A STUDY OF DIABETIC RETINOPATHY IN PATIENTS WITH DIABETIC FOOT ULCER DISEASE

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LIST OF ABBREVATIONS

ABBREVATION	FULL FORM
DFU	Diabetic Foot Ulcer
DU	Deemed to be University
BLDE	Bijapur Lingayat District Educational
DR	Diabetic Retinopathy
ETDRS	Early Treatment Diabetic Retinopathy study
SD-OCT	Spectral Domain- Optical Coherence Tomography
OCT	Optical Coherence Tomography
DM	Diabetes Mellitus
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
IDF	International Diabetes Federation
ICMR	Indian Council of Medical Research
WHO	World Health Organisation
IFG	Impaired Fasting Glucose
PG	Plasma Glucose
FPG	Fasting Plasma Glucose
IGT	Impaired Glucose Tolerance
OGTT	Oral Glucose Tolerance Test
DME	Diabetic Macular Edema

DRS	Diabetic Retinopathy Study
WESDR	Wisconsin Epidemiologic Study on Diabetic Retinopathy
DRVS	Diabetic Retinopathy Vitrectomy Study
UKPDS	United Kingdom Prospective Diabetic Retinopathy Study
DCCT	Diabetes Control and Complications Trial
PDR	Proliferative Diabetic Retinopathy
NPDR	Non-Proliferative Diabetic Retinopathy
BP	Blood Pressure
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
OHA	Oral Hypoglycemic Agents
HLA	Human Leucocyte Antigen
NFL	Nerve Fiber Layer
GCL	Ganglion Cell Layer
ILM	Internal Limiting Membrane
ELM	External Limiting Membrane
IPL	Inner Plexiform Layer
OPL	Outer Plexiform Layer
INL	Inner Nuclear Layer
ONL	Outer Nuclear Layer
RPE	Retinal Pigment Epithelium
DAG	Diacyl Glycerol

PKC	Protein Kinase C
VEGF	Vascular Endothelial Growth Factor
IGF-1	Insulin like Growth Factor-1
AGEs	Advanced Glycation End Products
RAAS	Renin Angiotensin Aldosterone System
ROS	Reactive Oxygen Species
NO	Nitric Oxide
DNA	Deoxy-ribo Nucleic Acid
AR	Aldose Reductase
NADPH	Nicotinamide Adenine Dinucleotide Phosphate Hydrogen
NADH	Nicotinamide Adenine Dinucleotide+ Hydrogen
NAD	Nicotinamide Adenine Dinucleotide
RAGEs	Receptors for Advanced Glycation End Products
GAP	Glyceraldehyde 3 Phosphate
eNOS	Endothelial Nitric Oxide Synthase
AGAT	Acetyl glucosaminyl transferase
SOD	Super Oxide Dismutase
bFGF	Basic Fibroblast Growth Factor
EGF	Epidermal Growth Factor
TGF	Transforming Growth Factor
PDGF	Platelet Derived Growth Factor

CA	Carbonic Anhydrase
MA	Micro Aneurysms
PAS	Periodic Acid Schiff
BRB	Blood Retinal Barrier
ICAM	Intercellular Adhesion Molecule
NVD	New Vessels on the Disc
NVE	New Vessels Elsewhere
IRMA	Intra Retinal Microvascular Abnormalities
CSME	Clinically Significant Macular Edema
RCT	Randomised Controlled Trial
PRP	Pan Retinal Photocoagulation
SVL	Severe Visual Loss
FA	Fluorescein Angiography
CME	Cystoid Macular Edema
FAZ	Foveal Avascular Zone
RD	Retinal Detachment
PVD	Posterior Vitreous Detachment
TRD	Tractional Retinal Detachment
HRC	High Risk Characteristics
CiDME	Center-involving Diabetic Mavular Edema
MI	Myocardial Infarction
BCVA	Best Corrected Visual Acuity
IOP	Intra Ocular Pressure
IDO	Indirect Ophthalmoscopy

VMT	Vitreo Macular Traction
PPV	Pars Plana Vitrectomy
LVA	Low Vision Aids
NDCP	National Diabetes Control Programme
PAD	Peripheral Arterial Disease
CVI	Chronic Venous Insufficiency
OIS	Ocular Ischemic Syndrome
VTDR	Vision Threatening Diabetic Retinopathy
SUA	Serum Uric Acid
OR	Odds Ratio
CI	Confidence Interval
BUN	Blood Urea Nitrogen
OPD	Out Patient Department
IPD	In Patient Department
SPSS	Statistical Package for Social Sciences
ANOVA	Analysis of Variance
SD	Standard Deviation
CFT	Central Foveal Thickness
TMV	Total Macular Volume
AMT	Average Macular Thickness
GLUT1	Glucose Transporter 1
RBS	Random Blood Sugar
HbA1C	Glycosylated Hemoglobin

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ABSTRACT

AIMS AND OBJECTIVES:

The goal of this study was to compare and analyze the grades of Diabetic Foot Ulcer (DFU) with the severity of Diabetic Retinopathy (DR).

MATERIAL AND METHODS:

A cross-sectional study was carried out on 234 eyes of 117 subjects with various grades of DFU consulting BLDE (Bijapur Lingayat District Educational) (Deemed to be University)'s Shri BM Patil Medical College, Hospital and Research Centre, Vijayapura, Karnataka, from August 2022 to August 2023. A detailed history was taken, including demographics. Snellen's visual Acuity, anterior segment examination under slit lamp, mydriatic fundus examination with indirect ophthalmoscopy, and digital fundus photography were performed on all the subjects. DFU grading was done using the "Wagner's classification system of diabetic foot ulcers"[1]. Diabetic Retinopathy (DR) grading was based on the Early Treatment Diabetic Retinopathy Study (ETDRS) classification[2]. Optical Coherence Tomography (OCT) scanning of the macula was performed in all subjects using Spectral Domain- OCT (SD-OCT). Biochemical parameters HbA1C (%), Serum uric acid (mg/dl), Blood urea (mg/dl), Serum creatinine (mg/dl) were all compared against the grade of retinopathy along with the grade of DFU. SPSS (Statistical package for social sciences) software version 20 was used to present descriptive statistics for categorical parameters using frequency and percentage. Mean and standard deviation were used for continuous parametric data. Dependent and independent variables are differentiated using the ANOVA (Analysis of Variance) test.

The chi-square test was used to find out the association between the parameters. P value < 0.001 was considered highly statistically significant.

RESULTS:

The mean age of the patients was 55.63+/- 12.820 years. There were 80 males (68.4%) and 37 females (31.6%). Duration of diabetes mellitus (DM), biochemical parameters like HbA1C (%), Serum Creatinine (mg/dl), Blood Urea (mg/dl), and Serum Uric acid (mg/dl) were all directly proportionate to the severity of retinopathy, which was significant statistically with a P value < 0.001. Comparison of DFU grade with the severity of retinopathy showed a strong positive correlation with a P value < 0.001, which was highly statistically significant. Also, a comparison of DFU grade with OCT-measured Central Foveal Thickness (CFT) and Total macular volume, overall average macular thickness showed a strong positive correlation with a P value < 0.001.

CONCLUSION:

Our study reports a highly statistically significant correlation between the grades of DFU and severity of DR in all the subjects, thus concluding that patients with DFU have a higher risk of DR and vice-versa, pointing the significance of prompt and early screening for these two DM consequences to prevent further serious outcomes.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease, involving inappropriately elevated blood glucose levels[3]. Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM) are the two primary subtypes of diabetes mellitus (DM)[3]. T1DM and T2DM are primarily caused by faulty insulin production and/or action, respectively[3]. Low levels of insulin, insulin resistance of body tissues like striated muscles, fat tissues, and, to a lesser extent, liver genes are responsible for these metabolic abnormalities[4]. A number of different vascular disorders have a roughly doubled risk when diabetes mellitus is present[5]. DM is a major global public health problem. As of 2019, 463 million persons worldwide had been diagnosed with diabetes (DM), and the number is expected to rise in the years to come, according to the International Diabetes Federation (IDF)[6]. Globally, the prevalence of diabetes is predicted to reach 9.9% by 2045, affecting over 770 million people[6,7]. DM affects an individual's physical health and heavily burdens society and the economy[7]. In India, 10.1 crore people have diabetes, as per a 2023 study conducted by the Indian Council of Medical Research - India Diabetes (ICMR INDIAB)[8]. The glycation hemoglobin (HbA1c) test can be used to measure the nonenzymatic glycation of proteins and lipids that occurs as a result of chronic hyperglycemia[3]. Elevated glucose levels accelerate the glycation-induced damage to tiny blood vessels in the retina, kidney, and peripheral nerves[3]. This harm results in the avoidable consequences of blindness, dialysis, and amputation, as well as the traditional diabetic sequelae of diabetic retinopathy, nephropathy, and neuropathy[3]. A Diabetic Foot Ulcer (DFU) is an open sore or wound that most usually forms at the bottom of the foot or toes where repetitive trauma and pressure are faced[9]. It is the main uncontrolled diabetes mellitus complication that has a high rate of morbidity and

mortality[9]. DFUs frequently develop in foot areas that are vulnerable to pressure, which may result in osteomyelitis and amputations[10]. DFUs are extremely common; they harm 25% of diabetics over the course of their lives and result in around 1 million foot amputations globally[11,12]. Every 20 seconds, a limb is amputated due to a DFU[11,12]. DFUs carry a high risk of recurrence: around 40% within a year and 65% within three years[13].

A microvascular condition called diabetic retinopathy (DR) is brought on by the long-term consequences of diabetes mellitus[14]. Diabetic retinopathy can cause retinal damage that could potentially result in blindness and pose a hazard to eyesight[14]. In working-age individuals in the western world, it is the most prevalent cause of significant vision loss[14]. Recent epidemiological figures released by the American Academy of Ophthalmology indicate that 387 million people worldwide currently suffer from diabetes mellitus, and by 2035, that number is expected to rise to 592 million[15]. Diabetes-related retinopathy affects 93 million individuals worldwide[15]. People with DR might not feel any symptoms until severe damage happens to the retina. As the problem gets worse, new blood vessels grow on the retinal surface. Unfortunately, the damage to the retina happens to be in both eyes, so the vision is deteriorated gradually in these patients[16]. The onset of severe visual loss resulting from DR can be kept under control by reasonable control of blood sugars by early screening and treatment initiation with regular follow-ups[16]. Appropriate management of factors like blood pressure, blood glucose levels and lipid levels control the advancement of microvasculopathy.

NEED FOR THE STUDY

The link between DR and DFU has been the subject of more and more investigation in recent years. In DFU that is not mending, there is a chance that the disease will advance more quickly due to persistent inflammation and accompanying infections. Hence, patients with DFUs should be monitored by an ophthalmologist. Since DR is the most common complication of diabetes and is expected to be more in number in the future[17]. Early identification of DFU and DR would enhance the quality of life and reduce physical, mental, and visual handicap in this population[18]. In a study conducted on DR in patients with DFU in South India by Thoiba Karam et al[19] it was found that there was an increased presence of the South Indian cohort with DFU disease. Establishing the association between the two will help establish an integrated management strategy for these two consequences of diabetes.

Despite the magnitude and impact of the two debilitating consequences of DM, not enough research results are available considering the association between the two entities. Considering the pathogenic mechanisms shared between the two conditions, there is a possibility for a relationship in the clinical features between the two entities. Few studies on the same subject proved no correlation between the two entities. In comparison, few other studies on the same proposed a direct proportional relationship between the severities of the two entities. There exists a lot of ambiguity on this subject, which needs to be looked into further by more studies. Therefore, the present study has been conducted to investigate the potential correlation between the severities of the DFU and DR entities.

AIMS AND OBJECTIVES OF THE STUDY

The goal of this study was to compare and analyze the grades of Diabetic Foot Ulcer (DFU) with the severity of Diabetic Retinopathy (DR).

REVIEW OF LITERATURE

DIABETES MELLITUS

DEFINITION

A class of metabolic disorders known as diabetes is defined by elevated blood sugar levels brought on by deficiencies in either insulin production, insulin action, or both[20]. Diabetes's chronic hyperglycemia is linked to long-term harm, malfunction, and organ failure, particularly to the kidneys, eyes, heart, nerves, and blood vessels[20].

DIAGNOSTIC CRITERIA FOR DIABETES MELLITUS

The Expert Committee on Diagnosis and Classification of Diabetes Mellitus identified an intermediate category of people in 1997 and 2003 whose blood glucose levels are higher than normal but do not match the criteria for diabetes[21,22]. These individuals were classified as having impaired glucose tolerance (IGT) [2-hour oral glucose tolerance test (OGTT) values ranging from 140 mg/dl to 199 mg/dl] or impaired fasting glucose (IFG) [fasting plasma glucose (FPG) levels 100 mg/dl to 125 mg/dl][21,22].

It has been stated that those who have IFG and/or IGT are pre-diabetic, meaning that they have a comparatively greater chance of developing diabetes in the future[20].

In 1997, the first Expert Committee on the Diagnosis and Classification of Diabetes Mellitus revised the diagnostic criteria, using the observed association between FPG levels and the presence of retinopathy as the key factor with which to identify threshold glucose level[20]. For decades, the diagnosis of diabetes has been based on glucose criteria, either the 75-g OGTT or the FPG[20]. The Committee analyzed information from three cross-sectional epidemiologic studies that measured glycemia as FPG, 2-h PG (2

hourly plasma glucose), and HbA1c (glycosylated hemoglobin), and evaluated retinopathy using fundus photography or direct ophthalmoscopy[20]. These investigations showed glycemic thresholds below which retinopathy was not as common and at which retinopathy grew in a seemingly linear manner[20]. For each measure within each group, the deciles of the three measurements at which retinopathy started to grow were the same[20]. Furthermore, there were similarities in the glycemic levels among the populations above which retinopathy increased[20]. These results validated the established diagnostic 2-hour PG value of ≥ 200 mg/dl and contributed to the development of a new diagnostic cut point for FPG of ≥ 126 mg/dl[20]. As with the diagnostic thresholds for FPG and 2-h PG, there is an inflection point for the prevalence of retinopathy related with the diagnostic HbA1c cut point of 6.5%[23].

DIABETIC FOOT

DEFINITION

Diabetic foot ulcer, as defined by the World Health Organisation (WHO), is an infection, ulceration, and profound tissue destruction associated with peripheral neurological abnormalities secondary to multiple degrees of peripheral vascular abnormalities in the lower extremities in people with DM.

DFU GRADING

Wagner's classification of diabetic foot ulcers[1]

Wagner's system of classification of diabetic foot ulcers

Wagner's Classification[1]	
Grade 0	Skin intact, but bony deformities lead to "foot at risk."
Grade 1	Superficial ulcer
Grade 2	Deeper, full-thickness extension
Grade 3	Deep abscess formation or osteomyelitis
Grade 4	Partial Gangrene of forefoot
Grade 5	Extensive Gangrene

Table 1: Wagner's classification of diabetic foot ulcers[1]

(*Note: Table source*[1])

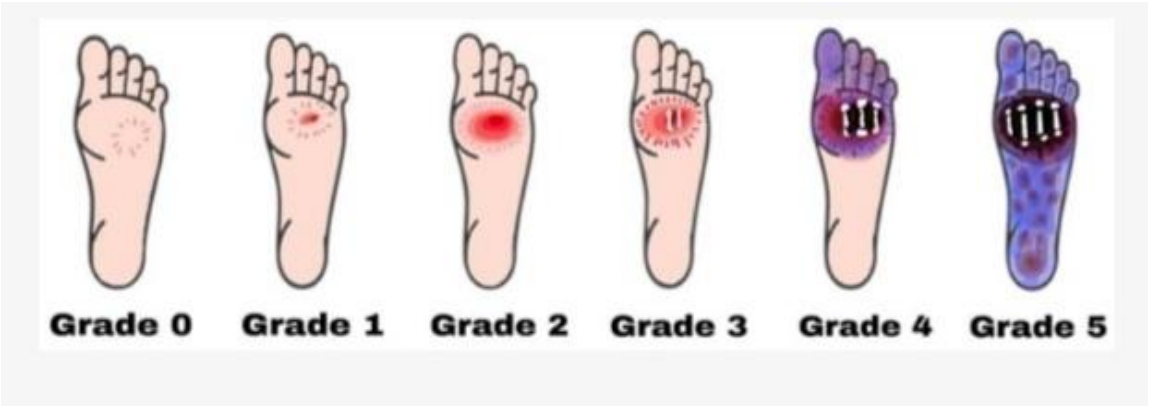


Figure 1: Pictorial representation of Wagner's system of classification of diabetic foot ulcers

(Note: Image source[24])

OCULAR MANIFESTATIONS OF DM

Lids: Boils, chalazia, xanthelasma, cranial nerve palsies (seventh, sixth, third, and fourth) and cellulitis are orbital and lid features[25].

Conjunctiva: Pingueculae, pterygia, and convoluted and dilated vessels—which are frequently located in the inferior bulbar region—are examples of conjunctival characteristics[26]. Diabetes-related microvascular problems include tortuosity and vein dilation[26].

Cornea: Patients with diabetes mellitus also frequently have corneal abnormalities, including damage to the corneal endothelium, recurrent corneal erosion, chronic epithelial defects, and superficial punctate keratitis[27]. Reduced corneal sensitivity has also been observed in diabetic patients as a component of global sensory neuropathy[28].

Iris: Four grades of diabetic iridopathy were distinguished on the extent of rubeosis: I- Peri-pupillary vessel dilatations with leakage, II- Early neovascularisation mainly in the chamber angle, III- Prominent rubeosis with or without neovascular glaucoma, and IV- Florid rubeosis[29]. Diabetes patients also have sluggishly reacting pupil due to autonomic neuropathy.

Pupil: Patients who have diabetes usually have greater miotic tendency for pupils[30]. The histological studies showed the loss of nerve terminals from the dilator muscle[31]. Diabetes patients hence have sluggishly reacting pupil to the light.

Changes in refraction: Duke-Elder had earlier reported a shift towards myopia or hyperopia associated with hyperglycemia or hypoglycemia, respectively[32]. Variations in the eye's refractive condition could be a sign of diabetes[33]. These may be myopia or hypermetropia[33]. An increase in the crystalline lens's thickness and curvature could be the cause of myopia[33]. But most patients show hyperopic changes.

Diabetes's impact on the posterior cornea's refractive power was documented by Wiemer et al[34]. Since this alteration had no effect on the total corneal power, it is most likely the result of lens-related refractive changes that diabetic patients experience[34]. Waite and Beetham[35] examined the paralysis of accommodation in 21% of diabetes patients, with the majority of these individuals falling between the 20–50 age range[35].

Changes in lens:

Diabetes also affects pharmacological pupil dilatation and lens transparency[33]. Patients with diabetes may get cataracts as a result of the diabetes itself or from accelerated senile cataract, in which case the cataract develops sooner than usual[33]. Similar to retinopathy, the length of time and degree of diabetes control play a significant role in the development and treatment of cataracts[33]. 987 participants (53%) in one research developed cataracts in one or both of their eyes[36].

DIABETIC RETINOPATHY

The most frequent ocular microvascular consequence of diabetes mellitus is diabetic retinopathy (DR). DR is still a global burden, affecting over 100 million people globally and predicted to rise in number despite a few recent studies suggesting a reduction in

the incidence of visual impairment from DR in developed countries due to improved treatment modalities[16,17].

HISTORY

Table 2: History of diabetic retinopathy

YEAR	SCIENTIST/ STUDY	CONTRIBUTION
2nd Century AD	Aretaeus of Cappadocia[37]	Introduced term Diabetes[37]
1846	Appokinaire Bouchardat[38]	Development of visual loss in absence of cataract in diabetes[38]
1855	Eduard Jager[39]	First observed diabetic macular changes[39]
1869	Henry Nayes[40]	Link between DM and Maculopathy[40]
1872	Edward Nettleship[41]	Cystoid macular degeneration in diabetic patients[41]
1876	Nettleship and Sir Steven Mackenzie[42]	Description of abnormal retinal changes induced by diabetes[42]
1876	Wilhalm Menz[43]	Paper on "Retinitis Proliferans"[43]
1890	Julius Hirschberg[44]	Classified DR into 4 types[44]: 1. Retinitis centralis punctuate 2. Hemorrhagic form 3. Retinal infarction 4. Hemorrhagic glaucoma
1943	Arthur James Ballantyne[45]	Role of capillary wall alterations in diabetic patients[45]
1950	Gerhard Meyer Schwickerath[46]	Treatment with photocoagulation[46]
1953	Poulsen[47]	PDR progression decreased in postpartum pituitary necrosis (Simmond's disease)[47]
1963	Paul Wetzig and colleagues[48]	Clinical application of photocoagulation for DR[48]

1970	William Beetham and Lloyd Aiello[49]	Effectiveness of photocoagulation in diabetic neovascular retinopathy[49]
1976	Diabetic Retinopathy Study (DRS)[50]	Preliminary report on effects of photocoagulation[50]
1984	WESDR (Wisconsin Epidemiological Study on Diabetic Retinopathy)[51]	DR prevalence[51]
1985	DRVS (Diabetic Retinopathy Vitrectomy Study)[52]	Effect of early vitrectomy for severe vitreous hemorrhage[52]
1989	ETDRS (Early Treatment Diabetic Retinopathy Study)[53]	Effect of argon laser and aspirin on DR[53]
1993	DCCT (Diabetes Control and Complications Trial)[54]	Effect of intensive glycemic control on DR[54]
1998	UKPDS (United Kingdom Prospective Diabetes Study)[55]	Effect of Blood Pressure (BP) and blood sugar levels on DR[55]

EPIDEMIOLOGY:

About 77 million people in India have diabetes, and by 2045, that figure is expected to rise to 125 million[56].

In India, the current estimate is that one in five adults has diabetes[56,57,58,59].

The majority of people with type 2 diabetes are diagnosed in their working years; other people are diagnosed later on, once problems start to arise[56,58]. The rate of blindness from VTDR is expected to climb in tandem with the nation's exponential rise in the

prevalence of diabetes if screening and treatment for diabetic retinopathy are not given top priority[56,58].

Globally, the number of people with visual impairment has reduced, but the number of diabetic retinopathy blind individuals has increased from 0.2 million to 0.4 million[60]. Diabetic retinopathy is the primary cause of blindness in persons of working age and one of the leading worldwide causes of irreversible blindness[61,62]. About 80% of individuals with type 2 diabetes are estimated to experience retinopathy[61,62].

RISK FACTORS

1. HbA1C[63]: In a retrospective cohort research involving 1125 diabetic patients, HbA1c values were considerably greater in individuals with retinopathy than in those without[63].

2. Elevated serum lipids[64]: The Diabetes Control and Complications Trial (DCCT) showed a relationship with the occurrence of retinopathy and elevated very low and low density lipoproteins[64].

3. Blood pressure[65]: The UKPDS showed that the incidence of retinopathy was associated with systolic blood pressure[65].

4. BMI[66]: It has been demonstrated that obesity and being overweight are two risk factors for developing diabetes mellitus[66].

5. Pregnancy[67]: A woman's pregnancy could raise her risk of developing DR by 2.3 times, and 29% of women would experience DR regression in the postpartum period[67]. Pregnant women who have retinopathy have a significantly increased chance of developing DR; 47% of cases advance, and 50% of cases require laser treatment[67].

ANATOMY OF RETINA [68,18]

With the exception of the optic nerve region, the retina lines the whole posterior region of the eye. It then extends anteriorly and finishes 360 degrees circumferentially at the ora Serrata, where it joins the ciliary body[68,18].

There are 10 different layers of neurons in the retina, and these layers are joined by synapses. The cells can be further classified into three primary cell types: glial, neuronal, and photoreceptor[68,18]. The following are the layers that go from the nearest to the front anterior to the posterior[68,18]:

1. The ILM, or inner limiting membrane
2. Layer of nerve fibers (NFL)
3. Layer of ganglion cells (GCL)
4. The IPL, or inner plexiform layer
5. The INL, or inner nuclear layer
6. The middle limiting membrane
7. The OPL, or outer plexiform layer
8. The ONL, or outer nuclear layer
9. The ELM, or external limiting membrane
10. The rod and cone layer

These retinal layers contain a variety of cell types, each with a specialized function that aids in converting incoming photons into action potentials that the brain's cortices interpret as three-dimensional vision[68,18].

The six different cell types in the retina include[68,18]:

1. Rods
2. Cones

3. Retinal Ganglion cells

4. Bipolar cells

5. Horizontal cells

6. Amacrine cells

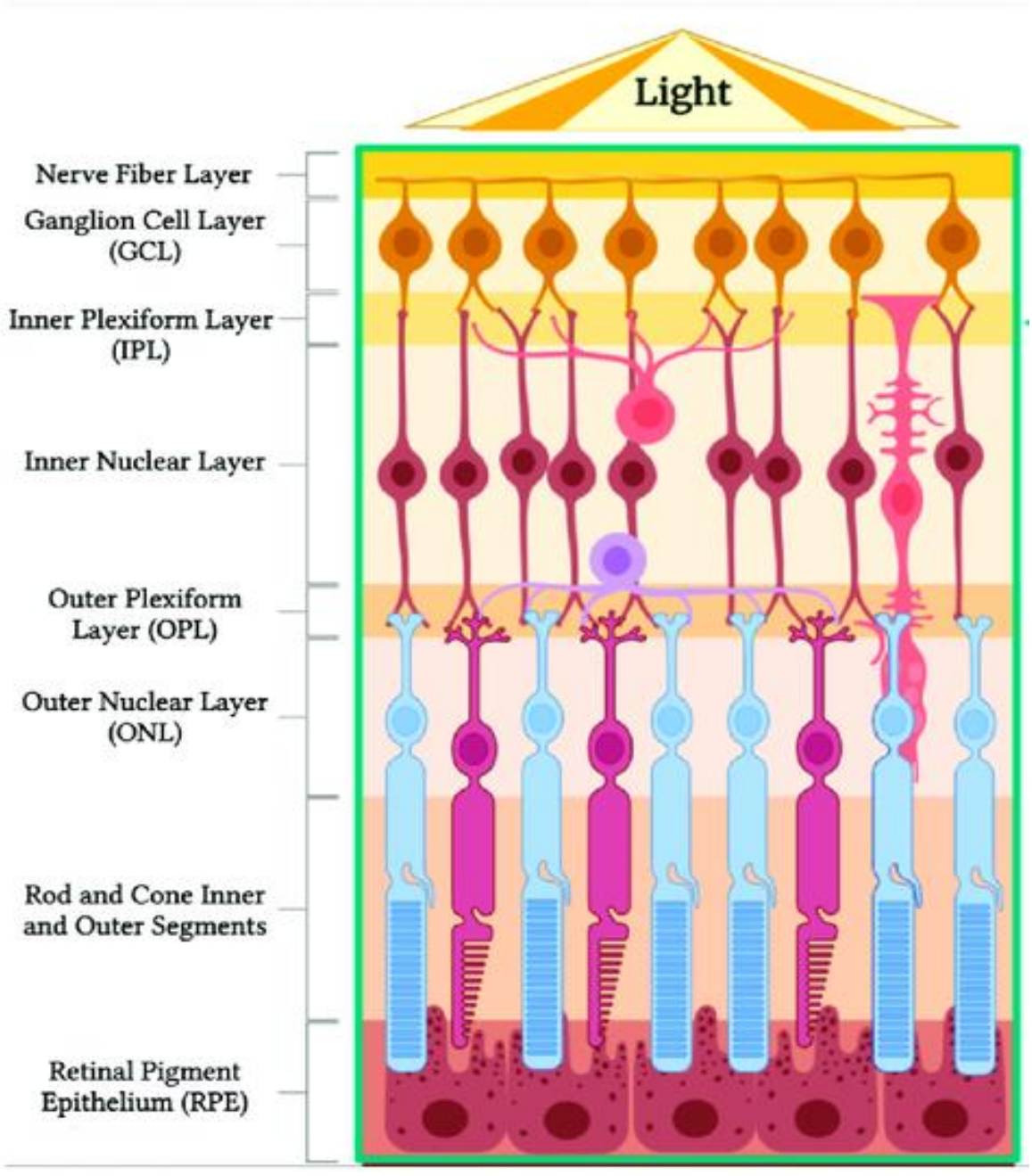


Figure 2: Gross anatomical depiction of layers of retina

(*Note: Image source*[69])

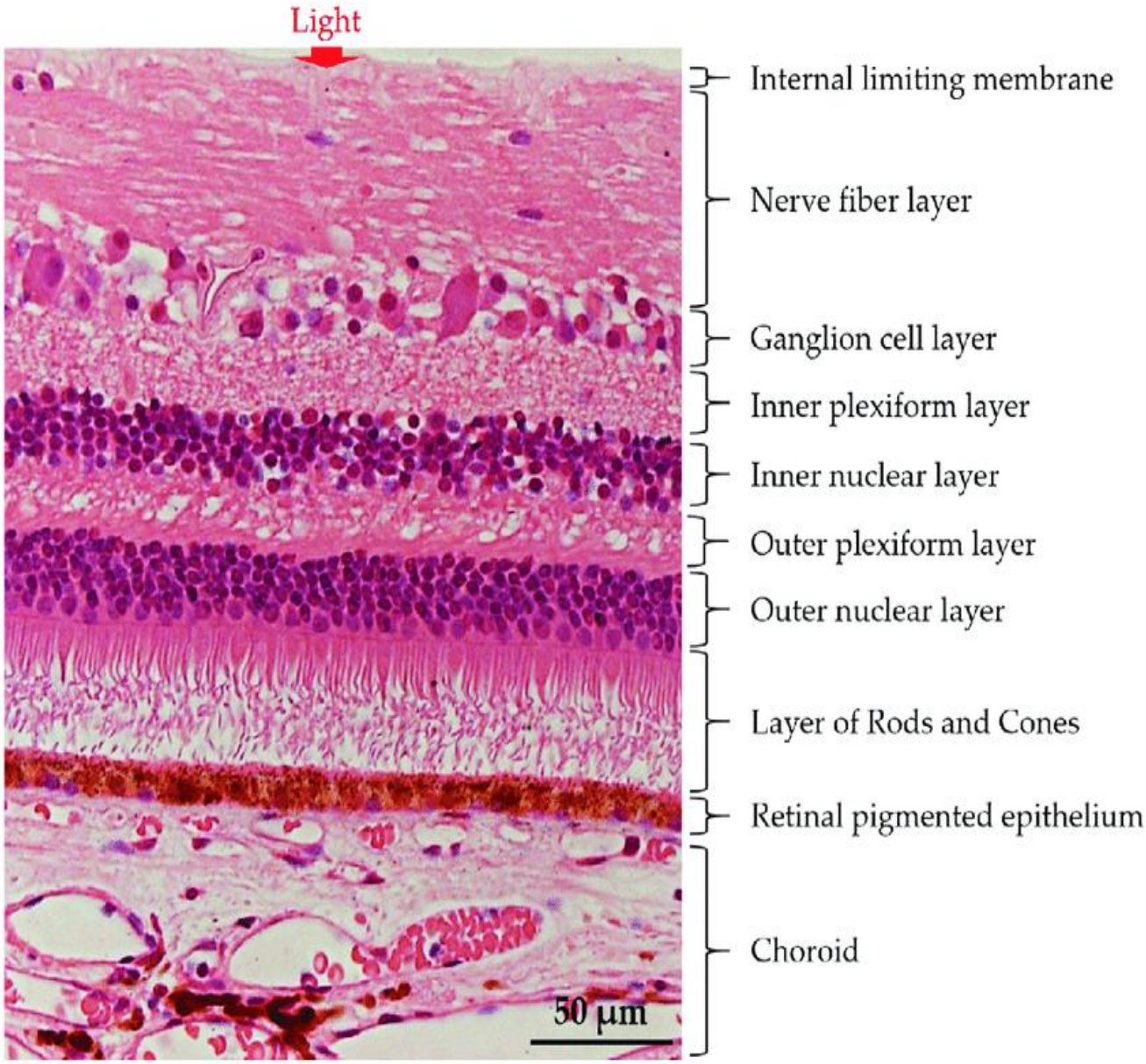


Figure 3: Histological depiction of layers of retina

(Note: Image source[70])

PATHOGENESIS

The following biochemical pathways are involved in the pathogenesis of diabetic retinopathy:

Polyol Pathway:

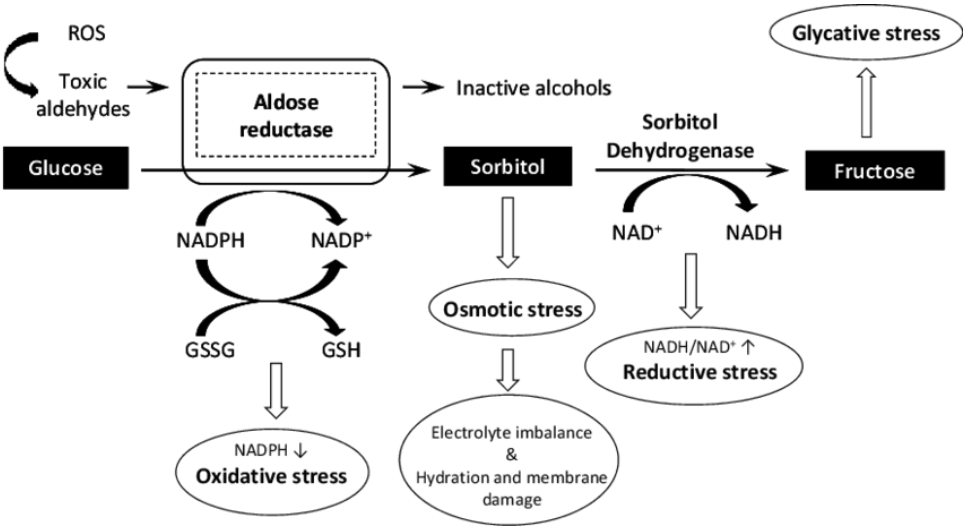


Figure 4: Polyol Pathway

(*Note: Image source*[71])

Excess glucose is diverted into the polyol pathway[72]. Aldose reductase (AR) in the retina uses the cofactor NADPH to convert glucose to sorbitol[72]. Sorbitol is transformed into fructose by Sorbitol Dehydrogenase (SDH)[72]. Cell membranes are impermeable to sorbitol; hence, they accumulate within the cell, resulting in a slow sorbitol metabolism to fructose[72]. Cofactor NADPH is also required for glutathione reductase to regenerate glutathione in cells[72]. The cells ability to function as antioxidants is diminished as a result of the decreased availability of NADPH[72]. Osmotic injury is one of the many detrimental effects of sorbitol accumulation on retinal cells[72]. Moreover, the fructose produced by this pathway can be converted to 3-deoxyglucosone by phosphorylating it to form fructose-3-phosphate[72]. Both of these processes culminate in the formation of solid glycating agents and AGEs. The abnormal change in the NADH/NAD+ ratio

caused by the drop in NADPH levels activates the enzyme NADH oxidase, which in turn elevates the production of Reactive Oxygen Species (ROS) in the cell[72].

Non-enzymatic Protein Glycation:

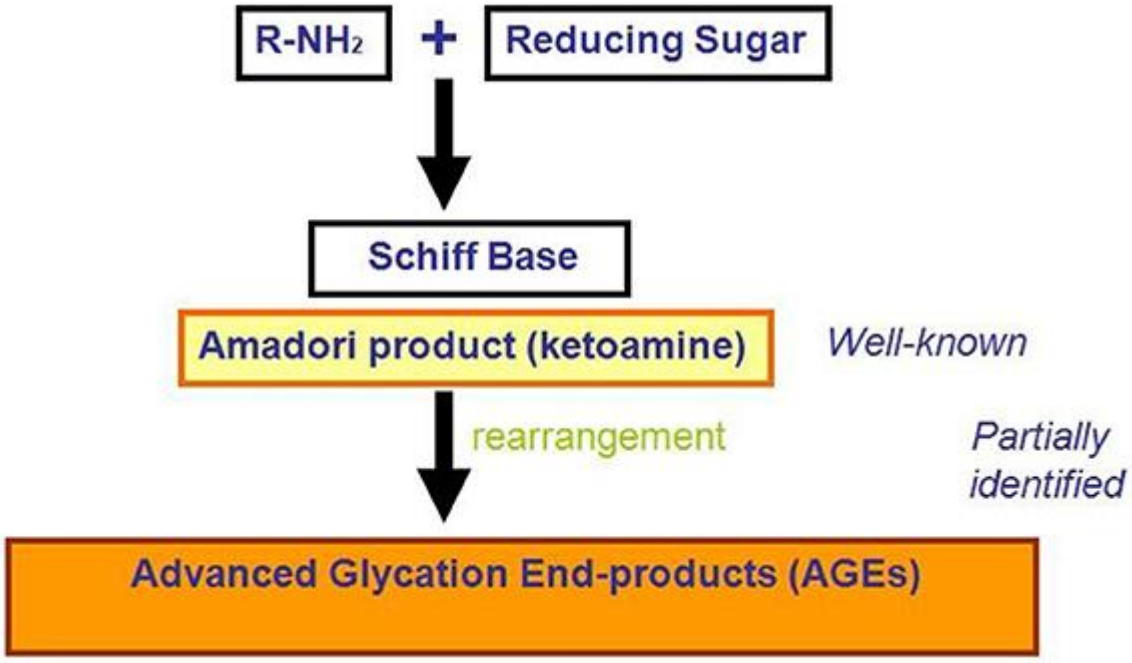


Figure 5: Formation of AGEs

(*Note: Image source*[73])

AGEs form slowly but constantly in the human body, starting from embryonic development[74]. Their production accelerates in DM due to increased glucose availability[74]. AGEs are a group of molecules produced due to a non-enzymatic reaction between reducing sugars and amino groups of proteins[74]. The first product of this pathway is known as Schiff's base[74].

A key feature of AGEs is their ability to covalently crosslink the proteins, altering their anatomy and functionality in cell matrix, basement membranes, and vessel walls[74]. They also interact with several cell-surface receptors like Receptor for Advanced

Glycation Endproducts (RAGEs), activating the cell towards pro-oxidant and pro-inflammatory events[74].

Protein Kinase C (PKC) Activation:

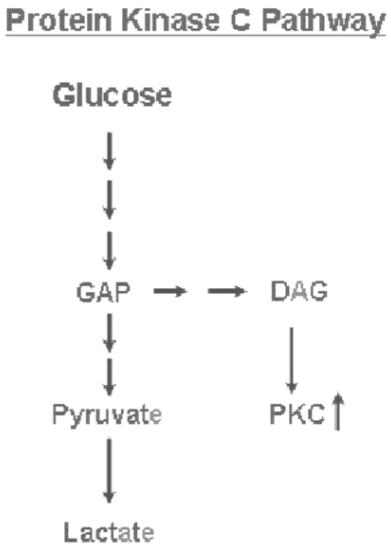


Figure 6: Protein Kinase C pathway

(*Note: Image source*[75])

GAP- Glyceraldeyde 3 phosphate

DAG- Diacyl glycerol

PKC- Protein kinase C

The ten distinct enzymes that make up the PKC family have an isoform called PKC-beta that is thought to be directly linked to the onset of DR[76]. It is a serine/threonine kinase linked to signal transduction processes in response to growth factor, hormone, and neural cues[76]. Hyperglycaemia increases glucose flux by glycolysis, increasing the synthesis of Diacyl glycerol (DAG), a key activator of PKC[76]. Several studies reported an increased expression of DAG and PKC in DM[76]. Activated PKC alters vascular endothelial permeability, retinal hemodynamics, leukostasis and VEGF expression in the retina[76].

Hemodynamic Changes[77]:

The WESDR and the UKPDS have reported the significant role of BP in the progression of PDR. According to published research, those with diabetes are more likely to develop hypertension. Hypertension contributes to the progression of DR through mechanical stretch on the endothelial cells, increased retinal perfusion, and increased blood viscosity, leading to severe endothelial dysfunction[18].

Subclinical inflammation and leukostasis:

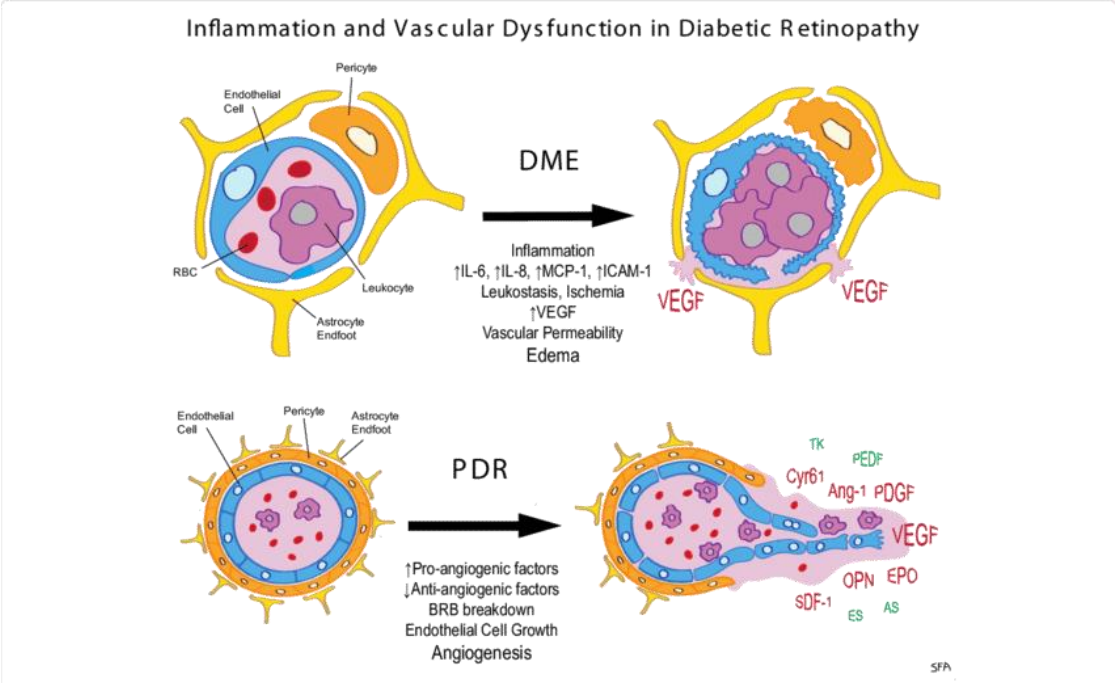


Figure 7: Subclinical inflammation

(*Note: Image source*[78])

Hoorn Study highlighted the role of subclinical inflammation in the development of DR[79]. Retinal hemorrhages result from the activation of endothelial nitric oxide synthase (eNOS), the development of new, weak vessels, and enhanced permeability caused by VEGF as a result of subclinical inflammation in the retinal tissue[79]. Conversely, leukostasis increases the local inflammatory response in the retinal tissue by causing capillary blockage and ROS-mediated cell death[79,18].

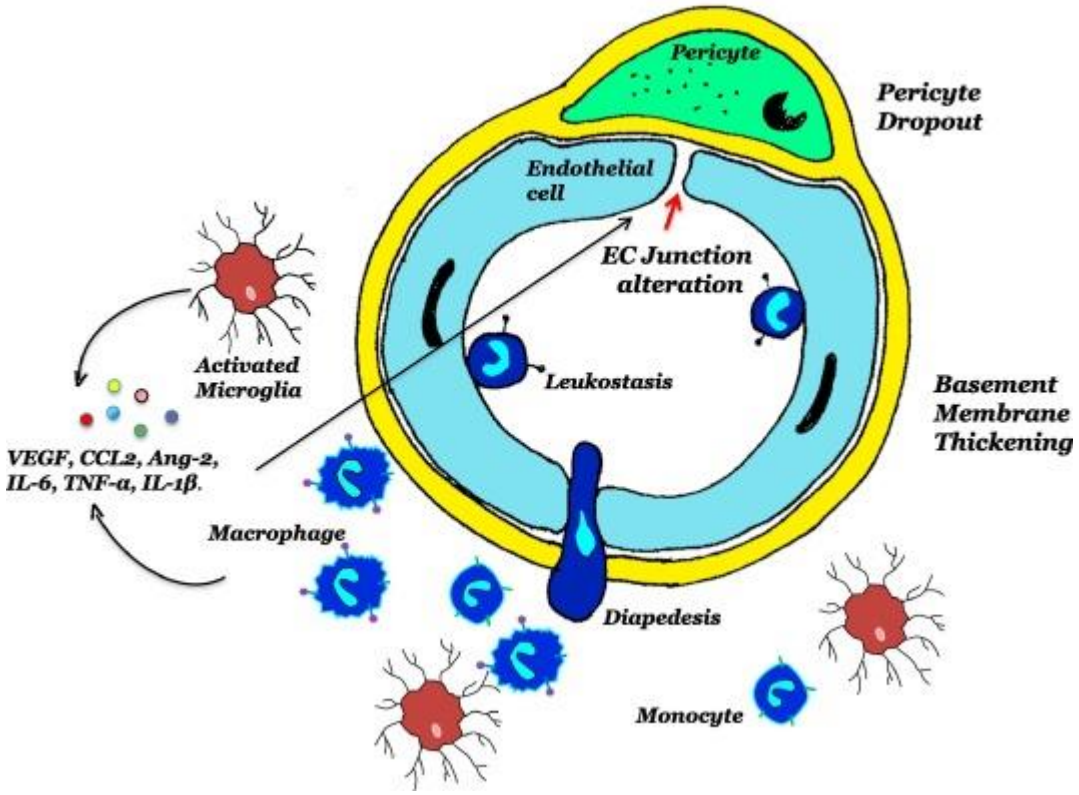


Figure 8: Leukostasis

(*Note: Image source*[80])

In several studies, inflammatory activity positively correlates with the progression of DR[81]. Patients with diabetes exhibit increased activity of the inflammatory enzyme Acetylglucosaminyltransferase (AGAT). Increased leukostasis results from this enzyme's increased O-glycosylation type changes in the carbohydrate chains that cover leukocyte surfaces.

Peripheral neuropathy and DR advancement were positively linked with this enzyme's activity[82,18].

Oxidative Stress:

Oxidative stress is a gross imbalance between reactive oxygen radicals and the antioxidant defenses in a biological system[83]. Tissue damage secondary to oxidative stress is the chief cause of chronic disease state of the cell and cell death[83].

Typically, ROSs are detoxified by interaction with sequestering agents like thioredoxin, glutathione, vitamin E, Superoxide Dismutases (SODs), catalase, glutathione peroxidase, and thioredoxin reductase. Hyperglycemia increases oxidative stress in the pathogenesis of DR[84].

Growth Factors:

During puberty, there was clinical evidence of retinopathy due to growth factors and the same pathology was rarely observed in growth hormone-deficient dwarfs[18]. Also, few studies in the 1970s showed that pituitary ablation slowed the progression of DR[18].

The main growth factors that are involved include the following: erythropoietin, stromal-derived factor-1, epidermal growth factor (EGF), platelet-derived growth factors (PDGFs), transforming growth factor-beta 2 (TGF-B2), angiopoietin-1 and 2, basic fibroblast growth factor (bFGF), and Insulin-like Growth Factor-1 (IGF-1)[85,18].

Carbonic Anhydrase:

Intraocular VEGF increment is correlated to increased vascular permeability, contributing to hemorrhages and exudates leading to NPDR, angiogenesis, and vasculogenesis leading to PDR, respectively.

Ubiquitous metalloenzymes, the Carbonic anhydrases (CAs), function by conversion of carbon dioxide to proton ions and bicarbonate. According to recent research by Gao et al., the concentrations of CA in diabetes patients were significantly greater than those in healthy controls. Furthermore, acetazolamide and other CA inhibitors were demonstrated to decrease the progression of DR. CA inhibitors can help DR patients by

decreasing humour secretion, promoting vasodilatation, enhancing blood flow to the eye area, preventing platelet aggregation, and lowering vascular permeability[86,18].

Retinal Neurodegeneration:

Structural and functional damage to non-vascular cells like ganglion cells, glial cells, and microglia also contribute to the pathogenesis of DR. Literature reports that retinal neuronal degeneration takes place even before the development of Micro-Aneurysms (MAs).[87-91]

PATHOLOGY

1. Capillary basement membrane thickening[92-95]

Electron microscopic studies showed a thickened capillary basement membrane with an increased type IV collagen and Swiss cheese vacuolization. Basement membrane functions are deranged in diabetes.

2. Loss of microvascular intramural pericytes[94]

Endothelial cells of capillary walls are surrounded by pericytes, which contain the enzyme aldose reductase lacking in endothelial cells, which causes sorbitol accumulation in the pericytes. The dead pericyte resembles an empty, balloon-like space bulging from the capillary wall. The average ratio of pericytes and endothelial cells is 1:1. In DR, pericyte count drops severely[94].

3. Microaneurysms

Retinal preparations processed with trypsin revealed MAs as hypercellular saccular protrusions of the capillary wall that may hyalinize and become Periodic Acid Schiff stained [PAS].

4. Capillary acellularity

Retinal microvasculature loses all its cellularity.

5. Breakdown of Blood-Retinal Barrier (BRB)

Opening of Zonulae occludentes between adjacent endothelial cells causes the breakdown of BRB. Increased transport across the cells was noted via endocytic vesicles and cytoplasmic fenestrations of endothelial cells.

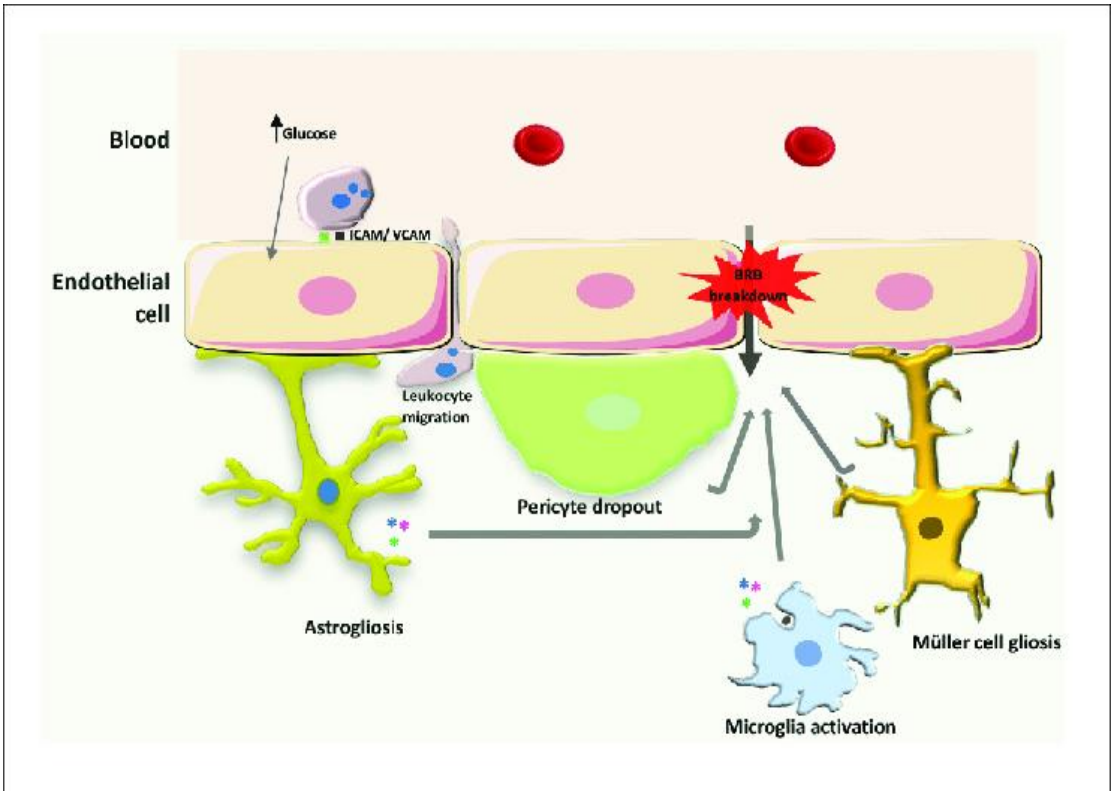


Figure 9: Breakdown of BRB

(*Note: Image source*[96])

Exudates

1. Hard exudates: Henle's layer lesions that are hard, yellow, and waxy and contain proteinaceous and fatty materials

2. Soft exudates or Cotton wool spots: Axon clusters of ganglion cells in the Nerve Fiber Layer (NFL). At the ischemic location, bullous dilatation (cytoid bodies) can be observed.

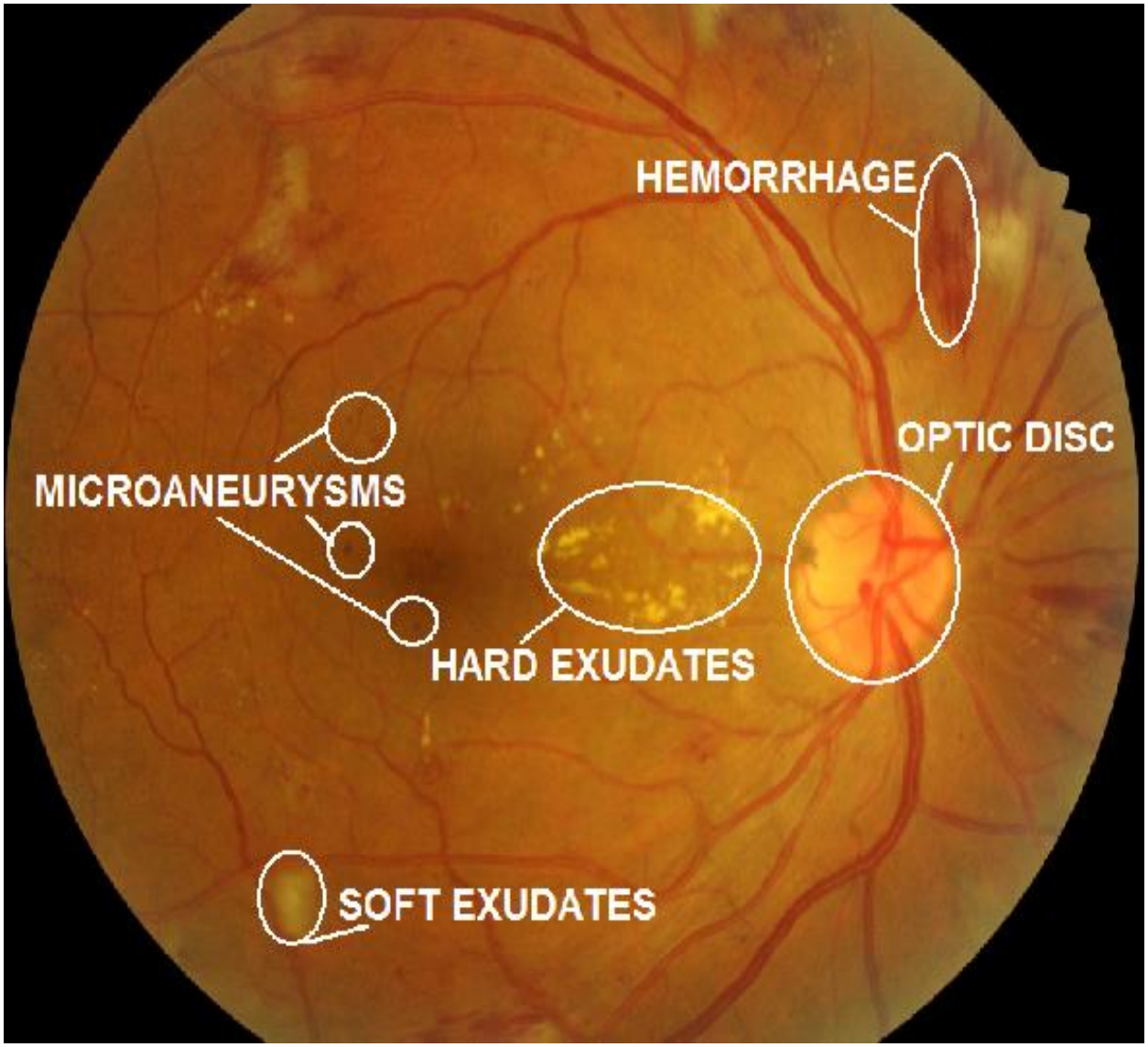
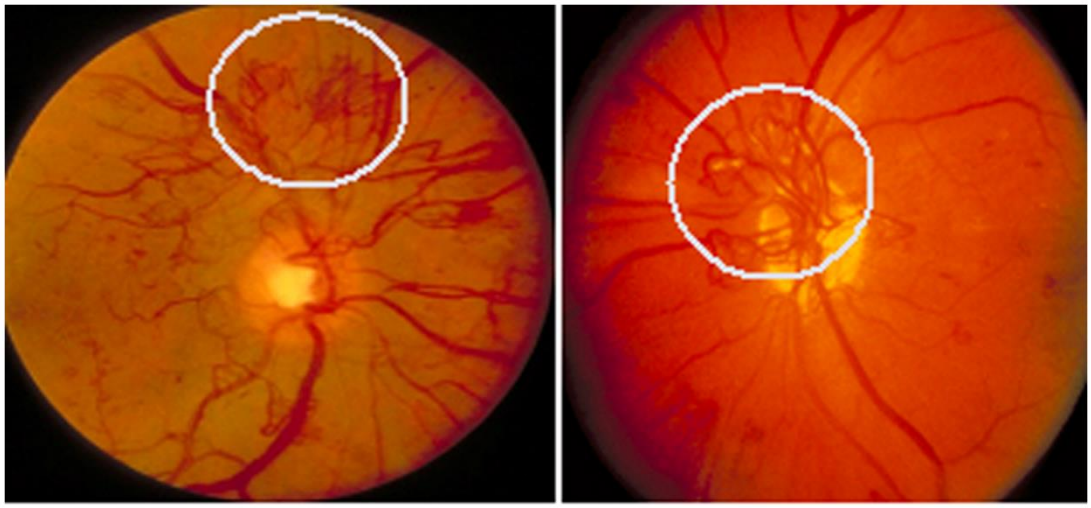


Figure 10: Clinical manifestations of posterior pole in moderate NPDR

(*Note: Image source*[97])

Neovascularisation[94,95]



(a) New vessels elsewhere (NVE) (b) New vessels on disc (NVD)

Figure 11: Neovascularisation in PDR

(*Note: Image source*[98])

The term "neovascularization" refers to the development of new, weak vascular channels in the retina, either outside or on the optic disc.

Stage 1: Naked vessel stage: Fine, new blood vessels lacking supportive connective tissue originating from the capillaries. They grow in the retinal plane, at times invading the vitreous cavity.

Stage 2: Connective tissue condensation stage: Connective tissue is laid down around the naked vessels, which eventually begin to condense.

Stage 3: Cicatrization stage. The size and number of new vessels decrease with an increase in the density of condensed connective tissue. Contraction of this tissue forms contraction bands.

DIABETIC RETINOPATHY CLASSIFICATION [2]

Based on the Early Treatment Diabetic Retinopathy Study (ETDRS)

ETDRS Level	Disease Severity	Definition
10	No retinopathy	Diabetic retinopathy absent
20	Very mild NPDR	MA only
35	Mild NPDR	MA plus hard exudates, soft exudates (cotton wool spots) and mild retinal hemorrhages
43	Moderate NPDR	MA plus mild IRMA or moderate retinal hemorrhages
47	Moderate NPDR	More extensive IRMA. Severe retinal hemorrhages or venous beading in 1 quadrant only
53	Severe NPDR	Severe retinal hemorrhages in 4 quadrants, venous beading in at least two quadrants, or moderately severe IRMA in at least one quadrant
61	Mild PDR	NVE < 1/2nd disc area in 1 or more quadrants
65	Moderate PDR	NVE ≥ 1/2nd disc area in 1 or more quadrants or NVD < 1/4–1/3rd disc area
71-75	High-Risk PDR	NVD ≥ 1/4–1/3rd disc area and vitreous hemorrhage
81-85	Advanced PDR	Fundus partially obscured

Table 3: ETDRS Final Scale of DR Severity[2]

(*Note: Table Source*[2])

Clinically Significant Macular Edema (CSME) is defined by ETDRS as follows: 1. Retinal thickening within 500 micrometres of the macula centre.

2. Hard exudates within 500 micrometres of the macular centre with adjacent retinal thickening. (or)

3. Retinal thickening of one disc area or more, with a portion of it residing within one disc diameter of the macula centre.

STUDIES ON DIABETIC RETINOPATHY

Early Treatment Diabetic Retinopathy Study (ETDRS)[99]

To determine the impact of laser in DR, a Randomised Clinical Trial (RCT) was conducted.

Results of ETDRS study:

1. Aspirin did not alter the progression of DR or vitreous hemorrhage.

2. Early Pan Retinal Photocoagulation (PRP) is not indicated in eyes with mild-moderate DR.

3. Early PRP reduced the risk of severe visual loss.

4. For DME, focal photocoagulation decreased the chance of mild vision loss.

Diabetic Retinopathy Study (DRS) [100]

This study assessed PRP's impact on DR.

One of the DRS's findings was a 50% decrease in the rates of severe vision loss (SVL) using xenon arc photocoagulation.

2. Patients with high-risk PDR benefited from it the most.

United Kingdom Prospected Diabetic Retinopathy Study (UKPDS)[101]

This RCT evaluated the effectiveness of intense BP and blood sugar control in type II diabetes patients.

Results of UKPDS:

Intense control of BP and blood glucose delayed DR progression and reduced the risk of microvascular complications.

Diabetes Control and Complications Trial (DCCT)[102]

This study evaluated the results of intense blood sugar control in DM-Type I.

Results of DCCT:

1. Strict blood sugar management slowed the development of DR by 76% and stopped it from progressing by 54%.
2. Additionally, it decreased the chances of nephropathy and peripheral neuropathy by 54% and 60%, respectively.

Diabetic Retinopathy Vitrectomy Study (DRVS)[103]

Investigating the function of vitrectomy in DR was the goal of this randomised prospective clinical study.

Results of DRVS:

Severe PDR benefitted more from early vitrectomy in Type I DM.

Wisconsin Epidemiologic Study on Diabetic Retinopathy (WESDR)[104]

The study reported the risk factors associated with DR and its prevalence.

CLINICAL FEATURES

I. NON-PROLIFERATIVE DIABETIC RETINOPATHY

Retinal capillary MAs, elevated endothelial permeability, and eventual capillary closure are among the pathophysiological processes associated with NPDR.

1. Microaneurysms

Localized enlargements of the capillary wall known as microaneurysms are frequently observed in diabetic individuals[105]. A greater diameter of 61 μm or more in a microaneurysm is linked to reduced visual acuity[106].

2. Hard exudates

Lipid and proteinaceous materials, including albumin and fibrinogen, that seep out of the compromised blood-retinal barrier make up the hard exudates. They are mostly found in the retina's outer plexiform layer[107,108,109].

3.Intra-retinal haemorrhages[110]

Superficial hemorrhages are flame-shaped as the blood accumulates in the superficial retinal layers parallel to the coursing nerve fibers.

Deep hemorrhages, also known as “Dot and blot hemorrhages,” are seen in the outer plexiform and inner nuclear layers, breaking through the confines of Muller cell processes.

4. Capillary closure

Patchy regions of the non-perfused retina with IRMA, haemorrhages, cotton wool spots, clusters of MAs, and venous beading are caused by capillary closure.

5. Cotton wool spots:

These white patches, which are also referred to as "soft exudates," are seen in regions of ischemia and vascular non-perfusion. Their edges extend into the surrounding retina.

6. Intra-retinal Mirovascular Abnormalities (IRMA):

Unlike new PDR arteries, intra-retinal microvascular shunts do not leak during fluorescein angiography (FA)[111].

II. MACULOPATHY

It is the principal cause of visual loss in DR, more commonly associated with non-insulin-dependent DM with an increased duration of DM. Maculopathy can present either as ischemia or edema. Edema can be focal or diffuse and can be clinically significant[111].

1. Focal macular edema:

a) Leakage spots from MAs and IRMAs.

b) Associated with rings of hard exudates and MAs.

2. Diffuse Macular Edema:

Diffuse retinal thickening with widespread capillary abnormality and diffuse leakage due to breakdown of BRB, often seen with Cystoid Macular Edema (CME).

3. Macular Ischaemia:

a) Areas of Capillary non-perfusion.

b) Clusters of MAs at the margins of nonperfusion.

c) Increased visual loss with normal appearing macula on clinical examination.

d) Foveal Avascular Zone (FAZ) enlargement.

4. Clinically Significant Macular Edema (CSME):

10% of DM patients have macular edema, of which 40% present with involvement of the center of the macula with significant visual loss[111].

PROLIFERATIVE DIABETIC RETINOPATHY (PDR)

PDR is the formation of NVD or NVE in the retina, and the most plausible explanation is the occlusion of parts of the retinal capillary bed, eventually leading to inner retinal layer ischemia. New vessels can be on the disc or elsewhere on the retina or even involve anterior chamber structures but are commonly seen within 45 degrees of the optic disc.

45% of cases develop new vessels elsewhere on the retina alone, and 45% create new boats both in and outside the optic zone[111].

STAGES OF PDR

Stage of proliferation

a) Fine new vessels are noted at the margins of the disc of size 1/8th to 1/4th caliber of a major retinal vein.

b) Seen more frequently along super-temporal veins growing along the plane of the retina or invading the vitreous.

c) Fibrous tissue deposition is noted around new blood vessels.

Stage of regression

At this point, the quantity and quality of vessels decline, and fibrous tissue replaces them.

PDR is classified as early, high-risk, and advanced according on the presence of phthisis bulbi, significant vitreous haemorrhage, and retinal detachment with macular involvement. Enucleation may be necessary as a result of a DR complication[111].

SEQUELAE

1. **Contraction of the vitreous**

a) Fibrous tissue production thickens the posterior vitreous next to the new formed veins.

b) The posterior vitreous is pulled forward by vitreous contraction.

d) Eventual Posterior Vitreous Detachment (PVD), which frequently happens temporally to the macula, usually happens along superotemporal arteries. Intraretinal haemorrhage is caused by traction over these veins[111].

2. Retinal Detachment with Traction (TRD)

The degree of vitreoretinal adhesions and vitreous shrinkage affect the severity of RD. The macula, which is often pulled nasally and vertically, is distorted and displaced as these adhesion bands contract.

3. Involutional DR

It is characterized by complete vitreous contraction, detachment, and reduced vessel caliber. Severe retinal ischemia eventually results in marked visual loss[112].

MILD NPDR

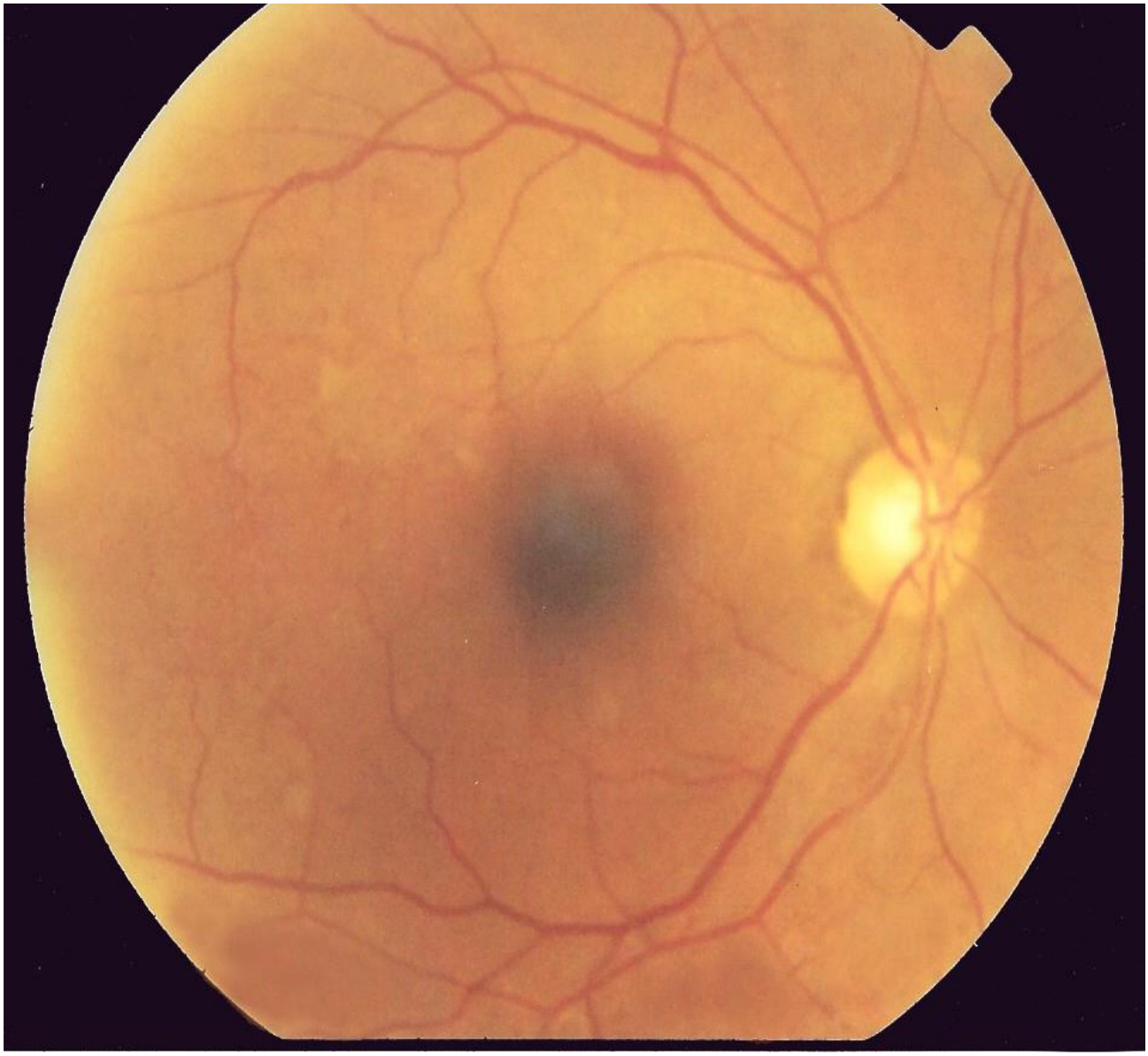


Figure 12: Mild NPDR

(*Note: Image source*[114])

MODERATE NPDR

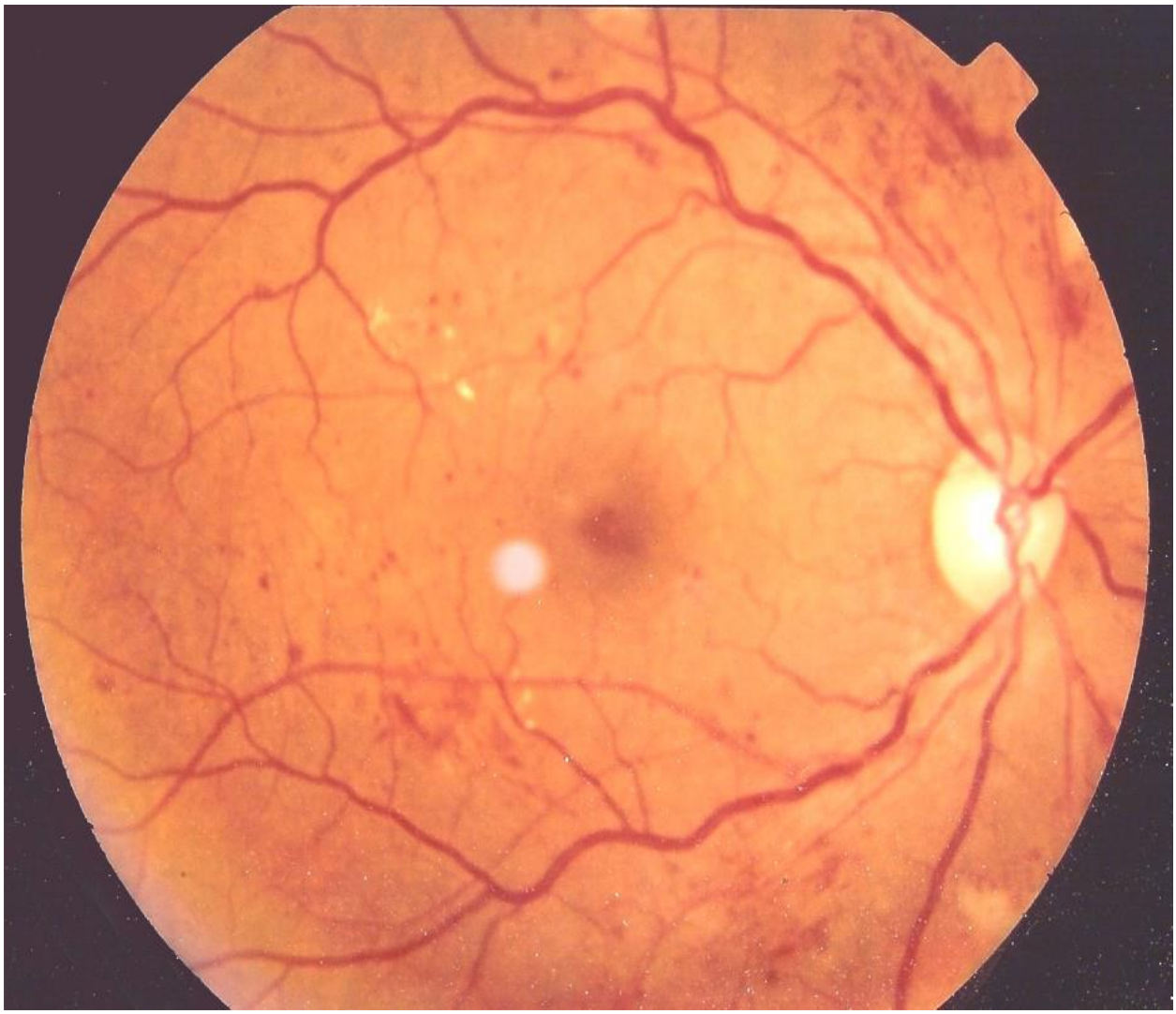


Figure 13: Moderate NPDR

(*Note: Image source*[114])

SEVERE NPDR

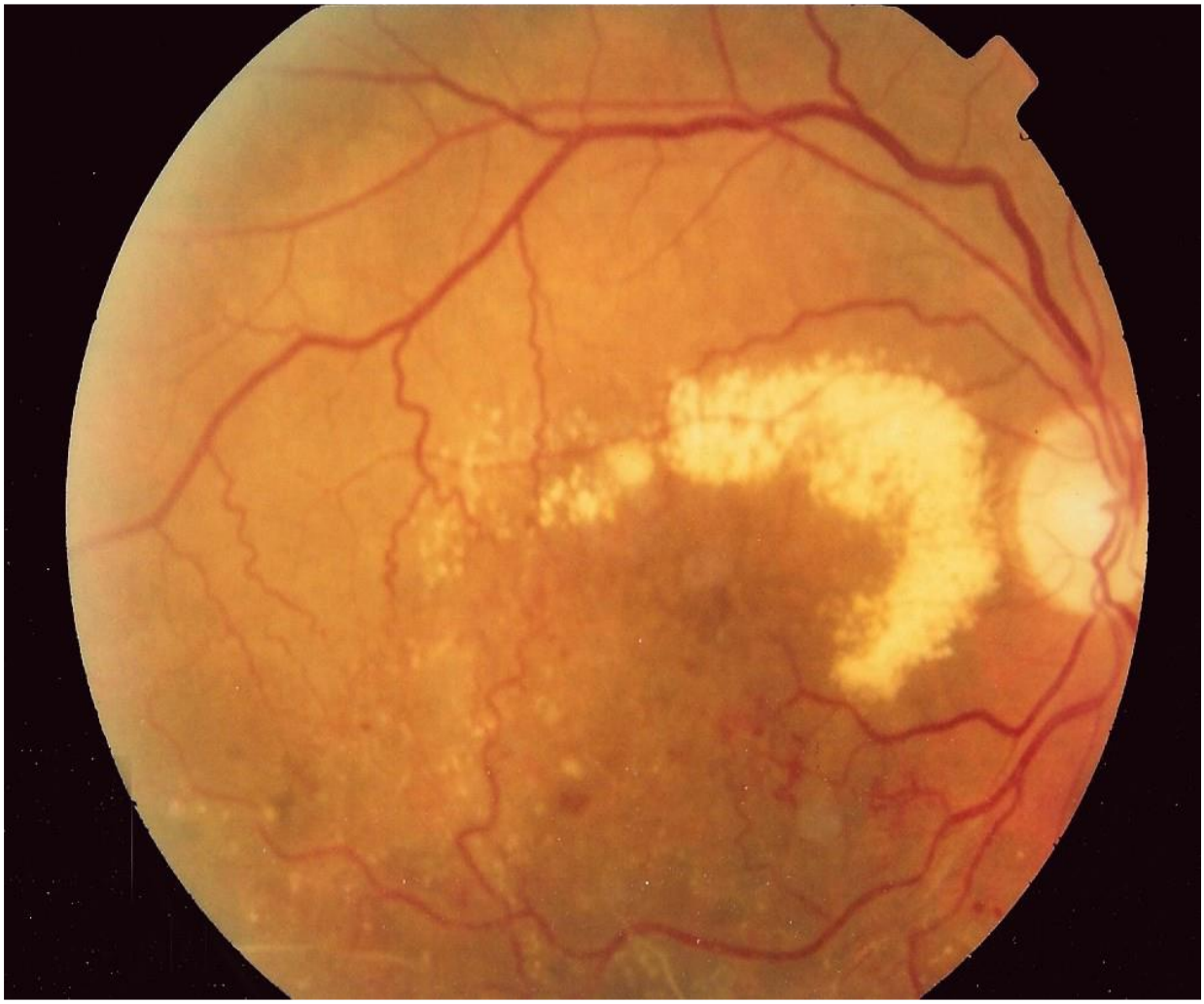


Figure 14: Severe NPDR

(*Note: Image source*[114])

VERY SEVERE NPDR

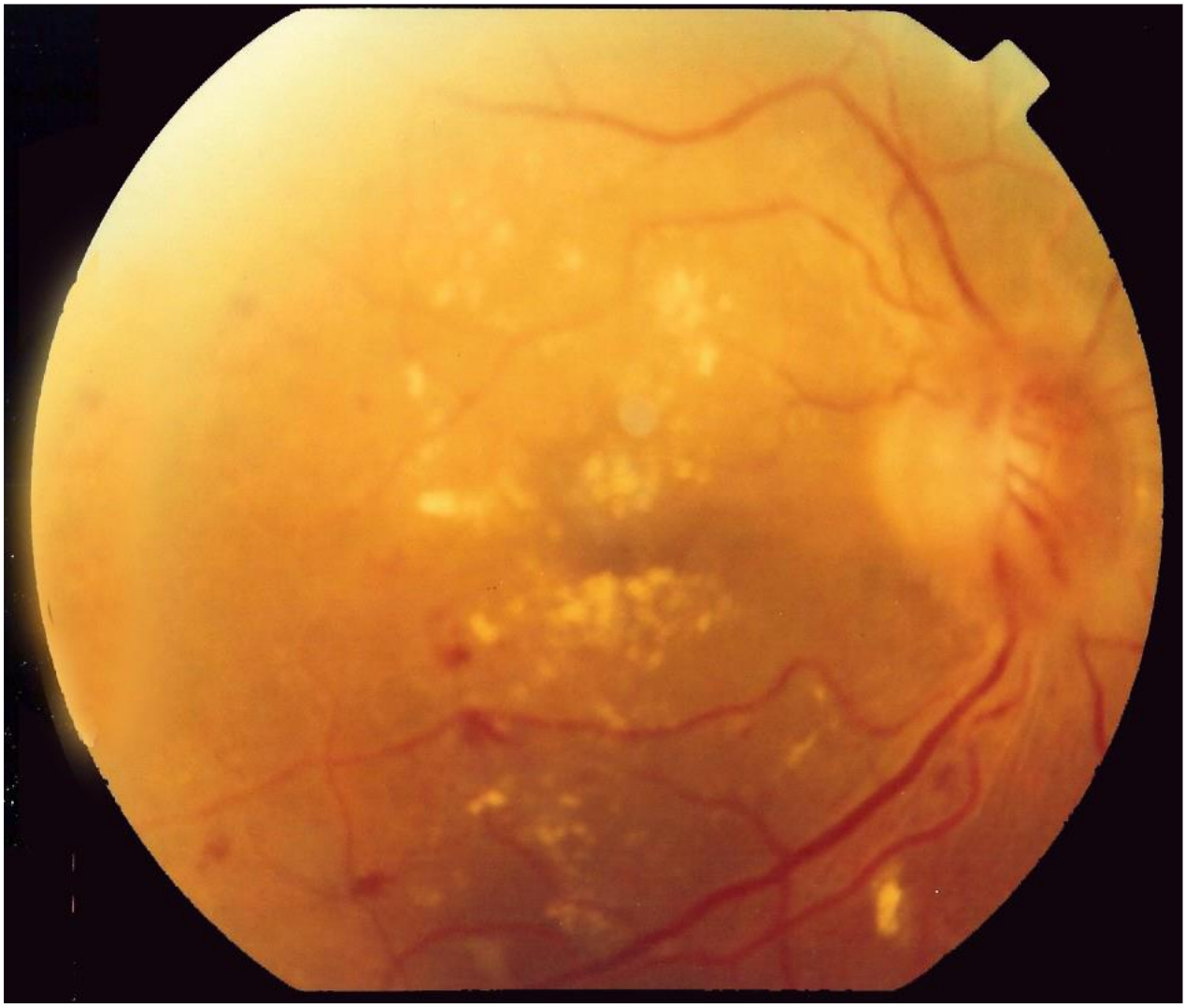


Figure 15: Very Severe NPDR

(*Note: Image source*[114])

VENOUS LOOPING

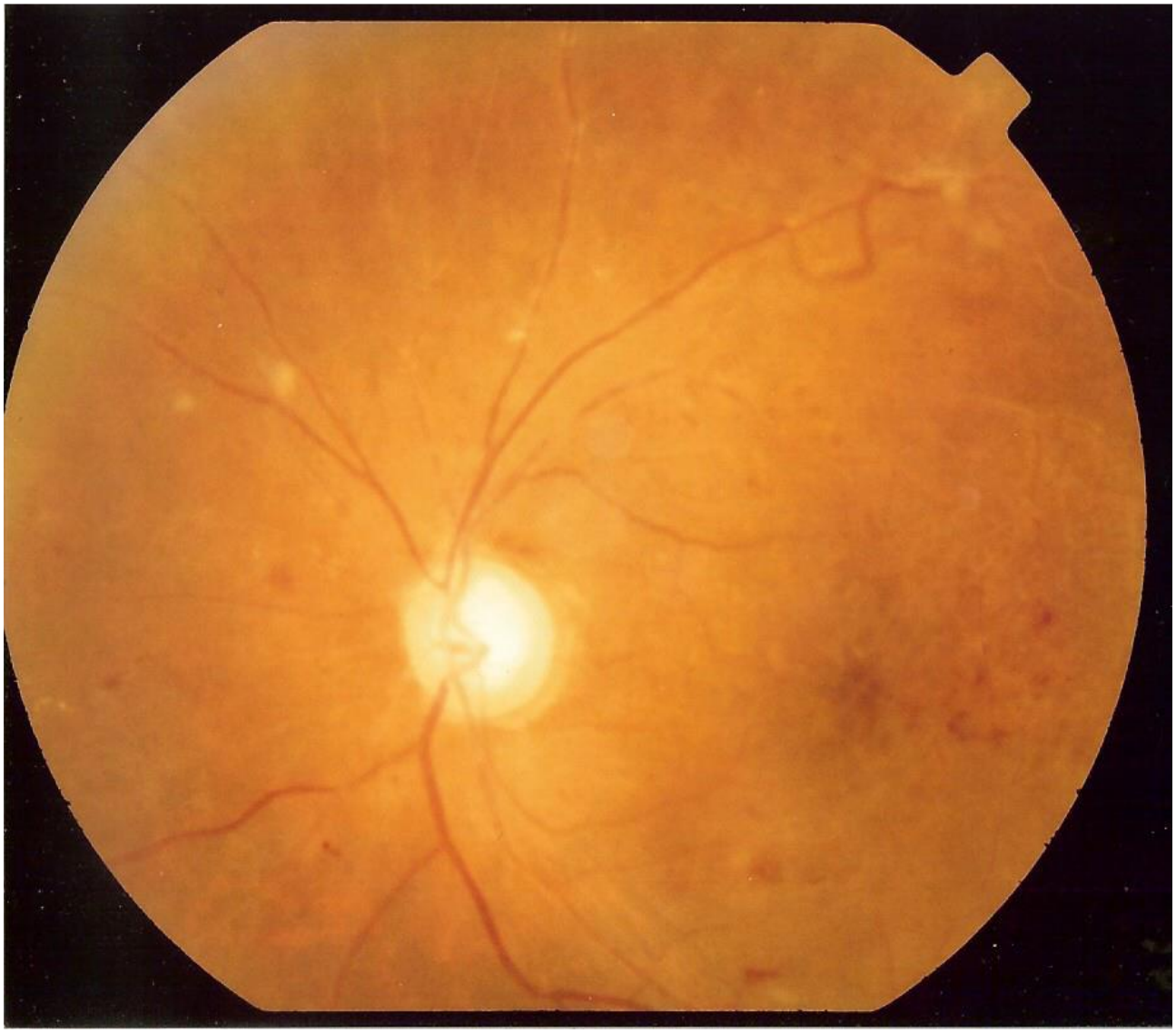


Figure 16: Venous looping

(*Note: Image source*[114])

PDR

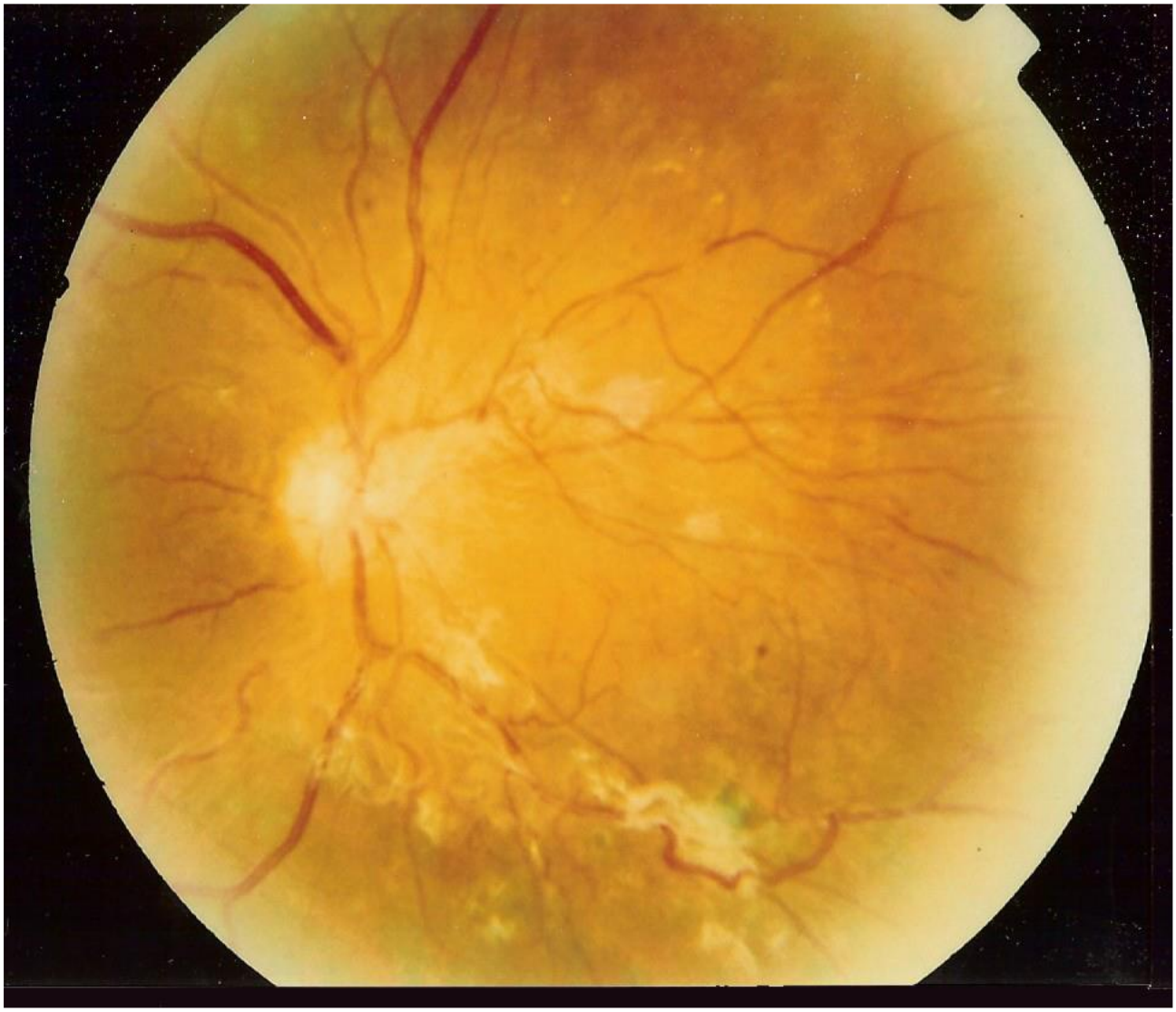


Figure 17: PDR

(*Note: Image source*[114])

ADVANCED PDR

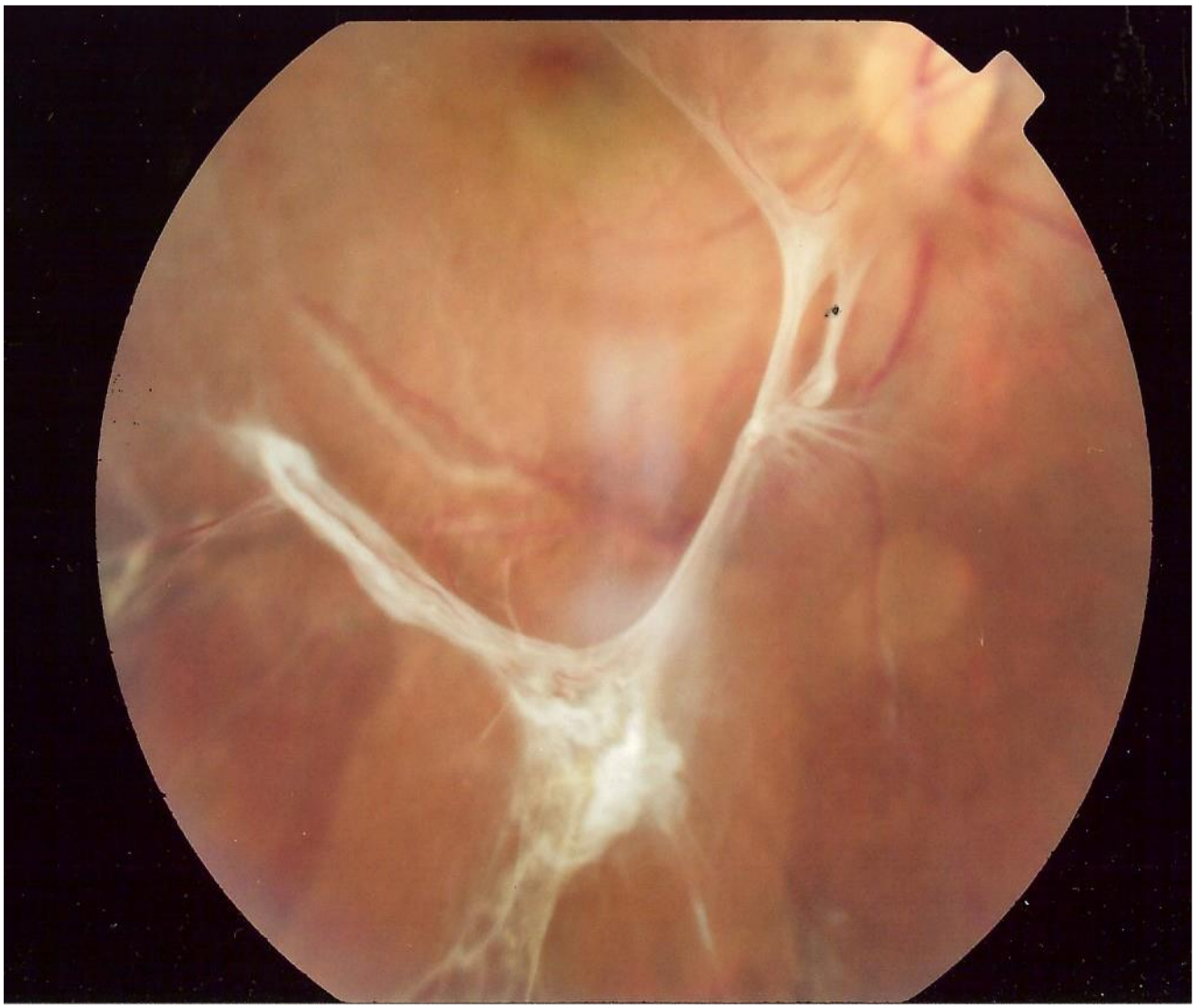


Figure 18: Advanced PDR with RD (Retinal Detachment)

(*Note: Image source*[114])

MACULOPATHY

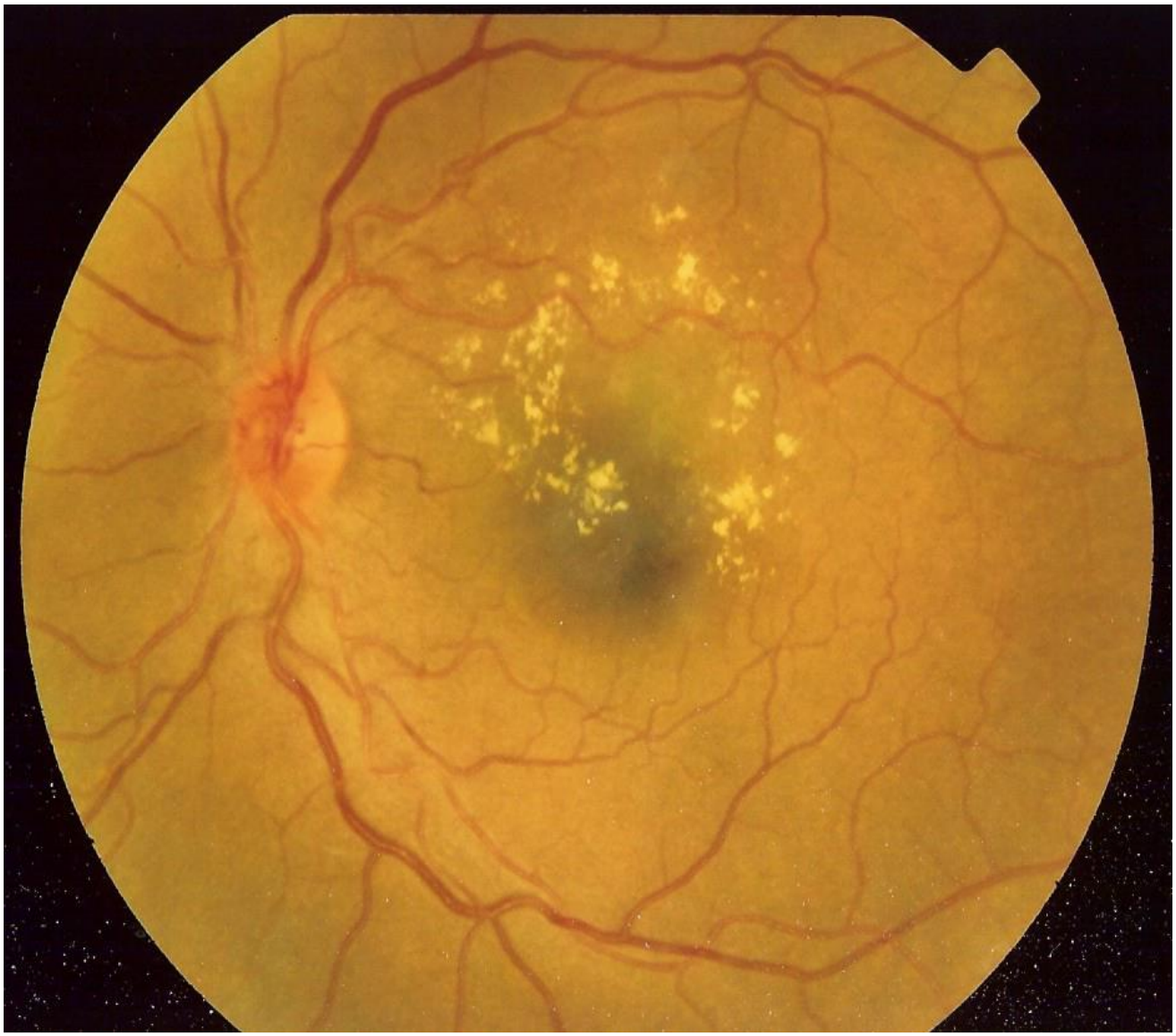


Figure 19: Maculopathy

(*Note: Image source*[114])

OPHTHALMIC ASSESSMENT

Visual Acuity

The first step in an ophthalmic evaluation is to measure visual acuity. Documentation of Best Corrected Visual Acuity (BCVA) is required[112,113].

Color vision

Blue cone sensitivity declines in diabetes, and the most frequently seen abnormality is in the blue-yellow spectrum. It is best detected using Farnsworth Munsell's hundred hue test[112,113].

Fields

Perimetry is done to observe scotomata corresponding to abnormal retinal areas[112,113].

Intraocular pressure (IOP)

People with diabetes have their IOP assessed to rule out neovascular glaucoma[112,113].

Ophthalmoscopy

Indirect Ophthalmoscopy is performed to visualize the entire retina, including the peripheral retina[112,113].

Light from the illumination system is "condensed" into the patient's pupil by the lens. A true, laterally and horizontally inverted image of the fundus, which is located between the lens and the examiner, is produced when light reflected from the retina travels back through the lens. It creates a stereoscopic image with magnification ranging from 2 to 5 times[115].

Slit Lamp Examination

Fundus examination under a slit lamp is done using a +78D or +90D lens[112,113].

Macular Function Tests

The following tests are used to observe the macular function.

a) Amsler grid test b) Photo Stress Test c) 2-point discrimination d) Blue field entoptoscopy.

Fluorescein angiography (FA)

Indications in DR

a) To describe the diffuse and localised leaks in maculopathy caused by diabetes.
b) To define the maculopathy's ischemic zone's boundaries.
c) To identify regions in the proliferative stage when capillary non-perfusion and leakage from nascent capillaries occur.
d) To track the development, resolution, or persistence of macular edema after photocoagulation.
e) It is possible to see microaneurysms smaller than 20 microns.

Fluorescein absorbs shorter wavelengths, higher energy blue light, and emits longer wavelengths, with lesser energy green light over a brief period of less than 10 seconds. This property is called fluorescence and is used in FA[112,114,117].

<u>Features</u>

1. MAs: Clearly defined hyperfluorescence set against a background of dark choroidal light.

2. Well-defined regions of hypo-fluorescence indicate retinal hemorrhages.

3. Blocked retinal and choroidal fluorescence due to superficial hemorrhages.

4. Blocked choroidal fluorescence alone in deep hemorrhages.

5. Hard exudates: Fluorescence-blocking regions.

6. Cotton wool spots: Fluorescence-blocking areas.

7. Capillary non-perfusion: distinct regions of low fluorescence that exist between the retinal arteries and the capillaries that are not visible.

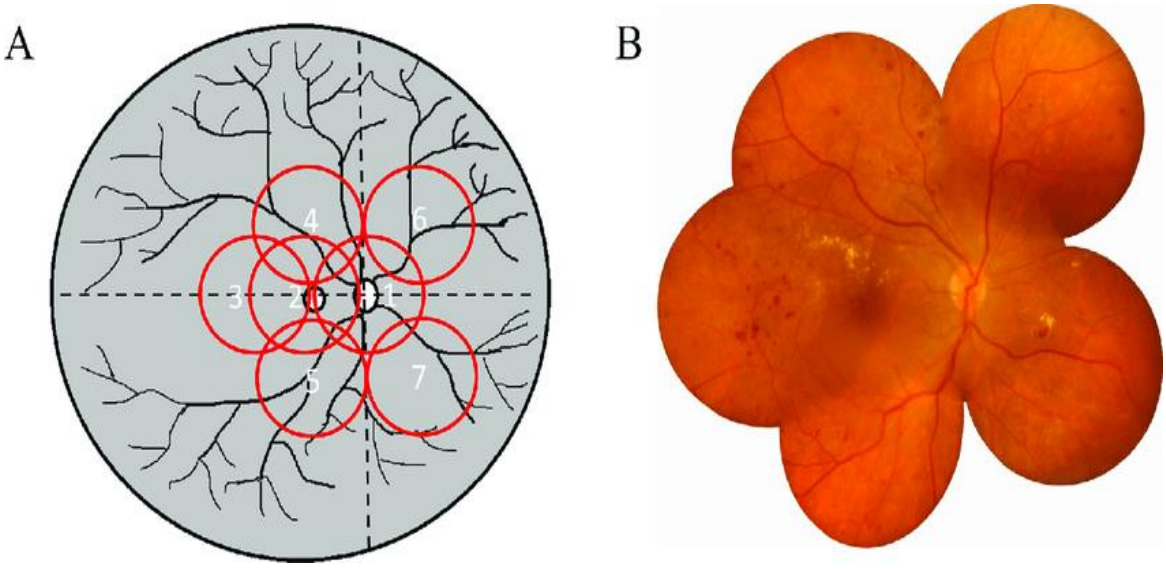
8. NVD/NVE: Leakage-related hyper-fluorescence that is becoming more extreme.

9. Focal macular edema: Hemorrhages, hard exudates that obstruct fluorescence, and focal leaks from MAs.

10. DME: Dilatation of capillaries and diffuse leaks in the early venous phase. Floral pattern in CME.

11. Ischemic maculopathy: Enlarged and irregular FAZ, capillary dropouts in perifoveal area[112,116,117].

Fundus Photography:



(*Note: Image source*[118])

Figure 20: Seven standard-field fundus photography. (A) Pattern diagram, Field 1 is centered on the optic disc, field 2 on the macula, field 3 is temporal to the macula and fields 4-7 are tangential to horizontal lines passing through the upper and lower poles

of the disc and to a vertical line passing through its center. (B) Stitched fundus photograph.

Optical Coherence Tomography (OCT)

Using low coherence interferometry, optical coherence tomography (OCT) is an optical equivalent of ultrasound imaging that creates cross-sectional images of the retina. It decodes the spatial information of tissue microstructures by capturing optical scattering from the tissue[118]

Without adjusting the reference mirror, SD-OCT captures the depth scan using a photo-detector array. Consequently, just a lateral scan needs to be done[119]. The scan speed significantly enhanced as a result. Subsequent technological advancements resulted in the near-infrared broadband super-luminescent diode light source of SD-OCT being replaced with a tunable laser source with a 1050 nm wavelength centre[120].

TREATMENT

The treatment is based on retinopathy severity[114].

NPDR

For both mild and severe NPDR, strict adherence to normal blood pressure, cholesterol, and glucose status levels is essential. In general, scatter laser photocoagulation is not advised. Laser photocoagulation is advised by the ETDRS for CSME and severe forms of retinopathy[114,121].

Severe NPDR

Scatter laser treatment is used for severe NPDR if,

a) Disease progression is rapid and

b) Close follow-up unlikely.

Macular edema

According to ETDRS, laser photocoagulation offers a 50% reduction in the likelihood of visual deterioration.

a) Focal macular edema: MAs 500–3000μm from the macula's center are covered with a green or yellow wavelength laser. The targeted treatment settings are as follows: 1. Spot size: 50-100μm

2. Length: less than 0.1 seconds

3. Power: Enough to turn MA blanching

b) Diffuse macular edema: A grid-patterned green or yellow wavelength laser is used to treat areas with diffuse leakage that are more than 500μm from the temporal limit of the optic disc and 500μm from the macular center.

The grid pattern's parameters are as follows: 1. Spot size: 50–100μm

2. Length: less than 0.1 seconds

3. Power: Enough to cause MAs and dot hemorrhage to blanch. At least one burn width separates each spot. The laser has a greater benefit for CSME.

c) Ischemic maculopathy: Focal or grid laser is not recommended when there is nonperfusion of the macula[114,121].

PDR Management

Medical management:

Both systemic and local factors causing the progression of NPDR to PDR must be targeted, which involves proper blood sugar control, blood pressure control, and treatment of renal and cardiac diseases.

According to DCCT and UKPDS, intensive blood sugar control reduces the risk of newly diagnosed retinopathy and progression of pre-existing retinopathy[114,121].

Pan-retinal Photocoagulation (PRP)

One can manage neovascularization using PRP.

The following factors are included in the ETDRS and DRS research model: 1. Number of burns: ≥1200

2. The size of the spot is 500μm

3. It lasts for 0.1 seconds.

4. Spaces between spots are at least one burn width apart.

5. There are more than two sessions. With PRP, a 57% decrease in the rate of vision loss has been observed.

Surgical management

The cornerstone of modern treatment for tractional retinal detachment (TRD) and vitreous hemorrhage is surgery. The advantages of early vitrectomy are shown by type I DM patients with severe vitreous hemorrhage[114,121].

Indications for Pars Plana Vitrectomy (PPV):

a) Dense non-clearing vitreous hemorrhage.

b) TRD threatening macula.

c) Combined tractional and rhegmatogenous retinal detachment.

d) DME with post-hyaloid traction.

e) Recurrent vitreous hemorrhage.

Recent Advances

Refractory CSME patients can be treated with intravitreal corticosteroid administration. Currently, various modalities of drug delivery are under clinical trials to investigate their efficacy[122].

Table 4: Screening recommendations for Diabetic Retinopathy (DR)

(*Note: Table source*[123])

Status of retinopathy	**Referral to ophthalmologist**	**Follow-up**	**Recommended ocular treatment**
No Diabetic Retinopathy (DR)	Within 1 year	Every 1-2 years	None
Mild Non-Proliferative DR (NPDR)	Within 1 year	Every year	None
Moderate NPDR	Within 3-6 months	Every 6 months	None
Severe NPDR	Immediate	Every 3 months	Can consider pan-retinal photocoagulation (PRP) under specific circumstances

Status of retinopathy	**Referral to ophthalmologist**	**Follow-up**	**Recommended ocular treatment**
Proliferative DR	Immediate	Every 3 months	Pan-retinal photocoagulation (PRP) and/or intravitreal anti-VEGF* therapy, especially if HRCs† are present
No Diabetic macular edema (DME)	Within 1 year	Every year	None
Non-CiDME (non-center involving DME)	Immediate	Every 3 months	Focal laser photocoagulation, and observe carefully for progression to CiDME
Centre involving	Immediate	Every 1-2 months	Anti-VEGF as first-line therapy. Consider focal macular laser as an rescue therapy in eyes with persistent

Status of retinopathy	**Referral to ophthalmologist**	**Follow-up**	**Recommended ocular treatment**
DME (CiDME)			CiDME despite anti-VEGF. Intravitreal steroids can be used as an alternative in pseudophakic eyes or in select cases if anti-VEGF is contraindicated (like recent MI)

(VEGF- Vascular Endothelial Growth Factor, HRC-High Risk Characteristics)

LEVELS OF PREVENTION OF DIABETIC RETINOPATHY

Primary prevention

Diet, physical activity, and medication achieve strict control of blood sugars. Periodic ophthalmic examination must be carried out on diabetic patients, and they should be promptly referred to ophthalmologists.

Secondary prevention

In NPDR patients, blindness can be avoided by altering the risk factors. Early on, FA is used to identify the kind of maculopathy. For maculopathy and PDR, laser photocoagulation is administered to avoid vision loss.

Tertiary prevention

Surgical treatment appropriate to the patient's stage of advanced proliferative illness is administered. Low vision aids provide more thorough visual recovery[124,125].

National Diabetes Control Programme[126,127,128]

Preventing diabetes involves identifying high-risk individuals and putting them on early intervention through health education, early disease diagnosis and treatment, lowering

morbidity and mortality in the high-risk population, preventing acute and chronic complications related to the metabolism, cardiovascular system, kidneys, and eyes, providing equal opportunities for diabetic patients to become physically fit, and rehabilitating those who are partially or completely disabled as a result of their diabetes.

ASSOCIATION BETWEEN DFU and DR:

There is a strong association between DFUs and PDR, with 31% to 55% of individuals with DFU progressing to PDR.

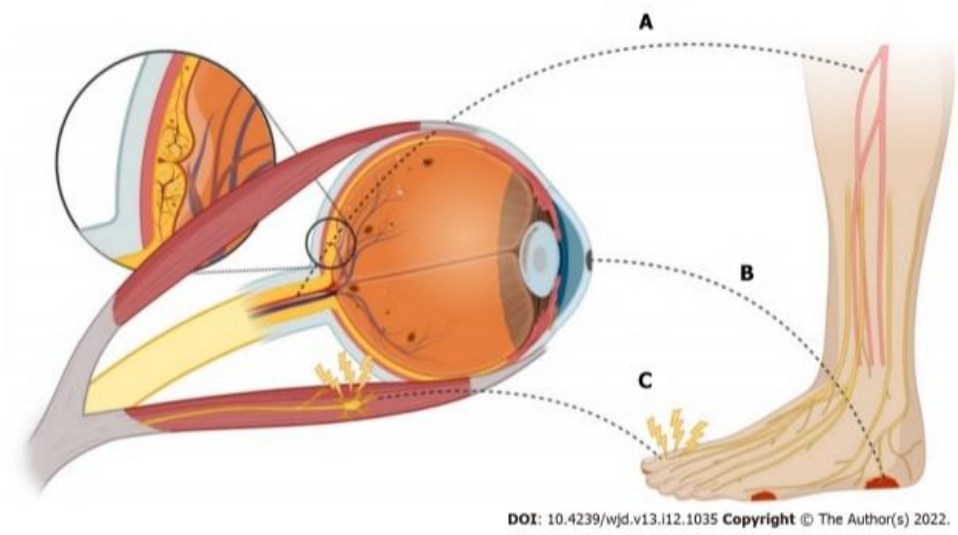


Figure 21: Association between DFU and DR

(*Note: Image source*[129])

A- Diabetic micro and macrovascular complications

B- Diabetic ulcers

C- Diabetic neuropathy

MICROVASCULAR COMPLICATIONS OF DIABETES

Microaneurysms are biomarkers of microvascular injury in diabetic retinopathy (DR)[129]. Impaired retinal capillary perfusion is a critical pathogenic mechanism in the development of microvascular abnormalities[129]. As the disease progresses, the production of VEGF promotes further dysfunction, vascular leakage, and bleeding (dot

and blot hemorrhages). Visual acuity is increasingly affected by disease progression and is often further limited by macular involvement- DME[130].

The disease's most vision-threatening consequence, PDR, is predominantly caused by the expression of VEGF and is indicated by NVD or NVE. These new, weak blood vessels have the potential to develop into the vitreous and bleed, leading to traction, RD, or vitreous hemorrhages, all of which can impair vision[131,132].

MACROVASCULAR COMPLICATIONS OF DIABETES

Peripheral Arterial Disease (PAD) and Chronic Venous Insufficiency (CVI) are common macrovascular problems that affect the lower extremities and can result in lower extremity amputation[18,133].

In hyperglycemic conditions, there is less NO available, a possible vasodilator generated in the endothelium that mediates local vascular endothelial tone. Additionally, DM increases endothelin-1 synthesis, which in turn causes vasoconstriction and vascular smooth muscle growth[18,134].

The result may be overt occlusion, acute thrombus formation, and increasingly stenotic vessels, resulting in reduced perfusion[18].

Ocular Ischemic Syndrome (OIS), a rare vision-threatening syndrome linked to carotid artery obstruction that causes ocular hypoperfusion, is a manifestation of DM-associated macrovascular alteration in the eye[18,133,134].

The combination of hyperglycemia, insulin resistance, dyslipidemia, hypertension, and chronic inflammation in individuals with type 2 diabetes can harm the vascular endothelium and cause macrovasculopathy[18,133].

STUDIES RELATED TO ASSOCIATION BETWEEN DFU AND DR:

1. A systematic review study was done by Ziye Li[8] in 2023 to study the association between DR and DFU to provide evidence for preventing diabetic complications. The literature was individually reviewed by two researchers, and data was retrieved based on the inclusion and exclusion criteria. Eleven publications covering 10,208 participants were examined; 2191 of them had DFU, while 8017 did not. The meta-analysis's findings demonstrated a substantial increase in DR with higher DFU incidence. The study's findings indicated that DR patients had a higher chance of developing DFU, emphasizing the vital need of early detection and routine screening for these two diabetic complications in order to stop more negative consequences[8].

2. A systematic review by Dragos Serban et al[135], 2020, assessed nine articles for correlations between DR and DFU. In all cases, DR, especially PDR, was significantly higher in rate in the presence of DFU. DFU and higher rates of DR were found to be significantly correlated, and in non-healing DFUs, DR progressed more quickly. This could be because to chronic inflammation and related infections[135].

3. Dr. Vaishnavi R, Dr. Ansu Ann John, Dr. Ponniah Iyyapan, and Dr. Mary Thomas (2020) performed a cross-sectional study in a university teaching hospital over six months on 100 type 2 DM patients with DFU. They examined the correlation between other risk factors and the prevalence of DR in patients with DFU diagnoses. The data indicated a stronger correlation between the severity of DFU and the existence of retinopathy. According to the study's findings, patients with DFU that was getting worse had worse retinopathy than other related risk factors[136].

4. Matsushita Y et al[137], conducted a study on 2921 Japanese men between 2008 and 2009 with fasting. They had been examined by an ophthalmologist. A simplified diabetic retinopathy scale was utilized to categorize retinopathy into seven distinct groups. Each parameter related to the presence or absence of retinopathy was assessed using receiver operator characteristic analysis. The odds ratios increased significantly with HbA1C > 6.8%. It was made evident that there was no clear threshold and that the prevalence of retinopathy increased with the amount of HbA1c, suggesting the possibility of detecting DR with HbA1c levels alone[137].

5. Thoiba Karam et al[19], 2018, conducted a cross-sectional study on one hundred and eighty-two patients diagnosed with a risk profile for DFU, visiting a South Indian tertiary care hospital to study DR in patients with a risk of DFU. Of the 182 patients, 67.58% had retinopathy changes. PDR constituted 17.88% of the total patients with retinopathy. The study found that the South Indian cohort with DF syndrome had a higher prevalence of DR. Patients with higher DF risk grades experienced a greater degree of severity[19].

6. Duck Jin Hwang et al[17], 2017 conducted a retrospective review on 100 type 2 diabetic patients with DFU. Within six months, they underwent ocular and vascular tests; control data came from the medical records of 2496 Type II DM patients who did not have DFU. Regarding each clinical characteristic, the prevalence and severity of DR in DFU patients were evaluated and contrasted with a control group. The findings demonstrated that compared to the NPDR group, the PDR patients had greater serum creatinine, BUN, and length of DM. Additionally, it was found that almost 50% of DFU

patients had PDR upon presentation. In DFU patients, only a greater serum creatinine level was linked to PDR in the multivariable analysis. According to the study's findings, around half of DFU patients also had PDR, and DR is common in DFU patients. No noteworthy correlation was discovered with respect to severity of the two complications of DM[17].

7. Hu Y et al[138], conducted a cross-sectional study on 3481 type 2 DM patients in China between 2016 and 2019. Severe NPDR, PDR, CSME were classified as vision-threatening diabetic retinopathy (VTDR). Multivariable logistic regression was utilized to investigate any possible correlation between SUA and VTDR. A total of 305 participants had VTDR. Both higher Serum Uric Acid (SUA) and hyperuricemia. were positively associated with VTDR after adjustment for relevant covariates. Higher SUA levels were linked to a higher risk of VTDR in patients with type 2 diabetes in both sexes, according to the study's findings, while women appeared to be more susceptible to high SUA than men[138].

MATERIALS AND METHODS

Two hundred and thirty four eyes of 117 DFU subjects were included in this study. Both eyes of all subjects were selected. The study was approved by Institutional Ethical committee. Informed and written consent was obtained from all the study participants. Demographic data, medical and ocular history were documented. All subjects underwent BCVA (Best Corrected Visual Acuity), anterior segment evaluation under slit-lamp biomicroscopy, dilated fundus examination using indirect ophthalmoscopy. Fundus image was captured using a digital fundus camera. All subjects underwent OCT (Cirrus HD OCT, Spectral Domain technology, Zeiss) scan.

The following parameters were measured on the SD-OCT scan:

1. Central Foveal Thickness (CFT) (Micrometer): The central 1mm zone which is the distance between vitreoretinal interface and anterior surface of RPE is measured. Following manual adjustment, automated measurement was done using measurement software in SD-OCT.

Overall average macular thickness (Micrometer) and total volume of the macula (Cubic mm): The modified ETDRS grid shows a circular map over 6mm square scanned area in 9 sectors. Centered on the fovea with central 1mm zone. Middle 3mm and outer 6mm concentric zones have superior, inferior, nasal and temporal quadrants. The automated program that was obtained from the 3D scan methodology provides these measurements.

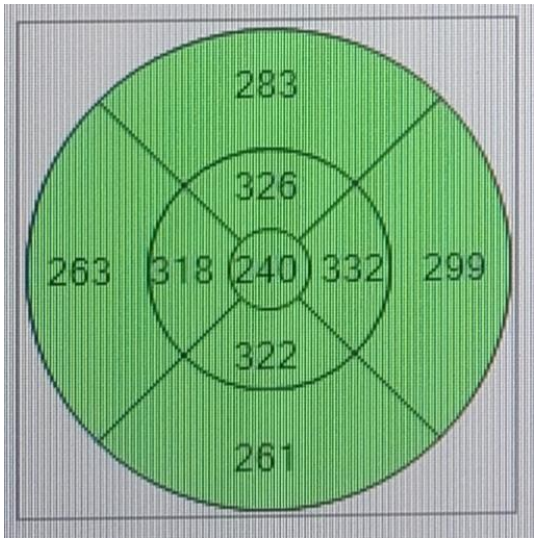


Figure 22: Average macular thickness measured in ETDRS grid circular map of 9 sectors. Central 1mm zone corresponds to fovea. Surrounding 3mm and 6mm concentric zones are divided into superior, inferior, nasal and temporal quadrants.

All scans were performed using same OCT machine by a single operator. Procedure carried out in a dim room. Rescanning was done in those subjects with poor centration and motion artifacts and considered. Right eye was scanned first followed by left eye.

Inclusion Criteria:

Patients with DFU who are attending Ophthalmology and General Surgery Out Patient Department (OPD) and In-Patient Department (IPD) in BLDE deemed to be university's hospital, Karnataka, are included in the study.

Exclusion Criteria:

Patients with a previous history of treatment for diabetic retinopathy, like laser photocoagulations and intravitreal anti-VEGF injections, ocular surgeries for DR, patients who are totally immobile with severe grades of DFU with sepsis admitted into intensive care units are excluded from the study.

STATISTICAL ANALYSIS

Statistical Package for Social Sciences (SPSS) software version 20 was used to analyze data from both the eyes of all 117 subjects. Descriptive statistics for categorical parameters were presented using frequency and percentage. Mean and standard deviation were used for continuous parametric data. Dependent and independent variables are differentiated using the ANOVA test. The chi-square test was used to find out the association between the parameters. P value < 0.001 was considered highly statistically significant.

ANOVA:

One-way ANOVA (Analysis of Variance) on ranks test, Kruskal Wallis test by ranks, and Kruskal Wallis H test are non-parametric methods to determine if the samples originate from the same distribution. It compares more than two independent samples of equal or unequal sample sizes, unlike the Mann-Whitney U test, which cannot compare beyond two groups. Kruskal-Wallis H test is parametrically equivalent to the one-way analysis of variance (ANOVA).

Chi square test:[139]

Researchers must conduct a significance test called the Chi-Square test to determine the linkage between two qualitative variables. The five steps to conduct this test are:

Step 1: Formulate the hypotheses

Step 2: Expected values for every cell of the table were specified (considering the null hypothesis is true)

Step 3: Compare the observed counts with the expected counts to see if the data gives convincing evidence against the null hypothesis

Step 4: Compute the test statistic

Step 5: Confirm if chi-square is statistically significant

DR status graded in all subjects using ETDRS classification of Diabetic Retinopathy. The eyes whose posterior pole could not be visualized due to hazy, dense cataractous media, vitreous hemorrhage leading to poor scan quality were categorized under “Non-Visualized” category in data interpretation of the results.

RESULTS

1) MEAN AGE OF SUBJECTS

AGE	Mean	Std. Deviation	Minimum	Maximum
	55.63	12.820	18	85

Table 5: Mean age of all subjects in Mean+/- Standard deviation.

Mean age of subjects was 55.63±12.820

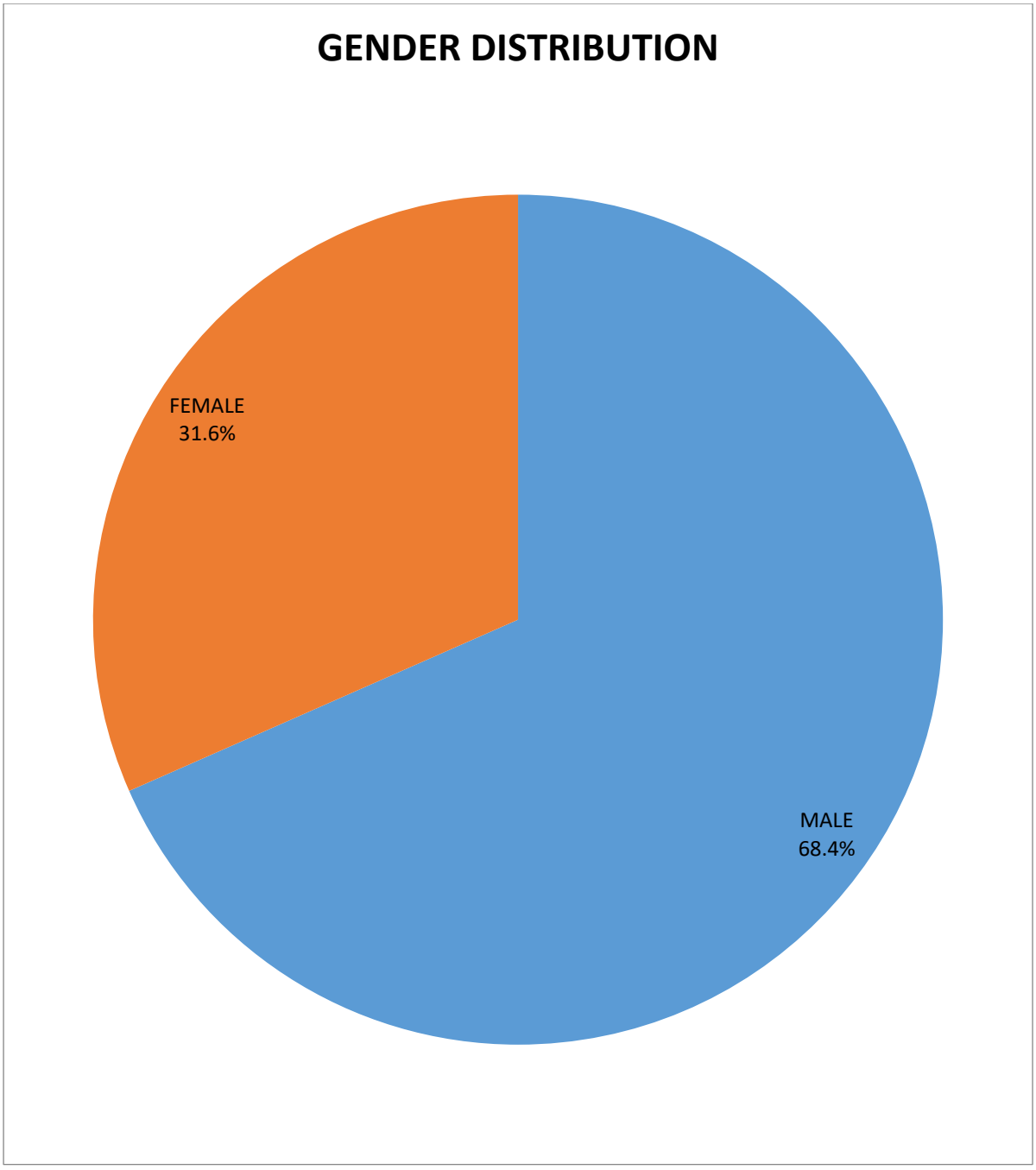
Retinopathy rates were greater (46.67%) in the 51–60 age group and 23.3% in the 61–70 age group.

2) GENDER DISTRIBUTION

GENDER	Frequency	Percent
MALE	80	68.4
FEMALE	37	31.6
TOTAL	117	100.0

Table 6: Frequency distribution of gender among all study subjects.

Among the subjects, 80 (68.4%) were males and 37 (31.6%) were females. The gender wise distribution showed a preponderance for male sex.

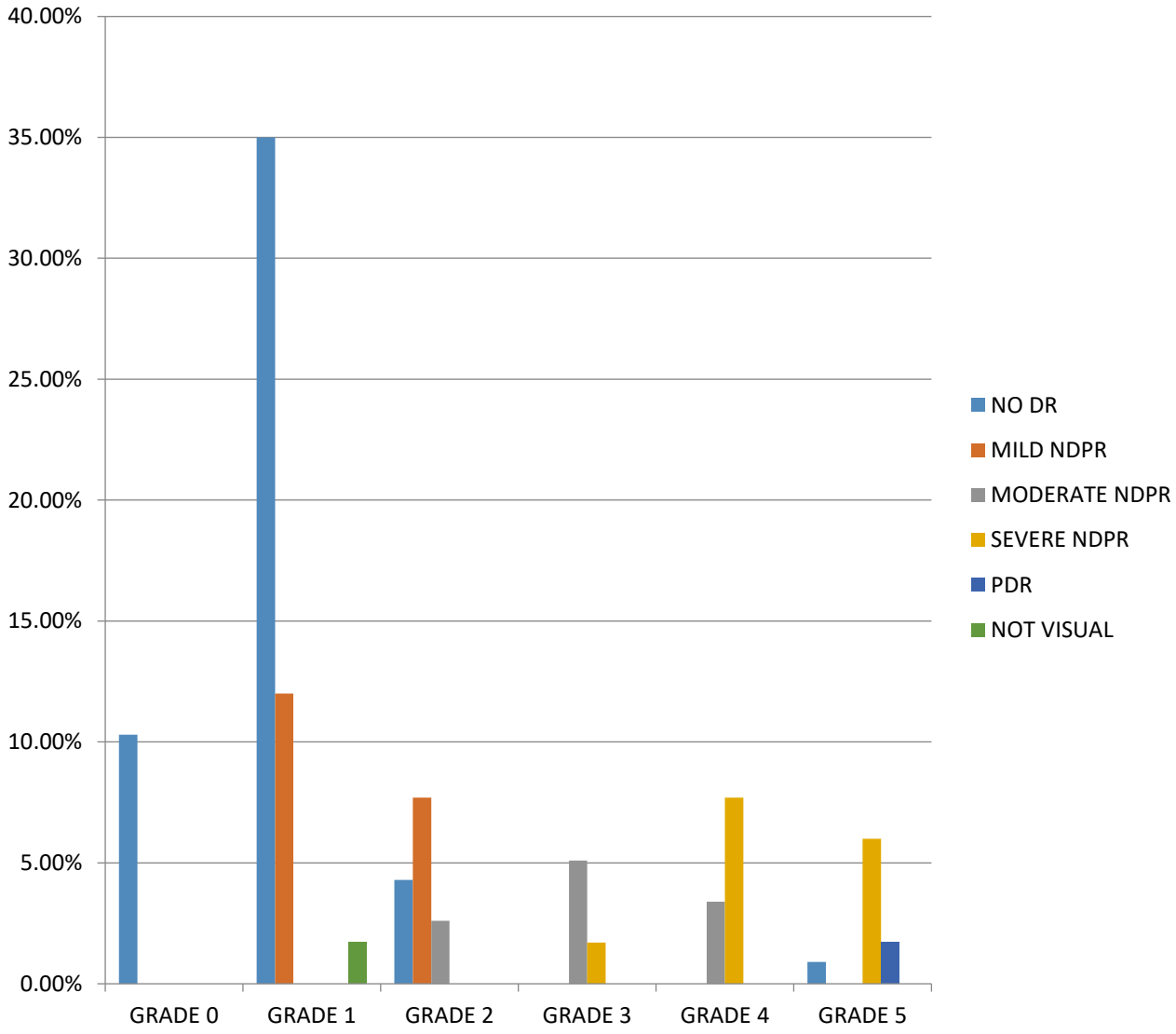


Graph 1: Pie chart depicting the gender distribution of study subject

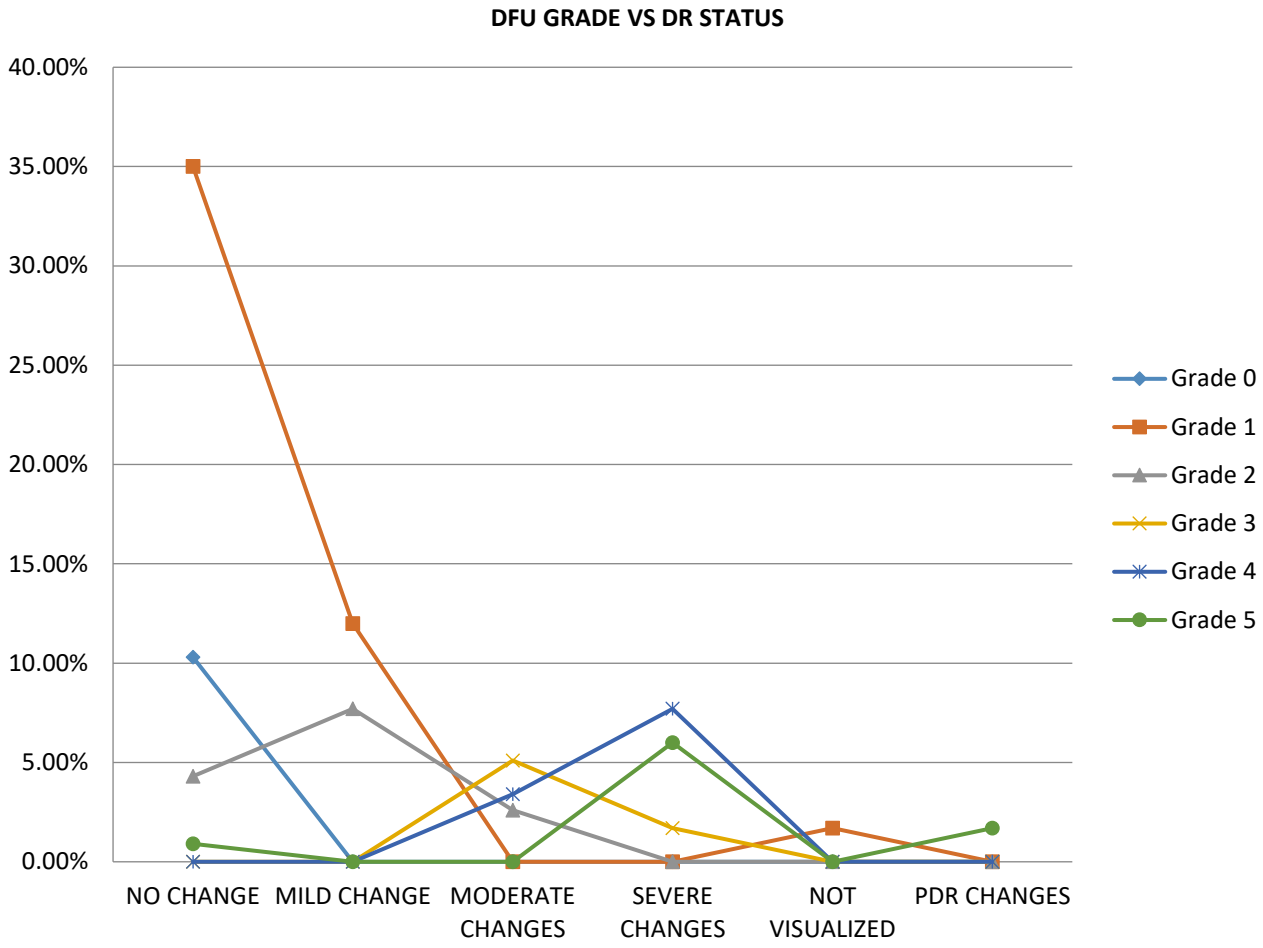
3. DFU GRADES COMPARISON WITH DR STATUS

DFU GRADE	NO DR	MILD NDPR	MODERATE NDPR	SEVERE NDPR	PDR	NOT VISUALIZED	TOTAL	CHI-VALUE	P VALUE
GRADE 0	24 10.3 % 	0 0.0% 	0 0.0% 	0 0.0% 	0 0.0% 	0 0.0% 	24 10.3% 	339.141	<0.001
GRADE 1	82 35.0 % 	28 12.0% 	0 0.0% 	0 0.0% 	0 0.0% 	4 1.7% 	114 48.7% 		
GRADE 2	10 4.3% 	18 7.7% 	6 2.6% 	0 0.0% 	0 0.0% 	0 0.0% 	34 14.5% 		
GRADE 3	0 0.0% 	0 0.0% 	12 5.1% 	4 1.7% 	0 0.0% 	0 0.0% 	16 6.8% 		
GRADE 4	0 0.0% 	0 0.0% 	8 3.4% 	18 7.7% 	0 0.0% 	0 0.0% 	26 11.1% 		
GRADE 5	2 0.9% 	0 0.0% 	0 0.0% 	14 6.0% 	4 1.7% 	0 0.0% 	20 8.5% 		
TOTAL	118 50.4 % 	46 19.7% 	26 11.1% 	36 15.4% 	4 1.7% 	4 1.7% 	234 100.0% 		

Table 7: Comparison of DFU grades with DR status. Test used- chi square, P< 0.05 is significant and P< 0.001 is highly significant



Graph 2: Bar graph depicting rate of presentation of DR status in various DFU groups.



Graph 3: A line graph depicting the relationship between DR status and DFU grades. With increase in the DFU grades, increased severity of DR status is noted from the graph.

4. DFU GRADES COMPARISON WITH DURATION OF DM

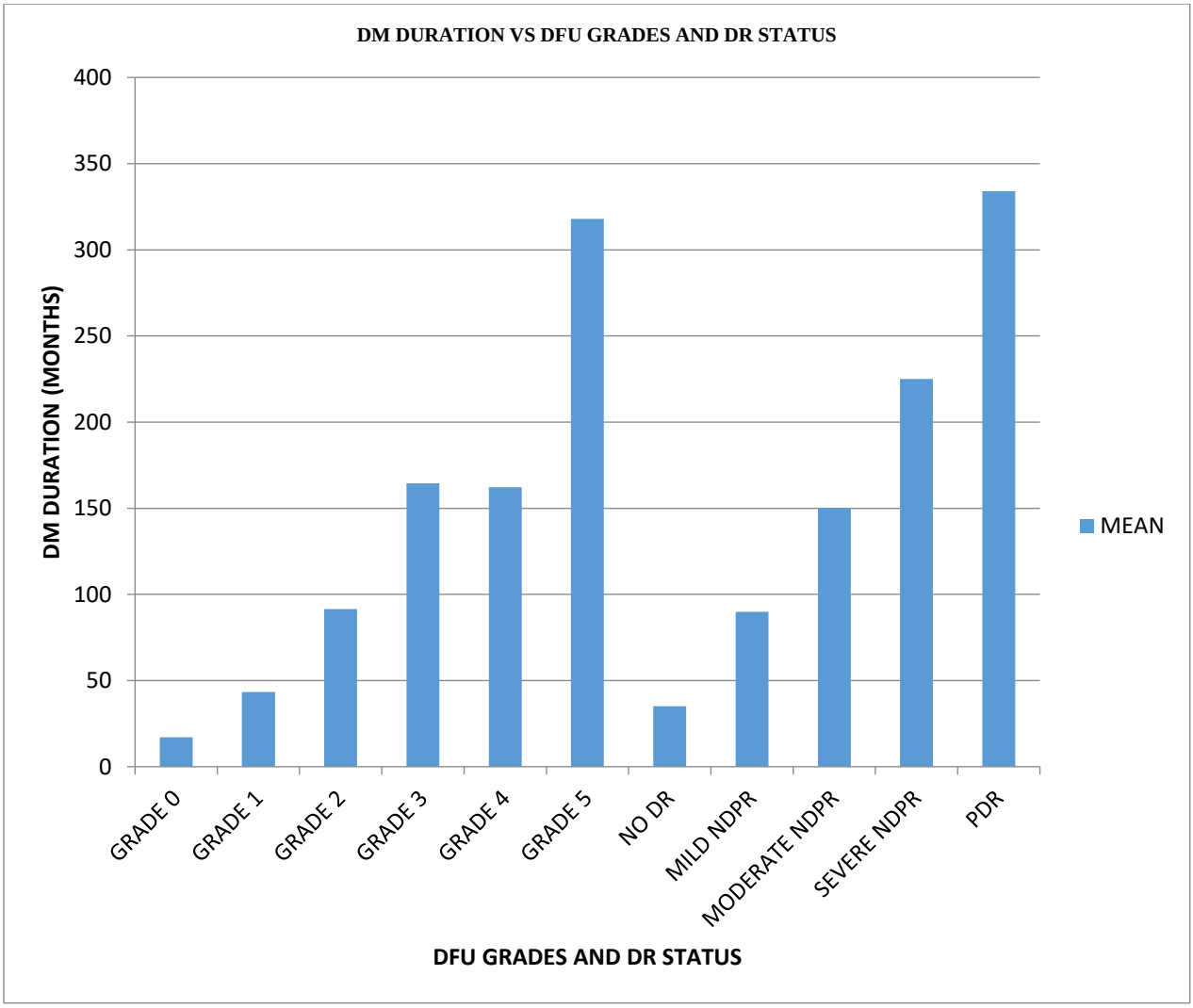
DFU GRADES	MEAN	STANDARD DEVIATION	F VALUE	P VALUE
GRADE 0	17.17	15.603	68.883	< 0.001
GRADE 1	43.33	48.753		
GRADE 2	91.53	85.601		
GRADE 3	164.50	66.190		
GRADE 4	162.23	63.252		
GRADE 5	318.00	146.302		

Table 8: Comparison of DFU grades with duration of DM (in months). Test used- ANOVA, P< 0.05 is significant and P< 0.001 is highly significant.

5. DR STATUS COMPARISON WITH DURATION OF DM

DR STATUS	MEAN	STANDARD DEVIATION	F VALUE	P VALUE
NO DR	35.10	56.314	68.883	<0.001
MILD NDPR	89.96	79.572		
MODERATE NDPR	150.23	34.190		
SEVERE NDPR	225.06	128.933		
PDR	334.00	175.514		
NOT VISUALISED	12.50	.577		

Table 9: Comparison of DR status with duration of DM (in months). Test used- ANOVA, P< 0.05 is significant and P < 0.001 is highly significant.



Graph 4: Bar graph depicting the relationship between grades of DFU and DR status with the duration of DM (in months). It is clear from the graph that higher grades of DFU and increased severity of DR were associated with longer duration of DM.

6. DFU GRADES COMPARISON WITH HbA1C LEVELS

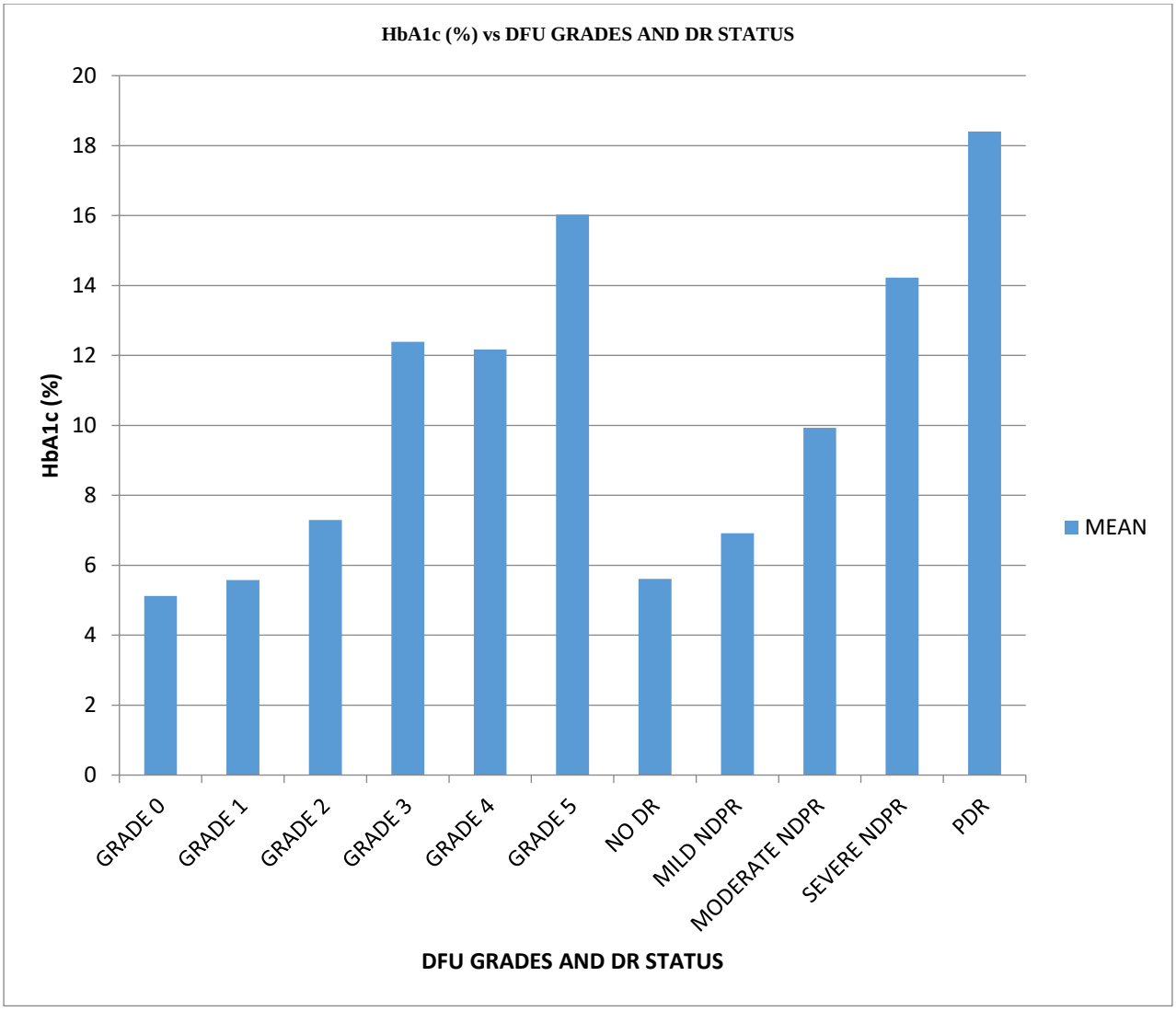
DFU GRADES	MEAN	STANDARD DEVIATION	F VALUE	P VALUE
GRADE 0	5.125	.9665	191.207	< 0.001
GRADE 1	5.575	.7446		
GRADE 2	7.294	2.0646		
GRADE 3	12.388	3.8458		
GRADE 4	12.169	2.0370		
GRADE 5	16.030	2.7970		

Table 10: Comparison of DFU grades with HbA1C levels (%). Test used- ANOVA, P< 0.05 is significant and P< 0.001 is highly significant.

7. **DR STATUS COMPARISON WITH HbA1C**

DR STATUS	**MEAN**	**STANDARD DEVIATION**	**F VALUE**	**P VALUE**
NO DR	5.607	1.8552	191.207	<0.001
MILD NDPR	6.913	1.8705		
MODERATE NDPR	9.931	2.2423		
SEVERE NDPR	14.228	2.6068		
PDR	18.400	1.5011		
NOT VISUALISED	4.550	.0577		

Table 11: Comparison of DR status with HbA1C (%). Test used- ANOVA, $P < 0.05$ is significant and $P < 0.001$ is highly significant.



Graph 5: Bar graph depicting the relationship between grades of DFU and DR severity with the levels of HbA1C (%). It is clear from the graph that higher HbA1C levels were found in patients with severe grades of DFU and DR.

8. DFU GRADES COMPARISON WITH CENTRAL FOVEAL THICKNESS (CFT)

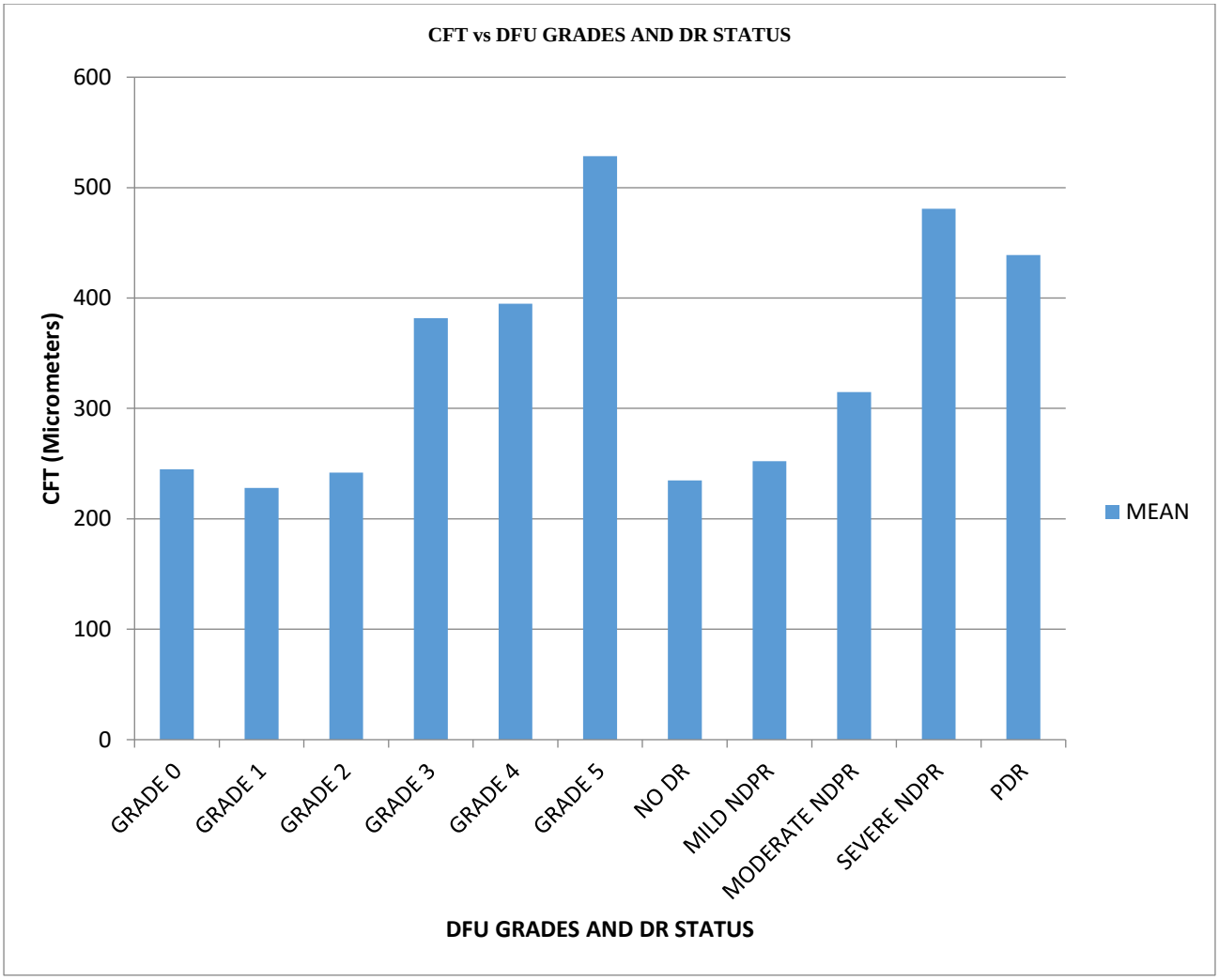
DFU GRADES	MEAN	STANDARD DEVIATION	F VALUE	P VALUE
GRADE 0	244.79	23.596	38.870	<0.001
GRADE 1	227.91	62.252		
GRADE 2	241.91	43.846		
GRADE 3	381.75	141.530		
GRADE 4	394.96	191.185		
GRADE 5	528.55	191.974		

Table 12: Comparison of DFU grades with CFT (in micrometers). Test used- ANOVA, P< 0.05 is significant and P< 0.001 is highly significant.

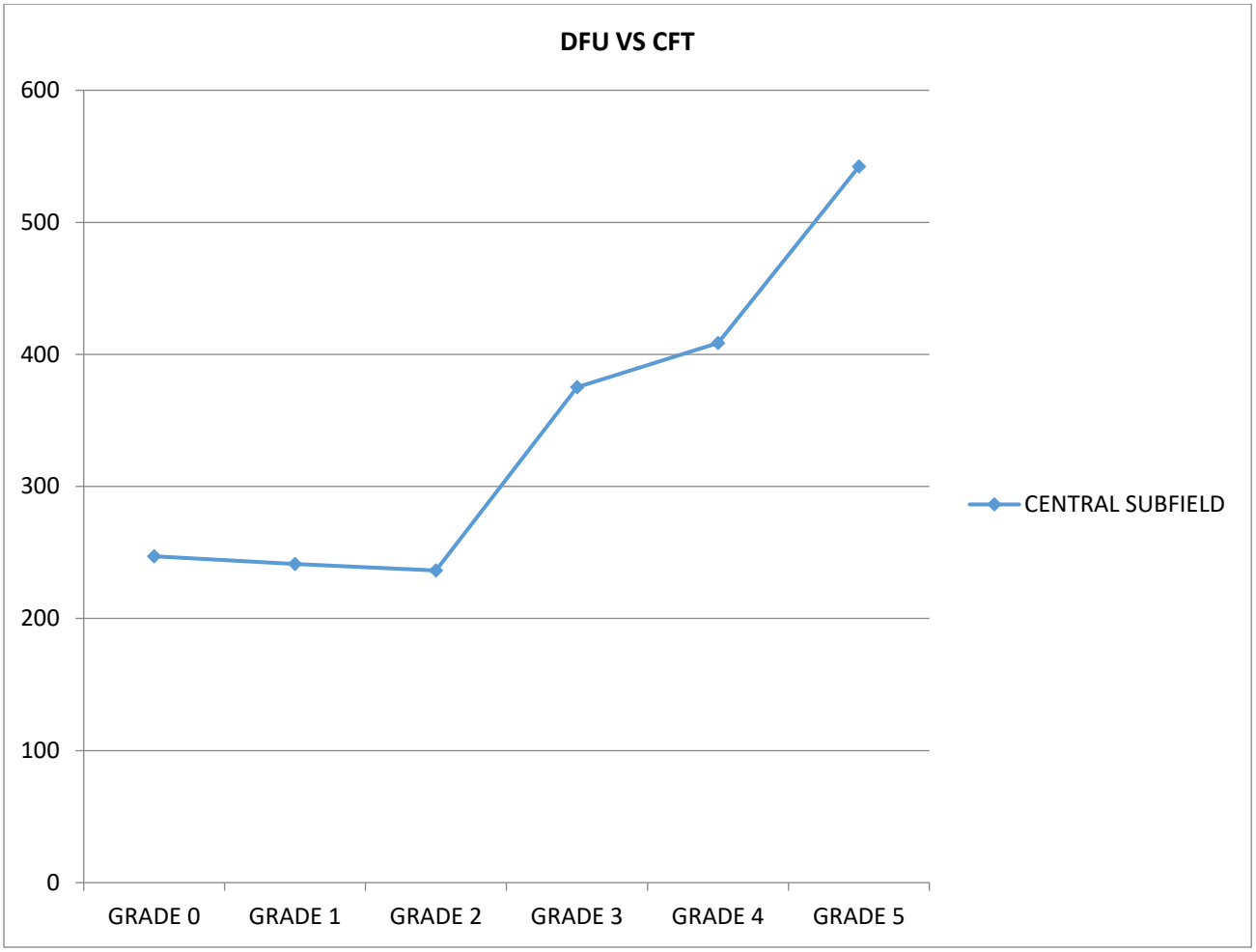
9. DR STATUS COMPARISON WITH CENTRAL FOVEAL THICKNESS (CFT)

DR STATUS	MEAN	STANDARD DEVIATION	F VALUE	P VALUE
NO DR	234.76	74.462	38.870	< 0.001
MILD NDPR	252.15	47.481		
MODERATE NDPR	314.88	70.597		
SEVERE NDPR	480.86	205.966		
PDR	439.00	244.574		
NOT VISUALISED	118.75	137.223		

Table 13: Comparison of DR status with CFT (in micrometers). Test used- ANOVA, P< 0.05 is significant and P< 0.001 is highly significant.



Graph 6: Bar graph depicting the relationship between grades of DFU and DR to Central Foveal Thickness/ CFT (in micrometers). It is clear from the graph that increased CFT was seen in patients with higher grades of DFU and DR.



Graph 7: Line graph depicting the relationship between DFU grades and CFT (in micrometers). It is clear from the graph that with increased grades of DFU, increased CFT is noted.

10. DFU GRADES COMPARISON WITH TOTAL MACULAR VOLUME

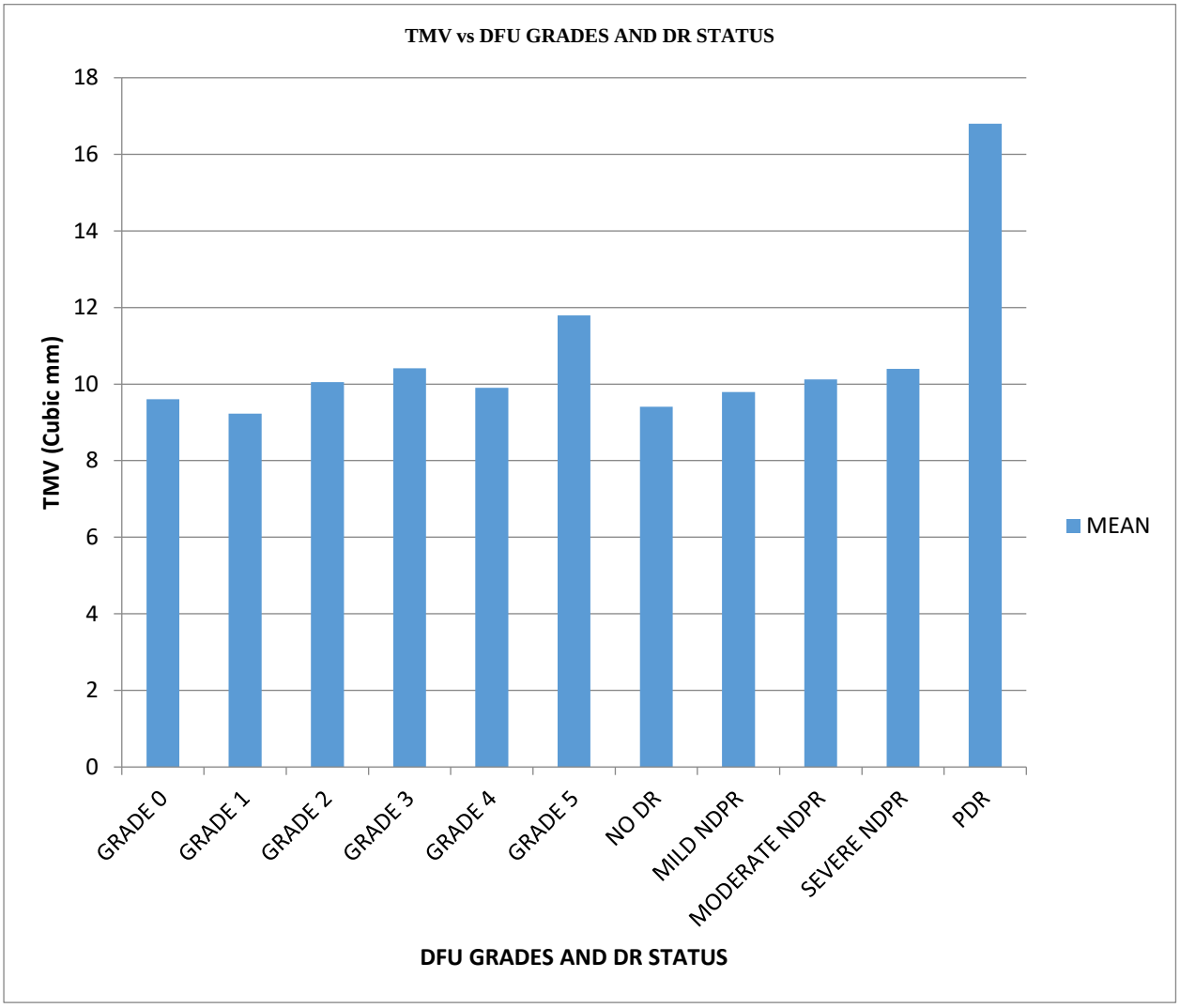
DFU GRADES	MEAN	STANDARD DEVIATION	F VALUE	P VALUE
GRADE 0	9.604	1.0610	3.844	0.002
GRADE 1	9.229	2.4790		
GRADE 2	10.053	1.1540		
GRADE 3	10.413	1.4245		
GRADE 4	9.900	2.3636		
GRADE 5	11.795	5.4184		

Table 14: Comparison of DFU grades with total macular volume (in cubic mm). Test used- ANOVA, P <0.05 is significant and P <0.001 is highly significant

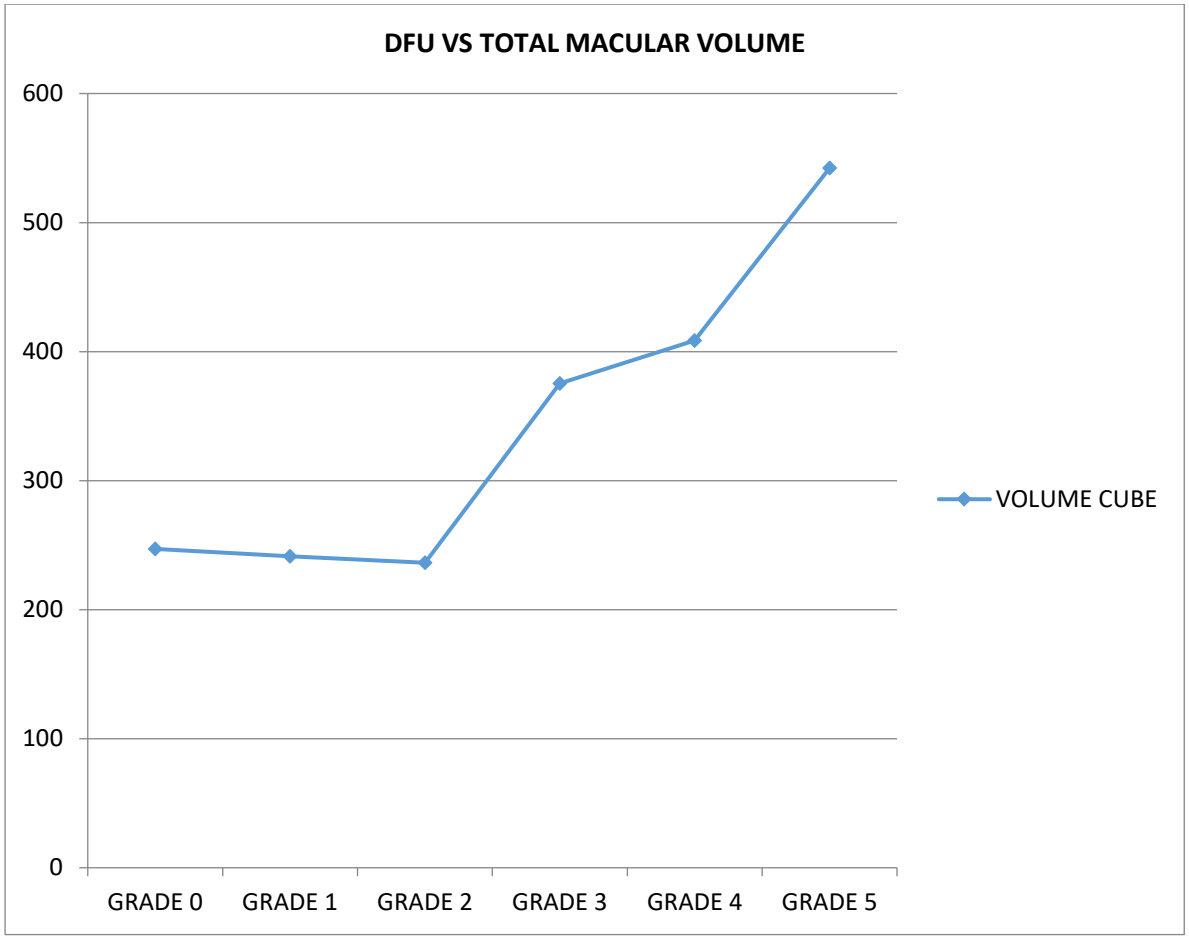
11. DR STATUS COMPARISON WITH TOTAL MACULAR VOLUME

DR STATUS	MEAN	STANDARD DEVIATION	F VALUE	P VALUE
NO DR	9.408	1.9714	3.844	0.002
MILD NDPR	9.791	1.7221		
MODERATE NDPR	10.123	.7361		
SEVERE NDPR	10.397	2.9682		
PDR	16.800	9.7690		
NOT VISUALISED	4.750	5.4854		

Table 15: Comparison of DR status with total macular volume (in cubic mm). Test used- ANOVA, P< 0.05 is significant and P< 0.001 is highly significant.



Graph 8: Bar graph depicting the relationship between the grades of DFU and DR to Total Macular Volume/ TMV (in cubic mm). It is clear from the graph that the volume of the macula increased with increased grades of DFU and DR.



Graph 9: A line graph depicting the relationship between DFU grade and total macular volume/ TMV (in cubic mm). It is clear from the graph that with increased grade of DFU, increased volume of macula is noted.

12. DFU GRADES COMPARISON WITH AVERAGE MACULAR THICKNESS

DFU GRADES	MEAN	STANDARD DEVIATION	F VALUE	P VALUE
GRADE 0	267.88	29.797	4.643	<0.001
GRADE 1	254.06	71.972		
GRADE 2	278.09	34.558		
GRADE 3	274.50	76.778		
GRADE 4	274.92	65.593		
GRADE 5	340.65	154.933		

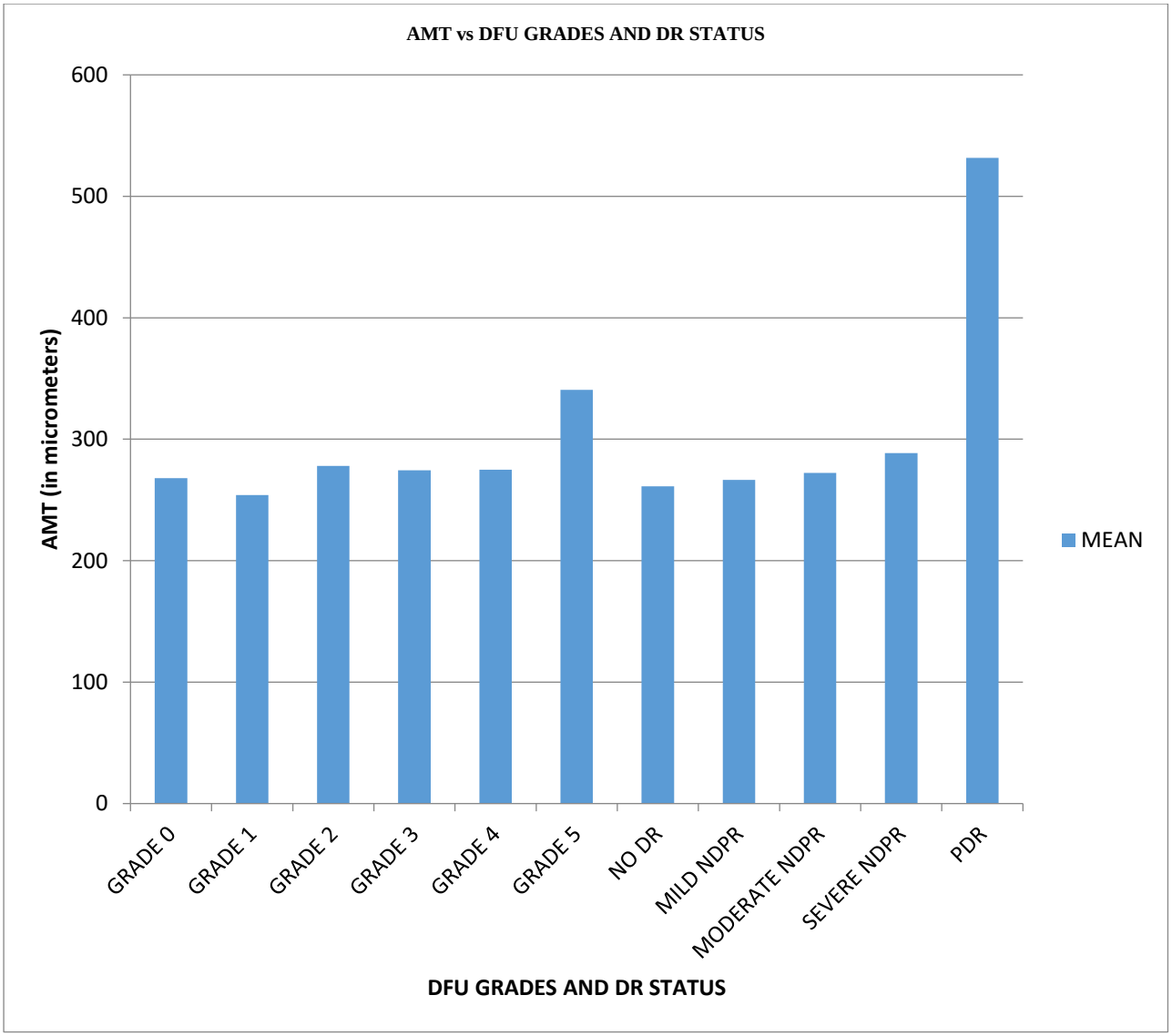
Table 16: Comparison of DFU grades with average macular thickness (in micrometers).

Test used- ANOVA, P< 0.05 is significant and P< 0.001 is highly significant.

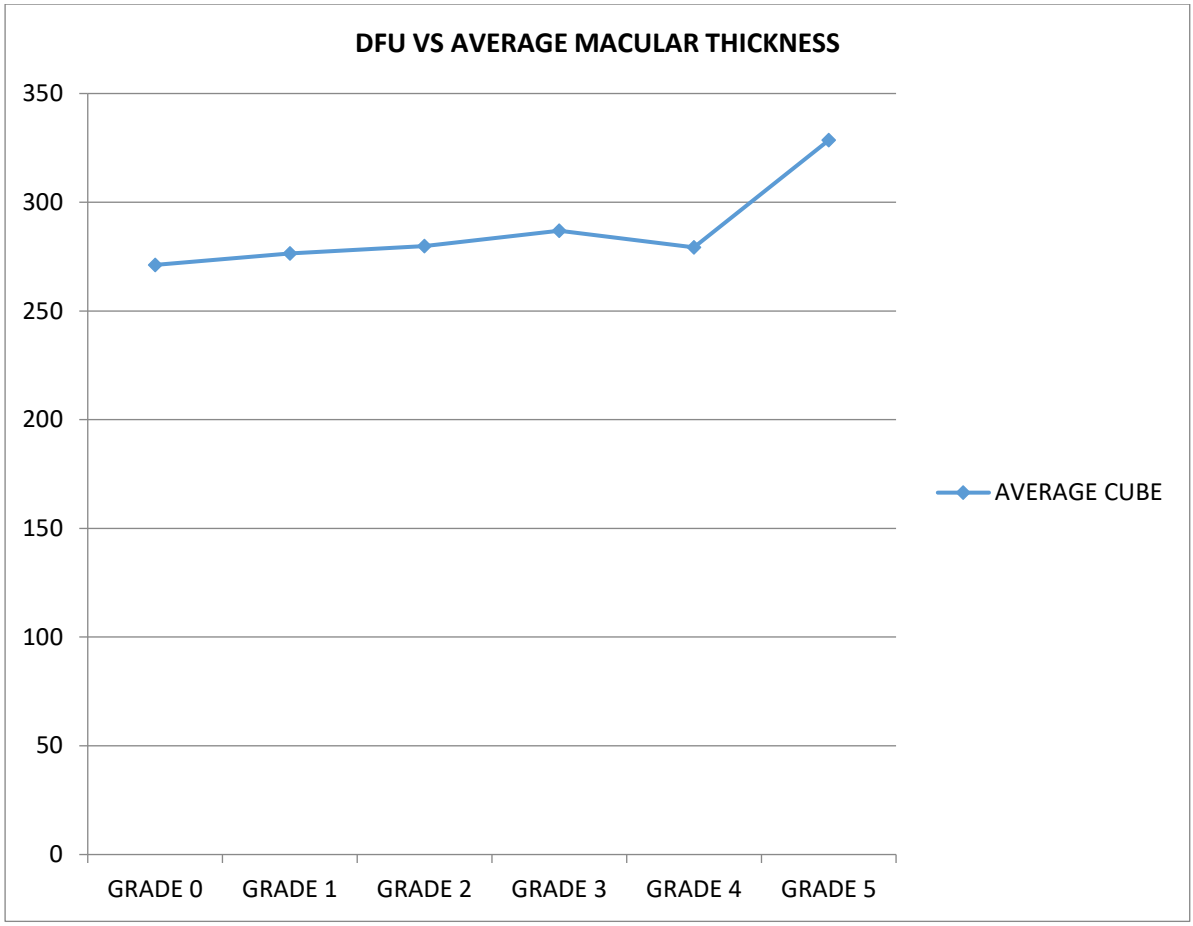
13. DR STATUS COMPARISON WITH AVERAGE MACULAR THICKNESS

DR STATUS	MEAN	STANDARD DEVIATION	F VALUE	P VALUE
NO DR	261.17	55.130	4.643	< 0.001
MILD NDPR	266.43	59.596		
MODERATE NDPR	272.31	54.237		
SEVERE NDPR	288.64	82.425		
PDR	531.75	231.081		
NOT VISUALISED	132.00	152.429		

Table 17: Comparison of DR status with average macular thickness/ AMT (in micrometers). Test used- ANOVA, P< 0.05 is significant and P< 0.001 is highly significant.



Graph 10: Bar graph depicting the relationship between DFU grades and DR status with overall average macular thickness/ AMT (in micrometers). It is clear from the graph that average macular thickness increased with increase in the severity of DFU and DR.



Graph 11: A line graph depicting the relationship between the DFU grade and average macular thickness (in micrometers). It is clear from the graph that the average macular thickness increased with an increase in the DFU grade.

14. DFU GRADES COMPARISON WITH BLOOD UREA

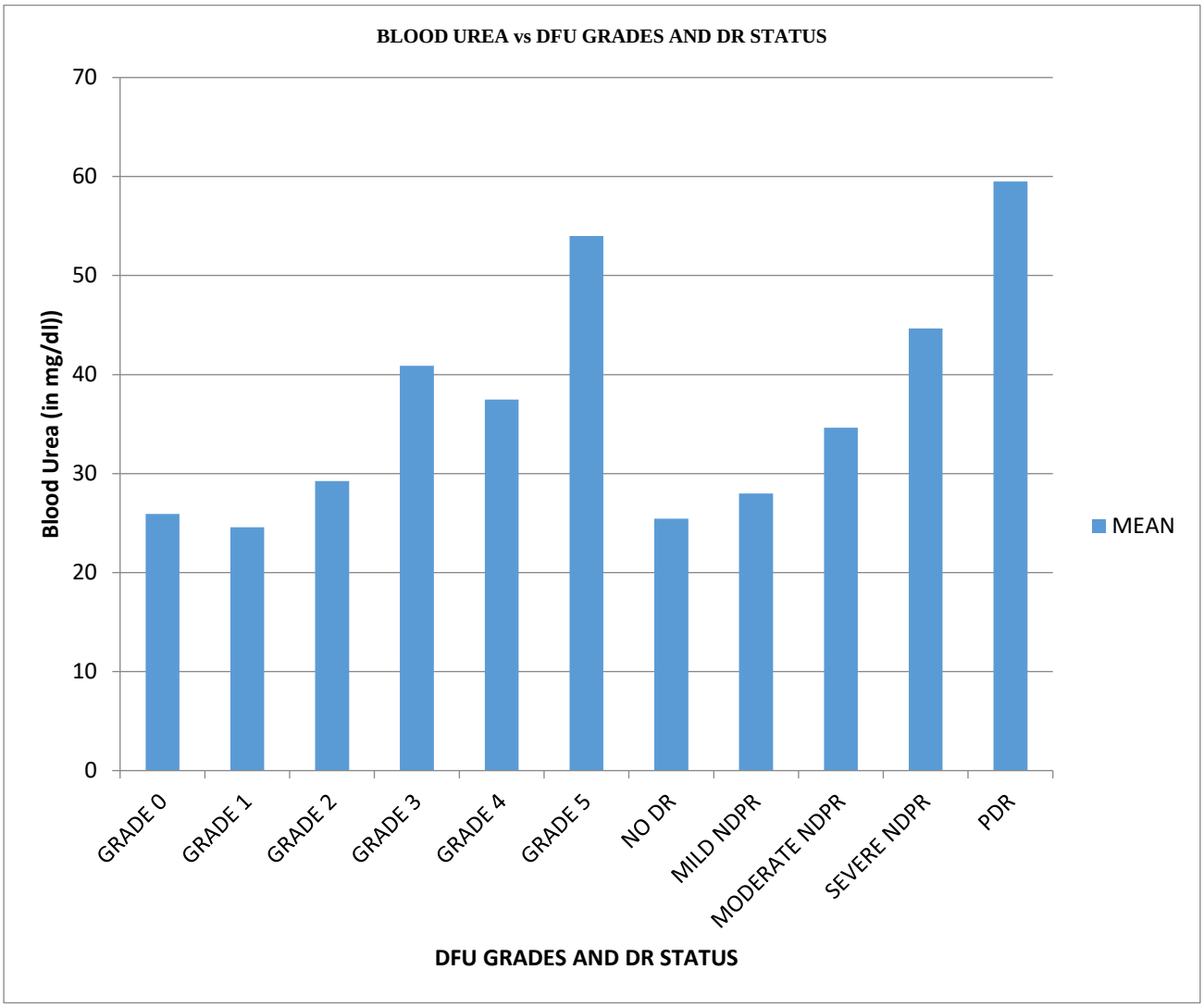
DFU GRADES	MEAN	STANDARD DEVIATION	F VALUE	P VALUE
GRADE 0	25.92	6.345	34.132	<0.001
GRADE 1	24.59	8.360		
GRADE 2	29.24	12.780		
GRADE 3	40.88	14.971		
GRADE 4	37.46	14.089		
GRADE 5	54.00	10.906		

Table 18: Comparison of DFU grades with Blood Urea (mg/dl). Test used- ANOVA, P< 0.05 is significant and P< 0.001 is highly significant.

15. DR STATUS COMPARISON WITH BLOOD UREA

DR STATUS	MEAN	STANDARD DEVIATION	F VALUE	P VALUE
NO DR	25.44	9.735	34.132	< 0.001
MILD NDPR	28.00	10.285		
MODERATE NDPR	34.62	13.063		
SEVERE NDPR	44.67	15.470		
PDR	59.50	9.815		
NOT VISUALISED	23.00	2.309		

Table 19: Comparison of DR status with Blood urea (mg/dl). Test used- ANOVA, P< 0.05 is significant and P< 0.001 is highly significant



Graph 12: Bar graph depicting the relationship between DFU grades and DR status with blood urea levels (in mg/dl). It is clear from the graph that the blood urea levels increased with increase in the grades of DFU and DR.

16. DFU GRADES COMPARISON WITH SERUM CREATININE

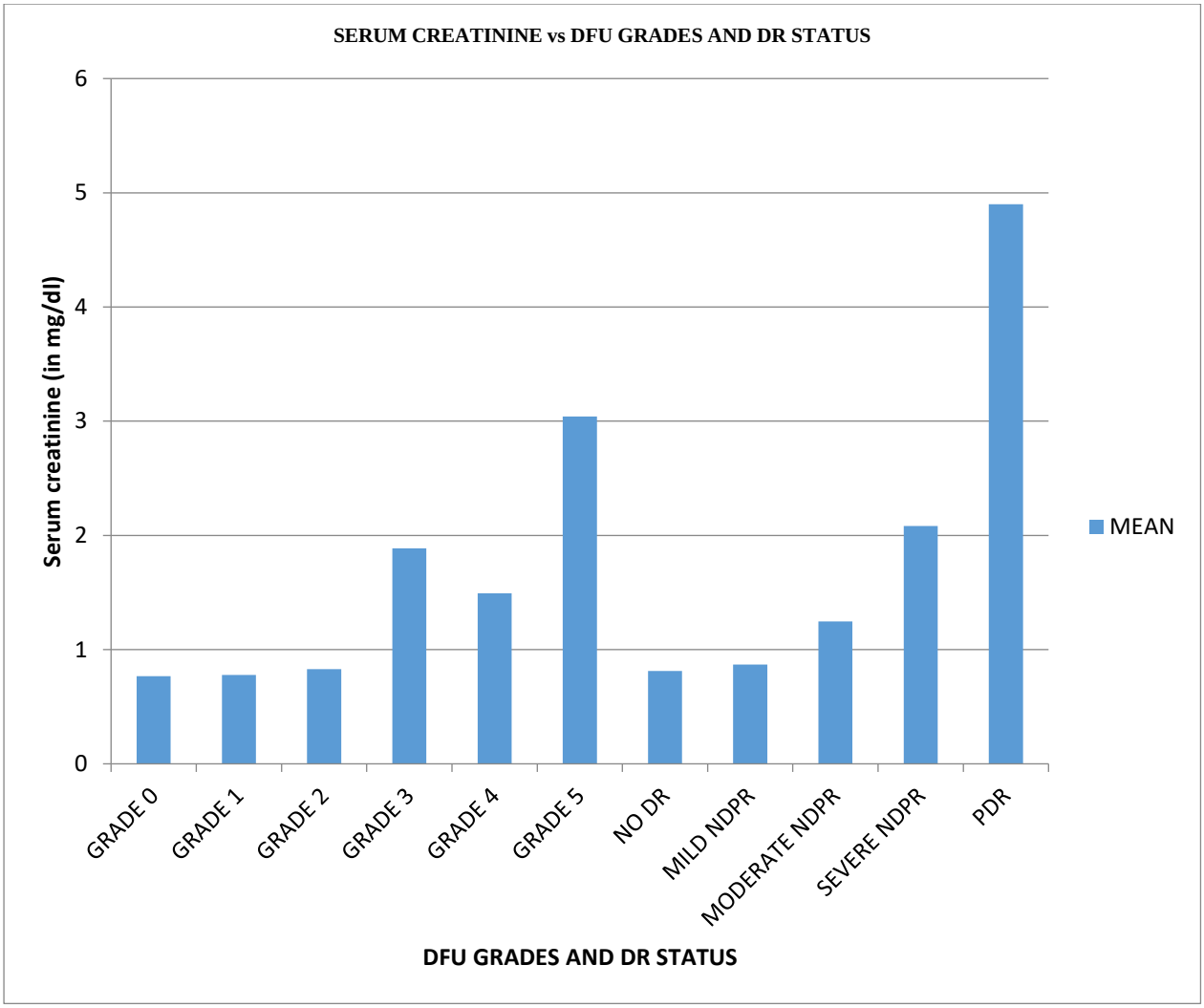
DFU GRADES	MEAN	STANDARD DEVIATION	F VALUE	P VALUE
GRADE 0	.767	.3919	58.547	<0.001
GRADE 1	.779	.2024		
GRADE 2	.829	.2303		
GRADE 3	1.888	1.3832		
GRADE 4	1.492	.5238		
GRADE 5	3.040	1.3949		

Table 20: Comparison of DFU grades with Serum creatinine (mg/dl). Test used- ANOVA, P< 0.05 is significant and P< 0.001 is highly significant.

17. DR STATUS COMPARISON WITH SERUM CREATININE

DR STATUS	MEAN	STANDARD DEVIATION	F VALUE	P VALUE
NO DR	.814	.4908	58.547	< 0.001
MILD NDPR	.870	.1824		
MODERATE NDPR	1.246	.5116		
SEVERE NDPR	2.083	1.0924		
PDR	4.900	1.1547		
NOT VISUALISED	.550	.1732		

Table 21: Comparison of DR status with Serum creatinine (in mg/dl). Test used- ANOVA, P< 0.05 is significant and P< 0.001 is highly significant.



Graph 13: Bar graph depicting the relationship between the serum creatinine levels (in mg/dl) with the DFU grades and DR status. It is clear from the graph that the serum creatinine levels increased with increased grades of DFU and DR.

18. DFU GRADES COMPARISON WITH SERUM URIC ACID

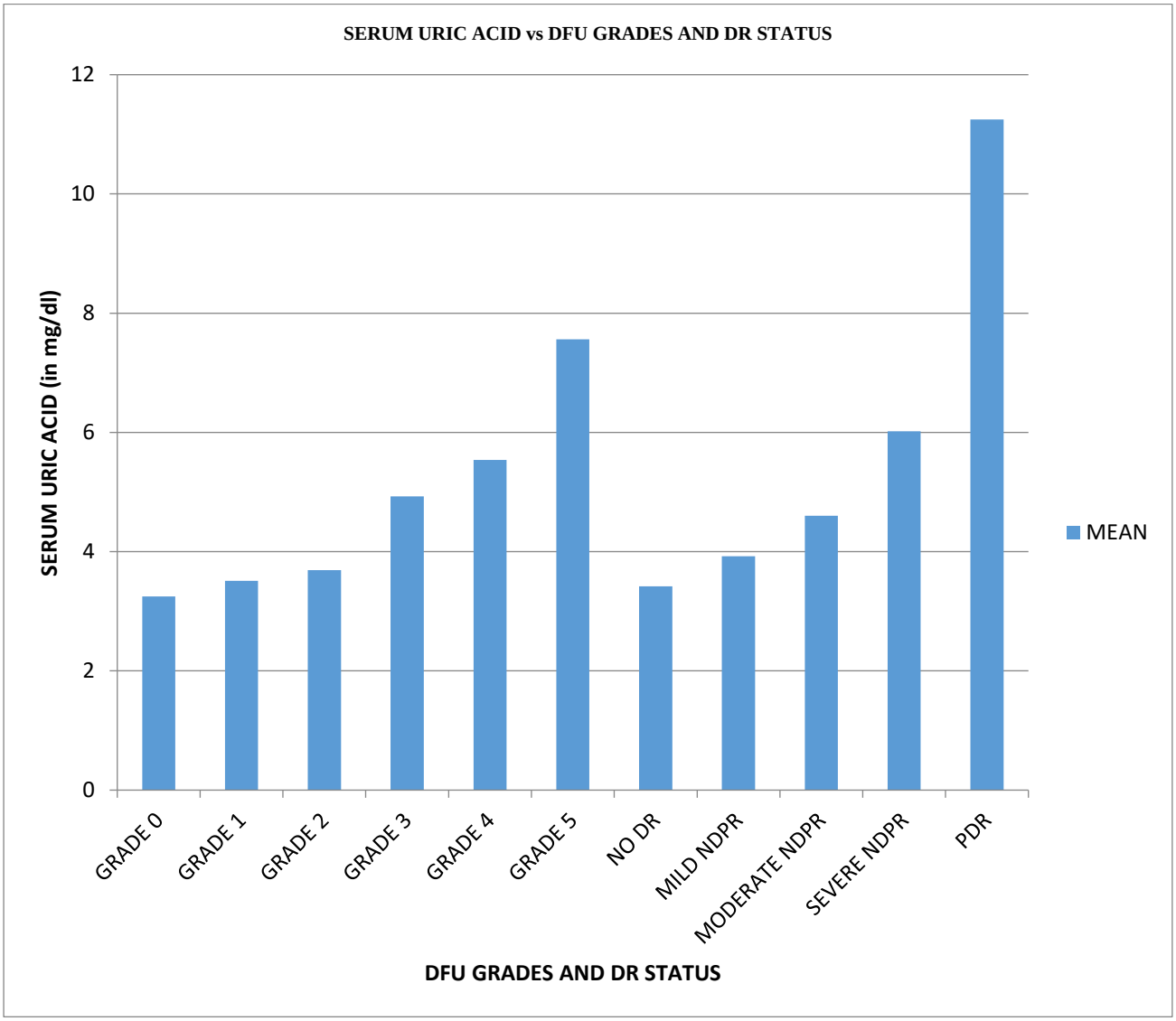
DFU GRADES	MEAN	STANDARD DEVIATION	F VALUE	P VALUE
GRADE 0	3.250	.6627	42.595	< 0.001
GRADE 1	3.512	1.0226		
GRADE 2	3.688	.8238		
GRADE 3	4.925	.8714		
GRADE 4	5.538	2.1915		
GRADE 5	7.560	2.3931		

Table 22: Comparison of DFU grades with Serum Uric acid (in mg/dl). Test used- ANOVA, P< 0.05 is significant and P< 0.001 is highly significant.

19. DR STATUS COMPARISON WITH SERUM URIC ACID

DR STATUS	MEAN	STANDARD DEVIATION	F VALUE	P VALUE
NO DR	3.419	1.0693	42.595	< 0.001
MILD NDPR	3.922	1.0220		
MODERATE NDPR	4.600	1.2918		
SEVERE NDPR	6.017	1.9350		
PDR	11.250	.2887		
NOT VISUALISED	3.200	.5774		

Table 23: Comparison of DR status with Serum uric acid (mg/dl). Test used- ANOVA, P< 0.05 is significant and P< 0.001 is highly significant**.**



Graph 14: Bar graph depicting the relationship between DFU grades and DR status with serum uric acid levels (in mg/dl). It is clear from the graph that the serum uric acid levels increased with increase in the grades of DFU and DR.

DISCUSSION

In people with diabetes mellitus, peripheral neuropathy and various degrees of vascular dysfunction can result in foot infections, ulcerations, and significant tissue destruction. These conditions are referred to as diabetic foot ulcers (DFUs). One of the main causes of blindness around the world, DR is characterized by hyperglycemia, retinal neovascularization, microaneurysms, lipid exudation, thickening of the basement membrane, pericyte loss, and IRMA. DR can eventually result in total blindness. Lack of glucose control is thought to be a major beginning factor in DR, which has been the subject of much discussion since it was originally reported in 1977.

Numerous putative mechanisms, including as the polyol pathway, non-enzymatic glycation, oxidative stress, and PKC activation, have been connected to the development of DR.

The primary means by which these systems raise intracellular glucose levels are by increased glucose transport into retinal cells. The only glucose transporter capable of allowing glucose to pass through the inner blood-retinal barrier is GLUT1. Retinal endothelial cells in the early stages of diabetic retinopathy (DR) surprisingly show decreased GLUT1 expression, suggesting that GLUT1 is not closely associated with the development of retinopathy.

Diabetes does not alter the expression of GLUT1 in the retinal pigment epithelium (RPE), suggesting that glucose enters the retina more through the RPE than through the retinal endothelial cells. On the other hand, it has been suggested that vascular endothelial growth factor (VEGF), a factor increased in DR, increases the density of relocalized GLUT1 in the inner blood-retinal barrier.

Microvascular problems can have a synergistic effect and significantly increase healthcare expenses if they are not addressed appropriately.

Thus, the present study aims to find an answer to the question of the relationship between DR and DFU. In the present study, people with diabetes with DFU attending the ophthalmology department of Shri B. M. Patil Medical Hospital, Bijapur, from August 2022 to August 2023 were enrolled and studied for the pattern of presentation of DR. A total of 234 eyes from 117 DFU patients were considered for the study.

DR predominantly affected the average age group of 55.63 years, with a minimum of 28 years and a maximum of 85 years (*Table 5*). DR rates were higher (46.67%) among subjects 51-60 years of age. 23.3% of DR was noted in subjects 61-70 years of age. A study by Khandekar et al[140], 2003 reported DR rates commonly in 50-69 years, which is confirmed in yet other studies by Dandona et al[141], 1999, Agrawal et al[142], 2003 and WESDR by Klein et al[143], 1984.

The gender distribution showed a male preponderance (*Table 6, Graph 1)*. In the present study, 80 (68.4%) subjects were males, and 37 (31.6%) were females, which correlated with studies by Bodansky et al[144], 1982 which reported the gender ratio as 2:1 and Rema et al[145],2005, Dandona et al[141], 1999 and Kohner et al[146,] 1998.

The magnitude of retinopathy;

In the present study, the fundus of 234 eyes was compared to DFU severity. DR and DFU changes were maximum in all eyes when comparing with duration of diabetes mellitus (in months) (*Table 8,9, Graph 4),* HbA1C (%) (*Table 10,11, Graph 5*), blood urea (mg/dl) (*Table 18,19, Graph 12),* serum creatinine (mg/dl) (*Table 20,21, graph 13*), and uric acid (mg/dl) (*Table 22,23, Graph 14*). In the present study, most of the

patients with severe grades of DFU were at high risk for DR and maculopathy (*Table 7, Graph 2,3*). This study correlates with the study done by Agarwal et al[142], 2003.

When comparing DFU grade (Wagner's) and DR status with ILM-RPE central foveal thickness (CFT) of all eyes on SD-OCT, it was evident that a strong positive correlation exists, and these results were significant (*Table 12,13, Graph 6,7*). On comparing the DFU grade (Wagner's) and DR status with ILM-RPE total macular volume (TMV) of all eyes, it was evident that a strong positive correlation exists, and these results were significant (*Table 14,15, Graph 8,9*).

In the comparison of DFU grade (Wagner's) with ILM-RPE average macular thickness (AMT), it was evident in that a strong positive correlation exists, and these results were significant (*Table 16,17, Graph 10,11*).

Thus, all the above findings show a high risk of diabetic maculopathy among the study patients of DFU.

A study by Gong et al[147] examined 189 DM patients. They discovered that there was a substantial link between DFU and DR, with the incidence of DR in non-diabetic feet being 48.7% and that in diabetic feet being 90%. A different cross-sectional investigation with 62681 patients revealed that, with a relative risk of 4.45, DR was a significant risk factor for DFU[148]. DFU and DR are both closely related complications of diabetes mellitus. Studies have indicated a favourable association between the occurrence of DFU and DR[16,148]. According to a study by Gu et al[149], there is a favourable correlation between the incidence of DFU and microvascular pathology in diabetes. The results of this study are consistent with the significantly higher incidence of DFU in people with DR. The development and progression of DR and chronic kidney disease have been strongly linked to chronically high blood sugar levels, as documented by the DCCT and UKPDS trials.

Numerous biochemical pathways, including increased polyol pathway flux, diacylglycerol (DAG) activation, PKC pathway, growth factor expression such as VEGF and IGF-1, formation of advanced glycation end products (AGEs), RAAS system activation, oxidative stress, hemodynamic changes, and leukostasis, were identified as potential links between hyperglycemia and DR.

These two kinds of problems frequently work in concert, and if left untreated, they can have a negative effect on the prognosis of the illness and significantly increase healthcare expenses.

The present study shows that DR can significantly increase the incidence of DFU and vice-versa. Studies revealed a favourable relationship between the duration of DM and DR, with an increased risk of 1.89 times for each extra five years of DM.

Thus, the present study helps clinical prevention and treatment of DM patients who develop further complications.

CONCLUSION

Diabetic retinopathy is more common after 50, with a preponderance of males. There is a positive correlation between the grades of DR and the DM progression with increased HbA1C, serum urea, uric acid, and creatinine levels. Increased lipids, fasting blood glucose and elevated blood pressure are important risk factors for diabetic retinopathy.

The majority of patients in this study exhibited retinopathy, and every case showed a positive correlation with the degree of DFU. Consistent with the results of this investigation, patients with DFU have a considerably higher chance of developing DR. Early diagnosis of maculopathy and its early treatment reduces significant visual loss. Timely intervention saves the individual from severe visual loss by controlling the progression of retinopathy. Thus, in conclusion, patients with DFU have a higher risk of DR since severe forms of DFU are associated with higher grades of DR. This highlights the significance of regular screening of all DFU patients by dilated fundus examination for DR changes for early initiation of treatment to prevent significant ocular morbidity. Also, it is equally important to refer all DR patients to DFU clinics to screen for early manifestations of DFU by vascular and neurologic assessments of the foot to prevent serious adverse outcomes of DFU, like amputations. Nevertheless, additional research is necessary to verify the findings of this investigation.

Limitations of the study:

- Patients need follow-ups.
- Smaller sample size
- Single centre study with restricted geographical territory
- Single ethnic group

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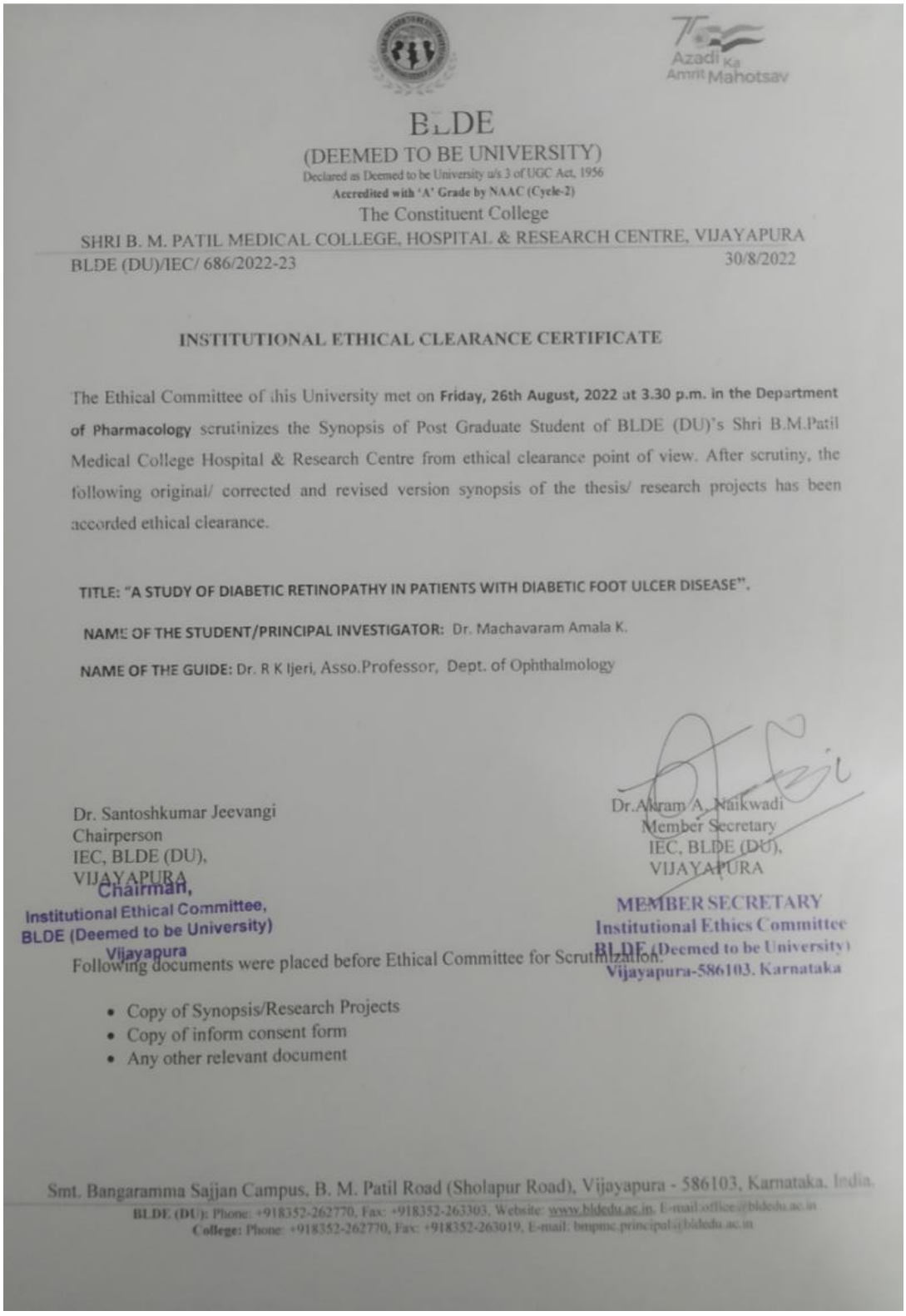
ANNEXURES

ETHICAL COMMITTEE CLEARANCE



BLDE
(DEEMED TO BE UNIVERSITY)
Declared as Deemed to be University u/s 3 of UGC Act, 1956
Accredited with 'A' Grade by NAAC (Cycle-2)
The Constituent College
SHRI B. M. PATIL MEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE, VIJAYAPURA

BLDE (DU)/IEC/ 686/2022-23 30/8/2022

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this University met on **Friday, 26th August, 2022 at 3.30 p.m. in the Department of Pharmacology** scrutinizes the Synopsis of Post Graduate Student of BLDE (DU)'s Shri B.M.Patil Medical College Hospital & Research Centre from ethical clearance point of view. After scrutiny, the following original/ corrected and revised version synopsis of the thesis/ research projects has been accorded ethical clearance.

TITLE: "A STUDY OF DIABETIC RETINOPATHY IN PATIENTS WITH DIABETIC FOOT ULCER DISEASE".

NAME OF THE STUDENT/PRINCIPAL INVESTIGATOR: Dr. Machavaram Amala K.

NAME OF THE GUIDE: Dr. R K Ijeri, Asso.Professor, Dept. of Ophthalmology

Dr. Santoshkumar Jeevangi
Chairperson
IEC, BLDE (DU),
VIJAYAPURA

Chairman,
Institutional Ethical Committee,
BLDE (Deemed to be University)
Vijayapura

Dr.Akram A. Naikwadi
Member Secretary
IEC, BLDE (DU),
VIJAYAPURA

MEMBER SECRETARY
Institutional Ethics Committee
BLDE (Deemed to be University)
Vijayapura-586103. Karnataka

Following documents were placed before Ethical Committee for Scrutinization:

- Copy of Synopsis/Research Projects
- Copy of inform consent form
- Any other relevant document

Smt. Bangaramma Sajjan Campus, B. M. Patil Road (Sholapur Road), Vijayapura - 586103, Karnataka. India.
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STUDY SUBJECT CONSENT FORM

Dr. M. AMALA KRISHNA has explained the purpose of the research, the study procedure, the benefits, and the possible discomfort in the language I best understand. Therefore, Dr. M. AMALA KRISHNA may consider me a subject to participate in this research project, and I willfully consent for the same.

_____ _____

(Participant) (Date)

_____ _____

(Witness to above signature) (Date)

ಅಧ್ಯಯನವಿಷಯಕಾನ್ಸೆಂಟ್ಫಾರ್ಮ್

ಡಾ. ಎಂ. ಅಮಲಾ ಕೃಷ್ಣ, ನನಗೆ ಸಂಶೋಧನೆಯ ಉದ್ದೇಶ, ಅಧ್ಯಯನದ ವಿಧಾನ ಮತ್ತು ಸಂಭವನೀಯ ಅಸ್ವಸ್ಥತೆಗಳು ಮತ್ತು ನನ್ನ ಸ್ವಂತಭಾಷೆಯಲ್ಲಿ ನಾನು ಅನುಭವಿಸಬಹುದಾದ ಪ್ರಯೋಜನಗಳನ್ನು ವಿವರಿಸಿದ್ದೇನೆ ಎಂದು ನಾನು ಖಚಿತ ಪಡಿಸುತ್ತೇನೆ. ಮೇಲಿನ ಎಲ್ಲಾ ವಿಷಯಗಳನ್ನು ನನ್ನ ಸ್ವಂತ ಭಾಷೆಯಲ್ಲಿ ವಿವರವಾಗಿ ವಿವರಿಸಲಾಗಿದೆ ಮತ್ತು ನಾನು ಅದನ್ನು ಅರ್ಥಮಾಡಿಕೊಂಡಿದ್ದೇನೆ. ಆದ್ದರಿಂದ, ಈ ಸಂಶೋಧನಾಯೋಜನೆಯಲ್ಲಿ ವಿಷಯವಾಗಿ ಭಾಗವಹಿಸಲು ಒಪ್ಪಿಗೆ ನೀಡಲು ನಾನು ಒಪ್ಪುತ್ತೇನ

_____ _____

(ಭಾಗವಹಿಸುವವರು) (ದಿನಾಂಕ)

RISK AND DISCOMFORTS:

I understand that I may undergo some pain and discomfort during the examination or the treatment. This study's procedures are not expected to amplify these feelings associated with the usual course of treatment.

BENEFITS:

I know that my participation in "A STUDY OF DIABETIC RETINOPATHY IN PATIENTS WITH DIABETIC FOOT ULCER DISEASE" would help in the early diagnosis of the disease, which would help initiate early and effective treatment. I understand and accept the benefits, risks, and costs involved. I willingly give consent to take part in the study.

CONFIDENTIALITY*:*

I understand that this study's medical information will be subject to the required privacy and become a part of hospital records.

Suppose the data are used for teaching purposes or publication in the medical literature, no name will be used in that case, and other identifiers such as photographic images will be used only with written permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study to DR. RAGHAVENDRA K IJERI in the Department of Ophthalmology, DR. MANJUNATH S KOTENNAVAR in the Department of General Surgery, who will answer my queries or worries. I understand that I will be well informed of any significant new findings discovered during the study, which might influence my continued participation. A copy of this consent form is given to me for careful reading.

REFUSAL FOR WITHDRAWAL OF PARTICIPATION:

I understand that I am participating in this study voluntarily and may withdraw consent or refuse to participate and discontinue participation at any time without prejudice. I also understand that DR. M. AMALA KRISHNA may terminate my study's participation after explaining the reasons.

INJURY STATEMENT:

I understand that in any unlikely event of injury to me resulting directly from my study's participation, and if any such damage were reported promptly, I would be treated appropriately. However, no further compensation or reimbursement would be provided by the doctor or the hospital. I understand my agreement to participate in this study and not waive any of my legal rights.

_____ _____

(Participant) (Date)

I have explained to the patient name _____the purpose of the research, the procedures required and the possible risks to the best of my ability.

_____ _____

(Investigator) (Date)

PROFORMA FOR CASE TAKING

DEPARTMENT OF OPHTHALMOLOGY

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

DATE

CASE NO: OPD/IPD NO:

NAME: AGE:

SEX: OCCUPATION:

ADDRESS: CONTACT NUMBER:

CHIEF COMPLAINTS:

HISTORY OF PRESENT ILLNESS:

HISTORY OF PAST MEDICAL ILLNESS:

1. K/C/O DIABETES MELLITUS SINCE
2. PATIENT IS ON MEDICATION-
3. REGULARITY OF MEDICATION- REGULAR ☐

   IRREGULAR ☐
4. OTHER MEDICAL ILLNESSES-

HISTORY OF PAST SURGICAL ILLNESS:

FAMILY HISTORY:

PERSONAL HISTORY

- DIET
- SLEEP
- HABITS
- BOWEL MOVEMENTS
- BLADDER HABITS

GENERAL PHYSICAL EXAMINATION

- PALLOR
- ICTERUS
- CYANOSIS
- CLUBBING
- KOILONYCHIA
- LYMPHADENOPATHY
- EDEMA

- BP
- PULSE
- TEMPERATURE

PERIPHERAL PULSES

1. DORSALIS PEDIS
2. ANTERIOR TIBIAL
3. POSTERIOR TIBIAL
4. POPLITEAL
5. FEMORAL

LOCAL EXAMINATION OF THE DIABETIC FOOT ULCER

- LOCAL RISE OF TEMPERATURE
- TENDERNESS
- LOCATION OF THE ULCER
- NUMBER OF ULCERS
- SIZE
- SHAPE
- MARGINS
- EDGES
- FLOOR
- SKIN SURROUNDING THE ULCER

GRADE OF THE ULCER

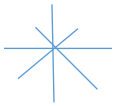
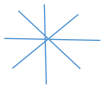
1. WAGNER'S SYSTEM OF CLASSIFICATION

2. THE INTERNATIONAL WORKING GROUP OF THE DIABETIC FOOT(IWGDF)

OCULAR EXAMINATION

RIGHT EYE

LEFT EYE

	EXTERNAL APPEARANCE	
	OCULAR MOTILITY	
	LIDS	
	SCLERA	
	CONJUNCTIVA	
	CORNEA	
	IRIS	
	ANTERIOR CHAMBER	
	PUPIL	
	LENS	
	BEST CORRECTED VISUAL ACUITY	
	INTRAOCULAR PRESSURE	

DILATED FUNDUS EXAMINATION

RIGHT EYE

LEFT EYE

	MEDIA	
	DISC	
	BACKGROUND	
	BLOODVESSELS	
	MACULA	

IMPRESSION:

OPTICAL COHERENCE TOMOGRAPHY

FUNDUS PHOTO

INVESTIGATIONS

- HBA1C
- SERUM URIC ACID
- BLOOD UREA
- SERUM CREATININE
- RANDOM BLOOD SUGAR

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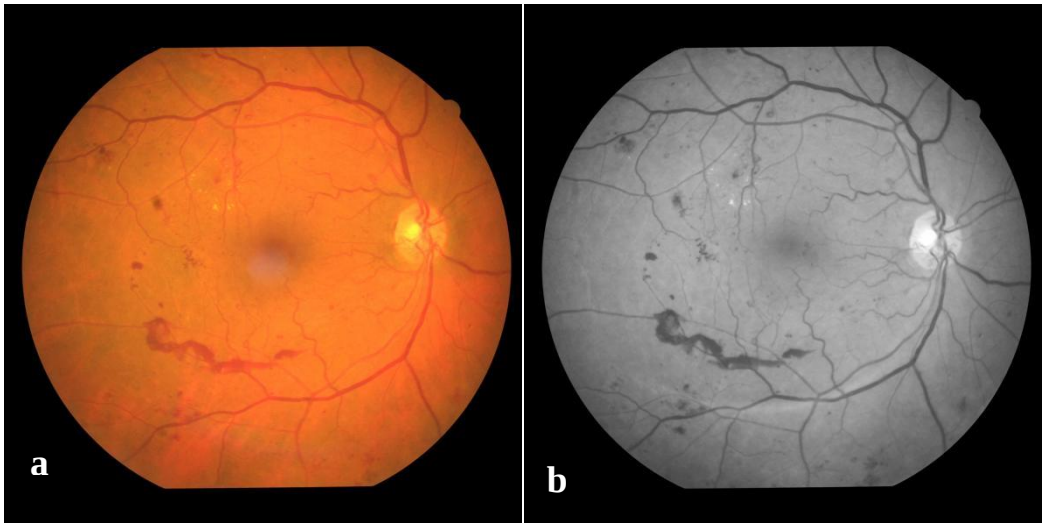
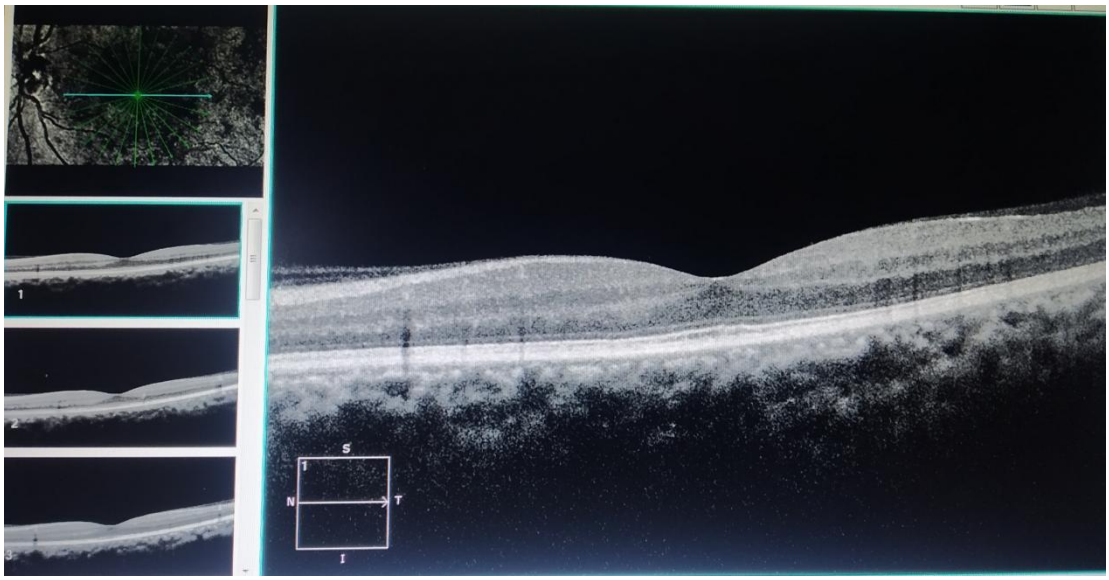
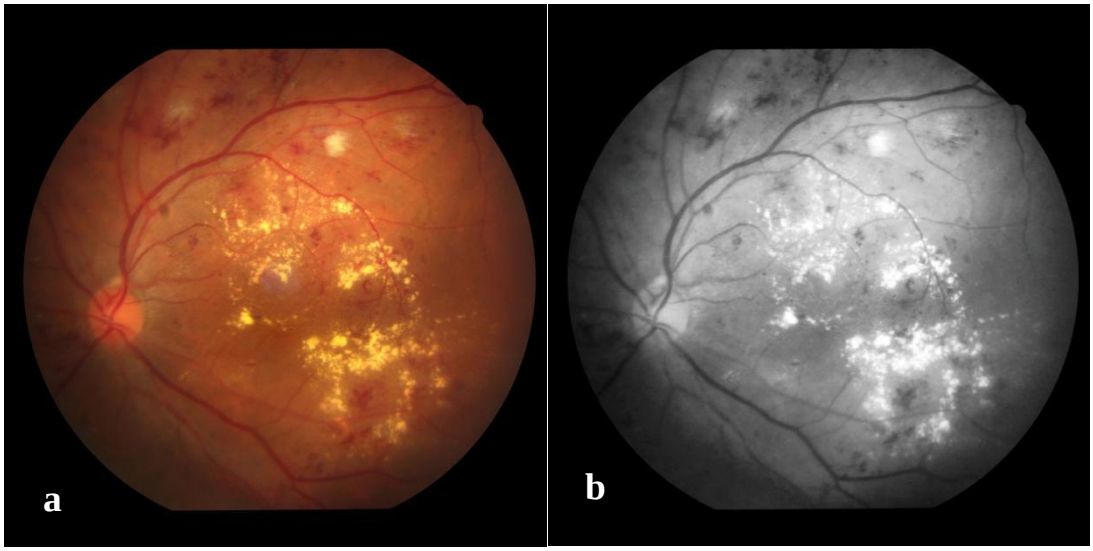
COLOUR PLATES



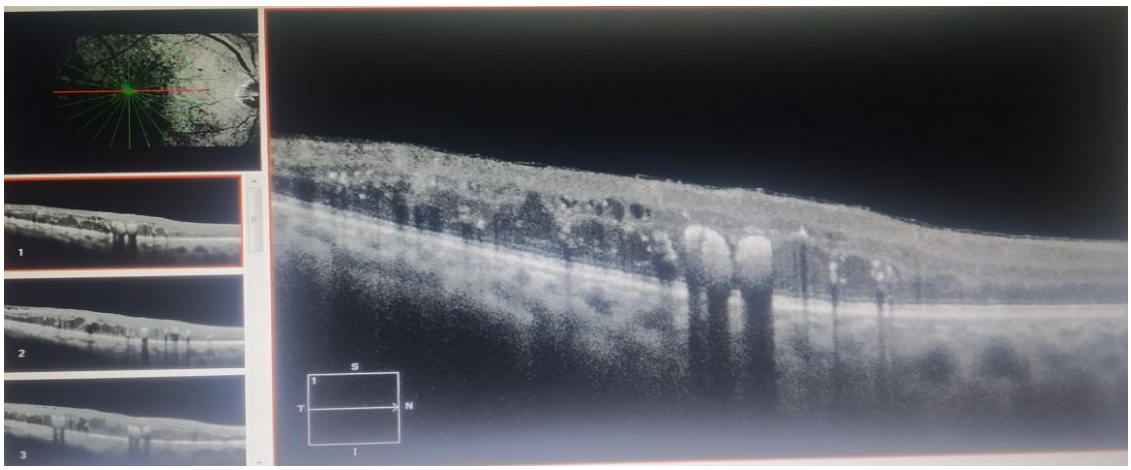
Colour plate 1: a) Right eye color fundus photograph of a 47-year-old male (patient-1) with Grade 2 DFU. Moderate NPDR was noted. b) Right eye red-free fundus photograph of the same patient



Colour plate 2: Right eye OCT scan of patient-1.



Colour plate 3: a) Left eye color fundus photograph with Severe NPDR with CSME of a 71-year-old male (patient-2) with Grade 4 DFU. b) Left eye red-free fundus image of the same patient.



Colour plate 4: Left eye OCT image of patient 2 showing multiple hyperreflective foci of hard exudates with back shadowing, intraretinal edema secondary to leakage from microaneurysms in the cysts, multiple intraretinal fluid pockets and loss of retinal layer integrity.

Colour plate 5: High Density Spectral Domain Optical Coherence tomography scanning of a patient on Cirrus HD OCT (Zeiss).

Colour plate 6: Digital fundus photography of a patient with handheld fundus camera after full pharmacological dilatation of pupils.

KEY TO MASTERCHART

1. OP NO.- Out Patient Number
2. IP NO.- In Patient Number
3. M- Male
4. F- Female
5. BU- Blood Urea
6. SC- Serum Creatinine
7. SUA- Serum Uric Acid
8. DFU- Diabetic Foot Ulcer
9. R- Right eye
10. L-Left eye
11. DR- Diabetic Retinopathy
12. NPDR- Non-proliferative Diabetic Retinopathy
13. PDR- Proliferative Diabetic Retinopathy
14. CFT- Central Foveal Thickness
15. TMV- Total Macular Volume
16. AMT- Average Macular Thickness

CASE NO.	PT. NAME	IP/OPD N(	AGE	SEX	Duration	HBA1C	BU	SC	SUA	DFU	GRAC	FUNDUS	R FUNDUS	L CFT (R)	CFT (L)	TMV (R)	TMV (L)	AMT (R)	AMT (L)
1	SHRISAIL	245726	65	M	1	5	53	1.2	3.5	2		NO DR	NO DR	137	268	8.5	6.6	235	183
2	SAHADEV	278523	70	M	1	6.1	40	0.5	2.9	2		NO DR	NO DR	130	130	9.2	8.3	255	190
3	RAVINDRA	203294	45	M	60	6.3	68	1	3.8	1		NO DR	NO DR	253	256	10.5	10.5	292	293
4	SURESH	264479	29	M	121	11	65	1.3	4.2	2		VILD NPDF	VILD NPDF	267	272	10.7	10.8	298	299
5	RAVIKANT	186307	48	M	188	13.2	37	1.2	2.9	4		EVERE NPE	EVERE NPD	614	609	8.8	9.9	245	275
6	GANGABAI	217342	49	F	48	14.3	20	0.7	3.5	4		EVERE NPE	NPDR CH	639	624	12.5	13.8	347	382
7	AKATUNSA	050877	49	M	133	11.2	42	1.5	7.9	4		EVERE NPE	EVERE NPD	684	679	9.3	10.5	258	290
8	IRANNA	090259	58	M	146	5.6	19	0.9	3.7	1		NO DR	NO DR	230	221	9.2	9.2	255	256
9	MALAPPA	285895	38	M	12	7	42	1.9	3.9	0		NO DR	NO DR	217	213	7.9	8.5	221	237
10	HAKUNTAL	308362	67	F	170	8.3	56	2.2	4.5	3		DERATE NI	DERATE NI	359	380	9.4	9.8	262	272
11	DATTA	306440	60	M	304	6.9	24	0.9	2.9	2		VILD NPDF	VILD NPDF	237	247	10.3	10.3	285	287
12	HANDRAPF	300110	45	M	36	12.5	16	1	3.2	2		VILD NPDF	VILD NPDF	283	279	9.1	8.9	252	248
13	SUSHILA	362420	50	F	148	11.6	10	0.5	4.1	3		DERATE NI	DERATE NI	451	460	9.5	9.3	265	259
14	SAVITRI	325941	35	F	188	12.2	12	0.7	3.9	4		EVERE NPE	EVERE NPD	666	685	10.1	11.6	280	323
15	RUDRAYYA	339706	72	M	73	5.6	9.9	0.5	2.1	1		NO DR	NO DR	237	231	10.8	10.7	300	298
16	HARANAPF	296621	70	M	73	5.8	27	0.6	2	1		NO DR	NO DR	185	181	9.2	9.2	256	256
17	HIVANANI	369098	70	M	12	5.6	29	0.8	1.3	1		NO DR	NO DR	216	227	10.4	10.8	289	301
18	BASANNA	363523	65	M	18	5.2	9	1.3	1.6	1		NO DR	NO DR	216	205	10.2	9	283	250
19	GADEVAPI	367555	55	M	4	4.9	16	0.8	2.3	1		NO DR	NO DR	220	205	10.7	3.2	297	89
20	VENDRAPI	192571	54	M	73	4.9	23	0.5	2.3	1		NO DR	NO DR	226	205	9.7	10.6	270	294
21	MALLANNA	356344	65	M	60	5.7	10	0.6	4.1	1		NO DR	NO DR	216	203	10.4	8.9	289	249

22	VAGAMMA	370660	60	F	73	8.8	30	0.6	4.9	2	VILD NPDR	MILD NPDR	228	240	8.9	9.4	248	262
23	NNABASA	380628	54	M	36	5.2	26	0.7	5.7	1	NO DR	NO DR	134	300	10.5	9.4	290	260
24	HANTABA	382620	66	F	303	10	24	1	3.7	4	EVERE NPDR	EVERE NPDR	268	208	11	9.5	306	263
25	RAYAPPA	437962	72	M	36	7.5	29	0.9	3.6	1	VILD NPDR	MILD NPDR	205	202	10	10	278	278
26	ANAMANT	133181	28	M	267	4.4	29	0.7	3.2	1	VILD NPDR	MILD NPDR	259	204	9.6	9.1	268	254
27	KRISHNA	029571	62	M	24	6.9	21	0.9	6	2	VILD NPDR	MILD NPDR	262	266	11.8	12	327	334
28	BALABAI	112950	70	F	34	6	26	0.6	3	1	VILD NPDR	MILD NPDR	320	273	9.5	10.3	265	285
29	KALAMMA	398951	72	F	121	7	28	1.2	3.5	1	VILD NPDR	MILD NPDR	277	248	11	10.4	305	29
30	AMALABA	020418	55	F	133	6.9	49	1.1	3.3	1	VILD NPDR	MILD NPDR	272	270	9.9	9.9	274	274
31	MADDUMA	049287	74	M	60	6.9	22	1	4	1	VILD NPDR	MILD NPDR	274	256	10.8	8.9	299	247
32	AVVAPPA	437974	68	M	109	6.1	17	0.9	6.5	1	VILD NPDR	MILD NPDR	271	257	10.4	10.1	289	280
33	SHIVARAY	415566	62	M	243	6.7	26	0.9	4.5	2	VILD NPDR	MILD NPDR	236	237	10.4	10.4	288	290
34	VALLAPPA	411562	32	M	36	5	20	0.6	3	2	VILD NPDR	MILD NPDR	252	250	11.3	11.5	314	319
35	BHARATI	372703	49	F	73	8.9	31	0.7	3.5	2	VILD NPDR	MILD NPDR	185	182	9.2	8.5	257	237
36	JAYANNA	020084	47	M	24	7.2	22	0.9	6	1	VILD NPDR	MILD NPDR	272	270	9.9	9.9	274	274
37	ENCHAPPA	418696	65	M	73	6	24	0.8	4	1	VILD NPDR	MILD NPDR	265	307	9.6	10.6	265	295
38	ASAMMA	017704	61	F	12	5.1	21	0.7	4.5	1	NO DR	NO DR	206	205	9.9	10.1	276	279
39	IRUAMMA	008765	60	F	24	6	25	0.8	4.8	1	NO DR	NO DR	295	233	10.3	10.1	286	281
40	ULATRAY	038019	58	F	6	6.2	28	0.8	4	1	NO DR	NO DR	202	208	10.3	10.2	285	284
41	ANDRAKA	114661	69	F	60	6	29	1	5	1	NO DR	NO DR	198	205	9.9	10.1	274	282
42	ANGAPPA	436375	85	M	36	6.7	26	1.1	4.8	0	NO DR	NO DR	272	264	10.6	9.9	294	275
43	SHIVAPPA	029839	66	M	24	7	30	1.2	5	1	NO DR	NO DR	223	234	9.4	9.2	260	255
44	LAXMIBAI	112866	60	F	73	6	19	0.8	3	2	NO DR	NO DR	266	236	10.3	10	285	278

44	LAXMIBAI	112866	60	F	73	6	19	0.8	3	2	NO DR	NO DR	266	236	10.3	10	285	278
45	HIVANANI	445156	64	M	24	5.7	26	1	3.8	1	NO DR	NO DR	260	254	9.9	10.2	276	285
46	ANIL	322327	38	M	36	4.1	23	0.7	2.9	1	NO DR	NO DR	220	209	9	9	249	249
47	BASAPPA	060480	48	M	12	6.2	32	1	5.6	1	NO DR	NO DR	223	224	9.8	10	271	279
48	HANNAPP/	043032	61	M	13	5.5	22	0.5	3.3	1	NO DR	NO DR	210	208	8.9	9.4	248	250
49	IANDAWV	232889	61	F	6	4.5	20	0.9	3	1	NO DR	NO DR	214	217	9.6	9.4	268	261
50	KASTURI	417051	38	F	6	6.1	21	0.7	3.2	2	NO DR	NO DR	212	210	9.8	9.8	272	273
51	ANGABAI	024861	68	F	12	4.6	27	0.5	3.3	2	NO DR	NO DR	275	253	10.9	10.5	304	290
52	OURAMM/	052716	37	F	18	4.9	22	0.7	2.9	1	NO DR	NO DR	196	200	9.6	9.6	267	267
53	GADEVAPI	367555	55	M	4	4.9	16	0.8	2.3	1	NO DR	NO DR	220	205	10.7	3.2	297	89
54	SAROJINI	446750	57	M	109	15	46	2.1	9	4	EVERE NPD	NV	226 NV		7.7 NV		213 NV	
55	ANKARAPI	388033	62	M	133	11.2	39	1.6	4.9	4	EVERE NPD	EVERE NPD	240	227	9.4	9.4	262	260
56	VARASING	041469	62	M	146	14	59	2	7.5	4	EVERE NPD	EVERE NPD	241	226	9.4	9.2	261	257
57	INGAREVV	001869	55	F	243	15.1	62	2.2	8	4	EVERE NPD	EVERE NPD	330	316	11	11	304	306
58	IASHIKANT	217301	41	M	255	16.3	62	2	7.9	5	EVERE NPD	NV	253 NV		10.1 NV		280 NV	
59	RAMBABAI	003706	65	F	142	14.1	47	1.1	5.2	3	DERATE NI	DERATE NI	345	344	10.5	10.2	291	283
60	ANGAMES	436282	58	M	219	13.1	41	1.1	5.9	3	DERATE NI	DERATE NI	209	274	8.2	9.9	228	274
61	VANAGOU	400589	44	M	127	8	28	1	4	3	DERATE NI	DERATE NI	232	237	10.3	9.3	286	25
62	BHUTALI	427616	60	M	160	8	32	1	4	2	DERATE NI	DERATE NI	236	290	10.6	11.6	294	323
63	ADIVAYYA	411718	45	M	206	9	28	1.2	3.7	4	DERATE NI	DERATE NI	272	271	10	10.1	278	280
64	BASAPPA	400621	58	M	136	7.9	17	0.6	3.5	2	DERATE NI	DERATE NI	278	282	10.9	10.8	303	300
65	RUDRAYYA	037492	65	M	85	8.9	49	1.3	3.9	3	DERATE NI	DERATE NI	239	246	9.7	10	268	279

66	HARADABA	418990	55	M	148	7.2	24	1	4	2	DERATE NI	DERATE NI	267	271	10	9.9	278	274		
67	SANGAYYA	210750	50	M	133	11.3	39	1.2	5.8	4	DERATE NI	DERATE NI	369	364	10.6	10.5	295	291		
68	SIDDAPPA	116086	55	M	182	14.1	69	1.9	8.7	5	EVERE NPD	EVERE NPD	610	606	14	12.4	389	345		
69	ANAND	112008	67	M	194	16.1	59	2	8	5	EVERE NPD	EVERE NPD	567	550	10.8	11.1	300	309		
70	AMALABA	430170	58	M	121	9.2	33	1.9	8	4	DERATE NI	DERATE NI	360	348	11.1	11.5	309	320		
71	VIM AWAT	040761	77	M	158	12.5	46	2.1	3.2	4	DERATE NI	DERATE NI	403	400	9.8	9.7	272	271		
72	BASAPPA	068624	58	M	24	5.5	21	0.6	3	1	NO DR	NO DR	301	279	11	10.8	304	301		
73	SHRISHAIL	084707	70	M	42	5.9	25	0.9	3.9	1	NO DR	NO DR	232	230	10.3	10.2	285	283		
74	MBAWWA	068231	49	F	12	4.9	29	0.7	3.2	0	NO DR	NO DR	273	277	10.5	10.7	293	298		
75	RENUKA	083477	40	F	3	5.1	28	0.8	3.9	0	NO DR	NO DR	249	239	9.7	10.2	296	282		
76	ANITA	092154	35	F	8	5	27	0.5	3.1	0	NO DR	NO DR	255	240	9.1	10.2	254	283		
77	RAMESH	107155	38	M	12	5.1	29	0.8	3.7	1	NO DR	NO DR	257	241	10.7	10.8	296	300		
78	URALIDHA	066445	73	M	486	17.1	51	3.9	11	5	PDR	PDR	223	232	11.5	11.2	417	473		
79	VITTAL	037768	50	M	24	5.5	21	0.8	3.7	1	NO DR	NV	241	NV	9.7	NV	268	NV		
80	NAMANT	047755	47	M	36	5.9	28	0.9	4.1	1	NO DR	NO DR	237	288	10.2	9.7	283	269		
81	PEERU	065604	47	M	11	5.1	21	0.6	3.3	1	NO DR	NO DR	241	237	9.2	10.8	257	301		
82	PRABHU	064302	67	M	42	5.4	27	0.9	3.9	1	NO DR	NO DR	257	241	10.7	10.8	296	300		
83	HOSAPPA	057306	66	M	121	15.9	40	3.1	5.9	3	EVERE NPD	EVERE NPD	578	566	12.7	12.4	352	345		
84	VITTHAL	254473	70	M	304	19.2	56	4.8	5.9	3	EVERE NPD	EVERE NPD	589	599	12.4	13	343	360		
85	KALMESH	092875	38	M	12	4.4	21	0.6	3.1	0	NO DR	NO DR	230	229	9	9.4	250	262		
86	ALAKA	295249	67	F	60	5.6	30	0.9	4.2	1	MILD NPDR	MILD NPDR	291	281	9.8	10.2	273	283		
87	NNAPURN	093391	57	F	12	4.8	20	0.4	2.9	1	NO DR	NO DR	279	280	10.5	7.9	293	221		

88	GIRISH	090505	37	M	54	5	21	0.8	3.3	1	MILD NPDR	MILD NPDR	267	265	10.4	10.3	290		287
89	NAGAMMA	118220	60	F	13	4.6	25	0.7	3.7	1	NV	NO DR	NV	231	NV	9.4	NV		262
90	ALLAMMA	086849	61	F	24	4.9	23	0.7	3.4	1	NO DR	NO DR	239	238	10.4	9.1	290		254
91	KAREPPA	014376	30	M	6	5	22	0.6	3.9	1	NO DR	NO DR	281	234	9.9	9.8	274		272
92	VITTAL	084957	63	M	9	6	25	0.9	4	1	NO DR	NO DR	277	322	10.6	10.2	295		284
93	OLLALAPP/	076627	48	M	7	5.9	19	0.4	2.8	1	NO DR	NO DR	240	233	10.1	10	280		277
94	SHRISHAIL	096449	53	M	13	6.3	27	0.6	3.9	1	MILD NPDR	NV	272	NV	7.1	NV	198	NV	
95	HANTABA	203410	80	F	36	6.2	29	0.8	3.4	0	NO DR	NO DR	237	209	10.2	9.8	282		271
96	HAKUNTAL	044244	68	F	377	18.7	54	4	7.9	5	NO DR	EVERE NPD	647	671	9.5	9.5	264		263
97	AKINABEG	173208	56	F	36	5.6	22	0.7	3.4	1	NO DR	NO DR	223	234	9.4	9.2	260		255
98	HULAMM/	176806	55	F	30	4.9	20	0.6	3.1	0	NO DR	NO DR	279	279	10.5	10.9	291		302
99	MALANNA	158904	37	M	5	4	18	0.4	2.7	0	NO DR	NO DR	251	275	10	5.9	277		164
100	HILVALEEL	120847	30	F	1	4.4	21	0.6	2.9	0	NO DR	NO DR	211	206	9.4	9.3	260		259
101	A. B. NAIK	094148	50	F	515	15.3	49	3.8	5.5	5	EVERE NPD	EVERE NPD	642	627	10.4	9.2	289		254
102	VITTAL	088022	65	M	36	6.1	29	0.7	2.9	1	NO DR	NV	228	NV	8.8	NV	244	NV	
103	MASWAN	141843	65	F	48	6	27	0.9	3.1	1	MILD NPDR	MILD NPDR	258	260	9.7	9.7	270		270
104	MUDKAPP/	370058	48	M	3	4.1	29	0.7	2.5	0	NO DR	NO DR	239	237	9.9	10.1	276		280
105	HAVURAY/	025492	45	M	1	5	27	0.9	2.9	1	NO DR	NO DR	251	261	10.5	5.2	291		146
106	HIDANANI	131319	37	M	479	14.3	42	3.1	5.6	5	EVERE NPD	EVERE NPD	520	523	11.7	13	326		361
107	RABHUDE\	039827	35	M	12	4.5	21	0.4	2.7	1	NV	NO DR	NV	244	NV	9.6	NV		266
108	SRIDHAR	062291	62	M	401	18.8	53	2.9	5.6	5	EVERE NPD	EVERE NPD	631	622	12.7	12.1	353		337
109	ULASABAI	075124	61	F	42	4.9	22	0.6	2.4	1	NO DR	NO DR	240	228	10.3	10.1	287		281

109	TULASABAI	075124	61	F	42	4.9	22	0.6	2.4	1	NO DR	NO DR	240	228	10.3	10.1	287	281
110	HAKUNTAL	009756	55	F	18	5	29	0.9	3.3	1	MILD NPDR	MILD NPDF	239	280	9.4	9.8	262	272
111	MASHANK	065295	40	M	182	19.7	68	5.9	11.5	5	PDR	PDR	635	666	13.1	31.4	365	872
112	KASAPPA	008641	65	M	7	5.6	20	0.5	2.7	1	NO DR	NV	236	NV	9.5	NV	264	NV
113	ARANAPP	018514	69	M	109	9.9	33	0.9	3.9	5	VERE NPD	VERE NPD	694	652	10.9	11.3	302	314
114	MAHADEV	180364	65	M	36	4.8	22	0.5	2.4	1	NO DR	NO DR	253	246	9.3	9.1	259	254
115	PRAJWAL	223825	28	M	194	4.9	22	0.9	3.6	1	NO DR	NO DR	222	229	10.5	10.6	293	295
116	MAHADEV/	111226	71	M	48	4.8	21	0.5	2.4	0	NO DR	NO DR	252	242	9.4	9.4	260	262
117	ANGAYYA	310835	50	M	109	6.4	31	0.9	3.1	2	MILD NPDR	MILD NPDF	267	294	9.4	11.2	262	311

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