"A ONE YEAR CROSS SECTIONAL STUDY TO DETERMINE THE RELATIONSHIP BETWEEN SERUM LIPID PROFILE AND DIABETIC RETINOPATHY"

By

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Under the Guidance of

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“ Arise ! Awake ! And stop not till the goal is reached”

- Swami Vivekananda.

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Dr. K.RAMA KRISHNA

LIST OF ABBREVIATIONS

AGE	Advanced glycation end products
BDR	Background Diabetic Retinopathy
CRA	Central retinal artery
CSME	Clinically Significant Macular Edema
DAG	Diacylglycerol
DR	Diabetic retinopathy
DM	Diabetes Mellitus
ETDRS	Early Treatment of Diabetic Retinopathy Study
FBS	Fasting blood sugar
FFA	Fundus Fluorescein Angiography
GFAT	Fructose-6-phosphate amidotransferase
HBA_{1C}	Glycosylated hemoglobin
HDL	High density lipoproteins
HS	Highly significant
IDDM	Insulin dependant diabetes mellitus
IGF	Insulin like growth factor
IRMA	Intra Retinal Microvascular Abnormalities
LDL	Low density lipoproteins

mg/dl	milligrams per deciliter
mm Hg	millimeters of mercury
NIDDM	Non Insulin dependant diabetes mellitus
NS	Not Significant
NV	Neovascularization
NVD	Neovascularization at disc
PDR	Proliferative Diabetic Retinopathy
PKC	Protein Kinase C
PPBS	Post prandial blood sugar
PPDR	Pre Proliferative Diabetic Retinopathy
S	Significant
VEGF	Vascular Endothelial Growth Factor
VS	Very Significant
WHO	World Health Organization
$\chi 2$	Chi Square Test Value
Lp (a)	Lipoprotein A

ABSTRACT

INTRODUCTION

Diabetic retinopathy remains the number one cause of new blindness in developed countries. The trend is catching up in developing countries such as ours where this clinical entity is fast gaining importance as a disease of major public health importance. Dyslipidemia in diabetes patients may act as predisposing risk factor, an aggravating or complicating risk factor. Its clear role in microvascular complications however is yet to be understood.

An understanding of the relationship between various grades of diabetic retinopathy with the lipid profile will be helpful in stratification and tailoring of anti diabetic and lipid lowering treatment for diabetic retinopathy.

OBJECTIVE OF THE STUDY:

To determine the relationship of serum lipid profile and glycemic control with the fundus changes in patients with type II diabetes mellitus and also to correlate the severity of diabetic retinopathy with duration of diabetes.

METHODOLOGY

It was a one year cross sectional study which included 100 patients of diabetic retinopathy whose retinopathy was classified into different grades based on Kanski's classification.

After taking informed consent all patients were examined according to a pre designed proforma. Relevant history was taken and general physical examination was performed followed by a complete ophthalmic examination. A detailed fundus evaluation was performed using a direct, indirect ophthalmoscopy along with slitlamp biomicroscopy with +90D lens.

Patients with ocular media haze, other degenerative lesions of the fundus, uncontrolled hypertension, pregnancy, coronary heart disease, hepatic diseases and on lipid lowering drugs were excluded from the study.

Investigations performed in these patients were fasting blood sugar levels, Glycosylated hemoglobin (HbA_{1C}) levels to determine the glycaemic control and estimation of serum Lipid profile. (Total cholesterol, LDL, HDL, Triglycerides & LDL/HDL Ratio)

OBSERVATIONS AND RESULTS

Progression of retinopathy was more with raised total cholesterol and decreased HDL-cholesterol levels. There was a significant increase of LDL / HDL ratio and serum triglycerides with increasing severity of retinopathy.

Patients with longer duration of diabetes had more severe grades of diabetic retinopathy and poor glycemic control led to the worsening of the retinopathy.

CONCLUSION

The raised Total cholesterol, LDL, Triglycerides and lower HDL cholesterol levels were clearly associated with progression of severity of diabetic retinopathy. The results in our study indicate the hope of pharmacological intervention to reduce the lipid levels in patients of diabetic retinopathy with raised total cholesterol levels inorder to retard its progression.

Key words: Total cholesterol, HDL, LDL-Cholesterol, FBS, HbA_{1C}, Diabetic Retinopathy.

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INTRODUCTION

The human eye is a highly specialized sensory organ. The eye is an externalized portion of the brain.[1]When light falls upon the retina it acts as a stimulus to rods and cones which serve as the sensory nerve endings.[2]It serves the purpose of photoreception , the process by which the light energy from the environment produces changes in specialized nerve cells of retina- rods and cones.

These changes result in nerve action potential which via the optic nerve reaches the brain where the information is processed and consciously perceived as vision.[3]

Few diseases have the potential to widely and profoundly affect the entire visual apparatus like that of diabetes mellitus.

Successful management of diabetic retinopathy via a combination of glucose control, laser therapy and vitrectomy represents one of the most striking achievements of modern ophthalmology.

Despite this, diabetic retinopathy remains the number one cause of new blindness in developed countries.[4]The trend is catching up in developing countries such as ours where this clinical entity is fast gaining importance as a disease of major public health importance. The prevalence of diabetic retinopathy was found to be 1.78% in a population based study in south India and is supposed to become a significant cause of blindness during the coming decade.[5]

In spite of extensive research, the final metabolic pathway that causes diabetic retinopathy is still unknown. However there are several theories to explain the pathogenesis, one of the main mechanisms involved in the pathogenesis of diabetic

retinopathy is microvascular occlusion.[6] Alteration in the biochemical & physiological environment in the vessel wall may lead to the above state.

Though the pathogenesis of diabetic retinopathy is not fully understood the established risk factors are duration of diabetes, poor metabolic control, hypertension, nephropathy and other risk factors like smoking and obesity[7].

Further identification of risk factors and determinants for retinopathy is important to improve the understanding of disease mechanisms and to provide new treatment and preventive strategies[8].

Dyslipidaemia in diabetes patients may act as predisposing risk factor, an aggravating or a complicating risk factor. Its clear role in microvascular complications however is yet to be understood[9].

An understanding of the relationship between various grades of diabetic retinopathy with the lipid profile will be helpful in stratification and tailoring of anti diabetic and lipid lowering treatment for diabetic retinopathy to retard its progression[10].

AIMS & OBJECTIVES

1. To determine the relationship of serum lipid profile with the fundus changes in patients with type II diabetes mellitus.
2. To correlate the severity of diabetic retinopathy with duration of diabetes.
3. To correlate the severity of diabetic retinopathy with glycemic control.

REVIEW OF LITERATURE

Diabetes mellitus (DM) comprises a group of common metabolic disorders that share the phenotype of hyperglycemia. Various types of DM exist and are caused by a complex interaction of genetic, environmental factors and life style choices. 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 caresystem.[11]

Diabetes mellitus has emerged as a major public health problem in India. The first authentic data on the prevalence of diabetes in India came from the multi-centric study conducted by Indian council of medical research (ICMR) in the early seventies. This study reported a prevalence of 2.3% in the urban and 1.5% in rural areas.[12]

Work done by other researchers more recently using the WHO criteria showed a prevalence of 5% in urban township in south India .[13,14] All the studies clearly point to a rising prevalence of NIDDM in India, which is probably related to improving living conditions and changing lifestyles in urbanized regions. In the year 2000, there were 300 million people with diabetes mellitus in India .[15] By the year 2024 more than two-thirds of people with diabetes will be in the developing world of which a majority would be residing in India and China.[15] The age of onset of type-2 diabetes in Indo- Asians is a decade earlier than their western counterparts. It affects individuals in the most productive period of their life.[15]

In two studies from south India, the prevalence rates of diabetic retinopathy in NIDDM patients were 34.1% and 37%.[16 & 17] India has 31.7 million diabetic subjects at present as per World Health Organization estimates. [18]

Classification of diabetes mellitus[19]

1) Diabetes Mellitus:

- Insulin dependent diabetes mellitus (type 1).
- Non-Insulin dependent diabetes mellitus (type2).
- Malnutrition related diabetes mellitus.
- Other types, associated with certain conditions and syndromes:

Pancreatic disease, disease of hormonal etiology, drug or chemical induced conditions, abnormalities of insulin or its receptors, certain genetic syndromes and other miscellaneous conditions.

2) Impaired glucose tolerance:

Obese, non obese or associated with certain conditions and syndromes.

3) Gestational diabetes mellitus

Diabetic retinopathy

Diabetic retinopathy is one of the most common microvascular complications of diabetes causing severe morbidity. It is the number one cause of new blindness in developed countries.[4]

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.[20]

In an epidemiological study done at Chennai, the over all 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.[21] In a clinic based study the overall prevalence of diabetic retinopathy was 33.4% in type 2 diabetic patients.[21]

Clinical features of diabetic retinopathy

The exact pathophysiological events in this clinical entity is still to be elucidated and the clinical presentation is quite variable. Various systems of classification were developed to help us study the natural course of disease and assist us in taking decisions regarding treatment for the patient.

Some of the important ones are Duke-Elder's classification[22], Kanski's classification[6], Airlee-House classification and modified Airlee-House classification or modern ETDRS classification[23]. In this study Kanski classification was followed.

Kanski's classification

A) Background Diabetic Retinopathy (BDR)

B) Pre Proliferative Diabetic Retinopathy (PPDR)

C) Proliferative Diabetic Retinopathy (PDR)

A) Background diabetic retinopathy

This stage is equivalent to the stage of mild non proliferative diabetic retinopathy (according to the Modified Airlee-House Classification) and is recognized

by the following features. Microaneurysms are among the earliest ophthalmoscopically detectable lesions, seen commonly in the posterior pole. These are round when young and irregular in shape when old. They represent distension of the venous end of the capillaries due to loss of pericytes. They are surrounded by capillary loss and may be occluded or ruptured. Ruptured microaneurysms are difficult to distinguish from dot hemorrhages. They leak fluorescein and have a life span of a few months to many years. Hard exudates are waxy yellow material with relatively indistinct borders seen in the outer plexiform and inner nuclear layers. They result from abnormal vascular leakage with breakdown lipid products from degenerating neural retinal elements. They may be discrete, confluent or may form a circinate pattern around a cluster of leaking microaneurysms or microvascular abnormalities. If present in the foveal region, they may impair vision.

Retinal hemorrhages may either show a “dot and blot” configuration when they arise from the outer capillary network in the outer plexiform and inner nuclear layers or may be flame shaped when arising from the inner capillary network in the nerve fiber layer. Retinal oedema is located in the outer plexiform and inner nuclear layers and is seen on slit lamp biomicroscopic examination with a fundus contact lens or a + 78 D lens as a thickening and whitening of the retina in which the normal retinal capillary network is indistinct and the underlying RPE and choroidal vessels are obscured. It is often possible to identify one or more microaneurysms within the area of macular oedema, which are the probable sources of leakage of fluid in this area. The oedema may be focal or diffuse and may impair vision if the fovea is involved.

B) Pre - proliferative diabetic retinopathy

With time, background diabetic retinopathy progresses with an increase in the number of microaneurysms and hemorrhages and the occurrence of soft exudates as a consequence of retinal hypoxia. Pre proliferative diabetic retinopathy may have different grades of severity, which range from moderate to severe non proliferative diabetic retinopathy (as per the ETDRS grading system).

Vascular changes are marked, showing venous dilatation, tortuosity, looping, coiling, beading and "sausage like" segmentation with capillary drop- out and subsequent neovascularization. Dark blot hemorrhages represent retinal infarcts and are located in the outer layers of the retina. Soft exudates are located in the nerve fiber layer and represent infarcts with derangement of axoplasmic flow in the neurons. They are white and opaque in appearance and can appear in the absence of hypertension. Intra- retinal microvascular abnormalities (IRMA) are seen adjacent to areas of capillary non- perfusion and can be distinguished from new vessels by their intra- retinal location, failure to cross over major vessels and absence of leakage of fluorescein.

Fluorescein Angiography may

1. Show more microaneurysms compared to ophthalmoscopy.
2. Delineate intra- retinal microvascular abnormalities.
3. Document leakage from these lesions
4. Document the extent and severity of the capillary closure.
5. Help to rule out neovascularization.

These changes represent "Non- Proliferative diabetic retinopathy" and are confined to the retinal layers. These lesions may remain stationary, regress without sequelae or progress to proliferative diabetic retinopathy. Once proliferative changes set in, the internal limiting membrane is broken and the vitreous participates in the process.

C) Proliferative diabetic retinopathy

The retinal hypoxia seen in the preproliferative stage may increase further, resulting in the progression to the proliferative stage of diabetic retinopathy. This is characterized by areas of neovascularization at the disc or elsewhere. In neovascularization, the hypoxic retina provides stimulus for release of angiogenic factors, which result in the formation of new vessels. Activated macrophages in the tissues, probably derived from a circulating pool of cells and from a resident microglial population provide a rich source of growth factors and other molecules such as matrix modifying enzymes which ultimately lead to an angiogenic response in surrounding healthy endothelial cells[24].

An inhibitor of angiogenesis has been identified in the vitreous and the balance between these substances may affect the development of ocular neovascularization in diabetics[25]. These new vessels probably arise from IRMA (preneovascular stage) and may be located at the disc (NVD) or along the vascular arcades of the retina at the junction of the perfused and non-perfused retina. They may lie flat after disrupting the internal limiting membrane or proliferate along the detached posterior hyaloid. These new vessels leak fluorescein from the periphery to the center and are asymptomatic until they bleed. A rise in the venous pressure or

posterior vitreous detachment can precipitate a bleed. Unabated proliferative retinopathy can manifest dangerous sequelae such as vitreous hemorrhage, fibrovascular proliferations and tractional retinal detachment.

D) <u>End stage diabetic eye disease (Involutiona1 PDR):</u>

Fibrous proliferation and tractional retinal detachment tend to stagnate or progress very slowly and seldom regress. Thrombotic glaucoma, inoperable detachment of the retina and complicated cataract may result from untreated or unsuccessfully treated severe proliferative diabetic retinopathy. Finally, extensive and severe vitreoretinal derangement supervenes with gross structural and functional damage.

Diabetic Maculopathy is defined as the involvement of the macula by hard exudates and / or oedema within one disc diameter (1500µ) from the center of the fovea.

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

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

Macular oedema of severity, which is less than that defined by these parameters is not regarded as clinically significant macular oedema. Diabetic maculopathy is the most common cause of visual loss in non- proliferative diabetic

retinopathy[4,6,26].

The various forms of diabetic maculopathy[6] based on FFA include:

1. Focal exudative maculopathy: There is focal leakage with hard exudates, sparing the foveal center, and the prognosis is good.
2. Diffuse exudative maculopathy: There is diffuse macular oedema and the prognosis is often poor.
3. Ischemic maculopathy: There are extensive areas of macular non-perfusion, soft exudates and large deep retinal hemorrhages with retinal thickening seen on ophthalmoscopy. There is reduced visual acuity with a relatively normal appearance of the fovea.
4. Mixed maculopathy: characterized by features of both ischaemia and exudation.

Kanski's classification

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[23]:

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: NVD/NVE Pre-retinal or Vitreous Hemorrhage, Fibrous tissue proliferation.	E. Early PDR	1. New vessels present but definition not met for F
	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

The other established risk factors for development of diabetic retinopathy are: [6]

1) Poor metabolic control is said to correlate with more severe forms of retinopathy.
2) Pregnancy is occasionally associated with rapid progression of diabetic retinopathy.
3) Hypertension if poorly controlled is associated with worsening of DR.
4) Nephropathy if severe is associated with worsening of DR.
5) Other risk factors include smoking, obesity, hyperlipidemia.
6) Ocular factors: glaucoma and myopia are associated with a less severe form of

diabetic retinopathy.

Pathogenesis

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

a. Microvascular occlusion
b. Microvascular leakage[6]

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

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: Is associated with significant capillary occlusion (Dropout), which runs from arterioles to venules. As it is unclear whether or not these lesions represent new vessels, they are often referred to as 'intraretinal microvascular 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.

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.

Microaneurysms are the saccular pouches, which may form as a result of local capillary distension. 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

Chronic localized retinal oedema leads to the deposition of hard exudates at the junction of healthy and edematous retina. The exudates, which are composed of lipoprotein and lipid filled macrophages, typically surround leaking microvascular

lesions forming a circinate pattern. In some eyes they absorb spontaneously over a period of months or years, either into the healthy surrounding capillaries or by phagocytosis of their lipid content. In other cases, more chronic extravasation leads to enlargement of the exudates and deposition of cholesterol.

Concepts in the pathogenesis: Past and Present

With the current focus in any disease today on primary prevention/secondary prevention, there has been a lot of work done to exactly understand the pathogenic mechanism of the disease. There is no doubt as to the pathology in the vessels which is microvascular occlusion, microvascular leakage, [27] the question is regarding the causative mechanism of the above. This is not only due to retinal vascular abnormalities, but also probably due to the effects of systemic metabolic abnormalities that accompany diabetes mellitus.

The first evidence[28] of retinal vascular closure in Diabetic retinopathy was reported in 1950. Earliest detectable vessel closure in diabetic retinopathy occurs at the level of the retinal capillary bed. Fluorescein angiograms show that microaneurysms tend to cluster around small areas of capillary non-perfusion, suggesting that microaneurysms formation may be a response to focal capillary closure. It is likely that the capillary dilatation is a physiological response to focal retinal hypoxia caused by the closure of adjacent capillaries[1] However, in later stages of the disease, larger arterioles also become occluded and intensive areas of non perfusion develop.[27]

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

- Intra luminal
- Intra mural
- Extra mural

Possible intra luminal factors include abnormalities of the blood elements [29] and which could promote thrombosis within the small retinal vessels. These factors [24] are:

- 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 [27].

Possible intramural factors include abnormalities of endothelium and basement membrane of retinal vessels[1]. 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.[27]

The extramural factor that has been proposed for capillary closure is compression of the capillary wall by interstitial fluid swelling of the retina.[27]

Microvascular leakage occurs due to the breakdown of the inner blood retinal barrier leading to the leakage of plasma constituents into the retina[6]. One of the main aspects of this process is the formation of microaneurysms. They may be formed as a result of endothelial proliferation or due to weaknesses in the capillary walls due to

the loss of pericytes[30].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. Biochemical factors

Multiple biochemical pathways have been proposed to explain the pathogenesis of diabetic retinopathy all starting initially from hyperglycemia. These mainly include [21]

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

1. <u>Increased polyol pathway</u>

The polyol pathway consists of two steps, the reduction of glucose to sorbitol by aldose reductase and NADPH, followed by oxidation of sorbitol to fructose by sorbitol dehydrogenase and NAD+. In tissues such as nerve, lens, retina and kidney, which do not require insulin for the intracellular transport of glucose, aldose reductase activity has been shown to be increased in a hyperglycemic environment[21] with concomitant sorbitol accumulation in tissues. The potential detrimental effects of this

include sorbitol-induced osmotic stress, decreased Na+/K+ ATPase activity, an increase in cytosolic NADH/NAD+ and a decrease in cytosolic NADPH, as well as activation of PKC, decreased glutathione and depletion of other antioxidant defenses. These metabolic changes culminate in tissue damage and defined structural changes in the retinal vasculature[18].

The contribution of polyol pathway to diabetic complications may be very much species, site and tissue-dependent[21]. Although animal data convincingly shows that aldose reductase plays an early role in the pathogenesis of diabetic retinopathy, studies of inhibition of the polyol pathway in vivo have yielded inconsistent results. The long-term Sorbinil Trial[21] 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.

However, the positive effect of aldose reductase inhibition on diabetic neuropathy with zenarestat[18] provides vested hopes in the use of these compounds in diabetic retinopathy[21]which needs to be tested and validated by future studies.

2. <u>Increased AGE formation</u>

Increased formation of advanced glycation end products (AGE's) correlate with poor glycemic control and these reactive adducts form on DNA, lipids and proteins representing pathophysiological modifications that precipitate dysfunction at a cellular and molecular level. 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[21]. AGEs can arise from intracellular auto oxidation of glucose to glyoxal, decomposition of the Amadori product (glucose-derived 1-amino-1-deoxyfructose lysine) to 3-deoxyglucosone and fragmentation of glyceraldehyde-3-phosphate and dihydroxyacetone phosphate to methylglyoxal. These reactive intracellular dicarbonyl's (glyoxal, methylglyoxal and 3-deoxyglucosone) react with amino groups of intracellular and extracellular proteins to form AGEs (pyrraline, pentosidine, crossline, etc).

The potential importance of AGEs in the pathogenesis of diabetic complications is indicated by the observation in animal models that two structurally unrelated AGE inhibitors partially prevented various functional and structural manifestations of diabetic microvascular disease in retina, kidney and nerve.[21] As more therapeutic agents are developed to inhibit AGE formation or limit their pathogenic influence during chronic diabetes, it is becoming clear that these anti-AGE strategies have an important role to play in the treatment of diabetic complications with special reference to retinopathy.

3. <u>Hexosamine pathway</u>

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.[21] During normal physiology, only about 3% glucose is channeled into the hexosamine pathway.Fructose-6-phosphate amidotransferase (GFAT) catalyses the conversion of fructose-6-phosphate to glucoseamine-6-phosphate. The latter is rapidly metabolized

to UDP-N-acetyl-glucosamine and is, along with other hexosamines, used as essential substrates for the synthesis of glycoprotein's, proteoglycans, gangliosides and glycolipids.

During hyperglycemia, increased glucose flux follows hexosamine pathway and results in raised glucosamines that may cause insulin resistance in skeletal muscle and adipocytes. However, 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[21]. This report emphasizes that hexosamine pathway may be involved in retinal neurodegeneration in diabetes.

4. Increased PKC activation

The protein kinase C (PKC) family is a large group of structurally related enzymes that are involved in multiple cellular functions, they are also referred to as 'microchips' in the cell signaling machinery[21]. It appears that increased de novo DAG synthesis arises from the altered glycolysis that occurs in diabetes. Increased formation of a-glycerol-3-phosphate serves as a readily available precursor of DAG that stimulates PKC. Hyperglycemia may also activate PKC isoforms indirectly through both ligation of AGE receptors and increased activity of the polyol pathway. Activation of PKC-b isoforms has been shown to mediate retinal and renal blood flow abnormalities in experimental diabetes[18] and this led to the development of specific inhibitors of PKC-b isoforms.

An investigational compound known as LY333531, a protein kinase C-b inhibitor is presently in Phase III clinical trials for severe preproliferative diabetic retinopathy and for diabetic macular edema. In experimental diabetes, these inhibitors prevented the slowing of retinal blood flow, induced regression of retinal neovascularization that is produced by laser-induced major branch vein occlusions[21] and inhibited vascular leakage induced by VEGF.[21] Preclinical and initial clinical studies evaluating LY333531 are thus far promising, as it did ameliorate diabetes-associated abnormalities in retinal vascular function. Patient identification for PKC-b inhibitor therapy, cost effectiveness and toxicity if any, are some of the issues that await results of the currently undergoing clinical trials.

B. Endocrine factors

It was found that retinopathy in patients with diabetes regresses after infarction of the pituitary gland. [31] 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[32]. 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[33] and vitreous.[34] 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.[35]

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.[36] 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, which through a series of events may lead to the formation of micro thrombi and other pathological changes in the retinal vasculature.

Further more in the involvement of haemodynamic and biochemical factors in the causation of diabetic retinopathy is the change in the concept of the clinical entity called diabetes, with some authors calling it a disease of immune system, and the complications are as a result low grade sub clinical inflammation that happens at the level of the capillary endothelium.[37]

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. [38]

There is an indirect relationship between the glycemic control and the

development and progression of DR. 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 was associated with a significant decrease in the progression of DR as well as the incidence of PDR. [39] Intensive diabetic control leads to reduction in the development and progression of all diabetic complications. [40]

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. [41]

There is a direct correlation between the frequency and severity of DR and the duration of DM. [42] A steady increase in the prevalence of retinopathy with increasing duration of diabetes & the prevalence of retinopathy was 52.2%, in patients with diabetes of >15yrs duration. [43]

In patients with having HbA_{1c} levels <8%, the retinopathy was seen only in 0.04% patients and in patients with HbA_{1c} levels more than 10%, the prevalence of retinopathy was 36.4%.[43]

Lipid profile & Diabetic retinopathy

Mechanisms of Retinal Damage Due to Hyperlipidemia

The proposed mechanisms by which elevated levels of lipids can cause or exacerbate diabetic retinopathy in patients with DM are as follows:

i) Elevation of blood viscosity and alterations in the fibrinolytic system. [44]

ii) Incorporation of TG in the cellular membrane, which may change membrane fluidity[45] and cause leakage in the retina resulting in edema and hemorrhage.

iii) Accumulation of basal linear deposits in the Bruch's membrane due to high serum levels of total cholesterol (TC). [46]

iv) Damage to endothelial cells and pericytes by an oxidized form of LDL-C, as shown in the bovine model. [47]

v) High serum levels of Lp (a), resulting in a procoagulant state that may be related to diabetic retinopathy, similar to that seen in other procoagulant states. [48,49] Elevated serum levels of Lp(a) interacting synergistically with other lipid and non-lipid factors to increase atherosclerosis-related damage and may also contribute to microvascular damage. [50-52]

Role of serum lipids

Nearly 30% of patients with DM have a dyslipidemic profile consisting of high serum levels of triglycerides (TG) and small-dense low density lipoprotein-cholesterol (LDL-C), and low serum levels of high density lipoprotein-cholesterol (HDL-C). Such a dyslipidemic profile and/or high serum levels of LDL-C play a significant role in the acceleration of atherosclerosis in patients with DM. [53]

Serum levels of TC and TG were positively associated with any grade of DR in nine and eight studies, respectively, while no association was shown in three studies each. Serum LDL-C levels showed good association with DR in five studies, while no association was reported in one study. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy, serum TC levels were a significant factor in describing the severity of hard exudates but not retinopathy. [54]

In a large cross-sectional study, Sjolie et al. [55]reported that serum levels of TG were a significant risk factor for the development of moderately severe proliferative and non-proliferative retinopathy after adjustment for age, duration of DM, blood glycosylated hemoglobin (HbA_{1c}) levels . Increased serum levels of LDL-C were less important, but showed significant positive association with the time taken for the development of hard exudates. [56]

Cholesterol is probably an important factor associated with atherosclerosis, which may be directly related to the venous status in diabetes. The control of serum cholesterol has equivocal role in checking vascular complications or their severity. Serum cholesterol levels were higher in poorly controlled diabetics compared to the controlled ones & serum cholesterol levels of blood showed an upward trend in the higher grades of retinopathy [57]

Likewise, patients in the ETDRS who had elevated serum cholesterol or LDL levels at baseline were more likely to have retinal hard exudates than those with normal levels . [56]

Development of retinal hard exudates was also 50% more likely in those patients with elevated serum total cholesterol or triglyceride levels. Because the risk of loss in visual acuity was correlated with the degree of retinal hard exudates, reducing serum lipid levels in patients with diabetes and retinopathy may be particularly important. In addition, severe hard exudates can lead to the development of subretinal fibrosis, a complication that can lead to permanent loss of vision. [58]

Patients with retinopathy had significantly elevated serum cholesterol, triglycerides, and phospholipid levels as compared with the controls. [41]

Hence the purpose of this study is to make clear the role of serum lipid profile in diabetic retinopathy, its progression and plan for further treatment modalities.

METHODOLOGY

Source of Data

1. Patients attending ophthalmic OPD and IPD in KLES PK Hospital and MRC, Belgaum
2. Patients referred from medicine clinic attached to KLESPK Hospital , Belgaum.

Method of Collection of Data

Study Design: Cross sectional study.

Sample Size: 100

Based on previous statistics of patients input.

Duration: One year (01st Jan ,2007 to 31st Dec,2007).

Inclusion criteria:

1.Patients diagnosed to have type 2 diabetes mellitus with retinopathy changes in the fundus were included in the study.

Exclusion criteria :

1. Patients with ocular media haze were excluded from the study.
2. Known patients of other degenerative lesions of the fundus, as the presence of these will mask the fundus appearance of diabetic retinopathy.
3. Patients with ocular media haze, other degenerative lesions of the fundus, uncontrolled hypertension, pregnancy, coronary heart disease, hepatic diseases and on lipid lowering drugs.

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, 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 Kanski's system of classification as follows[6].

a) BDR (background diabetic retinopathy)

b) PPDR (pre-proliferative diabetic retinopathy)

c) PDR (proliferative diabetic retinopathy)

In case of patients with asymmetric fundus findings the eye with a more severe grade of diabetic retinopathy was taken into consideration. Fundus fluorescein angiography was performed only when clinically necessary.

Laboratory investigations done were as follows:

- FBS levels
- Glycosylated hemoglobin (HbA_{1C}) levels to determine the glycemic control.
- Estimation of serum Lipid profile. (Total cholesterol, LDL,HDL, Triglycerides, LDL/HDL Ratio).

Estimation of Lipid Profile :

Various parameters of the lipid profile were estimated by commercially available enzymatic *in vitro* assay kits using Flex reagent cartridge on the dimension clinical chemistry system and were expressed as mg/dl.

Statistical methods :

Analysis of variance test was used to determine the relationship between serum lipid profile and fundus changes in patients of type 2 DM.

Chi Square test was used to determine the relationship between severity of diabetic retinopathy with duration of diabetes and glycemic control.

OBSERVATIONS AND RESULTS

The present study "**A ONE YEAR CROSS SECTIONAL STUDY TO DETERMINE THE RELATIONSHIP BETWEEN SERUM LIPID PROFILE AND DIABETIC RETINOPATHY.**" was conducted in KLES PK Hospital and MRC, Belgaum in J.N. Medical College during the period of 01st Jan to 31st Dec-2007. During this period 100 patients, who satisfied the selection criteria were included in this study.

Table No. 1 : Characteristics of the Study Population

Average Parameters	Study Group
Total number included	100
Age (Yrs) Sex -70/30 (M/F)	62.38 ± 7.05
Onset of diabetes (Yrs)	49.92 ± 5.56
Duration of diabetes (Yrs)	12.48 ±4.65
FBS (mg / dl)	139.92 ± 31.44
Total cholesterol (mg / dl)	195.41 ± 39.11
HDL- cholesterol (mg / dl)	45.50 ± 8.25
LDL-cholesterol (mg / dl)	146.01 ± 27.09
Serum triglycerides	150.56 ± 27.56
LDL : HDL ratio	3.34 ± 1.01
Glycosylated haemoglobin (Hb A1c)	8.06 ± 2.41

The above table shows the demographic data with the mean values for the chief parameters used for comparisons during this study. Age of the patients, Onset of diabetes, Duration of Diabetes, Fasting Blood Sugars (FBS), Glycosylated hemoglobin (HbA_{1C}) and serum Lipid profile levels were the chief parameters in this study.

The mean values of the parameters have been represented in the 3 retinopathy groups of Background Diabetic retinopathy (BDR), Pre Proliferative Diabetic Retinopathy (PPDR) and Proliferative Diabetic Retinopathy (PDR).

Table 2: Prevalence of Retinopathies

Retinopathy	No of patients	Percentage (%)
BDR	47	47
PPDR	32	32
PDR	21	21
Total	100	100

According to the observations made by this table, the highest prevalence percentage was that of background retinopathy, amounting to 47%. This was followed by the pre proliferative retinopathy group, which accounted for 32% of the study population. The smallest group was the proliferative retinopathy group, accounting for 21% of the patients studied. Out of 100 retinopathy patients studied it can be seen that BDR accounted for nearly half the patients while the other half consisted of PPDR and PDR, the former being higher than the latter.

Table 3: Retinopathy in Relation to Sex Distribution

Sex	BDR	PPDR	PDR	Total
Male	36	23	11	70
Female	11	9	10	30
Total	**47**	**32**	**21**	**100**

$\chi^2 = 4.132$, $p < 0.1267$ (NS).

There were 70 males and 30 females in our study group. *Statistical analysis of the above table did not yield anything significant* .

Table 4: Mean Age of study population , Age of onset & Duration of Diabetes in different groups.

Retinopathy	Mean age of patients in groups (yrs)	Retinopathy	Average onset of diabetes (yrs)
BDR	61.04 ± 8.07	BDR	50.31±5.84
PPDR	63.12 ± 6.05	PPDR	49.81±5.53
PDR	64.23 ± 5.44	PDR	49.19±5.12
TOTAL	62.38 ± 7.05	TOTAL	49.92 ± 5.56

P = 0.1728, (NS). P = 0.7393, (NS)

From the above table, it can be seen that the mean ages of onset of diabetes in the study groups of background, pre proliferative and proliferative diabetic retinopathies were found to be 50.31±5.84, 49.81±5.53, 49.23±5.17 respectively. The mean age in different groups were also calculated and tabulated. *Statistical analysis of the above table did not yield any significant relation between the groups.*

Table 5 : Relationship between Retinopathy and Duration of diabetes

Grade of retinopathy	Duration of diabetes (Yrs)				Total
	0-5	6-10	11-15	> 15	
BDR	6	12	23	06	47
PPDR	0	6	19	07	32
PDR	2	01	5	13	21
Total	**8**	**19**	**47**	**26**	**100**

$\chi^2 = 24.523$, p = 0.004 (S).

From the above table it can be gathered that among the BDR group, which consisted of 47 of the total 100 patients, higher numbers were seen in the 6-10y and 11-15y duration of diabetes. It was also noted that a total of 29 patients out of 47 that developed BDR had diabetic age of more than 10 years. Only 6 patients of the total 47 BDR patients had diabetic age of more than 15 yrs.

In contrast to this, the PPDR group showed 6 patients who developed retinopathy in less than 10 years of diabetes. More number of patients had diabetes duration of 11-15y and >15 years. Similarly even the PDR group showed higher numbers of patients in the 11-15y and >15y diabetes duration groups, that is 5 and 13 patients respectively.

The chi square test was used to analyze this table. From this, a 'p' value of 0.004 was obtained which was significant.

Table 5B: Mean duration of diabetes in the retinopathy groups

Retinopathy	Mean duration of diabetes (yrs)
BDR	10.72±3.96
PPDR	13.31±4.71
PDR	15.14 ±4.59
TOTAL	12.48 ±4.65

P < 0.0001, (S).

Table 5C : Statistical Comparisons

Comparisons	'p'	SIG
BDR – PPDR	P<0.05	S
PPDR – PDR	P>0.05	NS
BDR – PDR	P<0.001	HS

With regard to duration of diabetes in the groups, when BDR and PDR groups were compared a 'p' value of <0.05 was found and similarly comparing the groups of BDR and PDR yielded a 'p' value of <0.001, which indicates there was a significant relationship between severity of retinopathy and mean duration of diabetes in these groups. However when PPDR & PDR groups were compared, there was no significant relation found between these two groups (P>0.05).

Table 6: Relationship between Grade of Retinopathy and Fasting Blood Sugars

Retinopathy	Mean Fasting Blood Sugars
BDR	135.0 ± 31.73
PPDR	142.88 ± 30.29
PDR	146.43 ± 32.24
TOTAL	139.92 ± 31.44

P=0.3145, (NS).

The mean fasting blood sugar levels were estimated in the three retinopathy groups. There was no statistically significant relation between the groups noted in our study.

Table 7A : Relationship between Grade of Retinopathy and Glycaemic Control

	Well controlled	**Uncontrolled[59]**	**Total**
	(HbA_{1C}: 6.2 - 8.3)	(HbA_{1C}: >8.3)	
BDR	36	11	47
PPDR	16	16	32
PDR	6	15	21
Total	**58**	**42**	**100**

$\chi^2 = 14.978$, p = 0.0006 (S).

Regarding the glycemic control, on tabulation we noted that 58% of the study population belonged to well controlled group and remaining belonged to uncontrolled group.

Table 7B: Relationship between Grade of Retinopathy and Mean HbA_{1C}.

	Mean Glycosylated hemoglobin with std deviation	Cases
BDR	7.13 ± 2.17	47
PPDR	8.40 ± 2.13	32
PDR	9.62±2.47	21
TOTAL	8.06±2.41	100

The mean HbA_{1C} levels in the 3 retinopathy groups were estimated.

Table7C: Statistical Comparisons

Comparisons	'p'	SIG
BDR - PPDR	P<0.05	S
PPDR - PDR	P>0.05	NS
BDR - PDR	P<0.001	HS

When statistical comparisons were done between the retinopathy groups it was seen that the comparison of mean HbA_{1C} values of PPDR with PDR group showed a 'p' value of > 0.05 indicating no correlation. *Whereas the comparison of mean HbA_{1C} values between the BDR and PPDR group yielded a p value of <0.05 and between BDR and PDR group $P<0.001$, which was significant.*

Table 8 : Relationship of Retinopathy with Serum Total Cholesterol

Grades of Diabetic retinopathy	Serum total cholesterol levels (mg / dl) [59]				Mean
	< 200 (Desirable)	200-239 (Borderline)	> 240 (Abnormal)	Total	
BDR	33	14	0	47	185.43 ± 28.35
PPDR	11	20	01	32	196.38 ± 39.44
PDR	07	06	08	21	216.29 ± 51.16
Total	**51**	**40**	**09**	**100**	195.41 ± 39.11

$\chi^2 = 37.592$, $p < 0.0001$ (S).

The patients were divided into subgroups based on serum total cholesterol levels into those having desirable levels, borderline & abnormal levels. The mean cholesterol level in each retinopathy group was also noted. This was then compared among the 3 retinopathy groups.

Table 8B : Statistical Comparisons

Comparisons	'p'	SIG
BDR - PPDR	P>0.05	NS
PPDR - PDR	P>0.05	NS
BDR - PDR	P<0.01	S

When statistically compared, there was no relation found between BDR and PPDR groups and also between PPDR and PDR groups (P>0.05). But there was statistically significant relation between BDR and PDR groups (P<0.01).

Table 9 : Relationship between Serum HDL Cholesterol with Retinopathy

Retinopathy	Serum HDL cholesterol (mg / dl) [59]			Total	Mean
	> 60 (Desirable)	36-60 (Borderline)	<35 (Abnormal)		
BDR	01	45	01	47	50.76 ± 6.33
PPDR	00	31	01	32	43.15 ± 6.78
PDR	00	15	06	21	37.28 ± 5.36
Total	**01**	**91**	**08**	**100**	45.50 ± 8.25

$\chi^2 = 16.334$, p = 0.0026 (S)

Table 9B : Statistical Comparisons

COMPARISONS	'p'	SIG
BDR – PPDR	P<0.001	HS
PPDR – PDR	P<0.01	S
BDR – PDR	P<0.001	HS

The mean HDL- cholesterol levels in BDR, PPDR and PDR groups were 50.76 ± 6.33, 43.15 ± 6.78, 37.28 ± 5.36 respectively. When statistically compared, there was significant relation found between all three groups, as shown in the table above.

Table No. 10 : Relationship of Serum LDL Cholesterol with Retinopathy

Retinopathy	Serum LDL cholesterol (mg / dl) [59]			Total	Mean
	< 130 (Normal)	130-159 (Borderline)	> 160 (Abnormal)		
BDR	19	20	08	47	136.17 ± 22.15
PPDR	06	15	11	32	148.13 ± 26.41
PDR	03	02	16	21	164.81 ± 28.58
Total	**28**	**37**	**35**	**100**	146.04± 27.08

$\chi^2 = 25.024$, $p < 0.0001$ (S).

The serum LDL cholesterol levels were estimated & categorized as normal, borderline and abnormal. The mean value of LDL cholesterol in each retinopathy group was noted & comparison was done between the 3 groups.

Table 10 B : Statistical Comparisons

COMPARISONS	'p'	SIG
BDR – PPDR	P>0.05	NS
PPDR – PDR	P>0.05	NS
BDR – PDR	P<0.001	HS

When statistically compared, there was no relation found between BDR/PPDR and PPDR/ PDR (P>0.05). But there was highly significant relation between BDR and PDR groups (P<0.001).

Table 11 : Relationship between LDL / HDL Ratio with Retinopathy

Retinopathy	Serum LDL : HDL cholesterol ratio [59]			Total	Mean
	< 2.5	2.5-5.0	> 5.00		
BDR	19	28	00	47	2.71 ± 0.55
PPDR	6	26	00	32	3.50 ± 0.82
PDR	01	14	06	21	4.49 ± 0.96
Total	**26**	**68**	**06**	**100**	**3.34 ± 1.01**

$\chi^2 = 31.946$, $p < 0.0001$ (S).

Out of 100 patients, 26 (26%) patients with varying grades of retinopathy had LDL : HDL ratio of < 2.5.The next group of 68 patients had serum LDL / HDL ratio between 2.5-5.0 and only 6 patients had serum LDL / HDL ratio more than 5.00.

Table 11 B : Statistical Comparisons

COMPARISONS	'p'	SIG
BDR - PPDR	P<0.001	HS
PPDR - PDR	P<0.001	HS
BDR - PDR	P<0.001	HS

Overall, the increasing levels of LDL / HDL ratio correlated positively with increasing severity of retinopathy, which was statistically highly significant between all 3 retinopathy groups ($p<0.001$).

Table 12 : Relationship of Serum Triglycerides with Retinopathy

Retinopathy	Serum Triglycerides Levels (mg/dl)[59]		Total	Mean
	< 150	> 150		
BDR	32	15	47	138.85±22.27
PPDR	11	21	32	152.69±25.39
PDR	04	17	21	173.52±27.13
Total	**47**	**53**	**100**	**150.56**±27.56

$\chi^2 = 17.023$, p = 0.002 (S).

Table 12B : Statistical Comparisons

COMPARISONS	'p'	SIG
BDR – PPDR	P<0.05	S
PPDR – PDR	P<0.01	S
BDR – PDR	P<0.001	HS

Out of 100 patients, 47 patients had serum triglycerides levels of < 150 mg/dl and the remaining 53 patients had more than 150 mg/dl.

Overall, serum triglycerides levels correlated positively with increasing severity of retinopathy which was statistically significant .

Table 13 : Comparison of Maculopathy with stage Diabetic Retinopathy

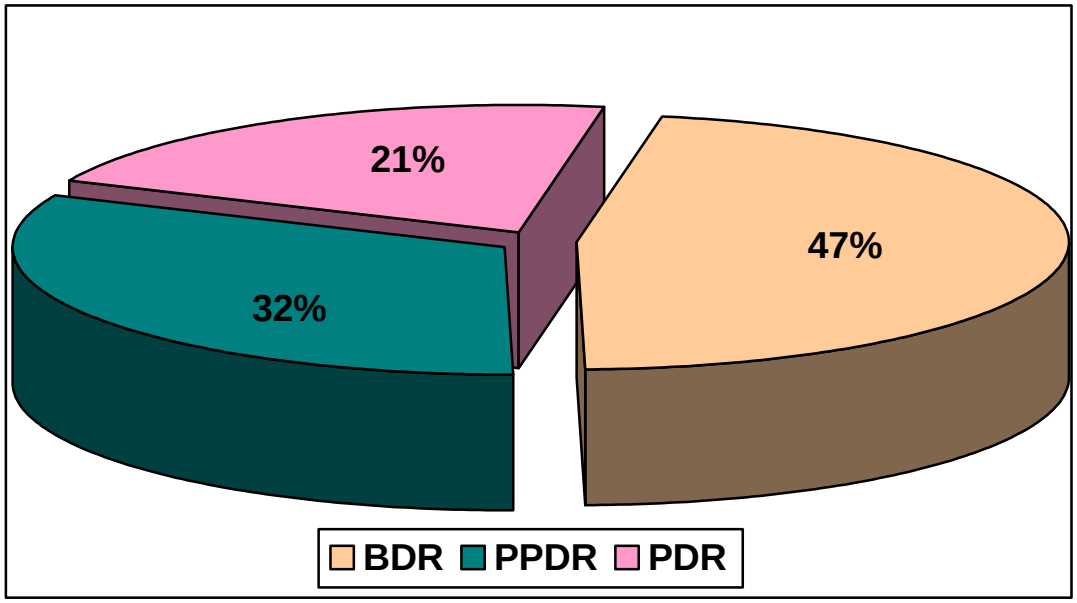
Maculopathy	Grades of Retinopathy			
	BDR	**PPDR**	**PDR**	**Total**
Maculopathy	5	4	6	15
No Maculopathy	42	28	15	85
No. of patients	**47**	**32**	**21**	**100**

$\chi^2 = 3.892$, $p = 0.1429$ (NS).

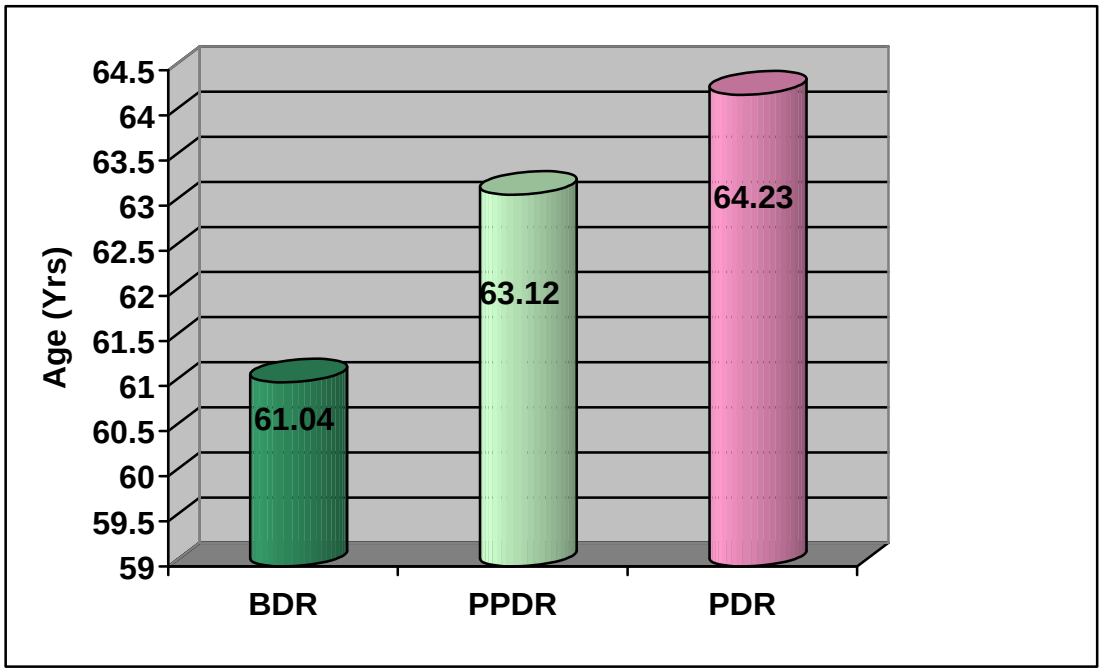
It was found that the number of patients who had evidence of maculopathy were 5, 4 and 6 in the BDR, PPDR and PDR groups respectively. *Statistical analysis did not yield anything significant.*

GRAPHS

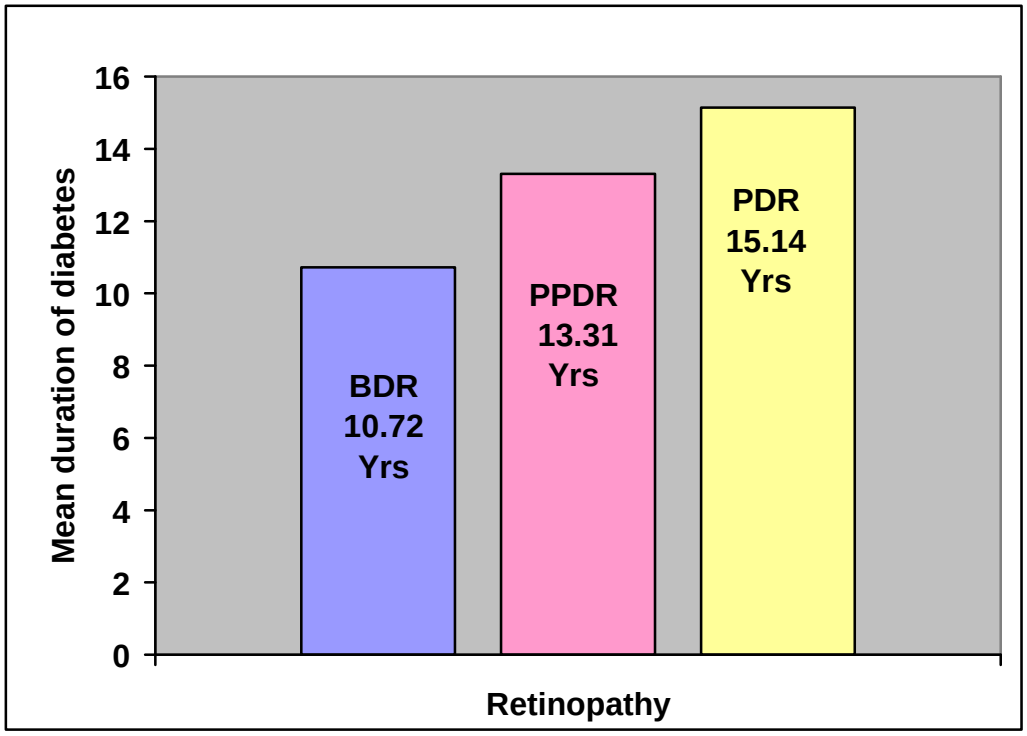
1. Prevalence of retinopathy



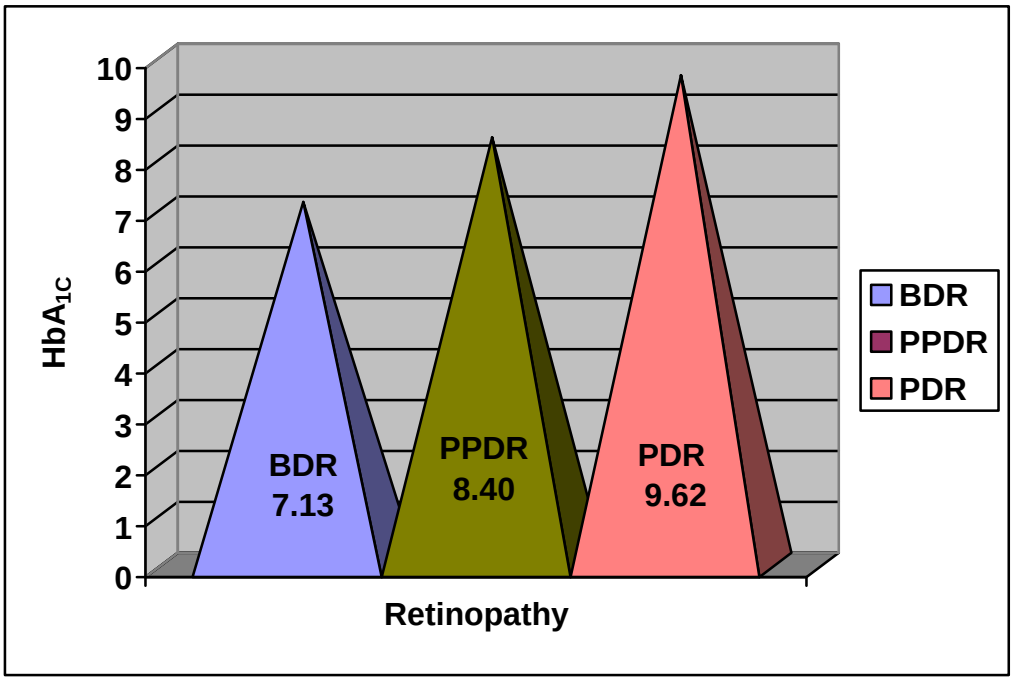
Graph 2 : Mean age of patients in study groups.



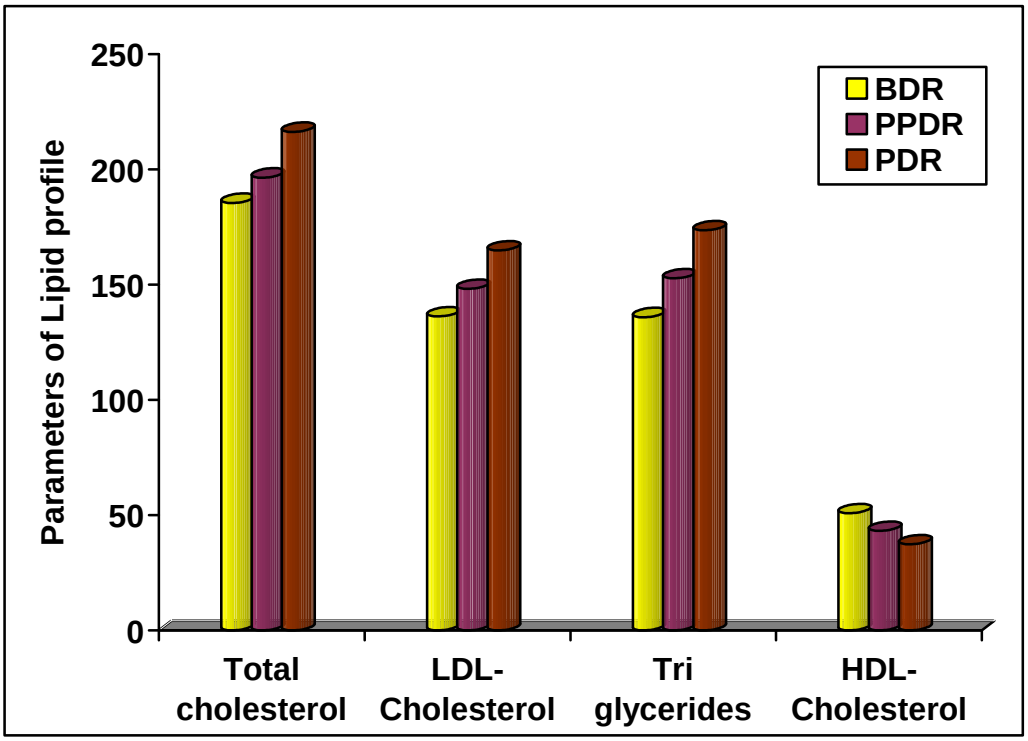
Graph 3 : Mean duration of diabetes in different groups



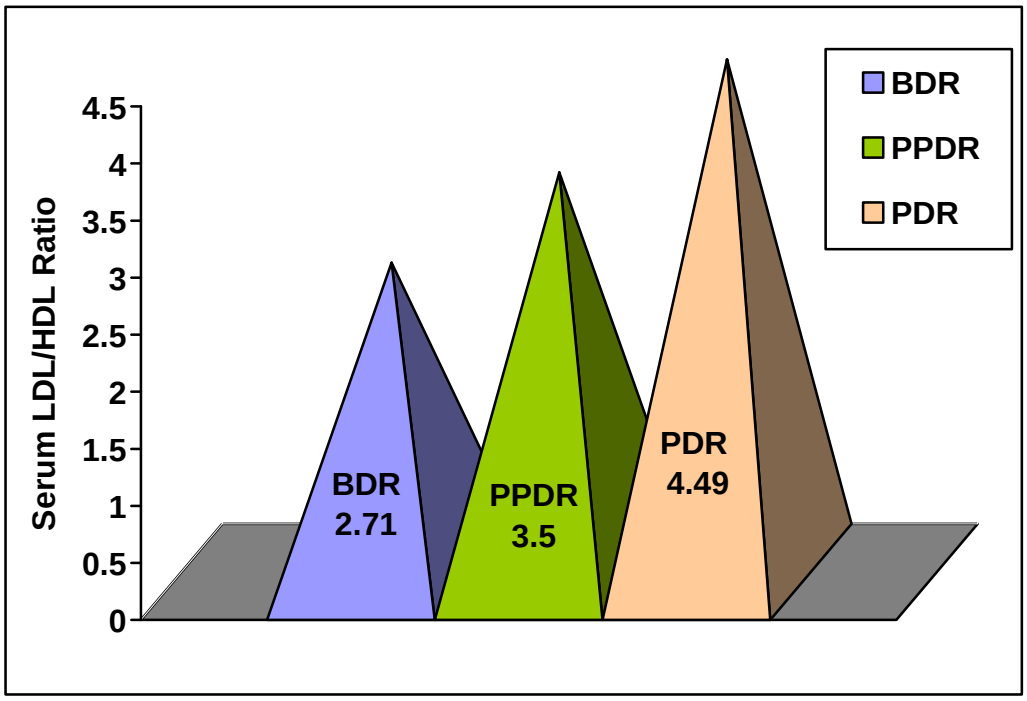
Graph 4 : Mean HbA1c in different groups



Graph 5 : Various parameters of Lipid profile in different groups of retinopathy.



Graph 6 : Mean values of LDL / HDL ratio in different retinopathy groups


Serum LDL/HDL Ratio
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
BDR
PPDR
PDR
BDR
2.71
PPDR
3.5
PDR
4.49

DISCUSSION

Prevalence of the Retinopathies

The present study, which was cross sectional in design, included 100 patients of diabetic retinopathy. Among these, 47 patients had background diabetic retinopathy (BDR), 32 patients had pre proliferative diabetic retinopathy (PPDR) and 21 patients had proliferative diabetic retinopathy (PDR). Thus the prevalence of different grades of retinopathies in this study were 47%, 32% and 21% respectively.

Patient Age and Type of Retinopathy

The mean age of study groups, age of onset of diabetes in relation with the different stages of retinopathy among the 100 patients were studied and tabulated in table 1 and 4.

Although there was no statistical relation found, it appears from these tables that the severity of the retinopathy was increasing with the increasing age of the patients. This could probably be attributed to the fact that the older patients would have also had longer duration of diabetes.

This finding is similar to another finding in a recent study which mentioned that, once the type of diabetes and duration of diabetes are considered, age of the patient has little significance in the progression of retinopathy[60].

The mean age of onset of diabetes was almost similar in all the groups.

Retinopathy and Sex of the Patient:

The sex distribution of the study population has been depicted in table 3. Although, in our study there was a higher number of males than females which was

contrary to another study[41], the analysis showed that there was no significant variation in the stages of retinopathy based on sex of the patient.

Duration of diabetes and type of retinopathy:

The 100 patients of diabetic retinopathy who were studied were categorized based on their duration of diabetes.

Most of the BDR cases (87%) had diabetic age of more than 10 years, whereas most of PPDR cases were among 11-15yrs (59%) diabetic age and those patients with PDR had diabetic age of more than 15 years (61%) (Table no-5).

It is evident from these findings that there was statistically significant worsening of the retinopathy with the increasing duration of diabetes in these individuals ($p = 0.004$) (S).

When compared, there was a statistically significant relation between the mean duration of all the groups of retinopathy and there was a linear correlation between the severity of retinopathy and duration of diabetes found in our study which is similar to the findings of other study.[41] This observation has also favourable correlation with another longitudinal study [61] and a cross sectional study [62] which noted similar findings.

Fasting blood sugars and Retinopathy

Regarding the FBS relationship with the severity of the retinopathy, it was observed that though the mean values in all the 3 groups were above normal limits and mean fasting sugar levels were more with increasing severity of retinopathy, there was no statistically significant relation between different groups noted in our study ($P = 0.3145$) (NS) (Table no-6).

Glycosylated haemoglobin and Grade of 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 is protective for all levels of retinopathy and there is no glycemic threshold below which a reduction in microvascular complications is not observed**.** [63,64]

The DCCT showed that strict control of blood sugar could reduce the occurrence of diabetic retinopathy and slowdown the progression of any retinopathy. [65]

The glycemic status of the patients was studied by measuring HbA_{1C} levels. When the HbA_{1C} values were compared in the groups with increasing severity of retinopathy from BDR to PDR, increasing levels of HbA_{1C} (table 7A, B & C) were noted showing a significant correlation ($p = 0.0006$) (S). Therefore it was noted that poor glycemic control led to the worsening of the retinopathy.

One of the studies conducted previously in this regard showed that the risk of PDR was six times greater among patients with poor glycemic control.[66]

SERUM LIPIDS & DIABETIC RETINOPATHY

Total Cholesterol & Retinopathy

The mean total cholesterol levels were compared between the groups which showed no significant relation when BDR was compared with PPDR and when PPDR was compared with PDR. But when BDR was compared with PDR there was statistically significant relation indicating that elevated total cholesterol levels were

associated with increasing severity of retinopathy. (Table no-8 & 8B)

A previous study which indicated a similar association quoted "elevated cholesterol and triglycerides were associated with an increased risk for any grade of retinopathy". [67]

Similarly, few workers like Joslin and Babel found that these cholesterol levels were higher in cases of diabetes with retinopathy. [68]

Contrary to this, Wang et al mentioned that the rise in serum cholesterol levels are insignificant in cases of diabetes with retinopathy. [69]

HDL-Cholesterol & Retinopathy

In our study we found a decrease in the mean HDL cholesterol levels in all the groups as the severity of retinopathy progressed. A significant relation was found between all three groups when compared indicating that reduced levels of HDL cholesterol is associated with severity of retinopathy (Table no-9 & 9B).

Similarly in a recent cross sectional study an inverse relation between HDL cholesterol and severity of diabetic retinopathy was detected. [70]

In the above two groups (Total cholesterol & HDL cholesterol), even though the cholesterol levels were borderline, we still found a significant difference on comparing BDR group with the PDR group of patients.

LDL-Cholesterol & Retinopathy :

ETDRS identified elevated levels of serum cholesterol and low density lipoproteins (LDL) as independent risk factors for the development of hard exudates. [56]

The mean LDL cholesterol levels were compared between the groups which showed no significant relation when BDR was compared with PPDR and when PPDR was compared with PDR. But when BDR was compared with PDR there was statistically significant relation indicating the association of raised LDL cholesterol levels with severe retinopathy like PDR (Table no-10 & 10B).

LDL / HDL Ratio & Diabetic retinopathy

In our study we found a significantly elevated LDL / HDL ratio in all the three groups. When we compared there was a statistically significant relation between all the three groups showing the association of elevated LDL / HDL ratio in patients of retinopathy with increasing severity. (Table no-11 & 11B). We could not find other similar studies for comparison.

Triglycerides & Retinopathy

Triglycerides are a significant risk factor for presence of diabetic retinopathy according to two previous cross sectional studies. [55,71]

In our study we noted elevated triglyceride levels in the groups as retinopathy progressed. On comparison we found a statistically significant relation between all the three groups (Table no-12 & 12B).

Lipid profile & Maculopathy

In our study we did not find any significant difference in the lipid profile of patients with maculopathy when compared to those without maculopathy..

We also found almost an equal incidence of maculopathy in all the three groups and could not come to a clear conclusion regarding this.

Visual acuity

Even though visual acuity was recorded in all the patients of the study group, we did not do any analysis because there were so many causes like refractive errors, early cataracts and age related degenerations which account for some amount of decrease of visual acuity in these patients.

CONCLUSIONS

At the end of our study, we were able to conclude that:-

- Progression of retinopathy was more with raised Total cholesterol and decreased HDL cholesterol levels.
- Even though there was no significant relation between all the groups on comparison, there was a significant increase of LDL cholesterol levels between BDR and PDR groups.
- There was a significant increase of LDL / HDL ratio and serum triglycerides with increasing severity of retinopathy.
- Patients with longer duration of diabetes had more severe grades of diabetic retinopathy.
- Poor glycemic control led to the worsening of the retinopathy.
- In addition to glycemic control, lowering of serum lipids may be effective in retarding the progression of diabetic retinopathy.

SUMMARY

Diabetes mellitus is a public health problem which has reached epidemic proportions. Diabetic retinopathy remains a serious vision threatening complication of diabetes mellitus. While strides in modern medicine have been successful in increasing life expectancy in diabetics, antecedent end organ damage especially that of diabetic retinopathy continues to be one of the most important concerns of the present decade.

This study titled "A ONE YEAR CROSS SECTIONAL STUDY TO DETERMINE THE RELATIONSHIP BETWEEN SERUM LIPID PROFILE AND DIABETIC RETINOPATHY." was conducted in KLES PK Hospital and MRC, Belgaum in J.N.Medical College during the period of 01st Jan to 31st Dec-2007.

In this study**,** 100 patients of various grades of retinopathy were examined and categorized based on their grade of retinopathy as per the Kanski's system of classification.

The different grades of diabetic retinopathy of these patients were compared with various parameters such as mean fasting lipid profile levels, age of onset of diabetes, duration of diabetes, sex of the patient, fasting blood sugars and HbA_{1C} levels.

The summary of the results obtained is as follows:

- The study group included 100 diabetic retinopathy patients consisting of 47 cases (47%) of background diabetic retinopathy, 32 cases (32%) of pre proliferative retinopathy and 21 cases (21%) of proliferative retinopathy
- Older patients had more severe grades of retinopathy

- There was no significant association between the sex of the patients and severity of retinopathy.
- It was found that the mean age of onset of diabetes was almost similar in all the groups and patients with longer duration of diabetes had more severe grades of diabetic retinopathy.
- It was noted that the mean FBS levels in different groups were more with increasing severity of retinopathy. But the association was not statistically significant.
- The mean total cholesterol was significantly higher in those patients with longer duration of diabetes indicating poorer metabolic control of their diabetes.
- It was noted that with the increase in severity of the features of the retinopathy, there was a significant decrease of HDL cholesterol levels in the different groups.
- Even though there was no significant relation between other groups, there was significant increase of LDL cholesterol levels between BDR and PDR groups.
- There was a significant increase of LDL / HDL ratio with increasing severity of retinopathy.
- Patients with CSME did not have a significant change in their lipid profile when compared with those patients without CSME.

Most of the current therapy regarding the management of diabetic retinopathy is targeted at the retina once the disease is already evolving. The conventional modalities of treatment such as fundus fluorescein angiography and laser photocoagulation although successful to an extent in controlling the disease, come into the picture of treatment only after the clinical retinopathy has already set in. Even

though the most stringent glycemic control in a retinopathy patient slows down the progression of the retinopathy, it does not eliminate the retinopathy completely. While glycemic control still holds good as a very important aspect in preventing retinopathy and other diabetic complications, current concepts are inclining towards possible molecular or pharmacological interventions.

The results in our study indicate the hope of pharmacological intervention to reduce the lipid levels in patients of diabetic retinopathy with raised total cholesterol levels. Although a positive association was found between the levels of serum Lipid profile and severity of retinopathy, larger studies are required to exactly delineate the role of lipid lowering recommendations in the management of diabetic retinopathy to retard the progression of the disease.

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ANNEXURE – I: PROFORMA

1) NAME :

2) AGE:

3) SEX:

4) ADDRESS:

5) AGE OF ONSET OF DIABETES:

6) DURATION OF DIABETES(YRS):

7) BRIEF HISTORY OF PRESENTING COMPLAINTS:

8) SIGNIFICANT PAST HISTORY:

9) SIGNIFICANT FAMILY HISTORY:

10) GENERAL PHYSICAL EXAMINATION:

INVESTIGATIONS:

1) FBS mg/dl :

2) Hb A_1C :

3) TOTAL CHOLESTEROL:

4) HDL mg/dl :

5) LDL :

6) TRIGLYCERIDES ;

7) LDL/HDL RATIO:

8) BEST CORRECTED VISUAL ACQUITY:

OD :

OS :

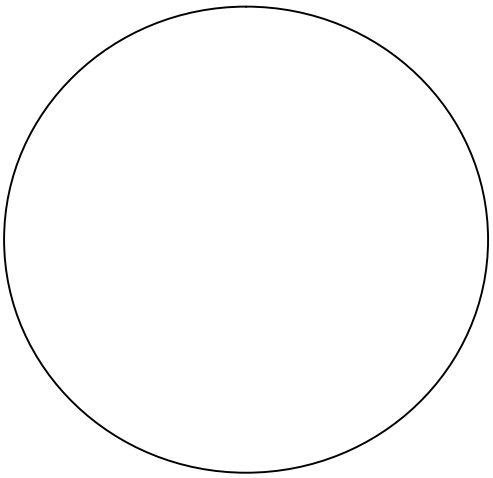
A) OCULAR EXAMINATION: OD OS

1. ADENEXA
2. SCLERA
3. CONJUNCTIVA
4. CORNEA
5. ANTERIOR CHAMBER
6. IRIS
7. PUPIL
8. LENS:

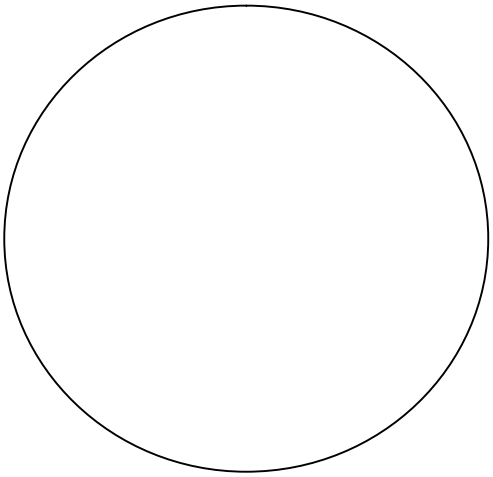
B) FUNDUS EXAMINATION

1. GLOW
2. MEDIA
3. DISC
4. CUP : DISC RATIO
5. BLOOD VESSELS:
6. BACK GROUND OD OS
    a) Haemorrhages:
    b) Cotton-wool spots:
    c) Hard Exudates:
    d) Any other positive finding :

7. MACULA:



OD



OS

DIAGNOSIS :

Signature of candidate **signature of guide**

ANNEXURE-II: CONSENT FOR PARTICIPATION IN RESEARCH

Mr./Mrs._____we are requesting you to enroll yourself in study titiled -A ONE YEAR CROSS SECTIONAL STUDY TO DETERMINE THE RELATIONSHIP BETWEEN SERUM LIPID PROFILE AND DIABETIC RETINOPATHY IN PATIENTS ATTENDING KLESPK HOSPITAL & MRC, BELGAUM, conducted by DR K.RAMA KRISHNA, postgraduate student in M.S Ophthalmology under the guidance of DR U.S.DANDAVATIMATH at J.N Medical College, Belgaum under KLE University, Belgaum.

You have been requested to participate in research because you are into the study group. During the study you will be asked some questions and you are supposed to answer to the best of your knowledge.

Your participation in research is voluntary. Your decision whether or not to participate in the study will not affect your relationship with J.N.M.C. If you decide to participate you are free to withdraw at any time.

The purpose of research is to determine the relationship between serum lipid profile and diabetic retinopathy.

PROCEDURE INVOLVED:

Investigated serum lipid profile levels are documented and correlated with the grade of diabetic retinopathy.

RISKS AND BENEFITS:

There are no extra risks involved and benefits are to be evaluated.

ALTERNATIVES:

Even if you decline the participation, you will get the routine line of management.

PRIVACY AND CONFIDENTIALITY:

The only people to know that you are a research subject are members of the research team. No information about you or provided by you during the research will be disclosed to others without your written permission except:

1. In emergency to protect your rights and welfare.
2. If required by law.

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. Any information that is obtained in connection with this study and that can be identified with you will remain confidential.

FINANCIAL INCENTIVES FOR PARTICIPATION:

You will not be paid/offered any free gifts for participating in the research. You will not be reimbursed for expenses.

CONSENT STATEMENT:

I undersigned_____ have been explained in my vernacular language about the study and my participation in the study is voluntary. If I want, I can withdraw at any time. Also I have been given enough time to clear my doubts and rights as study participant.

In case you have any questions related to the study, you can contact Dr K Rama Krishna (Phone No 9986154113)

In case you have any questions about your rights as a study participant, you can contact Dr V.D Patil (0831-2471350)

Signature or the Left Thumb print of Participant or legally authorized representative

Participants Name_____ Signature_____

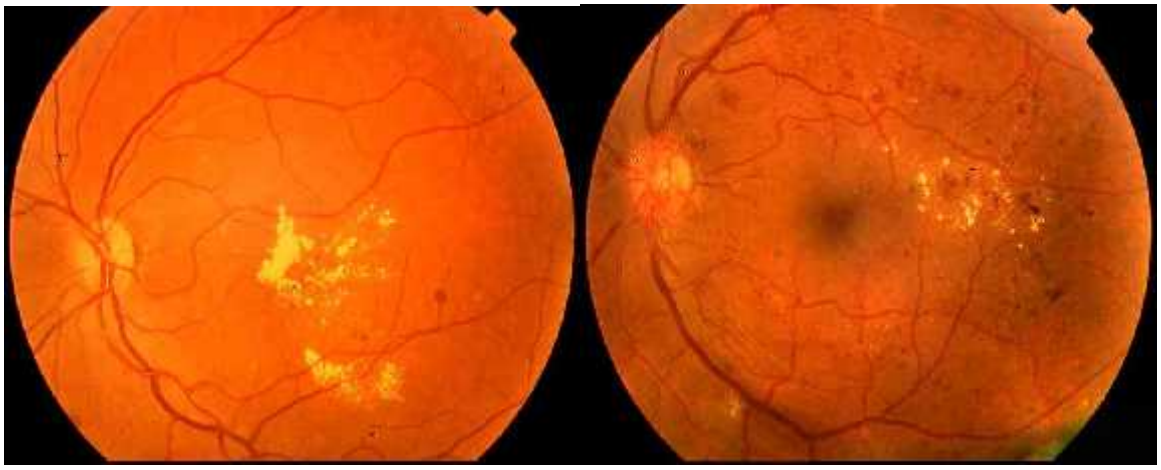
Witness Name_____ Signature_____

Date_____

Place_____

ANNEXURE – III: PHOTOGRAPHS

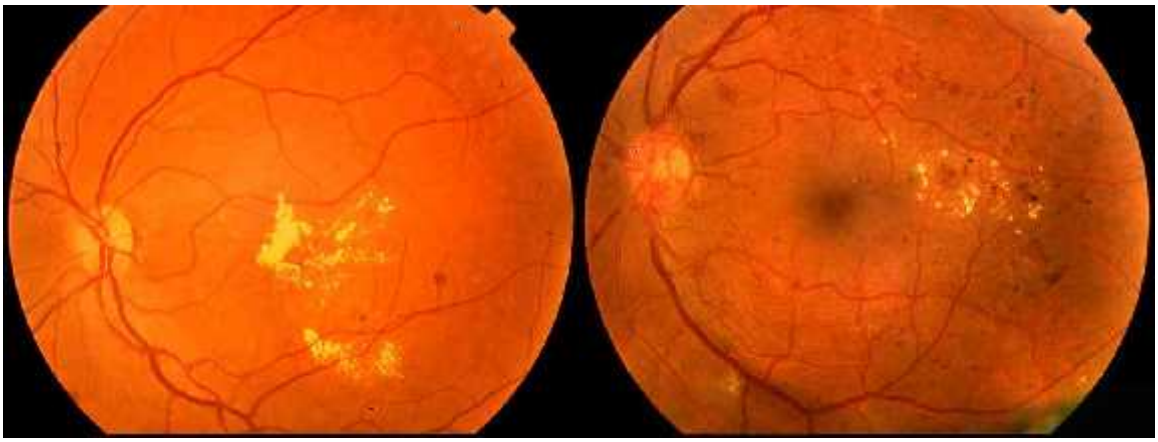
Background Diabetic Retinopathy **Pre-Proliferative Diabetic Retinopathy**



Clinically Significant Macular Oedema **Proliferative Diabetic Retinopathy**

PHOTOGRAPHS

Background Diabetic Retinopathy | Pre-Proliferative Diabetic Retinopathy



Clinically Significant Macular Oedema | Proliferative Diabetic Retinopathy

PROFORMA

1) NAME :

2) AGE:

3) SEX:

4) ADDRESS:

5) AGE OF ONSET OF DIABETES:

6) DURATION OF DIABETES(YRS):

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8) SIGNIFICANT PAST HISTORY:

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2) Hb A_1C :

3) TOTAL CHOLESTEROL:

4) HDL mg/dl :

5) LDL :

6) TRIGLYCERIDES ;

7) LDL/HDL RATIO:

8) BEST CORRECTED VISUAL ACQUITY:

OD :

OS :

A) OCULAR EXAMINATION: OD OS

1. ADENEXA
2. SCLERA
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5. ANTERIOR CHAMBER
6. IRIS
7. PUPIL
8. LENS:

B) FUNDUS EXAMINATION

1. GLOW
2. MEDIA
3. DISC
4. CUP : DISC RATIO

5. BLOOD VESSELS:

6. BACK GROUND OD OS

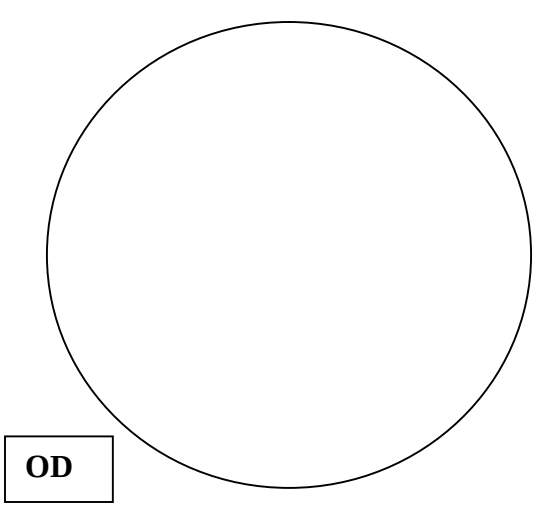
   a) Haemorrhages:

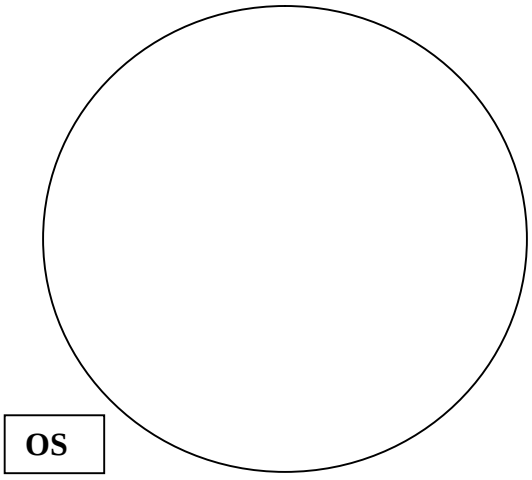
   b) Cotton-wool spots:

   c) Hard Exudates:

   d) Any other positive finding :

7. MACULA:





DIAGNOSIS :

Signature of candidate **signature of guide**

CONSENT FOR PARTICIPATION IN RESEARCH

Mr./Mrs._____we are requesting you to enroll yourself in study titiled -A ONE YEAR CROSS SECTIONAL STUDY TO DETERMINE THE RELATIONSHIP BETWEEN SERUM LIPID PROFILE AND DIABETIC RETINOPATHY IN PATIENTS ATTENDING KLESPK HOSPITAL & MRC, BELGAUM, conducted by DR K.RAMA KRISHNA, postgraduate student in M.S Ophthalmology under the guidance of DR U.S.DANDAVATIMATH at J.N Medical College, Belgaum under KLE University, Belgaum.

You have been requested to participate in research because you are into the study group. During the study you will be asked some questions and you are supposed to answer to the best of your knowledge.

Your participation in research is voluntary. Your decision whether or not to participate in the study will not affect your relationship with J.N.M.C. If you decide to participate you are free to withdraw at any time.

The purpose of research is to determine the relationship between serum lipid profile and diabetic retinopathy.

PROCEDURE INVOLVED:

Investigated serum lipid profile levels are documented and correlated with the grade of diabetic retinopathy.

RISKS AND BENEFITS:

There are no extra risks involved and benefits are to be evaluated.

ALTERNATIVES:

Even if you decline the participation, you will get the routine line of management.

PRIVACY AND CONFIDENTIALITY:

The only people to know that you are a research subject are members of the research team. No information about you or provided by you during the research will be disclosed to others without your written permission except:

1. In emergency to protect your rights and welfare.
2. If required by law.

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. Any information that is obtained in connection with this study and that can be identified with you will remain confidential.

FINANCIAL INCENTIVES FOR PARTICIPATION:

You will not be paid/offered any free gifts for participating in the research. You will not be reimbursed for expenses.

CONSENT STATEMENT:

I undersigned_____ have been explained in my vernacular language about the study and my participation in the study is voluntary. If I want, I can withdraw at any time. Also I have been given enough time to clear my doubts and rights as study participant.

In case you have any questions related to the study, you can contact Dr K Rama Krishna (Phone No 9986154113)

In case you have any questions about your rights as a study participant, you can contact Dr V.D Patil (0831-2471350)

Signature or the Left Thumb print of Participant or legally authorized representative

Participants Name_____ Signature_____

Witness Name_____ Signature_____

Candidates Name_____ Signature_____

Date_____

Place_____

Sl. No.	Name	Age (Yrs)	Sex	IP No.	Age of Onset (Yrs)	Duration (Yrs)	Hb A1c	FBS	Cholestrol					BCVA		adnexa		conjunctiva		Cornea		AC		Pupil		Lens		Retinopathy grades
									Total	HDL mg/dl	LDL	TG	ldl: hdl	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS	
1	AN	76	F	270213	61	15	5.6	174	201	41	113	101	2.75	6/12,N10	6/12,N10	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	BDR
2	PA	77	M	269282	56	21	4.8	121	108	46	131	116	2.84	6/18,N10	6/60,N18	N	N	N	N	arcus	arcus	N	N	RRR	RRR	IOL	CAT,	BDR
3	SH	63	F	270531	49	14	11.3	162	119	43	159	142	3.69	6/12,N10	6/12,N10	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	PDR
4	SI	72	M	268823	56	16	7.3	96	204	39	158	169	4.05	6/24,N12	6/9,N8	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	PPDR
5	SA	73	M	268763	59	14	6.4	127	238	43	186	151	4.32	6/18,N12	6/18,N18	N	N	N	N	arcus	arcus	N	N	RRR	RRR	PSC	PSC	PPDR
6	SV	69	M	268281	54	15	5.9	86	192	49	96	149	1.95	6/24,N18	6/60,N36	N	N	N	N	arcus	arcus	N	N	RRR	SLUG	N	N	BDR+LE M
7	MA	72	M	268803	58	14	8.3	201	129	43	128	82	3	6/18,N18	6/24,N18	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	BDR
8	ML	52	M	265587	44	8	4.2	82	176	58	135	138	2.32	6/24,N18	6/18,N12	N	N	N	N	N	N	N	N	RRR	RRR	N	N	BDR
9	RU	74	F	268315	58	16	4.1	121	231	41	163	132	3.97	6/36,N36	6/24P,N18	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	IOL	PPDR
10	HA	67	M	268171	48	19	9.4	174	216	33	79	171	2.39	6/60,N36	6/36,N36	N	N	N	N	arcus	arcus	N	N	SLUG	SLUG	IOL	IOL	PPDR+RE M
11	MD	70	M	268721	57	13	6.3	143	119	49	128	181	2.63	6/18,N12	6/18,N12	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	BDR
12	KO	63	M	267914	51	12	9.7	165	198	56	117	127	2.08	6/24,N18,	618,N12	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	BDR
13	BA	65	F	267895	56	9	10.1	101	205	48	168	151	3.5	6/36,N18	6/24,N12	N	N	PTER	PTER	arcus	arcus	N	N	RRR	RRR	N	N	BDR
14	PA	69	F	267981	56	13	8.9	92	261	41	189	176	4.6	6/24,N18,	6/18,N12	N	N	N	N	arcus	arcus	N	N	RRR	RRR	CAT	IOL	PDR
15	SF	72	M	268861	59	13	9.6	174	196	30	96	182	3.2	6/12,N18	6/24,N18	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	PDR
16	BS	61	M	268132	57	4	5.3	147	125	53	131	136	2.47	6/24,N10	6/60,N36	N	N	N	N	arcus	arcus	N	N	RRR	SLUG	CAT	IOL	BDR+LE M
17	LI	69	M	270252	53	16	7.6	138	138	48	167	128	3.47	6/9,N8	6/6P,N8	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	BDR
18	BN	70	M	268308	56	14	5.1	92	211	39	158	115	4.05	6/24,N18	6/24.N18	N	N	N	N	arcus	arcus	N	N	RRR	RRR	NS	NS	BDR
19	SU	65	F	267946	53	12	7.4	107	121	43	149	156	3.46	6/18,N18	6/24,N18	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	PPDR
20	SN	57	F	270531	51	6	6.9	141	241	38	171	175	4.5	6/18,N10	6/24,N18	N	N	N	N	N	N	N	N	RRR	RRR	NS	IOL	PPDR
21	RE	67	F	270283	52	15	10.8	121	146	39	164	146	4.2	6/9,N6	6/36,N36	N	N	N	N	arcus	arcus	N	N	RRR	RRR	NC	NC+PSC	PPDR
22	AD	63	M	267745	52	11	11.1	162	188	51	140	119	2.74	6/12,N6	6/36,N18	N	N	N	N	arcus	arcus	N	N	RRR	RRR	IOL	CAT,	BDR
23	ST	61	F	267521	51	10	9.8	141	165	33	132	166	4	6/18,N12	6/18,N12	N	N	N	N	arcus	arcus	N	N	RRR	RRR	CAT	IOL	BDR
24	MP	55	M	267450	46	9	4.3	132	199	41	127	132	3.09	6/12,N6	6/12,N6	N	N	N	N	N	N	N	N	RRR	RRR	N	N	BDR
25	NE	58	F	266972	53	5	11.3	147	183	57	91	137	1.59	6/18,N12	6/18,N12	N	N	N	N	N	N	N	N	RRR	RRR	N	N	BDR
26	MR	62	M	268923	44	18	7.3	161	102	38	184	92	4.84	6/24,N18	6/60,N36	N	N	N	N	arcus	arcus	N	N	RRR	SLUG	N	N	PDR+LE M
27	KD	68	M	268831	52	16	12.1	138	255	24	152	144	6.33	6/18,N10	6/18,N10	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	PDR
28	SI	57	M	268937	43	14	7.3	109	231	53	156	161	2.94	6/24,N18	6/12,N12	N	N	N	N	N	N	N	N	RRR	RRR	CAT	IOL	PPDR
29	BI	65	M	268784	54	11	10.8	152	131	44	138	118	3.13	6/12,N10	6/24,N10	N	N	N	N	arcus	arcus	N	N	RRR	RRR	IOL	IOL	PPDR
30	FA	72	F	268709	59	13	9.4	124	177	38	149	156	3.92	6/36,N18	6/12,N10	N	N	N	N	arcus	arcus	N	N	IRR,SR	RRR	CAT	IOL	PPDR
31	MW	58	M	268400	42	16	7.5	149	232	43	181	173	4.2	6/12,N10	6/9,N6	N	N	N	N	N	N	N	N	RRR	RRR	N	N	PPDR
32	BN	65	F	265654	53	12	5.9	133	209	48	139	147	2.89	6/12,N10	6/18,N12	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	BDR
33	SIV	66	M	259208	55	11	12.6	126	206	52	146	137	2.8	6/9,N8	6/12,N10	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	BDR

Sl. No.	Name	Age (Yrs)	Sex	IP No.	Age of Onset (Yrs)	Duration (Yrs)	Hb A1c	FBS	Cholestrol					BCVA		adnexa		conjunctiva		Cornea		AC		Pupil		Lens		Retinopathy grades
									Total	HDL mg/dl	LDL	TG	ldl: hdl	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS	
34	DH	62	F	259013	53	9	5.7	141	184	59	154	166	2.61	6/18,N10	6/18,N10	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	BDR
35	TU	70	F	265809	54	16	9.3	173	238	33	168	181	5.09	6/12,N6	6/12,N10	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	PDR
36	SVL	68	M	266063	57	11	10.9	176	203	54	163	181	3.01	6/12,N6	6/60,N6	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	PPDR
37	KUT	69	M	264960	54	15	5.6	163	219	49	98	126	2	6/18,N10	6/36,N18	N	N	N	N	arcus	arcus	N	N	RRR	RRR	IOL	CAT,	PPDR
38	GA	70	M	259621	47	23	10.4	134	184	59	147	158	2.49	6/18,N10	6/6,N6	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	PPDR
39	AKM	64	F	259126	51	13	5.7	84	211	37	159	169	4.29	6/12P,N6	6/60,N36	N	N	N	N	arcus	arcus	N	N	RRR	RRR	IOL	IOL	PPDR
40	STP	67	M	261496	49	18	6.9	213	162	49	181	131	3.69	CF3MT	6/60,N36	N	N	N	N	arcus	arcus	N	N	SLUG	RRR	N	CAT,	PDR+RE M
41	PAR	66	F	261277	48	18	10.1	96	228	36	163	183	4.52	6/18,N18	6/18,N10	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	PDR
42	MRT	61	M	261504	55	6	7.6	124	175	37	89	92	2.4	6/60,N18	6/36,N18	N	N	N	N	arcus	arcus	N	N	RRR	RRR	PSC	PSC	BDR
43	MH	62	M	258978	51	11	6.1	96	142	53	109	168	2.05	6/6,N6	6/12,N6	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	BDR
44	SG	61	M	263423	54	7	5.6	134	179	57	163	125	2.85	6/9,N6	6/18,N10	N	N	PTER	N	arcus	arcus	N	N	RRR	RRR	N	N	BDR
45	KHS	63	M	257192	50	13	6.8	143	208	52	126	137	2.42	6/12,N10	6/18,N10	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	BDR
46	VK	52	M	261998	44	8	5.2	113	208	58	142	134	2.44	6/12N10	6/18,N18	N	N	N	N	OPAC	arcus	N	N	RRR	RRR	N	CAT,	BDR
47	APA	75	M	239659	54	21	5.7	103	234	39	178	159	4.56	6/24,N36	6/60,N36	N	N	N	N	arcus	arcus	N	N	RRR	SLUG	N	N	PDR+LE M
48	NK	68	M	240721	48	20	14.4	146	178	41	123	171	3	6/36,N18	6/24,N12	N	N	N	N	arcus	arcus	N	N	RRR	RRR	IOL	IOL	PDR
49	VB	60	M	257147	42	18	7.1	136	171	54	114	173	2.11	6/9,N6	6/9,N8	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	PPDR
50	KLV	58	F	241135	51	7	8.6	203	205	39	135	138	3.46	6/60,N36	CF2MT	N	N	N	N	N	N	N	N	RRR	RRR	IOL	CAT,	PPDR
51	SOM	65	M	239731	44	21	8.1	134	113	42	157	158	3.73	6/12,N10	6/18,N10	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	PPDR
52	MHD	64	M	236835	54	10	12.3	125	191	42	129	89	3.07	6/12,N10	6/36,N18	N	N	N	N	arcus	arcus	N	N	RRR	SLUG	IOL	CAT,	PPDR+LE M
53	SHB	58	F	235694	40	18	9.7	152	208	38	171	169	4.5	6/9,N8	6/24,N8	N	N	N	N	N	N	N	N	RRR	RRR	IOL	CAT,	PPDR
54	ANJ	54	F	259429	43	11	6.1	102	187	50	137	159	2.74	6/18,N10	6/24,N12	N	N	N	N	N	OPAC	N	N	RRR	RRR	PSC	PSC	BDR
55	PRK	54	M	257412	48	6	9.6	159	193	47	133	183	2.82	6/12,N10	6/12,N10	N	N	N	PTER	N	N	N	N	RRR	RRR	N	N	BDR
56	SUJ	64	F	256879	51	13	4.9	129	187	48	119	121	2.47	6/18,N12	6/36,N18	N	N	N	N	arcus	arcus	N	N	RRR	RRR	IOL	CAT,	BDR
57	PAT	62	M	241695	51	11	4.8	123	231	51	129	98	2.52	6/9,N6	6/9,N6	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	BDR
58	NAG	55	F	258891	47	8	9.1	173	129	32	189	184	5.9	6/24,N18	CF1MT	N	N	N	N	N	N	N	N	RRR	RAPD	N	CAT,	PDR
59	RUD	60	F	248431	43	17	12.1	145	239	38	179	191	4.71	6/18,N12	6/18,N12	N	N	N	N	arcus	arcus	N	N	RRR	RRR	PSC	PSC	PDR
60	NAR	63	M	248412	46	19	6.3	113	244	37	184	169	4.97	CF2MT	6/12,N10	N	N	N	N	arcus	arcus	N	N	SLUG	RRR	N	N	PDR+RE M
61	ASH	51	M	241494	40	11	6.1	211	179	58	172	134	2.96	CF1MT	6/9,N6	N	N	N	N	N	N	N	N	RAPD	RRR	N	N	BDR
62	TUKR	62	M	241490	50	12	4.4	127	189	49	148	129	3.02	6/18,N10	6/18,N10	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	BDR
63	MLPA	54	M	261694	42	12	9.8	117	156	52	127	139	2.44	6/12P,N6	6/12,N12	N	N	N	N	N	N	N	N	RRR	RRR	N	N	BDR
64	SMT	65	F	241332	53	12	6.8	145	188	47	141	158	3	6/12,N10	6/9,N6	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	BDR
65	MDY	65	M	256980	51	14	7.1	106	193	59	116	163	1.96	PL,PR	6/12,N10	N	N	N	N	arcus	arcus	N	N	RAPD	RRR	N	N	BDR+RE M
66	DEV	55	M	241758	43	12	6.3	135	217	48	148	126	3.08	6/12,N10	6/9,N6	N	N	N	N	N	N	N	N	RRR	RRR	N	N	PPDR
67	ANS	59	F	248762	49	10	11.8	108	157	36	179	107	4.97	6/12,N6	6/12,N10	N	N	PTER	PTER	N	N	N	N	RRR	RRR	N	N	PPDR

Sl. No.	Name	Age (Yrs)	Sex	IP No.	Age of Onset (Yrs)	Duration (Yrs)	Hb A1c	FBS	Cholestrol					BCVA		adnexa		conjunctiva		Cornea		AC		Pupil		Lens		Retinopathy grades
									Total	HDL mg/dl	LDL	TG	ldl: hdl	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS	
68	RYP	50	M	248690	44	6	12.1	147	212	43	144	123	3.34	6/12,N6	6/60,N6	N	N	N	N	N	N	N	N	RRR	RRR	N	N	PPDR
69	VLB	61	M	256691	43	18	9.2	136	239	39	141	206	3.61	6/18,N10	6/9,N6	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	PPDR
70	VIT	61	M	248309	41	20	11.4	178	261	36	168	202	4.66	6/18,N10	6/6,N6	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	PDR
71	BLB	62	F	246689	51	11	9.3	159	239	33	173	187	5.24	CF3MT	CF1MT	N	N	N	N	arcus	arcus	N	N	SLUG	SLUG	CAT	IOL	PDR+BE M
72	PRT	65	F	242315	60	5	9.8	129	248	35	181	193	5.17	6/24,N18	6/18,N12	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	PDR
73	SID	48	M	246775	44	4	6.9	89	199	46	136	121	2.95	6/12,N10	6/12,N12	N	N	N	N	N	N	N	N	RRR	RRR	IOL	IOL	BDR
74	HAJ	48	M	248295	43	5	5.8	132	203	52	175	169	3.36	6/12,N10	CF1MT	N	N	N	N	N	N	N	N	RRR	SLUG	N	N	BDR + LE M
75	BBJ	67	M	246732	53	14	6.3	171	210	56	158	157	2.82	6/18,N18	6/24,N18	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	BDR
76	ABD	57	M	241987	50	7	10.8	203	197	58	143	148	2.46	6/12,N10	6/12,N10	N	N	N	N	N	N	N	N	RRR	RRR	N	N	BDR
77	NIS	62	M	246717	50	12	11.6	79	174	48	128	153	2.66	6/9,N6	6/12,N10	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	BDR
78	MRTI	57	M	241623	49	8	5.3	148	218	48	153	161	3.18	6/9,N6	6/12,N10	N	N	N	N	N	N	N	N	RRR	RRR	N	N	PPDR
79	SHTM	64	F	259316	50	14	7.6	137	123	34	166	169	4.88	6/12,N10	6/9,N6	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	PPDR
80	PRB	54	M	257412	48	6	10.3	153	226	49	118	156	2.4	6/9,N6	6/9,N6	N	N	N	N	N	N	N	N	RRR	RRR	N	N	PPDR
81	PRR	61	M	257954	54	7	8.4	145	235	51	149	193	2.92	6/12,N10	6/12,N10	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	PPDR
82	ARN	50	M	241293	42	8	9.33	142	231	46	169	129	3.67	6/9,N6	6/12,N10	N	N	N	N	N	N	N	N	RRR	RRR	N	N	BDR
83	CHD	60	M	241723	47	13	5.6	134	181	53	101	158	1.9	6/9,N6	6/12,N10	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	BDR
84	BPA	62	M	241653	44	18	8.1	123	211	57	128	143	2.24	6/12,N10	6/9,N6	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	BDR
85	BBR	76	M	241439	60	16	7.8	115	198	61	132	109	2.16	6/9,N6	6/9,N6	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	BDR
86	BSRV	63	M	257305	47	16	7.1	168	183	39	89	179	2.28	6/9,N8	6/12,N8	N	N	N	N	arcus	arcus	N	N	RRR	RR,SLU	IOL	IOL	PDR
87	STYV	65	F	239811	47	18	14.6	174	258	44	169	211	3.84	6/36,N18	6/36,N12	N	N	N	N	arcus	arcus	N	N	RRR	RRR	PSC	PSC	PDR
88	BAB	46	M	256996	41	5	6.3	154	168	59	128	161	2.16	6/9,N10	6/60,N36	N	N	PTER	N	arcus	arcus	N	N	RRR	SLUG	IOL	CAT,	BDR+LE M
89	GUL	55	F	258564	47	8	5.8	214	218	56	116	147	2.07	6/60,N36	6/60,N36	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	BDR
90	THO	75	M	258372	63	12	5.9	145	172	48	136	138	2.83	6/60,N36	6/60,N36	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	BDR
91	APJ	65	M	257189	43	22	7.6	178	128	38	163	159	4.28	PLPR	PLPR	N	N	N	N	arcus	arcus	N	N	IRR,SR	RR,SLU	N	N	PPDR+BE M
92	SHET	61	M	257986	48	13	8.5	231	206	54	178	121	3.29	6/18,N18	6/60,N36	N	N	N	N	arcus	arcus	N	N	RRR	SLUG	N	N	PPDR+LE M
93	SDN	60	M	258973	52	8	5.9	145	218	36	153	161	4.25	6/12,N10	6/12,N10	N	N	N	N	arcus	arcus	N	N	RRR	RRR	N	N	PPDR
94	GNP	70	M	259621	56	14	10.3	181	232	37	81	135	2.18	6/18P,N8	6/9,N6	N	N	PTER	PTER	arcus	arcus	N	N	RRR	RRR	N	N	PPDR
95	BPL	51	M	258113	46	5	8.9	152	273	37	193	189	5.21	6/12,N10	6/18,N12	N	N	N	N	N	N	N	N	RRR	RRR	N	N	PDR
96	ZAB	64	F	260868	49	15	6.9	103	239	42	164	191	3.9	CF5MT	6/18P,N18	N	N	N	N	arcus	arcus	N	N	SLUG	RRR	CAT	IOL	PDR+RE M
97	SND	60	M	258973	43	17	11.1	123	256	36	179	187	4.97	6/24,N18	6/18,N12	N	N	N		arcus	arcus	N	N	RRR	RRR	N	N	PDR
98	BHSK	43	M	254642	40	3	6.9	127	231	51	178	144	3.49	6/36,N18	6/24,N18	N	N	N	N	N	N	N	N	RRR	RRR	CAT	PSC	BDR
99	RNG	57	M	254739	41	16	8.1	121	197	58	139	128	2.39	6/18,N36	6/9,N6	N	N	N	N	N	N	N	N	RRR	RRR	N	N	BDR
100	RKM	59	F	241746	51	8	5.7	135	174	48	181	153	3.77	6/12,N10	6/9,N6	N	N	N	N	N	N	N	N	RRR	RRR	N	N	BDR