

"A ONE YEAR LONGITUDINAL STUDY TO KNOW  
THE PROGRESSION OF DIABETIC RETINOPATHY  
AFTER INTRA OCULAR LENS IMPLANTATION"

**By**

Dr. AFIYA WAHID KACHRU  
REG NO. BK0112001

**Dissertation**

Submitted to the  
KLE University, Belgaum, Karnataka

In Partial Fulfillment  
of the requirements for the degree of

MASTER OF SURGERY (M.S.)  
in  
OPHTHALMOLOGY

**Under the Guidance of**

**Dr. S. B. PATIL** MS,DOMS  
Professor and Head

**DEPARTMENT OF OPHTHALMOLOGY,  
JAWAHARLAL NEHRU MEDICAL COLLEGE,  
BELGAUM, KARNATAKA**

**APRIL - 2015**

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**KLE UNIVERSITY, BELGAUM,  
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I hereby declare that this dissertation entitled “**A ONE YEAR LONGITUDINAL STUDY TO KNOW THE PROGRESSION OF DIABETIC RETINOPATHY AFTER INTRA OCULAR LENS IMPLANTATION**” is a bonafide and genuine research work carried out by me under the guidance of **Dr. S. B. PATIL** MS,DOMS Professor and Head, Department of Ophthalmology, Jawaharlal Nehru Medical College, Nehru Nagar, Belgaum – 590010.

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## LIST OF ABBREVIATIONS USED

µm	-	Micro meter
AD	-	Anno domini
AGE	-	Advanced glycation end
APEDS	-	Andhra Pradesh Eye Disease Study
ASDIAB	-	Asian Young Diabetes Research
B.C.	-	Before Christ
BAB	-	Blood-aqueous barrier
BMI	-	Body mass index
CAD	-	Coronary artery disease
CI	-	Confidence interval
CME	-	Cystoid macular edema
CSME	-	Clinically significant macular edema
CURES	-	Chennai Urban Rural Epidemiology Study
DCCT	-	Diabetes Control and Complications Trial
DKA	-	Diabetic ketoacidosis
DM	-	Diabetes mellitus
CDC	-	Centers for Disease Control and Prevention
DME	-	Diabetic macular edema
DR	-	Diabetic retinopathy
DRS	-	Diabetic Retinopathy study
ECCE	-	Extraction to extracapsular cataract extraction
ESRD	-	End-stage renal disease
ETDRS	-	Early Treatment Diabetic Retinopathy Study
FFA	-	Fundus fluorescein angiography

FPG	-	Fasting plasma glucose
g	-	Gram
GAD	-	Glutamic acid decarboxylase
GIP	-	Glucose-dependent insulintropic polypeptide
GLP-1	-	Glucagonlike peptide-1
h	-	Hour
HbA1C	-	Hemoglobin A1C (glycated haemoglobin)
HMGA1	-	High mobility group A1
HRC	-	High-risk characteristics
HSS	-	Hyperglycemic hyperosmolar state
ICMR	-	Indian Council of Medical Research
IDDM	-	Insulin-dependent diabetes mellitus
IDF	-	International Diabetes Federation
IFG	-	Impaired fasting glucose
IGT	-	Impaired glucose tolerance
INSR	-	Insulin receptor gene
IOL	-	Intraocular lens
IRMA	-	Intraretinal microvascular abnormalities
LDL	-	Low-density lipoprotein
mg/dL	-	Milligram per deciliter
mmol/L	-	Millimole per liter
n	-	Total number
NGSP	-	National Glycohemoglobin Standardization Program
NIDDM	-	Non insulin dependent diabetes mellitus
NPDR	-	Non proliferative diabetic retinopathy

NVD	-	New vessel disc
NVE	-	New vessel elsewhere
OCT	-	Optical coherence tomography
OGTT	-	Oral glucose tolerance test
p	-	Probability
SVL	-	Severe visual loss
PAD	-	Peripheral arterial disease
PDR	-	Proliferative diabetic retinopathy
PKC	-	Protein kinase C
PRP	-	Panretinal photocoagulation
PVD	-	Posterior vitreous detachment
ROS	-	Reactive oxygen species
SD	-	Standard deviation
SICS	-	Small Incision Cataract Surgery
SNPs	-	Single-nucleotide polymorphisms
UKPDS	-	The United Kingdom Prospective Diabetes Study
VEGF	-	Vascular endothelial growth factor
VEGF	-	Vascular endothelial growth factor
WESDR	-	Wisconsin Epidemiologic Study of Diabetic Retinopathy
WHO	-	World Health Organization
WHR	-	Waist hip ratio

## **ABSTRACT**

### **Background and Objective**

Cataract surgery in diabetic patients is performed to improve the vision. However, there is higher incidence of post operative complications and progression of DR. Considering the scanty data on the progression of diabetic retinopathy after IOL implantation the present study was aimed to know the progression of diabetic retinopathy after intra-ocular lens implantation.

### **Methods**

This longitudinal study was carried out at Department of Ophthalmology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2013 to December 2013. A total of 50 patients with diabetes undergoing cataract surgery were included in the study. Patients were assessed at baseline and four months post operatively for the diabetic retinopathy based on EDTRS classification.

### **Results**

Most of the patients (44%) presented with age between 51 to 60 years and mean age was  $60.60 \pm 7.47$  years. The male to female ratio was 1:1 with 50% of the patients each being males and females. The mean duration of diabetes was  $5.16 \pm 4.15$  years and majority (66%) of the patients were on one oral hypoglycaemic agent. The mean blood sugar levels were noted as  $107.56 \pm 19.39$  mg/dL. Most of the patients had visual acuity of  $> 6/60$  in right (64%) and left eye (46%). Right eye cataract surgery was done in 64% of the patients and majority of the cases (98%) underwent SICS as it was done in free OT.

Progression of DR from normal to mild was noted in 14.29%, mild to moderate in 8.08% and moderate to severe in 6.12% of the patients.

### **Conclusion and interpretation**

The present study showed progression of diabetic retinopathy in 24.49% of the patients who underwent cataract surgery.

### **Key Words:**

Cataract; Diabetes mellitus; Diabetic retinopathy; Small Incision Cataract Surgery;

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## **INTRODUCTION**

Diabetes, a disease of developed countries, is one of the endocrine disorders that has reached epidemic proportions worldwide.<sup>1</sup> It is a major and growing threat to global public health.<sup>2</sup>

Worldwide type 2 diabetes mellitus (DM) accounts for more than 90% of the diabetic population and about 79 million Americans have prediabetes. The International Diabetes Federation predicts that the number of people living with diabetes will rise from 366 million in 2011 to 552 million by 2030.<sup>3</sup> According to the Centers for Disease Control and Prevention (CDC) report in 2011 nearly, 26 million Americans have diabetes.<sup>4</sup>

The top 10 countries with highest number of people with diabetes are currently India, China, the United States, Indonesia, Japan, Pakistan, Russia, Brazil, Italy, and Bangladesh. The prevalence of diabetes and its adverse health effects have risen more rapidly in South Asia than in any other region of the world.<sup>5</sup>

According to an ICMR survey in adults over 30 years,<sup>6</sup> prevalence of DM was two percent in urban India and one percent in rural India. The last three decades witnessed prevalence rates shooting up to 12 to 16% in urban India and 3 to 8% in rural India which means a 600 to 800% increase in prevalence rates of diabetes something which is unparalleled in any Western nation. Indeed, India is now referred to as the “Diabetic Capital” of the world.

The chronic hyperglycemia of diabetes is associated with long term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart

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and blood vessels. It is a chronic and potentially disabling disease which is reaching an epidemic proportion in many parts of the world.

Diabetic retinopathy (DR) is one of the commonest and easily demonstrable examples of microvascular damage that diabetes inflicts throughout the body. DR is among the leading causes of blindness in people of working age, affecting both the genders equally. Patients with type 1 diabetes may show evidence of retinopathy as early as 5 years after the onset of diabetes, and almost all patients will show varying degrees of retinopathy 20 years after the onset of diabetes. Background retinopathy may even be present at the time of diagnosis of type 2 diabetic patients, consistent with the usually long duration of subclinical hyperglycemia in such patients and more than 60% of type 2 diabetic patients will have some degree of retinopathy after 20 years of onset of diabetes.<sup>7</sup>

The retina is particularly vulnerable to microvascular damage in diabetes due to its high metabolic and oxygen demands and its dependence on an intact blood-retinal barrier. Damage is caused by both microvascular leakage from breakdown of the inner blood-retinal barrier and microvascular occlusion both of which can be distinguished from each other by fluorescein angiography. This may result in different stages from background retinopathy to advanced eye disease.<sup>7</sup>

The treatment modalities for the management of DR include laser and surgical interventions. However, it is known that diabetic eyes have more complications after cataract surgery than nondiabetic eyes, particularly more pronounced postoperative inflammation and a poorer visual acuity. Many authors have tried to identify risk factors for visual prognosis and progression of DR

following cataract surgery in diabetic eyes. Diabetic eyes have many disturbances within the anterior segment, such as a bigger lens, a steeper anterior lens curvature, and a shallower anterior chamber, especially in eyes with diabetic retinopathy. These changes may make surgery more difficult. The diabetic eye is also more susceptible to surgical trauma than the non-diabetic eye. Surgically more pronounced miosis, a longer duration of surgery, a more fragile lens capsule with a higher rate of rupture, a higher postoperative flare intensity, a transient elevation of intraocular pressure, and a higher incidence of angiographic cystoid macular oedema have been found in diabetic eyes. Surgical technique contributes to the incidence of postoperative complications in the anterior and the posterior segment of the eye. The breakdown of blood-aqueous barrier (BAB) by surgical trauma produces postoperative inflammation with a pigment dispersion, a fibrinoid reaction, and development of posterior synechiae.<sup>8</sup>

Progress in surgical technique from intracapsular cataract extraction to extracapsular cataract extraction (ECCE) and improvements in intraocular lens (IOL) technology have increased the indications for cataract surgery in diabetic patients. However, ECCE requires a large incision and the nucleus is expressed through the pupil with a certain degree of iris trauma. Phacoemulsification technique allows the surgeon to remove a cataract through a smaller incision than with manual ECCE.<sup>8</sup>

Phacoemulsification also has an advantage over previous cataract surgical procedures because of quick recovery of vision and less postoperative inflammation. Heparin coated IOLs, may also be suitable for diabetic eyes because of decreased postoperative inflammation.<sup>8</sup>

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However, recent studies have reported progression of DR and vision deterioration inspite of cataract removal because of increased vascular leak and post operative cystoid macular oedema secondary to vascular endothelial growth factor.<sup>9</sup> In contrast, it is also hypothesized that uncomplicated cataract surgery does not cause any progression of diabetic retinopathy post operatively and progression observed may be due to the natural history of the disease.<sup>10</sup> These controversies demonstrate the need of further evaluation for the progression of DR after IOL implantation. Hence the present study was undertaken to know the progression of DR after IOL implantation.

## **OBJECTIVES**

The objective of this study was to know the progression of diabetic retinopathy after intra-ocular lens implantation.

## **REVIEW OF LITERATURE**

### **DIABETES MELLITUS**

Diabetes Mellitus, a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both.<sup>2</sup>

Diabetes mellitus (DM) an epidemic in many parts of the world is a chronic and potentially disabling disease. The biggest impact of the disease is particularly in developing countries among adults. The vast majority of patients fall into two broad categories: those having little or no endogenous insulin secretory capacity (IDDM or type 1 DM) and those who retain endogenous insulin secretory capacity but have a combination of resistance to insulin action and an inadequate compensatory insulin secretory response (NIDDM, or Type 2 DM).<sup>2,11</sup>

### **Historical Review**

Diabetes is perhaps as old as mankind. Cognizance of symptoms related to diabetes and recognition of the disorder was confined to a few geographic and cultural locations in the Ancient Era (up to 600 AD).

During the later decades of the 19<sup>th</sup> and first half of the 20<sup>th</sup> century, round progress was achieved in the knowledge of pathology, predisposing factors, management, course and complications of diabetes mellitus. Advancements have been made the last century (contemporary period) involving epidemiology, genetics, immunology and molecular biology which has led to a vast information on various aspects of this versatile disorder.<sup>6,12</sup>

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Some key developments in scientific and clinical understanding of diabetes may be summarized as follows:

The earliest mention of diabetes like illness characterized by polyuria can be traced to Egyptian Papyrus dating back to around 1550 B.C.<sup>12</sup>

The sweet taste of diabetic urine was noted in the 5<sup>th</sup> and 6<sup>th</sup> century AD by the Indian physicians and in the 17<sup>th</sup> century by Thomas Willis. The term ‘Diabetes mellitus’, an allusion to the honeyed taste of urine, was first used in the late 18<sup>th</sup> century by John Rollo and others, to distinguish it from other polyuric states in which urine was tasteless.<sup>12</sup>

In 1893, Edovard Laguesse named that pancreatic islets after Paul Langerhans, who had described them in 1869, and suggested that they produced a glucose lowering substance. Then this hypothetical hormone was named ‘insulin’ by Jean de Meyer in 1909, over a decade before its discovery.<sup>12</sup>

Insulin was discovered at the University of Toronto in 1921, through collaboration between Frederick G. Banting, Charles H. Best, James B. Collip and J.J.R. Macleod. Insulin was extracted from chilled pancreas in an acid / ethanol mixture; the extracts were found to lower blood glucose levels in pancreatectomized dogs and were first tested in a human diabetic in January 1922.<sup>12</sup>

### **Diabetes mellitus today**

Diabetes mellitus refers to a group of common metabolic disorder that shares the phenotype of hyperglycemia. Several distinct types of DM exist and are caused by a complex interaction of genetics and environmental factors. Depending on the

etiology of the DM, factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production.<sup>2,13</sup>

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. In the United States, DM is the leading cause of end-stage renal disease (ESRD), non traumatic lower extremity amputations, and adult blindness.<sup>2,6,13-15</sup>

## **CLASSIFICATION OF DIABETES MELLITUS**

DM is classified on the basis of the pathogenic process that leads to hyperglycemia, as opposed to earlier criteria such as age of onset or type of therapy. The two broad categories of DM are designated as Type 1 & Type 2.<sup>6</sup> Both types of diabetes are preceded by a phase of abnormal glucose homeostasis as the pathogenic processes.

Type 1 diabetes is the result of complete or near-total insulin deficiency whereas, type 2 DM is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production. Distinct genetic and metabolic defects in insulin action and/or secretion give rise to the common phenotype of hyperglycemia in type 2 DM and have important potential therapeutic implications.

Type 2 DM is preceded by a period of abnormal glucose homeostasis classified as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT).<sup>6</sup>

## **Epidemiology**

### Worldwide

It is estimated that 366 million people had DM in 2011 and by 2030 this will rise to 552 million. The number of people with type 2 DM is increasing in every country with 80% of people with DM living in low- and middle-income countries. DM caused 4.6 million deaths in 2011. It is estimated that 439 million people would have type 2 DM by the year 2030.<sup>16</sup> The incidence of type 2 DM varies substantially from one geographical region to the other as a result of environmental and lifestyle risk factors.<sup>17</sup>

A 2011 Centre for Disease Control and Prevention (CDC) reported that DM affects about 25.8 million people in the US (7.8% of the population) in 2010 with 90% to 95% of them being type 2 DM.<sup>18</sup>

Globally, age-standardized prevalence of DM was found to be 9.8% in men and 9.2% in women with observed regional disparity, as a high prevalence of DM was found in South Asia, Latin America, the Caribbean, Central Asia, North Africa, and the Middle East.<sup>19</sup>

### Indian scenario

India is often referred as the diabetes capital of the world as currently its experiencing an epidemic of type 2 diabetes mellitus with the largest number of diabetic patients. The International Diabetes Federation 2009 report reveals that the total number of diabetic subjects in India is 50.8 million.<sup>20</sup>

Diabetes mellitus is a disease of grave concern not only because of its rapidly increasing prevalence, but also because various studies have shown rising prevalence of diabetes in young and middle aged people. Increased prevalence of diabetes mellitus would also increase the disease burden and put socio-economic pressure on the most productive age group and health systems in the country.<sup>21</sup>

Disparity exist across the country as in urban areas the prevalence of DM is from 5.9% to 12.1% (North: 8.6% to 11.6%; South: 13.5% to 19.5%). Rural India also has high prevalence of DM (about 2.0% to 10.0%).<sup>20</sup> A systematic review for DM in tribal population of India observed a ranging prevalence of 0.7% to 10.0%, with a final estimate of 5.9%.<sup>22</sup>

A review<sup>22</sup> showed higher prevalence of diabetes (19.78%) in Karnataka as well as another study<sup>23</sup> also showed higher prevalence of diabetes (12.5%) in Kerala, South India. Many villages in south India especially Kerala and Karnataka have undergone a marked change in living standards and lifestyles on account of the influx of money in recent years from people working abroad in the Gulf States and other affluent countries. Higher prevalence of diabetes could be expected in south India especially Kerala since it has the highest proportion of elderly in India.<sup>23</sup> In Karnataka, the prevalence of diabetes was more in women (22.04%) compare to men (16.06%).<sup>23</sup>

Asian Indians are more susceptible to risk factors like age, adiposity (based on BMI), and central obesity (WHR). Despite the low BMI among Asian Indians as compared to other ethnic groups, BMI is strongly associated with glucose tolerance.<sup>20</sup>

### Race

The prevalence of type 2 diabetes mellitus varies widely among various racial and ethnic groups. Type 2 diabetes mellitus is becoming virtually pandemic in some groups of Native Americans and Hispanic people. The risk of retinopathy and nephropathy appears to be greater in blacks, Native Americans, and Hispanics.<sup>24</sup>

### Sex

Type 2 DM is slightly more common in older women than men.<sup>24</sup> A nationwide survey across India showed 1.3% prevalence of self-reported DM, which was more in men (1.5%) as compared to women (1.0%) [23].

### Age

While type 2 diabetes mellitus traditionally has been thought to affect individuals older than 40 years, it is being recognized increasingly in younger persons, particularly in highly susceptible racial and ethnic groups and in obese. In some areas, more type 2 than type 1 diabetes mellitus is being diagnosed in prepubertal children, teenagers, and young adults. Virtually all cases of diabetes mellitus in older individuals are type 2.<sup>24</sup>

Prevalence of diabetes in India study reported an age-standardized prevalence of 4.3%, 4.4% and 4.5% for all adults, and males and females, respectively.<sup>25</sup>

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## CRITERIA FOR THE DIAGNOSIS OF DIABETES MELLITUS<sup>12,13</sup>

- Symptoms of diabetes plus random blood glucose concentration more than 11.1 mmol/L (200 mg/dL)<sup>a</sup> *or*
- Fasting plasma glucose more than 7.0 mmol/L (126 mg/dL)<sup>b</sup> *or*
- Two-hour plasma glucose more than 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test<sup>c</sup>

**Note:** In the absence of unequivocal hyperglycemia and acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day.

<sup>a</sup>Random is defined as without regard to time since the last meal.

<sup>b</sup>Fasting is defined as no caloric intake for at least 8 h.

<sup>c</sup>The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water; not recommended for routine clinical use.

### Pathophysiology

#### Type 1

Type 1 DM is the culmination of lymphocytic infiltration and destruction of insulin-secreting beta cells of the islets of Langerhans in the pancreas. As beta-cell mass declines, insulin secretion decreases until the available insulin no longer is adequate to maintain normal blood glucose levels. After 80-90% of the beta cells are destroyed, hyperglycemia develops and diabetes may be diagnosed.

Currently, autoimmunity is considered the major factor in the pathophysiology of type 1 DM.

Approximately 85% of type 1 DM patients have circulating islet cell antibodies, and the majority also have detectable anti-insulin antibodies before receiving insulin therapy. The most commonly found islet cell antibodies are those

directed against glutamic acid decarboxylase (GAD), an enzyme found within pancreatic beta cells.

#### *Sensory and autonomic neuropathy*

Sensory and autonomic neuropathy in people with diabetes are caused by axonal degeneration and segmental demyelination. Many factors are involved, including the accumulation of sorbitol in peripheral sensory nerves from sustained hyperglycemia. Motor neuropathy and cranial mononeuropathy result from vascular disease in blood vessels supplying nerves.

#### *Angiopathy*

Using nailfold video capillaroscopy, a study detected a high prevalence of capillary changes in patients with diabetes, particularly those with retinal damage. This reflects a generalized microvessel involvement in both type 1 and type 2 DM.<sup>26</sup>

Microvascular disease causes multiple pathologic complications in people with diabetes. Hyaline arteriosclerosis, a characteristic pattern of wall thickening of small arterioles and capillaries, is widespread and is responsible for ischemic changes in the kidney, retina, brain, and peripheral nerves.

Atherosclerosis of the main renal arteries and their intrarenal branches causes chronic nephron ischemia. It is a significant component of multiple renal lesions in diabetes.

## *Nephropathy*

In the kidneys, the characteristic wall thickening of small arterioles and capillaries leads to diabetic nephropathy, which is characterized by proteinuria, glomerular hyalinization (Kimmelstiel-Wilson), and chronic renal failure.

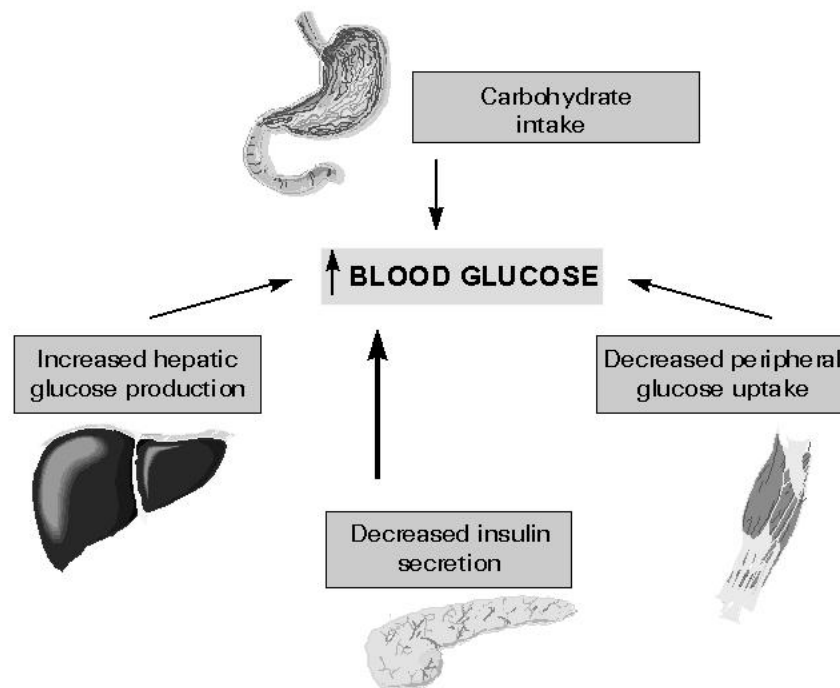
Genetic factors influence the development of diabetic nephropathy. Single-nucleotide polymorphisms affecting the factors involved in its pathogenesis appear to influence the risk for diabetic nephropathy in different people with type 1 DM.<sup>27</sup>

## Type 2

Type 2 diabetes is characterized by a combination of peripheral insulin resistance and inadequate insulin secretion by pancreatic beta cells. Insulin resistance, which has been attributed to elevated levels of free fatty acids and proinflammatory cytokines in plasma, leads to decreased glucose transport into muscle cells, elevated hepatic glucose production, and increased breakdown of fat.

A role for excess glucagon cannot be underestimated; indeed, type 2 diabetes is an islet paracrinopathy in which the reciprocal relationship between the glucagon-secreting alpha cell and the insulin-secreting beta cell is lost, leading to hyperglucagonemia and hence the consequent hyperglycemia.<sup>28</sup>

For type 2 diabetes mellitus to occur, both insulin resistance and inadequate insulin secretion must exist.



**Figure 1. Simplified scheme for the pathophysiology of type 2 diabetes mellitus**

#### *Beta-cell dysfunction*

Beta-cell dysfunction is a major factor across the spectrum of prediabetes to diabetes. A study of obese adolescents confirms what is increasingly being stressed in adults as well: Beta-cell dysfunction develops early in the pathologic process and does not necessarily follow the stage of insulin resistance.<sup>29</sup>

#### *Insulin resistance*

In the progression from normal to abnormal glucose tolerance, first postprandial blood glucose levels increase followed by fasting hyperglycemia as suppression of hepatic gluconeogenesis fails. During the induction of insulin resistance (such as occurs with a high-calorie diet, steroid administration, or physical inactivity), increased glucagon levels and increased glucose-dependent

insulinotropic polypeptide (GIP) levels accompany glucose intolerance. However, the postprandial glucagonlike peptide-1 (GLP-1) response is unaltered.<sup>30</sup>

#### *Genomic factors*

Genome-wide association studies of single-nucleotide polymorphisms (SNPs) have identified a number of genetic variants that are associated with beta-cell function and insulin resistance. Some of these SNPs appear to increase the risk for type 2 diabetes. Over 40 independent loci demonstrating an association with an increased risk for type 2 diabetes have been shown.<sup>31</sup> A subset of the most potent are as below:<sup>32</sup>

- Decreased beta-cell responsiveness, leading to impaired insulin processing and decreased insulin secretion (*TCF7L2*)
- Lowered early glucose-stimulated insulin release (*MTNR1B, FADS1, DGKB, GCK*)
- Altered metabolism of unsaturated fatty acids (*FSADS1*)
- Dysregulation of fat metabolism (*PPARG*)
- Inhibition of serum glucose release (*KCNJ11*)
- Increased adiposity and insulin resistance (*FTO* and *IGF2BP2*)
- Control of the development of pancreatic structures, including beta-islet cells (*HHEX*)
- Transport of zinc into the beta-islet cells, which influences the production and secretion of insulin (*SLC30A8*)
- Survival and function of beta-islet cells (*WFS1*)

The high mobility group A1 (HMGA1) protein is a key regulator of the insulin receptor gene (*INSR*).<sup>33</sup> Functional variants of the *HMGA1* gene are associated with an increased risk of diabetes.

#### *Amino acid metabolism*

Amino acid metabolism may play a key role early in the development of type 2 diabetes. A study reported that the risk of future diabetes was at least 4-fold higher in normoglycemic individuals with high fasting plasma concentrations of 3 amino acids (isoleucine, phenylalanine, and tyrosine). Concentrations of these amino acids were elevated up to 12 years prior to the onset of diabetes.<sup>34</sup>

## **SCREENING<sup>2</sup>**

Diabetes was originally identified by the presence of glucose in the urine. Almost 2,500 years ago it was noticed that ants were attracted to the urine of some individuals. In the 18th and 19th centuries the sweet taste of urine was used for diagnosis before chemical methods became available to detect sugars in the urine. Tests to measure glucose in the blood were developed over 100 years ago, and hyperglycemia subsequently was criterion recommended for the diagnosis of diabetes.

The most widely accepted glucose-based criteria for diagnosis are fasting plasma glucose (FPG)  $\geq 126$  mg/dL or a 2-h plasma glucose  $\geq 200$  mg/dL during an oral glucose tolerance test (OGTT) on more than one occasion. In a patient with classic symptoms of diabetes, a single random plasma glucose  $\geq 200$  mg/dL is considered diagnostic. Before 2010 virtually all diabetes societies recommended blood glucose analysis as the exclusive method to diagnose diabetes. However, over

the last few years many physicians have been using hemoglobin A1C for screening and diagnosing diabetes. Although considered the “gold standard” for diagnosis, measurement of glucose in the blood is subject to several limitations, many of which are not widely appreciated. Further measurement of HbA1C for diagnosis has some inherent limitations.<sup>35</sup>

*Current criteria for the diagnosis of diabetes*<sup>36</sup>

- A1C  $\geq 6.5\%$ . The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP)-certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay
- Fasting plasma glucose (FPG)  $\geq 126$  mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h, or
- 2-h plasma glucose  $\geq 200$  mg/dl (11.1 mmol/l) during an oral glucose tolerance test (OGTT). The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water
- In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose  $\geq 200$  mg/dl (11.1 mmol/l)
- In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing.

Oral Glucose Tolerance Test

The OGTT evaluates the efficiency of the body to metabolize glucose and is the “gold standard” for diagnosis of diabetes. An increase in postprandial glucose

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concentration usually occurs before fasting glucose increases. Therefore, postprandial glucose is a sensitive indicator of the risk for developing diabetes and an early marker of impaired glucose homeostasis.<sup>35</sup>

The OGTT is accepted as a diagnostic modality by the ADA, WHO/International Diabetes Federation (IDF),<sup>37</sup> and other organizations. However, extensive patient preparation is necessary to perform an OGTT. Important conditions include, among others, ingestion of at least 150 g of dietary carbohydrate per day for 3 days prior to the test, a 10- to 16-h fast, and commencement of the test between 7:00 a.m. and 9:00 a.m.<sup>35</sup>

*Advantages*

- Sensitive indicator of risk of developing diabetes.
- Early marker of impaired glucose homeostasis

*WHO Diabetes criteria - Interpretation of Oral Glucose Tolerance Test (1999)*<sup>38</sup>

Glucose levels	NORMAL		Impaired fasting glycaemia (IFG)		Impaired glucose tolerance (IGT)		Diabetes Mellitus (DM)	
	Fasting	2hrs	Fasting	2hrs	Fasting	2hrs	Fasting	2hrs
(mmol/L)	<6.1	<7.8	≥ 6.1 & <7.0	<7.8	<7.0	≥7.8	≥7.0	≥11.1
(mg/dL)	<110	<140	≥110 & <126	<140	<126	≥140	≥126	≥200

*ADA criteria for diagnosis of diabetes mellitus*<sup>39</sup>

Summarized Interpretation of Oral Glucose Tolerance Test (OGTT)

- 2 hour postload glucose of < 140 mg/dl = normal glucose tolerance

- 2 hour postload glucose between 140 mg/dl and 199 mg/dl = impaired glucose tolerance
- 2 hour postload glucose > 200 mg/dl = provisional diagnosis of diabetes (Must be confirmed on a subsequent day by any of the above criteria for diagnosis of Diabetes Mellitus.)

## **Complications of diabetes mellitus**

### ***Acute Complications of DM***

Acute complications of DM are diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are acute complications of diabetes. DKA was formerly considered a hallmark of type 1 DM, but it also occurs in individuals who lack immunologic features of type 1 DM and who can subsequently be treated with oral glucose-lowering agents (these obese individuals with type 2 DM are often of Hispanic or African-American descent). HHS is primarily seen in individuals with type 2 DM. Both disorders are associated with absolute or relative insulin deficiency, volume depletion, and acid-base abnormalities. DKA and HHS exist along a continuum of hyperglycemia, with or without ketosis.<sup>6,13</sup>

### ***Chronic Complications of DM***

The chronic complications of DM affect many organ systems and are responsible for the majority of morbidity and mortality associated with the disease. Chronic complications can be divided into vascular and nonvascular complications. The vascular complications of DM are further subdivided into microvascular (retinopathy, neuropathy, nephropathy) and macrovascular complications [coronary

artery disease (CAD), peripheral arterial disease (PAD), cerebrovascular disease]. Nonvascular complications include problems such as gastroparesis, infections, and skin changes. Long-standing diabetes may be associated with hearing loss. Whether type 2 DM in elderly individuals is associated with impaired mental function is not clear.<sup>13</sup>

### **Chronic complications of diabetes mellitus**

1. Microvascular
  - a. Eye disease
    - i. Retinopathy (nonproliferative/proliferative)
    - ii. Macular edema
  - b. Neuropathy
    - i. Sensory and motor (mono- and polyneuropathy)
    - ii. Autonomic
  - c. Nephropathy
2. Macrovascular
  - a. Coronary artery disease
  - b. Peripheral arterial disease
  - c. Cerebrovascular disease
3. Other
  - a. Gastrointestinal (gastroparesis, diarrhea)
  - b. Genitourinary (uropathy/sexual dysfunction)
  - c. Dermatologic
  - d. Infectious
  - e. Cataracts

- f. Glaucoma
- g. Periodontal disease

The risk of chronic complications increases as a function of the duration of hyperglycemia; they usually become apparent in the second decade of hyperglycemia. Since type 2 DM often has a long asymptomatic period of hyperglycemia, many individuals with type 2 DM have complications at the time of diagnosis.<sup>16</sup>

The Microvascular complications of both type 1 and type 2 DM result from chronic hyperglycemia. Large, randomized clinical trials of individuals with type 1 or type 2 DM have conclusively demonstrated that a reduction in chronic hyperglycemia prevents or delays retinopathy, neuropathy and nephropathy. Other incompletely defined factors may modulate the development of complications.<sup>40</sup>

## **DIABETIC RETINOPATHY**

Diabetic retinopathy (DR) is one of the commonest and easily demonstrable examples of microvascular damage that diabetes inflicts throughout the body. DR is among the leading causes of blindness in people of working age, affecting both the genders equally.<sup>7</sup>

Patients with type 1 diabetes may show evidence of retinopathy as early as 5 years after the onset of diabetes, and almost all patients will show varying degrees of retinopathy 20 years after the onset of diabetes. Background retinopathy may even be present at the time of diagnosis of type 2 diabetic patients, consistent with the usually long duration of subclinical hyperglycemia in such patients and more than

60% of type 2 diabetic patients will have some degree of retinopathy after 20 years of onset of diabetes.<sup>7</sup>

### **Epidemiology**

In 1981, a study of the natural history of diabetic retinopathy in 461 people with juvenile-onset insulin-dependent diabetes mellitus (IDDM) was done. At diagnosis no DR was found, with prevalence of 50% at 7 yrs duration and 90% at 17-50 yrs duration. Proliferative diabetic retinopathy (PDR) was first seen at 13 yrs, with 26% prevalence at 26-50 yrs duration.<sup>41</sup>

A longitudinal analysis of the WESDR study in 1984 reported that for the 154 people with IDDM diagnosed > 30 yrs. with no DR at first visit, 47% developed DR after 4 yrs.<sup>42,43</sup> For the 418 people with IDDM diagnosed > 30 yrs. with no PDR at first visit, 7% developed PDR after 4 years and worsening of DR in 34%. For the 320 non IDDM diagnosed > 30 yrs. with no DR at first visit, 34% (developed DR after 4 yrs. For the 486 non IDDM diagnosed > 30 yrs. with no PDR at first visit, 2% developed PDR after 4 years and worsening of DR in 25%. Further there is clear evidence that sight-threatening diabetic retinopathy has a recognisable latent or early symptomatic stage.<sup>44</sup>

The Diabetes Control and Complications Trial (DCCT)<sup>45-47</sup> included 1441 people with type 1 DM, 726 with no DR at base line (the primary-prevention cohort), and 715 with mild to moderateretinopathy (the secondary-intervention cohort), with mean follow-up of 6.5 years. For the primary-prevention cohort, intensive therapy reduced the mean risk for the development of DR by 76 % (CI 62-85 %), compared with conventional therapy. For the secondary-intervention cohort, intensive therapy

slowed the progression of DR by 54 % (CI 39-66 %) and reduced the development of PDR or severe NPDR by 47 % (CI 14-67 %).

The United Kingdom Prospective Diabetes Study<sup>42,48</sup> recruited 3867 with type 2 DM and the effect of intensive blood-glucose control with sulphonylureas or insulin was compared with conventional treatment. Compared with the conventional group, there was a 25% risk reduction (7-40, p=0.0099) in the intensive group in microvascular endpoints, including the need for retinal photocoagulation. Patients allocated metformin, compared with the conventional group, had risk reductions of 32% (95% CI 13-47, p=0.002) for any diabetes-related endpoint.

A systematic review published by Williams<sup>49</sup> in 2004 on the epidemiology of diabetic retinopathy and macular oedema concluded that studies of sufficient size to stratify for age and duration of eye disease show an increase in DR in older age groups with long-standing disease.

A study<sup>50</sup> reported the 25 year incidence of proliferative retinopathy among population-based cohort of 727 type 1 Danish diabetic patients was 42.9%.

In 2009, a systematic review<sup>51</sup> was conducted on rates of progression in diabetic retinopathy during different time periods. The authors concluded that since 1985, lower rates of progression to PDR and severe visual loss (SVL) were being reported by the studies included in the review. These findings may reflect an increased awareness of retinopathy risk factors; earlier identification and initiation of care for patients with retinopathy; and improved medical management of glucose, blood pressure, and serum lipids.

### Indian scenario

In India with the epidemic increase in type 2 diabetes mellitus as reported by the World Health Organization (WHO),<sup>52</sup> diabetic retinopathy is fast becoming an important cause of visual disability.

An earlier study done in a clinic-based population reported an overall prevalence of 14%. NPDR was observed in 6%, while 4% had macular oedema and 4% had PDR.<sup>53</sup> Asian Young Diabetes Research (ASDIAB) Study, reported the prevalence of DR in 724 young diabetic subjects of age 12-40 yr with duration of diabetes < 12 months in 7 centres of four Asian countries. It is interesting to note that DR prevalence was least among Indians (5.3%) as compared to other ethnic groups like Malays (10%) and Chinese (15.1%).<sup>54</sup> Higher levels of fasting C-peptide and glucagon stimulated C-peptide among the Indians in this study, may partly explain the lower prevalence of DR in this group.

In India, the Andhra Pradesh Eye Disease Study (APEDS) of self-reported diabetics, the prevalence of DR was 22.4%.<sup>55</sup> The Chennai Urban Rural Epidemiology Study (CURES), evaluated urban sample of diabetic patients and estimated the overall prevalence of DR as 17.6%.<sup>56</sup>

### **Risk factors**

#### Duration of diabetes

There is a direct correlation between the frequency and severity of DR and the duration of DM.<sup>42</sup>

In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), the widest and most prolonged population based ophthalmologic survey, reported that higher prevalence of DR was associated with longer duration of diabetes. In persons with type 1 diabetes with less than 5 yr of duration, the prevalence of retinopathy was about 10%, whereas it ranged from 25 to 40% in individuals with type 2 diabetes.<sup>57</sup>

In India, virtually all studies have shown an increased prevalence of DR as the duration of diabetes increased.<sup>58</sup> In a study among type 2 diabetes, it was reported that 87.5% of those with >15 yr duration of diabetes had DR compared with 18.9% of those who had <15 yr duration.<sup>55</sup> In the CURES Eye study, 41.8 % had DR after 15 yr of diabetes and severity of DR proportionally increased with longer duration of diabetes. In addition, it has been demonstrated that for every five year increase in duration of diabetes, the risk for DR increased by 1.89 times.<sup>56</sup>

### Glycemic control

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 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.<sup>45</sup> Intensive diabetic control leads to reduction in the development and progression of all diabetic complications.<sup>59</sup>

There is strong evidence to suggest that the development and progression of DR is influenced by the level of hyperglycaemia. The protective effect of glycaemic

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control on the development and progression of DR has been investigated in both type 1 (WESDR and Diabetes Control and Complications Trial- DCCT) and type 2 diabetic patients (UKPDS).<sup>58</sup> In the 14 yr progression of retinopathy study (WESDR), the prevalence of retinopathy in type 1 diabetic subjects was 12 % when glycated haemoglobin (HbA1c) was <7% as compared to 40.7% when HbA1c levels were >10% and an increased risk of PDR was associated with more severe baseline retinopathy and higher HbA1c levels.<sup>60</sup> The DCCT Research Group<sup>45</sup> demonstrated that intensive therapy reduced the mean risk of retinopathy by 76% as compared with conventional therapy in the primary-prevention cohort. While in the secondary intervention cohort, intensive therapy reduced the risk of eye complications by 54% for the development of DR, decreased progression of NPDR to PDR or severe NPDR by 47% and the need for laser therapy by 56%. Another study<sup>61</sup> also showed that the visual outcome of laser photocoagulation for eyes with PDR was also dependent on the degree of glycaemic control.

In the CURES Eye Study, a linear trend in the prevalence of retinopathy with increase in quartiles of HbA1c (trend Chi square: 51.6,  $P < 0.001$ ) from 8.1 % (HbA1c level < 6.9%) to 31.7% (HbA1c level >10.3%) was observed. For every 2 % elevation of HbA1c, the risk for DR increased by a factor of 1.7.<sup>56</sup> In the UKPDS,<sup>62</sup> the risk reduction in eye complications for every 1% decrease in HbA1c was 19%. Thus it is observed that long term glycemic control plays an important role in delaying the onset and lowering down the progression of DR.

### Age and sex

The prevalence and severity of DR increases with increasing age in type 1 DM but not in type 2 DM.<sup>42</sup>

Studies have shown varying results when predicting gender as a risk factor for developing DR. In the Joslin clinic patients, there appeared to be excess females over males in the older-onset group, however among those with PDR, males were equal to females.<sup>63</sup> In the clinic cohort in Chennai DR appeared to be prevalent more in the males compared to females (sex ratio 2:1).<sup>64</sup> A similar preponderance has been reported from the CURES Eye study,<sup>56</sup> UKPDS study<sup>20</sup> and the Hyderabad study.<sup>55</sup>

### Hypertension

Studies, such as WESDR and UKPDS, suggest that hypertension increases the risk and progression of DR and DME. In UKPDS, tight control of blood pressure resulted in 34% reduction in progression of retinopathy with 47% reduced risk of deterioration in visual acuity of three lines.<sup>62</sup>

Increased blood pressure has been hypothesized, through the effects of increased sheer stress of blood flow, to damage the retinal capillary endothelial cells in eyes of people with diabetes. The possible mechanisms by which hypertension may affect DR are haemodynamic (impaired auto regulation and hyperperfusion) and through VEGF (vascular endothelial growth factor). This hypothesis has been supported by observations from clinical studies which showed an association between hypertension and the presence and severity of retinopathy in people with diabetes.<sup>58</sup>

The UKPDS showed that the incidence of retinopathy was associated with systolic blood pressure,<sup>66</sup> while in the WESDR, diastolic blood pressure was a significant predictor of progression of diabetic retinopathy to PDR over 14 yr of follow up in patients with type 1 diabetes.<sup>60</sup> In the Indian context, hypertension was not a significant confounding factor in the CURES Eye study, however uncontrolled hypertension did influence the progression of DR.<sup>56</sup>

### Nephropathy

The presence of gross proteinuria at baseline has been reported to be associated with 95% increased risk of developing DME among type I patients in the WESDR. The prevalence of PDR was much higher in patients with persistent microalbuminuria.<sup>67</sup>

A link between renal and retinal angiopathy in diabetes has been recognized, an effect that may be mediated through an increase in blood pressure, fibrinogen levels and lipoproteins.<sup>68</sup> Cross-sectional and longitudinal studies report a relationship between microalbuminuria, proteinuria and retinopathy.<sup>58</sup> Proteinuria was present in 29.2% of the subjects with DR in the CURES Eye study,<sup>56</sup> while studies from north India have suggested a correlation between DR and microalbuminuria.<sup>58</sup> A study from South Indian reported that the prevalence of proliferative retinopathy was significantly higher in type 2 diabetic patients with macroproteinuria (35%) compared with those with microproteinuria (4%).<sup>53</sup> Another study<sup>43</sup> demonstrated a significant association between DR and preclinical morphologic changes of diabetic nephropathy in type 1 diabetic patients.

### Genetics

In WESDR, patients with HLA DR4 and absent HLA DR3 were found to be at a greater risk of having PDR. Data from the DCCT also suggested genetic predisposition to diabetes. However, it is probable that both genetic and environmental factors play a role in the expression of DR.<sup>50</sup>

### Serum lipid

In WESDR, higher total serum cholesterol was associated with increased risk of having retinal hard exudates. ETDRS has reported a positive correlation between serum lipids and risk of retinal hard exudates in type 2 DM. Recently, a study reported reduction in edema, severity of hard exudates and subfoveal lipid migration in patients with type 2 diabetes and dyslipidaemia, using a lipid-lowering drug, atorvastatin, as an adjunct to macular photocoagulation.<sup>70</sup>

Individuals with elevated total serum cholesterol, low-density lipoprotein (LDL) cholesterol or triglyceride levels are more likely to have or develop retinal hard exudates, which can be associated with risk of vision loss, independent of the extent of macular oedema.<sup>58</sup> Several investigators have reported on the association of lipids with DR, but the results have not been consistent. The ETDRS<sup>71</sup> and the WESDR group<sup>72</sup> found a statistically significant association between elevated serum total cholesterol and LDL cholesterol and the severity of retinal hard exudation in patients with DR. An earlier study<sup>73</sup> showed an association of DME in type 2 diabetic subjects with increased LDL levels. Other studies have demonstrated that decreasing dietary polyunsaturated fats may have an association with shrinkage of exudates and a treatment to lower plasma lipid levels reduced the risk size of

perimacular hard exudates. It has also been shown that in type 2 diabetic subjects there was an increase in the lipid peroxidation in plasma and this is accentuated in patients with diabetic complications.<sup>58</sup>

A recent paper from the CURES eye study<sup>74</sup> showed an association of DR with total cholesterol and serum triglycerides. This association was maintained even after adjusting for age, as age by itself is a significant risk factor for hyperlipidaemia. The other significant finding in type 2 diabetes was that DME also showed a strong correlation with high LDL levels in the study.

### Anemia

Anaemia is considered as another risk factor, because of smaller amounts of oxygen for the retinal tissue.<sup>58</sup> A study<sup>75</sup> reported spontaneous closure of the microaneurysms on correction of anaemia and metabolic control in type 1 diabetic patient with coexisting nutritional anaemia.

In ETDRS, low hematocrit levels at baseline were identified as independent risk factor for the development of high-risk PDR and severe visual loss. It showed an increased risk of retinopathy in patients with the hemoglobin level of less than 12 g/dl.<sup>76</sup> Anemia-induced retinal hypoxia is speculated as cause of development of microaneurysms and other retinopathy changes.<sup>77</sup> The low haematocrit was an independent risk factor for development of high risk PDR and visual impairment.<sup>58</sup>

A Finnish study<sup>78</sup> showed that the odds ratio of having any retinopathy was two-fold among subjects with a haemoglobin level of less than 12 g/ dl, as compared with those having a higher haemoglobin level, even after controlling for serum creatinine levels, proteinuria, and other prognostic factors associated with diabetes.

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In addition, DR patients with low haemoglobin levels, had over fivefold increased risk of severe retinopathy compared to those with higher haemoglobin levels.

### Puberty

In WESDR, younger onset subjects who were post-menarchal stood a 3.2 times greater risk of developing DR as compared to pre-menarchal subjects.<sup>79</sup> Those who were older than 13 years at the time of diagnosis were more likely to have retinopathy than those who were younger. The exact mechanism by which puberty might exert its effect on the development of early retinopathy is not yet understood, but a possible role of hormonal factors is suspected.

### Socioeconomic status

Although educational attainment was inversely associated with retinopathy in women in the WESDR, socioeconomic status was not associated with increased risk of worsening of retinopathy. Once the level of glycemia is accounted for, social factors have little or no influence on this complication of diabetes.<sup>80</sup>

### Alcohol

A few studies have examined the effect of alcohol consumption on DR. The Casteldaccia Eye Study<sup>81</sup> demonstrated that duration of alcohol intake was associated with DR. In contrast, WESDR showed no significant association with incidence or progression of retinopathy.<sup>82</sup>

### Obesity

Recent studies have shown that DR may not only be associated with glycaemic control and blood pressure, but also to body mass index (BMI) in patients with type 2 diabetes.<sup>58</sup> Perhaps variation in ethnicity may explain the fact that BMI did not manifest as a risk factor for DR in the CURES Eye study. On the contrary subjects with type 2 diabetes and PDR had a lower BMI<sup>10</sup>. In the diabetes control and complications trial (DCCT) a study observed that besides diabetes duration and metabolic control, BMI had a significant predictive value in developing retinopathy.<sup>83</sup>

### Ocular factors

Posterior vitreous detachment (PVD) significantly common in diabetic subjects is a phenomenon, which occurs due to degenerative changes in the vitreous. It has been shown that a complete PVD may prevent the development of PDR because the hyaloid is needed as a scaffold for retinal neovascularization. An attached posterior hyaloid has also been associated with an increased risk for DME.<sup>58</sup>

High myopia with choroidal degeneration and extensive old chorioretinopathy protect against DR and are believed to act in the same manner as panretinal photocoagulation by reducing the metabolic needs of the retina.<sup>58</sup>

Removal of a cataract may aggravate both existing DME and NPDR and may hasten the onset of rubeosis.<sup>58</sup> In the Palakkad Eye Disease Survey, which looked at visual impairment and blindness in the population reported that cataract (27.8%) was one of the major causes for visual disability among subjects with

diabetes.<sup>84</sup> In a retrospective analysis done in 223 eyes of 184 type 2 diabetic subjects who underwent cataract surgery, it has been reported that 44 % had progression of DR after cataract surgery and 8.0 % developed DR for the first time, this was mainly in patients who underwent extra capsular cataract extraction with intra ocular lens (IOL) implantation.<sup>85</sup> This emphasizes the need of routine retinal documentation and detecting DR before cataract extraction.

### **Etiology and Pathogenesis**

Various studies have shown that chronic hyperglycemia, hypertension and hyperlipidemia contribute to the pathogenesis of DR. Hyperglycemia damages retinal vasculature in several ways and progression of DR is generally related to the severity and duration of hyperglycemia. The exact mechanism by which raised glucose levels lead to vascular disruption seen in retinopathy is poorly defined. However, various biochemical pathways have been suggested to demonstrate correlation between hyperglycemia and microvascular complications of retinopathy. Among these pathways, increased activity of protein kinase C (PKC) and glycation of key proteins that lead to formation of advanced glycation end (AGEs) products are more important than polyol accumulation or oxidative stress.<sup>7</sup>

### **Role of PKC activation**

The increased activity of various PKC isoforms plays an important role in the pathogenesis of DR. Activation of PKC causes cellular changes, leading to enhanced permeability of retinal vasculature, alterations in retinal blood flow, basement membrane thickening and cellular signaling by vascular endothelial growth factors (VEGFs) leading to ocular neovascularization.<sup>7</sup>

### **Role of AGEs**

Increased blood glucose concentration in diabetes can lead to formation of AGEs by non enzymatic binding of glucose to protein side chains. Animal studies have demonstrated that accumulation of AGEs is associated with microaneurysm formation and pericyte loss whereas animals treated with AGE formation inhibitor (aminoguanidine) show reduced retinal damage.<sup>7</sup>

### **Role of polyol accumulation**

Experimental studies have demonstrated that accumulation of polyol in animals is associated with changes similar to those seen in DR in humans. In the presence of increased polyol concentrations, hyperglycemia of diabetes leads to high intracellular sorbitol concentrations through enzymatic activity of aldose reductase. This increase in sorbitol concentration has been hypothesized to cause osmotic damage to vasculature of retina.<sup>7</sup>

### **Oxidative damage**

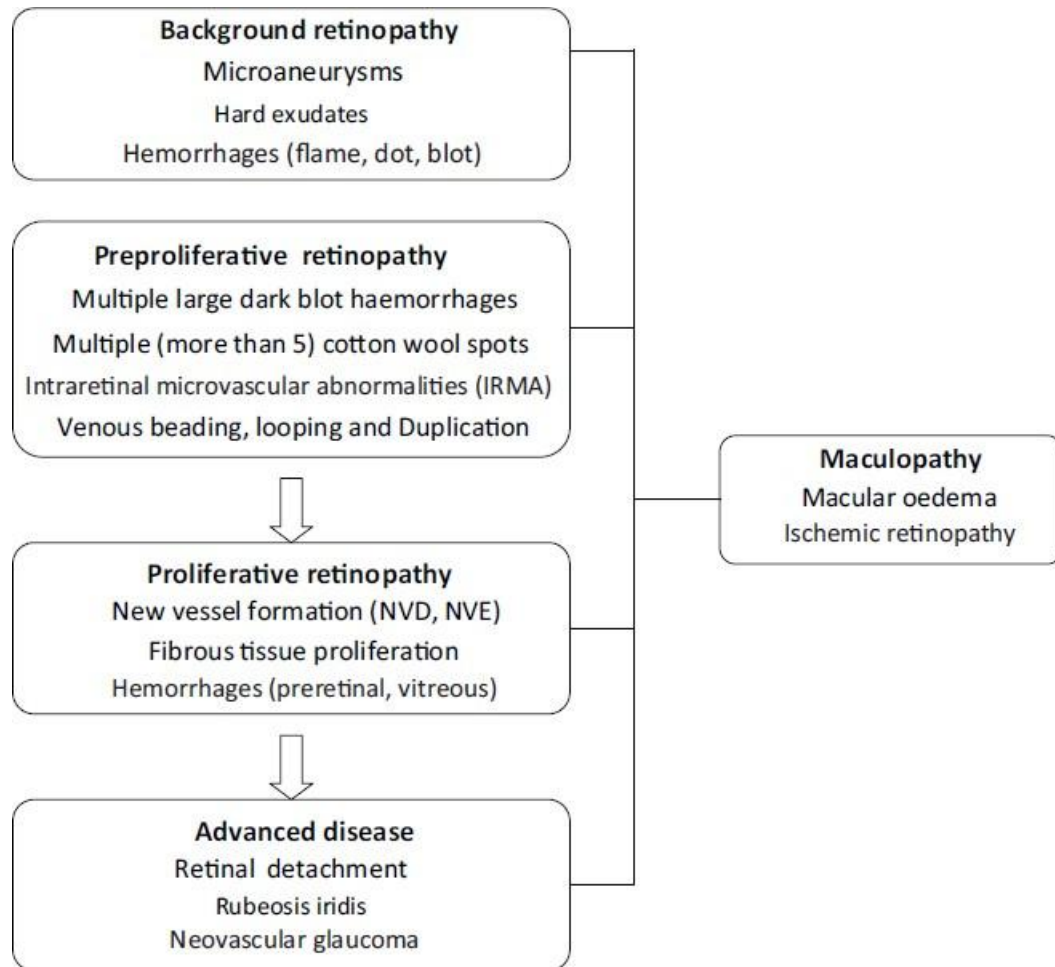
Hyperglycemia of diabetes and other biochemical pathways described above can lead to formation of reactive oxygen species (ROS) (free radicals) that leads to oxidative stress and damage to retinal vasculature. Further, normalization of glucose-induced superoxide production has been shown to block at least three independent pathways of hyperglycemia- induced vascular damage.<sup>7</sup> Animal and human studies have also suggested that antioxidants such as vitamin E may prevent some of the vascular dysfunction associated with diabetes.<sup>86</sup>

### **Role of Growth factors**

Understanding of the biochemical pathways underlying DR has clearly demonstrated the important role of a number of growth factors (vascular endothelial growth factor (VEGF), growth hormone, insulin-like growth factor-1, PKC, transforming growth factor- and pigment epithelium derived factor) in the development of structural changes in the retinal vasculature (increased retinal vascular permeability, retinal ischemia, neovascularisation) and progression of DR.<sup>87</sup>

### **Clinical Stages of Diabetic Retinopathy**

The retina is particularly vulnerable to microvascular damage in diabetes due to its high metabolic and oxygen demands and its dependence on an intact blood-retinal barrier. Damage is caused by both microvascular leakage from breakdown of the inner blood-retinal barrier and microvascular occlusion both of which can be distinguished from each other by fluorescein angiography. The stages of DR are summarized and shown in Figure.



**Figure 2. Stages of diabetic retinopathy<sup>7</sup>**

### **Background retinopathy**

Individual lesions of background retinopathy may appear and regress but their total density tends to increase with lengthening duration of diabetes. Vision is not damaged unless maculopathy coexists; over 50% of patients do not progress beyond this stage.<sup>7</sup>

Microaneurysms are outpouchings of capillaries and are among the first clinically detectable signs of retinopathy.<sup>88</sup> They arise due to ballooning of

weakened capillary walls or endothelial buds attempting to revascularize ischemic retina. They appear as tiny red dots, commonly temporal to the macula. Although microaneurysms are not fixed features and may even disappear, sudden appearance of numerous microaneurysms is an indication of worsening retinal ischemia.<sup>7</sup>

Hard exudates are the result of precipitation of lipoproteins and other circulating proteins through abnormally leaky retinal vessels. They appear as yellow lipid deposits with a waxy or shiny appearance and may form a circinate pattern around foci of leaking capillaries. Hard exudates encroaching upon the macula may affect the vision.<sup>88</sup>

Hemorrhages occur due to rupture of weakened capillaries. Small dots or larger blot hemorrhages are present within the densely packed deeper layers of retina while hemorrhages occurring in the superficial nerve fiber layer appear flame shaped.<sup>7</sup>

### **Maculopathy**

Maculopathy is a disease of macula and can accompany any stage of DR including background retinopathy. Maculopathy is a serious condition and may affect central vision.<sup>89</sup> It is characterized by macular edema and ischemic maculopathy. Macular edema is due to extravasation of plasma proteins due to damage of blood-retinal barrier. Clinically significant macular edema is defined as any one of the following:<sup>7</sup>

- Retinal edema within 500  $\mu\text{m}$  (one third of a disc diameter) of the fovea

- Hard exudates within 500  $\mu\text{m}$  of the fovea if associated with adjacent retinal thickening
- Retinal edema that is one disc diameter (1500  $\mu\text{m}$ ) or larger, any part of which is within one disc diameter of the fovea.

A substantial proportion of patients with clinically significant macular edema will show serious visual loss, highlighting the importance of treatment of this condition.<sup>88</sup> Ischemic maculopathy arises due to extensive microvascular occlusion and may cause severe loss of central vision.<sup>89</sup>

### **Preproliferative retinopathy<sup>90</sup>**

This stage is characterized by worsening retinal ischemia, which may lead to formation of new vessels (neovascularization). It is characterized by the presence of one of the following:

- Multiple large dark blot hemorrhages
- Multiple (more than 5) cotton wool spots appearing as dead white patches with vague margins and representing microinfarcts in the nerve fiber layer
- Venous beading, looping and duplication
- Intraretinal microvascular abnormalities (IRMA).

### **Proliferative retinopathy**

This stage is characterized by new vessel formation which appears as arcade of abnormal structures commonly arising on the optic disc (new vessel disc or NVD)

or elsewhere on the retina (new vessel elsewhere or NVE). Fibrous tissue and hemorrhages may also accompany. Abnormal new vasculature may threaten vision due to complications such as retinal detachment, hemorrhage and glaucoma. NVD carries a worse prognosis than NVE and if left untreated often leads to vitreous hemorrhage and increases chances of blindness.<sup>88</sup>

### **Advanced eye disease**

This represents advanced retinal damage that leads to blindness in the absence of intervention. This stage is characterized by vitreous hemorrhage, progressive fibrovascular proliferation, retinal detachment, rubeosis iridis and neovascular glaucoma which may lead to a painful blind eye.<sup>88</sup>

### **Pathophysiology**

The final metabolic pathway causing DR is unknown. There are several theories. Electrolytic imbalance caused by the high aldose reductase levels leads to cell death, especially retinal pericytes, which cause microaneurysm formation. Apart from this, thickening of the capillary basement membrane and increased deposition of extracellular matrix components contribute to the development of abnormal retinal hemodynamics. In diffuse type of diabetic macular edema (DME), breakdown of the inner blood- retinal barrier results in accumulation of extracellular fluid.<sup>91</sup>

Increased retinal leukostasis has been reported and it causes capillary occlusions and dropout, non-perfusion, endothelial cell damage and vascular leakage due to its less deformable nature.<sup>91</sup>

Currently, there has been a great interest in vasoproliferative factors, which induce neovascularization. It has been shown that retinal ischemia stimulates a pathologic neovascularization mediated by angiogenic factors, such as vascular endothelial growth factor (VEGF), which results in proliferative diabetic retinopathy (PDR).<sup>91</sup> VEGFs are released by retinal pigment epithelium, pericytes and endothelial cells of the retina.

### **Clinical Features of Diabetic Retinopathy**

#### Non-proliferative and proliferative diabetic retinopathy

Non-proliferative diabetic retinopathy (NPDR) is characterized by the presence of: (i) microaneurysms, which are the first clinically detectable lesions of DR located in the inner nuclear layer of the retina, (ii) dot and blot hemorrhages, which are located in the middle retinal layers, (iii) hard exudates, which are located between the inner plexiform and inner nuclear layer of the retina, (iv) vascular changes such as beading, looping and sausage like segmentation of the veins, (v) cotton wool spots, also called soft exudates or nerve fiber infarcts, result from capillary occlusion of the retinal nerve fiber layer, (vi) intraretinal microvascular abnormalities (IRMA), which are dilated capillaries that seem to function as collateral channels, frequently seen adjacent to the areas of capillary closure, (vii) retinal edema characterized by accumulation of fluid between the outer plexiform layer and inner nuclear layer, which may later involve the entire layers of the retina.<sup>91</sup>

In the natural course, approximately 50% of patients with very severe NPDR progress to PDR within 1 year. PDR is characterized by the presence of

neovascularization. New vessels may proliferate on the optic nerve head (new vessels at disc - NVD) and along the course of the major vascular arcades (new vessels elsewhere - NVE). The new vessels mostly grow along the posterior hyaloid and sudden vitreous contraction may result in rupture of these fragile vessels. When the vitreous detachment occurs, the new vessels are pulled anteriorly along with the underlying retina, resulting in tractional retinal detachment. On the other hand, vitreous might detach completely without any pull on the retina and new vessels regress, thus resulting in the development of an end-stage disease.<sup>91</sup>

ETDRS has classified NPDR into mild, moderate, severe and very severe and PDR into early PDR and high-risk PDR. This is as follows:<sup>92</sup>

- A. Mild NPDR: Presence of at least one microaneurysm, definition not met for B, C, D, E, or F.
- B. Moderate NPDR: Hemorrhages and/or microaneurysms, presence of soft exudates, venous beading, IRMA definitely present, definition not met for C, D, E, or F.
- C. Severe NPDR: Hemorrhages and/or microaneurysms in all four quadrants, or venous beading in two or more quadrants, or IRMA in at least one quadrant, definition not met for D, E, or F.
- D. Very severe NPDR: Any two or more of the changes seen in severe NPDR, definition not met for E, or F.
- E. Early PDR: Presence of new vessels, definition not met for F.
- F. High-risk PDR: Includes any of the following characteristics
  - I. Neovascularization of disc (NVD)  $> 1/3^{\text{rd}}$  to  $1/4^{\text{th}}$  disc diameter

- II. NVD < 1/3<sup>rd</sup> to 1/4<sup>th</sup> disc diameter with vitreous/ pre-retinal hemorrhage
- III. NVE with vitreous/pre-retinal hemorrhage. High-risk characteristics (HRC) were defined by DRS, as the patient, if not treated urgently, is at a high risk of severe visual loss.

International Clinical Diabetic Retinopathy Disease Severity scale<sup>32</sup> has developed an easily understandable scale to classify NPDR. This scale is based on findings observed upon dilated ophthalmoscopy, which includes no apparent retinopathy - no abnormalities, mild NPDR - microaneurysms only, moderate NPDR - more than just microaneurysms but less than severe NPDR and severe NPDR includes any of the following such as 20 intraretinal hemorrhages in each of four quadrants, definite venous beading in two or more quadrants, prominent IRMA in one or more quadrants and no signs of PDR.<sup>91</sup>

#### Diabetic macular edema

Macular edema or retinal thickening is an important manifestation of DR and the most common cause of moderate visual loss. The intraretinal fluid comes from leaking microaneurysms or diffuses from capillary incompetence areas. Sometimes the pockets of fluid are so large that they can be seen as cystoid macular edema (CME).<sup>91</sup>

Diabetic macular edema is retinal thickening within two disc diameters of the center of macula. DME patients were categorized into clinically significant macular edema (CSME) or non-CSME by ETDRS. CSME includes any one of the following lesions:<sup>91</sup>

- Retinal thickening at or within 500 microns from the center of macula.
- Hard exudates at or within 500 microns from the center of macula associated with thickening of the adjacent retina.
- An area or areas of retinal thickening at least one disc area in size, at least a part of which is within one disc diameter of the center of macula.

International clinical diabetic macular edema severity scale<sup>32</sup> has devised a simpler classification for the understanding of general ophthalmologist. The severity scale includes no DME present (no retinal thickening or hard exudates in the posterior pole), DME present (retinal thickening or hard exudates in the posterior pole). It is further classified as mild, moderate or severe depending upon the severity of macular edema.<sup>91</sup>

### **Ancillary investigations**

Diabetic retinopathy is essentially a clinical diagnosis. Slit lamp biomicroscopy, dilated fundus evaluation with a direct ophthalmoscope and indirect ophthalmoscope or contact/non- contact slit lamp biomicroscopic examination are essential in the diagnosis of DR. However, several ancillary investigations are required to aid the diagnosis, plan and execute the treatment and to document the lesions for research purposes. Stereoscopic fundus photographs may be required for research purposes and are especially useful for the assessment of macular edema.<sup>91</sup>

### **Fundus fluorescein angiography**

Fundus fluorescein angiography (FFA) is a well-established technique in ophthalmic practice. The common uses of fluorescein angiography are in retinal and

choroidal vascular diseases such as diabetic retinopathy, macular degeneration, hypertensive retinopathy and vascular occlusions. The angiogram is used to determine the extent of damage, to develop treatment plan and to monitor the results of treatment.<sup>93</sup>

In diabetic retinopathy the angiogram is useful in identifying the extent of ischemia, the location of micro aneurysms, the presence of intraretinal microvascular abnormalities (IRMA) that can only be confirmed on angiogram; neovascularization and the extent of macular edema.<sup>93</sup>

Fluorescein angiography is an excellent method to display the retinal capillaries in detail to show the pathologic changes because the retinal pigment epithelium provides a good background. FFA is not only useful for diagnosis but also to gauge the progression and management of diabetic retinopathy<sup>4</sup> (DR). FFA is a therapeutic guide to laser photocoagulation treatment for several retinal vascular diseases. Clinical investigations of DR are necessary using fundus photographs and fluorescein angiograms.<sup>93</sup>

#### Optical coherence tomography

Optical coherence tomography (OCT) generates cross-sectional image of the retina, which is comparable to histological sections. OCT is more sensitive than clinical fundus evaluation in diagnosing CSME. OCT provides us with quantitative measurement of thickness in the posterior pole area with reasonable accuracy, thus aiding in establishing the diagnosis of CSME. The repeatability and accuracy of OCT is very helpful in assessing and prognosticating the response of CSME to any treatment.<sup>93</sup>

Diabetic macular edema is classified into different morphological patterns based on OCT.<sup>93</sup> In a study it has been shown that OCT findings correlate reasonably with FFA features.<sup>94</sup>

#### Non-mydriatic fundus photography

Digital non-mydriatic camera is being increasingly used for screening patients that can be subsequently reviewed by the experts to determine the need for referral to an ophthalmologist.<sup>93</sup>

#### **Screening**

#### Ophthalmoscopy

Ophthalmoscopy is the most commonly used technique to screen for DR. When performed by an ophthalmologist, the specificity of direct and indirect ophthalmoscopy was high, but the sensitivity was low (34-50%), particularly for early retinopathy, in comparison to 7-field stereo photographic assessment.<sup>93</sup>

#### Digital imaging

Digital imaging makes fundus photography easier and more widely accessible. It may be used to obtain fundus images through non-dilated pupils. Mydriasis is usually necessary in older patients. Single-field fundus photography with interpretation by trained readers could serve as a screening tool to identify patients with DR.<sup>93</sup>

## **Management**

It may involve any or combination of laser, vitrectomy and/or pharmacological therapy.<sup>7</sup>

Laser photocoagulation is accomplished by directing a focused laser (**L**ight **A**mplification by the **S**timulated **E**mission of **R**adiation) beam of a discrete wavelength onto specified parts of the retina. Its absorption in a variety of intra-ocular pigmented retinal layers, causes a local rise in temperature which in turn causes denaturation of tissue proteins and coagulative necrosis. Laser treatment is used to treat diabetic macular edema either in the form of focal or grid using small spot size, short duration and low power enough to produce whitening of the retina. Focal treatment is required for focal lesions (e.g., microaneurysms, IRMA) located between 500 and 3000  $\mu\text{m}$  from the center of the macula, which causes the hard exudates and retinal thickening.<sup>95</sup>

Photocoagulation may also be used in a form of a grid pattern sparing the fovea and the maculopapillary area to treat diffuse areas of leakage in the macula. Panretinal photocoagulation (PRP) is indicated for the treatment of high-risk proliferative diabetic retinopathy and eyes with severe non-proliferative diabetic retinopathy and early proliferative diabetic retinopathy that are at high risk for progression or for poor outcome. Results of Diabetic Retinopathy study (DRS) and the Early Treatment Diabetic Retinopathy Study (ETDRS) have provided the strongest evidence to establish the place of panretinal photocoagulation as a standard technique for treating severe non-proliferative and proliferative diabetic retinopathy. It also had shown that panretinal photocoagulation reduces the risk of moderate and

severe visual loss by 50% in patients with severe non-proliferative and proliferative retinopathy.<sup>95</sup>

The aim of panretinal photocoagulation is to prevent the onset or induce the regression of neovascularization without vitreous hemorrhage or fibrovascular proliferation. This is done by destroying the ischemic peripheral retina with 1500–3000 burns that spare the disk, the macula and maculopapillary nerve bundle. It is done using enough power to produce a mild-to-moderate white burn, using shorter burn duration for patients comfort. This will result in concentrating the remaining retinal blood flow onto the macula and adjacent important areas. Laser photocoagulation is not without adverse effect. The adverse effects of PRP include visual field constriction, night blindness, color vision changes, accidental laser burn to macula.<sup>95</sup>

### **Intra-ocular lens implantation and progression of diabetic retinopathy**

Cataract surgery in diabetic patients may be performed to improve vision or to allow assessment and treatment of retinopathy.<sup>96,97</sup> The prognosis of cataract surgery in diabetic patients (with little/no retinopathy) and non-diabetic patients is same. However, in the presence of significant diabetic retinopathy the results can be disappointing.<sup>98</sup>

Studies have reported progression of diabetic retinopathy with risk factors such as young age, background retinopathy, active proliferative retinopathy, insulin therapy, and poor control of blood glucose. Severe visual loss following cataract surgery in diabetics may be due to worsening macular edema, continuing anterior and posterior segment proliferation, posterior capsule opacification level.<sup>99,100</sup>

Adequate panretinal laser photocoagulation is therefore essential if there is severe peripheral retinal ischaemia or early retinal neovascularisation.<sup>98</sup> Evidence suggests that diabetic retinopathy may worsen after cataract surgery and that the visual prognosis after cataract surgery is poor in patients with diabetes.

A growing body of literature supports the idea that diabetic retinopathy (DR) progresses more rapidly after phacoemulsification cataract surgery. Recent reports present different opinions about whether cataract surgery itself might influence the risk of retinopathy progression.

A recent report describes a clinic-based cohort study by a team of Australian researchers at Westmead Hospital in Sydney, which found that progression rate of DR doubled in diabetic patients 12 months after surgery compared with nonoperated eyes.<sup>101</sup> Of the 169 patients followed for 12 months postoperatively, incident DR, or DR newly developed since baseline, occurred in 28.2% of operated eyes compared with 13.8% of nonoperated eyes. And in a paired-eye comparison of 45 patients who remained unilaterally operated for at least 12 months and who were at risk of DR progression, 35.6% of operated eyes exhibited DR progression compared with 20.0% of fellow nonoperated eyes. The authors observed DR progression in 81 eyes (both surgical and nonsurgical) during 12 months of follow-up. Of these, 33 eyes (40.7 percent) progressed by one ETDRS step, 12 (14.8%) by two ETDRS steps and 36 (44.4%) by three or more ETDRS steps.<sup>102</sup>

These findings were consistent with other studies that looked at the DR progression rate after phacoemulsification. Earlier studies<sup>8</sup> that compared operated eyes to non-operated eyes found consistently higher rates of progression in the

operated eyes, although the difference was not significant. Why DR progresses after surgery is not clear, though poor glycemic control in diabetic patients has been associated with both cataract and DR. Therefore, the presence of cataract may be a marker for greater severity of DR or increased likelihood of progression of DR. In addition to the need for adequate control of blood glucose and blood pressure levels prior to surgery, these patients will require close monitoring after cataract surgery reminding clinicians that current practice includes preoperative laser to adequately control active DR features and diabetic macular edema.<sup>102</sup>

Patients with DM have a higher prevalence of lens opacities and develop cataract at an earlier age than non diabetics. Cataract in diabetic patients decreases the visual acuity, makes an adequate examination of the retina harder or impossible and photocoagulation of diabetic patients difficult. So it is important to perform cataract surgery for improvement of vision. For diagnostic and therapeutic reasons, if there is potential risk of aggravation of retinopathy cataract surgery should be performed. Progress in surgical technique from intra capsular cataract extraction to extra capsular extraction and improvement in IOL technology have increased the indications of cataract surgery in diabetic patients.<sup>8</sup>

ECCE requires a large incision and the nucleus is expressed through the pupil with a certain degree of iris trauma. Phacoemulsification technique allow the surgeon to remove a cataract though a smaller incision than with manual ECCE. There is quick recovery of vision to less post operative inflammation.<sup>8</sup>

It is known that diabetic eyes have more complications after cataract surgery than non diabetic eyes, particularly post operative inflammation and poorer visual

acuity. These cause of complications and progression of DR is attributed to the disturbances within the anterior segment, such as bigger lens, a steeper anterior curvature and shallow anterior chamber. These are the causes which make surgery more difficult to and the diabetic eye is more susceptible to surgical trauma than non diabetic eye. Surgically more pronounced moisis, a longer duration of surgery, a more fragile lens capsule with a flare intensity, a transient elevation of intraocular pressure and higher incidence of angiographic cystoid macula edema.<sup>8</sup>

The cause of post cataract cystoid macular oedema is mechanical (vitreous or iris incarceration in the surgical wound), inflammatory (continuous iris irritation by an iris fixated IOL), physical ultraviolet radiation reaching the retina when lens is removed and the presence of integrity of the posterior lens capsule is an important element. Surgical technique contributes to the incidence of post operative complications in the anterior and posterior segment of eye.<sup>8</sup>

The breakdown of blood aqueous barriers by surgical trauma produces post operative inflammation with a pigment dispersion, fibrinoid reaction and development of posterior synechiae. The advantage of phacoemulsification is that, this technique with a small incision reduces the post operative breakdown of blood aqueous barrier. Thus surgical procedure also may contribute to the progression of diabetic retinopathy and deterioration of pre existing diabetic maculopathy.<sup>103</sup>

Diabetic patients have an increased risk of developing cataract. This risk is related to age, severity of retinopathy, duration of the disease and, possibly, systemic hypertension. In 1992, using data from the Oxford Region in the UK, a study

demonstrated that diabetes mellitus is associated with a fivefold increase in the risk of developing cataract.<sup>103</sup>

Cataract surgery in diabetics with little or no retinopathy has the same prognosis as cataract surgery in non-diabetics. However, in the presence of significant diabetic retinopathy the results can be disappointing. Severe visual loss following cataract surgery in diabetics may be due to worsening macular oedema, continuing anterior and posterior segment proliferation, posterior capsule opacification, or unrelated events, such as retinal vein occlusion.<sup>103</sup>

Neovascular glaucoma and rapidly progressive proliferative diabetic retinopathy can occur after extracapsular cataract surgery in treated and untreated proliferative diabetic retinopathy. A study<sup>104</sup> described the rapid development of severe retinal ischaemia confirmed by fluorescein angiography within 3 months following uncomplicated extracapsular cataract surgery. The visual results of extracapsular cataract surgery in treated proliferative diabetic retinopathy with maculopathy are frequently poor.<sup>103</sup>

These results indicate that the activity and severity of pre-existing retinopathy seem to be one of the major risk factors for postoperative complications. Some previous clinical studies showed that patients with maculopathy at the time of surgery had the worst postoperative prognosis relative to visual acuity after ECCE<sup>105-107</sup> or phacoemulsification.<sup>108</sup> A study,<sup>8</sup> also found that the postoperative visual acuity reflects the status of the macula at one week postoperatively. The activity of diabetic retinopathy at the time of surgery appears to be a major factor causing the progression of retinopathy after cataract surgery.<sup>103</sup>

Patients who have long standing diabetes often have irregularities and abnormalities of the retinal pigment epithelium in the macular area. For these patients the intraocular lens with its minimal image magnification produces the smallest possible central or paracentral scotoma after cataract extraction, thus restoring visual function to as close to normal levels as possible.<sup>103</sup>

## **METHODOLOGY**

The present study was carried out in the Department of Ophthalmology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2013 to December 2013.

### **Study design**

A one year longitudinal study.

### **Place**

This study was carried out at Department of Ophthalmology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum a tertiary care teaching hospital attached to Jawaharlal Nehru Medical College, Belgaum.

### **Source of Data**

Patients with diabetes mellitus undergoing cataract surgery in the Department of Ophthalmology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum were included in the study.

### **Study Period**

January 2013 to December 2013

### **Sample Size**

A total of 50 patients with diabetes mellitus undergoing cataract surgery were studied.

### **Sampling procedure**

The sample size was calculated based on the following formula.

$$n = (Z1 - ( / 2) / e)^2$$

That is,

$$n = (1.96 / 0.28)^2 = 49$$

Hence a total of 50 patients were enrolled in the study.

### **Selection criteria**

#### Inclusion criteria

- Diabetic patients willing to participate in the study.
- Uneventful surgical procedure.
- Post operative follow up period of four months.

#### Exclusion criteria

- Patients with glaucoma.
- Patients with uveitis.
- Patients with history of trauma.
- Laser treatment for established DR applied before surgery.

### **Ethical clearance**

Prior to the commencement of the study Ethical clearance was sought from Research Committee, Jawaharlal Nehru Medical College, Belgaum.

### **Informed Consent**

All the patients satisfying the selection criteria were explained about the nature of the study and its implications and a written informed consent was obtained before enrollment (Annexure I).

### **Method of collection of data**

After the enrollment, patients were interviewed for the demographic data such as age, sex and diabetic history including type, duration and treatment were obtained through a questionnaire. Further the patients were investigated for fasting blood sugar, serum creatinine and blood urea. These findings were recorded on a predesigned and pretested proforma (Annexure II).

### **Ocular examination**

Ocular examination included recording visual acuity with snellen's chart (in patients with visual acuity less than 6/60, acuity was recorded as counting fingers at particular distance or hand movements or perception of light or projection of rays).

Detailed anterior segment examination was done and IOP was measured using Schiottz tonometer. Through fully dilated pupil fundus was examined before surgery or within three days of surgery (If ocular media is not visible) by consultant. Further posterior segment examination was done to evaluate the diabetic changes and classified according to EDTRS classification<sup>109</sup> as below.

a. Mild nonproliferative retinopathy

At least one microaneurysm, and definition not met for moderate nonproliferative retinopathy, severe nonproliferative retinopathy, early proliferative retinopathy, or high-risk proliferative retinopathy.

b. Moderate nonproliferative retinopathy

Hemorrhages and/or microaneurysms; and/or soft exudates, venous beading, or intraretinal microvascular abnormalities definitely present; and definition not met for severe nonproliferative retinopathy, early proliferative retinopathy, or high-risk proliferative retinopathy were classified as moderate non proliferative retinopathy.

c. Severe nonproliferative retinopathy

Soft exudates, venous beading, and intraretinal microvascular abnormalities all definitely present in at least; or two of the preceding three lesions present in at least two and hemorrhages and microaneurysms present in these four fields, equaling or exceeding standard photo 2A in at least one of them; or intraretinal microvascular abnormalities present in each of fields four through seven and equaling or exceeding standard photograph 8A in at least two of them; and definition not met for early proliferative retinopathy or high-risk proliferative retinopathy were grouped under severe non proliferative diabetic retinopathy.

d. Early proliferative retinopathy (Proliferative retinopathy without Diabetic Retinopathy Study high-risk characteristics)

New vessels; and definition not met for high-risk proliferative retinopathy

e. High-risk proliferative retinopathy (proliferative retinopathy with Diabetic Retinopathy Study high-risk characteristics)

New vessels on or within one disc diameter of the optic disc (NVD) standard photograph 10A\* (about one-quarter to one-third disc area), with or without vitreous or preretinal hemorrhage; or vitreous and/or preretinal hemorrhage accompanied by new vessels, either NVD < standard photograph 10A or new vessels elsewhere (NVE) one-quarter disc area

**Follow-up**

First follow up

All patients were followed on post operative day three. The patients were subjected to visual acuity and detailed anterior segment evaluation. Further patient's fundus photograph and fundus fluorescence angiography were done in retina clinic as baseline examination.

Second follow up

The second follow up was scheduled at fourth month and following recordings were done: Visual acuity, anterior segment examination, IOP and fundus. Fundus fluorescence angiography was repeated and the findings were noted.

**Progression of diabetic retinopathy**

The progression of diabetic retinopathy was assessed by comparing fundus fluorescence angiography findings at first and second follow up (Fourth month).

### **Statistical analysis**

The data was coded and compiled on Microsoft Excel spreadsheet. Categorical data was expressed in terms of rates, ratios and percentages. Continuous variables were expressed as mean  $\pm$  standard deviation (SD). The data was analysed by test of proportion and chi-square test. A probability value ('p' value) of  $< 0.05$  was considered as statistically significant.

## **RESULTS**

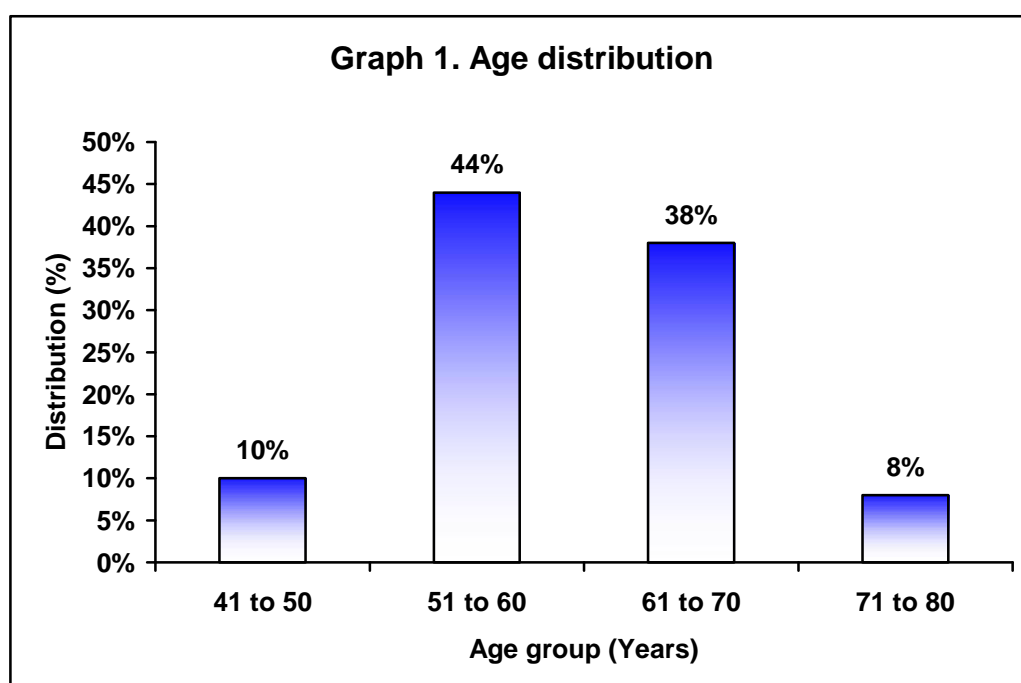
This one year longitudinal study was conducted in the Department of Ophthalmology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2013 to December 2013. A total of 50 patients with diabetes undergoing cataract surgery were included in the study.

Of the 50 patients, one patient (2%) was lost during first month follow up. Hence the outcome data was available in 49 patients.

The data obtained was coded and entered into the Microsoft Excel Spread (Annexure 3). The data was analysed and the final results and observations were tabulated as below.

**Table 1. Age distribution**

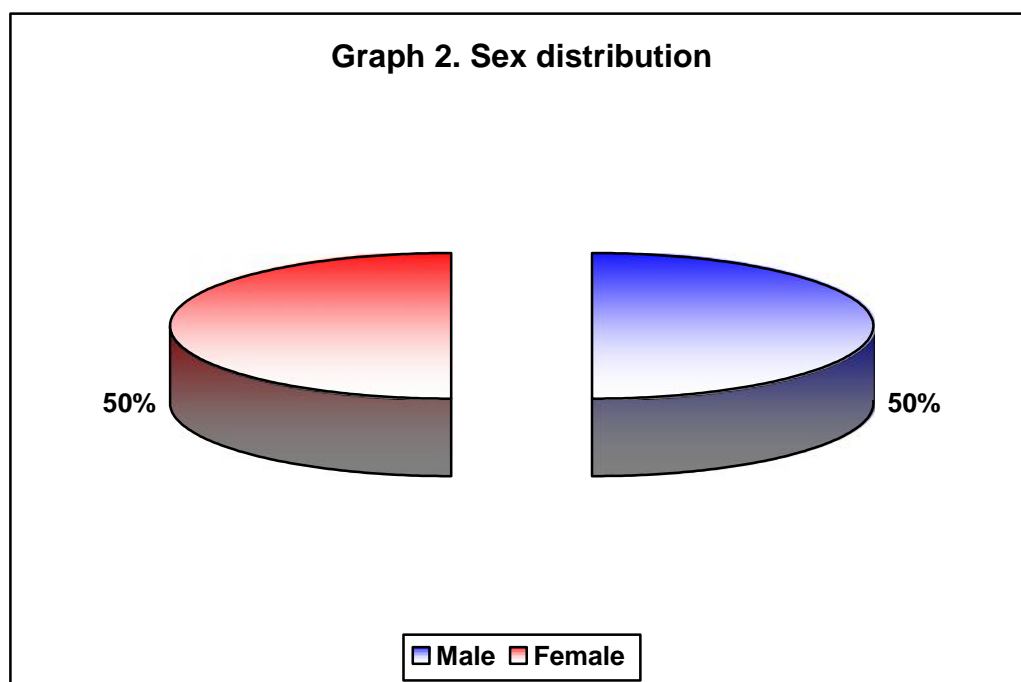
Age group (Years)	Distribution (n=50)	
	Number	Percentage
41 to 50	5	10.00
51 to 60	22	44.00
61 to 70	19	38.00
71 to 80	4	8.00
<b>Total</b>	<b>50</b>	<b>100.00</b>



In this study 44% of the patients presented with age between 51 to 60 years and 38% with 61 to 70 years. The mean age was noted as  $60.60 \pm 7.47$  years with range of 42 years being minimum and 80 years being maximum. Overall the commonest age group in this study was 51 to 60 years with 44% of the patients

**Table 2. Sex distribution**

Sex	Distribution (n=50)	
	Number	Percentage
Male	25	50.00
Female	25	50.00
<b>Total</b>	<b>50</b>	<b>100.00</b>



In the present study 50% of the patients each were males and females with the male to female ratio of 1:1.

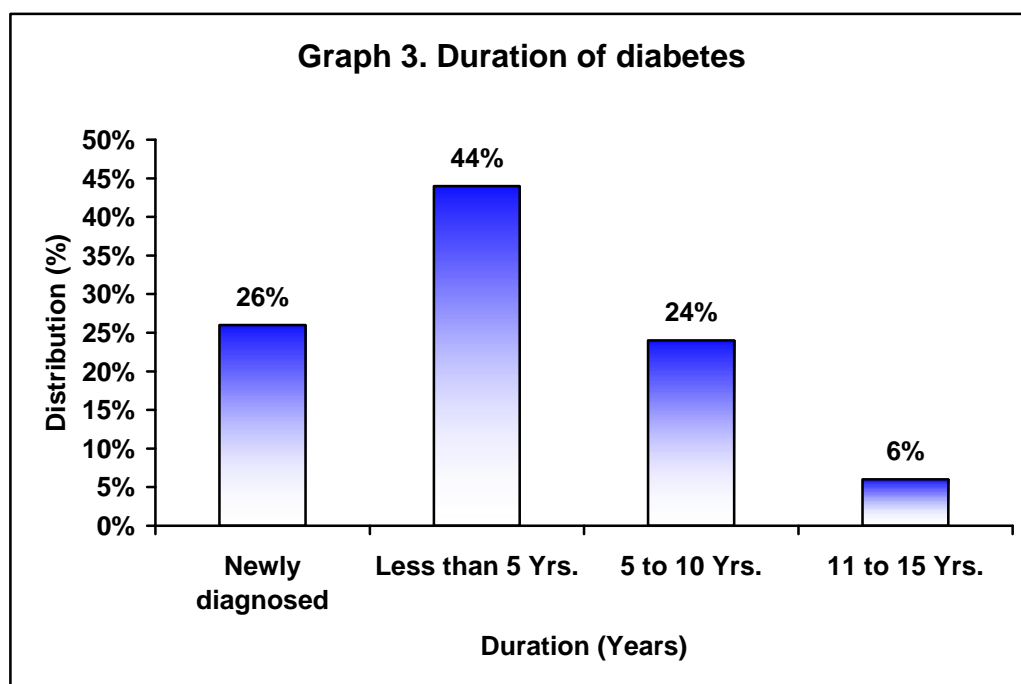
**Table 3. Diminution of vision**

Vision	Diminution	Right (n=50)		Left (n=50)	
		Number	Percentage	Number	Percentage
<b>Distance</b>	Yes	33	66.00	28	56.00
	No	17	34.00	22	44.00
	<b>Total</b>	<b>50</b>	<b>100.00</b>	<b>50</b>	<b>100.00</b>
<b>Near</b>	Yes	33	66.00	28	56.00
	No	17	34.00	22	44.00
	<b>Total</b>	<b>50</b>	<b>100.00</b>	<b>50</b>	<b>100.00</b>

In the present study diminution of near and distance vision was reported by 66% of the patients each.

**Table 4. Duration of diabetes**

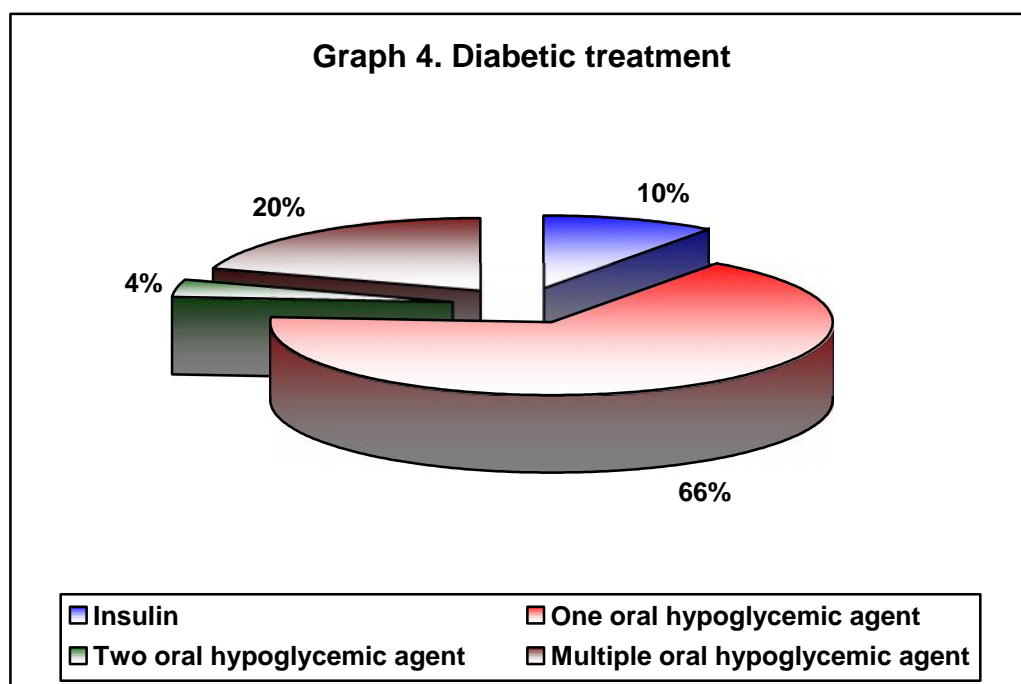
Duration (years)	Distribution (n=50)	
	Number	Percentage
Newly diagnosed	13	26.00
Less than 5	22	44.00
5 to 10	12	24.00
11 to 15	3	6.00
<b>Total</b>	<b>50</b>	<b>100.00</b>



In this study most of the patients (44%) presented with duration of diabetes of less than five years. The mean duration was noted as  $5.16 \pm 4.15$  years.

**Table 5. Diabetic treatment**

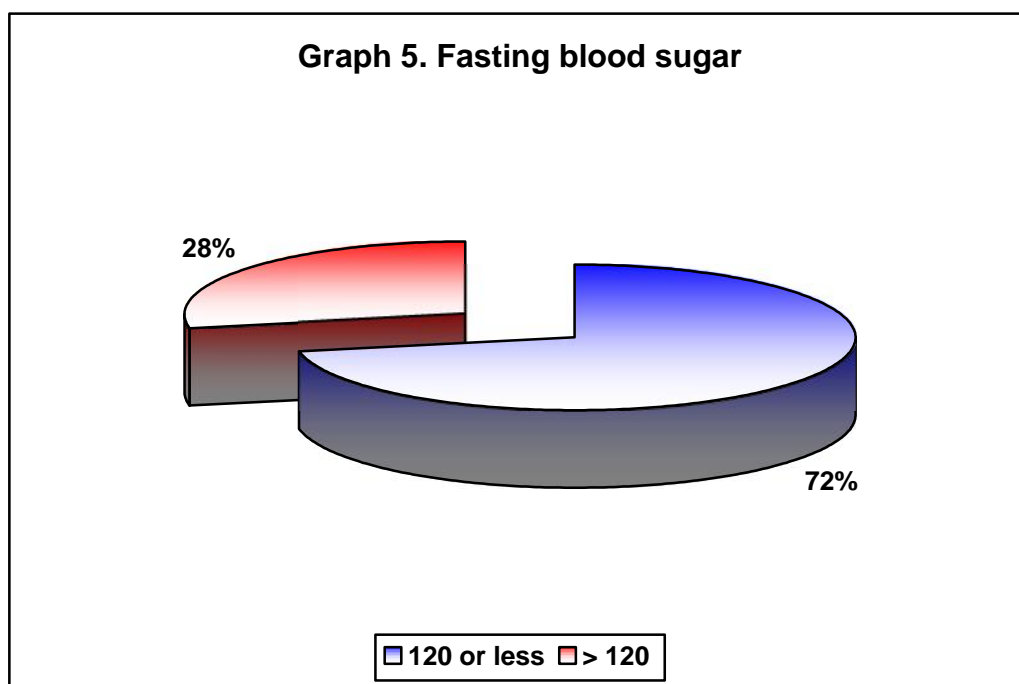
Treatment	Distribution (n=50)	
	Number	Percentage
Insulin	5	10.00
One oral hypoglycemic agent	33	66.00
Two oral hypoglycemic agent	2	4.00
Multiple oral hypoglycemic agent	10	20.00
<b>Total</b>	<b>50</b>	<b>100.00</b>



In the present study 66% of the patients were on one oral hypoglycaemic agent while 20% of the patients reported multiple oral hypoglycaemic agents.

**Table 6. Fasting blood sugar**

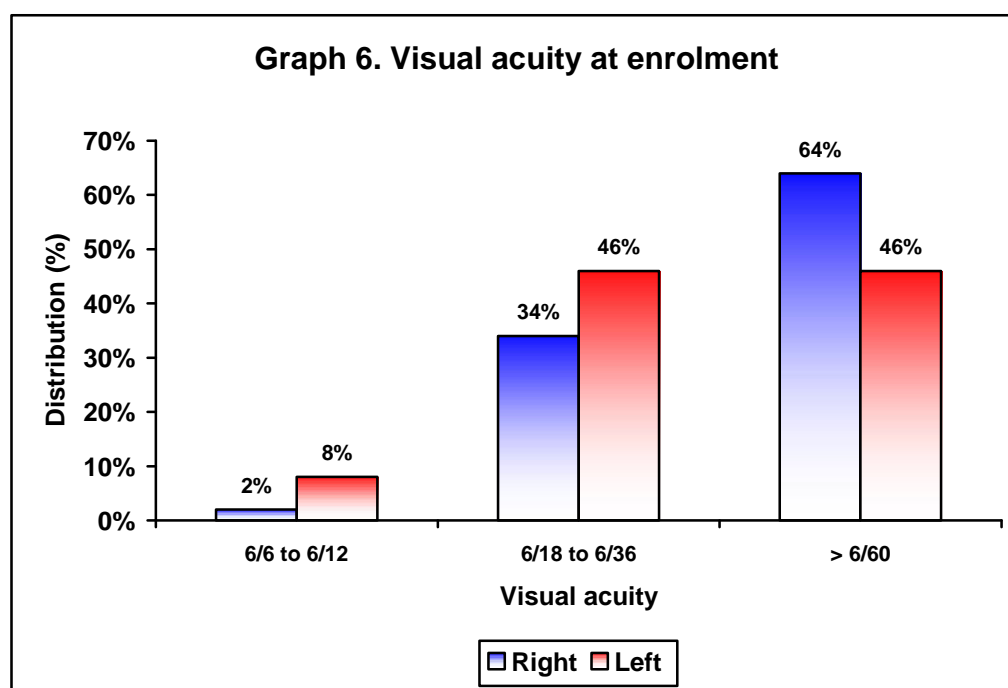
FBS (mg/dL)	Distribution (n=50)	
	Number	Percentage
120 or less	36	72.00
> 120	14	28.00
<b>Total</b>	<b>50</b>	<b>100.00</b>



In this study fasting blood sugar levels were 120 mg/dL or less in 72% of the patients and 28% of the patients had fasting blood sugar above 120 mg/dL. The mean blood sugar levels were noted as  $107.56 \pm 19.39$  mg/dL. Overall majority of the patients were found to have FBS levels within normal limit.

Table 7. Visual acuity at enrolment

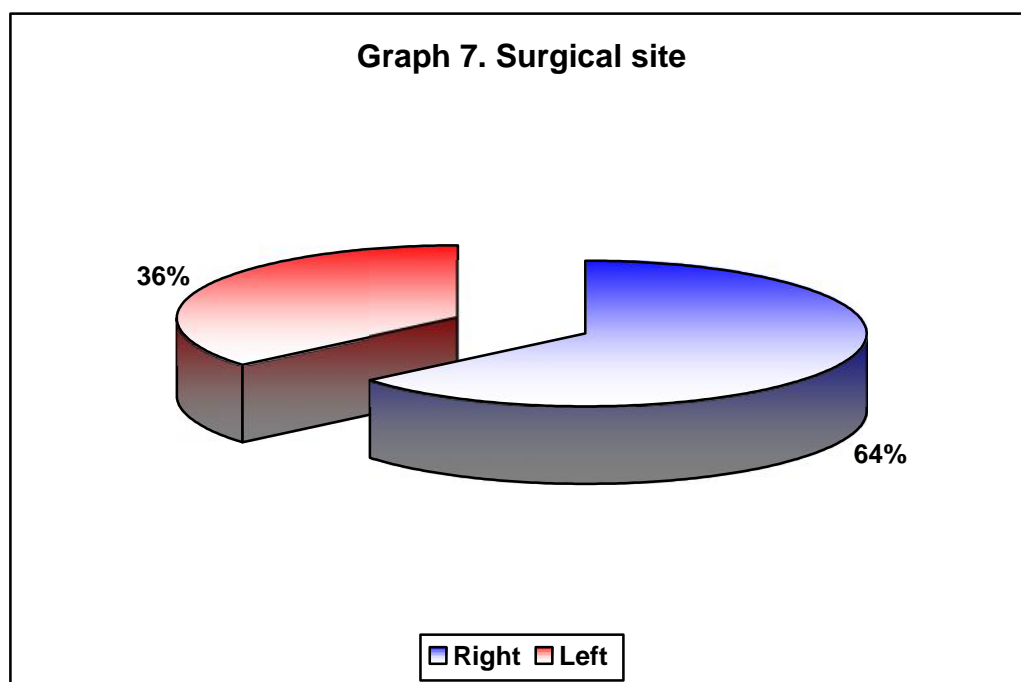
Visual acuity	Right (n=50)		Left (n=50)	
	Number	Percentage	Number	Percentage
6/6 to 6/12	1	2.00	4	8.00
6/18 to 6/36	17	34.00	23	46.00
< 6/60	32	64.00	23	46.00
<b>Total</b>	<b>50</b>	<b>100.00</b>	<b>50</b>	<b>100.00</b>



In the present study most of the patients had visual acuity of > 6/60 in right (64%) and left eye (46%).

**Table 8. Surgical site**

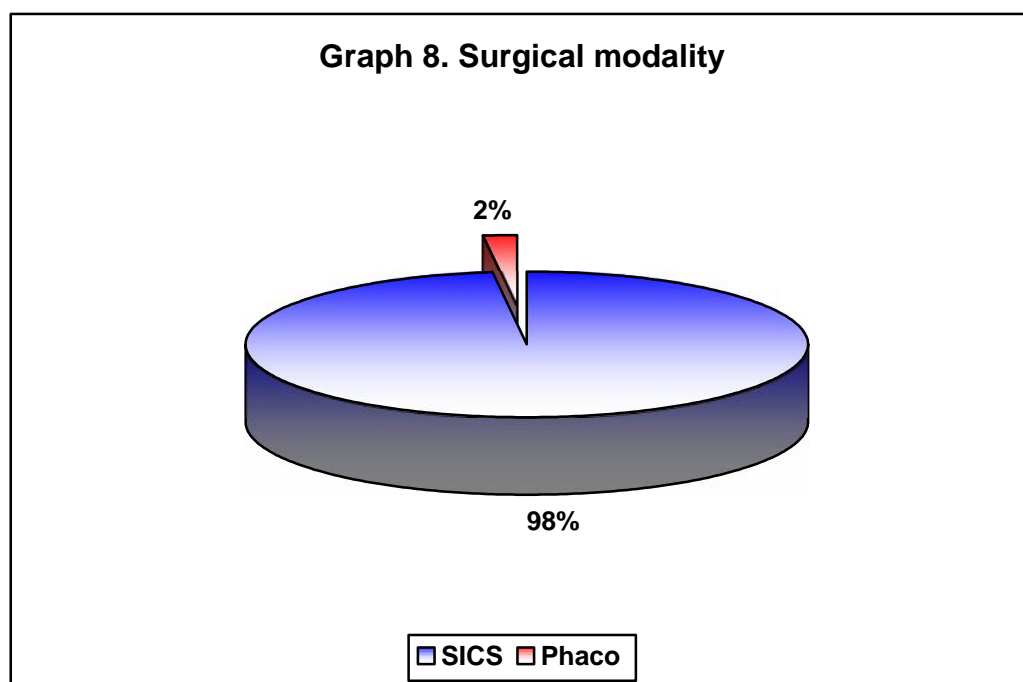
Side	Distribution (n=50)	
	Number	Percentage
Right	32	64.00
Left	18	36.00
<b>Total</b>	<b>50</b>	<b>100.00</b>



In the present study 64% of the patients underwent right eye cataract surgery while 36% of the patient had surgery for left eye.

**Table 9. Surgical modality**

Surgery	Distribution (n=50)	
	Number	Percentage
SICS	49	98.00
Phaco	1	2.00
<b>Total</b>	<b>50</b>	<b>100.00</b>



In this study majority of the cases (98%) underwent SICS as it was done in free OT.

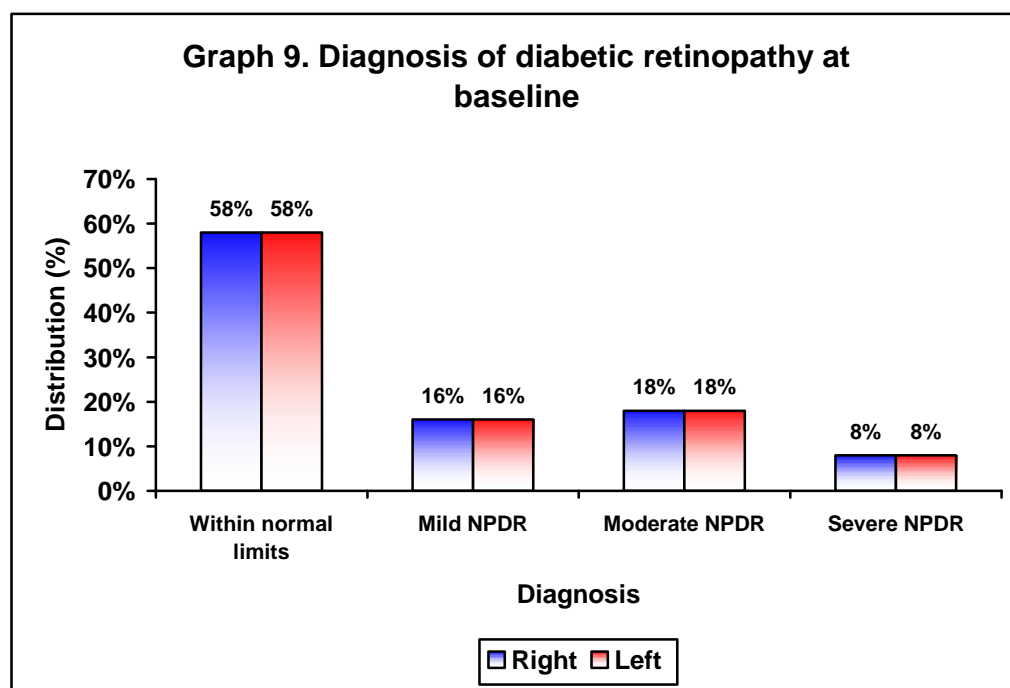
**Table 10. Post operative visual acuity of affected eye**

Interval	Visual acuity	Distribution	
		Number	Percentage
<b>Day 1 (n=50)</b>	6/6 to 6/12	5	10.00
	6/18 to 6/36	37	74.00
	< 6/60	8	16.00
	<b>Total</b>	<b>50</b>	<b>100.00</b>
<b>One month (n=50)</b>	6/6 to 6/12	8	16.33
	6/18 to 6/36	38	77.55
	< 6/60	3	6.12
	<b>Total</b>	<b>49</b>	<b>100.00</b>
<b>Three months (n=49)</b>	6/6 to 6/12	9	18.37
	6/18 to 6/36	38	77.55
	< 6/60	2	4.08
	<b>Total</b>	<b>49</b>	<b>100.00</b>

Table 10 shows assessment of post operative visual acuity of the operated eye. On day one 74% of the patients had visual acuity of 6/18 to 6/36. Further, of the 50 patients, one patient (2%) was lost during first month follow up and outcome data was available only in 49 patients. At one month and three months follow up 77.55% of the patients had visual acuity of 6/18 to 6/36.

**Table 11. Diagnosis of diabetic retinopathy at baseline**

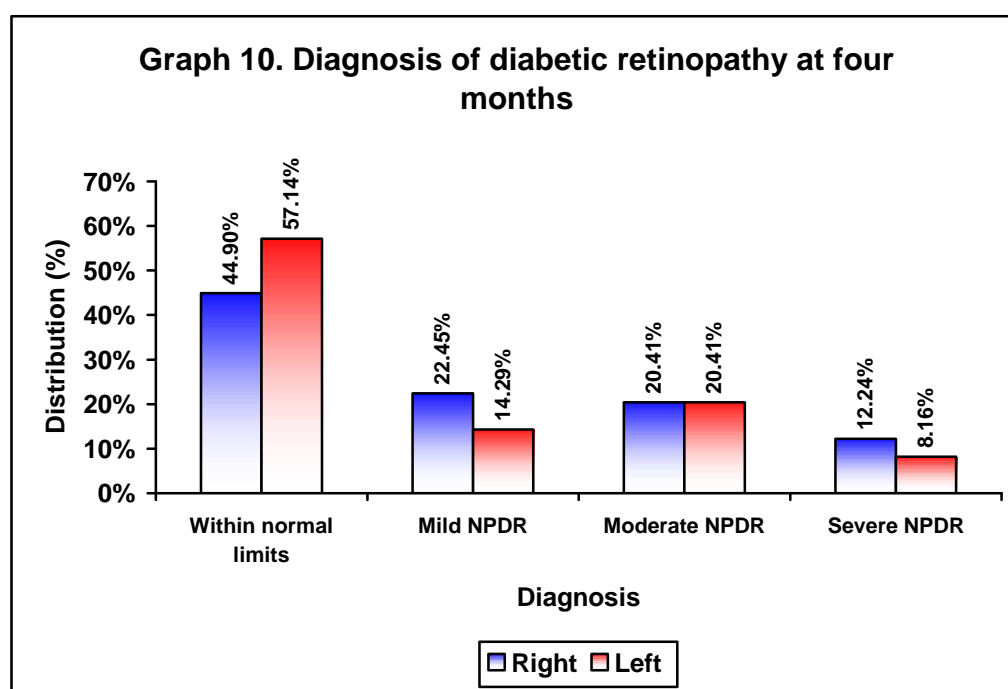
Diagnosis	Right (n=50)		Left (n=50)	
	Number	Percentage	Number	Percentage
Within normal limits	29	58.00	29	58.00
Mild NPDR	8	16.00	8	16.00
Moderate NPDR	9	18.00	9	18.00
Severe NPDR	4	8.00	4	8.00
<b>Total</b>	<b>50</b>	<b>100.00</b>	<b>53</b>	<b>100.00</b>



In the present study, at baseline, mild, moderate and severe NPDR was noted in 16%, 18% and 8% of the patients in right and left eyes respectively while 58% of the patients were normal.

**Table 12. Diagnosis of diabetic retinopathy at four months**

Diagnosis	Right (n=49)		Left (n=49)	
	Number	Percentage	Number	Percentage
Within normal limits	22	44.90	28	57.14
Mild NPDR	11	22.45	7	14.29
Moderate NPDR	10	20.41	10	20.41
Severe NPDR	6	12.24	4	8.16
<b>Total</b>	<b>49</b>	<b>100.00</b>	<b>49</b>	<b>100.00</b>



In this study during four months follow up mild, moderate and severe NPDR was noted in 22.45%, 20.41% and 12.24% of the patients in right eye respectively and in left eye the same was noted in 14.29%, 20.41% and 8.16% respectively. In 49.9% and 57.14% the right and left eyes were normal. Cataract surgery may be the possible explanation for the progression of DR.

**Table 13. Diagnosis at four months**

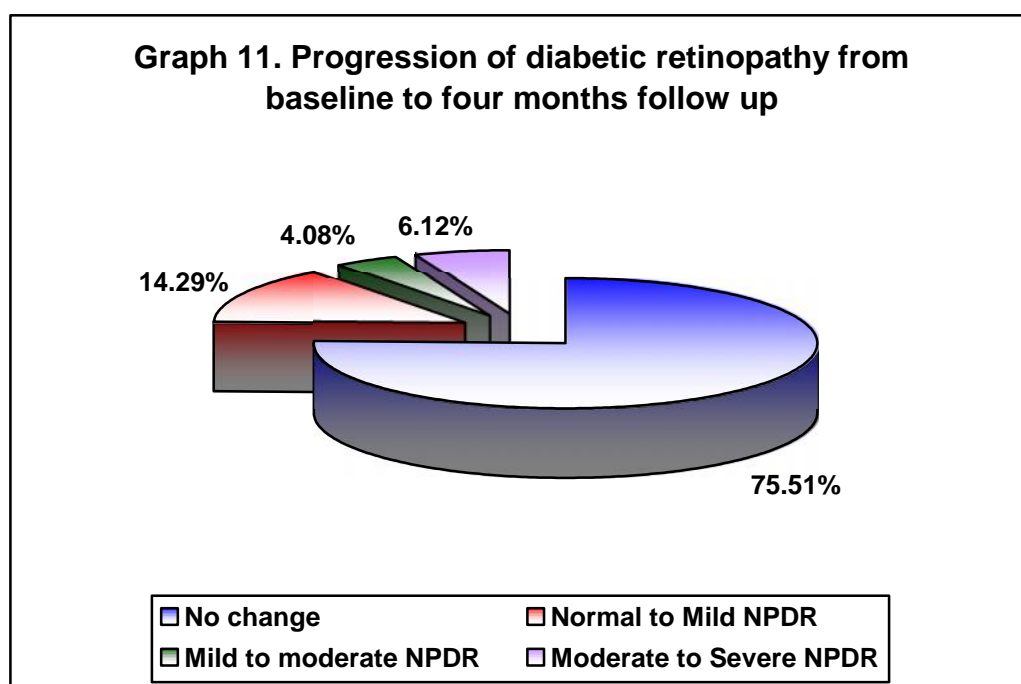
NPDR at baseline	Diabetic retinopathy at four months follow up (n=49)									
	WNL		Mild		Moderate		Severe		Total	
	No	%	No	%	No	%	No	%	No	%
Normal	22	44.90	7	14.29	0	0.00	0	0.00	29	59.18
Mild	0	0.00	4	8.16	5	10.20	0	0.00	9	18.37
Moderate	0	0.00	0	0.00	5	10.20	3	6.12	8	16.33
Severe	0	0.00	0	0.00	0	0.00	3	6.12	3	6.12
<b>Total</b>	<b>22</b>	<b>44.90</b>	<b>11</b>	<b>22.45</b>	<b>10</b>	<b>20.41</b>	<b>6</b>	<b>12.24</b>	<b>49</b>	<b>100.00</b>

Table 13 shows the comparison of baseline and four months status of diabetic retinopathy in the operated eye among the study population. It was observed that,

- Of the 29 (59.18%) normal eyes at baseline, 22 (44.9%) were within normal limits at third follow up.
- Of the 9 (18.37%) mild NPDR patients at baseline, 8 had (16.33%) moderate NPDR at second follow up.
- Of the 3 patients with severe NPDR at baseline, number patients increased to 11 (22.45%) with mild NPDR, 10 (20.41%) with moderate NPDR and 6 (12.24%) with severe NPDR.

**Table 14. Progression of diabetic retinopathy from baseline to four months follow up**

Progression of NPDR	Distribution (n=49)	
	Number	Percentage
No change	37	75.51
Normal to Mild NPDR	7	14.29
Mild to Moderate NPDR	2	4.08
Moderate to Severe NPDR	3	6.12
<b>Total</b>	<b>49</b>	<b>100.00</b>



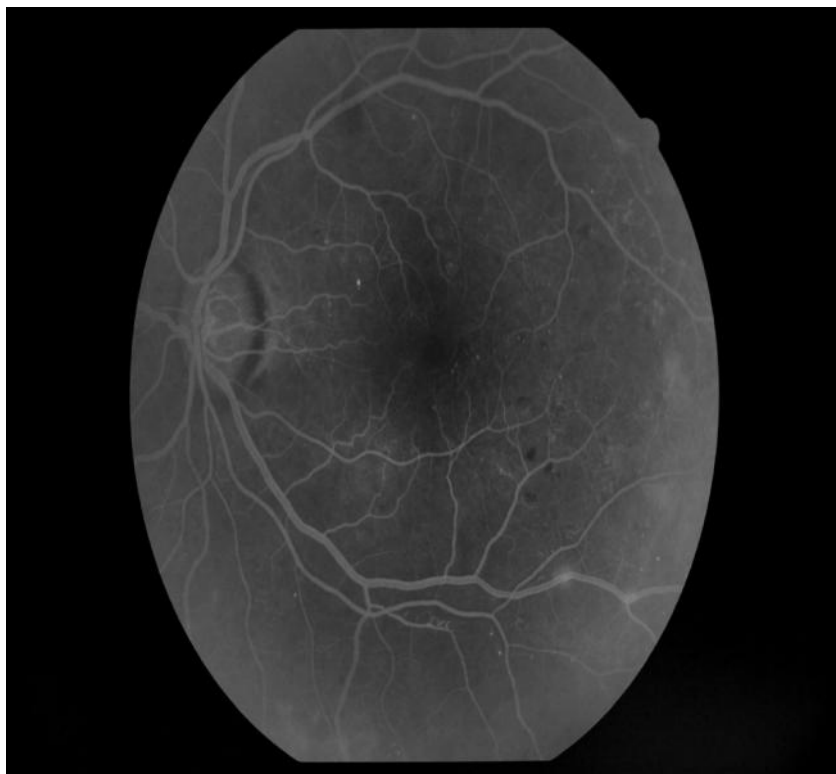
In the present study 14.29% of the patients progressed from normal to mild NPDR, 4.08% from Mild to Moderate NPDR and 6.12% from moderate to severe NPDR. However, 75.51% of the patients had no progression.



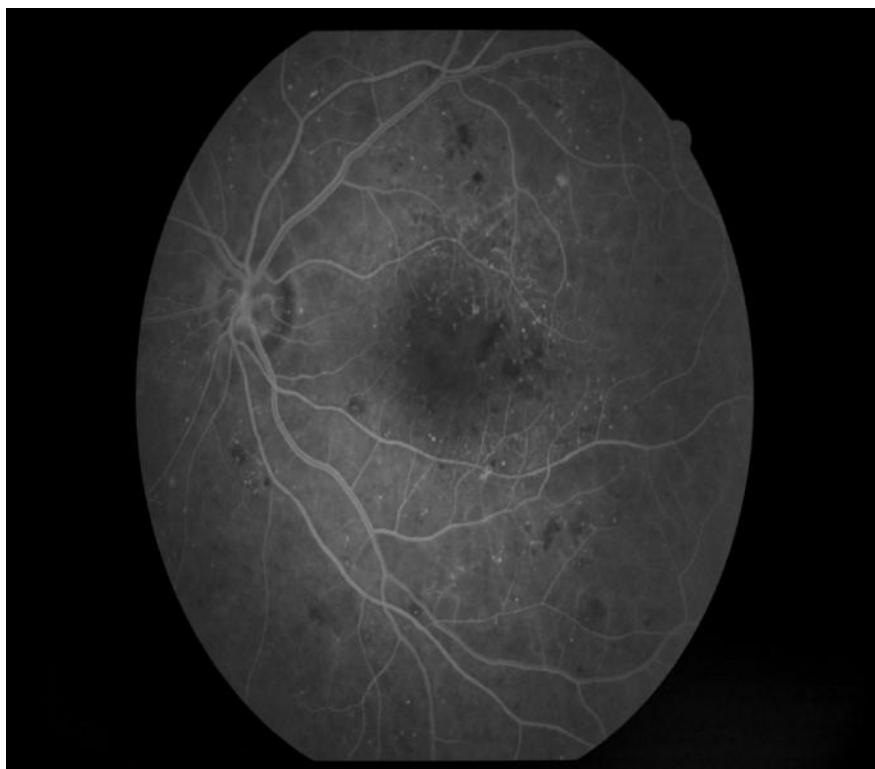
**Figure 3. FFA findings at baseline**



**Figure 4. Post operative FFA findings**



**Figure 5. FFA findings at baseline**



**Figure 6. Post operative FFA findings**

## **DISCUSSION**

Diabetes mellitus (DM) is a common condition of great public health importance. In DM, cataract occurs earlier in diabetics than in non-diabetics, and both cataract and retinopathy are related to the age of the patient and the duration of the diabetes. Cataract surgery in diabetic patients may be performed to improve vision or to allow assessment of retinopathy.<sup>105,106</sup> However, retinopathy also increases with age and duration of diabetes,<sup>99</sup> Iris vessels have been shown to be more permeable in diabetics and diabetic iridopathy is usually associated with significant retinopathy. Cataract seen in diabetic eyes is expected to respond poorly to IOL implantation. When cataract extraction with intraocular lens (IOL) implantation was introduced, diabetes was considered to be a contraindication. Subsequent studies have shown that use of the procedure for diabetic patients provides a good visual rehabilitation, and the laser photocoagulation can be done with better fundus visualization.

However, there is evidence of a high incidence of intraoperative and/or postoperative complications, and of postoperative progression of retinopathy.<sup>8,103,111</sup> Considering the scanty data on the progression of diabetic retinopathy after IOL implantation the present study was aimed to know the progression of diabetic retinopathy after intra-ocular lens implantation.

The present one year longitudinal study recruited 50 patients with diabetes undergoing cataract surgery in the Department of Ophthalmology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period

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of January 2013 to December 2013. Of the 50 patients, outcome data was available in 49 patients (98%) as one patient (2%) did not turn up for the second follow up.

In the present study on ocular examination at baseline 42% of the patients had DR and 16% had mild, 18% had moderate and 8% had severe DR in both eyes. Of the 49 patients who completed second follow up, 22.45% had mild, 20.41% had moderate and 12.24% had severe DR in right eye and in left eye, mild DR was noted in 14.29%, moderate in 20.41% and severe in 8.16%. Based on these findings the rate of progression 24.49% and in 75.51% of the patients no progression in diabetic retinopathy status was noted. Among those who progressed to advanced stage of NPDR, 14.29% of the patients progressed from normal to mild, 4.08% from Mild to Moderate and 6.12% from moderate to severe NPDR. These findings indicate that diabetic retinopathy progresses frequently in patients who undergo cataract extraction and IOL implantation. Whatever the aetiology, the retinal capillaries appear to react with a pathological response to the surgery, resulting in disruption of the blood-retinal barrier and/or occlusion of the capillaries.<sup>111</sup> The clinical correlation of these events are transudation and macular oedema and/or induction of retinal ischemia leading to neovascularization.<sup>104</sup>

In previous studies, the progression of retinopathy occurred at the rate of 42% in 70 eyes,<sup>112</sup> 13% in 91 eyes<sup>103</sup> and 21% in 47 eyes,<sup>8</sup> and 20.4% in 93 eyes.<sup>111</sup> Studies<sup>113,114</sup> carried out previously suggested that the removal of the lens contributes to worsening of diabetic retinopathy. Many patients including those with diabetic retinopathy may have very high expectations from cataract surgery. For this reason, patients with diabetic retinopathy and cataract need to be advised preoperatively that retinopathy and vision may worsen after cataract extraction. In

most cases, retinopathy progression was characterised by worsening of non-proliferative retinopathy. Risk factors associated with worsening retinopathy after cataract surgery include pre-existing severely treated or untreated retinopathy, poor glysemic control, increasing age, and posterior capsule disruption.<sup>114</sup>

However, whether cataract surgery itself increased the risk of progression to DR is still controversial. Some authors observed increased risks,<sup>113,115-117</sup> whereas others reported no difference,<sup>10,99,110,112</sup> and postulated that the retinopathy progression may simply represent the natural history of the disease.<sup>10,99</sup>

In the present study the overall rate of progression of NPDR observed was slightly low compared to a study<sup>108</sup> in 1997 where authors reported 25 out of 74 eyes with progression of retinopathy post-operatively. Another study<sup>112</sup> in 1996 reported progression of the retinopathy in 30 out of the 70 eyes. In 1991 authors studied the course of diabetic retinopathy following extracapsular cataract extraction with posterior chamber lens implantation in eyes previously treated by laser photocoagulation for diabetic retinopathy retrospectively in 33 eyes (33 patients). In 20 eyes (61%) there was no change in the retinal status postoperatively. In 13 (39%) there was postoperative progression of diabetic retinopathy compared with the fellow non-operated eye, in which progression occurred in nine eyes (27%).<sup>116</sup> However, lower rate of progression of diabetic retinopathy in the present study may be considerably due to the shorter follow-up time as the follow up period in previous studies ranged from six months to five years and the shorter duration of diabetes which was found to average  $5.16 \pm 4.15$  years.

In the present study we encountered equal number of males and females that is 50% each with male to female ratio of 1:1 suggesting equal distribution of sex. In contrast a study<sup>111</sup> in 2003 to assess the influence of cataract surgery and posterior chamber intraocular lens implantation on retinopathy progression, reported 44 women and 32 men. Similarly another study<sup>108</sup> in 1996 also reported 30 men and 44 women. The disparity of the male to female ratio in the present study compared to other studies may be attributed to the smaller sample size of the present study.

In the present study the commonest age group was 51 to 60 years comprised of 44% of the patients while 38% of the patients were aged between 61 to 70 years and the mean age was  $60.60 \pm 7.47$  years. These findings indicate predominant involvement of elderly population in the present study. These findings were consistent with a study<sup>108</sup> from Cambridge which reported mean age of 67 years and another study<sup>111</sup> where mean age at the time of surgery as 63.7 years.

In the present study nearly half of the study population (44%) had less than five years duration of diabetes and mean duration was  $5.16 \pm 4.15$  years. In contrast a study from Samsun reported mean duration of diabetes as 10.8 years.

Overall the findings of this study indicate that diabetic retinopathy progresses frequently in patients who undergo cataract extraction and IOL implantation.

The present study has several limitations namely, shorter follow up period, the risk factors associated with worsening retinopathy after cataract surgery including untreated retinopathy, poor glycemic control, increasing age, and posterior capsule disruption were not considered as they were beyond the scope of this study

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and due to shorter follow up period. Further studies considering the longer follow up duration, different cataract surgery and risk factors would focus the progression of DR after cataract extraction and IOL implantation.

## **CONCLUSION**

The present study showed progression of diabetic retinopathy in 24.49% of the patients who underwent IOL implantation. These results indicate that diabetic retinopathy may worsen after IOL implantation in considerable subset of patients undergoing cataract surgery.

## SUMMARY

Cataract surgery in diabetic patients is performed to improve the vision. However, there is higher incidence of post operative complications and progression of DR. Considering the scanty data on the progression of diabetic retinopathy after IOL implantation the present study was aimed to know the progression of diabetic retinopathy after intra-ocular lens implantation.

This longitudinal study was carried out at Department of Ophthalmology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2013 to December 2013. A total of 50 patients with diabetes undergoing cataract surgery were included in the study. Patients were assessed at baseline and four months post operatively for the diabetic retinopathy based on EDTRS classification.

Most of the patients (44%) presented with age between 51 to 60 years and mean age was  $60.60 \pm 7.47$  years. The male to female ratio was 1:1 with 50% of the patients each being males and females. The mean duration of diabetes was  $5.16 \pm 4.15$  years and majority (66%) of the patients were on one oral hypoglycaemic agent. The mean blood sugar levels were noted as  $107.56 \pm 19.39$  mg/dL. Most of the patients had visual acuity of  $> 6/60$  in right (64%) and left eye (46%). Right eye cataract surgery was done in 64% of the patients and majority of the cases (98%) underwent SICS as it was done in free OT. Progression of DR from normal to mild was noted in 14.29%, mild to moderate in 8.08% and moderate to severe in 6.12% of the patients.

Based on findings of this study it may be concluded that, diabetic retinopathy may worsen after IOL implantation in considerable subset of patients undergoing cataract surgery as rate of progression was 24.49%.

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## ANNEXURE I – CONSENT FORM

ID NO:

Mr/Mrs/Ms \_\_\_\_\_

You are invited to participate in our research study titled “A one year longitudinal study to know the progression of diabetic retinopathy after IOL implantation” conducted by Dr. Afiya Wahid Kachru, Post Graduate student in M.S. Ophthalmology, under the guidance of Dr. S.B. Patil, Professor in the Department of Ophthalmology, J N Medical College, Belgaum.

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

**Purpose of the Study:** There are some studies which show the fact that after IOL implantation diabetic retinopathy progresses and vision deteriorates inspite of cataract removal because of increased vascular leak and postoperative cystoid macular edema and there are also some studies which show the fact that uncomplicated cataract surgery does not cause any progression of diabetic retinopathy, so the purpose of my study is to know the progression of diabetic retinopathy after IOL implantation.

**Procedure Involved:** If you agree to enroll yourself in this study, you will be asked your present, past and family history. You will be clinically examined and relevant investigations will be done. Investigations include fasting blood sugar, serum creatinine, blood urea, and fundus fluorescein angiography. You would be asked to

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come for follow up on specified dates when your progress would be monitored documented and photographed.

**Risks and Benefits:** There are no major risks involved in this study. Your participation may benefit you and others undergoing cataract surgery to know and follow up the course of diabetic retinopathy after IOL.

**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:** There will not be any extra cost incurred by you. You will, however, have to pay for the investigations which are part of the existing management protocol for the condition. There is no commitment for any reimbursement or any other compensation.

**Privacy and Confidentiality:** Your privacy is guaranteed. However, your medical records can be directly accessed and reviewed by authorized individuals or by the ethics committee. Records, which could reveal your identity, will be kept confidential. Personal data will remain anonymous if data is being published or written as a dissertation.

**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:** 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. Investigator, Dr. Afiya Wahid Kachru, Post Graduate student, Department of Ophthalmology, JNMC, Belgaum, Contact No. 8722955922
2. Guide, Dr. S. B. Patil, Professor, Department of Ophthalmology, JNMC, Belgaum. Contact No. 9448138855
3. Chairperson Dr. JNMC Institutional Ethics Committee and Human Reseech, JNMC, Belgaum Dr. Ganga S. Pilli, Professor and Head, Department of Pathology Contact No. 9448863866

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**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 at 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 : \_\_\_\_\_

Name of guide: Dr. S. B. Patil

Signature of Guide: \_\_\_\_\_

Date:

Place:

## ANNEXURE II – PROFORMA

PROGRESSION OF DIABETIC RETINOPATHY AFTER IOL IMPLANTATION LONGITUDINAL STUDY .

DATA COLLECTION INSTRUMENT

I.D. NO :

NAME :

AGE :

SEX : 1=MALE 2=FEMALE

RELIGION :

1- HINDU 2-MUSLIM 3-CHRISTIAN 4- OTHERS

ADDRESS :

OPD NO :

IPD NO :

PROVISIONAL DIAGNOSIS:-

1- Diabetes Mellitus

INCLUSION CRITERIA

1- Met 2-Non Met.

Criteria of Inclusion : Diabetic patients who are willing to participate in the study

INFORMED CONSENT

1- Taken 2- Not Taken

Approval of the Guide : \_\_\_\_\_

CHIEF COMPLAINTS:

1= YES 2= NO

	RE	LE	BE
1) Diminution of vision-distance	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2) Diminution of vision-near	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3) Pain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4) Flashes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5) Floaters	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6) Metamorphosia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7) ANY OTHER COMPLAINTS –			

IF ANY : \_\_\_\_\_

## PAST HISTORY

1= YES, 2=NO, a=&gt;0-5Yrs, b=&gt;5-10Yrs, c=&gt;10-15Yrs, d=&gt;15-20Yrs, e=&gt;20Yrs

- 8) H/O WEARING GLASSES  If yes, Duration
- 9) H/O HYPERTENTION  If yes, Duration
- 10) DIABETES MELLITUS  If yes, Duration
- 11) H/O ANY OCULAR SURGERY  If 1, SPECIFY \_\_\_\_\_
- 12) H/O AUTOIMMUNE DISEASE
- 13) H/O DRUG ALLERGY

14) ANY OTHER :

IF YES: \_\_\_\_\_

15) FAMILY HISTORY : 

1= SIGNIFICANT 2= NOT SIGNIFICANT

16) LIFESTYLE :

1= YES 2= NO

ACTIVE SEDENTARY 

YES 2=NO a=&gt;0-5 yrs b=&gt;5-10yrs c=&gt;10-15 yrs d=&gt;15-20yrs e=&gt;20yrs

.) ALCOHOL  IF YES, DURATION ) SMOKING  IF YES, DURATION ) DIET-VEG/MIXED  (1=VEG,2=MIXED)

DIABETIC HISTORY :

- 20.) Age of onset of diabetes \_\_\_\_\_ Years  
 21.) Duration of diabetes \_\_\_\_\_ Years  
 22.) Any significant events \_\_\_\_\_ Years

TREATMENT HISTORY :

1=yes      2=no

a=&gt;0-5 yrs   b=&gt;5-10 yrs   c=&gt;10-15 yrs   d=&gt; 15-20 yrs   e=&gt;20 yrs.

- 23.) Oral hypoglycemic: Single  If yes, Duration   
 Multiple  If yes, Duration

Group of drug used:

- a. 1<sup>st</sup> Generation sulfonylureas  
 b. 2<sup>nd</sup> Generation sulfonylureas  
 c. Biguanides  
 d. Miglitinide analogues  
 e. Thiazolidinediones  
 f. Glucosidase Inhibitor  
 g. Others, Specify: \_\_\_\_\_

24) Insulin Injections :  If yes, Duration

25) Any Other :

GENERAL PHYSICAL EXAMINATION :

26) PULSE RATE ( Per Min )

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27) RESPIRATORY RATE ( Per Min )

--	--	--

BLOOD PRESSURE (in mm Hg )

28) Systolic

--	--	--

29) Diastolic

--	--	--

30) TEMPERATURE ( in deg F )

--	--	--

Systemic examination:

1=Normal 2=Abnormal

31) CVS  if Abnormal

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32) R/S  if abnormal

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33) P/A  if abnormal

---

34) CNS  if abnormal

---

35) Renal  if abnormal

---

36) Skin  if abnormal

---

37) Foot  if abnormal

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OCULAR EXAMINATION

38) HEAD POSTURE:

1=ERECT 2=TILTED

39) VISUAL AXIS:

1=PARALLEL 2=DEVIATED

40) FACIAL SYMMETRY:

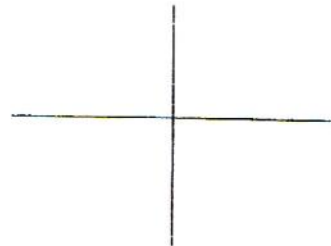
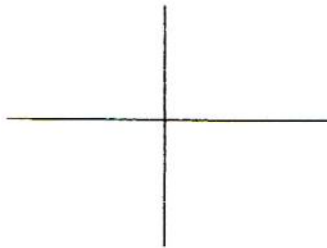
1= SYMMETRICAL 2= DEVIATED

EXTRAOCULAR MOVEMENTS:

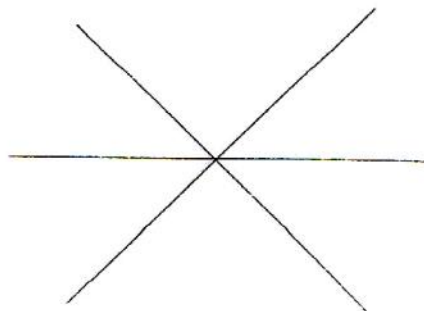
1=NORMAL 2= RESTRICTED

41) UNIOCCULAR : RE

LE



42) BINOCULAR



## OCULAR EXAMINATION :

	RIGHT EYE	LEFT EYE
<b>43) VISUAL ACUTTY</b> 1: 6/6 – 6/12   2: 6/18 – 6/36   3: ≤6/60  <u>Unaided vision :</u>  With pinhole :  With spectacles :	<input type="checkbox"/>	<input type="checkbox"/>
<b>44) ADNEXA</b>  1- Normal   2 – Abnormal  If 2, Specify _____	<input type="checkbox"/>	<input type="checkbox"/>
<b>45) LIDS</b>  1- Normal   2 – Abnormal  If 2, Specify _____	<input type="checkbox"/>	<input type="checkbox"/>
<b>46) CONJUNCTIVA</b>  1- Normal   2- Congested   3- Others  If 3, Specify : _____	<input type="checkbox"/>	<input type="checkbox"/>
<b>47) CORNEA</b> 1- Clear   2- Hazy   3-Other  If 3, Specify : _____	<input type="checkbox"/>	<input type="checkbox"/>
<b>ANTERIOR CHAMBER</b>  <b>48) DEPTH</b>  1- Normal   2- Shallow   3- Deep	<input type="checkbox"/>	<input type="checkbox"/>



**OBSERVATION:**

58) FBS (mg/dl)		
<b>FUNDUS EXAMINATION</b>	<b>OD</b>	<b>OS</b>
59) Glow 1- Present, 2- Faint, 3- Absent		
60) MEDIA 1- Clear, 2- Hazy  Corneal Lenticular Vitreous		
61) DISC 1- Normal 2- Pallor 3- NVD 4- Disc Haemorrhage  Other, Specify _____		
62) Cup : Disc Ratio 1- Normal (0.3) 2- Abnormal  If 2, Specify _____		
63) VESSELS 1. Normal 2. V. Beading 3. V. Dilatation 4. V. Lopping 5. V. Tortuosity 6. Venous sheathing  Other, Specify _____		

<p><b>64) Background</b>                  1- Normal, 2- Abnormal                   If 2, Specify _____</p>		
<p><b>65) Haemorrhages</b>                  1- Present, 2- Absent                   If 1 : ( Specify quadrants in brackets )                  a) Superiorasal                  b) Superiotemporal                  c) Inferionasal                  d) Inferiotemporal</p>		
<p><b>66) Types of h'rage</b>                  1. Microaneurysms                  2. Superioial                  3. Deep h.                  4. Flame shaped h.                  5. Pre-retinal h.                  6. Vitreous h.</p>		
<p><b>67) Hard Exudates</b>                   1- Present 2- Absent                   If 1, Specify quadrants as above.</p>		
<p><b>68)</b> a = NVE                  b = Collaterals                  c = IRMAs                  1 – Present, 2- Absent                   If 1, Specify quadrants as above.</p>		
<p><b>69) Soft exudates</b>                  1- Present, 2- Absent                   If 1, Specify quadrants as above.</p>		

**SURGERY:** Phaeo-comulsification   
 SICS   
 ECCE

## OCULAR EXAMINATION ON FIRST POST OPERATIVE DAY

Ocular Examination :                      Right Eye                      Left Eye

<b>1) visual acuity</b> 1:6/6-6/12    2: 6/8 – 6.36    3: < 6/60	<input type="checkbox"/>	<input type="checkbox"/>
United vision :  With pinhole :  With spectacles	<input type="checkbox"/>	<input type="checkbox"/>
<b>2) ADNEXA</b>  1-Normal 2 – Abnormal If 2, specify _____	<input type="checkbox"/>	<input type="checkbox"/>
<b>3) Lids</b> 1-Normal 2 – Abnormal If 2, specify _____	<input type="checkbox"/>	<input type="checkbox"/>
<b>4) CONJUNCTIVA</b>  1 – Normal 2- congested 3 – other  If 3, specify : _____	<input type="checkbox"/>	<input type="checkbox"/>
<b>5) Cornea</b>  1- Clear    2 – Hazy    3-other  If 3 specify : _____	<input type="checkbox"/>	<input type="checkbox"/>
<b>6) ANTERIOR CHAMBER :</b>  DEPTH  1-Normal 2- shallow 3 – deep	<input type="checkbox"/>	<input type="checkbox"/>

<p>7) IRIS :</p> <p>COLOUR AND PATTERN</p> <p>1- Normal 2- Atrophic Patches</p>	<input type="checkbox"/>	<input type="checkbox"/>
<p>8) PUPIL</p> <p>SIZE</p> <p>1-Normal 2 - constricted 3 - Dilated</p>	<input type="checkbox"/>	<input type="checkbox"/>
<p>9) REACTION :    DIRECT                           INDIRECT</p> <p>1-Present 2 - Absent 3 - Sluggish</p>	<input type="checkbox"/>	<input type="checkbox"/>
<p>10) PUPILLARY MARGIN</p> <p>1-Normal 2 - Abnormal If 2,specify _____</p>	<input type="checkbox"/>	<input type="checkbox"/>
<p>11) POSTERIOR SYNECHIAE</p> <p>1-present 2 - Abnormal If 2 , specify _____</p>	<input type="checkbox"/>	<input type="checkbox"/>
<p>12) ACCOMODATION</p> <p>1- Present 2-Absent</p>	<input type="checkbox"/>	<input type="checkbox"/>
<p>13) LENS</p> <p>1-Clear 2 - cataractous 3 - pseudophakia 4- Aphakia</p>	<input type="checkbox"/>	<input type="checkbox"/>
<p>14) IOP :</p>		

**FFAWITHIN 3 DAYS OF IOL IMPLATATION(BASELINE)****Observation :**

1.) Serum creatinine Blood urea.		
Fundus examination	OD	OS
2.) Glow 1=present, 2=faint, 3=absent		
3.) Media 1=clear, 2=hazy Conreal Lenticular Vitreos		
4.) Disc 1= normal 2= pallor 3= NVD 4= disc haemorrhage Other,specify_____		
5.) Cup : disc ratio 1= normal (0.3) 2= abnormal if 2,specify_____		
6.) Vessels 1= normal 2= V.Beading 3= V.dilatation 4= V.looping 5= V.tortuosity 6= Venous Sheething. Other,specify_____		

<p>7.) Background 1=normal, 2=abnormal If 2,specify_____</p>		
<p>8.) Haemorrhages 1=present, 2=absent If 1 :- (specify quadrant inbracket) (a)= superiorasal (b)= superiotemporal (C)= inferionasaal (d)= inferiotemporal</p>		
<p>9.) Types of h'рге 1= Microaneuysing. 2= Superfioal h. 3= Deep h. 4= Flame shaped h. 5= Vitreous h.</p>		
<p>10.) Hard exudates 1=present, 2= absent If 1, specify quadrants as above.</p>		
<p>11.) a= NVE     b= Collateral     c= IRAMs 1=preent, 2=absent If 1, specify quadrants as above.</p>		
<p>12.) Soft exudates 1=present, 2=absent If 1, specify quadrants as above.</p>		

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**OCULAR EXAMINATION AFTER ONE MONTH OF IOL IMPLANTATION**

OCULAR EXAMINATION :	Right Eye	Left Eye
<b>1) <u>VISUAL ACUITY</u></b> 1: 6/6 – 6/12    2: 6/18 – 6/36    3: ≤6/60	<input type="checkbox"/>	<input type="checkbox"/>
<u>Unaided vision :</u>  With pinhole :  With spectacles :		
<b>2) <u>ADNEXA</u></b>  1- Normal    2 – Abnormal  If 2, Specify _____	<input type="checkbox"/>	<input type="checkbox"/>
<b>3) <u>LIDS</u></b>  1- Normal    2 – Abnormal  If 2, Specify _____	<input type="checkbox"/>	<input type="checkbox"/>
<b>4) <u>CONJUNCTIVA</u></b>  1- Normal    2- Congested    3- Others  If 3, Specify : _____	<input type="checkbox"/>	<input type="checkbox"/>
<b>5) <u>CORNEA</u></b> 1- Clear    2- Hazy    3-Other  If 3, Specify : _____	<input type="checkbox"/>	<input type="checkbox"/>
<b><u>ANTERIOR CHAMBER</u></b>		
<b>6) DEPTH</b>	<input type="checkbox"/>	<input type="checkbox"/>

1- Normal 2- Shallow 3- Deep		
7) IRIS:  COLOUR AND PATTERN 1- NORMAL 2- ATROPHIC	<input type="checkbox"/>	<input type="checkbox"/>
8) PUPIL : <u>SIZE</u>  2- Normal 2- Constricted 3- Dilated	<input type="checkbox"/>	<input type="checkbox"/>
9) REACTION : DIRECT	<input type="checkbox"/>	<input type="checkbox"/>
INDIRECT	<input type="checkbox"/>	<input type="checkbox"/>
2- Present 2- Absent 3- Sluggish		
10) <u>PUPILLARY MARGIN</u>  2- Normal 2- Abnormal If 2, Specify _____	<input type="checkbox"/>	<input type="checkbox"/>
	<input type="checkbox"/>	<input type="checkbox"/>
11) <u>POSTERIOR SYNECHIAE</u>  2- Present 2- Absent	<input type="checkbox"/>	<input type="checkbox"/>
12) <u>ACCOMODATION</u>  2- Present 2- Absent		
13) <u>LENS</u> :  2- Clear 2- Cataractous 3- Pseudophakia 4- Aphakia.	<input type="checkbox"/>	<input type="checkbox"/>
14) IOP		

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OCULAR EXAMINATION AFTER 3 MONTHS OF IOL IMPLANTATION

SERUM CREATININE

BLOOD UREA

Ocular Examination

	Right Eye	Left Eye
1.) <u>VISUAL ACUITY</u> 1 : 6/6    2 : 6/18-6?36    3: ≤6/60  Unaided vision : With pimhole : With spectacles :	<input type="checkbox"/>	<input type="checkbox"/>
2.) <u>ADNEXA</u>  1-Normal 2-Abnormal If 2,specify _____	<input type="checkbox"/>	<input type="checkbox"/>
3.) <u>LIDS</u>  1-Normal 2-Abnormal If 2,specify _____	<input type="checkbox"/>	<input type="checkbox"/>
4.) <u>CONJUNCTIVA</u>  1-Normal 2-Abnormal If 2,specify _____	<input type="checkbox"/>	<input type="checkbox"/>
5.) <u>CORNEA</u>  1-Normal 2-Abnormal If 2,specify _____	<input type="checkbox"/>	<input type="checkbox"/>
6.) <u>ANTERIOR CHAMBER :</u> DEPTH	<input type="checkbox"/>	<input type="checkbox"/>

1-Normal 2-Shallow 3-Deep		
7.) <u>IRIS:</u>  COLOUR AND PATTERN 1-Normal 2- Atrophic Patches	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>
8.) <u>PUPIL:</u> <u>SIZE</u> 1-NORMAL 2-Constricted 3-Dilated	<input type="checkbox"/>	<input type="checkbox"/>
9.) REACTION: DIRECT INDIRECT  1-Present 2-Absent 3- Sluggish	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>
10.) <u>PUPILLARY MARGIN</u>  1-Normal 2-Abnormal  If2, specify _____	<input type="checkbox"/>	<input type="checkbox"/>
11.) <u>POSTERIOR SYNECHIAE</u>  1-Present 2- Absent	<input type="checkbox"/>	<input type="checkbox"/>
12.) <u>ACCOMODATION</u>  1-Present 2- Absent		
13.) <u>LENS:</u>  1-Clear 2-Cataractous 3-Pseudophakia 4- Aphakia.	<input type="checkbox"/>	<input type="checkbox"/>
14. IOP.-		

AFTER 3 MONTHS

SERUM CREATININE

BLOOD UREA

Observation :

60.)		
61.) FBS(mg/dl)		
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 4=disc haemorrhage Other,specify_____		
65.) Cup : disc ratio 1=normal (0.3) 2=abnormal If 2,specify_____		
66.) Vessels 1=normal 2=V.Beading 3=V.dilatation 4=V.looping 5=V.tortuosity 6=Venous sheathing. Other, specify_____		

<p><b>67.)Background</b>  1=normal, 2=abnormal  If 2,specify _____</p>		
<p><b>68.)Haemorrhages</b>  1=present , 2=absent  If 1:- (specify quadrants in brackets )  (a)=superionasal  (b)=superiotemporal  (c)= inferionasal  (d)=inferiotemporal</p>		
<p><b>69.)Types of h'рге</b>  1= Microaneurysms.  2=Superfioial h.  3=Deep h.  4=Flame shaped h.  5=pre-retinal h.  6=Vitreous h.</p>		
<p><b>70.) Hard exudates</b>  1=present, 2=absent  If 1, specify quadrants as above.</p>		
<p><b>71.) a= NVE  b=Collaterals  c=IRMAs</b>  1=present, 2=absent as above.</p>		
<p><b>72.) Soft exudates</b>  1=present, 2=absent  If 1, specify quadrants as above.</p>		

**ANNEXURE III – KEY TO MASTER CHART**

-	-	Absent
Adnexa		
1	-	Normal
2	-	Abnormal
Anterior chamber		
1	-	Normal
2	-	Shallow
3	-	Deep
Background		
1	-	Normal
2	-	Abnormal
Conjunctiva		
1	-	Normal
2	-	Congested
3	-	Others
Cornea		
1	-	Clear
2	-	Hazy
3	-	Other
Cup:disc ratio		
1	-	Normal
2	-	Abnormal

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Disc			
	1	-	Normal
	2	-	Pallor
	3	-	NVD
	4	-	Disc haemorrhage
F		-	Female
Glow			
	1	-	Present
	2	-	Faint
	3	-	Absent
Haemorrhages			
	1	-	Present
	2	-	Absent
Hard exudates			
	1	-	Present
	2	-	Absent
Iris			
	1	-	Normal
	2	-	Atrophic
Lens			
	1	-	Clear
	2	-	Cataractus
	3	-	Pseudophakia
	4	-	Aphakia
LOF		-	Lost to follow up

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M	-	Male
m	-	Months
MDNPDR	-	Moderate non proliferative diabetic retinopathy
Media		
1	-	Clear
2	-	Hazy
mg/dL	-	Milligram per deciliter
MNPDR	-	Mild non proliferative diabetic retinopathy
mu	-	Multiple
N	-	No
OHA	-	Oral hyperglycaemic agent
Pupil		
1	-	Normal
2	-	Constricted
3	-	Dilated
SNPDR	-	Severe non proliferative diabetic retinopathy
Soft exudates		
1	-	Present
2	-	Absent
Visual acuity		
1	-	6/6
2	-	6/18
3	-	6/36
4	-	6/60
WNL	-	Within normal limits
Y	-	Yes

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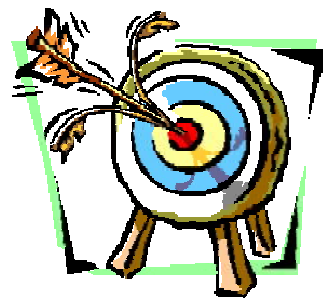
ANNEXURE III - MASTER CHART

Serial Number	Post operative																														
	Four months																														
	Visual acuity	Pin hole	Adnexa	Conjunctiva	Cornea	Anterior chamber	Iris	Pupil	Lens	Glow		Media		Disc		Cup disc ratio		Blood vessels		Back-ground		Haemorrhages		Exudates		Macula		Diagnosis			
										Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left
26	1	1	1	1	1	1	1	1	3	2	1	2	1	1	1	1	1	1	1	1	1	2	2	2	2	1	1	WNL	WNL		
27	1	1	1	1	1	1	1	1	3	1	2	1	2	1	-	1	-	1	-	1	-	1	-	2	2	2	2	1	1	WNL	WNL
28	2	1	1	1	1	1	1	1	3	1	1	1	2	1	1	1	1	1	1	2	2	1 a,b	1 a,b	2	2	2	2	1	1	MDNPDR	MNPDR
29	2	2	1	1	1	1	1	1	3	1	1	1	1	1	1	1	1	1	2	2	a,b	1 a,b	1	1	2	2	1	1	SNPDR	MDNPDR	
30	2	1	1	1	1	1	1	1	3	1	1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	1	1	WNL	WNL	
31	2	1	1	1	1	1	1	1	3	1	1	1	1	1	1	1	1	1	2	2	1 a,c	1 b,c	1	1	2	2	2	2	MDNPDR	MDNPDR	
32	2	1	1	1	1	1	1	1	3	1	1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	1	1	WNL	WNL	
33	2	1	1	1	1	1	1	1	3	1	1	1	1	1	1	1	1	1	2	2	b,c	a,b	2	2	a,b	a,c	1	1	SNPDR	SNPDR	
34	2	2	1	1	1	1	1	1	3	1	3	1	-	1	-	1	-	1	-	1	-	2	-	2	-	2	-	1	-	WNL	WNL
35	2	2	1	1	1	1	1	1	3	3	1	-	1	-	1	-	1	-	1	-	1	-	2	-	2	-	2	-	1	WNL	WNL
36	2	1	1	1	1	1	1	1	3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	2	1 a	1	1	1	MDNPDR	MDNPDR
37	2	1	1	1	1	1	1	1	3	1	1	1	1	1	1	1	1	1	1	1	1	1	2	2	2	2	1	1	WNL	WNL	
38	2	1	1	1	1	1	1	1	3	1	1	1	1	1	1	1	1	1	1	1	1	1	2	2	2	2	1	1	WNL	WNL	
39	2	1	1	1	1	1	1	1	3	1	1	1	1	1	1	1	1	1	1	1	1	1	2	2	2	2	1	1	WNL	WNL	
40	2	1	1	1	1	1	1	1	3	1	1	1	1	1	1	1	1	1	1	1	1	1	2	2	2	2	1	1	MNPDR	WNL	
41	2	1	1	1	1	1	1	1	3	1	1	1	1	1	1	1	1	1	2	2	1	1	1 a,c	1 a,b	2	2	1	1	MDNPDR	MDNPDR	
42	2	1	1	1	1	1	1	1	3	1	1	1	1	1	1	1	1	1	2	2	1	1	2	2	2	2	1	1	MNPDR	MNPDR	
43	2	1	1	1	1	1	1	1	3	1	1	2	1	1	1	1	1	1	1	1	1	2	2	2	2	2	1	1	WNL	WNL	
44	2	1	1	1	1	1	1	1	3	1	1	1	1	1	1	1	1	1	2	2	1	1	2	2	2	2	1	1	MNPDR	MNPDR	
45	2	1	1	1	1	1	1	1	3	1	1	1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	1	1	WNL	WNL	
46	2	1	1	1	1	1	1	1	3	1	1	1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	1	1	WNL	WNL	
47	2	1	1	1	1	1	1	1	3	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	1	1	MNPDR	MNPDR	
48	2	2	1	1	1	1	1	1	3	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	1	1	MDNPDR	MDNPDR		
49	2	1	1	1	1	1	1	1	3	1	1	1	2	1	1	1	1	1	1	1	1	2	2	2	2	2	1	1	WNL	WNL	
50	2	2	1	1	1	1	1	1	3	1	1	1	1	1	1	1	1	1	2	2	1	1	2	2	2	2	1	1	MNPDR	MNPDR	



## *Introduction*

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## *Objectives*

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# *Review of Literature*

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# *Methodology*

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*Results*

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## *Discussion*

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*Conclusion*

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*Summary*

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## *Bibliography*

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*Annexure-I*

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## *Annexure-II*

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## *Annexure-III*

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