The Role of Diabetic Retinopathy Pathogenesis in Diabetic Retinopathy Therapy
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ABSTRACT
Introduction: The estimation of diabetes mellitus (DM) patients nowadays are 486 million people. Diabetic retinopathy (DR) serves as one of the most common microvascular disease complications. About 2.6 million people with DM are suffered from visual disturbance. The pathogenesis of DR consists of several mechanisms. These mechanisms are the basics of the DR standard therapies. This review is conducted to observe the pathogenesis of diabetic retinopathy related to the treatment that existed through current literature.

Methods: An online literature search was conducted in PubMed for relevant publications between 2011 and 2021 by combining the following search terms: retina, diabetic retinopathy, pathogenesis, hyperglycemia, oxidative stress, and management.

Results: Retinal neurodegeneration consists of several steps that cause ROS elevation. Retinal microvasculopathy causes increase microvasculature. Chronic inflammation cause progressive damage to the retina. Based on diabetic retinopathy pathogenesis, the therapy includes pharmacological and nonpharmacological treatment. Pharmacological treatment aims to reduce blood glucose and progress through anti-VEGF and anti-inflammatory drugs. Non-pharmacological treatment is the option to treat severe DR and acts as conjunctive therapy towards pharmacological therapy.

Conclusions: Based on the current literature, it can be concluded that the pathogenesis of diabetic retinopathy plays an important role in the DR therapy that already existed, especially in the microvasculopathy and inflammation stage.

Keywords: hyperglycemia, diabetic retinopathy, pathogenesis, treatment

INTRODUCTION
Diabetes prevalence is a major public health concern. Since 1980 age-standardized diabetes mellitus (DM) prevalence has increased by over 110% in men and 58% in women older than 45 years old, reaching, respectively, 9% and 7.9% global prevalence in 2014.1 Such an alarmingly high increasing rate, coupled with population growth and aging, has led to a near quadrupling of the number of adults with diabetes worldwide who are now estimated to be 422 million and projected to rise to 629 million by 2045. The highest DM burden is concentrated in low-income and middle-income countries.1

Diabetic eye disease, resulting from chronic high blood glucose levels causing damage to the retinal capillaries, is the most common microvascular complication of DM and includes diabetic retinopathy (DR) and diabetic macular edema (DME).1 Wisconsin Epidemiology Study of Diabetic Retinopathy (WESDR) reports 99% of patients with Type 1 DM and 60% of patients with type 2 DM will have diabetic retinopathy within 20 years. Proliferative RD occurs in 50% of patients with type 1 DM in 15 years.1

With the increasing global incidence of diabetes mellitus (DM) in both developed and developing countries, diabetic retinopathy (DR) has likewise increased in prevalence. Recent estimates suggest that approximately 486 million people worldwide have DM and that roughly one-third demonstrate evidence of DR, including diabetic macular edema (DME).1 In the working adult population, DR remains a major cause of blindness in the
US, causing 12,000–24,000 new cases each year. DR is the leading cause of vision loss in working-age adults; two recent meta-analysis pooling data from, respectively, 2437 and 2888 population-based studies estimated the global burden of visual impairment and blindness attributable to DR, reporting that in 2015 2.6 million people were visually impaired because of DR.\(^1\)^\(^2\)

Riset kesehatan dasar (RISKESDAS) 2013 found around 6.9% of the Indonesian population who are over 15 years old suffer from DM and Cipto Mangunkusumo Hospital Jakarta recorded the second percentage of complications most common after neuropathy is retinopathy. Other study conducted by Sasonko et al reported that the prevalence of DR in Indonesia was 43.1%, while the prevalence of visual threatening diabetic retinopathy was 26.3%.\(^3\) This shows that diabetic retinopathy is still one of the nation's health concerns.

The current study aims to carry out a systematic review to summarize the current pathogenesis and treatment of diabetic retinopathy. These data will hopefully contribute to reducing DR morbidity and mortality.

**METHODS**

We conducted the online literature search in PubMed for relevant publications between 2011 and 2021 by combining the following terms: retina, diabetic retinopathy, pathogenesis, hyperglycemia, oxidative stress, and management. We found 100 articles according to the keywords, then, we exclude 80 similar articles and which did not accompanied with abstract. We also excluded 19 articles which published more than 10 years and selected only the articles written in English language. According to critical review, we exclude 6 articles which did not match to our topics, and include 15 articles for further review.

![Figure 1. Literature selection diagram](image)

**RESULT**

Structure and Function of the Retina

The retina consists of several structures that are used to convert light energy to form a three-dimensional image.\(^4\) The retina is the innermost structure. It is formed from a structure with the highest metabolic function compared to other tissues in the...
human body. Cells in the retina have more oxygen requirements than other tissues. The retina is composed of six types of cells spread over 10 different layers. Each cell functions to continue the stimulus. The retina covers the entire posterior part of the eye. The area of the optic nerve is the only part of the retina that extends anteriorly to around the ora Serrata. The retina is composed of ten layers of nerves connected by synapses. These ten layers consist of three types of cell types, namely photoreceptor cells, neuronal cells, and glial cells. The retinal layers starting from the most superficial layer to the most caudal layer consist of the inner limiting membrane, nerve fiber layer (NFL), ganglion cell layer, inner plexiform layer, inner nuclear layer, middle limiting membrane, outer plexiform layer, outer nuclear layer, external limiting membrane, and rods & cones layer. The histology of retina are available in figure below.

Figure 2. Histology of the retina (available from: Mahabadi et. al)

The retina receives its blood supply from two sources, the choroid and the ophthalmic artery. Branches of the ophthalmic artery provide blood supply to the macula and posterior uveal tract. Blood flow to the retina remains stable influenced by intraocular pressure, systemic blood pressure, and sympathetic autoregulation. Several factors that can affect perfusion through the ophthalmic artery in the retina include nitric oxide, prostaglandins, and endothelin. In addition to the ophthalmic artery, the choroid is another structure that contributes to the retina's blood supply. The choroid is a structure in the posterior part of the uveal tract. The choroid serves to provide blood supply to the outer layer of the retina. The choroid receives its blood supply from the posterior ciliary artery. The inner retinal layer is very sensitive to hypoxia conditions, while the outer retina has a better ability to withstand hypoxia and cell stress environments.

The nervous system of the retina originates from the optic nerve. The optic nerve then continues through the optic stalks to the optic chiasm, lateral geniculate nucleus, and the visual cortex in the posterior occiput.

Diabetic Retinopathy Definition, Epidemiology and Risk Factor

Diabetic retinopathy is one of the complications in patients with diabetes mellitus which is characterized by vision-threatening damage to the retina to blindness. Diabetic retinopathy is one of the most common complications of microvascular disease in people with diabetes mellitus, especially in the elderly population. Diabetic retinopathy is considered as one of the health-associated economic burdens. Duh et al. states that the prevalence of diabetic retinopathy is relatively high. According to the survey conducted in the United States showed that the prevalence of diabetic retinopathy between 1990-2010 showed that cases of visual impairment and blindness associated with diabetic retinopathy increased by 64% and 27%, respectively. The number of diabetic retinopathy patients is expected to be increased over time. According to study conducted by Shukla et al, several countries have been estimated the prevalence of diabetic retinopathy in the future, for example, the United States with an estimated 16 million diabetic retinopathy sufferers in 2050.
Assessment of risk factors is important in patients with diabetes mellitus to prevent complications such as diabetic retinopathy. Diabetic retinopathy is often detected in undiagnosed individuals with diabetes mellitus. Uncontrolled blood glucose level in people with diabetes mellitus is known as a major risk factor for diabetic retinopathy. Several comorbid conditions such as hypertension, dyslipidemia, male sex, and obesity can increase the risk of diabetic retinopathy in people with diabetes mellitus up to 10%. Diabetic Retinopathy Pathophysiology

Retinal neurodegeneration

Retinal neurodegeneration is an early stage of diabetic retinopathy. Wang et al states that this stage is related to neuronal cell apoptosis due to an increase in caspase-3, Bax, and Fas as pro-apoptotic molecules. Wang et al also states that pro-apoptotic protein expression in mitochondria such as cytochrome c and apoptosis-inducing factor (AIP) is also known to be increased in diabetic retinopathy patients. Damage to mitochondria causes the formation of reactive oxygen species (ROS) significantly.

According to Dehdashtian et al article, increased levels of ROS can be caused by other mechanisms. Retinal ischemia and chronic hyperglycemia cause increased expression of NADPH oxidase (Nox) 2 and Nox 4. Decreased levels of antioxidant enzymes such as superoxide dismutase, glutathione reductase, glutathione peroxidase, and catalase were also found in people with diabetes mellitus. Both of these mechanisms also play an important role in increasing ROS. Increased ROS causes mitochondrial dysfunction so that it disrupts the membrane potential of the mitochondria as well as damages mitochondrial DNA. Mitochondria are the site of adenosine triphosphate (ATP) formation, so mitochondrial damage causes a decrease in ATP production. The decrease in ATP causes an increase in mitochondrial membrane permeability and the release of apoptotic factors such as cytochrome c from the mitochondria to the cytoplasm.

Reactive oxygen species can activate the transcription factor nuclear factor B (NF-κB) thereby increasing levels of nitric oxide (NO) and proinflammatory cytokines. These two substances trigger an increase in VEGF expression as well as metabolic pathways such as the hexosamine pathway, polyol pathway, formation of the advanced glycation end product (AGE), protein kinase C (PKC) pathway, and p38 MAPK pathway.

A. P38 MAPK Pathway

P38 is a type of mitogen-activated protein kinase (MAPK). This enzyme is activated in response to stress, lipopolysaccharide, TNF, platelet-activating factor, interleukin-1, and in response to ischemia. Kang et al. states that activation of the p38 enzyme causes nuclear transposition followed by activation of protein kinases and transcription factors such as NF-κB and SHP-1. Both substances are able to inhibit platelet-derived growth factor (PDGF) and stimulate caspase activation, causing pericyte damage.

B. Polyol Pathway

The polyol pathway is often referred to as the sorbitol-aldose reductase pathway. This process involves the enzyme aldose reductase to catalyze the reduction of glucose to sorbitol and the enzyme sorbitol dehydrogenase to convert sorbitol to form fructose through an oxidation process. Both reactions require nicotinamide adenine dinucleotide phosphate (NADPH) and nicotinamide adenine dinucleotide (NAD+). Hyperglycemia conditions cause an increase in the polyol pathway following the decrease of NADPH levels. NADPH is required for the formation of intracellular antioxidants. Kang et al also states that the reduction of NADPH levels increased ROS.
formation and caused oxidative stress environment. Accumulation of sorbitol and fructose in cells causes an increase in osmotic pressure, edema in cells, and damage to cell membranes. Both substances cause the reduction of NAD+ to NADH due to an imbalance in the redox reaction, increased intracellular NADH, cell edema, changes in retinal structure, and microvascular lesions that interfere with retinal function.

C. Hesoxamine pathway

The fructose formation in the polyol pathway will undergo a process of phosphorylation to form fructose-6-phosphate. The addition of a glutamine molecule catalyzed by the enzyme fructose-6-phosphate amidotransferase (GFAT) causes the conversion of fructose-6-phosphate to glucosamine 6-phosphate. Glucosamine is converted to glucosamine 6-phosphate and catalyzed by hexokinase enzyme, then it is converted to UDP-GlcNAc. Kang et al concluded that glucosamine increases the production of H2O2 causing oxidative stress, changes in endothelial cells, increased vascular permeability, and angiogenesis.

D. PKC Pathway

Protein kinase C (PKC) is a type of serine kinase. This enzyme is activated by certain stimuli such as hormones, the nervous system, and growth factors. Kang et al states that hyperglycemia conditions cause an increase in the synthesis of diacylglycerol (DAG), this component plays a role in the mechanism of PKC activation in cells. PKC can increase the activity of NADPH oxidase thereby increasing the production of ROS in cells, including endothelial cells, muscle cells, pericytes, and mesangial cells. This process causes the increase of oxidative stress and aggravates apoptosis.

E. Accumulation of Advanced Glycation End Products (AGEs)

Chronic hyperglycemia also causes a series of non-enzymatic processes in the human body. Nonenzymatic processes can occur in other macromolecules. Hyperglycemia causes glucose to react with other macromolecules such as proteins and lipids, causing the formation of intermediate products with stable properties with the main component being a carbon component. This product can be overhauled through a series of oxidation and dehydration processes to form advanced glycation end products (AGEs). Several types of AGEs have been studied, but according to Kang et al carboxymethyl lysine (CML) is one of the most detectable AGEs in retinal blood vessels.

The nonenzymatic reaction between glucose, protein structures, and other amino acids can change the protein structure. The pathogenesis of microvascular disease in patients with diabetic retinopathy also involves AGEs. The interaction between AGEs and protein structures in blood vessels such as elastin and collagen causes stiffness in blood vessels. AGEs bind to receptors for AGEs (RAGE) on the cell surface. The binding between AGE and RAGE stimulates NF-B activation and causes pericyte apoptosis. Activation of NF-B also causes an increase in VEGF thereby increasing vascular permeability.

Retinal microvasculopathy

Diabetic retinopathy is one of the microvascular diseases following complications of diabetes mellitus. Chronic hyperglycemia state is known to play important role in the pathogenesis of diabetic retinopathy. Microvascular disease mechanisms in diabetic retinopathy include the polyol pathway, accumulation of advanced glycation end products (AGE), protein kinase C pathway,
and the hexosamine pathway. Wang et al stated that hyperglycemia causes changes in blood flow and the elasticity of blood vessels as the compensatory mechanism. Damage to the pericyte followed by apoptosis of the pericyte is an early stage in the pathogenesis of diabetic retinopathy. Damage to the pericyte occurs progressively, causing localized loss of vascular elasticity and triggering the formation of microaneurysms. This process is followed by apoptosis in endothelial cells and the thickening of the basement membrane. Chronic progression of these mechanisms causes blockage of the capillary blood vessels resulting in ischemia of the retina. The compensatory mechanism following ischemia of the retina is the activation of hypoxia-inducible factor-1 (HIF-1) to increase levels of vascular endothelial growth factor (VEGF). The role of VEGF as an angiogenic factor triggers the proliferation of endothelial cells. Increased vascular permeability is known to occur due to other angiogenic factors such as Ang-1 and Ang-2. Both of these factors interact with endothelial receptor tyrosine kinase, causing vascular leakage in diabetic retinopathy patients. Increased VEGF stimulates the release of endothelial progenitor cells (EPCs) from the bone marrow to the retina, then stimulates the release of stem cell factor (SCF) causing neovascularization.

**Inflammation**

The microvascular disease causes impairment of the blood-retina barrier and damage to endothelial cells. These mechanisms are followed by an increase in the number of leukocytes. Dehdastian et al said that the immune system will be activated through recognition of endogenous stress signals called damage-associated molecular patterns (DAMPs). These molecules interact with tool-like receptors (TLRs) thereby activating nuclear factor B (NF-κB) and mitogen-activated protein kinase (MAPK) resulting in the continuous release of cytokines. Leukocytes adhere to endothelial cells through the role of adhesion molecules. Several types of adhesion molecules include intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and selectins (E-selectin). Several studies such as Wu et al, Kang et al, and Shukla et al have shown that adhesion molecules increase in people with diabetes mellitus. The attachment of leukocytes to endothelial cells progressively causes leukostasis. Leukostasis plays a role in the mechanism of endothelium damage and damage to the blood-retinal barrier through the Fas-ligand pathway.

Retinal ischemia triggers the release of other mediators such as chemokines. Wang et al states that chemokines, especially monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein 1α (MIP-1α), and macrophage inflammatory protein 1β (MIP-1β), cause monocyte recruitment through the chemotaxis process. Other mediators such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, IL-6, and IL-8 are also pre-regulated and play a role in diabetic pathogenesis according to Wang et al. Periodic release of mediators causes a chronic inflammatory response causing tissue damage and triggering a program of cell death. At a certain stage, the capillaries and the blood-retinal barrier will be progressively damaged. The pathogenesis of diabetic retinopathy is summarized on figure 3.
Diabetic Retinopathy Classification

The International Clinical Disease Severity Scale (ICDSS) for diabetic retinopathy has been published through a meeting of experts based on the aim of simplifying the differences between each diabetic retinopathy stage. Staurenghi et al had been reviewed the classification of DR based on ICDSS. This classification divides diabetic retinopathy into five stages. The first stage found no abnormalities in the fundus. The second stage, called mild non-proliferative diabetic retinopathy (NPDR), is characterized by the presence of microaneurysms. The third stage, called moderate NPDR, is characterized by the presence of a microaneurysm, internal hemorrhage, or venous bleeding. The fourth stage is called severe non-proliferative diabetic retinopathy. At this stage, the criteria can be determined through the appearance of internal hemorrhage, and venous bleeding with the 4:2:1 formula on the standard photograph. A 4:2:1 formula means four or more quadrants of internal hemorrhages (Figure 4A), two or more venous bleeding (Figure 4B), or 1 or more intraretinal microvascular abnormalities (Figure 4C).

The fifth stage is called proliferative diabetic retinopathy (PDR). This stage is characterized by neovascularization of the optic disc, retina, iris, and angle. This stage may also be accompanied by vitreous hemorrhage or retinal detachment. This stage can be divided according to the severity of the image following macular edema. Mild diabetic macular edema is characterized by hard exudates located far from the center of the fovea (Figure 5A). Moderate diabetic macular edema is characterized by hard exudate surrounding the center of the fovea without thickening of the center of the fovea (Figure 5B). Severe diabetic macular edema is characterized by the presence of hard exudate and thickening of the center of the fovea (Figure 5C).
Diabetic Retinopathy Therapy

Recent studies have evaluated the pharmacological, laser, and surgical therapeutic strategies for the treatment and prevention of DR and DME. Based on article by Mansour et al pharmacological therapies for both DR and DME include both systemic and ocular agents. Systemic agents that promote intensive glycemic control, control of dyslipidemia, and antagonists of the renin-angiotensin system demonstrate beneficial effects for both DR and DME. Ocular therapies include anti-VEGF agents, corticosteroids, and nonsteroidal anti-inflammatory drugs. Laser therapy, both as panretinal and focal or grid applications continues to be employed in the management of DR and DME. Recent attempts to lessen the burden of anti-VEGF injections by integrating laser therapy have met with mixed results. Increasingly, vitreoretinal surgical techniques are employed for less advanced stages of DR and DME.²

**Pharmacological therapy**

**A. Systemic pharmacological therapy**

The basis for the medical management of diabetic retinopathy consists of intensive medical control of blood glucose, blood pressure, and blood lipids.² The UK Prospective Diabetes Study in Type II diabetes also states for every 1% decrease in hemoglobin A1C, there was a 35% reduction in the risk of microvascular complications.² Newer adjunctive therapies such as Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are increasingly being employed to better regulate serum glucose fluctuations in DM and also appear to confer some benefit in severity reduction of DR.²

The Actions to Control Cardiovascular Risk in Diabetes (ACCORD) Study showed that intensive glycemic control, control of dyslipidemia with fenofibrate, and simvastatin reduced the proportion of eyes that had progression of retinopathy by one-third. Intensive blood pressure control did not have a statistically significant effect. Over four years, the progression of retinopathy was reduced by 40% in the fenofibrate group.¹² Simultaneous with the ACCORD study, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study concluded that a potential therapeutic role existed for fenofibrate in the prevention of retinopathy alongside intensive management of hyperglycemia and high blood pressure. Studies with statins and their role in delaying the onset and severity of DR have yielded similar results to those obtained with the fibrates.²

**B. Ocular pharmacological therapy**

*Anti-VEGF*
VEGF is also an important link between the neurodegenerative process that occurs in the early stages of diabetic retinopathy, including angiogenesis and the BRB breakdown. This might be the reason anti-VEGF considered as one of the DR therapy recently. Current evidence indicates that three anti-VEGF agents could be useful for diabetic retinopathy, bevacizumab, ranibizumab, and aflibercept. Recent clinical trials with anti-VEGF therapies have demonstrated significantly improved visual acuity for patients suffering from DME, ranibizumab being the most thoroughly tested. A prospective, randomized, comparative effectiveness trial of bevacizumab, ranibizumab, and aflibercept showed no difference in efficacy of the three drugs in eyes with center-involved DME and VA of 20/40 or better at one or two years of follow-up. However, in eyes with VA of 20/50 or worse, aflibercept was superior to ranibizumab and bevacizumab at one year, whereas at two years aflibercept was no longer superior to ranibizumab, but remained superior to bevacizumab. Approaches aimed at increasing the intravitreal concentration of anti-VEGF agents have not proved beneficial. The READ-3 clinical trial examining two doses of ranibizumab (0.5 and 2.0 mg) in DME showed that at 1 year there were no significant differences between the two groups. Intravitreal ranibizumab injections given monthly for DME increase the proportion of 2 or 3 step improvement in the severity of diabetic retinopathy, reduce the proportion of eyes with 2 or 3 steps worsening in severity of diabetic retinopathy, and reduce the proportion of eyes progressing to proliferative diabetic retinopathy. Anti-inflammatory agent Typical clinical signs of DR, such as edema and neovascularization, are hallmarks of inflammation and suggest a possible role of inflammation in the pathology. The potential role of inflammatory mediators in DR has been supported by extensive evidence in the past two decades. The increase in neutrophils was found to correlate with upregulation of ICAM-1 immunoreactivity in the vessels. Triamcinolone, dexamethasone, and fluocinolone have been used in many forms, including particulate suspensions, viscoelastic mixtures, and solid slow-release devices. Topical difluprednate for persistent DME has demonstrated short-term improvement in both VA and reduction in macular thickness, but this has been accompanied by an incidence of approximately 20% increase in intraocular pressure. Nonsteroidal anti-inflammatory drugs (NSAIDs) for DME have not been studied in-depth, but available investigations suggest that they have little role in its management. One small randomized trial used intravitreal diclofenac 500 µg in one of the treatment arms for patients with DME. DME improved, but VA did not. In another small case series, there was no effect on macular edema or VA. Non-pharmacological treatment A. Laser therapy Laser photocoagulation elevates the temperature of retinal and choroidal tissues, resulting in necrosis and scars thus sealing leaking vessels in these tissues. It is currently the principal treatment for severe DR, such as diabetic macular edema and proliferative DR. It can be applied as a focal, grid, and panretinal treatment, depending on the lesions to be treated. In general, focal treatment is indicated to coagulate vascular leakage through a series of local burns, while grid laser treatment is employed in regions of diffuse leakage due to the breakdown of the blood-retinal barrier (BRB). Intense panretinal photocoagulation (PRP) is aimed at the regression of existing new vessels and preventing the onset of newly
formed ones, therefore it is indicated for treating proliferative DR.\textsuperscript{2}

Recent studies state that there was a little short-term benefit in combining prompt macular laser with anti-VEGF therapy for center-involved DME.\textsuperscript{2} However in that same protocol, patients who were treated with deferred laser therapy achieved the best outcome in terms of sustained visual improvement. Preliminary data examining widefield targeted PRP in conjunction with intravitreal ranibizumab for DME, have demonstrated no significant reduction in the frequency of PRN injections.\textsuperscript{2} Combination therapy with intravitreal corticosteroids has likewise yielded mixed results in terms of both VA stabilization or improvement and reduction in overall treatment burden.\textsuperscript{2}

B. Surgery
Surgery for late complications of proliferative diabetic retinopathy remains the cornerstone of management even in patients who have received optimal laser photocoagulation and medical therapy.\textsuperscript{6} Currently, vitrectomy continues to play a critical role in the management of certain scenarios in DR. With improvisation in the surgical techniques and development of micro-incision surgical techniques for vitrectomy, the indications for surgical intervention are expanding to include diabetic macular edema with a greater number of patients undergoing early intervention.\textsuperscript{6} The indications of surgery include: vitreous hemorrhage, tractional retinal detachment, combined tractional and rhegmatogenous retinal detachment, pre-macular hemorrhage, and diabetic macular edema.\textsuperscript{6,16} Pretreatment with intravitreal anti-VEGF, 3-4 days before surgery helps in reducing intraoperative bleeding, thus facilitating fibrovascular membrane peeling. It is also reported to reduce postoperative vitreous hemorrhage.\textsuperscript{2,6,16}

DISCUSSION
Pathogenesis of Diabetic retinopathy consists of several mechanism as the results of hyperglycemia condition. Hyperglycemia is a major cause of retinal neurodegeneration. Based on this statement, it can be concluded that reducing blood sugar levels is very crucial as the target therapy for treating and preventing diabetic retinopathy. This also include the supportive therapies such as lowering cholesterol levels to prevent gluconeogenesis as the part of hyperglycemia pathway in type 2 diabetes. According the literature conducted by Mansour et al, Simo et al, and Zhang et al, Pharmacological therapy also includes ocular therapy consisting of anti-VEGF, corticosteroids, and NSAIDs. VEGF is one of the mediators in retinal vasculopathy. Study conducted by Simo et al shown that anti-VEGF is known to affect increasing visual acuity in patients with DME. Diabetic retinopathy also involves a chronic inflammatory process in the retina. This statement is the main reason for giving corticosteroids or NSAIDs to patients with DME according to Mansour et al and Zhang et al. In the severe stage of DR, a combination of pharmacological therapy with more advanced therapy is required. Laser therapy is the main option in patients with severe DR. For sealing leaking vessels in DME and PDR. Shukla et al states that PDR with advanced complications is best treated with vitrectomy preceded by anti-VEGF pretreatment as the best option.

CONCLUSION
Diabetic retinopathy occurs following several mechanisms, retinal neurodegeneration, retinal microvasculopathy, and inflammation. Retinal neurodegeneration consists of several steps that cause ROS to be increased. Retinal microvasculopathy causes increase microvasculature. Chronic
inflammation progressively damaged the retina. The DR therapy related to the pathogenesis includes pharmacological and nonpharmacological treatment. Pharmacological treatment is aimed to reduce blood glucose and reduce the progress through anti-VEGF and anti-inflammatory drugs, while non-pharmacological treatment act as conjunctive therapy towards pharmacological therapy.

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