"CLINICAL CORRELATION BETWEEN DIABETIC RETINOPATHY, DIABETIC NEUROPATHY AND GLYCATED HEMOGLOBIN LEVELS"

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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LIST OF ABBREVATIONS

DM	Diabetes Mellitus
DR	Diabetic retinopathy
DPN	Diabetic peripheral neuropathy
RE	Right Eye
LE	Left eye
HbA1c	Glycosylated hemoglobin
ESRD	End stage renal disease
MODY	Maturity onset diabetes of the young
GDM	Gestational diabetes mellitus
LIC	Low income countries
LMIC	Middle income countries
NCD	Non-communicable diseases
GT	Glucose tolerance
FPG	Fasting plasma glucose
RBS	Random blood sugars
FBS	Fasting blood sugars
PPBS	Post prandial blood sugars
WESDR	Wisconsin Epidemiologic Study of Diabetic Retinopathy
VEGF	Vascular endothelial growth factor
NPDR	Non proliferative diabetic retinopathy
PDR	Proliferative diabetic retinopathy

VH	Vitreous hemorrhage
DME	Diabetic macular edema
IRMA	Intraretinal microvascular abnormalities
ETDRS	Early treatment of diabetic retinopathy study
OCT	Optical Coherence Tomography
TCNS	Toronto Clinical neuropathy Scoring System

ABSTRACT

Background and Objective

Diabetic retinopathy(DR) and Diabetic peripheral neuropathy(DPN) is the commonest complication which occur in diabetes mellitus. Both are microvascular complications and is said to share a common pathophysiology. It was noticed that the patients with either one may be missed by the treating doctor as both these complications are dealt by two different specialties. Hence, this study was undertaken to look for a clinical correlation between both DR and DPN and their relation to the glycemic inconsistency and the glycated hemoglobin levels.

Methods

This is a hospital based Cross-sectional observational study involving 156 attending the ophthalmology OPD and the in-patients department at R L Jalapa hospital attached to Devaraj Urs Medical College, Tamaka, Kolar from between December 2019 and May 2021.

Results

The DR severity in both the eyes was found to considerably increase with increase in duration of Type II DM among the patients ($p<0.001$). Similarly mean FBS and mean PPBS is seen to be significantly high amid patients with diabetic DPN compared to those without ($p<0.001$). The mean FBS and the mean PPBS were higher in the PDR group compared to other patients with DR ($p<0.001$). Proportion of patients with DPN was found to pointedly increase with increasing severity of DR in both eyes among the patients ($p<0.001$). A statistically significant association was seen to be present between DR and DPN**.**

Conclusion and interpretation

This study, demonstrated a positive correlation between severity of DR and existence of DPN and its relationship with the HbA1c variability. And it emphasized the need for a interdepartmental involvement for the complete evaluation and management.

Keywords: Diabetes mellitus, diabetic retinopathy, peripheral neuropathy, glycated hemoglobin

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INTRODUCTION

INTRODUCTION

Diabetes mellitus (DM) is a non-communicable disease and it is the most rampant one all through the world and has turned out to be one of the biggest threat to the health of the public across the globe.

The worldwide prevalence of DM is said to increase in the coming decades, from an approximated 382 million in the year 2013 to 592 million by year of 2035.[1, 2]

Type II diabetes has been said to have already reached an epidemic level, while type I diabetes is said to have been displaying an increased incidence over the previous few years.[3]

Patients with diagnosis of DM have been found to suffer from many complications which is found to be both life limiting and life threatening, these complications include macrovascular which include stroke, ischemic heart disease, peripheral artery disease and microvascular complications like retinopathy, neuropathy, and nephropathy.

Frequently encountered microvascular complication of DM are DR and DPN. Both of these microvascular complications are dealt by two different specialities and hence a better understanding of the relationship of the two will help us in early management and deterring the onset of complications.[4]

DM is characterized by hyperglycaemia which is said to be due to underlying insulin deficiency. In type I DM, the hyperglycemia is caused due to T cell-mediated autoimmune damage of the pancreatic-beta cells which are insulin-secreting and thereby there is an absolute deficiency of insulin. In type II DM, there is relative deficiency of insulin because of resistance to action of insulin and it therefore belongs to a group of conditions which are being called the ‘insulin resistance syndrome‘ or ‘metabolic syndrome‘.[5]Among the two it has been perceived that Type II DM is existent in 90% to 95% of patients.[6]

Retinal small blood vessels, which are named as the vasa-nervorum and the glomeruli of kidneys are at a very high risk to damage due to chronic hyperglycaemia and undergo characteristic changes such as thickening of capillary basement that finally lead to microangiopathy.[7] Diabetic retinopathy is due to progressive vascular dysfunction in the retina, and vascular dysfunction in the peripheral nerves which leads to diabetic neuropathy and in the vascular dysfunction of kidneys ultimately leads to diabetic nephropathy. The chronic complications linked with the disease are the leading cause for the majority of morbidity, mortality and health care expenditure connected with DM.[8]

The most frequently encountered complications of a patient suffering from DM is retinopathy and neuropathy. The worldwide prevalence of DR was reported with type 1 DM to be 60% in and with type 2 DM with 25.2 %.[9] DPN was said to have an effect in about one third with type 1 DM and more than half in those with type 2 DM.[10] DR is known to be an illustration of microvascular complications and said to be the root cause of blindness which is irreversible in the working age population.[10] DPN is a microvascular complication which is commonly come across and a prime risk factor for lower extremity amputation following foot ulcers.[11]

Both DR and DPN are microangiopathies and have the same pathophysiology, thus the existence and severity of either one could reflect on that of the other.[12] The eye is said to act as a window for the diabetic microangiopathic complications this relationship is noted between retinopathy, neuropathy and nephropathy. [13-15] And since they are diagnosed and managed by different specialties, the patients often tend to receive only one mode of care and treatment and may not be referred for the other systemic complication and thus they tend to be untreated for a longer duration leading to increased complication and debilitation. A better insight to the interrelationship between DR and DPN will emphasize the need for screening for other complications.

Previous studies carried out to look for the interrelationship between DR and DPN have found a positive correlation which is significant statistically between the two. But it has been observed that such studies correlating grades in DR with that of the severity of DPN are found to be highly limited. [19-23]

The glycosylated hemoglobin (HbA1c) levels also help us to identify the glycemic control of the individual and, the interrelation between the two complications along with their grades are correlated with their levels of HbA1c.

So, this study was marshaled with the aim of correlating the grade of DR with that of DPN and gauging their link with the glycated hemoglobin levels.

AIMS & OBJECTIVES

OBJECTVES OF STUDY

To establish a correlation between diabetic retinopathy, diabetic neuropathy and glycated hemoglobin levels.

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.[21]

Factors contributing to hyperglycemia include in DM.[22]

1. Reduced insulin production

2. Decreased glucose uptake

3. Increased 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 diabetes and on their health care. DM is said to be one among the major cause of end stage renal disease (ESRD), non-trauma related lower limb amputations and adult onset irreversible blindness. It also said to make patient prone to a risk for cardiovascular diseases. With an increasing incidence throughout the world, DM is presumably going to continue to be a foremost cause of morbidity and mortality across the globe in the upcoming days of the future.[22]

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.[21]

Types of diabetes

1. **Type 1 diabetes**: presents at a very early age which is commonly acute in onset, but it can have an onset later on during adult life.[23] Islet-specific autoimmunity is said to be the reason for the majority of people. 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 diabetes:** most common, accounts for >90 percent 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 age, it is known as youth-onset Type 2 diabetes, is seen to be rising in the recent years.[21]
3. **Hyperglycaemia in pregnancy** (gestational diabetes) is when women with no known previous history of diabetes develop high blood sugar levels in the later parts of their pregnancy. This condition is usually is seen to resolve after the delivery.
4. Diabetes secondary to other systemic conditions, such as chronic pancreatic illness, or secondary to intake of certain medication for example use of steroids .

   A newer classification has been proposed recently, which delineate five subgroups of diabetes formulated on six biomedical markers (including beta-cell function and insulin resistance) and the complications risks.[25]

Diabetes Mellitus classification based on etiology. [22]

I. Type 1 diabetes (due to reduced beta cell numbers)

a. Immune-mediated

b. Idiopathic

II. Type 2 DM (due to insulin resistance or decreased insulin production)

III. Other types of diabetes.

a. Genetic deficiencies of β cell function characterized by mutations in:

i. Hepatocyte nuclear transcription factor (HNF) 4 (Maturity onset diabetes of the young 1(MODY 1)).

ii. Glucokinase (MODY 2).

iii. HNF-1 (MODY 3).

iv. Insulin promoter factor-1 (IPF-1; MODY 4).

v. HNF-1 (MODY 5).

vi. NeuroD1 (MODY 6).

vii. Mitochondrial DNA.

viii. Subunits of ATP-sensitive potassium channel.

ix. Proinsulin or insulin conversion.

b. Genetic defects in action of insulin

i. Type A insulin resistance.

ii. Leprechaunism.

iii. Rabson-Mendenhall syndrome.

iv. Lipodystrophy syndromes.

c. pancreas related disease-pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy, mutations in carboxyl ester lipase.

d. Endocrinopathies-acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma.

e. Drug or chemical induced-vacor, pentamidine, nicotinic acid, glucocorticoids, thyroid hormone, diazoxide, β-adrenergic agonists, thiazides, phenytoin, α-interferon, protease inhibitors, clozapine.

f. Infections - Congenital rubella, cytomegalovirus, coxsackie.

g. Unusual forms of immune-mediated diabetes "stiff-person" syndrome, anti-insulin receptor antibodies.

h. genetic syndromes occasionally associated with diabetes— Down's syndrome, Klinefelter's syndrome, Turner's syndrome, Wolfram's syndrome, Friedreich's ataxia, Huntington's chorea, Laurence-Moon-Biedl syndrome, myotonic dystrophy, porphyria, Prader-Willi syndrome

IV. Gestational diabetes mellitus (GDM).

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.[26]

In 2014 it was roughly calculated that there are 422 million grown persons with DM universally, and the widespread presence is increasing in most nations because of advanced years, life-style changes and the interactions between the two parameters.[27] The universal

occurrence is seen to be greater in men (9%) than when compared with women (7.9%). In the year of 2016 DM was categorized 8th highest in terms of years existed with disability,[28] and the years of lifespan lost from diabetes increased 31% between the years of 2006 and 2016 (ranked in 9th place in lower middle income nations).[29] The frequency of diabetes increases with age, affecting 13–20% of those aged 50 years and above. It was further noted that 352 million people have impaired glucose tolerance, which sharply increases the risk of diabetes.[30] The amount of grown person aged 20–79 years with diabetes is said to surge to 629 million by 2045.[30] It was also discovered that three quarters of persons with diabetes live in low income and middle income countries (LIC, LMIC) and close to half are not detected with the disease till much later in life.[30] Children and adolescents more than 1 million have type 1 diabetes, and 1 in 6 births are to mothers with hyperglycaemia of pregnancy.[30] Roughly 4 million demises were attributable to diabetes in 2012,[31] and 12% of worldwide health expenses is spent on diabetes care ($727 billion).[30] The World Health Organization (WHO) projects that diabetes will be the 7th leading cause of death by 2030.

Diabetes in India

In the year of 2016 there were a projected 65 million people suffering from DM in India with the age of ≥20 years, which has seen to be amplified by 2.5 million since 1990.[32] In 2016 through out the country the occurrence was maximal in the states of Tamil Nadu, Kerala and Delhi, and lowest in the states of Rajasthan, Bihar, Himachal Pradesh and North Eastern States. The general age-standardized prevalence of DM is 7.9% (95% confidence interval 7.1–8.6%).[32] The overall predominance of diabetes is greater in males than females, and the occurrence increases with age in men and in women, with a greater increase in men over time. The driver for escalation in diabetes is increasing overweight, which has increased from 9% to 20.4% between 1990 and 2016. For every 100 overweight Indians aged 20 years or above, 38 have diabetes, which is larger than the global average of 19.[32]

In India almost half of all people suffering with DM (47%) are not identified, as in many other nations,[33] and are not attaining any form of treatment. As in other nations, in India the majority of DM patients have type 2 DM, and in 2017 there were projected to be 128,500 young people (< 20 years) with Type 1 diabetes.[30]

Impact of diabetes in India and the response needed: A study conducted in India estimated that between the year 2001 and 2003, 2.1% of all demises (136,000) were among persons aged 15–69 years were attributable to kidney failure, and rising to 2.9% by 2010-13. Diabetes was the maximal contributor of death from renal failure, with a higher odds in the second time period than the first. 15 people born in the 1970s had a larger risk unlike those born in the 1950s, suggestive of that it is becoming an important progressive cause of untimely death in India.[34]

Economic impact of diabetes in India: A World Economic Forum report on the monetary implications of non-communicable diseases (NCDs) estimated that India stands to lose $4.58 trillion before 2030 due to NCDs and mental health conditions with diabetes alone being responsible for US$0.15 trillion.[36] Health care spending for people with DM is 2–3 times greater than people without. The average cost per person is projected to be INR 3,000–10,000 per annum. The high cost of treatment leads to a greater incidence of non-compliance, particularly among the lower socio-economic groups. Diabetes and its complications also imposes an economic burden in terms of lost productivity and opportunity costs which impact on the individual, families and society .[34]

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 The frequency of type II DM shifts broadly amid different racial and ethnic gatherings. Type II DM is getting for all intents and purposes pandemic in certain gatherings of Native Americans and Hispanic individuals. The blacks, Native Americans and Hispanics are at the higher level of danger of retinopathy and nephropathy.[43]

Sex in older women than men Type II DM is marginally more common. [43]

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.[43]

Pathophysiology

Hyperglycemia is a consequence of absence of intrinsic insulin which is either complete as in type 1 DM, or partial as in type II DM. Partial insulin insufficiency as a rule happens due to decreased activities of insulin in structures such as muscle, body fat and the liver and a lacking reaction by the beta cell present in the pancreas. Insulin resistance which has been ascribed to raised degrees of free unsaturated fats in plasma prompts diminished glucose transference in muscle, raised hepatic glucose creation, with expanded breakdown of fat. Additionally, type 2 DM occur when a lifestyle which is conducive for DM (unwarranted caloric intake, insufficient caloric expenditure, obesity) is overlaid upon a vulnerable genotype. The body mass index at which surplus weight rises risk for diabetes varies with different races. In an example compared with people of European ancestry individuals of Asian ancestry are at bigger risk for diabetes at lower levels of overweight.[44] The pathophysiology of irregular glucose breakdown in type II DM is represented in the picture below.

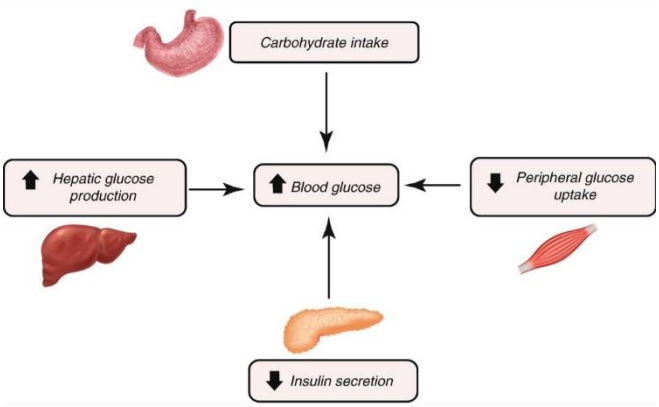


Figure 1: Pathophysiology in type II DM

Microvascular and metabolic complications is determined by the amount of hyperglycemia. However, it is much less related when it comes to macrovascular disease.

Diagnosis[22]

Glucose tolerance is categorized into three extensive categories:

- Normal glucose homeostasis
- Impaired glucose homeostasis
- DM

Glucose tolerance can be calculated using the fasting plasma glucose (FPG), the response to oral glucose challenge, or the hemoglobin A1c (HbA1c).

FPG <5.6 mmol/L(100 mg/dL), a plasma glucose < 7.9 mmol/L (140 mg/dL) following an oral glucose challenge, and an HbA1c <5.7% are reflected to define normal glucose tolerance.

Criteria for the Diagnosis of DM. [22]

- Symptoms of diabetes plus random blood glucose concentration ≥ 11.1 mmol/L (200 mg/dL)[a] or
- Fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dL)[b] or
- Two-hour plasma glucose ≥ 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test[c]

a Random blood sugars (RBS) taken without regard to time since the last meal.

b Fasting blood sugars(FBS) is taken as no caloric intake for the last 6 hours.

c The test is be done after a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water; not recommended for routine clinical use.

Risk factors associated with Type II DM. [22]

- Familial history of diabetes (Parents or sibling with type 2 diabetes)
- 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.

COMPLICATIONS [22]

Diabetes-related complications distress many organs in the human systems and are accountable for majority of morbidity and mortality linked with the disease. For countless years in the United States, diabetes has been the foremost cause of new blindness in adults, kidney failure, and non-traumatic lower limb amputation. Since recent years, diabetes has also materialized as a foremost contributor to coronary heart disease (CHD). The complications linked with the diabetes related to hyperglycemia usually do not start until the second decade of the disease.

Diabetes-Related Complications [22]

Microvascular

- **Eye disease**

Retinopathy (nonproliferative/proliferative)

Macular edema

- **Neuropathy**

Sensory and motor (mono- and polyneuropathy)

Autonomic Nephropathy (albuminuria and declining renal function)

Macrovascular

- Coronary heart disease
- Peripheral arterial disease
- Cerebrovascular disease

Others

- Gastrointestinal (gastroparesis, diarrhea)
- Genitourinary (uropathy/sexual dysfunction)
- Dermatologic Infectious
- Cataracts
- Glaucoma
- Cheiroarthropathy
- Periodontal disease
- Hearing loss

Ophthalmic Complications of Diabetes Mellitus [45]

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

6) Accelerated senile cataract

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.[46] It is an example of microvascular complications and is thought to be a crucial indicator of the impact diabetes has.[47] 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.[48]

Diabetic Retinopathy Epidemiology [49]

DM is a mounting worldwide epidemic that is anticipated to affect 642 million persons by the year 2040, leading to a concomitant amplified predominance of diabetic retinopathy globally. One- third of the worldwide population with diabetes mellitus is projected to have diabetic retinopathy; of that group, one- third is expected to have vision threatening diabetic

retinopathy. An important discovery of the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) was the direct connotation of an increased occurrence in diabetic retinopathy with longer duration of diabetes mellitus in patients with both type I and type II diabetes. In the WESDR cohort, "after 20 years of diabetes mellitus, nearly 99% of patients with type I and 60% with type II disease demonstrated some degree of diabetic retinopathy". Proliferative diabetic retinopathy was found in 50% of type 1 patients who had 20 years' duration of disease and in 25% of type 2 patients who had 25 years' duration of disease.[50] Moreover, 3.6% of younger- onset patients (aged< 30 years at diagnosis) and 1.6% of older-onset patients (aged 30 years or older at diagnosis) were found to have a visual acuity of 20/200 or worse. Such loss of vision was inferable to diabetic retinopathy in 86% of the younger- onset of diabetes patients and in 33% of the older-onset group.[51] Latest studies have advocated that rates of diabetic retinopathy evolution and vision loss are lesser in the modern era due to advances in systemic control and treatment advances.

Applied Anatomy of The Retina

The over-all area of the retina is roughly 1,100 mm^2. The healthy retina on an average is about 250-μm thick closely adjacent to the temporal margin of the optic nerve, it then thickens to nearly 400 μm in the macular area surrounding the fovea and then thins to 150 μm in the fovea.[52]

The retinal layers are shown below commencement with the outermost layer (contiguous to the choroid & sclera) and ensuing inwards in the direction of the vitreous.

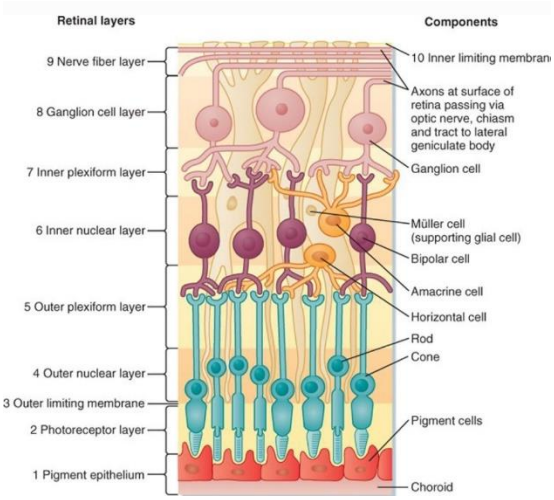


Figure 2: Layers of the retina

Vascular anatomy of the Retina: [42]

The blood vessels present in the retina nourish the innermost two thirds of the retina and the choroidal vessels supply the outer retina (Retinal pigment epithelium and outer segments and nuclei of rods and cones). The central retinal artery, the first branch of the ophthalmic artery, which is an end artery. It splits into the superior and inferior papillary arteries, which in turn bifurcates into nasal and temporal quadrantic branches. The retinal vessels normally hardly ever cross the horizontal raphe and the hemispheric division of vessels is usually maintained throughout the retina. In about 25% of eyes, an artery named as cilioretinal artery, which is derived from posterior ciliary arteries hooks around the temporal margin of the optic disc and is said to supply a portion of the macula. Arteries and veins are said to be present in the nerve fiber layer. The capillaries are arranged in laminar meshworks:

- The ganglion cell layer is the location for the superficial inner capillary plexus
- The inner nuclear layer is the location for the deep outer capillary plexus.

A capillary free zone up to 100 microns in diameter is present around each arteriole. Retinal capillaries are absent in the region of the fovea and the remote retinal periphery. The foveal

avascular zone (FAZ) is normally 400 to 500 microns in diameter. Venous drainage of the retina by and large are along the same path as the arterial supply. The retinal veins drain into central retinal vein, which also acts as the major efferent channel for veins of the optic nerve and drains into the cavernous sinus

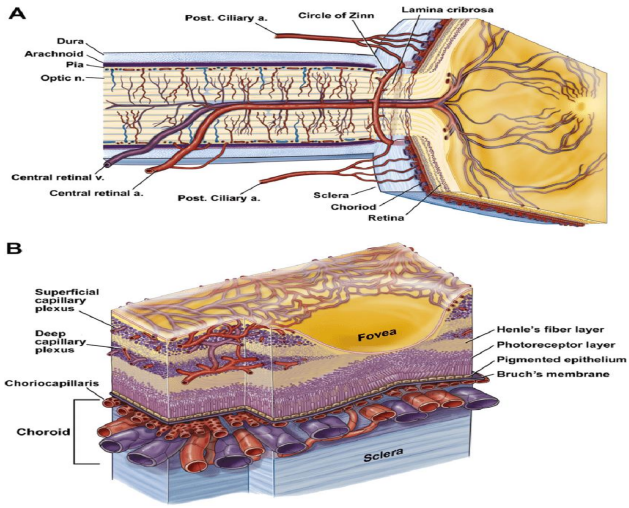


Figure 3: Vascular anatomy of retina

Structure of the retinal capillaries:[46]

Retinal capillaries are bereft of smooth muscle and elastic tissue.

Their walls comprise of:

- Endothelial cells: form a solitary layer on the basement membrane and are linked by tight junctions that form the inner blood–retinal barrier.
- The basement membrane: a highly specialized extracellular matrix rich in type IV collagen that provides structural support to the vessel wall and also serves as a reservoir of growth factors that modulate cell function and regulate tissue development.
- Pericytes: have multiple pseudopodial processes that envelop the capillaries. They have contractile properties and participate in autoregulation of microvascular

circulation. The BRB controls exchange of metabolites between vascular lumen and neural retina and maintains specialized environment in the neural retina. It has two components: the inner BRB and the outer BRB.

Pathogenesis of Diabetic Retinopathy [49]

Even though the principal cause of diabetic microvascular disease remains understood poorly, exposure to hyperglycemia over a long-drawn-out period results in biochemical pathway and molecular pathway variations, including escalations in inflammatory oxidative stress, advanced glycation end products, and protein kinase C pathways that in due course cause endothelial damage and pericyte loss. Abundant hematologic idiosyncrasies are also linked with the onset and progression of retinopathy, together with increased platelet adhesion, amplified erythrocyte aggregation, and flawed fibrinolysis. Nevertheless, the precise role of each of these abnormalities in the pathogenesis of retinopathy— individually or in combination— is not well defined. Over certain time period, retinal capillary changes such as basement membrane thickening and selective loss of pericytes lead to capillary occlusion and retinal nonperfusion. High resolution imaging of the retinal vasculature, now available through Optical Coherence Tomography angiography (OCTA) and adaptive optics scanning laser ophthalmoscopy, often discloses areas of vascular remodeling in eyes with clinically mild diabetic retinopathy. Vascular irregularities take place in both the superficial and deeper retinal capillary plexuses. These modifications deteriorate with increasing levels of diabetic retinopathy severity.[53] In addition, endothelial barrier decompensation leads to serum leakage and retinal edema. In late stages of the disease, retinal neovascularization develops in response to increases in intraocular vascular endothelial growth factor (VEGF), which is produced by ischemic retinal tissue.

The Pathophysiology of Microvascular Complications of Diabetes Mellitus

- Chronic hyperglycemia causes raised intracellular glucose concentration and the excess intracellular glucose is compelled to enter abnormal biochemical pathways including amplified anaerobic glycolysis, polyol pathway, AGE formation and amplified lipid peroxidation.
- The resulting molecular changes including increased oxidative stress and release of growth factors lead to structural & functional abnormalities of the vasculature.[7]
- Small blood vessels in the retina, the vasa nervorum and the renal glomeruli are for the most part vulnerable to damage from hyperglycemia and endure pathognomonic changes such as capillary basement thickening leading to microangiopathy.
- While retinal arteriolar changes, such as narrowing and arteriovenous nicking reflect microvascular changes associated with HTN, venular dilatation reflects retinal hypoxia and lactic acidosis due to inflammatory, atherosclerotic and other processes and possibly associated by means of similar changes in the cerebral, coronary, peripheral, and renal vessels.[54]

Even though chronic hyperglycemia is a noteworthy etiologic factor leading to the complications of DM, the mechanism by which it leads to such varied cellular and organ dysfunction is unidentified.[22, 46, 55] There are several theories that are not equally exclusive

1) **Polyol pathway or sorbitol-aldose reductase pathway:** [22,46]

   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.

2) **Increased anaerobic glycolysis:**

Excessive generation of lactic acid increases expression of VEGF in a concentration-dependent way.[56-58] It also decreases the pH of the cell's microenvironment and weakens the activity of L-glutamate/L-aspartate transporter (GLAST) causing glutamate excitotoxicity.[58, 59] Glutamate excitotoxicity has been projected as a mechanism of neural apoptosis.

3) **Formation of advanced glycosylation end products (AGEs):** [22]

Excess unutilized glucose stimulates non-enzymatic glycosylation of proteins and lipids resulting in the formation of AGEs which bind to cell surface receptors causing a range of pathological effects including: endothelial dysfunction and increased endothelial permeability to macromolecules; glomerular dysfunction; altered extracellular matrix composition which might also damage the nerve fibers; crosslinking of proteins including collagen causing vascular stiffening and entrapment of LDL in the vessel walls causing accelerated atherosclerosis.

4) **Activation of protein kinase C (PKC):** [22]

Hyperglycemia increases the formation of diacylglycerol, leading to PKC activation. PKC activation leads to the release of vascular endothelial growth factor and also alters the transcription of genes for fibronectin, type IV collagen, contractile proteins, and extracellular matrix proteins in endothelial cells and neurons leading to increased vascular disease.

5) **Production of growth factors and neovascularization:**

Growth factors has an titural role in some microvascular complications, and their production is increased by most of these proposed pathways. Hypoxia stimulates the initial angiogenic response in the adventitial vasa vasorum.[60] Neovascularization develops by growth from the adventitial layer (outward) and arterial lumen (inward) toward the intima.[61]

VEGF is a multifunctional cytokine that promotes neovascularization, increases vascular permeability to macromolecules, causes monocyte chemotaxis, and tissue factor production.[62] In the eye, a neurotropic factor-pigment epithelium-derived factor (PEDF) may offset VEGF action by its potent angiogenic inhibition.[63] In proliferative DR PEDF level is decreased and VEGF- A is increased locally. Other growth factors such as tissue growth factor-beta (TGF-β), connective tissue growth factor (CTGF), insulin-like growth factor 1, basic fibroblast growth factor, and hepatocyte growth factor may also foster proliferative retinopathy.[64]

Tesfaye et al. demonstrated that proliferation of new leaky neural vessels in diabetic patients led to arteriovenous shunting among epineural vessels causing vascular endoneurial hypoxia.[65] However, contrary to this, rodent VEGF gene transfer experiment showed that VEGF restored microcirculation in the vasa nervorum and limited diabetic neuropathy.[66]

6) **Oxidative stress and mitochondrial dysfunction:** Hyperglycemia promotes the formation of ROS, which interact with DNA and proteins causing cellular damage and epigenetic changes that influence gene expression. This could be a form of pathologic―memory‖ in the microvasculature persisting even after glucose

normalization.[46] Oral administration of antioxidants has shown to inhibit the diabetes-induced degeneration of retinal capillaries in animal studies.[67]

7) **Inflammation:** Hyperglycemia induces low-grade inflammation by causing macrophage and complement activation. This results in endothelial damage and thickening of choriocapillaries and Bruch's membrane due to deposition of extra-cellular matrix. The dramatic effect of corticosteroids on DME is evidence that inflammatory processes play a titular role in DR pathogenesis.[68]

8) **Abnormalities of platelet function and alterations in blood viscosity:** induced by hyperglycemia may cause focal capillary occlusion and focal areas of ischaemia.[46]

9) **Effects of Chronic Hyperglycemia on the Retina:**

The retina is highly prone to damage from oxidative stress because of its high lipid content, tremendous oxygen supply and the existence of chromophores in the photoreceptors.[69] Hyperglycemia induced biochemical changes cause accelerated death of retinal neural cells and vascular cells (capillary pericytes & endothelial cells), basement membrane thickening and capillary drop out.[70,71]

TABLE 1: Recommended eye examination schedule for patients with DM [49]

Diabetes types	Recommended time of first eye examination	Routine minimum follow-up interval
Type 1	5 year after diagnosis	Annually
Type 2	Upon diagnosis	Annually
Type 1 or type 2 and pregnancy	Soon after conception and early in first trimester	No retinopathy to mild/moderate Non proliferative diabetic retinopathy(NPDR): every 3-12 months Severe NPDR or worse : every 1-3 months

Table 2: ETDRS CLASSIFICATION OF DIABETIC RETINOPATHY[49]

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. [68-70]

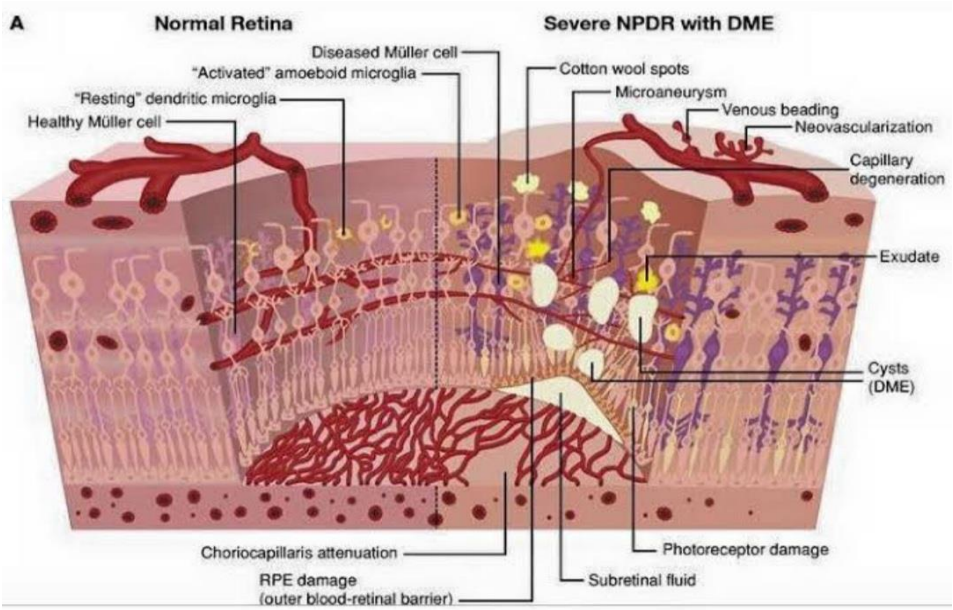


Figure 4 :Pathological changes in DM

Diabetic macular edema(DME)

Diabetic maculopathy (foveal, exudative or ischemic) is one of predominant reason of decreased visualization in a diabetic. Diffuse edema is caused by capillary leakage and focal edema is caused by microaneurysms fluid being present between the outer plexiform layer and the inner nuclear layers.

Clinically significant macular oedema detected on clinical examination as defined by ETDRS:

1. Retinal thickening within 500μm of the center of the macula.

2. Exudates within 500μm of the center of the macula, if associated with retinal thickening .

3. Retinal thickening one optic disc area(1500 μm) or larger any part of which is within one disc diameter of the center of the macula.

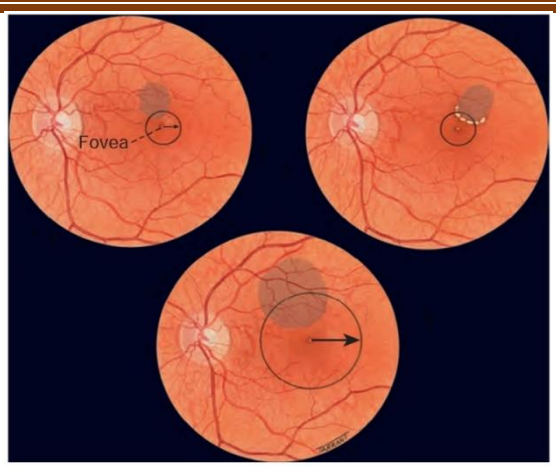


Figure 5: Clinically significant macular edema

Ophthalmoscopic features of NPDR:[46]

Microaneurysms: are the first ophthalmoscopically detectable changes in DR. These exist as localized (mainly saccular) outpouchings of the capillary wall occurring due to focal dilations of the capillary wall or endothothelial cell proliferation at sites of retinal capillary pericyte loss. They may thrombose or become leaky due to break down of the inner BRB.

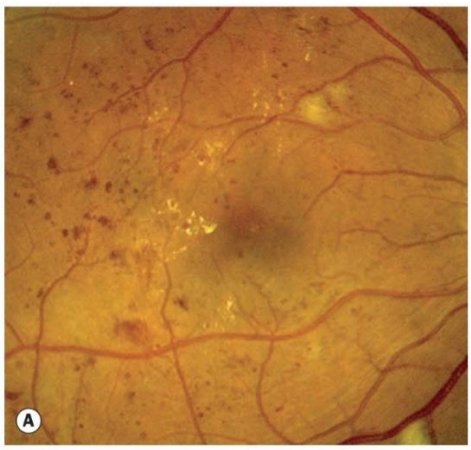


Figure 6: Microaneursym

Intraretinal haemorrhages: Rupture of weakened capillary walls or microaneurysms causes intraretinal haemorrhages- predominantly deep dot and blot haemorrhages (from venous ends of capillaries in the inner nuclear and outer plexiform layers) and sometimes, superficial flame-shaped haemorrhages from (precapillary arterioles in the nerve fibre layer).

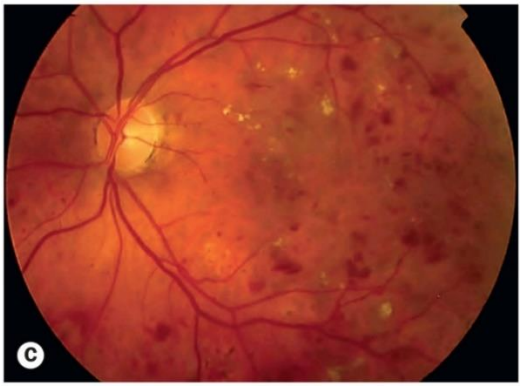


Figure 7: Dot and blot hemorrhages

Hard exudates made of lipoprotein and lipid filled macrophages are perceived as waxy yellow lesions with relatively distinct margins that may be arranged in clumps and/or rings around a group of leaking microaneurysms (circinate retinopathy). They occur due to chronic localized edema and develop at the junction of normal and edematous retina within the inner and outer plexiform layers.

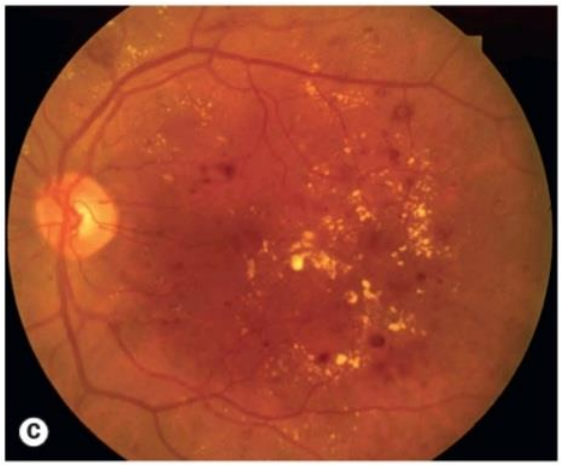


Figure 8: Hard exudates

Cotton wool spots/ soft exudates/ nerve fiber infarcts occur as a consequence of local ischaemia causing obstruction of axoplasmic flow; consequent swelling of the nerve fibers gives cotton wool spots their distinctive white fluffy appearance. They are not related with an increased risk of progression to PDR.

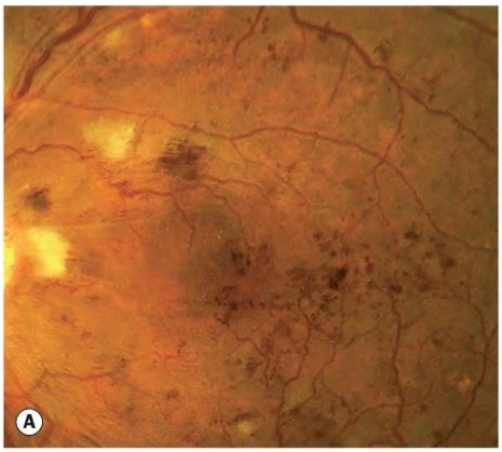


Figure 9: Cotton wool spots

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.

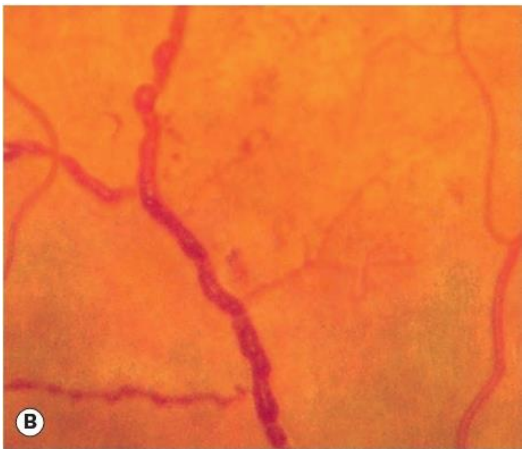


Figure 10: Venous beading

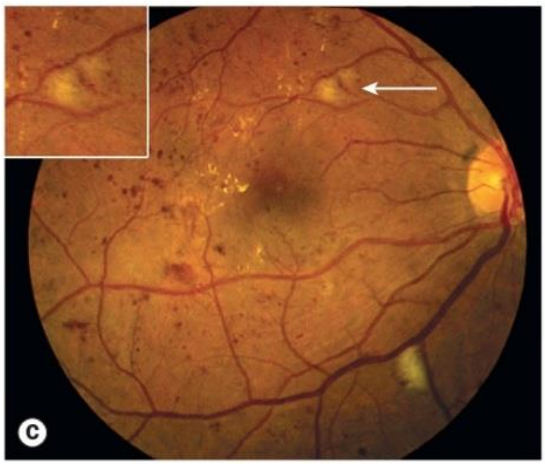


Figure 11: IRMA

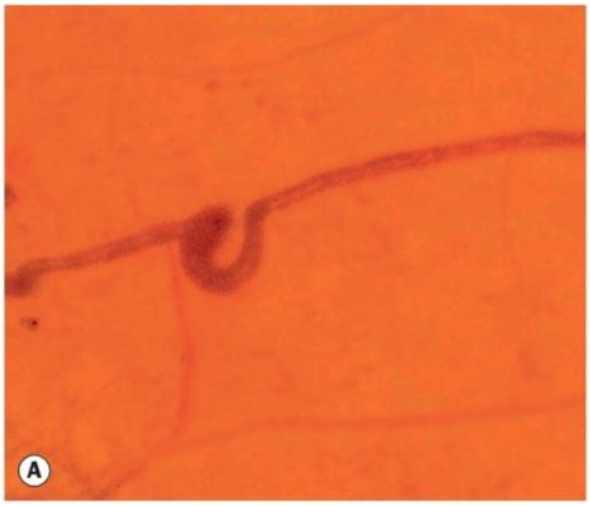
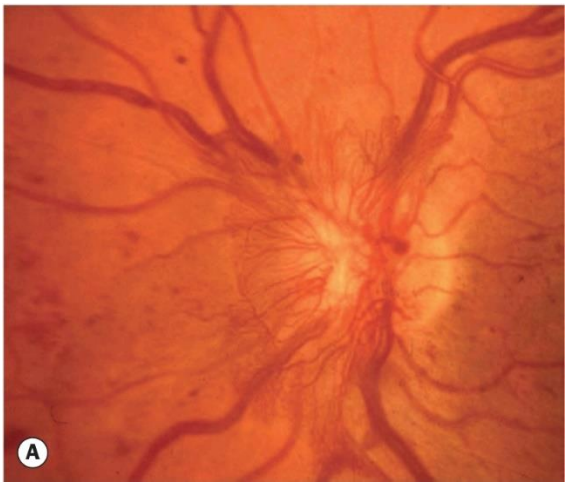


Figure 12: Venous looping

Proliferative diabetic retinopathy:

- Severe retinal ischemia from capillary closure triggers the release of vascular growth factors and the development of retinal neovascularization. It has been estimated that more than one quarter of the retina must be non-perfused before PDR develops.[45]
- Proliferative vessels usually arise from retinal veins as a collection of multiple fine vessels that leak fluorescein into the vitreous.[46]
- As PDR progresses, these new vessels grow along the route of least resistance into zones of retinal ischemia and undergo (vascular or avascular) fibrous proliferation. Once posterior vitreous detachment occurs they get lifted into the vitreous cavity, adhere to the vitreous and are pulled in by the contracting vitreous.[46]
- The fibrovascular proliferations may transmit vitreous traction to the retina leading to traction retinal detachment.
- Sudden vitreous contractions may tear the fragile new vessels causing vitreous haemorrhage and may also cause retinal tears and rhegmatogenous or traction retinal detachment.[46]

- Diffusion of the angiogenic growth factors into the aqueous followed by neovascularization of the iris and anterior chamber angle structures causes neovascular glaucoma



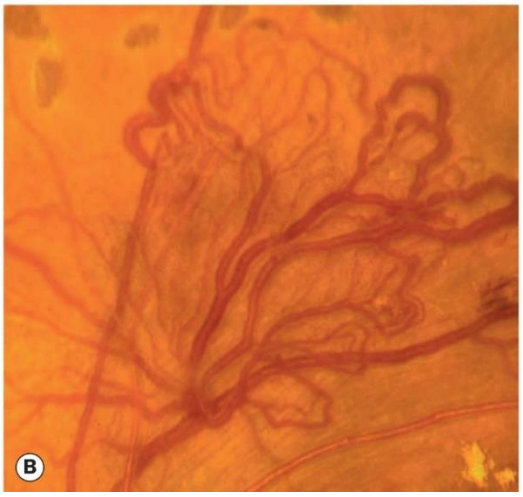


Figure 13: Neovascularization of disc **Figure 14: Neovascularization elsewhere**

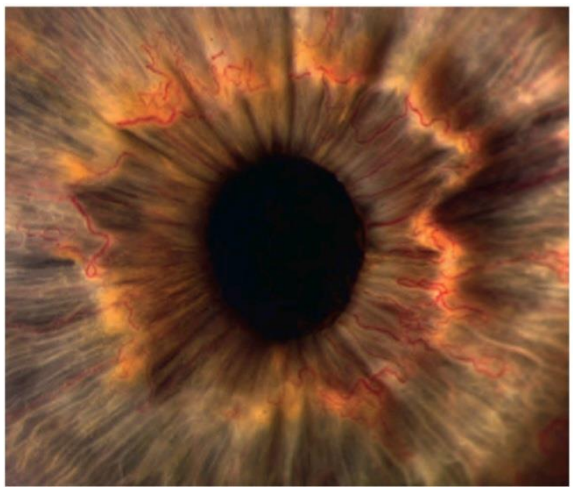


Figure 15: Rubeosis iridis

DME classification based on OCT(Optical Coherence Tomography)findings:[75]

a) Sponge like Thickening

• Most common presentation

• Mostly in outer retinal layers while internal layers maintain their normal reflectivity

• Cross-sectional scans show swelling of the retina giving it a spongy appearance with increased retinal thickness

• Backscattering seen from intra-retinal fluid accumulation

b) Cystoid Spaces

• Second most common pattern

• Intra-retinal cystoid spaces

• Involves variable depth of retina and has intervening septa in between

• Progresses gradually to involve the whole of retinal thickness

c) **Serous Detachment**

• Seen as a hypo-reflective area between neurosensory retina and RPE

d) **Taut Posterior Hyaloid Membrane**

• Taut, thickened, shiny, glistening hyper-reflective membrane with striations on retina over the posterior pole with attachment to the disc and the top of the elevated macular surface

• Retinal thickness is greatly increased with intra-retinal hypo-reflective cyst like cavities (corresponding to fluid accumulation)

• May also present as macular edema with foveal detachment

DIABETIC NEUROPATHY

Diabetic neuropathy, which ensues in ~50% of persons with long standing type I and type II DM, manifests as a diffuse neuropathy. Similar to other complications of DM, the development of neuropathy draw a parallel with the period of diabetes and glycemic control. Supplementary risk factors are body mass index (BMI) (the bigger the BMI, the bigger the

risk of neuropathy) and smoking. The presence of Cardiovascular disease (CVD), elevated triglycerides, and hypertension is also related with diabetic peripheral neuropathy. Both myelinated and unmyelinated nerve fibers are lost. Because the features of diabetic neuropathy are similar to neuropathies of other other causes , the diagnosis of diabetic neuropathy should be made only after other likely etiologies are exclude [22]

Effects Of Chronic Hyperglycemia On The Peripheral Nerves

Persistent hyperglycemia causes microvascular insufficiency, oxidative stress, glutamate excitotoxicity, nitrosative stress, autoimmune-mediated nerve destruction and impaired neurotrophism, axonal transport and gene expression resulting in diabetic neuropathy.

Diabetic neuropathy Classification of diabetic neuropathies:[79]

A. Diffuse neuropathy:

1) Chronic sensorimotor distal symmetric polyneuropathy (typical DPN) : (Most common form; accounts for ~ 75% of the diabetic neuropathies) [(80, 76)]

- Primarily small-fiber neuropathy
- Primarily large-fiber neuropathy
- Mixed small- and large-fiber neuropathy (most common)

2) Autonomic neuropathy:

- Abnormal pupillary function
- Cardiovascular: resting tachycardia, orthostatic hypotension, malignant arrhythmia
- Gastrointestinal: gastropathy/ diarrhea / constipation
- Urogenital: diabetic cystopathy (neurogenic bladder), erectile dysfunction
- Sudomotor dysfunction: Distal hypohydrosis/anhidrosis, gustatory sweating

B. Mononeuropathy (mononeuritis multiplex) (atypical forms)

- Isolated cranial or peripheral nerve (e.g., CN III, IV, VI, ulnar, median, femoral)
- Mononeuritis multiplex (if confluent may resemble polyneuropathy)

C. Radiculopathy or poly radiculopathy (atypical forms) Radiculo plexus neuropathy & Thoracic radiculopathy

Definition of Diabetic peripheral neuropathy (DPN): An internationally approved upon definition of DPN for clinical practice is ―the presence of symptoms and/or signs of peripheral nerve dysfunction in individuals with diabetes after excluding other causes.[76]

DPN is a common form of diabetic neuropathy, frequently presents with distal sensory loss and pain, > 50% do not have symptoms of neuropathy. Symptoms may include a sensation of numbness, tingling, sharpness, or burning that begins in the feet and spreads proximally. Hyperesthesia, paresthesia, and dysesthesia also may occur. Pain encompasses the lower extremities, is present usually at rest, worsens at night. Both an acute (lasting < 12months) and a chronic form of painful diabetic neuropathy may occur.

The acute form is sometimes treatment-related, occurring in the context of improved glycemic control. As diabetic neuropathy progresses, the pain subsides and eventually disappears, but a sensory deficit persists and motor defects may develop.

Annual screening for DSPN should begin 5 years after diagnosis of type 1 DM and at the time of diagnosis of type 2 DM and is aimed at detecting loss of protective sensation (LOPS).[25]

DSPN are major risk factors for foot ulceration and falls due to small and large nerve fiber dysfunction.

DPN is a diagnosis of exclusion.

Other cause of neuropathy, counting chronic inflammatory demyelinating polyneuropathy (CIDP), B12 deficiency, hypothyroidism, and uremia, ensue more regularly in diabetes and should be ruled out. The pathological hallmark of DPN is progressive loss of both large and small nerve fibers. [77]

Changes in Sural nerve fiber density have been documented as the major change in DPN.[77, 78]

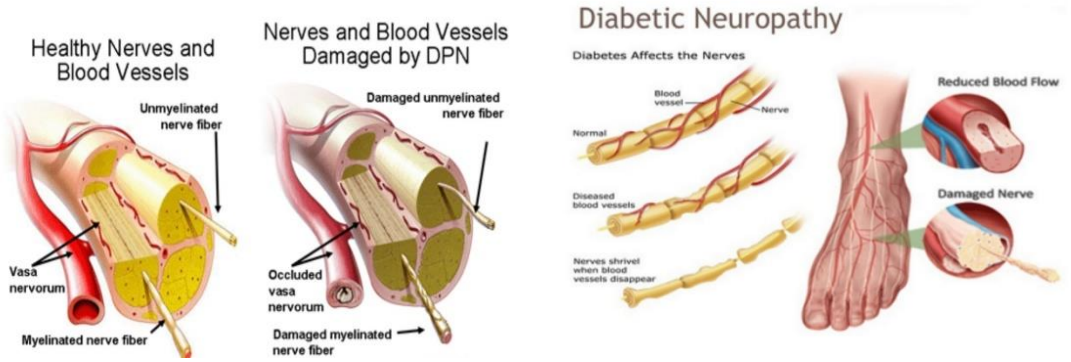


Figure 16: Pathogenesis of DPN

Table 3: Symptoms and signs of DPN: [79,81]

	Large myelinated nerve fibers	Small myelinated nerve fibers
Function	Pressure, balance	Nociception, protective sensation
Symptoms	Numbness, tingling, poor balance	Neuropathic pain
Examination	Reduced or absent: 1) Deep tendon reflexes (ankle jerk and knee jerk) 2) Vibration perception (with 128 Hz tuning fork) 3) Pressure sensation (with 10-g monofilament) & 4) Proprioception (last to be lost)	Reduced or absent: 1) Thermal discrimination & 2) Pinprick sensation

Neuropathic ache is the most common early indicator of DPN and is present in up to 25% of individuals with DPN. It is characteristically a burning, lancinating, tingling, or shooting type of pain, most commonly in the feet and characteristically worse at night.

It may be accompanied by hyperalgesia and allodynia .

- Up to 50% of the patients may be asymptomatic so, lack of symptoms should not be presumed to point to an absence of signs.
- The feet must be inspected for ulcers, calluses, and deformities, and footwear should be examined.
- Small and large fiber function should be assessed. Combining at least two examinations will increase the sensitivity and specificity of detecting DPN.[82-85]
- Validation can be recognized with quantitative electrophysiology, sensory, and autonomic function testing.

Complications of DPN: Foot deformities, such as hammertoes and collapse of the mid foot may happen. Blisters and sores may appear on numb areas of the foot because of pressure or injuries going undetected. Failure to treat infections promptly may result in spread of infection to deeper tissues and the bone. It is the most important contributor to falls and fractures [85]. Late complications of DPN include foot ulceration (due to insensate injury) and Charcot neuroarthropathy [86]. These increase the risk of amputation and are also predictors of mortality.

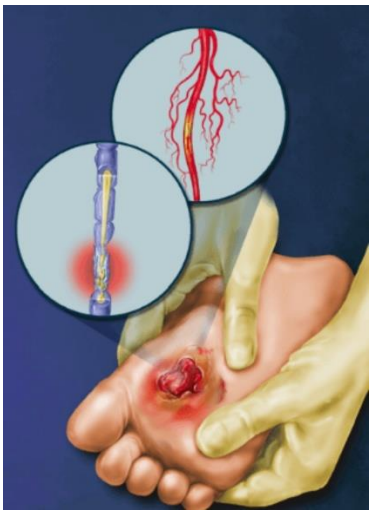


Figure 17: Diabetic foot

Clinical scoring Systems for DPN

As nerve conduction tests are expensive and time consuming, various clinical scoring systems have been developed to grade DPN severity and monitor progression or response to intervention. These include: [82-84, 83]

- Toronto clinical neuropathy score (TCNS)
- Michigan neuropathy screening instrument (MNSI)
- Neuropathy symptom score (NSS)
- Neuropathy disability score (NDS)

The Toronto Clinical neuropathy Scoring System (TCNS) consisting of symptom scores, reflex scores and sensory test scores was validated by comparison with results of sciatic nerve biopsies and closely correlated with electrophysiological studies.[78]

The socioeconomic impact of DR and DPN:

DR is the foremost cause of avoidable impaired vision in the working age residents across the world.[10]

Significant vision loss can take place at any stage of DR due to CSME and in advanced disease due to PDR with vitreous hemorrhage, retinal detachment, or neovascular glaucoma. Visual impairment in DR affects people capacity to execute day-to-day living vision-dependent activities, such as reading, domestic everyday jobs, and driving, consequential in having more risk of falls. [84] DR also has a considerable socio-emotional bearing, being linked with social seclusion and greater rates of depression. [85]

The foremost risk factor for lower extremity amputation following foot ulcers is DPN.[11] Equal to 50% may be with no symptoms and at a risk of unconscious injury. Loss of the ―perception of pain permits patients with foot ulcers to move around and walk although lesion is present, leading to chronicity, often complicated by infection and an greater than before risk of amputation and mortality.[11] Neuropathic pain is a common symptom taking place in 40–50% of the patients with DPN and can hamper with day-to-day activities and lead to disability.[86] Loss of proprioception and unsteadiness of gait in DPN is a major contributor to falls and fractures.[81] A combination of DR and DPN will dramatically increase the economic burden associated with DM both directly (cost of management of neuropathy & retinopathy) as well as indirectly by leading to disability, work absence and change in employment. With the growing occurrence of DM, occurrence of its microvascular complications is also anticipated to increase, resulting in increased morbidity, mortality and health care expenditure.[19]

TREATMENT

Deterrence of diabetic neuropathy is important through enhanced glycemic control. Treatment of DN is less than agreeable. Standard of living alterations (exercise, diet) has some effectiveness in DSPN in type 2 DM and increased blood pressure and

hypertriglyceridemia should be treated. Hard work put to improve glycemic control in long-standing diabetes may be addled by unawareness of hypoglycemia. Averting of neurotoxins (alcohol) and smoking, supplementation in possible deficiencies with vitamins (B12, folate;). Patients should be educated that loss of sensation in the lower extremities surges the threat for ulceration and its sequelae and that deterrence of such problems is vital. Patients with symptoms or signs of neuropathy or LOPS should check their feet daily and take precautions (footwear) aimed at preventing calluses or ulcerations. If foot deformities are present, a podiatrist should be involved. Chronic, painful diabetic neuropathy is challenging to treat with only symptomatic treatment being available; indication of the efficiency of better glycemic control in painful diabetic neuropathy is not there. Two agents, duloxetine and pregabalin, have been approved by the U.S. Food and Drug Administration (FDA) for pain related with diabetic neuropathy. Tapentadol, a centrally acting opioid, is also FDA-approved, but has only uncertain efficacy and poses risk of addiction, making it and other opioids less desirable and not a first-line therapy.[19]

Glycated haemoglobin (HbA1c)

It was said to be documented as an "unusual" haemoglobin in those with diabetes several years back[144] . After which multiple studies were carried out correlating it with glucose values concluding that it maybe used as an objective measure of glycaemic control. HbA1c was brought into use for clinical purpose in the 1980s and consequently it has become a foundation of checking for glycemic control among diabetics.[145]. It mirrors the average glycemic index over 3 months.[146] The test can be carried out during any given time of the day and does not need any requirement of fasting. Thus, due to such ease of performing the test and its reflection of an overall long period of glycemic index it has become the preferred test

to check for glycemic control among diabetics. In the recent years it has become the standard diagnostic test among diabetics to screen among those with higher risk.[147]

Due to the vast inconvenience in quantifying the FPG levels, and the everyday change in the glucose values, an alternate to measurement of glucose for diabetes has been pursued for a long time. It has now been HbA1c has now been endorsed by an International Committee and by the ADA as a tool to screen and diagnose diabetes.[147]

The link between HbA1c and retinopathy is same as that to that of plasma glucose. [148] This relation was initially reported in the Pima Indians.[149]and observed amongst several other people in various parts of the world.[150] Even though HbA1c gives equal sensitivity and specificity to the glycemic index values as a predictor of prevalent retinopathy,but the drawback is its unavailability in many of the different regions in the world.

It is uncertain whether HbA1c or blood glucose is superior for predicting the development of retinopathy, in one of the recent reports from Australia it was observed that HbA1c for predicting incidence of retinopathy is as good as or possibly better than one including fasting plasma glucose.[151]

HbA1c has an advantage that it can help in avoiding problems such as the everyday variability of glucose values, and notably it circumvents the necessity for the person to fast prior to taking the test don't have to make any previous dietary preparations. Thus, it has a benefit of having the insinuations for early identification and treatment which have been strongly be in favor of in recent years. Conversely, HbA1c may be affected by a variety of factors such as their underlying genetics, haematologic and illness-related factors.[152] Hemoglobinopathies is an important factor affecting the levels of glycated haemoglobin.[153] Levels of HbA1c just below 6.5% may indicate the presence of intermediate hyperglycaemia. While recognizing the continuum of risk that may be captured by the HbA1c assay, the

International Expert Committee recommended that persons with a HbA1c level between 6.0 and 6.5% were at particularly high risk and might be considered for diabetes prevention interventions.

Role of therapeutic drugs on microvascular complications:

Management of DR is a multidimensional and multipronged pattern which consist of systemic glycemic control, laser treatment, intravitreal injections, and surgery.

Insulin therapy: may be beneficial not only by improving glycemic control but also by improving retinal blood flow and the tone of retinal microvasculature.[87]

Oral hypoglycemic agents:

- Studies have shown metformin to have a protective effect on DPN.[88]
- Sitagliptin may have a protective effect by decreasing the retinal inflammatory state and neuronal apoptosis.[89]
- Glitazones should be used with caution in DR as it‘s use give the impression to be a cause for macular edema, and drug termination look as if to result in rapid resolution. [90]

Lipid lowering agents: In the FIELD and the ACCORD Eye Study, slight or no outcome of fenofibrate was seen in those with no retinopathy at baseline, but a strong protective effect was seen in those with concomitant mild NPDR, thwarting its progression to macular edema or PDR.[91] In the FIELD study, nonetheless, the protective effects of fenofibrate did not correlate with serum lipid levels.[92]

Anti-Hypertensive agents: In patients with DR, a local renin-angiotensin system (RAS) in the eye is found to be up-regulated resulting in increased VEGF. Angiotensin converting enzyme inhibitors like lisinopril and angiotensin receptor blockers such as candesartan may

have a protective effect on DR (independent of their anti-HTN action) by inhibiting the RAS.[93]

NSAIDs: Acetylsalicylic acid-aspirin therapy worsens diabetic nephropathy but has no effect on DR.[93]

MATERIAL & METHODS

MATERIALS AND METHODS:

SOURCE OF DATA:

A total 156 patients diagnosed with Type I and Type II diabetes mellitus will be 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: December 2019 and May 2021

INCLUSION CRITERA:

All patients diagnosed with diabetic retinopathy.

EXCLUSION CRITERIA:

1. Patients with retinopathy due to other causes like hypertensive retinopathy, HIV retinopathy, anemic retinopathy.
2. Patients with DPN due to other causes like vitamin B12 deficiency, traumatic neuropathy, HIV neuropathy . (ruled out by examining clinical features related to the disease.)
3. Ocular co-morbidities like myopia and glaucoma,corneal opacities

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

A. Demographic details, detailed ophthalmological examination, duration of diabetes, and visual acuity by Snellen's chart will be recorded, followed by assessment of diabetic status by fasting blood sugar (FBS), post prandial blood sugar(PPBS), glycated hemoglobin (Hb1Ac). (Annexure I and IV).

B. Diabetic retinopathy will be determined through fundus examination and graded clinically using the "Early Treatment of Diabetic Retinopathy Study"(ETDRS) classification for DR.

   Grade 0: No apparent retinopathy

   Grade 1: Mild non-proliferative retinopathy (NPDR) –few micro aneurysms. Grade 2: Moderate NPDR –micro aneurysms, intra-retinal hemorrhages or

   venous beading

   Grade 3: Severe NPDR – based on the 4:2:1 rule of the ETDRS, hemorrhages

   in all 4 quadrants, venous beading in two quadrants or intraretinal

   microvascular abnormalities(IRMA) in one quadrant.

   Grade 4: Very severe NPDR- Two or more of the criteria for severe NPDR

   Proliferative diabetic retinopathy (PDR) – characterized by neovascularization of the disc, retina, iris &of the angle, vitreous hemorrhage or tractional retinal detachment.

Diabetic maculopathy was classified as clinically significant macular edema (CSME) , diffuse macular edema , Focal macular edema and ischemic maculopathy.

Neurological examination will be done Based on **Toronto clinical Neurological scoring system** which includes extent of paresthesia, tingling or numbness, presence of burning, vibration , light touch, temperature and relevant examination.

Examinaion was conducted and the person was graded accordingly as

0-5 POINTS: NO NEUROPATHY

6-8 POINTS : MILD NEUROPATHY

9-11 POINTS:MODERATE NEUROPATHY

12+POINTS: SEVERE NEUROPATHY.

HbA1c was measured by High Performance Liquid Chromatography (HPLC) technique from the Department of Pathology. The American Cardiology Association referred values for HbA1c were categorised into four groups.

0- Less than 6.

1- 6.1 - 7 (well controlled).

2- 7.1 - 8 (fair control).

3- More than 8 (poor control).

SAMPLE SIZE ESTIMATION

Sample size calculated based on prevalance of diabetic retinopathy is 27.% according to the study [7]

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

Where

d = absolute error = 7%

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

P = 27%

Q = 100-P

By utilising the above formula sample size came to be around 155 at 7 % of absolute error.

STATISTICAL METHODS USED FOR THIS STUDY

Data will be entered into excel sheet 13 and analyzed using SPSS 22 version. Chi-square test (Fischer's Exact test) will be used as the test of significance to test the p value <0.05 will be considered as statistically significant

RESULTS

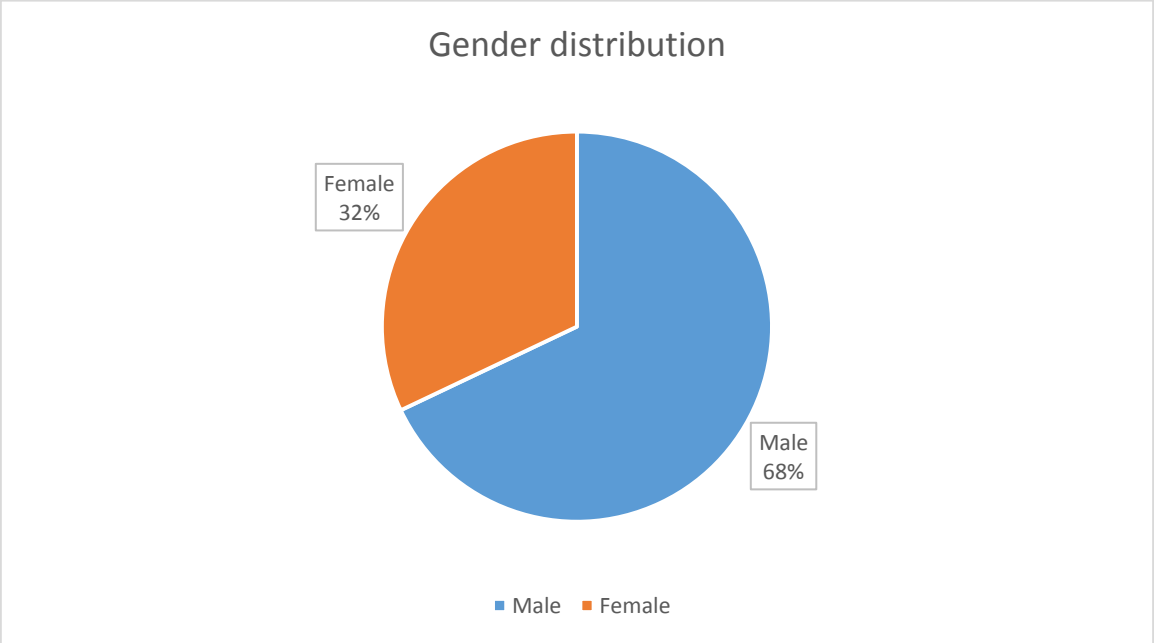
RESULTS

This study was done to compare severity of diabetic retinopathy (DR) with occurrence of Diabetic peripheral neuropathy (DPN) in Diabetic patients. A total of 156 patients who attended The OPD at the setting and having fulfilled the earlier stated inclusion criteria were enrolled in this study. Study considered the severity of both eyes separately for better statistical analysis.

Study had 106 (67.9%) male and 50 (32.1%) female.

Table 4: Gender wise distribution of patients with DR

Gender	Number	Percentage
Male	106	67.9
Female	50	32.1
Total	156	100.0

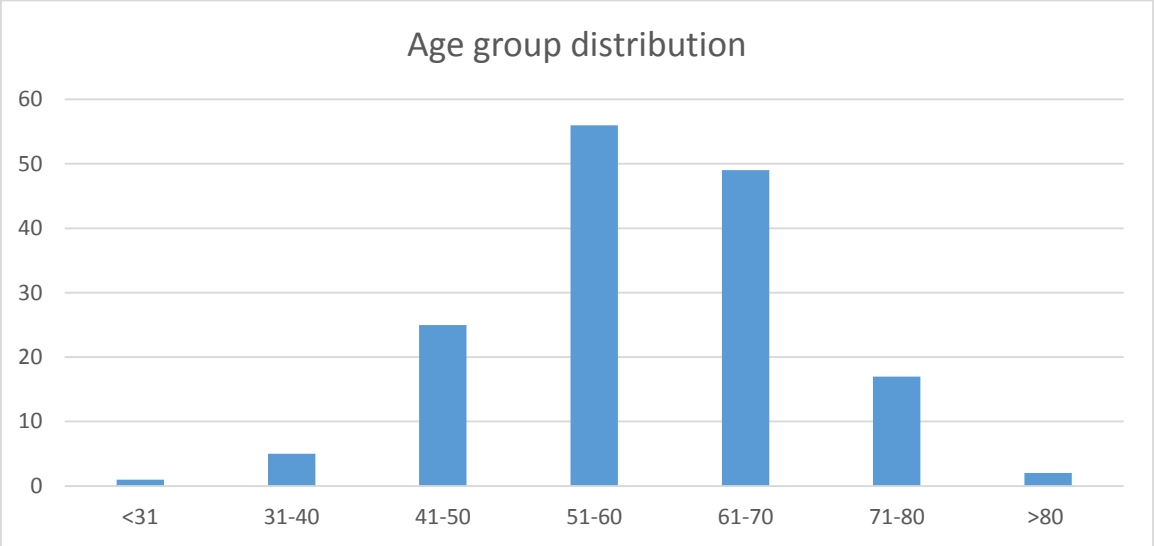


GRAPH 1: Gender wise distribution of patients with DR

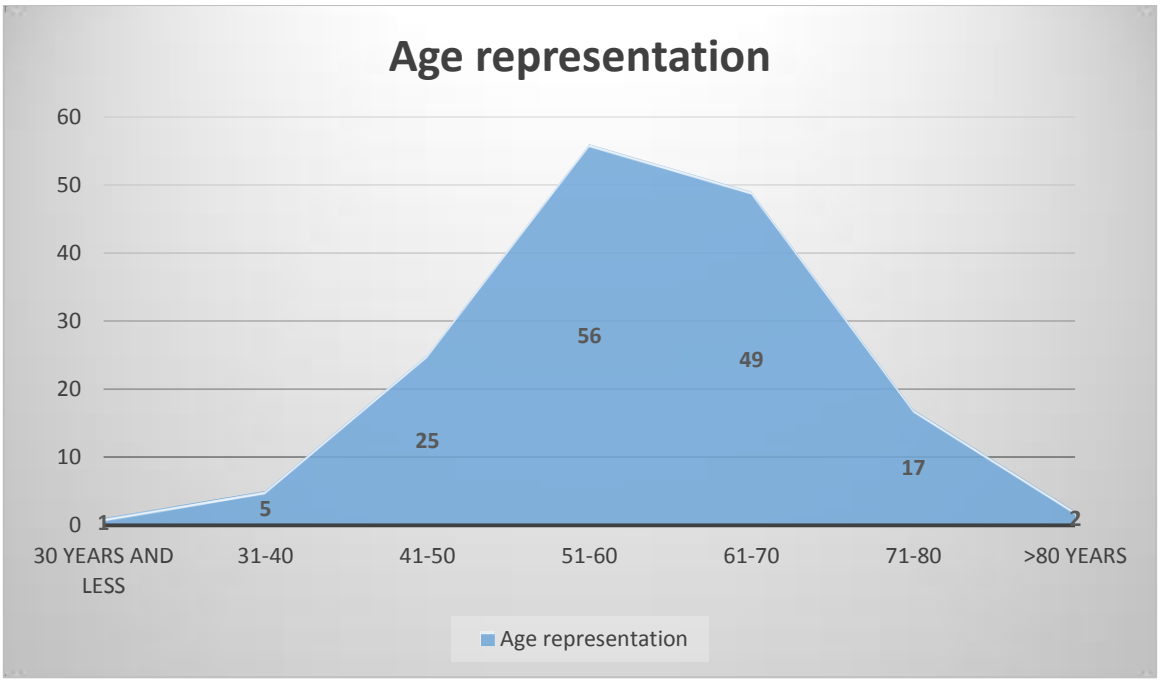
Study group had a mean age group of 58.85 years (SD 10.1 years) with most of the population falling into 5th (36%) and 6th (32%) decade in both male and female categories with maximum of 82 years and youngest included patient into the study with diabetic retinopathy was 22 years.

Table 5: Age group distribution

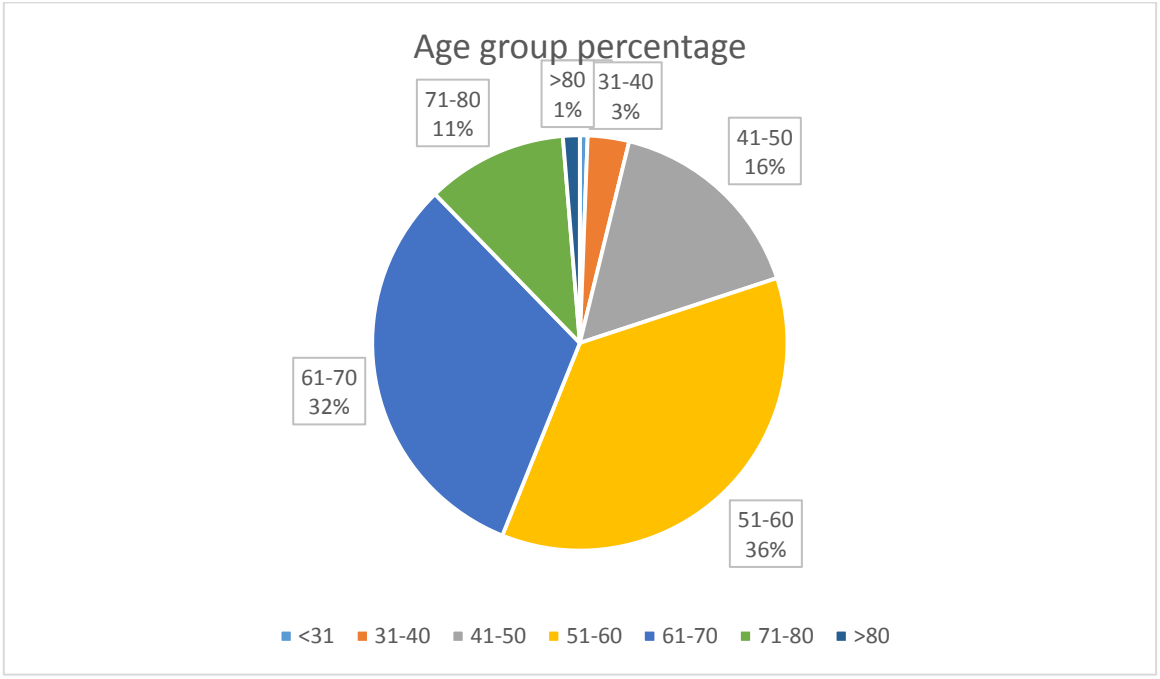
Decade of age group	Number of patients
<31	1
31-40	5
41-50	25
51-60	56
61-70	49
71-80	17
>80	2
Total	156



GRAPH 2a: Age Distribution



GRAPH 2b: Age Distribution

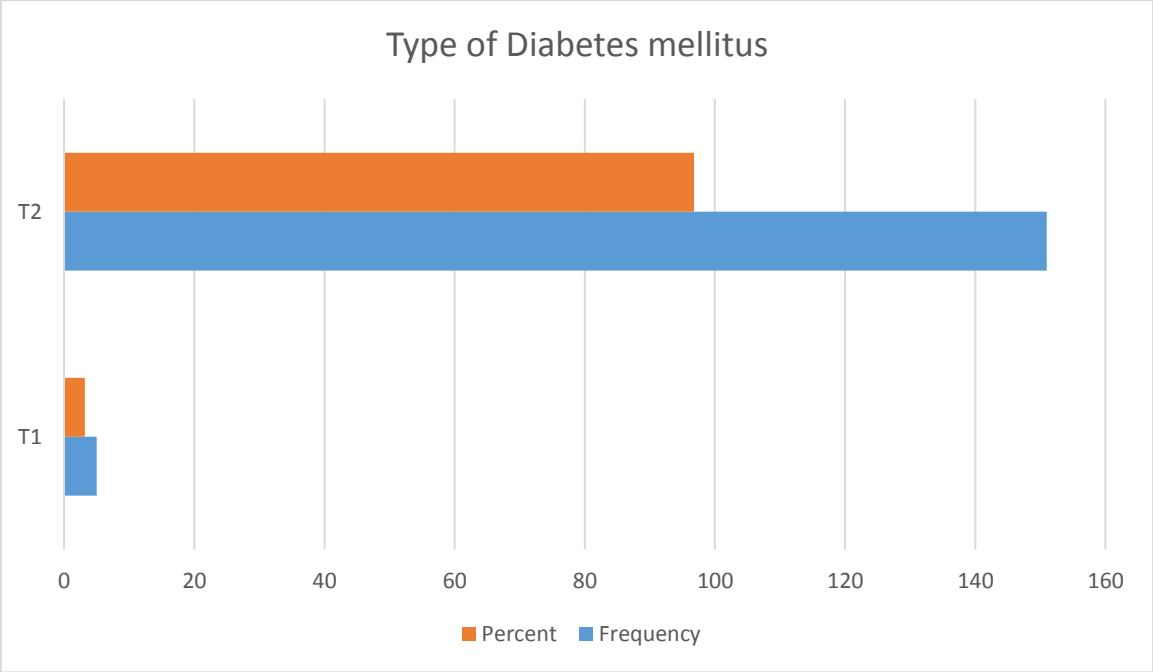


GRAPH 3 : PERCENTAGE DISTRIBUTION OF AGE

Majority of the patients 152 (96.8%) were Type 2 diabetes mellitus, and rest Type 1 (3.2%).

Table 6: Type of Diabetes mellitus

Diabetes mellitus	Number	Percentage
T1	5	3.2
T2	151	96.8

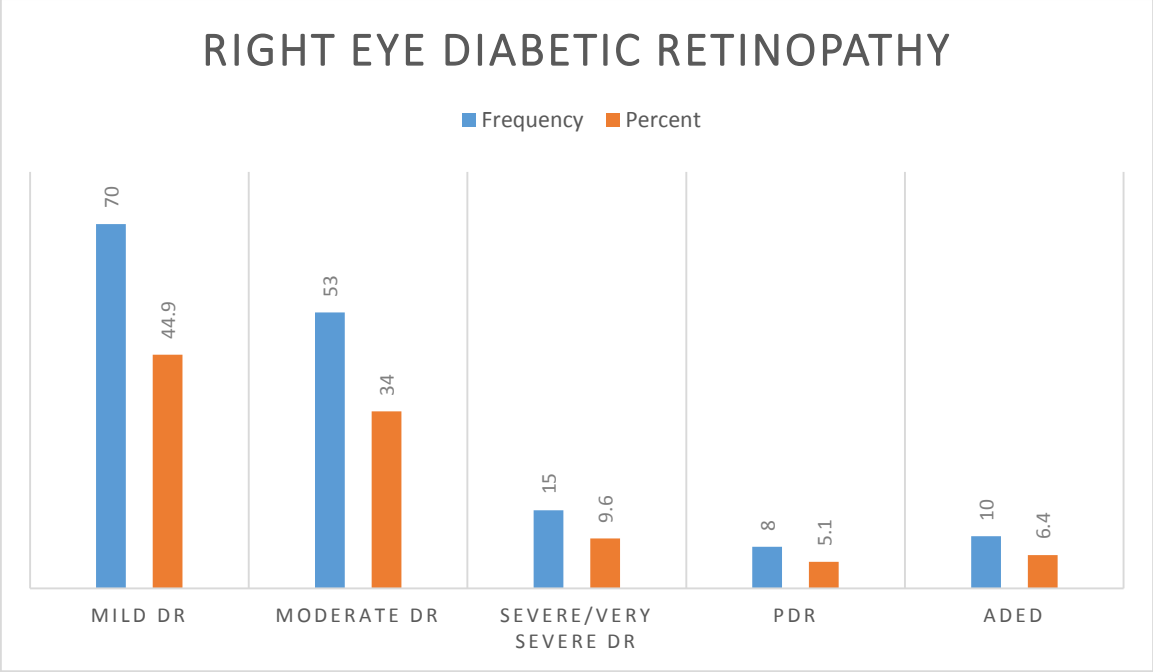


GRAPH 4: Type of Diabetes mellitus

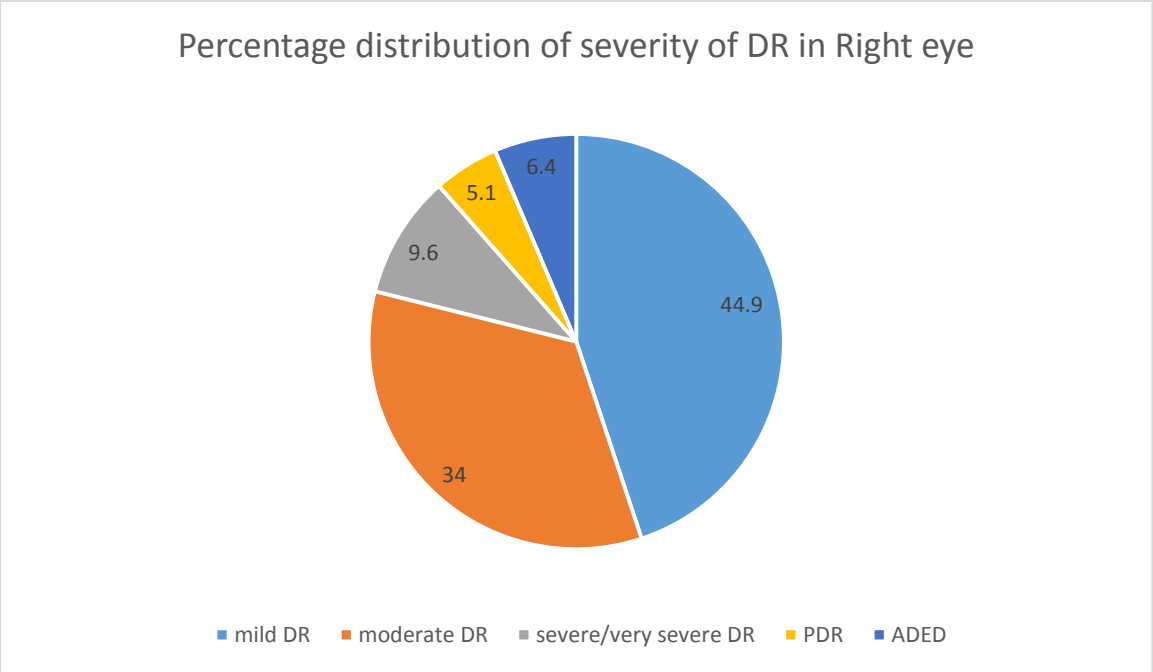
Diabetic retinopathy (DR) severity was assessed separately in both the eyes for better statistical significance in comparison to diabetes and peripheral neuropathy. As shown I graph most of the patient fall into category of mild DR right eye 70 (45%), left eye 67 (43%) followed by moderate DR right eye 53 (34%) Left eye 55 (35.3%).Severe DR corresponds to 15 (10%) in both eyes, proliferative DR in 8 (5%) of patients in right eye and slightly higher percentage of 6.4%. Advanced diabetic eye disease in right eye is seen in 10 patients and 9 amounting to 5.8% in left eye.

Table 7: Frequency of severity of DR in Right eye

Grading of DR	Frequency(n)	Percent (%)
Mild DR	70	44.9
Moderate DR	53	34.0
Severe/very severe DR	15	9.6
PDR	8	5.1
ADED	10	6.4



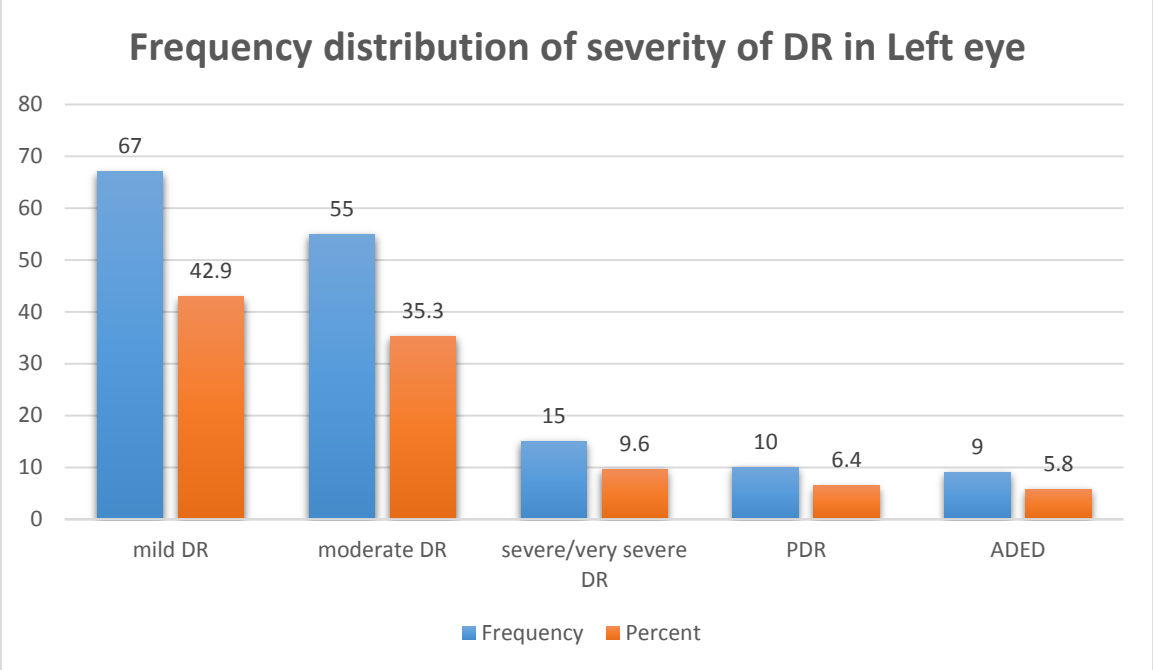
GRAPH 5a: Right eye diabetic retinopathy severity grading



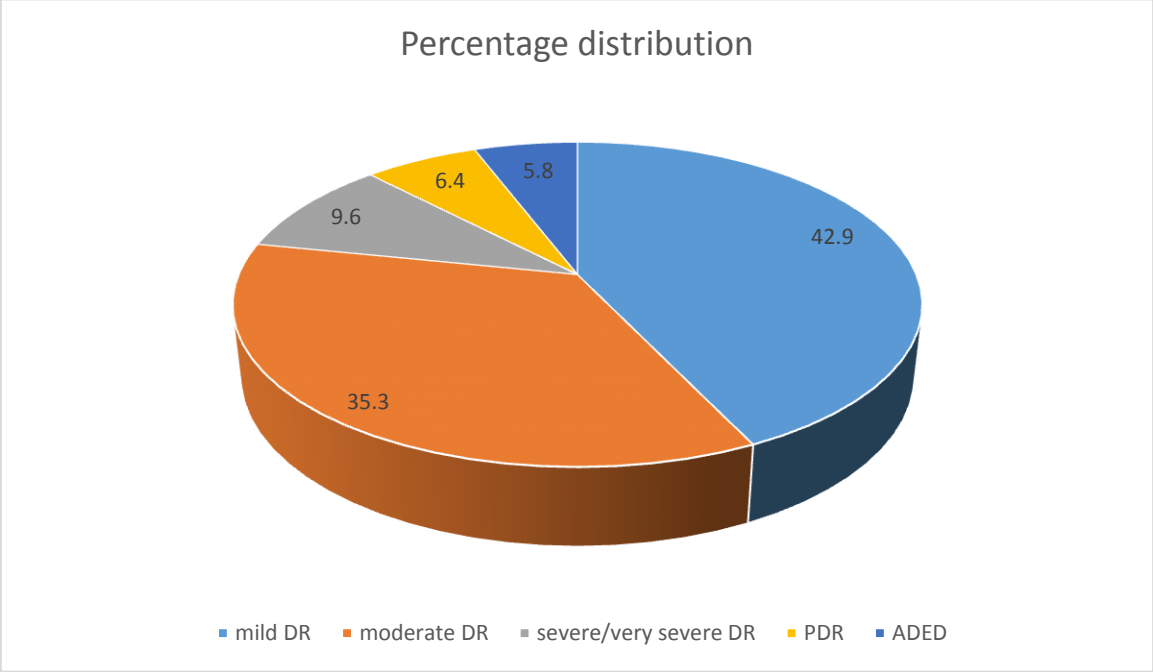
GRAPH 5b: Percentage distribution of severity of DR in Right eye

Table 8: Frequency distribution of severity of DR in Left eye

Grading of DR	Frequency	Percent
Mild DR	67	42.9
Moderate DR	55	35.3
Severe/very severe DR	15	9.6
PDR	10	6.4
ADED	9	5.8



GRAPH 6: Frequency distribution of severity of DR in Left eye



GRAPH 7: Percentage distribution of severity of DR in Left eye

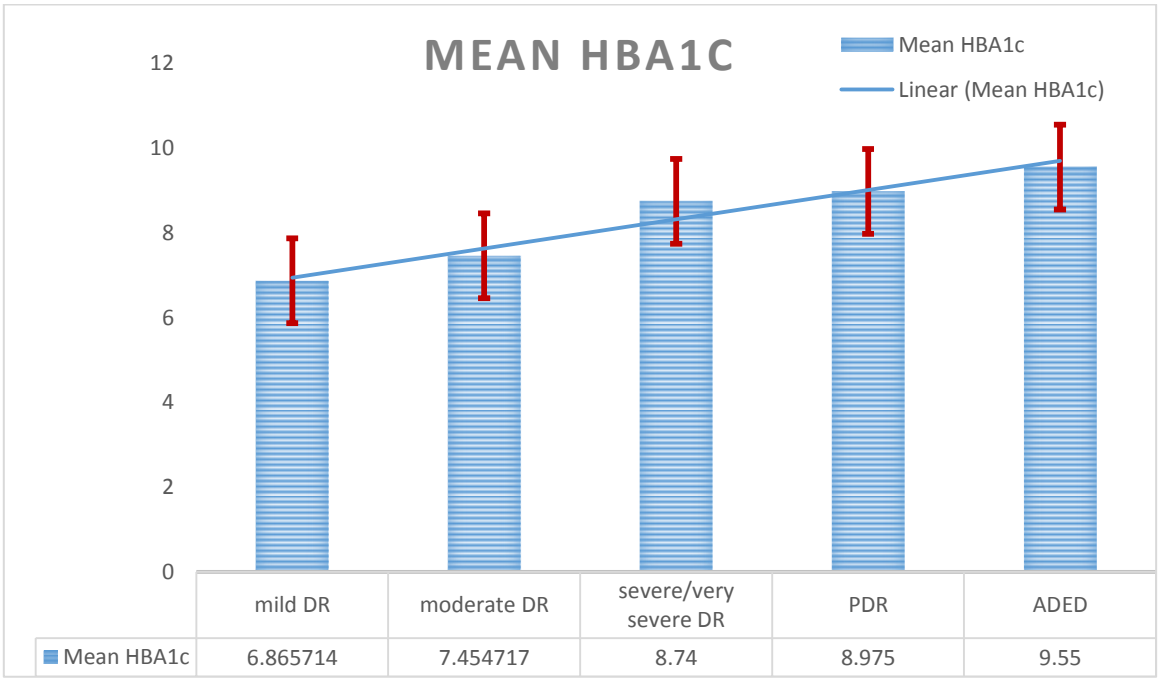
Our study noted that there is striking significance of increase in severity of retinopathy with increase in HbA1c levels and also overlap of the HbA1c levels with severity of retinopathy. The mean HbA1c in both right and left eye for mild and moderate DR was 6.8(+/-1.8) and

7.4 (+/-1.4) respectively. Even though mean Levels in ADED 9.5 (+/-1.7) is same in both eyes, in severe DR right eye shows slightly higher levels of mean HbA1c of 8.7 in comparison to 8.5 of left eye.

Table 9: Association between HBA1c values and severity of diabetic retinopathy in the right eye among patients

Right eye Severity	Mean HBA1c	Standard Deviation
Mild DR	6.865714	1.8380744
Moderate DR	7.454717	1.4493455
Severe/very severe DR	8.740000	1.9245779
PDR	8.975000	1.3530389
ADED	9.550000	1.7677670

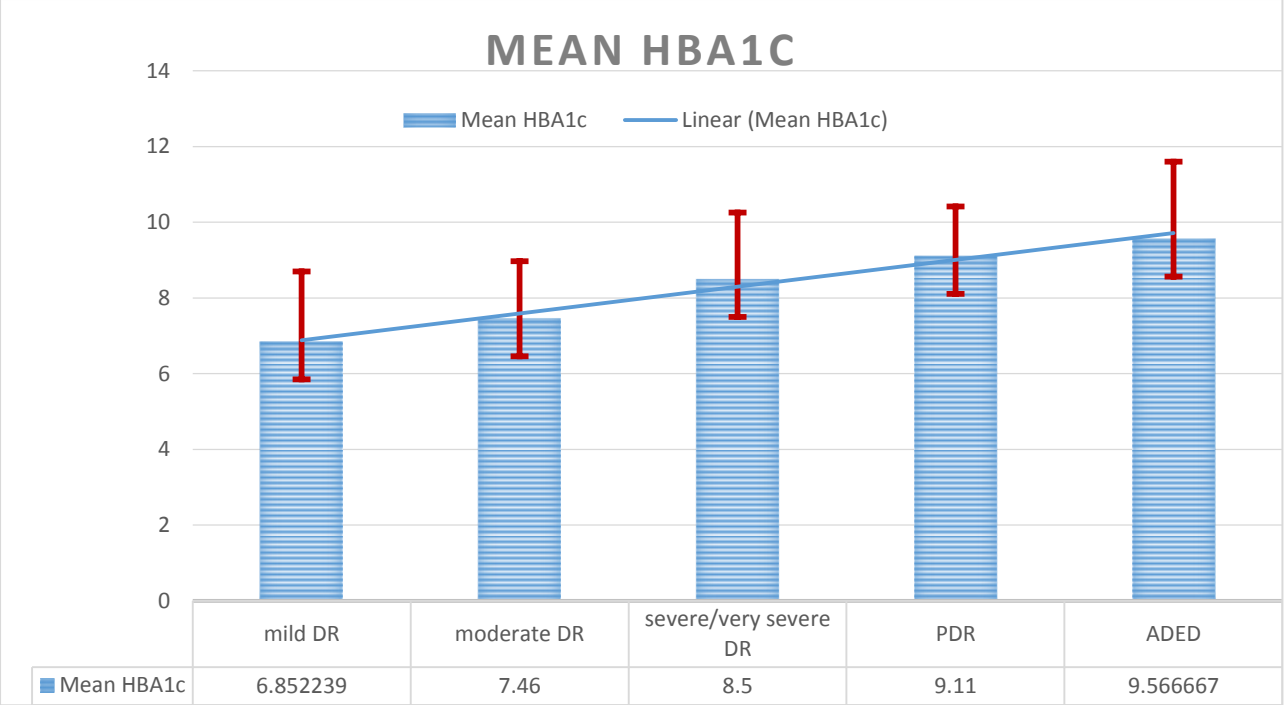
(F=9.6, p<0.001).



GRAPH 8: Association between HBA1c values and severity of diabetic retinopathy in the right eye among patients

Table 10: Left Eye Diabetic retinopathy severity and mean HBA1c Level

Left eye Severity	Mean HBA1c	Standard Deviation
Mild DR	6.852239	1.8428698
Moderate DR	7.460000	1.5093045
Severe/very severe DR	8.500000	1.7521415
PDR	9.110000	1.3033717
ADED	9.566667	2.0285463



GRAPH 9 : Association between HBA1c values and severity of diabetic retinopathy in the Left eye

On further application of independent t test and ANNOVA found that the mean HbA1c in patients with ADED was 9.5±1.8, PDR was 9±1.3, severe/ very severe DR was 8.7±1.9, moderate DR was 7.4±1.4 and mild DR was 6.9±1.8 ($F=9.6$, $p<0.001$).

FBS AND PPBS LEVEL

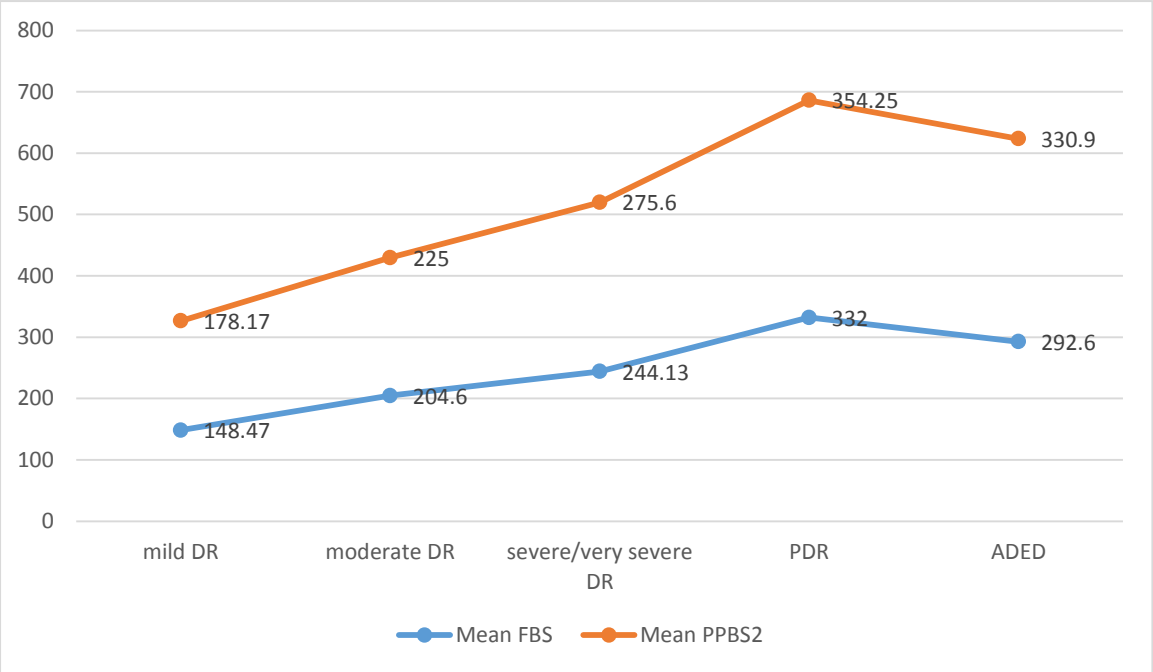
Fasting blood sugar average in retinopathy patients is found to be 178 and PPBS 222, but has increasing trend of levels with increasing severity. Mild and moderate DR 148 (+/- 45) and 203 (+/- 69), ADED patients had an average FBS of 292(+/- 68)

Similarly PPBS is noted to be 178 (+/-61) in mild DR and 275 and 332 in Severe and PDR category respectively, which also has linear upward trend with plateauing due to overlap with ADED patients.

Table 11: FBS and PPBS level in comparison to severity of DR of Right Eye

Right eye	Number of patients	Mean FBS	SD
Mild DR	70	148.47	45.502
Moderate DR	53	204.60	69.207
Severe/very severe DR	15	244.13	47.265
PDR	8	332.00	85.988
ADED	10	292.60	68.434
Total	156	195.39	78.499
Right eye	Number of patients	Mean PPBS	SD
Mild DR	70	178.17	62.565
Moderate DR	53	225.00	67.745
Severe/very severe DR	15	275.60	48.425
PDR	8	354.25	63.073
ADED	10	330.90	67.167
Total	156	222.27	82.171

With Independent sample T test FBS F value is 14.433 with p value <0.001, PPBS F value is 3.184 with p value of 0.076



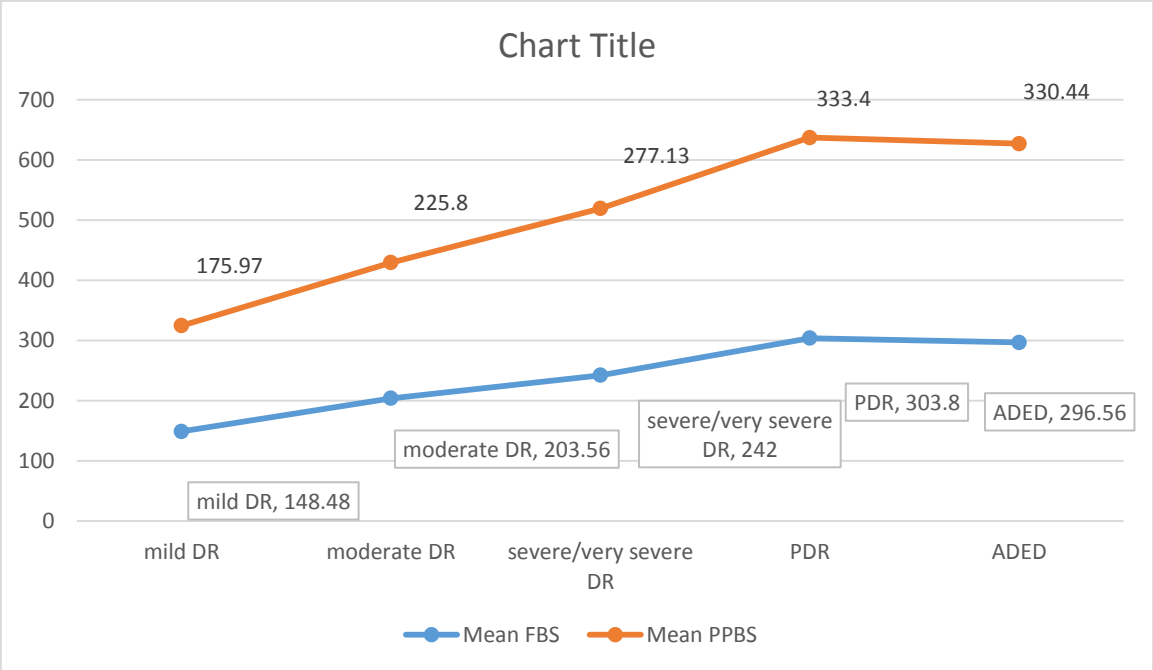
GRAPH 10: FBS and PPBS level in comparison to severity of DR of Right Eye

Table 12: FBS and PPBS level in comparison to severity of DR of Left Eye

Left eye	Number of patients	Mean FBS	SD
Mild DR	67	148.48	45.134
Moderate DR	55	203.56	69.116
Severe/very severe DR	15	242.00	57.101
PDR	10	303.80	100.407
ADED	9	296.56	64.221
Total	156	195.39	78.499

Left eye	Number of patients	Mean PPBS	SD
Mild DR	67	175.97	61.687
Moderate DR	55	225.80	69.982
Severe/very severe DR	15	277.13	51.553
PDR	10	333.40	74.911
ADED	9	330.44	55.864
Total	156	222.27	82.171

ANOVA showed FBS F value is 31.977 and p value <0.001, PPBS F value is 27.014 and p value <0.001for right eye, and for left eye FBS F value is 26.432 and p value <0.001 PPBS F value is 25.132 with p value <0.001



GRAPH 11: FBS and PPBS level in comparison to severity of DR of Left Eye

Duration of Diabetes Mellitus

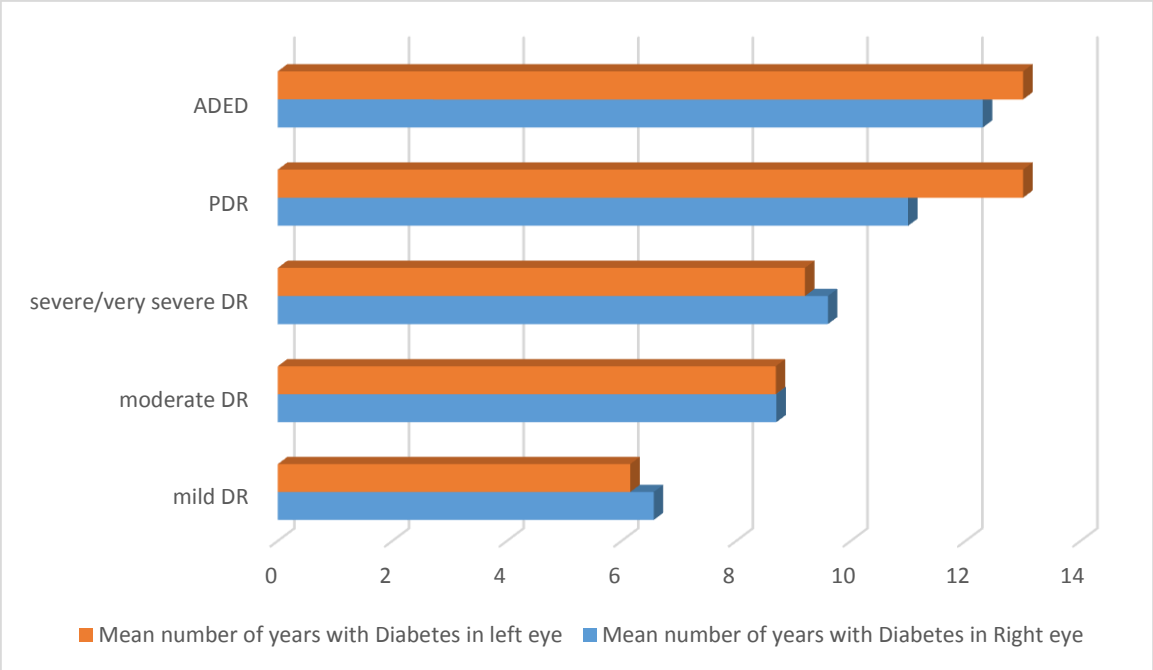
The number of years of diabetes and severity of retinopathy was studied and mild and moderate DR had 6.5 and 8.7 years of diabetes respectively. 9.2 years in severe DR in left eye and mean of 13 years are noted in both PDR and ADED patients in left eye whereas 11 and 12.3 years in right eye. Severity of DR in both the eyes was found to increase with increasing duration of Type II DM among the patients ($p<0.001$).

Table 13: Duration of diabetes right eye

Grading of DR	Number	Mean in years	SD	95% Confidence interval lower limit- upper limit
Mild DR	70	6.56	4.238	5.55
Moderate DR	53	8.70	4.436	7.48
Severe/Very Severe DR	15	9.60	3.397	7.72
PDR	8	11.00	3.381	8.17
ADED	10	12.30	3.164	10.04
Total	156	8.17	4.441	7.47

Table 14: Duration of diabetes Left eye

	Number	Mean in years	SD	Standard Error	95% Confidence interval lower bound
Mild DR	67	6.15	3.197	.391	5.37
Moderate DR	55	8.69	4.149	.560	7.57
Severe/very severe DR	15	9.20	3.278	.846	7.38
PDR	10	13.00	6.633	2.098	8.25
ADED	9	13.00	4.444	1.481	9.58
Total	156	8.17	4.441	.356	7.47



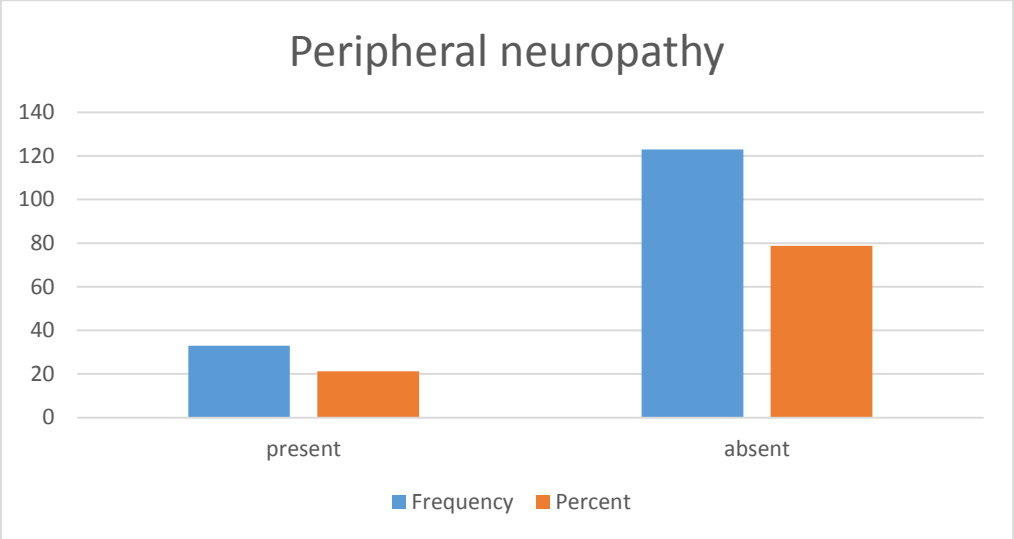
GRAPH 12 : Duration Of DM and Severity of DR

The mean HbA1c in those with diabetic peripheral neuropathy (n=33) was 9.7±1.6 in comparison to 6.9±1.5 among patients without diabetic peripheral neuropathy (n=123) (t=9.395, p<0.001).

Diabetic Peripheral neuropathy(DPN) is noticed in 33 patients (21.2%) of the study group with varying severity and has direct correlation of HbA1c as noticed by the fact that mean in those with DPN is noted to be 9.7(+/- 1.6) and 6.9 (+/- 1.46) in non-peripheral neuropathy having diabetic retinopathy patients.

Table 15: Peripheral neuropathy

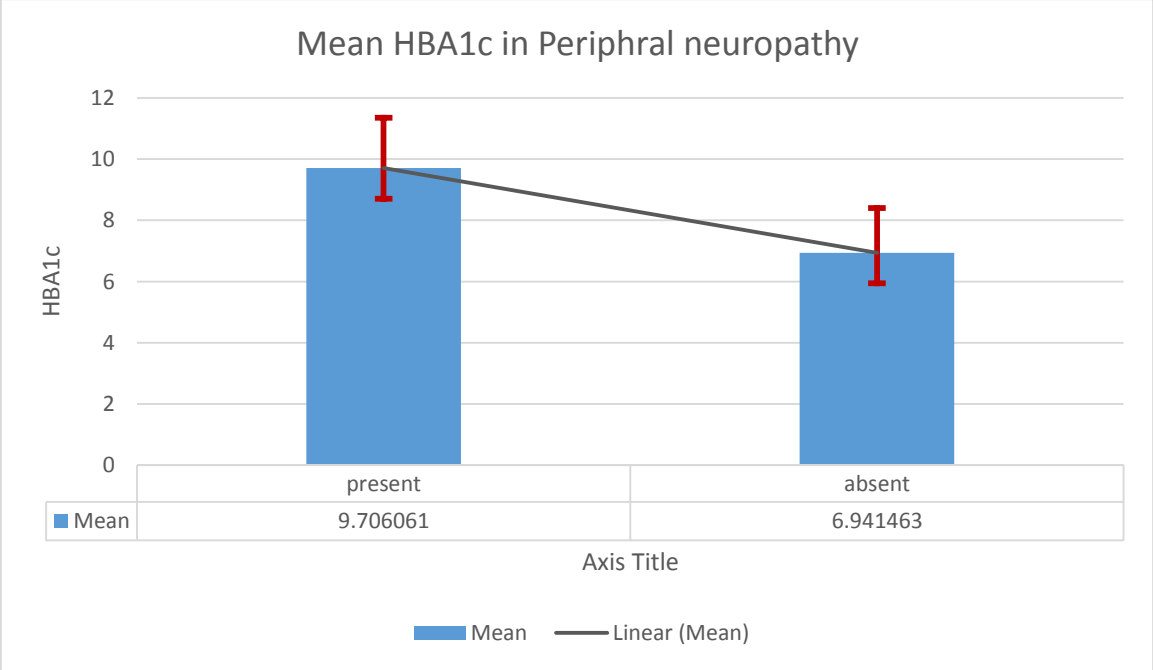
Peripheral neuropathy	Frequency	Percent
Present	33	21.2
Absent	123	78.8



GRAPH 13 : Frequency and percentage distribution of peripheral neuropathy

Table 16: Peripheral neuropathy and HBA1c

Peripheral neuropathy	Number	Mean	Std. Deviation
Present	33	9.706061	1.6435365
Absent	123	6.941463	1.4612440



GRAPH 14: Peripheral neuropathy and HBA1c

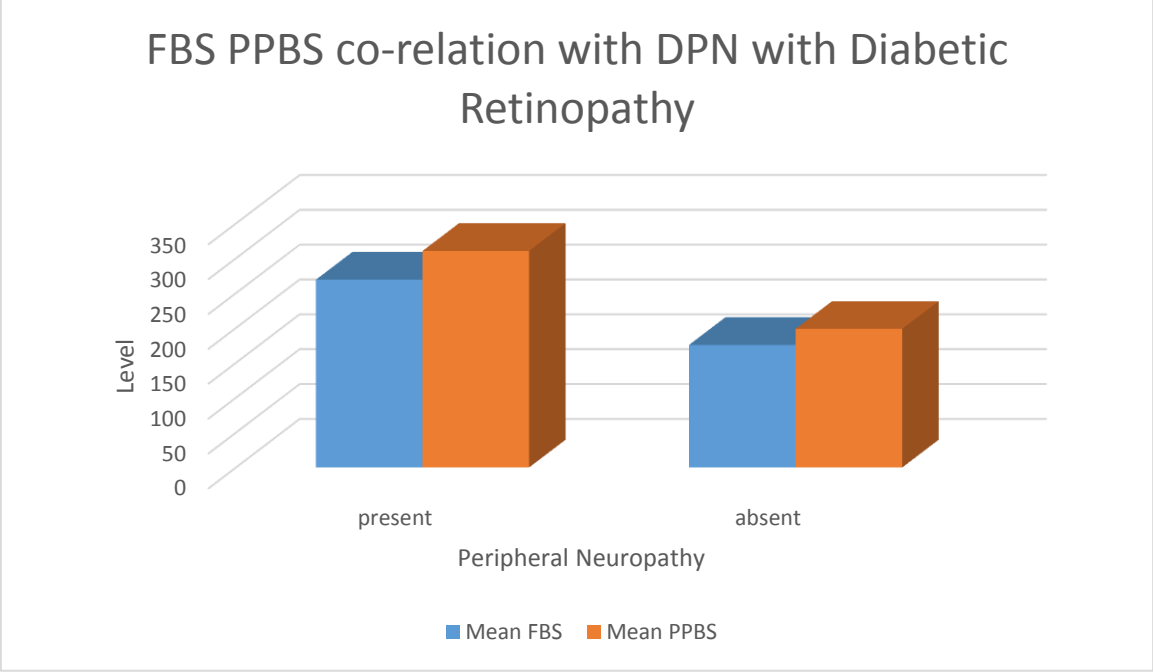
Table 17: FBS PPBS co-relation with DPN with Diabetic Retinopathy

FBS and PPBS were seen to be high in patient with peripheral neuropathy in comparison to patients having only Diabetic retinopathy, our study shows 269 (+/-94) and 310 (+/- 78) respectively. Mean FBS and mean PPBS were seen to be significantly high among patients with DPN compared to those without ($p<0.001$). The mean FBS and the mean PPBS were higher in the PDR group compared to other patients with DR ($p<0.001$).

Peripheral Neuropathy	Number of patient	Mean FBS	Standard deviation
Present	33	269.24	94.228
Absent	123	175.58	60.241

Peripheral Neuropathy	Number of patient	Mean PPBS	Standard deviation
Present	33	310.55	78.847
Absent	123	198.59	65.379

t=9.395, p<0.001



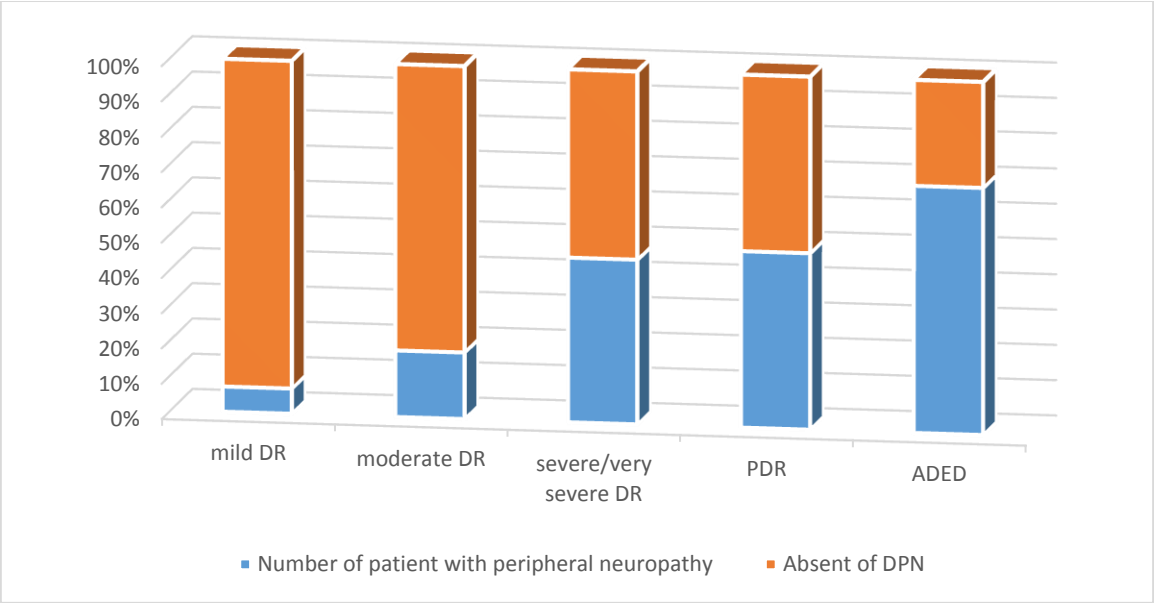
GRAPH 15: FBS, PPBS co-relation with DPN with Diabetic Retinopathy

Table 18: Incidence of Peripheral neuropathy with Severity of DR of Right eye

Percentage Presence of DPN increases as the severity increases as 50% PDR in right and 70% in left eye has Diabetic peripheral neuropathy. Whereas it increases to 70% and 77% in ADED patients. Proportion of patients with peripheral neuropathy was found to increase with increasing severity of DR in both eyes among the patients ($p<0.001$).

Right eye	DPN present	DPN Absent
Mild DR	5	65
Percentage	7.1%	92.9%
Moderate DR	10	43
Percentage	18.9%	81.1%
Severe/very severe DR	7	8
Percentage	46.7%	53.3%
PDR	4	4
Percentage	50.0%	50.0%
ADED	7	3
Percentage	70.0%	30.0%
Total	33	123
Percentage	21.2%	78.8%

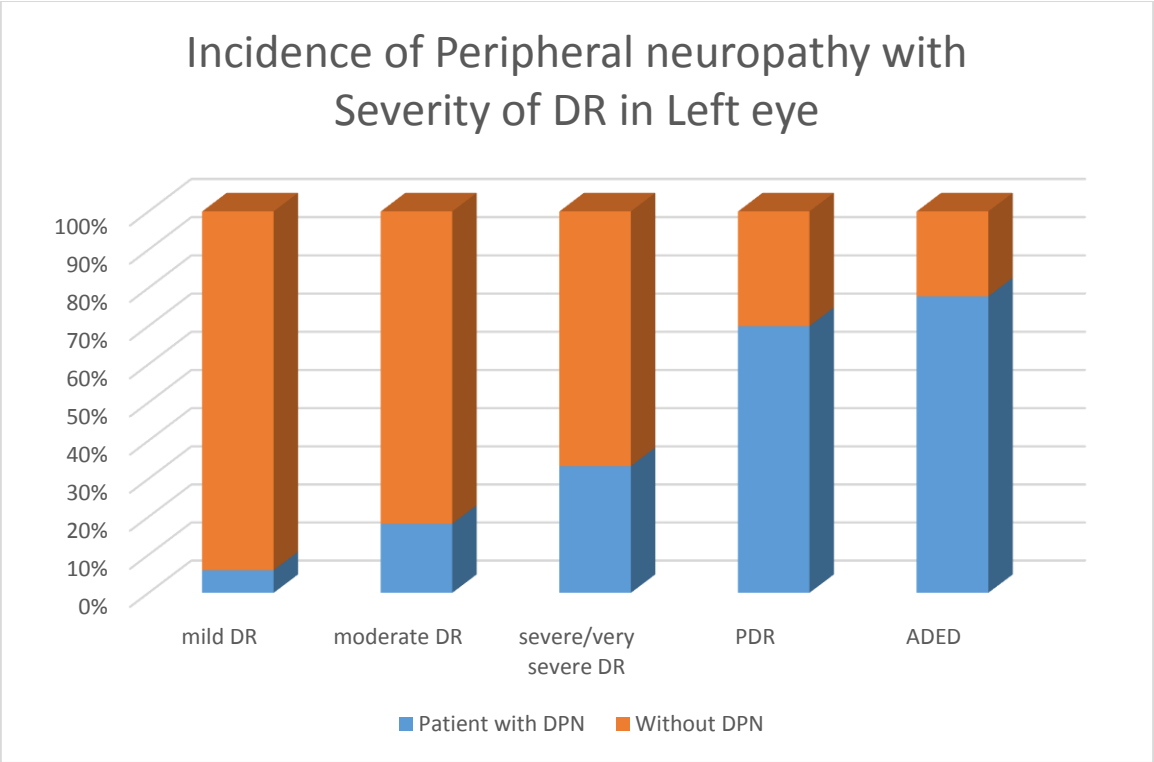
$X^2=32.555$, $p<0.001$



GRAPH 16: Incidence of Peripheral neuropathy with Severity of DR of Right eye

Table 19: Incidence of Peripheral neuropathy with Severity of DR in Left eye

Left eye	DPN present	DPN Absent
Mild DR	4	63
Percentage	6.0%	94.0%
Moderate DR	10	45
Percentage	18.2%	81.8%
Severe/very severe DR	5	10
Percentage	33.3%	66.7%
PDR	7	3
Percentage	70.0%	30.0%
ADED	7	2
Percentage	77.8%	22.2%
TOTAL	33	123
	21.2%	78.8%



GRAPH 17: Incidence of Peripheral neuropathy with Severity of DR in Left eye

- The mean HbA1c in both right and left eye for mild and moderate DR was 6.8(+/-1.8) and 7.4 (+/-1.4) respectively.
- Even though mean Levels in ADED 9.5 (+/-1.7) is same in both eyes, in severe DR right eye shows slightly higher levels of mean HbA1c of 8.7 in comparison to 8.5 of left eye.
- On further application of independent t test and ANNOVA we found that the mean HbA1c in patients with ADED was 9.5±1.8, PDR was 9±1.3, severe/ very severe DR was 8.7±1.9, moderate DR was 7.4±1.4 and mild DR was 6.9±1.8 ($F=9.6$, $p<0.001$).
- Severity of diabetic retinopathy in both the eyes was found to significantly increase with increasing duration of Type II DM among the patients ($p<0.001$).
- Similarly mean FBS and mean PPBS were seen to be significantly high among patients with DPN compared to those without ($p<0.001$).

- The mean FBS and the mean PPBS were significantly higher in the PDR group compared to other patients with DR ($p<0.001$).
- Proportion of patients with peripheral neuropathy was found to significantly increase with increasing severity of DR in both eyes among the patients ($p<0.001$).

DISCUSSION

DISCUSSION

The current cross-sectional observational study was carried out in the Department of Ophthalmology, R.L.Jalappa. Hospital and Research Centre, attached to Sri Devaraj Urs Medical College , Tamka, Kolar between December 2019 and May 2021 with the aim of correlating the grade of diabetic retinopathy (DR) with the severity of DPN and gauging their relationship with glycated hemoglobin levels . The study included 156 patients with both type 1 DM and type 2 DM who fulfilled the selection criteria and gave written informed consent.

Two clinic-based studies revealed occurrence rates of DR in DM type II patients in South India 34.1% and 37%, respectively. [94,95] Agarwal et al in their study revealed that the prevalence rate of 28.9% of DR.[96] In a another study done by Narendran et al revealed an general prevalence rate of DR to be 26.2%. Out of which NPDR was seen in 94.1% cases.[97]

Kalpana. R et al. [98] found that males were affected more than females. In a another study by Sharma VK. et al [17] it was observed that the number of males with retinopathy were more when compared with female . Similarly, in our study we had 106 (67.9%) male and 50 (32.1%) female patients suffering from retinopathy thereby it was observed that a higher incidence of DR was present among the males in comparison to the females.

Katulanda *et al.*[88] found the occurrence of DPN almost same in both the sexes. In our study also had a similar finding with slight higher male preponderance.

JI *et al.* [100] in their study conducted in the year 2012 found the occurrence of DPN more or less same in both males and females, which consist of of 43.3% males and 49.8% females. Katu landa *et al.*[88] in their study on occurrence of DPN in the year 2012 found that the occurrence in males and females was 20.0% and 26.4%, respectively, which was much less when compared with our study.

Katulanda P et al [88] and Narendra *et al*. [97] in the study conducted at Arvind Eye Care in 2002 found that the occurrence of DR was not significantly associated with sex, JI *et al*.[100]in their study found that incidence in females was to some extent greater than that of males (52.2% and 47.8%, respectively), which did not correlate with the findings of our study.

Won *et al*., [102] and JI *et al*. [100] also concluded that DPN was more in individuals who had a longer course of disease.

The period of DM, an essential predictor of DR decides the contact time of other risk factors. Rema *et al*. [103] in their CURES study-risk of DR amplified by 1.89 for every 5 years increase in duration. Al-Sarraf et al. [104] detected that patients with the duration of 10 to 19 years of disease are twice as to be anticipated to have DR and approximately 3 times more when the exposure is more than 20 years. In a study conducted in USA each year it was found that DM represents a 6% increase in chance of DR. This connection with duration of diabetes was first established in the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) with a advanced prevalence in 25, 60 and 80% for 5, 10 and 15 years of development of DM, respectively.[105] Additionally to afore stated, numerous other studies have exhibited statistical significance for this factor both in type I and type II DM, perchance the most important independent risk factor for DR.[106,107,108,109]

Agarwal et al study has shown the maximum prevalence of DR in patients of >15 years of diabetes to be 52.2%. [110]

Bansal et al.[111] 62% prevalence of DR with period of DM of 16-20 years, but then again higher prevalence in 20-25years duration of DM and retinopathy was seen to be maximum in patients with DM of more than 25 years.

Sharma VK et al. found that both DR and DPN were associated with longer duration of DM and poor glycaemic control but were not associated with BMI (obesity).[98]

Kumar KH et al.[14] in their study found that with growing age, duration of DM and higher HBA1c acted as common risk factors for both DR and DPN while low body weight predisposed to retinopathy over DPN. In a study studies conducted by Feldman et al.,[113] Gill et al.,[114] and Ashok et al.[115] it was found that the period of diabetes was a significant determinant for neuropathy .In our study it was observed that severity of DR in both the eyes was found to increase with increasing duration of Type II DM among the patients ($p<0.001$).

In a study conducted by Meena N et al.[116] it was found that increase in the FBS,PPBS and Hba1c biochemical parameters, there is also increase in the DR grade of severity .

In the VERONA study,[123] no association of FPG variability with the onset or the progression of retinopathy was observed. 2 studies by Japanese from the same clinic, confirm the link between the variability of FPG in relation to both non proliferative retinopathy and proliferative retinopathy in Type II diabetis mellitus patients.[117,118] In our study it was found that the Fasting blood sugar average in retinopathy patients is found to be 178 and PPBS 222, it was observed that with the increasing trend of levels of FBS there was an increasing severity in the grade of DR. In Mild and moderate NPDR it was 148 (+/- 45) and 203 (+/- 69), ADED patients had an average FBS of 292(+/- 68). Similarly PPBS is noted to be 178 (+/-61) in mild DR and 275 and 332 in Severe and PDR category respectively, which also has linear upward trend with plateauing due to overlap with ADED patients.

HbA1c inconsistency was related with macrovascular disease ($p = 0.02$) in Type II diabetic patients, in the ADVANCE trial however short-term glucose variability was associated with both macrovascular ($P = 0.005$) and microvascular events ($P < 0.001$).[129]

Kilpatrick et al.[130] In the DCCT study recognized a significantly increased risk of retinopathy, not only with higher HbA1c mean value , but also with higher fluctuation. It was observed that for every increase in the SD of HbA1c by a value of one the absolute %, the

hazard ratio of both the development and progression of DR increased by more than 100 percent.

In a study conducted by Zavrelova et al.[135] with a large cohort of patients with type II DM (n = 3343) who were screened every twelve months for six years helped to identify the DR progression patterns, which showed that patients with higher HbA1c levels, fast progression from NPDR to PDR may occur. Meena N et al.[116] in their study found that with the rise in the value of HbA1c largely affects the severity of the diabetic retinopathy stages. Therefore, they suggested an exceedingly significant correlation (P=<0.001) between HbA1c level and the severity of DR stages. Raman R et al.[126] calculated, a strong association of HbA1c with DR (P-value < 0.001).

In relation to CURES [103] Eye study it was observed that as the level of HbA1c increases by 2 percent,the risk of DR increases by 1.7. In another study carried out by Nanda PK et al.[127]it was understood that HbA1c is a strong predictor of the manifestation of severity of diabetic retinopathy. In the study by CURES [103] and Rema *et al*. [94] they also similarly found that with the increasing HbA1c numbers there is an increase in the prevalence of retinopathy. Rajendra Prasad et al observed in their study that there was an increase in the severity of retinopathy with higher levels of HbA1c.[134] Our study noted that there is striking significance of increase in severity of retinopathy with increase in HbA1c levels and also overlap of the HbA1c levels with severity of retinopathy. The mean HbA1c in both right and left eye for mild and moderate DR was 6.8(+/-1.8) and 7.4 (+/-1.4) respectively. Even though mean Levels in ADED 9.5 (+/-1.7) is same in both eyes, in severe DR right eye shows slightly higher levels of mean HbA1c of 8.7 in comparison to 8.5 of left eye.

Kumar *et al*.[14] in their study came to a conclusion risk of developing microvascular complications will increase in those with a larger value of HbA1c. Salwa et al. [128] in their

study acknowledged HbA1c as a modifiable risk factor for diabetic neuropathy. Won *et al*., [102] Ji *et al*.,[100] and Rema *et al*.[103] in their corresponding studies found DPN to be more in those diabetics with a higher values of HbA1c. It was perceived that the rate of rise of DPN is much higher than of DR. In cases with mild derangement (HbA1c 7-9%), the occurrence of DPN increases up to the level achieved by retinopathy in cases with severe derangement.

Foo et al.[131] and Takao et al.[132] in their study indicated that HbA1c variability measured as HbA1c-standard deviation or HbA1c-Coefficeint of Variation was predictive for the developing diabetic retinopathy and neuropathy. Su et al.[133] in a study which was cross sectional conducted over 1-year period of time amongst 563 type II diabetes patients to examine the relationship between HbA1c fluctuation measured as HbA1c-CV and DPN. In their study it was seen that the neuropathy incidence increased with a higher variability of HbA1c.

Lee WJ et al.[135] conducted a study which revealed that HbA1c level was a quantitative indicator of the severity of polyneuropathy; and poor glycemic control (HbA1c level >6.5%) and that it may perhaps increase incidence of polyneuropathy in DM by more than 5-fold. Through their study it was concluded close relationships between glycemic erraticism parameters and DPN in type II diabetes. Vikendra et al.[136] in their study revealed that the overall prevalence of DPN in patients with DM 56% and 27%. Pai et al.[138] showed that those with a higher Coffecient of Variability of fasting plasma glucose had an evidently greater risk of DPN. Venkatesh et al.[139] in their study on patients with different grades of retinopathy, a greater yield was seen with nerve conduction when compared to other clinical tests for DPN. In our study the mean HbA1c in patients with DPN (n=33) was 9.7±1.6 in comparison to 6.9±1.5 among patients without diabetic peripheral neuropathy (n=123) ($t=9.395$, $p<0.001$).

DPN was noticed in 33 patients (21.2%) of the study group with varying severity and it was seen to have a direct correlation to HbA1c values. In our study the FBS and PPBS were found to be high in patient with peripheral neuropathy in comparison to patients having only Diabetic retinopathy. Mean FBS and mean PPBS were seen to be significantly high among patients with DPN compared to those without ($p<0.001$). The mean FBS and the mean PPBS were significantly higher in the PDR group compared to other patients with DR ($p<0.001$).

Sharma VK et al.[17] showed that prevalence of DPN in cases with DR was 2.75 times than in cases without DR (14%). Kumar *et al.* [14] and Won *et al.* [102] established that incidence of DPN was observed to be increased in patients with retinopathy. Salwa et al.[128] and Katulanda *et al.* [88] indicated that DR as most significant risk factors for a patient with DPN and their ratio of association was almost similar to the findings of our study. JI *et al.* [100]in their study proved that DR is an independent risk factor for DPN. The percentage of cases suffering from both the microvascular complication was found almost equal to that of our study.

Gavin et al.[140] studied the association of prevalence of DR in individuals with and without DPN and it was seen to be 2 times more. Ashok et al.[115]in a study to perceive prevalence of neuropathy, compared incidence of retinopathy in patients with and without neuropathy and found a higher incidence in those with neuropathy.

In our study it was found that the percentage presence of DPN increases as the severity increases as 50% PDR in right and 70% in left eye has Diabetic peripheral neuropathy. Whereas it increases to 70% and 77% in ADED patients. Proportion of patients with peripheral neuropathy was seen to increase significantly with rise in severity of DR in both eyes among the patients ($p<0.001$).

CONCLUSION

CONCLUSION

In the present study which was conducted it was observed that there was a clinical correlation between the severity of the diabetic retinopathy and the presence of diabetic peripheral neuropathy.

DPN was seen to be remarkably more common in those diabetics with retinopathy than in those without retinopathy. A statistically significant positive correlation was found between severity of DR and the incidence of DPN.

DM when present for a longer duration was concluded to be a common risk factor for both DR and DPN.

Higher glycemic index variability and elevated Hba1c levels were associated with both DR and DPN.

SUMMARY

SUMMARY

DR and DPN are the common complication which occur in diabetes mellitus. Both are microvascular complications and is said to share a common pathophysiology. DR and DPN related complications lead to a large number of mortality and morbidity, one causes irreversible blindness and the other may lead to lower limb amputations. Studies have found that presence of any one complication may help in diagnosing the other. However, there is limited studies carried out to show the correlation between the two and its relationship with glycated hemoglobin levels.

The current cross-sectional observational study was carried out in the Department of Ophthalmology, R.L.Jalappa. Hospital and Research Centre, attached to Sri Devaraj Urs Medical College , Tamka, Kolar between December 2019 and May 2021.

In the pesent study the mean HbA1c in both right and left eye for mild and moderate DR was 6.8(+/-1.8) and 7.4 (+/-1.4) respectively. Even though mean Levels in ADED 9.5 (+/-1.7) is same in both eyes, in severe DR right eye shows slightly higher levels of mean HbA1c of 8.7 in comparison to 8.5 of left eye. On further application of independent t test and ANNOVA it was observed that the mean HbA1c in patients with ADED was 9.5±1.8, PDR was 9±1.3, severe/ very severe DR was 8.7±1.9, moderate DR was 7.4±1.4 and mild DR was 6.9±1.8 ($F=9.6$, $p<0.001$).

Severity of diabetic retinopathy in both the eyes was found to increase with increase in duration of Type II DM among the patients ($p<0.001$).

Similarly mean FBS and mean PPBS were shown to be high among patients with diabetic neuropathy compared to those without ($p<0.001$).

The mean FBS and the mean PPBS were higher in the PDR group compared to other patients with DR ($p<0.001$).

Proportion of patients with peripheral neuropathy was found to increase with increase in severity of DR in both eyes among the patients ($p<0.001$).

Our study, by proving a correlation between the DR and DPN with Hba1c values, give emphasis to the importance of an interdepartmental level of screening and treatment,irrespective of the symptoms and the reason for the visit.

The treating doctor should encourage a screening test of HbA1c for all patients with DM and should be referred to an ophthalmologist for screening for retinopathy. Hence, both the general physicians and ophthalmologist play a very important role in the overall care of patient with DM.

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ANNEXURE

ANNEXURE-1

STUDY PROFORMA

Case no: **Date:**

Name: **OP no:**

Age: **IP no:**

Sex: **Address:**

Occupation:

Past history:

Diabetic status

- Duration of DM –
- Diabetes treatment –

Personal history: Tobacco/ Alcohol/ Smoking/ Computer use/ others

GPE:

Vital signs:

Pulse – RR –

BP – Temp –

Systemic examination:

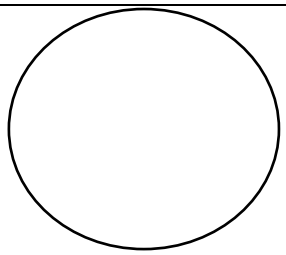
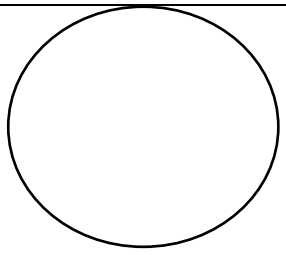
a) CVS – c) RS –

b) PA – d) CNS –

Hematological investigation:

FBS, PPBS, HbA1C

OCULAR EXAMINATION

TESTS	RE	LE
1. HEAD POSTURE 2. OCULAR POSTURE 3. FACIAL SYMMETRY		
4. EXTRAOCULAR MOVEMENTS a) Ductions b) Versions c) Vergence		
5. VISUAL ACUITY: a) Distant b) Near		
6. **ANTERIOR SEGMENT** a. Lids and Adnexa b. Conjunctiva c. Cornea d. Anterior chamber e. Iris f. Pupil g. Lens h. Anterior Vitreous		
7. FUNDUS a. Indirect ophthalmoscopy b. 90 D examination c. B SCAN when indicated d. Gonioscopy when indicated		
Fundus		

Toronto clinical neuropathy scoring system:

A) Symptom scores: Present=1; Absent= 0	**Right**	**Left**
1.Pain(Foot)		
2.Numbness(foot)		
3.Tingiling(foot)		
4.Weakness(foot)		
5.Ataxia		
6.Upper limb symptoms		
B) Sensory test scores: (sensory testing on 1st toe) Normal=0; Abnormal=1		
1)Pinprick		
2)Temp		
3) Light Touch		
4) Vibration		
5)Position		
C) Reflex scores: Normal=0; Reduced=1; Absent=2		
Knee reflex		
Ankle reflex		
Total score		
Severity: 0-5: No neuropathy 6-8: Mild neuropathy 9-11: Moderate neuropathy 12+: Severe neuropathy		

ANNEXURE-II

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

INFORMED CONSENT FORM

Case no:

IP no:

TITLE: STUDY OF THE CLINICAL CORRELATION BETWEEN DIABETIC RETINOPATHY, DIABETIC NEUROPATHY AND GLYCATED HEMOGLOBIN LEVELS

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.

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:			

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

ತಿಳಿವಳಿಕೆ ಸಮ್ಮತಿನಮೂನೆ

ಈ ಸಂಶೋಧನೆಗೆ ರೋಗಿಯ ಗುರುತಿನ ಸಂಖ್ಯೆ:

ಐಪಿ ಸಂಖ್ಯೆ:

ಶೀರ್ಷಿಕೆ:"ಡಯಾಬಿಟಿಕ್ ರೆಟಿನೋಪತಿ, ಡಯಾಬಿಟಿಕ್ ನ್ಯೂರೋಪತಿ ಮತ್ತು ಗ್ಲೈಕೇಟೆಡ್ ಹಿಮೋಗ್ಲೋಬಿನ್ ಮಟ್ಟಗಳ ನಡುವಿನ ಕ್ಲಿನಿಕಲ್ ಕೊರೆಲೇಷನ್"

ಅಂಗೀಕರಿಸಿದ ನಾನು, ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳಲು ಒಪ್ಪುತ್ತೇನೆ ಮತ್ತು ಈ ಸಮ್ಮತಿಯ ರೂಪದಲ್ಲಿ ವಿವರಿಸಿರುವಂತೆ ನನ್ನ ವೈಯಕ್ತಿಕ ಮಾಹಿತಿಯ ಸಂಗ್ರಹಣೆ ಮತ್ತು ಬಹಿರಂಗಪಡಿಸುವಿಕೆಯನ್ನು ದೃಢೀಕರಿಸುತ್ತೇನೆ.

ನಾನು ಈ ಅಧ್ಯಯನದ ಉದ್ದೇಶ, ತಂತ್ರಗಳ ಅಪಾಯಗಳು ಮತ್ತು ಪ್ರಯೋಜನಗಳನ್ನು ಮತ್ತು ಅಧ್ಯಯನದಲ್ಲಿ ಸಂಗ್ರಹಿಸಿದ ಮತ್ತು ಬಹಿರಂಗಪಡಿಸುವ ಮಾಹಿತಿಯ ಗೌಪ್ಯತೆ ನಾನು ಅರ್ಥಮಾಡಿಕೊಂಡಿದ್ದೇನೆ.

ಸಂಗ್ರಹಿಸಿದ ಮಾಹಿತಿಯನ್ನು ಸಂಶೋಧನೆಗೆ ಮಾತ್ರ ಬಳಸಲಾಗುತ್ತದೆ.

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

ನಾನು ಈ ಅಧ್ಯಯನದಿಂದ ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ಹಿಂತೆಗೆದುಕೊಳ್ಳಲು ಮುಕ್ತವಾಗಿರುತ್ತೇನೆ ಮತ್ತು ಇದು ನನ್ನ ಮುಂದಿನ ಕಾಳಜಿಯನ್ನು ಬದಲಿಸುವುದಿಲ್ಲ ಎಂದು ನಾನು ಅರ್ಥಮಾಡಿಕೊಂಡಿದ್ದೇನೆ.

ಈ ಸಂಶೋಧನಾ ಯೋಜನೆಯ ಭಾಗವಹಿಸುವಿಕೆ ನನಗೆ ಯಾವುದೇ ಹಣಕಾಸಿನ ಹೊರೆ ಒಳಗೊಂಡಿರುವುದಿಲ್ಲ.

ಹೆಸರು	ಸಹಿ	ದಿನಾಂಕ	ಸಮಯ
ರೋಗಿಯ:			
ಸಾಕ್ಷಿ 1:			
ಸಾಕ್ಷಿ 2:			
ಪ್ರಾಥಮಿಕ ತನಿಖೆದಾರ / ಡಾಕ್ಟರ್:			

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 " STUDY OF THE CLINICAL CORRELATION BETWEEN DIABETIC RETINOPATHY, DIABETIC NEUROPATHY AND GLYCATED HEMOGLOBIN LEVELS". 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?

   To evaluate the interelation between diabetic retinopathy, neuropathy and glycated hemoglobin levels.

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 Best Corrected Visual Acuity done with Snellen's chart, Slit lamp bio-microscopy and dilated fundus examination, peripheral neuropathy examination, FBS, PPBS and HbA1c.

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 Sri Archana.
post graduate student
Department of ophthalmology
SRI DEVARAJ URS MEDICAL ACADEMY
TAMAKA, KOLAR
Contact no:9591343716.

ರೋಗಿಯ ಮಾಹಿತಿ ಹಾಳೆ

ಈ ಮಾಹಿತಿಯು ''ಡಯಾಬಿಟಿಕ್ ರೆಟಿನೋಪತಿ, ಡಯಾಬಿಟಿಕ್ ನ್ಯೂರೋಪತಿ ಮತ್ತು ಗ್ಲೈಕೇಟೆಡ್ ಹಿಮೋಗ್ಲೋಬಿನ್ ಮಟ್ಟಗಳ ನಡುವಿನ ಕ್ಲಿನಿಕಲ್ ಕೊರೆಲೇಷನ್''

ಎಂಬ ಅಧ್ಯಯನದ ಉದ್ದೇಶವನ್ನು ಅರ್ಥಮಾಡಿಕೊಳ್ಳಲು ಸಹಾಯ ಮಾಡುತ್ತದೆ. ಈ ಸಂಶೋಧನಾ ಅಧ್ಯಯನದಲ್ಲಿ ಸ್ವಯಂಪ್ರೇರಿತವಾಗಿ ಪಾಲ್ಗೊಳ್ಳಲು ನಿಮ್ಮನ್ನು ಆಹ್ವಾನಿಸಲಾಗಿದೆ, ಅಧ್ಯಯನದ ಉದ್ದೇಶ, ಕಾರ್ಯವಿಧಾನ, ಪ್ರಯೋಜನಗಳು ಮತ್ತು ಅಸ್ವಸ್ಥತೆಗಳನ್ನು ನೀವು ಓದುವುದು ಮತ್ತು ಅರ್ಥಮಾಡಿಕೊಳ್ಳುವುದು ಮುಖ್ಯವಾಗಿದೆ.

1. ಈ ಅಧ್ಯಯನದ ಉದ್ದೇಶವೇನು?

ಮಧುಮೇಹ ರೆಟಿನೋಪತಿ, ನರರೋಗ ಮತ್ತು ಗ್ಲೈಕೇಟೆಡ್ ಹಿಮೋಗ್ಲೋಬಿನ್ ಮಟ್ಟಗಳ ನಡುವಿನ ಪರಸ್ಪರ ಸಂಬಂಧವನ್ನು ಮೌಲ್ಯಮಾಪನ ಮಾಡಲು

2. ವಿವಿಧ ತನಿಖೆಗಳನ್ನು ಬಳಸಲಾಗುತ್ತಿದೆ? ಯಾವುದೇ ಸಂಬಂಧಿತ ಅಪಾಯಗಳಿವೆಯೇ?

ಸ್ನೆಲೆನ್‌ನ ಚಾರ್ಟ್, ಸ್ಲಿಟ್ ಲ್ಯಾಂಪ್ ಬಯೋ-ಮೈಕ್ರೋಸ್ಕೋಪಿ ಮತ್ತು ಡೈಲೇಟೆಡ್ ಫಂಡಸ್ ಪರೀಕ್ಷೆ, ಬಾಹ್ಯ ನರರೋಗ ಪರೀಕ್ಷೆ, ಎಫ್‌ಬಿಎಸ್, ಪಿಪಿಬಿಎಸ್ ಮತ್ತು ಎಚ್‌ಬಿಎ 1 ಸಿ ಯೊಂದಿಗೆ ಮಾಡಿದ ಅತ್ಯುತ್ತಮ ಸರಿಪಡಿಸಿದ ವಿಷುಯಲ್ ಆಕ್ಯುಟಿ ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗಿಯಾಗಿರುವ ವಿವಿಧ ತನಿಖೆಗಳೊಂದಿಗೆ ಯಾವುದೇ ಅಪಾಯಗಳು ಸಂಬಂಧಿಸಿಲ್ಲ.

3. ಭಾಗವಹಿಸುವವನಾಗಿ ನನಗೆ ಏನು ಪ್ರಯೋಜನ?

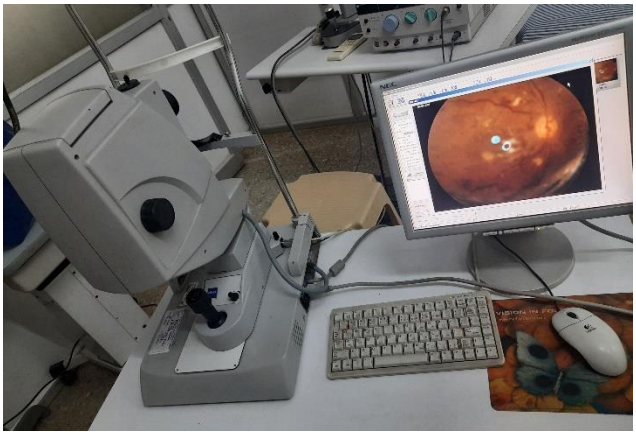
ಈ ಸಂಶೋಧನಾ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸುವಿಕೆಯು ನಿಮ್ಮ ಕಣ್ಣಿನ ಸ್ಥಿತಿಯ ಅಂತಿಮ ಫಲಿತಾಂಶವನ್ನು ಬದಲಿಸಬಾರದು. ಆದಾಗ್ಯೂ, ಭವಿಷ್ಯದಲ್ಲಿ ರೋಗಿಗಳು ಈ ಅಧ್ಯಯನದಿಂದ ಪಡೆದ ಜ್ಞಾನದ ಫಲಿತಾಂಶವಾಗಿ ಪ್ರಯೋಜನ ಪಡೆಯಬಹುದು. ಸಂಶೋಧನಾ ಅಧ್ಯಯನದ ಸಮಯದಲ್ಲಿ ನಡೆಸಿದ ಯಾವುದೇ ಪ್ರಕ್ರಿಯೆಗಳಿಗೆ ನಿಮಗೆ ಹೆಚ್ಚುವರಿ ಶುಲ್ಕ ವಿಧಿಸಲಾಗುವುದಿಲ್ಲ. ಈ ಅಧ್ಯಯನದಲ್ಲಿ ನಿಮ್ಮ ಪಾಲ್ಗೊಳ್ಳುವಿಕೆಯು ಸಂಪೂರ್ಣವಾಗಿ ಸ್ವಯಂಪ್ರೇರಿತವಾಗಿದೆ. ಅಧ್ಯಯನದಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳಲು ನೀವು ನಿರಾಕರಿಸಬಹುದು ಅಥವಾ ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳುವುದಕ್ಕೆ ಮುಂಚಿತವಾಗಿ ನೀವು ಯಾವುದೇ ಅರ್ಹತೆಯಿಂದ ಯಾವುದೇ ದಂಡ ಅಥವಾ ನಷ್ಟವಿಲ್ಲದೆಯೇ, ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ನಿಮ್ಮ ಪಾಲ್ಗೊಳ್ಳುವಿಕೆಯನ್ನು ಅಧ್ಯಯನದಲ್ಲಿ ನಿಲ್ಲಿಸಬಹುದು.

ಗೌಪ್ಯತೆ

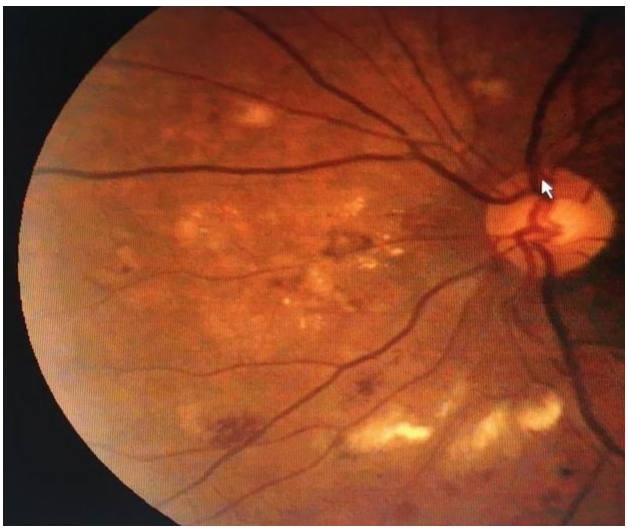
ನಿಮ್ಮ ವೈದ್ಯಕೀಯ ಮಾಹಿತಿಯನ್ನು ಅಧ್ಯಯನದ ವೈದ್ಯರು ಮತ್ತು ಸಿಬ್ಬಂದಿ ಗೌಪ್ಯವಾಗಿಡಲಾಗುವುದು ಮತ್ತು ಸಾರ್ವಜನಿಕವಾಗಿ ಲಭ್ಯವಿರುವುದಿಲ್ಲ. ನಿಮ್ಮ ಮೂಲ ದಾಖಲೆಗಳನ್ನು ನಿಮ್ಮ ವೈದ್ಯರು ಅಥವಾ ನೈತಿಕ ವಿಮರ್ಶೆ ಮಂಡಳಿ ಪರಿಶೀಲಿಸಬಹುದು. ಹೆಚ್ಚಿನ ಮಾಹಿತಿಗಾಗಿ / ಸ್ಪಷ್ಟೀಕರಣಕ್ಕಾಗಿ ದಯವಿಟ್ಟು

ಡಾ ಶ್ರೀ ಅರ್ಚನಾ.
ಸ್ನಾತಕೊತ್ತರ ವಿದ್ಯಾರ್ಥಿ
ನೇತ್ರವಿಜ್ಞಾನ ವಿಭಾಗ
ಶ್ರೀ ದೇವರಾಜ್ ಯುಆರ್ಎಸ್ ಮೆಡಿಕಲ್ ಅಕಾಡೆಮಿ
ತಮಕ, ಕೋಲಾರ
ಸಂಪರ್ಕ ಸಂಖ್ಯೆ:9591343716.

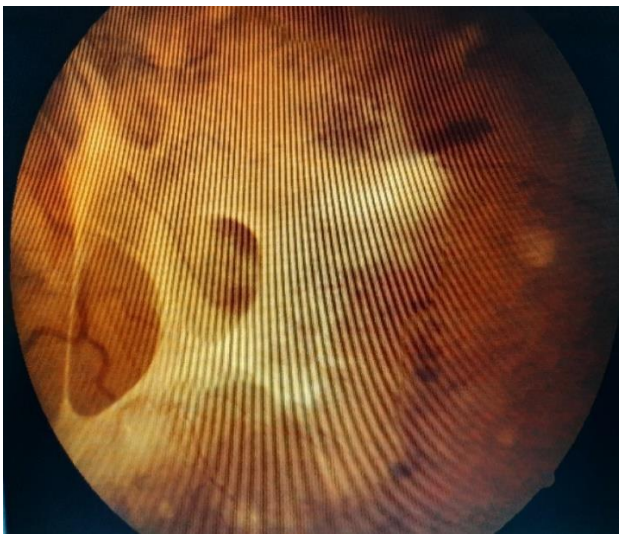
ANNEXURE-IV



PHOTOGRAPH 1: FUNDUS CAMERA

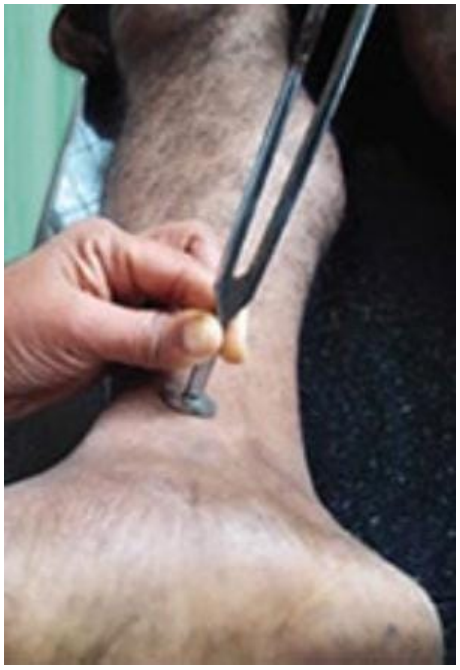


PHOTOGRAPH 2: RE-MODERATE NPDR



PHOTOGRAPH 3: LE-ADED

PHOTOGRAPH 4: 90D Examination



PHOTOGRAPH 5: EXAMINATION OF VIBRATION SENSATION

KEY TO MASTER CHART

NPDR - Non Proliferative Diabetic Retinopathy

PDR - Proliferative Diabetic Retinopathy

ADED - Advanced Diabetic Eye Disease

CSME - Clinically Significant Macular Edema

1 - POSITIVE

0 - NEGATIVE

MASTER CHART

UHID	AGE	SEX	RIGHT EYE	LEFT EYE	MACULA	FBS	PPBS	HBA1C	PERIPHERAL NEUROPATHY	TYPE OF DM	DURATION
828038	63	F	SEVERE NPDR	SEVERE NPDR		256	263	9.5	1	T2	13
828671	55	F	MOD NPDR+CSME	MILD NPDR	CSME	200	214	8.7	1	T2	5
850762	60	F	V.SEVERE NPDR	ADED		298	310	9.2	1	T2	9
822836	30	M	ADED	MOD NPDR		212	237	8.3	1	T1	11
830629	60	M	MILD NPDR	MILD NPDR		201	222	7.2	0	T2	3
698307	62	F	SEVERE NPDR +CSME	SEVERE NPDR CSME		198	213	8	0	T2	8
824865	80	M	MOD NPDR	MOD NPDR		160	168	6.9	0	T2	6
824165	70	M	MILD NPDR	MILD NPDR		132	142	6.2	0	T2	4
831461	72	F	MILD NPDR	MILD NPDR		129	136	5.5	0	T2	4
831463	60	F	MILD NPDR	MILD NPDR		142	132	5.9	0	T2	9
849987	55	F	MODERATE NPDR	MODERATE NPDR	CSME	175	183	5.6	0	T2	15
836412	60	M	MILD NPDR	MILD NPDR		141	148	6.2	0	T2	10
833806	50	F	MILD NPDR	MILD NPDR		158	173	6.3	0	T2	3
506490	65	F	MILD NPDR	MILD NPDR		258	290	8	1	T2	10
830629	51	M	MILD NPDR	MILD NPDR		176	183	7	0	T2	6
830130	65	F	MOD NPDR	MOD NPDR		149	159	6.9	0	T2	8
830147	65	M	SEVERE NPDR+CSME	SEVER NPDR	CSME	258	299	8.5	1	T2	15
827681	46	M	MILD NPDR	MILD NPDR		144	158	5.9	0	T2	7
845977	55	M	MILD NPDR	MILD NPDR		129	140	5.5	0	T2	4
848737	46	M	MOD NPDR	MOD NPDR		242	263	8.2	1	T2	12
847808	55	M	MILD NPDR	MILD NPDR		132	136	5.1	0	T2	7
852804	61	F	MOD NPDR	MOD NPDR	CSME	202	280	6.4	0	T2	8
856389	55	F	MILD NPDR	MILD NPDR		156	188	5.8	0	T2	11
885432	60	M	MOD NPDR	MOD NPDR		440	234	11.6	0	T2	5
812074	55	F	MILD NPDR	MILD NPDR		285	334	13	0	T2	3

UHID	AGE	SEX	RIGHT EYE	LEFT EYE	MACULA	FBS	PPBS	HBA1C	PERIPHERAL NEUROPATHY	TYPE OF DM	DURATION
895200	47	F	MILD NPDR	MILD NPDR		156	188	11.1	0	T2	6
895204	74	M	MOD NPDR	MOD NPDR		98	170	8.8	1	T2	20
898328	67	M	MOD NPDR	MOD NPDR	CSME	107	217	9.6	0	T2	3
898339	70	M	MILD NPDR	MILD NPDR		180	244	11	1	T2	15
856896	65	M	MOD NPDR	MOD NPDR		107	163	8.9	1	T2	12
893850	76	M	SEVERE NPDR	ADED		151	247	11.6	1	T2	6
873110	50	M	MOD NPDR	MOD NPDR		189	267	10.2	1	T2	9
901794	65	F	MILD NPDR	MILD NPDR		69	142	9.2	0	T2	10
886198	58	F	MILD NPDR	MILD NPDR		113	332	10.7	0	T2	2
901797	55	F	MILD NPDR	MILD NPDR		106	282	8.5	0	T2	3
901800	73	M	MILD NPDR	MILD NPDR		71	205	12	1	T2	5
858831	55	M	MILD NPDR	MILD NPDR		189	204	6.2	0	T2	6
820819	60	M	MILD NPDR	MOD NPDR		213	256	7.3	0	T2	6
859859	75	F	MILD NPDR	MILD NPDR		102	126	5.3	0	T2	6
860119	54	M	MILD NPDR	MILD NPDR		111	136	6.4	0	T2	9
860470	54	M	ADED	PDR		298	342	9.2	1	T2	11
860522	48	F	MOD NPDR	MOD NPDR	CSME	168	204	7.5	0	T2	3
861422	63	F	MILD NPDR	MILD NPDR		118	209	6.7	0	T2	7
862784	65	M	MILD NPDR	MILD NPDR		165	232	6.5	0	T2	1
865218	71	M	MILD NPDR	MILD NPDR		122	163	5.7	0	T2	5
863659	65	M	MILD NPDR	MILD NPDR		136	195	6.1	0	T2	7
868881	49	M	MILD NPDR	MILD NPDR		179	203	5.9	0	T2	9
867474	56	M	MILD NPDR	MILD NPDR		206	213	6.2	0	T2	3
869849	55	F	MILD NPDR	MILD NPDR		183	205	5.9	0	T2	4
870384	66	M	MILD NPDR	MOD NPDR		211	256	6.4	0	T2	7

UHID	AGE	SEX	RIGHT EYE	LEFT EYE	MACULA	FBS	PPBS	HBA1C	PERIPHERAL NEUROPATHY	TYPE OF DM	DURATION
874926	22	F	MILD NPDR	MILD NPDR		146	280	5.4	0	T1	4
874537	71	F	MILD NPDR	MILD NPR		201	354	6.3	0	T2	9
881676	65	F	MOD NPDR	MOD NPDR		269	322	7	0	T2	7
874040	53	M	MOD NPDR	MOD NPDR		259	310	6.9	0	T2	6
877190	55	F	ADED	ADED		311	359	7.1	0	T2	11
876484	63	M	MOD NPDR	MOD NPDR		187	263	6.1	0	T2	7
876859	71	M	MOD NPDR	MOD NPDR	CSME	214	261	6.9	0	T2	10
877031	68	F	MILD NPDR	MOD NPDR		98	105	5.1	0	T2	9
879001	68	M	SEVERE NPDR	SEVERE NPDR	CSME	301	322	8.2	1	T2	11
886193	50	F	MOD NPDR	MOD NPDR		215	278	6.4	0	T2	4
891572	63	M	MOD NPDR	MOD NPDR		119	126	5.9	0	T2	7
896452	60	M	MOD NPDR	MOD NPDR		174	215	6.1	0	T2	9
881936	55	M	MOD NPDR MOD NPDR			348	403	11.4	1	T2	19
902859	65	M	MILD NPDR	MILD NPDR		240	266	8.5	0	T2	6
873110	50	M	MOD NPDR	MOD NPDR	CSME	313	298	9.1	1	T2	11
911010	55	F	MILD NPDR	MILD NPDR		176	198	6.4	0	T2	6
908309	45	M	SEVERE NPDR	SEVERE NPDR	CSME	237	288	7.9	0	T2	4
911471	53	M	PDR	PDR		360	397	8.1	1	T2	10
908487	53	M	PDR	PDR		401	412	8.7	1	T2	13
907260	65	M	MILD NPDR	MILD NPDR		111	119	5.1	0	T2	7
906131	40	M	MILD NPDR	MILD NPDR+CSME	CSME	138	143	6.3	0	T2	5
906698	45	F	MODERATE NPDR	MOD NPDR		146	168	6.8	0	T2	7
906173	68	M	MOD NPDR	MOD NPDR		188	192	6.6	0	T2	9
906587	59	M	SEVERE NPDR +CSME	SEVERE NPDR CSME	CSME	213	222	7.2	0	T2	11
903842	64	F	SEVERE NPDR+CSME	SEVERE NPDR CSME	CSME	254	263	7.5	0	T2	7

UHID	AGE	SEX	RIGHT EYE	LEFT EYE	MACULA	FBS	PPBS	HBA1C	PERIPHERAL NEUROPATHY	TYPE OF DM	DURATION
901842	63	M	MILD NPDR	MILD NPDR		117	123	5.7	0	T2	6
887081	65	M	MILD NPDR	MILD NPDR		102	115	5.1	0	T2	4
881892	68	F	MOD NPDR	MOD NPDR	CSME	131	145	6.2	0	T2	10
902795	54	M	MILD NPDR	MILD NPDR		127	135	6.9	0	T2	4
897906	60	M	MOD NPDR	MOD NPDR		149	187	5.9	0	T2	7
899202	66	F	MILD NPDR	MILD NPDR		122	134	5.2	0	T2	8
896895	85	M	MOD NPDR	MOD NPDR		203	211	7.1	0	T2	12
879001	60	M	SEVERE NPDR	SEVERE NPDR	CSME	215	229	7	0	T2	8
896869	66	M	MILD NPDR	MILD NPDR		115	123	5.1	0	T2	4
896291	52	M	MILD NPDR	MILD NPDR		134	147	6	0	T2	6
896519	36	M	SEVERE NPDR	SEVERE NPDR		211	232	7.7	0	T2	5
668558	49	M	PDR	SEVERE NPDR	CSME	342	345	8.7	0	T2	8
893986	65	M	MILD NPDR	MILD NPDR		101	113	5	0	T2	6
864271	64	F	MOD NPDR	MOD NPDR		139	157	6.8	0	T2	9
894847	54	F	MILD NPDR	MILD NPDR		119	124	5.8	0	T2	4
894818	71	M	MILD NPDR	MILD NPDR		126	132	6.1	0	T2	7
890073	60	M	MILD NPDR	MILD NPDR		107	116	5.4	0	T2	4
881807	48	M	PDR	PDR		312	354	8.6	0	T2	11
700605	77	M	MOD NPDR	MOD NPDR		259	301	7.7	0	T2	13
937161	70	M	MOD NPDR	MOD NPDR	CSME	336	431	9	1	T2	8
929291	46	M	MILD PDR	HIGH RISK PDR		143	223	7.2	1	T2	5
927711	53	M	SEVERE NPDR	SEVERE NPDR		306	380	14.4	1	T2	10
911471	52	M	MILD PDR	MILD PDR		128	210	10	1	T1	30
942599	58	F	PDR	PDR		398	400	12	1	T2	12
941214	51	M	SEVERE NPDR	SEVERE NPDR	CSME	212	275	8.1	0	T2	9

UHID	AGE	SEX	RIGHT EYE	LEFT EYE	MACULA	FBS	PPBS	HBA1C	PERIPHERAL NEUROPATHY	TYPE OF DM	DURATION
939906	55	M	ADED	MOD NPDR		352	407	11	1	T2	10
938102	88	M	MILD NPDR	MILD NPDR		153	189	7.1	0	T2	20
938770	58	F	MILD NPDR	MILD NPDR		181	283	7.8	0	T2	10
934111	53	M	ADED	ADED		397	413	9.8	1	T2	18
939906	55	M	ADED	SEVERE NPDR		153	240	8.7	0	T2	10
941968	63	M	MOD NPDR	MOD NPDR		247	254	7.3	0	T2	7
921729	47	M	ADED	HIGH RISK PDR		308	310	9.3	0	T2	9
948745	38	F	ADED	ADED		274	277	13.7	1	T1	15
933386	46	M	PDR	SEVERE NPDR		153	240	7.7	0	T2	5
980112	60	F	MILD NPDR	MILD NPDR		197	86	5.1	0	T2	4
945009	60	M	MOD NPDR	MOD NPDR	CSME	198	118	8.1	0	T2	7
941267	60	F	MILD NPDR	MILD NPDR		128	123	6.5	0	T2	3
977143	61	F	MOD NPDR	MOD NPDR		212	163	6.9	0	T2	6
943750	52	M	MILD NPDR	MILD NPDR		181	108	10.5	0	T2	2
943766	69	M	MILD NPDR	MILD NPDR		282	130	9.9	0	T2	2
943754	72	M	MILD NPDR	MILD NPDR		181	252	10.7	0	T2	7
943771	72	M	MILD NPDR	MILD NPDR		179	217	5.7	0	T2	3
930391	72	M	MILD NPDR	MILD NPDR		97	101	5.7	0	T2	1
814048	66	M	MOD NPDR	MOD NPDR	CSME	126	149	5.5	0	T2	8
813983	50	F	PDR	PDR		278	283	8.3	0	T2	13
817830	49	M	MOD NPDR	MOD NPDR		218	225	7.9	0	T2	9
816148	52	M	MILD NPDR	MILD NPDR		146	154	6.9	0	T2	6
711982	39	M	MOD NPDR	MOD NPDR	CSME	187	195	6.7	0	T2	8
812123	71	M	MOD NPDR	MOD NPDR	CSME	176	198	5.9	0	T2	5
813893	53	F	MOD NPDR	MOD NPDR		212	219	7.7	0	T2	5

UHID	AGE	SEX	RIGHT EYE	LEFT EYE	MACULA	FBS	PPBS	HBA1C	PERIPHERAL NEUROPATHY	TYPE OF DM	DURATION
802189	45	M	ADED	ADED		302	313	9.1	1	T2	11
803590	60	M	MOD NPDR	MOD NPDR		208	214	7.5	0	T2	6
802702	64	M	MOD NPDR	MOD NPDR		198	209	7.1	0	T2	9
577924	46	M	MOD NPDR	MOD NPDR		186	210	6.8	0	T2	9
793638	60	M	SEVERE NPDR	MOD NPDR	CSME	231	245	7.9	0	T2	14
603421	63	F	MILD NPDR	MILD NPDR		121	132	7.5	0	T2	7
793523	74	M	MOD NPDR	MOD NPDR		201	211	7.7	0	T2	5
797761	37	F	MOD NPDR	ADED		318	331	8.9	1	T1	19
790423	54	M	MOD NPDR	MILD NPDR		148	154	5.8	0	T2	5
792665	62	M	MOD NPDR	MOD NPDR	CSME	199	207	6.9	0	T2	7
787429	70	F	MOD NPDR	ADED		299	313	7.4	0	T2	11
788909	50	M	MILD NPDR	MILD NPDR		129	134	6.4	0	T2	6
787898	54	F	MOD NPDR	MOD NPDR	CSME	221	234	7.3	0	T2	8
791795	48	M	PDR	PDR		412	403	9.7	1	T2	16
7877706	68	M	MOD NPDR	MOD NPDR	CSME	165	189	6.5	0	T2	5
758566	70	M	MILD NPDR	MILD NPDR	CSME	105	123	5.9	0	T2	7
786321	70	M	MILD NPDR	MILD NPDR	CSME	189	213	6.1	0	T2	9
708498	60	F	SEVERE NPDR	SEVERE NPDR	CSME	321	346	8.4	1	T2	14
762432	65	F	MILD NPDR	MILD NPDR		97	115	5.2	0	T2	9
948417	54	M	MILD NPDR	MILD NPDR		105	161	7	0	T2	4
948427	65	M	MOD NPDR	MOD NPDR	CSME	132	158	7.8	0	T2	11
956717	61	F	MILD NPDR	MILD NPDR	CSME	177	198	6.6	0	T2	8
967143	63	M	MILD NPDR	MILD NPDR		101	111	6.7	0	T2	10
948644	47	M	MOD NPDR	MOD NPDR	CSME	113	139	5.8	0	T2	4
948338	45	M	MOD NPDR	MOD NPDR	CSME	220	213	7.1	0	T2	12

UHID	AGE	SEX	RIGHT EYE	LEFT EYE	MACULA	FBS	PPBS	HBA1C	PERIPHERAL NEUROPATHY	TYPE OF DM	DURATION
945507	62	M	MILD NPDR	MILD NPDR		177	198	5.9	0	T2	9
944967	50	F	MILD NPDR	MILD NPDR		103	111	6.1	0	T2	6
940421	53	M	MOD NPDR	MOD NPDR		201	212	5.4	0	T2	4
950236	61	m	MOD NPDR	MOD NPDR	CSME	235	263	9.7	0	T2	5
950343	74	M	MOD NPDR	MOD NPDR	CSME	338	357	10.2	1	T2	25
950920	55	M	ADED	ADED		319	411	9.3	1	T2	17