The prevalence of diabetic retinopathy is 77% in type 1 diabetic patients and 25% in type 2 diabetic patients.⁴ The importance of increasing number of diabetic patients and its complications increases day after day.

Although the mechanisms of the pathogenesis of diabetic retinopathy are not fully understood, chronic hyperglycemia is thought to lead to series of biochemical and molecular changes resulting in vascular endothelial damage. Prolonged biochemical and molecular changes result in decreased visual acuity.⁵ Randomized clinical trials have shown that early treatment reduces severe visual loss by 57%.⁶

It is important to compile up-to-date information, especially in ophthalmology, due to the current advances in the diagnosis and treatment methods of diseases. Therefore, the pathogenesis of diabetic retinopathy and current treatment methods were reviewed in this review.

2. DIABETIC RETINOPATHY PATHOGENESIS

DR is defined as a microangiopathy due to hyperglycemia, especially with microvascular tissue. Capillary endothelial cell damage, loss of pericyte cells, capillary basal membrane thickening, and deterioration of the blood-retina barrier lead to clinical findings of diabetic retinopathy.⁵ It has emphasized that neurodegeneration is an important component of diabetic retinopathy in recent years. Hyperglycemia disturbs the metabolic balance in the retina and signals from the insulin receptors decrease. These signals are important for neural development, growth, and survival and lead to neural apoptosis when reduced. In addition, increased oxidative stress, inflammation and loss of neuroprotective factors contribute to neurodegeneration. Glial cells play a crucial role in retinal blood flow, vascular permeability, and cell survival.^{5,7}

Various mechanisms have been proposed in diabetic retina that lead to capillary obstruction and impaired vessel permeability. These mechanisms include polyol pathway, advanced glycation end products pathway, protein kinase C (PKC) pathway, and hexosamine

pathway. These mechanisms lead to increased oxidative stress, inflammation and vascular dysfunction. The result is blood retinal breakdown and diabetic retinopathy.^{8,9}

All lesions that occur as a result of the diabetic microangiopathy that affects primarily the precapillary arterioles, capillaries, and venules of the retina are the result of two main events:

1. Microvascular obstruction
2. Microvascular leakage

Microvascular Obstruction:

The changes leading to microvascular obstruction can be briefly summarized as follows:

- Capillary basement membrane thickening,
- Capillary endothelial cell injury and proliferation
- Changes in red blood cells leading to impairment of oxygen transport.¹⁰⁻¹²

All these changes result in the occlusion of the capillaries that causes ischemic islets in the retina. The result is retinal hypoxia. First, arteriovenous shunts, collaterals that normally do not exist are developed with the aim of blood circulation. While this leads to the abnormal development of the retinal hemodynamics, a substance that stimulates the formation of new blood vessels, that is supposed to be released from hypoxic retina, initiates neovascularization with the aim of the hypoxic retina. Thus, it is shifted to proliferative phase.⁸⁻¹²

Microvascular Leakage:

The pathological process called microvascular leakage is the penetration of retinal tissue with blood contents by deterioration of the vessels' wall permeability. The result is hemorrhage or edema. Changes leading to microvascular leakage⁸⁻¹²:

1. Pericyte cell loss,
2. Endothelial cell injury,
3. Blood-retinal barrier deterioration
4. Micro-aneurysm formation

Aldose reductase activity is high in tissues (cornea, nerve tissue, vesicle seminalis) that do not require insulin for glucose uptake in diabetics. Accordingly, the formation of sorbitol and galactitol is also high. These polyols can not pass through the cell membrane and accumulate in the cell. Intracellular polyol accumulation creates

osmotic stress and ultimately capillary endothelial cell damage occurs.¹³

2.1. Clinical Findings

2.1.1 Microaneurysms

Microaneurysms is the first clinical finding of DR. It is developed from retinal capillaries and is usually found in occluded capillary areas. They have 12-125 microns diameter. Small aneurysms occur as a result of weakness and disconnection in capillary walls caused by the loss of pericyte cells. While microaneurysms are stained, bleeds are not stained in fundus fluorescein angiography (FFA).¹⁴⁻¹⁷

2.1.2. Intra Retinal Hemorrhages

Rupture of microaneurysms, decompensated capillaries and IRMAs cause retinal hemorrhages. Their clinical appearance varies from place to place in retina. The outer plexiform and inner nuclear layers have rounded and paw shaped hemorrhages, while the hemorrhages in superficial layers of nerve fibers are seen as flames. These hemorrhages are absorbed between 6 weeks and 4 months.¹⁴⁻¹⁷

2.1.3. Hard Exudates

It is a yellowish-white, sharp-bordered, lipid / lipoprotein accumulation. They are located in the outer plexiform layer. They are in the form of clustered or circinated ring which surround the microaneurysms. They do not mask of paint like druse in FFA. They are resorbed spontaneously or after laser treatment. Chronically hard exudates turn into hard plaques forming disciform type scars.¹⁴⁻¹⁷

2.1.4. Soft Exudates

Thrown cotton-like exudates are small infarcts in the nerve fibers. As a result of the regional hypoxia, the slowing of the axonal transmission causes accumulation of cell organelles in the axons and cystoid bodies occur. At an average of 6 weeks, they disappear with an atrophic areas due to nerve fibers and ganglion cells loss. They show hyperfluorescence in FFA.¹⁴⁻¹⁷

2.1.5. Occlusion in Arterioles

First, it starts in the end point arterioles, then the large arterioles are involved. White colored string like occluded vessels are observed. The involvement of the macula causes irreversible visual loss.

2.1.6. Venous Disorders

Venous disorders that are seen in the diabetic retinopathy; venous beading, ring formation, sheathing, exudation around the vein, and

venous occlusions are seen in as venous disorders. Venous beading is the area of focal venous enlargement associated with thinning in the vein wall. Ring formation is deviated from the normal course of venous. Branch and central retinal vein occlusion are more common in people with diabetes.

2.1.7. Intra Retinal Microvascular Abnormalities (IRMA)

IRMA is dilated, curved, and telangiectatic vessels between the arterioles and venules. The vessels show endothelial proliferation and result as shunting towards the nonperfused area. Numerous IRMA existence demonstrates the severe period of NPDR and the upcoming of mild neovascularization in a short time.¹⁴⁻¹⁷

2.1.8. Neovascularization (NV)

They are irregularly shaped veins (Figure 1). They are extremely fragile, permeable, and wrapped by a contractile characterized fibrous tissue (due to the fibroblasts). This fibrous tissue, which is initially undefined, becomes visible by maturation over time. The NV may develop on the optical disc and / or anywhere in the retina. NVs located on the retina surface are often localized in the posterior pole and along the main temporal arches. 15% of the PDR lesions are located either on the NV optical disc or in a disc-diameter distance, 40% on the outside of this area, and 45% on both areas.¹⁴⁻¹⁷

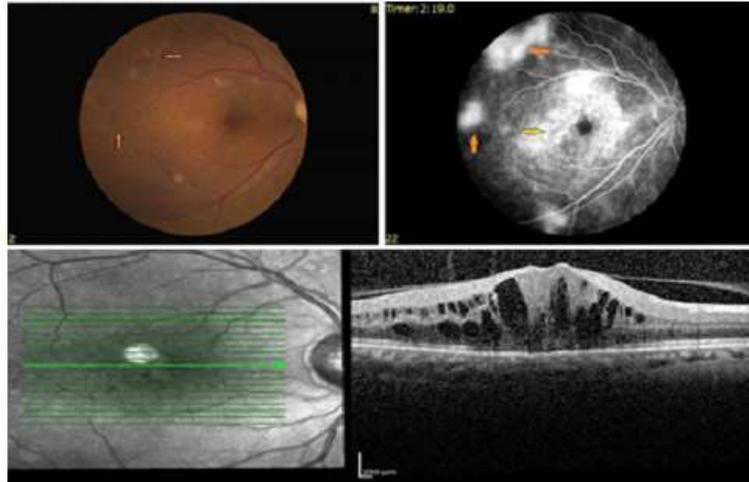
2.1.9. Vitreous Hemorrhage

In DR, hemorrhage is caused by neovascular tissue. There are two types of hemorrhage. The anterior hemorrhage of the retina is located between the detached vitreous and the retina surface during the current vitreous detachment. It can resorb or spread into the vitreous. Intravitreal bleeding causes severe vision loss. Second type hemorrhage is occur into the vitreous cavity due to the growth of NV into the vitreous, or the spread of the formed preretinal hemorrhage. Spontaneous resorption is expected in the first three months for the first vitreous hemorrhages.¹⁸ Presence of tractional detachment with bleeding and special condition of the disease (single eye, young age) requires early vitreoretinal surgery.

2.1.10. Macular Edema

Macular edema is extracellular fluid accumulation in the retina in the macula zone. Diabetic macular edema may be seen in every stage of diabetic retinopathy, in both NPDR and PDR stages. There are many factors that contribute to macular edema. First, the functional damage and necrosis occur of retinal capillaries, which cause deterioration of the inner blood retinal barrier. Intraretinal

Figure 1: Orange arrows in the fundus image on the left side show neovascularizations. Fluorescein angiography on the right side shows leakage as hyperfluorescence in neovascularization areas. Diffuse macular edema is also seen with the yellow arrow. At the lower optical coherence tomography, intraretinal cysts are seen in the macula of the same patient.



microvascular abnormalities and microaneurysms cause leakage of serum lipoproteins.^{19,20} Vitreous is considered to have an effect on macular edema. In fact, macular edema is less common in patients with posterior vitreous detachment. Macular edema is evaluated in two subgroups as focal and diffuse.

Focal Macular Edema:

Any retinal thickening or hard exudate formation that is located at a disk-diameter distance from the center of the macula is called focal diabetic macular edema. Focal macular edema is usually caused by leaks from microaneurysms and dilate capillaries. As the liquid components of these leakage resorb over time, but the lipid and lipoprotein derivatives accumulate in the inner and outer plexiform layers of retina and form hard exudates. Clinically significant macular edema is defined by the presence of at least one of the following three edema localizations:^{19,20}

- retinal edema within 500 μm of the center of the fovea
- presence of hard exudate within 500 μm from the center of the fovea and presence of retinal edema at the adjacent retina
- at least 1 optic disc diameter retinal edema, extending to the zone that is 1 optic disc diameter to the center of retina

Diffuse macular edema:

The retinal thickening of two or more optic disc sizes, including the macula center is called diffuse diabetic macular edema (Figure 1). Diffuse diabetic macular edema is closely associated with uncontrolled hyperglycaemia, renal insufficiency, systemic factors such as high diastolic blood pressure. Physiopathologically, RPE pump function impairment may contribute. In addition to

microaneurysms in this type of edema, intra-retinal microvascular abnormalities also can be a cause by leakage. Unlike focal diabetic macular edema, hard exudate plaques are rarely seen because the blood-retina barrier prevent the diffusion of the big molecules in diffuse type. In addition, diffuse type macular edema includes cystoid changes. Another feature that distinguishes diffuse diabetic retinopathy is the increased visibility of retinal capillary bed in early phase of FFA. In angiography, as well as occluded capillaries, adjacent capillary areas to these areas appear to be distinct. Diffuse diabetic macular edema is unlikely to regress spontaneously. Early detection and treatment of diabetic macular edema may improve recovery and stabilization of vision.^{9,19,20}

2.2. Classification of Diabetic Retinopathy

Diabetic retinopathy is evaluated in two subgroups as non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). While the lesions are only limited in the retina in NPDR, the lesions extend outside of the retina in PDR.²¹

2.2.1. Non-Proliferative Diabetic Retinopathy

It is classified into 4 sub-categories according to the severity of clinical findings.²¹

1- Mild NPDR

Retinopathy is the initial period. Microaneurysms and a small number of small retinal hemorrhages are seen. The risk of development of PDR within one year is 5% and 15% within 5 years.

2- Moderate NPDR

The number of microaneurysms and / or retinal haemorrhage is increased and is widely available in at least one quadrant. Soft

exudates, venous nodules and intraretinal microvascular anomalies (IRMA) have begun to occur. The risk of development of PDR within one year is 12-27%, 33% within 5 years.

3-Severe NPDR

Microaneurysms, retinal hemorrhages, venous changes and IRMA are dominant in the picture. Soft exudates are also detected. Hemorrhages and microaneurysms in all retinal quadrants, venous calibration changes in at least two retinal quadrants, IRMA in at least one retinal quadrant are detectable. The risk of development of PDR within one year is 52%, 60% within 5 years.

4- Very Severe NPDR

It is the more common and more severe form of severe NPDR. Common arteriolar occlusions, soft exudates, venous changes and especially increase in IRMA intensity and width are seen. The risk of development of PDR within one year is 75%.

2.2.2. Proliferative Diabetic Retinopathy

The pathologic events have gone beyond the retina in this type of diabetic retinopathy. Neovascularization, the main finding of the PDR, is located on the retina surface, especially along the upper and lower arches and on the optic disc. Neovascularization advances between the retina and the internal limiting membrane and then penetrates the internal limiting membrane into the vitreous cavity. It is clinically examined in two phases.²¹

1. Early Stage PDR

It is characterized by neovascularizations on the retinal surface and preretinal hemorrhages arising from them. Fluorescein angiography has hyperfluorescence sites associated with wide ischemic areas and neovascularizations.

2. High-risk PDR

On the retinal surface, neovascularization proceeded into the vitreous. In addition, there is prominent fibrous tissue proliferation. Localized tractional detachments, severe preretinal hemorrhages, and vitreous hemorrhages are associated with optic disc neovascularization. Fluorescein angiography shows extensive ischemic areas and hyperfluorescence areas due to neovascularization and fibrous proliferation.

3. DIABETIC RETINOPATHY TREATMENT

Currently, there is no proven pharmacological treatment that can be used in the treatment or prevention of diabetic retinopathy.

Regulation of blood glucose levels and metabolic control, and photocoagulation and intravitreal medicines when necessary are effective methods. Regular screening of diabetic patients and early treatment have been shown to reduce the risk of severe vision loss. Diabetes mellitus should be examined with contact or non-contact lenses by dilating the pupil once a year until retinopathy develops. Patients with maculopathy or retinopathy should be monitored more closely by fluorescein angiography.

3.1. Control of Blood Glucose Levels and Systemic Factors

In mild NPDR, blood glucose regulation and metabolic control, and monitoring of patients at regular intervals are often sufficient. It has been reported that severe glucose control slows down DR progression in both type 1 and type 2 diabetic patients. Therefore, blood glucose levels and HbA1c follow-up and control are very important in DR patients. Control of blood pressure in HT patients has been shown to slow the progression of the DR and reduce vision loss. High blood lipid levels have been reported in diabetic patients with diffuse macular edema and severe exudates. Therefore, blood lipid control is important in the progression of DR. In addition, the control of cardiovascular disease and diabetic nephropathy is important to slow down the progression of DR.⁹

Aspirin use has been tried due to the increased role of platelet adhesiveness in the pathogenesis of diabetic retinopathy, but beneficial effects were not found on nonproliferative or proliferative diabetic retinopathy. Although aspirin has no place in the treatment of diabetic retinopathy, there is no obstacle for diabetic patients to use aspirin for other reasons.⁶

3.2. Retinal Laser Photocoagulation

Photocoagulation is a devastating type of treatment where light energy is absorbed into the target cells and turned into heat and irreversible thermal denaturation occurs. Burning of the ischemic areas in the retina is the main objective. When the outer retina layers are destroyed with laser photocoagulation, the oxygen requirement of the retina decreases and the reduced oxygen supply from the damaged vessels to the retina gets sufficient. In this way, VEGF release from ischemic tissues stimulating neovascularization is reduced and perfusion of the functional areas is increased. Argon laser is often used. It has been shown that retinal laser therapy can prevent 95% of legal blindness due to diabetic retinopathy during randomized studies.²² The results of the ETDRS study show that focal laser application of diabetic macular edema is beneficial.²³ Good timing in laser treatment and regular follow-up after treatment

are important. Laser therapy has not helped to recover lost sight. Therefore, regular screening examination; is important for the detection of diabetic retinopathy in the period of asymptomatic vision threat.

3.2.1. Macular Edema Laser Treatment

In the laser treatment of this type of maculopathy, the microaneurysm and dilated capillary vessels causing the leakage should be closed. Laser photocoagulation should be performed to microangiopathy that is located in the circinated retinopathy. Green argon and yellow dye lasers, which are absorbed by hemoglobin but not absorbed by the xanthophyll pigment in the macula, should be preferred.²⁴ Usually a spot diameter of 50-100 microns is used. In focal diabetic macular edema, the exudates are removed by macrophages within a few months after laser treatment, they can be lost for 5-6 months. Therefore, the success of the treatment is followed by decrease retinal thickness, not followed by disappearance of hard exudates.²⁵ Grid laser is used for diffuse macular edema. The goal is to stimulate retinal cells to increase fluid transport through the retina. Both focal and grid laser photocoagulation can be applied in combination for the same case. Focal or grid laser therapy, which can be applied as a first-line treatment for macular edema, is now often combined with intravitreal anti-VEGF or steroid treatments. The laser treatment is often added to the medical treatment if these medications are not responded or if insufficient response received from them.⁹

3.2.2. Severe NPDR Laser Therapy

Common blot-dot retinal hemorrhages, venules beading, arteriolar and capillary obstruction, intraretinal microvascular abnormal vessels and exudates are signs of severe ischemia in the retina. In these cases, that is to say in the pre-proliferative phase, laser photocoagulation should be performed after the findings of fluorescein angiography reflecting the recent state are seen. Panretinal light coagulation prevents both retinal ischemia and development of neovascularization and reduces the risk of anterior segment neovascularization. Green argon and red krypton laser are used at 200mW power, 200-500 micron spot diameter and 0.2-0.5 second. After the panretinal light coagulation is performed, the vessels expansion and retinopathy progression is stopped. However, in some cases, progression of retinopathy may occur again months later. In these cases vitreous contraction and posterior vitreous detachment accompany the table. For this reason, the presence of posterior vitreous detachment during photocoagulation of

preproliferative retinopathy suggests that retinopathy may have a better progress.²⁶

3.2.3. PDR Laser Therapy

When the outer retina layers, especially photoreceptors, are destroyed with argon laser, the oxygen requirement of the retina decreases and the reduced oxygen supply from the damaged vessels to the retina gets sufficient. In this way VEGF inhibition occurs and neovascularization is prevented. It is reported that impaired autoregulation in the retinal vessels has been improved and oxygen delivery to retina has been increased after photocoagulation.¹²

3.3. Medical Treatment

Intravitreal steroids and anti-VEGF agents are the most common medical treatments in DR. These treatments are often used in diabetic macular edema. Intravitreal steroids may be injected or implanted. The most common use of intravitreal steroids was triamcinolone acetonide earlier, but dexamethasone implant is now. Complications of steroid drugs such as glaucoma, cataracts and endophthalmitis limit the use of these drugs. In dexamethasone implant, these risks are lower, especially the risk of glaucoma, compared with triamcinolone acetonide. Because of the antiproliferative, anti-edematous, anti-inflammatory and angiostatic effects of the steroids, it is used in macular edema and its effect lasts for about 3-6 months. Another medical treatment is intravitreal administration of anti-VEGF drugs, which are now being used more widely. The vascular endothelial growth factor (VEGF) is produced in response to hypoxia from capillary loss and / or microaneurysm formation. VEGF binds to specific receptors in vascular endothelial cells to increase vascular permeability. Clinically applied anti-VEGF agents include bevacizumab, ranibizumab and aflibercept. They can be combined with macular laser therapy. Anti-VEGF therapy may play an important role in the prevention of PDR.^{9,12}

3.4. Surgical Treatment

Vitreous contraction is a late complication of proliferative diabetic retinopathy. This leads to vision loss by tractional detachment which includes macula and intravitreal hemorrhage. According to the results of the diabetic retinopathy vitrectomy study group; successful results have been obtained with vitrectomy treatment with appropriate timing in eyes with uncleared vitreous hemorrhage or tractional retinal detachment. Photocoagulation therapy, which can not be performed due to vitreous haemorrhage or detachment, can also be performed simultaneously with vitrectomy.^{9,12}

4. CONCLUSION

Diabetic retinopathy is one of the most important causes of preventable blindness worldwide. Although there have been many studies to understand the pathogenesis of diabetic retinopathy, it has not been fully elucidated. However, good blood glucose regulation and control of other systemic factors such as hypertension and hyperlipidemia are very important in stopping the progression of the disease. Despite all the advances in the treatment of diabetic retinopathy, there is no treatment yet that removes retinopathy and leads to sequel-free recovery. Nevertheless, current treatment modalities can prevent legal blindness and allow patients to continue their lives with a level of acceptable vision.

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