

A Review: Diagnosis of Diabetic Retinopathy by using Machine Learning & Deep Learning Techniques

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Abstract:

This study focuses to detect all the stages of diabetic retinopathy (DR) using end-to-end deep ensemble networks. One of the most prominent and significant micro-vascular ramifications of diabetes mellitus involves diabetic retinopathy (DR). If the treatment is not received for this degenerative condition on time, it damages the retina, visual impairment and blindness may result. It impacts on the affected persons can be lessened by having a thorough understanding of the pathophysiology, on receiving a quick diagnosis, and using efficient management techniques. The complex pathophysiology of diabetic retinopathy (DR) is reviewed in this abstract, which includes a range of biochemical, molecular, and hemodynamic mechanisms brought on by persistent hyperglycaemia. Chronic hyperglycaemia contributes to the onset and progression of diabetic disease DR by causing microvascular changes, oxidative stress, inflammation, and neurodegeneration. Many hand-on engineering and end-to-end learning-based approaches are used to detect the DR using Kaggle dataset. The detection of the mild stage is important for the early control of this fatal disease. This study focuses to detect all the stages of DR using end-to-end deep ensemble networks. The results show that the proposed approach outperforms state-of-the-art methods. To get the finest mass image dataset to train models, it takes Pre-processing steps, like data augmentation will increase the number of training examples, and data normalization will precisely predict classification. So, they could train the latest CNNs model (AlexNet, VggNet, GoogleNet and ResNet) to recognize the slight differences between the image classes for DR Detection. Transfer learning and hyper-parameter tuning methods are adopted and the experimental results have demonstrated the better accuracy than non-transferring learning methodology on DR image classification.

Keywords: Diabetic Retinopathy (DR), Convolutional Neural Networks (CNN), Neurodegeneration, Hyperglycemia, Chronic Hyperglycemia.

INTRODUCTION

Diabetic Retinopathy (DR) is one of the major causes of blindness. DR mutilates the retinal blood vessels of a patient having diabetes. The DR had two major types: the Non-Proliferative Diabetic Retinopathy (NPDR) and Proliferative Diabetic Retinopathy (PDR) [9]. The DR in the early stages was called NPDR which was further divided into Mild, Moderate, and Severe stages. Where the mild stage has one Microaneurysma (MA), which is a small circular red dot at the end of blood

vessels. In the Moderate stage the MAs rupture into deeper layers and form a flame-shaped hemorrhage in the retina. The severe stage contains more than 20 intra retinal hemorrhages in each of the four quadrants, having definite venous bleeding with prominent intra retinal micro vascular abnormalities [10]. PDR was the advanced stage of DR which leads to neo vascularization, a natural formation of new blood vessels in the form of functional micro vascular networks that grow on the inside surface of the retina [11]. Globally, the number of DR patients was expected to increase from 382 million to 592 million by 2025 [12].

In the early stages of the DR the patients were asymptomatic but in advanced stages, it leads to floaters, blurred vision, distortions, and progressive visual acuity loss [13]. Hence, it was difficult but utmost important to detect the DR in early stages to avoid the worse effect of latter stages. As explained in the previous section, the color fundus images were used for the diagnosis of DR. The manual analysis could only be done by highly trained domain experts but expensive in terms of time and cost [14]. Therefore, it was important to use computer vision methods to automatically analyze the fundus images and assist the physicians/radiologists. The computer vision-based methods were divided into hand-on engineering [15] and end-to-end learning. The hand-on engineering methods extract features using traditional approaches such as HoG, SIFT, LBP, Gabor filters and etc which failed to encode the variations in scale, rotation, and illumination. The end-to-end learning automatically learns the hidden rich features and thus performs better classification [16]. Many hand-on engineering and end-to-end learning-based approaches were used to detect the DR in Kaggle dataset but no approach was able to detect the Mild stage. The detection of the mild stage was important for the early control of this fatal disease [17]. This study focuses to detect all the stages of DR (including the mild stage) using end-to-end deep ensemble networks. The results show that the proposed approach outperforms state-of-the-art methods [18].

To get the finest mass image dataset to train models, it takes preprocessing steps, like data augmentation will increase the number of training examples, and data normalization will denoise to precisely predict classification [19]. So, they could train the latest CNNs model (AlexNet, VggNet, GoogleNet and ResNet) to recognize the slight differences between the image classes for DR Detection. Transfer learning and hyper-parameter tuning are adopted and the experimental results have demonstrated the better accuracy than non-transferring learning methodology on DR image classification [20]. In the recent studies, several intelligence methods have been proposed by the researchers to detect DR as well as to get preclusion for progressive damage. MAs turnover was a noninvasive early detection method for analysis of DR have been described in [21] with a high accuracy, where two different approaches took place under the proposed methodology to diagnose the progression of DR [22]. A variety of attempts has been made to produce algorithms to automatically classify and track micro-aneurysmal in the ocular fundus to resolve this variability [23]. DCNN a deep learning branch has impressive data on image analysis and interpretation applications, including medical imaging [24]. Currently, large CNNs can successfully perform highly complex image recognition tasks with an outstanding norm for many object classes [26][27].

Other medications have had rare reports of macular edema. These include

- Prostaglandin analogs commonly used to treat glaucoma (Xalatan, Lumigan, and Travatan)
- Tamoxifen, taxanes, and interferon (used in some cancer treatments)
- Fingolimod (Gilenya) used in relapsing multiple sclerosis
- Various herbal and vitamin supplements that include high doses of niacin (vitamin B3). Most people do not have eye side effects. Check with your physician for more information about prescription medications that could put you at risk.

Diagnostic Testing: The best way to diagnose diabetic retinopathy is a dilated eye exam. During this exam, the physician places drop in the eyes to make the pupils dilate (open widely) to allow a better view of the inside of the eye, especially the retinal

tissue.

The physician will look for:

- Swelling in the retina that threatens vision (diabetic macular edema).
- Evidence of poor retina blood vessel circulation (retinal ischemia-pronounced is KEY me uh)
- Abnormal blood vessels that may predict an increased risk of developing new blood vessels.
- New blood vessels or scar tissue on the surface of the retina (proliferative diabetic retinopathy)

Regular dilated eye exams by an ophthalmologist are important, especially for those who are at a higher risk for diabetic retinopathy or diabetes. If you are over age 50, an exam every 1 to 2 years is a good idea

so the physician can look for signs of diabetes or diabetic retinopathy before any vision loss has occurred. In addition to checking for signs of diabetic eye disease, a comprehensive dilated eye exam will evaluate your vision/need for corrective lenses, eye

pressure (looking for glaucoma), the “front” of the eye (eyelids, cornea, checking for dry eye), lens (looking for cataracts), as well as a complete exam

of the retina and vitreous. In addition to this exam, physicians use other tests to detect and manage diabetic retinopathy: An optical coherence tomography (OCT) test provides highly detailed cross-sectional images of the retina that show its thickness, helping determine whether fluid has leaked into retinal tissue. The physician may take fundus photographs of the back of the eye to help detect and document diabetic retinopathy. These photos make it easier for the physician to monitor the disease on follow-up visits to determine if it is worsening. To evaluate retina blood vessel circulation, the physician may conduct a retinal photography test called fluorescein angiography (FA). After dilating the pupils, the physician will inject a dye into the patient’s arm. The dye then circulates through the eyes and works like a food coloring; however, it does not affect the kidneys and is unlike the dye that is used with MRIs and CAT scans. As the dye circulates, the physician takes pictures of the retina to

accurately detect blood vessels that are closed, damaged, or leaking fluid. The pictures are black and white to help the doctor detect these changes more easily, but the process is not the same as having an x-ray. Prior to examination, ask your physician to discuss the risks and benefits of obtaining these images. With proper examinations, diabetic retinopathy can be detected before vision loss begins. If the physician detects signs of diabetic retinopathy, she/he will determine how frequently follow-up examinations will be required to detect changes that would require treatment. Treatment and Prognosis: As a result of major government- and industry-

sponsored studies, there are many approved treatments for diabetic retinopathy, including intravitreal injections (small injections of medications into the middle cavity of the eye), laser treatments, and vitreous and retina surgery. These procedures can be done in an office or hospital setting to prevent, treat, or reverse damage from diabetes in the retina. Research has shown that eye injections often result in better vision than laser treatment alone for patients with diabetic macular edema. The key to these treatments is their ability to block vascular endothelial growth factor (VEGF), a chemical signal that stimulates leakage and abnormal blood vessel growth. Repeated doses of anti-VEGF medications may be needed to prevent blood vessels from leaking fluid and causing vision loss.

Prevention: Patients with diabetes frequently ask, “Is there anything I can do to keep from getting diabetic retinopathy or to prevent or treat vision loss once it occurs?” If you have diabetes, the National Eye Institute suggests that you keep your health on TRACK:

- Take your medicines as prescribed by your doctor.
- Reach and maintain a healthy weight.
- Add physical activity to your day.
- Control your ABCs—A1C, blood pressure, and cholesterol.

- Kick the smoking habit.

Regular dilated eye exams reduce the risk of developing more severe complications from the disease. It is extremely important for diabetic patients to maintain the eye examination schedule put in place by the retina specialist. How often an examination is needed depends on the severity of your disease. Through early detection, the retina specialist can begin a treatment regimen to help prevent vision loss in almost all patients and preserve the activities you most enjoy.

Clinical Terms:

Diabetic macular edema (DME): The term used for swelling in the macula in eyes, or the center part of the retina which is responsible for providing the sharp, straight-ahead vision used for reading and recognizing faces as well as color vision.

Fluorescein angiography (FA): An imaging technique where a yellow dye called sodium fluorescein is injected into a vein in the arm. The dye allows a special camera to record circulation in the retina and choroid in the back of the eye. This test can be very useful in diagnosing a number of retinal disorders.

Fundus photography: Involves the use of specialized cameras equipped with lenses that capture images of the back of the eye where the retina, macula, vitreous, choroid and optic nerve are located. Intraocular injection: Treatment where a medication is injected into the vitreous cavity in the middle of the eye.

Macula: A small area at the center of the retina where light is sharply focused to produce the detailed color vision needed for tasks such as reading and driving.

Neovascularization: Excessive growth of new blood vessels on abnormal tissue as a result of oxygen deprivation that can cause vision loss.

Optical coherence tomography (OCT): A non-invasive imaging technique that uses light to create a 3-dimensional image of your eye for physician evaluation.

Proliferative diabetic retinopathy (PDR): An advanced stage of diabetic retinopathy in which new abnormal blood vessels and scar tissue form on the surface of the retina. The scar tissue can pull on the retina and cause retinal detachment and loss of vision. If blood vessels grow on the **iris** it can clog the drainage system of the eye causing glaucoma (high pressure in the eye), pain and vision loss.

Retinal detachment: A condition where the retina separates from the back of the eye cavity. This may be caused by vitreous gel or fluid leaking through a retinal tear or hole and collecting under the retina, causing it to separate from the tissue around it.

Mechanism of Diabetic Retinopathy and Classification:

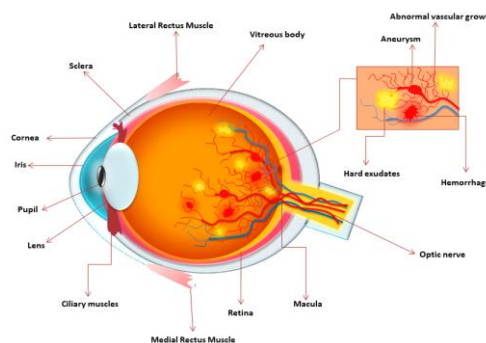


Fig1: Classification of DR

DR has been classified as the most commonly occurring major secondary complication in individuals diagnosed with DM. It has also been classified as the most documented microvascular threat to

diabetic patients. A lack of diagnosis or timely therapeutic intervention could result in visual impairment, partial blindness, and ophthalmic complications beyond these effect. Thus, understanding the mechanisms involved in DR is of great importance in order to ensure the proper diagnosis, assessment, and treatment of this disease. Depending on the pathophysiology of microvascular aneurysms, pre-retinal vascularization, retinal hemorrhages, Intraretinal microvascular abnormalities (IRMA) in Fig1, and other clinical patterns, DR can be differentiated into two major classes, namely, PDR and NPDR. PDR primarily begins with the abnormal growth of fibrous connective tissue on the retinal surface, whereas NPDR occurs due to lesions inside the retinal capillaries resulting from edema, hemorrhage, microaneurysms of the blood vessels, and/or capillary blockage in Fig1. In addition, persistent DME as well as vascular leakage causes the formation of hard exudates at the core of the macula.

These patterns can range from mild to severe, depending upon the onset and duration of the complications. Multiple types of research have been conducted and are ongoing, yet the pathological mechanism of DR remains unclear as a result of the absence of retinal samples of animals and the unavailability of human samples. In DR formation pattern of different mediators including cytokines, growth factors, coagulation factors, neurotrophic factors, vasoactive agents, and inflammatory mediators are affected due to metabolite disturbances thus can be used as therapeutic targets.

Hyperglycaemia in Diabetic Retinopathy:

Hyperglycemia is a clinical manifestation in diabetes and refers to an escalated level of blood glucose due to an insufficiency of insulin. An escalated glucose level causes non-enzymatic glycosylation that causes an increase of complex cross-linked substances known as advanced glycation end products (AGE). AGE formation leads to numerous secondary complications, for example, the augmentation of intracellular reactive oxygen species (ROS), which causes oxidative-stress-induced damage to retinal cells. In addition, the escalating production of AGE have shown reduction in standard mRNA levels of pigment epithelium-derived factor (PEDF), which coherently initiates inflammation and damage inside the microvascular endothelial cells of the retina since PEDF has a protective role. Due to its hydrophilic characteristics, hyperproduction of sorbitol does damage to retinal cells by causing an intracellular osmotic imbalance. Furthermore, the metabolism of fructose produces its glycosylating derivatives 3-deoxyglucosone and fructose-3-phosphate, which subsequently escalates oxidative stress at the pericytes and other retinal cells via the promotion of AGE. It is evident from the prior literature that the induction of oxidative stress, compromising the retinal cells, is a direct pathway for hyperglycemia to develop into DR. This increasing oxidative stress causes the loss of neuronal and pericyte cells, resulting in blocked capillaries. The blocked capillaries and increased number of blood vessels cause distortion and deformation of the microvascular structure of the retina.

Malfunction of Insulin Signaling in Retinopathy:

The peptide anabolic hormone, insulin has a major influence on the absorption of different macromolecules, such as fatty acids, carbohydrates, proteins, etc., in the cells. Insulin inversely interacts with glucagon to regulate glucose metabolism in the liver. These reactions are mediated by the signal transduction pathway. The blood–retina barrier acts naturally providing immune privilege to the eye; thus, at the physiological standard level of insulin the transport mechanism across this barrier works potently. However, with abnormal coagulation or a lack of insulin, this mechanism is disrupted.

The results of research conducted on exsanguinated animals to examine insulin transport levels suggested a decline in the transport rate of insulin as the physiological function of glial, neuronal, and vascular cells of the retina were disrupted. However, the exact pathway in which the mechanism of

transport is compromised has not entirely been elucidated but some plausible causes have been proposed. Recent investigations have found that activation of the insulin receptor in retinal microvascular cells has various effects such as overlapping of insulin receptor, insulin receptor substrate-1 (IRS-1), phosphatidylinositol 3-kinase (PI3K), and phosphor-tyrosine in neuronal cells of rats. Since the insulin signaling pathway is regulated by various proteins, different IR subsets are likely to signal differently than the above-mentioned routes. Another study, conducted on hyperglycemic rats showed an increase in insulin receptor levels in the cells of the retina. Thus, it is evident that there is a correlation of insulin level with retinopathy; however, further research needs to be conducted to elucidate the mechanism.

Pathophysiology:

Diabetic retinopathy is a microvascular disease, characterized in various ways based on elevated vascular flow and vascular leakage due to the presence of vascular lesions, cell inflammation, edema in tissues, adhesion molecule expression and cytokines, reactive glia, apoptosis of inner retinal cell, and neovascularization. In the pathogenesis of DR, hyperglycemia plays an important role. The biochemical pathways associated with hyperglycemia-induced vascular damage include elevated glucose flux by means of the polyol pathway, AGE-product accumulation, inflammation, as well as the activation of protein kinase C (hexosamine pathway).

The overabundance of superoxide in the mitochondria induced by hyperglycemia leads to oxidative stress, which acts as a stressor, linking all these metabolic pathways. Oxidative stress gives rise to multiple early clinical hallmarks of DR that include a thickened basement membrane, pericyte apoptosis, and mitochondrial dysfunction, which altogether result in BRB breakdown. BRB impairment thickens the retina, as well as increasing leukocytosis, which is an intravascular immune response and one of the early clinically recognizable pathologies of DR. It causes the adherence of white blood cells (WBCs) to the endothelial cells lining the blood vessels that influence the plugging of capillaries and vascular leakage. The summary of the pathophysiology is shown below.

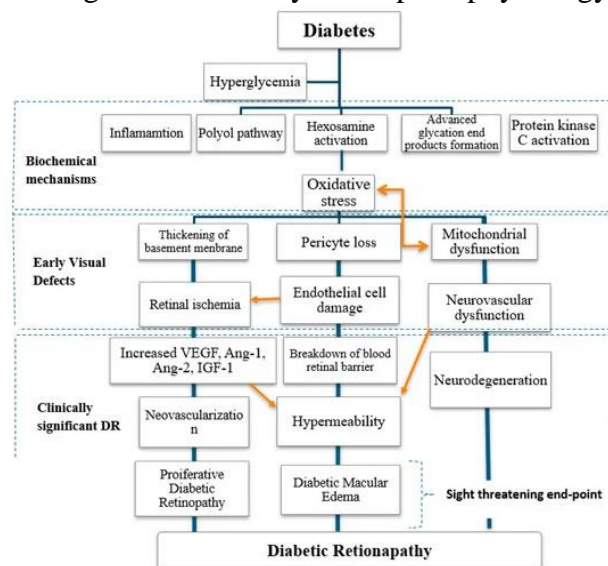


Fig2: DR Pathophysiology.

Risk Factors of Diabetic Retinopathy

DR is a persistent ocular fundus condition that accounts for 80% of visual loss in individuals with diabetes and therefore affects the quality of life, as well as elevating the financial burden on society. Risk factors of diabetic retinopathy include its duration, the presence of diabetic nephropathy, neuropathy, foot ulcer and amputation, along with hypertension, the level of cholesterol and

triglyceride in the serum, fasting blood glucose, the level of HbA1c and the age of the patient.

A study was carried out with 71 diabetic out-patients receiving insulin treatment who suffered from the illness for one to two decades, to determine the serum magnesium content. As per the extremity of retinopathy of the patients, they were split into two groups. Group A comprised patients having normal fundi or minimal alterations (microaneurysms and/or exudates smaller than microaneurysms), whereas group B included patients with more extreme abnormalities, including microaneurysms with larger hemorrhages and/or exudates, as well as proliferative retinopathy. Subjects as a whole had definite hypomagnesemia ($p < 0.001$), which was markedly evident among the segment with the most severe retinopathy ($p < 0.01$). In terms of established risk factors for DR, the segments were comparable. As a result, hypomagnesemia appeared to represent a new risk factor associated with the offset and development of the condition. In reality, investigations on the influence of lipids on the growth and genesis of PDR and DME have provided mixed results. Moreover, a complex and significant correlation was discovered amid glycemic control and alcohol intake. The progress of severe retinopathy (exudative and proliferative) was shown to be associated with excessive alcohol intake in 9 out of a total of 70 heavy drinkers (13%) in contrast to the remaining ten (4.4%). Alcohol intake might be a key independent factor in the development of diabetic retinopathy that threatens the sight. Hyperglycemia is the most common cause of DM.

Genetic Risk Factors of Retinopathy:

In accordance with various twin studies, DR is classified as a polygenic disorder that is genetically inherited, with researchers having discovered an obvious familial clustering. DR and PDR are found to be 27% and 52% heritable, respectively. Studies have shown that a family history of DR increased the risk of DR among individuals by almost two- to three-fold. The occurrence of diabetic retinopathy is also influenced by ethnicity according to the Multi-Ethnic Study of Atherosclerosis (MESA) which reported prevalence rates of 36.7% in African Americans, 37.4% in Hispanics, 24.8% in whites, and 25.7% in Chinese-Americans. A sub-linkage analysis for DR was conducted in Pima Indians among individuals with T2D (type 2 diabetes) and found a faint possibility of a linkage at chromosomes 3 and 9 with LOD (logarithm of the odds) scores of 1.36 and 1.46, respectively. A genome-wide meta-analysis identified a close association between the intergenic SNP (single-nucleotide polymorphism) rs476141 and DR. However, the results were not consistent with the Wisconsin Epidemiologic Study of Diabetic Retinopathy, which instead identified that in the gene CEP125, an intronic SNP at rs4865047 has a potential linkage with DR.

Other Risk Factors:

Dyslipidemia, a high BMI, puberty, pregnancy, and cataract surgery are all risk factors for diabetic retinopathy. In research conducted in Asia, BMI was shown to have a non-significant or negative relationship with DR. No proportional links were observed between DR and BMI in the study from China, but studies from South Korea and Singapore indicated a link between BMI and the occurrence of DR. Lower BMI might indicate a poorly-handled and severely complicated condition of diabetes that leads to DR and weight reduction; however, an elevated BMI can lead to a smaller duration for the milder stage of diabetes, reducing its prevalence. Other research has shown that the amount of time spent viewing television is linked to aberrant retinal vascular signals on its own. The proportionality in these links is not accurate as a result of the lack measures in physical exercises, sedentary lifestyles, longitudinal data in studies, and because of studies dealing with only type 1 diabetes. Diabetic retinopathy was found to be present in 17.6% of the population from rural areas who reported their illness themselves. Referable (sight-threatening) retinopathy was found in 5.3% of the population. Male gender (OR = 1.37), a longer duration of diabetes (per year, OR = 1.07), lean body mass index (OR = 1.30), higher systolic blood pressure (per 10 mm Hg, OR = 1.18), and insulin treatment (OR = 1.34) were all linked with the development of any DR. The study discovered risk factors for DR in diabetics living in rural areas. The research suggested that effective preventative

strategies were needed in rural regions to reduce avoidable blindness related to diabetes.

Diagnosis and Management of Diabetic Retinopathy:

Diagnosis:

Diabetic patients, along with their relatives, friends, and healthcare providers, must be informed about the significance of regular eye examinations to check for DR early. Some of the diagnostic techniques that may be used to diagnose, identify, and examine DR, as well as the efficacy of treatment, are direct and indirect ophthalmoscopy, stereoscopic digital and Fundus photography, mydriatic or nonmydriatic digital color or monochromatic single-field photography, ultrawide-field fundus fluorescein angiography (UWFA), optic coherence tomography (OCT), and optic coherence tomography-angiography (OCT-A), as well as fluorescein angiography. The most common method of diagnosis of diabetic retinopathy is ophthalmoscopy. However, compared to stereoscopic seven-field color photography, un-dilated ophthalmoscopy has low sensitivity, especially when performed by practitioners not involved with eye care. Direct ophthalmoscopy, when performed by non-ophthalmologists, can detect approximately 50% of cases of proliferative retinopathy under normal clinical situations. The Early Treatment Diabetic Retinopathy Study (ETDRS) group certified the grading of stereoscopic color fundus photographs in seven standard fields (SSFs) as a recognized standard for the diagnosis of DR. Although this method is precise and repeatable, it requires the use of professional photographers and photo readers, as well as advanced photographic equipment, film processing, and archiving. A diabetic retinopathy diagnosis methodology on the basis of single-field fundus photography has also been used. Patients with type 1 or type 2 diabetes were photographed consecutively through a non-pharmacologically dilated pupil using single-field digital monochromatic non-mydriatic photography (SNMDP), and then pharmacologically dilated before being examined by an ophthalmologist using ophthalmoscopy and having 30° color stereoscopic photographs taken in SSFs.

CONCLUSION:

The possibility of occurrence of diabetic retinopathy in individuals continues to escalate at a significant rate. However, research is ongoing to apprehend the underlying pathophysiology. This review discusses several mechanisms and prospective therapeutic targets to intervene in retinopathy progression. Despite a few limitations, the current management of DR, including glycemic control, control in blood pressure levels, use of anti-inflammatory corticosteroids, and focal laser treatment, have proven to be beneficial in the preceding research. Nevertheless, medications such as AGE inhibitors, antiplatelet and antioxidant medicines, and others have shown potential as well. Further research is required to overcome the drawbacks and develop effective treatments with reduced side effects.

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