Retinal disorder as a biomarker for detection of human diseases

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***Abstract*—The rapid development of digital imaging and computer vision has extended the potential of using these technologies in the diagnosis of human diseases. Medical image analysis is a non-invasive way to identify human diseases which are usually manually marked by medical experts or automatically detected by the Computer-Aided Diagnostic (CAD) system. The fundus images provide facts and information about visual disorders (diabetic retinopathy, glaucoma, age-related macular degeneration, etc.), brain disease (Alzheimer's), and heart-related diseases (cardiovascular, hypertension, and stroke). Extensive research has been done in the last two decades in developing automated methods for the identification of various human disorders from fundus images. This survey paper provides the reader with a broad review of the fundus image processing for the identification of various human disorders. In this paper, human diseases that can be diagnosed through fundus images are reviewed. Several publicly available fundus datasets which are helpful in the screening of these abnormalities are briefly discussed. This work aims to show the importance of retinal images in the diagnosis of different human diseases. The main challenges and difficulties faced in effective diagnosis are presented and discussed. We believe that this work will guide the researchers in addressing the challenges in existing solutions and assist doctors in the proper diagnosis of various diseases.**

***Index Terms*—Segmentation, Fundus Imaging, Diabetic Retinopathy (DR), Glaucoma, Age Macular Degeneration (AMD), Alzheimer's disease (AD), Cardiovascular Disease, Medical Diagnosis.**

I. Introduction

Eyes are the most important sensory organs of the human body to observe this beautiful world, without which life seems colorless. The health of this organ is indeed very important to live a normal life. Retinal images can provide a snapshot of everything which is happening inside the human body. The retina is the innermost, light-sensitive layer of the human eye. Structural format of the retina (optic disc (OD), macula, fovea, retinal vessels and abnormalities like microaneurysms (MAs), hemorrhages, exudates, cotton wool spots), macular hole, drusens, perivascular sheathing and exudation, retinal detachment, and subretinal fluid is revealed by fundus imaging [1]. Extraction and characterization of retinal vessels such as shape, diameter, tortuosity can be utilized in diagnosis, evaluation, and treatment of different retinal abnormalities. Automatic precise diagnosis of these structural changes and their timely medication can help to avoid severe consequences. An anatomical structure of the retina is shown in Fig. 1.

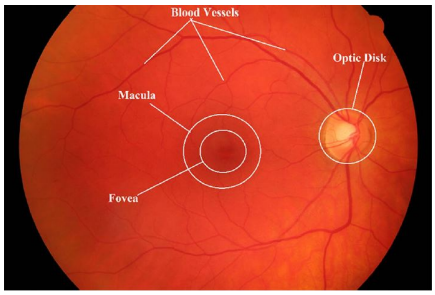

Fig. 1. Anatomical structure of retina image taken from HRF database.

The eye disease which leads to blindness is one of the major issues of mankind. Commonly encountered eye diseases are Diabetic Retinopathy (DR), Glaucoma, Age-related Macular Degeneration (AMD), macular hole, central serous retinopathy, retinal detachment, retinal vasculitides which occur due to the structural variations in the vascular network of the human retina [2]. Alzheimer's disease (AD) is a neurodegenerative disorder that arises as a result of the aging process. Retina being part of the central nervous system, it may reflect physiologic processes and abnormalities related to brain diseases. Ocular features in Alzheimer's disease include a decrease in vision, abnormal pupillary reactions, changes in visual fields, decreased contrast sensitivity, loss of ganglion cells, retinal thinning, etc. [3]. Cardiovascular diseases are also major health issues in the human body and can cause death in a short period. High blood pressure and stiffening of arteries are two main

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reasons that lead to cardiovascular disease. The cardiovascular condition of the human body can be examined from high-quality retinal images.

Various researchers worldwide are putting their untiring efforts to diagnose human diseases using medical images. Medical image analysis is a non-invasive way to identify human diseases by Computer-Aided Diagnostic (CAD) system. Considering the importance of human eye-related diseases, ophthalmology research is a topic of interest for various researchers across the globe, which represents the wide scope of this area. The retinal vasculature detection and extraction are very important for the identification of various diseases. In this paper, various human diseases related to the eye, brain, and heart that can be diagnosed through the eyes as well as their associated datasets available in the literature are briefly discussed.

The rest of the paper is organized as follows: In Section II, we discuss ophthalmological diseases and diagnostic methods. Section III and IV discuses cardiovascular and brain diseases respectively. Finally, the paper is concluded with perspectives in Section V.

II. Eye diseases

Eyes are the most important sensory organs of the human body without which life seems colorless. The health of this organ is indeed very important to live a normal life as an eye disorder may lead to blindness. Commonly observed eye diseases are DR, Glaucoma, AMD, macular hole, central serous retinopathy, retinal detachment, retinal vasculitides resulting from the structural variations in retinal vessels. These eye diseases and their diagnosis using non-invasive ways are briefly discussed in the following sections.

A. Diabetic retinopathy

Diabetic retinopathy is one of the eye diseases that causes severe vision problems n diabetes, more commonly in type 1 diabetes than in type 2 diabetes. Damage of blood vessels, growth of abnormal vessels, new vessels (neovascularization), cotton wool spots, and width variations of vessels (narrow or wider) are common signs of DR. The DR can be classified into non-proliferative DR (NPDR) in which signs of diabetic retinopathy occur without neovascularization (very mild, mild, moderate, severe, very severe) and proliferative DR (PDR) characterized by neovascularization.

Diabetes can also cause vascular permeability to increase, resulting in leakage of fluid from vessels into subretinal space. Microaneurysms, hemorrhages, venous irregularities, hard exudates, macular edema are retinal changes that are caused due to leakage of fluid in subretinal space. Microaneurysms are localized outpouchings formed by focal dilatation of capillary walls. At initial stages, recognition of Microaneurysms (MA) is very crucial and it can be considered as the first step in inhibiting diabetic retinopathy [4].

Diabetic Macular Edema (DME) is the most common cause of visual impairment in diabetic patients, especially in type 2 diabetics. It can be diffuse by extensive capillary leakage or local by localized leakage from microaneurysms. Hard exudates in the fundus image are indications of DME. Early detection of DME can prevent blindness so it is important to diagnose it early. A slight sign of DME is crucial to detect and it has no external symptoms. Computer-based methods have been developed for the diagnosis of DME. General steps of detection include image pre-processing, localization and masking of OD (optic disc), fovea detection, extraction of ROI, motion pattern generation, and severity of disease determination. A major problem faced for detection of DME is that color of optic disc and exudates is the same thus optic disc is masked to avoid considering optic disc as exudates [5].

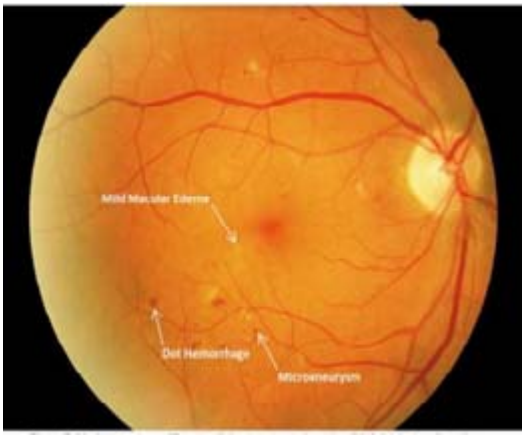
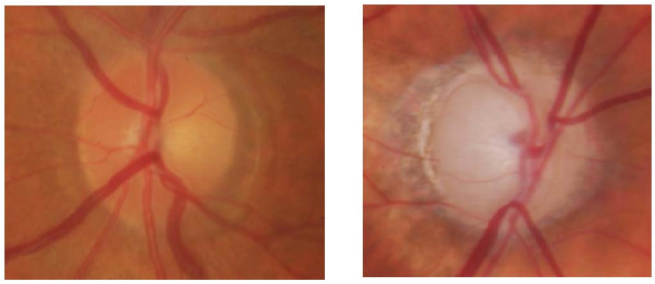


Fig. 2. Moderate non-proliferative DR with mild diabetic macular edema.

B. Glaucoma

Glaucoma is the second leading cause of blindness [6]. It causes blindness mostly for people over the age of 60 but it can occur at any age. The worst thing is that many forms of this disease have no warning signs and is given the nickname of ”sneak thief of sight”. Glaucoma causes irrecoverable blindness so it is necessary to have a regular eye examination and to get intraocular pressure checked. If it is diagnosed early then it is possible to prevent vision loss.

Glaucoma is due to the irreversible damage of retinal ganglion cells. The health of the optic nerve is vital for better vision. One of the risk factors associated with glaucoma is raised intraocular pressure (IOP) which leads to progressive and irreversible vision loss [7]. Accumulation of a fluid called aqueous humor which flows inside the eyes is the reason for raised eye pressure. Overproduction of this fluid and poor drainage system forbids the fluid to flow out and this creates high intraocular pressure. Another risk factor of glaucoma is the large size of the optic disc (OD) or optic nerve head (ONH). The OD is the beginning of the optic nerve and is circular. Changes in the shape of ONH and increment in the cup to disc ratio are indications of glaucoma. Fig. 3 (b) (a) shows ONH when no glaucoma is present while Fig. 3 (b) shows ONH with deep glaucoma. The difference in the shape of ONH can be seen clearly.



(a) (b)

Fig. 3. Example fundus images of ONH with a) No Glaucoma, (b) Deep Glaucoma

Studies have suggested that glaucoma can be diagnosed by a variety of criteria i.e. size of the cup, the narrowness of the remaining rim of the disc, vertical ovalness of the cup, and progressive changes in the cup. Glaucoma can be detected by measuring Cup to Disc Ratio (CDR) of the fundus. The CDR of the normal fundus is expected to be less than 0.5 while the CDR of the fundus suffering from glaucoma is more than 0.5. Many methods have been developed for measuring CDR. Common steps used for measuring CDR are: (i) Pre-processing of image (ii) Determination of Region of Interest (ROI) and (iii) Localization of OD and optic-cup (OC) [5]. Pre-processing of the image may include illumination correction (enhancing the contrast and removing blurring effect) and removal of blood vessels. For localization of ONH, Hough transform can be used. Deep learning methods can also be employed for the segmentation of OD and OC [7].

C. Age Macular Degeneration (AMD)

The macular disease damages the macula and causes blindness. AMD is caused due to macula which is the functional center of the retina. The leakage of fluid into the retina causes swelling of the surrounding tissues which may include macula. The macula is responsible for focusing central vision in the eye and the macula controls our ability to see objects in fine detail. Macular Degeneration (the leading cause of vision loss) is affecting more than 10 million Americans which is even more than glaucoma and cataracts combined. Macular degeneration in the early stages does not affect vision, as the disease progresses vision becomes wavy or blur and if the condition worsens then central vision may be completely lost. This is may get worse over time. Figure 4 shows intermediate and advanced AMD according to the Age-Related Eye Disease Study (AREDS) [8]. Figure 4 shows drusens in AMD: (a) Intermediate AMD (b) Advanced AMD.

D. Macular hole

A full-thickness macular hole can present with central vision impairment in one eye or it can be asymptomatic discovered on routine examination. Metamorphopsia can be present. The role of vitreomacular traction in the pathogenesis of macular hole has been studied. Other causes include high myopia, blunt ocular trauma. Imaging techniques such as Optical Coherence Tomography (OCT) is highly useful in the diagnosis. Other imaging modalities include FAF and FA.

E. Central Serous Retinopathy

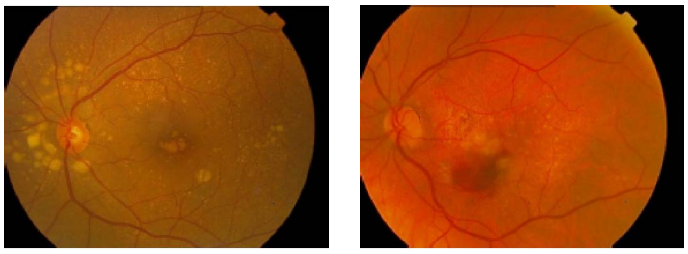
It is an idiopathic disorder characterized by localized detachment of the sensory retina at the macula due to leakage from the choriocapillaris through hyper permeable RPE sites. OCT shows an optically empty neurosensory elevation. Fluorescein angiography (FA) shows an ink blot and smokestack appearance. Other imaging techniques include Fundus Autofluorescence (FAF) and Indocyanine green angiography (ICGA).

F. Retinal Detachment

Accumulation of fluid in the space between retinal pigment epithelium and neurosensory retina secondary to a hole or break in the retina (Rhegmatogenous) leads to detachment of the neurosensory retina. Other types of retinal detachment include tractional retinal detachment and exudative detachment. Detailed fundoscopy using the non-contact lens on slit lamp, indirect ophthalmoscopy, and fundus photography are used to image the retina.

G. Retinal Vasculitides

FAF and FA are used to detect leakage, pooling, ischemia which are one of the common features in various retinal vasculitides.



(a) (b)

Fig. 4. (a) Intermediate AMD,(b) Advanced AMD

Two types of macular degeneration are dry (atrophic type) and wet (exudative type). In dry macular degeneration, yellow deposits (drusen) are found in the macula. In dry or atrophic form blind spots are found in the center of vision, if the disease gets worse result is a complete loss of central vision. In wet macular degeneration, blood vessels grow from underneath of macula. These vessels leak blood and fluid to the retina. Vision is distorted and as a result, straight lines appear wavy. This exudative form of macular degeneration also causes permanent central vision loss.

Macular disorders are diseases that damage the macula and cause blindness. The most common disease related to the macula is Macular Edema (ME). Other macular diseases include macular hole, AMD, diabetic macular edema, macular dystrophies, Stargardt disease, central serous retinopathy, and myopic macular degeneration. Different techniques are used to diagnose macular disorders i.e. Fundoscopy, Fundus Fluorescein Angiography (FFA), and OCT [5].

III. Cardiovascular Diseases

Cardiovascular Diseases (CVD) are major health issues in the human body and can cause death in a short period. High blood pressure and stiffening of arteries are two main reasons that lead to cardiovascular diseases. The cardiovascular condition of the human body can be monitored by examining the changes in the parameters of retinal blood vessels from high-quality retinal images [9].

The Central Retinal Artery Equivalent (CRAE) and Central Retinal Vein Equivalent (CRVE) tell about the diameter of major arteries and veins in retinal images respectively. Measurements of CRAE and CRVE are linked with coronary heart diseases, hypertension, and stroke. Another parameter of retinal blood vessel morphology is retinal vascular tortuosity which is basically characterized by abnormal twists and kinks of retinal blood vessels. This tortuosity is correlated with hypertension (high blood pressure) and other cardiovascular diseases. Measurement of Artery-Vein Ratio (AVR) in retinal images is used for the diagnosis of hypertension because low AVR reflects arteriolar narrowing. Arteriolar to venular diameter ratio is basically the ratio between the width of retinal arteries and veins. If this ratio is decreased then there are high chances of stroke and other cardiovascular diseases in adults and there are also high risks of retinopathy of prematurity in premature infants [10].

For the diagnosis of cardiovascular diseases from retinal images, we require high-quality retinal images for identifying true vessels because wrong identification leads to wrong clinical diagnosis. True vessels are identified through the segmentation of retinal blood vessels. Methods have been developed to measure AVR automatically. The steps involved are automatic detection of the optic disc, determining the AVR measurement Region of Interest (ROI), segmentation of vasculature, estimation of vessel width, classification of detected vessels into arteries and veins [10].

IV. Brain Diseases

Alzheimer's disease (AD) is a neurodegenerative disorder that arises from the aging process. In 2015, 46.8 million people were suffering from dementia in the world. It is predicted that the number of patients will be doubled every 20 years which will result in reaching 131.5 million in 2050. The disease which is considered as the most common cause of senile dementia is known as Alzheimer's and contributes to 60-80 percent of the total cases of dementia worldwide [3].

For diagnosis of Alzheimer's disease, some prominent clinical symptoms are short-term memory loss, poor visuospatial perception, impaired judgment and learning, and reduced executive functions progressing to a stage where it is difficult for a patient to recall previously well-remembered information. There are 3 stages of Alzheimer's disease i.e., mild, moderate, and severe. In the mild stage, the patient suffers from forgetfulness and confusion in unfamiliar situations. In the moderate stage problems with sleep and difficulty in remembering recently learned information are faced while in the last stage there is poor ability to think, difficulty in speaking and the patient becomes dependent on caregivers [3].

Alzheimer's disease can be diagnosed with retinal images and its indications are increased cup to disc ratio, retinal thinning, tortuosity of blood vessels, and deposition of beta-amyloid in the retina. Retina being part of the central nervous system, may reflect physiologic processes and abnormalities related to brain diseases. Enhancements in ophthalmologic techniques for studying retina have produced evidence of retinal degeneration in AD diagnosed patients [11]. Ocular changes in Alzheimer's disease include a decrease in vision, abnormal pupillary reaction, changes in visual fields, decreased contrast sensitivity, loss of ganglion cells, loss of retinal nerve fiber layer, increased cup to disc ratio, retinal thinning, tortuosity of blood vessels and deposition of beta-amyloid in the retina [3].

V. Datasets

Datasets are significant in pattern recognition studies because developed algorithms need to be verified on sample images. For fundus image analysis many research groups have proposed several algorithms and segmentation techniques. To check the accuracy and reliability of approaches, widely accepted fundus image databases and evaluation protocol exists. Many datasets are publicly available for comparing the results of different methods [1].

Digital Retinal Images for Vessel Extraction (DRIVE) [12] and Structured Analysis of the Retina (STARE) databases are two most commonly used publicly available databases [1]. The DRIVE contains 40 color fundus images taken for screening of DR. Standard DR database calibration level 0 and level 1 namely DIARETDB0 and DIARETDB1 respectively are also used for DR screening [13]. DIARETDB0 contains a total of 130 images in which 20 are normal and 110 are abnormal whereas, DIARETDB1 has a total of 89 fundus images, 5 are normal and 84 are abnormal. An example of fundus images from DIARETB1 with and without signs of DR are shown in Fig. 5.

Another publicly available database High-Resolution Fundus (HRF) contains 15 normal fundus images, 15 images of patients suffering from DR, and 15 images of glaucomatous patients [1]. DR HAGIS (a publicly available database for testing of automatic vessel extraction algorithms) contains 39 high-resolution color fundus images. These images were obtained from the DR screening program in the UK. DR HAGIS contains 4 comorbidity subgroups: diabetic retinopathy, hypertension, age-related macular degeneration, and Glaucoma image set [14]. RIM-ONE publicly available database contains 118 images of the normal eye (non-glaucomatous), 12 images of early glaucoma, 14 images of moderate glaucoma, 14 images of deep glaucoma, and 11 images of ocular hypertension (OHT) [15].

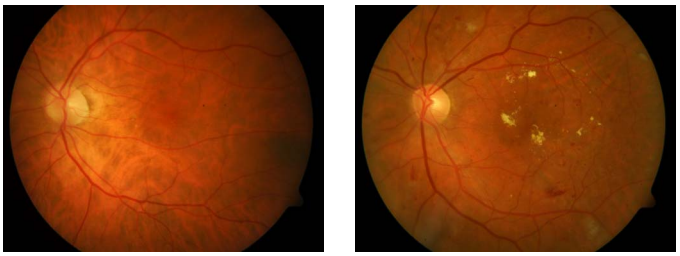
Retinal fundus images for glaucoma analysis (RIGA) is also an openly accessible database that includes three different files: 1) MESSIDOR dataset file has 3220 images, 2) Bin Rushed Ophthalmic center file has 1365 images, 3) Magrabi Eye center

TABLE I
SUMMARY OF VARIOUS RETINA DATASETS.

Sr. No.	Database	DR	Glaucoma	AMD	Cardiovascular
1	DRIVE	✓	✓		✓
2	STARE				
3	ImageRet	✓			
4	HRF	✓	✓		✓
5	DR HAGIS	✓	✓	✓	✓
6	DRIMDB	✓			
7	DRiDB	✓			
8	ARIA	✓		✓	
9	MESSIDOR	✓			✓
10	RIM-ONE		✓		
11	RIGA		✓		
12	SCES		✓		

file has 665 images. In this complete database, 750 images are original and 4500 images are manually marked [16].

Automated retinal image analyzer (ARIA) project aims to predict eye diseases. This database contains 92 photographs with AMD, 59 photographs with diabetes and 61 control group photographs [1]. A summary of various state-of-the-art retina datasets publicly available to diagnose various human diseases is shown in Table I.



(a) (b)

Fig. 5. Examples of DIARETDB1 fundus images: (a) Normal (b) Abnormal

VI. CONCLUSION AND PERSPECTIVES

In this paper, we briefly discussed various human diseases (eye, cardiac, and brain) that can be diagnosed from fundus images. We further discussed publicly available retina datasets particularly used for the diagnosis of various diseases.

Challenges in diagnosis using retinal images include lack of availability of appropriate publicly available databases covering large range of diseases. There is also a lack of consensus that which database is highly recommended for the target disease.

Another challenge in diagnosis of diseases through retinal images is acquisition of good quality fundus images. A good quality image is an image that has clarity and content. To address this issue image quality assessment tools are required. Image quality assessment is one of the important measures for proper diagnosis of diseases using medical image analysis. Major drawback which has been identified is that approximately 10% and 21% of retinal images, captured via fundus cameras for dilated and undilated pupils, respectively which are not suitable for authentic diagnosis and screening and make them useless for Automatic retinal screening system (ARSS). The robustness of ARSS can be increased by performing image quality assessment at the time of image acquisition, which otherwise will introduce an inconsistency in performance metrics. Artifacts which may deteriorate quality of fundus image are presence of dust or eyelashes on the lens of a fundus camera, eye blinking, bad illumination, out-of-focus imaging or blurring. Image quality represented by its sharpness, illumination, and homogeneity is suffered by these artifacts.

Additionally, a dataset that covers appropriate parts of the retina and highlights important structures related to the pathology is required for ARSS. Therefore, in the development of ARSS significant efforts were made but their performance is strongly dependant upon quality of processed retinal images. Two important characteristics of retinal images are: 1) Clarity: Retinal images should be sharp and homogeneously illuminated so that retinal structures and lesions can be separated by automatic systems, 2) Content: Retinal images must contain all the necessary retinal structures, image with incomplete retinal structures is not suitable for medical diagnosis [17]. Our work suggests that there is a need to develop a comprehensive dataset which contains high-quality images covering important structures related to pathology automatic screening of various human diseases.

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