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# **Optic Nerve Changes in Diabetic Retinopathy**

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http://dx.doi.org/10.5772/intechopen.81221

#### Abstract

Diabetic retinopathy (DR) is a devastating sight-threatening complication of diabetes mellitus (DM). Besides damaging the vascular system of the retina, DM will also destruct the tissue surrounding the retina, including the optic nerve. DR impairs the optic nerve by damaging its conduction and integrity. There are few clinical manifestations of optic nerve changes in DR such as diabetic papillopathy, neovascularization of optic disc, and optic nerve atrophy. These involve metabolic alterations related to DM, production of advanced glycation end products (AGEs), oxidative stress, and hemodynamic changes. Diagnostic tests including visual evoked potential (VEP) and optical coherence tomography (OCT) can detect functional and structural changes. This finding is important as it may reflect the early loss of retinal ganglion cell axons. As the neuronal loss is irreversible, it is pivotal to be able to screen these nervous system changes in the early stage of DR and prevent further deterioration.

**Keywords:** diabetes mellitus, diabetic papillopathy, diabetic retinopathy, neovascularization of optic disc, optical coherence tomography, optic nerve, optic atrophy, visual evoked potential

# 1. Introduction

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Diabetic retinopathy (DR), a devastating sight-threatening complication of diabetes mellitus (DM), is one of the most prevalent health diseases worldwide with an incidence of 6.9% [1–3]. The number of people with diabetes is estimated to rise from 171 million in 2000 to 366 million in 2030. A study by Jin et al. in DM type 2 population showed that within 5 years, the cumulative incidence of DR was 46.9% with 13.9% population suffering from severe nonproliferative DR (NPDR) and 4.6% from proliferative DR (PDR). Hence, more people will be at risk of developing DR and in danger of losing their sight [4, 5].

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DM endangers sight by damaging the neurovascular system of the eye, including the optic nerve [6, 7]. The damages include changes in angioarchitecture, blood flow and degenerative loss of neural tissue, morphological changes, changed protein expression, and changed neuro-transmission and neurotransmitters [6–9]. Recently, not so many studies have been conducted to elucidate damage due to DM and DR in the optic nerve and central visual pathway. We hypothesize that optic nerve damage occurs due to few processes in DM. Such processes are metabolic alteration, oxidative stress, and ischemia [10]. These changes could be detected via modalities such as visual evoked potential, biomicroscopy, and fundus photography [11–13]. These changes usually occur after persistent metabolic alterations, which may lead to late detection [2, 14]. Therefore, early detection of optic nerve involvement in DR may be beneficial to provide timely recognition and management for patients at greater risk of DR progression [14].

# 2. Pathophysiology

There are few processes in DR affecting the optic nerve. Such processes are metabolic alterations related to DM, production of advanced glycation end products (AGEs), oxidative stress, and hemodynamic changes. These processes will be discussed in detail below.

#### 2.1. Metabolic alterations

Findings from animal studies suggest that neurodegeneration in DR is caused by both diminished insulin receptor signaling and systemic hyperglycemia [15–17]. Insulin plays an important role, as insulin receptors in the retina stimulate neuronal development, growth, and anabolic synthesis [18, 19]. Therefore, a defect in insulin function either due to a low level of insulin or impaired sensitivity would hamper neuroretinal cells' survival. As diabetes progresses, retinal neurons start to degenerate by apoptosis within weeks after the onset [20, 21]. Metabolic alteration and hormonal factors might affect balance of some mediators including growth factors, cytokines, inflammatory, and adhesion molecules [22]. These alterations result in abnormal capillary permeability, apoptosis of capillary cells, and angiogenesis [23].

Metabolic alteration also damages neural conduction in the postretinal central visual pathway [10]. A recent study in diabetic rats showed that there is reduction of Na<sup>+</sup>/K<sup>+</sup>/ATPase enzyme in the optic nerve [24]. This enzyme is important for maintaining sodium potassium gradient within cells and controls the membrane axon depolarization/repolarization. When impaired, it suggests that the neuronal conduction and integrity are damaged.

#### 2.2. Advanced glycation end products

Hyperglycemia induces reaction of sugar and protein via Maillard reaction and produces advanced glycation end products (AGEs) [25, 26]. AGEs play a huge role in complications of DM as it triggers further oxidative stress and vascular cross-linking and activates pro-inflammatory cytokines [20, 21]. Neriyanuri et al. reported that AGEs were independent predictors of development of DR in addition to blood glucose and glycated hemoglobin [14].

AGEs are long-lasting, irreversible products that can modify blood vessel elasticity [25]. Highlevel AGEs in the optic disc affect elasticity of lamina cribrosa. As the intraocular pressure increases, cribriform plates become unable to bear the strain. This condition may develop into glaucoma in DR [27].

#### 2.3. Oxidative stress

Hyperglycemia stimulates increased flux through the glycolytic and tricarboxylic acid cycle pathways, hence resulting in excessive electrons within mitochondria [28]. These electrons would react with oxygen and form reactive oxygen species (ROS). Since mitochondria as cells' powerhouse also generate ROS on their own, they are also the first ones to be damaged by increased ROS. This results in reduced mitochondrial energy production, later causing loss of cellular and tissue function [29].

Oxidative stress also contributes to neural retinal ganglion cell and optic nerve injury through the impairment of L-glutamate/L-aspartate transporter (GLAST), which increases extracellular accumulation of glutamate and promotes excitotoxicity [30–32]. Glutamate is a neurotransmitter that plays a role in the regulation of neurohormonal activity and is found in high levels in the central nervous system. Upon stimulation of nerve cells, glutamate molecules are released from the glutamatergic synaptic vesicles and cause depolarization of the postsynaptic neuronal membrane, which generates signal. Accumulated glutamate in the synaptic space is then collected by adjacent astrocytes, afterward being broken down into glutamine [21].

In patients with DR, glutamate accumulates in extracellular space due to the following mechanisms: (1) reduction of Müller cell–specific enzyme glutamine synthetase, which converts glutamate to glutamine; (2) decrease in the retinal ability to oxidize glutamate to  $\alpha$ -ketoglutarate; and (3) impairment of glutamate uptake by the glial cells [29]. The accumulation of glutamate results in overactivity of ionotropic glutamate receptors, such as  $\alpha$ -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) and N-methyl-D-aspartate (NMDA) receptors, which later causes uncontrolled intracellular calcium response in postsynaptic neurons and eventually cell death [33, 34]. Recent studies suggest that glutamate excitotoxicity results in apoptotic degenerative lesions [25]. Glutamate toxicity also causes depletion of glutathione, which is an antioxidant, thus contributing to oxidative stress [35].

A recent study in diabetic rats also showed marked increase in oxidative stress level shown by malondialdehyde (MDA) level in the optic nerve and visual cortex. In addition, they also found reduced antioxidant, glutathione (GSH), in both the optic nerve and visual cortex [24]. These results suggest significant oxidative stress in the optic nerve and visual cortex along with impairment in neuronal conduction and integrity. Other studies have also found similar result, showing impaired retrograde and anterograde axonal transport in the optic nerve of diabetic rats along with retinal ganglion cell axonopathy [36, 37]. A study by Sokol et al. showed that when induced with ischemia, myelinated axons degenerated and became disordered [38]. Further changes are swollen and collapsed axons, and by 90th minute, myelin sheaths were fragmented. Joachim et al. found axonal damage and gliosis of the optic nerve after ocular ischemia. Renner et al. found damaged optic nerve in an ischemic rat model. Histologic examination revealed demyelination and subsequent loss of myelin sheaths after ischemia [39]. In addition, they also found marked microglia activation, upregulation of astrocytes, reduction of myelin basic protein and myelin oligodendrocyte glycoprotein (MOG), as well as the reduction in oligodendrocytes [40]. The optic nerve structure was also affected as neurofilament was found to be distorted after 21 days of ischemia/reperfusion induction. Ischemia also seemed to impair neuronal immune system as the study found destroyed astroglia structure, hence leaving the nerve tissue susceptible to insults, i.e., oxidative stress [40].

#### 2.4. Hemodynamic changes

Chronic hyperglycemia damages the retinal blood vessels and causes pericyte loss due to elevated sorbitol level. These result in involution of the vascular changes in microcirculation and loss of normal capillary exchange [12–14]. Microvascular anomalies and chronic inflammation may develop dysfunctional barriers permitting leakage of inflammatory molecules and immune cells from systemic circulation and cause further deterioration of the tissue [12, 41].

Another process that plays a major part in DR is capillary degeneration due to weakness and dilation of capillary walls' saccular outpouching, commonly known as microaneurysms. Rupture of these microaneurysms leads to leakage of endovascular products, including blood [9]. In DR, blood viscosity was significantly higher, thus resulting in reductions in blood flow. Persistent uncorrected blood flow causes chronic mild hypoperfusion, which might lead to ischemia and a rise in waste products [42, 43].

Accumulation of these molecules and cells leads to retinal occlusion, which later progresses into hypoxia [44]. Hypoxia results in upregulation of vascular endothelial growth factor (VEGF) platelet adhesiveness, erythrocyte aggregation, serum lipids, and fibrinolysis [45, 46]. VEGF promotes new blood vessel growth resulting in abnormal neovascularization [47].

# 3. Clinical manifestation

There are few clinical manifestations of optic nerve damage related to DM and DR that can be observed. Those are diabetic papillopathy, neovascularization of optic disc, and optic nerve atrophy [48]. Those will be discussed further below.

#### 3.1. Diabetic papillopathy

#### 3.1.1. Definition

Diabetic papillopathy (DP) is an ocular manifestation of both type 1 and type 2 DM characterized by unilateral or bilateral hyperemic disc swelling with minimal or no optic nerve dysfunction, which generally resolves without medical intervention [49, 50]. Patients with DP are often asymptomatic, but may sometimes experience transient decrease in visual acuity [50]. It is usually self-limiting and tends to resolve over a period of 2–10 months with the average time of 3.7 months, leaving minimal sequelae [51, 52]. Visual acuity generally recovers to better than 20/30 in most patients [53]. DP typically affects young people with type 1 DM, but it has also been reported to occur in elderly patients with type 2 DM. The prevalence of DP in both types of DM is 0.5% and the percentage of DP patients presenting with nonproliferative diabetic retinopathy (NPDR) is higher than in the proliferative diabetic retinopathy (PDR) [49].

#### 3.1.2. Pathophysiology

The pathophysiology of diabetic papillopathy remains poorly understood and several theories have been suggested [49]. Some researchers suggest that DP is a subtype of anterior ischemic optic neuropathy (AION), but there are different features between DP and AION that others argue that it is a completely different pathological process [49, 50]. For instance, DP is an asymptomatic optic disc edema, whereas AION is an acute optic disc infarction [54, 55]. Researchers support the argument that the pathophysiology of DP is distinguishable from AION [50]. A study evaluating fluroangiographic aspects by Brancato et al. showed robust leakage of fluorescein, suggesting that DP is a local nonhypotensive vasculopathy [56]. These findings are supported by Bayraktar et al. and Regillo et al., who showed notable telangiectatic vasculature and fluroangiographic hyperfluorescence [54, 57]. Meanwhile, case studies of AION by Hayreh et al. and Shin et al. demonstrated notable filling defects in fluroangiography [55, 58]. These findings of AION contrast with the hyperfluorescence that has been noted in cases of DP.

In patients with DP, the degree of DR tends to be mild. Regillo et al. observed that DP might be a separate entity rather than extension of DR [57]. Otherwise, a case series by Ostri et al. reported that three out of four patients with DP who already had DR before proceeded to develop high-risk PDR. This condition is called "early worsening phenomenon of DR " where progression of retinopathy and papillopathy was accelerated, while adaptation was remarkably slow in the very first year [59]. Bayraktar et al. also reported two cases of nonproliferative diabetic retinopathy (NPDR), which later on were also diagnosed as having DP. A 3-month follow-up showed that retinopathy worsened and developed into proliferative diabetic retinopathy (PDR) [54]. Lubow et al. found that two of three patients with DP subsequently developed PDR and vitreous hemorrhage [60]. Hayreh et al. reported similar findings and observed three patients with DP, who later on were also diagnosed as having PDR [55]. Hence, DP should be considered as a risk factor for progression to PDR and patients should be observed closely taking into account this possibility [54].

Early DP study by Appen et al. hypothesized that DP patients sustain a local vasculopathy of the optic disc, presumably in relation to diabetes [61]. This vasculopathy induces transient leakage of fluid, which results in disc edema. The authors also suggest that the presence of edema causes axoplasmic flow turmoil. An earlier study by Freund et al. showed that prolonged hyperglycemia and anoxia due to the failure of glucose utilization cause damages to the optic nerve [62]. Recent study by Slagle et al. suggested that clinically visible interstitial edema of the optic nerve head due to vascular hyperpermeability initiates the pathology of DP [50].

Slagle et al. elucidate that tissue perfusion depends on two main factors: (1) the ability of the blood to reach the tissue through patent vessels and (2) the dispersion of nutrients to the tissue via fluid movement through the capillary bed. There are four primary forces that determine perfusion: (1) capillary pressure, (2) interstitial fluid pressure, (3) plasma colloid osmotic pressure,

and (4) interstitial fluid colloid osmotic pressure [50]. The authors hypothesized that impairment in the transportation and reabsorption of fluid through the capillary walls causes capillary vasostatic perfusion pathology. Diabetes causes damages to vascular endothelium, which leads to initial vasculopathy characterized by increased vascular permeability [53]. Along with loss of pericytes, this causes hemodynamics and autoregulation derangements [53, 63].

In the early stage of diabetic vasculopathy, the hyperpermeability of diabetic capillaries causes excessive protein to spill from the plasma into the interstitium. This leads to the offsets of physiological osmotic gradient, creating deficiency in fluid reabsorption on the venule end of the capillary bed. Edema occurs when the lymphatic system is unable to correct this imbalance [50]. The typical transient initial edematous course of DP suggests that optic nerve capillaries are susceptible to this vasculopathy. Edema compresses vessels leading to ischemia as well as stagnates and prolongs cellular exposure to toxic effects from free radicals and cellular waste. In addition, edema might also compress nerve fibers causing axoplasmic flow derangements [61, 62, 64]. These hypotheses would explain the reported fluroangiographic hyperfluorescence in DP, its relatively benign nature compared to AION, and its transient course [50].

In the later stage of DP, ischemia may result from leukostasis-derived capillary occlusion due to retinal leukostasis effect and thickened capillary basement membranes, which affect retinal capillary endothelial function, perfusion, angiogenesis, and vascular permeability [64]. This results in a clinical picture resembling more like traditional AION sequelae with optic atrophy [50].

#### 3.1.3. Clinical features

The main features of DP are painless visual loss, macular edema, disc hyperfluorescence on fluroangiography, and significant visual improvement after treatment [49, 54]. Differential diagnoses include infection, inflammation, metastatic infiltration, hypertension, and papilledema [52, 57, 65].

#### 3.1.4. Diagnostic studies

Certain diagnostic criteria have to be met in order to recognize diabetic papillopathy. The current accepted diagnostic criteria include (1) confirmed diagnosis of diabetes; (2) unilateral or bilateral presence of optic disc edema; (3) normal intracranial pressure; (4) absence of inflammation, infiltration, or infection in the optic disc; and (5) a lack of substantial optic nerve dysfunction [50, 51]. Supportive examination to confirm DP includes fluorescein angiography (FA), orbital magnetic resonance imaging (MRI), and blood tests ranging from serum angiotensin-converting enzyme (ACE), antinuclear antibody (ANA), vitamin B12, folate, erythrocyte sedimentation rate (ESR), C reactive protein (CRP) to fluorescent treponemal antibody test [49].

#### 3.1.5. Treatment

There is no evidence that the resolution of DP and the prevention of permanent visual loss can be promoted by definitive treatment. As stated before, in most cases, the edema resolves within a few months (average of 3.7 months) to no visual impairment [49]. Because of its self-limiting

nature, the most common management is serial examinations. However, due to potential visual sequelae noted in certain cases, more efforts have to be made to identify at-risk patients and effective treatment to prevent this sequela.

Although originally thought to be related to glycemic control, systemic glucose manipulation has not shown any benefits in DP [51]. Hence, how diabetes treatment should be titrated to protect visual function in DP remains uncertain [59]. Current treatment aims to reduce disc edema in DP, including intravitreal anti-VEGF, which has been shown to increase visual acuity and decrease disc edema, and also periocular corticosteroids, which stabilizes the blood-ocular barrier at the disc [65–69].

#### 3.2. Neovascularization of optic disc

#### 3.2.1. Definition

Diabetic retinopathy is often associated with neovascular proliferation due to ischemia in the retina and release of angiogenic factors. These conditions cause neovascularization of the optic disc (NVD), also neovascularization elsewhere (NVE) [70, 71]. Patients with NVD have a poor visual prognosis due to high incidence of complication, such as vitreous hemorrhage, fibrous proliferation, and traction retinal detachment. NVD occurring in DR can be accompanied by NVE and NVI (neovascularization of the iris), which later on may develop into neovascular glaucoma (NVG), which is an optic neuropathy defined by changes in the optic nerve and associated with visual field defects and elevated intraocular pressure [70]. Recent studies have shown that PDR is the leading cause of neovascular glaucoma [72].

#### 3.2.2. Pathophysiology

In DR, capillary occlusion and reduced perfusion in retina provoke cascade events related to hypoxia and lead to angiogenesis. Normally, pro-angiogenic factors (VEGF and angiopoietin-2) and antiangiogenic factors (pigment epithelium-derived growth factor) are in equilibrium [71]. Imbalance between those factors might trigger activation, proliferation, and migration of endothelial cells and pericytes and lead to neovascularization [71–73]. VEGF is produced in a variety of neuroretinal cells and plays a major part in promoting intraocular neovascularization. Inflammatory cytokines interleukin-6 (IL-6) is also correlated with the degree of neovascularization (bFGF), transforming growth factor-beta 1 and -beta 2, nitric oxide, and endothelin-1 [73].

The new vessels at the disc can bleed spontaneously or with minimal trauma. The blood spills into the retina and between the retina and vitreous causing vitreoretinal hemorrhage. This condition attracts fibroglial elements and finally resulting in separation between inner layers of the retina and the underlying retinal pigment epithelium, which is known as tractional retinal detachment [3]. NVD and NVI do not always develop into NVG, although neovas-cularization always develops prior to intraocular pressure increase. This is primarily due to fibrovascular membrane that develops on the iris and iridocorneal angle, which later causes anterior synechiae, angle closure, and intraocular pressure elevation [49, 74].

#### 3.2.3. Clinical features

In early stages of neovascularization, patients may be asymptomatic or may present with low vision. Ocular findings can be subtle in early stage, so case history and complete ocular examination are important to make early diagnosis [71–73].

#### 3.2.4. Diagnostic studies

Fundus examination might trace the new vessels of the optic disc and reveal glaucomatous optic nerve damage [73–75]. In fluorescein angiography (FA), leakage from damaged vessels could be detected before development of visible neovascularization. Even though FA can aid early detection, the test is not always available [73, 76]. Using OCT angiography (OCTA), neovascularization around the optic disc at the level of the vitreous cavity might be observed in a faster and safer way [75]. Electroretinography and retinal angiography can be necessary to determine the origin of neovascularization in the retina. Meanwhile, gonioscopy is a low-cost and fast test, which can reveal NVI [73, 76].

#### 3.2.5. Treatment

Early diagnosis will enable early treatment and prevent blindness due to optic nerve neovascularization. Tight glycemic control is also important [75]. Medical intervention to prevent further visual loss related to NVG is associated with lowering the IOP levels using topical  $\beta$ -adrenergic antagonists,  $\alpha$ -2 agonists, and carbonic anhydrase inhibitors. Topical corticosteroid can also be used to reduce inflammation [73]. The main treatment for preventing NVD and NVE in DR is laser photocoagulation. Panretinal photocoagulation laser therapy in early stages is beneficial by inhibiting and reversing neovascularization [74]. Use of anti-VEGF, cyclophotocoagulation, cryotherapy, and surgery are among other therapeutic options.

#### 3.3. Optic nerve atrophy

#### 3.3.1. Definition

Optic nerve atrophy is the end result of any disease that causes optic nerve damage anywhere along the path from the retina to the lateral geniculate. Degeneration of axon will manifest as changes in color and structure of the optic disc. It is associated with variable degrees of visual dysfunction, including congenital, vascular, metabolic, inflammatory condition, trauma, and neoplasm [77, 78].

#### 3.3.2. Pathophysiology

Optic nerve atrophy could result from many processes related to DM and DR. Such processes include neurodegeneration, oxidative stress, and ischemia. It may also develop as a result of optic nerve abnormalities mentioned above. Further study should be carried out to distinguish whether optic nerve atrophy occurs as a result of DR or complications of laser photocoagulation [10, 24, 36].

#### 3.3.3. Clinical features

The main symptom of optic atrophy is vision loss. In optic nerve atrophy, axon loss and myelin shrinkage will show the pallor-appearing disc, widening of the optic cup, and decreased Kestenbaum index (less than 6) [78].

#### 3.3.4. Diagnostic studies

Optic nerve atrophy is easy to diagnose, but finding the etiology is challenging. Further diagnostic test is necessary to identify the etiology of optic atrophy. Imaging study, such as ultrasonography, CT, and MRI, is used depending on the disease process. Other diagnostic tests are visual acuity testing, color vision testing, contrast sensitivity test, visual field testing, electroretinography, optical coherence tomography, and visual evoked response [78].

#### 3.3.5. Treatment

No proven treatment is able to return the function of atrophic optic nerve. Experts believe that treatment initiated before the development of optic nerve atrophy can be very useful to save the remaining function. The goal of primary intervention is to prevent axon degeneration by finding and treating the cause of optic atrophy. In diabetic patients, tight glycemic control and early detection of DR are very important. If the main problem is found and well-treated, further damage can be prevented [78].

# 4. Diagnostic approach for detecting optic nerve changes in diabetic retinopathy

Various examination methods have been used to detect functional and structural optic nerve changes in patients with diabetic retinopathy.

#### 4.1. Visual functional test

#### 4.1.1. Visual acuity

As has been known, neurodegeneration is a progressive loss of structure and function of neurons. The quality of visual acuity (VA) depends on the normal condition of visual pathway. Visual acuity test is the standard test of visual function. There are two commonly used tools for evaluating VA, including the Snellen VA chart and the Early Treatment Diabetic Retinopathy Study (ETDRS) VA chart. The Snellen VA chart is a frequently used chart for measuring VA. This consists of different type, size, and number of letters in each row. In contrast, ETDRS-VA chart has an equal number of characters per row with relatively uniform legibility. Some studies agree that ETDRS-VA chart has more advantages over the Snellen VA chart. Moreover, besides VA tests, some experts suggested that psychophysical tests, such as visual field and contrast sensitivity test, should also be evaluated in DR patients with optic nerve complication. They found that those examinations were more sensitive than VA test only [13].

#### 4.1.2. Contrast sensitivity

Contrast sensitivity is a test of the inner retina, with different spatial frequencies in specific neural pathways [13]. There is no algorithm to define the pattern of contrast sensitivity alteration in the early stage of DR. Adachi, Jochim, and Renner. observed reduced contrast sensitivity only at single low spatial frequency in cases of non–insulin-dependent diabetes mellitus without DR [79–81]. Meanwhile, Joltikov et al. and Safi et al reported decline in contrast sensitivity at all spatial frequencies early in the course of diabetic retinal sensory neuropathy [14, 82]. Joltikov et al. suggested that contrast sensitivity might be the most sensitive test for detection of subtle functional impairment in diabetic patients with or without retinopathy. In addition, contrast sensitivity ity test is more practical than electroretinography [13]. However, longitudinal study showed that reduced contrast sensitivity in the earlier stage of the disease might be reversible [82].

#### 4.1.3. Visual fields

Another visual function affected by neurodegeneration is visual fields. A common test for evaluating the visual field in diabetic retinopathy is perimetry. Various perimetry methods have been applied including white-on-white standard automated perimetry (SAP), frequency doubling technology perimetry (FDP), short-wavelength automated perimetry (SWAP), and rarebit perimetry (RBP) [83, 84]. Bengtsson et al. suggested that SAP and SWAP are more sensitive to neuroretinal impairment than ETDRS-VA chart [85]. Safi et al. reported that by using microperimetry, it might detect a reduction of foveal sensitivity in diabetic patients with preclinical stage of DR [82].

#### 4.1.4. Color vision test

Many color vision tests have been assessed in diabetic patients with and without retinopathy diabetes, including Lanthony desaturated D-15, Farnsworth-Munsell 100-Hue, and chromatog-raphy tests. However, studies recommended that Farnsworth-Munsell 100-hue test has higher sensitivity than the other tests. This test has been recommended as a screening test for DR patients [82].

#### 4.1.5. Visual evoked potential

Visual evoked potential (VEP) is a noninvasive test that evaluates the visual pathways by recording the electric signal in response to a bright flash of light [86, 87]. Changes of amplitudes and latencies in VEP reflects impairment in ganglion cells and optic nerve [88]. Clinical conditions that cause a delay in VEP latencies include papillitis, neuritis, toxic optic neuropathies, multiple sclerosis, glaucoma, and conditions affecting conducting media [89].

Khatoon observed that the pattern of VEP responses may provide early diagnosis of optic nerve involvement in DR and define the prognosis [88]. Onset of diabetes blood glucose control might affect the result of VEP [89]. In diabetic patients, VEP amplitude was reduced progressively with an increase of latency as the years pass [87]. Farisa et al. showed that P100 latency was prolonged among diabetic patients compared to nondiabetic subjects [88].

Progressive delay in VEP latency reflects damage of ganglion cell, even before the first ophthalmoscopically noticeable signs arise. VEP should be done as a screening tool for detecting optic nerve involvement in DR. Thus, early and proper management can be done to prevent further ocular damage [88].

#### 4.2. Structural test

#### 4.2.1. Fundus photography

Fundus photography is a noninvasive examination for documenting clinical signs and monitoring the progression or improvement of retinal diseases over time. One of the purposes of fundus photography is screening DR in diabetic patients. This method is useful for illustrating normal and abnormal morphology of the retina [90, 91]. Some signs of neurodegeneration in DR patients could be screened by fundus photography, including papilledema and macular edema. However, the result of fundus photography is a two-dimensional image; thus, it is difficult to accurately assess the detailed morphology of the retina leading to a high false-positive rate. In addition, in the condition of vitreous hemorrhage or low-quality image, some part of the retina could not be evaluated [10, 48].

#### 4.2.2. Fundus fluorescein angiography

Fundus fluorescein angiography (FFA) is an invaluable imaging method demonstrating an interaction of fluorescent within the anatomic structure of ocular fundus. FFA is the gold standard in evaluating retinal vascularization. FFA has early and late phase. Early phase demonstrates following the injection until complete filling of retinal arteries, arterioles, and capillaries, while the late phase demonstrates filling of veins until gradual elimination of the fluorescent from the retinal vasculature. Hypofluorescence occurs due to a vascular filling defect or a secondary condition of a blocking effect, while hyperfluorescence may occur due to fluorescein leakage, staining, or pooling [10, 24, 36].

#### 4.2.3. Optical coherence tomography

Optical coherence tomography (OCT) is a high-resolution imaging modality to measure retinal morphology, including vitreoretinal interface, neurosensory retina, and subretinal space [48]. We can measure the retinal layer thickness and segmentation [92, 93]. OCT provides an accurate assessment with low specificity value [48]. OCT is divided into two types: spectral domain (SD) and time domain (TD) [2]. TD-OCT is mostly used in neuro-ophthalmology to measure peripapillary retinal nerve fiber layer (RNFL) thickness. Peripapillary RNFL thickness increases in disc edema and decreases in optic nerve atrophy [94]. The results of OCT can be used as a guide for making therapeutic decision.

#### 4.2.4. Optical coherence tomography angiography

Optical coherence tomography angiography (OCT-A) is a three-dimensional noninvasive chorioretinal vascular imaging to observe the microvascular structures of new vessels, including NVD and NVE [95]. OCT-A can analyze blood flow in the vessels without dye injections. In FFA, it sometimes showed artifacts due to dye leakage effect. OCT-A is superior to FFA in determining the number, course, size, and extension of NVD [96].

### 5. Conclusion

Changes in the optic nervous system may start prior to classic clinical manifestation of DR. The development of an integrated multimodal approach for detecting optic nerve involvement in DR is important for early diagnosis in preclinical stage DR and reducing diabetic complications.

# **Conflict of interest**

There are no conflicts of interest in this chapter.

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