"TO DETERMINE THE CORRELATION OF HAEMOGLOBIN A1c LEVELS WITH DIABETIC RETINOPATHY IN TYPE II DIABETES MELLITUS."

By

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Under the Guidance of

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MAY - 2012

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I hereby declare that this dissertation entitled ***"TO DETERMINE THE CORRELATION OF HAEMOGLOBIN A1c LEVELS WITH DIABETIC RETINOPATHY IN TYPE II DIABETES MELLITUS."*** is a bonafide and genuine research work carried out by me under the guidance of **Dr. REKHA.B.K.** **M.S.,D.O.M.S,** Professor, Department of Ophthalmology, Jawaharlal Nehru Medical College, Nehru Nagar, Belgaum-590010.

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I bow my head in respect before God Almighty.

Dr. Rishi Bhardwaj

LIST OF ABBREVIATIONS

ADEPS	Amrita Diabetes and Endocrine Population Survey.
AGEs	Advanced glycation end products.
ASDIAB	Asian young diabetes research study.
BMI	Body mass index.
CSME	Clinically significant macular oedema.
CURES	The Chennai urban rural epidemiology study.
DCCT	Diabetes control and complications trial.
DR	Diabetic retinopathy.
ETDRS	Early treatment diabetic retinopathy study.
FBS	Fasting blood sugar.
HbA1c	Haemoglobin A1c.
IGF-I	Insulin-like growth factor – I.
IRMAs	Intra-retinal microvascular abnormalities.
MODY	Maturity onset diabetes mellitus.
NIDDM	Non-Insulin dependent diabetes mellitus.
NPDR	Non-proliferative diabetic retinopathy.
NVD	Neovascularization of disc.
NVE	Neovascularization elsewhere in retina.
PDR	Proliferative diabetic retinopathy.
PEDF	Pigment epithelium derived growth factor.
S.D	Standard deviation.
TGF	Transforming growth factor.
UKPDS	United kingdom prospective diabetes study.
WESDR	Wisconsin epidemiologic study of diabetic retinopathy.

ABSTRACT

BACKGROUND:

Diabetes is the commonest metabolic abnormality in the world. Type II diabetes (NIDDM) is the commonest form of diabetes constituting nearly 90% of diabetic population. Diabetic retinopathy is a common and specific microvascular complication of diabetes, and remains the leading cause of preventable blindness in working-aged people. HbA1c is a powerful univariate correlate of retinopathy. Decrease in glycosylated haemoglobin levels is associated with a significant decrease in the progression of DR. The existence of thresholds of glycaemia has not been studied often in patients with type II diabetes mellitus.

OBJECTIVES:

1. To determine the correlation of blood levels of haemoglobin A1c to the presence of diabetic retinopathy in patients with type II diabetes mellitus.
2. To correlate the severity of diabetic retinopathy with levels of haemoglobin A1c.

METHODOLOGY:

The present study was carried out as a one year cross sectional descriptive observational design between January 1, 2010 and December 31, 2010 at KLES Hospital and MRC. A total of 100 type II diabetes patients with retinopathy changes and recent HbA1c levels known were included. Participants with very hazy ocular media and pregnant women were excluded.

Informed consent were taken followed by relevant history, general physical examination, complete ophthalmic examination and detailed fundus evaluation and seven field fundus photography. The retinopathies were documented in accordance with the modified ETDRS classification. FBS levels and HbA1c levels by high

performance liquid chromatography were noted. Statistical correlations were done by SPSS statistical data package editor, version 17.0

OBSERVATIONS AND RESULTS:

100 patients included in our study. The mean age of participants in this study was 61.74 ± 8.83 and out of the 100 participants, 72 males and 28 females with M:F ratio of 2.57 : 1. The mean age of 100 patients at diagnosis was 46.82 ± 6.94 and mean duration of diabetic age was 12.48 ±4.65. The mean of Glycosylated haemoglobin (HbA1c) in the study population is 9.29 ± 1.57.

Our study included 13% mild NPDR, 21% moderate NPDR, 49% severe NPDR, 13% PDR and 4% high risk PDR. 15% participants had CSME, 11% in NPDR and 4% in PDR. The age at diagnosis was significantly associated with the severity of retinopathy ($p<0.0001$). The severity of retinopathy and the duration of diabetes was found to be statistically significant ($p=0.0267$). There was significant association between visual acuity of the patient and the severity of retinopathy ($p=0.006$). Severity of retinopathy was not associated with life style ($P=0.5869$) and smoking ($p=0.28915$). There was noted a highly significant increasing trend of severity of retinopathy with raise in HbA1c ($p=0.0003$), with shift of HbA1c from mild NPDR to severe NPDR is highly significant ($p<0.0001$) and from moderate NPDR to severe NPDR is very significant ($p=0.007$). HbA1c was also significantly associated with presence of CSME ($p=0.0166$). FBS was not associated with severity of retinopathy and presence of CSME. The severity of retinopathy was significantly associated with duration of treatment by oral hypoglycaemic drugs ($p=0.030$) and not with insulin therapy ($p=0.880$). The threshold of HbA1c for occurrence of mild NPDR with 95% C.I was 7.6%.

CONCLUSION:

The poor metabolic control as demonstrated by high HbA1c is significantly associated with severity of retinopathy and presence of CSME. From the analysis of our study, we recommend to maintain HbA1c levels below 7.6% which may reduce the risk of development and progression of diabetic retinopathy. Duration of diabetes and high HbA1c levels are found to be the major predictors of diabetic retinopathy in type II diabetes mellitus.

Key words:

Diabetic retinopathy, CSME, HbA1c, Duration of diabetes, Age at onset of diabetes.

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INTRODUCTION

Diabetes is a disease characterized by abnormal metabolism, most notably hyperglycaemia, and an associated heightened risk for relatively specific long-term complications affecting the eyes, kidney and nervous system.[1] Diabetes is the commonest metabolic abnormality in the world.[2]Type 2 diabetes (NIDDM) is the commonest form of diabetes constituting nearly 90% of diabetic population.[3]

Diabetic retinopathy is a common and specific microvascular complication of diabetes, and remains the leading cause of preventable blindness in working-aged people. As the world-wide prevalence of diabetes continues to increase, diabetic retinopathy remains a leading cause of vision loss.[4,5]

Diabetic retinopathy is one of the most frequent causes of blindness world-wide. In India, retinopathy was the 17th cause of blindness but has now ascended to the 6th position. The estimated population of diabetic retinopathy is 5.8 million.[6]

Hyperglycaemia instigates the cascade of events that eventually lead to development of retinopathy. The validity of HbA1c as a measure of glucose control over a preceding 8 to 12 weeks period is well established. **HbA1c** is a powerful univariate correlate of retinopathy. Decrease in glycosylated haemoglobin levels is associated with a significant decrease in the progression of DR.[72]However,initial worsening of retinopathy has been reported after rapidly improved glycaemic control.[95] Moreover, although race and ethnicity may reduce the validity of HbA1C as a diagnostic tool, HbA1C level has less variability than FBS.[80.81]

Although previous and ongoing studies examined the relationship between glucose control and diabetic retinopathy in IDDM, relatively few studies have

attempted to examine the relationship in NIDDM. The existence of thresholds of glycaemia has not been studied often in patients with type II diabetes mellitus.[92]

Thus relationship between glucose control and development of diabetic complications remains an area of active investigation. As the relationship between HbA1c and risk of microvascular complications is exponential with no obvious "threshold" value, it means that targets aimed for are still to some extent arbitrary. The trend to lower targets seems to be continuing.[90]

The present study is to investigate the relationship of glycosylated haemoglobin (HbA1c) with the severity of diabetic retinopathy.

AIMS & OBJECTIVES

1. To determine the correlation of blood levels of haemoglobin A1c to the presence of diabetic retinopathy in patients with type II diabetes mellitus.
2. To correlate the severity of diabetic retinopathy with levels of haemoglobin A1c.

REVIEW OF LITERATURE

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels.[1] Diabetes is the single most important metabolic disease which can affect nearly every organ system in the body.[2]

Ancient Egypt, Hesy-Ra, recognized the disease that we now know as diabetes. The term diabetes was introduced by Aretaeus of Cappadocia, during the 2nd century AD.[3]**Sushruta (6th century BC)** identified diabetes and classified it as "Medhumedha", the "sweet urine disease". In medieval Persia, Avicenna (980–1037) provided a detailed account on diabetes mellitus in "The Canon of Medicine". Diabetes is first recorded in English, in the form diabetes, in a medical text written around 1425. In 1675, **Thomas Willis** added the word "mellitus", from the Latin word meaning "honey", a reference to the sweet taste of the urine. In 1910, Sir Edward Albert Sharpey-Schafer suggested that people with diabetes were deficient in a single chemical that was normally produced by the pancreas—he proposed calling this substance "insulin'.[4]

EPIDEMIOLOGY:

The worldwide prevalence of diabetes mellitus has risen dramatically over the past two decades, from an estimated 30 million cases in 1985 to 177 million in the year 2000. Based on current trends, it has been projected that 300 million individuals would be affected with diabetes by the year 2025 and more than 360 million individuals will have diabetes by the year 2030. Type 2 diabetes is the most common

type, accounting for approximately 85% of cases in most Caucasian populations and western countries and up to 95% of diabetes in developing countries.[5]The prevalence is similar in men and women throughout most age ranges (10.5% and 8.8% in individuals >20 years) but is slightly greater in men >60 years.

EVOLUTION OF DIABETIC EPIDEMIC IN INDIA:

The first national study on the prevalence of type 2 diabetes in India was done between 1972 and 1975 by the Indian Council Medical Research (**ICMR, New Delhi**). The prevalence was 2.1% in urban population and 1.5% in the rural population while in those above 40 year of age, the prevalence was 5% in urban and 2.8% in rural areas.[6]Subsequent studies showed a **rising trend** in the prevalence of diabetes across different parts of India. In 1988, a study done in south India reported a prevalence of 5%.[7]

A national rural diabetes survey was done between 1989 and 1991 in different parts of the country in selected rural populations which used the 1985 WHO criteria, reported a crude prevalence of 2.8 per cent.[8]

The **Eluru survey** in Andhra Pradesh showed a prevalence of 1.5%.[9] A study done in 1988 in Chennai reported a prevalence of 8.2% in the urban and 2.4% in the rural areas.[10] A subsequent study in the same urban area done after five years showed an age standardized prevalence of 11.6% indicating a rising trend in prevalence of diabetes.[11] A very high prevalence of 16.3% was reported in Thiruvanathapuram in Kerala.[12] In the same year, a prevalence of 8.2% was reported from Guwahati. A cross-sectional population survey was done in the Kashmir valley in the year 2000 and the prevalence of 'known diabetes' among adults aged above 40 years was found to be 1.9%.[13]

The **National Urban Diabetes Survey** (NUDS) reported that the age standardized prevalence of type 2 diabetes was 12.1%. This study also revealed that the prevalence in the southern part of India to be higher-13.5% in Chennai, 12.4%, in Bangalore, and 16.6% Hyderabad; compared to eastern India (Kolkatta), 11.7%; northern India (New Delhi), 11.6%; and western India (Mumbai), 9.3%.[14]

THE CURRENT SCENARIO:

India leads the world with largest number of diabetic subjects earning the dubious distinction of being termed the "diabetes capital of the world". Nowhere is the diabetes epidemic more pronounced than in India as the World Health Organization (WHO) reports show that 32 million people had diabetes in the year 2000. According to the Diabetes Atlas 2006 published by the International Diabetes Federation, the number of people with diabetes in India currently around 40.9 million in 2007 and is expected to rise to 69.9 million by 2025.

UNDIAGNOSED DIABETES – THE HIDDEN DANGER:

It is important to note that the studies that have shown an increase in prevalence of diabetes have also reported a very high prevalence of undiagnosed diabetes in the community. While in **CURES**, the prevalence of known diabetes was 6.1%, that of undiagnosed diabetes was 9.1%. Similarly, in **ADEPS**, the prevalence of known and undiagnosed diabetes were 9.0% and 10.5% respectively.[15] The **Kashmir valley study** showed that the prevalence of undiagnosed diabetes was 4.25 per cent, which was more than double to that of the known diabetes (1.9%).[16] The individuals who are unaware of their disease status are left untreated and are thus **more prone** to microvascular as well as macrovascular complications. Hence, it is necessary to detect the large pool of undiagnosed diabetic subjects in India and offer early therapy to these individuals.[17]

CLASSIFICATION OF DIABETES:[5]

I. Type 1 diabetes.

A. Immune-mediated

B. Idiopathic

II. Type 2 diabetes.

III. Other specific types of diabetes

A. Genetic defects of beta cell function characterized by mutations.

B. Genetic defects in insulin action.

C. Diseases of the exocrine pancreas.

D. Endocrinopathies.

E. Drug- or chemical-induced.

F. Infections.

G. Uncommon forms of immune-mediated diabetes.

H. Other genetic syndromes sometimes associated with diabetes.

IV. Gestational diabetes mellitus (GDM).

Type 1 diabetes: It is the result of complete or near-total insulin deficiency.

Type 2 Diabetes: It is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production.

Other types of diabetes: Other etiologies for DM include specific genetic defects in insulin secretion or action, metabolic abnormalities that impair insulin secretion, mitochondrial abnormalities, and a host of conditions that impair glucose tolerance. Maturity onset diabetes of the young (MODY) is a subtype of DM characterized by autosomal dominant inheritance, early onset of hyperglycemia (usually <25 years),

and impairment in insulin secretion. Mutations in the insulin receptor cause a group of rare disorders characterized by severe insulin resistance.

Gestational diabetes mellitus (GDM): Glucose intolerance may develop during pregnancy. Insulin resistance is related to the metabolic changes of late pregnancy, and the increased insulin requirements may lead to impaired glucose tolerance.

TYPE 2 DIABETES MELLITUS

This form of diabetes, which accounts for ~**90-95%** of those with diabetes, encompasses individuals who have insulin resistance and usually have relative (rather than absolute) insulin deficiency.

There are probably many different causes of this form of diabetes. Specific etiologies have not been identified. Most patients with type-2 diabetes mellitus are obese, and obesity itself causes some degree of insulin resistance. Ketoacidosis seldom occurs spontaneously. This form of diabetes frequently goes undiagnosed for many years, as the hyperglycemia develops gradually. Nevertheless, such patients are at increased risk of developing macrovascular and microvascular complications.[5]

CRITERIA FOR THE DIAGNOSIS OF DIABETES MELLITUS.[5]

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

COMPLICATIONS:

The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system. The major diabetes

related complications are coronary artery disease, peripheral vascular disease, neuropathy, **retinopathy** and nephropathy. Diabetic patients are 25 times more likely than the general population to become blind.[18]

DIABETIC RETINOPATHY:

In **1846**, the French ophthalmologist, Appolinaire Bouchardat (1806-1886) reported the development of visual loss in the absence of cataract in diabetics.[19]

Eduard Jäger was the first to observe diabetic macular changes in 1855.[20] His observations were confirmed in 1872 by Edward Nettleship, who expanded this in his paper entitled 'Oedema or cystic disease of the retina'.[21]Jäger produced one of the first atlases containing 21 colour plates of fundus paintings, which were drawn after 20-40 clinical sessions per patient.[22]

In 1876, WilhelmManz published **'Retinitis proliferans'** containing several drawings of fibrovascular degeneration of the optic disc and vitreoretinal adhesions in the retina.[23] Arthur J. Ballantyne of Glasgow suggested that diabetic retinopathy represents a unique form of vasculopathy and showed for the first time the role of capillary wall alterations in the development of diabetic retinopathy, as well as the presence of deep waxy exudates in the outer plexiform layer.

Diabetic retinopathy (DR) is a chronic progressive sight-threatening disease of the retinal microvasculature associated with prolonged hyperglycaemia. DR is a potentially blinding disease. The presence of diabetic retinopathy may indicate microcirculatory dysfunction in other organ systems.[24]DR can be defined as damage to microvascular system in the retina due to prolonged hyperglycaemia.[25]

DR is the most frequent cause of new cases of blindness among adults aged 24–74 years. Up to 21% of patients with type 2 diabetes have retinopathy at the time

of diagnosis of diabetes and most develop some degree of retinopathy over time. During the first two decades of disease, nearly all patients with type I diabetes and over 60% of patients with type II diabetes develop DR.

One of the largest epidemiological studies conducted on the progression of diabetic retinopathy in the area of southern Wisconsin concluded that the duration of diabetes is directly associated with an increased prevalence of diabetic retinopathy with nearly 99% of patients with type-1 and 60% of type-2 diabetics having some degree of retinopathy. In an epidemiological study done at Chennai, the overall prevalence of diabetic retinopathy among the 1262 eligible subjects was 19% which included 17.5% with non-proliferative diabetic retinopathy and 1.5% with proliferative diabetic retinopathy. Investigating the prevalence of diabetic retinopathy is important because it is a key indicator of systemic diabetic microvascular complications, and as such, a sentinel indicator of the impact of diabetes.[25]

THE INDIAN PERSPECTIVE:

In India with the epidemic increase in type 2 diabetes mellitus as reported by the World Health Organization **(WHO)**, diabetic retinopathy is fast becoming an important cause of visual disability; however this morbidity is largely preventable and treatable.

In India, there is a paucity of data on the prevalence of DR. An earlier study reported an overall prevalence of 14 per cent, NPDR 6%, while 4% had macular oedema and 4% had PDR.[26]Asian Young Diabetes Research **(ASDIAB)** Study, reported that DR prevalence was least among Indians (5.3%) as compared to other ethnic groups like Malays (10%) and Chinese (15.1%).[27] In a center at Chennai in south India the prevalence of DR was 34.1%. The prevalence included 30.8% with

NPDR, 3.4% with PDR and 6.4% had DME.[28] However, in the **CURES Eye Study**, the overall prevalence of DR was 17.6%.[29] Two other population-based studies conducted in south India, reported overall prevalence of DR as 22.4% and 26.8% respectively.[30]

Although urban Indian population based studies suggest that the prevalence of DR is lower compared to other ethnic groups, given the large number of diabetic subjects in India (31.7 million), even with the lower prevalence rates (17.6%), this would translate to over 5.6 million subjects with DR. This underscores the need for routine retinal screening of diabetic individuals annually to detect DR and prevent visual impairment.[31,32,33]

PATHOPHYSIOLOGY OF DIABETIC RETINOPATHY:

The unique retinal structure imparts special physiologic constraints compared with other nervous system tissues because of the requirement for transparency, and these features may contribute to its susceptibility to diabetes.[34]

First and foremost, retinal axons are unmyelinated, require more energy to maintain membrane potentials than myelinated axons.[35] Second, the pO_2 gradient of the retina declines from the outer retina to the inner retina.[36]. Third, the inner retina relies heavily on glycolysis, a less efficient means of generating ATP than oxidative phosphorylation, which predominates in the outer retina.[37]

In spite of this sparse vascularity and low pO_2, the retina has one of the highest metabolic demands of any tissue.[38]The combination of high metabolic demand and minimal vascular supply may limit the inner retina's ability to adapt to the metabolic stress of diabetes. By contrast, the outer retina receives its oxygen and nutrients by

diffusion from the choroid through the pigmented epithelium and is relatively spared from the early insults of diabetes.

These unique anatomic and physiologic specializations predispose the retina to diabetes-induced damage if the metabolic derangements typical of diabetes interfere with the generation of neurotransmitters, macromolecule synthesis, or induce proapoptotic or pro-inflammatory responses.

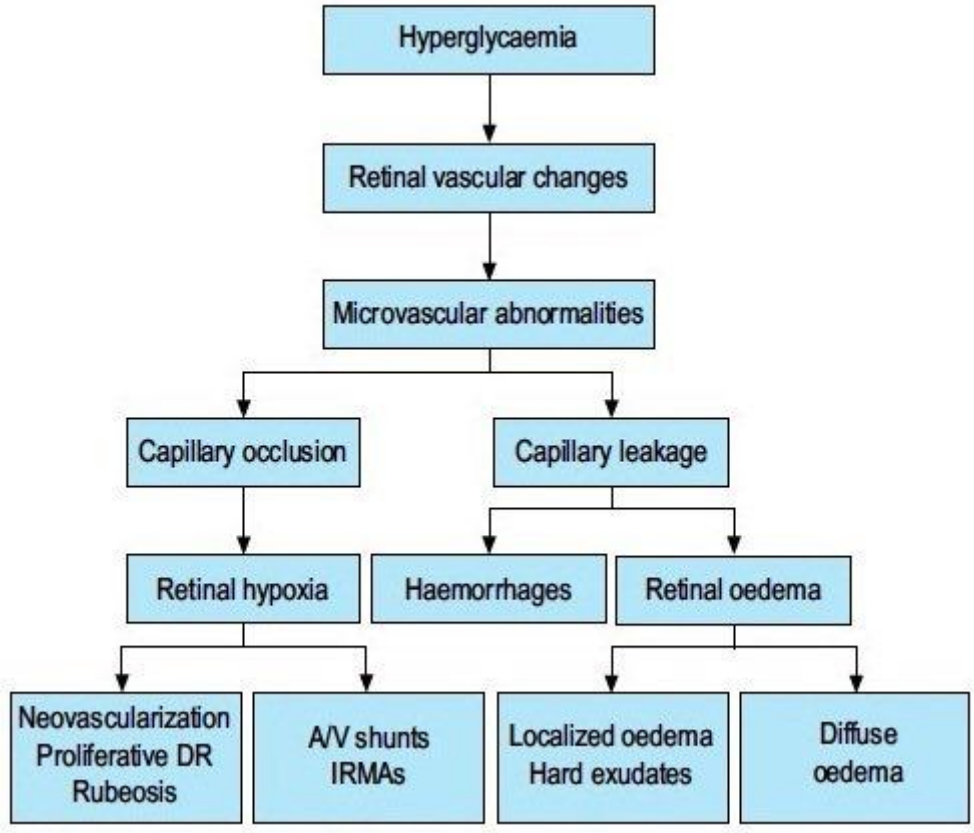


Figure No. 1: Pathogenesis of retinopathy lesions.

In diabetic retinopathy possible pathogenic mechanisms for capillary and arteriolar closure can be divided into three general categories:

1. Intra luminal
2. Intra mural
3. Extra mural

Possible **intra luminal factors** include abnormalities of the blood elements[39] which could promote thrombosis within the small retinal vessels. These factors are: [40]

- Abnormal erythrocyte aggregation
- Elevated plasma fibrinogen
- Increased platelet adhesiveness and aggregation.

In each instance, studies have shown correlations between the severity of retinopathy and degree of abnormalities of the blood elements. However a cause and effect relationship has not been proved.[41]

Possible **intramural factors** include abnormalities of endothelium and basement membrane of retinal vessels. Basement membrane thickening in diabetic patients is found in the retinal vessels as well as in small vessels elsewhere in the body. Progressive basement membrane thickening could cause luminal narrowing and haemodynamic alterations.[41]

The **extramural factor** that has been proposed for capillary closure is compression of the capillary wall by interstitial fluid swelling of the retina.[41]

No purely biochemical or physiological mechanism alone is sufficient to justify the progression of retinal lesions in diabetes. Possible causes of these changes can be grouped into three categories:

a) Biochemical

b) Endocrinal

c) Haemodynamic

Most possibly there is more than one mechanism occurring in one patient.

A. <u>Biochemical factors</u>:[42]

1. Multiple biochemical pathways have been proposed to link hyperglycemia and microvascular complications the pathogenesis of diabetic retinopathy all starting initially from hyperglycemia. These mainly include:

1. Increased polyol pathway
2. Increased advanced glycation end-products (AGE)
3. Increased hexosamine pathway flux
4. Formation of activated protein kinase C (PKC)
5. Oxidative stress

These processes are thought to modulate the disease process through effects on cellular metabolism, signaling, and growth factors.

Increased Polyol accumulation pathway:

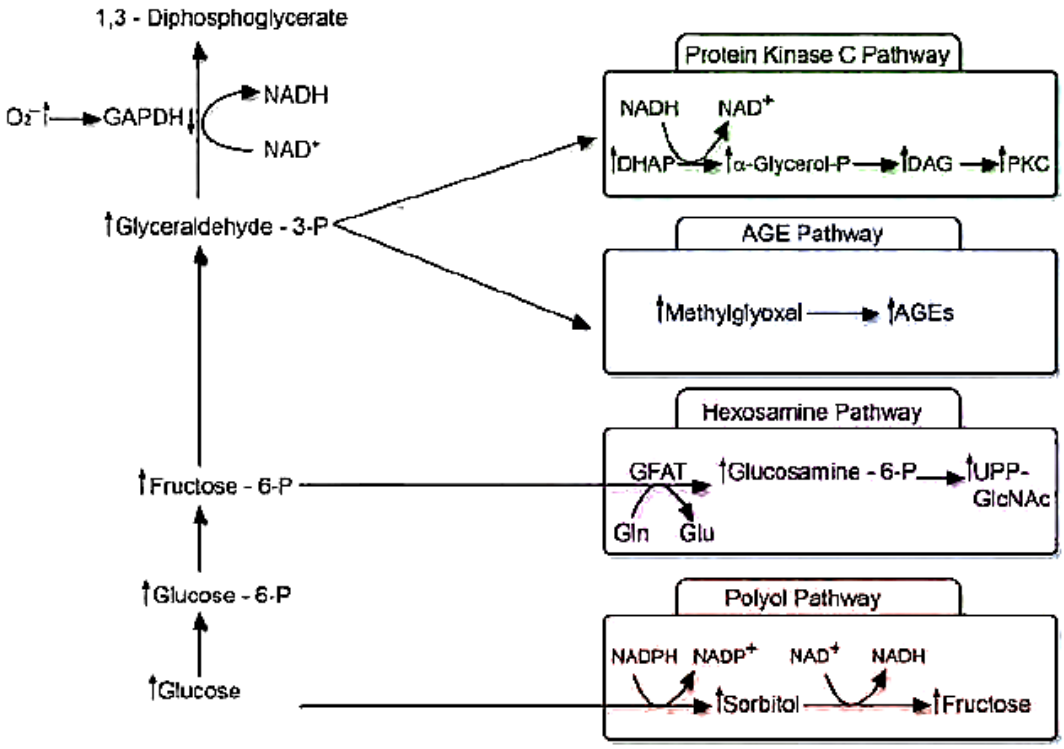


Figure No. 2: Polyol accumulation pathway.

High concentrations of glucose increase the flux through the polyol pathway with the enzymatic activity of aldose reductase, leading to an elevation of intracellular sorbitol concentrations. This rise in intracellular sorbitol accumulation has been hypothesized to cause osmotic damage to vascular cells.[43]

The contribution of polyol pathway to diabetic complications may be very much species, site and tissue-dependent. The long-term Sorbinil Trial also indicated that Sorbinil (an inhibitor of aldose reductase) did not prevent the worsening of the disease except for a slower progression rate in the number of microaneurysms.[44] However, the positive effect of aldose reductase inhibition on diabetic neuropathy with zenarestat[45] provides vested hopes in the use of these compounds in diabetic retinopathy[46]which needs to be tested and validated by future studies.

Increased AGEs formation:

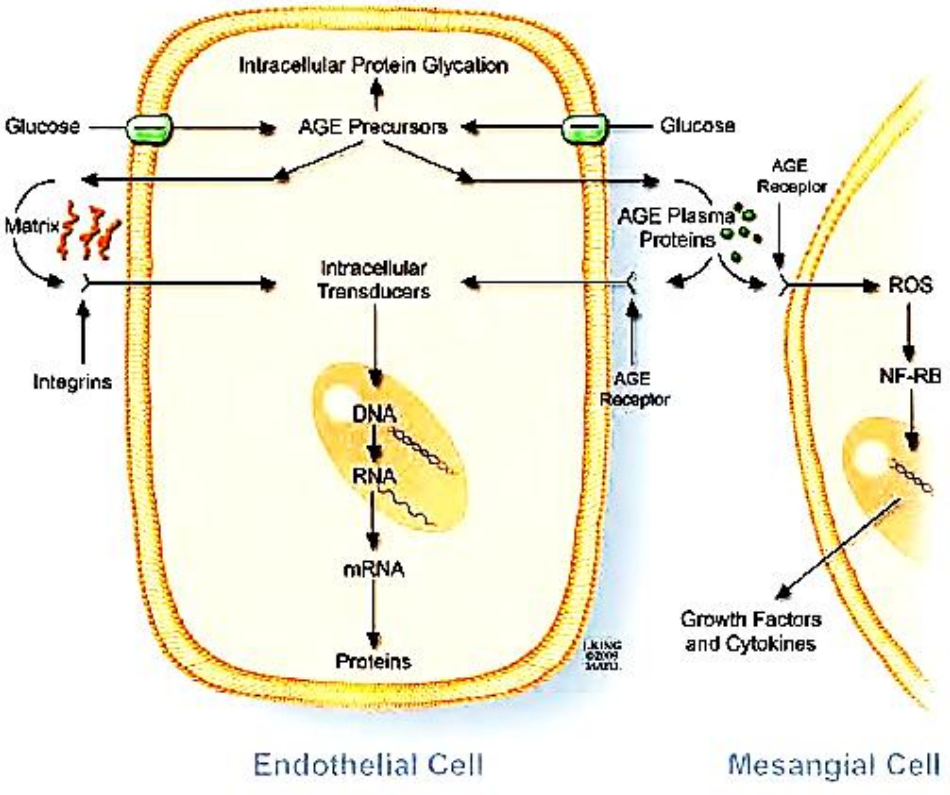


Figure No. 3: Advanced glycation end products formation.

Another well-characterized pathway is damage resulting from accumulation of AGEs. High serum glucose can lead to nonenzymatic binding of glucose to protein side chains, resulting in the formation of compounds termed AGEs.[46,47]

Increased formation of advanced glycation end products (AGEs) correlate with poor glycemic control. Glucose derived AGE formation readily explains the development of diabetic complications in kidney, nerve, retina and vasculature – tissues in which glucose transport is relatively independent of insulin, but which are rich in long lived proteins, such as collagen, elastin and myelin.

It is now recognized that intracellular hyperglycemia is the primary initiating event in the formation of both intracellular and extra cellular AGE's.[44]

Increased hexosamine flux pathway:

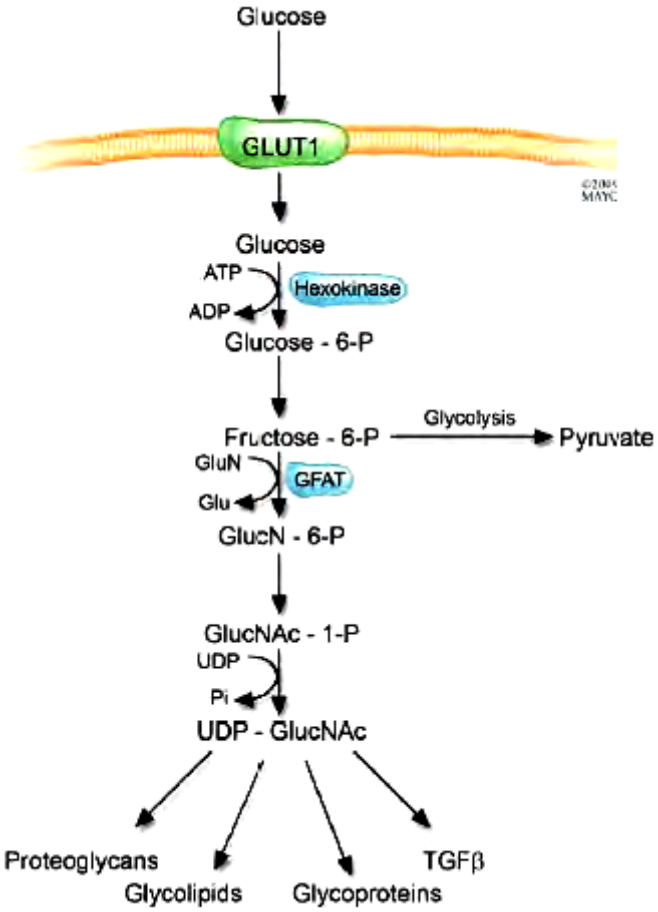


Figure No. 4: Hexosamine flux pathway.

Recent in vitro and in vivo studies suggested that the increased flux of glucose through the hexosamine pathway may contribute to insulin resistance, diabetic vascular complications and to the induction of the synthesis of growth factors.[44]

A recent study suggests that the excessive glucose flux through the hexosamine pathway may direct retinal neurons to undergo apoptosis in a bimodal fashion, i.e. via perturbation of the neuroprotective effect of insulin mediated by ALT and via induction of apoptosis possibly by altered glycosylation of proteins.[44] This emphasizes that hexosamine pathway may be involved in retinal neurodegeneration in diabetes.

Formation of activated protein kinase C (PKC):

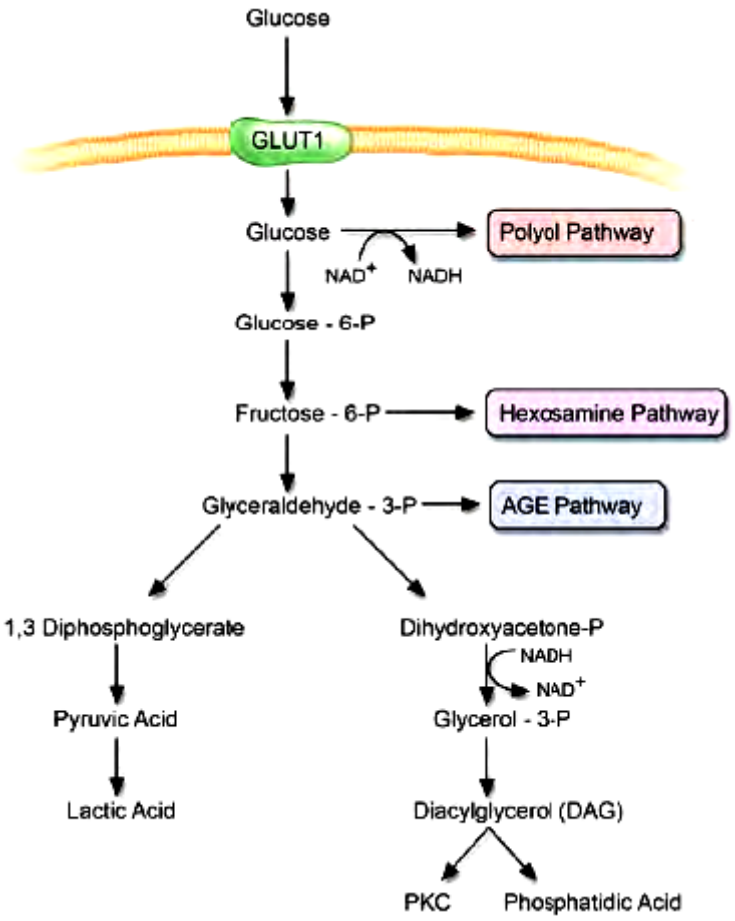


Figure No. 5: Activated protein kinase C pathway.

There is increasing evidence that PKC activation is related to hyperglycemia-induced microvascular dysfunction in diabetes.[48]Activation of PKC results in numerous cellular changes. The changes are seen as thickening of the basement membrane, increased retinal vascular permeability, and alterations in retinal blood flow. Moreover, PKC-β has been shown to be an integral component of cellular signaling by vascular endothelial growth factors (VEGFs), important mediators of ocular neovascularization, secondary to retinal ischemia and diabetic macular edema (DME).[49,50]

Oxidative damage

Diabetes and hyperglycemia can also lead to oxidative stress and formation of reactive oxygen species (ROS), leading to vascular damage. Production of ROS (free radicals) may result from glucose auto-oxidation, protein glycation, increased flux through the polyol pathway, and prostanoid production.[51]Normalization of glucose-stimulated superoxide production has been found to block at least three independent pathways of hyperglycemia-induced vascular damage.[52] Antioxidant deficiency appears to be associated with a risk for diabetic retinopathy.

Growth factors

Serum growth hormone (GH) abnormalities in diabetics have long suggested to be responsible for the retinal changes.[53]

The biochemical pathways mentioned above are associated with production and signaling of growth factors such as VEFG, growth hormone, IGF-I, transforming growth factor-β (TGF-β), and pigment epithelium–derived growth factor (PEDF).[54]

VEGF has been shown to be upregulated by hypoxia, with increasing levels of VEGF in the vitreous associated with increasing retinal ischemia. Growth hormone

and IGF-I have been suspected of playing a role in the progression of diabetic retinopathy. TGF-β is produced by pericytes and may inhibit endothelial proliferation. Active PDR and patients with rubeosis have lower levels of TGF-β. Lower levels may promote angiogenesis by removal of an inhibitor.[55]PEDF is produced by the retinal pigment epithelium and inhibits neovascularization.[56]

B. <u>Endocrine factors</u>:

It was found that retinopathy in patients with diabetes regresses after infarction of the pituitary gland.[57]This observation led to the suggestion that hormones other than insulin may influence the course of diabetic retinopathy.

Growth hormone could contribute to the development of diabetic retinopathy by augmenting thrombus formation and thus contributing to the closure of capillaries. This could be due to variations in the plasma levels of Von Willebrand factor, which is dependent in part on growth hormone.[58]

It also influences the composition of arterial and arteriolar walls so as to increase the likelihood of vascular occlusion. Eyes with rapidly accelerating neovascularization often have high IGF-1 values in serum and vitreous.[59,60]

Other growth factors could also be involved in the pathogenesis of diabetic retinopathy. Growth factors, IGF-I, epidermal growth factor and fibroblast growth factor have all been reported to stimulate both chemotaxis and proliferation of vascular endothelial cells.[61]

Despite striking evidence for the above it does not explain all the features of diabetic retinopathy, which can be better explained by other mechanisms.

C. Haemodynamic factors:

The first indication that haemodynamic abnormalities might contribute to the development of diabetic retinopathy was the finding that injury to the endothelium of a vessel could result from shear stress and did not require an antecedent defect in vessel wall.[62] Lot of research has been done on the rheological properties of blood in patients with diabetes. Shear stress is increased in patients with diabetes because of an increase in blood viscosity and roulex formation, which through a series of events may lead to the formation of micro thrombi and other pathological changes in the retinal vasculature. Furthermore in the involvement of haemodynamic and biochemical factors in the causation of diabetic retinopathy are as a result low grade sub-clinical inflammation that happens at the level of the capillary endothelium.[63]

Genes and diabetic retinopathy:

Although prolonged exposure to hyperglycaemia is the primary factor associated with the development of most microvascular complications, additional risk factors also play a role. Supportive evidence for a genetic role for retinopathy derives from twin, family and transracial studies demonstrating the importance of inherited factors in the aetiology of diabetes and its complications.

The possible candidate genes contributing to the development of diabetic retinopathy are genes for Aldose Reductase (ALR), Nitric Oxide Synthase (NOS) genes, genes for Receptor for Advanced Glycation End products (RAGE), genes coding for Angiotensin Converting Enzyme (ACE gene), Human Leucocyte Antigen (HLA) genes and genes for Vascular Endothelial Growth Factors (VEGF).[64]

CLINICAL FEATURES:

Diabetic retinopathy is a microangiopathy primarily affecting the retinal pre-capillary arterioles, capillaries, post-capillary venules and larger vessels may also be involved.

Retinopathy exhibits features of [44]

a. Microvascular occlusion

b. Microvascular leakage [65]

a. **Microvascular occlusion:** The factors thought to be responsible for the microvascular occlusion include

i. Thickening of the capillary basement membrane

ii. Capillary endothelial cell damage and proliferation

iii. Changes in RBC leading to defective oxygen transport

iv. Increased stickiness and aggregation of the platelets

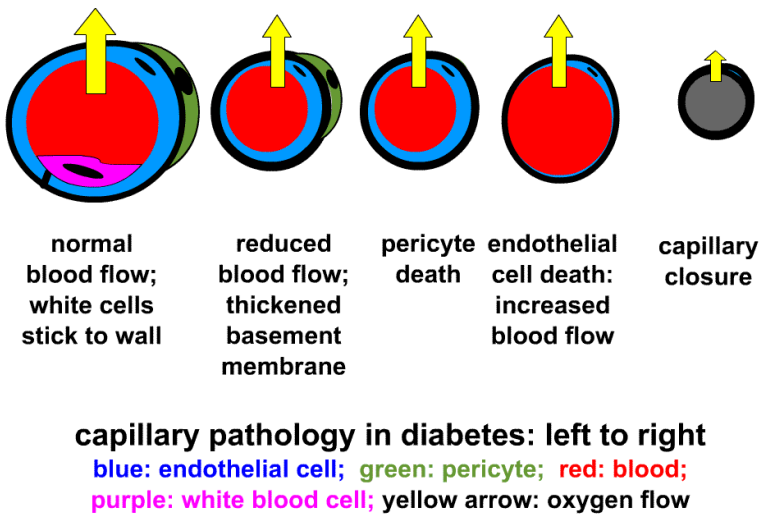


Figure No. 6: Development of capillary closure.

The consequence of retinal capillary non-perfusion is retinal ischemia, which leads to retinal hypoxia.

The two main effects of retinal hypoxia are as follows

Arterio-venous Shunts: These are associated with significant capillary occlusion (Dropout), which runs from the arterioles to venules. As it is unclear whether or not these lesions represent new vessels, they are often referred to as 'intraretinalmicrovascular abnormalities' (IRMA).

Neovascularization: Is thought to be caused by 'vasoformative substances', elaborated by the hypoxic retinal tissue in an attempt to revascularize hypoxic areas of the retina. These substances promote neovascularization on the retina (NVE) and optic nerve head (NVD) (proliferative diabetic retinopathy) and on the iris 'Rubeosis Iridis'.

b. Microvascular leakage: The cellular elements of retinal capillaries consist of endothelial cells and pericytes (Mural cells) with a ratio of 1:1. Pericytes are thought to be responsible for the structural integrity of vessel wall, which are wrapped around the capillaries.

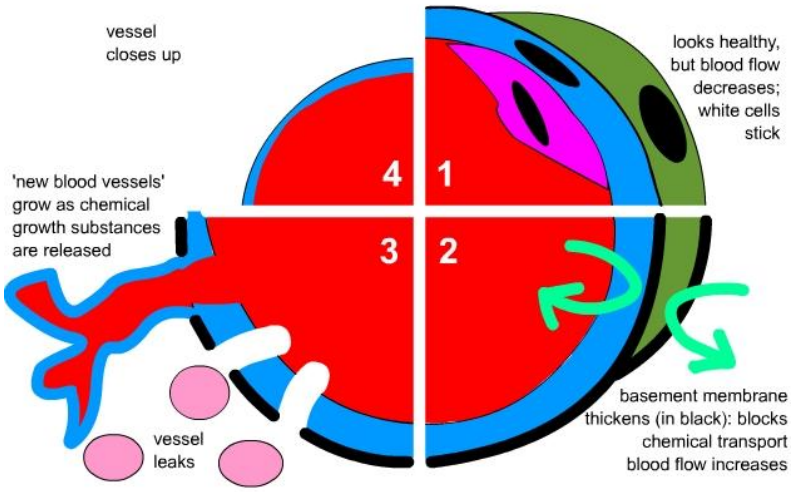


Figure No. 7: Progression of microvascular leakage.

In diabetic patients, there is a reduction in the number of pericytes altering the ratio. This reduction in pericytes is thought to be responsible for distension of the capillary walls and a breakdown of the blood retinal barrier, leading to the leakage of plasma constituents into the retina.

LESIONS OF DIABETIC RETINOPATHY:[66]

Microaneurysm: The earliest clinically visible changes that develop are microaneurysms, usually temporal to the fovea. They can be classified into two distinct types:

- Saccular — sac-like extensions presumed to evolve from weak points in the capillary wall and abetted by intra-luminal pressure. Reduced structural support from pericytes has been suggested as a contributory factor to their formation. An active cellular response, possibly as a result of a reduced inhibitory action by pericytes, has been proposed as a model for microaneurysm formation.
- Loop — originate as kinks in a capillary, these appear to be uncommon in non-diabetics in contrast to saccular microaneurysms which are common in many vascular disorders. They are thought to develop from the fusion of contiguous arms of kinked segments of a capillary.

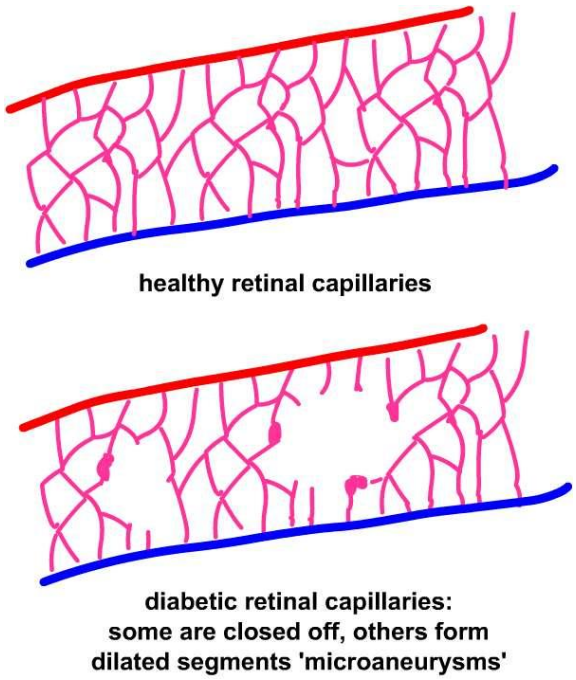


Figure No. 8: Formation of microaneurysms.

Microaneurysms may occur at any level between the superficial and deeper retinal capillary networks or even from the choroidal circulation, though the inner nuclear layer is the usual location. They vary in size from around 10 to 100 µm but only those greater than 30 um are visible clinically. The ETDRS gives an upper limit of 125 µm diameter and the requirement of sharp borders to be considered a microaneurysm. They may either leak or become thrombosed.

The consequences of **increased vascular permeability** are hemorrhages and retinal edema, which may be diffuse or localized.

1. Diffuse retinal edema is caused by extensive capillary dilatation and leakage.
2. Localized retinal edema is caused by focal leakage from micro aneurysms and dilated capillary segments

Flame-shaped haemorrhages occur in the superficial nerve fiber layer where the blood tends to follow the course of the nerve fibers.

Dot haemorrhages are located in the outer-plexiform and inner nuclear layers of the retina. On fluorescein angiography, dot haemorrhages exhibit hypofluorescence as opposed to hyperfluorescence of microaneurysms. Dot haemorrhages can be indistinguishable from microaneurysms on fundoscopy.

Blot haemorrhages are similar to dot haemorrhages but with less distinct borders. These originate from the deep capillary plexus. They are located in the inner plexiform and outer plexiform layers of the retina. Due to the compact structure of the retinal elements in this region and the relative depth at these locations, the haemorrhages assume a dark, blot-like appearance. Some haemorrhages have white centres due to the presence of platelets and fibrin.

Hard exudates consist of accumulated and condensed plasma and so are made up of mainly serum lipoproteins. They represent a leakage from the circulation

indicating structural damage to vascular endothelium. Capillaries with microaneurysms are the principal source.

As exudates become progressively concentrated they give rise to semi-solid residues that acquire a characteristic hard or waxy appearance.

Hard exudates consist of accumulated and condensed plasma and so are made up of mainly serum lipoproteins. Fluid plasma leaks through the abnormal permeable vascular wall and seeps into the outer-plexiform layer where it collects. It is thought that the inter-photoreceptor Muller cell junctional complexes present an obstacle to the further movement of molecules the size of lipids and proteins, whilst allowing the unimpeded passage of water towards the choroid. The exudate becomes progressively concentrated to leave semi-solid residues which acquire a characteristic hard or waxy appearance.

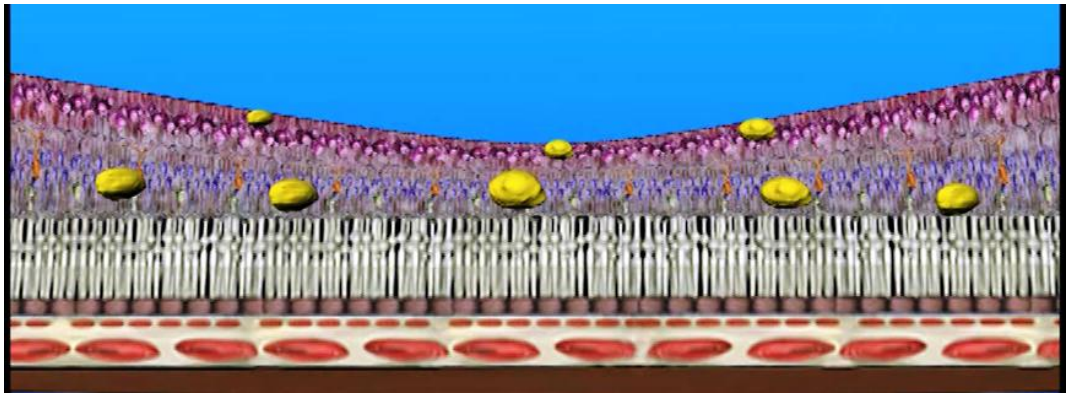


Figure No. 9: Formation of hard exudates.

Hard exudates may be re-absorbed either spontaneously or following laser photocoagulation. This is due to phagocytosis by macrophages.

Cotton wool spots: These are a consequence of capillary occlusion in the nerve fiber layer and are arranged along its long axis. This results in a stasis of axoplasmic flow within nerve fibers and a subsequent swelling of the neural tissue supplied by the arteriole. This gives rise to the fluffy white cotton wool-like lesions.

Most cotton wool spots have fairly common dimensions, being less than half a disc diameter in size. On very rare occasions they can be much larger ranging in size from 2 to 4 DDs. Cotton wool spots are almost always confined to the area adjacent to the major vascular arcades of the posterior pole.

Venous changes:

Tortuosity and dilatation occur when there is sluggish retinal circulation and are the most important signs of pre-proliferative disease. **Beading and looping** are caused by increasing hypoxia. Focal vitreous traction may contribute to the formation of venous loops.

Intra-retinal microvascular anomalies (IRMA) are a hallmark of severe NPDR and they are a precursor to PDR. Progressive vessel damage leads to blood being forced along alternative routes i.e. via capillary networks not intended for such increased blood flows. This can result in capillary distension and irregularity.

Diabetic maculopathy:

One of the ways in which blindness occurs is when the central macular area of the retina is damaged, causing diabetic maculopathy. The macula is defined as the central area of retina between the superior and inferior temporal arcades, from the disc and 2-DDs temporal to the fovea. Increased permeability of retinal vessels allows leakage of plasma constituents which accumulate in the extracellular spaces, initially at the outer-plexiform layer and inner nuclear layer level and later extending to involve the entire retinal thickness.

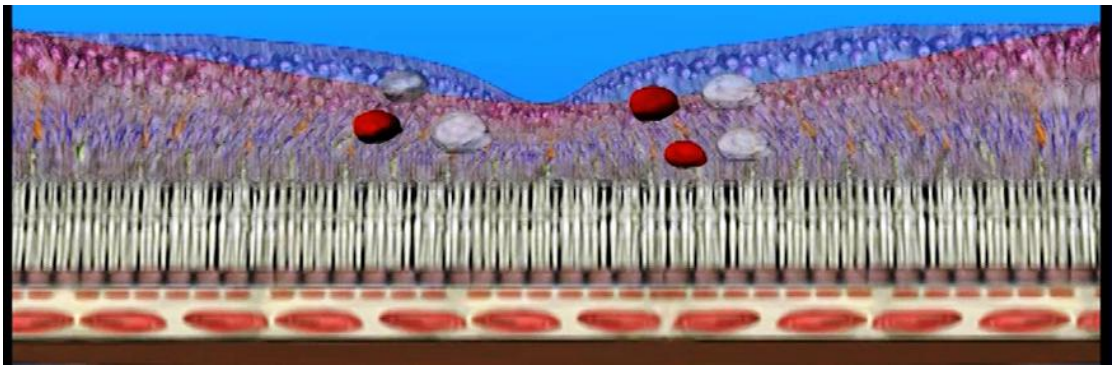


Figure No. 10: Formation of macular oedema.

Classification of DME:

There are four main types of maculopathy according to clinical examination and fluorescein angiography. These are:

- Focal: Leakage from dilated segments of capillaries and microaneurysms.
- Diffuse: Characterized by the presence of diffuse oedema.
- Ischaemic: Capillary shut down results in retinal non-perfusion and ischaemia. It is chararacterized by the presence of large blot haemorrhages, multiple cotton wool spots and IRMAs.
- Mixed: It is not uncommon to see a combination of focal, diffuse and ischaemic maculopathy.

Neovascularisation:

New vessels represent a serious threat to vision because they can bleed, causing pre-retinal and vitreous haemorrhages. Fibrous tissue accompanies the development of the new vessels and can lead to tractional retinal detachment.

Neovascularisation (NV) can be on the disc or elsewhere on the retina.[68]

NV disc can be: [67]

- Epipapillary
- Peripapillary
- Papillovitreal

NV elsewhere can be

- Surface
- Retinal
- Retinovitreal

Stages of neovascularisation:

Stage I: The stage of naked vessels.

Initially fine new vessels without supporting connective tissue arise from the capillary plexus on the disc or from superficial plexus of retina and grow either in the plane of disc and retina or invade the vitreous.

Stage II: Marked condensation of connective tissue around the naked vessels. There is considerable increase in the size of vascular arcades. Those arising from disc either extend into the subhyaloid space and follow the general course of the main trunks or pass forward into the vitreous where the festoons of arcade often take on a net – like appearance (rete mirabile). The clothing of connective tissue first appear as cloud-like condensations around the older elements and gradually increases in density so that at the end of this stage which marks the greatest development of proliferative tendency, there is a mass of new vessels ensheathed in a connective tissue matrix.

Stage III: The stage of cicatrisation.

There is gradual regression in type and number of new vessels and connective tissue surrounding them increases in density and contracts into sheaths or bands.

Signs of activity in new vessels include neovascular buds and paucity of fibrous tissue.

Signs of inactive new vessels include general reduction in vascular caliber in both the new vessels and the neighboring retinal vessels with increase in the fibrous component in the new vessels. [67]

Pre-retinal haemorrhage:

Pre-retinal haemorrhage is a dark mass of blood settling in the space between the retina and vitreo-retinal membrane forming a characteristic (boat) shape. The haemorrhage has a flat top due to the blood settling under the force of gravity. Although not discernible always, there must be leaking NVEs to produce pre-retinal haemorrhage. [67]

CLASSIFICATION OF DIABETIC RETINOPATHY:

Airlee house classification.

This system proposes fundus pathology, angiography, ophthalmoscopy, slit lamp biomicroscopy, fundus drawings and detailed written descriptions.

Grade 0 - Components absent

Grade I - Components less severe

Grade II - Components more severe

Non proliferative	• Hemorrhage and/or microaneurysms
	• Hard and soft exudates
	• Venous abnormalities
	• Intra-retinal microvascular abnormalities (IRMA)
	• Retinal oedema with or without macular oedema
Proliferative	• Neovascularisation within 1 disc diameter of disc
	• Neovascularisation in area other than the optic disc.
	• Fibrous proliferation within 1 disc diameter of disc.
	• Fibrous proliferation in areas other than the optic disc.

- Phase of proliferation: Grade 0 – within in one fourth disc diameter of surface of attached retina.
- Retinal elevation.

Vitreous hemorrhage
- Pre-retinal hemorrhage
- Vitreous hemorrhage
- History of vitreous hemorrhage

Kanski's Classification.

It is basically a management oriented classification with the recognition of an additional pre-proliferative stage.

Background Diabetic Retinopathy (BDR)	1. Microaneurysms (usually temporal to macula) 2. Hard exudates 3. Retinal oedema 4. Dot and blot hemorrhages
Pre-Proliferative Diabetic Retinopathy (PPDR)	1. Vascular changes- Venous beading, looping, sausaging, arteriolar narrowing or obliteration 2. Dark-blot hemorrhages representing retinal infarcts. 3. Multiple cotton-wool spots 4. Intra-retinal microvascular abnormalities (IRMA)
Proliferative Diabetic Retinopathy (PDR)	1. Neovascularization may develop along the vascular arcades (NVE) or at the optic disc (NVD) 2. Vitreous detachment 3. Pre-retinal or vitreous hemorrhage

	4. Retinal detachment and retinitis proliferans

Modified Airlee - House classification or Modern ETDRS classification:

Modern ETDRS classification is now universally accepted. Retinopathy status is graded in standard 7-field stereoscopic color photographs using the Early Treatment of Diabetic Retinopathy Scale (ETDRS) modification of the Airlie House Classification scheme which assesses the level of retinopathy for each eye. This grading system has been used extensively in clinical and epidemiological studies of diabetic retinopathy, including the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS), to assess baseline status of retinopathy and progression of disease.

The ETDRS modification of the Airlie House classification scheme of diabetic retinopathy proposed for use in this study has been validated as a means of measuring progression of disease in prospective studies.

Non-Proliferative Diabetic Retinopathy	A. Mild	1. At least 1 microaneurysm (MA) 2. Definition not met for B, C, D, E and F.
	B. Moderate	1. Soft exudates, venous beading and IRMA definitely present 2. Definition not met for C, D, E and F.
	C. Severe	1. Hemorrhages / MA > standard photograph in all four quadrants 2. Venous beading in 2 or more quadrants 3. IRMA in at least 1 quadrant
	D. Very severe	1. Any two or more of C 2. Definition not met for F
Proliferative diabetic retinopathy:	E. Early PDR	1. New vessels present but definition not met for F

NVD/NVE Pre-retinal or Vitreous Hemorrhage, Fibrous tissue proliferation.	F. High risk PDR	1. NVD ≥ 1/3-1/2 disc area or 2. NVD ¼-1/3 disc area with or without Pre-retinal/Vitreous hemorrhage 3. NVE ≥ 1/2 disc area and preretinal / vitreous hemorrhage

Clinical Significant Macular Oedema is defined as the involvement of the macula:

- With retinal oedema within 500µ of the center of the fovea, or
- With hard exudates within 500µ of the center of the fovea, with thickening of the adjacent retina with oedema, or
- With hard exudates or oedema, 1 disc diameter or larger, any part which is within 1 disc diameter from the center of the fovea.

VAHEX classification:[68]

Nonproliferative.	**Proliferative.**			
	Neovascularization.		**Glial Proliferation.**	**Vitroeretinal Traction.**
	Disc.	**Retinal.**		
Venous dilatation	Epipapillary	Surface.	Grade 1	Grade 1
Aneurysms	Peripapillary	Retina.	Grade 2	Grade 2
Haemorrhages	Papillovitreal	Retinovitreal	Grade 3	Grade 3
Edema			Grade 4	Grade 4
E**x**udate				Grade 5
				Grade 6
				Grade 7
				Grade 8
Duration of the disease. →				

Glial proliferation on retinal surface is graded as follows:

Grade 1: patchy gliosis in posterior retina or along the midportion or distal aspect of the vascular arcades, not involving the disc.

Grade 2: gliosis involving optic disc area only.

Grade 3: gliosis of arcade region and the optic disc.

Grade 4: a circular band of gliosis involving the optic disc, vascular arcades and temporal inter-arcade retinal area.

Vitreoretinal traction is graded as follows:

Grade 1: traction of vitreous on retinal structures in sectional or regional areas but not along any well-organised path or zones.

Grade 2:vitreoretinal adhesions in one major arcade, usually temporal. Traction is not generalised but concentrated in one geographic or segmental zone of posterior fundus.

Grade 3: more than one segmental sections of posterior retina is involved, usually superior and inferior vascular arcades, with severe vitreous contraction. It may form a circular or ring like area of retinal tenting.

Grade 4: tractional retinal detachment, usually small at first.

Grade 5: entire central portion of retina is moderately detached by a shallow detached posterior hyaloid.

Grade 6: moderately elevated detachment of retina by a highly detached cone-shaped posterior hyaloid.

Grade 7: markedly elevated totally detached retina by traction from a highly detached posterior hyaloid adherent to the vitreous base.

Grade 8: entire retina pulled forward into retrolenticular space by a highly detached posterior hyaloid, so-called triangular syndrome.

GLYCAEMIC CONTROL, DURATION OF DIABETES & DIABETIC RETINOPATHY:

Several interrelated biochemical pathways involving aldose reductase, advanced glycation end products, and protein kinase C link chronic hyperglycemia with retinal capillary endothelial cell damage and dysfunction in patients with diabetic retinopathy.[69] DCCT and Early Treatment of Diabetic Retinopathy Study (ETDRS) have convincingly shown the reduction in risk of progression of DR with intensive treatment. Decrease in glycosylated hemoglobin levels is associated with a significant decrease in the progression of DR as well as the incidence of PDR.[70] Intensive diabetic control leads to reduction in the development and progression of all diabetic complications.[71]

The severity of retinopathy was also found to have a linear correlation with the duration of the disease. It was also observed that the incidence of retinopathy increased with the increase in the duration of diabetes mellitus, from 16.7 per cent, in less than one year duration to 100 per cent where the duration of diabetes was above 16 years.[72] There is a direct correlation between the frequency and severity of DR and the duration of DM.[73]

GLYCOSYLATED HAEMOGLOBIN (HbA1C):

N-TERMINAL VALINE residues of erythrocyte haemoglobin become irreversibly glycosylated in proportion to circulating glucose concentrations, and the resultant product is commonly referred to as haemoglobin A 1c (HbA1c).[74]

In 1962, Huisman and Dozy reported an increase in one of the minor fractions of haemoglobin in four of their patients with diabetes.[75] Five years later Rahbar rediscovered this fraction in two patients with diabetes being screened for abnormal haemoglobins. Further investigation found abnormal band, all occurring in patients

with poorly controlled diabetes, and thus the finding of a ‘‘diabetic haemoglobin component’’ was reported in 1968.Soon it was demonstrated that the diabetic component had a chromatographic characteristic similar to that of haemoglobin A 1c (HbA1c).

Glycation of haemoglobin occurs over the entire 120-day lifespan of the red cell, but within this 120 days recent glycaemia has the largest influence on the HbA1c value.[76]

The clinical utility of HbA1c as a tool to assess the risk of diabetes complications was cemented by the UKPDS that confirmed that a relationship between HbA1c and microvascular complication risk existed in 3867 patients with type 2 diabetes.[77]

The use of hemoglobin A1c (HbA1c) to diagnose prediabetes and diabetes recently was recommended by the American Diabetes Association (ADA).[1]

There are several advantages to HbA1c as a diagnostic criterion for diabetes. HbA1c is less affected by short-term lifestyle changes, and its measurement has been improved and standardized during the last decade. While hemoglobinopathies and race/ethnicity may reduce the validity of HbA1c as a diagnostic tool, HbA1c level has less variability than FBS.[79] HbA1c is standardized and aligned to the DCCT/ UKPDS, has better index of overall glycemic exposure and risk for long-term complications, substantially less biologic variability, substantially less preanalytic instability, no need for fasting or timed samples, relatively unaffected by acute (e.g., stress or illness related) perturbations in glucose levels and is used to guide management and adjust therapy.[80] Nevertheless, the inter-individual variability of HbA1c is far more complicated than that of FBS. Genetic factors account for a significant part of the variation in HbA1c among people without diabetes.[81]

Recent study has shown that retinopathy prevalence began to rise precipitously when HbA1c exceeded 5.5% (corresponding to the 5th decile) and that the change points are helpful in finding the lowest cut point for the diagnosis of retinopathy. However, to be used clinically, at a minimum, further analyses to determine cut points for the diagnosis of retinopathy would need to include sensitivity and specificity analyses.[82]

But lower than that observed in some previous studies, including the Pima Indian study (6.2%), the Egyptian study (6.3%), and NHANES III (6.0%).[83] In the Multi-Ethnic Study of Atherosclerosis (MESA) population, there was a continuous relation between prevalent retinopathy (defined as ETDRS level 20) and HbA1c and, based on change point analysis, no clear evidence of a threshold.[84]

In the overall population, retinopathy prevalence increased precipitously after FBS levels of 5.8 mmol/l, but the change point was higher (7.0 mol/l) among those not receiving hypoglycemic treatment. This suggests that treatment affects FBS level and shifts the FBS distribution among people with diabetes to the left.[85]

Examining the prevalence of more advanced retinopathy by HbA1c levels may help in the identification of diagnostic cut points. Thus relationship between glucose control and development of diabetic complications remains an area of active investigation.[86]

As the relationship between HbA1c and microvascular complications risk are exponential with no obvious “threshold” value, it means that targets aimed for are still to some extent arbitrary. The trend to lower targets seems to be continuing. The present study thereby is to evaluate the relationship of HbA1c with the severity of diabetic retinopathy.

METHODOLOGY

The present study was carried out as a one year cross sectional descriptive observational design to correlate the levels of HbA1c with the severity of diabetic retinopathy in patients with type2 diabetes mellitus at KLES hospital and MRC.

All patients attending the out-patient, in-patient and referrals to ophthalmology department at KLES hospital and MRC between January 1, 2010 and December 31, 2010 were included in the study.

Sample Size: 100

Inclusion criteria:

1. Participants diagnosed to have type 2 diabetes mellitus with retinopathy changes in the fundus are included in this study.
2. Recent HbA1c levels of the participants known.

Exclusion criteria :

1. Participants with very hazy ocular media (i.e. ocular fundus not clearly visible by indirect ophthalmoscopy) are excluded from the study.
2. Participants not accepting the informed consent.
3. Pregnant women.

Evaluation of patients:

After taking informed consent all patients were examined according to a predesigned proforma. Relevant history regarding the diabetes with respect to age of onset, duration, nature and effect of treatment received were taken.

A general physical examination was performed followed by a complete ophthalmic examination. A detailed fundus evaluation was performed using a direct ophthalmoscopy, indirect ophthalmoscopy along with slitlamp biomicroscopy with +90D lens. All the findings were documented in the proforma verified by the guide.

The retinopathies were observed and documented in accordance with the modified ETDRS classification as follows:

1. Mild NPDR.
2. Moderate NPDR.
3. Severe NPDR.
4. Very Severe NPDR.
5. Early PDR.
6. High Risk PDR.

All patients were subjected to seven field fundus photography. Fundus fluorescein angiography was performed only when clinically necessary.

Laboratory investigations observed were as follows:

- FBS levels
- Glycosylated hemoglobin (HbA_{1C}) levels to determine the glycemic control.

Estimation of HbA1c :

Glycosylated haemoglobin (HbA1c) was measured by high performance liquid chromatography (HPLC) method, using the Biored D-10 model. It is expressed in percentage (%).

Statistical methods :

Analysis of variance test was used to determine the relationship between HbA1c and severity of retinopathy in patients of type 2 DM.

Chi Square test was used to determine the relationship between severity of diabetic retinopathy with visual acuity, life style, duration of diabetes and smoking.

All the calculations were done using SPSS statistical data package editor, version 17.0.

OBSERVATIONS AND RESULTS

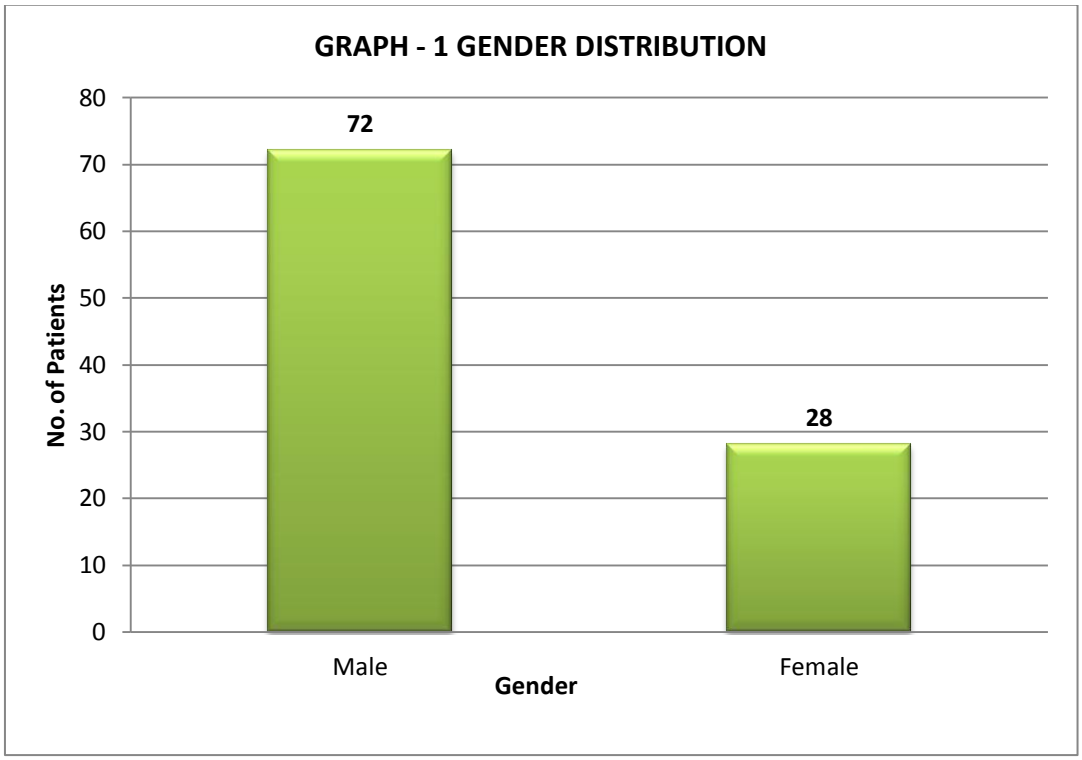
Table.1. Demographic and clinical data of study population

Parameters	Observation
Total number included	100
M:F	2.57:1
Mean age (years)	61.74 ± 8.83
Mean age at diagnosis (years)	46.82 ± 6.94
Mean duration of diabetes (years)	12.48 ±4.65
Mean HbA1c (%)	9.29 ± 1.57

The above table shows the demographic data of 100 patients were included in our study. The mean age of participants in this study was 61.74 ± 8.83 and out of the 100 participants, M:F ratio was 2.57 : 1. The mean age of 100 patients at diagnosis was 46.82 ± 6.94 and mean duration of diabetic age was 12.48 ± 4.65. The mean of Glycosylated haemoglobin (HbA1c) in the study population was 9.29 ± 1.57.

Table.2. Gender distribution

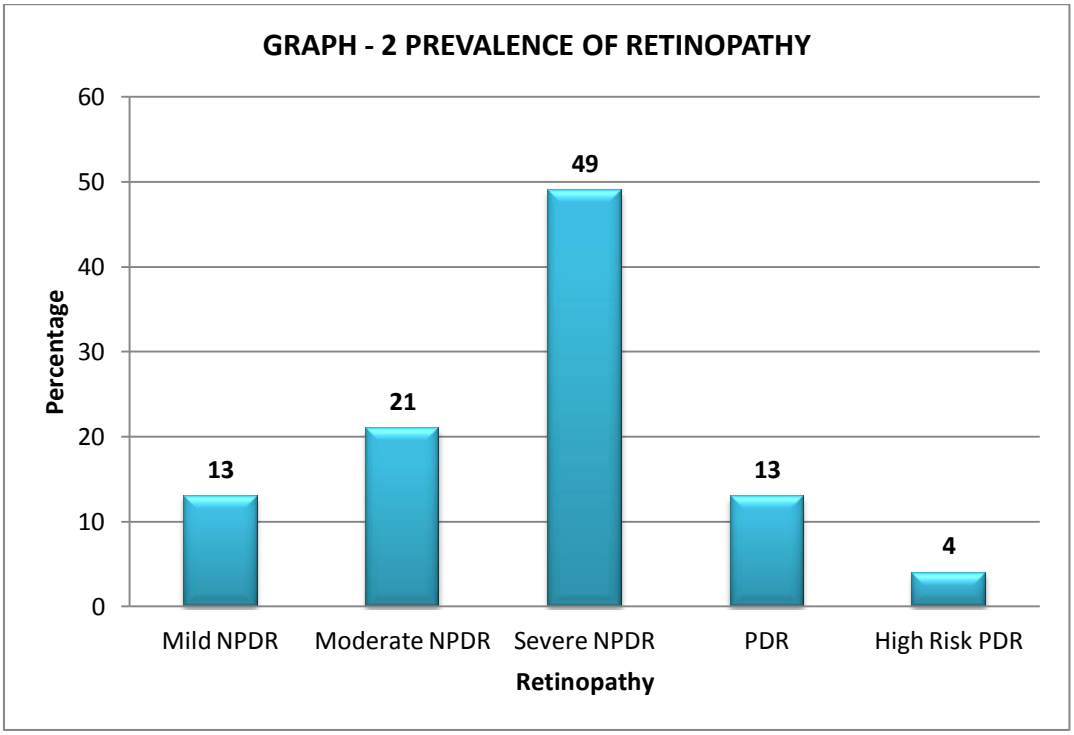
Gender	Total	M:F
Male	72	**2.57:1**
Female	28	
Total	**100**	



There were 72 males and 28 females in our study group, revealing a male preponderance in our recruited study population. The male : female ratio was 2.57 : 1.

Table.3.A. Prevalence of retinopathy

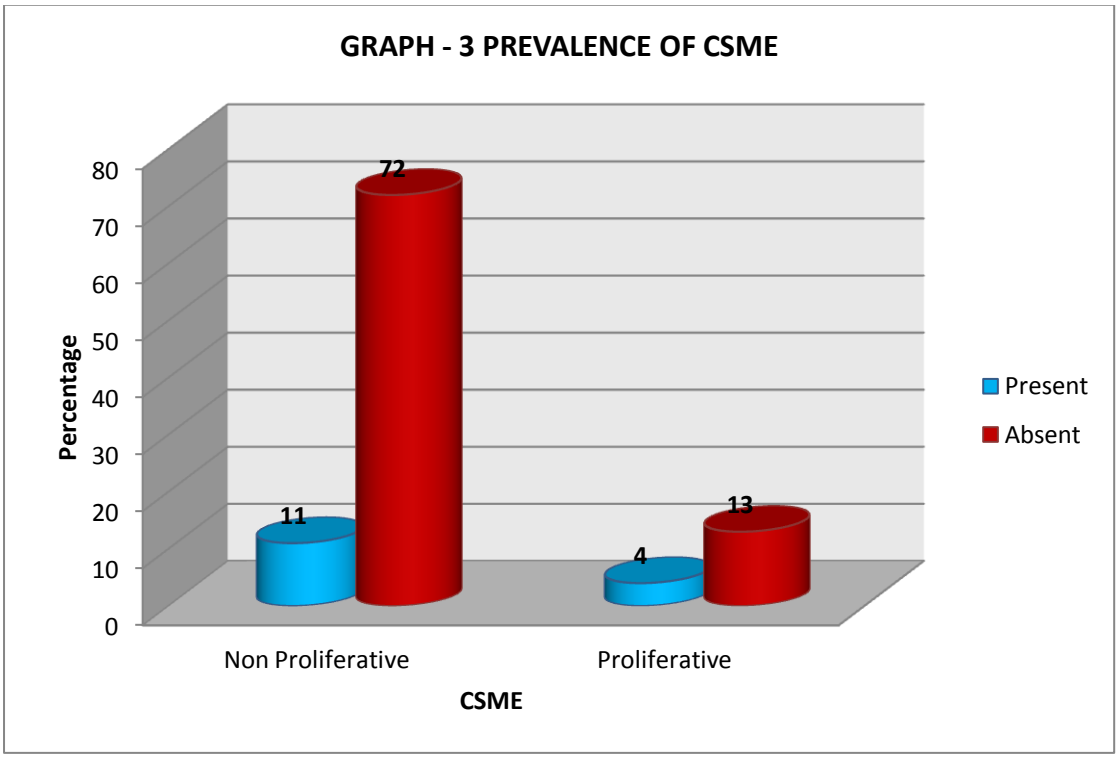
Retinopathy	No of patients	Percentage (%)
Mild NPDR	13	13
Moderate NPDR	21	21
Severe NPDR	49	49
Early PDR	13	13
High Risk PDR	4	4
Total	100	100



The present study constituted 13% mild NPDR, 21% moderate NPDR, 49% severe NPDR, 13% PDR and 4% high risk PDR. Out of 100 retinopathy patients studied severe NPDR accounted for nearly half the patients while the other half consisted of early PDR, mild and moderate NPDR, the latter being higher than the former.

Table.3B. Prevalence of CSME:

CSME	Non Proliferative	Proliferative	Total
Present	11	4	15
Absent	72	13	85
Total	83	17	100

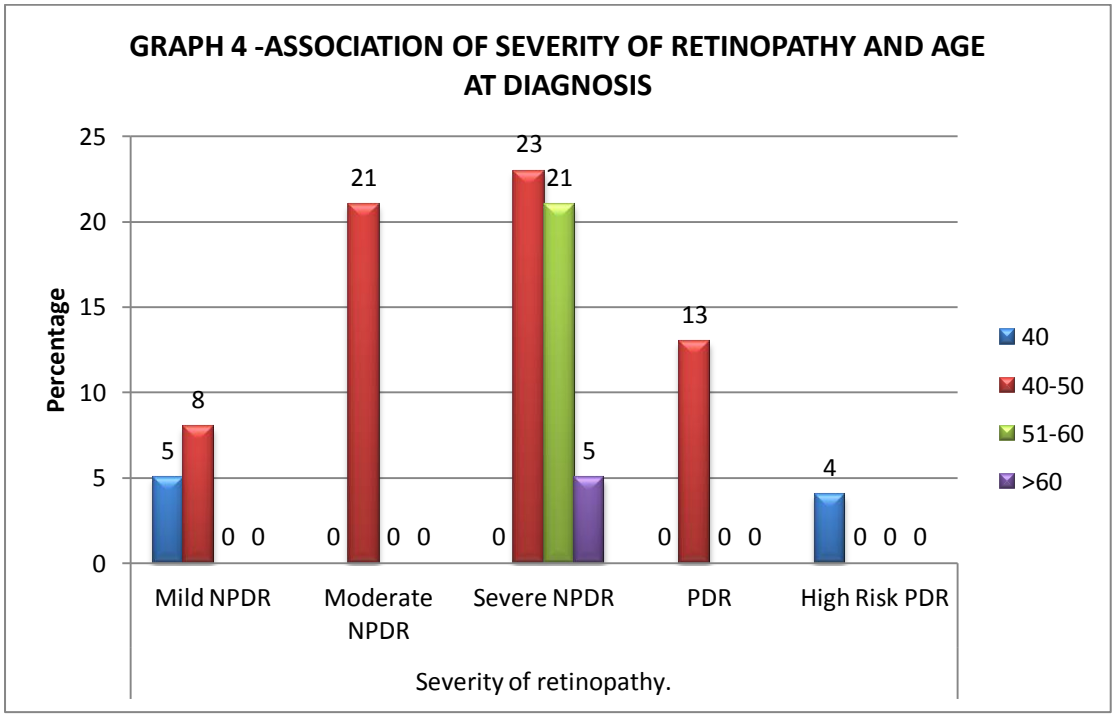


Out of the 100 cases of diabetic retinopathy, 15% had CSME, 11% in NPDR and 4% in PDR.

Table.4. Association of severity of retinopathy and age at diagnosis:

Age at diagnosis (years)	Severity of retinopathy					Total
	Mild NPDR	Moderate NPDR	Severe NPDR	Early PDR	High Risk PDR	
40	5	0	0	0	4	9
41-50	8	21	23	13	0	65
51-60	0	0	21	0	0	21
>60	0	0	5	0	0	5
Total	13	21	49	13	4	100

p <0.0001 (HS)

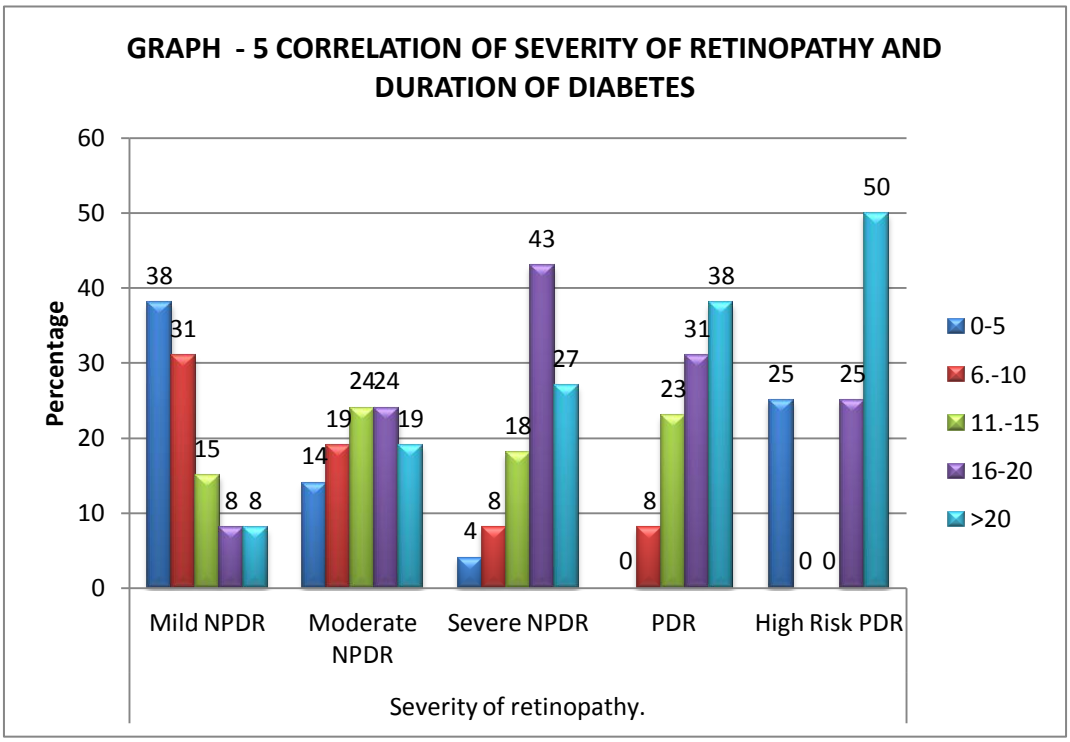


Age at diagnosis was calculated as patient's age at point of examination minus duration of diabetes. The above table shows that around 5 out of 13 (40%) cases with mild NPDR were in age of 40 years, all of the 21cases (100%) of moderate NPDR patients were in 40-50 years age group, 21 out of 49 cases (43%) patients with severe NPDR were in 51-60 years age group and all 5 cases above 60 years age had severe NPDR. This revealed that as the age at diagnosis of diabetes increases, severity of retinopathy increases. The age at diagnosis was significantly associated with the severity of retinopathy.

Table.5. Correlation of severity of retinopathy and duration of diabetes:

Duration of diabetes (years)	Severity of retinopathy.					Total
	Mild NPDR	Moderate NPDR	Severe NPDR	Early PDR	High Risk PDR	
0-5	5(38%)	3(14%)	2(4%)	0	1(25%)	11
6-10	4(31%)	4(19%)	4(8%)	1(8%)	0	13
11-15	2(15%)	5(24%)	9(18%)	3(23%)	0	19
16-20	1(8%)	5(24%)	21(43%)	4(31%)	1(25%)	32
>20	1(8%)	4(19%)	13(27%)	5(38%)	2(50%)	25
Total	13	21	49	13	4	100

p = 0.0267 (S)

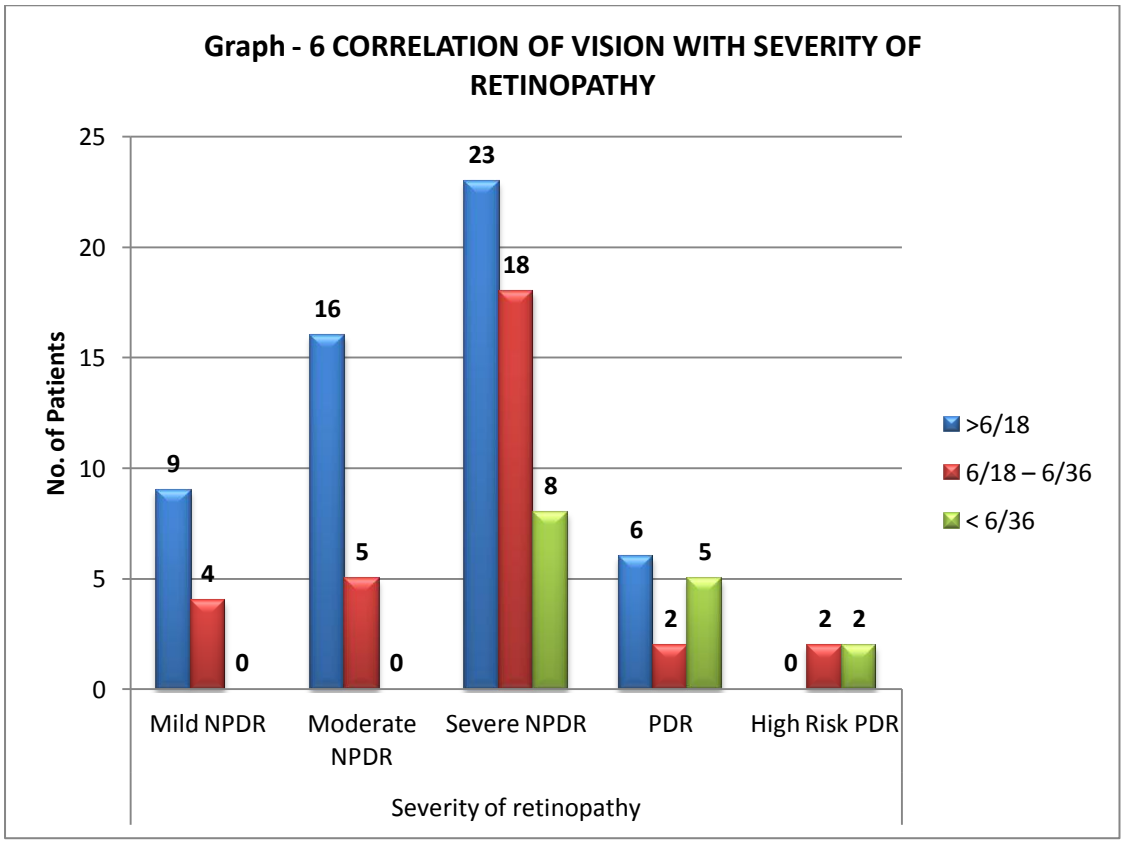


From the above table it can be observed that while the mild NPDR cases progressively reduced from 38% to 8% as the duration of diabetes increased from 5 years to more than 20 years, severe NPDR and early PDR cases increased from 4% to 27% and 0% to 38% respectively as the duration of diabetes increased from 5 years to more than 20 years.The distribution of retinopathy along the duration of diabetes was found to be statistically very significant.

Table 6. Correlation of vision with severity of retinopathy

Visual acuity (Snellen's)	Severity of retinopathy					Total
	Mild NPDR	Moderate NPDR	Severe NPDR	Early PDR	High Risk PDR	
>6/18	9	16	23	6	0	54
6/18 – 6/36	4	5	18	2	2	31
< 6/36	0	0	8	5	2	15
Total	13	21	49	13	4	100

P=0.006

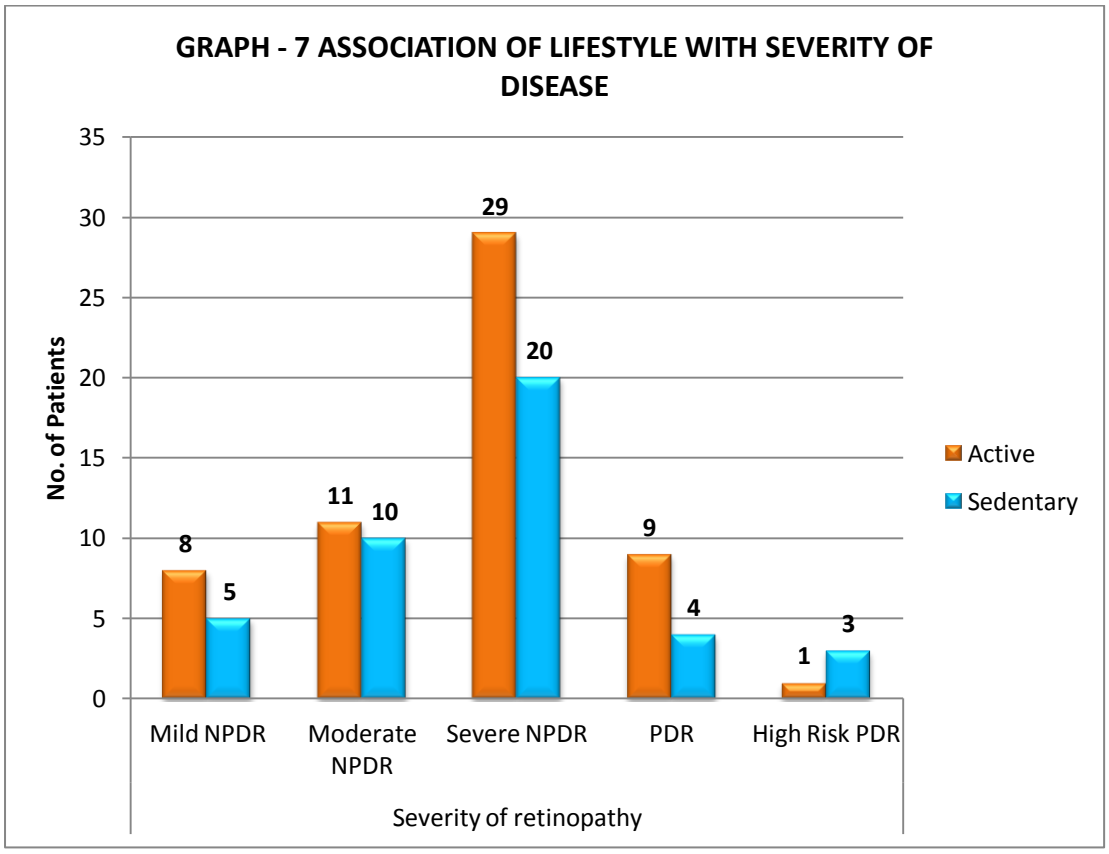


The above table reveals a significant association between best corrected visual acuity of the patient and the severity of retinopathy. Higher the level of retinopathy, lesser is the vision. These observations include all the cases with CSME also.

Table.7. Association of lifestyle with severity of disease:

Life style	Severity of retinopathy					Total
	Mild NPDR	Moderate NPDR	Severe NPDR	Early PDR	High Risk PDR	
Active	8	11	29	9	1	58
Sedentary	5	10	20	4	3	42
Total	13	21	49	13	4	100

P=0.5869



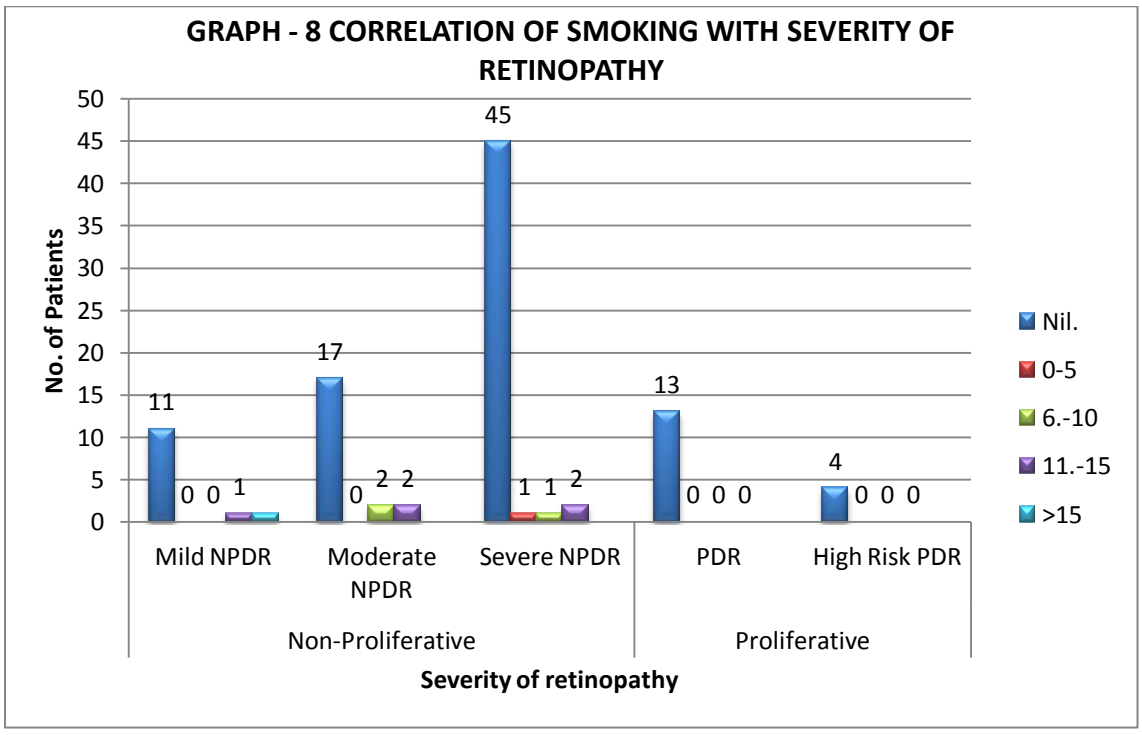
The distribution of the study population were almost equal among active and sedentary lifestyles with 58 participants in active group and 42 in sedentary. The

distribution of the study population in the severity of retinopathy was found to be statistically not significant.

Table.8. Correlation of smoking with severity of retinopathy:

Years of smoking.	Severity of retinopathy					
	Non-Proliferative			Proliferative		Total
	Mild NPDR	Moderate NPDR	Severe NPDR	Early PDR	High Risk PDR	
Nil.	11	17	45	13	4	90
0-5	0	0	1	0	0	1
6-10	0	2	1	0	0	3
11-15	1	2	2	0	0	5
>15	1	0	0	0	0	1
Total	13	21	49	13	4	100

p = 0.28915 (NS)



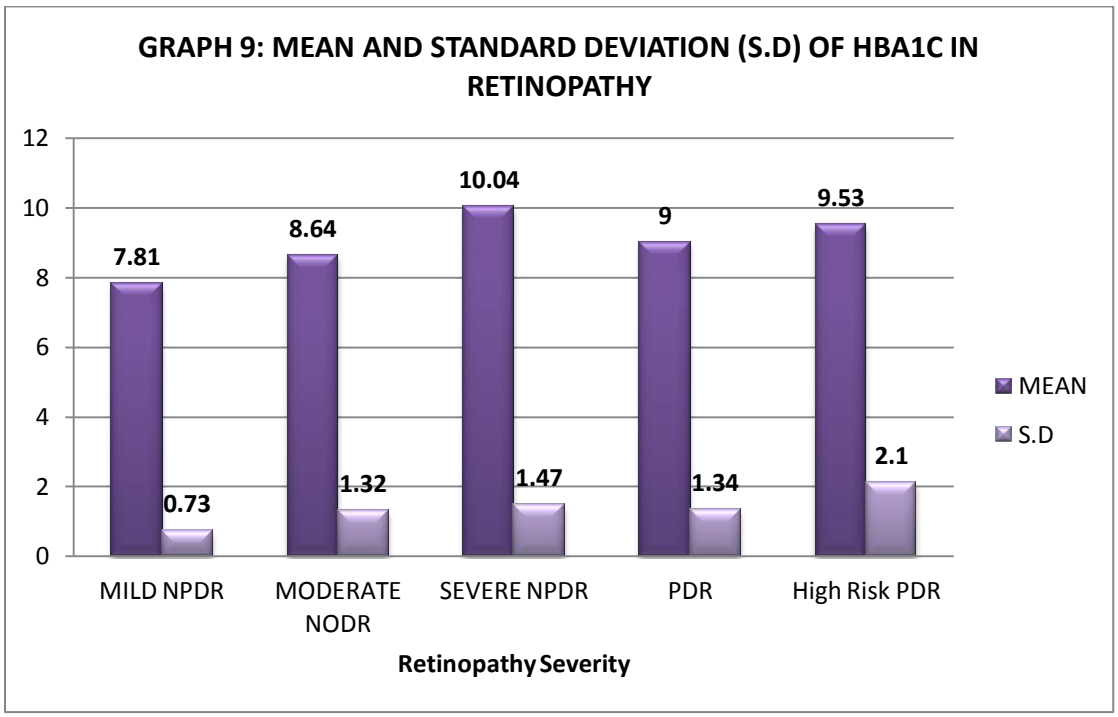
In our study population, 90 out of 100 patients were non-smokers. Most of the smokers were evenly clustered between 6-15 years duration of smoking with moderate and severe NPDR. The distribution revealed no variation with increasing

severity of retinopathy. Analysis of the 10 smokers in study population revealed no statistical significance with severity of retinopathy.

Table.9. Association of HbA1c with severity of retinopathy:

Table 9.A. Mean and standard deviation (S.D) of HbA1c in retinopathy:

Retinopathy Severity	HbA1C	
	MEAN	S.D
MILD NPDR	7.81	0.73
MODERATE NODR	8.64	1.32
SEVERE NPDR	10.04	1.47
Early PDR	9.00	1.34
High Risk PDR	9.53	2.10



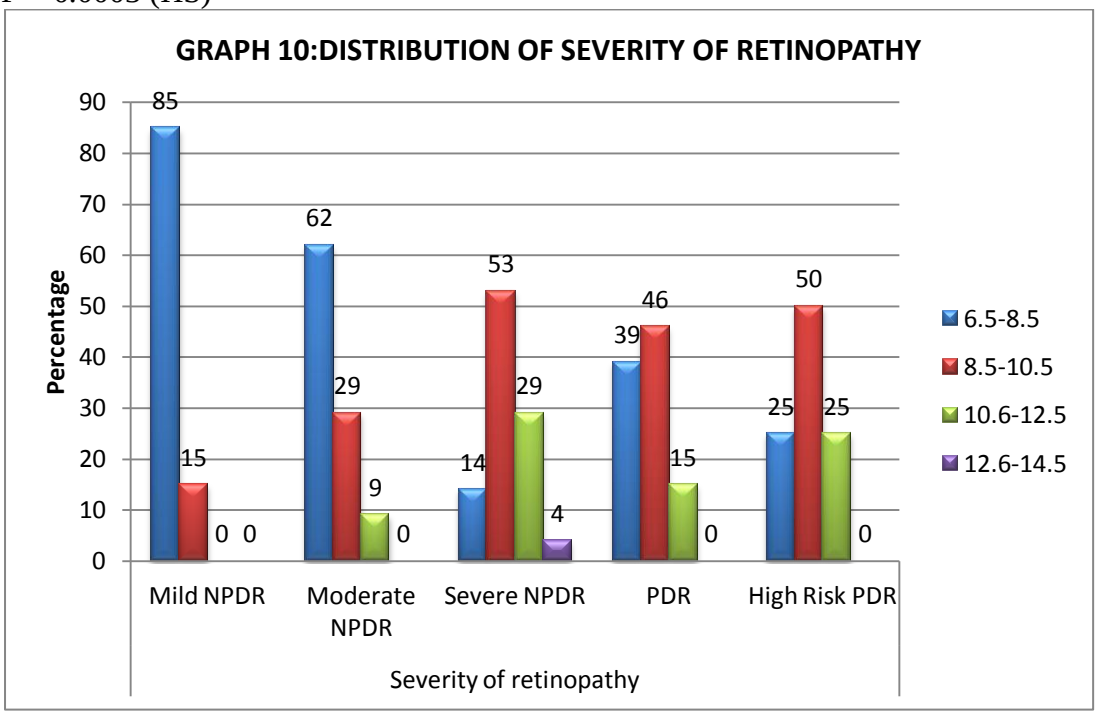
The table shows the means of HbA1c in each level of severity of diabetic retinopathy. The mean of HbA1c in mild NPDR was 7.81 $\pm$ 0.73, in moderate NPDR was 8.64 $\pm$ 1.32, in severe NPDR was 10.04 $\pm$ 1.47, in Early PDR was 9.0 $\pm$ 1.34 and in High risk PDR was 9.53 $\pm$ 2.10. Therefore, as the severity of retinopathy increased,

the mean HbA1c for that level of severity also increased. The standard deviation (S.D) in each group being small.

Table 9.B.Distribution of severity of retinopathy

HbA1c range (%).	Severity of retinopathy					Total
	Mild NPDR	Moderate NPDR	Severe NPDR	Early PDR	High Risk PDR	
6.5-8.5	11 (85%)	13 (62%)	7 (14%)	5 (39%)	1 (25%)	37
8.5-10.5	2 (15%)	6 (29%)	26 (53%)	6 (46%)	2 (50%)	42
10.6-12.5	0	2 (9%)	14 (29%)	2 (15%)	1 (25%)	19
12.6-14.5	0	0	2 (4%)	0	0	2
Total	13(100%)	21(100%)	49(100%)	13(100%)	4 (100%)	100

P = 0.0003 (HS)



The above table reveals that there were 85% of mild NPDR cases, 62% of moderate NPDR cases and 14% of PDR cases in 6.5% – 8.5% range of HbA1c.Whereas in HbA1c range of 8.6 % – 10.5%, mild and moderate NPDR cases reduced to 15% and 29% respectively and severe NPDR cases increased to 53%. Early PDR cases raised from 38% in 6.5% – 8.5% range of HbA1c to 46% in 8.6 % – 10.5%. And high-risk PDR cases raised from 25% to 50% when HbA1c raises form

6.5% - 8.5% range to 8.6 % – 10.5%. This revealed an increasing trend of severity of retinopathy with raise in HbA1c.

Table 9.C. Variance of HbA1c in retinopathy:

HbA1c	Sum of Squares (total variation in entire data)	df (degree of freedom)	Mean Square (sum of squares / degree of freedom)	F (ratio of mean squares)	P value
Between Groups	65.988	4	16.497	8.762	.000
Within Groups	178.862	95	1.883		
Total	244.850	99			

The above table of ANOVA test reveals that the variance of HbA1c in different levels of retinopathy severity was statistically highly significant. One way distribution of HbA1c among the groups show significant non homogeneity.

SCHEFFE'S TEST FOR PAIRWISE COMPARISON:

Comparison of mild NPDR with other levels of retinopathy:

GROUP (from)	GROUP (to)	Mean Difference	P value
Mild NPDR	Moderate NPDR	-.83516	.565
Mild NPDR	**Severe NPDR**	**-2.22904***	**.000**
Mild NPDR	Early PDR	-1.19231	.305
Mild NPDR	High Risk PDR	-1.71731	.317

Comparison of moderate NPDR with other levels of retinopathy:

Moderate NPDR	**Severe NPDR**	**-1.39388***	**.007**
Moderate NPDR	Early PDR	-.35714	.969
Moderate NPDR	High Risk PDR	-.88214	.845

Comparison of severe NPDR with other levels of retinopathy:

Severe NPDR	Early PDR	1.03673	.219
Severe NPDR	High Risk PDR	.51173	.972

Comparison of PDR with other levels of retinopathy:

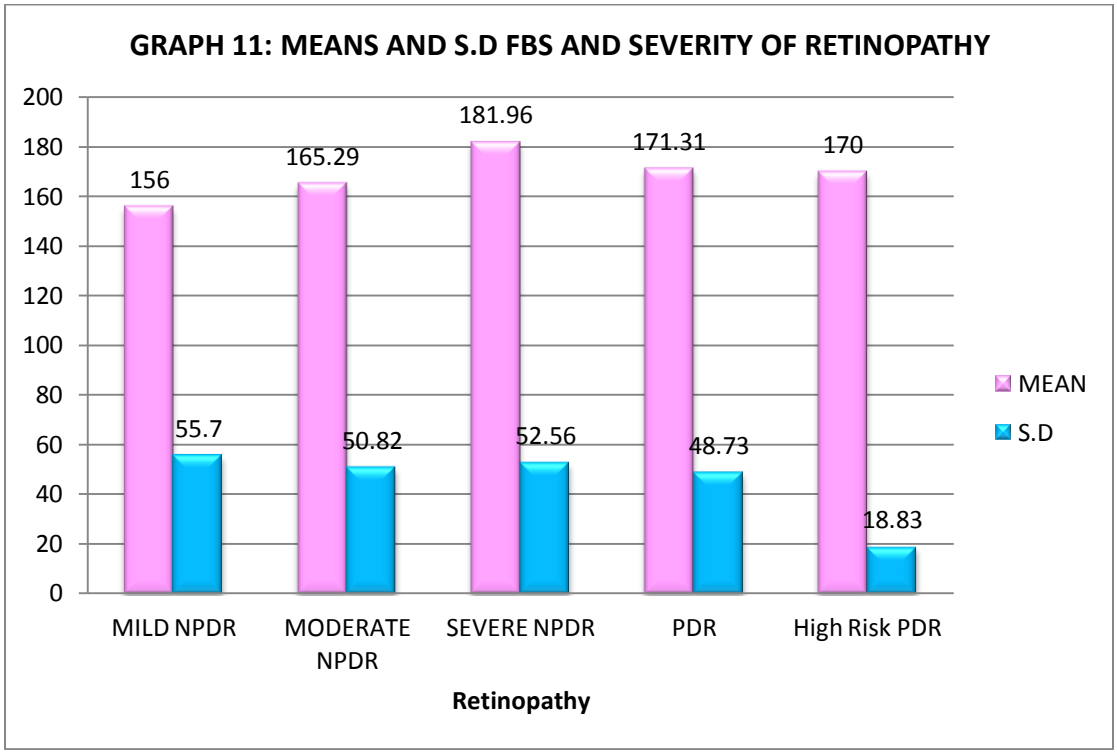
Early PDR	High Risk PDR	-.52500	.978

The above pair wise comparison of HbA1c in intergroup variability revealed that shift of HbA1c from mild NPDR to severe NPDR was highly significant and from moderate NPDR to severe NPDR was very significant.

Two way distribution of retinopathy among ranges of HbA1c revealed highly significant association with the severity of retinopathy.

Table.10.A. Means and S.D of FBS and severity of retinopathy

Retinopathy	MEAN	S.D
MILD NPDR	156.00	55.70
MODERATE NPDR	165.29	50.82
SEVERE NPDR	181.96	52.56
Early PDR	171.31	48.73
High Risk PDR	170.00	18.83



The table shows the means of FBS in each level of severity of diabetic retinopathy. The mean of FBS in mild NPDR was 156.00 ± 55.70, in moderate NPDR was 165.29 ±50.82, in severe NPDR was 181.96 ± 52.56, in Early PDR was 171.31± 48.73 and in High risk PDR was 170 ± 18.83. Therefore, as the severity of retinopathy

increased, the mean FBS for that level of severity also increased. The standard deviation (S.D) in each group being considerably large.

Table.10.B. Variance of FBS and severity of retinopathy:

FBS	Sum of Squares (total variation in entire data)	df (degree of freedom)	Mean Square (sum of squares / degree of freedom)	F (ratio of mean squares)	P value	
Between Groups	9008.187	4	2252.047	.852	.496	NS
Within Groups	251040.973	95	2642.537			
Total	260049.160	99				

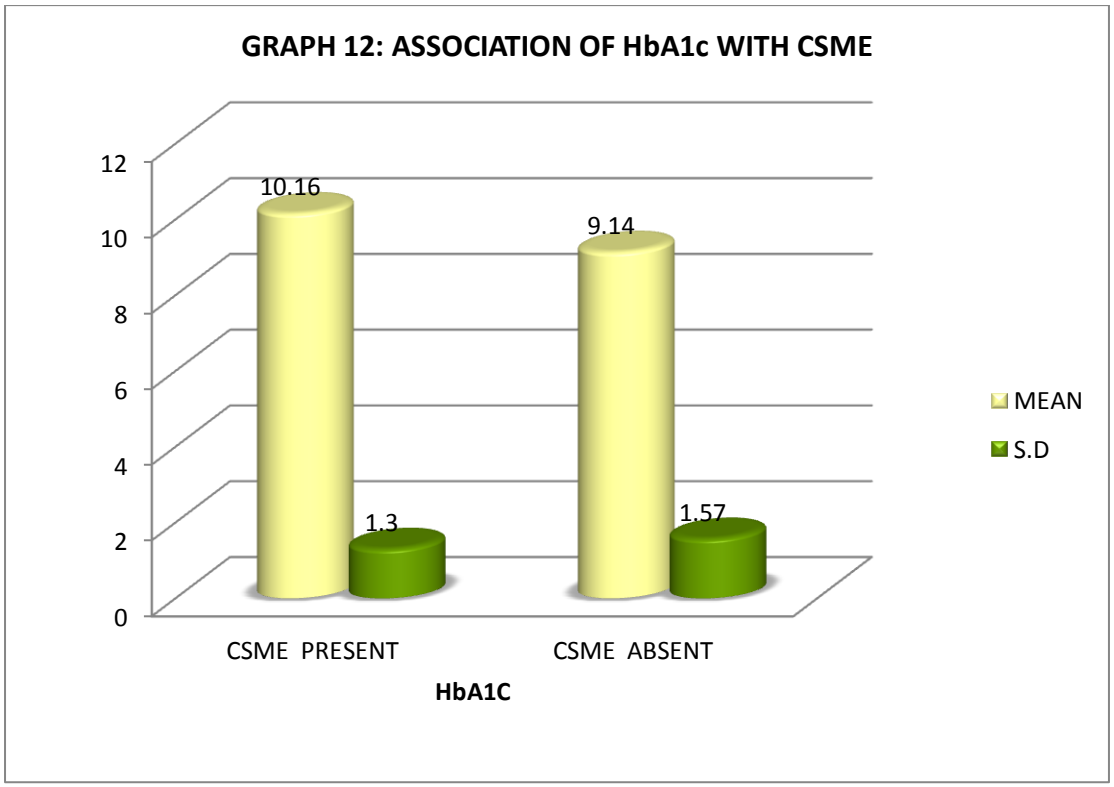
There was homogeneity among the groups, thereby the variance of FBS along the severity of retinopathy was not considerably high. Thus pair-wise comparison was not advisable.

Distribution of FBS along the severity of retinopathy shows homogeneity among all groups and thus the association was found to be statistically non-significant.

Table 11.Association of HbA1c with CSME:

PRESENCE OR ABSENCE OFCSME		
RETINOPATHY	**HbA1C**	
	MEAN	**S.D**
CSME PRESENT	10.16	1.30
CSME ABSENT	9.14	1.57

p VALUE BY STUDENT'S UNPAIRED t TEST IS 0.0166 (S)

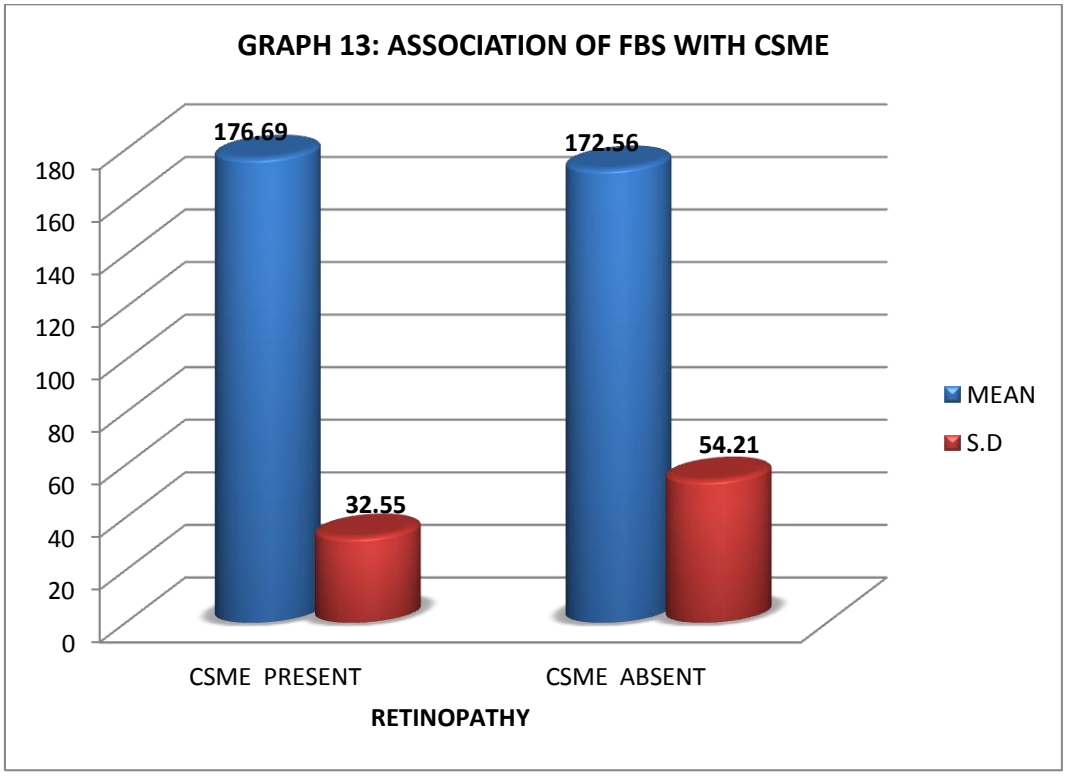


The above table shows that the mean HbA1c of cases with CSME was 10.16 ± 1.30 and that of cases without CSME was 9.14 ± 1.57. Comparison of the means of HbA1c in patients with and without CSME revealed statistically significant association of CSME with HbA1c.

Table.12. Association of FBS with CSME:

PRESENCE OR ABSENCE OFCSME		
RETINOPATHY	**FBS**	
	MEAN	**S.D.**
CSME PRESENT	176.69	32.55
CSME ABSENT	172.56	54.21

p = 0.7695 (NS)



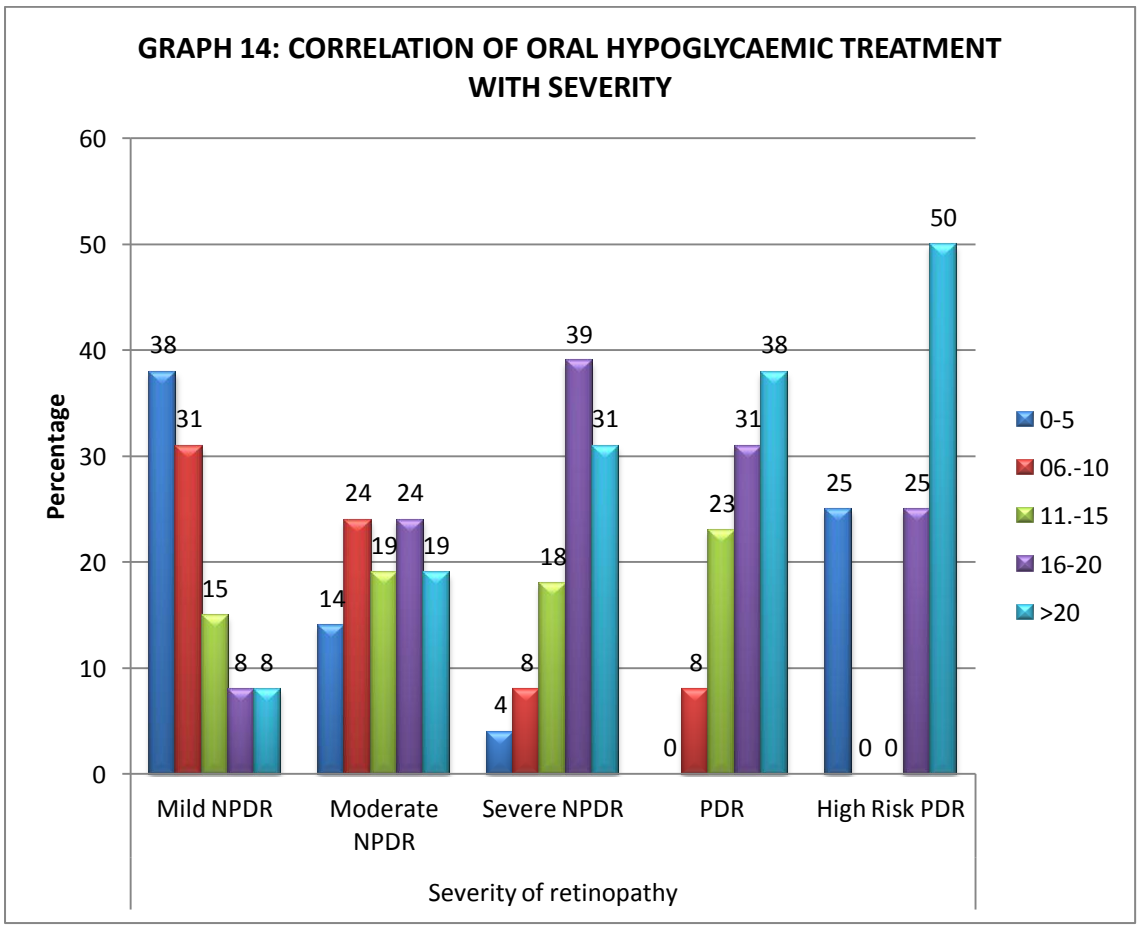
This table shows that the mean FBS of cases with CSME was 176.69 $\pm$ 32.55 and that of cases without CSME was 172.56 $\pm$ 54.21.

Comparison of the means of FBS in patients with and without CSME revealed no statistically significant association between CSME and FBS.

Table. 13. Correlation of oral hypoglycaemic treatment with severity of retinopathy:

Treatment duration (years)	Severity of retinopathy.					Total
	Mild NPDR	Moderate NPDR	Severe NPDR	Early PDR	High Risk PDR	
0-5	5 (38%)	3 (14%)	2 (4%)	0	1 (25%)	11
6-10	4 (31%)	5 (24%)	4 (8%)	1 (8%)	0	14
11-15	2 (15%)	4 (19%)	9 (18%)	3 (23%)	0	18
16-20	1 (8%)	5 (24%)	19 (39%)	4 (31%)	1 (25%)	30
>20	1 (8%)	4 (19%)	15 (31%)	5 (38%)	2 (50%)	27
Total	13(100%)	21(100%)	49(100%)	13(100%)	4 (100%)	100

p= 0.030



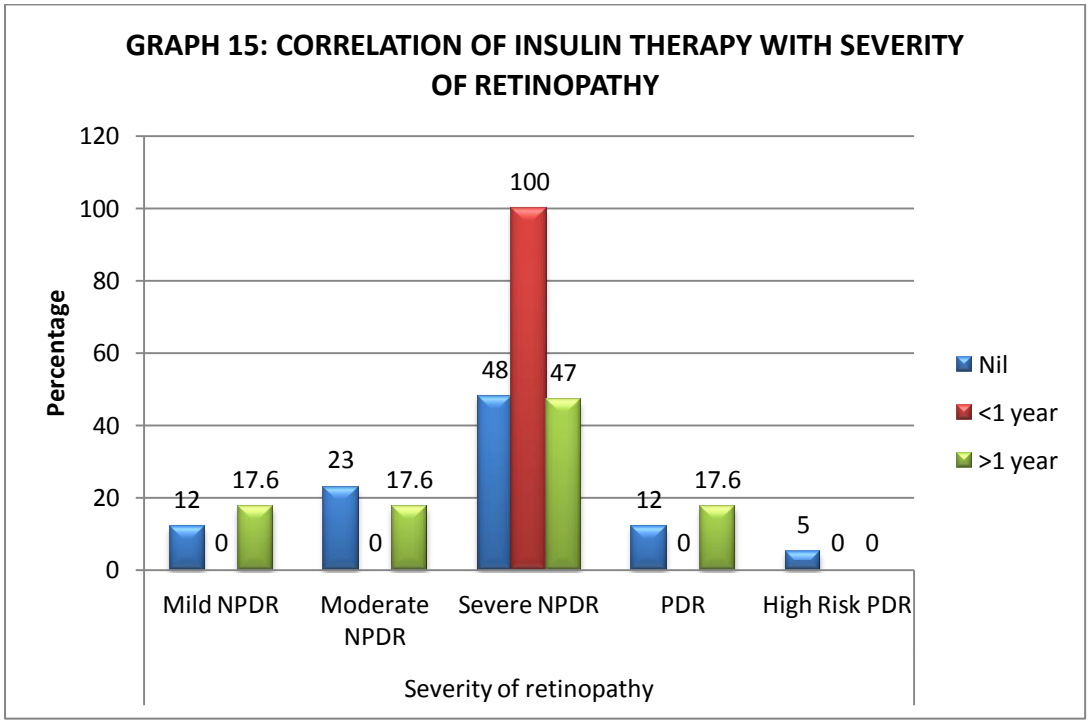
The above table reveals that in mild NPDR group, there was considerable reduction of cases from 38% to 8% as the duration of treatment increases from 5 years to more than 20 years. In moderate NPDR group, the cases were nearly maintained as 14% in 5 years treatment duration and19% in more than 20 years treatment duration. Similar consistency was seen in high risk PDR group.

The present study shows a significant association between the severity of retinopathy and duration of treatment by oral hypoglycaemic drugs. This means that treatment effectively retards or maintains the severity of retinopathy.

Table. 14. Correlation of Insulin therapy with severity of retinopathy.

Age at diagnosis (yrs)	Severity of retinopathy.					Total
	Mild NPDR	Moderate NPDR	Severe NPDR	EARLY PDR	High Risk PDR	
Nil	10(12%)	18(23%)	39(48%)	10(12%)	4(5%)	81 (100%)
<1 year	0	0	2 (100%)	0	0	2 (100%)
>1 year	3 (17.6%)	3 (17.6%)	8 (47%)	3 (17.6%)	0	17 (100%)
Total	13	21	49	13	4	100

p=0.880



The above table shows that all cases (100%) with insulin treatment of less than 1year had severe NPDR and in insulin treatment more than 1 year, there was increase in total cases from 17.6% in mild NPDR to 47% in severe NPDR revealing worsening of retinopathy with increased duration of insulin use. The observations of present study revealed no significant association between treatment by insulin and severity of retinopathy.

Table 15: HbA1c threshold for retinopathy:

Study	HbA1c threshold	Relation of HbA1c with retinopathy
Pima Indian study 1994	6.2%	Significant
Egyptian study 1997	6.3%	Significant
NHANES III 1999	6.0%	Significant
MESA study 1999	Unclear	Significant
Central India study 2004	7%	Significant
Wong et al. 2008	5.5%	Significant
Present study2011	7.6%	Significant

The analysis of our study reveals that the lower limit of HbA1c for occurrence of mild NPDR with 95% C.I in our study was 7.6%.

DISCUSSION

The present study was conducted as a descriptive observational study to determine the correlation of HbA1c levels with diabetic retinopathy.

Demographic details:

Our study included 100 patients. The mean age of participants in this study was 61.74 ± 8.83 and the M:F ratio is 2.57 : 1. The mean age of onset of 100 participants was 46.82 ± 6.94 and the mean duration of diabetic age was 12.48 ±4.65. The mean of Glycosylated haemoglobin (HbA1c) in the study population was 9.29 ± 1.57.

An earlier Indian study had shown the mean age diagnosis or onset to be 46.5 ± 10.25 years and the mean duration of diabetes as 7.6 ± 5 years.[7]The UKPDS revealed a mean HbA1c of 8.6%, the values ranging from 5.3% to 15.6%. These findings are close to the findings of our study.[91]

Gender distribution:

There were 72 males and 28 females in our study group, with a male : female ratio of 2.57:1.

Similar results of DR prevalence being more in males were depicted in WESDR study.[73] Contrary to this, Bajpai et al[72] revealed higher female preponderance, the analysis showed that there was no significant variation in the stages of retinopathy based on sex of the patient.

Prevalence of retinopathy:

The present study included 100 cases of retinopathy which constituted 13% mild NPDR, 21% moderate NPDR, 49% severe NPDR, 13% PDR and 4% high risk PDR. Out of 100 retinopathy patients studied severe NPDR accounted for nearly half

the patients while the other half consisted of PDR, mild and moderate NPDR, the latter being higher than the former. Regardless of the severity of retinopathy, 15% cases had CSME.

A south Indian study by Mohan R. reported an overall prevalence of 14 per cent, NPDR 6%, while 4% had macular oedema and 4% had PDR.[26]A Chennai study revealed the prevalence of DR was 34.1%. The prevalence included 30.8% with NPDR, 3.4% with PDR and 6.4% had DME.[28]

The differences in the findings could be attributed to variable population characteristics as age of onset, diabetic duration, treatment and its adherence.

Age at diagnosis and severity of retinopathy:

In our study around 40% patients with mild NPDR were aged 40 years, 100% of moderate NPDR patients were in 40-50 years age group and around 90% patients with severe NPDR were in 40-60 years age group. This revealed that as the age at diagnosis of diabetes increases, severity of retinopathy increases. The age at diagnosis was significantly associated with the severity of retinopathy.

Similar results in Minnesota study was in favor which said that the risk of retinopathy increases per year of diabetes after puberty.[87] On the other hand another study revealed that once duration and type of diabetes were considered, age of the patient had little significance in the progression of retinopathy.[86]

Duration of diabetes and severity of retinopathy:

It can be gathered from our study that 69% of mild NPDR were seen upto 10 years of diabetic duration, almost 67% moderate NPDR were in between 6 to 20 years of diabetic duration, almost 69% severe NPDR were seen in 16-20 years interval and almost 70% PDR were seen in diabetic duration of more than 16 years.

The distribution of retinopathy along the duration of diabetes was found to be statistically very significant. It is evident from these findings that there was statistically significant worsening of the retinopathy with the increasing duration of diabetes in these individuals. When compared, there was a statistically significant relation between the duration of diabetes in all the groups of retinopathy.

Duration of diabetes found in our study which was similar to the findings of another study by HS Bajpai[72] showing 51 per cent of diabetics with less than ten years of duration of the disease, had grade I changes, while only 11.7 percent had grade I changes with diabetes of more than 10 years duration ($P<0.001$). This observation also had favorable correlation with another longitudinal study by Palmberg[88] and a cross sectional study by Bender AP[89] which noted similar findings.

It was also observed that the incidence of retinopathy increased with the increase in the duration of diabetes mellitus, from 16.7 per cent, in less than one year duration to 100 per cent where the duration of diabetes was above 16 years.[72] WESDR study revealed that the prevalence of diabetic retinopathy varied from 17% to 97.5% in persons with diabetes for less than five years and 15 or more years, respectively. Proliferative retinopathy varied from 1.2% to 67% in persons with diabetes for less than ten years and 35 or more years, respectively concluding a direct correlation between the frequency and severity of DR and the duration of DM.[73]

Visual acuity and severity of retinopathy:

The present study revealed a significant association between visual acuity of the patient and the severity of retinopathy. Higher the level of retinopathy, lesser is the vision. These observations include all the cases with CSME also.

Lifestyle and severity of retinopathy:

The distribution of the study population with active and sedentary lifestyles through the stages of retinopathy found no statistically significant association between lifestyle and severity of retinopathy.

The extent of the relationship between diet, exercise, and tobacco use and diabetic retinopathy, either directly or indirectly, via increase in blood pressure, lipids, HbA1c, body mass index (BMI), or insulin utilization has not been determined.[90]

Smoking and severity of retinopathy:

In our study population, 90 out of 100 patients were non-smokers. Distribution of the 10 smokers in the stages of retinopathy revealed no statistical significance with severity of retinopathy.

Similar results had been shown in study by Ramchandran et.al. revealing that the smoking status was not significantly associated with retinopathy.[7]

HbA1c and severity of retinopathy:

Our study revealed that mean values of HbA1c in non-proliferative levels of diabetic retinopathy have indisputable difference. The S.D of each level being considerably small, made the difference more relevant.

One way distribution of HbA1c in our study among the levels of retinopathy revealed significant non homogeneity and further revealed that the transition from mild to severe NPDR was statistically highly significant and that from moderate to severe NPDR was very significant.

Two way distribution of retinopathy among ranges of HbA1c revealed highly significant association with the severity of retinopathy.

The glycemic status of the patients in this study was studied by measuring HbA1C levels. When the HbA1C values were compared in the groups with increasing

severity of retinopathy, increasing levels of HbA1C were noted showing a significant correlation. Therefore it was noted that poor glycemic control led to the worsening of the retinopathy.

The Diabetes Control and Complications Trial (DCCT) and the U.K. Prospective Diabetes study (UKPDS) were two randomized clinical trials which conclusively showed the efficacy of glycemic control in preventing diabetic retinopathy. These studies mentioned that glycemic control was protective for all levels of retinopathy and there was no glycemic threshold below which a reduction in microvascular complications was not observed.[65,91]

FBS and severity of retinopathy:

Our study revealed that mean values of HbA1c in non-proliferative levels of diabetic retinopathy had indisputable difference. The S.D of each level being considerably small, made the difference more relevant.

Distribution of FBS along the severity of retinopathy revealed homogeneity among all groups and thus the association was found to be statistically non-significant.

Similar results had been concluded by previous study by Yiling et.al. revealed a stronger correlation between HbA1c and retinopathy than between fasting glucose levels and retinopathy.[81]

Same study had also observed that the variability of FBS levels is more, with day-to-day with-in person variance of 12-15% as opposed to <2% with HbA1c.

HbA1c with CSME:

Comparison of the means of HbA1c in patients with and without CSME revealed statistically significant association of CSME with HbA1c.

High glycosylated hemoglobin (HbA1c) level is a well-known risk factor for diabetic macular oedema. In addition, the DCCT had demonstrated that intensive treatment to maintain blood glucose levels at a normal range reduced the risk of clinically significant macular oedema at the rate of 23%.[70,78]

A recent study in this regard has shown that mean HbA1c in patients with persistent unilateral CSME was 8.6% and that in bilateral CSME was 9.1%. Same study also revealed that type2 diabetics with persistent CSME have higher HbA1c at time of their disease than patients with resolved CSME.[91]

FBS with CSME:

Comparison of the means of FBS in patients with and without CSME revealed no statistically significant association between CSME and FBS.

No studies have found to be quoting FBS as an independent risk correlating factor for presence or absence of CSME. Recent guidelines had recommended HbA1c as a better criteria for glycaemic control over FBS owing to the variability of the latter.[79]

Oral treatment with severity of retinopathy:

The present study revealed a significant association between the levels of retinopathy and duration of treatment. This means that treatment effectively retards or maintains the severity of retinopathy.

Similar results had been consistent in DCCT trials[70] that revealed better control of the strict control group revealing effect of treatment on retinopathy.

Insulin treatment with severity of retinopathy:

The observations of present study gave no significant association between treatment by insulin and severity of retinopathy.

Similar observations had been shown in other study which revealed that initial improvement in glycaemic control in insulin treated diabetics may have favored the early progression of retinopathy.[94]

HbA1c cut-off level:

Average of HbA1c in mild NPDR cases = 7.81

S.D of HbA1c in mild NPDR cases = 0.73

Standard Error (S.E) = S.D / sq.root of "n" (13) = 0.20

Lower limit of HbA1c in mild NPDR (95% confidence interval, C.I)

= Mean – (1.96 x S.E) = 7.6.

Our study revealed that threshold of HbA1c for occurrence of mild NPDR was 7.6% (with 95% C.I).[90] Similar threshold of HbA1c 7% were revealed in a central Indian study. A recent study had shown that retinopathy prevalence began to rise precipitously when HbA1C exceeded 5.5% (corresponding to the 5th decile).[82] Some previous studies had given differing thresholds, including the Pima Indian study (6.2%), the Egyptian study (6.3%), and NHANES III (6.0%).[83] Another multi-ethnic study could conclude no clear evidence of a threshold.[84]

CONCLUSION

The poor metabolic control as demonstrated by high HbA1c is significantly associated with severity of retinopathy and presence of CSME. From the analysis of our study, we recommend to maintain HbA1c levels below 7.6% which may reduce the risk of development and progression of diabetic retinopathy. Duration of diabetes and high HbA1c levels are found to be the major predictors of diabetic retinopathy in type II diabetes mellitus.

SUMMARY

Diabetes mellitus is a public health problem which has reached epidemic proportions. Diabetic retinopathy remains a serious vision threatening complication of diabetes mellitus.

This study aimed "TO DETERMINE THE CORRELATION OF HAEMOGLOBIN A1c LEVELS WITH DIABETIC RETINOPATHY IN TYPE II DIABETES MELITUS." was conducted in KLES Hospital and MRC, Belgaum in J.N.Medical College during the period of 01st Jan to 31st Dec-2010

The summary of the results obtained is as follows:

- The mean age of participants in this study was 61.74 ± 8.83. The mean age at diagnosis was 46.82 ± 6.94 and mean duration of diabetic age was 12.48 ± 4.65. The mean of Glycosylated haemoglobin (HbA1c) in the study population was 9.29 ± 1.57.
- The study group included 100 diabetic retinopathy patients consisting of 13% mild NPDR, 21% moderate NPDR, 49% severe NPDR, 13% PDR and 4% high risk PDR. Out of the 100 cases of diabetic retinopathy, 15% had CSME.
- There was notable male preponderance, male : female ratio being 2.57 : 1.
- Visual acuity was significantly associated with severity of retinopathy. Higher the level of retinopathy, lesser is the visual acuity.
- There was no association of lifestyle and smoking with severity of retinopathy.
- Age at diagnosis of diabetes was significantly associated with severity of retinopathy increases.

- Severity of retinopathy also increases with increase in the duration of diabetes, the two having a statistically significant relation.
- The study revealed strong association between HbA1c and severity of retinopathy. Better glycaemic control was associated with less severe retinopathy and worsening of glycaemic control (HbA1c) was associated with worsening of diabetic retinopathy.
- Presence of CSME was also significantly associated with poorer glycaemic control.
- Conversely, the severity of retinopathy and presence of CSME were not closely associated with FBS.
- Oral hypoglycaemic treatment retarded or maintained the severity of retinopathy, while insulin therapy for sudden glycaemic control was not associated with severity of retinopathy.
- Lastly, the analysis from our study had found that the lower limit of HbA1c for occurrence of mild NPDR is 7.6 %, with 95% C.I.

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ANNEXURE – I
To determine the correlation of HbA1c levels with diabetic retinopathy in type II diabetes mellitus.

DATA COLLECTION INSTRUMENT

I.D.NO ☐☐☐

NAME ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐
(First name)(Surname)

AGE (in yrs.) ☐☐

SEX ☐ 1=Male 2 = Female

RELIGION ☐
1-Hindu 2-Muslim 3-Christian 4-Others

ADDRESS ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

OPD NO. ☐☐☐☐☐☐

IPD NO. ☐☐☐☐☐☐

PROVISIONAL DIAGNOSIS: ☐ ________________________________

1- Type I diabetes mellitus.

2- Type II diabetes mellitus.

3- Maturity onset diabetes of the young (MODY).

INCLUSION CRITERIA ☐
1- met 2- not met

Criteria of inclusion : diagnosed to have type II diabetes mellitus with retinopathy changes in the fundus.

INFORMED CONSENT

1-taken 2- not taken ☐

Approval of the guide: _____

CHIEF COMPLAINTS:

1= YES 2= NO

	RE	**LE**	**BE**
1.) Diminution of vision	☐	☐	☐
2.) Pain	☐	☐	☐
3.) Flashes	☐	☐	☐
4.) Floaters	☐	☐	☐
5.) Metamorphopsia	☐	☐	☐
6.) Polyuria	☐	☐	☐
7.) Polydypsia	☐	☐	☐
8.) Polyphagia	☐	☐	☐
9.) ANY OTHER COMPLAINTS:	☐	☐	☐

IF YES:_____

PAST HISTORY:

1= YES, 2= NO a= >0-5 yrs b= >5-10 yrs c= >10-15 yrs d= >15-20 yrs e= >20 yrs.

10.) H/O WEARING GLASSES ☐ If yes, duration ☐

11.) H/O HYPERTENSION ☐ If yes, duration ☐

12.) H/O DIABETES MELLITUS ☐ If yes, duration ☐

13.) H/O ANY OCULAR SURGERY ☐ If 1, specify _____

14.) H/O AUTOIMMUNE DISEASE ☐

15.) H/O DRUG ALLERGY ☐ If yes, specify _____

☐

16.) ANY OTHER IF YES: _____

17.) FAMILY HISTORY:

1-Significant 2- Not significant ☐

18.) Life style:

1= YES 2 = NO ☐

Active ☐

Sedentary ☐

Personal history:

1-yes 2-no a= >0-5 yrs b= >5-10 yrs c= >10-15 yrs d= >15-20 yrs e= >20 yrs.

19.) Alcohol ☐ If yes, duration ☐

20.) Smoking ☐ If yes, duration ☐

21.) Diet : Veg/Mixed ☐ (1 = veg. , 2 = mixed) ☐

DIABETIC HISTORY :

22.) Age of onset of diabetes _____years

23.) Duration of diabetes _____years

24.) Any significant events _____years

TREATMENT HISTORY : 1=yes 2=no

a= >0-5 yrs b= >5-10 yrs c= >10-15 yrs d= >15-20 yrs e= >20 yrs.

25.) Oral hypoglycaemic: Single ☐ If yes, duration ☐

Multiple ☐ If yes, duration ☐

Groups of drug used: a. 1st generation sulfonylureas

b. 1st generation sulfonylureas

c. Biguanides

d. Miglitinide analogues.

e. Thiazolidinediones.

f. Glucosidase inhibitor.

g. Others. Specify : _____

26.) Insulin injections : ☐ If yes, duration ☐

27.) Laser : RE : ☐ If yes, duration ☐

LE : ☐ If yes, duration ☐

28.) Any other : ☐

GENERAL PHYSICAL EXAMINATION:

29.) PULSE RATE(per min.) ☐☐☐

30.) RESPIRATORY RATE(per min.) ☐☐☐

BLOOD PRESSURE(in mm Hg)

31.) Systolic ☐☐☐

32.) Diastolic ☐☐☐

33.) TEMPERATURE(in deg F) ☐☐☐

SYSTEMIC EXAMINATION : 1= Normal 2= Abnormal

34.) CVS: ☐ If abnormal_____

35.) R/S: ☐ If abnormal_____

36.) P/A: ☐ If abnormal_____

37.) CNS: ☐ If abnormal _____

38.) Renal: ☐ If abnormal_____

39.) Skin: ☐ If abnormal_____

40.) Foot: ☐ If abnormal _____

OCULAR EXAMINATION

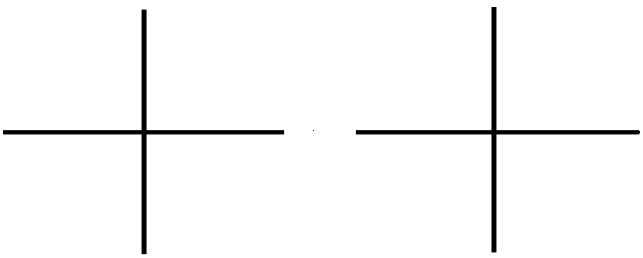
41.) HEAD POSTURE: ☐ 1= ERECT 2=TILTED

42.) VISUAL AXIS: ☐ 1=PARALLEL 2= DEVIATED

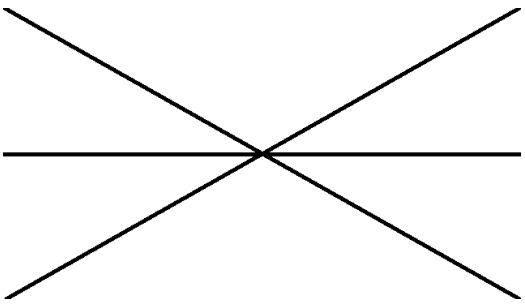
43.) FACIAL SYMMETRY: ☐ 1=SYMMETRICAL 2=DEVIATED

EXTRAOCULAR MOVEMENTS: ☐ NORMAL 2=RESTRICTED

44.) UNIOCULAR: RE ☐ LE ☐



45.) BINOCULAR ☐



Ocular examination : **Right eye** **Left eye**

46.) VISUAL ACUITY 1: 6/6 – 6/12 2: 6/18 – 6/36 3:≤ 6/60 Unaided vision : With pinhole : With spectacles :	☐	☐
47.) ADNEXA 1- Normal 2- Abnormal If 2,specify_____	☐	☐
48.) Lids 1-Normal 2-Abnormal If 2,specify_____	☐	☐
49.) **CONJUNCTIVA** 1 – Normal 2- Congested 3 – Other If 3,Specify : _____	☐	☐
50.) Cornea 1- Clear 2- Hazy 3- other If 3,Specify : _____	☐	☐
ANTERIOR CHAMBER: 51.) **DEPTH** 1- Normal 2- Shallow 3- Deep	☐	☐
52.) **IRIS:** COLOUR AND PATTERN 1- Normal 2- Atrophic Patches	☐	☐

53.) **PUPIL:** SIZE 1-normal 2- Constricted 3- Dilated	☐	☐
54.) **REACTION:** DIRECT INDIRECT 1- Present 2- Absent 3- Sluggish	☐ ☐	☐ ☐
55.) PUPILLARY MARGIN 1-Normal 2- Abnormal If 2,specify_____	☐	☐
56.) POSTERIOR SYNECHIAE 1- Present 2- Absent	☐	☐
57.) ACCOMODATION 1-Present 2- Absent	☐	☐
58.) LENS: 1- Clear 2- Cataractous 3-Pseudophakia 4-Aphakia.	☐ ☐	☐ ☐
59.) If Cataractous: 1- Immature 2- Mature 3- Hypermature	☐ ☐	☐

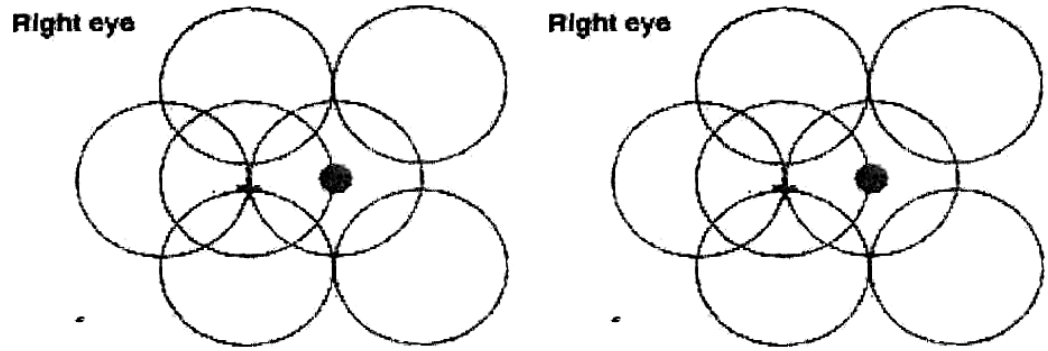
Observations :

60.) HbA1c (%)		
61.) FBS		
Fundus examination	**OD**	**OS**
62.) Glow 1=present, 2=faint, 3=absent		
63.) Media 1=clear, 2=hazy Corneal Lenticular Vitreous		
64.) Disc 1= normal 2 = Pallor 3 = NVD other, specify_____		
65.) Cup : disc ratio 1=normal (0.3) 2=abnormal If 2,specify_____		
66.) Vessels 1=normal 2 = Venous Beading 3 = Venous dilatation 4 = Venous looping 5 = Venous tortuosity Other, specify_____		
67.) Background 1=normal, 2=abnormal If 2,specify_____		

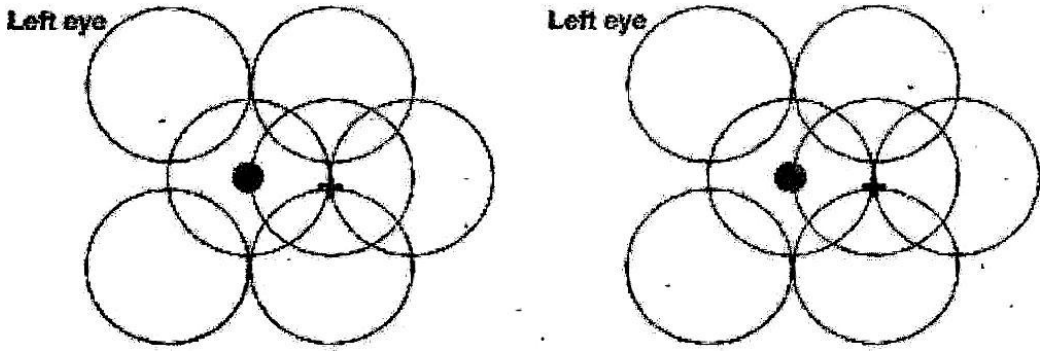
68.) **Haemorrhages** 1=present , 2=absent If 1 :- (specify quadrants in brackets) (a) = superionasal (b) = superiotemporal (c) = inferionasal (d) = inferiotemporal		
69.) Types of h'rge 1=Dot haemorrhages 2=Blot haemorrhages 3=Dark blot haemorrhages 4=Flame shaped haemorrhages 5=pre-retinal haemorrhages 6=Vitreous haemorrhages		
70.) Hard exudates 1=present , 2=absent If 1, specify quadrants as above.		
71.) A= NVE B= collaterals C= IRMAs 1 = present, 2 = absent. If 1, specify quadrants as above.		
72.) Soft exudates. 1 = present, 2 = absent. If 1, specify quadrants as above.		
73.) Fibrovascular proliferation: 1 = present, 2 = absent. If 1, specify quadrants as above.		
74.) **Others**		

75.) Macula 1= normal 2 = microaneurysms 3 = haemorrhare 4 = hard exudates 5 = thickening in 500um or less from center of macula. 6 = hard exudates in 500um or less from center of macula. 7 = thickening >/= 1 disc area, any portion of which is </= 1 disc diameter from center of macula. Others, specify _____		

Right eye:Fundus diagram FFA diagram



Left eye: Fundus diagram FFA diagram



Funduscopic Diagnosis :

Angiographic diagnosis :

ANNEXURE - II

CONSENT FOR PARTICIPATION IN RESEARCH STUDY

Mr/Mrs/Ms_____

You are invited to participate in our research study titled "**TO DETERMINE THE CORRELATION OF HAEMOGLOBIN Alc LEVELS WITH DIABETIC RETINOPATHY IN TYPE II DIABETES MELLITUS"** conducted by Dr. Rishi Bhardwaj, Post Graduate in M.S. Ophthalmology under the guidance of Dr. Rekha B.K., M.S., D.O.M.S, Professor in the Department of Ophthalmology, J .N. Medical College, Belgaum.

Respected Sir/Madam we request you to enroll yourself to participate in our study as you are eligible for participating in the study. Your participation in research is voluntary. If you decide to participate you are free to withdraw at any time.

Purpose of the Study: The purpose of research is TO DETERMINE THE CORRELATION OF HAEMOGLOBIN Alc LEVELS WITH DIABETIC RETINOPATHY IN TYPE II DIABETES MELLITUS.

Procedure Involved : If you agree to enroll yourself in this study, I will ask your present, past and family history. You will be clinically examined and relevant investigations will be accessed. Then you will be subjected to direct and indirect ophthalmoscopy, slit lamp biomicroscopy, fundus photography and fundus fluorescein angiography if required. The hence obtained data will be monitored, documented and reproduced as required.

Risks and Benefits : There are no major risks involved in the above mentioned procedures however some discomfort may occur, for which all precautions will be taken.

Your participation may benefit you and others suffering from the same ailment in future, by helping us learn more about the disease process and better treatment modalities.

Alternatives : If you are not willing to participate you will be treated according to the existing protocol & it will not affect your relationship with this hospital.

Costs for participating in this research: The participant will have to pay for the investigations which are the part of the existing management protocol for this ailment.

Privacy and Confidentiality: No information about you or information provided by you during the research will be disclosed to others without your written permission.

Authorization to Publish Results: When the results of the research are published or discussed, in a conference, no information will be displayed that would disclose your identity.

Compensation: In the event of injury related to the study, treatment will be made available through KLES Prabhakar Kore Hospital & MRC, Belgaum. There is no compensation or payment for such medical treatment by law. The doctors and the staff will provide facilities and medical attention to you.

Questions:

If you have any questions about the research you may please contact:

1) Chief investigator, **Dr. Rishi Bhardwaj**, P.G., Department of Ophthalmology, JNMC,Belgaum. Contact No. 9964728297.
2) **Dr. Rekha B.K.**, Professor, Guide, Department of Ophthalmology, JNMC, Belgaum. Ph: 9449938997

3) **Dr. V.D.Patil** ,Principal, JNMC,Belgaum and chairman of Institutional Ethics Committee. Ph. 0831-2471350

CONSENT FOR PARTICIPATION IN RESEARCH TRIAL

I, Mr./Ms./Mrs _____ voluntarily agree for the participation as a subject of this study. By signing this consent form I am not giving up any of my legal rights, I may withdraw from the study anytime. I am signing the consent form after having read or been read for me in my own vernacular language, including the risks and the benefits and having all my questions answered.

Subject Name : _____

Signature or the Left Thumb Print of Subject : _____

Witness Name:_____

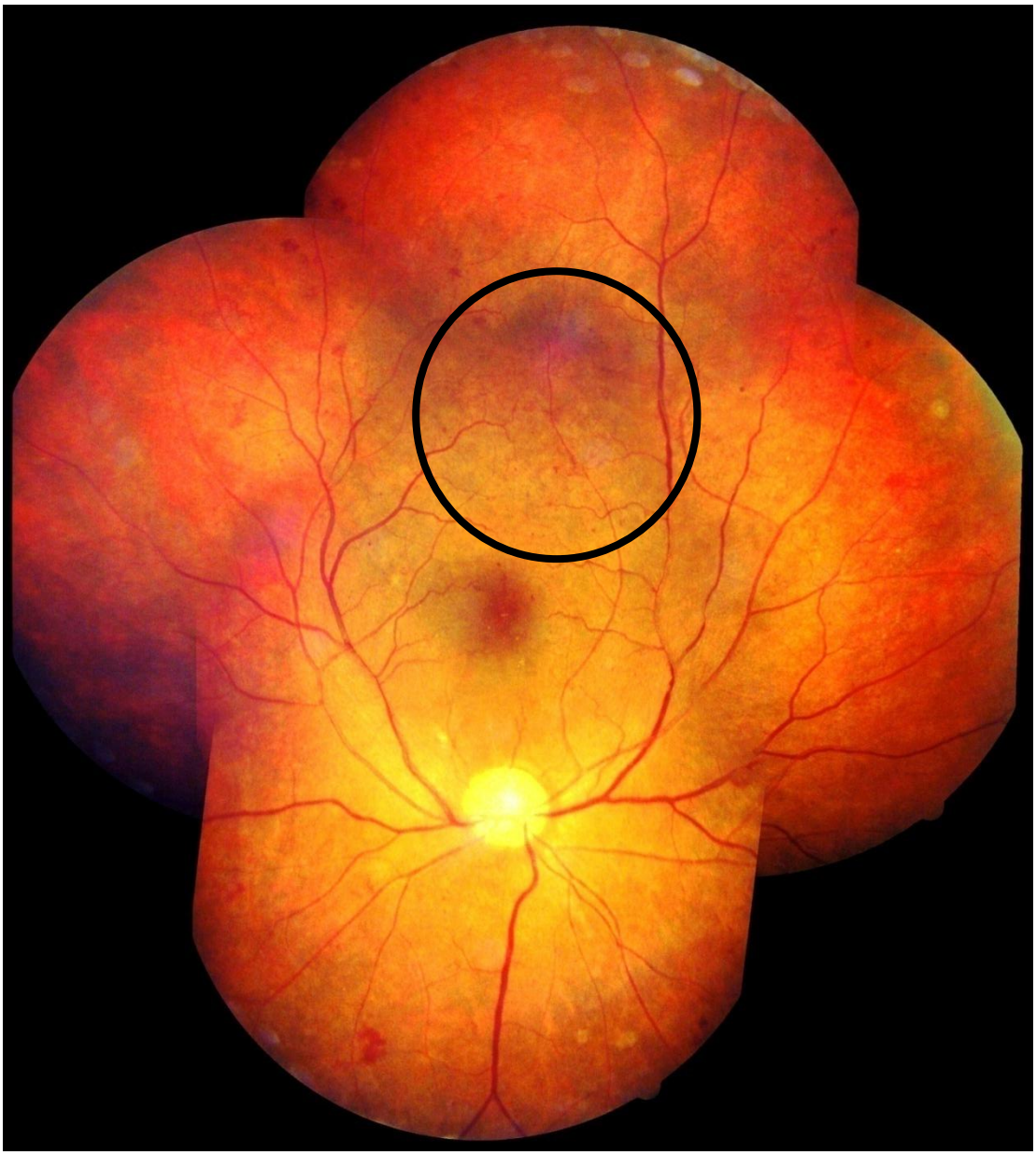
Signature of Witness:_____

Investigators Name: _____

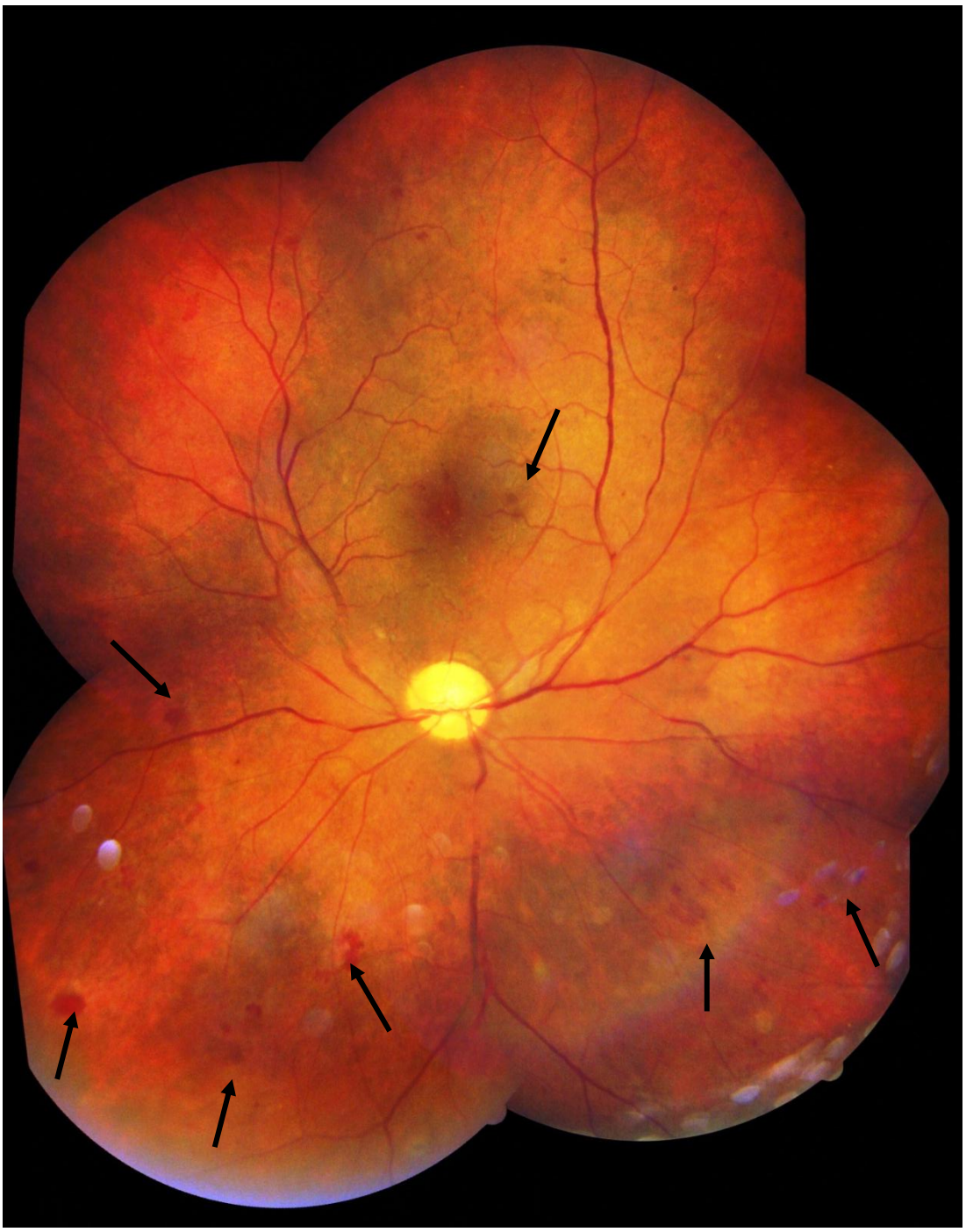
Signature of Investigator : _____

Date : _____

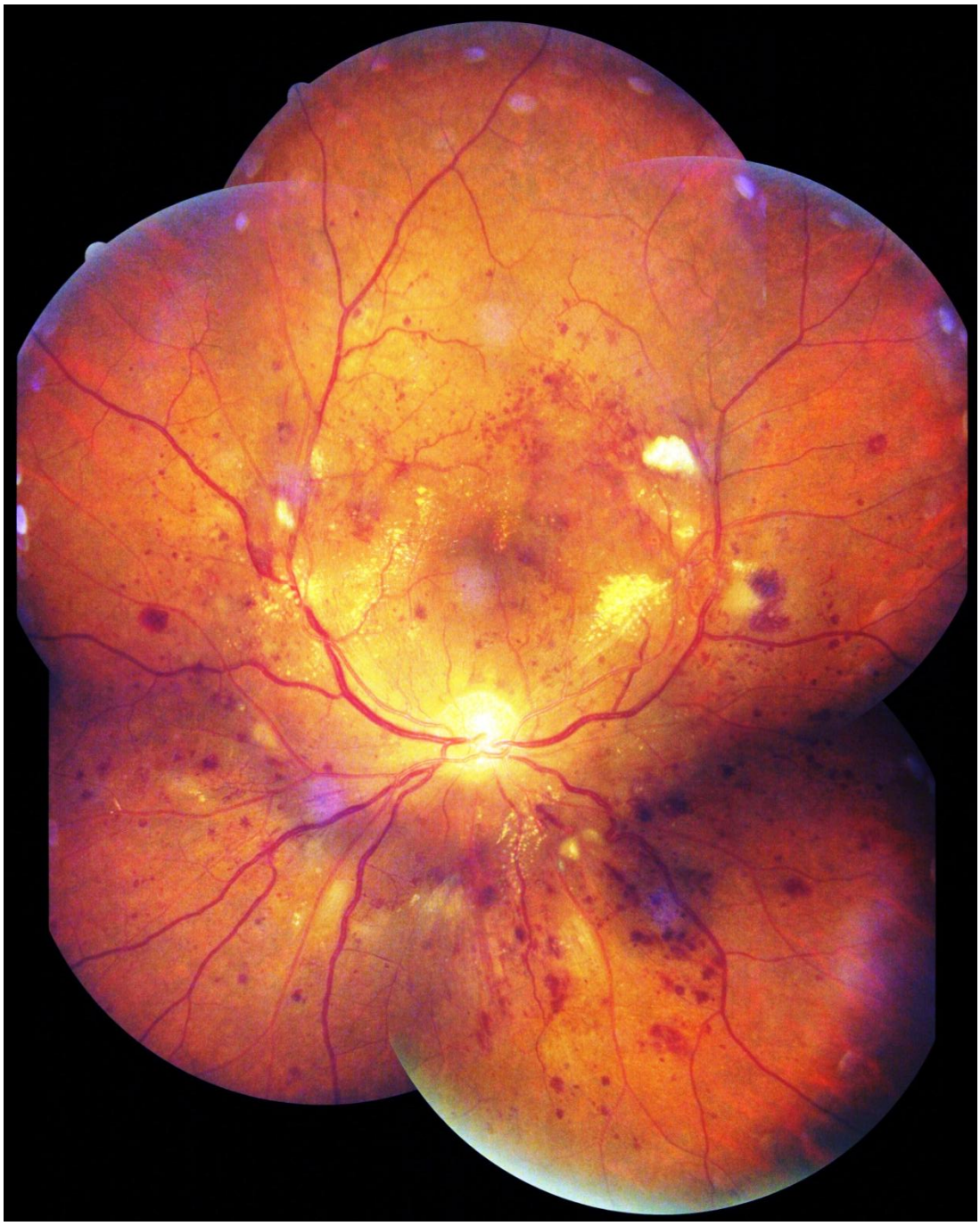
Place : _____



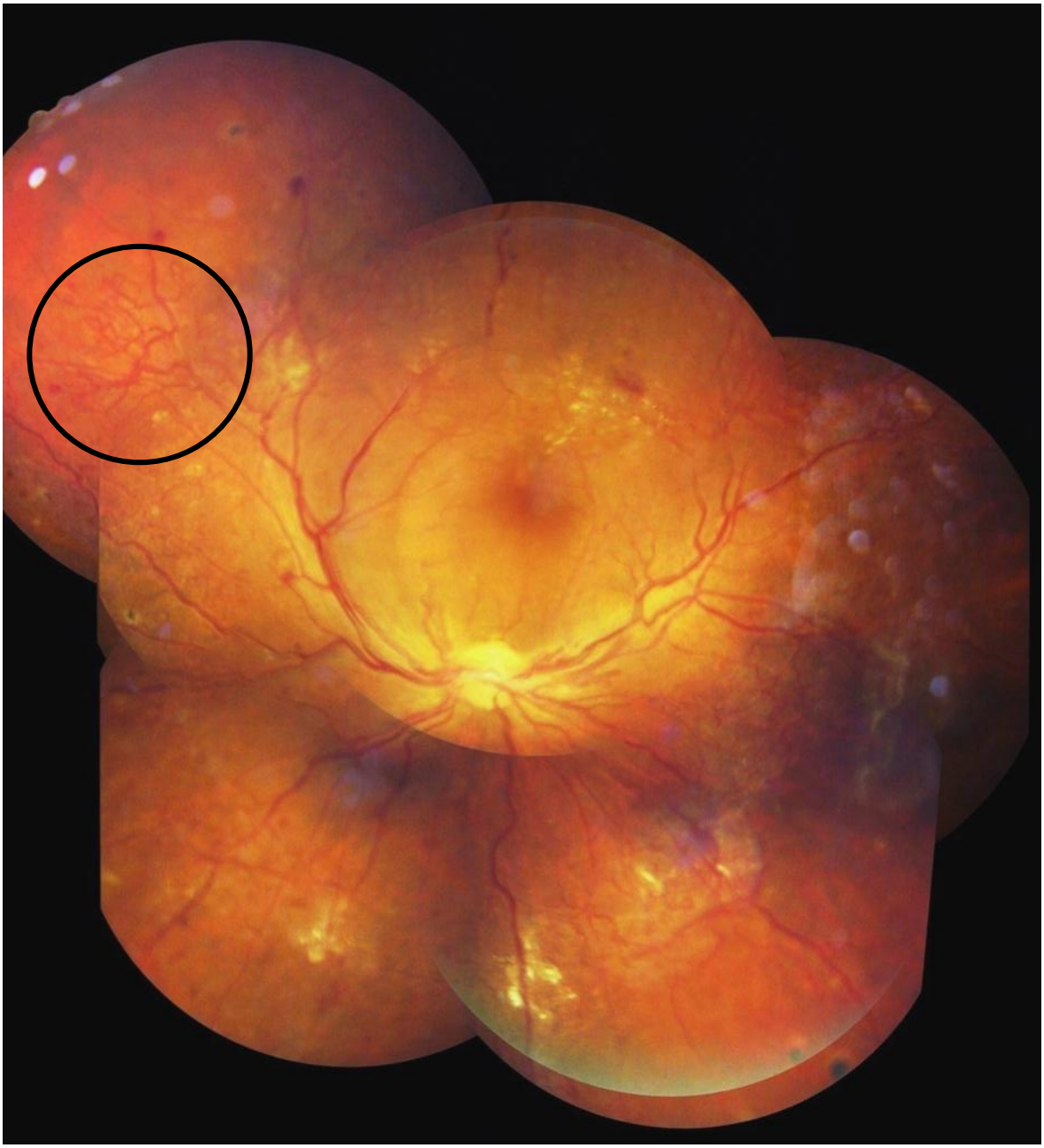
PHOTOGRAPH NO.1: MILD NPDR



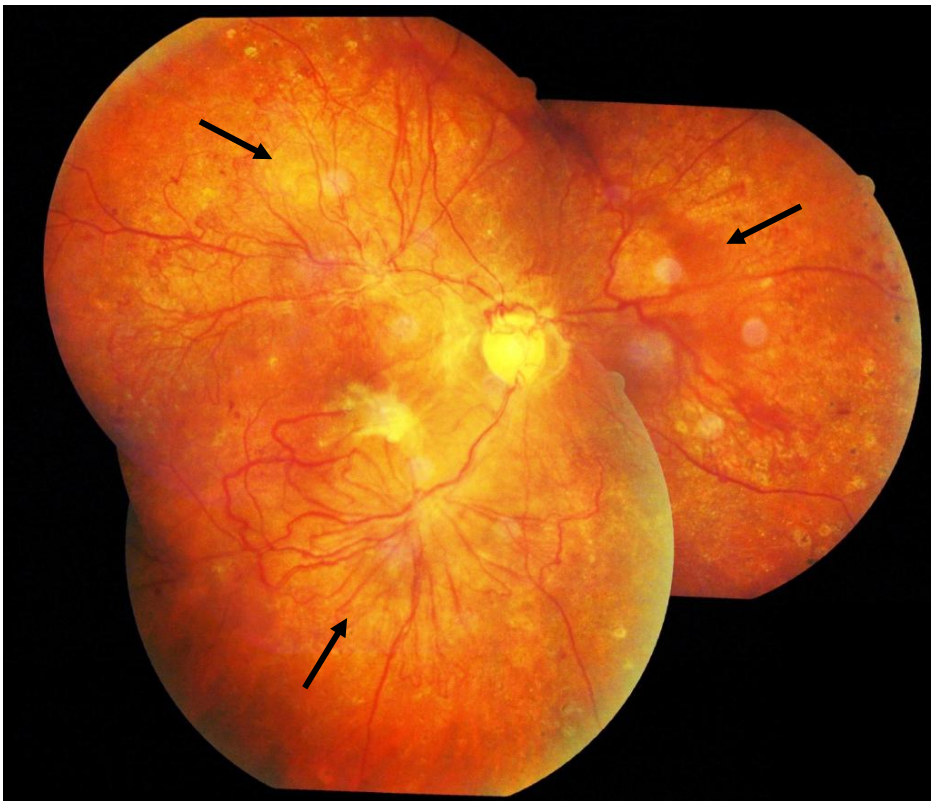
PHOTOGRAPH NO.2: MODERATE NPDR



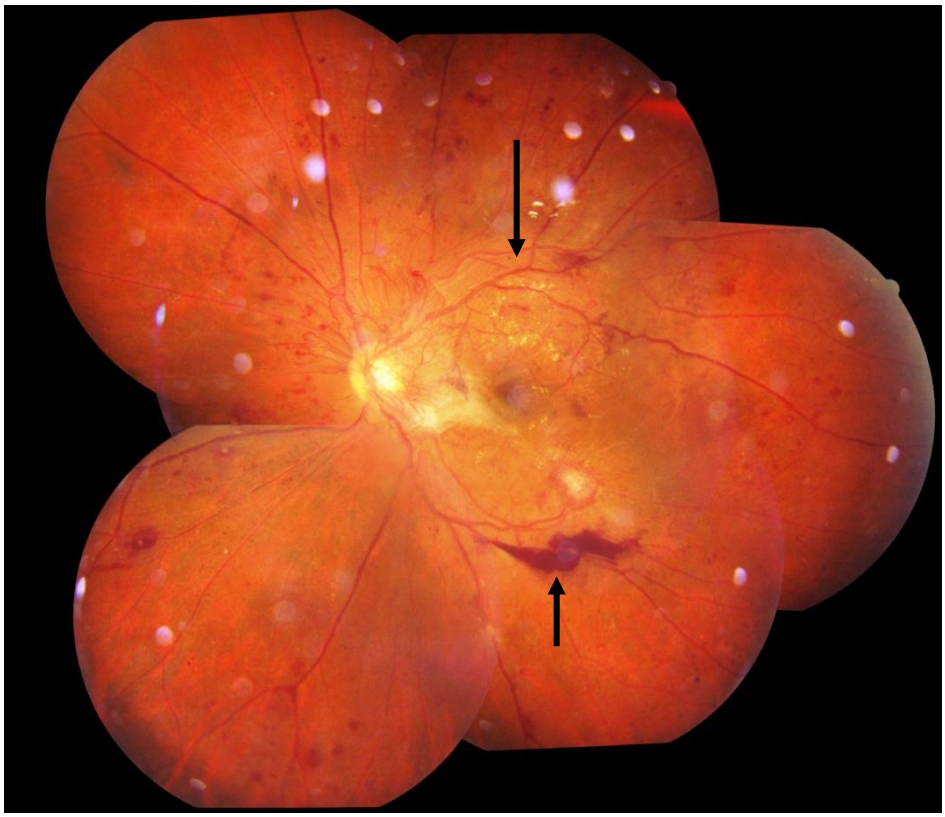
PHOTOGRAPH NO.3: SEVERE NPDR



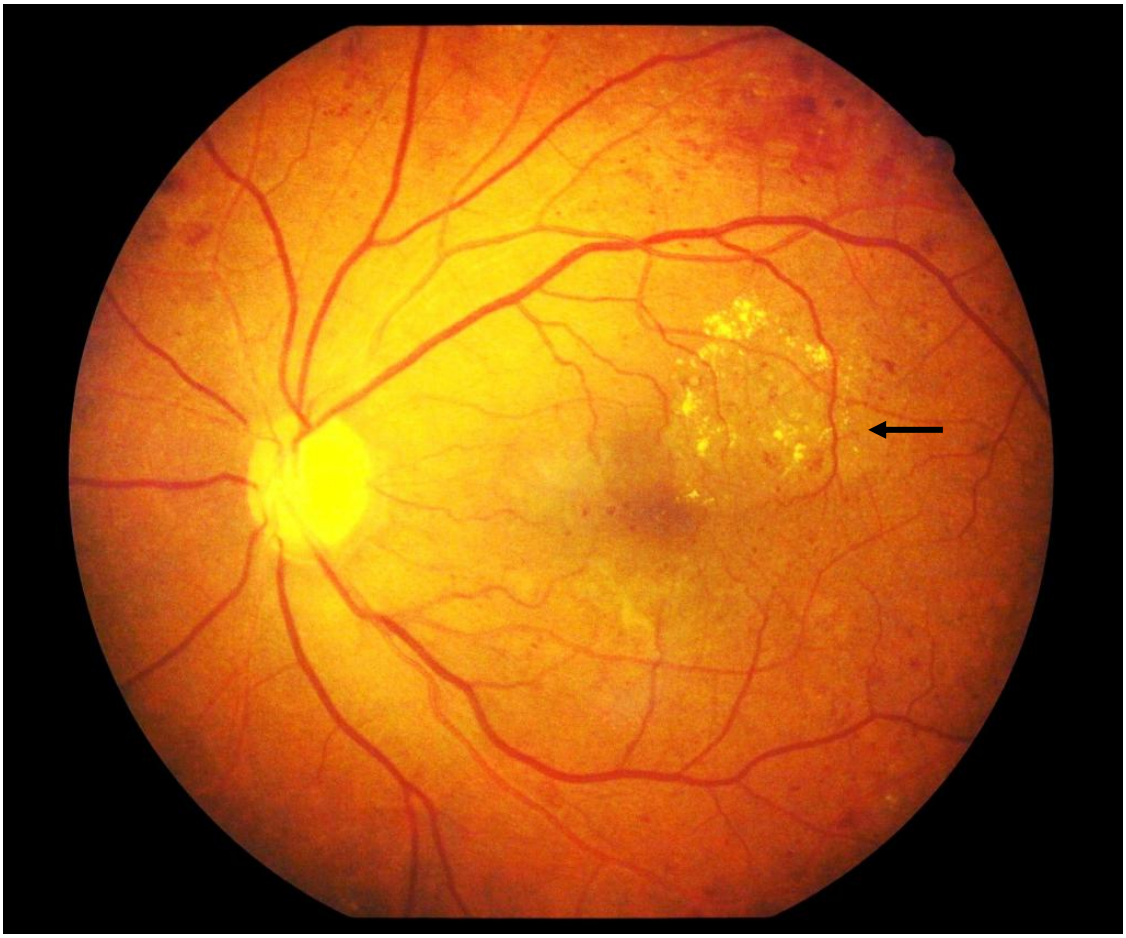
PHOTOGRAPH NO.4: EARLY PDR



PHOTOGRAPH NO. 5: HIGH RISK PDR (NVD).



PHOTOGRAPH NO. 6: HIGH RISK PDR (PRE-RETINAL HAEMORRHAGE).



PHOTOGRAPH NO. 7: CSME WITH CIRCINATE RETINOPATHY

PHOTOGRAPH NO. 8: CANON FUNDUS CAMERA USED FOR 7 FIELD PHOTOGRAPHY

ANNEXURE – IV: MATER CHART

Sl.No.	initials of patient	IP/OP no.	Sex	Age (years)	DM onset age (years)	DM duration (years)	Va RE	Va LE	Lifestyle	Smoking (years)	HbA1c (%)	FBS (mg/dl)	RE severity	LE severity	CSME	OHD single (years)	OHD multiple (years)	Insulin (years)
1	RA	1243168	M	51	40	11	L4	L4	A	N	10.3	153	Se	Se	N	R	N	N
2	RBT	347283	M	61	55	6	L4	L4	S	>15	7.8	132	M	M	LE	R	N	N
3	PSP	1160473	M	70	50	25	L6	L6	A	N	9.8	164	HRP	HRP	N	R	N	N
4	MBH	346612	M	49	49	R	L4	L4	A	N	7.4	128	M	M	N	R	N	N
5	PSM	353323	M	59	44	15	L4	L4	A	<15	8.1	182	Mo	Mo	N	<5	<10	N
6	RHB	1262223	F	62	40	22	L4	L4	S	N	9.7	173	Se	Se	N	<5	<10	>1
7	APK	1271131	F	57	40	17	L6	L6	S	N	9.2	186	HRP	HRP	N	<5	<15	N
8	SDA	1247760	F	52	48	3	L8	L8	S	N	12.1	184	HRP	HRP	BE	N	R	N
9	RHB	1274236	M	52	44	8	L4	L4	A	N	6.9	182	Se	Se	N	R	N	N
10	VAJ	1275909	M	56	41	15	L6	L6	A	N	8.4	210	Se	Se	N	N	R	>1
11	JBH	1276116	F	61	40	21	L8	L8	S	N	7	146	HRP	HRP	N	R	N	N
12	SSP	1299373	F	60	40	20	L6	L6	S	N	7.1	154	Mo	Mo	N	<10	<10	N
13	GNM	1265038	F	46	40	6	L4	L4	A	N	12.5	266	Mo	Mo	LE	<5	N	>1
14	SMSP	356644	M	68	47	21	L4	L4	A	N	11	159	Mo	Mo	N	R	N	>1
15	NSHS	1287322	M	70	54	16	L6	L6	S	N	7.2	128	Se	Se	N	R	N	N
16	BBK	1279010	F	59	44	15	L8	L8	S	N	7.6	125	Se	Se	N	<5	<10	N
17	TAR	1286106	M	54	47	7	L4	L4	A	N	6.7	128	P	P	N	<15	N	>1
18	MVM	1242069	M	59	49	10	L4	L4	A	<10	9.3	110	Mo	Mo	N	<10	N	<1

19	ACS	1239726	M	65	40	25	L4	L4	S	N	9.2	164	Se	Se	N	<5	N	>1
20	MDV	359605	M	73	56	17	L6	L6	A	N	6.9	124	Mo	Mo	N	N	<10	N
21	SCJ	1146527	M	70	56	14	L6	L6	A	N	7.9	256	P	P	N	<5	N	>1
22	UBD	361471	F	62	40	22	L4	L4	S	N	6.8	124	Mo	Mo	N	<5	<10	N
23	RKD	1307587	F	56	41	15	L6	L6	S	N	8.1	256	Se	Se	N	<5	<10	N
24	ECK	13072821	M	58	40	18	L6	L4	A	<15	9.5	241	Se	Se	N	<5	<15	N
25	VRK	1308940	F	59	42	17	L6	L6	A	N	8.2	164	Se	Se	N	<15	<10	N
26	SSK	1170772	M	65	45	20	L8	L8	A	N	10.1	184	Se	Se	BE	<15	N	N
27	MV	356477	M	65	42	23	L4	L4	A	N	8.4	138	Mo	Mo	N	<10	N	N
28	LVA	1337856	M	54	43	11	L4	L4	A	N	7.8	237	M	M	N	<10	<5	N
29	ISB	1291139	M	57	40	17	L6	L8	A	N	8.7	172	Se	Se	N	<10	N	N
30	SVK	1335214	M	54	54	R	L4	L4	S	N	8.5	127	M	M	N	<5	N	N
31	MBP	1337097	M	65	44	21	L6	L6	A	<15	7.6	134	M	M	N	<5	<10	>1
32	PSK	1332338	M	52	40	12	L4	L4	A	N	10.7	188	Se	Se	N	<5	<10	N
33	JDN	421135	F	55	48	7	L4	L4	S	N	8.3	164	Mo	Mo	N	<10	N	N
34	LSH	1319771	F	55	43	12	L4	L4	S	N	10.1	298	Mo	Mo	N	<10	<5	N
35	MDD	1327707	M	61	61	R	L6	L6	A	N	9.2	204	M	M	N	<5	N	>1
36	DSC	1320537	M	62	46	16	L4	L4	A	N	9.1	148	M	M	N	<5	<15	>1
37	VCB	1154014	F	52	48	4	L4	L4	S	N	8.7	268	Mo	Mo	N	<5	N	N
38	MFG	1317645	M	74	49	25	L4	L4	A	N	14.2	440	Se	Se	N	<5	<5	N
39	YMH	1269330	M	67	45	12	L6	L6	A	N	7.4	124	M	M	N	N	R	N
40	MPR	752175	M	49	49	R	L6	L6	A	N	11.7	149	Se	Se	N	<5	N	N
41	ABW	1348403	M	74	67	7	L6	L6	A	N	10.1	201	Se	Se	N	<5	N	N
42	GBP	1340931	M	52	40	12	L4	L4	A	N	9.9	132	Se	Se	N	<15	N	N

43	SBP	407043	M	64	46	18	L8	L8	A	N	10.9	353	Se	Se	N	<10	N	N
44	UV	1376113	M	67	44	23	L8	L6	A	N	9.2	164	P	P	RE	<10	<5	N
45	RGD	1406325	M	59	39	20	L4	L4	A	<15	10.6	182	Se	Se	N	<10	<10	>1
46	SDM	1510631	M	53	40	13	L8	L6	A	N	10.2	191	P	P	BE	<10	<5	N
47	FTF	604552	M	63	54	9	L4	L6	A	N	11.4	187	Se	Se	N	<5	N	N
48	SPD	384743	F	41	41	R	L4	L4	S	N	7.4	297	M	M	N	<5	N	N
49	LRG	1401532	F	44	34	10	L4	L4	S	N	10.7	164	Se	Se	N	<5	<10	>1
50	NSS	1322728	F	64	49	15	L6	L6	S	N	14.3	148	Se	Se	N	<5	<15	>1
51	KP	1380609	F	56	40	16	L8	L8	S	N	10.1	182	Se	Se	N	<5	<5	N
52	RBN	384582	M	61	42	19	L6	L6	A	N	9.7	173	Se	Se	N	<5	<5	N
53	MMP	1341739	M	63	46	17	L4	L4	A	N	9.6	184	Se	Se	N	<10	N	N
54	SYM	1379989	F	79	58	21	L8	L8	S	N	8.7	146	Se	Se	N	<5	N	N
55	KS	379404	M	58	43	15	L6	L6	S	N	11.3	184	Se	Se	N	<10	<10	N
56	VRM	1390854	M	43	43	R	L6	L6	A	N	8.9	142	Mo	Mo	N	<5	N	N
57	GAH	405810	F	51	45	6	L4	L4	S	N	7.8	142	M	M	N	<5	N	N
58	AMH	405811	M	59	47	12	L4	L4	A	N	8.6	172	Mo	Mo	N	<15	N	N
59	BN	380307	M	65	47	18	L4	L4	A	N	9.5	184	Mo	Mo	N	<10	N	N
60	SBB	1417214	M	72	49	23	L6	L6	A	N	11.8	216	Se	Se	BE	<10	N	N
61	RNS	1274819	M	67	53	14	L6	L6	S	N	7.8	148	Mo	Mo	N	<10	<10	N
62	GH	1557647	M	75	59	16	L4	L4	A	N	11.1	184	Se	Se	N	<10	<15	N
63	CN	1451513	M	55	43	12	L8	L8	A	N	8.9	142	P	P	BE	<5	<10	N
64	SB	1319628	M	67	49	18	L6	L6	A	N	10.2	182	Se	Se	N	<5	<10	N
65	PSK	1420610	M	68	68	R	L8	L6	S	N	9.4	164	Se	Se	RE	<5	N	N
66	BY	1319628	M	64	40	24	L6	L6	A	N	10.2	172	Se	Se	N	<10	N	N

67	NR	358556	M	77	55	22	L4	L4	A	<15	8.4	152	Mo	Mo	N	<5	N	N
68	RB	416256	M	59	40	19	L4	L4	A	N	9.2	184	P	P	N	<5	N	N
69	SDK	1558318	F	80	63	17	L6	L6	S	N	10.6	156	Se	Se	LE	<5	N	N
70	TL	1429115	M	62	47	15	L4	L4	S	N	10.7	186	Se	Se	N	<10	<10	N
71	VLH	1404634	M	59	42	17	L4	L6	A	N	11.2	284	P	P	N	<5	<5	>1
72	FT	392406	M	60	43	17	L4	L4	A	<10	9.9	157	Se	Se	N	<10	N	N
73	AN	964206	M	56	40	16	L4	L4	S	N	11.4	126	P	P	N	<10	<10	N
74	BNP	418361	M	67	45	21	L8	L6	S	N	8.9	148	P	P	N	<10	N	N
75	MGB	1069964	M	49	41	8	L4	L4	S	N	8.4	132	Mo	Mo	N	N	N	N
76	RSP	1565666	F	61	54	7	L4	L4	A	N	6.9	107	M	M	N	<5	N	N
77	GSP	389949	F	52	52	R	L6	L6	S	N	7.2	118	M	M	N	<5	N	N
78	CS	389974	M	77	59	18	L8	L8	A	N	9.9	171	Se	Se	BE	<10	N	N
79	GM	4754761	F	61	40	21	L4	L4	S	N	10.2	167	Se	Se	N	<10	R	>1
80	NB	1431608	F	60	40	20	L4	L8	S	<5	10.1	189	Se	Se	LE	<5	<15	N
81	VP	1452097	M	71	55	16	L4	L4	A	N	7.9	146	Mo	Mo	N	<5	N	N
82	VT	1600275	M	52	52	R	L4	L4	S	<10	8.3	148	Mo	Mo	N	<5	N	N
83	AP	1356508	M	71	54	17	L6	L8	S	N	8.1	128	Mo	Mo	N	<5	<15	N
84	BBM	1497681	M	66	40	26	L8	L8	A	N	8.2	178	P	P	N	<15	N	N
85	EDS	1468102	M	90	65	25	L4	L6	A	N	10.3	164	Se	Se	BE	<5	N	N
86	NB	1481396	F	61	40	21	L4	L4	S	N	9.4	162	Se	Se	N	<5	<10	N
87	STC	1476983	M	67	43	24	L4	L4	A	N	9.4	181	Se	Se	N	<5	<5	N
88	RBK	1471824	M	58	40	18	L4	L4	A	N	7.6	142	P	P	N	<10	<10	N
89	SYR	1455734	M	61	48	23	L4	L4	A	N	7.1	124	Se	Se	N	<5	N	>1
90	BRH	1257956	M	58	49	9	L4	L4	A	N	7.4	130	M	M	N	<10	N	N

91	TP	1492059	M	78	56	22	L4	L4	A	N	9.7	124	Se	Se	N	<5	N	N
92	MB	1301927	M	63	41	22	L4	L4	S	N	9.9	184	Se	Se	BE	<5	<5	<1
93	SP	1472922	F	68	44	24	L4	L4	S	N	9.2	148	P	P	N	<5	N	N
94	HC	1305906	F	67	50	17	L6	L4	S	N	11.3	184	Se	Se	LE	<10	<10	>1
95	LGK	1468658	F	78	57	21	L4	L4	S	N	9.8	162	Se	Se	N	<10	N	N
96	SBS	720462	M	70	48	22	L6	L6	S	N	11.1	191	Se	Se	N	N	N	N
97	VSM	401875	M	71	50	21	L6	L6	S	N	8.4	136	P	P	BE	<10	<10	N
98	BK	665945	M	49	41	8	L4	L4	S	N	8.4	132	Mo	Mo	N	N	N	N
99	NRP	1319628	M	68	49	19	L6	L6	A	N	10.2	182	Se	Se	N	<5	<10	N
100	RBH	752175	M	67	49	18	L6	L6	A	N	11.7	149	Se	Se	N	<5	N	N

KEY TO MASTER CHART

<10 = 6 to 10 years duration.

<15 = 11 to 15 years duration.

<5 = less than and equal to 5 years duration.

>15 = more than 15 years duration.

A= active life style.

BE = both eye.

F=female

HRP = high risk PDR.

IP=In-patient

L4= < 6/18 visual acuity.

L4= < 6/36 visual acuity.

L6= 6/18 to 6/36 visual acuity.

LE = left eye.

M=male

Mi = mild NPDR.

Mo = moderate NPDR.

N = no / nil.

OP=Out-patient

P = Early PDR.

R = recent.

RE = right eye.

Se = severe NPDR.

S= sedentary life style.