"ASSESSMENT OF THE EFFECT OF DIABETIC RETINOPATHY ON RETINAL NERVE FIBER THICKNESS "

By

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Dissertation submitted to

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH,CENTRE, TAMAKA, KOLAR

In partial fulfilment of the requirements for the degree of

MASTER OF SURGERY

IN

OPHTHALMOLOGY

Under the guidance of

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DEPARTMENT OF OPHTHALMOLOGY SRI DEVARAJ URS MEDICAL COLLEGETAMAKA, KOLAR.

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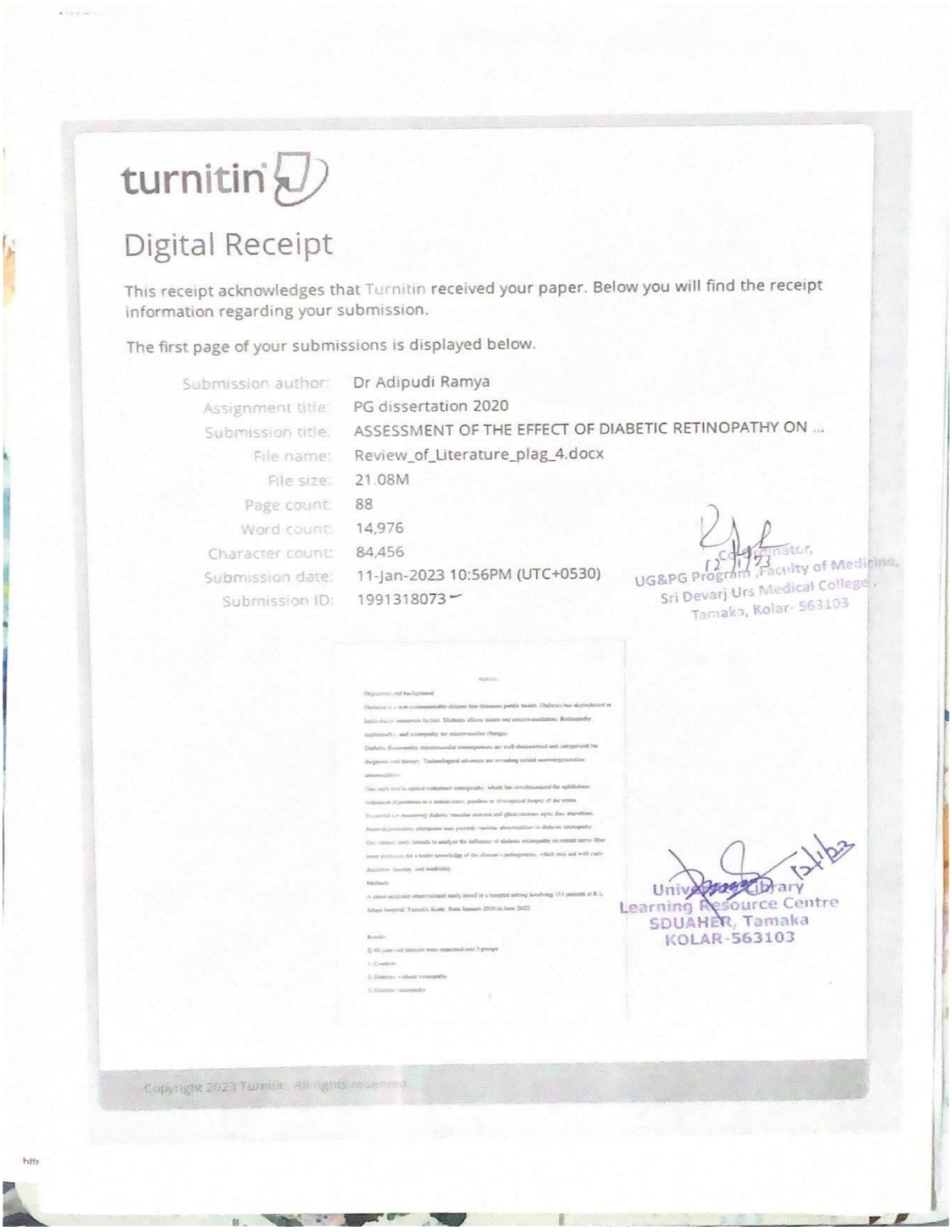

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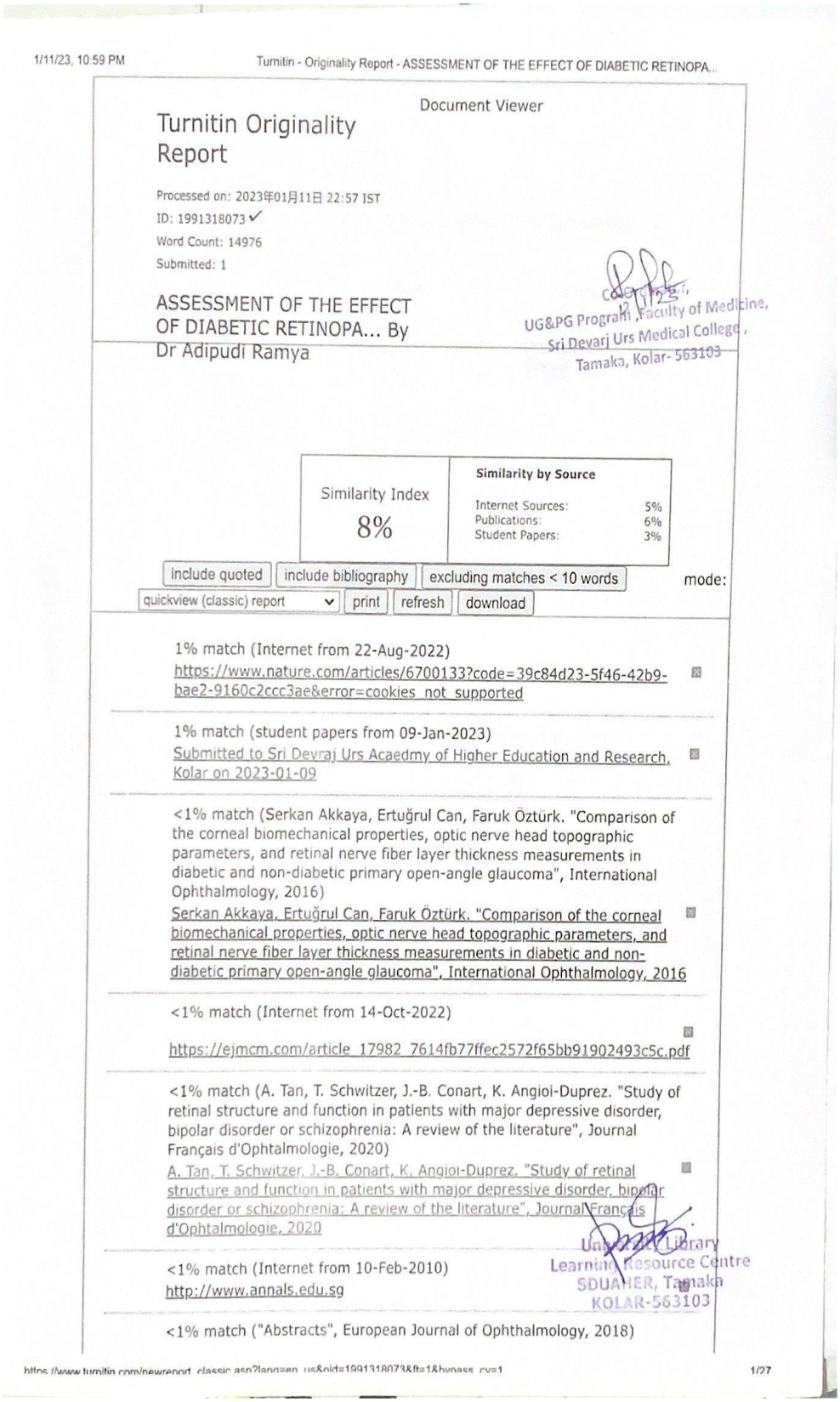

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LIST OF ABBREVATIONS

DM	Diabetes Mellitus
DR	Diabetic retinopathy
RE	Right Eye
LE	Left eye
RNFL	Retinal nerve fiber layer
MODY	Maturity onset diabetes of the young
GDM	Gestational diabetes mellitus
LIC	Low income countries
LMIC	Middle income countries
NCD	Non-communicable diseases
VEGF	Vascular endothelial growth factor
NPDR	Non proliferative diabetic retinopathy
PDR	Proliferative diabetic retinopathy
CSME	Clinically significant macular oedema
VH	Vitreous hemorrhage
DME	Diabetic macular edema
IRMA	Intraretinal microvascular abnormalities
ETDRS	Early treatment of diabetic retinopathy study
ONH	Optic Nerve Head
OCT	Optical Coherence Tomography
SLP	Scanning Laser Polarimetry

ETDRS	Early Treatment Diabetic retinopathy Study
HRT	Heidelberg Retinal Tomography

ABSTRACT

Objectives and background

Diabetes is a non-communicable disease that threatens public health. Diabetes has skyrocketed in India due to numerous factors. Diabetes affects micro and macrovasculature. Retinopathy, nephropathy, and neuropathy are microvascular changes.

Diabetic Retinopathy microvascular consequences are well-documented and categorized for diagnosis and therapy. Technological advances are revealing retinal neurodegenerative abnormalities.

One such tool is optical coherence tomography, which has revolutionized the ophthalmic outpatient department as a noninvasive, painless in vivo optical biopsy of the retina.

It's useful for measuring diabetic macular oedema and glaucomatous optic disc alterations. Neurodegenerative alterations may precede vascular abnormalities in diabetic retinopathy.

Our current study intends to analyze the influence of diabetic retinopathy on retinal nerve fibre layer thickness for a better knowledge of the disease's pathogenesis, which may aid with early detection, therapy, and morbidity.

Methods

A cross-sectional observational study based in a hospital setting involving 111 patients at R L Jalapa hospital, Tamaka, Kolar, from January 2020 to June 2022.

Results

≧ 40-year-old patients were separated into 3 groups:

1. Controls

2. Diabetes without retinopathy

3. Diabetic retinopathy

All 111 patients' OCTs were compared.

Mean Global and superior RNFL thickness decreased significantly which is denoted statistically in diabetic patients. Inferior, nasal, and temporal RNFL thickness changes are not significant. Superior RNFL thickness and disease duration are inversely correlated.

Out of 111 individuals, 37 had NPRD, 37 had no DR, and 37 were controls. This study found that there is a depletion in RNFL thickness in diabetics.

Superior quadrant RNFL and global RNFL thickness is where the maximum amount of depletion was observed.

Keywords: Diabetes mellitus, diabetic retinopathy, RNFL thickness, Optical coherence tomography.

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INTRODUCTION

INTRODUCTION

One in ten persons (20-79) have diabetes, which would be estimated to be around 537 million people worldwide. This makes diabetes mellitus (DM) the most predominant non-communicable disease and a major danger to public health worldwide. This number is predicted to reach 643 million by the year 2030 and 783 million by the year 2045. Eighty per cent or more of the world's diabetics live in developing countries in low, and middle-income families.[1]

Type I diabetes is believed to have been showing an increased occurrence over the preceding several years, whilst diabetes type II is said to have already reached an epidemic level. [2]

According to estimates from an organization of world health in Geneva (WHO), India has the highest prevalence of diabetes patients than any other country in the world. [3] This increase can be attributable to suburbanization and societal progress in addition to rapid epidemiological change. In India, the diabetes mellitus prevalence in the population aged 20 to 79 is 6.2–7.6%. (41 million).[1]

Patients who have been diagnosed with diabetes are more likely to experience a variety of problems, some of which can be both life-limiting and life-threatening. These complications can be divided into two categories: macrovascular and microvascular. Macrovascular complications include conditions such as ischemic stroke, heart disease and peripheral artery disease. Microvascular complications include retinopathy, neuropathy, and nephropathy.

As diabetic mellitus affects a large population in India.[4] Diabetic retinopathy (DR) is the most prevalent consequence of diabetes, affecting 5% of diabetics and leading to severe vision loss at the end stages (vision of 5/200 or lower).[5]

It is well recognized that diabetes causes long-term consequences on vascular tissues, which

alter the retina. The severity of these consequences ranges from mild to moderate grades of non-proliferative diabetic retinopathy to advanced proliferative retinopathy with or without clinically significant macular

oedemaIn locations where the technology is available, stereoscopic fundus photos are taken o f patients for documentation and follow-up

purposes. The procedure for the care of diabetic retinopathy, which has been thoroughly

detailed in the relevant body of literature, focuses on

the vascular consequences of diabetic retinopathy.

Nonetheless, it appears difficult to describe the changes that occur at the tissue level in DR. These modifications may have been more completely recorded if histological tissue sections had been available. We can now obtain optical section biopsies utilising non-invasive techniques such as Scanning Laser Polarimetry (SLP) and Optical Coherence Tomography (OCT) . Quantifying the direct effects of DR on neurons is also beneficial. Technologies have opened up fresh perspectives on disaster recovery management and comprehension.

In spite of identifiable evidence of retinal nerve fiber layer (RNFL) deficiencies, the cup disc ratio was not enlarged in diabetic eyes, which is what distinguishes diabetic retinopathy from glaucomatous optic nerve damage. [6]

Modern technologies such as the Heidelberg Retina Tomograph (HRT-III), Glaucoma Diagnostics- Variable Corneal Compensation (GDx VCC), and OCT have transformed the examination of the optic nerve head, peripapillary region, macula, and Retinal Nerve FL. We can effectively obtain a histological analysis of the tissue or location in the retina due to the excellent resolution and repeatability of these technologies. The parameters for the optic nerve head (ONH) and its rim, the thickness of the Retinal NFL with a diameter of 3.2 to 3.4 mm surrounding the ONH, and the macular thickness are among the most recent scientific

developments made when evaluating the ONH and retina.[7]

The goal of this research is to gain insight on the OCT properties of the retinal NFL in diabetics with diabetic retinopathy. We desire to determine whether there is a correlation between the thickness of the RNFL and DR. Early detection of retinal nerve FL thinning, which appears to be a characteristic of both diabetes and glaucoma, could be a significant tool in understanding the progression of diabetic retinopathy.[8-13]

AIMS & OBJECTIVES

OBJECTVES OF STUDY

- To determine the effect of Diabetic Retinopathy on Retinal nerve fiber layer thickness by using Ocular Coherence Tomography.
- To correlate the retinal nerve fiber layer thickness with duration of diabetes

REVIEW OF LITERATURE

REVIEW OF LITERATURE

DM a metabolic disorder involving all the systems and whose hallmark trait include an increase in blood sugar levels due to an absolute or relative inadequacy in the production of insulin.[14]

Factors contributing to hyperglycemia include in DM.[15]

1. Reduced insulin production
2. Decreased glucose uptake
3. Elevated glucose synthesis.

The metabolic dysregulation present with DM causes a series of pathological and physiological changes in the different organ frameworks that forces a enormous load on the person suffering with DM and on their health care.

CLASSIFICATION OF DIABETES MELLITUS

The older classification divided the disease depending on the mode of treatment into insulin dependent and non-insulin-dependent forms, but this classification was complicated when different subgroups needed to be considered.[16]

Types of diabetes

1. Type 1 diabetes: It usually appears at a very young age and has an immediate onset, but it might manifest later in life.[16] Autoimmunity specific to islet is thought to be the cause of the majority of cases. The requirement for the controlling of the hyperglycaemia in this DM is insulin. It is said to account for almost 10% of all diabetes.

2. Type 2 DM: most common, accounts for > 90% of all diabetes and seen to have a gradual onset. The risk factors included are obesity, absent physical activity, unhealthy diet, stressful life, urbanisation and in certain people genetic predisposition. When it occurs in a younger

3.**Hyperglycemia Pregnancy** (gestational diabetes) occurs when women with no known history of diabetes have elevated blood sugar levels in the advanced stages of their pregnancy. This issue is normally resolved after the delivery.

4. Diabetes as a result of other systemic illnesses, such as chronic pancreatic illness, or as a result of the use of certain medications, such as steroids. A novel classification has recently been developed, which divides diabetes into five subgroups based on six biological markers (including β –cell function and insulin resistance) and the risk of complications.[18]

EPIDEMIOLOGY

Diabetes – a global epidemic

Diabetes is very swiftly becoming the epidemic of the century across the globe. Type 2 diabetes mellitus, which is more rampant (>90% of all cases) and the main carter of the diabetes epidemic, now influences 5.9% of the world's adult population with upto 80% seen in the developing countries.[19]

In 2014, it was estimated that 422 million adults worldwide have DM, with the prevalence growing in most countries due to advanced age, lifestyle changes, and interactions among the 2 factors.[20]Diabetes was placed eighth in terms of years lived with disability in 2016, and the number of years of life lost due to diabetes climbed 31% between 2006 and 2016. (ranked in ninth place in lower middle-income nations).[21,]22 Diabetes becomes more common with

age, affecting 13-20% of persons aged 50 and above. It was also discovered that three hundred and fifty two million people had reduced glucose tolerance, which significantly raises the risk of diabetes.[23] Diabetes is expected to affect 629 million adults between the ages of 20 and 79 by 2045.[23] It was also observed that three-quarters of diabetics live in low and middle-income countries (LIC, LMIC), and nearly half are not diagnosed with the disease until they are significantly older.[23] More than one million children and adolescents have type 1 DM and one in every six births is to a mother who has hyperglycemia during pregnancy.[23] Diabetes was responsible for around 4 million deaths in 2012 and diabetes healthcare accounts for 12% of global health expenditures ($727 billion).[23, 24] Diabetes is expected to be the seventh leading cause of mortality by 2030, according to the WHO.

Diabetes in India

In 2016, there were an estimated 65 million persons in India under the age of 20 suffering with diabetes, a figure that has amplified by 2.5 million since 1990. [25] In 2016, the occurrence was highest in the states of Tamil Nadu, Kerala, and Delhi, and lowest in Rajasthan, Bihar, Himachal Pradesh, and the North Eastern States. The overall age-standardized prevalence of diabetes is 7.9% (95% Confidence interval 7.1-8.6%). [25] Diabetes predominates more in men than in women, and the prevalence rises with age in both men and women, with a higher increase in men with time. Diabetes escalation is being driven by rising obesity, which has risen from nine % to 20.4% between 1990 and 2016. Diabetes affects 38 out of every 100 obese individuals in Indians aged 20 and up, which is higher than the global average of 19. [25]In India, nearly half of all diabetics (47%) are not recognised, as in many other countries, and do not receive any type of treatment.[26] In India, as in other countries, the large percentage of Diabetics have type 2 diabetes, and in 2017 there were projected to be 128,500 young people (< 20 years) with Type 1 diabetes. [23]

Impact of diabetes in India and the response needed: A research conducted in India projected that between 2001 and 2003, 2.1 percent of all deaths (136,000) among those aged 15 to 69 years were due to kidney failure, rising to 2.9 percent by 2010-13. Diabetes was the leading cause of renal failure death, with a larger risk in the 2 time period than the first. 15 individuals born in the 1970s had a higher risk than those born in the 1950s, indicating that it is becoming an important progressive cause of untimely death in India. [27]

Economic impact of diabetes in India: According to a World Economic Forum analysis on the monetary implications of noncommunicable diseases (NCDs), India is expected to lose $4.58 trillion by 2030 due to NCDs and mental health disorders, with diabetes alone accounting for $0.15 trillion. [28] People with diabetes spend 2-3 times more on health care than those who do not. The average annual cost per individual is estimated to be between INR 3,000 and 10,000. The high expense of treatment increases the likelihood of noncompliance, particularly among lower socioeconomic groups. Diabetes and its associated complications impose a monetary burden in terms of missed performance and opportunity costs on individuals, families, and society. [27]

A few epidemiological investigations in migratory Indians and India itself make evident that the general population has a high hereditary inclination for diabetes, which is hastened by means of natural factors like, suburbanization.[37] Predominance of diabetes is 4-6 times lesser in rural regions probably accredited to a customary way of life which has valuable impact on glucose tolerance (GT). National Urban Diabetes Survey piloted in 6 cities found age standardized preponderance rates of 12 percent for diabetes with a slender male dominance and 14 percent for impaired glucose tolerance. Individuals less than 40 years, occurrence of 5 percent for DM and 13 percent occurrence of impaired glucose tolerance.[38] The International Diabetes Federation (IDF) approximates in the country that 40.9 million

people with DM and predicted to increase to 69.9 million by 2025.[39] In recent twenty years, an increment of proportion of diabetes amongst urban just as regional Indians with a proposition that Southern India has perceived the most intense percentage increase. Consequent contemplates affirmed this increased preponderance of DM in urban south India. Regardless the fact that in rural India preponderance of diabetes is a lot

of inferior to urban inhabitants, even here the frequency are quickly mounting nevertheless unambiguously more examinations are required. Change in the predominance of diabetes in numerous urban India are standard in view of the enormous variety in the pervasiveness of cardiovascular hazard factors in various districts and states.[40,41] There is a palpable alteration in age of inception to younger aged individuals, which is disturbing and this can have an adverse consequence on the country's economy. Therefore, the earlier to identify individuals at-risk of the disease and suitable intervention to increase exercise, changing their dietary habits into a more healthy approach and be a great magnitude of help to delay or counter, the occurrence of diabetes and consequently lessen the load due to its allied complications in India.[42]

Race: Different racial and ethnic groups have widely varying rates of type II DM occurrence. In some communities of Native Americans and Hispanics, type II diabetes has reached epidemic proportions. Retinopathy and nephropathy pose a greater threat to people of African, Native American, and Hispanic descent.[35]

Sex in older women than men Type II DM is marginally more common. [35]

Age Type II DM customarily has been believed to influence in people > 40 years of age it is being perceived progressively in more young individuals especially in specific races and

ethnicity and in people suffering from obesity. In certain territories, more type 2 than type 1 diabetes mellitus is being studied in pre-pubertal youths, adolescents and youthful grown-ups. For all intents and purposes all instances of diabetes mellitus in more seasoned people are type 2.[35]

Familial history of diabetes (Parents or sibling with type 2 DM)
Obesity (Body Mass Index ≥ 25 kg/m2)
Habitual physical inactivity
Racial (e.g. African, American, Asian American, Pacific Islander)
Gestational diabetes
Hypertension (blood pressure ≥ 140/90 mHg)
HDL cholesterol level ≤ 35mg/dL (0.90mmol/L) or triglyceride level ≥ 250mg/dL (2.82 mol/L)
Polycystic ovary syndrome or acanthosis nigricans.
History of vascular disease.

Table 1:- Risk factors associated with Type II DM.[15]

COMPLICATIONS [15]

Complications related to DM are responsible for the bulk of morbidity and death that are associated with the condition. These complications affect a wide variety of organs throughout the human body. Diabetes has been the leading cause of new cases of blindness in adults, renal failure, and non-traumatic amputations of the lower limbs in the United States for an incalculable number of years. In current history, diabetes has also emerged as a primary factor in the development of coronary heart disease (CHD). The hyperglycemia-related consequences of diabetes typically do not manifest themselves until the 2 decade of the patient's battle with the disease.

Microvascular	Macrovascular
- Eye disease 1. Retinopathy (non-proliferative/proliferative) 2. Macular oedema - Neuropathy 1. Sensory and motor (mono- and polyneuropathy) 2. Autonomic Nephropathy (albuminuria and declining renal function)	Coronary heart disease Peripheral arterial disease Cerebrovascular disease

Diabetes-Related Complications [15]

Ophthalmic Complications of Diabetes Mellitus [36]

Common:

1) Retinopathy

2) Iridopathy (minor iris transillumination defects)

3) Unstable refraction

4) Dry eye syndrome

5) Recurrent corneal abrasions

Uncommon:

1) Ocular motor nerve palsies

2) Recurrent styes

3) Xanthelasmata

4) Reduced corneal sensitivity

5) Neovascular glaucoma

Rare:

1) pupillary light-near dissociation

2) Acute onset cataract

3) Rhino-orbital mucormycosis

4) Diabetic papillopathy/ papillitis

5) Wolfram syndrome (progressive optic atrophy with multiple neurological & systemic abnormalities)

DIABETIC RETINOPATHY

Definition: "Diabetic retinopathy(DR) is said to be defined as a progressive dysfunction of the vasculature in the retina caused due long standing hyperglycaemia which results in damage to the structures of the neural retina".[37] It is an example of microvascular complications and is thought to be a crucial indicator of the impact diabetes has˙ to begin with the norms for diagnosis of diabetes was developed depending on the glycemic level above which there was noteworthy risk of developing microvascular complications, particularly DR in Pima Indians.[38,39]

Diabetic Retinopathy Epidemiology [40]

Diabetes is a growing global epidemic that is expected to affect 642 million people by 2040, resulting in an increased prevalence of diabetic retinopathy globally. One-third of the global population with diabetes mellitus is likely to have diabetic retinopathy, with one-third having vision-threatening diabetic retinopathy. The direct association of an increased prevalence of diabetic retinopathy with longer duration of diabetes mellitus in individuals with both type I and type II diabetes was an important discovery of the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR). After 20 years of diabetes mellitus, over 99% of patients with type I and 60% of patients with type II illness had diabetic retinopathy, according to the WESDR cohort. Proliferative diabetic retinopathy was identified in 50% of type 1 patients with a disease duration of 20 years and 25% of type 2 patients with a disease duration of 25 years. [41] Furthermore, 3.6% of younger-onset patients (aged 30 years or less at diagnosis) and 1.6% of elder-onset patients (aged 30 years or older at diagnosis) had visual acuity of 20/200 or worse. Diabetic retinopathy was responsible for such vision loss in 86% of younger-onset diabetes patients and 33% of older-onset diabetes patients. [42]

Pathogenesis of Diabetic Microangiopathy

Long-term hyperglycemia is required to cause alterations in the retinal vasculature. Within the first 6 weeks, hyperglycemia does not cause pathogenic alterations in the retinal vasculature. [43] Hyperglycemia controls the evolution of retinopathy through many mechanisms.

1. **Retinal endothelial cell glucose transport** - Retinal-endothelial cell glucose transport - It has been postulated that vascular endothelial growth factor (VEGF), a factor increased in retinopathy, promotes an increase in the concentration of relocalized GLUT1 in the inner blood-retinal barrier.[44]

2. Endothelium-derived relaxing factors

a) *Nitric oxide*- There are at least 3 mechanisms for decreasing production and/or increasing quenching of NO by hyperglycaemia. First, hyperglycaemia causes *de novo* synthesis of diacylglycerol (DAG), leading to activation of Protein kinase C (PKC).Second, hyperglycaemia activates the polyol pathway by increasing substrate- glucose for endothelial aldose reductase.[45] Third, hyperglycaemia generates non- enzymatic glycated proteins which lead to subsequent superoxide generation resulting in inactivation of NO.[46] Additionally, glycated proteins can directly quench NO.[47]

b) *Prostacyclin (PGI2)* PGI2 stimulates enhanced production of cyclic adenosine 3',5'- monophspate (cAMP) through adenylcyclase in smooth muscle cells and pericytes, leading to relaxation of those cells.[48] Hyperglycaemia also inhibits PGI2 synthesis through generating lipid peroxide and arachidonic acid via microsomal desaturase.

Endothelium-derived hyperpolarizing factor (EDHF)- mediate endothelium-dependent hyperpolarisation of vascular smooth muscle cells or pericytes . Endothelium-dependent hyperpolarization is reduced by hyperglycemia in diabetes, owing to a dysfunctional vascular response to EDHF. [49]

3. Endothelium-derived contracting factors

a) *Endothelin-1 (ET-1)*- ET-1 is an extremely potent vasoconstrictor peptide. ET-1 levels in retinal vascular cells are most likely to rise in response to hyperglycemia.[49]

b) Cyclooxygenase products

Cyclooxygenase products induce vasoconstriction and include thromboxane (TX), prostaglandin (PG) [50] and lipid peroxides (LPO) which can be found in endothelial cells and

platelets. However, overproduction of these factors has been detected in diabetic retinopathy.

4. Retinal capillary cell death

Histological analyses of diabetic retina demonstrate localised regions of non- perfused acellular 'vessels' consisting solely of basement membrane. Retinal capillary cell death unquestionably has a major impact on retinal vessels in diabetes and in the case of pericyte loss, occurs long before the onset of proliferative diabetic retinopathy (PDR) Hyperglycaemia has been shown to induce pericyte apoptosis both *in vivo* and in *vitro*, with *in vitro* evidence that cell death is exacerbated when glucose levels fluctuate between hyper- and normoglycaemia as often occurs in poorly controlled diabetes.[51,52]

5. Polyol pathway

The enzyme aldose reductase changes sugars into their alcohols (e.g. glucose to sorbitol and galactose to galactitol). As sorbitol and galactitol are unable to diffuse out of cells without difficulty, their intracellular concentration rises and water is drawn into the cells by osmotic forces. Retinal pericytes and Schwann cells have a high concentration of aldose reductase. So, it has been suggested that DR and DPN may be mediated by aldose reductase mediated damage. However clinical trials have not demonstrated any beneficial effects of aldose reductase inhibitors so far. [15,37]

6. Glycation pathway

During normal ageing, glucose binds non-enzymatically to free amino groups in proteins and forms advanced glycation end products (AGEs) through a series of oxidative and non- oxidative reactions. Hyperglycaemia and oxidative stress probably confer on the opportunity to continue to rearrange and generate irreversible advanced glycation end products (AGEs) in diabetes.[53] The impact of AGEs on retinal capillary cells is related to

their capacity to accumulate in tissues over time, to form cross-links and to generate oxygen-derived free radicals.[54]

7. Oxidative stress

Oxidative stress is defined as an increase in the steady-state levels of reactive oxygen species. There are decreased levels of super oxide dismutase (SOD) and glutathione peroxidase (GSH-Px) in both clinical and experimental diabetes, indicating an impaired defense system for free radical scavenging.[55] Oxygen derived free radicals may impair endothelium dependent vasodilatation through inactivation of NO.[56] In addition, oxidative stress can cause an increase in the conversion of deoxyguanosine to 8-oxo 2-deoxyguanosine in DNA. Both the altered gene profile of scavenging enzymes and overexpression of the cell death protease gene are believed to increase apoptosis of retinal capillary cells in diabetic retinopathy.[57]

Retinal ischemia

Retinal ischemia is generally believed to result from structural and functional derangement of the retinal microcirculation. The formation of acellular capillaries is a major histological feature of the ischaemic retina.[57] Several possible mechanisms have been proposed for the appearance of retinal ischaemia in diabetes. These include thickened basement membranes, platelet aggregation, leukocyte activation/adherence or a combination thereof. Furthermore, hyperglycaemia is likely to be a major risk facto**r.**

a) Retinal basement membrane thickening

In diabetes, early hyperglycaemia is sufficient to increase the synthesis of basement membrane components in the retina which in turn may contribute to the closure of capillaries. The expression of tenascin, an extracellular matrix glycoprotein, originally found to modulate organogenesis in tendinous and glial tissue, suggests that this

glycoprotein may promote retinal basement membrane thickening.[58]

b) Platelet aggregation

Diabetic retinopathy is associated with an increased number and size of platelet-fibrin thrombi in the retinal capillaries compared to normal. These thrombi can contribute to capillary obliteration and retinal ischemia.

c) Leukocyte activation and adherence

Excess activation of endothelial PKC promotes platelet-activating factor (PAF) synthesis in diabetes. PAF stimulates PAF receptors on peripheral leukocytes rolling on the luminal endothelial membrane leading to their activation. 2 integrins on activated leukocytes enable the leukocytes to adhere tightly to the endothelial cell via binding intercellular adhesion molecule-1 (ICAM-1). Furthermore, leukocytes in diabetes have been reported to be less deformable due to actin polymerization and increase in their viscosity. Alteration in retinal blood flow could reduce pressure gradients across retinal capillaries owing to stenotic or constricted arterioles resulting in activated leukocytes becoming wedged in capillaries and postcapillaries and obstructing retinal microvessels.[59]

Importance of retinal hypoxia

Capillary nonperfusion, loss of retinal capillaries, AGEs and/or oxidative stress can lead to progressive retinal hypoxia. Acute hypoxia rapidly activates retinal vascular endothelial cells to release inflammatory cytokines. These inflammatory mediators are able to recruit and promote the activation and adherence of leukocytes, which contribute to the obstruction of retinal capillaries, leading to further hypoxia. Chronic hypoxia in the retina, sufficient to

induce the expression of angiogenic growth factors results in the characteristic retinal neovascularization associated with proliferative diabetic retinopathy (PDR).

A cytosolic flavoheme protein acts as an oxygen sensor that detects decreased oxygen tension and activates transcription factors (mainly Hypoxia inducible factor 1) through signal transduction pathways.

Role of growth factors in diabetic retinopathy

a) *Vascular endothelial growth factor (VEGF)*

VEGF is a potent angiogenic factor capable of stimulating endothelial cells to degrade extracellular matrix, migrate, proliferate and form tubes. Recently, it also has been found to act as a survival factor for newly formed vessels. Hypoxia is also reported to induce expression of VEGF receptors in endothelial cells indicating that sensitivity to VEGF which is enhanced in the

ischaemic retina. VEGF also appears to play an early role in the development of diabetic retinopathy. VEGF has long been known to increase the permeability of vascular endothelium. Such effects presumably underlie the increased risks of vessel leakage and macular edema in diabetic retinopathy.[60,61,62]

b) *Alternative angiogenic factors*

A plethora of other angiogenic factors including insulin-like growth factor-I (IGF-I), basic fibroblast growth factors (bFGF or FGF2), platelet-derived growth factor (PDGF), hepatocyte growth factor/scatter factor (HGF/SF), placenta growth factor (PGF) and angiopoietin2 (Ang2) have been implicated in retinal neovascularization.

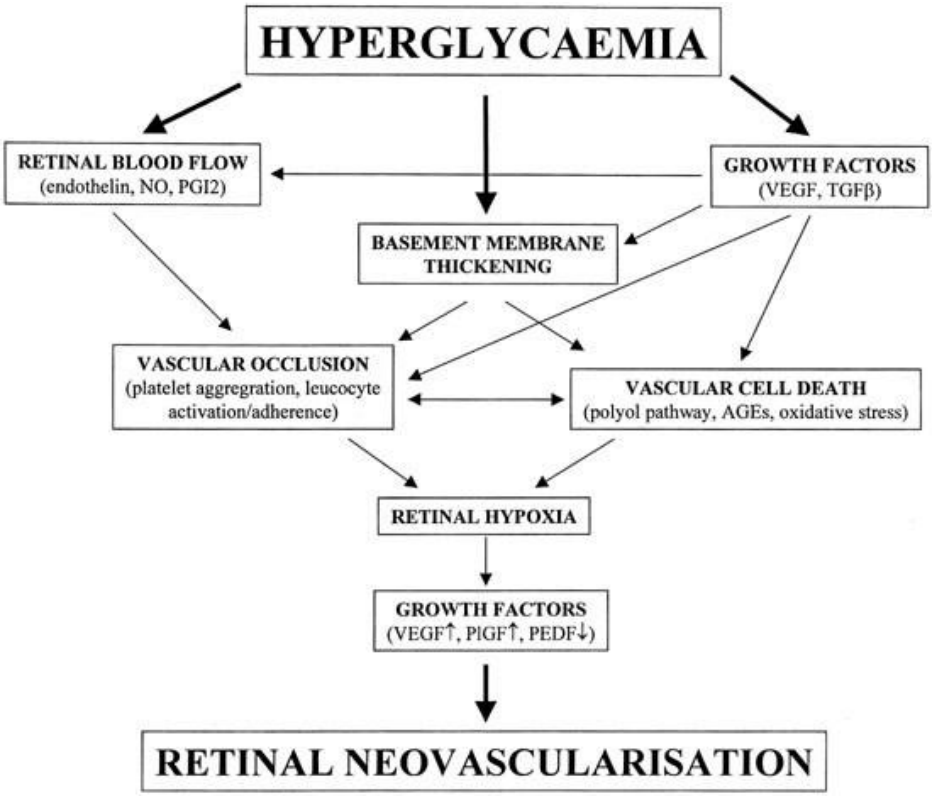


Fig 1: Schematic diagram of the pathogenesis of diabetic retinopathy.[63] Abbreviations: NO, nitric oxide; PGI2, prostacyclin;

VEGF, vascular endothelial growth factor;

TGF β, transforming growth factor beta; AGEs, advanced glycation end products; PGF, placenta growth factor;

PEDF, pigment epithelium-derived factor.

Table 2: ETDRS CLASSIFICATION OF DIABETIC RETINOPATHY[40]

Proposed Disease Severity Level Findings	Dilated Ophthalmoscopy
No apparent retinopathy	No abnormalities
Very Mild NPDR	Microaneurysms only
Mild NPDR	Any or all of: microaneurysms, retinal haemorrhages, exudates, cotton-wool spots, up to the level of moderate NPDR. No intraretinal microvascular anomalies (IRMA) or significant beading
Moderate NPDR	• Severe retinal haemorrhages (more than ETDRS standard photograph 2A: about 20 medium–large per quadrant) in 1–3 quadrants or mild IRMA • • Significant venous beading can be present in no more than 1 quadrant • Cotton-wool spots commonly presen
Severe NPDR	Any of the following (4-2-1 rule) and no signs of proliferative retinopathy •□> 20 intraretinal hemorrhages/quadrant in all 4 quadrants •□Definite venous beading in 2 or more quadrants •□Prominent IRMA in 1 or more quadrants
Very severe NPDR	>2 criteria for severe NPDR in absence of frank neovascularization
Proliferative diabetic retinopathy (PDR)	Mild–moderate PDR New vessels on the disc (NVD) or new vessels elsewhere (NVE), but extent insufficient to meet the high-risk criteria High-risk PDR • NVD greater than ETDRS standard photograph 10A (about 1 3 disc area) • Any NVD with vitreous haemorrhage • NVE greater than 1 2 disc area with vitreous haemorrhage

Advanced diabetic eye disease:

Persistent VH/ neovascular glaucoma/ tractional retinal detachment

The International clinical disease severity scale for DR and DME was developed in 2002 in an effort to improve communication between ophthalmologists and primary care physicians worldwide. It is based on the ETDRS classification of DR and on data collected from clinical trials and epidemiologic studies of DR. [64,65]

Retinal changes in diabetes [66]

Microaneurysms- Retinal microaneurysms are focal dilatations of retinal capillaries, 10 to 100 microns in diameter, and appear as red dots. They are usually seen at the posterior pole, especially temporal to the fovea. They may apparently disappear whilst new lesions appear at the edge of areas of widening capillary non-perfusion. Microaneurysms are the first ophthalmoscopically detectable change in diabetic retinopathy. Beginning as dilatations in areas in the capillary wall where pericytes are absent, microaneurysms are initially thin-walled. Later, endothelial cells proliferate and lay down layers of basement membrane material around themselves. Fibrin and erythrocytes may accumulate within the aneurysm. Despite multiple layers of basement membrane, they are permeable to water and large molecules, allowing the accumulation of water and lipid in the retina. Since fluorescein passes easily through them, many more microaneurysms are usually seen on fluorescein angiography than are apparent on ophthalmoscopy.[66]

Fig 2: Microaneurysms

Retinal Haemorrhages- When the wall of a capillary or microaneurysm is sufficiently weakened, it may rupture, giving rise to an intraretinal haemorrhage. If the haemorrhage is deep (i.e., in the inner nuclear layer or outer plexiform layer), it usually is round or oval ("dot or blot"). Dot haemorrhages appear as bright red dots and are the same size as large microaneurysms. Blot haemorrhages are larger lesions. They are located within the mid retina and often within or surrounding areas of ischaemia. If the haemorrhage is more superficial and in the nerve fiber layer, it takes a flame or splinter shape, which is indistinguishable from a haemorrhage seen in hypertensive retinopathy. They often absorb slowly after several weeks. Their presence strongly suggests the co-existence of systemic hypertension. Diabetics with normal blood pressure may have multiple splinter haemorrhages. Nevertheless, when an ophthalmologist sees numerous splinter haemorrhages in a diabetic patient, the patient's blood pressure must be checked because a frequent association of diabetes is systemic hypertension.[66]

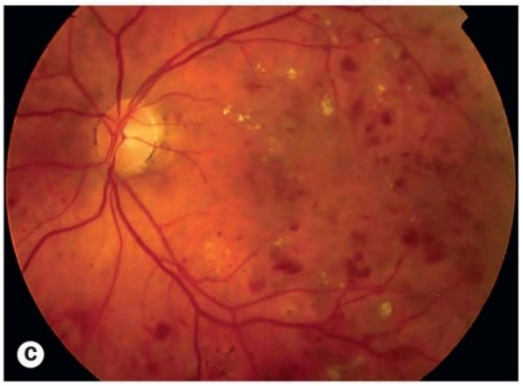
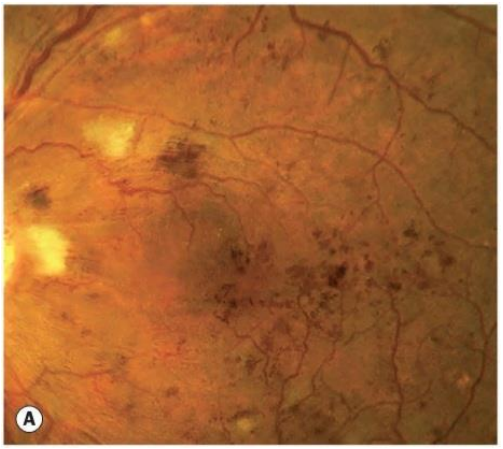


Fig 3: Retinal hemorrhages

Cotton Wool Spots- Cotton wool spots result from occlusion of retinal pre- capillary arterioles supplying the nerve fibre layer with concomitant swelling of local nerve fibre axons. Also called "soft exudates" or "nerve fibre layer infarctions" they are white, fluffy lesions in the nerve fibre layer. Fluorescein angiography shows no capillary perfusion in the area of the soft exudate. They are very common in DR, especially if the patient is also hypertensive.[66]



IMG 3: Cotton wool Spots

Hard exudates (Intra-retinal lipid exudates) - Hard exudates (Intra-retinal lipid exudates) are yellow deposits of lipid and protein within the outer plexiform layer in the sensory retina . Hyperlipidaemia may correlate with the development of hard exudates. Accumulations of lipids leak from surrounding capillaries and microaneurysms and they may form a circinate pattern.

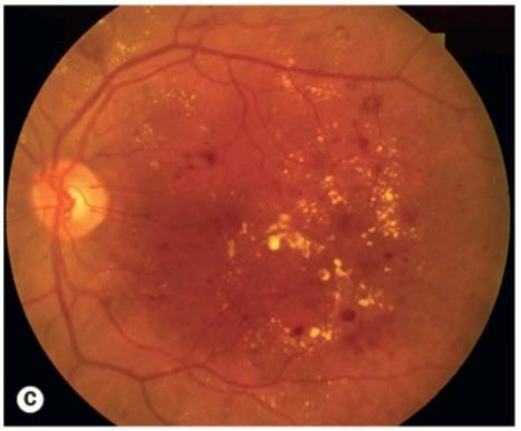


Fig 4: Hard Exhudates

Late non proliferative changes-Intra-retinal microvascular abnormalities (IRMA) are abnormal, dilated retinal capillaries or may represent intraretinal neovascularization which has not breached the internal limiting membrane of the retina. They indicate severe non-proliferative diabetic retinopathy that may rapidly progress to proliferative retinopathy.

Venous beading has an appearance resembling sausage-shaped dilatation of the retinal veins. It is another sign of severe non proliferative diabetic retinopathy

Inner retinal hypoxia causes venous changes including, generalized venous dilatation and tortuosity, venous looping, venous beading (focal narrowing and dilation due to sluggish circulation) and intraretinal microvascular abnormalities (IRMA). IRMAs are dilated (pre-existing) capillaries that function as arteriolar-venular shunts. They appear as spidery vessels within the retina that do not leak fluorescein dye. Areas of capillary hypoperfusion often surround IRMAs.

The ETDRS found IRMA, venous beading and loops, widespread capillary non-perfusion and widespread leakage on FFA to be significant risk factors for the development of PDR.[66]

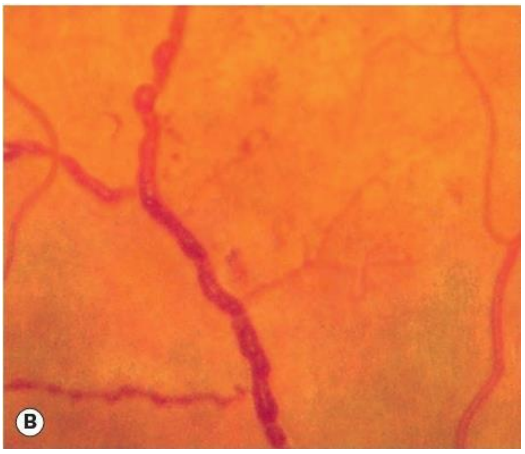


Fig 5:Venous beading

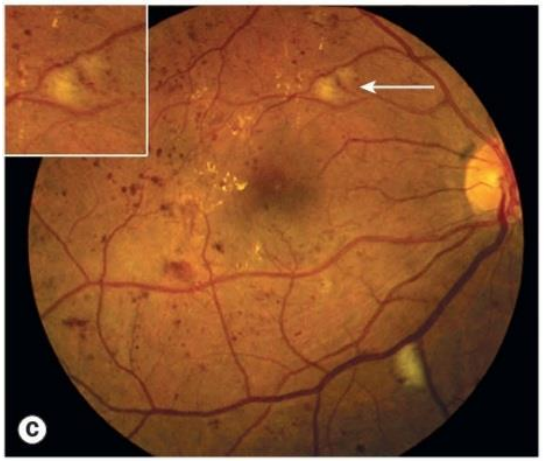


Fig 6: IRMA

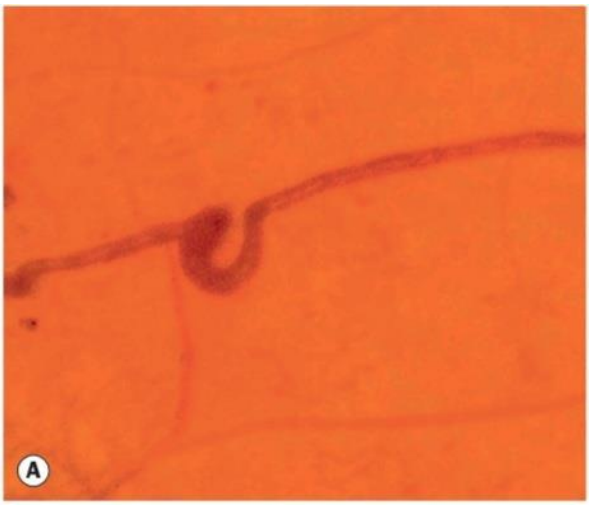


Fig 7: Venous Looping

Clinically Significant Macular Edema (CSME)

Diabetic maculopathy may be classified into: focal (subdivided into focal exudates and focal/multifocal oedema); diffuse; and ischaemic types.

In focal maculopathy focal leakage tends to occur from microaneurysms, often with extravascular lipoprotein in a circinate pattern around the focal leakage .

In the diffuse variety there is a generalised breakdown of the blood-retina barrier and profuse early leakage from the entire capillary bed of the posterior pole, often accompanied by cystoid macular changes[67]. As well as considering macular treatment, it is important to consider correction of systemic abnormalities such as hypertension and severe fluid retention.

In ischaemic maculopathy , enlargement of the foveal avascular zone (FAZ) due to capillary closure is found but may not have any visual consequences. However, extensive capillary and arteriolar closure is more serious and is more commonly associated with visual loss. The ischaemic areas appear hypofluorescent with capillary drop-out in fluorescein angiography and may show late leakage. Severe ischaemic maculopathy is often suspected when the level of vision loss does not correlate with the extent of DMO. Foveal ischaemia may also be

associated with visual field defects, reduction in contrast sensitivity and poor functional response to intravitreal pharmacotherapy despite anatomical improvements .67 Macular ischaemia usually correlates with the severity and duration of hyperglycaemia and is more common in patients with systemic circulatory disturbances, particularly hypertension . Fluorescein angiography is the standard method for evaluation of macular ischaemia; however, OCT may depict some changes as photoreceptor outer segment shortening, inner segment ellipsoid band disruption and thinning of the retinal nerve fibre layer[67]

Macular oedema is thus an important manifestation of DR because it is now the leading cause of legal blindness in diabetics. The intercellular fluid comes from leaking microaneurysms or from diffuse capillary leakage. Characteristics of Clinically Significant Macular Edema (CSME)

diagnosed by stereoscopic assessment of retinal thickening, usually by slit lamp biomicroscopy with a 78D or 90 D lens. Defined as the presence of one or more of the following (Modified Airlie –House Criteria) -

1. Retinal oedema within 500 microns of the centre fovea.
2. Hard exudates within 500 microns of fovea if associated with adjacent retinal thickening
3. Retinal oedema that is one disc diameter (1500 microns) or larger, any part of which is within one disc diameter of the centre of the fovea.

Laser grid photocoagulation reduces the risk of visual loss by 50% at 2 years

Proliferative diabetic retinopathy- Retinal ischaemia due to widespread capillary non perfusion results in the production of vasoproliferative substances and to the development of neovascularization. Neovascularization can involve the retina, optic disc or the iris *(rubeosis iridis).* Rubeosis iridis is a sign of severe proliferative disease, it may cause intractable glaucoma. Bleeding from fragile new vessels involving the retina or optic disc can result in

vitreous or retinal haemorrhage. Retinal damage can result from persistent vitreous haemorrhage. Pre-retinal haemorrhages are often associated with retinal neovascularization; they may dramatically reduce vision within a few minutes[66]

Late Disease- Contraction of associated fibrous tissue formed by proliferative

disease tissue can result in deformation of the retina and tractional retinal detachment There are two types of diabetic retinal detachments:

Those caused by traction alone (nonrhegmatogenous) and those caused by traction and retinal break formation (rhegmatogenous).

Characteristics of nonrhegmatogenous detachment in PDR include the following:

1. The detached retina is usually confined to the posterior fundus and infrequently extends more than two thirds of the distance to the equator;
2. It has a taut and shiny surface;
3. It is concave toward the pupil; and
4. There is no shifting of subretinal fluid

Characteristics of rhegmatogenous detachment in PDR include the following:

1. It is bullous and convex in nature
2. Retinal mobility- Undulating bullae or folds
3. Extends to ora early
4. Vitreous changes- PVD, traction on the flap of the tear

ANATOMY OF RETINAL NERVE FIBRE LAYER :-

The normal human optic nerve is made up of 1.0-1.2 million axons of retinal ganglion cells, which converge at the optic disc. These fibers make up the retinal nerve fiber layer and lie in the inner retina, just below the internal limiting membrane. Fibers from the superior and inferior halves of the retina do not cross the horizontal midline

and are separated from each other by a horizontal raphe. Macular fibers are oriented horizontally and make up the papillomacular bundle, which enters the optic nerve on the temporal side. Fibers on the temporal side of the disc that arise peripheral to the papillomacular bundle have to arch over the bundle to reach the optic nerve and are thus known as arcuate fibers. Fibers from the nasal side of the disc are oriented in a more radial fashion.[68]

The papillomacular bundle and nasal fibers that subserve the temporal field are affected relatively late in the disease process, which accounts for the preservation of central and temporal islands until the end stage is reached. The anterior-posterior orientation of the nerve fibers with regard to the positions within the optic nerve head is not clear. Fibers from the more peripheral portions of the retina occupy more peripheral locations in the nerve head, and those from the more central locations are more central within the nerve. Fibers from the peripheral retina are thought to occupy more superficial positions within the nerve fiber layer (i.e., closer to the vitreous), while more central fibers are thought to lie closer to the sclera. The fibers are thought to cross each other (i.e., the more superficial peripheral fibers cross the deeper central fibers to become more peripheral in the optic nerve, while the deeper fibers become more central in the nerve) somewhere in the anterior portion of the nerve head. The layer of nerve fibers is expected to be thickest just before the fibers make the 90-degree turn into the nerve head, and progressively thinner peripherally.

The distribution of fibers is not uniform around the nerve head, because the nerve fiber layer is thicker at the superior and inferior poles and thinner nasally and temporally. The appearance of the nerve fiber layer is dependent upon the method used to visualize it. Ophthalmoscopically, this layer is seen most easily in eyes that are darkly pigmented and have clear media, particularly if the red-free filter is used. The nerve fiber layer pattern appears as bright striations, most obvious where the layer is thickest. The bright striations of

the fiber bundles are offset by darker, elongated fibre like processes of the Müller cell origins that surround these nerve fibres.

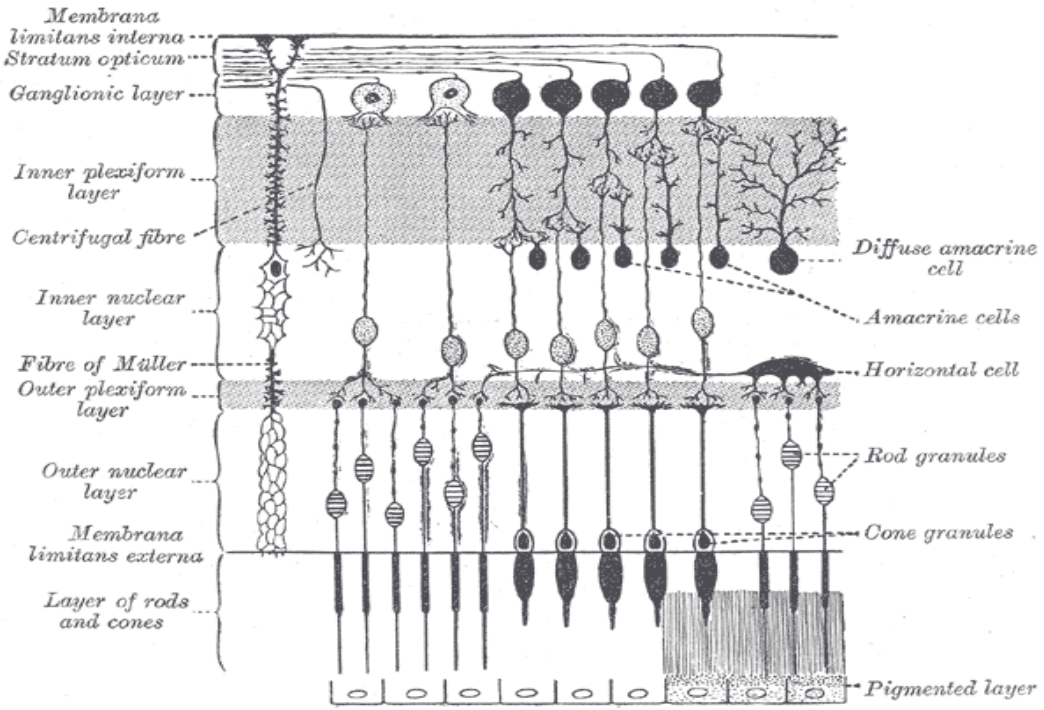


Fig 8: ANATOMY OF THE RETINA

Various modes of assessment of RNFL

Stereoscopic optic nerve head photography is a simple and low-cost method that is extremely useful to the clinician. It allows a 3-dimensional and permanent recording of the optic nerve head appearance. The interpretation of conventional photography however, remains subjective and differences sometimes arise even amongst experts examining the photographs on issues pertaining to discrimination between normal and abnormal discs.[60] Furthermore, the technique of acquiring the photographs may be difficult in patients with small pupils and media opacities. Accurate and objective methods of detecting disc and RNFL abnormalities, and their progression, would facilitate the diagnosis and monitoring of glaucomatous optic neuropathy.

The development of optic nerve head analysers such as the Glaucoma-scope (Ophthalmic Imaging Systems, Inc, Sacramento, CA) was an early attempt to provide a quantitative assessment of optic nerve head and peripapillary topography.[69] This technology using computer raster stereography technique to determine the depth of the disc was however limited by variability and poor resolution of images. In recent years, innovations in computer-based ocular imaging technologies utilising the optical properties of the optic nerve and retinal nerve fiber layer provide a potential means of obtaining quantitative measurements of the optic nerve head topography and RNFL thickness. These technologies employ the use of lasers and exhibit some of the characteristics of a good diagnostic tool such as high sensitivity and specificity, good reproducibility, ability to detect change over time, simplicity in usage and interpretation and convenience for both patient and doctor.

Device	Resolution	Data Obtained	Acquisition Time per Scan	Dilation Required?
Heidelberg Retina Tomograph III	11 micro m	ONH and rim parameters	1.6 sec	No
Stratus Optical Coherence Tomography (time domain OCT) Spectral Domain OCT	7–8 micro m (axial) higher axial resolution (5 micro m),	RNFL thickness along 3.4- mm-diameter circle around ONH; ONH parameters; macular thickness	2sec per structure	In cases Most
GDx Nerve fiber Analyzer VCC	13 micro m	RNFL thickness along 3.2-mm-diameter Circle around ONH	1 sec for corneal baseline; 1 sec for RNFL scan	No

Table 3. Devices to measure Retinal nerve fibers and Optic nerve heads [70]

Confocal Scanning Laser Ophthalmoscopy

The Heidelberg Retina Tomograph (newest version, HRT III; Heidelberg Engineering, Heidelberg, Germany) is a confocal laser scanning microscope for acquisition and analysis of 3-dimensional images of the posterior segment. It enables quantitative assessment of retinal and optic nerve head topography and precise follow-up of topographic changes. The HRT uses a 670 nm diode laser beam to scan the retina in a raster-like fashion. The presence of a confocal aperture ensures that only light originating from a particular plane is captured at any point in time. Planes which are out of focus are blocked by the aperture and do not reach the detector.[71]

Thirty-two consecutive 2-dimensional coronal section images, each at a fixed focal plane equidistant to one another are acquired from the anterior portion of the optic nerve head to the retrolaminar portion. Each image contains 256 x 256 pixels, with each pixel representing the retinal height at that location relative to the focal plane of the eye. Stacking these images together layer-by-layer results in a 3-dimensional image. The (retinal) surface height at each point is computed; resulting in a matrix of height measurements that is visualised as the topography image. This allows quantitative assessment of the 3-dimensional properties of the retinal/optic nerve surface. A *standard reference plane* is established. This plane is parallel to the peripapillary retinal surface and is located 50 microns posterior to the retinal surface in a temporal segment between 350 degrees and 356 degrees. The operator outlines the optic disc margin. This outline of the disc is known as the *contour line*. The reference plane serves as a boundary between the neural rim and cup. Tissue within the optic disc margin and above the reference plane is considered to be the neural rim. Tissue within the disc margin and below the reference plane is

optic cup. A topographic map of the optic nerve head is generated using a software algorithm (Fig. 3). In the figure the regions coloured blue and green are above the reference plane and represent the neuroretinal rim. The red region is below the reference plane and represents the optic cup. The graphical display at the bottom displays the surface height variation along the contour line (optic disc margin).Stereometric analysis provides a set of parameters useful for diagnosis of glaucoma and for monitoring of disease progression. These include disc area, cup-to-disc ratio, cup shape, height variation contour, rim area, rim volume, maximum cup depth, cup area, cup volume, RNFL cross-section area and mean RNFL thickness.

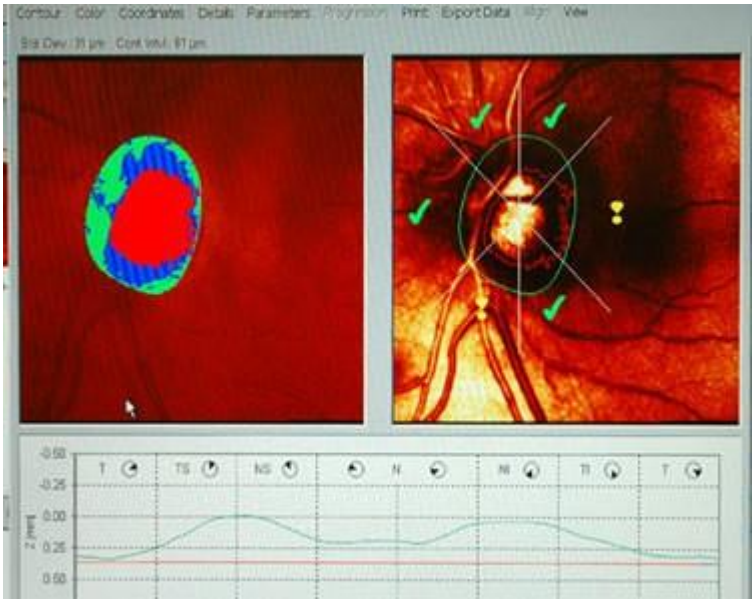


Fig.9. Topographic map (left) and reflectance image (right) display of the confocal scanning laser ophthalmoscope.

Reproducibility

Good reproducibility has been shown in normals, glaucomatous subjects and glaucoma suspects with coefficients of variation ranging from 2.9% to 6.4%.[71] Improved measurement reproducibility is achieved when a series of 3 examinations are obtained instead of a single image analysis.[72] Therefore, it is recommended that 3 images are obtained and averaged to create a mean topographic image.

Clinical Correlation

Several studies have shown strong correlation between various optic disc measurements measured by HRT and functional measurements obtained using automated static perimetry. Brigatti and Caprioli showed statistical correlation between cup shape measure and chromatic visual field indices in patients with early to moderate glaucoma.[73] Teesalu et al found a strong correlation between cup shape measure and short-wavelength automated perimetry.[74] Mistlberger et al found that RNFL thickness measured with HRT correlated with mean deviation of automated static perimetry and was able to differentiate glaucomatous from non-glaucomatous eyes.[75]

Sensitivity/Specificity

Stereometric parameters obtained were able to differentiate normal and glaucomatous subjects. By combining several parameters obtained from the HRT, Wollstein et al reported a highest specificity of 96.3% and sensitivity of 84.3% to separate normal subjects and those patients with early glaucoma using the 99% prediction interval from the linear regression between the optic disc area and log of the neuroretinal rim area.[76]This analysis, known as the Moorfields regression analysis has been incorporated into the software.(Fig. 4).

In the figure three measured rim area is compared to normal ranges for the whole disc (right panel, first column) and six predefined segments (left panel and remaining columns, right panel). The green check mark indicates 'within normal limits', yellow exclamation mark 'borderline' and the red cross 'outside normal limits'. The most abnormal segment gives the overall classification of the disc.

Fig 10: Moorfields regression analysis in the HRT II (Heidelberg Engineering, Heidelberg, Germany).

Clinical Use

The HRT has potential clinical use in screening, diagnosis and detection of progression. Presence of an age-matched normative database and software programme incorporating the Moorfields regression analysis allow differentiation of normal from abnormal optic nerve heads. A fast, noncontact, non-invasive method for screening is possible.HRT provides an additional parameter to aid the clinician in making the differentiating glaucoma from glaucoma suspect. HRT provides objective parameters for monitoring and longitudinal follow-up of patients, in addition to the other conventional parameters described above.

Limitations

The main limitations for the HRT are the need to establish a reference plane and the need for correct placement of the disc contour line. Any change in these two factors can influence many of the stereometric parameters. The current normative database is limited and is based on Caucasian eyes. An ethnicity based normative data may be required for it to be more useful for Asian eyes.

Scanning Laser Polarimetry

Scanning laser polarimetry (SLP) is a non-invasive method for objective evaluation of peripapillary retinal nerve fiber layer (RNFL) thickness by utilising the birefringent properties of retinal ganglion cell axons. The parallel arrangement of microtubules within

the nerve fibre provides linear birefringence.

Essentially, the system consists of a confocal scanning laser ophthalmoscope with an integrated polarimeter. As polarised light from a diode laser light source (780 nm) passes the RNFL and is reflected back from the deeper layer, it undergoes a phase shift. This change, referred to as "retardation" is linearly correlated to the thickness of the polarizing medium, and is computed to give an index of RNFL thickness. A detection unit measures the retardation of light returning from the eye and calculates the RNFL thickness at each retinal location on a 256 x 256 pixel image. Retardation measurements correspond with known properties of the RNFL, with areas of increased retardation in the superior and inferior arcuate regions, decreased retardation toward the periphery and overlying blood vessels, and decreased retardation with age.[77]

Use of a near-infrared light beam (wavelength 780 nm) minimises reflectance from the retinal nerve fibers and absorption by the lens. An anterior segment

compensating device has been incorporated into the machine to compensate for the polarization effects of other ocular birefringent structures such as the lens and cornea. The earlier versions of the instrument have a fixed system for compensation and assume a fixed slow axis of corneal birefringence 15 degrees nasally downward and a magnitude of 60 nm. Recent studies have shown that the magnitude and axis of corneal compensation are variable for different subjects.[78] This has prompted a change towards using a system with a variable corneal compensating device. This newer system has been renamed the GDx-VCC (Laser Diagnostic Technologies, Inc., San Diego, CA) (fig 5).

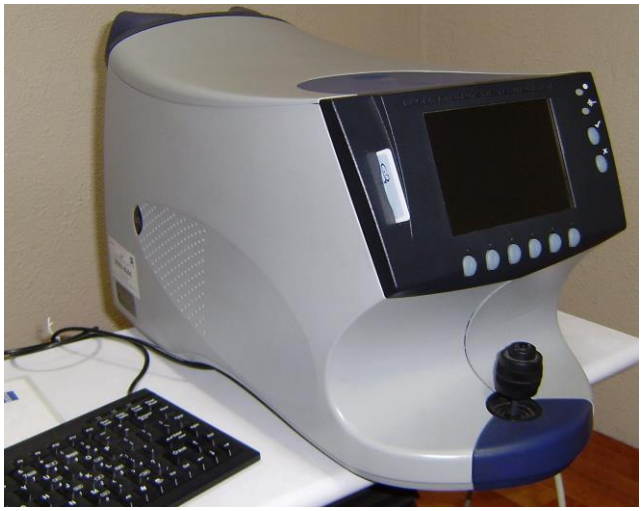


Fig 11: Glaucoma Diagnostics VCC

The GDx provides a set of parameters which include RNFL thickness measurements, modulation measurements and ratio measurements (Fig. 6). In the figure below the top image shows the fundus or reflectance image. The second image from the top shows the retardation map which is converted to a retinal nerve fibre layer (RNFL) thickness image. The RNFL thickness is colour coded based on the colour spectrum, with thinner regions displayed in blue and green and thicker regions displayed in yellow and red. The third image from the top is the deviation map. The location and severity of the RNFL loss are shown. Areas that fall below the normal range are colour coded according to the probability of normality. The graph at the bottom shows RNFL thickness measured along a measurement ellipse. The normal range is shown in the shaded area. There is also a neural network derived value (GDx Nerve Fiber Indicator, NFI) which gives an indication of likelihood of glaucoma. The manufacturer is currently improving its normative database to allow for cross-sectional comparison and diagnosis. With an improved database which is age and ethnicity specific, this technology can potentially be a fast and objective screening tool for glaucomatous patients.

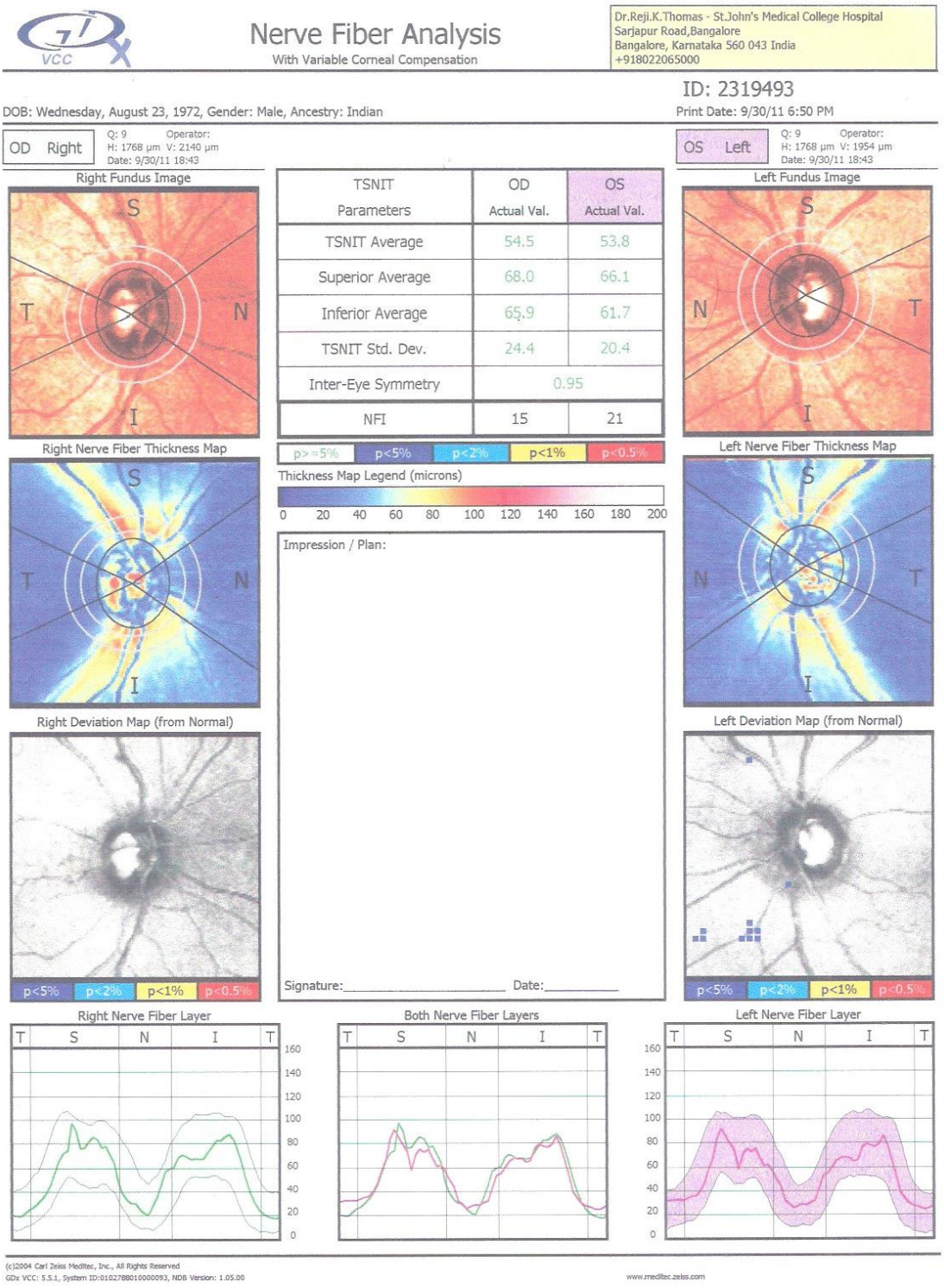


Fig. 12. Nerve fibre analysis of the right and left eyes with the GDx-VCC

The GDxPRO is the latest model in GDx technology.[79]

It has following features:

a) Intuitive Touch Screen or mouse driven operation requires virtually no experience

b) Live Fundus View ensures proper patient fixation prior to scan acquisition

c) Low Vision Target accommodates patients with compromised central vision

d) Iris Image Check to rule out alignment issues after the scan

e) Enhanced Corneal Compensation (ECC) available standard

f) GPA available standard with two options: Fast mode or extended mode

Reproducibility

Good intraoperator measurement reproducibility with low coefficient of Variation has been demonstrated with SLP measurements. Hoh et al described excellent intra-operator reproducibility and showed that inter- operator variability can be minimised by using a single measurement ellipse from the baseline image and exporting it to subsequent images[80].

Sensitivity and Specificity

In a study comparing the summary data of HRT, GDx and OCT, the sensitivity and specificity of GDx has been shown to range from 72 to 82% and 56 to 82%, respectively.[81] Positive predictive value of GDx is 14.0 to 17.7. [82] In a cross- sectional study comparing OCT and SLP, Hoh et al showed that SLP measurements was capable of differentiating glaucomatous from non- glaucomatous eyes, however, considerable measurement overlap exist between the 2 groups. Later work by Greenfield et al showed that correction for corneal polarisation axis has been shown to significantly improve the discriminating power of SLP for detection of mild to moderate glaucoma

Limitations

The early versions of the instrument used fixed corneal compensator devices. Variability in corneal polarisation axis and magnitude may affect retardation measurements.[85] However; this has been addressed in the newer version of the machine. As an improvement to the earlier versions of the GDx, the GDx- VCC has a built-in variable corneal compensator to determine and correct for anterior segment birefringence, from both the cornea and lens. Spurious RNFL thickness measurements may be obtained with anterior and posterior segment pathology such as ocular surface disease, media opacification and extensive peripapillary atrophy.[86] Caution should be exercised when interpreting data in cases with previous keratorefractive surgery.[87]

Optical Coherence Tomography

Optical Coherence Tomography device which is available commercially is manufactured by (Zeiss Humphrey System, Dublin, CA). The early development of the prototype system was a result of collaborative work between scientists and clinicians at the New England Eye Center, Massachusetts Institute of Technology and Lincoln Laboratories.

Generations of the OCT:[88] First generation

The first commercial instrument, OCT 1, was launched in 1996. This instrument gave researchers around the world the opportunity to investigate clinical applications of OCT. By today's standards, the performance of OCT 1 is modest, and there was a steep learning curve for interpreting images of retinal pathology.

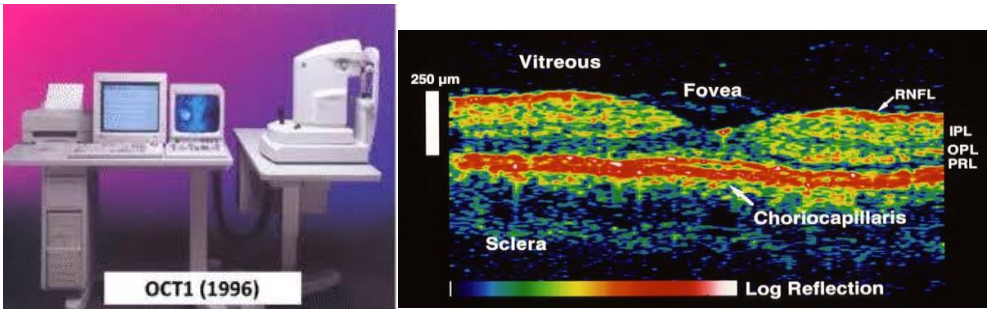


Figure 13: OCT1 (Lab tool)

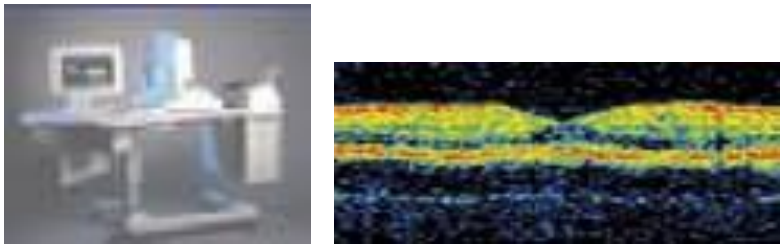


Figure 14: OCT2 (Upgraded)

Second generation

Stratus OCT was launched in 2002. It is based on Time Domain (TD).Faster scanning, speed and better axial resolution of Stratus OCT, based on the RSOD(rapid scanning optical delay line) principle, gave even higher-quality images, thus accelerating this process. Quantitative analyses of the data improved as well with inclusion of normative data for both glaucoma and retinal analysis.

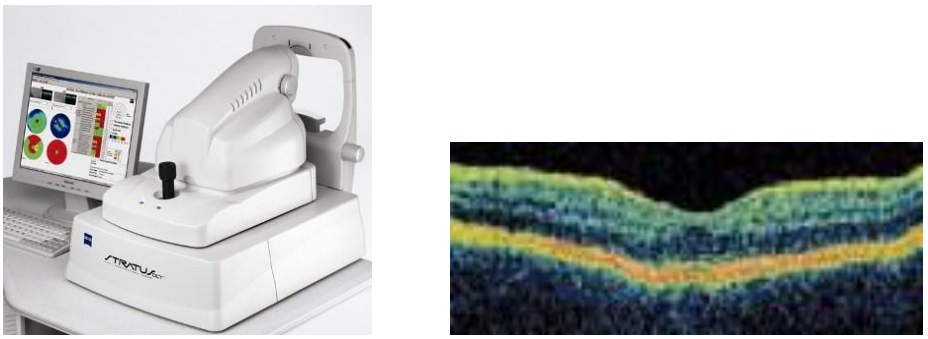


Fig 15 Stratus OCT

Third generation

A practical demonstration of spectral-domain OCT (SD-OCT)/Cirrus in an ophthalmic application was reported in 2003. Sometimes also known as Fourier Domain (FD)-OCT dramatically increases efficiency by acquiring scattering information for all depths simultaneously. The backscattered light is collected and combined with the reference light .The capability of this current generation of OCT to visualize the retina in three dimensions and to provide automated analysis of complex retinal pathologies is clear. Recent cirrus HD-OCT model 400 and 4000 has scan speed of 27,000 A-scans / sec , A-scan depth of 2.0 mm (in tissue) , axial resolution of 5 µm (in tissue) and Transverse resolution of 15 µm (in tissue) .[79]

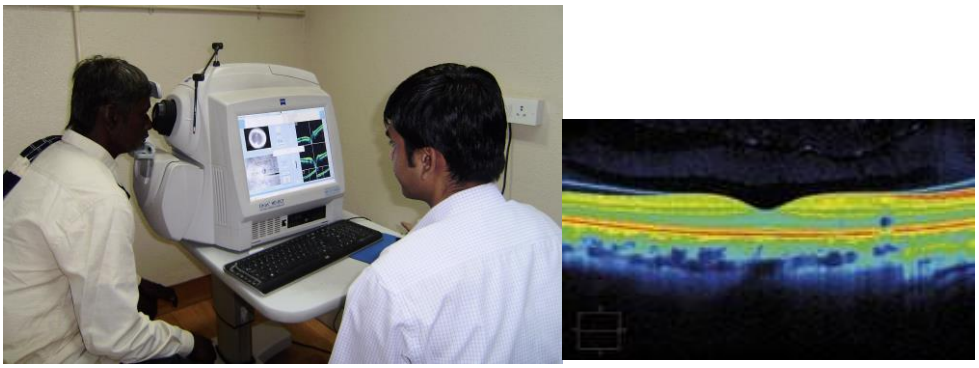


Fig 16: Cirrus OCT

Table 4 : Differences between stratus and cirrus OCT

Time Domain(Stratus) OCT	**Spectral Domain(Cirrus OCT)**
Mirror moves	Mirror Fixed
Sensor captures 1 image at a time	Sensor image Able to capture Multiple
Resolution limited by time	High resolution image capture quick

Low coherence near-infrared light (850 nm) from a super-luminescent diode laser is transmitted to the retina via a fibre optic delivery system. Backscatter from the retina is captured and resolved using a fiber-optic interferometer. Modulating the reference mirror allows longitudinal data to be extracted. Cross-sectional OCT images of the retina are constructed from the backscattering information provided by 100 individual axial A-scans. A digitised, composite image of the 100 A-scans, is produced on a monitor with a false colour scale representing the degree of light backscattering from tissues at different depths within the retina. Images are corrected for movement artefacts during scan acquisition using an image processing technique of cross correlation scan registration. A newer version developed by Zeiss-Humphrey Systems(Spectral Domain (SD) allows scanning with up to 512 A-scans within a similar duration of scan time of approximately 1 second. Patients should have a minimum pupillary diameter of 5 mm in order to obtain satisfactory OCT image quality.

OCT anatomy of the RNFL

The retinal nerve fiber layer (nerve fibre layer, RNFL) is formed by the expansion of the fibers of the optic nerve; it is thickest near peripapillary area, gradually diminishing toward the ora serrata. As the nerve fibers pass through the lamina cribrosa sclera they lose their medullary sheaths and are continued onward through the choroid and retina. When they reach the internal surface of the retina they radiate from their point of entrance over this surface grouped in bundles, and in many places arranged in plexuses. Most of the fibers are centripetal, and are the direct continuations of the axis-cylinder processes of the cells of the ganglionic layer, but a few of them are centrifugal and ramify in the inner plexiform and inner nuclear layers, where they end in enlarged extremities.

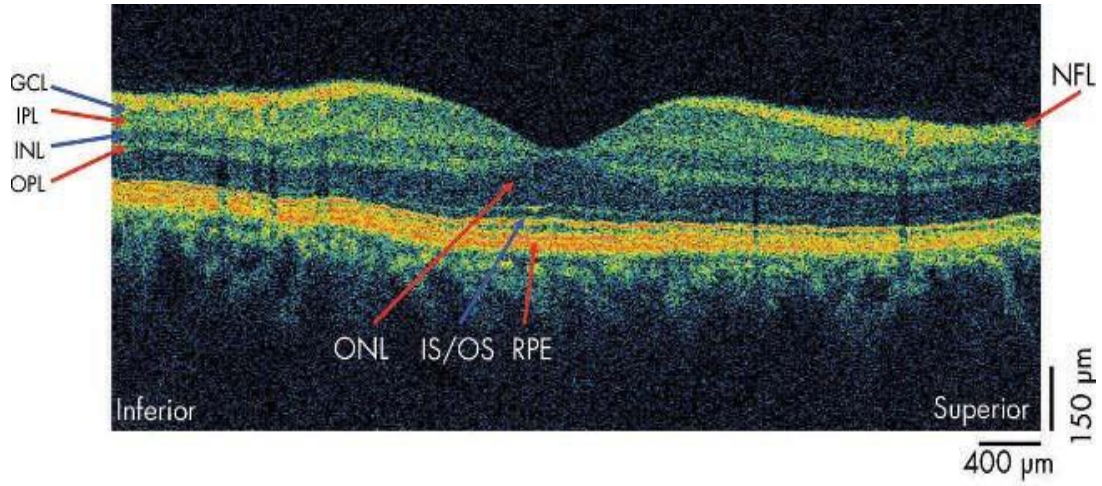


Fig 17: OCT Imaging and Layer Segmentation

The layers that could be identified between intraretinal surfaces were interpreted as follows (from the inner to outer surface, as labelled in Fig.11): NFL layer- Nerve fibre layer GCL- Ganglion Cell layer IPL- Inner Plexiform layer INL- Inner Nuclear Layer OPL- Outer Plexiform layer ONL- Outer Nuclear layer IS/OS junction- Inner segment/ Outer segment junction RPE- Retinal pigment Epithelium

Image acquisition:[89]

There are 2 basic OCT scan patterns- lines and circles.

1. Scan placement for RNFL protocols: These are circle scans centred in the middle of the optic disc.
2. Optic Nerve head Protocols: These are line scans arranged like spokes of a wheel the center of which should be in the middle of the optic disc.

Glaucoma scans protocols:

The OCT scan protocols described for glaucoma detection and management include the following:

1. RNFL Protocols

a. RNFL thickness (3.4): Consists of 3 circle scans of 3.4 mm diameter around the optic

disc which are averaged. (Fig. 12) The image displayed corresponds with the circular scan starting temporally and moving superiorly, nasally and inferiorly and ending temporally.

b. RNFL thickness (2.27 x disc): a single circular scan around the optic disc that is 2.27 times the radius of the aiming circle.

c. Fast RNFL thickness (3.4): acquires three 3.4 mm diameter scans in 1.92 seconds and compresses them into one scan.

d. RNFL Map: consists of a set of six concentric circle scans at increasing distances from the disc margin.

2. ONH Protocols

(a) Optic Disc

(b) Fast optic disc: Compresses six optic disc scans into one scan in 1.92 seconds.

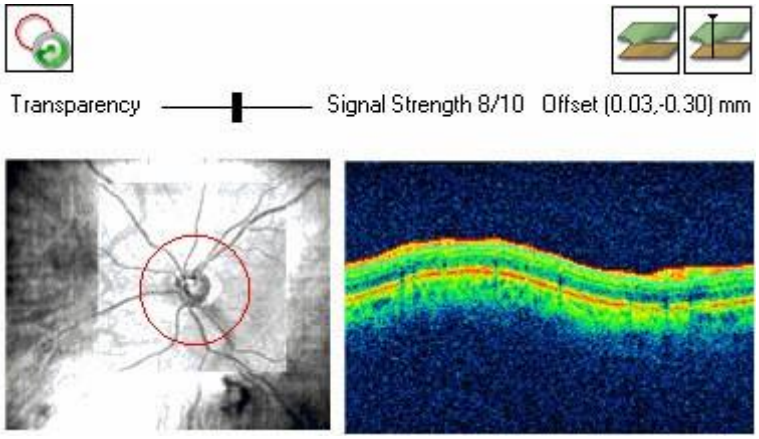


Fig 12. Circular around the optic disc with optical coherence tomography (Zeiss Humphrey System,)

ANALYSIS PROTOCOLS FOR GLAUCOMA

1. RNFL Thickness (Single Eye):

The normal RNFL graphs appear as a "double hump": due to increased RNFL thickness at the superior and inferior poles of the disc. The output chart includes circle characteristics like quadrant and clock hour RNFL thickness averages. The RNFL is depicted in hot colours i.e. a red band superficial to the green retina (Fig. 19)

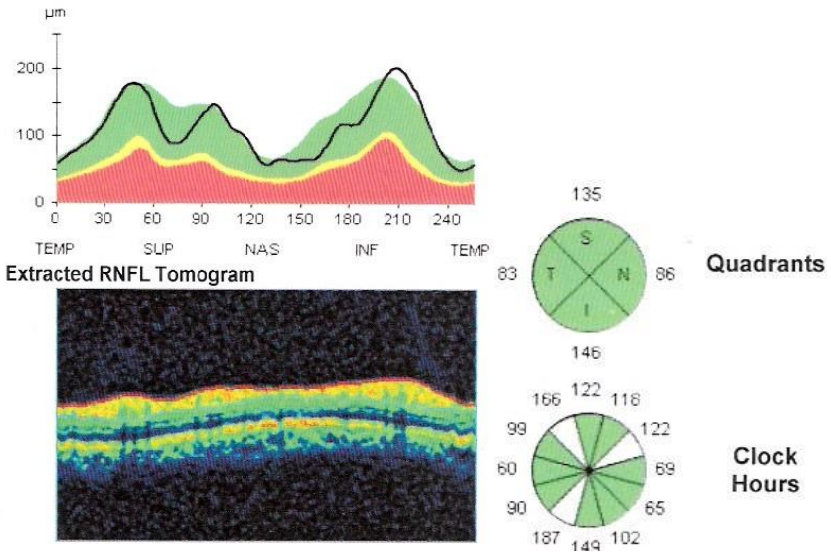


Fig 19: Retinal nerve fibre layer (RNFL) thickness measured with a circular optical coherence tomography scan around the optic disc.

2. RNFL Thickness Average (OU):

Two maps, one showing RNFL thickness using a colour code and the other showing average RNFL thickness in microns are created (Fig 19).The black graph represents the RNFL thickness of the eye being tested in the nasal, superior, temporal and inferior quadrants. The OCT has incorporated normative age- matched RNFL thickness data. The software displays graphs which are colour coded according to the probability of the RNFL thickness measured in the particular patient being normal when compared to age- matched controls.

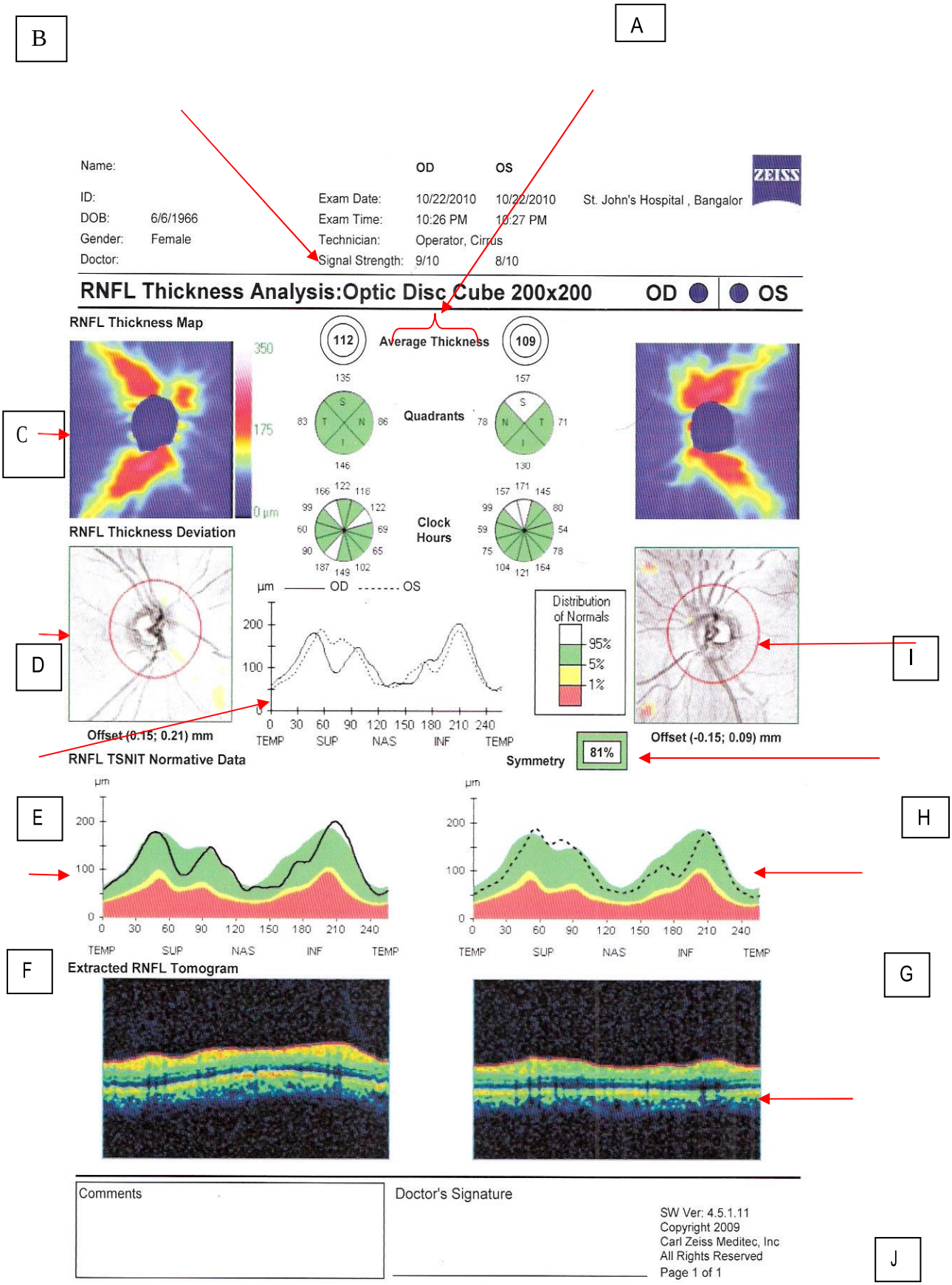


Fig 20: RNFL Thickness analysis

A. Average thickness along calculation circle

B. Signal strength

C. RNFL Thickness map

D. Deviation from Normal Map

E. Left and right eye thickness graph for symmetry comparison

F. Right eye thickness graph with TSNIT normative data

G. Left eye thickness graph with TSNIT normative data

H. Symmetry

I. Fundus image with red Calculation Circle

J. RNFL circle scan extracted along 3.46 mm diameter calculation circle Of the normal population (Fig 20)

: 5 % fall within the white band

: 5 to 95% fall within the green band

: 1 to 5 % falls within the yellow band.

: 1 % falls within the red band (Outside normal limits)

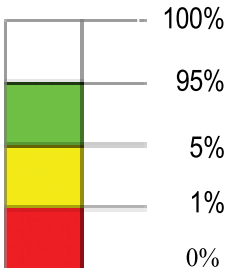


Fig 21: colour coding of probability of patient having disease in OCT

The output chart (fig214) also provides RNFL thickness values in clock hours and quadrants using the same colour code. Summary parameters which include average thickness in each quadrant, maximum RNFL thickness in superior and inferior quadrants and ratios of RNFL thickness in various quadrants (I max/S max, S max/I max; S max/ T avg; I max/ T avg) are also provided. Usually the inferior

RNFL is the thickest and the I max/ S max ratio is greater than 1.0. In glaucoma, the ratio may be less than 1.0 due to inferior RNFL loss.

3. RNFL Thickness Serial Analysis (OU)

   This allows comparison of RNFL thickness over time for up to 4 visits which are superimposed on the same chart and each visit is colour coded. RNFL thickness change analysis shows the difference in RNFL thickness in two visits.

4. Optic Nerve Head (Single Eye)

   The algorithm detects and measures all features of the disc anatomy based on the anatomical markers (disc reference points) on each side of the disc where the RPE ends. It locates and measures the disc diameter by tracing a straight line between the two disc reference points (Blue line) and measures cup diameter on a line parallel to the disc line and offset anteriorly by 150 µ (Red line, B). The output chart measures the optic disc, optic cup, and neuroretinal rim and cup/disc ratio using these measurements. (Fig.16).In the figure below the disc diameter is indicated by the *green line* joining the top and inner edges of RPE on each side of the optic disc. The reference plane (the cup offset) is determined by tracing a line parallel to the disc diameter with an anterior offset of 150micro meter (*white line*). *Red area*: the neuroretinal rim, estimated by using the reference plane as the posterior border and the lines extending perpendicularly from the ends of the disc diameter as the lateral boundaries. *Yellow lines*: nerve bundle widths on each side of the disc. They are straight lines from each disc reference point to the nearest point on the anterior surface.

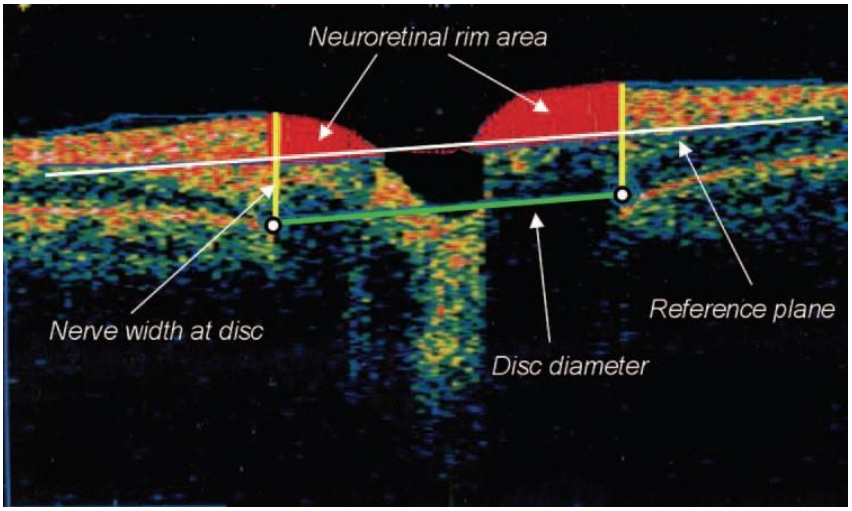


FIGURE 22. A vertical cross-sectional scan of the ONH.

5) RNFL Thickness Map (OU)(fig223)

Two maps, one representing RNFL thickness using a colour code and the other the average RNFL thickness in the inner and outer areas of eight map sectors are generated. OCT also reports a percentage calculation of thickness *symmetry* between the eyes. The color associated with each measurement derives from comparison to the age-matched RNFL normative data. The symmetry (fig 22) parameter is the correlation coefficient converted to a percentage, that results from comparing the OD profile (256 points) with the OS profile (256 points). Normative data was collected for both eyes and the Normal limits for this symmetry parameter were determined. When the symmetry parameter is close to 100%, the two eyes have similar profiles. As one profile becomes different from the other, the reported symmetry value decreases. If there is no relationship between the two eyes, the symmetry approaches 0%. It is possible for the symmetry to report a value below zero if the two profiles are very different, but this is rare.

6. Macular Thickness Map

Two maps, the upper one showing retinal thickness using a colour code and the lower one showing average retinal thickness in microns in each area are seen.

Reproducibility

Several studies have reported good reproducibility for the OCT.[90,91] Schumann et Al compared measurements of RNFL thickness and retinal thickness using circular scan diameters of 2.9 mm, 3.4 mm and 4.5 mm.[91] He also evaluated the use of internal fixation as compared with external fixation targets. He found that a circle diameter of 3.4 mm to be superior and that scans obtained with internal fixation targets were less variable compared with those obtained with external fixation targets. In a study by Gurses-Ozden et al, it was shown that a 4-fold increase in sampling density from 25 sampling points per quadrant to 100 sampling points per quadrant significantly improved measurement reproducibility in glaucomatous eyes.[92]

Sensitivity and specificity

In a cross-sectional study, comparing OCT with SLP in normal, ocular hypertensive and glaucomatous eyes, Hoh et al[59] found that OCT and SLP were capable of differentiating glaucomatous from non-glaucomatous eyes. However, considerable overlap was observed among normal, ocular hypertensive and glaucomatous eyes. Retinal nerve fibre layer thickness measurements obtained with OCT and SLP also demonstrated good correlation with visual field indices. Retinal nerve fibre layer thickness measurements obtained with OCT also demonstrated significant correlation with topographic measurements using CSLO.[75] The sensitivity and specificity of the OCT has been reported to range from 76% to 79% and 68% to 81% respectively.[81]

Limitation

The earlier versions of the OCT were limited by the number of sampling points which is 100 points per scan and speed of scanning. This has however been addressed in the later

versions of the instrument which saw an increase of sampling points to 512 points per scan within an almost similar scan duration. Pupillary dilatation is required for a satisfactory peripapillary circular scan.

RNFL AND DIABETIC CHANGES

Topographic features of eyes with diabetic optic neuropathy were reported to be very different from those with glaucomatous optic neuropathy in spite of the similar appearance of RNFL defects. The cup of the disc was not enlarged in diabetic eyes in spite of discrete signs of RNFL defects.[93]The reduced visibility of the RNFL, the increased optic disc pallor and the unchanged size of the neuroretinal rim and parapapillary atrophy suggest that diabetes mellitus may be associated with nonglaucomatous optic nerve atrophy.[94] Chihara reported the risk factors for RNFL defect as a higher level of diabetic retinopathy, systemic hypertension, and advanced age, but visual acuity, disc size, axial length, and HbA1c level at the time of examination were reported to be not correlated with these defects[95]

The mechanism for the development of optic neuropathy in diabetic patients is very complex. Several abnormalities in visual pathway functions in diabetic humans and animals have been reported. Amano *et al* reported that accumulation of advanced glycation end products in cribriform plates and around vessels in the optic nerve may contribute to the development of optic neuropathy in diabetic patients.[96] Animal studies have demonstrated that diabetes affects retrograde axonal transport progressively through selective impairment of retinal ganglion cells and this impairment of retrograde axonal transport in large- and medium- sized retinal ganglion cells preceded optic nerve involvement.[97,98]

The effect of metabolic control of diabetes on optic nerve functions and RNFL seems positive. In a study on newly diagnosed young diabetics, the P100 latency in visual

evoked potentials was significantly delayed as compared with the control group, which was seen to be normalized following good metabolic control.[99] On the other hand, there are case reports reporting acute bilateral visual loss caused by diabetic ketoacidosis.[100] This implies that optic neural tissue is vulnerable to hemodynamic and metabolic complications of diabetes. Hammes *et al* demonstrated that diabetes induces apoptosis in retinal ganglion cells and Müller cells in an experimental diabetes model.[101] According to an experimental report, impairment in retrograde axonal transport and a reduction in the cross-sectional size of large optic nerve fibers in diabetic rats were found.[97] The apoptosis-promoting actors in retinal ganglion cells (RGCs) are enhanced in the sensory retina in diabetes, and the death of the RGCs occurs early in diabetic eyes.[103] Other morphologic studies using TUNEL(terminal dUTP nick end labelling) staining have reported that enhanced apoptosis of neuroglial elements may affect the early onset of diabetes- associated RNFL loss.[103]

Generally, in glaucomatous eyes, the RNFL is initially damaged in superior area.[88,104-05] Sugimoto et al , found a decrease of RNFL thickness in superior area around the optic disc in 32 patients with no diabetic retinopathy versus in normal eyes using OCT 1. [106] Additionally, in vivo study using diabetic animal showed that there were more micro aneurysms seen in superior than in inferior area.[107] So this area is more susceptible to damage than other areas and may have a tendency for higher rates of cell death, which results in RNFL thinning. Compromised vascular reactivity and perfusion in this area has been proposed as a possible cause.[108] There remains a question that thinning of the RNFL does not necessarily mean a loss of retinal nerve fibers and the RNFL may have been swollen due to a partial blockade of the axoplasmic flow in the hyperglycaemic state. Masahiko Sugimoto et al conducted a study to assess the effect of glycemic control on RNFL thickness in type 2 diabetes mellitus, using OCT.[109] They found a significant RNFL thickness decrease in the superior area

between initial and 4 months examination. This study implies that the glycemic control affects RNFL within 4 months. Hence superior RNFL thickness is an indicator for retinal damage under the glycemic control. It should be noted that several reports also have shown interaction between glycemic control and retinal change including the blood-retinal barrier (BRB) or macula edema progression.[110-12] Such vascular breakdown may change the tissue construction and it is reasonable to propose that RNFL damage is followed by this change as an aspect of neurodegenerative change. Some molecular mechanism may participate in this change and some experimental studies have shown that insulin stimulates a cascade of neovascularization. Vascular endothelial growth factor (VEGF) is one of the major mediators of neovascularization or ischemia.[61] Insulin up-regulates VEGF in vitro and enhances vascular permeability or its proliferative effects, which results in proliferative retinal changes.[113] Thus, insulin itself plays an important role in neovascularization or BRB breakdown and may be one of the causes of several complications during glycemic control, including early worsening (intensive glycemic control sometimes induces worsening of DR). As several studies mentioned about importance of BP control for prevention of DR , it is important to consider BP control.[114] There is a possibility that increased BP and secondary increase in cerebrospinal fluid pressure may also relate with RNFL change.

Hille W. van Dijk et el found that the thinning of the inner retina in patients with minimal retinopathy is caused primarily by a thinning of the Ganglion Cell Layer (GCL) in the pericentral area of the macula, and secondary thinning of the RNFL more peripherally in the macula, because of axonal loss from the central ganglion cells.[115] The ganglion cell axons in the RNFL travel in bundles toward the optic nerve head without any tendency to cross to adjacent bundles or disperse.[116] Therefore , the most pronounced difference in RNFL thickness due to loss of ganglion cells in the pericentral area is expected to be found in the nasal region of the peripheral area of the macula. The RNFL thickness measured by OCT,

which includes not only ganglion cell axons but also Muller cell processes and astrocytes, did not show a significant reduction in subjects with diabetes compared with age- matched healthy subjects.[117-18] The neural retina, including the RNFL, may be substantially thickened by intraretinal fluid accumulation, exudates, and haemorrhages from leaking blood vessels in eyes with mild to moderate NPDR. This prospect might explain the significantly reduced RNFL thickness on a previous OCT report, in which only diabetic eyes without retinopathy were analyzed. It may also contribute to changes in reflectance or contrast characteristics in the reconstructed b-scan of OCT and age-related retinal nerve fiber loss only between diabetic eyes and diabetic eyes with glaucoma.[106] Moreover, *in vivo* use of scanning laser polarimetry and other techniques found a thinning of the nerve fibre layer in diabetes, further consistent with loss of RGCs and their axons in diabetes. In diabetes, there was structural remodelling of dendrites, including an increase in the total length, density, and number of terminals. Diabetes has been reported to impair axonal retrograde transport in large- and medium-sized RGCs in type 1 diabetic rats, but not type 2 diabetic rats.[97]

Loss of retinal function in diabetes

The onset of vision loss is insidious in diabetes, commonly beginning with a reduction in night vision or the ability to see details in lowlight conditions.[119] While clinical diagnosis of diabetic retinopathy requires detection of vascular pathology, the disease also includes deficits in the electroretinogram, and other measures of function such as contrast sensitivity , suggesting that acquisition or processing of the visual signal is impaired .[120-22] Such functional changes can occur before the gross vascular defects become detectable clinically.[123] The oscillatory potentials of the electroretinogram, which are likely to be due to inner retinal neurotransmission, have prolonged peak latencies and/or decreased amplitudes in diabetic rats suggesting abnormal inner retinal function.[124]

Apoptotic loss of RGCs combined with morphological changes in the surviving RGCs may account for some of the functional deficits in diabetes. Nevertheless, diabetes-induced deficits in RGC function might occur before morphologic changes.

Lopes de Faria and co-workers used the GDx nerve fiber analyzer to provide the first quantitative assessment of nerve fibre layer thickness in diabetics.[122]

They demonstrated that the diabetic group has statistically significant thinning of the nerve fibre layer in the quadrant superior to the optic disc. A study by Skarf.B points at the possibility of RNFL thickness measurement being helpful to detect early changes in diabetics.[125]

Chihara et al photographed the retinal nerve fibre layer of the right eye of 137 patients with diabetes and 144 healthy control subjects.[95] The level of diabetic retinopathy ranged from levels 1 (no micro aneurysm) to 4 (eyes with localized intra-retinal micro vascular abnormalities or venous beading) .[126] Defects of the retinal nerve fibre layer were found in 6/30 (20%) eyes with level 1 retinopathy, 8/14 (57%) eyes with level 2 retinopathy, 24/47 (51%) eyes with level 3 retinopathy, and 36/46 (78%) eyes with level 4 retinopathy. These findings suggest that the retinal nerve fibre layer abnormalities are common in patients with early diabetic retinopathy.

Gentile RC et al concluded that poor metabolic control of diabetes mellitus adversely affects the thickness of RNFL and this effect does not seem to be acute since it was not reversed by short-term blood glucose regulation.[127] This issue needs to be kept in mind when assessing glaucomatous progress in diabetic patients.

A study was done by S Özdek et al prospectively assessed RNFL thicknesses in four groups of patients, who were all age matched.[128] Diabetic patients without diabetic retinopathy were grouped according to their blood glucose regulation level into two, as: blood

glucose-regulated group and blood glucose-non regulated group. A group of patients with non proliferative diabetic retinopathy (NPDR) formed the 3rd group. The 4th group consisted of healthy subjects and acted as a control group. The mean superior maximum and ellipse modulation values were statistically significantly lower than the control group, in blood glucose -non-regulated and NPDR groups (P <0.05).The average thickness value was also statistically significantly lower than the control group in NPDR group. These values in the blood glucose-regulated group were not statistically significantly different from the control group (P > 0.05). RNFL thickness decreased with development of diabetic retinopathy and with impairment of metabolic regulation. This issue should be taken into account while assessing RNFL in diabetic glaucomatous patients.

In a study done by Jee Taek Kim et al, Retinal nerve fibre layer thickness and Optic nerve head (ONH) in diabetic patients with normal tension were analyzed using optical coherence tomography (OCT).[129] There was an increase in the temporal average thickness of RNFL in the proliferative diabetic retinopathy group. As the duration of diabetes increased, the mean average and nasal average of RNFL thickness also decreased. The severity of diabetic retinopathy did not show statistically significant differences in a topographic analysis of the optic nerve head. Diabetic changes should be considered when diabetes patients are diagnosed with glaucoma or glaucoma progression.

Diabetes-associated RNFL loss may enhance the cumulative damage of GON (Glaucomatous optic neuropathy).[130] RNFL thinning in diabetes mellitus does not result in the development of optic disc structural changes such as disc rim notching, splinter haemorrhages and progressive enlargement of the cup.[85] The sudden-onset painless visual loss with papilledema and RNFL defects at the large sector surrounding a pale disc are typical findings of diabetic optic neuropathy and are different from diabetes associated RNFL defects. The visual field defect patterns in eyes with moderate – severe NPDR were

amorphous and did not show glaucomatous features such as early nasal step and paracentral scotoma.[130]

Considering a significant optic nerve loss induced by GON, intraretinal architectural changes may have little impact on the detection of glaucoma in diabetic eyes without evident maculopathy. Although visual field losses in eyes with glaucoma and coexisting diabetic retinopathy often have amorphous patterns that are affected by retinal haemorrhage, exudates, and diabetes-associated retinal nerve fiber impairment, subjective optic nerve head assessment in clinical practice, combined with supplemental quantitative RNFL measurements, can have higher diagnostic value in glaucoma screening.

MATERAIL & METHODS

MATERIALS AND METHODS:

SOURCE OF DATA:

A total 111 patients diagnosed with diabetes mellitus was included in this cross sectional study, visiting the outpatient department of Ophthalmology at R.L.J. HOSPITAL AND RESEARCH CENTRE, attached to SRI DEVARAJ URS MEDICAL COLLEGE.

STUDY DESIGN: Cross sectional observational study.

STUDY PERIOD: January 2021 and June 2022

INCLUSION CRITERA:

1. Patients with diabetes mellitus
2. Age > 40 years of age

EXCLUSION CRITERIA:

1. Patient with Glaucoma.
2. History of any ocular surgery.
3. High myopia
4. Clinical diagnosis of diabetic macular oedema
5. Systemic Hypertension
6. Any other optic nerve pathology and intracranial diseases.

Ethical clearance

Prior to the commencement, the study was approved by the Ethics and Research Committee, Sri Devraj Urs medical college, Kolar.

Informed Consent

All the patients fulfilling selection criteria were explained about the nature of the study. A written informed consent was obtained from all the participants before enrolment (Annexure II and III).

METHOD OF COLLECTION OF DATA

Patients with diabetes presenting to the department of Ophthalmology in R.L.J hospital and research center, attached to Sri Devaraj Urs Medical College between January 2021 and June 2022.

Each patient was asked a detailed history and clinical examination of both the eyes was done.

The clinical examination included : -

- Visual acuity by Snellen chart for distant vision
- Near vision by Jaeger chart.
- Slit lamp examination
- Fundus examination by indirect ophthalmoscopy and 90D examination.

Following which patients were segregated and classified into:-

Group 1- Control group

Group 2- Diabetic Patients without DR

Group 3- Diabetic Patients with Diabatic retinopathy

These groups were decided on the basis of the findings documented which are as follows:-

Non-Diabetic Retinopathy (NDR) is defined as the absence of all features of diabetic retinopathy in diabetic eyes.

Non-Proliferative Diabetic Retinopathy (NPDR) is defined as the presence of microaneurysms, hard exudates, dot and blot hemorrhages, cotton wool spots, venous beading and intraretinal microvascular abnormalities.

Proliferative Diabetic Retinopathy (PDR) is defined as the presence of neovascularization on optic disc or elsewhere, vitreous or preretinal hemorrhage, and fibrovascular proliferative tissue.

Further these patients will be subjected to a non-invasive investigation.

- OCT to assess RNFL thickness

The OCT scan creates an image via the use of light waves. During the examination, the patient was instructed to sit in the chair provided with their chin placed on the chin rest. The OCT scan was performed on both eyes, uniocularly, and the patient was instructed to fixate their attention on a green target in order to obtain a macular scan. After that, the patient was instructed to concentrate on a moving red line in order to collect the RNFL thickness measurements.

Parameter measured under OCT are

- Retinal nerve fiber thickness: -

1. Superior retinal nerve fiber layer thickness
2. Nasal retinal nerve fiber layer thickness
3. Temporal retinal nerve fiber layer thickness
4. Inferior retinal nerve fiber layer thickness

SAMPLE SIZE ESTIMATION

Sample size calculated based on prevalence of diabetic retinopathy is 27.% according to thestudy [131]

Sample size(n) = $\frac{Z\alpha^2 PQ}{(d)^2}$

Where

d = absolute error = 7%

Z_α = critical value of Normal Distribution at ($\alpha = 0.05$) = 1.96P = 27%

Q = 100-P

By utilising the above formula sample size came to be around 111 at 7 % of absolute error.

STATISTICAL METHODS USED FOR THIS STUDY

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. **Chi-square test or Fischer's exact test** (for 2x2 tables only) was used as test of significance for qualitative data.

Continuous data was represented as mean and standard deviation. **ANOVA** was used as test of significance to identify the mean difference between more than two quantitative variables

Correlations were performed with **Pearson Correlation coefficient**

Graphical representation of data: MS Excel and MS word was used to obtain various types of graphs

P value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

Statistical software: MS Excel**,** SPSS version 22 **(**IBM SPSS Statistics, Somers NY, USA)

was used to analyze data.

- Group 1- Control group
- Group 2- Diabetic Patients without DR
- Group 3- Diabetic Patients with Diabetic retinopathy (NPDR)

RESULTS

RESULTS

Table 5:- Distribution of subjects according to sex among three groups.

	Group 1	Group 2	Group 3
Female	13	19	22
	35.1%	51.4%	59.5%
Male	24	18	15
	64.9%	48.6%	40.5%
Total	37	37	37
	100.0%	100.0%	100.0%

P value 0.103, there was no statistically significant difference found between the groups with respect to sex.

Figure 1:- Graph showing Distribution of subjects according to sex among three groups.

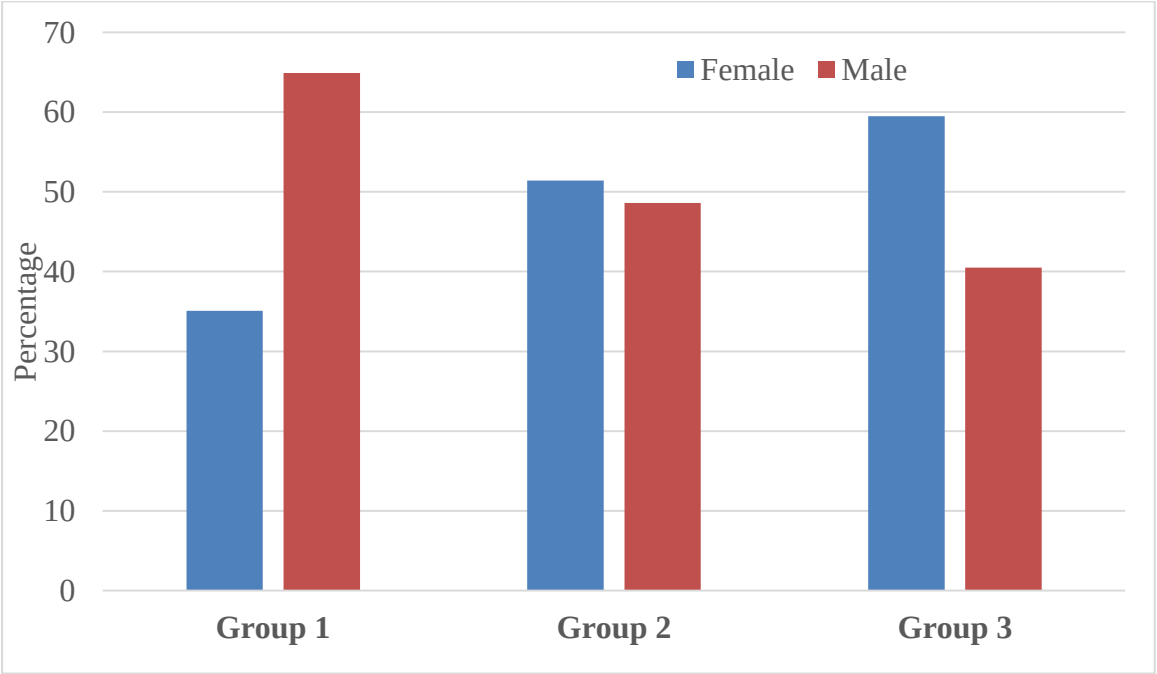
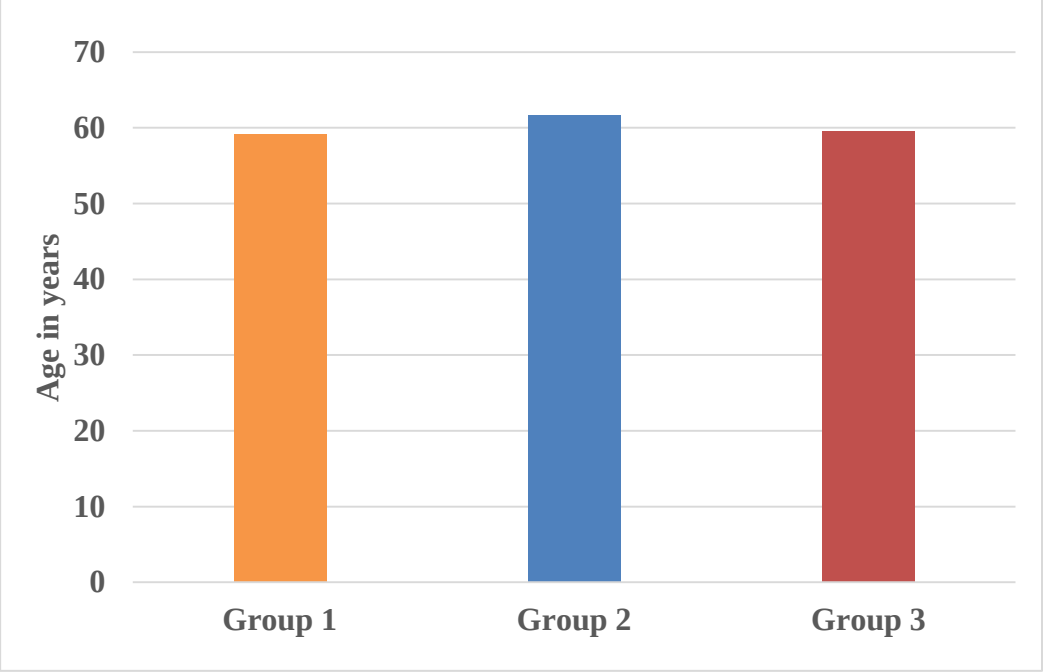


Table 6:- Comparison of mean age among three groups.

	Mean	Std. Deviation
Group 1	59.11	10.703
Group 2	61.68	11.451
Group 3	59.51	8.474

P value 0.516, there was no statistically significant difference found between the groups with respect to age.

Graph 2:- Graph showing Comparison of mean age among three groups.

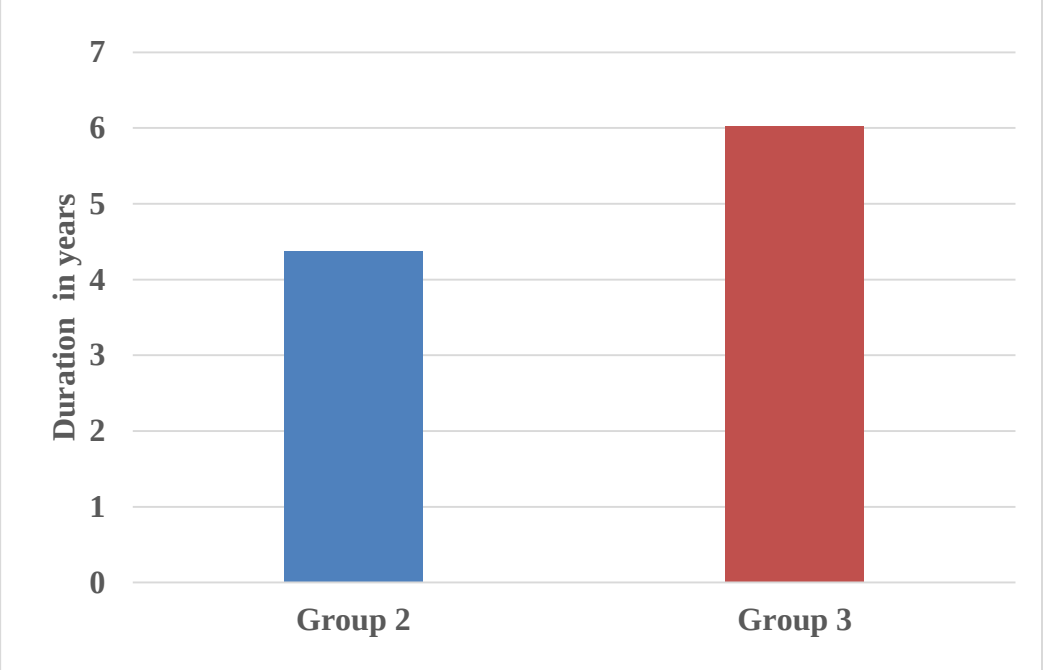


The mean age in group 1 is 59.11 years, 13 females and 24 males, in group 2 mean age is 61.68 with 19 females and 18 males and in group 3 mean age of 59.51 years with 22 females and 15 males. In our study it is seen that there is not statistical significance in age and gender.

Table 7:- Comparison of mean duration of DM among two groups.

	Mean	Std. Deviation
Group 2	4.38	2.046
Group 3	6.03	2.555

Graph 3:- Graph showing Comparison of mean duration of DM among two groups.



The patients suffering from diabetic retinopathy have seen to be suffering from the diabetes mellitus for a longer duration of time than the diabetic patients without diabetic retinopathy. There isn't any statistically significant difference in the two groups.

Table 8:- Comparison of mean global RNFL thickness among three groups.

	Mean	Std. Deviation
Group 1	91.20	19.48
Group 2	84.57	22.89
Group 3	80.95	22.43

P value 0.015, there was a statistically significant difference found between the groups with respect to mean global RNFL thickness

Graph 4:- Graph showing Comparison of mean global RNFL thickness among three groups.

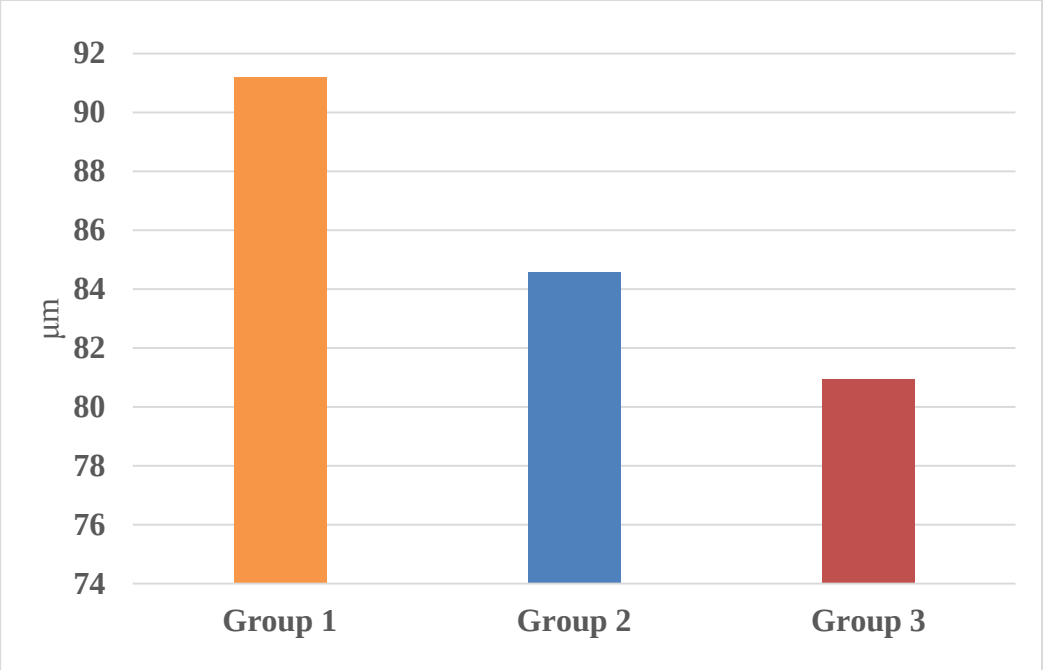


Table 9:- Comparison of mean superior RNFL thickness among three groups.

	Mean	Std. Deviation
Group 1	118.61	28.27
Group 2	106.64	38.94
Group 3	95.69	32.67

P value <0.001, there was a statistically significant difference found between the groups with respect to mean superior RNFL thickness.

Graph5:- Graph showing Comparison of mean superior RNFL thickness among three groups.

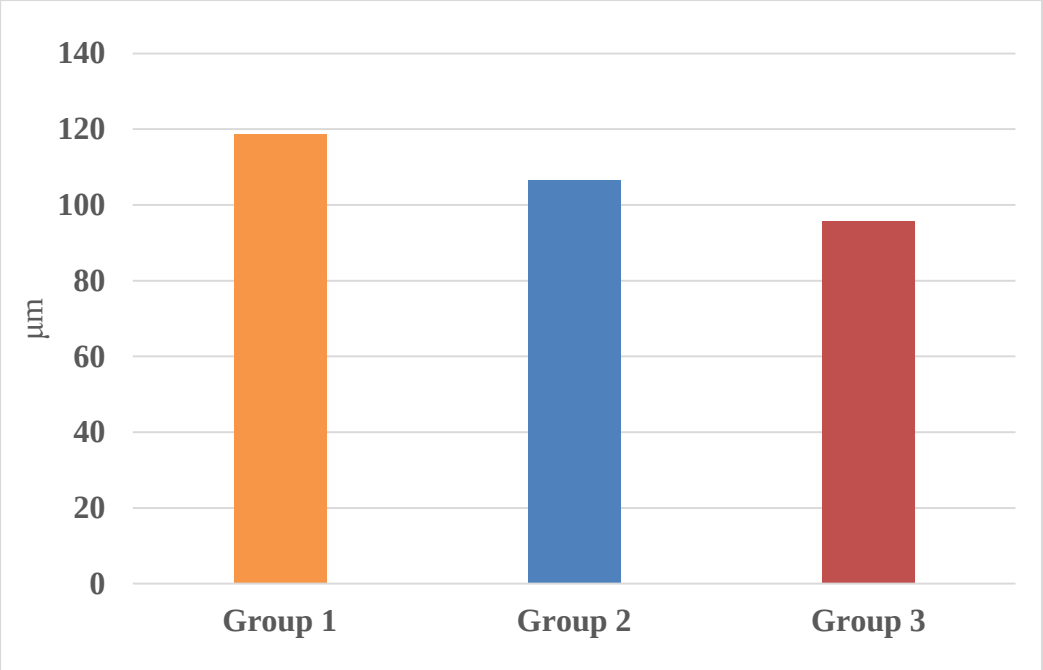


Table 10:- Comparison of mean inferior RNFL thickness among three groups.

	Mean	Std. Deviation
Group 1	109.51	37.40
Group 2	101.43	39.18
Group 3	99.27	42.68

P value 0.259, there was no statistically significant difference found between the groups with respect to mean inferior RNFL thickness.

Graph 6:- Graph showing Comparison of mean inferior RNFL thickness among three groups.

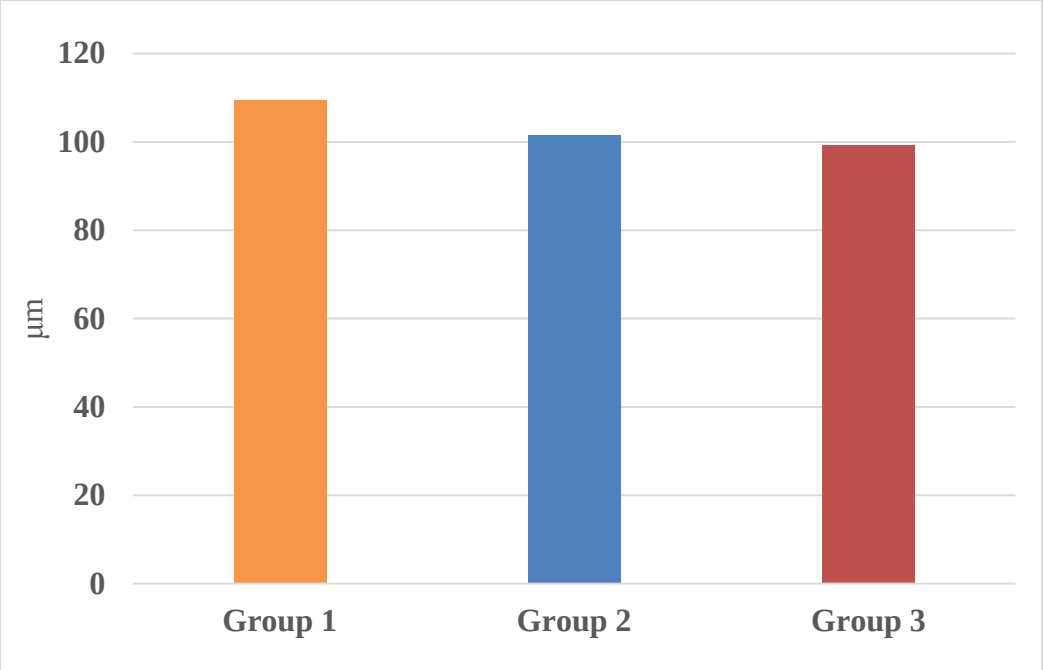


Table 11:- Comparison of mean nasal RNFL thickness among three groups.

	Mean	Std. Deviation
Group 1	67.00	20.07
Group 2	62.73	18.64
Group 3	66.76	23.68

P value 0.379, there was no statistically significant difference found between the groups with respect to mean nasal RNFL thickness.

Graph7:- Graph showing Comparison of mean nasal RNFL thickness among three groups.

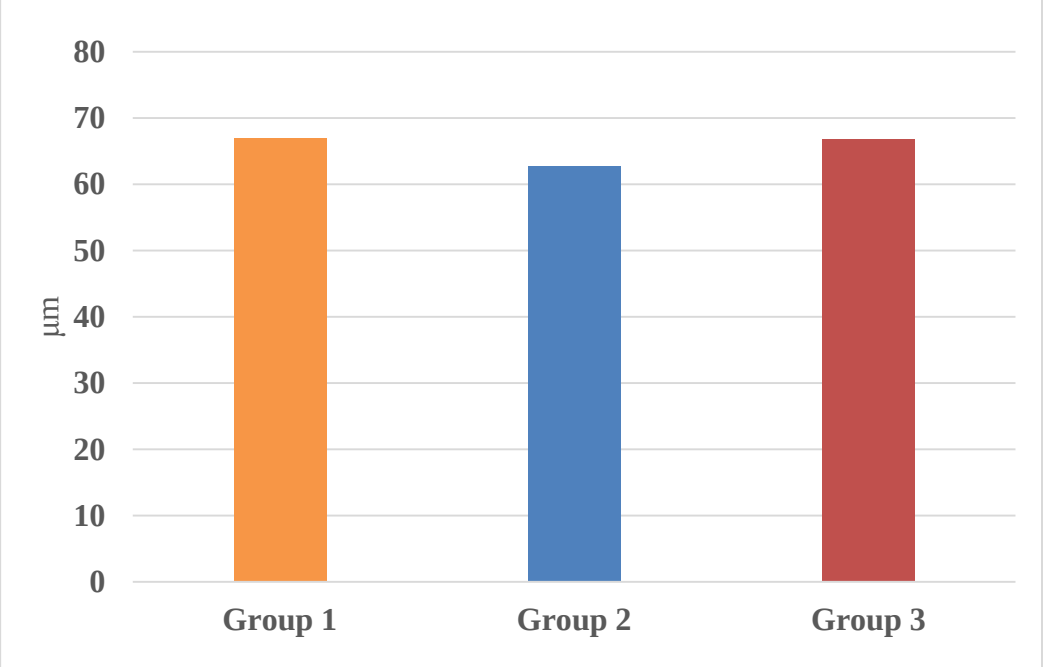
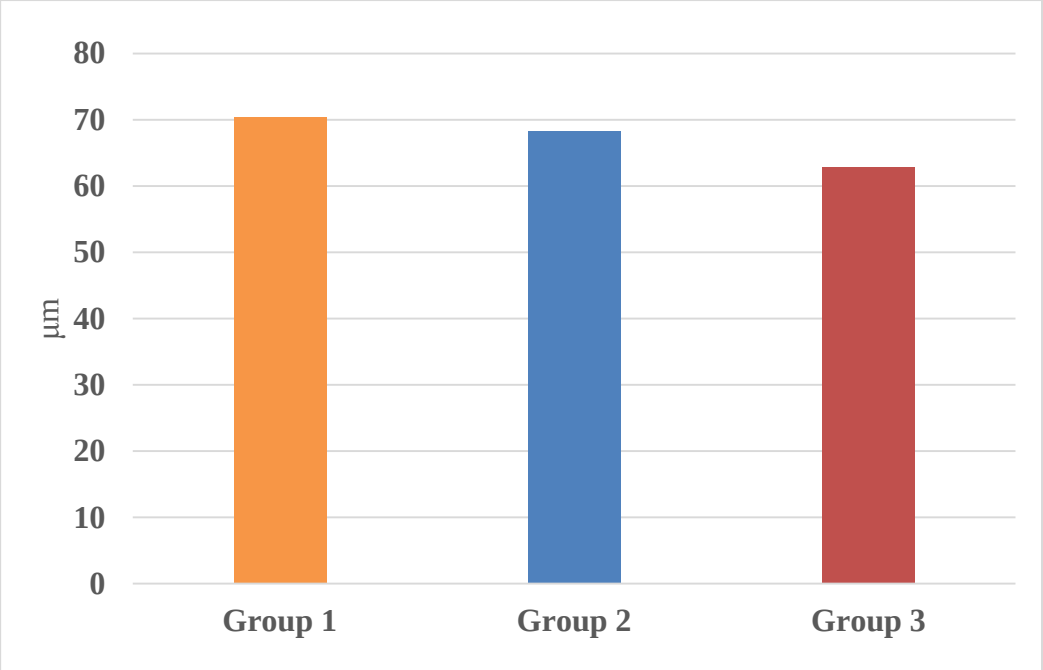


Table 12:- Comparison of mean temporal RNFL thickness among three groups.

	Mean	Std. Deviation
Group 1	70.43	22.16
Group 2	68.30	23.51
Group 3	62.91	18.67

P value 0.093, there was no statistically significant difference found between the groups with respect to mean temporal RNFL thickness.

Graph 8:- Graph showing Comparison of mean temporal RNFL thickness among three groups.



The mean average thickness of the global and superior quadrant show statistically significant difference by this we can defer that RNFL thickness decreased in patients with diabetic retinopathy the maximum and the group 2 containing diabetic patients without diabetic retinopathy also showed a decrease than the control group. RNFL thickness in the temporal, inferior and nasal showed no statically significant changes between the three groups.

Table 13:- Correlation of RNFL thickness with Duration of diabetes

		Duration of diabetes
Global	Pearson Correlation	-0.189*
	P Value	**0.022**
Superior	Pearson Correlation	-0.270**
	P Value	**0.001**
Inferior	Pearson Correlation	-0.072
	P Value	.388
Nasal	Pearson Correlation	-0.102
	P Value	.215
Temporal	Pearson Correlation	-0.109
	P Value	0.187

Global RNFL thickness has negative correlation with Duration of diabetes which was statistically significant.

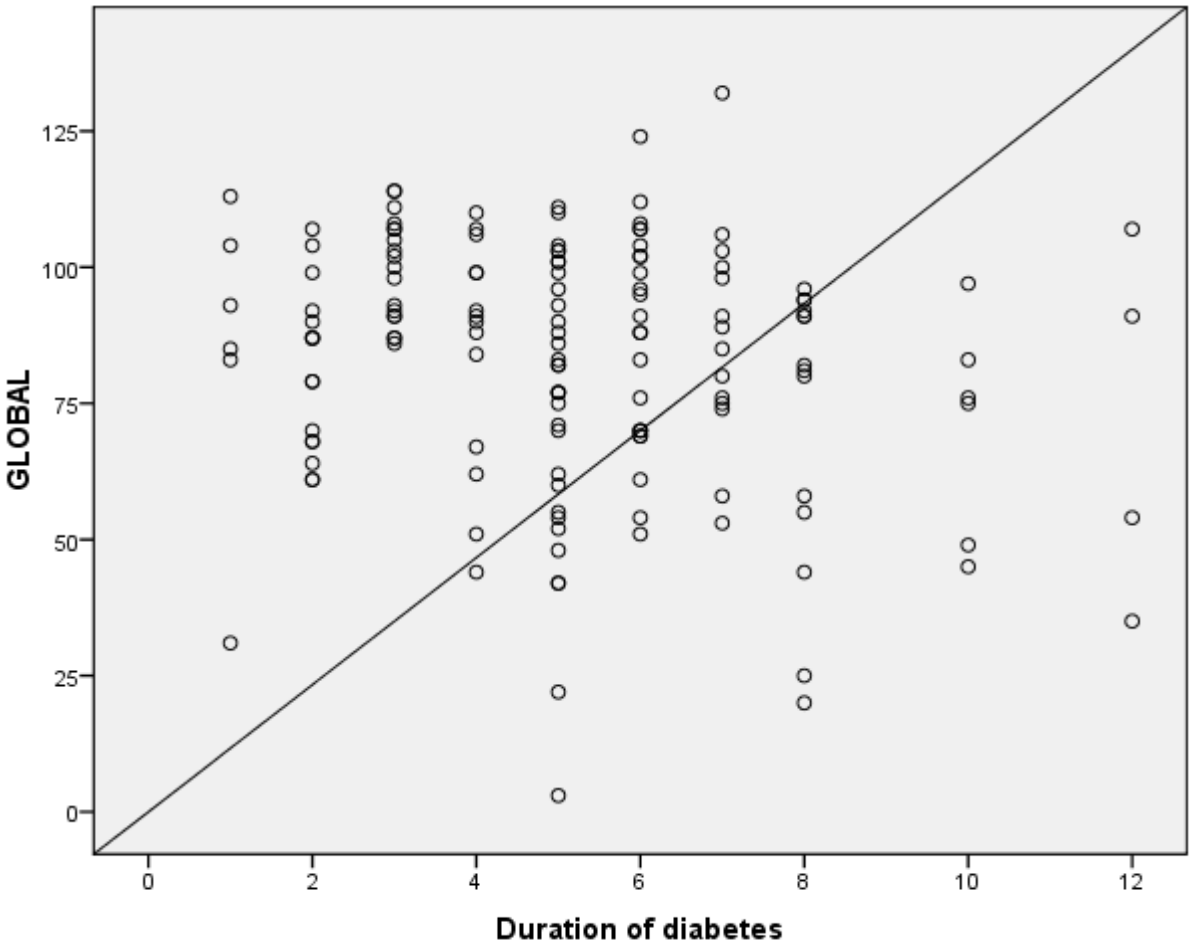
Superior RNFL thickness has negative correlation with Duration of diabetes which was statistically significant.

Inferior RNFL thickness has negative correlation with Duration of diabetes which not was statistically significant.

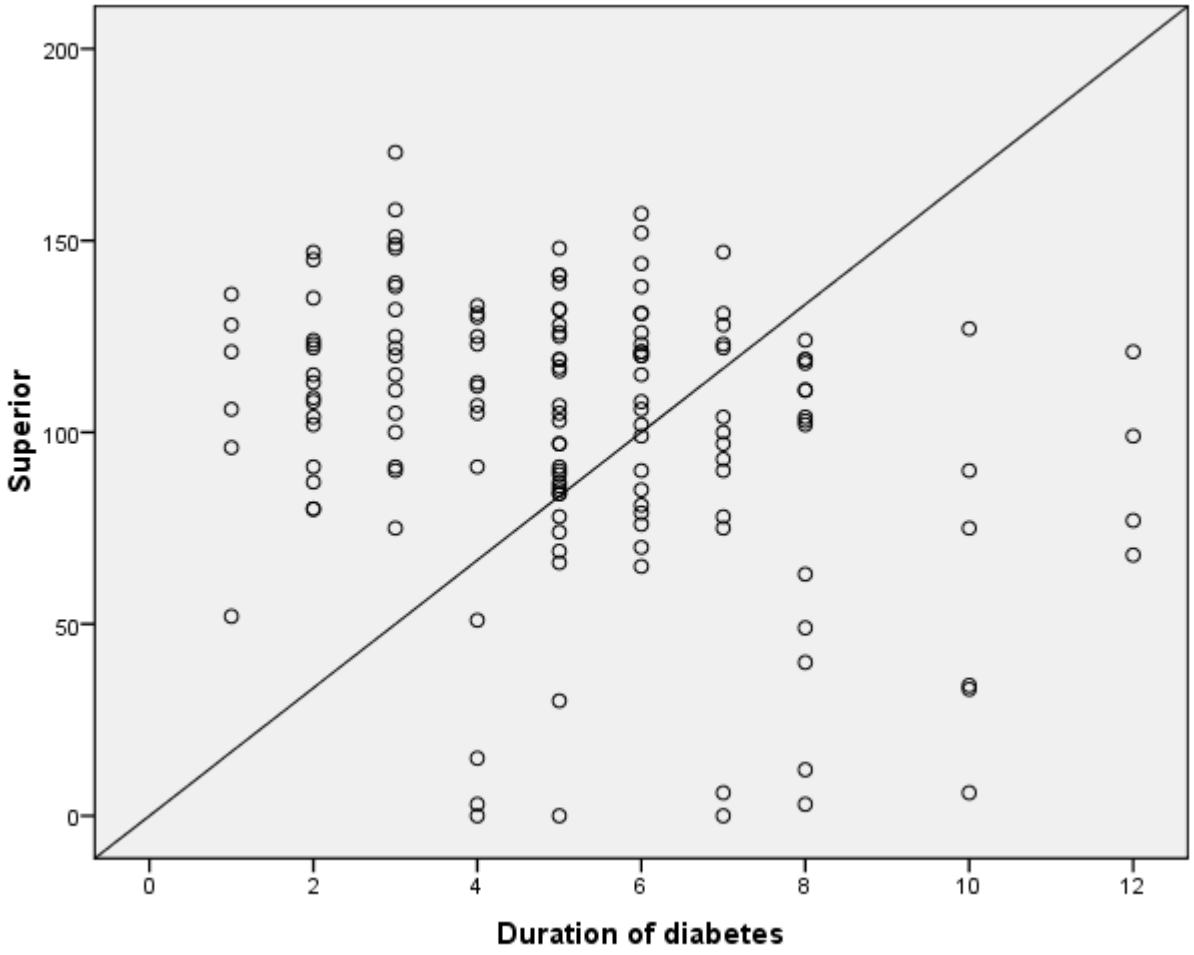
Nasal RNFL thickness has negative correlation with Duration of diabetes which not was statistically significant.

Temporal RNFL thickness has negative correlation with Duration of diabetes which not was statistically significant.

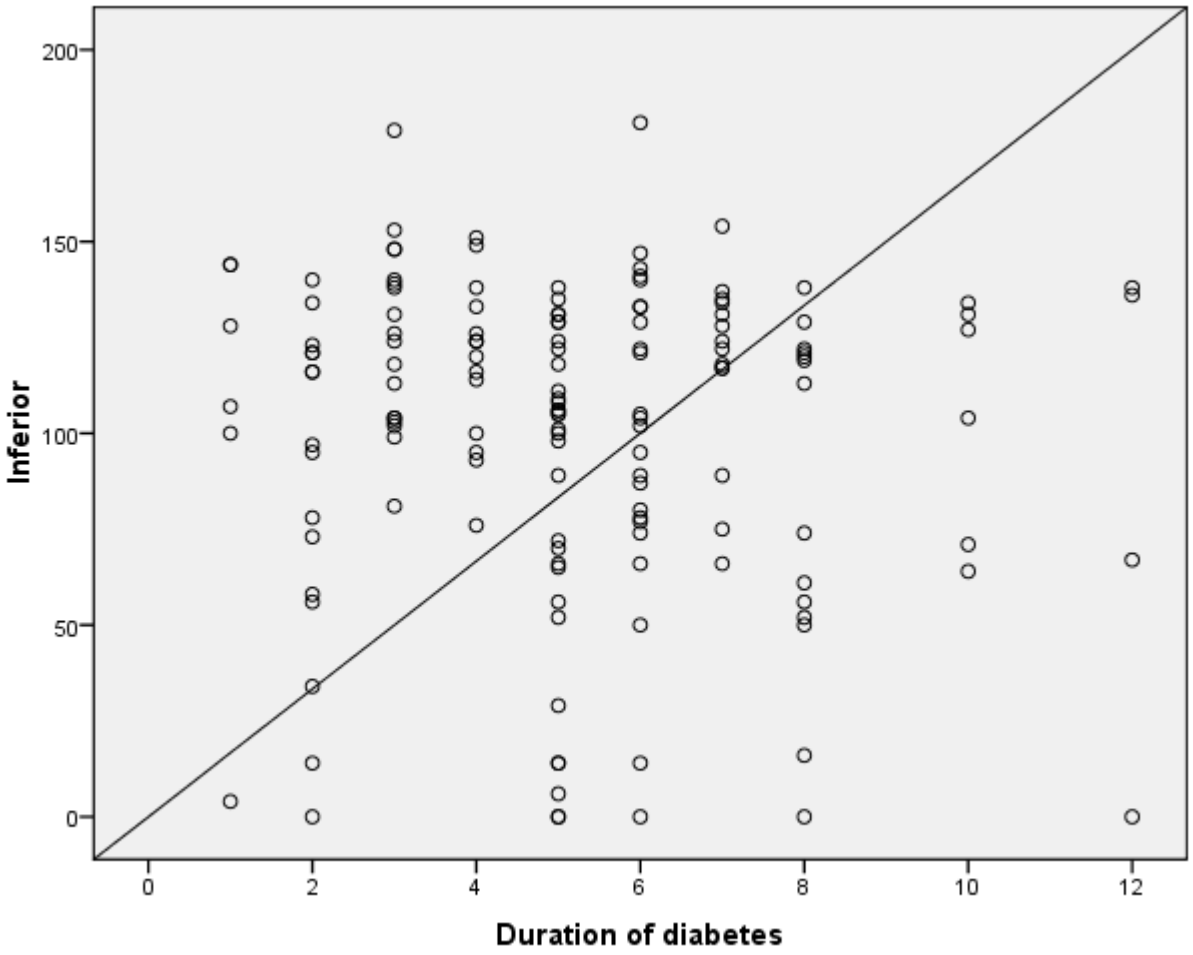
Graphs 9:- Scatter plot showing correlation between Duration of Diabetes with global RNFL thickness



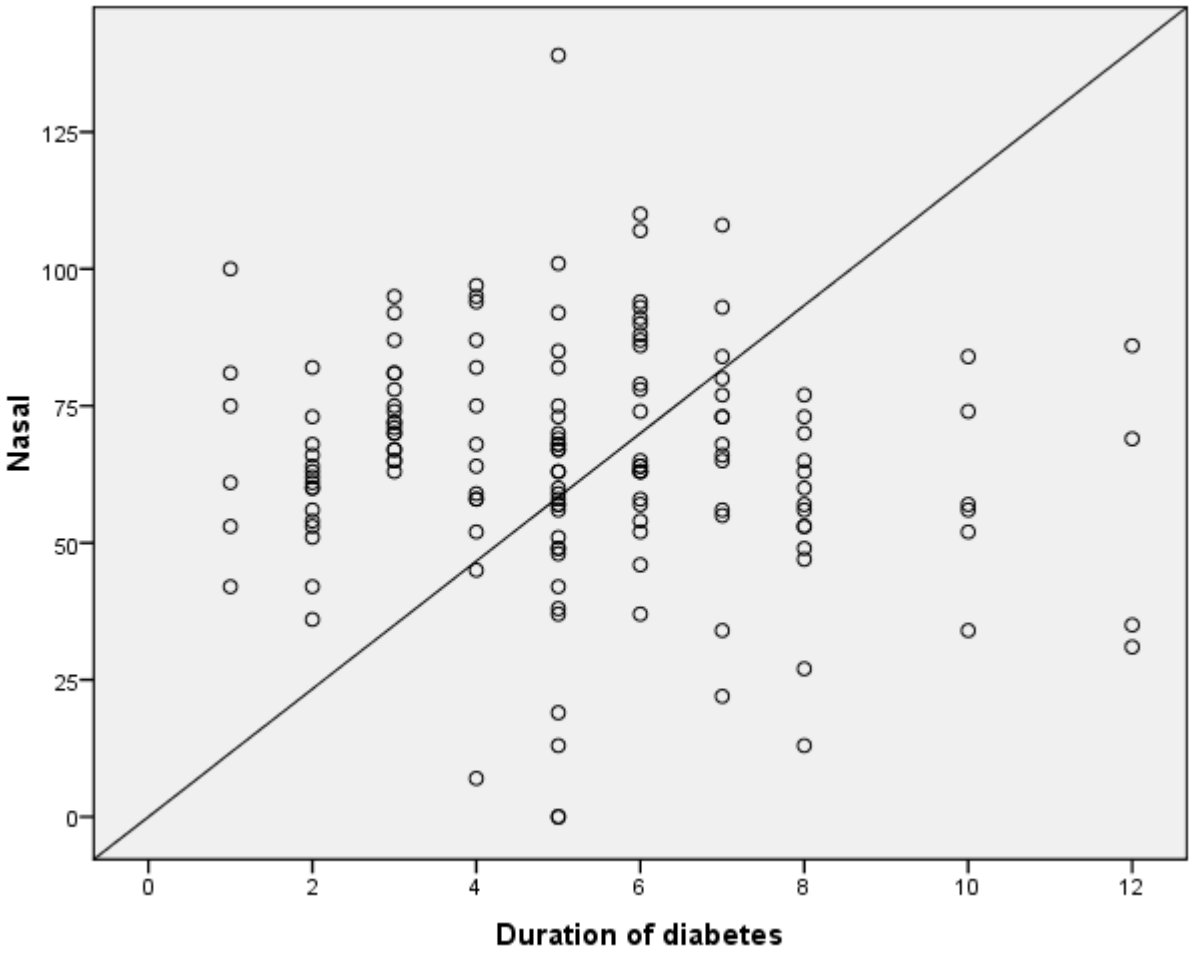
Graph 10:- Scatter plot showing correlation between Duration of Diabetes with superior RNFL thickness



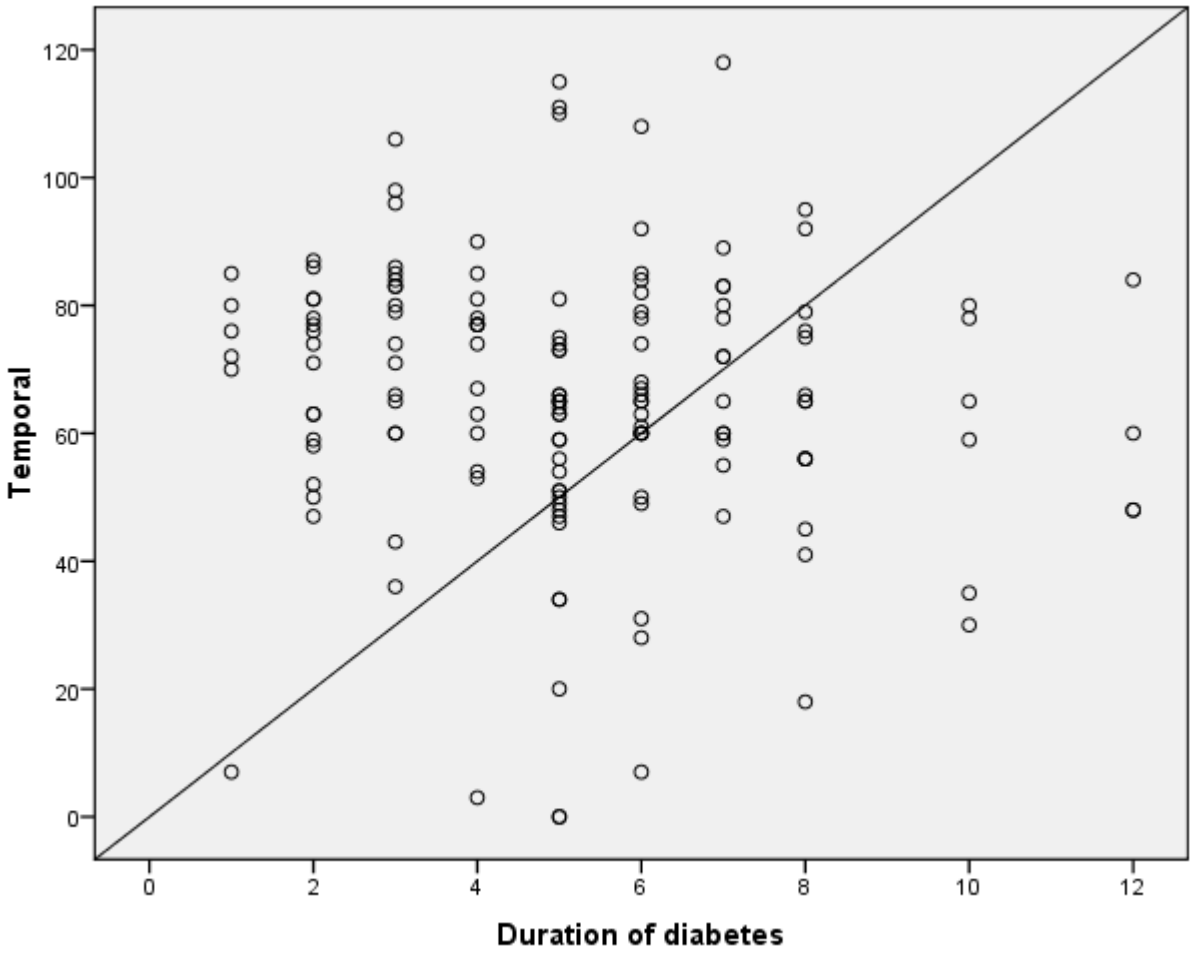
Graph 11:- Scatter plot showing correlation between Duration of Diabetes with inferior RNFL thickness



Graph 12:- Scatter plot showing a correlation between Duration of Diabetes with Nasal RNFL thickness.



Graph 13:- Scatter plot showing correlation between Duration of Diabetes with temporal RNFL thickness.



DISCUSSION

DISCUSSION

The vast bulk of research that has been published on retina pertaining to diabetic patients has focused on determining the impact of vascular alterations of diabetes on the retina .[133-35] On the other hand, in a study by Della Sala and in another study by Sokol found that patients with moderate DR changes having normal visual acuity also showed functional deficits. [136-37]

Bresnick debated that retinopathy should not be considered as a vascular pathology in isolation and that a similar argument can be applied to neuropathy. In turn, the author concluded that diabetic retinopathic changes are by a culmination of vascular and neurodegenerative pathology .[138] The anatomical and physiological changes that occur in the retina as a result of diabetes underscore the significance of taking into consideration the possibility that neuronal and vascular problems are a connected processes .[138]

The dysfunction of the retina has been proven using psychophysical and functional visual tests prior to the onset of clinically obvious alterations in the retinal blood vessels .[139-40] There is diminished contrast senstivity, including altered mesopic foveal contrast sensitivity, in diabetic patients who do not have diabetic retinopathy, according to clinical data .[141]

Neuronal apoptosis, the loss of ganglion cell bodies, a deficiency in glial responsiveness, and a reduction in the thickness of the inner retina are all symptoms of retinal neurodegeneration. The breakdown of the barrier between the blood and the retina as well as abnormalities in neurovascular interaction can both be caused by retinal neurodegeneration, which can also contribute to capillary degeneration. In the context of DR, the primary contributors to the development of neurodegeneration are an accumulation of glutamate in the extracellular space, oxidative stress, an imbalance in the synthesis of neuroprotective molecules in the retina, and inflammation. [142-45]

One of the initial signs of diabetic retinopathy is retinal hypoxia. The hyperglycaemia over a extended period of time will lead to build-up of sorbitol, an increase in the ratio of lactate to pyruvate, and a disruption in the redox balance, all of which led to cell damage. Extracellular glucose levels that are in elevated levels cause an increase in the oxidative metabolism of glucose in the mitochondria. This results in the generation of free radicals, which causes direct damage to the nerve axons. Diabetes impairs the retina's capacity to control glutamate, which may result in chronic excitotoxicity as a result of permitting a progressive increase in the levels of extracellular glutamate. Diabetes also causes the retina to become more sensitive to glutamate. An increase in the rate of apoptosis can be caused by excessive stimulation of neurons.[146-47]

Due to the fact that they express multiple proapoptotic genes, ganglion cells in diabetic retinas are particularly susceptible to apoptosis caspase-3, Fas, or Bax-like molecular structure thereby reducing the number of retinal neurons that survive, which in turn produces reactive alterations in the retinal glia and leads to the development of aberrant swellings on centrifugal axons. Kern and Engerman et al. came to the conclusion that certain regions of the retina do not have the typical vasoconstrictor response that occurs in response to noxious stimuli like hypoxia. Because of this, individuals have a greater risk of developing oxidative damage as well as losing nerve cells[146-147]

In the research carried out by Barber and colleagues, streptozotocin-induced diabetic rats showed a 10% decrease in the number of cells that made up the ganglion cell layer.[148] In addition to this, they discovered significant reductions in the thickness of the inner plexiform layers (IPLs) and the inner nuclear layers (INLs), as well as a tenfold rise in the number of nonvascular cells that had undergone apoptosis. A decrease in the number of axons in the optic nerve is another sign that the number of ganglion cell bodies in the retina has been

lost.[146] Both Dijk et al. and Oshitari et al. demonstrated that the thickness of the RNFL and RGC layers becomes thinner with time in DR patients, and that the degree of this thinning was proportional to the severity of the disease.[147]

According to Cho et al's findings, the macular and peripapillary retinal thicknesses of diabetic patients were substantially higher than those of healthy controls (p less than 0.05). There was a significant correlation between the severity of DR and an upward trend in all retinal thickness metrics, notably peripapillary circular scans (p 0.05). In contrast to the findings of prior investigations, Dhasmana and colleagues discovered that diabetic patients' eyes exhibited thinning of the RNFL in the supero-temporal (p-value = 0.001) and upper nasal sectors (p-value = 0.031) sectors around the optic disc. Lower RNFL thickness was shown to be lower in diabetics, according to Takis et al., but the two-year follow-up indicated no significant decline of RNFL thickness in diabetic or normal groups. This suggests that RNFL damage may start early on in diabetes patients. In the early stages of glaucoma, diabetes is a predisposing factor that causes RNFL thinning. However, glaucoma can be prevented or delayed by maintaining adequate glycaemic control and treatment compliance, which can avoid additional RNFL damage. [148-50] Peripapillary retinal oedema, which is impacted by diabetic macula oedema, was reported to be the cause of fluctuations in the RNFL thickness measurement by Hyun Seung Yang et al. The peripapillary RNFL thickness is substantially impacted by retinal oedema, particularly in the peripapillary area. As a result, the peripapillary RNFL thickness itself does not reveal the true RNFL gain or loss in DR patients. [145,151] There is diminished contrast senstivity, including altered mesopic foveal contrast sensitivity, in diabetic patients who do not have diabetic retinopathy, according to clinical data. Paul and his colleagues employed an HRA-OCT Spectralis machine to analyse the RNFL in patients with type 2 diabetes mellitus. They reported that the majority of their patients with RNFL thinning had lesions in the temporal quadrant of their eyes.[152]

Patients with type 1 diabetes mellitus who did not have diabetic retinopathy were shown to have a considerable loss of nerve fibre layer in the superior region of the retina when analysed with the nerve fibre analyzer (GDx), as reported by Lopes de Faria and colleagues .[153] Where as in our study patients with diabetic retinopathy also showed a decrease in the mean of superior RNFL quadrant.

Sugimoto and his colleagues employed Stratus OCT to evaluate RNFL in patients with type 2 diabetes mellitus while the patients were undergoing glycaemic management. At the initial appointment, as well as at one month, two months, and four months after the initial evaluation, each patient was re examined. At each visit , glycosylated haemoglobin(HbA1c) levels as well as OCT scans measuring RNFL thickness were analysed. Between the initial exam and either the one-month or the two-month follow-up, there was no discernible change in RNFL. Between the initial evaluation and the examination after four months, a considerable improvement was noticed in the upper quadrant. There was not observed to be any substantial change in the other quadrants .[154]

A combination of microvascular anomalies and a neurotoxic effect on retinal ganglion cells led to diabetic retinopathy, according to the findings of a study carried out by Altman C and associates. In addition to this, they brought to light the fact that the neurodegenerative effects of diabetes may develop before the micro vascular abnormalities.[155] Another study came to the same conclusion, arguing that the diabetic neurodegenerative effect on ganglion cells and RNFL thickness is caused first and foremost by diabetes mellitus and secondly as a secondary effect of damage to the blood retinal barrier and the resultant damage to retinal ganglions caused by oedema and an increase in extracellular fluid levels. This was supported by the findings of the first study. [156]

The findings of this study are consistent with those of an experimental study that Kern and Engerman carried out in two animal models of DR. That study found that the early events of diabetic retinal disease (microaneurysms and acellular capillaries) were not distributed uniformly across the retina, and that both lesions were significantly more prevalent in the superior temporal retina rather than in the inferior nasal areas of the retina. The findings of the present study corroborate the findings of the experimental study as there is a decrease in RNFL thickness in the superior quadrant but no significant change in the temporal quadrant.[157] A study done by Chung et al. in order to evaluate the blood flow response to hyperoxia and hypercapnia in peripapillary retinal tissue that was located superior and inferior to the optic nerve head using confocal scanning laser Doppler flowmetry. [157]According to the findings of their study, the superior temporal regions were more sensitive to vasoconstriction and less sensitive to vasodilatation; as a result, these regions were more likely to experience oxidative damage and loss of nerve cells.

When eyes with DR changes were compared to healthy eyes of the same age that served as a control group, the researchers found that there was a statistically significant difference in the thickness of the RNFL in all quadrant of eyes with early NPDR.

Patients with diabetes mellitus who did not have diabetic retinopathy were found to have thinner ganglion cell layers and RNFLs than age-matched controls, according to the findings of a study that was carried out by Sohn EH and colleagues. In addition to this, they discovered that the thinning was noticed over the course of four years and was unrelated to factors such as age, gender, or glycosylated haemoglobin levels. [158] Therefore, given the available evidence, we can hypothesise that the neurodegeneration of the retina may come before the onset of diabetic retinopathy. A comparable difference in RNFL thickness was discovered in a different investigation that was carried out on patients with type I diabetes

who did not have retinopathy. [159] Another study indicated that the thickness of the retinal nerve fibre layer (RNFL) and ganglion cells was much lower in Type I diabetic children who did not have retinopathy. This was in comparison to normal children. Therefore, there is evidence that diabetes mellitus has a neurogenerative effect on ganglion cells prior to the formation of the vascular component of diabetic retinopathy.[160]

Only the supero-nasal and supero-temporal quadrants of the retinal nerve fibre layer (RNFL) were found to be thinner in diabetic patients with type II diabetes and diabetic retinopathy, according to the findings of a study that compared these patients to normal people. They argue that neurodegeneration is an early stage of diabetes mellitus and that it may occur in conjunction with diabetic retinopathy. [161]

In a study that was very similar to this one, which was carried out on diabetic patients with Type 1 DM who did not have retinopathy, the RNFL thickness was measured with the assistance of scanning laser polarimetry, and it was observed that the superior quadrant showed thinning in comparison to the normative data base. [162]

These two investigations have revealed that the superior quadrants show RNFL thinning in Type-1 diabetic patients, regardless of existence of retinopathy, and regardless of age. Additionally, the neurodegeneration may predate the development of diabetic retinopathy vascular component.[163]

Our findings contradict those of research that was carried out by Srinivasan S and his colleagues. They discovered that the thickness of the RNFL and the thickness of the ganglion cell layer in healthy individuals, as well as diabetics with or without retinopathy, was not statistically different in any quadrant. [138] It was found in another study of this kind, which examined the neuronal structural integrity of cornea and retina as markers for neuronal

degeneration in diabetic individuals, that the RNFL thickness was the same in groups with or without retinopathy, as well as in the control group. [164] It was found that the RNFL had a distinct pattern of becoming thinner as the retinopathy advanced. [165] As a result, the assumption has been made that the vascular progression of diabetic retinopathy is accompanied by a comparable progression in the neurodegeneration of ganglion cells, which causes additional thinning of the RNFL. Another study concluded that the duration diabetes had an adverse effect on the thickness of the retinal nerve fibre layer (RNFL), and that as retinopathy progressed and diabetes lasted longer, the RNFL became thinner. [166]

There is a strong connection between neuronal cells, glial cells, and vascular cells in the neurovascular unit of the retina. This connection is crucial for the maintenance of homeostasis, which is required for appropriate neuroretinal function, including the blood-retinal barrier and neural signalling.[167,168] Neurodegeneration in diabetic patients manifests both structurally and functionally. Structurally, it appears as inner retinal thinning; functionally, it appears as abnormalities on electroretinography, loss of dark adaptation and contrast sensitivity, colour vision disturbance and abnormal microperimetry findings. [169-70] According to previous research, retinal ganglion and amacrine cells were the first neurons in which diabetes–induced apoptosis was observed as a result, the thickness of the inner retinal layers, such as the GC-IPL and the pRNFL, was reduced.[171-72] According to the findings of one long term study, the GC-IPL and RNFL thicknesses in the macular area, as evaluated by time-domain OCT using an open-source, gradually decreased in 45 diabetic individuals with limited to no DR.[173]

Although the RNFL thickness in patients with diabetes decreases with the severity of DR the influence of ischemic injury on the RNFL thickness reduction rate in the early stage of DR might be smaller than that of diabetic retinal neurodegeneration.[174] This is despite the fact

that the RNFL thickness in patients with diabetes decreases with the severity of DR. However, it's possible that the difference wasn't discovered because there wasn't enough statistical power to discern between the two groups' respective reduction rates.

According to the findings of Lee and his colleagues, eyes with high myopia had a higher drop in pRNFL over the course of 2 years when compared with healthy eyes.[174]

In the research carried out by Barber and colleagues, streptozotocin-induced diabetic rats showed a 10% decrease in the number of cells that made up the ganglion cell layer. In addition to this, they discovered significant reductions in the thickness of the inner plexiform layers (IPLs) and the inner nuclear layers (INLs), as well as a tenfold rise in the number of nonvascular cells that had undergone apoptosis. A decrease in the number of axons in the optic nerve is another sign that the number of ganglion cell bodies in the retina has been lost. Both Dijk et al. and Oshitari et al. demonstrated that the thickness of the RNFL and RGC layers becomes thinner with time in DR patients, and that the degree of this thinning was proportional to the severity of the disease. [145,146,147]

Significant connections were found by Vujosevic and colleagues between the thickness of the pRNFL and OCTA metrics in the parapapillary areas of patients with type 2 diabetes. These measures include perfusion and vascular density It is well established that alterations in the peripapillary microvasculature are connected with a deterioration in patients' visual function.

Previous longitudinal studies have revealed that age is not a major factor related with changes in the peripheral retinal nerve fibre layer (pRNFL) thickness of T2DM patients.[154] According to Lee et al. findings as well, age is not a significant factor associated with retinal microvasculature in Type 2 Diabetes.

Some of the strengths of the study are that it was possible to take into account confounding factors like the length of time someone has had diabetes.

This study has a number of limitations, including a small sample size and an uneven distribution of patients throughout the various phases of diabetic retinopathy. It is not possible to take into account confounding factors like the length of time someone has had other systemic factors like neurodegenerative disorders. This study did not have a large enough sample size to take into account of retinal dysfuction before the onset of clinically evident retinal vascular changes .

CONCLUSION

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The study titled "ASSESSMENT OF THE EFFECT OF DIABETIC RETINOPATHY ON RETINAL NERVE FIBER THICKNESS". OCT was done in 111 patients

In this study patients were divided into 4 groups:

-Controls (normal patients without Diabetes)-37 patients

-Diabetics without retinopathy (NDR group)-37 patients

- Non proliferative diabetic retinopathy (NPDR group) - 37 patients

In the OCT reports it was noted that

- Mean **Global** retinal nerve fibre layer thickness among the three groups in the study was statistically significant , p value - <0.015
- Mean **superior** retinal nerve fibre layer thickness among the three groups in the study was statistically significant, p- value - <0.001
- Mean **inferior** retinal nerve fibre layer thickness among the three groups in the study was not significant.
- Mean **Nasal** retinal nerve fibre layer thickness among the three groups in the study was not significant.
- Mean **Temporal** retinal nerve fibre layer thickness among the three groups in the study was not significant.

When the Diabetic patients RNFL was correlated with Duration of diabetes:-

Global RNFL thickness has negative correlation with Duration of diabetes which was statistically significant.

Superior RNFL thickness has negative correlation with Duration of diabetes which was statistically significant.

Age and sex did not have any statistically significant changes in RNFL thickness in patients with diabetes. Patients suffering from diabetic retinopathy can have their neurodegeneration advancement monitored with optical coherence tomography (OCT) by objectively assessing the thickness of their peripapillary retinal nerve fibre layer (RNFL). This is a diagnostic technique that can also be used to track the progression of DR, which can be used to determine the prognosis of DR.

SUMMARY

SUMMARY

The study titled "ASSESSMENT OF THE EFFECT OF DIABETIC RETINOPATHY ON RETINAL NERVE FIBER THICKNESS". This is a Cross sectional prospective study done in R.L. Jalappa Hospital during January 2021 to June 2022, OCT was done in 111 patients . The present study showed that the RNFL thickness was significantly less in diabetic patients than in the control group and the patient's RNFL thickness in global (G), superior quadrants showed statistical decrease . It was also noted that a negative correlation is present with the duration of diabetes. Age and sex did not show any statistical significance in change in RNFL thickness. This leads us to believe that neurodegenarative changes are present in the retinas of diabetic patients. As one of the assessment of neurodegeneration is OCT , OCT will prove to be a useful tool to quantitatively assess the effect of Diabetes on the retina. Therefore OCT should be conducted from the earliest detection period of Diabetes to follow the patients neurodegeneration and for early start of treatment.

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ANNEXURES

ANNEXURE - I

CASE PROFORMA	
Patient Name: -	UHID: -
Age: -	Gender: -
Address: -	

BRIEF HISTORY: -	
PAST HISTORY: -	
FAMILY HISTORY:	
PERSONAL HISTORY: -	a. Appetite/ Diet b. Bowel and bladder c. Sleep d. Habits
GENERAL PHYSICAL EXAMINATION Vitals: -	Pallor / Icterus/ Cyanosis/ Clubbing/ Edema PR: - BP: - RR: - Temp: -
Systemic examination: -	1. CVS: - 2. RS: - 3. P/A: - 4. CNS: -

OCULAR EXAMINATION		
TESTS	**RE**	**LE**
1. HEAD POSTURE 2. OCULAR POSTURE 3. FACIAL SYMMETRY		
4. EXTRAOCULAR MOVEMENTS a) Ductions b) Versions		
5. VISUAL ACUITY: a) Distant • Without spectacles • With spectacles b) Near		
6. FUNDUS a. Direct ophthalmoscopy b. Indirect ophthalmoscopy		
7. OCT (RNFL thickness - µm): - • Superior RNFL thickness • Inferior RNFL Thickness • Nasal RNFL Thickness • Temporal RNFL Thickness		

ANNEXURE-II

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, TAMAKA, KOLAR - 563101.

INFORMED CONSENT FORM

Case no:

IP no:

TITLE:
ASSESSMENT OF THE EFFECT OF DIABETIC RETINOPATHY ON RENTINAL NERVE FIBER THICKNESS

I, the undersigned, agree to participate in this study and authorize the collection and disclosure of personal information as outlined in this consent form.

I understand the purpose of this study, the risks and benefits of the technique and the confidential nature of the information that will be collected and disclosed during the study. The information collected will be used only for research.

I have had the opportunity to ask questions regarding the various aspects of this study and my questions have been answered to my satisfaction.3

I understand that I remain free to withdraw the participation from this study at any time and this will not change the future care.

Participation in this study does not involve any extra cost to me.

Name	Signature	Date	Time
Patient:			
Witness:			
Primary Investigator/ Doctor:			

ಶ್ರೀ ದೇವರಾಜ್ ಅರಸ್ ವೈದ್ಯಕೀಯ ಕಾಲೇಜು, ಟಮಕ, ಕೋಲಾರ

ತಿಳಿವಳಿಕೆಯ ಸಮ್ಮತಿ ನಮೂನೆ

ಕೇಸ್ ಸಂಖ್ಯೆ:

ಐಪಿ ಸಂಖ್ಯೆ:

ಶೀರ್ಷಿಕೆ: ದ್ರಿಷ್ಟಿ ಪಟಲದ ನರ ತಂತುಗಳ ಗಾತ್ರದ ಮೇಲೆ ಸಕ್ಕರೆ ಖಾಹಿಲೆ ಪರಿಣಾಮದ ಮಾಪನ

ನಾನು, ಅಂಗೀಕರಿಸಿದ, ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳಲು ಮತ್ತು ಈ ಸಮ್ಮತಿಯ ರೂಪದಲ್ಲಿ ವಿವರಿಸಿರುವಂತೆ ವೈಯಕ್ತಿಕ ಮಾಹಿತಿಯ ಸಂಗ್ರಹ ಮತ್ತು ಬಹಿರಂಗಪಡಿಸುವಿಕೆಯನ್ನು ಅನುಮೋದಿಸಲು ಒಪ್ಪುತ್ತೇನೆ.

ಈ ಅಧ್ಯಯನದ ಉದ್ದೇಶ, ತಂತ್ರದ ಅಪಾಯಗಳು ಮತ್ತು ಪ್ರಯೋಜನಗಳನ್ನು ಮತ್ತು ಅಧ್ಯಯನದ ಸಮಯದಲ್ಲಿ ಸಂಗ್ರಹಿಸಲ್ಪಟ್ಟಿರುವ ಮತ್ತು ಬಹಿರಂಗಪಡಿಸುವ ಮಾಹಿತಿಯ ಗೌಪ್ಯತೆಗೆ ನಾನು ಅರ್ಥಮಾಡಿಕೊಂಡಿದ್ದೇನೆ. ಸಂಗ್ರಹಿಸಿದ ಮಾಹಿತಿಯನ್ನು ಸಂಶೋಧನೆಗೆ ಮಾತ್ರ ಬಳಸಲಾಗುತ್ತದೆ.

ಈ ಅಧ್ಯಯನದ ವಿವಿಧ ಅಂಶಗಳನ್ನು ಕುರಿತು ಪ್ರಶ್ನೆಗಳನ್ನು ಕೇಳಲು ನನಗೆ ಅವಕಾಶವಿದೆ ಮತ್ತು ನನ್ನ ತೃಪ್ತಿಗೆ ನನ್ನ ಪ್ರಶ್ನೆಗಳಿಗೆ ಉತ್ತರ ನೀಡಲಾಗಿದೆ.

ಈ ಅಧ್ಯಯನದಿಂದ ಭಾಗವಹಿಸುವಿಕೆಯನ್ನು ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ನಾನು ಹಿಂಪಡೆಯಲು ಮುಕ್ತವಾಗಿರುತ್ತೇನೆ ಮತ್ತು ಇದು ಭವಿಷ್ಯದ ಕಾಳಜಿಯನ್ನು ಬದಲಿಸುವುದಿಲ್ಲ ಎಂದು ನಾನು ಅರ್ಥಮಾಡಿಕೊಂಡಿದ್ದೇನೆ.

ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸುವಿಕೆ ನನಗೆ ಯಾವುದೇ ಹೆಚ್ಚುವರಿ ವೆಚ್ಚ ಒಳಗೊಳ್ಳುವುದಿಲ್ಲ.

ಹೆಸರು	ಸಹಿ/ಹೆಬ್ಬೆಟ್ಟಿನ ಗುರುತು	ದಿನಾಂಕ	ಸಮಯ
ರೋಗಿಯ ಹೆಸರು			
ಸಾಕ್ಷಿಗಳ ಹೆಸರು			
ಪ್ರಾಥಮಿಕ ಸಂಶೋಧಕರು/ ವೈದ್ಯರು			

ANNEXURE-III

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, TAMAKA, KOLAR - 563101.

PATIENT INFORMATION SHEET

This information is to help you understand the purpose of the study "ASSESSMENT OF THE EFFECT OF DIABETIC RETINOTHAY ON RENTINAL NERVE FIBER THICKNESS". You are invited to take part voluntarily in this research study, it is important that you read and understand the purpose, procedure, benefits and discomforts of the study.

1. What is the purpose of this study?

   The study of RNFL thickness can help us understand the progression of the Diabetic retinopathy, which might assist in the early detection and management of the disease .

2.What are the various investigations being used? Are there any associated risks?

Absolutely no risks are associated with various investigations involved in this study such as

1. Ocular coherence tomography

3. What is the benefit for me as a participant?

Participation in this research study may not change the final outcome of your eye condition. However, patients in the future may benefit as a result of knowledge gained from this study. You will not be charged extra for any of the procedures performed during the research study. Your taking part in this study is entirely voluntary. You may refuse to take part in the study or you may stop your participation in the study at any time, without a penalty or loss of any benefits to which you were otherwise entitled before taking part in this study.

CONFIDENTIALITY

Your medical information will be kept confidential by the study doctor and staff and will not be made publicly available. Your original records may be reviewed by your doctor or ethics review board. For further information/ clarification please contact.

Dr. RASHMI G,

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, TAMAKA, KOLAR - 563101.

Contact no: 9886998871 or 7893782676 to Dr Ramya.

<u>ಶ್ರೀ ದೇವರಾಜ್ ಅರಸ್ ಉನ್ನತ ಶಿಕ್ಷಣ ಮತ್ತು ಸಂಶೋಧನಾ ಸಂಸ್ಥೆ,</u>

<u>ಟಮಕ, ಕೋಲಾರ - 563101.</u>

ರೋಗಿಯ ಮಾಹಿತಿ ಪತ್ರ

ಈ ಮಾಹಿತಿಯು " ದ್ರಿಷ್ಟಿ ಪಟಲದ ನರ ತಂತುಗಳ ಗಾತ್ರದ ಮೇಲೆ ಸಕ್ಕರೆ ಖಾಹಿಲೆ ಪರಿಣಾಮದ ಮಾಪನ". ಈ ಅಧ್ಯಯನದ ಉದ್ದೇಶವನ್ನು ಅರ್ಥಮಾಡಿಕೊಳ್ಳಲು ಸಹಾಯ ಮಾಡುವುದು. ಈ ಸಂಶೋಧನಾ ಅಧ್ಯಯನದಲ್ಲಿ ಸ್ವಯಂಪ್ರೇರಿತವಾಗಿ ಪಾಲ್ಗೊಳ್ಳಲು ನಿಮ್ಮನ್ನು ಆಹ್ವಾನಿಸಲಾಗಿದೆ, ಅಧ್ಯಯನದ ಉದ್ದೇಶ, ಕಾರ್ಯವಿಧಾನ, ಪ್ರಯೋಜನಗಳು ಮತ್ತು ಅಸ್ವಸ್ಥತೆಗಳನ್ನು ನೀವು ಓದುವುದು ಮತ್ತು ಅರ್ಥಮಾಡಿಕೊಳ್ಳುವುದು ಮುಖ್ಯವಾಗಿದೆ.

1. ಈ ಅಧ್ಯಯನದ ಉದ್ದೇಶವೇನು?

ಆರ್ಎನ್ಎಫ್ಎಲ್ ದಪ್ಪದ ಅಧ್ಯಯನವು ಡಯಾಬಿಟಿಕ್ ರೆಟಿನೋಪತಿಯ ಪ್ರಗತಿಯನ್ನು ಅರ್ಥಮಾಡಿಕೊಳ್ಳಲು ನಮಗೆ ಸಹಾಯ ಮಾಡುತ್ತದೆ, ಇದು ರೋಗದ ಆರಂಭಿಕ ಪತ್ತೆ ಮತ್ತು ನಿರ್ವಹಣೆಗೆ ಸಹಾಯ ಮಾಡುತ್ತದೆ.

2. ವಿವಿಧ ತನಿಖೆಗಳನ್ನು ಬಳಸಲಾಗುತ್ತಿದೆ? ಯಾವುದೇ ಸಂಬಂಧಿತ ಅಪಾಯಗಳಿವೆಯೇ?

ಸಂಪೂರ್ಣವಾಗಿ ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಒಳಗೊಂಡಿರುವ ವಿವಿಧ ತನಿಖೆಗಳೊಂದಿಗೆ ಯಾವುದೇ ಅಪಾಯಗಳಿಲ್ಲ

1. ಒಕ್ಯುಲರ್ ಕೋಹೆರೆನ್ಸ್ ಟೊಮೊಗ್ರಫಿ

3. ಭಾಗವಹಿಸುವವನಾಗಿ ನನಗೆ ಏನು ಪ್ರಯೋಜನ?

ಈ ಸಂಶೋಧನಾ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸುವಿಕೆಯು ನಿಮ್ಮ ಕಣ್ಣಿನ ಸ್ಥಿತಿಯ ಅಂತಿಮ ಫಲಿತಾಂಶವನ್ನು ಬದಲಿಸಬಾರದು. ಆದಾಗ್ಯೂ, ಭವಿಷ್ಯದಲ್ಲಿ ರೋಗಿಗಳು ಈ ಅಧ್ಯಯನದಿಂದ ಪಡೆದ ಜ್ಞಾನದ ಫಲಿತಾಂಶವಾಗಿ ಪ್ರಯೋಜನ ಪಡೆಯಬಹುದು. ಸಂಶೋಧನಾ ಅಧ್ಯಯನದ ಸಮಯದಲ್ಲಿ ನಡೆಸಿದ ಯಾವುದೇ ಪ್ರಕ್ರಿಯೆಗಳಿಗೆ ನಿಮಗೆ ಹೆಚ್ಚುವರಿ ಶುಲ್ಕ ವಿಧಿಸಲಾಗುವುದಿಲ್ಲ. ಈ ಅಧ್ಯಯನದಲ್ಲಿ ನಿಮ್ಮ ಪಾಲ್ಗೊಳ್ಳುವಿಕೆಯು ಸಂಪೂರ್ಣವಾಗಿ

ಸ್ವಯಂಪ್ರೇರಿತವಾಗಿದೆ. ಅಧ್ಯಯನದಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳಲು ನೀವು

ನಿರಾಕರಿಸಬಹುದು ಅಥವಾ ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳುವುದಕ್ಕೆ ಮುಂಚಿತವಾಗಿ ನೀವು ಯಾವುದೇ ಅರ್ಹತೆಯಿಂದ ಯಾವುದೇ ದಂಡ ಅಥವಾ ನಷ್ಟವಿಲ್ಲದೆಯೇ ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ನೀವು ಭಾಗವಹಿಸುವಿಕೆಯನ್ನು ನಿಲ್ಲಿಸಬಹುದು.

ಗೌಪ್ಯತೆ

ನಿಮ್ಮ ವೈದ್ಯಕೀಯ ಮಾಹಿತಿಯನ್ನು ಅಧ್ಯಯನದ ವೈದ್ಯರು ಮತ್ತು ಸಿಬ್ಬಂದಿ ಗೌಪ್ಯವಾಗಿಡಲಾಗುವುದು ಮತ್ತು ಸಾರ್ವಜನಿಕವಾಗಿ ಲಭ್ಯವಿರುವುದಿಲ್ಲ. ನಿಮ್ಮ ಮೂಲ ದಾಖಲೆಗಳನ್ನು ನಿಮ್ಮ ವೈದ್ಯರು ಅಥವಾ ನೈತಿಕ ವಿಮರ್ಶೆ ಮಂಡಳಿ ಪರಿಶೀಲಿಸಬಹುದು. ಹೆಚ್ಚಿನ ಮಾಹಿತಿಗಾಗಿ ಸಂಪರ್ಕಿಸಿ

ಡಾ. ರಾಶ್ಮಿ. ಜೀ ,

ಡಾ. ರಮ್ಯಾ

ಎಸ್ ಡಿ ಯು ಎಮ್ ಸಿ.

ಟಮಕ, ಕೋಲಾರ

ಸಂಪರ್ಕ ಸಂಖ್ಯೆ: 9886998871 ಅಥವಾ 7893782676.

ANNEXURE-IV

PHOTOGRAPH 1: 90D Examination

PHOTOGRAPH 2: OCT

MASTER CHART

KEY TO MASTER CHART

NPDR - Non Proliferative Diabetic Retinopathy

DR - Diabetic Retinopathy

S.no	UHID	age	sex	duration of diabetis	Retina	eye	global	superior	inferior	nasal	temporal
1	947462	70	F	5 years	mIld NPDR	Right	71	78	56	101	50
						left	62	89	52	58	49
2	942276	70	M	6 years	Mod NPDR	Right	70	81	80	57	61
						left	70	79	89	63	49
3	948644	51	f	7 years	Mild NPDR	Right	89	93	128	73	60
						left	80	90	117	65	83
4	944967	57	M	8 years	mod NPDR	Right	91	124	129	53	56
						left	44	40	16	47	75
5	944765	63	M	5 year	MOD NPDR	Right	42	103	0	19	47
						left	82	105	105	59	59
6	37914	60	m	12 years	Severe NPDR	Right	35	77	0	31	48
						left	54	68	67	35	48
7	42414	63	M	2 years	Mild NPDR	Right	90	124	123	51	63
						left	64	80	58	53	63
8	908309	62	F	5 years	mIld NPDR	Right	55	69	66	38	48
						left	54	66	65	49	65
9	48369	63	F	6 YEARS	Mild NPDR	Right	70	70	74	64	74
						left	69	76	66	65	66
10	46987	69	F	5 YEARS	MOD NPDR	Right	77	87	72	82	65
						left	70	91	70	68	51
11	46881	71	F	1 YEAR	MILD NPDR	Right	113	136	144	100	72
						left	104	121	144	81	70
12	50421	64	F	5 YEARS	MILD NPDR	Right	99	119	135	67	73
						left	48	84	106	0	0
13	50590	52	F	8 YEARS	MOD NPDR	Right	20	12	0	13	56
						left	96	111	121	73	66
14	50421	62	F	5 YEARS	MILD NPDR	Right	82	141	101	42	46
						left	96	128	122	73	59
15	48147	60	F	2 YEARS	MILD NPDR	Right	92	145	116	60	47
						left	99	135	134	68	58
16	58321	61	F	10 YEARS	SEVERE NPDR	Right	45	34	64	52	30
						left	49	33	71	56	35
17	57164	56	F	6 years	MOD NPDR	Right	69	85	78	52	60
						left	61	108	14	54	63
18	58214	46	M	6 years	MOD NPDR	Right	54	102	50	58	7
						left	51	126	0	46	31
19	60061	67	F	10 years	MOD NPDR	Right	76	6	134	84	80
						left	75	75	131	34	59
20	56488	71	M	12 years	MILD NPDR	Right	91	99	138	69	60
						left	107	121	136	86	84
21	55627	73	F	5 year	MILD NPDR	Right	110	86	106	139	111
						left	77	97	89	56	66

22	60980	48	F	7 years	Mild NPDR	Right	98	104	122	93	72
						left	91	100	117	80	65
23	62558	49	F	6 years	Mod NPDR	Right	107	131	122	90	85
						left	83	90	104	74	65
24	66102	53	M	8 years	Mod NPDR	Right	58	49	74	65	45
						left	55	63	56	60	41
25	20060	54	M	4 years	Mild NPDR	Right	110	130	149	94	67
						left	91	51	138	97	77
26	65578	55	M	6 years	MOD NPDR	Right	107	131	147	87	65
						left	104	121	143	91	60
27	68821	55	M	5 years	mild NPDR	Right	60	85	29	92	34
						left	101	126	131	85	63
28	47811	40	F	3 years	Mod npdr	Right	114	138	153	81	84
						left	108	91	179	78	83
29	88566	58	F	6 years	Mild NPDR	Right	108	121	140	79	92
						left	124	144	181	88	84
30	99051	60	M	7 yaers	Mod NPDR	Right	74	97	89	56	55
						left	53	78	66	22	47
31	90042	47	F	2 years	Mild NPDR	Right	87	104	97	66	81
						left	87	115	121	36	77
32	89567	55	M	4 years	Mild NPDR	Right	107	105	133	82	78
						left	99	123	124	95	85
33	106080	55	M	6 years	Mod NPDR	Right	112	120	133	86	108
						left	102	123	129	78	79
34	107713	67	F	7 years	Mod NPDR	Right	76	6	134	84	80
						left	75	75	131	34	59
35	120916	77	M	10 years	Severe NPDR	Right	97	127	127	57	78
						left	83	90	104	74	65
36	133809	65	F	5 years	Mild NPDR	Right	103	139	131	70	74
						left	88	107	111	68	66
37	141822	62	F	6 years	Mod NPDR	Right	99	138	87	110	60
						left	76	65	77	94	68

S.No	UHID	age	sex	duration of diabetis	Retina	Eye	global	superior	inferior	temporal	nasal
1	37776	80	M	5 years	NO DR	Right	77	90	98	48	73
						left	52	97	6	57	54
2	42574	72	F	2 years	NO DR	Right	79	80	116	42	78
						left	87	109	95	61	81
3	938604	40	M	4 years	NO DR	Right	99	125	95	87	90
						left	88	131	120	58	60
4	50060	42	M	7 years	NO DR	Right	100	123	124	77	78
						left	103	122	135	68	89
5	942181	64	M	1 year	NO DR	Right	85	128	128	53	76
						left	83	96	100	42	80
6	56182	40	f	3 years	NO DR	Right	86	75	140	92	36
						left	91	105	124	70	65
7	75392	59	F	3 years	NO DR	Right	100	151	104	65	79
						left	91	100	99	67	98
8	75988	59	F	6 years	NO DR	Right	102	157	102	63	82
						left	88	152	105	37	60
9	55981	62	F	3 years	NO DR	Right	87	158	81	67	43
						left	111	173	104	63	106
10	76546	64	M	8 years	NO DR	Right	94	104	122	56	92
						left	80	102	113	49	56
11	77141	63	M	4 YEAR	NO DR	Right	84	107	93	58	77
						left	90	112	114	59	74
12	72201	51	M	5 years	NO DR	Right	75	84	100	51	64
						left	83	117	109	49	56
13	78112	75	F	2 YEARS	NO DR	Right	70	113	34	56	76
						left	61	123	0	62	59
14	78362	75	M	4 YEARS	NO DR	Right	106	133	151	64	77
						left	62	15	126	52	53
15	84393	82	M	1 YEAR	NO DR	Right	31	52	4	61	7
						left	93	106	107	75	85
16	87293	72	M	8 YEAR	NO DR	Right	92	103	138	63	65
						left	81	119	50	77	76
17	83939	68	M	6 YEARS	NO DR	Right	91	99	133	64	67
						left	95	115	95	93	78
18	98298	52	F	3 YEARS	NO DR	Right	107	122	139	72	96
						left	98	120	126	65	83
19	107958	52	F	2 YEARS	NO DR	Right	79	91	78	60	87
						left	68	87	73	64	50
20	106243	45	M	3 YEARS	NO DR	Right	92	111	102	72	85
						left	93	115	113	74	71
21	98654	71	M	8 YEARS	NO DR	Right	25	3	52	27	18

						left	82	118	61	53	95
22	100679	71	M	5 years	NO DR	Right	3	0	14	0	0
						left	104	116	129	57	115
23	108789	77	M	3 YEARS	NO DR	Right	107	132	138	71	86
						left	87	90	103	95	60
24	108771	77	F	5 years	NO DR	Right	90	141	105	67	51
						left	111	132	138	63	110
25	90265	68	M	2 YEARS	NO DR	Right	107	122	140	82	86
						left	104	147	121	73	74
26	85250	68	M	7 YEARS	NO DR	Right	85	128	75	66	72
						left	106	131	137	73	83
27	116531	68	F	5 years	NO DR	Right	101	132	129	69	75
						left	103	148	118	63	81
28	122830	60	F	3 YEARS	NO DR	Right	103	139	131	70	74
						left	105	149	118	87	66
29	122931	60	F	4 YEARS	NO DR	Right	67	91	100	75	3
						left	44	0	116	7	54
30	120916	51	F	3 YEARS	NO DR	Right	114	148	148	81	80
						left	102	125	148	75	60
31	112702	61	F	4 YEARS	NO DR	Right	51	3	76	45	81
						left	92	113	124	68	63
32	128053	56	F	2 YEARS	NO DR	Right	61	108	14	54	71
						left	68	102	56	63	52
33	106987	52	F	5 YEARS	NO DR	Right	93	125	108	75	63
						left	42	74	14	13	65
34	111107	70	F	6 YEARS	NO DR	Right	88	120	121	63	50
						left	96	106	141	107	28
35	137181	47	M	7 YEARS	NO DR	Right	132	147	154	108	118
						left	58	0	118	55	60
36	135194	51	F	5 YEARS	NO DR	Right	22	30	0	37	20
						left	86	119	124	60	34
37	135801	57	F	8 YEARS	NO DR	Right	94	119	119	57	79
						left	91	111	120	70	65

S.no	Name	age	sex	duration of diabetis	Retina	EYE	global	superior	inferior	temporal	nasal
1	884847	51	F	no	normal	Right	84	96	83	74	81
						left	88	103	105	76	70
2	890073	41	M	no	normal	Right	94	128	115	76	57
						left	95	126	108	63	84
3	900306	44	M	no	normal	Right	99	109	116	84	86
						left	96	99	118	77	88
4	50060	55	F	no	normal	Right	81	95	95	50	57
						left	80	84	84	58	67
5	951195	66	F	no	normal	Right	88	99	99	75	70
						left	94	131	113	69	76
6	926438	75	M	no	normal	Right	89	120	120	53	75
						left	84	115	115	54	75
7	65410	52	F	NO	normal	RIGHT	94	140	125	52	60
						LEFT	96	129	122	60	70
8	68391	71	F	no	normal	Right	97	128	122	62	71
						left	63	120	5	69	74
9	74512	64	M	no	normal	Right	71	150	52	39	57
						left	94	129	129	56	43
10	81981	61	M	no	normal	Right	96	134	123	62	60
						left	34	131	0	4	65
11	76377	60	F	no	normal	Right	75	80	93	66	2
						left	84	108	100	64	61
12	81200	50	F	no	normal	Right	85	100	92	64	63
						left	83	100	103	64	92
13	84346	63	F	no	normal	Right	101	136	135	64	103
						left	102	131	136	66	73
14	87396	62	M	no	normal	Right	99	144	116	51	73
						left	97	142	121	53	52
15	88689	63	M	no	normal	Right	91	136	113	54	58
						left	98	138	130	58	46
16	88493	71	M	no	normal	Right	97	135	128	68	67
						left	95	136	124	57	67
17	91310	83	M	no	normal	Right	57	68	74	58	62
						left	56	102	51	39	49
18	90322	62	F	no	normal	Right	105	119	140	30	40
						left	109	142	135	95	64

19	90648	61	M	no	normal	Right	127	134	156	70	88
						left	108	133	142	110	108
20	85250	52	M	no	normal	Right	75	37	141	63	91
						left	89	117	145	65	56
21	44720	52	M	no	normal	Right	93	127	122	71	24
						left	102	134	140	56	66
22	91706	56	M	no	normal	Right	104	134	143	67	67
						left	101	135	125	63	75
23	88451	56	M	no	normal	Right	53	124	2	69	74
						left	101	128	130	57	29
24	88473	60	M	no	normal	Right	35	77	0	31	74
						left	54	58	67	35	118
25	87864	76	F	no	normal	Right	99	113	138	66	79
						left	98	126	136	59	70
26	88895	50	M	no	normal	Right	100	133	121	63	82
						left	97	127	127	57	78
27	98663	82	M	no	normal	Right	80	93	111	106	12
						left	111	145	122	69	109
28	88359	61	M	NO	normal	Right	134	166	198	87	86
						left	158	229	181	74	147
29	84570	71	M	no	normal	Right	111	124	118	118	85
						left	76	65	77	94	68
30	90071	66	M	no	normal	Right	88	101	99	75	76
						left	94	99	131	69	75
31	54370	40	F	NO	NO DR	Right	104	110	123	109	74
						left	99	138	87	110	60
32	53181	42	M	no	normal	Right	88	107	111	68	66
						left	89	115	111	64	67
33	72668	47	M	no	normal	Right	131	136	153	116	118
						left	77	53	110	66	77
34	72610	53	M	no	normal	Right	80	81	107	62	69
						left	85	97	110	62	71
35	78581	60	F	no	normal	Right	103	139	131	70	74
						left	105	149	118	66	87
36	93421	57	M	no	normal	Right	83	99	87	115	33
						left	93	115	113	71	74
37	100060	51	F	no	normal	Right	99	138	117	75	67

						left	74	158	14	46	80