CHOROIDAL THICKNESS ASSESSMENT IN DIABETES MELLITUS PATIENTS

By

Dr. MERVIN JONATHAN ISRAEL.

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Dr.RAGHAVENDRA.K

PROFESSOR

DEPARTMENT OF OPTHALMOLOGY

BLDE (Deemed to be University)

SHRI B.M.PATIL MEDICAL COLLEGE

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LIST OF ABBREVIATIONS

DR	Diabetic Retinopathy
T2 DM	Type 2 diabetes mellitus
IOP	Intraocular pressure
HbA1c	Glycoselated haemoglobin
NPDR	Non proliferative diabetic retinopathy
PDR	Proliferative diabetic retinopathy
AGEs	Advanced glycosylation end products
OCT	Optical coherence tomography
B scan	Brightness Scan
RBS	Random Blood Sugar
FBS	Fasting Blood Sugar
PPBS	Post Prandial Blood Sugar
FFA	Fundus Flourscein Angiography
ICG	Indocyanine Green Angiography

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ABSTRACT

BACKGROUND

Diabetes mellitus (D.M.) is a significant public health problem where about more than 300 million people are affected, with severe morbidity and mortality. Its long-term complications can decrease the quality of life of patients. It is one of the largest global health emergencies of this century leading to high mortality with cardiovascular disease (CVD), respiratory disease, and cancer

The choroid is a vital structure responsible for the supply of nourishment to the outer retinal layers, and any modifications in choroidal structure or vasculature may affect the retinal function. choroid being a vascular structure is extremely vulnerable to both microvascular and macro-vascular abnormalities caused by diabetes mellitus. change, choroidal vasculopathy might also play a role in the pathogenesis of diabetic retinopathy. recent studies have focused on the choroidal thickness as an indicator of the choroidal blood flow

Diabetic Mellitus includes several end-organ, one of the more pronounced organs to be affected is the kidneys leading to diabetic nephropathy. Developmentally the retinal and the renal vasculature share some similarities during organogenesis; thus, the vascular pathologies affecting either the retina or the kidney may have some correlation

AIM AND OBJECTIVES

This study aims to assess the choroidal thickness in Diabetes Mellitus patients.

MATERIALS AND METHODS

This is a cross-sectional and time-bound study conducted on patients attending the outpatient and inpatient departments of Ophthalmology, B.L.D.E. (D.U.).'s Shri B.M. Patil Medical College, Hospital and Research Centre, VIjayapura.

A total of 192 patients were included in this study, of which 96 were diabetic patients (cases) and 96 were normal patients (controls). Diabetic patients were grouped into patients with retinopathy and nephropathy. Patients were screened for Diabetes mellitus and retinopathy by complete examination, including detailed History. The following investigations were performed:

- Best-corrected visual acuity
- Slit-lamp examination
- Direct and Indirect Ophthalmoscopy
- Fundus Photography
- Relevant blood investigations like F.B.S., P.P.B.S., HBA1C, SR CREAT, ALBUMINUREA, UREA and eGFR were done
- Diabetic retinopathy was graded using E.T.D.R.S. (Early Treatment Diabetic Retinopathy Study).
- Choroidal thickness was assessed by SD- OCT with EDI

RESULTS

study included 96 cases and 96 controls, of which majority belonged to the 5th and 6th decade. male predominance was noted, while Majority of the diabetic had duration of diabetes of 5-10 years with severe PDR cases of 10-15 years. positive correlation was noted between duration of diabetes with severity of retinopathy.

HbA1c levels also showed significant relation with grades of retinopathy, with majority of patients with severe PDR and PDR had values >8%

On assessment of choroidal thickness controls had a mean choroidal thickness of 327.308 microns as compared to diabetic patients with overall thinner choroidal thickness. An overall decrease in choroidal thickness was also noted with increasing severity or higher grades of diabetic retinopathy. Thinnest choroids were observed in PDR patients with a mean thickness of 193 microns.

Statistically significant difference in choroidal thickness across all groups were noted with p value of < 0.001. in patients with nephropathy, thinner choroidal thickness was noted with a mean thickness of 211.838 microns. A statistically significant difference p value 0.001 was noted when compared to the control group as well as cases group with mild and moderate NPDR, with least choroidal thickness in patients with nephropathy.

CONCLUSION

the severity of diabetic retinopathy was influenced by the duration of diabetes and HbA1c levels. Choroidal thickness was maximum in control group. Diabetic patients showed decrease in choroidal thickness with increase in severity of retinopathy and nephropathy. Thinnest choroidal thickness was observed in patient with PDR and nephropathy. SD-OCT (EDI) proves to be a reliable method to assess choroidal thickness. Choroidal thickness can be used to assess the severity of diabetic retinopathy, as well as the prognosis with treatment. It can also n=be used as a screening tool for diabetic nephropathy in diabetics coming for ocular complaints.

INTRODUCTION

Diabetes mellitus (D.M.) is a significant public health problem where about more than 300 million people are affected, with severe morbidity and mortality. Its long-term complications can decrease the quality of life of patients [1].

A series of metabolic illnesses known as diabetes mellitus are characterized by chronic hyperglycemia brought on by the deficiencies in secreting insulin, faulty action of insulin, or both. [2].

Diabetes mellites being one of the largest global health emergencies of this century, ranking among the 10 leading causes of mortality together with cardiovascular disease (CVD), respiratory disease, and cancer [3].

Nearly 592 million people are anticipated to pass away from diabetes by 2035 [4].

8.8% of United States adult population have diabetes, with males having slightly higher rates (9.6%) than women (9.0%), the International Diabetes Federation claims (IDF) [5]. Impaired glucose tolerance (IGT), a prediabetic condition, affects 463 million and 374 million persons worldwide, respectively, according to the most recent data. It is predicted that by 2045, there will be 548 million people with IGT and 700 million people with diabetes, a 51% rise from 2019 [6].

Diabetes was divided into Type 1, Type 2, Additional Forms, and Gestational Diabetes Mellitus (GDM), which is currently the most common, by the American Diabetes Association (ADA) in 1997 [7].

Diabetes Mellitus Type 1 (insulin-dependent diabetes mellitus [IDDM]), which is brought on by the autoimmune-mediated death of the beta cells of the pancreas and the cells that produce insulin, is one of two types of diabetes mellitus.

Many recent studies have focused on the choroidal thickness as an indicator of the choroidal blood flow. Choroidal vasculature and blood flow can be altered in various conditions; however, the major condition affecting the choroid is diabetes mellitus. Diabetic retinopathy is one of the primary causes of preventable blindness in working-age adults, affecting more than 35% of diabetic patients, as the choroid being a vascular structure is extremely vulnerable to both microvascular and macro-vascular abnormalities caused by DM2

The choroid, also known as the choroid coat, is the vascular layer of the eye, which is positioned between the retina and sclera. The choroid receives a large percentage of ocular blood flow and is responsible for the supply of nourishment to the outer retinal layers, and any modifications in choroidal structure or vasculature may affect the retinal function [8]. It also provides nourishment to retinal pigment epithelium (RPE) and photoreceptors, which is responsible for maintaining the extremely metabolically active photoreceptor cells, as apparent from the absence of retinal vasculature in the foveal region [9] the fovea is the most sensitive area of the retina, responsible for sharp central vision, is also supplied by the choroidal vasculature, and thus also affected in choroidopathy. Damage of choriocapillaris may cause severe functional impairment to tissues in foveal region [10]

Scientific and experimental findings suggest that, along with retinal change, choroidal vasculopathy might also play a role in the pathogenesis of diabetic retinopathy. Various choroidal irregularities, including obstruction of the choriocapillaris, vascular degeneration, choroidal aneurysms, and choroidal neovascularization, have been observed in previous studies on diabetic eyes [10,11,12,] Thus, such choroidal vascular

irregularities can lead to serious complications and dysfunction of the outer retina. However, in recent times there have been very few studies carried out on choroidal vasculature assessment and associating features. Thus this study aims to assess and the choroid vasculature properties, its changes with diabetes, and its association with co-relatable pathologies.

Choroidal imaging has seen a lot of development in recent years. Previously invasive procedures such as indocyanine green choreography were used for the imaging and assessment of the choroid, which made it difficult to carry out studies of choroidal pathology at a large scale. However, in recent years a more non-invasive and convenient method for choroidal imaging has emerged. Since the invention of spectral-domain optical coherence tomography, the imaging of the choroid has been gradually improving (SD-OCT). Moreover, the emergence of SD-OCT enhanced depth imaging (EDI) has enabled improved visualization and clearer imaging of the choroid[13]. Enhanced depth imaging optical coherence tomography (EDI OCT) is unique in having foveal tracking ability and is used to measure the thickness of the choroid in normal and pathological states [13,14,15]

Diabetic Mellitus includes several end-organ pathologies that directly relate to the severity and chronicity of the disease. One of the more pronounced organs to be affected is the kidneys, which, due to the various microvascular changes, lead to the development of diabetic nephropathy. Developmentally the retinal and the renal vasculature share some similarities during organogenesis; thus, the vascular pathologies affecting either the retina or the kidney may have some correlation and

influence on each other, resulting in pathologies in either one being used as a marker or predictor for pathologies of the other.

Microalbuminuria is an initial marker of generalized endothelial damage and is also related to the microvascular chronic complications in diabetic patients. Annually, 5%–10% of type 2 diabetes mellitus patients with microalbuminuria develop diabetic nephropathy, presenting with an increased risk of developing DR [16,17]

Development of nephropathy, in turn, leads to a higher risk of development of retinopathy and choroidopathy. Diabetic nephropathy leads to changes in the eGFR, albumin excretion, serum creatinine, and urea. These can be used as markers or predictors for the increased risk of development of choroidal vascular changes and, in turn, diabetic choroidopathy.

NEED FOR STUDY

Many recent studies have focused on the choroidal thickness as an indicator of the choroidal blood flow which is suspectable to alteration in diabetes mellitus. Scientific and experimental findings suggest that, along with retinal change, choroidal vasculopathy might also play a role in the pathogenesis of diabetic retinopathy.

In our study the choroidal thickness was assessed using a more resent development, the EDI OCT. The development of Enhanced Depth Imaging Optical Coherence Tomography (EDI OCT) has made it possible to visualize and image the choroid more clearly [13] with unique foveal tracking ability and can be used to measure the thickness of the choroid in normal and pathological states [13].

Diabetic Mellitus includes several end-organ pathologies, and One of the more pronounced organs to be affected is the kidneys, which, due to the various microvascular changes, lead to the development of diabetic nephropathy. Developmentally similarities are also shared between the retinal and renal vasculature during organogenesis, thus we also focused on choroidal thickness assessment in patients with diabetic nephropathy

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REVIEW OF LITERATURE

HISTORY

In 1856, Eduard Jaeger noted the first signs of diabetes in the retina. This wasn't possible prior to the direct ophthalmoscope's invention in 1855. Jaeger's conclusions were refuted by Albrecht Von Graefe, who claimed there was no connection between diabetes and retinopathy.

Edward Nettleship demonstrated in his work from 1872 the first histological proof of "Cystoid Degeneration of the Macula" in diabetic individuals. Then, in 1876, Wilhelm Manz emphasised the significance of vitreous haemorrhages and tractional retinal detachments while describing the proliferative alterations connected to diabetic retinopathy. [18]

The debate over whether diabetes, hypertension, and arteriosclerosis were the more likely culprits for macular alterations persisted, into the early 20th century. However, greater proof that diabetes was the underlying cause of the retinopathy observed in these patients was presented by Arthur James Ballantyne in Glasgow in the second part of the 20th century.

Technically speaking, diabetic choroidopathy is a non-inflammatory degeneration of the choroid caused by diabetes, and the first study on it was conducted by Hidayat and Fine (1985) in a small cohort of advanced-stage, painfully blind diabetic eyes (Hidayat and Fine, 1985) [19]

In some of the arteries, they noticed choriocapillaris (CC) dropout, luminal constriction, and thickening of the basement membranes.

Fryczkowski created vascular casts of a small group of diabetic eyes and used scanning electron microscopy (SEM) to analyse the choroidal vasculature (Fryczkowski, 1988, Fryczkowski et al., 1989). [20]

In diabetic choroid, Lutty and McLeod used histochemical activity of the endogenous alkaline phosphatase (APase) enzyme to demonstrate the absence of functional choriocpillaries. (McLeod and Lutty, 1994; Lutty and McLeod, 2005) [21]

DIABETES MELLITUS

DEFINITION

A series of metabolic illnesses known as diabetes mellitus are characterized by chronic hyperglycemia brought on by deficiencies in insulin secretion, insulin action, or both.

Low insulin levels, insulin resistance in tissues including skeletal muscles and adipose tissue, as well as liver genes to a lesser extent, are to blame for these metabolic anomalies. [22]

According to the WHO, diabetes is a metabolic disease that is chronic and is defined by high blood glucose (or blood sugar) levels. Over time, this causes major harm to the heart, blood vessels, eyes, kidneys, and nerves.

EPIDEMIOLOGY

Ever since it was first recognized as a disease, diabetes mellitus has caused concern on a global scale. Diabetes mellitus has become more common worldwide, reaching epidemic levels in underdeveloped countries like India and China. With an estimated 77 million people affected, India has the second-highest prevalence of diabetes behind China. In India, it has been discovered that one out of every six individuals is impacted. [23]

I.D.F., the international organization for diabetes, mentioned in the year 2020, approximately 463 million people in the world have diabetes, of which Southeast Asia contributes 88 million people [24]. On analysis of the epidemiology of diabetic retinopathy, 16.9% of the population consisted of people below 50 years of age. On further analysis, reports stated that 18.6%, of diabetic retinopathy population belonged to the age group between 60-69 years and 18.3% of the age group 70-79-years. The lowest prevalence of 14.3% were found in the age groups of 50-59-years [25].

CLASSIFICATION OF DIABETES MELLITUS

The categories of diabetes mellitus include the following

1. **Type 1 diabetes** - It happens as a result of insulin shortage brought on by -cell destruction.
2. **Type 2 diabetes** - It results from problems with insulin secretion and insulin resistance.

3. **Gestational diabetes mellitus (G.D.M.)** – It is typically discovered in the second or third trimester of pregnancy and is not overt diabetes.
4. **Specific types of Diabetes** – Ex: because of chemically induced diabetes, exocrine pancreas disorders, and monogenic diabetes syndromes ([12).

CRITERIA FOR DIAGNOSIS OF TYPE 2 DIABETES MILLITUS

Type 2 Diabetes according to the American Diabetes Association Diagnostic criteria

"The American Diabetes Association Expert Panel recommends a diagnosis of diabetes Mellitus when one of the following four criteria are met and confirmed with retesting on a subsequent day:

- HbA1c ≥6.5% (<5.7% = normal)
- plasma glucose level 2 hourly ≥200 mg/dL (11.1 mmol/L) with 75-g OGTT
- Random plasma glucose levels ≥200 mg/dl in a patient with symptoms of hyperglycaemia, including polyphagia, polyuria, and polydipsia" [26]

World Health Organization and the International Diabetic Federation both claim

Measurement Diagnostic cut-off value Comment

- Fasting plasma glucose ≥7.0 mmol/L (126 mg/dL)
- post-load venous plasma glucose ≥11.1 mmol/L (200 mg/dL)
- 2-hour post-load capillary plasma glucose ≥12.2 mmol/L (220 mg/dL)
- Random plasma glucose ≥11.1 mmol/L (200 mg/dL)
- HbA1c - 6.5% (48 mmol/mol)

PREVENTION OF DIABETES

NATIONAL DIABETES CONTROL PROGRAM

The National Diabetes Control Program (N.D.C.P.) was initiated in 1987 in Tamil Nadu, Jammu and Kashmir, and Karnataka. Its objectives included:

- Identify high-risk population
- Introduction of the health education for early measures
- Aim for early diagnosis and treatment.
- Reduction in mortality and morbidity among the high-risks.
- Prevention of ocular metabolic, renal, cardiovascular complications.
- Rehabilitation of the people disabled people due to the disease [27]

INDIAN DIABETES PREVENTION PROGRAM

A three-year randomized control experiment called the Indian Diabetes Prevention Program (I.D.P.P.) used metformin and lifestyle changes to help people with impaired glucose tolerance avoid developing type 2 diabetes.

They came to the conclusion that altering one's lifestyle and taking metformin were affordable therapies that may be utilized to prevent diabetes in high-risk people in India and other developing nations. [28].

OCULAR MANIFESTATIONS OF DIABETES AND HYPERGLYCEMIA

Diabetes mellitus can lead to a number of complications that involves multiple systems. Ocular complications such as diabetic retinopathy, diabetic papillopathy, glaucoma, cataract, and ocular surface diseases [29]

Various ocular structures that are affected in diabetes:

EYE LIDS/LASHES

Individuals are generally prone to majority of acute infections, especially in the presence of uncontrolled diabetes. The eyelids being more susceptible to infection may give rise to ulcerative blepharitis and. Recurrent styes are sometimes the first indications of diabetes and hence should indicate for an immediate diabetic evaluation **30.**Staphylococcus epidermis was reported to be isolated from the lid margins of nearly all diabetic patients

EXTRAOCULAR MUSCLE ABNORMALITIES

The extraocular muscles involved in the movement of the eyeball are controlled by the 3rd, 4th, and 6th nerves. These nerves are susceptible to damage from high blood sugar, eventually leading to nerve palsy. These Nerve palsies tend to recover completely on normalization of blood sugar. [31,32]

CONJUNCTIVA

Patients with diabetes are susceptible to bacterial infections, such as acute infective conjunctivitis. Conjunctival pathological alterations in up to 86% of diabetic patients include higher squamous metaplasia rates and decreased goblet cell density. [33,34]

CORNEA

acceleration of ocular surface abnormalities has been noted, indicating diabetic keratopathy. Corneal abnormalities include symptomatic corneal conditions, such as punctate keratopathy and persistent corneal epithelial defect [35]. Minor Corneal abrasions in diabetic patients can lead to severe outcomes including non-healing corneal ulcers and detachment of the basement membrane.

IRIS

One of the most deleterious effects on the iris is neovascularization. It is often present around the pupillary margin, but in advanced cases, it may involve the angle of the anterior chamber and even the whole of the iris [36]. These changes result in neovascular glaucoma.

PUPIL

It has been observed that there is a Loss of nerve terminals in diabetes. These nerve loss affects the dilator muscle majorly as shown in histological studies [37], leading to pupils being more miotic [38]. In diabetic patients, surgically induced miosis that followed phacoemulsification was shown to be substantially more pronounced.

CHANGES IN REFRACTION

The posterior half of the cornea's refractive power was affected by diabetes, according to research by **Wiemer et al**. However, since the overall corneal power was unaffected, it is still most likely that lens modifications are to blame for the refractive abnormalities observed in diabetic patients. [39].

Prior to this, **Duke-Elder** had noted a change from hyperopia to myopia in relation to either hyperglycemia or hypoglycemia, respectively**.** [40]. According to recent studies, diabetic individuals changed more frequently toward hyperopia, especially when therapy first started.

In addition to refractive changes, recent onset diabetic patients also exhibit changes in accommodation. Waite and Beetham reported transient paralysis of accommodation in 21% of diabetic patients, most commonly in between 20 followed by 50 years of age group [41].

CHANGES IN LENS

One well-known side effect of cataract growth is visual impairments. According to the **Framingham Eye Study** [42] Those over 65 years old have a twofold rise in cataract occurrences, while patients under 65 years old have a fourfold increase. According to The **Blue Mountains Eye Study**, impaired fasting glucose is a risk factor for cortical cataract development even in the absence of clinical diabetes **43**. One potential pathogenic mechanism for diabetes cataracts has been proposed: the deposition of advanced glycation end products in the lens. [44.] Additionally, it has been noted that sorbitol builds up in the fibres of the cortical lens to provide an osmotic explanation for the lens enlargement and cataract. [45]

The following are the hypotheses that explain lens changes in diabetics

- In diabetics, the activation of a specific isoform of protein kinase C by glucose results in the development of early-onset cataracts
- increased flux mediated by aldose reductase.
- Production of advanced glycation end products has increased (A.G.E.s), which are produced by the non-enzymatic reaction of aldehydes like glucose [46].

RETINA

The retina is most suspectable to damage from diabetes, leading to severe complications and eventually visual loss. Diabetes mellitus majorly affects the microvasculature of the retina. The advanced glycation end products formed due to uncontrolled hyperglycaemia is responsible for the damaging effect of diabetes. Two pathways are responsible for the formation of these end products, the sorbitol and hexosamine pathways.

Diabetes-related microvascular damage also causes an increase in the synthesis of numerous growth factors, including vascular endothelial growth factor (VEGF), which worsens the disease's progression. The development of D.R. is primarily related to the duration and control of diabetes. Other factors known to influence the disease process are hyperglycaemia, hypertension, hyperlipidaemia, pregnancy, nephropathy, and anaemia [47,48].

Diabetic retinopathy (D.R.) being a microangiopathy mainly targets smaller retinal vessels leading to increased vascular permeability, ocular haemorrhages, lipid exudate, ischemia and formation of new vessels [49].

Along with retinal change, choroidal vasculopathy might also play a role in the pathogenesis of diabetic retinopathy. Various choroidal irregularities, including obstruction of the choriocapillaris, vascular degeneration, choroidal aneurysms, and choroidal neovascularization. Additionally seen in some arteries were choriocapillaris dropout, luminal constriction, and thickening of the basement membranes.

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BASIC ANATOMY

The retina makes up the eyeball's inner layer, where the eye's optical system creates the optical image. The macula is situated in the middle of the temporal vascular arcades and the optic nerve head, measuring roughly 5.5 mm in diameter. The 1.5 mm of the macula centrally, the fovea is specialized for color vision and high spatial acuity. The unborn depression, which has a diameter of 150–200 μm, is located in the foveola's middle.

A region devoid of retinal vessels within the fovea is known as the foveal avascular zone (F.A.Z.). The parafovea, which is 0.5 mm wide and surrounds the fovea, is the thickest part.

OPTIC DISC

Its diameter is roughly 1.5 mm. Except for the nerve fiber layer, all retinal layers terminate here. Due to the lack of photoreceptors, it is insensitive to light and is referred to as the blind spot. The extra-areal peripheral part of retina, sometimes denoted as peripheral retina, is typically split into several concentric sections, A 1.5-mm ring around the temporal major vascular arcades is the closest to the center.

Peripheral retina refers to the region that is anterior to the equatorial retina. The retina that encircles the equator is known as the equatorial retina. The retina and pars plana are divided from one other in the far peripheral retina by the Ora Serrata.

HISTOLOGY

Here is a list of the layers of the retina, from the inner to the outer retina.:

1. Internal limiting membrane (I.L.M.)
2. Nerve fibre layer
3. Ganglion cell layer
4. Inner plexiform layer (I.P.L.)
5. Inner nuclear layer (I.N.L.)
6. Middle limiting membrane (M.L.M.)
7. Outer plexiform layer (O.P.L.)
8. Layer of Henle fibre (HFL))
9. Outer nuclear layer (O.N.L.; the nuclei of the photoreceptors)
10. limiting membrane external (E.L.M.)
11. Inner segments Rod and cone (I.S.)
12. Outer segments Rod and cone (O.S.)

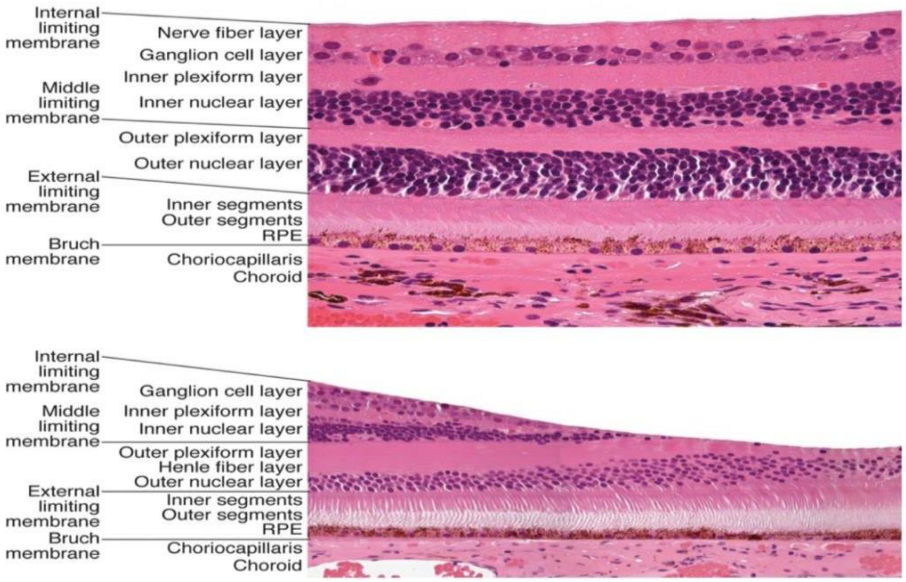

Figure 1. Schematic Cross-section of Retina Demonstrating Layers of Retina

OXYGEN SUPPLY AND RETINAL VASCULATURE

The avascular outer retina receives its vascular supply directly from the choroidal circulation, while the vascular supply of the inner retina receives it indirectly via the retinal circulation. The central retinal artery divides into four branches after entering the eye, each of which supplies blood to one of the retina's four quadrants. An area of the inner retina may occasionally receive blood flow from a cilioretinal artery that originates from the ciliary circulation.

The retina receives blood supply from up to four layers of vessels at the tissue level:

1. The radial peripapillary capillary network in the nerve fibre layer surrounds the optic nerve head.
2. In the retinal ganglion cell layer, the superficial vascular plexus,
3. A capillary bed on either side of the I.N.L. in the deep capillary plexus

The four layers that make up the outer lamina are the pigment epithelium, rods and cones, the outer nuclear layer, the external limiting membrane, and the choriocapillaris.

The remaining six layers that make up the inner lamina are the internal limiting membrane, the inner nuclear layer, the ganglion cell layer, and the nerve fibre layer supplied by the central retinal arteries and veins.

The choriocapillaris and central retinal artery both contribute to the supply of the outer plexiform layer.

RETINAL PIGMENT EPITHELIUM

RPE is a monolayer of pigmented cells that develops from the optic cup's outer layer. This layer is continuous with the pigment epithelium of the ciliary body and iris.

Each RPE cell has an apex and base; the apical portion envelops the outer segments of the photoreceptor cells with villous processes.

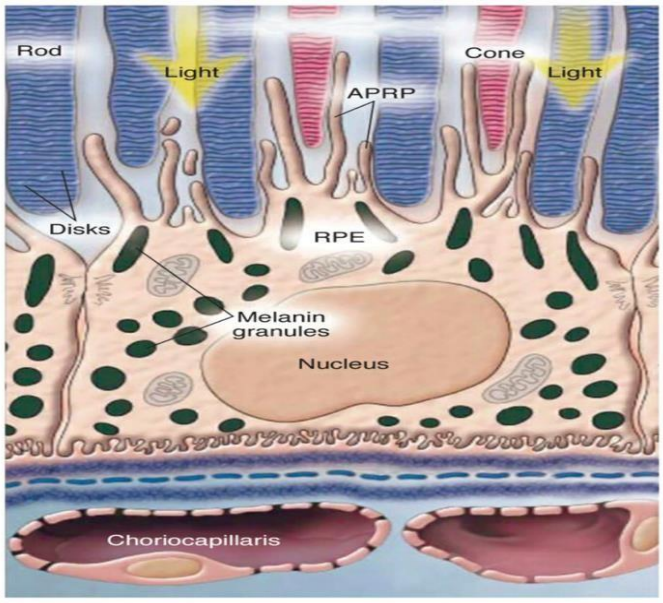

FIG 2. The Bruch membrane and the RPE's relationship to photoreceptors

The RPE supports retinal function in a number of ways, including:

- light absorption
- phagocytoses of cells in the outer segments of the rod and cone
- takes part in the metabolism of retinal fat and polyunsaturated fatty
- maintenance of subretinal space
- healing and scar tissue formation
- regeneration and recycling of visual pigment

BLOOD RETINAL BARRIER

Endothelial cells line the retinal capillaries, which are joined by zonula occludens-type intercellular connections. The blood-retinal barrier is made up of these junctions, which prevent solutes and fluids from freely moving from the retinal vessels into the interstitium. This blood-retinal barrier is weakened in diabetes, which causes the distinctive alterations seen in diabetic retinopathy.

ANATOMY OF CHOROID

he choroid is the term for the back of the uvea, the central tunic of the eye. The choroid is made up of blood vessels, melanocytes, fibroblasts, resident immune-competent cells, and supporting collagenous and elastic connective tissue. Its principal function has traditionally been considered to be providing oxygen and nutrients to the outer retina as well as the inner retina in animals with avascular retinas. One of the body's tissues with the most extensive vascularization is this one. Light absorption is a further conceivable purpose (in species with pigmented choroids). Thermoregulation and IOP adjustment are achieved through heat dissipation and vasomotor control of blood flow. It is noteworthy that the choroid is also engaged in the aqueous humor's uveoscleral route outflow from the anterior chamber. In humans, this route is responsible for about 35% of drainage, 40% to 60% in non-human primates, and significantly less drainage (about 3% and 3-8%, respectively) in cats and rabbits.

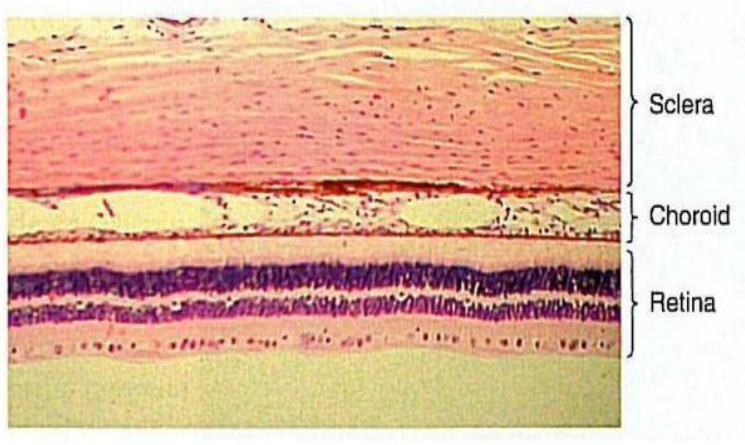

FIG ,3 SHOWING ANATOMY OF CHOROID

DEVELOPEMENT

In humans, towards the end of the first month, the two vesicles that later develop into the eyes, the uvea, bud off the embryonic forebrain. Around that time, melanocyte precursors start to travel from the neural crest into the uvea, but it takes them another 7-8 months of pregnancy for them to differentiate into pigmented melanocytes. The growing retinal pigment epithelium (RPE) must connect with the mesenchyme that creates the choriocapillaris at about two months in order to differentiate. As a result, the neural ectoderm serves as the origin of both the retina and the RPE, while other cell lines make up the choroid.

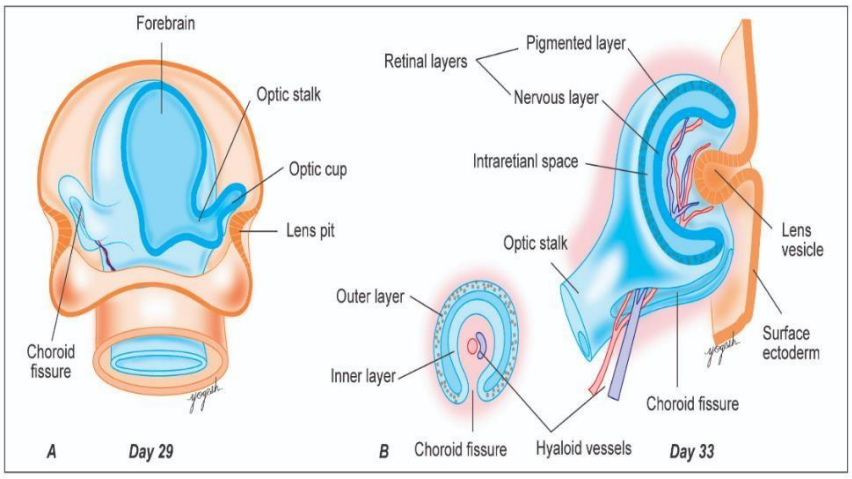

FIG 4 SHOWING DEVELOPMENT OF CHOROID

HISTOLOGY

The choroid continues anteriorly from the pars plana to the margins of the optic nerve before creating the ciliary body. Its deepest layer is the complex 5-laminar Bruch's

membrane structure, and its outermost layer is the suprachoroidal gap between the choroid and sclera.

It is 0.1 mm thick at the ora serrata and 0.22 mm thick in the central macular region, progressively getting thinner anteriorly, according to histologic study. With a mean age of 50 years old and healthy subjects, the average subfoveal choroidal thickness measured in vivo by SD-OCT is 287 m. However, as people get older and sicker, the thickness of their eyes varies. The presence of both thin (leptochoroid) and thick (pachychoroid) choroid is associated with ocular disease.

Depending on whether the vascular region is viewed as 1 or 2 layers (Sattler's and Haller's) and if the lamina fusca is believed to be of choroidal or scleral origin, the choroid has been histologically divided into 4 to 6 layers. The five layers that are most usually used to describe it are Bruch's membrane, the choriocapillaris, the two vascular layers (Haller's and Sattler's), and the suprachoroidea.

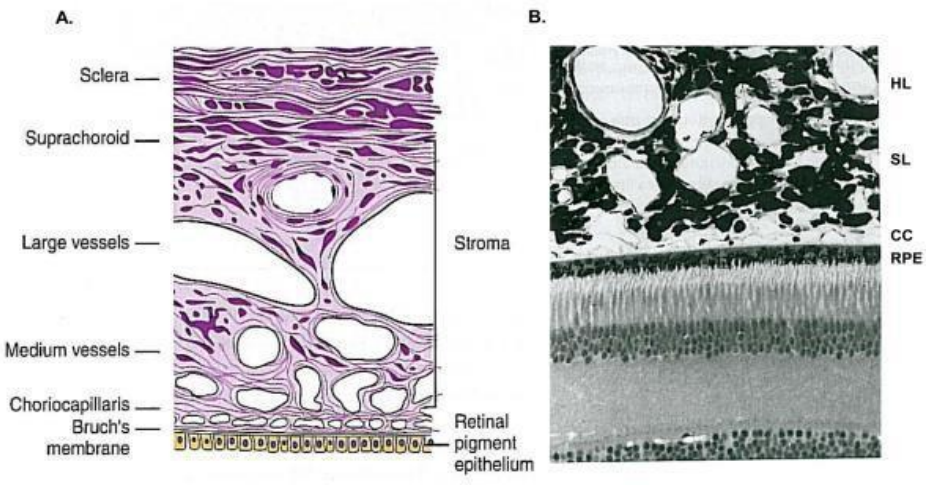

FIG 5 SHOWING HISTOLOGY OF CHORIOCAPILLARIS

CIRCULATION

The posterior ciliary arteries supply blood to the choroid. The Haller layer, the outermost layer of large-caliber choroidal arteries, is comparatively thick. The Sattler layer is the

division of the choroidal arteries into smaller-diameter vessels and precapillary arterioles. By distributing blood throughout the choroid, these blood vessels raise the choriocapillaris's relatively low arterial pressure. Backwards is where the choroid is thickest.

Even though the capillaries themselves are not precisely ordered into lobules, the choriocapillaris creates a plexus of capillaries in the posterior pole. The capillary pattern is more unequal close to the periphery, where the capillaries are directed more radially. There are small patches of fibroblasts, loose connective tissue, and melanocytes throughout the arteries of the choroid.

Blood is gathered in venules after it has passed through the choriocapillaris, and these venules eventually combine to form the ampullae, or collecting channels, of the vortex veins. The equator of most eyes is where four or five vortex veins exit the eye. The superior and inferior ophthalmic veins receive drain from the vortex veins.

The retina, which has one of the highest metabolic rates per gramme of tissue in the body, receives its metabolic requirements from the choroid. According to some estimates, 90% of the oxygen required by the retina, specifically by the photoreceptors, is provided by the choroidal circulation. The highest blood flow of any tissue occurs in the choroid, yet the venous blood that leaves it still has a very high oxygen tension.

The RPE cells receive the highest oxygen pressures of any perfused tissue because to their physical attachment to the choriocapillaris, which raises the possibility of oxidative injury. The choroid's rapid flow generates a heat sink by absorbing thermal energy from light absorption.

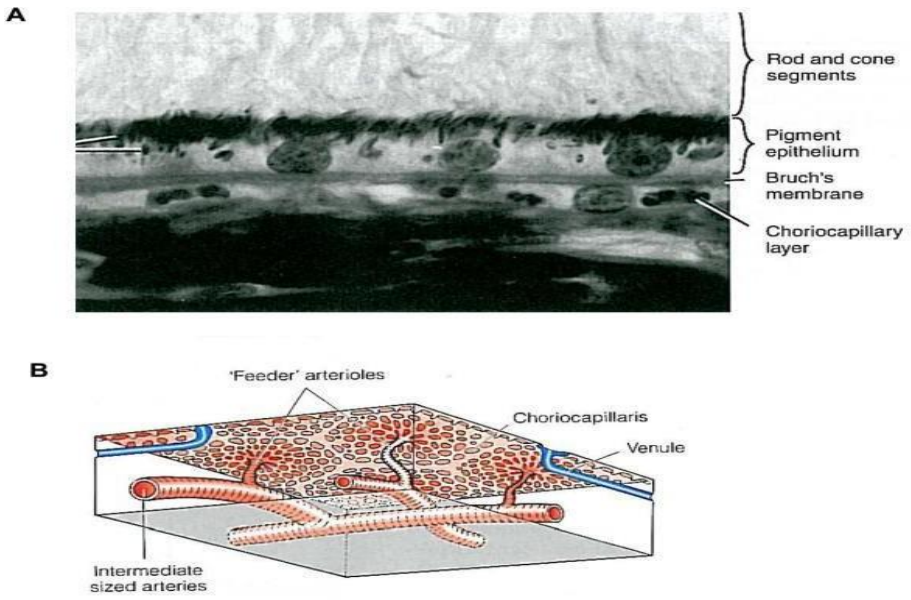

FIG 6 SHOWING CHOROIDAL CIRCULATION

ANATOMY OF KIDNEYS

The excretion of waste products like ammonia and urea, the management of electrolytes, and the maintenance of acid-base balance are just a few of the crucial tasks carried out by the kidneys. They are necessary for maintaining intravascular volume and managing blood pressure via the renin-angiotensin-aldosterone pathway. They are also in responsible of reabsorbing glucose, calcium, phosphate, erythropoietin, calcitriol, electrolytes, water, and amino acids [50,51].

The kidneys have a bean-like form with lateral convexity and medial concavity. Male kidneys typically weigh between 150 and 200 g, whereas female kidneys typically weigh between 120 and 135 g. The measurements are typically 10 to 12 cm in length, 5

to 7 cm in width, and 3 to 5 cm in thickness. Each kidney is about the size of a closed fist. They are situated between the transverse processes of T12 and L3 on the posterior abdominal wall, retroperitoneally. In comparison to the lower poles, the higher poles are frequently slightly medially and posteriorly inclined. A horseshoe kidney or a superior pole renal tumor may be present if the upper renal poles are positioned laterally. Due to the liver, the right kidney is typically positioned somewhat below the left kidney. [52]

EMBRYOLOGY

The intermediate mesoderm is where the mammalian kidney develops. Pronephros, mesonephros, and metanephros are the three sequential phases of kidney development (nephrogenesis). The cervical region's pronephros are comprised of vestibular excretory units (nephrotomes) during the beginning of the fourth week of development, but by the conclusion of the week, they have retreated. The intermediate mesoderm from the upper thoracic to upper lumbar segments gives birth to the mesonephros as the pronephros regresses. Bowman's capsule surrounds the glomerulus that makes up the renal corpuscle, and it extends, forms a loop, and develops capillaries. The mesonephric or Wolffian duct, which is a collecting duct, receives the excretory tubule. By around the sixth week, two bilateral organs are present. [53].

STRUCTURE AND FUNCTION

The two main parts of the kidney are the cortex and medulla. The cortex is composed of renal corpuscles, straight tubules, collecting tubules, collecting ducts, and vasculature.

Medullary rays are straight tubules and collecting ducts that the medulla projects into the cortex. The medulla also contains the vasa recta, a network of capillaries important to the countercurrent exchange system. Oriented with their bases facing the cortex and their apexes facing the hilum, pyramids are conical formations comprised of tubules that have gathered in the medulla. The papillae on the apices of the pyramids grow into smaller calyces and discharge into the cribrosa, a collection area, at the points of the structures. A lobule is a group of nephrons that a collecting duct drains. [54]

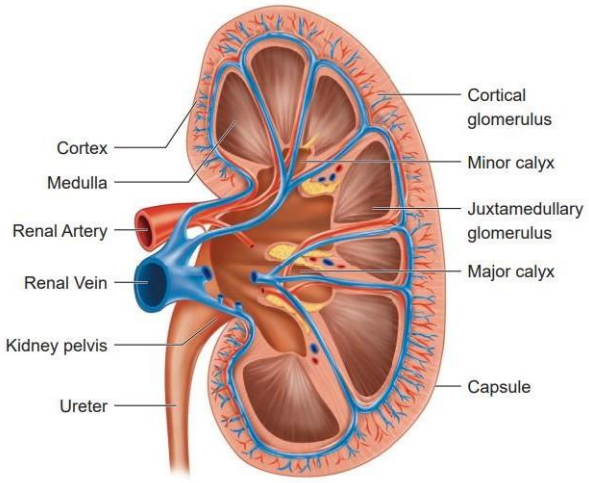

FIG 7 SHOWING ANATOMY OF KIDNEY

The functioning elements of the kidney are called nephrons. Per adult kidney, there are about 2 million nephrons. A renal corpuscle is created by an afferent arteriole supplying a network of capillary loops known as the glomerulus, which is encircled by a double-layered epithelium known as Bowman's capsule. The vasa recta, which develops from an efferent arteriole that drains the glomerulus, supplies the renal tubules. The following structures are located distal to Bowman's capsule: the proximal convoluted tubule, proximal straight tubule, or thick descending limb of the Henle loop, thin descending limb of the Henle loop, thin ascending limb of the Henle loop, distal straight tubule, or think ascending limb of the Henle loop, distal convoluted tubule, collecting

tubule, cortical collecting duct, medullary collecting duct, papillary duct, minor calyx, major calyx, renal pelvis, and ureter. The tubules begin in the brain, travel to the medulla, undergo a hairpin-like turn in the small limb of the loop of Henle, and then return to the cortex at the site of their starting renal corpuscle. [50,51]

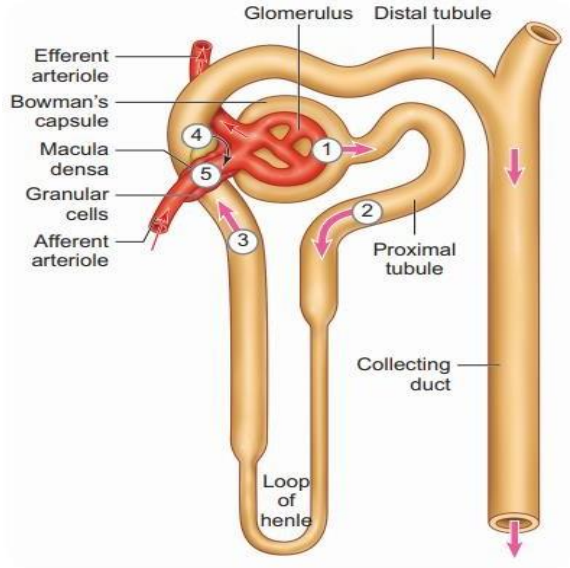

FIGURE 8 SHOWING STRUCTURE OF NEPHRON

The glomerular filtration barrier of the renal corpuscle is composed of the visceral layer of Bowman's capsule, the glomerular basement membrane (GBM), and the fenestrated endothelium of glomerular capillaries. Foot processes that stretch from the podocytes join, leaving filtration slits between them, that the slit diaphragm covers. The lamina rara externa, lamina rara interna, and lamina densa make up the GBM. Simple squamous epithelium makes up Bowman's capsule's parietal layer. It is separated from the visceral layer by Bowman's gap. Mesangial cells are present across the whole renal corpuscle, outside of the capillaries. Specialized mesangial cells outside of the renal corpuscle, juxtaglomerular cells, and the macula densa make up the juxtaglomerular apparatus. In its return to the original glomerulus, the thick ascending limb creates the macula densa, a wall of specialised cells enclosing the afferent arteriole. [55,56].

DIABETIC RETINOPATHY

RISK FACTORS OF DIABETIC RETINOPATHY CAN BE CLASSIFIED AS FOLLOWS:

Non-modifiable	Duration of Diabetes, Genetic Factors, Gender
Modifiable	Glycaemia, Blood Pressure, and Lipid Levels
Others	Carotid arterial disease, pregnancy, renal impairment, and smoking

TABLE .1 RISK FACTORS OF DIABETIC RETINOPATHY

NON-MODIFIABLE FACTORS

DURATION

The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) examined patients with both type 1 and type 2 diabetes mellitus and discovered a connection between the prevalence of diabetic retinopathy and the length of diabetes mellitus. After 20 years of having diabetes mellitus, nearly 99% of type 1 patients and 60% of type 2 patients in the **WESDR** cohort had some kind of diabetic retinopathy Proliferative diabetic retinopathy was discovered in 25% of type 2 patients with a 25-year history of the disease and 50% of type 1 individuals with a 20-year history of the condition**.** [57].

GENDER

In the WESDR trial, men who developed diabetes sooner than women did had a higher incidence of proliferative diabetic retinopathy. But in the **WESDR** trial, there was no discernible difference between males and females in terms of the prevalence or progression of retinopathy [57]. PDR was discovered in 33% of women and 50% of men after 20 years of diabetes, respectively.

GENETICS

Genetic influence has also known to factor in and influence the course of diabetic retinopathy by either altering the onset, progression or severity of DR. heredity plays a vital role leading to estimates ranging from 25% to 50% have been reported for proliferative DR [58].

Patients with the HLA DR 4 and DR 5 phenotypes have an increased chance of developing proliferative diabetic retinopathy.

Seventy loci were found to be related with type 2 diabetes in a study called the **Genome-wide association studies (GWAS)** that was carried out on several populations. Additionally, they found a strong correlation between a variety of mutations and SNPs that affected how linked proteins expressed and had physiological effects and an elevated risk of type 2 diabetes [59].

MODIFIABLE FACTORS

GLYCEMIA

In a study, the trial research group it was observed that for type 1 diabetic patients, a 10% reduction in the haemoglobin A1c (HbA1c) was associated with improvement of DR in the rigorous and traditional treatment group, [60].

Diabetes Control and Complications Trial (DCCT) [61] and the **United Kingdom Prospective Diabetes Study (UKPDS)** have both demonstrated the cost-effectiveness and efficacy of glycaemic control in reducing the incidence and progression of retinopathy. However, it was also observed that the data from these studies, as well as other other studies have confirmed the difficulty in achieving and maintaining good glycaemic control over an extended period of time [62].

The **(DCCT)** also found that a 10% drop in HbA1c (from 8% to 7.2%) causes a 35% to 40% drop in the prevalence of diabetic retinopathy. But rather of using data from **NIDDM** patients, this study used outcomes from **IDDM** patients.

The **ACCORD** Eye study confirmed the importance of maintaining good glycaemic control by lowering HbA1c levels from a mean of 58 to 46 mmol/mol, as well as its correlation with decreased incidences of proliferative retinopathy requiring

photocoagulation or vitrectomy from 10.2% to 6.5% and retinopathy progression was decreased by 42% [63].

BLOOD PRESSURE

Hypertension has been observed to be a causative factor for increased retinal capillary endothelial damage. The constant elevation in blood pressure is responsible for this in already susceptible retinal vasculature in diabetics [64].

The **UKPDS** revealed a link between elevated systolic blood pressure and the higher prevalence of retinopathy. [65].

The **UKPDS** also shown an association between a decrease in the mean systolic blood pressure from 154 to 144 mmHg and a decrease in the number of microaneurysms at 4.5 years of follow-up. At 7.5 years, there were also less hard exudates and cotton-wool spots, a lower need for photocoagulation, and less degeneration of 2-step or more on the ETDRS retinopathy scale [66].

LIPID LEVELS

High serum lipid levels in the ETDRS were linked to a higher occurrence of hard exudates at the macula and lower visual acuity at baseline

OTHER FACTORS

PREGNANCY

Pregnancy is associated with increased risk factor that leads to a progression in retinopathy. The severity of retinopathy is also known to increase, when compared to non-pregnant diabetic women.

It has been observed that Human placental lactogen (hPL) plays an important role in the influence of pregnancy on DR due to its increased production and similarity to growth hormone activity. Pregnancy being a Hyperdynamic circulatory is also known to cause mechanical endothelial damage at the capillary level [67].

SMOKING

Smoking is a significant risk factor, particularly for diabetic people. When difficulties arise early in the course of type 1 diabetes, smoking has been found to be connected to microangiopathy. [68,69]

PATHOGENESIS OF DIABETIC RETINOPATHY

1. ANATOMICAL

a) Thickening of the capillary basement membrane
b) According to electron microscopy, the basement membrane has significantly thickened, showing signs of vacuolization akin to Swiss cheese and the deposition of fibrillar collagen, which is positive for type III collagen.
c) Loss of intramural microvascular pericytes
d) They have been described as empty, balloon-like regions protruding from the capillary wall during digest preparation. This is probably connected to how the sorbitol pathway works.
e) Endothelial cell dysfunction and endothelial cell loss
f) The endothelial cell connections loosen, which may be connected to the ZO-1 protein's decreased expression. In the cytoplasm of endothelial cells, there are fenestrations.

2. BIOCHEMICAL MECHANISMS IN THE PATHOGENESIS OF DIABETIC RETINOPATHY

Individuals with DM experience microvascular abnormalities in the retinal vasculature, renal glomeruli, and peripheral nerve vasa vasorum.

Edema, ischemia, and hypoxia-driven neovascularization are caused by chronic hyperglycaemia's reduction in the production of neuronal cell and endothelium trophic factors. [70]

While atherosclerosis marks the beginning of endothelial dysfunction in non-diabetic patients, it appears that insulin resistance does so in diabetes patients.

Four hypotheses were used to investigate the mechanism of hyperglycaemia-induced microvascular injury.

These are:

I. Increase in polyol pathway flux
II. Build-up of advanced glycation end products (AGEs)
III. Protein kinase C activation (PKC)
IV. Enhanced flux via the hexosamine route

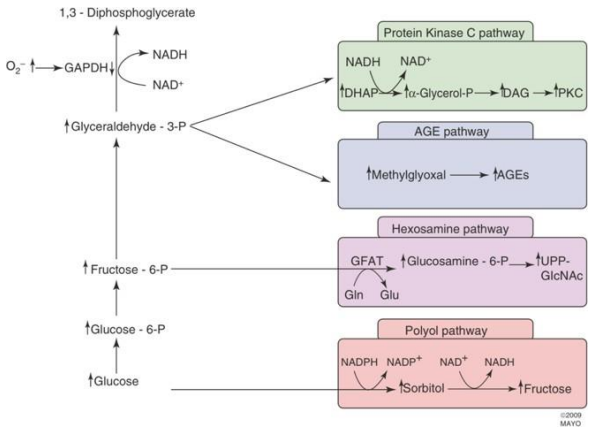

FIG 10. HYPERGLYCEMIA DYSREGULATES FOUR BIOCHEMICAL PATHWAYS.

Increased Polyol Pathway Flux

Aldose reductase in cases of high blood sugar, glucose is converted to sorbitol As NADH levels drop, . Sorbitol is then oxidised to fructose with NADH reconstitution. The oxygenation of sorbitol prevents the enzyme glyceraldehyde-3-aldehyde

dehydrogenase (GAPDH) from working, which raises triose phosphate concentrations and causes the synthesis of methylglyoxal and diacylglycerol (DAG) [71].
Reduction of glucose to sorbitol consumes NADPH, worsening oxidative stress.

Advanced Glycation End Products (AGEs)

AGE formation is promoted by intracellular hyperglycemia, which is found in increased concentrations in glomeruli and diabetic retinal blood vessels [72].
Critical proteins are altered and have their functions changed by AGE precursors. These alter integrins and elements of the extracellular matrix, changing the way that plasma proteins bind to AGE receptors.
By extending the molecular packing of type 1 collagen and altering the collagen type IV composition in basement membranes, advanced glycation end product-induced cross-linking alters blood vessel function.[73] .

Activation of Protein Kinase C (PKC)

When AGE receptors are ligated by hyperglycemia [and the polyol pathway becomes more active], PKC isoforms are indirectly activated. [74]. Nitric oxide production drops and endothelin-1 activity rises as a result of PKC-isoform activation, which is what causes aberrant blood flow in the kidney and retina.
A PKC-specific inhibitor reduces retinal activity and reduces diabetes-related increases in retinal mean circulation time. [75].

Hexosamine Pathway Flux Increased

Over-induction of the hexosamine pathway causes the activation of genes that cause vascular endothelial dysfunction and a variety of other changes that are seen in diabetic retinopathy.

The covalent modification of the transcription factor Sp1 by N-acetylglucosamine (G1cNAc) explains the relationship between the hexosamine pathway and hyperglycemia-induced changes in the transcription of the PAI-I gene, but it is unclear how increased hexosamine pathway flux results in hyperglycemia-induced increases in gene transcription. [76]

PATHOGENESIS OF DIABETIC MACULAR EDEMA

1. **BREAK DOWN OF BLOOD RETINAL BARRIER**
2. Damage to the junctional complexes between RPE cells and capillary endothelial cells, changes in the condition of the cell's membrane or its capacity to pump, or all three of these factors may be to blame. Leakage processes include increased transcellular transport via vesicles, the development of fenestrations across the cytoplasm of endothelial cells, and increased RPE infoldings that promote choroidal to subretinal space transudation.. [53]

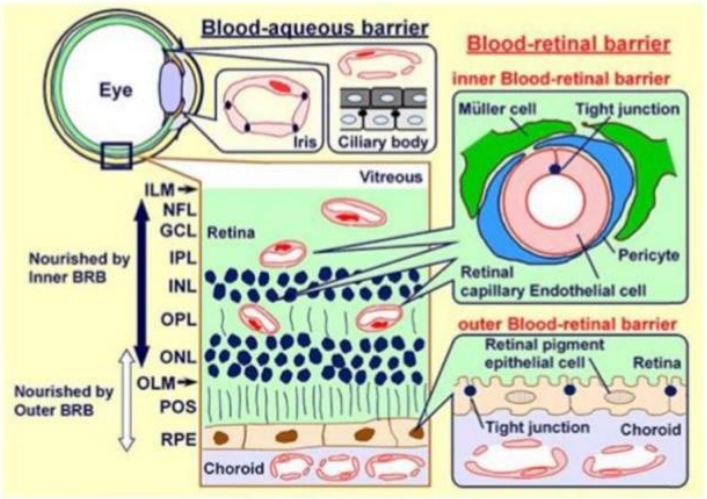

FIG 11. BREAKDOWN OF BLOOD RETINAL BARRIER

ROLE OF VASOACTIVE FACTORS

a. Vascular endothelial growth factor-A
b. Protein kinase C
c. Histamine
d. Angiotensin II

e. Matrix metalloproteinases
f. Pigment epithelium-derived factor.

Vascular endothelial growth factor

Through a number of processes, vascular endothelial growth factor raises vascular permeability (Fig.5)

The process starts by triggering inositol triphosphate (IP3), which releases intracellular calcium and relaxes vascular smooth muscle.

Second, VEGF promotes the synthesis of DAG, which directly raises cellular permeability via DAG-sensitive Ca2+ channels. Thirdly, elevated DAG production activates PKC. [77].

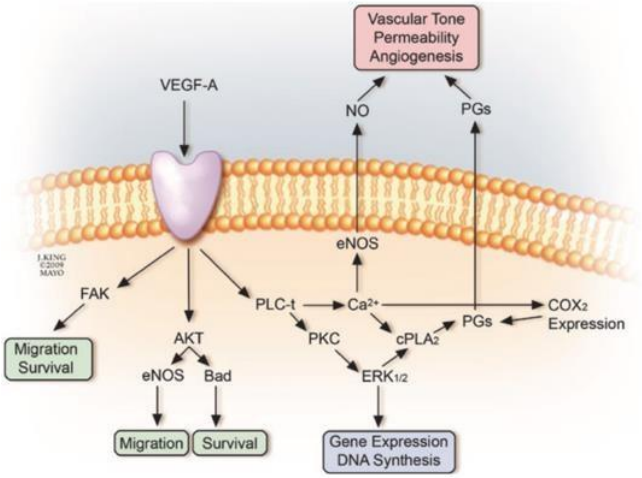

FIG 12. TRANSMEMBRANE RECEPTORS, SITE OF VASCULAR ENDOTHELIAL GROWTH FACTOR-A BINDING

Protein kinase C

Protein kinase C, a member of the serine/threonine protein kinase family, has been linked in three different ways to the aetiology of diabetic BRB breakdown:

VEGF-A mediates its impact.

It has been demonstrated that PKC- regulates and facilitates the regulation of VEGF-A gene expression in a transgenic mouse model.

Secondly, by oxidative stress through ROS produced by hyperglycemia or advanced glycation end-products (AGEs), PKC can be activated.

Thirdly, Phosphorylation of tight junction-associated proteins to induce BRB breakdown is triggered by PKC [78].

Histamine

·Vascular endothelial cells of the retina are very sensitive to histamine.

· Reduces the ZO1 protein expression.

Renin/Angiotensin System

Angiotensin has a major impact on vascular smooth muscle cells, causing them to expand, proliferate, and deposit extracellular matrix proteins. Some of the mediators of these include TGF-1, PDGF, VEGF, insulin-like growth factor, and connective tissue growth factor**. 79**.

Angiotensin II's pro-angiogenic effect on mammalian retinas with oxygen-induced retinopathy is mediated by VEGF. Pharmacological RAS suppression lowers angiogenesis by downregulating VEGF and VEGFR2. **80.** Angiotensin II levels are increased in diabetic macular edoema patients and are associated with vitreous VEGF concentrations. According to study, this may be regulated by the AT1-R/NF-B pathway, opening up new target sites for the prevention of diabetic retinopathy. **81**.

CLINICAL FINDINGS OF DIABETIC RETINOPATHY

Vascular malfunction and decreased perfusion remain the hallmarks of diabetic retinopathy, but a growing body of data suggests that neuroretinal function is impacted before overt vascular abnormalities are apparent.

1. MICROANEURYSM

Retinal capillary microaneurysms are frequently the earliest diabetic retinopathy symptoms to be seen under an ophthalmoscope. The dark red or white fundus patches that have a diameter of 25 to 100 m are saccular dilations of the capillaries. There is no known mechanism for how microaneurysms arise. Alterations in the retinal microenvironment caused by metabolic effects on neurons, glial cells, and endothelial cells, as well as endothelial cell injury related to leukostasis, may be contributory factors.

Perfused microaneurysms are seen on fluorescein angiography as distinct hyperfluorescent patches, with early dye pooling and late leakage.

2. RETINAL HAEMORRHAGES

Retinal haemorrhages come in two different shapes and can be either:

- ‘Flame-shaped," which typically develops from the superficial capillary plexus and occurs within the nerve fibre layer.
- "Dot and blot," which takes place in the spaces between the vertically oriented axons that emerge from the deep capillary plexus and are located in the inner plexiform layer.
- Unlike microaneurysms, haemorrhages typically signify a more serious form of DR.

3. HARD EXUDATES

Hard exudates are small, white or yellowish-white deposits with definite edges. The exudates are pathologically observed as fat-filled (lipoidal) histiocytes in the OPL or Henle fibre layer. Foamy histiocytes are present in massive exudation in the OPL. Circinate retinopathy is the term for the circular pattern caused by the accumulation of exudates around diseased vessels.

4. SOFT EXUDATES

Cotton-wool spots occur in the nerve fiber layer and under the ILM. Cotton-wool spots are indicative of backup of axoplasmic flow. Histopathological, the cotton-wool spots are cystoid bodies and are the swollen ends of ruptured axons in the nerve fiber layer in the infarcted area, just under the ILM

5. INTRARETINAL MICROVASCULAR ANOMALIES (IRMA)

Intraretinal microvascular abnormalities (IRMAs) are shunt vessels and appear as abnormal branching or dilation of existing blood vessels (capillaries) within the retina that act to supply areas of non-perfusion in diabetic retinopathy.

These vessels represent either new vessel growth within the retina or remodelling of pre-existing vessels through endothelial cell proliferation stimulated by hypoxia bordering areas of capillary nonperfusion.

Cotton wool patches and localised arteriolar blockage may coexist with the collateral creation process, which is a variation responsible for the development of IRMA. Cotton wool spots (CWS) and intraretinal microvascular abnormalities are frequently linked to early retinal ischemia (IRMA).

6. OPTIC DISC CHANGES

Diabetes papillopathy, which causes swollen optic discs, is common in diabetic patients but has no relationship to retinopathy levels. Diabetic papillopathy must be distinguished from neovascularization and ischemic optic neuropathy (NVD

7. RETINAL NEOVASCULARIZATION

Retinal neovascularization arises as a result of advanced retinal ischemia. Neovascularization elsewhere (NVE) or neovascularization of the disc (NVD) refers to generating new vasculature from retinal or disc vessels that already exist, which develop along the scaffolding of the posterior hyaloid surface.

The level of intraocular VEGF typically correlates with the rate of blood vessel growth. Although new vascular growth is the hallmark of proliferative diabetic retinopathy (PDR), patients may also have all the signs of non-proliferative diabetic retinopathy, including macular edoema .

8. VITREO-RETINAL INTERFACE ANGIOGENESIS

The inner side of the retina, which is most firmly adhered to the pars plana, and the posterior hyaloid face of the vitreous gel are where new blood vessels develop. Typically, they have no symptoms. The difficulties that result from the dynamic interplay at the vitreoretinal interface are what produce the symptoms. The contact raises the new vessel off the retinal surface and causes an inflammatory reaction and scarring. Additional contraction may result in vitreous haemorrhage and traction retinal detachment.

9. RETINAL DETACHMENTS

The vitreoretinal attachments determine the extent and location of tractional retinal detachment.

CLASSIFICATION OF DIABETIC RETINOPATHY

There are mainly two types of classification:

A. ETDRS CLASSIFICATION OF DIABETIC RETINOPATHY

"Disease severity level	Findings observable upon dilated ophthalmoscopy
MILD NPDR	• At least one microaneurysm, and definition not met for Moderate NPDR. • 5 % risk of progressing to PDR within 1 year and a 15 % risk of progressing to high-risk PDR within 5 years
MODERATE NPDR	• Haemorrhages and/or microaneurysms, and/or soft exudates, venous beading, or intraretinal microvascular abnormalities definitely present; • Definition not met for severe NPDR • The risk of progression to PDR is 12-27 % within 1 year, and 33 % within 5 years
SEVERE NPDR	The 4-2-1 rule; one or more of: • Severe haemorrhages in all 4 quadrants • Significant venous beading in 2 or more quadrants • Moderate IRMA in 1 or more quadrants • The risk of developing PDR is 52 % within 1 year and 60 % within 5 years.
VERY SEVERE NPDR	• Two or more of the criteria for severe NPDR. • The risk of developing PDR is 75 % within 1 year.
EARLY PDR	• New vessels; and definition not met for high-risk PDR
HIGH RISK PDR	• New vessels on or within one disc diameter of the optic disc (NVD with or without vitreous haemorrhage or pre retinal haemorrhage; • Accompanied by new vessels, either NVD< or new vessels elsewhere (NVE)>/= one quarter disc area"

Table 2. ETDRS Classification of Diabetic retinopathy

- **Clinically important macular oedema (CSME) was described as follows in ETDRS:**
  - ·Within 500 microns of the macula's center, the retina thickens.
  - ·If connected to thickening of the retina, exudates that are 500 microns or less from the macula's center (which may be outside the 500-micron range).
  - Any portion of the retina that is thicker than one disc area (1500 microns) and falls within one disc diameter of the macula's centre

.

MODIFIED AIRLIE HOUSE CLASSIFICATION

Seven standard photographic fields are shown for the right eye. Field 1 is centered on the disc, field 2 on the macula, and field 3 temporal to the macula so that its nasal edge passes through the center of the macula. Fields 4 to 7 are tangential to a vertical line passing through the center of the disc and to horizontal lines passing through its upper and lower poles.

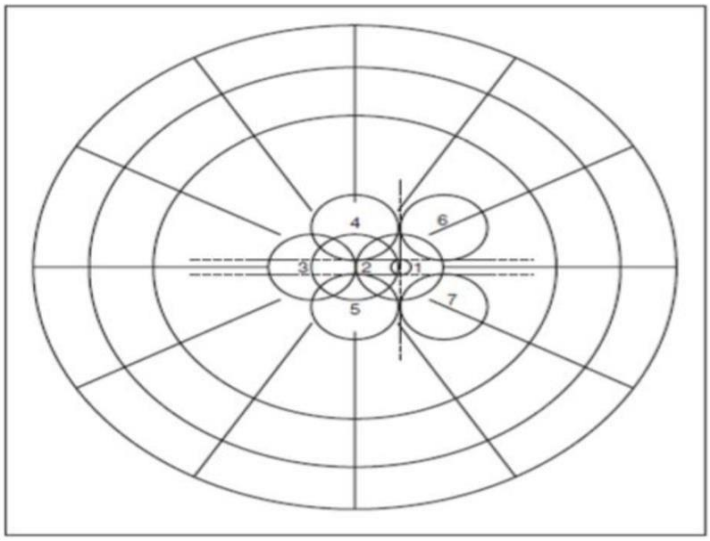

FIG 13. : MODIFIED AIRLIE HOUSE CLASSIFICATION

"ETDRS RECOMMENDATION FOR FOLLOW-UP"

CATEGORY	FOLLOW UP
NO DIABETIC RETINOPATHY	• Review in 12 months

MILD NPDR	• Review range of 6-12 months, depending stability, severity and associated systemic features
MODERATE NPDR	• Review in roughly six months
SEVERE NPDR	• Review in three months
VERY SEVERE NPDR	• Review in two to three months
EARLY PDR	• A therapy plan based on the stability, seriousness, and associated systemic difficulties Review in 2 months if the patient is not receiving treatment

Table 3: ETDRS RECOMMENDATION FOR FOLLOWUP IN DR

DIABETIC CHOROIDOPATHY

It has been suggested in previous literature that diabetes can cause a non-inflammatory deterioration of the choroid. a Hidayat and Fine study (1985) [19], It was observed that some arteries had arteriosclerotic alterations together with choriocapillaris (CC) dropout, luminal constriction, and thickening of basement membranes. Loss of CC, big and intermediate blood vessel tortuosity, vascular hypercellularity, and microaneurysms were reported in patients with diabetic choroids, according to a 1989 study by **Fryczkowski et al.**

CHOROIDAL VASCULAR LOSS

Endogenous alkaline phosphatase (APase) enzyme histochemical activity has shown decrease of functional CC in diabetic choroid (Lutty and McLeod, 2005)

Histochemical study of large fields of CC revealed malfunction in flat mount preparations of diabetic choroids in both diabetics with and without retinopathy at all stages of the disease (Lutty and McLeod, 2005; McLeod and Lutty, 1994) [21]

There are two different forms of choroidal vascular loss

1. Diffuse
2. Complete

In diffuse loss there is capillary loss but without any defined area, however in complete loss there was defined borders with atrophy.

ETIOLOGY

Diabetes is known to initiate an inflammatory response as part of its pathological process. TNF and IL1 levels had been found to be elevated (Lampeter et al., 1992) [82]

The presence of activated leukocytes, such as polymorphonuclear neutrophils (PMNs), circulating in diabetics in comparison to non-diabetic's nondiabetics (Wierusz-Wysocki et al., 1987) [83]. Compared to nondiabetics, diabetic PMNs have a stiffer cytoplasmic membrane, which increases the likelihood that they will become caught in the microvasculature and lead to capillary blockage (Kelly et al., 1993).

Firm adhesion to the endothelium cells is caused by PMNs adhering to them after rolling over the surface, which is mediated by P-selectin. ICAM-1 and activated PMNs are known to exhibit CD11/CD18 on their surfaces, which aids in their ability to bind to ICAM-1 (Springer, 1994)

CHOROIDAL NEOVASCULARIZATION IN DIABETIC CHOROIDOPATHY

CC depletion in diabetic choroid eventually led to development of hypoxia in the choroid and overlying RPE. this hypoxic causes the upregulating of VEGF production leading to angiogenesis (Shima et al., 1995) [84]

EVALUATION

1. ICG angiography
2. colour Doppler
3. Optical coherence tomography (OCT)

ICG angiography and FA shows areas with hypofluorescence and late choroidal nonperfusion regions, whereas OCT offers a better assessment of the blood vessels in the Sattler's and Haller's layer. OCT also helps with evaluation of choroidal nonperfusion or poor perfusion, as well as choroidal hypoxia areas. Additionally, localized dilatations and choroidal vascular remodeling in the form of crooked, tortuous, and beaded choroidal arteries have been reported.. examination and measurement of choroidal thickness in diabetic choroidopathy is also an effective method to assess the choroidal status. It has been observed, due to the hypoperfusion in diabetics there is a reduction in the choroidal thickness in time.

DIABETIC NEPHROPATHY

Diabetic nephropathy (DN) or diabetic kidney disease is a syndrome with characteristic features of urine albumin excretion in pathological quantities, diabetic glomerular lesions along with the loss of glomerular filtration rate (GFR) [85].

Diabetic kidney disease (DKD) is the major causative factor for end-stage kidney disease (ESKD). Diabetic retinopathy is majorly caused by the involvement of microvascular components, and can occur in both type 1 and type 2 diabetes mellitus. Albuminuria with a progressive decline in the glomerular filtration rate are some of the important presenting features. progression of the discord can be substantially reduced when treatment is initiated early [17].

PATHOPHYSIOLOGY

Similarly, to diabetic retinopathy and choroidopathy, Hyperglycemia tends to be the initiating factor. It causes the synthesis of harmful reactive oxygen species and the activation of many pathways. These pathways can include the protein kinase C, polyol and hexosamine pathway. Eventually there is formation of advanced glycation end products (AGE). Another crucial element is inflammation, which shows itself as a rise in cytokines and chemokines. These inflammatory mediators, which cause inflammation fibrosis and increased vascular permeability, include IL-6, MCP-1, TGF-beta (transforming growth factor-beta), and VEGF (vascular endothelial growth factor).

These different pathways culminate in A podocytopathy, which then prompts albuminuria. Proteinuria is the outcome of the resultant intraglomerular and systemic

hypertension. Proteinuria induces the transition of epithelial-mesenchymal cells into fibroblasts and persistent tubular damage.

INVESTIGATIONS

Urine albuminuria and estimated GFR (eGFR) are reliable diagnostic and monitoring assays. Urea, creatinine, and protein levels in urine are measured via urine analysis. A nephritic cause is ruled out using microscopy. To rule out multiple myeloma, serum and urine electrophoresis are performed, and renal ultrasonography is performed to measure the size of the kidneys. When the diagnosis is unclear, a kidney biopsy is performed.

DIAGNOSTIC TESTING

1. DIRECT OPHTHALMOSCOPE

In 1851, Helmholtz invented the first direct ophthalmoscope. The direct ophthalmoscope allows a highly magnified, monocular image of the retina and optic disk. The fundus is viewed through a tiny peephole located just above the illumination source of the instrument, producing an upright virtual image.

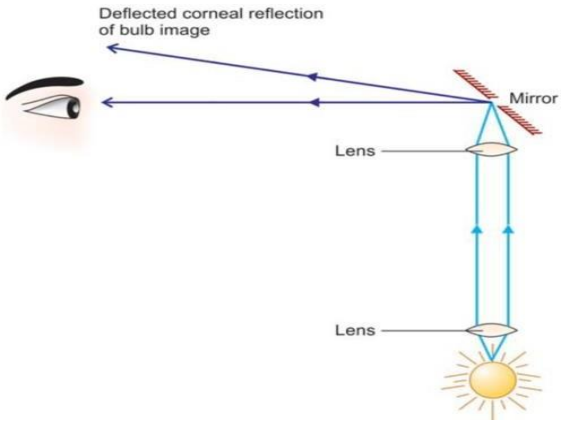

FIG 14 RAY DIAGRAM OF THE OPTICS OF THE DIRECT OPHTHALMOSCOPE

2. INDIRECT OPHTHALMOSCOPE

Introduced by Schepens, binocular indirect ophthalmoscopy offers an excellent resolution of fundus details. The binocular indirect ophthalmoscope provides a brightly illuminated, wide-angle, and stereoscopic view of the retina.

The power of the lens depends upon the magnification used and the refraction of the eye.

- 15D lens (magnifies four times and field is about 40°) is used for examination of the posterior pole.
- 20D lens (magnifies three times and field is about 45°) is most commonly used for the general overall examination of the fundus.
- 30D (magnifies 2.5 times and field is 60°) has a shorter working distance and is useful when examining the patient with small pupils.
- 40D lens (magnifies 1.5 times and field is about 65°) is used mainly to examine small children. Panretinal 2.2 lens magnifies three times, and the field observed is about 55°

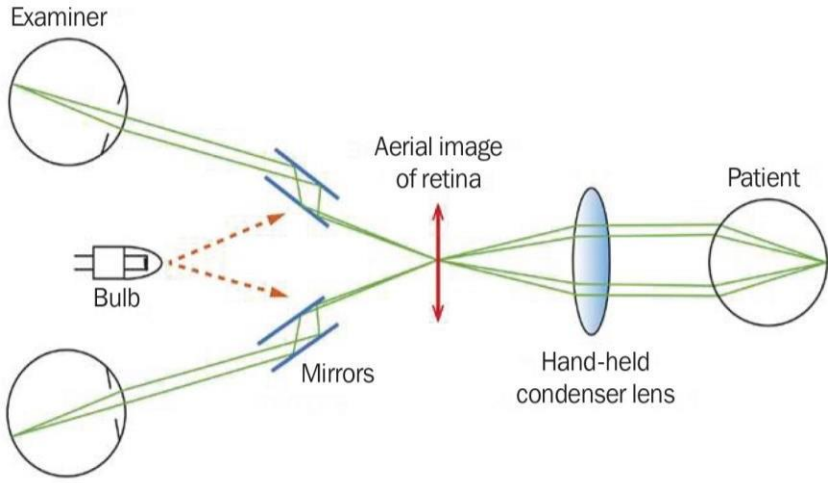

FIG.15 RAY DIAGRAM OF THE OPTICS OF THE INDIRECT OPHTHALMOSCOPE

3. FUNDUS PHOTOGRAPHY

- The digital fundus camera is a low-power microscope specialized with a camera attached. The optical design of the camera is similar to the monocular indirect ophthalmoscope principle.
- The fundus camera provides a magnified upright view of the fundus.

- In colour fundus photography, the retina is examined in full colour and illuminated by white light.
- Red colour is removed by filtration of imaged light, which improves the contrast of vessels and other structures in red-free photography. It shows small haemorrhage's, microaneurysms, and hard exudates with more clarity than colour fundus photos.

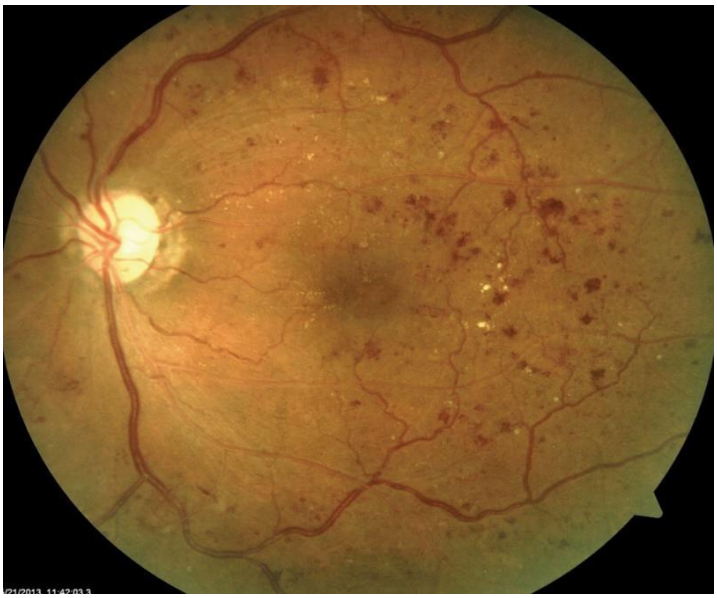

Fig 8. Fundus photography of Moderate NPDR

4. FLUORESCEIN ANGIOGRAPHY

In FA, through intravenous injection of a fluorescent dye, the vessels are brought into high contrast. With an excitation color, the retina is illuminated, which fluoresces the light of another color. By using a filter, the excitation color is excluded, and by passing the fluorescent stain, a higher contrast of the vessels is produced. Photos of the timed sequence show the dye's progression into the vessels reveals the flow dynamics and the different layers of the retina. Thus, different areas of the retinal architecture are delineated.

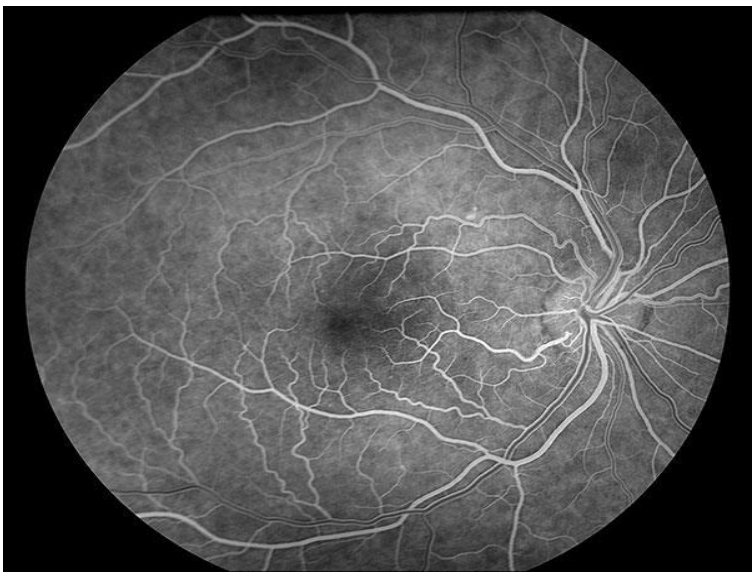

FIG 16. FLUORESCEIN ANGIOGRAM SEQUENCE, AVPHASE AND PROGRESSING TO MIDTRANSIT

Clinical Applications of Fluorescein Angiography

Macular edema and non- proliferative diabetic retinopathy and to evaluate areas of capillary nonperfusion. Neovascularization of the retina elsewhere would also be identified. Fluorescein angiography is also useful to monitor macular edema post-laser. To evaluate the progression and resolution of residual macular edema,

comparison photographs and angiographic frames from previous examinations can be used.

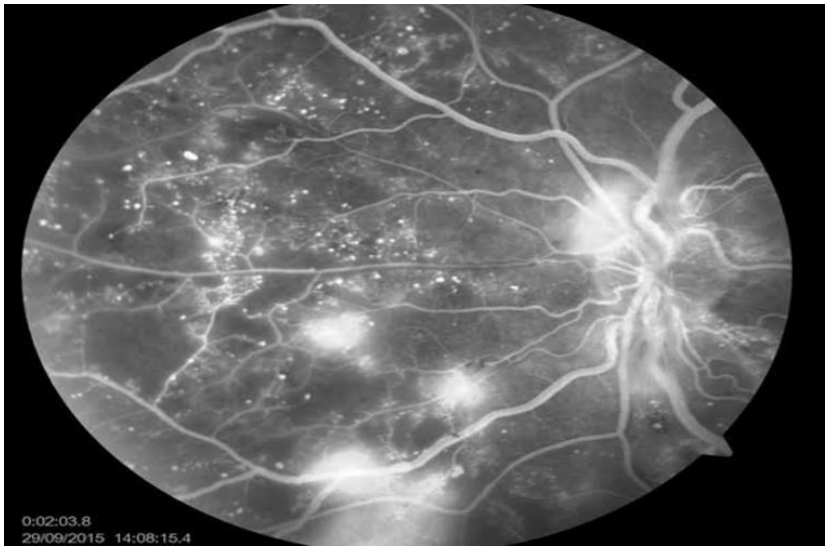

FIG 17. FFA IN PDR

5. INDOCYANINE GREEN ANGIOGRAPHY

Indocyanine green dye angiography (ICG) is a method to capture the flow of the dye in the choroid. In approximately 15% of patients with nonproliferative diabetic retinopathy, ICG can reveal additional microvascular complications in diabetes not seen with conventional fluorescein angiography

Clinical Applications of Indocyanine Green Angiography - ICG is used to follow in patients with choroidal lesions or those patients with diabetes with an abnormal presentation of diabetic retinopathy.

SEVEN STANDARD DIABETIC PHOTOGRAPHIC FIELDS

This is a technique of taking photos in a series using a digital fundus camera. A 35-degree field of view is utilized.

The fields are centered as follows:

FIELD 1	THE OPTIC NERVE IS CENTERED
FIELD 2	THE MACULA
FIELD 3	TEMPORAL TO THE MACULA
FIELD 4	SUPEROTEMPORALLY, EXCLUDING THE OPTIC DISC
FIELD 5	INFEROTEMPORALLY EXCLUDING THE OPTIC DISC;
FIELD 6	SUPRANASALLY ALONG THE ARCADES, EXCLUDING THE OPTIC
FIELS 7	INFERONASALLY- EXCLUDING THE OPTIC DISC.

TABLE 4 STANDARD DIABETIC PHOTOGRAPHIC FIELDS

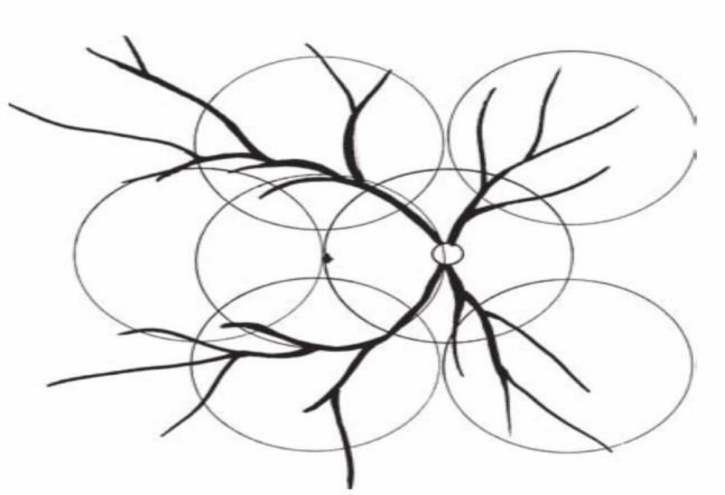

FIG 18. DIAGRAM OF SEVEN STANDARD PHOTOGRAPHIC FIELDS.

6. OPTICAL COHERENCE TOMOGRAPHY

An optical equivalent of the frequently used ultrasonic imaging is optical coherence tomography (OCT). It works by collecting and creating cross sections of the retina using low coherence interferometry. To obtain a decoded image of the tissue microstructures, light scattering from tissue is collected and processed.

It makes use of infrared light from a two-part super luminescent diode.

1. The light that a reference mirror reflects

2. light reflected by living tissue.

Along with their amplitude information, the two reflected light beams are created to produce interference patterns that aid in determining an echo time delay. A 2-dimensional image is created by combining scans taken by a transverse scanning mechanism at adjacent retinal regions. One can attain image resolutions of 1 to 15 m.

There are two primary OCT technologies used in point-scanning/point-detection technology,

1. time-domain OCT (TD-OCT)
2. Fourier-domain OCT (FD-OCT).
3. full-field OCT (FF-OCT) - Direct acquisition of 2D OCT

TD-OCT is based on a detection technique that uses a low-coherent light source and a scanning reference delay. The first OCT technology to be created was TD-OCT, which initially appeared in the 1990s. In TD-OCT measurements, light echoes are progressively caught by the step-movement of a reference mirror.

Fourier-domain OCT imaging can also be performed in two ways: by spectral-domain OCT (SD-OCT) and by swept-source OCT (SS-OCT). In FD-OCT, all of the spectral components of the source spectrum are concurrently recorded as light echoes that arrive at the same time from all axial depths. They are able to acquire data at faster rates. Before detection with SD-OCT, the interference pattern dissipates.

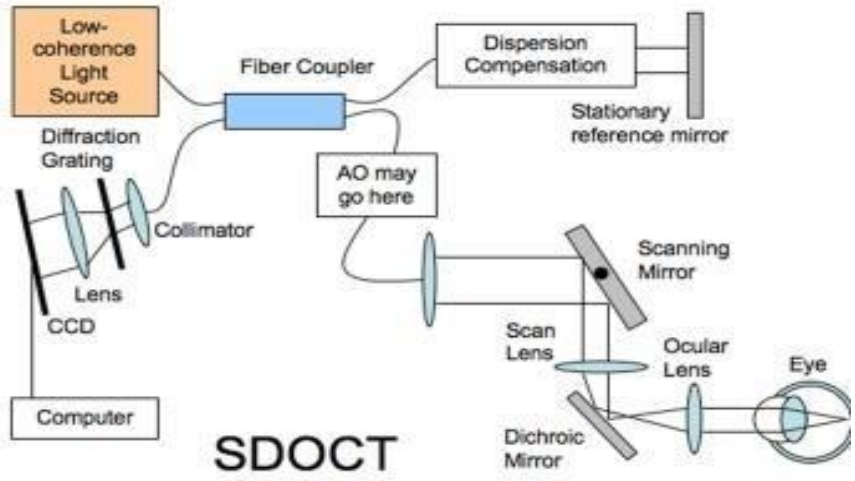

FIG 19. WORKING PRINCIPLE OF OCT

Konstantina Sampani et al, in their study "Comparison of SDOCT Scan Types for Grading Disorganization of Retinal Inner Layers and Other Morphologic Features of Diabetic Macular Edema" conducted in 2020, concluded that reproducibility for SDOCT parameters of DRIL and intraretinal cysts was high across all five SDOCT scan types; thus, evaluation of DRIL is feasible using multiple SDOCT models in eyes with DME [86].

Ahmed H. ElTanboly et al, in 2020 carried out a study to assess An automated approach for early detection of diabetic retinopathy using SD-OCT images [87]. They characterized Each layer of retina by its thickness, tortuosity, and normalized reflectivity and

concluded that SD-OCT is a novel automated method that enables quantitative analysis of the changes in each layer of the retina caused by diabetes. They also stated it was a reliable non-invasive diagnostic tool for early detection of DR

Gerard A. Lutty in his study on diabetic choroidopathy in 2017 stated that, The tortuosity and loss in intermediate and major blood vessels in Sattler's and Haller's layer that were previously observed with histological techniques have been documented by EDI-SD OCT and SS OCT. [88]

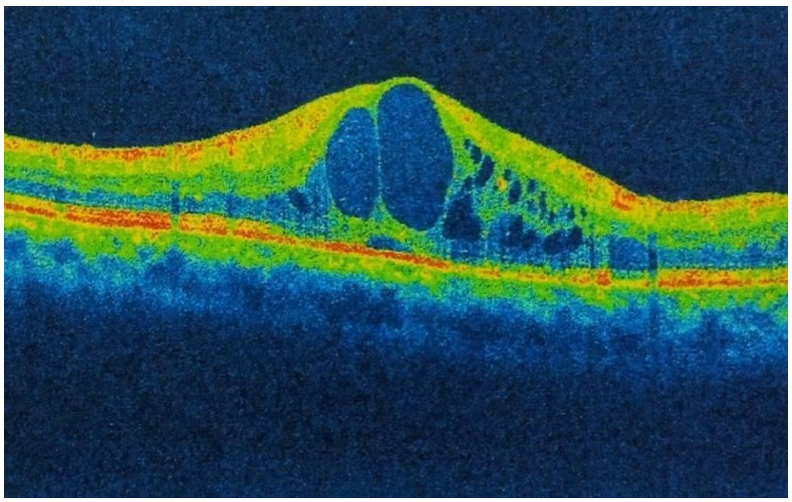

FIG 20. OCT SCAN OF MACULAR EDEMA

In their study on the role of biochemistry and molecular cell biology in the evolution of diabetic retinopathy, Brownlee M et al. identified increased polyol pathway flux, increased advanced glycation end products (A.G.E.s), activation of the isoform of protein kinase C (PKC), and increased hexosamine pathway flux as the mechanisms causing diabetic retinopathy[89].

The E.T.D.R.S. group developed the modified Airlie House classification of diabetic retinopathy, which was used in the D.R.S., based on the specific lesions seen. There are five levels of diabetic retinopathy: mild, moderate, severe, very severe, early PDR, and high-risk PDR. [90].

CHOROIDAL THICKNESS AND DIABETES MELLITUS

1. In 2012 Caio v. regatieri, Ph.D., laurenbranchini, jillcarmody, James g. Fujimoto, and jay s. Duker, in their study on choroidal thickness in patients with diabetic retinopathy analyzed by spectral-domain optical coherence tomography, concluded that choroidal thickness was altered in diabetics and may be related to the severity of retinopathy, and the presence of diabetic macular edema is associated with a significant decrease in the choroidal thickness [91]
2. In 2013 Hyo Kyung Lee ,Ji Won Lim , Min Cheol Shin1 . Concluded, a significant decrease in CT between mild-to-moderate NPDR, severe NPDR, and PDR groups ($p = 0.005$, $p < 0.001$, $p < 0.001$, respectively). There were no significant differences among the mild-to-moderate NPDR, severe NPDR, and PDR groups ($p > 0.05$). The retinal foveal thickness was significantly increased only in the severe NPDR and PDR groups compared with the controls ($p < 0.001$). In the no-diabetic-change and mild-to-moderate NPDR groups[92]
3. In 2015 Aditya Sudhalkar, et al. In their study to evaluate choroidal thickness (CT) change by SDOCT in various grades of diabetic retinopathy in125 diabetic patients and 110 age-matched normal patients. They found Subjects with diabetes without retinopathy had a greater subfoveal choroidal thickness (SFCT) than subjects with diabetes with retinopathy. And patients with PDR had thinner SFCT than those with NPDR. They concluded that control patients had a greater SFCT than patients with diabetes and that the thinning progressed with the severity of DR[93]
4. In 2019, Hamidreza Torabi1 reported that there is a substantial association between choroidal thickness and haemoglobin A1c levels in individuals with type 2

diabetes, and that better glycemic control with HbA1c <7% may prevent choroidal thinning.[94]

5. In 2020 Wei Wang, Sen Liu, ZhihanQiu, Miao He, Lanhua Wang, Yuting Li, and Wenyong Huang concluded. Choroidal thickness increased in the early stages of diabetes, and further decreased with diabetic retinopathy progression. Diabetic macular edema had no significant association with choroidal thickness. These findings provide more insight to suggest that choroid alterations have a role in the DR pathogenesis [95]

CHOROIDAL THICKNESS AND NEPHROPATHY

1. In 2014, Won June Lee, Lucia Sobrin, MinJeong Lee, Min-Ho Kang, Mincheol Seong, and Heeyoon Cho discovered that in Korean individuals with diabetes, proliferative diabetic retinopathy is linked to microalbuminuria and DR is linked to overt nephropathy. Their findings also indicated that prompt evaluation of the patient's renal condition should be advised when an ophthalmologist discovers the presence of DR or PDR. [96]

2. In 2019 Antonio Manuel Garrido-Hermosilla1 et al. in their study on Renal function and choroidal thickness did use swept-source optical coherence tomography in diabetic patients, concluded Choroidal thickness could represent an additional tool to help clinicians predicting the renal status in ocular treatment-naïve diabetic patients [97]

MATERIALS AND METHODS

This research is a cross-sectional and time-limited study on patients attending the outpatient and inpatient departments of Ophthalmology, BLDE (DU.).'s Shri B.M. Patil Medical College, Hospital and Research Centre, Vijayapura.

The study includes a total of 192 patients of which 96 patients with Type 2 Diabetes Mellitus and 96 age matched controls. the diabetic group are further grouped into three with those having diabetic retinopathy, those without diabetic retinopathy and those with diabetic nephropathy.

They will be screened for Diabetic Retinopathy by complete ophthalmic examination, including detailed History.

HISTORY:

An extensive history was used to screen every patient. It was also necessary to record the history of any past eye surgery, laser therapy, or other medical treatments, as well as the use of oral hypoglycemic medicines, insulin, and other medications.

OCULAR EXAMINATION

- Snellen's chart was used to measure visual acuity, and patients' refractive status was recorded.
- A biomicroscope with a slit lamp was used to evaluate the anterior segment.
- The Goldmann Applanation Tonometer was used to measure intraocular pressure.
- Diabetic retinopathy was examined by a dilated fundus examination using 90D & indirect ophthalmoscopy
- Photographs of the fundus were obtained for documentation.

- Retinopathy grades were then determined and categorised in accordance with the ETDRS (Early Treatment Diabetic Retinopathy Study) grading system.

The patients were explained about the study and patients' willful consent was taken. Details of the patients including history, clinical examination, investigations were recorded

INVESTIGATIONS

1. EVALUATION OF DIABETES MELLITUS

- Blood glucose levels at fasting (FBS)
- Levels of postprandial blood sugar (PPBS)
- Random blood sugar levels (RBS)
- Glycolsated haemoglobin (HBA1c) were done to evaluate the diabetic status of the patient.

➢ Biochemical parameters were analyzed in clinical biochemistry laboratory using commercial kit adapted to auto analyzer. Serum was separated by centrifugation at 4,000 rpm for 10 min.Plasma glucose level was estimated by glucose oxidase and peroxidase (GOD-POD) end point assay method.

➢ The biomarkers' normal ranges are as follows.:

✓ Fasting Blood Sugar: 70 to 110 mg/dl

✓ Post prandial Sugar: 110 to 140 mg/dl

✓ HbA1c:

2. ASSESSMENT OF NEPHROPATHY IN DIABETIC PATIENTS

- Albumin excretion in the form of microalbuminuria will be used as a marker of nephropathy changes
- Microalbuminuria will be defined as 24 hours excretion of albumin in the range of 30-300mg/dl
- Urinary albumin excretion less than 30mg/dl will be considered normal
- Urinry albumin excreation between 30mg/dl – 300mg/dl were considered significant microalbuminuria
- And urinary albumin excretion above 300mg/dl will be considered as macroalbuminuria
- Serum creatinine levels were measured On the EM 360, a Fully Automated Biochemistry Analyzer, creatinine was calculated using the modified Jaffe's Method and urea by the Urease-Berthelot's method.
- Serum urea was assessed
- eGFR will also be used in the assessment of nephropathy
- To estimate the GFR, an abridged equation that was created using data from the Modification of Diet in Renal Disease research was used to determine the kidney function level as follows:
- eGFR ¼ 186.3 x (serum creatinine)1.154 x age0.203 x (0.742 for women).

✓ An eGFR of less than 60 mL/min/1.73m2 was used to identify chronic kidney disease (CKD).

✓ The biomarkers' normal ranges were as follows:

✓ Serum Urea: 15 to 40 mg/dl

✓ Serum Creatinine:

- In Males 0.6 to 1.2 mg/dl and in
- Females 0.5 to 1.1 mg/dl

3. CHOROIDAL THICKNESS

- SDOCT ASSESSMENT OF THE CHOROIDAL THICKNESS
- SD-OCT; (ZEISS CIRRUS 500 HD-OCT) was carried out on day of blood sampling without pupillary dilation. using EDI-OCT imaging Each eye's central sub-foveal choroidal thickness will be measured with the available calliper (CIRRUS software version 8.0; ZEISS CIRRUS 500) From the hyper-reflective line corresponding to the Bruch's membrane under the retinal pigment epithelium (RPE) to the choroid and sclera inter face, the central horizontal B-scan travels directly through the foveal centre. The central subfoveal pol will therefore be 500 m in the nasal and temporal directions based on the measures of choroidal thickness.
- Sdoct scans will be performed in the EDI mode
- Choroidal thickness measurements will be taken from the area extending from the outer margins of the retinal pigment epithelium to the inner sclera
- Measurements will be taken at three points, the subfoveal area, the area temporal to the foveal center, and the area nasally to the foveal center
- Retinal status was documented by a post-pupillary dilation fundus camera

STATISTICAL ANALYSIS

- **Formula used to calculate the sample size:**

$$N = 2\left[\frac{(Z_a + z_\beta) * S}{d}\right]^2$$

- ✓ **Z**a - Level of significance=95%
- ✓ **Zβ** - the power of the study=90%
- ✓ **d**= clinically significant difference between two parameters
- ✓ **SD** = Common standard deviation

- The anticipated Mean ± SD of Nasal Choroidal thickness in non-diabetic patients is 200.5±51.5 and in Diabetic without Retinopathy patients 178.6±56 resp.
- The required minimum sample size is 96 per group (i.e., a total sample size of 192, assuming equal group sizes) to achieve a power of 95% and a level of significance of 5% (two-sided) for detecting a true difference in means between two groups.

- **CALCULATED SAMPLE SIZE - 192**

STATISTICAL TOOLS USED FOR DATA ANALYSIS AND RESULTS TABLES ARE EVOLVED THROUGH DATA ANALYSIS TOOL IN MS-EXCEL AS AN ADD ON TOOL

THEORETICAL CONCEPTS AND EQUATIONS

COVARIANCE:

- It is a systematic relationship where changes in one random variable are mirrored by comparable changes in the second random variable
- t can have any value between -∞ to +∞, with a positive value denoting a positive relationship, a negative value denoting a negative relationship, and a value of zero denoting no relationship.
- Calculation of Covariance:
- For the set of 'n' units of observations be given by the ordered pairs (x_1, y_1), (x_2, y_2).....(x_n, y_n), where n is the number of sets or observations.

  Calculate $\bar{x} = (x_1+x_2+\ldots\ldots\ldots +x_n)/n$ or $(\sum_{i=1}^{n} x_i)/n$

  Calculate $\bar{y} = (y_1+y_2+\ldots\ldots +y_n)/n$ or $(\sum_{i=1}^{n} y_i)/n$

Calculate: $\sum_{i=1}^{n}(x_i - \bar{X}) (y_i - \bar{y})$

Covariance: $(X, Y) = \dfrac{\sum_{i=1}^{n}(x_i - X) (y_i - y)}{n}$

CORRELATION:

- A measure which determines the change in one variable due to change in another variable.
- Correlation can range from -1 to +1, with close values to +1 indicating high positive correlation and close values to -1 indicating strong negative correlation.

$$\text{Correlation } (X, Y) = \frac{\dfrac{\sum_{i=1}^{n}(x_i - X) (y_i - y)}{n}}{\sqrt{\text{Variance of X} * \text{ Variance of Y}}}$$

ANALYSIS OF VARIANCE (ANOVA):

Analysis of variance is a collection of statistical models and their associated estimation procedures used to analyse the differences among group means in a sample. There are two types i.e., one-way anova and two-way anova.

a) <u>Calculation of Variance Between the Samples:</u>

It is the sum of the squares of the deviations of the means of various samples.

(i) Calculate the sample means $\overline{X_1}, \overline{X_2}$…….$\overline{X_k}$ of k samples.

(ii) Calculate mean for it i.e. $\frac{\overline{X_1} + \overline{X_2}\text{…….}\overline{X_k}}{K}$ = T/ N where

T= grand total of all observations and N = total No.of observations in K samples.

Calculate find. $\overline{X_1} - \overline{X}, \overline{X_2} - \overline{X},$ ……$\overline{X_k} - \overline{X},$

Calculate: SSB (or SSC) = Sum of the Squares of the variations between the samples (or between the columns)

$= \sum_{i=1}^{k} n_I (\overline{X_i} - \overline{X})^2$

(a) Calculations of Variance within the samples:

It is the sum of the squares of the deviations of the means of various samples.

(i) Calculate the sample means $\overline{X_1}, \overline{X_2}$…….$\overline{X_k}$ of k samples.

(ii) Calculate the deviations of various k samples from mean values and Square these deviations and obtain their total

Calculate: SSW = Sum of the squares of the variations within the samples.

$$\sum (X_1 - \overline{X_1})^2 + \sum (X_2 - \overline{X_2})^2 + \cdots\cdots\cdots\cdots\cdots\cdots\cdots \sum (X_K - \overline{X_K})^2$$

(C) **Calculation of the Test Statistic F**

Assuming that H_o is true, the Test Statistic

CONCEPT OF P VALUE

The p-value is calculated using the sampling distribution of test statistic under Null Hypothesis, the sample data, type of test being done.

What Is P-Value?

The probability of receiving outcomes as extreme as those of a statistical hypothesis test, assuming that the null hypothesis is true, is known as the p-value in statistics. The smallest level of significance at which the null hypothesis would be rejected is provided by the p-value, which is used as an alternative to rejection points. The alternative hypothesis is supported by more robust evidence when the p-value is lower.

How Is P-Value Calculated?

P-values are computed using spreadsheets, statistical software, or p-value tables. A reader could occasionally find it challenging to compare the outcomes of two distinct tests since different researchers employ various levels of significance when studying an issue. P-values offer an answer to this issue.

The researchers might give the reader the p-value of the hypothesis test to get around this problem and let them assess the statistical significance. A p-value method to hypothesis testing is what it is.

P-Value Approach to Hypothesis Testing

The p-value approach of hypothesis testing uses the estimated probability to determine whether there is enough data to reject the null hypothesis. The null hypothesis, often known as the conjecture, is the initial claim made about a population (or the process used to produce the data).

If the population parameter is different from the value of the population parameter specified in the conjecture, this is mentioned in the alternative hypothesis.

The significance level, which establishes the minimum p-value required to reject the null hypothesis, is typically established in advance

Type I Error

Falsely rejecting the null hypothesis is a type I error. This happens when the null hypothesis is rejected because the p-value is less than the significance level even though the null hypothesis is actually true (often 0.05). The significance level (often 0.05) and relative frequency of receiving a p-value that is less than the significance level together determine the risk of a type I error under the null hypothesis.

Real-World Example of P-Value

Let's say an investor says the performance of their investment portfolio is comparable to the Standard & Poor's (S&P) 500 Index. To determine this, the investor does a two-tailed test. The alternative hypothesis asserts that, in contrast to the null hypothesis, the returns of the portfolio and the S&P 500 are not equal during the relevant time period. (If the investor used a one-tailed test, the alternative hypothesis would be that the returns on the portfolio are either lower or higher than the returns on the S&P 500.)

0.05 is a typical significance level. If the investor finds out that the p-value is less than 0.05, the null hypothesis is disproved. The investor would thus favour the alternative hypothesis above the null hypothesis. The p-value decreases as the strength of the evidence against the null hypothesis increases. If the investor finds that the p-value is 0.001, which is strong evidence against the null hypothesis, they can be certain that the portfolio's returns and the returns of the S&P 500 are not equal.

If the p-value was less than 0.05, the investor would fail to reject the null hypothesis, indicating that there is (at best) scant evidence against the speculation. The disparities between the S&P 500 data and investment portfolio data in this scenario can only be explained by chance.

P Value	Conclusion	Level of Significance
0.001 to 0.010	Reject Null hypothesis at 1% level	Highly significant
0.011 to 0.050	Reject Null hypothesis at 5% level	Significant
0.051 to 1.00	Accept Null hypothesis at 5% level	Not Significant

Table 5: Concept of P value

STATISTICALLY SIGNIFICANT TESTS USED IN THE STATISTICAL ANALYSIS:

KRUSKAL–WALLIS TEST

The Kruskal-Wallis test on ranks, also known as the one-way ANOVA on ranks or the Kruskal-Wallis H test (after William Kruskal and W. Allen Wallis), is a non-parametric technique for determining if samples come from the same distribution. It is utilised to compare two or more distinct samples with similar or dissimilar sample sizes. The

Mann-Whitney U test, which is used to compare only two groups, is expanded by this method. The one-way analysis of variance is the Kruskal-Wallis test's parametric counterpart (ANOVA).

MANN–WHITNEY *U* TEST

In statistics, the **Mann–Whitney *U* test** (also called the **Mann–Whitney–Wilcoxon** (**MWW**), **Wilcoxon rank-sum test**, or **Wilcoxon–Mann–Whitney test**) is a nonparametric test of the null hypothesis that, for randomly selected values *X* and *Y* from two populations, the probability of *X* being greater than *Y* is equal to the probability of *Y* being greater than *X*.

Although Mann and Whitney developed the Mann–Whitney *U* test under the assumption of continuous responses with the alternative hypothesis being that one distribution is stochastically greater than the other, there are many other ways to

$$U = \sum_{i=1}^{n} \sum_{j=1}^{m} S(X_i, Y_j),$$

formulate the null and alternative hypotheses such that the Mann–Whitney *U* test will give a valid test.

The corresponding Mann-Whitney U statistic is defined as:

with

$$S(X,Y) = \begin{cases} 1, & \text{if } Y < X, \\ \frac{1}{2}, & \text{if } Y = X, \\ 0, & \text{if } Y > X. \end{cases}$$

INCLUSION CRITERIA

1. Individuals with type 2 diabetes mellitus who visit the OPD at the BLDE, Bijapur, Department of Ophthalmology.
2. Diabetic individuals coming to the medicine/ophthalmology OPD/IPD with and without nephropathy.
3. Patients without diabetes mellitus presenting to the OPD of the Department of Ophthalmology in BLDE, Bijapur.
4. Patients having different grades of diabetic retinopathy and ME.

EXCLUSION CRITERIA

1. Type 1 diabetes mellitus
2. Patients having a history of diabetic retinopathy who received treatment for the same
3. Patients with high myopia or any other developmental anomalies with increased axial length
4. Conditions causing hazy media such as corneal opacities, cataract, and vitreous hemorrhage that interfere with readings.
5. Patients with Choroidal detachment
6. Patients with macular and choroidal degeneration from any other cause
7. Inability to give informed consent

RESULTS

192 patients were enrolled in this study. 96 patients were diagnosed as diabetics and were considered as cases, while 96 were non-diabetics and were considered as controls. Of the 96 patients with diabetes mellitus 50 patients had some grade of diabetic retinopathy present, 26 patients had presence of diabetic nephropathy and 20 patients were normal

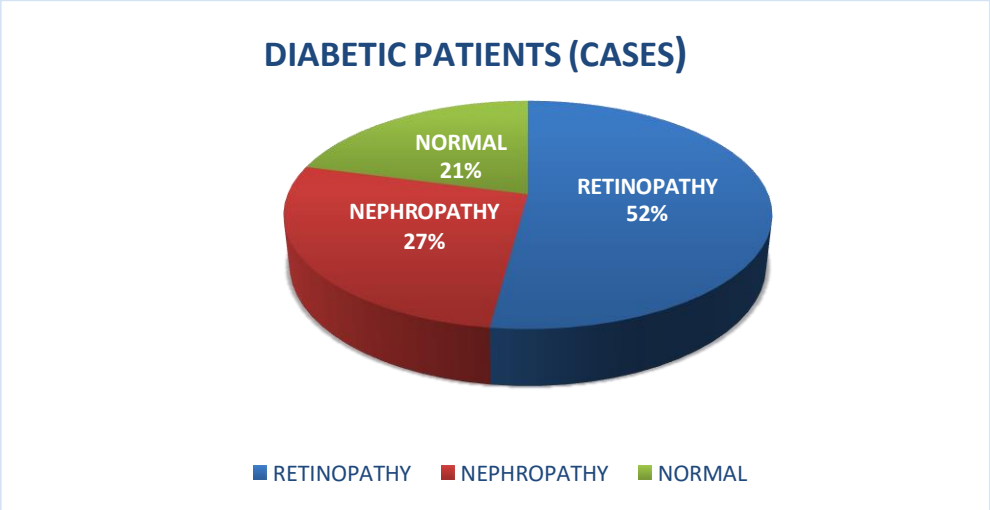

fig 1. pie chart showing distribution of retinopathy and nephropathy among diabetics

AGE DISTRIBUTION

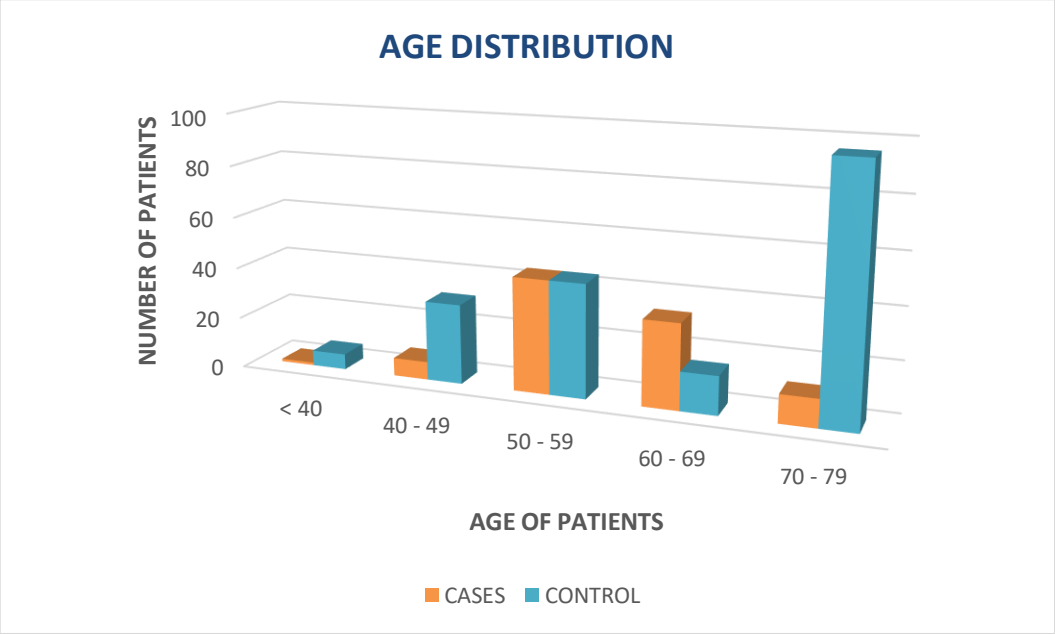

Fig 2. GRAPH SHOWING AGE DISTRIBUTION AMONG CASES AND CONTROLS

The ages of patients ranged from 39 years to 79 years. Majority of the patients belonged to the age group of 50-59 years of age.

SEX DISTRIBUTION

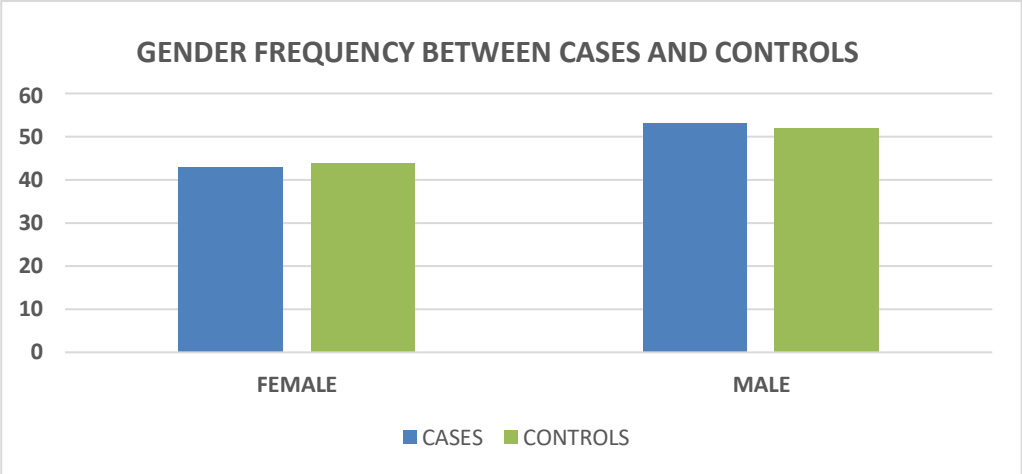

Fig 3. GRAPH SHOWING SEX DISTRIBUTION

Our study observed an increase in male patients in both cases and controls. While (55.8%) were males among the diabetic group when compared to females (44.2%). The control group also showed similar results

TREATMENT PATTERN AMONG DIABETIC PATIENTS

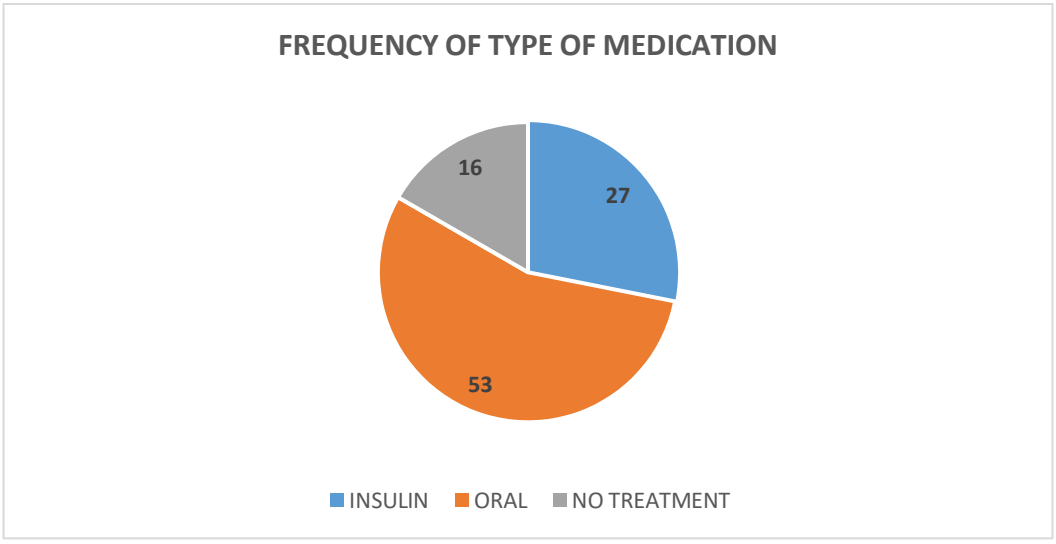

Fig 4. PIE CHART SHOWING DIABETIC TREATMENT PATTERN

In the study among the patients included in the study, majority 53 (55.2%) were under oral hyperglycaemic drugs, while 27 (28.12%) of the patients were on regular insulin therapy and 16 (16.6%) patients were not on any treatment for hyperglycaemia.

DURATION OF DIABETES

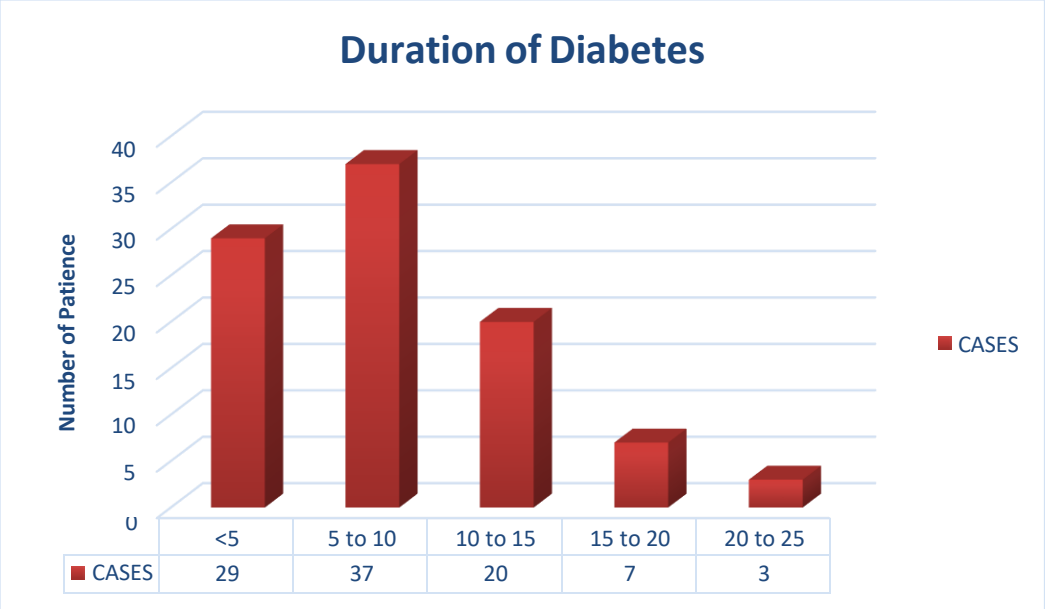

Fig 5. GRAPH REPRESENTING DURATION OF DIABETES

From the time of initial diagnosis of diabetes mellitus to the present study period. The duration of diabetes was categorized into 5 groups. The majority of patients (37) had diabetes for a duration of 5 to 10 years, followed by (29) patients with a duration of less than 5 years. While the duration of diabetes between 10 to 15 years and 15 to 20 years were 20 and 7 respectively. Only 3 patients were diabetics for more than 20 years

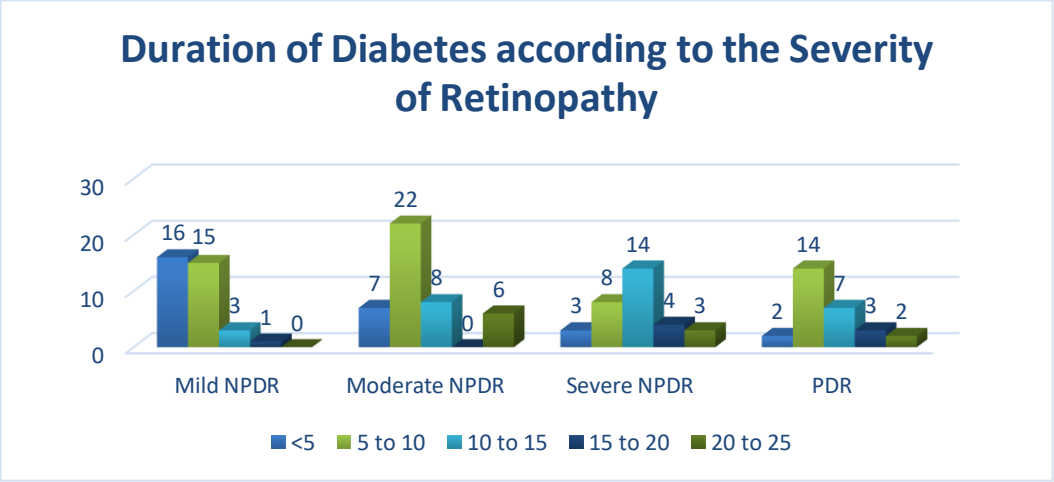

Fig 6. GRAPH SHOWING CORRELATION BETWEEN DURATION OF DIABETES AND GRADE OF RETINOPATHY

Reviewing the duration of diabetes according to the degree of retinopathy revealed that patients with mild NPDR had an average duration of less than five years (n=16), those with moderate NPDR had an average duration of five to ten years, and those with severe NPDR had an average duration of ten to fifteen years.

On the other hand, among the PDR cases, majority were included in 5 to 10 years but were among irregular treatment.

DISTRIBUTION OF HBA1C AMONG THE CASE

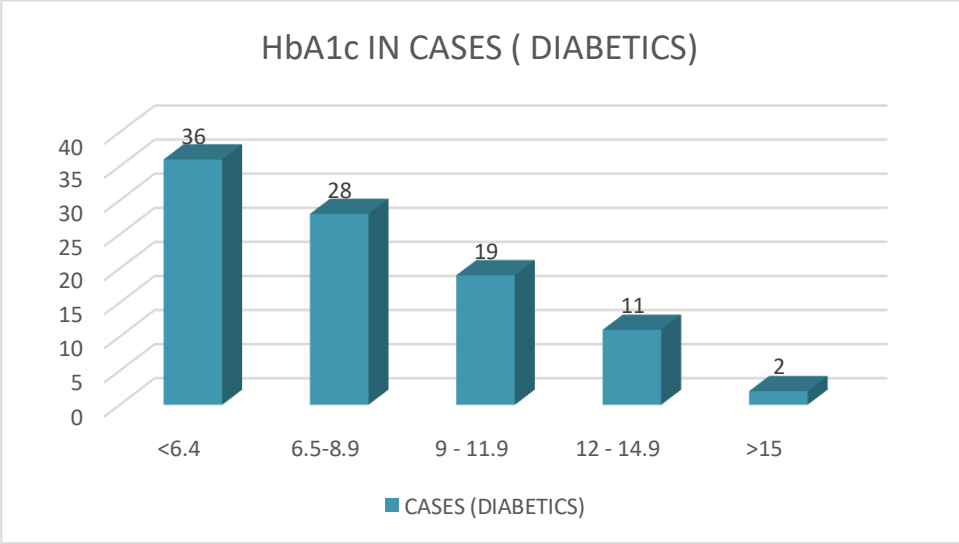

Fig 7. GRAPH REPRESENTING RELATION BETWEEN HBA1C AND CASES

The serum HbA1c levels were found to be statically significant among the cases. Majority of the diabetic patients 36(37.5) had serum HBA1c level below 6.4, followed by 28(29.1) patients who had HbA1c values ranging from 6.5 to 8.9. while patients with HbA1c values between 9 to 11.9 and 12 to 14.9 were 19(19.7) and 11(11.4) respectively. Only 2 patients had values above 15.

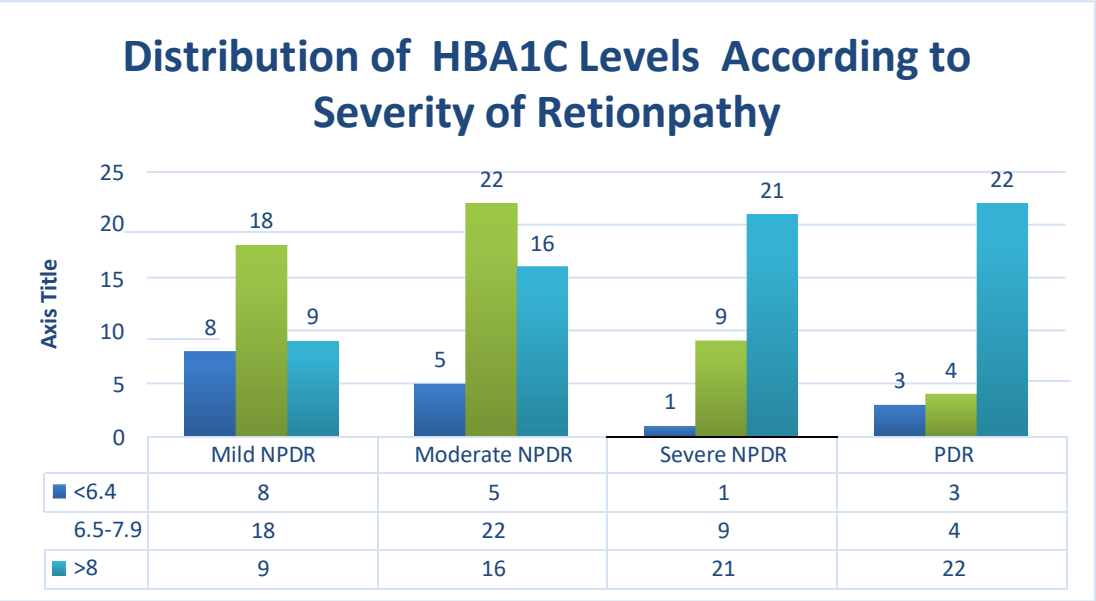

Fig 8. GRAPH SHOWING DISTRIBUTION OF HBA1C LEVELS ACCORDING TO SEVERITY OF RETINOPATHY

serum HbA1c levels were highest in patients with PDR in which 22 patients had HbA1c values above 8%. This was followed by patients in the sever NPDR group, where 21 patients had values above 8%. Both the mild NPDR and moderate NPDR groups had majority of patients with HbA1c between 6.5 to 7.9. it was also observed that minimum number of patients in all groups of retinopathies had HbA1c values of <6.4%.

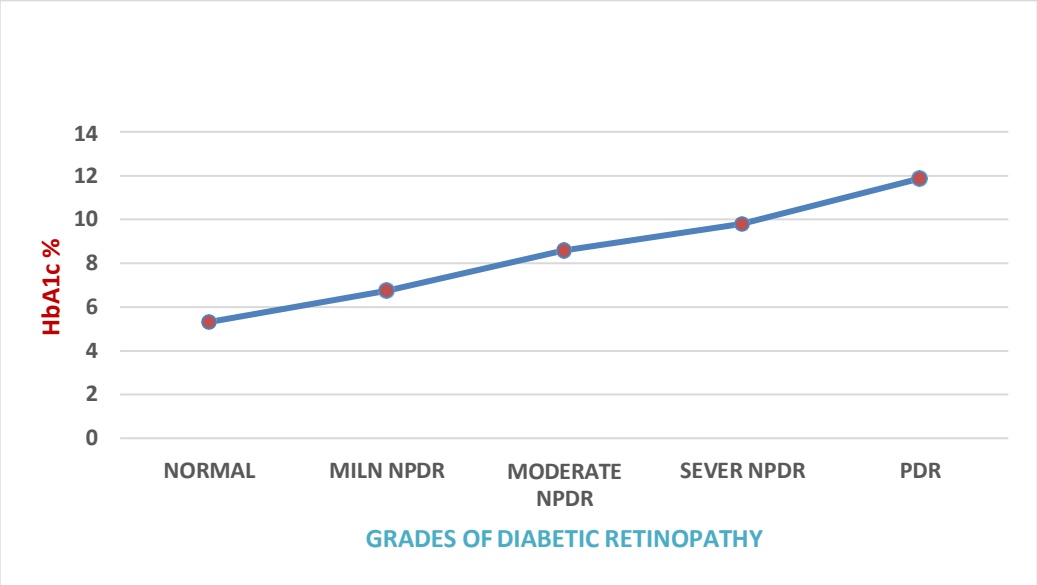

Fig 9 LINE GRAPH SHOWING THE TREND OF HBA1C LEVELS IN RELATION TO THE SEVERITY OF RETINOPATHY.

An increasing tread was observed when comparing HbA1c levels with the various groups of diabetic retinopathy severity, where a steep rise was seen in HbA1c values from diabetic patients without retinopathy to diabetic patients with PDR. The HbA1c levels ranged from 3.3 to 16.1 % with the minimum values seen in diabetic patients without retinopathy and the maximum value seen in patients with PDR

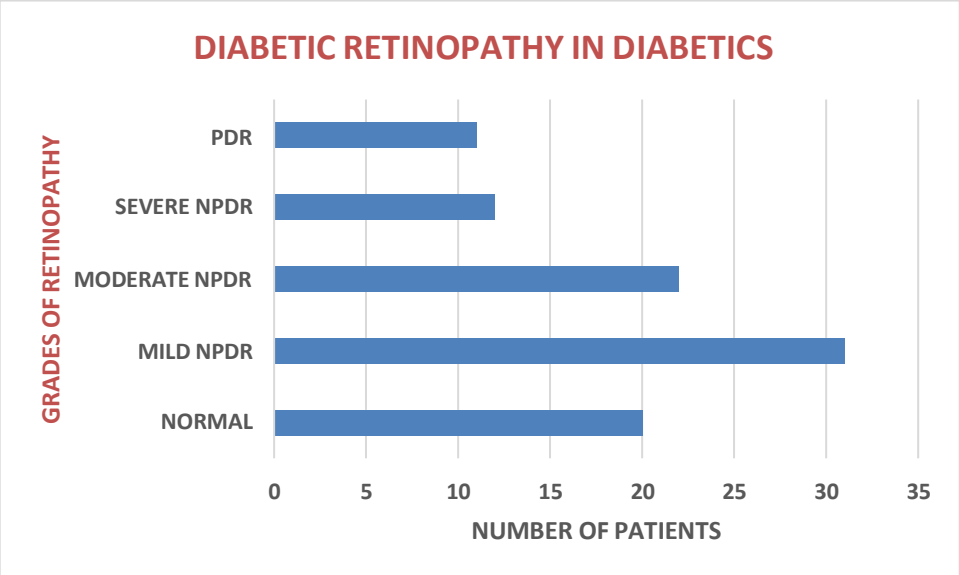

Fig .10 BAR GRAPH SHOWING GRADES OF DIABETIC RETINOPATHY

STATISTICAL TESTING PART

TABLE COMPARING VARIOUS PARAMETERS BETWEEN CASES AND CONTROLS				
	CASES		CONTROLLS	
	MEAN	STANDARD DEVATION	MEAN	STANDARD DEVATION
AGE	58.86	8.03	61.48	7.42
HbA1C	7.86	2.78	4.70	0.59
PPBS	229.07	78.41	164.22	14.7
FBS	172.76	68.68	94.47	9.07
SUBFOVAL THICKNESS	253.63	36.35	328.30	18.11

Table 6 COMPARISON OF PARAMETERS BETWEEN CASES AND CONTROLS

On comparing the means of various parameters in both cases and controls, it was observed the mean HbA1c in diabetics was 7.86% while it was only 4.7% in the control group. The mean subfoval thickness was 74.67 microns thicker in the control group in comparison with the diabetic group

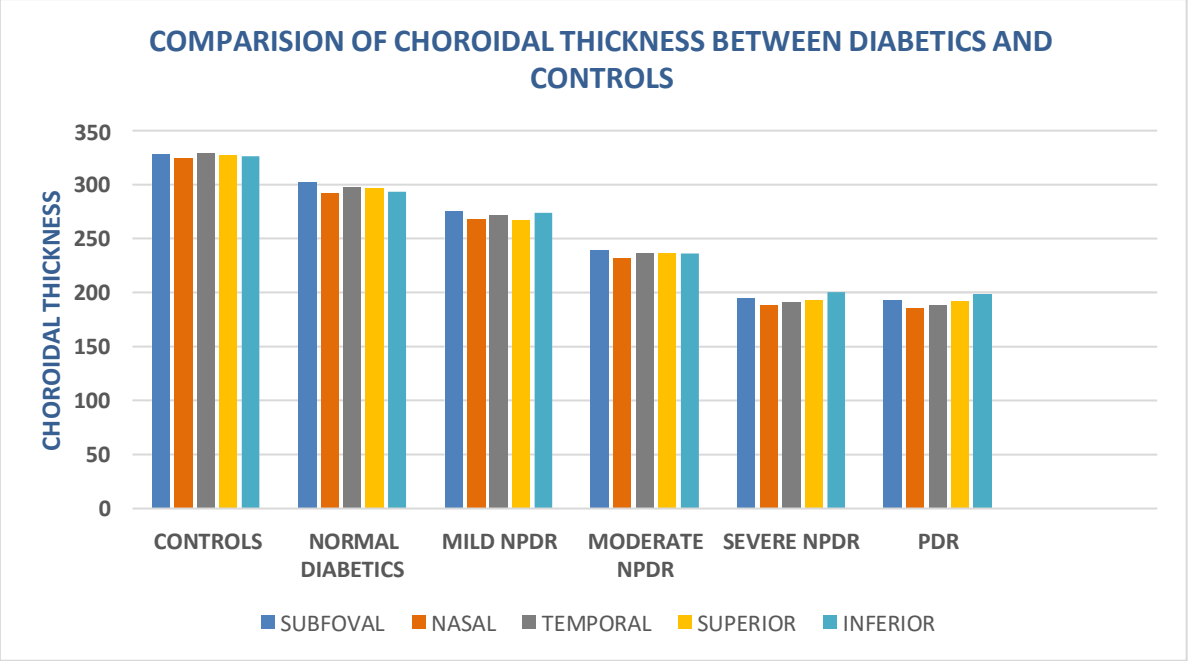

TABLE 7 COMPARISION OF CHOROIDAL THICKNESS BETWEEN DIABETICS AND CONTROLS

TABLE SHOWING COMPARRISION OF CHOROIDAL THICKNESS BETWEEN DIABETIC PATIENTS AND CONTROLS				
CHOROIDAL THICKNESS	**GROUPS**	**MEAN**	**SD**	**CHI-SQUARE**
SUBFOVAL	NO RETINOPATHY	302.70	10.063	145.674
	MILD NPDR	276.03	30.522	
	MODERATE NPDR	239.68	31.242	
	SEVERE	195.08	12.972	
	PDR	193.00	15.245	
	CONTROLLS	328.30	17.382	
NASAL	NO RETINOPATHY	291.80	13.477	147.556
	MILD NPDR	268.55	31.891	
	MODERATE NPDR	231.73	30.376	
	SEVERE	188.83	13.630	
	PDR	186.09	15.527	
	CONTROLLS	324.88	18.117	
TEMPORAL	NO RETINOPATHY	297.70	11.150	148.509
	MILD NPDR	272.13	30.407	
	MODERATE NPDR	236.50	31.567	
	SEVERE	191.25	11.537	
	PDR	188.55	14.767	
	CONTROLLS	329.18	21.819	
SUPERIOR	NO RETINOPATHY	297.00	12.048	147.136
	MILD NPDR	267.00	41.204	
	MODERATE NPDR	236.59	28.555	
	SEVERE	192.83	13.704	
	PDR	191.64	14.144	
	CONTROLLS	327.73	18.685	
INFERIOR	NO RETINOPATHY	293.35	28.673	130.012
	MILD NPDR	273.84	46.587	
	MODERATE NPDR	236.14	28.501	
	SEVERE	200.33	26.898	
	PDR	198.18	59.493	
	CONTROLLS	326.45	18.825	
STATISTICALLY SIGNIFICANT				

TABLE .8 SHOWING THE COMPARISON OF CHOROIDAL THICKNESS IN CASES AND CONTROLS

Comparison of choroidal thickness between control group and cases group were statistically significant. The choroidal thickness was maximum in the control group, while the PDR patients of the cases(diabetic) group had least choroidal thickness**.** The choroidal thickness decreased as

the severity of diabetic retinopathy increased. On comparison, the closest similarity in choroidal thickness between cases and controls was that of controls and diabetic patients without retinopathy

TABLE SHOWING COMPARRISION OF CHOROIDAL THICKNESS IN DIABETIC BETWEEN PATEINTS WITH NO RETINOPATHY, RETINOPATHY AND NEPHROPATHY				
CHOROIDAL THICKNESS	**GROUPS**	**MEAN**	**SD**	**CHI-SQUARE**
SUBFOVAL	NO RETINOPATHY	302.70	10.063	145.674
	RETINOPATHY	254.62	40968	
	NEPHROPATHY	213.96	35.113	
NASAL	NO RETINOPATHY	291.80	13.477	147.556
	RETINOPATHY	247.64	41.066	
	NEPHROPATHY	205.92	33.913	
TEMPORAL	NO RETINOPATHY	297.70	11.150	148.509
	RETINOPATHY	251.12	40.842	
	NEPHROPATHY	209.69	34.881	
SUPERIOR	NO RETINOPATHY	297.00	12.048	147.136
	RETINOPATHY	248.46	43.596	
	NEPHROPATHY	210.81	33.786	
INFERIOR	NO RETINOPATHY	293.35	28.67	130.012
	RETINOPATHY	251.58	46.853	
	NEPHROPATHY	218.81	54.228	
STATISTICALLY SIGNIFICANT				

TABLE. 9 SHOWING COMPARISON OF CHOROIDAL THICKNESS IN DIABETIC BETWEEN PATIENTS WITH NO RETINOPATHY, RETINOPATHY AND NEPHROPATHY

On comparing sub-groups in cases, Choroidal thickness showed significant difference in the subfoval, nasal, temporal, superior and inferior areas. In the diabetic group patients without retinopathy had the highest choroidal thickness, while patients with nephropathy had the least thickness in all areas. The mean choroidal thickness in diabetic patients

without retinopathy was 296 microns, while the mean in patients without retinopathy and nephropathy was 250 microns and 211 microns respectively

TABLE SHOWING THE COMPARRISION OF CHOROIDAL THICKNESS BETWEEN CONTROLLS AND DIABETIC NEPHROPATHY PATIENTS					
CHOROIDAL THICKNESS	**GROUPS**	**MEAN**	**SD**	**Mann-Whitney U Test**	**P VALUE**
SUBFOVAL	NEPHROPATHY	213.96	35.113	6.00	<0.001
	CONTROL	328.30	17.382		
NASAL	NEPHROPATHY	205.92	33.913	7.500	<0.001
	CONTROL	324.88	18.117		
TEMPORAL	NEPHROPATHY	209.69	34.881	7.0	<0.001
	CONTROL	329.18	21.819		
SUPERIOR	NEPHROPATHY	210.81	33.786	10.500	<0.001
	CONTROL	327.73	18.685		
INFERIOR	NEPHROPATHY	218.81	54.228	67.00	<0.001
	CONTROL	326.45	18.825		
STATISTICALLY SIGNIFICANT					

TABLE 10 COMPARISION OF CHOROIDAL THICKNESS BETWEEN CONTROLS AND NEPHROPATHY PATIENTS

There is statistically significant difference (p value <o.oo1) in the mean choroidal thickness between the control group and diabetic group with nephropathy. The difference in choroidal was noted in all areas (sub-foval, nasal, temporal, superior and inferior). The mean choroidal thickness in patients with nephropathy ranged from 205.92 microns to 218.81 microns, with a mean of 211.838 microns. While in the control group mean ranged from 329.18 microns to 324.88 microns, with a mean of 327.308 microns.

TABLE SHOWING THE COMPARRISION OF CHOROIDAL THICKNESS BETWEEN DIABETICS WITHOUT RETINOPATHY AND DIABETIC NEPHROPATHY PATIENTS					
CHOROIDAL THICKNESS	**GROUPS**	**MEAN**	**SD**	**Mann-Whitney U Test**	**P VALUE**
SUBFOVAL	NEPHROPATHY	213.96	35.113	6.00	<0.001
	NORMAL DIABETIC	302.70	10.063		
NASAL	NEPHROPATHY	205.92	33.913	7.500	<0.001
	NORMAL DIABETIC	291.80	13.477		
TEMPORAL	NEPHROPATHY	209.69	34.881	7.0	<0.001
	NORMAL DIABETIC	297.70	11.150		
SUPERIOR	NEPHROPATHY	210.81	33.786	10.500	<0.001
	NORMAL DIABETIC	297.00	12.048		
INFERIOR	NEPHROPATHY	218.81	54.228	67.00	<0.001
	NORMAL DIABETIC	293.35	28.673		
STATISTICALLY SIGNIFICANT					

TABLE 11 COMPARRISION OF CHOROIDAL THICKNESS BETWEEN DIABETICS WITHOUT RETINOPATHY AND DIABETIC NEPHROPATHY PATIENTS

A statistically significant difference was also observed when comparing the nephropathy group with the diabetic patients without retinopathy, with P value <0.001.

DISCUSSION

A structurally and functionally intact choroidal vasculature is essential for proper functioning of the retina. Any abnormalities in the choroidal circulation and blood volume leading to a compromised choroidal blood flow can eventually cause the dysfunction of photoreceptor leading to its death. Diabetes mellitus mainly targeting the microvasculature can affect multiple systems. The retina, choroid and kidneys are majorly affected and can influence each other leading co- related complication and outcomes.

In our study about 45.8 % of patients belonged to the 5th to 6th decades of life, suggesting the increased prevalence of systemic diseases such as diabetes among people in those age groups. Similar results were observed in a study by wei wang et al,on choroidal thickness in diabetes and diabetic retinopathy. They observed that maximum patients belonged to the 6th decade (80) Several studies reported that early onset diabetes was more aggressive and may be related to increased occurrence of diabetic microvascular dmage. Zou, W., Ni, L., Lu, Q. *et al* in their study on Diabetes Onset and its Association with an Increased Risk of Diabetic Retinopathy concluded that diabetes onset age of 31–45 years was considered an independent risk factor for development of DR in type 2 DM **[98]**.

Sex distribution saw a male predominance in both cases and controls. This increased male predominance can be attributed to the increased prevalence of diabetes in males. Results are similar to the results of a study by Nordstorm a et al in their study on higher prevalence of type 2 diabetes in men than in women is associated with differences in visceral fat mass

On evaluation of the duration of diabetes, it was observed that a maximum of 38.5 % of the diabetic group had a history of diabetes of 5-10 years. However, patients with a longer duration of diabetes were observed to have higher grades of diabetic retinopathy and subsequently a lower overall choroidal thickness. Similar observations were also made on evaluating medication history, where majority of patients (55.2) were on oral medications, however more severe grades of diabetic retinopathy were noted in patients on insulin therapy (16.5)

Hyperglycemia being the main initiating component for the microvascular alterations and disease progression in diabetic patients, makes it vital to monitor the diabetic status and control of the patient. HbA1c, PPBS and FBS were used to evaluate the diabetic status in both cases and controls, as well as the diabetic control in the diabetic group. Assessment of HbA1c levels showed concerning number of patients with levels >8 %. It was observed that higher HbA1c levels had statistically significant association with increased severity in grades of retinopathy. This can be attributed to the poor diabetic control that higher HbA1c levels represent, which in turn leads to increased severity in microvascular damage due to hyperglycemia. Similar observations were made on consideration of FBS and PPBS levels. On comparison with cases, it was noted that ta statistically significant difference in all three levels were present, implicating the importance of diabetic status and diabetic control of the patient

Diabetic patients were grouped into patients with retinopathy and without. The patients with retinopathy were further graded according to the severity of retinopathy. In our study majority of the patients had mild NPDR (32%). However, an alarming number of patients had severe NPDR (12.5%) and PDR (11.5%)

Choroidal thickness assessment was the major parameter evaluated in this study, and compared between the cases and control groups. Until recent times, insight pertaining to choroidal thickness was primarily based on histologic and histopathology. This however did not give which necessarily and vital measurements of the choroidal. Recent literature has proven the potential of spectral-domain OCT in imaging the choroidal. Manjunath V et al in their study on Choroidal thickness in normal eyes measured using Cirrus HD optical coherence tomography, demonstrated that choroidal thickness can be evaluated using SD-OCT [99]

In our study the mean choroidal thickness in controls was 327.308 microns, with the maximum thickness of 329.18 microns noted in the temporal area and minimum thickness of 324.88 microns in the nasal region. Similar results were observed in a study by Entezari M et al on choroidal thickness in healthy subjects [100].

According to our study's assessment of the choroidal thickness of diabetes patients (cases group), patients without retinopathy had the highest levels of choroidal thickness, with a mean thickness of 295 microns. Maximum reduction in choroidal thickness among patients with retinopathy was observed in patients with PDR, with a mean thickness of 191.492 microns. Mean choroidal thickness in the mild NPDR, moderate PDR, severe PDR was 271, 242, 193 microns respectively. A statistically significant reduction in mean choroidal thickness was noted with increasing severity of diabetic retinopathy

Study by Regatieri CV et al, also observed similar results in their study on Choroidal thickness in patients with diabetic retinopathy analyzed by spectral-domain optical coherence tomography. They observed presences of thinner choroids in patients with

proliferative diabetic retinopathy, as compared to patients with non-proliferative diabetic retinopathy. They also concluded that, diabetic choroidal angiopathy was related to the degree of severity of retinopathy because of a significant decrease in the CT in patients [101]. Another study by Ambiya, V et al concluded The SFCT was significantly lower in proliferative DR as compared to non-proliferative DR patients [102].

As our study is a case control-study, comparisons were made between the non-diabetic patients (control) and diabetic patients (cases). Mean choroidal thickness in controls was 327.308 microns, as compared to thinner mean choroidal thickness in diabetic patients of 295 microns in diabetic patients without retinopathy and 271, 242, 193 and 191.492 with mild NPDR, moderate PDR, severe PDR and PDR respectively. Statistically significant differences were on comparisons of choroidal thickness between controls and cases

Comparative findings between cases and controls in our study are similar to the results observed by Hyo Kyung Lee et al in their study, where they noted That sub-foveal choroidal thickness was thinner in eyes with non-proliferative or proliferative diabetic retinopathy than in normal eyes ($p < 0.01$) [103].

To the best of our knowledge, this work is the first to combine SD-OCT with EDI to look into the relationship between choroidal thickness and diabetic nephropathy.

The findings showed that diabetic individuals with nephropathy had considerably thinner CTs than diabetic patients without retinopathy or non-diabetic patients.

The choroid is a highly vascularized tissue that is crucial for controlling ocular metabolism. According to our study, diabetic patients with nephropathy had a mean choroidal thickness of 211.838 microns. When compared to the choroidal thickness in the control group, this was noticeably thinner. Additionally, there was a statistically significant difference in choroidal thickness between diabetics with nephropathy and those without, as well as between those with mild and those with moderate NPDR. Nephropathy patients had the thinnest choroidal tissue. This may be because the choroid is purely vascular and can thin to reflect microvascular disease throughout the body. Patients with severe NPDR and PDR had thinner choroids than those with nephropathy, it was also discovered.

Previous research has assessed the connection between CT and renal function as well as the impact of systemic vascular disease on choroid alterations. While Farias et al. discovered that the CT was thinner in patients with microalbuminuria, Kocasarac et al. revealed that the CT was lowered in diabetes patients with diabetic nephropathy, showing that patients with renal impairment had generally thinner CTs [104].

CONCLUSION

Choroidal and its vasculature is essential for proper functioning of the retina. Any abnormalities in the choroidal circulation and blood volume leads to a compromised choroidal blood flow and can eventually lead to the dysfunction and of photoreceptor. Our study mainly concentrated on the estimation of choroidal thickness in diabetic patients. This was designed a case control study for more reliable results.

Our study included 96 cases and 96 controls. The majority of individuals included in our study were male and primarily in their fifth and sixth decades of life. Majority of the diabetic patients had some grade of retinopathy 52%, while 27% had nephropathy. majority of the diabetic patients had mild NPDR (32%). However, an alarming number of patients had severe NPDR (12.5%) and PDR (11.5%)

Majority of the diabetic patients 37 had duration of diabetes of 5-10 years. The severity of retinopathy and the duration of diabetes were positively correlated, with patients with severe PDR having had diabetes for an average of 10-15 years. It has been hypothesised that prolonged diabetes increases the severity of retinopathy and eventually thins the choroid.

HbA1c levels were found to be below 6.4% in majority of diabetic patients 37.5%. HbA1c levels also showed significant relation with grades of retinopathy, in which majority of patients with severe PDR and PDR had values >8%, showing the importance of proper diabetic control in arresting progression of retinopathy and eventually choroidal dysfunction

Choroidal thickness was measured using the SD-OCT with EDI mode. Healthy non-diabetic patients showed a mean choroidal thickness of 327.308 microns, while diabetic patients had an overall thinner choroidal thickness. An overall decrease in choroidal thickness was noted with increasing severity or higher grades of diabetic retinopathy. Thinnest choroids were observed in PDR patients with a mean thickness of 193 microns. Thinning of the choroid can be attributed to the hypoperfusion of the choroid due to microvascular changes, eventually leading to choroidal dysfunction.

Presence of Nephropathy was noted in diabetic patients by assessing 24 hours microalbuminuria, Sr creatinine, urea, and eGFR. In our study a total 27% of the diabetic group patients had presence of nephropathy. On assessment of choroidal thickness in these patients, thinner choroidal thickness was noted with a mean thickness of 211.838 microns. A statistically significant difference was noted when compared to the control group as well as cases group with mild and moderate NPDR, with least choroidal thickness in patients with nephropathy. This can be attributed to the high vascular nature of the choroid which can be altered or reflect systemic microvascular dysfunction

SUMMARY

This was a time bound, case control study carried out on 192 patients, that include 96 non diabetic healthy patients as controls and 96 diabetic patients as cases done. The study was caried out on patients attending the outpatient and inpatient departments to determine the choroidal thickness.

This study aimed to assess the choroidal thickness in diabetes mellitus patients and compare it with healthy non diabetic controls

A total 196 patients, fulfilling the inclusion criteria were included in the study. The study parameters including: RBS, FBS, PPBS, HbA1c to assess diabetic asatus and control and SR creatinine, SR urea, microalbuminuria, eGFR for nephropathy. Diabetic retinopathy assessment and grading was done and choroidal thickness was measured using SD-OCT with EDI mode. A detailed history was taken from patients including duration of diabetes and treatment history. Thorough ocular examination was performed

Our study included 96 cases and 96 controls, of which majority belonged to the 5th and 6th decades of life in both cases and control groups. A male predominance was noted with 55.8% males and 44.2% females. Majority of the diabetic patients 37 had duration of diabetes of 5-10 years, while maximum patients with severe PDR having diabetes for 10-15 years. positive correlation was noted between duration of diabetes with severity of retinopathy.

96 patients were diabetic, of which 52% had retinopathy and 27% had retinopathy. Of the patients with retinopathy (32%) had mild NPDR, (12.5%) had severe NPDR and (11.5%) had PDR

HbA1c levels was below 6.4% in majority of diabetic patients 37.5%, while majority of patients with severe PDR and PDR had values >8% HbA1c levels also showed significant relation with grades of retinopathy

On assessment of choroidal thickness. Healthy non-diabetic patients showed a mean choroidal thickness of 327.308 microns in comparison to diabetic patients in which overall thinner choroidal thickness was noted. An overall decrease in choroidal thickness was also noted with increasing severity or higher grades of diabetic retinopathy. Thinnest choroids were observed in PDR patients with a mean thickness of 193 microns. Statistically significant difference in choroidal thickness across all groups were noted with p value of < 0.001. in patients with nephropathy, thinner choroidal thickness was noted with a mean thickness of 211.838 microns. A statistically significant difference p value 0.001 was noted when compared to the control group as well as cases group with mild and moderate NPDR, with least choroidal thickness in patients with nephropathy.

LIMITATIONS OF THE STUDY

- this study lacked patient follow up and choroidal assessment after diabetic control was achieved in an uncontrolled diabetic
- Patients were not evaluated for macular thickness

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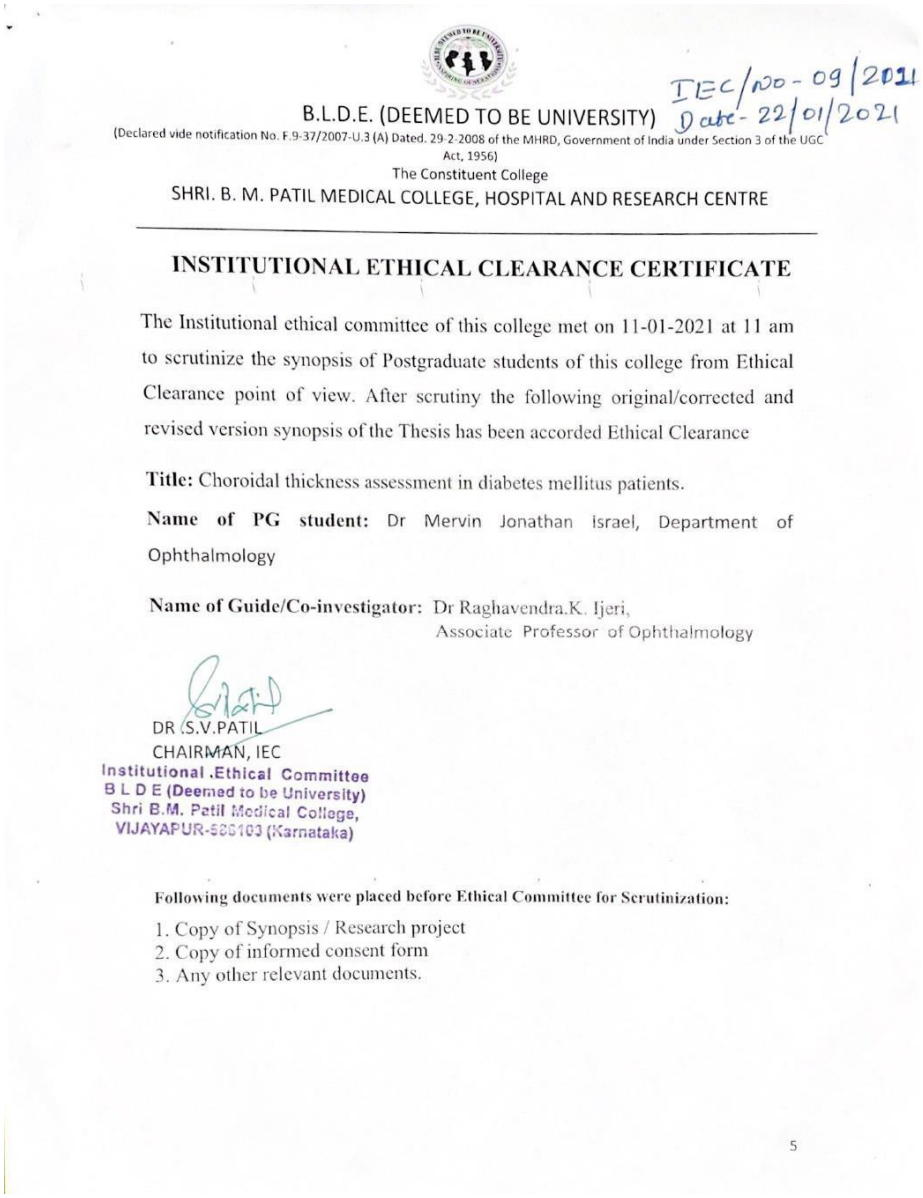
ANNEXURES

ETHICAL CLEARANCE CERTIFICATES



B.L.D.E. (DEEMED TO BE UNIVERSITY)

IEC/NO-09/2021
Date- 22/01/2021

(Declared vide notification No. F.9-37/2007-U.3 (A) Dated. 29-2-2008 of the MHRD, Government of India under Section 3 of the UGC Act, 1956)

The Constituent College

SHRI. B. M. PATIL MEDICAL COLLEGE, HOSPITAL AND RESEARCH CENTRE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Institutional ethical committee of this college met on 11-01-2021 at 11 am to scrutinize the synopsis of Postgraduate students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has been accorded Ethical Clearance

Title: Choroidal thickness assessment in diabetes mellitus patients.

Name of PG student: Dr Mervin Jonathan Israel, Department of Ophthalmology

Name of Guide/Co-investigator: Dr Raghavendra.K. Ijeri, Associate Professor of Ophthalmology

DR S.V.PATIL
CHAIRMAN, IEC
Institutional Ethical Committee
B L D E (Deemed to be University)
Shri B.M. Patil Medical College,
VIJAYAPUR-586103 (Karnataka)

Following documents were placed before Ethical Committee for Scrutinization:

1. Copy of Synopsis / Research project
2. Copy of informed consent form
3. Any other relevant documents.

5

SAMPLE INFORMED CONSENT FORM

B.L.D.E.U.'S SHRI B.M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, VIJAYAPUR–586103, KARNATAKA

TITLE OF THE PROJECT

: CHOROIDAL THICKNESS ASSESSMENT BY SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY IN DIABETES MELLITUS PATIENTS

PG GUIDE: Dr. RAGHAVENDRA. K. IJERI

ASST. Professor

Department of Ophthalmology

BLDE Deemed to be university ShriB.M.Patil Medical College Hospital & Research Centre, Solapurroad,vijayapura.

PRINCIPAL INVESTIGATOR: Dr. MERVIN JONATHN ISRAEL

First-year resident in Ophthalmology

Department of Ophthalmology BLDE Deemed to be university.

ShriB.M.Patil Medical College Hospital & Research Centre, Solapur Road Vijayapura-586103

Email: mervinisrael@yahoo.co.in / israelmervin@gmail.com

PURPOSE OF RESEARCH:

I have been informed that this study: CHOROIDAL THICKNESS ASSESSMENT BY SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY IN DIABETES MELLITUS PATIENTS.

I am briefing about the reason for doing this study and selecting me/my ward as a participant for this study. I have also been given free will for either being included or not in the study.

PROCEDURE:

I understand, that i will be taking part in this study: A STUDY TO ASSESS THE CHOROIDAL THICKNESS BY SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY IN PATIENTS WITH DIABETES MELLITUS

I understand that I may experience and discomfort during the examination. This mainly results from my condition, and the procedure of this study does not expect to exaggerate or worsen these feelings, which are usually associated with the usual course of treatment.

BENEFITS:

I understand my participation in this study:

CHOROIDAL THICKNESS ASSESSMENT BY SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY IN DIABETES MELLITUS PATIENTS

I Understand and accept the risks, benefits, and costs involved and I willingly give consent to take part in the study.

CONFIDENTIALITY:

I understand that the medical information acquired by this study will become a part of this Hospital's records and will be subjected to the confidentiality and privacy regulation of this hospital. If this data is used for publication in the medical literature or teaching purposes, no names and other identifying details such as photographs and audio or video will be used. Such usage will be allowed only with my documented permission. I also understand that I may see the photograph and videotapes and hear audiotapes before giving permission.

REQUEST FOR MORE INFORMATION:

I understand that I can ask more questions about the study at any time. **Dr. RAGHAVENDRA. K. IJERI** in the Department of ophthalmology will be available anytime to answer my questions or related concerns. I also understand that I will be informed of any significant new findings discovered during this study, which might influence my continued participation. If, during this study or later, I wish to discuss my participation in or concerns regarding this study with persons not directly involved, I am aware that the social worker of the hospital is available to talk with me.

And that a copy of this consent form will be given to me to keep for careful reading.

REFUSAL OR/AND WITHDRAWAL TO PARTICIPATE IN THE STUDY:

I understand that my participation will be voluntary, and I may refuse to participate or may withdraw consent and discontinue from participating in this study at any time without prejudice to my present or future care at this hospital.

I also understand that Dr. MERVIN JONATHAN ISRAEL will terminate my participation in this study at any time after he/she has explained the reasons for doing so and has helped arrange for my continued care by my physician or therapist if this is appropriate.

INJURY STATEMENT;

I understand that in the unlikely event of an injury to me, resulting directly due to my participation in this study, such injury will be reported promptly, then medical treatment would be available to me, but no further compensation will be provided.

I understand that by my agreement to participate in this study and not waiving any of my legal rights.

I have explained the purpose of this research, the procedures required, and the possible risks to the best of my ability in the patient's language.

Dr. MERVIN JONANTHA ISRAEL

(Investigator)

DATE

Patient’s signature Witness to above signature

STUDY SUBJECT CONSENT STATEMENT:

I confirm that Dr. MERVIN JONATHAN ISRAEL has explained to me the purpose of this research study, the study procedure that I will undergo, and the possible discomforts and benefits that I may experience in my language.

I have been explained all the above in detail in my language, and I understand the same. Therefore I agree to give my consent to participate as a subject in this research project.

(Participant) Date

(Witness to above signature) Date

ಡಾ. ಮೆರ್ವಿನ್ ಜೊನಾಥನ್ ಇಸ್ರ ೇಲ್ ನನಗೆ ಸಂಶೇಧನೆಯ ಉದ್ದ ೇಶ, ಅಧಯ ಂತ ವರ್ಧಾನ ಮತ್ತ ಸಂಭವನೇಯ ಅಸ್ವ ಸ್ಥ ತೆಗಳು ಮತ್ತ ನನನ ಸ್ವ ಂತಭಾಷೆಯಲ್ಲಿ ನಾನುಅನುಭವರ್ಸ್ಪಹುದಾದ ಪ್ರ ಯೇಜನಗಳನುನ ರ್ವವರಿಸಿದ್ದ ೇನೆ ಎಂದು ನಾನು
ಖಚಿತಪ್ಡಿಸುತೆೇನೆ. ಮೇಲ್ಲನ ಎಲ್ಲಿ ರ್ವಷಯಗಳನುನ ನನನ ಸ್ವ ಂತಭಾಷೆಯಲ್ಲಿ ರ್ವವರವಾR ರ್ವವರಿಸ್ಲ್ಲRದ್ ಮತ್ತ ನಾನು ಅದನುನ
ಅಥಿಮಾಡಿಕಂಡಿದ್ದ ೇನೆ. ಆದದ ರಿಂದ, ಈ ಸಂಶೇಧನಾಯೇಜನೆಯಲ್ಲಿ ರ್ವಷಯವಾR ಭಾಗವಹಿಸ್ಲ್ಲು ಒಪ್ಪಿ ಗೆ ನೇಡಲು ನಾನು ಒಪ್ಪಿ ತೆೇನ

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(ಭಾಗವಹಿಸುವವರು)
(Øನಾಂಕ)

PERFORMA

PRO-FORMA FOR CASE TAKING

TOPIC: CHOROIDAL THICKNESS ASSESSMENT IN DIABETES MELLITUS PATIENTS

DEPARTMENT OF OPHTHALMOLOGY

B.L.D.E UNIVERSITY'S SHRI B.M.PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, VIJAYAPURA-586103

CASE NO: OPD/IPD NO: DATE:

NAME: AGE: SEX:

KNOWN CASE OF TYPE 2 DM: YES / NO

DURATION OF TYPE 2 DM: ON REGULAR MEDICATION : YES/ NO

HISTORY OF HYPERTENSION : IF YES : ORAL / INSULIN:

ANY OTHER RELATED COMPLICATIONS: ANY OCULAR COMPLAINTS:

PERSONAL HISTORY PAST MEDICAL HISTORY:

PAST SURGICAL HISTORY: FAMILY HISTORY:

HBA1C level: RBS: FBS

Sr. CREAT UREA: URINE ALBUMIN

EGFR:

HISTORY OF PVD:

OPHTHALMIC EXAMINATION

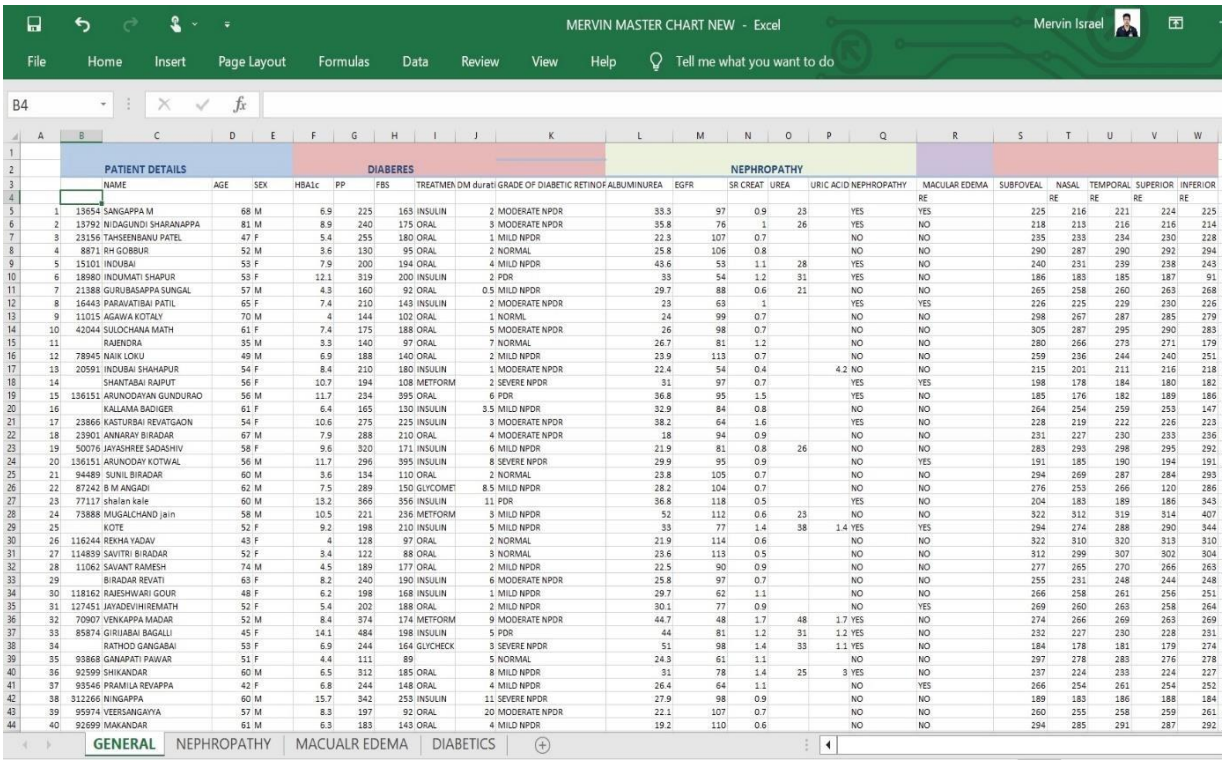
	RIGHT EYE	LEFT EYE
External Appearance		
Ocular Motility		
Lids		
Conjunctiva		
Cornea		
Anterior Chamber		
Iris		
Pupil		
Lens		
Unaided		
Pinhole		
Near Vision		

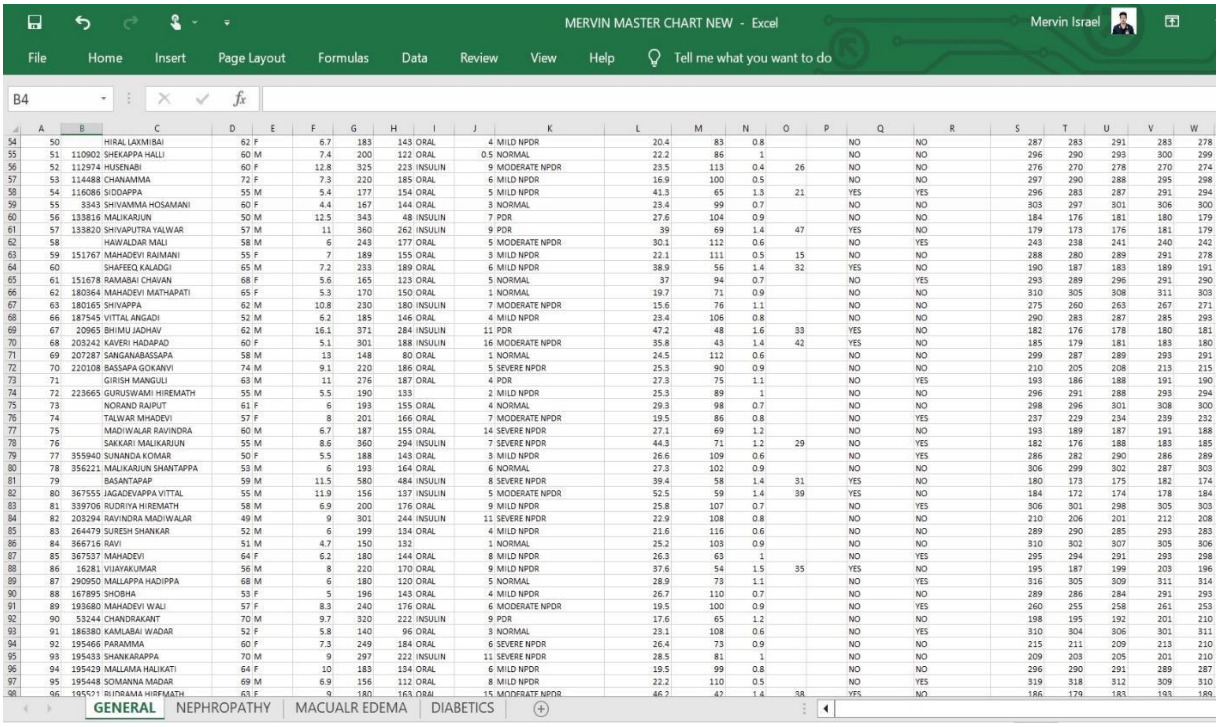
FUNDUS EXAMINATION

	RIGHT EYE	LEFT EYE
Media		
Disc		
Blood vessel		
Background		
macula		

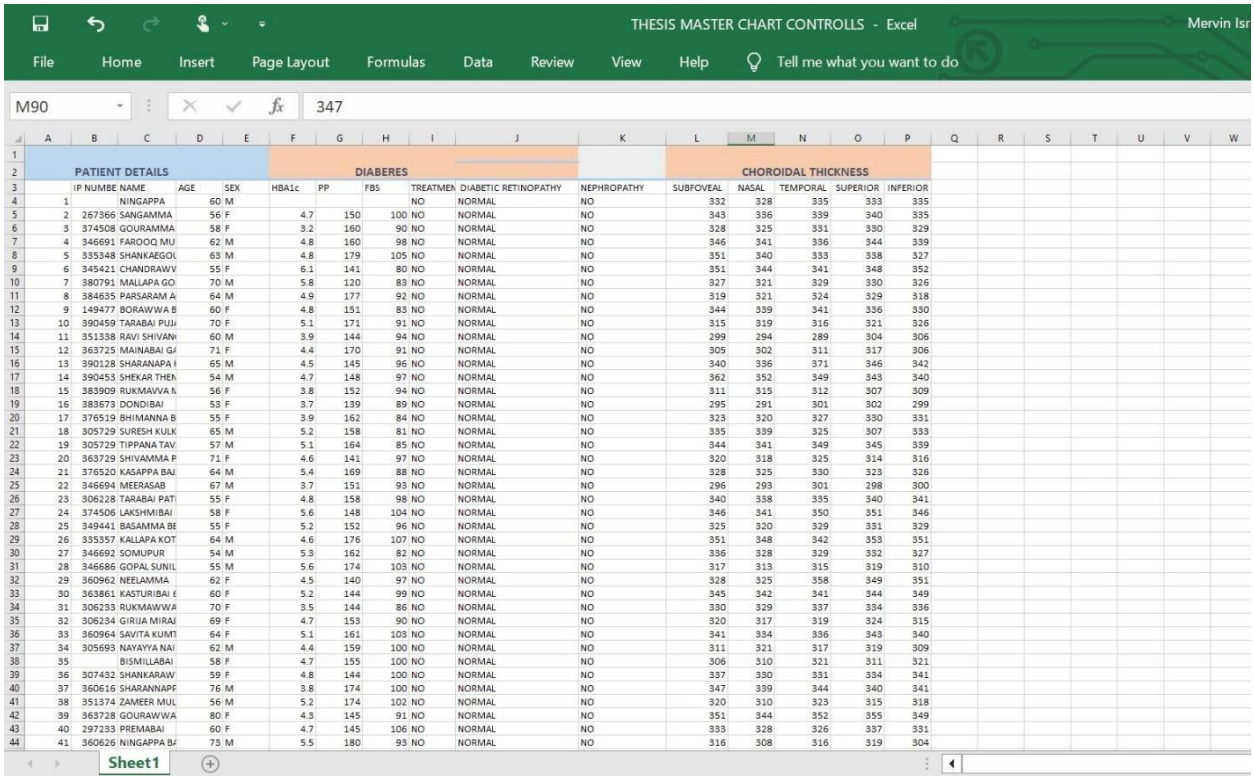
CHOROIDAL THICKNESS	RIGHR EYE	LEFT EYE
SUB FOVIAL		
NASAL		
TEMPORAL		
SUPERIOR		

MASTER CHART FOR CASES



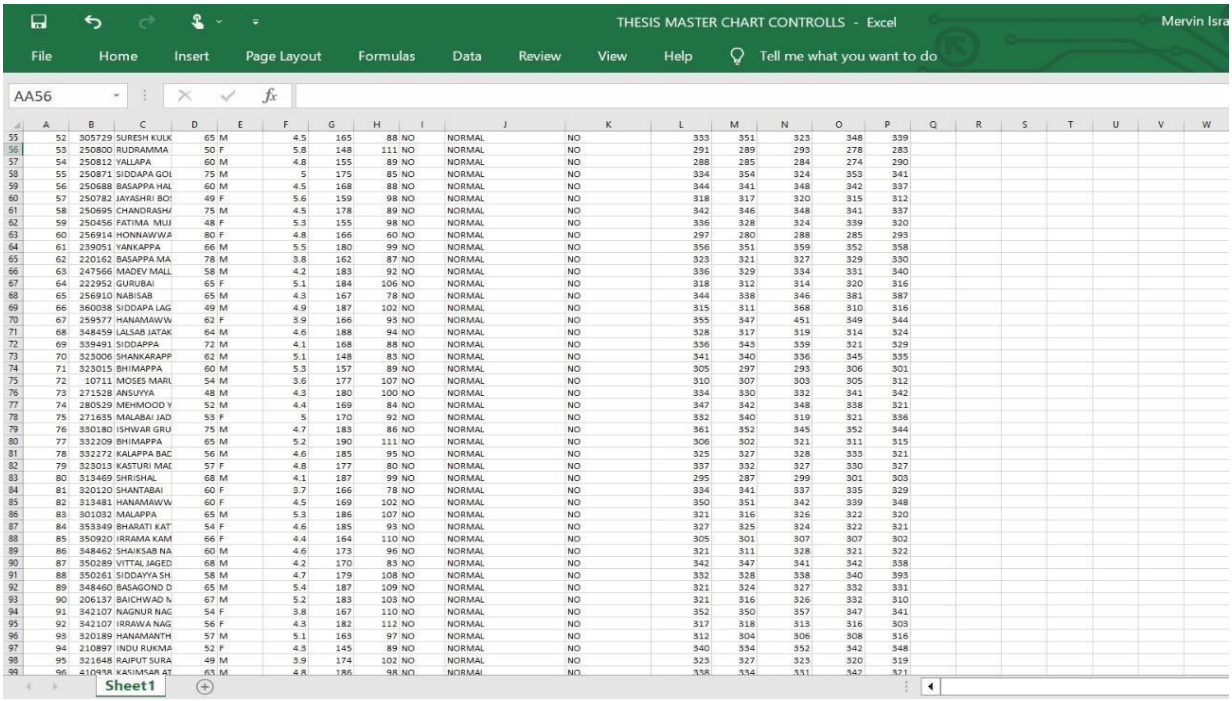


MASTER CHART FOR CONTROLS



THESIS MASTER CHART CONTROLLS - Excel

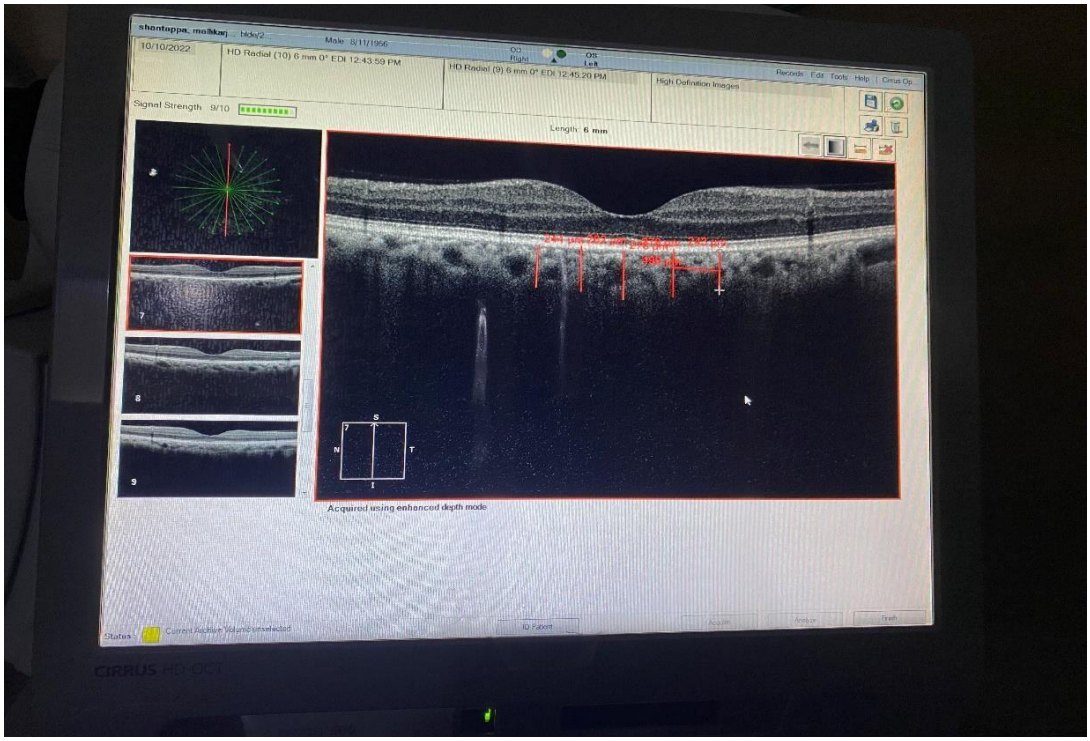
	PATIENT DETAILS				DIABERES						CHOROIDAL THICKNESS				
	IP NUMBE	NAME	AGE	SEX	HBA1c	PP	FBS	TREATMEN	DIABETIC RETINOPATHY	NEPHROPATHY	SUBFOVEAL	NASAL	TEMPORAL	SUPERIOR	INFERIOR
1		NINGAPPA	60	M				NO	NORMAL	NO	332	328	335	333	335
2	267366	SANGAMMA	56	F	4.7	150	100	NO	NORMAL	NO	343	336	339	340	335
3	374508	GOURAMMA	58	F	3.2	160	90	NO	NORMAL	NO	328	325	331	330	329
4	346691	FAROOQ MU	62	M	4.8	160	98	NO	NORMAL	NO	346	341	336	344	339
5	335348	SHANKAEGOL	63	M	4.8	179	105	NO	NORMAL	NO	351	340	333	338	327
6	345421	CHANDRAWV	55	F	6.1	141	80	NO	NORMAL	NO	351	344	341	348	352
7	380791	MALLAPA GO	70	M	5.8	120	83	NO	NORMAL	NO	327	321	329	330	326
8	384635	PARSARAM A	64	M	4.9	177	92	NO	NORMAL	NO	319	321	324	329	318
9	149477	BORAWWA B	60	F	4.8	151	83	NO	NORMAL	NO	344	339	341	336	330
10	390459	TARABAI PUJ	70	F	5.1	171	91	NO	NORMAL	NO	315	319	316	321	326
11	351338	RAVI SHIVAN	60	M	3.9	144	94	NO	NORMAL	NO	299	294	289	304	306
12	363725	MAINABAI GA	71	F	4.4	170	91	NO	NORMAL	NO	305	302	311	317	306
13	390128	SHARANAPA I	65	M	4.5	145	96	NO	NORMAL	NO	340	336	371	346	342
14	390453	SHEKAR THEN	54	M	4.7	148	97	NO	NORMAL	NO	362	352	349	343	340
15	383909	RUKMAVVA N	56	F	3.8	152	94	NO	NORMAL	NO	311	315	312	307	309
16	383673	DONDIBAI	53	F	3.7	139	89	NO	NORMAL	NO	295	291	301	302	299
17	376519	BHIMANNA B	55	F	3.9	162	84	NO	NORMAL	NO	323	320	327	330	331
18	305729	SURESH KULK	65	M	5.2	158	81	NO	NORMAL	NO	335	339	325	307	333
19	305729	TIPPANA TAV	57	M	5.1	164	85	NO	NORMAL	NO	344	341	349	345	339
20	363729	SHIVAMMA P	71	F	4.6	141	97	NO	NORMAL	NO	320	318	325	314	316
21	376520	KASAPPA BAJ	64	M	5.4	169	88	NO	NORMAL	NO	328	325	330	323	326
22	346694	MEERASAB	67	M	3.7	151	93	NO	NORMAL	NO	296	293	301	298	300
23	306228	TARABAI PAT	55	F	4.8	158	98	NO	NORMAL	NO	340	338	335	340	341
24	374506	LAKSHMIBAI	58	F	5.6	148	104	NO	NORMAL	NO	346	341	350	351	346
25	349441	BASAMMA BE	55	F	5.2	152	96	NO	NORMAL	NO	325	320	329	331	329
26	335357	KALLAPA KOT	64	M	4.6	176	107	NO	NORMAL	NO	351	348	342	353	351
27	346692	SOMUPUR	54	M	5.3	162	82	NO	NORMAL	NO	336	328	329	332	327
28	346686	GOPAL SUNIL	55	M	5.6	174	103	NO	NORMAL	NO	317	313	315	319	310
29	360962	NEELAMMA	62	F	4.5	140	97	NO	NORMAL	NO	328	325	358	349	351
30	363861	KASTURIBAI E	60	F	5.2	144	99	NO	NORMAL	NO	345	342	341	344	349
31	306233	RUKMAWWA	70	F	3.5	144	86	NO	NORMAL	NO	330	329	337	334	336
32	306234	GIRIJA MIRAJ	69	F	4.7	153	90	NO	NORMAL	NO	320	317	319	324	315
33	360964	SAVITA KUMT	64	F	5.1	161	103	NO	NORMAL	NO	341	334	336	343	340
34	305693	NAYAYYA NAI	62	M	4.4	159	100	NO	NORMAL	NO	311	321	317	319	309
35		BISMILLABAI	58	F	4.7	155	100	NO	NORMAL	NO	306	310	321	311	321
36	307432	SHANKARAW	59	F	4.8	144	100	NO	NORMAL	NO	337	330	331	334	341
37	360616	SHARANNAPF	76	M	3.8	174	100	NO	NORMAL	NO	347	339	344	340	341
38	351374	ZAMEER MUL	56	M	5.2	174	102	NO	NORMAL	NO	320	310	323	315	318
39	363728	GOURAWWA	80	F	4.3	145	91	NO	NORMAL	NO	351	344	352	355	349
40	297233	PREMABAI	60	F	4.7	145	106	NO	NORMAL	NO	333	328	326	337	331
41	360626	NINGAPPA BA	73	M	5.5	180	93	NO	NORMAL	NO	316	308	316	319	304



THESIS MASTER CHART CONTROLLS - Excel

52	305729	SURESH KULK	65	M	4.5	165	88	NO	NORMAL	NO	333	351	323	348	339	
53	250800	RUDRAMMA	50	F	5.8	148	111	NO	NORMAL	NO	291	289	293	278	283	
54	250812	YALLAPA	60	M	4.8	155	89	NO	NORMAL	NO	288	285	284	274	290	
55	250871	SIDDAPA GOI	75	M	5	175	85	NO	NORMAL	NO	334	354	324	353	341	
56	250688	BASAPPA HAL	60	M	4.5	168	88	NO	NORMAL	NO	344	341	348	342	337	
57	250782	JAYASHRI BO	49	F	5.6	159	98	NO	NORMAL	NO	318	317	320	315	312	
58	250695	CHANDRASH/	75	M	4.5	178	89	NO	NORMAL	NO	342	346	348	341	337	
59	250456	FATIMA MUJ	48	F	5.3	155	98	NO	NORMAL	NO	336	328	324	339	320	
60	256914	HONNAWWA	80	F	4.8	166	60	NO	NORMAL	NO	297	280	288	285	293	
61	239051	YANKAPPA	66	M	5.5	180	99	NO	NORMAL	NO	356	351	359	352	358	
62	220162	BASAPPA MA	78	M	3.8	162	87	NO	NORMAL	NO	323	321	327	329	330	
63	247566	MADEV MALL	58	M	4.2	183	92	NO	NORMAL	NO	336	329	334	331	340	
64	222952	GURUBAI	65	F	5.1	184	106	NO	NORMAL	NO	318	312	314	320	316	
65	256910	NABISAB	65	M	4.3	167	78	NO	NORMAL	NO	344	338	346	381	387	
66	360038	SIDDAPA LAG	49	M	4.9	187	102	NO	NORMAL	NO	315	311	368	310	316	
67	259577	HANAMAWW	62	F	3.9	166	93	NO	NORMAL	NO	355	347	451	349	344	
68	348459	LALSAB JATAK	64	M	4.6	188	94	NO	NORMAL	NO	328	317	319	314	324	
69	339491	SIDDAPPA	72	M	4.1	168	88	NO	NORMAL	NO	336	343	339	321	329	
70	323006	SHANKARAPP	62	M	5.1	148	83	NO	NORMAL	NO	341	340	336	345	335	
71	323015	BHIMAPPA	60	M	5.3	157	89	NO	NORMAL	NO	305	297	293	306	301	
72	10711	MOSES MARL	54	M	3.6	177	107	NO	NORMAL	NO	310	307	303	305	312	
73	271528	ANSUYYA	48	M	4.3	180	100	NO	NORMAL	NO	334	330	332	341	342	
74	280529	MEHMOOD Y	52	M	4.4	169	84	NO	NORMAL	NO	347	342	348	338	321	
75	271635	MALABAI JAD	53	F	5	170	92	NO	NORMAL	NO	332	340	319	321	336	
76	330180	ISHWAR GRU	75	M	4.7	183	86	NO	NORMAL	NO	361	352	345	352	344	
77	332209	BHIMAPPA	65	M	5.2	190	111	NO	NORMAL	NO	306	302	321	311	315	
78	332272	KALAPPA BAC	56	M	4.6	185	95	NO	NORMAL	NO	325	327	328	333	321	
79	323013	KASTURI MAC	57	F	4.8	177	80	NO	NORMAL	NO	337	332	327	330	327	
80	313469	SHRISHAL	68	M	4.1	187	99	NO	NORMAL	NO	295	287	299	301	303	
81	320120	SHANTABAI	60	F	3.7	166	78	NO	NORMAL	NO	334	341	337	335	329	
82	313481	HANAMAWW	60	F	4.5	169	102	NO	NORMAL	NO	350	351	342	339	348	
83	301032	MALAPPA	65	M	5.3	186	107	NO	NORMAL	NO	321	316	326	322	320	
84	353349	BHARATI KAT	54	F	4.6	185	93	NO	NORMAL	NO	327	325	324	322	321	
85	350920	IRRAMA KAM	66	F	4.4	164	110	NO	NORMAL	NO	305	301	307	307	302	
86	348462	SHAIKSAB NA	60	M	4.6	173	96	NO	NORMAL	NO	321	311	328	321	322	
87	350289	VITTAL JAGED	68	M	4.2	170	83	NO	NORMAL	NO	342	347	341	342	338	
88	350261	SIDDAYA SH	58	M	4.7	179	108	NO	NORMAL	NO	332	328	338	340	393	
89	348460	BASAGOND D	65	M	5.4	187	109	NO	NORMAL	NO	321	324	327	332	331	
90	206137	BAICHWAD N	67	M	5.2	183	103	NO	NORMAL	NO	321	316	326	332	310	
91	342107	NAGNUR NAG	54	F	3.8	167	110	NO	NORMAL	NO	352	350	357	347	341	
92	342107	IRRAWA NAG	56	F	4.3	182	112	NO	NORMAL	NO	317	318	313	316	303	
93	320189	HANAMANTH	57	M	5.1	163	97	NO	NORMAL	NO	312	304	306	308	316	
94	210897	INDU RUKMA	52	F	4.3	145	89	NO	NORMAL	NO	340	334	352	342	348	
95	321648	RAJPUT SURA	49	M	3.9	174	102	NO	NORMAL	NO	323	327	323	320	319	

COLOR PLATES



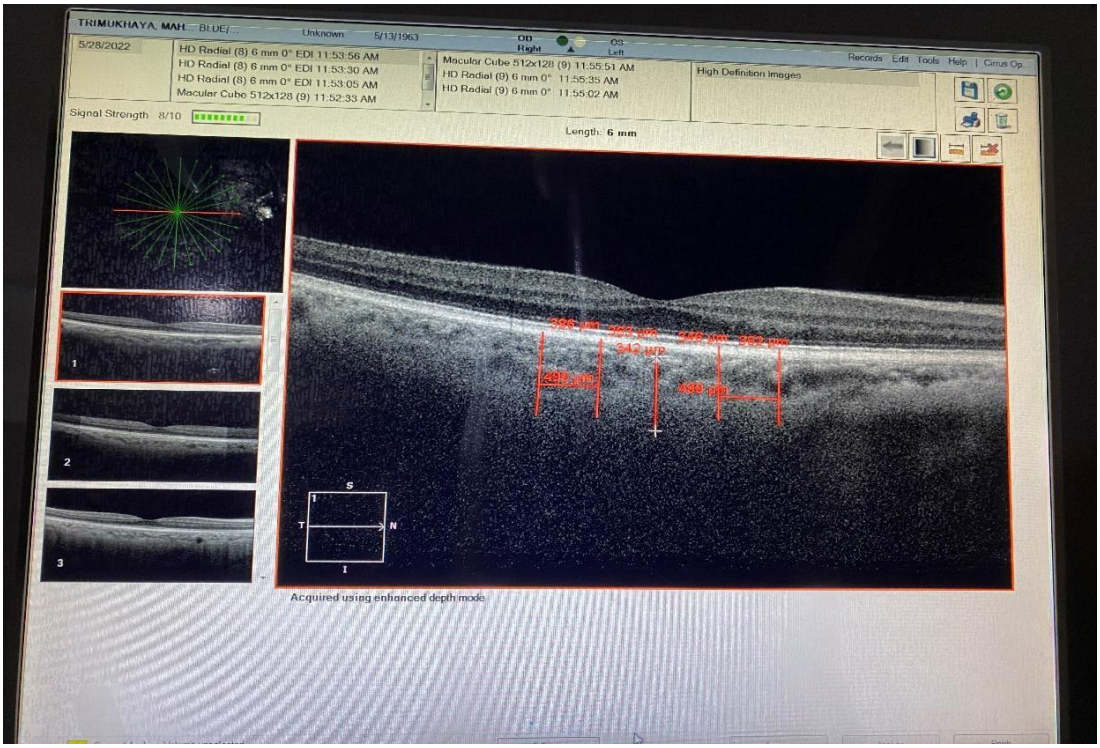


FIG 21 MEASUREMENT OF CHOROIDAL THICKNESS ON OCT SCANS

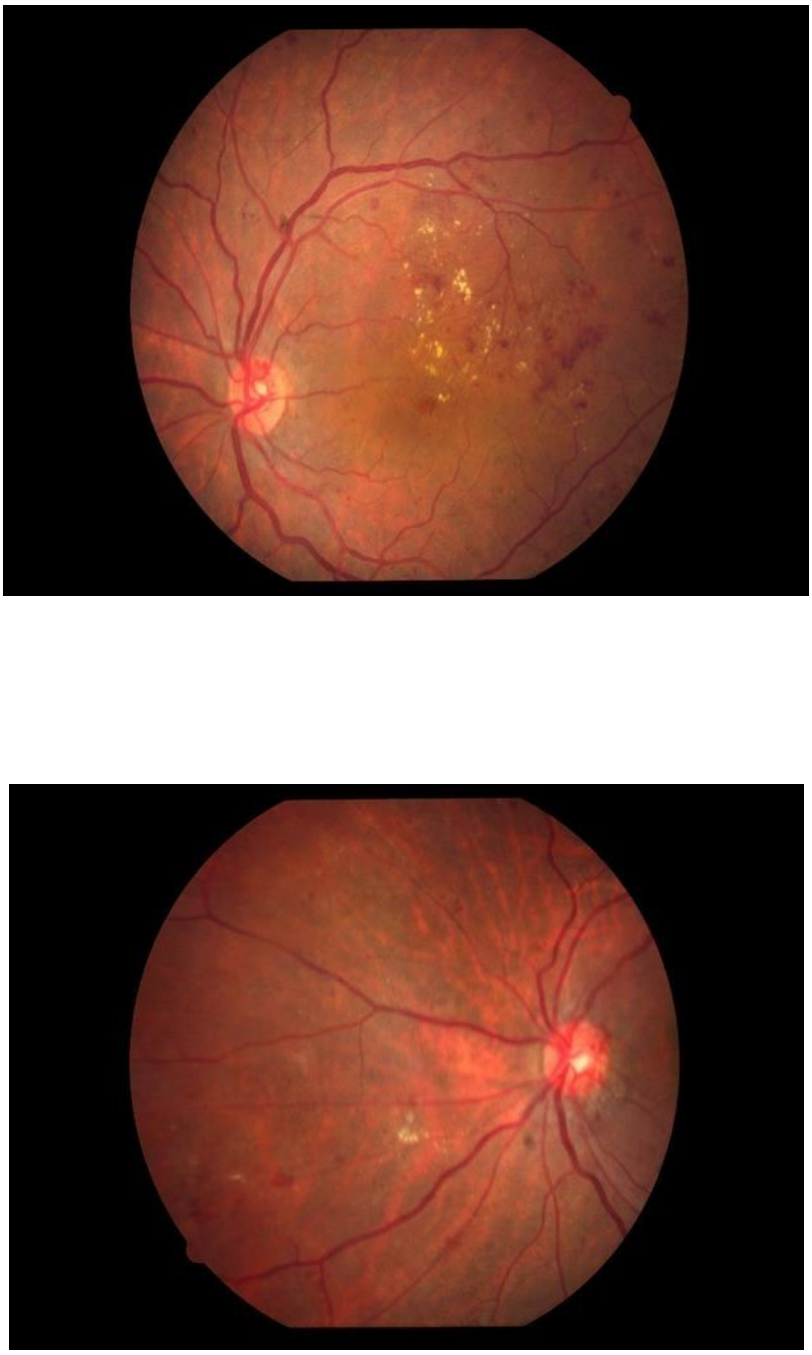


Fig 22. Fundus photograph of a Moderate – Severe NPDR patient