Different Clinical Parameters to Diagnose Glaucoma Disease: A Review

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ABSTRACT
Glaucoma is a severe human eye disease that causes permanent loss of vision. The main cause of glaucoma eye disease is the continuous loss of retinal nerve fiber layers due to the increase in the intra ocular pressure inside the eyes. The function of these retinal nerve fibers is the transformation of recognized object information in the form of signals to the brain, where these signals are recognized as object. Damages to these nerve fibers generate blind spots and these blind spots leads to permanent blindness. Therefore, Retinal Nerve Fiber Layer Thickness is the main parameter to diagnose glaucoma. Other parameters also leading to glaucoma are Intraocular Pressure, Vertical Cup to Disc Ratio, Neuro Retinal Rim Thickness, Central Cornea Thickness, Inferior Superior Nasal and Temporal Sector Ratio etc. Therefore, the identification of these parameters plays the major role in glaucoma assessment, since it allows timely treatment to prevent the vision loss caused by glaucoma. To estimate these parameters, clinical instruments such as Tonometry, Ophthalmoscopy, Heidelberg Retinal Tomography, Perimetry, Pachymetry, Optical Coherence Tomography, GDx etc are adopted. This paper presents the various parameters, as mentioned above, used to analyze and diagnose the Glaucoma disease and associated advantages, disadvantages and the different instruments used to analyze each clinical parameter.

General Terms
Glaucoma, Clinical Parameters

Keywords
Intraocular Pressure, Retinal Nerve Fiber Layer, Optical Coherence Tomography, Inferior (I) Superior (S) Nasal (N) and Temporal (T) Rule and Vertical Cup to Disc Ratio

1. INTRODUCTION
Human eyes are the most important organs in the human body. In human eyes, the retina converts light rays into electrical impulses. Then these signals or impulses are sent through the optic nerve to the brain, where they are recognized as images. This optic nerve of an eye consists of several retinal nerve fibers to connect retina to the brain. These retinal nerve fibers are damaged when intra ocular pressure inside human eyes increases and it leads to glaucoma. Glaucoma is a censorious eye health condition affecting up to 60.5 million people world-wide [1]. It is a time progressive disease and the leading cause of permanent blindness. Glaucoma is commonly found in urban and semi urban areas of industrial developed countries. According to a survey of World Health Organization glaucoma is the second leading cause of blindness. In India, 11 million people are affected by glaucoma. Out of the 11 million, 1.5 million people are blind [2]. In Figure 1, left hand side image illustrates normal eye with thick retinal nerve fiber layers or no damages to retinal nerve fiber. The right hand side image represents the glaucomatous eye with damaged retinal nerve fibers or thin retinal nerve fiber layers.

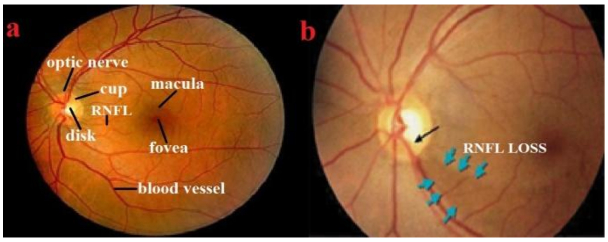


Fig 1: (a) Healthy Eye and (b) RNFL Loss Eye

2. GLAUCOMA DISEASE DIAGNOSIS PARAMETERS
There are several parameters to be considered in order to differentiate the healthy and glaucomatous eyes. Major parameters are as follows:

2.1 Intraocular Pressure
In the healthy eye, middle chamber of the eye produces the aqueous fluid. This fluid then flows around the lens, enters into the drainage meshwork and then comes out of the eye, as shown in the figure 2(a). If drainage meshwork is blocked, fluid does not move out of the eye, as shown in figure 2(b). As a result, fluid inside the eye increases. This increases the pressure inside the eye and causes damages to the optic nerve or retinal nerve fiber layers and in turn leads to loss of vision. Tonometry is the device used to measure the pressure inside eye. This device measures the pressure in terms of millimeters of mercury (mmHg). In normal eye, IOP is usually between 10-20 mmHg. Higher IOP inside the eye may increase the risk of glaucoma, but does not mean that the person has glaucoma because in some cases normal people may have higher IOP [3]. The following formula is used to calculate IOP of an eye.

$$IOP = \left[\frac{\text{aqueous fluid formation rate}}{\text{outflow rate}} \right] + \text{venous pressure}$$

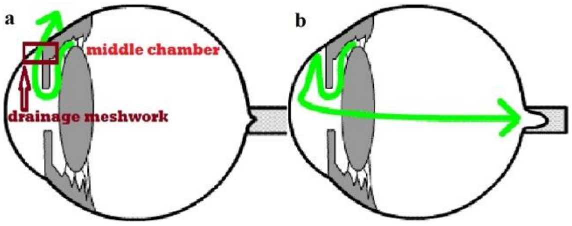


Fig 2: Process of retina (a) in healthy eye and (b) in glaucoma eye

2.2 Vertical Cup to Disc Ratio
In the human eye, Inner portion of the optic nerve is called optic disk, as shown in figure 1. The optic disk has an inner

portion called the optic cup. Disk of the optic nerve is always larger than the cup in normal and glaucomatous eyes. The major difference between normal eye and glaucoma with respect to optic disk and cup is that disk size may be same in both normal and glaucoma eye but cup size is usually larger in case of glaucoma eye compared to normal eye. Therefore, Glaucoma can be diagnosed by measuring the Vertical Cup to Disc Ratio (VCDR). Vertical cup to disk ratio is defined as the ratio of vertical cup diameter (VCD) to vertical disk diameter (VDD). In healthy eye, VCDR is always less than or equal to 0.5 [4]. In case of glaucomatous eye, the VCDR is greater than 0.5.This is because of loss of RNFL due to high pressure inside the eye causes an increase in cup size with constant disk size usually increasing the VCDR.

Ophthalmoscopy or Fundus camera is a device used to estimate VCDR. Different fundus cameras are available in the market such as Zeiss FF retinal camera, portable Nidek NM-100, canon Fundus camera etc. these fundus cameras are used to capture the eye images of the patients. These images are called as fundus eye images. Later, image processing techniques are used to extract cup area and disk area from these fundus eye images. Extracted cup and disk areas from fundus eye images are used to estimate the vertical cup diameter and the vertical disk diameter as shown in the figure 3. Finally VCDR is calculated using following formula.

$$\mathrm{VCDR} = \frac{\mathrm{VCD}}{\mathrm{VDD}}$$

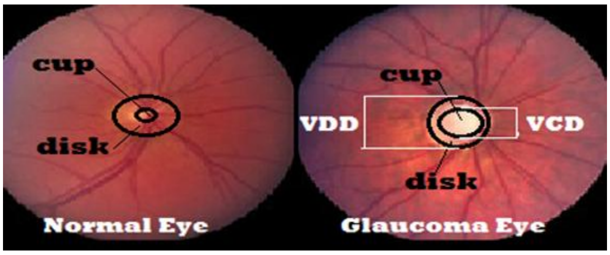
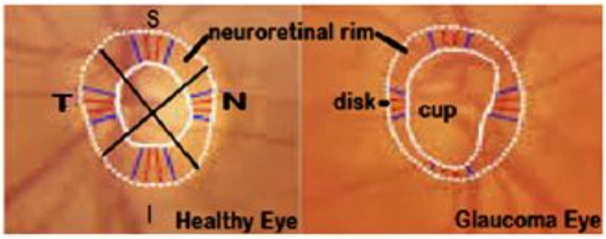


Fig 3: Healthy eye with small cup and glaucoma eye with larger cup

2.3 Neuro Retinal Rim Area

Neural retinal rim area is another parameter used in the glaucoma eye disease detection [5]. Figure 4 shows Neuro retinal rim area in healthy eye and in glaucoma eye.



a **b**

Fig 4: Neuro retinal rim area (a) in healthy eye and (b) in glaucoma eye

Neural retinal rim is an area located between disk boundary and cup boundary and it is obtained by subtracting cup area from disk area. In normal eyes, neural retinal rim area ranges from 0.80 to 4.66 mm2 [6]. In case of glaucoma eyes, area of cup increases due to increase of intra ocular pressure inside the eye. Therefore NRR is usually less than 0.80 mm^2. NRR of a human eye is extracted using image processing techniques from the fundus eye images captured by fundus camera device. The Neural retinal rim area is calculated by dividing the eye optic nerve head into 4 sectors superior, nasal, inferior and temporal. Initially each sector area is computed independently and total NRR area is computed by summing 4 sector areas. Superior and inferior rim areas are always smaller than the nasal and temporal in case of glaucoma eye, because it affects the superior and inferior regions more than inferior and temporal regions.

2.4 Central Cornea Thickness

The cornea is an extremely sensitive, transparent, clear and dome-shaped window covering the front part of the eye [7]. Thickness of Central cornea is one of the most important parameter in glaucoma diagnosis and management [8]. Ocular Hypertension Treatment Study says that Central cornea thickness and intraocular pressure are related to each other. Patients with thicker CCT may have a normal IOP value (10-20mmHg). Patients with thinner CCT may have a higher IOP value measured by tonometry than actual value (10-20mmHg). This means that higher IOP or thinner CCT indicates the sign of glaucoma [9] and lower IOP or thicker CCT indicates the healthy eye.

Currently, ultrasonic pachymetry, noncontact pachymetry instruments such as Orbscan II and SP3000P are used to determine the thickness of central cornea. In healthy eye, CCT is in between 0.50 and 0.54mm [10, 11] and in the case of glaucoma eye, CCT is usually less than 0.50mm.

2.5 Visual Field

Visual field of a human eye is the total area covered by the eye in which objects are visible from peripheral or side vision. Visual field varies from person to person. Visual field or field of vision is measured by the technique called visual field test and it is also called as perimetry test. This test makes use of the perimeter device for the measurement. Most of the ophthalmologists use the perimeter device to detect, monitor and examine the glaucoma disease by estimating visual field. Perimeter device detects the vision loss areas of patient eye to diagnose glaucoma and other diseases such as storks by regularly conducting the test.

Working principle of perimeter device is as follows:

1. Patient initially sits and looks inside the perimeter.

2. Light is flashed on one particular spot of eye.

3. Patient needs to press a button each time he sees the flash.

4. Device records spots in which patient pressed the button and also spots in which patient did not press the button.

5. Finally, the device shows the vision loss areas. These are the areas in which patient did not press the button.

In normal eye, vision loss areas are almost zero. But in case of glaucoma, vision loss areas are more. Therefore visual field test is helpful for finding the glaucoma disease in early stage.

2.6 ISNT Rule

ISNT RULE was first coined by Jonas et al [12] and it says that in a healthy eye, rim is the widest in the inferior sector, followed by the superior sector, the nasal and the temporal sectors [12, 13]. The ISNT rule is useful in the classification of normal and glaucomatous optic nerves [14]. In normal eye, the thickness of neural retinal rim changes from one sector to another and generally obeys the ISNT rule. Glaucoma eyes are normally violates the ISNT rule because it causes more structural damages to the inferior and superior sectors than nasal and the temporal. Therefore ISNT rule violation is the indication of glaucoma disease. The Heidelberg Retina Tomography (HRT) and Optical Coherence Tomography (OCT) are the most effective devices to find the thickness of retinal rim. HRT is a laser ophthalmoscope and it is a widely used technique to capture the optic disk images as shown in figure 5. It scans the retina in a few milliseconds to avoid artifacts of eye and generates the optic disk image by scanning optic disk using laser light and setting the field of view to 15 degrees. Later, HRT software is used to calculate the thickness of the inferior, superior, nasal and the temporal sectors.

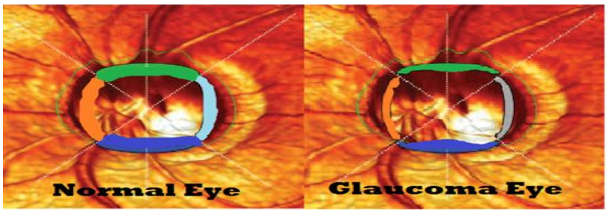


Fig 5: Optic nerve head captured by HRT

2.7 RNFL Thickness

The eye Retinal Nerve Fiber Layer (nerve fiber layer or RNFL) is formed by the expansion of the fibers of the optic nerve [15]. RNFL thickness is an important parameter for appraising glaucoma disease [16]. Thickness of RNFL is high around the optic nerve head (ONH) and gradually decreasing away from the optic nerve head. Thickness of RNFL decreases or RNFL loss occurs in glaucoma disease patients because of the high pressure inside the eye. Figure 6 shows the healthy eye without RNFL Loss and glaucoma eye with RNFL Loss.

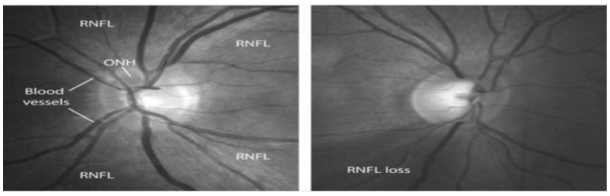


Fig 6: Healthy eye without RNFL Loss and glaucoma eye with RNFL Loss

RNFL thickness is measured using digital imaging technologies such as Optical Coherence Tomography, Heidelberg Retina Tomography and GDx.

The working principle of OCT is based on low coherence interferometry [17]. OCT device produces the high resolution cross sectional images (OCT images) by focusing light onto retinal structure of the patient eye and capturing the amount of light reflected from retinal structure using detectors present in the device based on the time and direction of the light [18]. OCT device is based on B-scans or cross sectional tomography, which is used to generate retinal OCT images [19]. OCT device allows the ophthalmologist to perform a B-scan at any degree of view. Widely used B-scans to identify the glaucoma are horizontal scan, vertical scan and circular scan. These scans are illustrated in the figure 7.

The Retinal Nerve Fiber Layer is the topmost layer of OCT image, which is shown in the figure 8 [20]. Steps involved in the estimation of RNFL thickness from OCT RBG image using image processing techniques, are as follows:

1. Convert RBG image into gray scale image.

2. Preprocess gray scale image to remove noises.

3. Enhance the gray scale image.

4. Detect the edges of RNFL.

5. Smooth the boundaries of RNFL.

6. Segment RNFL from gray scale image.

7. Convert segmented image into binary image.

8. Calculate RNFL thickness.

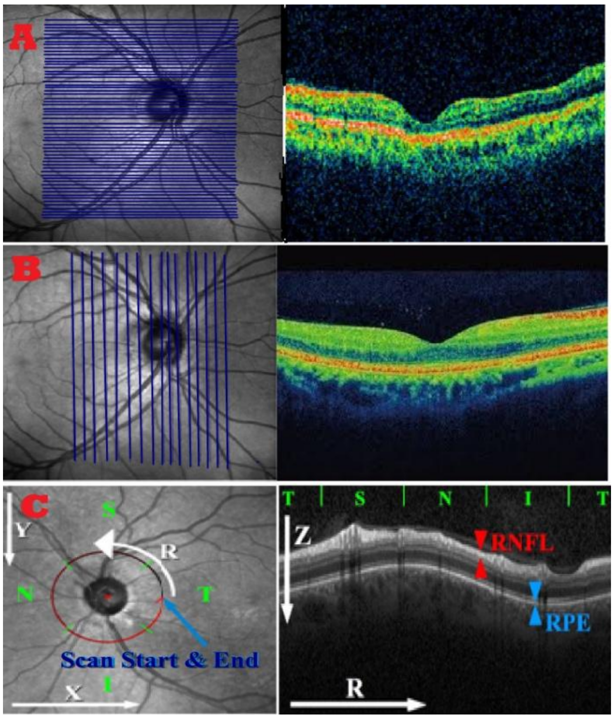


Fig 7: A) Horizontal Brightness Scan (B-Scan) of Eye and corresponding OCT image, B) Vertical B Scan of Eye and corresponding OCT image, C) Circular B Scan of Eye and corresponding OCT image

RNFL-retinal nerve fiber layer

R- Scan direction

X, Y, Z- axes

RPE- retinal pigment epithelium

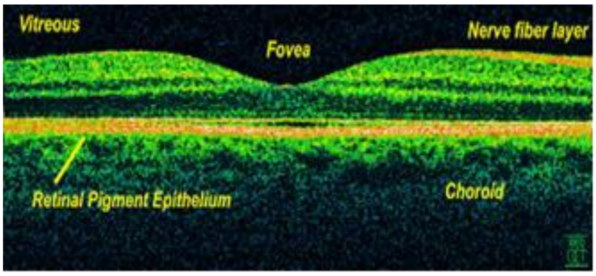


Fig 8: Structure of OCT image

RNFL thickness measurement is based on the number of pixels present in the RNFL [16]. Following formula is used to find the thickness of RNFL:

$$\mathrm{RNFLT} = \frac{\mathrm{RF}}{\mathrm{N}} \sum_{k=1}^{N} \left(\begin{array}{l} \text{number of pixels in kth column} \\ \text{of RNFL} \end{array} \right)$$

Where RNFLT = Retinal Nerve Fiber Layer thickness.

RF = resolution factor of OCT device.

N = number of columns present in RNFL

RNFL thickness in case of healthy eye is always greater than or equal to 90 micro meters and in case of glaucoma eye, it is usually less than 90 micro meters. RNFL thickness also obeys the ISNT rule which means, the RNFL thickness of Inferior (I) region ≥ Superior (S) region ≥ Nasal (N) region ≥ Temporal (T) region.

Heidelberg Retina Tomography and GDx are devices to measure RNFL thickness. Working procedure of HRT was already presented in previous section. GDx device uses the GaAIAs diode to produce the polarized laser beam. This laser beam is used to scan the human eye. It projects the laser beam onto the eye. As laser beam passes through the RNFL device estimates the thickness of the RNFL based on birefringent properties of layer [21]. Later, this thickness is used for glaucoma assessment.

3. CONCLUSIONS

In this work, authors have presented different parameters used to diagnose the glaucoma and devices used to measure the parameters. According to literature survey, authors observe that working principal of tonometry is based on the several factors such as shape and thickness of cornea. Therefore, Tonometry overestimates the IOP in thick cornea and underestimates the IOP in thin cornea [22]. In VCDR estimation, calculation of VCDR based on vertical cup to vertical disc diameters. But, these values are completely based on the region in which people live. This means VCD and VDD of Indians are usually different from European-Americans. In retinal rim area estimation, 71% of healthy eyes obey the rule ISNT but remaining 29% of normal eyes do not obey the ISNT rim area rule [23]. In central cornea thickness estimation, if CCT is less than 0.50mm, it indicates the sign of glaucoma. But it is difficult to conclude whether the patient is affected by glaucoma or not because some diseases like keratoconus also affect the thickness of cornea. In visual field test, test is based on the patient cooperation and it is time consuming compared to other parameters estimation. Because of these reasons, this parameter is not effective for glaucoma diagnosis. In ISNT estimation, 20% or more normal eyes may not obey of ISNT rule [24] and 25% of glaucoma eyes obey the ISNT rule. From all these reasons, final conclusion of this work is RNFL thickness measurement is the best parameter to analyze and detect the glaucoma. In the future work, the novel technique is developed to detect the glaucoma using RNFL parameter.

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