"OUTCOME OF INTRAVITREAL INJECTION OF BEVACIZUMAB ON VISUAL ACUITY AND CENTRAL MACULAR THICKNESS IN PATIENTS WITH DIABETIC MACULAR EDEMA– A ONE YEAR LONGITUDINAL STUDY AT KLES DR. PRABHAKAR KORE HOSPITAL AND MEDICAL RESEARCH CENTRE, BELAGAVI"

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ABSTRACT

Aim: To study the outcome intravitreal injection of bevacizumab (IVB) on best corrected visual acuity (BCVA) and central macular thickness (CMT) in patients with DME.

Design: A one year longitudinal study was carried out in Department of Ophthalmology, KLES Dr. Prabhakar Kore Hospital and MRC, Belagavi, from January 2019- December 2019.

50 eyes of known diabetics with DME with CMT > 260 microns and BCVA of 6/9 (0.18 logMAR units) or worse were recruited and given three monthly IVB. BCVA and CMT at the end of four months were assessed and compared to baseline values. Side effects were noted if any.

Results: The mean BCVA at baseline and at 4 months were 0.80 ± 0.49 and 0.51 ± 0.36 respectively (p value =0.0001). The mean baseline CMT (μm) and at 4 months were 448.40 ± 149.47 and 368.76 ± 131.49 (p value =0.0001) respectively. The improvement in BCVA and CMT were statistically significant. Various factors like duration of diabetes and value of HbA1c were not found to be significant for the improvement in BCVA and CMT.

Conclusion: IVI bevacizumab given as 3 injections at monthly intervals was safe, economical and effective in DME management. No major adverse effects were noted in this study.

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ACCEPTANCE LETTER

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LIST OF ABBREVIATIONS USED

AGEs	Advanced Glycation End Products
ALP	Alkaline Phosphatase
AST	Aspartate Transferase
BCVA	Best Corrected Visual Acuity
BRB	Blood Retinal Barrier
CFT	Central Foveal Thickness
CMT	Central Macular Thickness
CMV	Central Macular Volume
CRT	Central Retinal Thickness
CSME	Clinically Significant Macular Edema
DCCT	Diabetes Control And Complications Trial
DM	Diabetes Mellitus
DME	Diabetic Macular Edema
DR	Diabetic Retinopathy
ELISA	Enzyme Linked Immunosorbent Assay
ETDRS	Early Treatment Of Diabetic Retinopathy Study
FA	Fluorescein Angiography

Fab	Fragment Antibody
FcRn	Neonatal Fc Receptor
HIF	Hypoxia Inducible Factor
ICMR	Indian Council Of Medical Research
IOP	Intraocular Pressure
IRMA	Intra Retinal Microvascular Abnormalities
IVB	Intravitreal Bevacizumab
IVI	Intravitreal Injection
IVM	Intravitreal Methotrexate
IVTA	Intravitreal Triamcinolone Acetonide
KDR	Kinase Insert Domain Receptor
NPDR	Non Proliferative Diabetic Retinopathy
NRP	Neuropilin
NVD	Neovascularization On The Disc
NVE	Neovascularization Elsewhere
NVI	Neovascularization Of Iris
OCT	Optical Coherence Tomography
PCIOL	Posterior Chamber Intraocular Lens

PDR	Proliferative Diabetic Retinopathy
PlGF	Placental Growth Factor
PPV	Pars Plana Vitrectomy
PRP	Panretinal Photocoagulation
RESTORE	Ranibizumab Monotherapy Or Combined With Laser Versus Laser Monotherapy For Diabetic Macular Edema
RFT	Renal Function Test
RN	Retinal Neovascularization
SCDME	Subclinical Diabetic Macular Edema
SDOCT	Spectral Domain Optical Coherence Tomography
SNP	Single Nucleotide Polymorphism
TA	Triamcinolone Acetonide
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
VNTRS	Variable Number Tandem Repeats
VTDR	Vision Threatening Diabetic Retinopathy
WNL	Within Normal Limits

INTRODUCTION

INTRODUCTION

The word Diabetes mellitus is derived from the Greek word Diabetes, which literally means siphon - to pass through. In Latin language, Mellitus means sweet. Metabolically, it is associated with significant elevation and derangement of blood glucose levels. Broadly and commonly, it is classified into following main types: Type 1, Type 2, Maturity-onset diabetes of the young (MODY), Gestational diabetes, Neonatal diabetes, and Secondary causes. However; classically, types I and type II are the main clinically considered variants of DM which occur because of defective insulin secretion (T1DM) and/or action (T2DM).[1]

In 2011, across the globe, approximately a little less than 350 million subjects were affected with diabetes. Also, the number is expected to double by 2030.[2]

In diabetes, one of the major factors resulting in visual impairment is diabetic retinopathy (DR). Literature from past few decades has reported prevalence of DR to be varying from seventeen percent to twenty percent in Indian subcontinent. If it kept on growing at this pace, DR is expected to increase in coming few decades to approximately twenty two and a half million. On the basis of above analysis, there is an urgent need for implantation of definitive health programs for decreasing the socio-economic burden of DR on general population.[3]

Following the progression of disease, DR is assumed to follow following path of increasing severity: Mild type i.e. Non-proliferative stage, and → Proliferative stage. However; visual acuity might not follow similar severity pathway of progression.

There can be decrease in vision and hence Vision-threatening DR (VTDR) can occur during any stage of severity of DR. While analysing the data of a recent past study, it was seen that more than severity percent of the diabetic patients were affected with Non-proliferative DR, while approximately only fifty percent of the diabetic patients had good vision.[3]

DME is known to affect approximately twelve percent of subjects with DR and results in over ten thousand new cases of blindness annually. The prevalence and incidence rate of DME is directly affected by duration and type of diabetes. Cross-sectional data from past literature demonstrates that after initial 5 years of confirmed diagnosis of diabetes (Types I), patients are at higher risk of developing DME. Within thirty years, the incidence rate spikes up to forty percent. At the time of clinical presentation and confirmation of diagnosis of diabetes (Type II), approximately five percent of the patient population are already affected with DME.[4-8]

The retina is significant and one of the major structural and functional component of eye. It is anatomically present as thin layer in the eye's posterior segment in the vicinity of optic nerve. Photoreceptor cells are present in it.

It obtains focused light (directed from the lens) and transforms the light into neural signals. Hence; any damage to retina can lead to serious structural and functional consequences.

The macula is the center of the retina. It contains maximum concentration of photoreceptors. Occurrence of macular edema in diabetes is a multifactorial process. Anti-vascular endothelial growth factor (VEGF) therapy is the major treatment therapy employed in this group of patients.[9, 10]

Diabetes and subsequent hyperglycemia results in the formation of advanced glycation end products (AGEs). The specific etiology of diabetic retinopathy is unclear and likely, the result of many interplaying factors. AGEs are osmotically active, and they may be responsible for fluid accumulation in the macula. Diabetes also results in disruption of the blood-retinal barrier (BRB), and this is likely critical in the pathogenesis of diabetic associated macular edema. AGEs are also associated with increased inflammatory markers such as VEGF, leukocyte adhesion, and protein kinase C.[11, 12]

The underlying pathophysiology of diabetic macular edema is secondary to the disruption of the BRB. The BRB isolates the photoreceptors of the retina from the ophthalmic vasculature. The BRB functions in a complex manner that involves several factors that work in tandem; however, many of the specific physiologic processes are poorly understood.

The BRB involves two major compartments: an outer and inner barrier. Animal models have illustrated that the permeability of both compartments is disrupted after the onset of diabetes. Disruption of this barrier results in the accumulation of macular edema; however, the process is more complicated than this and also involves various inflammatory markers upregulated by AGEs, hyperglycaemia, and diabetes.

Diabetes also results in vasoconstriction, which upregulates VEGF expression. VEGF also results in macular edema and results in vasculogenesis, which results in further retinal disease.[13, 14]

One of the mainstays for diabetic macular edema treatment has historically involved laser photocoagulation, it has been shown to improve visual acuity in a small percentage of patients. The Early Treatment Diabetic Retinopathy Study (EDTRS) provides the guidelines for the laser photocoagulation for DME have provided by the ETDRS. Leaking microaneurysms are directly treated, while a combination of focal laser photocoagulation and scatter laser photocoagulation are described as the treatment for DME in certain instances of proliferative diabetic retinopathy and non-proliferative diabetic retinopathy. Although macular laser photocoagulation is a major treatment modality for clinically significant macular edema, it is not curative, and many cases are refractive to the laser therapies. Vitrectomies have been shown to improve DME; however, the science behind this is unclear.[15, 16]

DME patients are typically manifested by elevated vascular permeability. VEGF production is upregulated in DR patients due to hypoxia, further resulting in retinal capillary hyperpermeability. The anti-VEGF treatment protocols in the present health and medicine scenario includes: ranibizumab, bevacizumab, aflibercept and pegaptanib sodium.[17]

Bevacizumab is a type of antibody (monoclonal in nature) that is known to obstruct VEGF-A family isoforms within the extracellular space. It is one of the mainline drugs for treating metastatic carcinomas as approved by FDA. It is also employed as one of the major therapeutic option in treating neovascular age-related macular degeneration and retinal vascular disorders including retinal vein occlusion and diabetic macular edema.

Data from the studies and trials conducted in the past literature have shown that intravitreal pegaptanib and intravitreal ranibizumab leads to improvement in DME cases within 9 months' time.[18- 21]

Hence; under the light of above mentioned data, the present study was undertaken for assessing the outcome of intravitreal injection of bevacizumab on visual acuity and central macular thickness in patients with diabetic macular edema.

AIMS & OBJECTIVES

AIMS & OBJECTIVES

1. To study the outcome of intravitreal injection of bevacizumab on visual acuity and central macular thickness

2. To assess its safety in terms of its effects on eye in patients with diabetic macular edema.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Diabetic macular edema (DME) clinically presents in the form of retinal thickening because of intraretinal fluid leakage, mainly in the inner and outer plexiform layers. It is supposed to be occurring because of hyper-permeability of retinal vasculature.

Early Treatment of Diabetic Retinopathy Study (ETDRS) Criteria for Clinically Significant Macular Edema (CSME)[1]:

• Retinal thickening at the center of the macula

• Retinal thickening and/or adjacent hard exudates at or within 500 μ of the center of the macula

• An area of retinal thickening greater than or equal to one disc area, any part of which is within 1 disc diameter of the center of the macula

PATHOLOGY AND PATHOPHYSIOLOGY OF DME

Retina is a unique structural organ in terms of circulation pattern. Vascular supply of retina is non-fenestrated. Endothelial cells of the capillaries exhibit tight junctions. No fluid and blood leakage occurs from the retinal capillaries under normal conditions. There is absence of lymphatic drainage system in the retina. Hence; any retinal abnormality or pathology, which can cause fluid leakage, would lead to formation of edema or swelling. Retina reacts to ischemic stimuli by proliferating growth factors to cause neovascularization.

DME is the outcome of micro-vascular ischemic alterations in diabetic resulting because of incompetence of vessels and following edema. Hypoxic state further causes stimulation of VEGF resulting in aggregation of edema. [22]

Hence; two major characteristic alterations occur in DME:

• Vessel permeability

- Damaged endothelial wall becomes more leaky (porous)
- Vessel leaks fluid, lipids, erythrocytes
- Fluid accumulation results in edema (macular edema if situated within the central region of the retina) [22]

• Vessel closure

- Supply of oxygen and nutrients are reduced
- New abnormal and weak vessel formation occurs (secondary to ischemia)

CLINICAL DEFINITIONS

DME is regarded as thickening of the retina within one disc diameter of the center of the macula or definite hard exudates in this region.

CENTER-INVOLVING DIABETIC MACULAR EDEMA

- DME in which the fovea is involved.

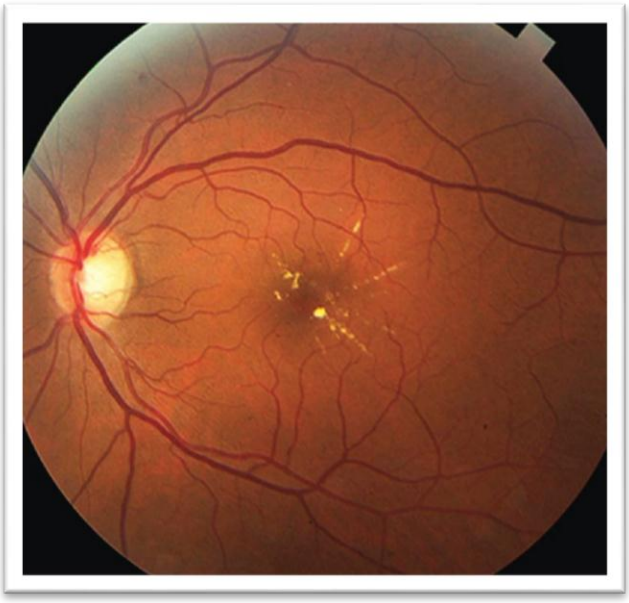


Fig. 1

Centre involving DME

CLINICALLY SIGNIFICANT MACULAR EDEMA

The situation in which at least one of the following criteria is fulfilled:

- Retinal thickening within 500 μm of the center of the macula
- Hard exudates within 500 μm of the center of the macula with adjacent retinal thickening
- One disk area of retinal thickening any part of which is within one disk diameter of the center of the macula. [22]

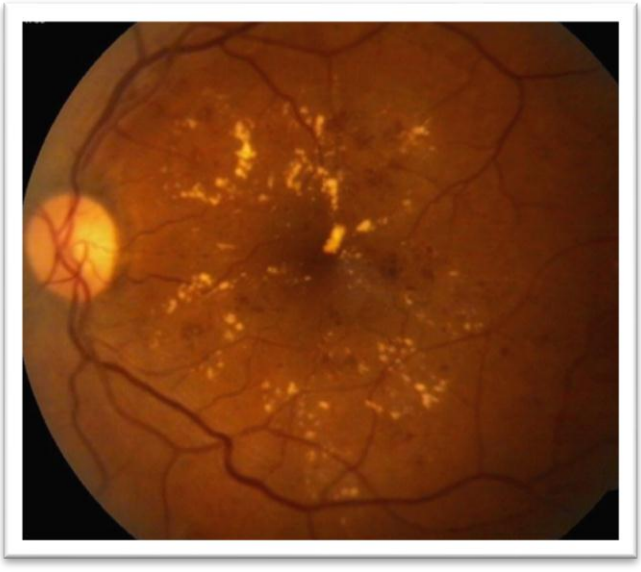


Fig. 2

CSME fundus photograph

FOCAL AND DIFFUSE DIABETIC MACULAR EDEMA

Data from the past literature does not define both these terms consistently. Focal edema is supposed to occur because of microaneurysms, while diffuse edema is projected to occur from dilation and hyper-permeability of vasculature throughout the macula.

In terms of prevalence, as per previous literature, focal DME is reported to have high prevalence rate in comparison with diffuse DME. However; there are numerous cases reported in the literature in which clear distinction in type of DME is very difficult because of overlapping symptoms. Extra misperception might occur because "focal" terminology is used to enumerate a technique of direct smearing of laser to micro-aneurysms when managing DME patients with focal/grid photocoagulation.

Several other authors have also proposed differential DME classifications from time to time. According to one such report, DME is divided into following subtypes: Diffuse Edema, Cystoid macular Edema, and serous retinal detachment.

Unpredictable results have been reported in the past literature and trials which have attempted in associating these subgroups to therapeutic outcome. Also, no unanimity protocol exists on interventions for the projected subtypes. [22]

SUBCLINICAL DIABETIC MACULAR EDEMA (SCDME)

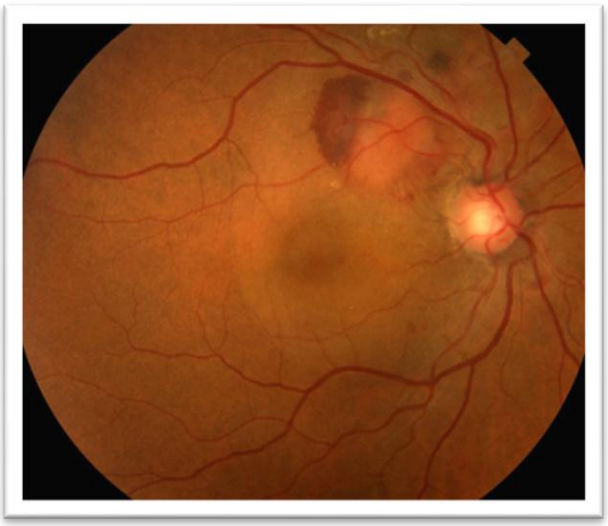
The severity of DME might not spread upto the description of CSME or CIDME. Clinical evaluation of DME and OCT analysis of DME often disagree in this spectrum of subjects.

Also, few eyes do not have confirmed diagnosed DME, but macular thickening is appreciable with the help of OCT. The term subclinical DME is employed for defining both of these classes of DME which are less severe in comparison to clinically significant DME. [22]

PERSISTENT DIABETIC MACULAR EDEMA

Persistent DME is defined as those DME cases which were treated without thorough resolution. Persistent DME are reported to be present in significant proportion of eyes treated by any therapeutic option like focal laser photocoagulation, intravitreal injection of anti-VEGF drugs/ steroids and vitrectomy. Dissimilar standards have been used for the number of therapeutic options or duration of treatment needed before smearing the term. Few eyes have obstinate edema instead of all known treatments for DME. [22]

Fig. 3 Persistent DME



RECURRENT DIABETIC MACULAR EDEMA

Recurrent DME is regarded as that type of DME in which pathology still exists after once resolution has occurred following completion of treatment. Or in other words, pathology has recurred. Although resolution of DME can occur impulsively without treatment, and then recur, the terminology of recurrent DME is employed in relation to treated eyes with recurrences.[22]

CLINICAL ASSOCIATIONS AND RISK FACTORS

DME is strongly directly correlated with severity of diabetic retinopathy in diabetic patients. Glycemic control decisively recognizes risk factors for progression of retinopathy along with progression of DME. A strong correlation of diabetes duration with prevalence macular edema, retinopathy progression, and other diabetic complications also exists.

The final diagnosis of diabetes in patients with presence of type 2 diabetes infrequently occurs a while after subclinical diabetes has manifested. This might yield a small amount of subjects which might present with DME at the time of diagnosis.

However; in contrast, subjects with type 1 diabetes are less likely to face advanced retinopathy and macular edema before five years of duration.

CLINICAL ASSOCIATIONS WITH DIABETIC MACULAR EDEMA SEVERITY [23, 24]

- Duration of Diabetes – increased risk of diabetic retinopathy
- Glycemic control – The Diabetes Control and Complication Trial (DCCT) clearly demonstrated that stricter control of blood sugar is associated with decreased incidence of diabetic retinopathy
- Nephropathy – proteinuria is an important indicator for DR development; thus, patients with diabetic nephropathy should be more closely monitored
- Hypertension – higher risk of retinopathy (diabetic retinopathy with superimposed hypertensive retinopathy)
- Dyslipidemia – normalization of lipid levels decreases leakage of retinal vasculature and deposition of exudates
- Pregnancy – diabetic retinopathy can progress rapidly in pregnant women, especially those with pre-existing diabetic retinopathy
- Intra-ocular surgery
- Uveitis
- Panretinal Photocoagulation

CLINICAL PRESENTATION OF DIABETIC MACULAR EDEMA

Subjects affected by DME usually present with a series of visual manifestations depending on the severity to which involvement of fovea occurs and the chronicity of the lesion. In case of non-involvement of macula center, patients are

usually asymptomatic; however, only a few subjects might observe relative paracentral scotomas consistent with focal edema and hard exudates. Few subjects with central macular involvement might show brilliant acuity with absence of visual complains. This might occur because of only recent involvement of the center.

Metamorphopsia is a common phenomenon. Commonly, subjects with center involved DME observe fluctuation of vision from routine daily life. In few cases, the subject might relate such alterations to fluid retention, hyper or hypoglycemia, or ambient lighting.[25, 26]

Retinal thickening might be demonstrated in common identifiable patterns on fundus examination. Focal edema frequently occurs in association with microaneurysms clusters, many a times enclosed by an incomplete circle of hard exudates. Diffuse DME might be extremely problematic to identify clinically under conditions in which retina is of constant thickness, because of lack of reference landmarks. Stereoscopic fundus examination provide an option for assessing the long-term alterations in the retina.[27- 29]

In highlighting the breakdown of the blood-retinal barrier by delineating retinal micro-vascular leakage and micro-vascular nonperfusion, Fluoresceine angiography has been proven to be highly useful. However; Fluorescein angiography is not useful in assisting the diagnosis of CSME but must be implemented if treatment of CMSE is being considered.

Optical coherence tomography (OCT) is also capable of demonstrating a moderate association between retinal thickness and BCVA, and it also demonstrates three basic structural alterations in the retina from diabetic macular edema, which are, retinal swelling, cystoid edema, and serous retinal detachment. Quantitative assessment of macular thickness and independent assessment of the foveal architecture permit a precise and reproducible method to observer macular edema. [27-29]

TREATMENT

For preventing the occurrence of DME and also preventing its progression, it is necessary to maintain strict glycemic control under all conditions. Also, at the same time, it is strictly essential to reduce blood lipid levels, and normalize systemic blood pressure. As recommended by the American Diabetes Association, HbA1c levels should be kept under seven percent, blood pressures should be kept under 130/80 mmHg, and total lipids levels should be maintained under one hundered mg/dL. Ocular therapeutic options include retinal laser photocoagulation, intravitreal administration of certain agents, and vitreoretinal surgery when required.[30]

LASER THERAPY

Laser therapeutic protocols have been obtained mainly from the Early Treatment Diabetic Retinopathy Study (ETDRS). In this study, authors analysed the photocoagulation in diabetic subjects of North America.

The results of the study demonstrated that patients with CSME who were treated by laser photocoagulation, exhibited improved visual acuity, decreased the risk of visual loss, and negligible visual field loss. Hence; it is essentially accepted as the existing line of treatment for DME by many researcheres.[31- 35]

Fewer adverse events associated with laser photocoagulation are described in the past literature. These include macular hemorrhage, choroidal neovascularization, decline in visual acuity and contrast sensitivity, and visual field defects.

The target of laser photocoagulation therapy is to abolish the outer segments of photoreceptors and lessen oxygen consumption; with the aim of minimising this impact, numerous efforts have been made to enhance the variable and application techniques.[36, 37]

ANTI–VEGF AGENTS

The VEGF family is a sub-group of growth factors. VEGF-A is also member of this family. It is proved to play a crucial and central role in patho-physiology of various ocular pathologies and its signalling promotes angiogenesis along with enhancing vascular permeability.[38, 39]

The function of VEGFR-1 is still unclear. Along with this, it also fixes PlGF and seems to be involved in monocyte chemotaxis along with the induction of MMP-9.[38- 40] VEGF-A expression can be prompted by hypoxic environment through the

transcription factor hypoxia-inducible factor (HIF) and it enhances the capillary permeability through numerous downstream effects.

VEGF-A initiates phosphorylation of the tight junction proteins occludin and zonula occludens-1, resulting in disruption of tight junctions. Each of these consequences results in enhanced vascular permeability. Ischemia induced by leukostasis and endothelial cell death can in turn further increase the expression of VEGF.[41- 43]

VEGF is considered as the main logical target for treating DME, mainly due to its principle role in the pathogenesis of DME. Pegaptanib, produced by OSI Pharmaceuticals, USA was the first anti-VEGF drug employed in the speciality of ophthalmology. It is a 28-nucleotide ribonucleic acid aptamer that fixes to the VEGF-A165 isoform and was originally accepted for treating neovascular age-linked macular degeneration. Its use has largely been displaced by the development of ranibizumab. Ranibizumab is a fragment antigen binding (Fab) anti-VEGF drug which functions for neutralizing all isoforms of VEGF-A. Bevacizumab, produced by Genentech, Inc., USA, is a monoclonal antibody that fixes to all isoforms of VEGF-A. It was initially developed in the year 1996 and was initially employed for treating human cancers.[38, 44]

There has been a tremendous increase in use of anti-VEGF agents in different fields of ophthalmology ever since the authorization of bevacizumab has come for colorectal cancer and ranibizumab for age-linked macular degeneration. For treating

retinal pathologies, few of the available therapeutic agents include Pegaptanib, bevacizumab, ranibizumab, aflibercept, and KH902. Each drug has been the topic of numerous trials and has shown constant improvement in patients DME.

At present, for treating DME, ranibizumab is the only therapeutic option approved by the US Food and Drug Administration. Aflibercept, also regarded as "VEGF trap" (due to its capability to neutralize all six VEGF proteins), is permitted for use in patients with wet age-linked macular degeneration, but not yet in DME.[46- 49]

Ranibizumab is a monoclonal antibody fragment which is obtained from a mouse monoclonal anti-VEGF antibody. It can restrict the metabolic activities of VEGF. Data from previous studies have authenticated its utility in reducing macular thickness. In a previous one year old clinical trial (the RESTORE study), authors validated the impacts of ranibizumab, laser, and a combination of the two. Results from this study demonstrated that ranibizumab monotherapy and a combination of ranibizumab with laser therapy were more beneficial in comparison to laser treatment alone when assessed for improving macular thickness and visual acuity gain. Furthermore, ranibizumab has minimal or negligible complications and is often regarded as a well-tolerated drug, even on long term follow-up.[50, 51]

In relapsed cases of DME, effectiveness of anti-VEGF agents is proven in few of clinical studies. In one such study conducted by **Gulkilik et al**, authors demonstrated the efficacy of bevacizumab in cases with recurrent DME after pan retinal photocoagulation.

Yuksel et al, in another study, demonstrated that IVB treatment is efficacious in patients which are unresponsive to focal laser photocoagulation or/and subtenon or intravitreal steroid injection. In few patients, therapeutic reaction to IVB or ranibizumab might be incomplete or absent. It has been demonstrated that switching to aflibercept delivers anatomical and visual enhancement in these patients because of differences in pharmacodynamics of the drugs.[52- 54]

INTRAVITREAL CORTICOSTEROIDS

The usefulness of glucocorticoids is dependent upon their anti-inflammatory and anti-VEGF influences. Triamcinolone acetonide (TA) has been routinely employed for different ocular inflammatory disorders (DME). Significant amount of studies have reported substantial improvements in DME with TA alone or in combination with anti-VEGF therapeutic options. Significant improvement in the visual acuity and decrease in CMT during post-injection follow-up period have been reported on a number of occasions by different authors. Nevertheless, the persistent impact of TA is still controversial, specifically in terms of anatomical outcome. Increased IOP and cataract formation are the few of the significant complications of TA injection. As per a previous report, while elevated IOP might need medical treatment, only two percent of treated eyes needed surgical therapy for reducing IOP.[56- 59]

PARS PLANA VITRECTOMY

Significant reductions in macular edema in selective DME patients in response to pars plana vitrectomy (PPV) have been demonstrated in various clinical trials. PPV eliminates traction forces and pro-inflammatory substances and enhance the oxygenation of inner retinal layers. The protocol is applicable when DME is resistant to laser treatment and anti-VEGF injections. It decreases the macular thickness and delivers visual acuity gain. All these effects are usually sustainable over considerable period of time.

Improved surgical results have been obtained by mixing medical and surgical therapeutic protocols. The presence of hard exudates, vitreous hemorrhage, and vitreomacular traction might be regarded as indications for PPV in DME cases.[60- 62]

BEVACIZUMAB

Bevacizumab (Avastin®; CA) is a humanized anti-VEGF monoclonal IgG1 antibody (molecular weight, 149 kDa).

MECHANISM OF ACTION

Malignant cells and organs frequently have high metabolic activity; this might lead to enhanced demand for oxygen and nutrients; disrupting the equilibrium and exceeding the supply. Consequently, these cells and tissues manifest by the creation of hypoxic environment, which is also the single major parameter controlling angiogenesis.

In hypoxic environment, hypoxia inducible factor (HIF) impasses to the hypoxic response element which are present in the VEGF gene. This further leads to induction of transcription of VEGF protein.

This is followed by binding of circulating VEGF to VEGF receptor (VEGFR)-1 and VEGFR-2 and to its co-receptors neuropilin (NRP)-1 and NRP-2 with high binding affinity. Expression of these receptors is significantly higher on endothelial cell surfaced, and they perform a crucial role in the process of neo-angiogenesis by activating recruitment and endothelial cell proliferation.

Mechanism of action of Bevacizumab is selectively binding to circulating VEGF. This further, inhibits binding of VEGF to its cell surface receptors. As a result of this inhibition process, there is a significant reduction in microvascular growth of tumour blood vessels. This considerably limits the tumour tissue's vascular supply. These consequences also decrease the tissue interstitial pressure, enhance the vascular permeability, might also enhance delivery of chemotherapeutic agents, and favour apoptosis of tumour endothelial cells.

Results of studies on rodent models have demonstrated that upon interruption of anti-VEGF therapy, the tumor capillaries recommenced multiplication and extended upto the baseline growth rate within a span of one week. Tumour vasculature regrowth occurs from the empty sleeves and pericytes of the vascular basement membrane. Under the environment of continued anti-VEGF
therapy, the tumor vasculature became sensitive once more as under baseline environment. [61-63]

PHARMACOKINETICS

ELISA technique has been suggested to be effective for analysing serum bevacizumab concentrations. In a previous research, four hundred and ninety one patients who received 1–20 mg/kg of bevacizumab every week (upto three weeks), the estimated half-life was approximately twenty days and the estimated time to reach steady-state was approximately one hundred days.[61-63]

PROTEIN BINDING

Data from recent researchers have suggested that bevacizumab binds >97% of serum VEGF. Platelets are responsible for producing predominant portion of Serum VEGF, which is demonstrated to be taken up bevacizumab. Platelets might discharge bevacizumab at areas of endothelial damage and hence deliver it to procoagulatory angiogenic tumor areas at relatively high concentrations, targeting the tumor cell VEGF.[61-63]

DISTRIBUTION

A bi-compartment prototype with first-order elimination assessed that the quantity of bevacizumab distributed was 2.3 in case of typical females and 3.2 in case of typical males. Bevacizumab circulation was restricted to the tumor angiogenic supply with negligible extravascular circulation. Along with this, scintigraphic imagining of VEGF expression in rodent demonstrated the accretion of radiolabelled bevacizumab enhanced in tumor tissues in comparison to normal counterpart, and that the uptake in normal tissues declines over a period of time.[61-63]

ELIMINATION

The neonatal Fc Receptor (FcRn) contributes significantly in clearing of bevacizumab. In catabolic cells, movement of antibodies into the endosomes occur by process of pinocytosis. Inside them, its binding to the FcRn occurs. This process of antibody binding defers the degradation process of antibody and saves it from systemic excretion, thereby prolonging half-life. The assessed clearance rate of bevacizumab is a little more than 0.2 per day.

A direct correlation of bevacizumab elimination is observed with weight, sex, serum albumin, ALP, and AST levels. In underweight subjects, bevacizumab's clearance rate could fall upto thirty percent. Also in obese subjects, bevacizumab's clearance rate could be enhanced upto thirty percent. Gender based variation has also been observed in relation to clearance of bevacizumab. On an average, males have approximately twenty six percent higher clearance rate in comparison to females.

A significantly low clearance rate has also been reported among subjects with low serum albumin levels. In contrast, subjects with higher ALP levels are reported to have approximately twenty three percent higher clearance rates. [61-63]

PHARMACO-GENETICS

Genetic aberrations in VEGF or VEGF receptors could possibly act as a differential marker for the assessing the therapeutic response. In VEGF, 5 functional SNPs have been identified in the 5′ and 3′ regions. These SNPs leads to decline in

VEGF production or enhanced promoter activity. Along with this, there are numerous non-synonymous SNPs in the coding region of KDR and HIF-1α, which are accountable for their enhanced expression.[61-63]

The enhanced plasma half-life of bevacizumab could be elucidated by variable alleles of FcRn. There are several numbers of tandem repeats (VNTRS) inside the promoter of the FCGRT gene (which codes Fc), comprising of five different alleles.

The VNTR3 allele is related with enhanced FcRn expression and it is feasible that subjects having this allele have a lengthier plasma half-life of bevacizumab.[61-63]

The haplotype associated with polymorphism at −460/+405 have been reported to correlated with changed in-vitro VEGF production. Presence of this kind of polymorphism suggestively modifies VEGF promoter activity. Since, these gene alterations and changes might contribute to disparity in VEGF production, subjects having one or more of these SNPs might exhibit differential effectiveness or even noxious reactions to anti-VEGF therapy. [61-63]

SIDE EFFECTS

Routinely encountered adverse events associated with bevacizumab include, blood pressure abnormalities, asymptomatic proteinuria, events occurring due to thromboembolic derangement, perforation of the gut, and often wound healing problems. Rarely, thrombo-embolitic serious manifestations are associated with

higher doses of bevacizumab. If any of the complication of higher severity appears following bevacizumab administration, it should be discontinued immediately.[61-63]

Haritoglou C et al in 2006 conducted a prospective analysis of effeteness of bevacizumab in treating patients with DME. Fifty one patients with mean age of sixty four years were included in the present study. Even in subjects with presence of diffuse DME not responding to preceding therapeutic protocols, significant improvement of visual acuity and decline of retinal thickness was appreciated after IVB.[64]

In another study conducted by **Kumar A et al in 2007,** authors described the anatomic and visual acuity therapeutic alteration following IVB therapy in patients with presence of DME. They analysed twenty eyes in subjects with stable diabetic status and presence of diffuse DME. Mean age of subjects of their study group was fifty nine years. They observed a highly significant alteration in the acuity from baseline value of 1.3 to final post-injection value of 1.09 on three months follow-up. A significant reduction in mean CMT was also observed varying from baseline value of 492 µm to final value of 369 µm. Their results demonstrated that patients with diffuse DME which do not respond to routine photocoagulation should be treated with IVB therapy.[65]

Arevalo JF et al (2007) studied the data records of eighty eight consecutive patients (one hundred ten eyes) with DME. After following the inclusion and exclusion criteria, 78 eyes of sixty four consecutive subjects (mean age: 59.7 years)

were enrolled. They observed a statistically significant improvement in the BCVA from baseline mean value of 0.87 to final follow-up value of 0.6. On final analysis, they observed that approximately forty percent of the eyes remained stable, improvement with ≥ 2 ETDRS lines of BCVA occurred in approximately fifty five percent of the patients, decline of ≥2 ETDRS lines of BCVA in approximately five percent of the patients. A significant decrease in mean CMT from baseline value of 387.0 to final follow-up value of 275.7 was also observed.[66]

Roh MI et al (2008) presented the data of IVB administration in twenty four patients (Thirty one eyes) with DME. No significant difference was observed while comparing the baseline and follow-up of VA and CMT values. From the results, they concluded that repeated IVB administration might lead to improvement of VA and CMT in DME patients.[67]

A Özkiriş in 2009 analysed the efficacy of IVB in treating patients with DME. A total of thirty eyes of thirty diabetic patients who presented with DME were enrolled. During a mean follow-up of approximately five to six months, a significant enhancement in the visual acuity was observed in eighty percent of the eyes. They concluded that IVB application delivers significant enhancement in visual acuity of diabetic patients and clinical course of DME.[68]

Arevalo JF et al in 2009 evaluated the impact of IVB on retinal neovascularization (RN) in patients with PDR. Analysis of 44 eyes in thirty three patients was done. Approximately sixty percent of the eyes demonstrated total

regression of RN on fundus examination with absence of fluorescein leakage. Approximately thirty four percent of the eyes showed partial regression of RN on fundus examination and FA. From the results, they concluded that IVB causes marked reduction of RN in patients with PDR.[69]

Al-Laftah FAW et al in 2010 evaluated treatment response of IVB in patients with DME. Forty five eyes (thirty eight patients) with presence of refractory DME were enrolled. They observed a significant improvement in LOGMAR and CRT in sixty seven percent and seventy percent of eyes respectively. Mean LOGMAR visual acuities values were 0.64 at pre-treatment value and were 0.60 at final post-treatment follow-up. The mean foveal thicknesses improved significantly from pre-treatment value of 444.95 μm to final post-treatment follow-up value of 378.32 μm (p- value < 0.05). They observed significant correlation while analysing the pre and post-treatment parametric values with diabetic duration and diabetic control.[70]

Shaikh et al in 2011 analysed the effectives of IVB on visual acuity and CMT in patients with DME. Only those patients were enrolled in their study that has been already subjected to macular laser photocoagulation. Significant improvement in BCVA was seen from pre-treatment baseline value of 1.03 to final value of 3 on follow-up. Also, significant improvement in the CMT was seen from baseline value of 520 μm to final follow-up value of 427 μm. They concluded that IVB resulted in significant enhancement clinical manifestations in DME patients.[71]

Rajendram R et al in 2012 described the results of outcome of IVB and modified ETDRS macular laser therapy in patients with CSME. Their research provided substantial data supporting the effeteness of IVB on long term basis in patients with CSME.[72]

Saif MYS et al in 2013 evaluated the efficacy of anti-VEGF therapy in patients with DME. They injected IVB in ninety patients (one hundred six eyes) with DME. Seventeen percent of the eyes received the IVB alone while twenty nine percent of the patients had macular grid in conjunction with the IVB. In the remaining fifty four percent of the eyes, PRP was given with the injection. They concluded that Anti-VEGF therapy is significantly effective in treating DME patients.[73]

Małgorzata W et al in 2013 analysed the efficacy of IVB in DME patients. They observed a significant reduction in the mean retinal thickness in comparison to the baseline values. They concluded that IVB in DME patients led to significant improvement in clinical and structural manifestations of the disease.[74]

Bakbak B et al in 2013 analysed and compared the effectiveness of bevacizumab and ranibizumab on contralateral, untreated, eyes in patients with bilateral DME. Their study comprised of two study groups; Group 1- Fifty patients (fifty eyes) who received bevacizumab, and Group 2- Thirty two patients (thirty two eyes) who received ranibizumab. They didn't observe any significant difference in the median BCVA value in the uninjected eye in either of the study groups on final post-treatment follow-up. From the results, they concluded that IVB showed better results in un-injected eyes in comparison with ranibizumab in patients with bilateral DME.[75]

Tareen IU et al in 2013 conducted a study for analysing the effectiveness of IVB on DME patients. They observed a significant reduction in the mean BCVA from pre-treatment value of 0.42 to post-treatment value of 0.16 (p- value < 0.05).

Significant improvement in the mean CMT was also observed from pre-treatment value of 452.9 to post-treatment follow-up value of 279.8. However; they didn't observed any pre-treatment or post-treatment complication. They concluded that IVB appears to deliver constancy and improvement in clinical symptoms in DME patients.[76]

Ateeq A et al in 2014 analysed the efficacy of IVB in DME patients. Fifty four patients with DME were enrolled. IVB (1.25 mg) was injected under topical anaesthesia. Approximately eighty percent of the patients demonstrated more than 10% decline in macular thickness. Approximately eighteen percent of the eyes demonstrated less than 10% decline in macular thickness. From the results, they concluded that IVB is an effective mode of therapeutic protocol in treating DME.[77]

Hanhart J et al in 2014 retrospectively analysed efficacy of unilateral IVB in bilateral DME patients. Evaluation of a total of 35 patients was done. They observed a significant reduction in the mean OCT by seventy two µm in the injected group and forty nine µm in the non-injected group. Approximately forty five percent of the injected eyes and twenty eight percent of the non-injected eyes showed a reduction of central subfield thickness by fifty microns.

From the results, they concluded that bilateral therapeutic response of unilateral bevacizumab is usually observed in bilateral DME patients.[78]

Lee K et al in 2014 evaluated the correlation of intravitreal anti VEGF/ steroid injection with fluid turbidity in DME patients. Reviewing of the data records of a total of 583 patients was done. Out of these patients, one hundred and four cases were analysed. IVB (Single dose) was given to sixty eyes while IVTA was given to remaining 44 eyes. In both the study groups, there was significant improvement in the visual acuity and central macular thickness.

Among the subjects of IVB group, less alteration in the visual acuity and CMT was seen because of higher turbidity of intra-retinal fluid. However; among the subjects of IVTA group, higher reduction was seen in relation to CMT due to more increased turbidity of intra-retinal fluid. They concluded that in DME patients, both were IVB and IVTA injections could be used with high efficacy in improving the course of the disease.[79]

In DME patients, predictors of ocular and systemic variables in response to treatment with IVB was analysed in a previous study conducted by **Joshi L et al in 2016.** Within a span of two years, they evaluated seventy eight eyes in fifty four patients. They defined the anatomic response to the treatment therapy as one fifth reduction in central macula thickness following three injections course of IVB. Appropriate anatomical response was seen in 28% of the patients after IVB's first course.

Systemic hypertension was found to be significant prognosticator of ideal response to IVB. However; poor response was found to be significantly associated with previous macular laser therapy. 68% of eyes experienced succeeding therapy for DME following first course of IVB.[80]

Elnahry AG et al in 2020 analysed macular perfusion alterations after IVB in DME patients using SD-OCT. They reported an approximately eight percent elevation in FAZ, approximately one and half percent decline in FD-Full and FD-SCP, approximately two percent decline in FD-DCP, 8% and approximately 25% decrease in skeleton VD-SCP following IVB injections.[81]

Fazel F et al in 2020 analysed the effectives of IVB in combination with intravitreal methotrexate (IVM) in patients with DME. 36 treatment-naive eyes were enrolled in their study. They observed a reduction in the BCVA from pre-treatment value of 0.95 to post-treatment follow-up value of 0.75 in the combination group. BCVA values also changed from pre-treatment value of 0.72 to final post-treatment value of 0.49 on follow-up in other group.

However; in both the study groups, the improvement was statistically non-significant in comparison to baseline values. Also, mean CMT and CMV values showed non-significant alterations in both the study groups. Results from their study demonstrated that no enhanced treatment effects for IVB combined with IVM compared to IVB alone in DME patients.[82]

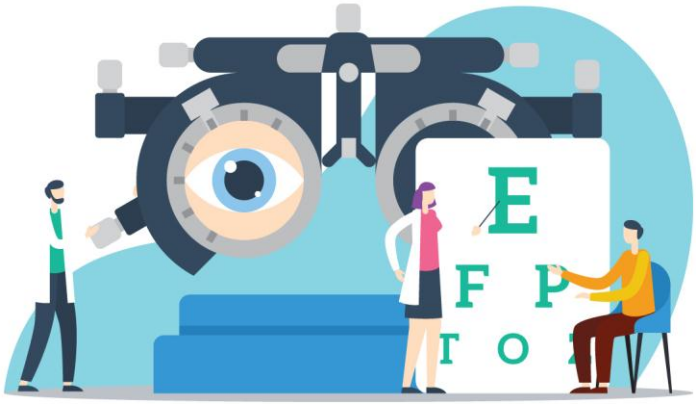
Sharma S et al in 2020 evaluated the impact of HbA1c on therapeutic follow-up response following bevacizumab therapy in DME patients. They analysed thirty seven patients (thirty seven eyes) which had history of vision loss because of DME and were treated with bevacizumab. Analysis of a total of 17 patients with HbA1c baseline concentration of less than or equal to seven percent and twenty patients with HbA1c baseline concentration of more than seven percent was done in their study.

In the group with HbA1c concentrations of less than or equal to seven percent, visual acuity showed mean improvement from pre-treatment value of 0.50 logMAR to final post-treatment value of 0.33 logMAR. Significant reduction in the mean central macular thickness in all the subjects was observed. Their results showed that treatment outcome in DME patients by IVB was affected by baseline glycaemic control.[83]

In another study conducted by **Badr SMJ et al in 2020**, authors analysed the impact of intravitreal (Avastin) in DME patients. Sample size in their study comprised of 15 patients (fifteen eyes with DME). They didn't observe any improvement in visual acuity. None of the patients exhibited any intra-treatment or post-treatment complication.

They observed significant reduction in central macular thickness from pre-treatment value of 492 µm to final post-treatment value of 369 µm. They concluded that Avastin led to significant decline in macular thickness and enhancement of visual acuity on follow up.[84]

MATERIALS & METHODS



MATERIALS & METHODS

The present study was undertaken for assessing the outcome of intravitreal injection of bevacizumab on visual acuity and central macular thickness in patients with DME.

Study population

Subjects attending the Ophthalmology OPD who were diagnosed with Diabetic Macular Edema at KLES Dr. Prabhakar Kore Hospital and MRC, Belagavi

Study Design

A one year longitudinal study

Duration

January 2019 – December 2019

Sample Size

50

Sample size formula

For confirmative results a sample of size 50 was taken. The above mentioned values have been obtained from study conducted by A. Dorukcan et al.[85]

$$n = \frac{(z_\alpha + z_\beta)^2(s_1^2 + s_2^2)}{(\bar{X}_1 - \bar{X}_2)^2}$$

- z_α =level of significance and
- z_β = power of the test.
- For 5% level of significance, z_α =1.96
- For 80% power of test, z_β =0.84
- $\bar{X}_1$ = mean of the first group (506.76)
- $\bar{X}_2$ = mean of the second group (341.36)
- s_1 = standard deviation of the first group (166.7)
- s_2 = standard deviation of the second group (146.2)

The mean for first group was the baseline CFT and mean for the second group was CFT values at 1 month.

SELECTION CRITERIA

Inclusion criteria—

Patients of either sex 25-75 years of age with any type of DM and having DME involving the centre, visual acuity of 6/9 or worse and CFT of 260 μm or more on Spectral Domain Optical Coherence Tomography (SD-OCT).

Exclusion criteria—

- Patients having bleeding disorders.
- Active ocular infections.
- Previous history of intravitreal bevacizumab or anti VEGF within 4 months in the past
- Recent myocardial infarction
- Glaucoma or ocular hypertension taking more than 2 topical medications
- Proliferative Diabetic Retinopathy with high risk characteristics
- Vitreous haemorrhage
- Vitreous Macular Traction/ Haemorrhage or Posterior Hyaloid thickening
- Significant media opacity
- Pregnancy
- Previous history of focal or grid laser

METHODOLOGY:

A total of 50 eyes of 38 patients with DME as selected by the inclusion criteria was enrolled into study after taking an informed and written consent and demographic data of patients was noted in a predesigned proforma. Study was conducted in the ophthalmology department at KLES Dr. Prabhakar Kore Hospital and MRC, Belagavi.

Preoperative assessment included medical history, visual acuity, refractive history and examination of anterior and posterior segments. OCT examination was done one week prior to procedure to assess the CMT. Other investigations included blood pressure monitoring.

Patients were followed up after the first injection at 1 week and then at 3 weeks and visual acuity was assessed; based on outcome of the first injection, the need of consecutive injection was assessed. If required, 2nd and 3rd consecutive injections were performed at 28- 35 days' intervals. Patients were followed up after each injection at 1 week and then at 3 weeks. BCVA and complete ophthalmic examination was repeated at all the 3 weekly visits after injection. At the end of 4 months after intravitreal injection, complete ophthalmic examination including BCVA & OCT was done.

Surgical technique:

Eye was identified and marked. Pre-operative dilatation was done with Tropicamide 0.8% + Phenylepherine 5%. Proparacaine 0.5% eyedrops and Povidone-iodine 5% instilled 4 times.

Eye was painted and draped and sterile speculum was inserted. 5% Povidone-iodine was applied to the site of injection with cotton tip applicator. 1.25mg (0.05cc) bevacizumab (Avastin) was injected intravitreally with a 30 gauge needle at a distance of 4mm from the limbus in phakic patients and at a distance of 3.5mm from the limbus in aphakic and pseudophakic patients.

Injection was given in mid-vitreous with needle directing towards optic nerve head. After removing the needle, the site of injection was pressed with sterile cotton applicator. Globe was checked for any hardness. 1 drop of 5% povidone-iodine was instilled. Eye patched for 4 hours. No antibiotic drops were prescribed.

BCVA in logMAR will be taken at first visit and at 4 months follow up & was compared by student t test. All the results were evaluated by employing SPSS software. Related samples- Wilcoxon Signed Rank Test was used for evaluating the level of significance. P- value of less than 0.05 was regarded as significant.

RESULTS

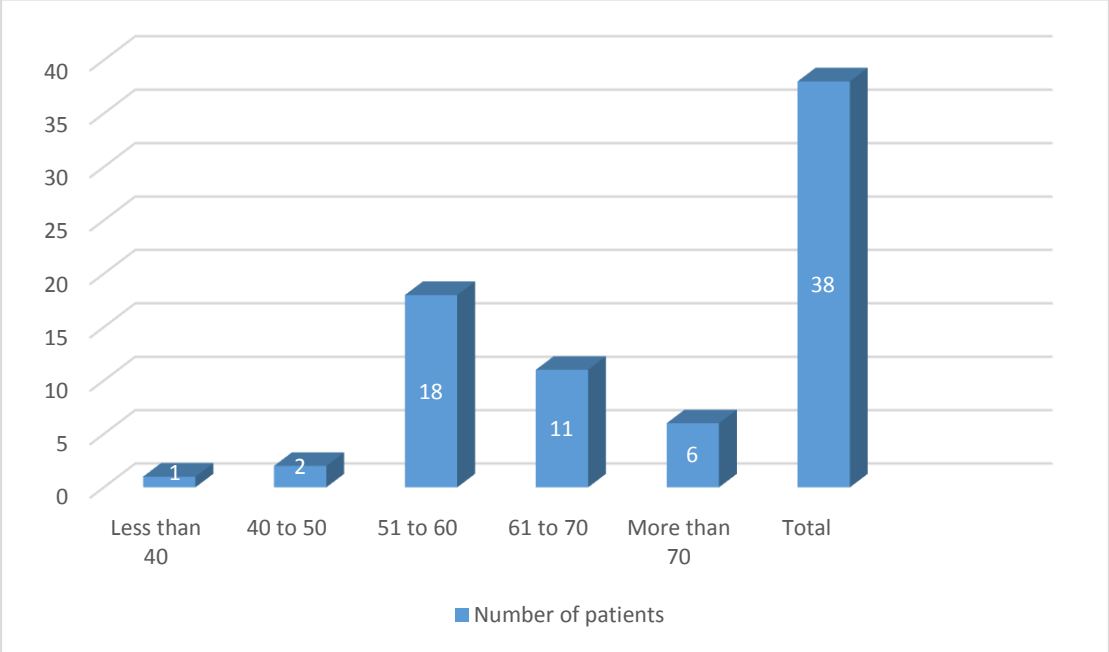
RESULTS

The present study was undertaken for assessing the outcome of intravitreal injection of bevacizumab on visual acuity and central macular thickness in patients with diabetic macular edema. Subjects attending the Ophthalmology OPD who were diagnosed with Diabetic Macular Edema at KLES Dr. Prabhakar Kore Hospital and MRC, Belagavi were enrolled. Following results were obtained:

Table 1: Age-wise distribution of patients

Age group (years)	Number of patients	Percentage of patients
Less than 40	1	2.63%
40 to 50	2	5.26%
51 to 60	18	47.37%
61 to 70	11	28.95%
More than 70	6	15.79%
Total	38	100
Mean age ±SD (years)	61.15 ± 9.0	

Graph 1: Age-wise distribution of patients

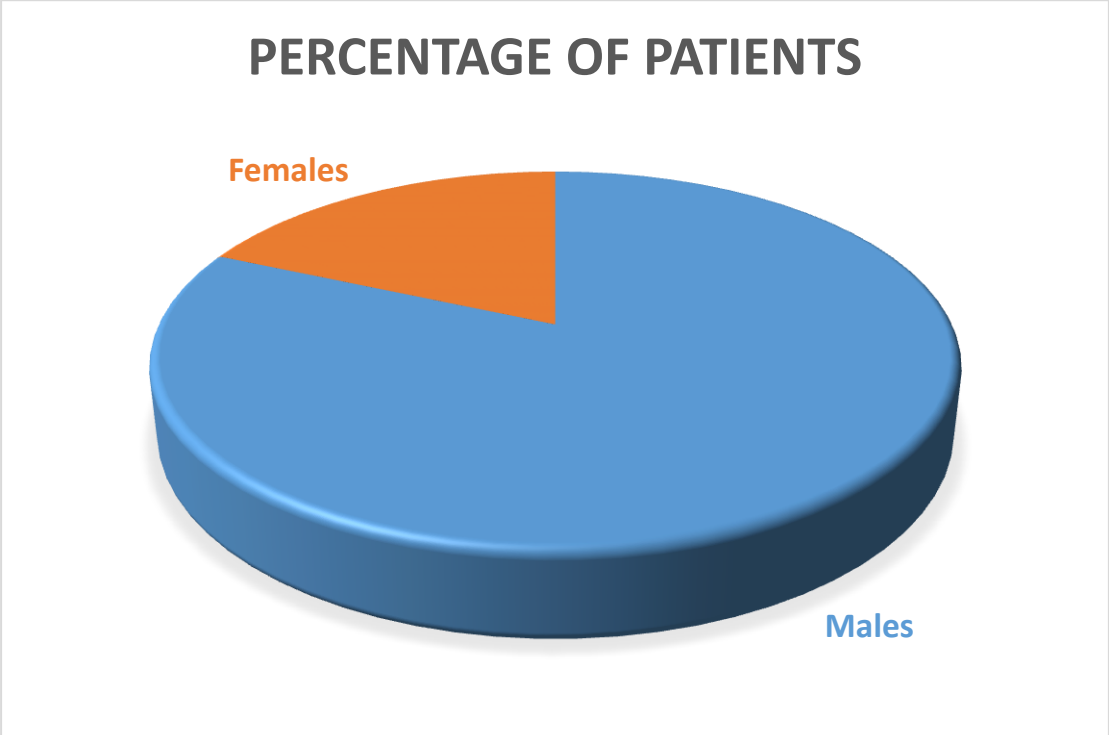


47.37 percent of the patients (18 patients) belonged to the age group of 51 to 60 years while 28.95 percent of the patients (11 patients) belonged to the age group of 61 to 70 years. Mean age of the patients was found to be 61.15 years (SD = 9.0). Range was from 38 to 75 years.

Table 2: Gender-wise distribution of patients

Gender	Number of patients	Percentage of patients
Males	31	81.6%
Females	7	18.4%
Total	38	100

Graph 2: Gender-wise distribution of patients

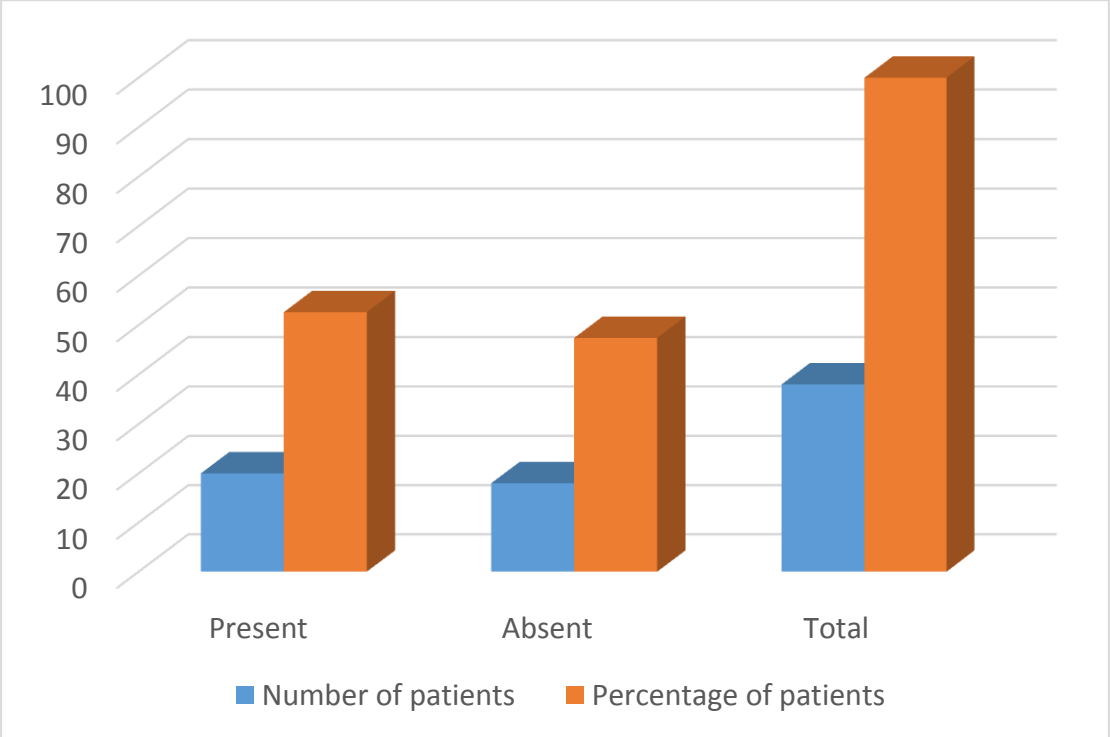


82 percent of the patients (41 patients) were males while the remaining 18 percent (9 patients) were females.

Table 3: Distribution of patients according to history of hypertension

Hypertension	Number of patients	Percentage of patients
Present	20	52.6
Absent	18	47.4
Total	38	100

Graph 3: Distribution of patients according to history of hypertension

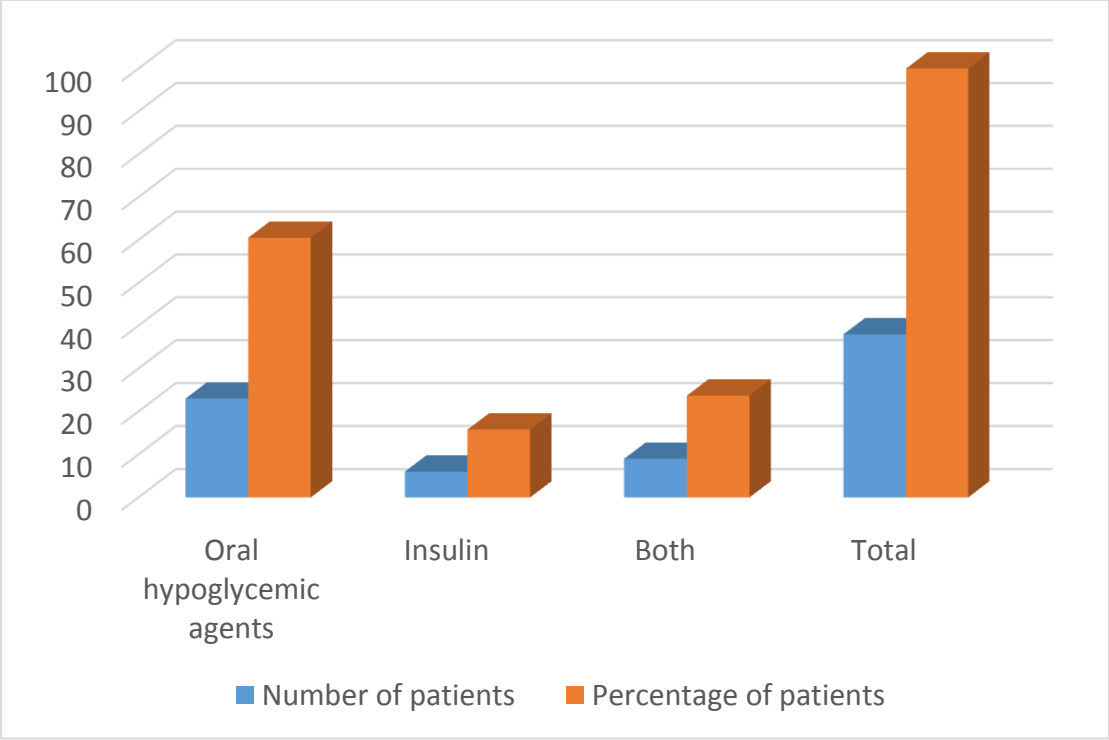


52.6 percent of the patients (20 patients) were found to be hypertensive.

Table 4: Distribution of patients according to treatment of diabetes

Diabetes treatment	Number of patients	Percentage of patients
Oral hypoglycemic agents	23	60.5
Insulin	6	15.8
Both	9	23.7
Total	38	100

Graph 4: Distribution of patients according to treatment of diabetes

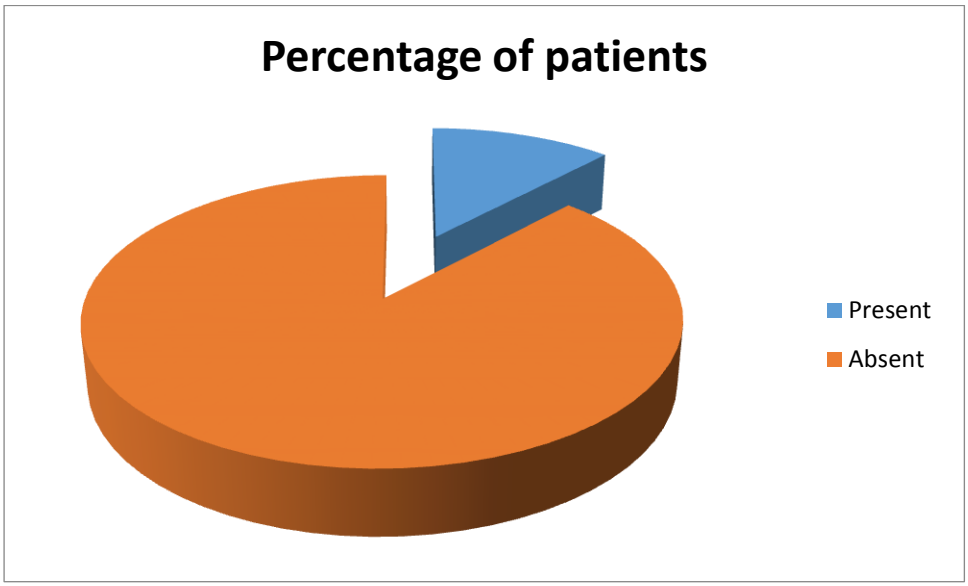


60.5 percent of the patients (23 patients) were on oral hypoglycemic agents, while 15.8 percent of the patients (6 patients) were on insulin. 23.7 percent of the patients (9 patients) were on combined oral hypoglycemic agents and insulin.

Table 5: Distribution of patients according to status of anticoagulant therapy

Anticoagulant therapy	Number of patients	Percentage of patients
Present	4	10.5
Absent	34	89.5
Total	38	100

Graph 5: Distribution of patients according to status of anticoagulant therapy

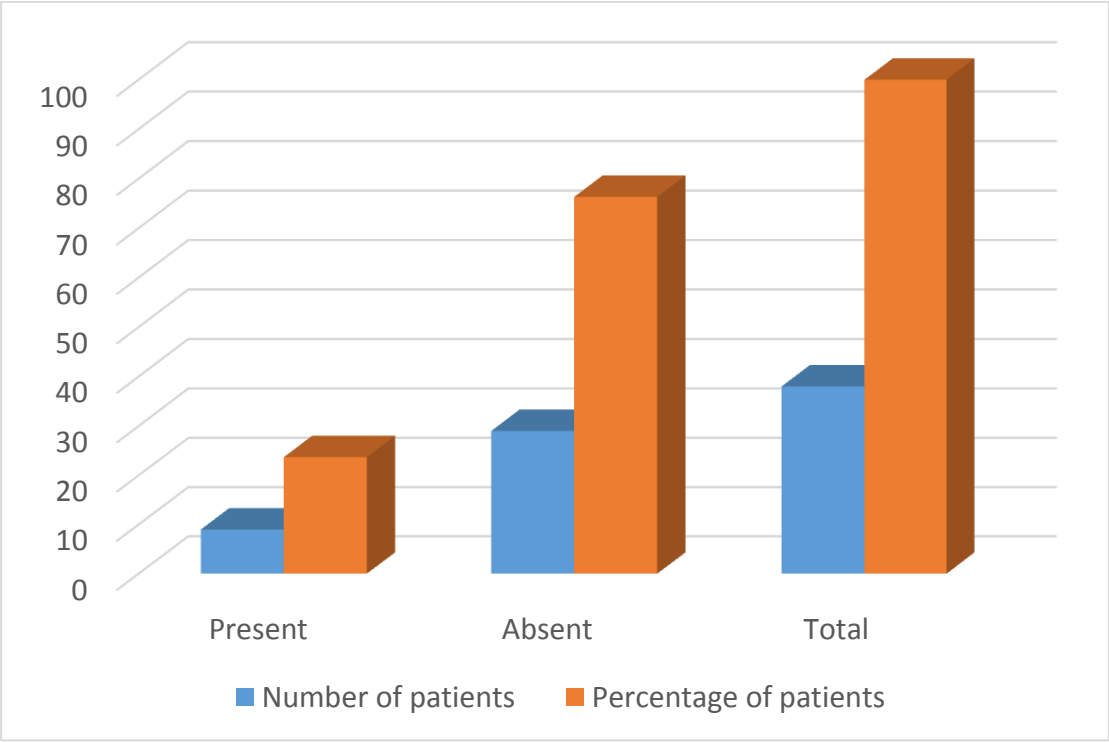


10.5 percent of the patients (4 patients) were on anticoagulant therapy.

Table 6: Distribution of patients according to status of hypercholesterolemia

Hypercholesterolemia	Number of patients	Percentage of patients
Present	9	23.7
Absent	29	76.3
Total	38	100

Graph 6: Distribution of patients according to status of hypercholesterolemia

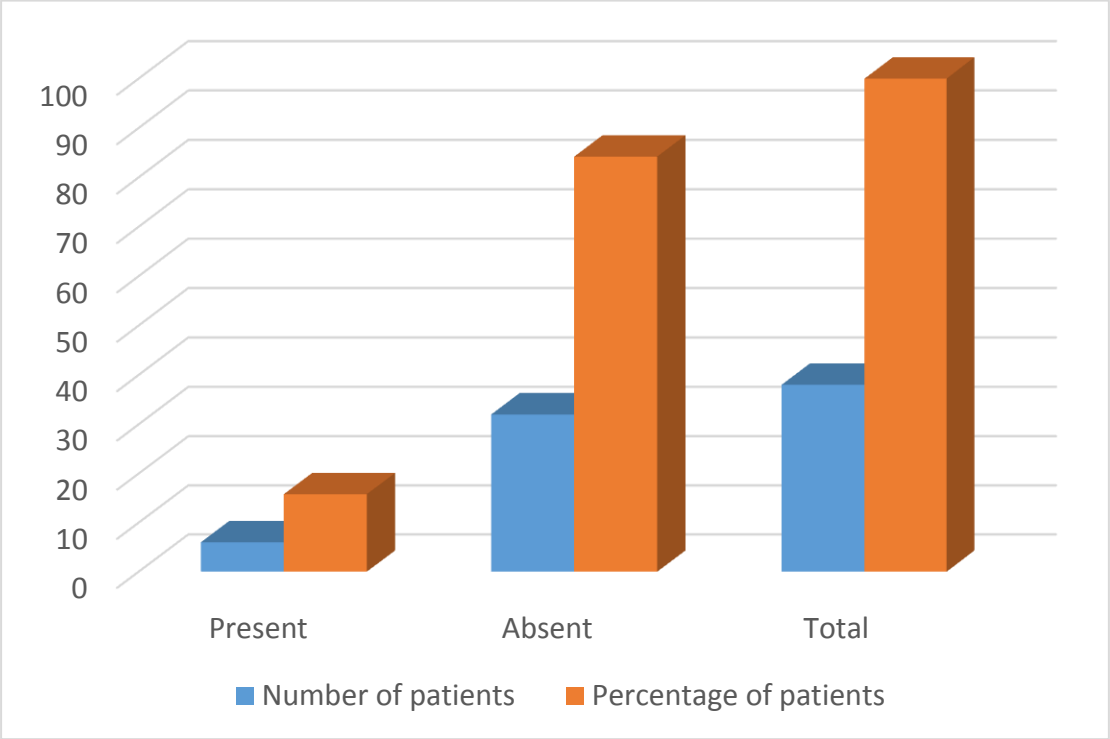


Hypercholesterolemia was present in 22 percent of the patients (11 patients)

Table 7: Distribution of patients according to status of nephropathy

Nephropathy	Number of patients	Percentage of patients
Present	6	15.8
Absent	32	84.2
Total	38	100

Graph 7: Distribution of patients according to status of Nephropathy

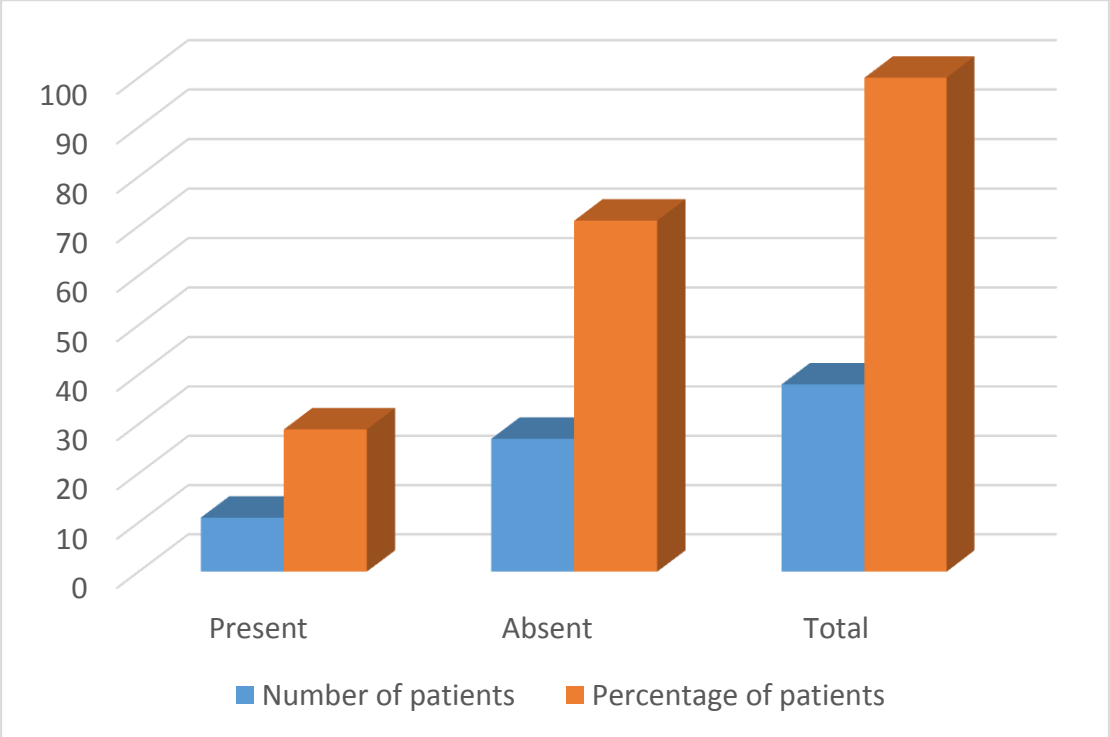


Nephropathy was present in 15.8 percent of the patients (6 patients).

Table 8: Distribution of patients according to smoking habit

Smoking habit	Number of patients	Percentage of patients
Present	11	28.9
Absent	27	71.1
Total	38	100

Graph 8: Distribution of patients according to smoking habit

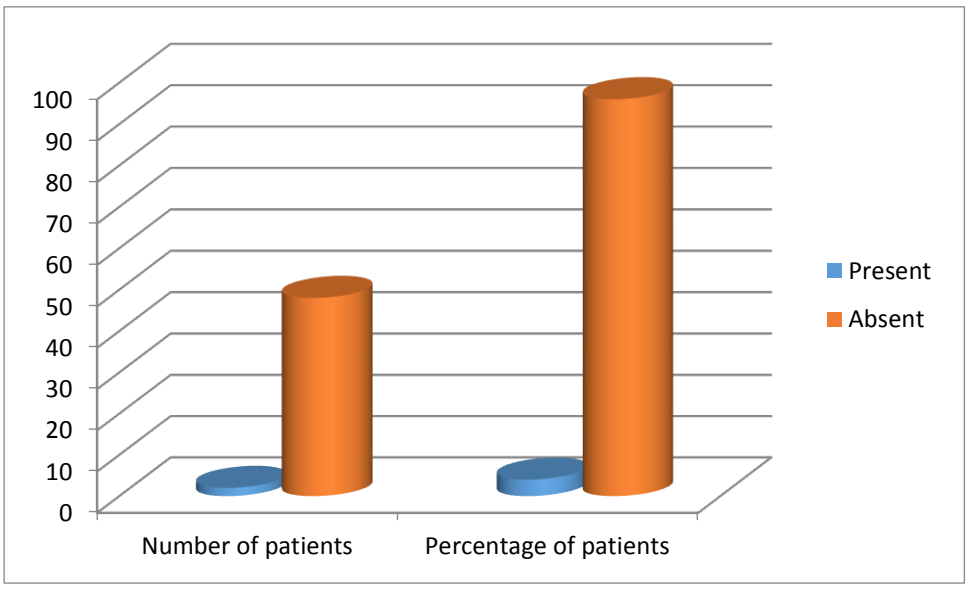


Smoking habit was found to be present in 28.9 percent of the patients (11 patients).

Table 9: Distribution of patients according to status of glaucoma

Glaucoma	Number of patients	Percentage of patients
Present	1	2.6
Absent	37	97.4
Total	38	100

Graph 9: Distribution of patients according to status of glaucoma

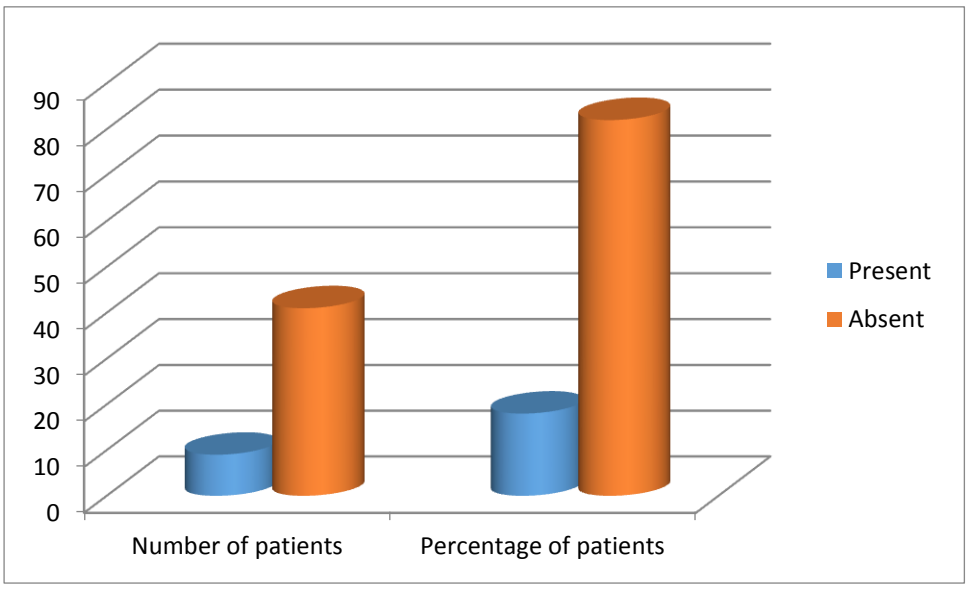


Glaucoma was present in 2.6 percent of the patients (1 patient).

Table 10: Distribution of patients according to history of panretinal photocoagulation

Panretinal photocoagulation	Number of patients	Percentage of patients
Present	6	15.8
Absent	32	84.2
Total	38	100

Graph 10: Distribution of patients according to history of panretinal photocoagulation

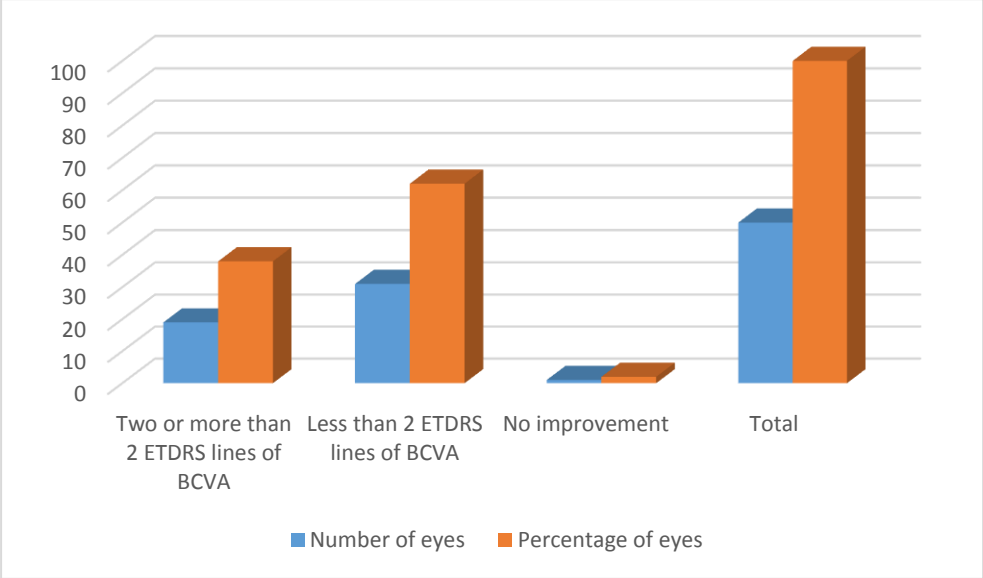


History of panretinal photocoagulation was present in 15.8 percent of the patients (6 patients).

Table 11: Distribution of eyes according to improvement in best corrected visual acuity

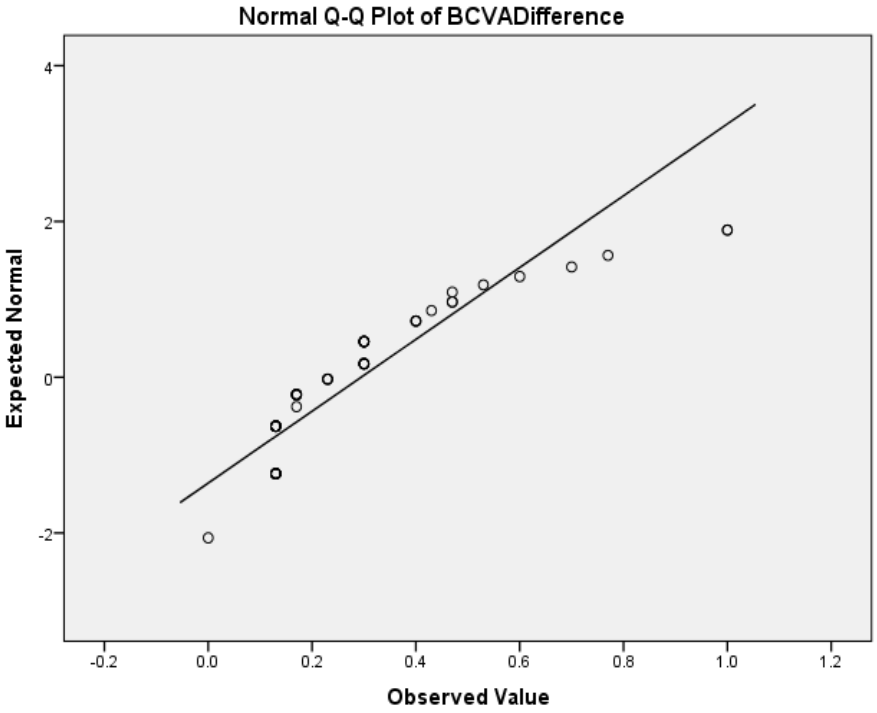
Improvement in best corrected visual acuity	Number of eyes	Percentage of eyes
Two or more than 2 ETDRS lines	19	38
Less than 2 ETDRS lines	30	60
No improvement	1	2
Total	50	100

Graph 11: Distribution of eyes according to improvement in best corrected visual acuity



In 38 percent of the cases (19 eyes), improvement in best corrected visual acuity was 2 or more than 2 ETDRS lines, while in remaining 60 percent of the cases (30 eyes), improvement in best corrected visual acuity was less than 2 ETDRS lines. One eye did not show any improvement after three injections.

Graph 11.1



Graph 11.2

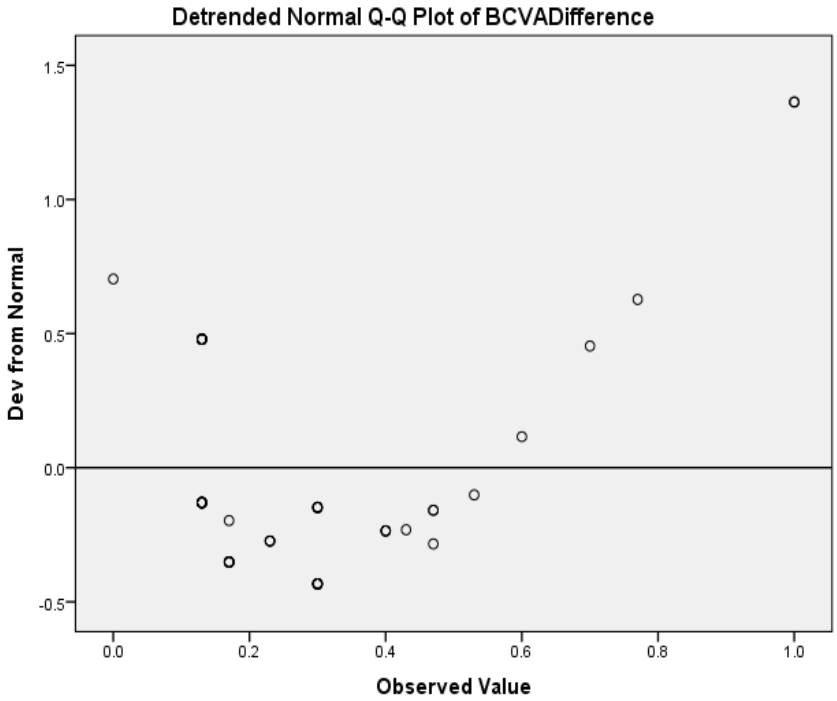
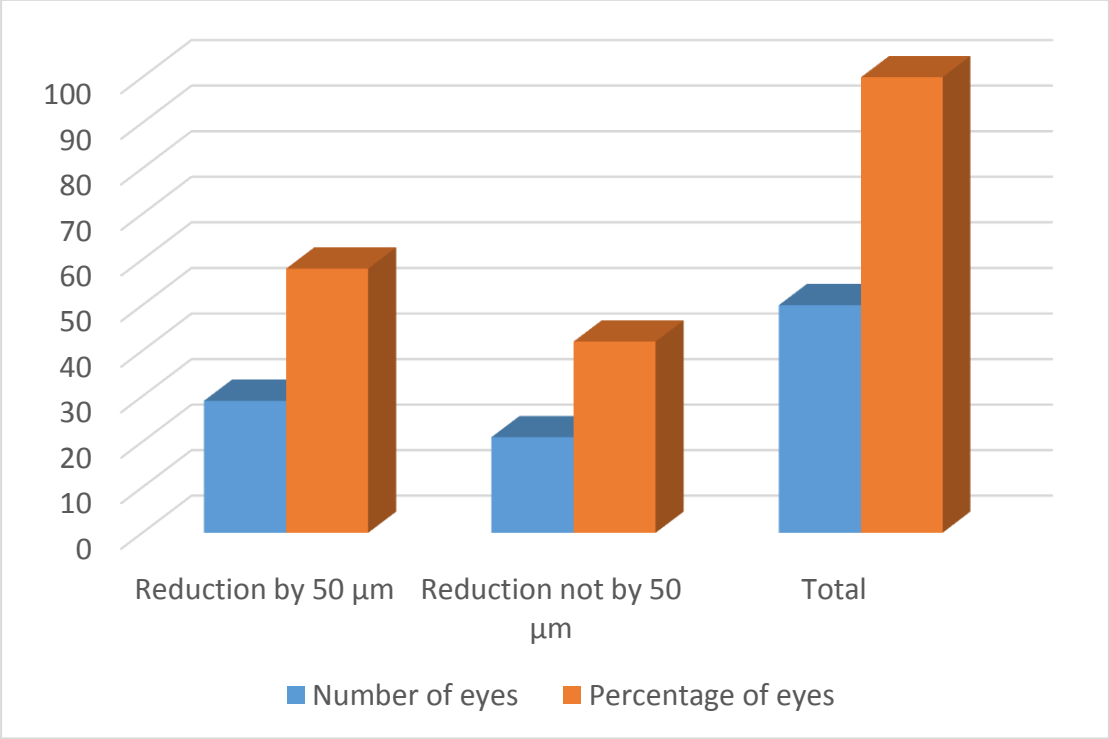


Table 12: Distribution of eyes according to reduction of central foveal thickness by 50 µm

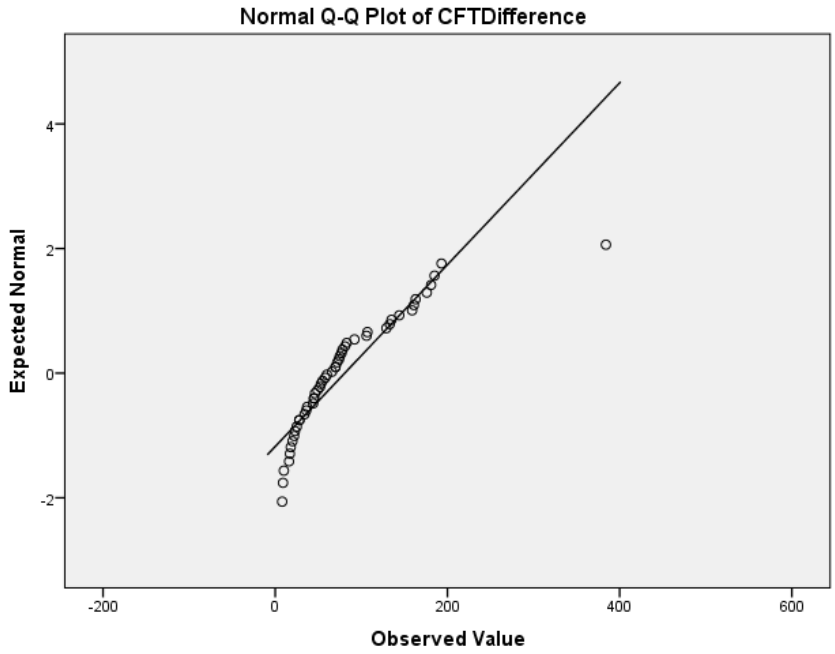
Reduction of central foveal thickness by 50 µm	Number of eyes	Percentage of eyes
Reduction by 50 µm	29	58
Reduction by < 50 µm	21	42
Total	50	100

Graph 12: Distribution of eyes according to reduction of central foveal thickness by 50 µm



In 58 percent of the cases (29 eyes), reduction of central foveal thickness was by 50 µm.

Graph 12.1



Graph 12.2

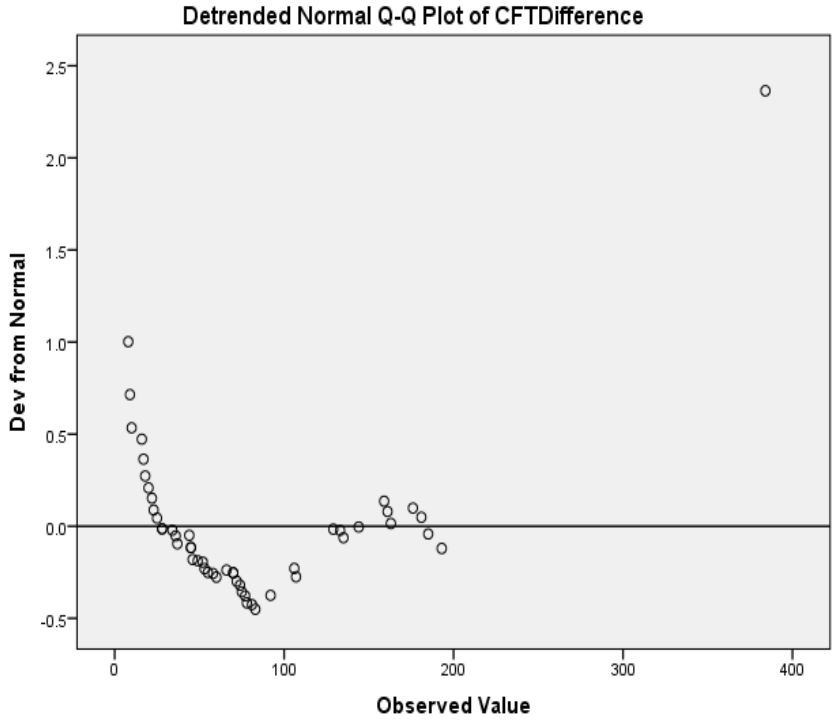
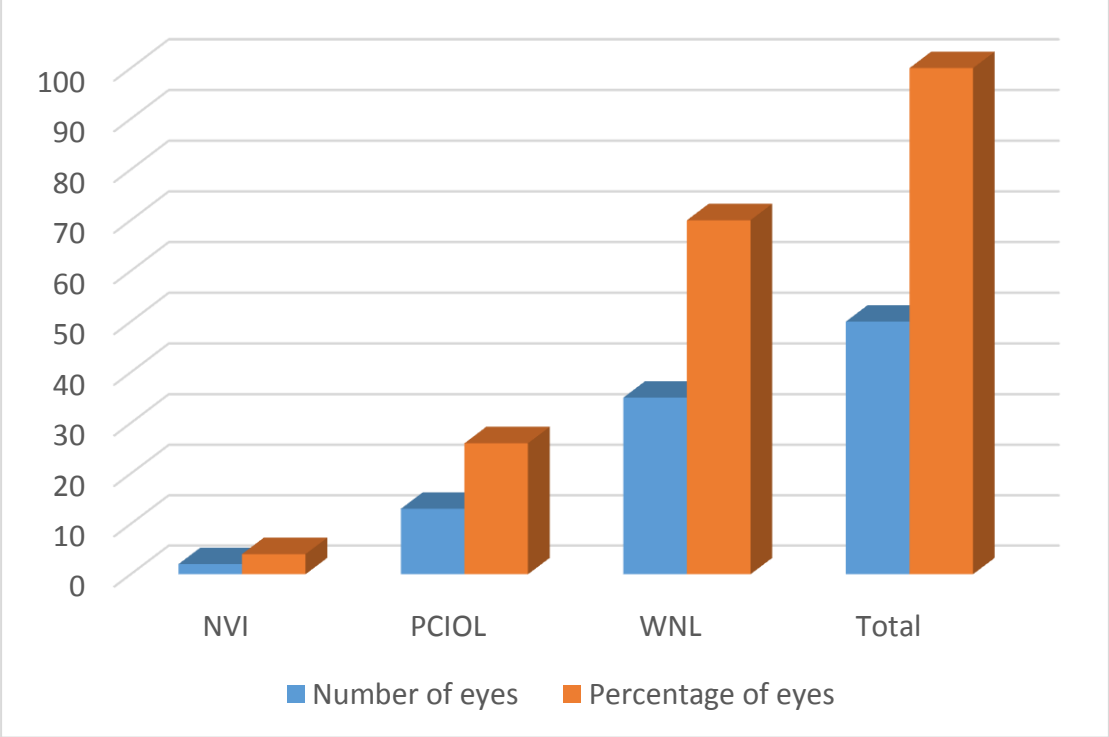


Table 13: Distribution of eyes according to findings of anterior segment

Anterior segment	Number of eyes	Percentage of eyes
NVI	2	4
PCIOL	13	26
WNL	35	70

Graph 13: Distribution of eyes according findings of anterior segment

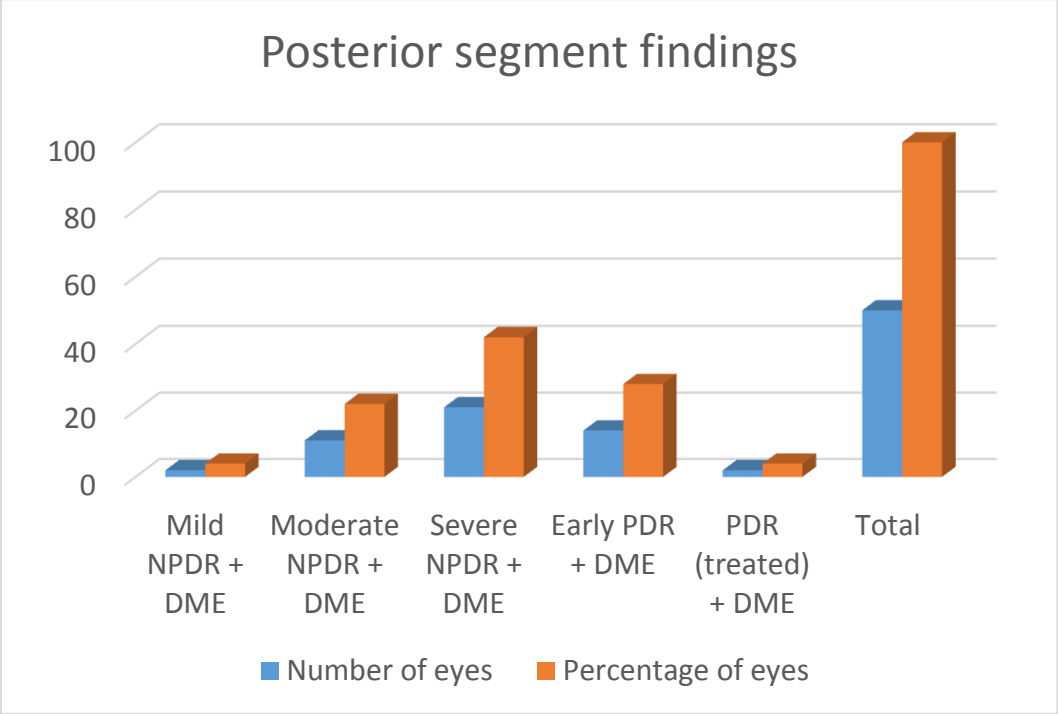


70 percent of the cases (35 eyes) were phakic and anterior segment was within normal limits. NVI was found in 4 percent cases which were phakic (2 eyes) and 26 percent of the cases (13 eyes) were pseudophakic.

Table 14: Distribution of eyes according to findings of posterior segment

Posterior segment	Number of eyes	Percentage of eyes
Mild NPDR + DME	1	2
Moderate NPDR + DME	8	16
Severe NPDR + DME	19	38
Early PDR + DME	13	26
PDR (treated) + DME	9	18
Total	50	100

Graph 14: Distribution of eyes according to findings of posterior segment



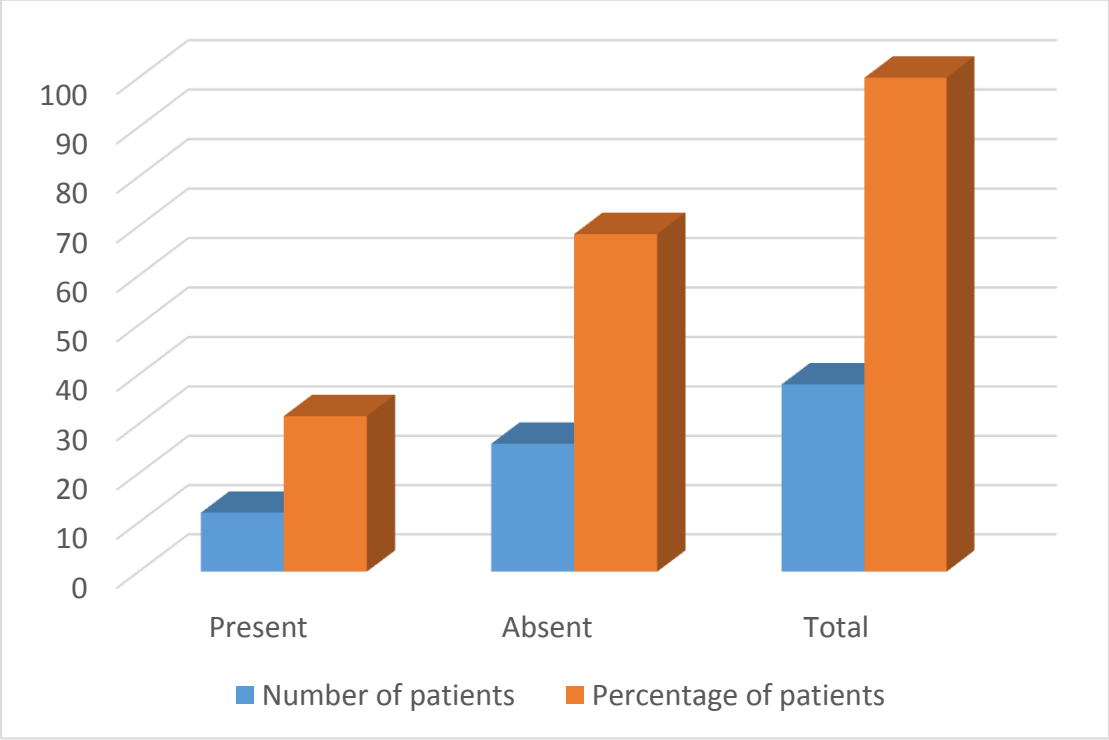
Severe NPDR + DME was the major finding of the posterior segment found to be present in 38 percent of the cases (19 eyes). Moderate NPDR + DME in the posterior segment were found to be present 16 percent of the cases (8 eyes).

Early PDR + DME in the posterior segment were found to be present in 26 percent of the cases (13 eyes) and 18 percent cases showed treated PDR (9 eyes).

Table 15: Distribution of patients according to family history of diabetic retinopathy

Family history of diabetic retinopathy	Number of patients	Percentage of patients
Present	12	31.6
Absent	26	68.4
Total	38	100

Graph 15: Distribution of patients according to family history of diabetic retinopathy



Positive family history of diabetic retinopathy was found to be present in 31.6 percent of the cases (12 patients).

Table 16: Distribution of eyes according to incidence of complications

Complications	Number of eyes	Percentage of eyes
Present	1	2
Absent	49	98
Total	50	100

Only one of the eyes showed anterior uveitis post operatively which was conservatively managed successfully. None of the other eyes showed any major complications.

Graph 16: Distribution of eyes according to incidence of complications

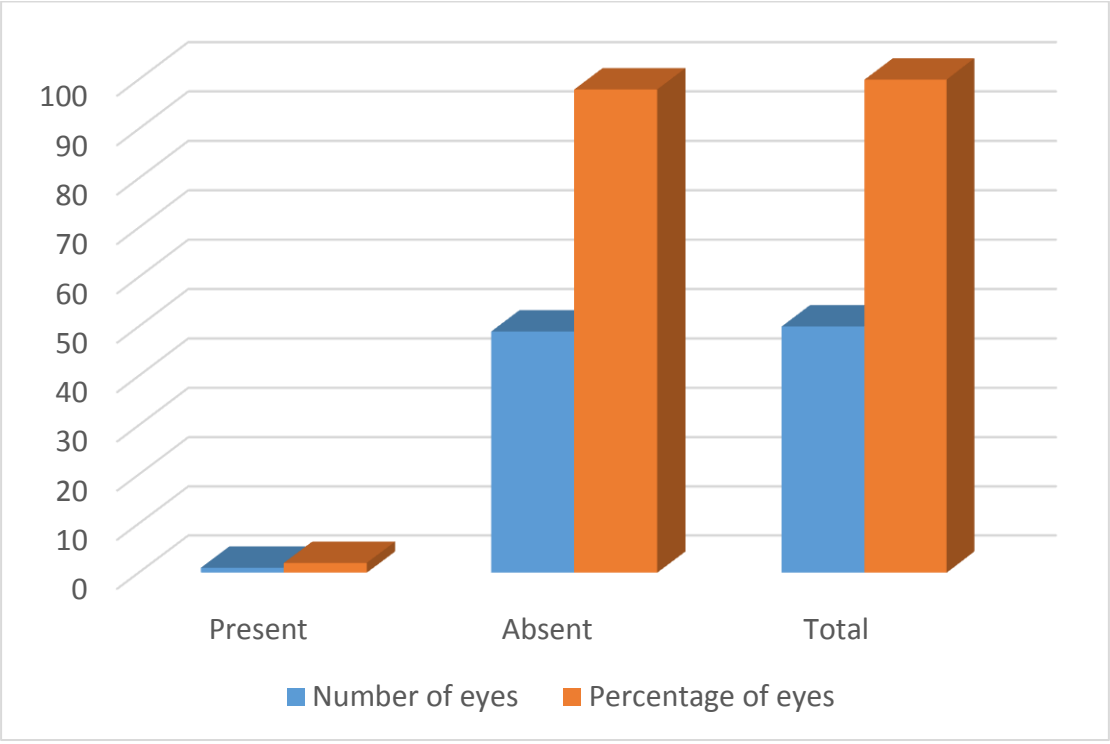
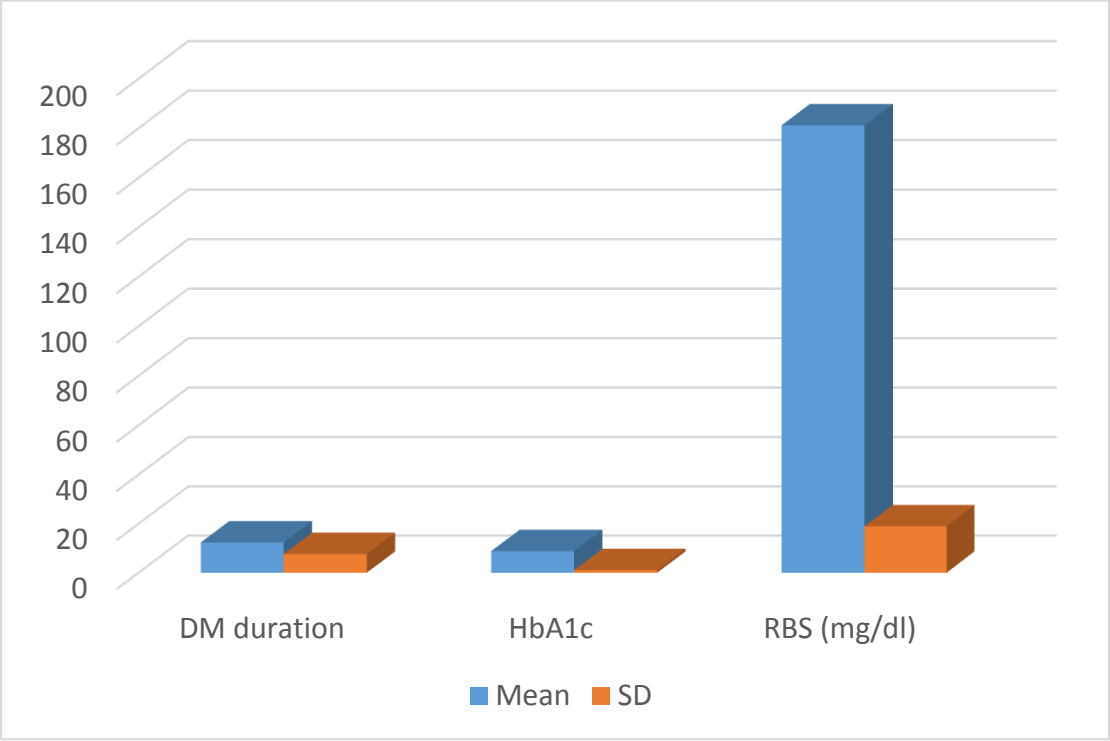


Table 17: Descriptive analysis

Variable	Mean	SD
DM duration	12.35	7.65
HbA1c	8.81	1.04
RBS (mg/dl)	181.15	18.92

Graph 17: Descriptive analysis

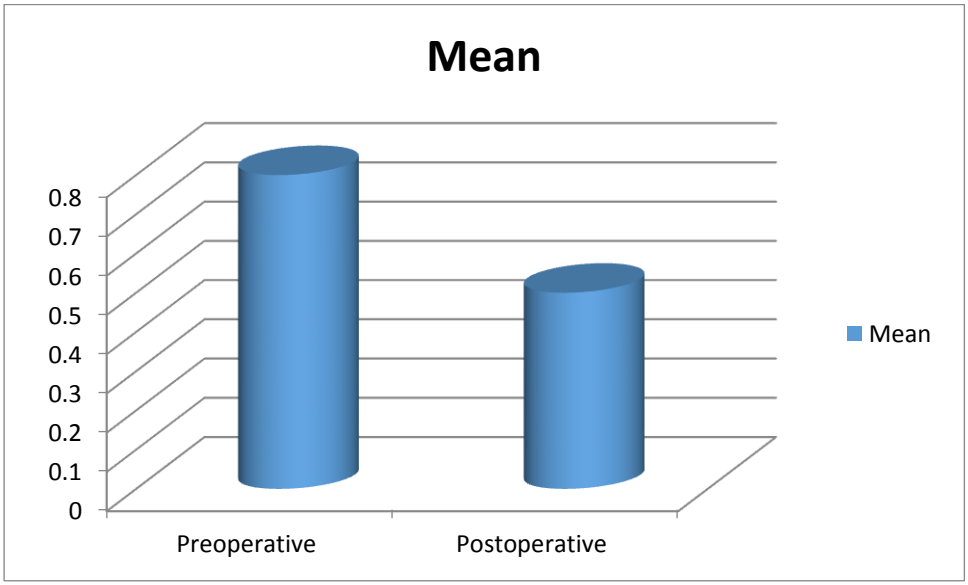


Mean duration of diabetes was 12.35 ± 7.6 years. Mean HbA1c concentration was found to be 8.81 ± 1.04 while mean RBS concentration was found to be 181.15 ± 18.92 mg/dL.

Table 18: Comparison of best corrected visual acuity

Best corrected visual acuity	Mean	SD
Preoperative	0.80	0.48
Postoperative	0.50	0.36
Statistical Test	Related samples- Wilcoxon Signed Rank Test	
p- value	0.00 (Significant)	

Graph 18: Comparison of best corrected visual acuity

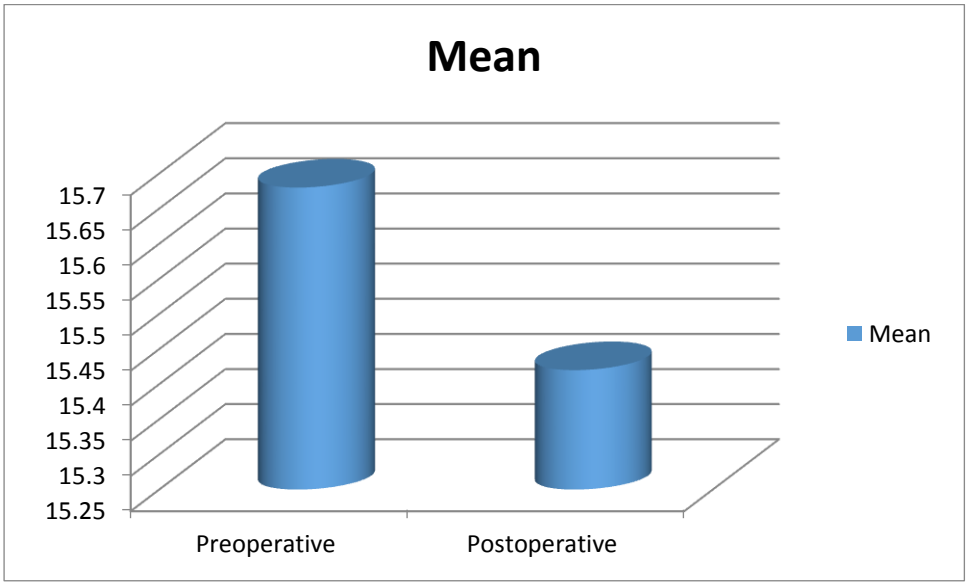


Mean preoperative BCVA (logMAR) was 0.80 while mean postoperative best corrected visual acuity (logMAR) was 0.50. While comparing the mean preoperative and postoperative best corrected visual acuity, significant results were obtained.

Table 19: Comparison of Intraocular pressure

Intra-ocular pressure (mm Hg)	Mean	SD
Preoperative	15.68	2.76
Postoperative	15.42	2.61
Statistical Test	Related samples- Wilcoxon Signed Rank Test	
p- value	0.700 (Non-significant)	

Graph 19: Comparison of Intraocular pressure

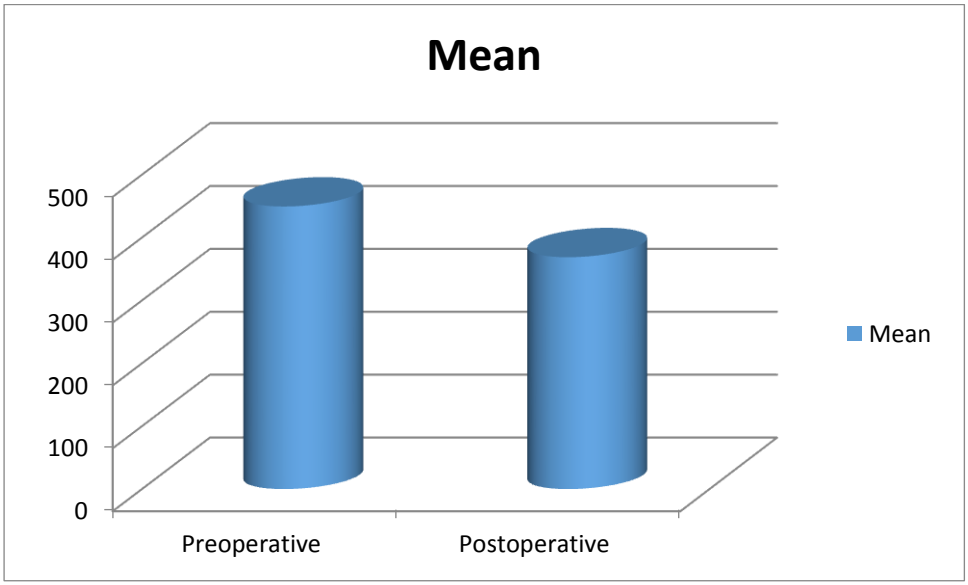


Mean preoperative intraocular pressure was 15.68 mm of Hg, while mean postoperative intraocular pressure was 15.42 mm of Hg. However; while comparing the mean intraocular pressure preoperatively and postoperatively, non-significant results were obtained.

Table 20: Comparison of Central foveal thickness (µm)

Central foveal thickness (µm)	Mean	SD
Preoperative	449.40	148.14
Postoperative	368.76	131.48
Statistical Test	Related samples- Wilcoxon Signed Rank Test	
p- value	0.000 (Significant)	

Graph 20: Comparison of Central foveal thickness (µm)



Mean preoperative Central foveal thickness (µm) was 449.40, while mean postoperative Central foveal thickness (µm) was 368.78. However; while comparing the mean Central foveal thickness (µm) preoperatively and postoperatively, significant results were obtained.

DISCUSSION

DISCUSSION

Diabetes mellitus is a one of the commonest pathological entity leading to more than four and a half million deaths across the globe per year. As per the data records of International Diabetes Federation, approximately three and a half million subjects across the globe are diabetic, out of which, approximately four-fifth are from lower economic countries. As per Indian data (Given by ICMR study, 2011) more than sixty million subjects were diabetic in 2011. Also, these numbers are expected to cross one hundred million by the end of 2030.[86]

Diabetic retinopathy is one of the commonest complication and manifestation of uncontrolled diabetes, and its incidence and prevalence is known to be directly proportional to the severity and duration of diabetes. The problem and manifestations are further known to be exaggerated with presence of other associated systemic problems like hypertension and hypercholesterolemia. Hence; it is necessary subjects with presence of diabetic retinopathy should be monitored very carefully and prompt treatment should be started in them.[87]

Diabetic retinopathy mostly results from abnormality of retinal vessels. This can occur because of two reasons: Proliferation of retinal vessels [also known as proliferative diabetic retinopathy (PDR)]; and functional incompetency of retinal vessels.[87]

Across the patients ranging from adolescents to geriatric subjects, DR is the major etiologic factors for vision loss. In the last three decades, DR was reported to be fifth major cause of preventable blindness.[88]

In DME, there is retinal swelling because of fluid leakage from blood vessels within the macula. The main target of therapeutic protocol for DME aims to maintain the current visual acuity and decrease the possibilities of progression to visual loss.[89]

The pathogenesis of diabetic retinopathy is multifactorial. The main mechanism is disruption of the blood-retinal barrier and increased vascular permeability. Other factors implicated in the pathophysiology of the disease include inflammation and ischemia. Systemic factors including hyperlipidemia, higher systolic blood pressure, renal dysfunction, and higher HbA1c may further complicate the underlying pathology and exaggerate the clinical picture.[89, 90]

Anti-angiogenic agents such as ranibizumab and bevacizumab are used to inhibit VEGF, and triamcinolone is used to suppress prostaglandin-induced inflammation. Out of bevacizumab and ranibizumab, bevacizumab is similar in effectiveness and is more cost effective in comparison to ranibizumab. Results from two year follow-up studies have demonstrated that intravitreal bevacizumab (IVB) gave significantly better results in comparison to laser in improving VA.[80, 91]

Hence; under the light of above mentioned data, the present study was undertaken for assessing the outcome of intravitreal injection of bevacizumab on visual acuity and central macular thickness and its safety in terms of its effects on eye in patients with DME.

AGE & GENDER-WISE DISTRIBUTION

In the present study, 47.37 percent of the patients belonged to the age group of 51 to 70 years. Mean age of the patients was found to be 61.15 years. 81.6 percent of the patients were males while the remaining were females. Our results were in concordance with the results obtained by previous studies who also reported similar demographic data. **Vyas S et al** reported the mean age of the patients with DME to be 59.59 years. 65.4 percent of the subjects were males while the remaining were females. In another study, conducted by **Ateeq A et al** on 54 patients with DME, 57.4 percent of the patients were males and mean age of the patients was found to be 55.44 years.[77, 92]

Joshi L et al, in their study reported that mean age of the patients with DME was 65 years with 69 percent of the patient population being males. In another study conducted by **Tareen IU et al**, authors reported that the patients were of a mean age of 53.5 ± 11.4 years, out of which 25(59.52%) were male, 17(40.47%) were female.[76, 80]

DIABETIC TREATMENT

60.5 percent of the patients were on oral hypoglycemic agents, while 15.8 percent of the patients were on insulin. 23.7 percent of the patients were on combined oral hypoglycemic agents and insulin. In a previous study conducted by **Joshi L et al**, authors reported that 24 percent of the patient population was on insulin, 14 percent of the patients were on oral hypoglycemic drugs while the remaining 62 percent of the patients were on combined oral hypoglycemic drugs and insulin.[80]

NEPHROPATHY

Nephropathy was present in 15.8 percent of the patients. In a previous study conducted by **Joshi L et al**, nephropathy was reported to be present in 13 percent of the cases.[80]

ANTERIOR SEGMENT & POSTERIOR SEGMENT FINDINGS

Anterior segment was within normal limits in 70 percent of the cases (35 eyes) which were phakic. NVI was found in 4 percent cases which were phakic (2 eyes). 26 percent of the cases (13 eyes) were pseudophakic. Severe NPDR + DME was the major finding of the posterior segment found to be present in 38 percent of the cases (19 eyes). Moderate NPDR + DME in the posterior segment were found to be present 16 percent of the cases (8 eyes). Early PDR + DME in the posterior segment were seen in 26 percent of the cases (13 eyes) and 18 percent cases showed treated PDR (9 eyes).

Vyas S et al, in their study, reported that most of the patients were in severe NPDR group followed by moderate PDR group and early PDR.[92]

DIABETES DURATION

Mean duration of diabetes was 12.35 years. The mean HbA1c concentration was found to be 8.81 while mean RBS concentration was found to be 181.15 mg/dL. Our results were in accordance with the results obtained previously by other studies authors. In a study conducted by **Vyas S et al**, mean duration of diabetes among the subjects with DME was found to be 11.88 years. **Ateeq A et al**, in their study reported that mean duration of diabetes among subjects with DME to be 10.15 years.[77, 92]

In a study conducted by **Mason et al** the mean duration of diabetes in 30 patients was 18.4 years with a range of 3 years to 27 years. Longer the duration of diabetes, the higher the prevalence of diabetic maculopathy.[93] **Joshi L et al** in their study reported the median duration of diabetes to be 13 years.[80]

MEAN BEST CORRECTED VISUAL ACUITY

In 38 percent of the cases (19 eyes), improvement in best corrected visual acuity was 2 or more than 2 ETDRS lines, while in remaining 62 percent of the cases (31 eyes), improvement in best corrected visual acuity was less than 2 ETDRS lines.

Mean preoperative best corrected visual acuity was 0.80 (SD=0.48) while mean postoperative best corrected visual acuity was 0.50 (SD=0.36). While comparing the mean preoperative and postoperative best corrected visual acuity, significant results were obtained.

In a previous study conducted by **Vyas S et al**, authors observed that the mean BCVA (at baseline) was 0.80 log MAR, with statistically significant improvement 0.68 (p=0.012), 0.63 (p=less than0.001) and 0.60 log MAR (p=less than0.001) at 6 weeks, 3 months, and 6 months respectively. In their study, final BCVA analysis showed that twenty five eyes (48.07%) remained stable and twenty two (42.30%) improved ≥ 2 lines on BCVA.[92]

Arevalo et al, in their study demonstrated that on six months follow-up, bevacizumab injections resulted in improvement of BCVA from the baseline value of 0.87 to the final post-treatment follow-up value of 0.60. In another study carried out by **Tareen IU et al**, authors also observed improvement in BCVA from pre-treatment value of 0.42 to the final post-treatment value of 0.34 (p- value < 0.05).[66, 76]

MEAN INTRAOCULAR PRESSURE

Mean preoperative intraocular pressure was 15.68 mm of Hg, while mean postoperative intraocular pressure was 15.42 mm of Hg. However; while comparing

the mean intraocular pressure preoperatively and postoperatively, non-significant results were obtained. Our results were similar to those obtained by **Paccola L et al**, who also reported a non-significant alteration in the mean intra-ocular pressure on 3 months follow-up.[94] In couple of clinical trials, enhancement of intraocular pressure occurred in approximately sixteen percent of the eyes on triamcinolone versus zero on bevacizumab.

Results from another set of trials also demonstrated that bevacizumab was beneficial in treating DME However; no leakage was reported on fluorescein angiography in any of these studies.[94- 96]

Ashwini G et al, in their study reported that mean IOP during pretreatment time was 17.28 while during post-treatment follow-up mean IOP was found to be 17.15. They also observed non-significant alteration in the mean IOP postoperatively. However; they observed a transitory non-significant rise in IOP during interim follow-ups. Several reports have documented elevation of IOP subsequent to intravitreal anti-VEGF drugs. Hence; it can be presumed that intravitreal bevacizumab is not associated with sustained IOP elevation over long term follow-up and IOP monitoring is mandatory in such patients.[97, 98]

Mazzulla DA et al devised a retrospective study design to delineate IOP fluctuation in patients subjected to intravitreal bevacizumab injection. They reviewed 29 patients who underwent successive intravitreal bevacizumab injections and

unveiled significant IOP elevation immediately after the injection, which reinstated to baseline levels within a week. Their study reported that bevacizumab injection of is considered to be safe in accordance with the outlook of short-term IOP elevation. They have illustrated early IOP elevation after bevacizumab injection. They have also reported the normalization of IOP by 1 week.[99]

Several studies have outlined protracted IOP elevation and suggested several presumptions related to risk factors associated with continued IOP elevation. According to these studies rise in IOP is connected with preexisting glaucoma, ocular hypertension and number of anti-VEGF injections. **Don Nguyen et al** designed a retrospective study to analyse longstanding effects of bevacizumab injection on IOP in patients with diabetic macular edema. Their study included 100 patients with mean injections ranging from 1 to 3 with a follow- up period of 1 year. The study concluded that there was no statistically significant elevation in IOP in those who received bevacizumab intravitreally, though there is persistent rise in IOP in glaucomatous patients.[100]

MEAN CENTRAL FOVEAL THICKNESS

Mean preoperative Central foveal thickness (μm) was 449.40 (SD=148.14), while mean postoperative central foveal thickness (μm) was 368.78 (SD=131.48). In 58 percent of the cases (29 eyes), reduction of central foveal thickness was by 50 μm.

While comparing the mean Central foveal thickness (μm) preoperatively and postoperatively, significant results were obtained. Our results were found to be in agreement with the results reported by other authors.

In a previous study by **Kook D**, authors observed that mean central retinal thickness (OCT) decreased from baseline value of 463 μm to 374 μm after 6 months ($P < 0.001$) and to 357 μm after 12 months ($P < 0.001$).[101]

A significant reduction in the mean central retinal thickness (on six months follow-up) from pre-treatment value of 449.03 μm to final post-treatment value of 326.51 μm was reported in the study conducted by **Vyas S et al**.[92]

Our results were in concordance with the results obtained by **Soheilian et al**, **Lam et al**, and **Joshi L et al**, who also observed reduction in the mean central foveal thickness following Bevacizumab therapy.[80, 102, 103]

Tareen IU et al, in their study, also observed significant improvement in the CMT from pre-treatment value of 452.9 μm to final post-treatment value of 279μm on half year follow-up. [76] In another study commenced by **Ateeq A et al**, authors reported significant improvement in the Macular thickness from 384.38 μm to final value of 323.19 μm on six months follow-up post-treatment.[77]

Haritoglou et al reported significant decrease in mean macular thickness post-treatment in patients with DME treated with Bevacizumab (Pre-treatment value: 498.96 µm; Post-treatment value of334.40).[64]

The conclusive pathologic process involved in DME is still uncertain. Retinal hypoxia and different physiologic disturbances are supposed to disrupt inner blood-retinal barrier correlating with metabolic derangement.

On long term basis, this derangement of circulatory function and physiology might results in functional vascular blockage, comparative retinal ischemia, and discharge of cytokines. **Funatsu et al** observed elevation in VEGF concentrations in vitreous fluid DME patients. VEGF resulted in conformational alterations in the retina's tight junctions (epithelial) and causes enhanced vascular permeability during the progression of DME.[104, 105]

Literature quotes considerable studies on the efficacy of intravitreal anti-VEGF for treating DME. In a recent study carried out by **Khan et al**, authors reported significant reduction in BCVA from mean pre-treatment value of 0.72 Log Mar to follow-up post-treatment value of 0.45 in DME patients. In another study conducted by **Kumar and Sinah**, authors observed that IVB led to significant reduction in macular thickness, along with significant improvement in BCVA on three months follow-up. **Ozkiris A**, in another previous study, observed enhanced visual acuity in eighty percent of the eyes on follow-up in DME patients following IVB injection.

They also reported significant reduction in the mean edema map values by one-third.[65, 106, 107]

In a phase II clinical trial analyzing the impact of IVD in DME patients, researchers demonstrated favorable results of bevacizumab on retinal thickness and VA.[108]

Małgorzata W et al, in their research, assessed the efficacy of IVB in patients with DME. They analysed twenty two eyes in twenty two patients with DME and observed that IVB injections led to enhancement of vision acuity followed by significant decrease in central retinal thickness.[109]

Impact of single bevacizumab injection in DME patients was assessed by **Soheilian et al**. Their results supported the results obtained in our study that bevacizumab might be an effective therapeutic option for treating DME patients.[103]

Hence; further clinical trials with longer follow-up and larger sample size are recommended for better exploration of this field of ophthalmology.

CONCLUSION

&

SUMMARY

CONCLUSION

Application of IVB offers significant enhancement and improvement in VA of diabetic patients with DME. Also, they considerably help in improving the clinical course of DME.

However, the minor decrease in enhancement of visual acuity and CFT during follow-up proposes that repeated bevacizumab injections may be required within three months for maintaining its effect, since the drug is well tolerated and there are no health issues and concerns.

SUMMARY

The present study was undertaken for assessing the outcome of intravitreal injection of bevacizumab on visual acuity and central macular thickness in patients with diabetic macular edema.

Subjects attending the Ophthalmology OPD who were diagnosed with Diabetic Macular Edema at KLES Dr. Prabhakar Kore Hospital and MRC, Belagavi were enrolled.

Patients of either sex 25-75 years of age with diabetes mellitus & with DME involving the centre, visual acuity of 6/9 or worse and CMT of 260μm or more on Spectral Domain Optical Coherence Tomography (SD-OCT).Patients were followed up after the first injection at 1 week and then at 3 weeks and visual acuity was assessed; 2nd and 3rd consecutive injections were performed at 28- 35 days intervals. At the end of 4 months after intravitreal injection, complete ophthalmic examination including BCVA & OCT was done.

Following results were obtained:

- The mean baseline BCVA (logMAR) and at 4 months of 1st injection = 0.80 ± 0.49 and 0.51 ± 0.36 respectively. The mean baseline CMT (μm) and at 4 months of 1st injection 448.40 ± 149.47 and 368.76 ± 131.49 respectively. The improvement in BCVA and CMT was statistically significant in our study. However, none of the other variables were significant by logistic regression analysis.

- In 38 percent of the cases (19 eyes), improvement in best corrected visual acuity was 2 or more than 2 ETDRS lines, while in remaining 62 percent of the cases (31 eyes), improvement in best corrected visual acuity was less than 2 ETDRS lines.
- In 58 percent of the cases (29 eyes), reduction of central foveal thickness was by 50 μm.
- Positive family history of diabetic retinopathy was present in 31.6 percent of the patients (12 patients).
- Uveitis was the only complication noted in 2 percent of the cases (1 patient) only.
- Mean duration of diabetes was 12.35 years.
- Mean HbA1c concentration was found to be 8.81 while mean RBS concentration was found to be 181.15 mg/dL.
- Mean preoperative intraocular pressure was 15.68 mm of Hg, while mean postoperative intraocular pressure was 15.42 mm of Hg. However; while comparing the mean intraocular pressure preoperatively and postoperatively, non-significant results were obtained.

- Mean preoperative Central foveal thickness (μm) was 449.40, while mean postoperative Central foveal thickness (μm) was 368.78. However; while comparing the mean Central foveal thickness (μm) preoperatively and postoperatively, significant results were obtained.

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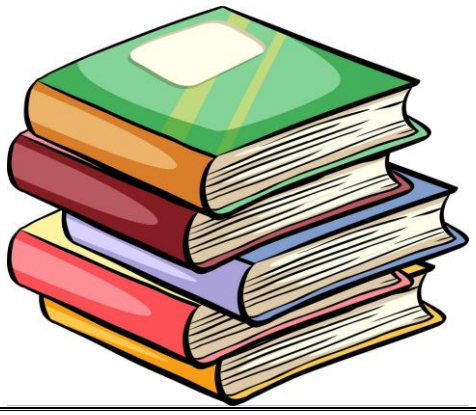

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ANNEXURE - I

Annexure I

K.L.E. ACADEMY OF HIGHER EDUCATION AND RESEARCH
(Deemed – to- be- University)
Accredited 'A' Grade by NAAC (2nd Cycle) Placed in Category 'A' by MHRD (GoI)
JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)
Website: http//www.jnmc.edu
E-Mail : dome@jnmc.edu
Phone: (+ 91-(0)831 Office : 2472550
Principal: 2471701
Fax No. +91 (0)831 – 2470759

Ref: MDC/DOME/ 66 **Date: 24/11/2018**

To,

REG. NO. BK0118001

PG student in Ophthalmology,
J.N.Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"OUTCOME OF INTRAVITREAL INJECTION OF BEVACIZUMAB ON VISUAL ACUITY AND CENTRAL MACULAR THICKNESS IN PATIENTS WITH DIABETIC MACULAR EDEMA – A ONE YEAR LONGITUDINAL STUDY AT KLES DR. PRABHAKAR KORE HOSPITAL AND MEDICAL RESEARCH CENTRE, BELAGAVI",** is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr. Arathi Darshan)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

(Dr. Roopa M Bellad)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

66

ANNEXURE - II

Annexure II

INFORMED CONSENT

STUDY ID NO: _____

TITLE OF THE STUDY:

"OUTCOME OF INTRAVITREAL INJECTION OF BEVACIZUMAB ON VISUAL ACUITY AND CENTRAL MACULAR THICKNESS IN PATIENTS WITH DIABETIC MACULAR EDEMA– A ONE YEAR LONGITUDINAL STUDY AT KLES DR. PRABHAKAR KORE HOSPITAL AND MEDICAL RESEARCH CENTRE, BELAGAVI"

PRINCIPLE INVESTIGATOR: REG. NO. BK0118001

GUIDE: Dr. _____

INTRODUCTION AND PURPOSE:

This study is designed to study outcome of intravitreal injection of bevacizumab on visual acuity and central macular thickness in patients with diabetic macular edema.

PROCEDURE:

I request you to kindly participate in the study titled 'OUTCOME OF INTRAVITREAL INJECTION OF BEVACIZUMAB ON VISUAL ACUITY AND CENTRAL MACULAR THICKNESS IN PATIENTS WITH DIABETIC MACULAR EDEMA– A ONE YEAR LONGITUDINAL STUDY AT KLES DR. PRABHAKAR KORE HOSPITAL AND MEDICAL RESEARCH CENTRE, BELAGAVI. If you agree to participate in the study please provide the details pertaining to the study. We will check do complete ophthalmic examination including examining optic disc changes and macular changes on OCT.

BENEFITS:

Results will help to study outcome of intravitreal injection of bevacizumab on visual acuity and central macular thickness in patients with diabetic macular edema.

Annexure II

RISKS: No proven side effects.

ALTERNATIVES:

If patient is not willing to take part in the study, his / her treatment or any other further investigations the patient wants to undergo, in future, in KLE will not be affected by his / her decision.

VOLUNTARY PARTICIPATION / WITHDRAWAL:

Taking part in this study is voluntary. I may choose not to take part in this study, or if I decide to take part I can later change my mind and withdraw from the study. My decision will not change the present or future health care or other services that I receive. The study doctor or the sponsor may stop my participation in this study. I will tell of any important new findings that may change my willingness to continue to take part. If I choose not to take part in the study I will receive the standard treatment for patients with my condition.

COMPENSATION:

In the event that I become injured as a result of taking part in this study, treatment will be offered to me. No reimbursement, compensation or free medical care is given.

CONFIDENTIALITY:

All information collected about me during the course of the study will be kept confidential to the extent permitted by the law. The code numbers will identify me in this research record. Information from this study may be published but my identity will be confidential in any publication.

CONSENT TO PARTICIPATE IN RESEARCH STUDY

I voluntarily agree to take part in this study by signing on the line below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicated that I have read this entire consent form or it has been read to me, and has been explained to me in my vernacular language and had all my questions answered. I will be given a copy of this consent form.

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

Annexure II

Participant's Name : ……

Signature/ Left Thumb impression: ……..……..

Name of the legally authorized representative: ……...

Signature/ Left Thumb impression: .……...……

Witness's Name: ……...

Signature/ Left Thumb impression: ……

Investigators name and Signature: ……

Date and Place: ……...

In this research record, information from this study may be published but my identity will be confidential in any publication.

QUESTION:

If any enquiries in the future or in case of research related injury illness, you may contact following persons:

1) PRINCIPLE INVESTIGATOR: **REG. NO. BK0118001**
   Post graduate student, Department of Ophthalmology,
   J N Medical College, Belagavi.

2) GUIDE: **DR.** _____ , Professor and Head, Department of Ophthalmology, J N Medical College, KLE University, Belagavi.

3) CO-GUIDE: **DR.** _____ , Consultant vitreo-retinal surgeon, Department of Ophthalmology, J N Medical College, KLE University, Belagavi.

4) For any further queries, you may contact: **Dr.ROOPA BELLAD** M.D.DCH, Professor of Pediatrics, Chairman of JNMC Institutional Ethics Committee on Human Subjects Research, J N Medical College, Belagavi.

ANNEXURE - III

Annexure III

PROFORMA

DATE: ☐☐ ☐☐ ☐☐☐☐

PATIENTS NAME: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

AGE:_____ Years

SEX: ☐ (1-Male; 2-Female)

S.No. ☐

ADDRESS: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐
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OP NUMBER: ☐☐☐☐☐☐☐☐

IP NUMBER: ☐☐☐☐☐☐☐☐

DATE OF ADMISSION: ☐☐ ☐☐ ☐☐☐☐

DATE OF DISCHARGE: ☐☐ ☐☐ ☐☐☐☐

IS THE PATIENT ELIGIBLE FOR STUDY? (1-YES; 2-NO) ☐

HAS INFORMED CONSENT BEEN GIVEN? (1-YES; 2-NO) ☐

GUIDE'S NAME:.

GUIDE'S SIGNATURE: _____

CO-GUIDE'S NAME:

CO-GUIDE'S SIGNATURE: _____

Annexure III

CHIEF COMPLAINTS:

DIMINUTION OF VISION RE ☐
Duration: _____ days/months/years

LE ☐
Duration: _____ days/ months/years

HISTORY OF PRESENT ILLNESS:

1. DIMINUTION OF VISION 1- Gradual; 2- Sudden ☐

1- Progressive; 2- Static ☐

PAST HISTORY: ☐

TRAUMA TO THE EYE: 1- Present; 2- Absent ☐

OCULAR SURGERY: 1- Present; 2- Absent

Type of surgery: _____
Duration: ☐☐ months/years

DIABETES:
Duration: ☐☐ months/years
Medications ☐

HYPERTENSION: 1- Present 2- Absent ☐

Duration: ☐☐ months/years

On Aspirin or Warfarin ☐

Annexure III

ANY OTHER MEDICAL DISORDERS:

_____

Hypercholesterolemia ____

Renal Failure ____

Smoking/tobacco addiction: 1-Present 2-Absent ☐

If yes, no. of years ___

H/O Treatment for DME _____

H/O PRPC _____

H/O (Intravitreal Avastin) IVA_____ Which eye_____ When _____

Cataract surgery___ Which eye ____When _____

H/O PPV_____ Which eye_____

Glaucoma treatment RE_____ LE_____

OCULAR EXAMINATION

1. Visual Acuity:

	RE	LE
DISTANT		
PINHOLE		
NEAR		
AIDED		

2. Adnexa (1- Normal; 2-Abnormal)	☐	☐

Annexure III

3. Sclera (1- Normal; 2- Congested)	☐	☐
4. Conjunctiva (1-normal; 2-conjunctival congestion; 3-ciliary congestion; 4-chemosis)	☐	☐
5. Cornea (1- normal; 2-opacity; 3-vascularisation)	☐	☐
6. Anterior chamber (1- normal depth; 2-shallow; 3-deep)	☐	☐
7. Iris (1-normal, colour & pattern; 2-Abnormal)	☐	☐
8. Pupil: Size- ____ in mm Shape- 1- Round & regular; 2.Abnormal Reaction: Direct (1. Present, 2. Absent) Indirect (1.Present, 2.Absent) Near reflex (1.Present, 2.Absent)	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
9. Lens Clarity- 1. Clear, 2. Opaque Cataract - (1) , PCIOL - (2) IOP: (mmHg)	☐ ☐	☐ ☐

Annexure III

FUNDUS	RE	LE
GLOW		
MEDIA		
DISC		
C:D RATIO		
BLOODVESSELS		
BACKGROUND		
MACULA		

Blood pressure: _____ mm hg
Random blood sugar: _____ mg/dl

Annexure III

OCT on date of examination just prior to bevacizumab injection and upon follow up :

DATE	RE VA	LE VA	RE CFT	LE CFT	REMARKS

DATE OF INJECTIONS

EYE INJECTED	1ST INJECTION DATE	2ND INJECTION DATE	3RD INJECTION DATE

Annexure III

POST-OP- IOP

Eye & Injection Date	One Month	Four Months

SUMMARY

a. Pre-op vision BCVA affected eye : RE____LE____

b. Post-op vision in affected eye BCVA : RE____ LE____

c. Pre-op CFT affected eye RE : ____LE____

d. Post-op CFT affected eye RE: ____LE____

ANNEXURE - IV

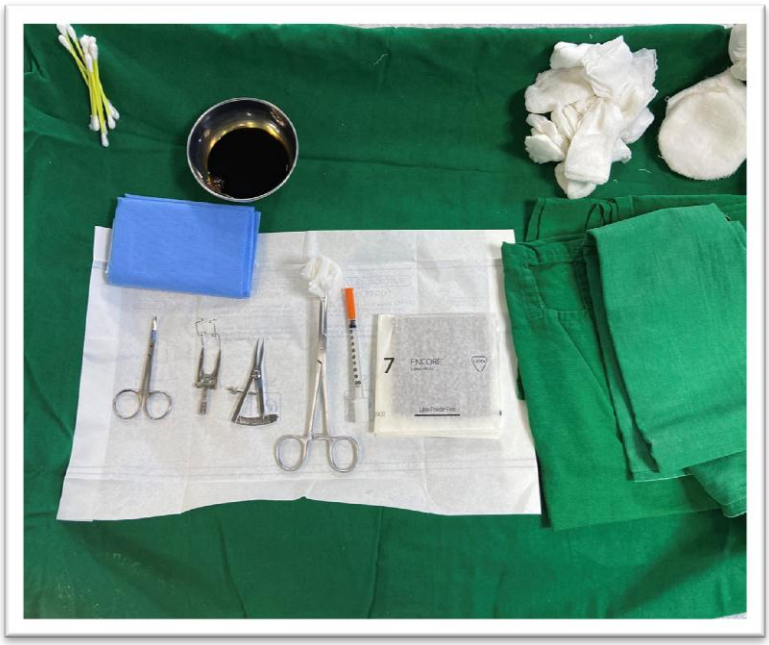
Annexure IV

PHOTOGRAPHS

1. Patient undergoing OCT examination

2. Intravitreal Anti VEGF Bevacizumab administration

2.1 Instrument set



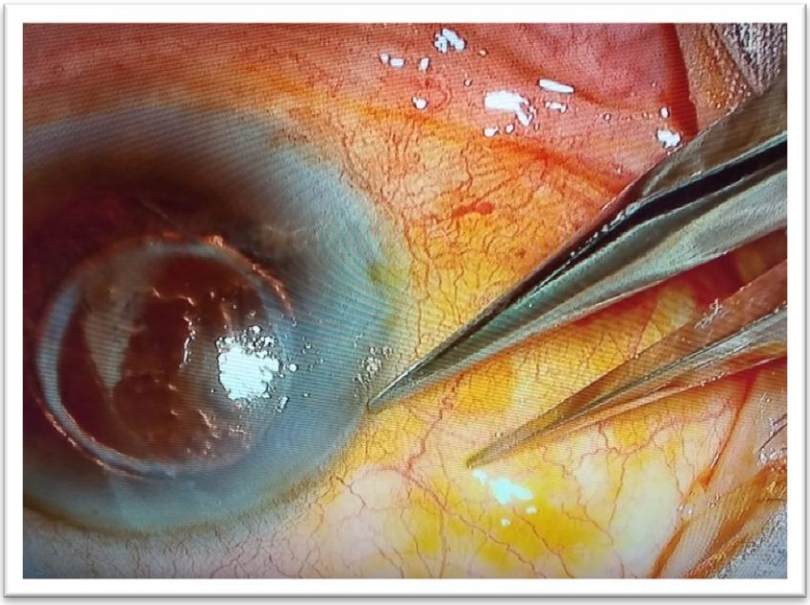
Annexure IV

2.2 Cleaning of the bevacizumab vial before and after withdrawal of drug

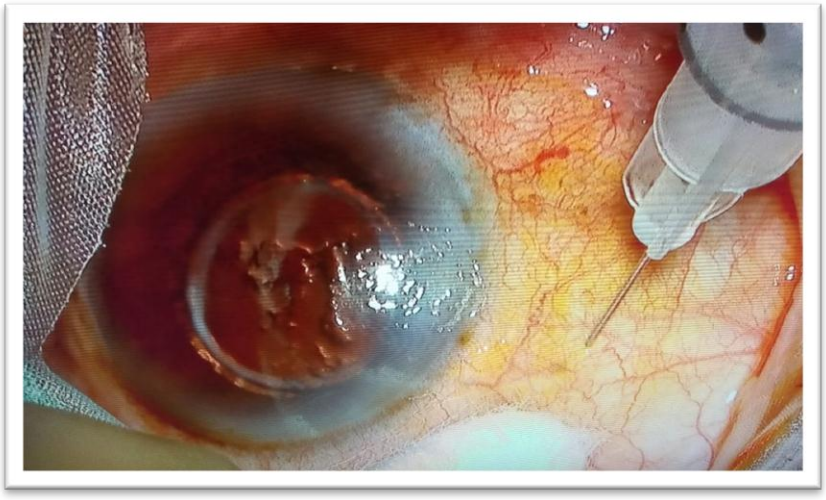
2.3 Preparation of surgical area

Annexure IV

2.3 Measurement of distance from limbus with caliper



2.4 Administration of IVI Bevacizumab



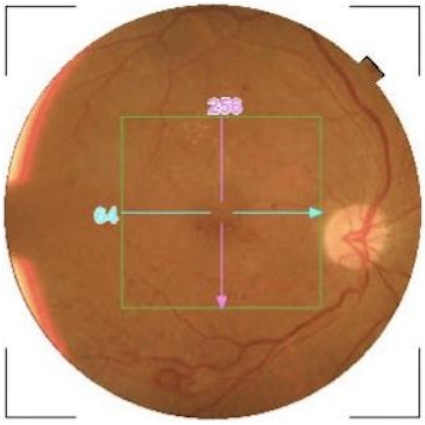
Annexure IV

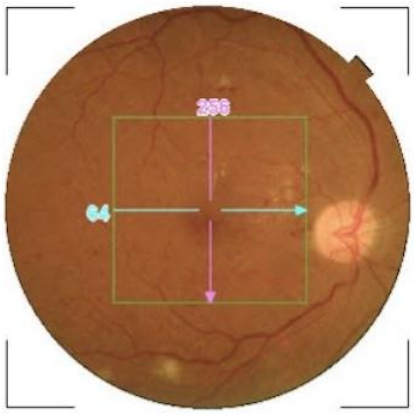
3 Representative cases : Fundus pictures and OCT scans showing decrease in CFT before and after 3 monthly IVB

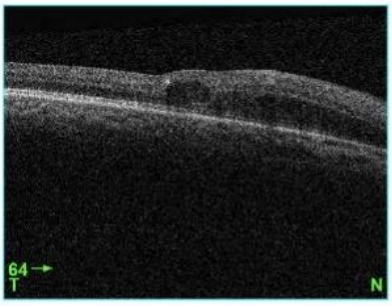
4

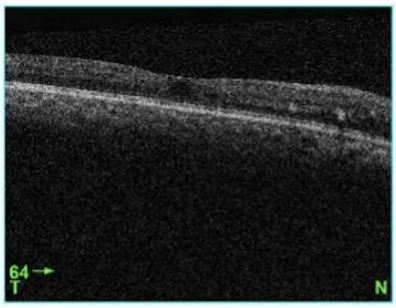
3.1 : **CASE 1**

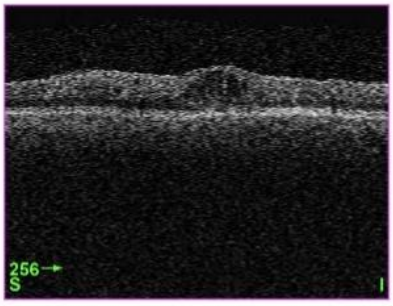
BEFORE **AFTER**

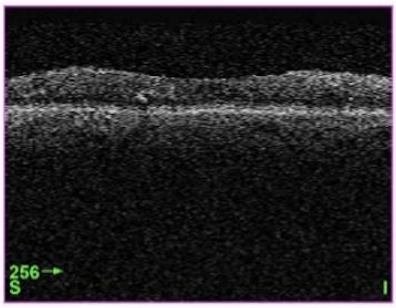


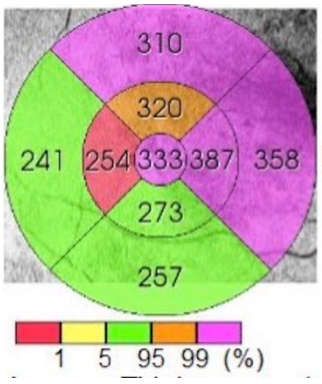


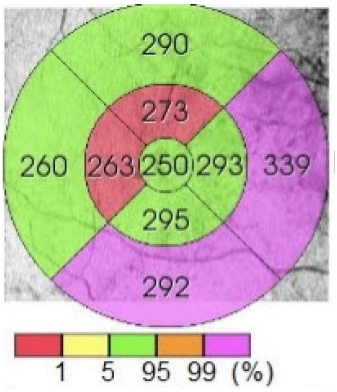






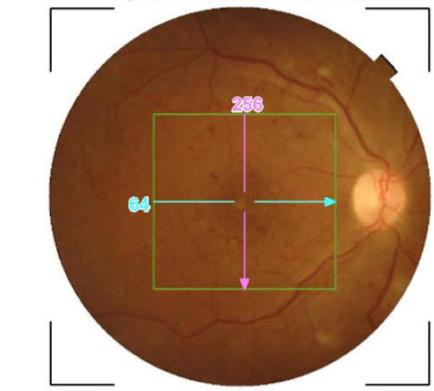


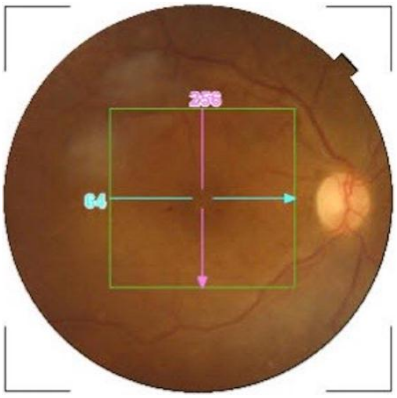


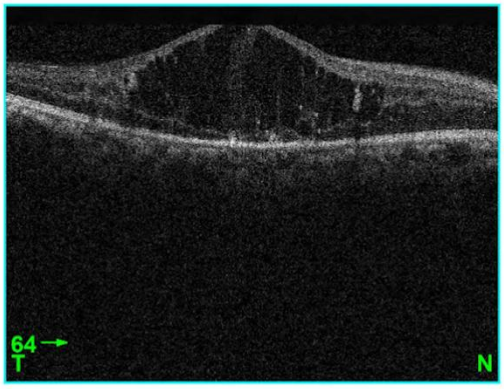


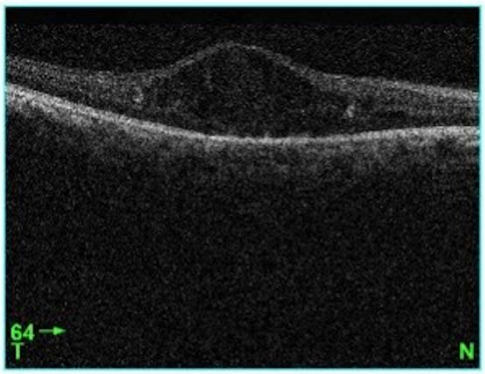
Annexure IV

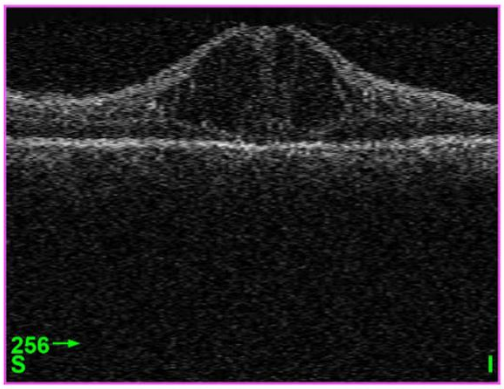
3.2 CASE 2 **BEFORE** **AFTER**

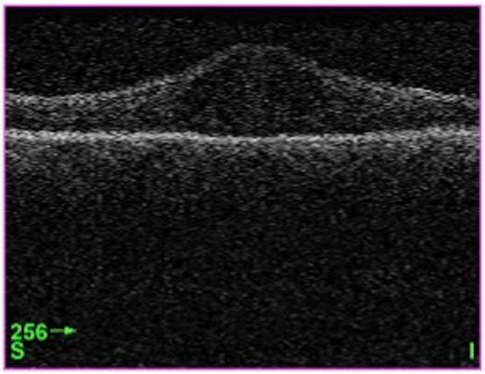


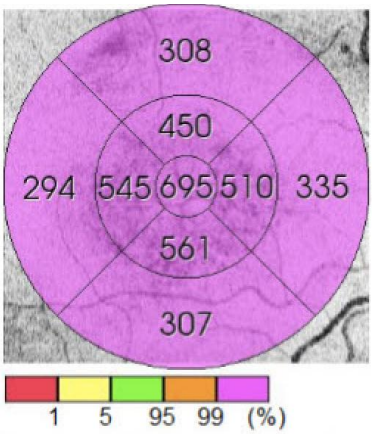


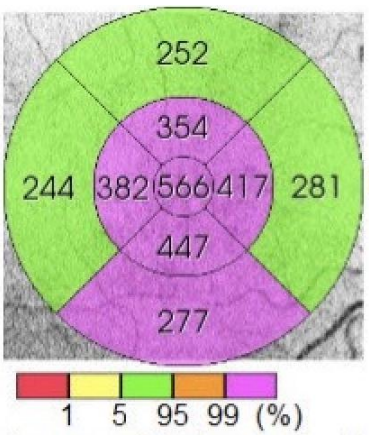












ANNEXURE - V

Annexure V

KEY TO MASTER CHART

Sex : 1 - Male

2 - Female

DM duration – Duration of diabetes mellitus

HTN – Hypertension

1 - Present

2 - Absent

Hba1c – Glycosylated haemoglobin

DM treatment – treatment taken for diabetes mellitus

1 - Oral hypoglycemic agents

2 - Insulin

3 - Oral hypoglycemic agents + Insulin

Anticoagulants – use of anticoagulants

1 - Present

2 - Absent

Hypercholesterolemia :

1 - Present

2 - Absent

Nephropathy :

1 - Present

2 - Absent

Annexure V

Smoking habit :

1 - Present

2 - Absent

Glaucoma :

1 - Present

2 - Absent

H/O PRPC – History of Panretinal photocoagulation

1 - Present

2 - Absent

Pre op BCVA (logMAR) – Preoperative best corrected visual acuity as logMAR

Post op BCVA (logMAR) – Postoperative best corrected visual acuity as logMAR

Improvement in BCVA – Improvement in best corrected visual acuity of > 2 lines

1 - Present

2 - Absent

Pre op IOP – Preoperative intraocular pressure (mmHg)

Post op IOP – Postoperative intraocular pressure (mmHg)

Pre op CFT – Preoperative Central foveal thickness

Post op CFT – Postoperative Central foveal thickness

Reduction of CFT by 50 μm :

1 - Present

2 - Absent

Annexure V

Anterior segment :

WNL – Within normal limits / Phakic eye

PCIOL – Posterior capsular intraocular lens / Pseudophakic eye

NVI – Neovascularization of iris

Posterior segment :

- Mild NPDR + DME = Mild Non proliferative diabetic retinopathy + diabetic macular edema
- Moderate NPDR + DME = Moderate Non proliferative diabetic retinopathy + diabetic macular edema
- Severe NPDR + DME = Severe Non proliferative diabetic retinopathy + diabetic macular edema
- PDR (treated) = Treated proliferative diabetic retinopathy
- Early PDR = Early proliferative diabetic retinopathy

DR Family history – family history of Diabetic retinopathy :

1 - Present

2 - Absent

Complications :

1 - Present

2 - Absent

ANNEXURE - VI

Annexure VI

Serial no.	Age(years)	Sex	DM duration	HTN	HbA1c	DM treatment	Anticoagulants	Hypercholesterolemia	Nephropahy	Smoking	Glaucoma	H/O PRPC	Pre op BCVA (logMAR)	Post op BCVA (logMAR)	Improvement in BCVA	Pre op IOP (mmHg)	Post op IOP (mmHg)	Pre op CFT (µm)	Post op CFT (µm)	Reduction of CFT by 50 µm	Anterior Segment	Posterior Segment	DR Family history	RBS (mg/dl)	Complications
1	47	2	15 years	2	8.00	3	2	2	2	2	2	2	0.6	0.17	1	17.7	16.8	414	386	2	WNL	Moderate NPDR + DME	2	177	2
2	70	1	4 years	1	9.20	1	2	1	2	1	2	2	1	0.6	1	18.1	14.6	406	386	2	WNL	Early PDR + DME	1	194	2
3	75	1	20 years	1	8.00	3	2	1	1	2	2	2	0.6	0.47	2	12	14.2	348	326	2	WNL	Moderate NPDR + DME	2	148	2
4	54	1	4 years	2	7.70	1	2	2	2	1	2	2	0.3	0.17	2	17.3	13.4	440	363	1	WNL	Moderate NPDR + DME	2	176	2
5	75	1	25 years	1	10.30	3	1	2	2	2	2	2	0.47	0.3	2	18.1	13.3	463	410	1	PCIOL	Severe NPDR + DME	1	174	2
6	60	1	20 years	1	9.90	1	2	2	2	1	2	2	1.47	1.3	2	15.8	17.2	695	566	1	PCIOL	Severe NPDR + DME	2	202	2
7	66	1	15 years	2	7.00	1	2	2	2	2	2	2	0.47	0.17	1	16.7	17.1	343	333	2	PCIOL	Mild NPDR + DME	1	166	2
8	75	2	20 years	1	8.10	3	2	2	2	2	1	1	0.47	0.3	2	14.3	14.4	349	216	1	WNL	PDR (treated) + DME	2	214	2
9	75	2	20 years	1	8.10	3	2	2	2	2	1	1	0.47	0.3	2	12.3	11.7	302	224	1	WNL	PDR (treated) + DME	2	214	2
10	52	2	10 years	2	10.10	1	2	2	2	2	2	2	0.6	0.47	2	10	11	354	247	1	WNL	Early PDR + DME	2	170	2
11	57	1	9 months	2	8.50	1	2	2	2	1	2	2	0.47	0.3	2	16.6	19	400	330	1	WNL	Severe NPDR + DME	1	184	2
12	57	1	9 months	2	8.50	1	2	2	2	1	2	2	0.47	0.17	1	18.7	18.6	359	313	2	WNL	Severe NPDR + DME	1	184	2
13	63	1	14 years	1	9.20	1	2	2	2	2	2	2	0.3	0.17	2	16.7	14	359	314	2	PCIOL	Severe NPDR + DME	2	170	1
14	64	1	10 years	1	8.30	1	2	1	1	2	2	2	0.47	0.17	1	11.4	16.7	427	251	1	**NVI**	Early PDR + DME	2	220	2

15	55	1	2 years	2	8.80	1	2	2	2	1	2	2	1.47	1	1	15.6	17.6	399	325	1	WNL	Moderate NPDR + DME	2	172	2
16	59	1	25 years	1	9.80	2	1	2	2	2	2	2	1.77	1.47	2	13.5	13.2	756	712	2	**NVI**	Early PDR + DME	1	198	2
17	59	1	25 years	1	9.80	2	1	2	2	2	2	2	0.17	0.17	2	15.7	15.4	464	455	2	WNL	Severe NPDR + DME	1	198	2
18	59	1	15 years	2	8.30	3	2	2	1	1	2	1	0.3	0.17	2	14.1	16.3	448	396	1	WNL	PDR (treated) + DME	1	201	2
19	60	2	17 years	2	8.10	3	2	1	2	2	2	2	0.6	0.47	2	15.8	14.1	547	455	1	PCIOL	Severe NPDR + DME	2	180	2
20	70	1	12 years	2	9.80	1	2	2	2	1	2	1	1.3	1	2	17.2	11.9	523	498	2	PCIOL	PDR (treated) + DME	1	124	2
21	70	1	12 years	2	9.80	1	2	2	2	1	2	1	0.3	0.17	2	18.1	10.7	333	317	2	PCIOL	PDR (treated) + DME	1	124	2
22	56	1	15 years	1	8.50	1	2	1	2	2	2	1	0.47	0.3	2	14.5	14.5	333	250	1	WNL	PDR (treated) + DME	2	170	2
23	38	1	10 years	2	8.30	2	2	2	2	1	2	1	0.77	0.47	2	12.7	13.4	620	602	2	WNL	PDR (treated) + DME	2	180	2
24	38	1	10 years	2	8.30	2	2	2	2	1	2	1	0.77	0.3	1	11.9	15.4	843	762	1	WNL	PDR (treated) + DME	2	180	2
25	75	1	15 years	2	8.00	1	2	2	1	1	2	2	0.6	0.47	2	20.3	20.3	354	346	2	WNL	Severe NPDR + DME	2	166	2
26	75	1	15 years	2	8.00	1	2	2	1	1	2	2	0.77	0.47	1	18	19.1	293	256	2	WNL	Severe NPDR + DME	2	166	2
27	58	1	24 years	1	7.40	2	2	1	2	2	2	2	0.6	0.47	**2**	16	17.2	415	343	1	WNL	Moderate NPDR + DME	1	160	2
28	52	1	6 years	2	10.40	1	2	2	2	2	2	2	0.47	0.17	1	14.6	12.1	313	277	2	WNL	Early PDR + DME	2	186	2
29	54	1	5 years	1	11.00	2	2	2	2	1	2	2	1.77	1.47	2	15.7	17.2	925	766	1	WNL	Early PDR + DME	2	201	2
30	54	1	5 years	1	11.00	2	2	2	2	1	2	2	1.77	0.77	1	16.6	18.6	622	459	1	WNL	Early PDR + DME	2	201	2
31	65	1	6 years	1	7.70	1	2	2	2	1	2	1	0.3	0.17	2	15.2	14	282	265	2	WNL	PDR (treated) + DME	1	180	2
32	59	1	7 months	1	9.80	1	2	1	2	2	2	2	0.77	0.47	2	14.1	13.8	469	325	1	PCIOL	Severe NPDR + DME	2	186	2
33	59	1	7 months	1	9.80	1	2	1	2	2	2	2	0.47	0.17	1	14.5	14.2	313	268	2	WNL	Severe NPDR + DME	2	186	2

34	55	1	10 years	1	9.20	1	2	2	2	2	2	2	0.3	0.17	2	13.8	17.3	575	390	1	WNL	Severe NPDR + DME	2	172	2
35	65	2	10 years	1	8.10	3	2	2	2	2	2	2	1.77	1.3	1	13.3	18.3	282	222	2	WNL	Severe NPDR + DME	2	182	2
36	65	2	10 years	1	8.10	3	2	2	2	2	2	2	1.77	1	1	12.9	12.8	465	304	1	WNL	Severe NPDR + DME	2	182	2
37	49	1	19 years	2	9.30	3	2	2	2	2	2	2	0.6	0.47	2	11.2	13.7	376	342	2	WNL	Early PDR + DME	2	220	2
38	49	1	19 years	2	9.30	3	2	2	2	2	2	2	0.6	0.47	2	11	13	500	442	1	WNL	Early PDR + DME	2	220	2
39	75	1	11 years	2	7.50	1	2	2	2	2	2	2	0.3	0.17	2	13.4	8	395	329	1	PCIOL	Moderate NPDR + DME	1	170	2
40	52	2	15 years	1	8.80	1	2	2	2	2	2	2	0.3	0.17	2	21.4	17.1	275	247	2	PCIOL	Severe NPDR + DME	2	202	2
41	69	1	12 years	2	10.10	1	2	2	1	2	2	2	0.6	0.47	2	18.4	17.6	419	349	1	PCIOL	Early PDR + DME	2	176	2
42	70	2	30 years	1	7.30	3	2	2	1	2	2	2	1	0.6	1	14.3	16.2	421	315	1	PCIOL	Moderate NPDR + DME	2	181	2
43	74	1	2 years	2	8.30	2	2	1	2	2	2	2	1.47	0.77	1	17.7	15.5	413	278	1	WNL	Moderate NPDR + DME	2	177	2
44	54	1	22 years	2	8.50	1	1	1	2	2	2	2	1	0.77	2	19.8	17.9	664	280	1	WNL	Early PDR + DME	1	174	2
45	54	1	22 years	2	8.50	1	1	1	2	2	2	2	1	0.6	1	22.5	19.9	488	307	1	WNL	Early PDR + DME	1	174	2
46	55	1	15 years	1	10.10	2	1	2	2	2	2	2	0.6	0.3	1	17.1	18.4	314	259	1	WNL	Severe NPDR + DME	2	164	2
47	58	1	9 years	1	7.70	1	2	2	2	2	2	2	1	0.77	2	15.6	15	656	463	1	WNL	Severe NPDR + DME	2	174	2
48	65	1	2 years	1	9.20	1	2	2	2	2	2	2	1	0.77	2	14.7	16	626	551	1	WNL	Severe NPDR + DME	2	192	2
49	65	1	2 years	2	10.60	1	2	2	2	2	2	2	1.77	0.77	1	18.8	17.6	365	316	2	PCIOL	Early PDR + DME	1	201	2
50	65	1	2 years	2	10.60	1	2	2	2	2	2	2	1.3	0.77	1	18.2	16	325	302	2	WNL	Severe NPDR + DME	1	201	2