Republic of Yemen
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21 September university of medical & applied sciences
Faculty of medicine

الجمهورية اليمنية
وزارة التعليم العالي والبحث العلمي
جامعة 12 سبتمبر للعلوم الطبية والتطبيقية
كلية الطب البشري

Evaluation of Efficiency of Intravitreal Injection (Bevacizumab) In Treatment of Diabetic Macular Edema

This Thesis is Submitted to the Department of Community Medicine, Faculty of medicine and Health Sciences, 21 September university of medical & applied sciences As A partial Fulfillment for MBBS. Graduation.

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تقييم كفائة الحقن المستخدمة في علاج وذمة الشبكية الناتجة عن مضاعفات امراض السكري

يتم تقديم هذه الأطروحة الى قسم طب المجتمع ، كلية الطب والعلوم الصحية ، جامعة 21سبتمبر للعلوم الطبية والتطبيقية ك ا ستكمال جزئي لمشروع التخرج بكالوريوس طب وجراحة عامة.

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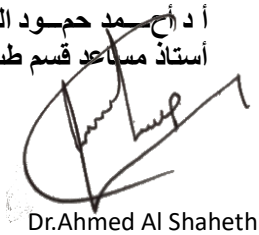

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List of abbreviation

FDA	Food And Drug Administration
US	United States
CNV	Choroidal Neovascularization
AMD	Age Related Macular Degeneration
DME	Diabetic Macular Edema

OCT	Optical Coherence Tomography
BCVA	Best-Corrected Visual Acuity
IVB	Intravitreal Bevacizumab
VEGF	Vascular Endothelial Growth Factor
DRP	Diabetic Retinopathy
PDRP	Proliferative Diabetic Retinopathy

Abstract

Background: Anti-VEGF agents have been proven to be effective in treating macular edema secondary to a multitude of pathological conditions. However, in large clinical trial settings, the results may be overstated. This study **aimed** to evaluate the efficacy of intravitreal injection Bevacizumab in patients with diabetic macular edema in term of detect the improvement of visual acuity, macular edema and thickness according to the ophthalmological parameters[Optical Coherence Tomography (OCT), Visual Acuity (VA) and BestCorrected Visual Acuity (BCVA)]

Methods: This is a Retrospective, Analytical study was conducted at Magrabi Eye Hospital, Sana'a, Yemen From June 2022 to December 2022. n:245 eyes of 173 patients with macular edema were treated with intravitreal Bevacizumab injections. Visual Acuity, Best-corrected visual acuity (BCVA), and OCT parameters including central retinal thickness (CRT) were assessed prior to the injections and then 4 weeks post injection and compared. Systematic random sampling method was used. The data were collected from the medical records of the patients. The data analysis was performed on the cleaned datasets using SPSS Software (SPSS inc., Chicago.II.USA, version 25.0)

Result: The study sample consisted of (n:245) eyes of 173 patients who had treated with intravitreal injection(Bevacizumab), the results showed that there is an improvement in the ophthalmological parameters Optical Coherence Tomography (OCT), Best-Corrected Visual Acuity (BCVA) and visual acuity as the following (75.1%), (71.8) and (55.1), respectively. The results also revealed that there is a statistically significant relationship at the level(p<0.05) between; (OCT before and after treatment), (Baseline VA and VA at last visit) and (Baseline VA and BCVA).

Conclusion:- Treatment with intravitreal Bevacizumab injections was found safe and resulted in clinically and statistically significant improvement in OCT parameters and visual acuity in patients with macular oedema secondary to various retinal pathologies.

Keywords: Bevacizumab; Macular Edema; Diabetic Retinopathy; Magrabi Eye Hospital; Sana'a, Yemen.

INTRODUCTION

1.1 Background

Diabetes mellitus (DM) stands out as a cause for morbidity and mortality. Global estimates indicate that 382 million people live with DM (8.3%), and this number can reach 592 million by 2035.[1] In 2015, the International Diabetes Federation (IDF) estimated that 8.8% of the world population aged between 20 and 79 years (415 million people) have DM, and this figure is projected to increase to 642 million by the year 2040.[2] Around 75% of the cases occur in developing countries, where an increase in number of DM patients is expected in the next decades.[2] Until the year 2045, the prevalence of DM can be estimated at 9.9%.[3]

One of the complications resulted from DM is diabetic retinopathy (DR). Actually, it is one of the major causes of blindness in patients aged between 20 and 64 years, which represent around 12% of new cases.[4] Besides, 80% of DM patients who have lived with the disease for over 20 years are frequently diagnosed with DR. At least 90% of the new cases, however, showed to have the retinal structure and function restored when proper treatment was provided.[5]

Diabetic retinopathy is a common cause of severe vision loss and the leading cause of blindness in individuals between 20 and 65 years of age in developed countries. Diabetic macular edema (DME) is the most common cause of visual loss in diabetic retinopathy,[6] affecting approximately 6.8% of people with diabetes.[7] Although laser treatment previously was the benchmark treatment for clinically significant DME, the limitations of laser treatment, together with intense clinical research over the last 10 years, have led to laser treatment being surpassed by intravitreal pharmacotherapy as first-line treatment for moderate to severe vision loss caused by DME.[8]

Bevacizumab (Avastin) is a tumor-starving (anti-angiogenic) therapy. was first approved by the Food and Drug Administration (FDA) to treat colon and different types of cancer.

1

Its use to treat eye diseases is considered an “off-label” use. The FDA allows “off label” drug use if doctors are well informed about the product and studies prove the drug is helpful. Many studies have shown Avastin as safe and effective for eye disease since it was first used in the US in February 2004.[9]

1.2 Problem statement

The problem to be addressed through this study are Poor glycemic control, Irregular follow up of patients post intravitreal bevacizumab inection and having been ill for more than ten years are strongly associated factors with macular edema and patients not improved or had deterioration.

1.3 hypothesis

In order to improve Visual Acuity and reduce macular thickness of diabetic macular edema. We wish to know whether the first dose of intravitreal bevacizumab injection is playing a role in improvement?

Is there any significant role in the improvement of visual acuity and reduce macular edema after the first dose of intravitreal bevacizumab injection?

Is the Regular follow up of the patients before and after treatment playing a role in the improvement?

1.4 Justifications

Recent studies have demonstrated the usefulness of intravitreal injections of bevacizumab in the reduction of macular edema secondary to central retinal vein occlusion, vascular

permeability, fibrovascular proliferation in retinal neovascularization secondary to proliferative diabetic retinopathy (PDR), and choroidal neovascularization secondary to

age-related macular degeneration (AMD) (Spaide and Fisher 2006, Wu, Martínez-Castellanos et al. 2008).

The present study aimed to assess the efficacy of Intravitreal bevacizumab injections for patients with diabetic macular edema in Magrabi eye hospital, Sana'a, Yemen

1.5 Objectives

1.5.1 General study objective

This study Aimed to evaluate the efficacy of intravitreal injections bevacizumab in the treatment of macular edema in Magrabi Eye Hospital, Retinal department, Sana'a, Yemen.

1.5.2 Specific study objectives

1-To evaluate the efficacy of bevacizumab in the improvement of visual acuity, macular edema and thickness according to the ophthalmological parameters Optical Coherence Tomography (OCT), Best-Corrected Visual (BCVA) and Visual Acuity.

CHAPTER 2: LITERATURE REVIEW

2.1 Review of Diabetic Macular Edema

Diabetic retinopathy remains the major threat to sight in the working age population in the developed world. Furthermore it is increasing as a major cause of blindness in other parts of the world especially in developing countries [10]. Diabetic macular edema (DME) is a manifestation of diabetic retinopathy that produces loss of central vision. Macular edema within 1 disk diameter of the fovea is present in 9% of the diabetic population [11]. Although visual loss secondary to proliferative changes is more common in patients with type 1 diabetes, visual loss in patients with type 2 diabetes is more commonly due to macular edema. [12] Proliferative diabetic retinopathy (PDR) is a major cause of visual loss in diabetic

patients. In PDR, the growth of new vessels from the retina or optic nerve, is thought to occur as a result of vascular endothelial growth factor (VEGF) release into the vitreous cavity as a response to ischemia. [13-14]

2.2 Epidemiology of Diabetic Macular Edema

Diabetes mellitus (DM) stands out as a cause for morbidity and mortality. Global estimates indicate that 382 million people live with DM (8.3%), and this number can reach 592 million by 2035.[1] In 2015, the International Diabetes Federation (IDF) estimated that 8.8% of the world population aged between 20 and 79 years (415 million people) have DM, and this figure is projected to increase to 642 million by the year 2040.[2] Around 75% of the cases occur in developing countries, where an increase in number of DM patients is expected in the next decades.[2] Until the year 2045, the prevalence of DM can be estimated at 9.9%.[3]

Prevalence of DR and DME

In many countries, DR is not only the most frequent cause of preventable blindness among individuals of working age (20-65 years), but also a frequent cause of vision loss in elderly populations. In the U.S.A., an estimated 29 % of adults with diabetes have DR and 3 % have DME [15]. The prevalence rates are similar between those aged 40–64 years and those aged 65 years and older (28 % vs 30 % for DR and 4 % vs 5 % for vision-threatening DR). Outside of the U.S.A., similarly high rates have been reported in other Western countries as well as in developing countries [16–17]. In particular, Asia has emerged as the global epicenter of the diabetes epidemic [18] and the proportion of individuals with DR will be on the rise with increasing numbers and lifespans of people with diabetes, especially in China and India. A study from rural China [19] showed that DR is common, with rates of 43 % for any DR and 3.5 % for DME. These estimates are higher than are those reported in

another study of mostly urban Chinese residents (37 % for DR and 2.6 % for DME) [8], suggesting that preventive efforts should be targeted in rural areas of China. On the basis of data from the former study, an estimated 9.2 million Chinese people aged 30 years and older living in rural areas have diabetic retinopathy, of whom 1.3 million suffer visionthreatening retinopathy and 0.7 million have DME [19].

More recently, a pooled individual participant meta analysis provided more up-to-date estimates of DR prevalence worldwide from the compilation of 35 separate population based studies in the U.S.A., Australia, Europe, and Asia conducted from 1980 to 2008 [20]. Based on the latest figures derived from this study, the overall prevalence is 35 % for any DR, 7.2 % for PDR and 7.5 % for DME among individuals with diabetes aged 20–79 years and all these prevalence end points are substantially higher in people with type 1 compared with type 2 diabetes (77 % vs 32 %, 32 % vs 3 %, 14 % vs 6 % for any DR, PDR and DME respectively), independent of diabetes duration. The likelihood of retinopathy is strongly related to duration of diabetes, and the prevalence of any DR ranges from 21 % among participants with less than 10 years of diabetes to 76 % in those with 20 years or more of disease. The prevalence of DME ranges from 3 % among participants within 10 years of diabetes to 20 % in those with 20 or more years of disease. The prevalence estimates of DR and DME are similar in men and women, and vary across ethnic groups—they are highest among African Americans and lowest among Asians. However, it is uncertain whether these apparent ethnic variations represent subpopulation differences associated with access to and the level of medical care, differential susceptibility to risk factors, or variability in genetic predisposition to microvascular damage [21]. Population-based studies incorporating host and environmental data would be helpful in further elucidating the effect of race and ethnicity on DR prevalence.

Incidence of DR and DME

Few population-based studies have reported the incidence and progression of DR or DME. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) in the U.S.A., the overall 10-year incidence of retinopathy was 74 %, and among those with retinopathy at baseline, 64 % developed more severe retinopathy and 17 % progressed to develop PDR [22]. About 20 % of type 1 diabetes and 14-25 % of type 2 diabetes developed DME over a 10-year follow-up period [23]. Data from the 25-year follow-up of the WESDR type 1 diabetes cohort show that virtually all patients (97 %) developed retinopathy over time, with a third to a half going on to develop vision-threatening disease (42 % developed PDR, 29 % developed DME and 17 % developed clinically significant DME [the more severe spectrum of DME]) [24-25]. Although the cumulative incidence of PDR or DME increased with duration of diabetes, their relationship was not linear, presumably due to the increased competing risk of death. Based on the WESDR data, it is estimated that over a 25-year period, of the 515,000 to 1.3 million Americans with known type 1 diabetes, approximately 185,000–466,000 will develop PDR and 149,000377,000 will develop DME

[24-25].

There are scarce other long-term population-based incidence data to compare with these findings. In the U.K., more recent data from the annual diabetic retinopathy screening program in England showed that the 5-year cumulative incidences of any DR, PDR and clinically significant DME were 36 %, 0.7 % and 0.6 % among people with type 2 diabetes who were free of retinopathy at baseline [26]. After 10 years of follow up, the respective cumulative incidences rose to 66 %, 1.5 % and 1.2 %.

2.3 Risk Factors of Diabetic Macular Oedema

Clinical associations and risk factors

Macular edema is strongly positively associated with diabetic retinopathy severity. Glycemic control is a conclusively identifies risk factor for retinopathy progression as well as for DME. Duration of diabetes is strongly correlated with prevalence and incidence of macular edema, retinopathy progression, and other diabetic complications. The diagnosis of diabetes in type 2 subjects occasionally occurs sometime after subclinical diabetes has been manifest, which yields a small proportion of patients who may present with macular edema at the time of diagnosis, or even have decreased vision from macular edema at the presenting sign. In contrast, persons with type 1 diabetes are very unlikely to experience advanced retinopathy and macular edema before 5 years of duration.

Clinical Associations with Diabetic Macular Edema Severity: [27] [28]

• **Duration of Diabetes** – increased risk of diabetic retinopathy

Thus, 2 key changes occur:
• **Vessel permeability**

• **Glycemic control** – The Diabetes Control and Complication Trial (DCCT) clearly demonstrated that tighter control of blood sugar is associated with reduced incidence of diabetic retinopathy (Glycosylated hemoglobin (HbA1c) should be less than 7%)

• **Nephropathy** – proteinuria is a good marker for development of diabetic retinopathy; thus, patients with diabetic with nephropathy should be observed more closely

• **Hypertension** – increased risk of retinopathy (diabetic retinopathy with superimposed hypertensive retinopathy)

- **Vessel closure**
- **Dyslipidemia** – normalization of lipid levels reduces retinal leakage and exudates deposition
- **Pregnancy** – diabetic retinopathy can progress rapidly in pregnant women, especially those with preexisting diabetic retinopathy
- **Intraocular surgery**
- **Uveitis**
- **Panretinal Photocoagulation**

2.4 Etiology of Diabetic Macular Edema

Causes of ME:

Macular edema is caused by pockets of fluid (usually leakage from damaged blood vessels) swelling up in the macula.

There are many conditions that can leak fluid into the retina and cause macular edema, including:

Diabetes. With diabetes, high blood sugar levels damage blood vessels, which leak into the macula.

Age-related macular degeneration (AMD). With AMD, abnormal blood vessels leak fluid and cause macular swelling.

Macular pucker/vitreomacular traction. When vitreous in the aging eye doesn't detach completely from the macula, the vitreous tugs on the macula or forms scar tissue, and pockets of fluid collect underneath it.

Retinal vein occlusion (RVO). With blood vessel diseases like RVO, veins in the retina become blocked. Blood and fluid then leak out into the macula.

Hereditary/genetic disorders (passed from parent to child), such as retinoschisis or retinitis pigmentosa.

Inflammatory eye diseases. Conditions like uveitis, where the body attacks its own tissues, can damage retinal blood vessels and cause swelling of the macula.

Medication. Certain drugs have side effects that can lead to macular edema.

Eye tumors. Both benign and malignant tumors can lead to macular edema.

Eye surgery. It's not common, but sometimes after glaucoma, retinal or cataract surgery, you can get macular edema.

Injuries. Trauma to the eye.

2.5 Pathophysiology of Diabetic Macular Oedema

Diabetic macular oedema (DME) is the accumulation of excess fluid in the extracellular space within the retina in the macular area, typically in the inner nuclear, outer plexiform, Henle's fiber layer, and subretinal space. [29] [30]

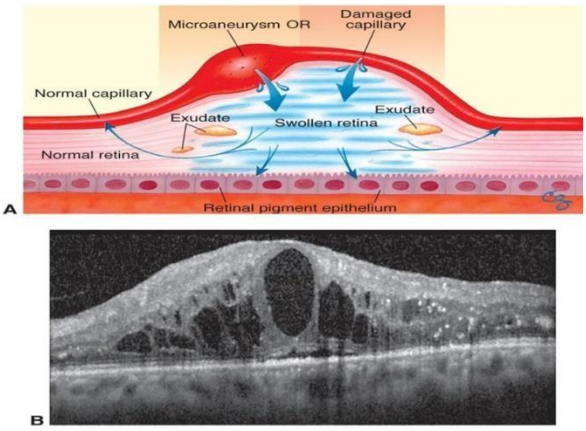

Figure 2.1: Diabetic macular edema. A: Schematic diagram of DME. Microaneurysms or damaged capillaries resulting from the breakdown of the blood-retina barrier leak fluid to the extracellular space, resulting in a swollen retina. Resorption of DME is dependent on the adjacent capillaries and retinal pigment epithelium. Resorption of fluid may leave behind lipoprotein residues seen as exudates. B: Optical Coherence Tomography image of DME. Published online with permission from the AAO.

Chronic hyperglycaemia-related accumulation of advanced glycated end products (AGEs) disrupts the blood retinal barrier (BRB) characterized by endothelial cell junction breakdown and pericyte loss. The inner BRB is composed of endothelial cells in the retinal capillaries, while the outer BRB is composed of retinal pigment epithelium (RPE) cells. Altered BRB leads to interstitial fluid accumulation within and underneath the retina through leakage of molecules dependent on intact cell to cell junctions **(Figure 1**). [31] Evidence also shows that DME has an inflammatory component to the disease, with several chemokines and cytokines involved in its development. These factors include vascular endothelial growth factor (VEGF), interleukins (ILs), matrix metalloproteinases (MMPs), and tumor necrosis factor (TNF). Upregulation of multiple pathways leads to increased inflammation, oxidative stress, and vascular dysfunction. [32] There are also significant changes in the neurovascular unit, altering the homeostasis between astrocytes, ganglion cells, Müller cells, retinal vascular endothelial cells, and amacrine cells. [33] Retinal vascular permeability changes also involve the kallikrein-kinin system, which induces vasorelaxation via bradykinin and nitric oxide.[34] [35] [36]

Natural History

DME can develop at any stage of diabetic retinopathy (DR), from mild **nonproliferative diabetic retinopathy (NPDR)** to **proliferative diabetic retinopathy (PDR),** but is more frequent as the severity of DR increases. DME threatening or at the fovea is more likely to result in blurred vision and metamorphopsia. When the DME involves or threatens the fovea, the risk of moderate visual loss (MVL, defined as a three-line or more decrease of visual acuity, equivalent to a doubling of the visual angle) over 3 years in the Early Treatment of Diabetic Retinopathy Study (ETDRS) was 24% without treatment.[37] The disease course is variable, with some eyes having chronic persistent DME spanning several years, while other eyes have rapid spontaneous resolution, although the risk of recurrence is always present.

2.6 Clinical Presentation of Diabetic Macular Edema

DR is the commonest cause of vision loss in adults aged 20–74 years. [38] An estimated 285 million people suffer from diabetes, and one-third of these are affected by vision threatening DR, which may include diabetic macular edema (DMO) or proliferative DR (pDR). [39]

In patients with type I diabetes, pDR is the most prevalent vision-threatening condition. In type II diabetics however, DMO is more common, and this explains the significant increase seen with the prevalence of DMO over recent years, in which ever increasing levels of obesity in the western world have been implicated. [38]

Clinically, pDR and DMO may present with a variety of symptomatic ailments and variability between patients is common. During the early stages of the disease, patients are often asymptomatic but progress over time to develop microaneurysms, hemorrhages, and

intraretinal microvascular abnormalities. [40] Upon examination, this can manifest as dark spots occluding vision, blurred vision, impaired color vision, and eventually vision loss if treatment is not effective. [41] As DR progresses, DMO may occur, defined as the presence of retinal thickening and hard exudates within 500 μ m of the center of the macula.[42] Additionally, some patients demonstrate severe pDR in which aberrant neovascularization leads to the formation of highly permeable blood vessels across the retina.

2.7 Investigation and Evaluation of Diabetic Macular Edema

History

DME is suspected in patients with any level of DR who present with blurred vision or metamorphopsias. A detailed history including the approximate date of onset of diabetes, the use of insulin versus oral antihyperglycemic agents, and the quality of metabolic control (e.g., HbA1c level) should be elicited. Any associated medical problems such as hypertension, hypercholesterolemia, renal disease, and thyroid disease should be identified, along with a thorough review of medications. It should be noted that mild to extensive DME may be present without symptoms evident to the patient.

Physical Examination

Patients undergo a detailed biomicroscopic examination using the **slit lamp biomicroscope** and **indirect ophthalmoscope.** Historically, DME classifications were based on the ETDRS definitions of clinically significant macular edema (CSME). The specific criteria for diagnosing CSME were:

Retinal thickening at or within 500 μm of the center of the fovea

Hard exudates at or within 500 μm of the center of the fovea if adjacent to an area of retinal thickening

Retinal thickening of at least 1-disc area any portion of which is within 1500 μm (approximately 1-disc diameter) from the center of the fovea

Thus, CSME as defined by the ETDRS in the 1980s is a clinical diagnosis made by slitlamp examination using a contact lens. While clinical examinations remain essential for the full evaluation of DME, **Optical Coherence Tomography (OCT)** is now routinely used to complement physical examination in the diagnosis of DME.

Signs

Macular thickening with or without hard exudates may be seen with **stereo biomicroscopy.** However, some eyes may present without apparent signs of retinal thickening on clinical examination despite significant DME as observed using OCT. Thickening can occur in various patterns: focal, multifocal, and diffuse areas of retina thickening. Despite these terms being frequently used, there are no well-established standard definitions, and different authors use them inconsistently.[43] In the ETDRS, focal leakage results from microaneurysms that may be treated with fluorescein angiography (FA) guided focal laser, while diffuse capillary leakage is from a more widespread breakdown of the BRB, which may be treated with grid laser.[44] Hard exudates in various patterns may also be seen, including circinate rings and focal aggregations of exudates. Hard exudates consist of lipoprotein residues of serous leakage from damaged vessels, serving as biomarkers for DME.

Symptoms

DME may present with decreased visual acuity (VA), metamorphopsia, changes in color perception, and difficulty reading, although it may also present asymptomatically.

Diagnostic Procedures

1. **Optical Coherence Tomography (OCT).**

   OCT within recent years has quickly become an important ancillary procedure in the diagnosis and treatment of DME. Three basic structural changes can be seen: retinal swelling, cystoid macular edema, and subretinal fluid (Figure 4). Macular scans can quickly and accurately identify even subtle areas of thickening, along with quantitative metrics for different areas. Changes in the anatomic distribution of DME can be monitored over time, especially the fluid's relationship to the fovea. This information has proven crucial regarding clinical and research implications for the evaluation and management of DME. More recently, the International Council of Ophthalmology (ICO) guidelines for diabetic eye care in 2018 have adopted the clinical entity of center-involved DME (ci-DME) versus non-center involved DME (non ci-DME) for the evaluation of macular fluid. The classification is:

   1.Center-involved DME: Retinal thickening in the macula that involves the central subfield zone (1 mm in diameter)

   2.Non-center involved DME: Retinal thickening in the macula that does not involve the central subfield zone (1 mm in diameter)

2. **Fluorescein Angiography.**

Fluorescein angiography (FA) is performed to identify leaking microaneurysms or capillaries to guide laser treatment, and areas of retinal ischemia. Leakage on the angiogram is not

synonymous with retinal oedema. Focal DME is characterized by focal leakage from microaneurysms or capillaries. In contrast, diffuse DME is diagnosed when

poorly demarcated areas of capillary leakage are present. Recently, there has been a decreasing trend in the use of FA in the management of DME, likely due to the procedure being more invasive and time-consuming compared to OCT. [45] Contraindications to the use of FA include pregnancy and allergy associated with the contrast dye.

Laboratory Testing

Primary: HbA1c (Glycated Haemoglobin), Blood pressure, Lipid Profile. Secondary: Haemoglobin (anaemia exacerbates diabetic retinopathy and may be associated with diabetic nephropathy), Fasting Blood Sugar (FBS), Post Prandial Blood Sugar (PPBS), Urea, Creatinine, Urine microalbumin levels, Thyroid panel.

Differential Diagnosis

Other causes of macular oedema include retinal vein occlusion, ruptured microaneurysm, Irvine-Gass syndrome, radiation retinopathy, hypertensive retinopathy, subfoveal choroidal neovascularization, retinal vein occlusion, and VMIA. OCT and FA ancillary diagnostics can help differentiate between these differential diagnoses.

2.8 Management of Diabetic Macular Edema

Medical therapy

- Strict control of diabetes, blood glucose, hypertension, and hypercholesterolemia [46]

- Diet Modification
- Weight Loss
- Exercise

Pharmacotherapy

At present, anti-VEGF agents are the first-line treatment for DME requiring treatment. Since 2005, intravitreal bevacizumab has been used off-label for ocular conditions. FDA approved ranibizumab for DME in 2012, Aflibercept in 2014 and Brolucizumab and Faricimab in 2022.

Pharmacotherapy Landmark Studies

Anti-VEGF

Bevacizumab: Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that binds VEGF. Bevacizumab is given off-label for the treatment of DME, and remains the most cost-effective treatment option among anti-VEGF medications.[47] In the BOLT study, intravitreal Bevacizumab (1.25 mg) at 6-week intervals was reported to be more effective than modified ETDRS focal/grid laser in terms of improvement in visual acuity at 12 months.[48] In DRCR Protocol T, a comparison between **bevacizumab, ranibizumab, and aflibercept**, 1-year results showed that bevacizumab thinned the retina the least.[49] However, all 3 medications had similar visual outcomes among eyes with baseline vision of 20/40 or better.[50] Intravitreal bevacizumab doses of 1.25 to 2.5mg have shown improvement in best-corrected visual acuity and reduced macular thickness on OCT at 24 months in The Pan-American Collaborative Retina Study Group.[51]

Steroids

Triamcinolone (1 mg or 4 mg) preservative-free intravitreal injection was less effective and had more side-effects for most patients with DME than focal/grid photocoagulation at 2years follow-up (Protocol B). [52]

Dexamethasone (Ozurdex) 0.7 mg biodegradable implant improved vision by at least 15 letters in 22% of patients at 3 years in the phase III MEAD study. [53] The FDA approved the 0.7 mg implant for DME, and at this dose, 41.5% of patients needed anti-glaucoma medications, with 0.6% needing glaucoma surgery. Around 60% of eyes in the 0.7 mg implant group had cataract surgery. The implant is effective for approximately 3-6 months intraocularly.

Fluocinolone acetonide (Iluvien) 0.19 mg non-biodegradable implant is a sustained release device effective for up to 3 years intraocularly. It is FDA approved to treat DME in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in IOP. [54][55] At the 0.2 μg/day dosage BCVA improvement of at least 15 letters was found in 28.7% of patients, with 38.4% needing anti-glaucoma medications and 4.8% needing glaucoma surgery. The latter figure was reduced to 0% among eyes that did not have a history of IOP elevation with a prior steroid challenge. The implant can have complications like the dexamethasone implant, including cataracts and implant migration.

Laser Photocoagulation

Before developing anti-VEGF for DME, the standard treatment for CSME was macular laser photocoagulation since the ETDRS was published in 1985. In "focal" CSME, a focal laser pattern is used to treat leaking microaneurysms identified on the FA that contribute to

the retinal oedema. In "diffuse" CSME, intraretinal leakage is noted on the FA from dilated retinal capillary beds or intraretinal microvascular abnormalities (IRMA) without isolated, discrete foci of leakage. Macular grid is done for diffuse macular oedema. Laser photocoagulation has been shown to decrease the risk of moderate visual loss (loss of 15 or more ETDRS letters) from 24% to 12% by 3 years. After laser treatment, the follow-up examination is at three months. If residual CSME is noted, OCT and FA may be performed to evaluate the benefit and location of repeat laser treatment. With the FDA approval of anti-VEGF for DME, focal/grid laser is only indicated in patients with non-ciDME. Especially in resource-limited countries with decreased access to anti-VEGF agents, macular laser remains a viable treatment option for patients with DME.

Surgery

No well-constructed studies show a definitive benefit of pars plana vitrectomy (PPV) for managing DME. The theoretical basis for PPV as a treatment option comes from reports that it increases vitreous oxygenation in ischemia, leading to decreased VEGF production, and from the observation that DME is less common among eyes with PVD.[99][100][101][102][103][104] Vitreous viscosity also significantly decreases, which may bring about a greater diffusion of pro-inflammatory cytokines away from the macula.[105] Other authors suggest PPV plus internal limiting membrane (ILM) peeling should be attempted, as its removal brings better resolution of the tractional forces at the vitreoretinal interface known to worsen DME. This procedure also prevents proliferating astrocytes from using the

ILM as a scaffold which may lead to ERM. [106] In a systematic review looking at PPV for DME, CST was significantly decreased by 102 μm, and a non-significant VA increase of 2 letters was observed. [107] However, the anatomic benefit was not maintained by the 12-month timepoint. A similar meta-analysis looking at PPV plus ILM peeling versus PPV

alone showed no significant difference in postoperative vision and macular thickness. [108] DRCR Protocol D, a prospective study of eyes with DME and VMT, found that at 6 months postop, 43% of eyes had a reduction in central subfield thickness to <250 μm. [109] However, the median VA did not change at 6 months. In 38% of eyes the median visual acuity improved by ≥10 letters, and in 22% the median VA decreased by ≥10 letters. Posthoc analysis of DRCR Protocol I showed that previously vitrectomized eyes given anti-VEGF for ci-DME had no improved clinical outcomes compared to non-vitrectomized

eyes. [110]

2.9 Previous Studies:

1-A Study was done in Department of Ophthalmology, Erciyes University Medical Faculty, Kayseri, Turkey in 2009 to study " Intravitreal bevacizumab (Avastin) for primary treatment of diabetic macular oedema"

Result: The visual acuity increased in 24 of 30 eyes (80%) during a mean follow-up time of 5.6 months. The mean baseline best-corrected LogMAR value for visual acuities of the patients before intravitreal bevacizumab injection was 1.09±0.23. After treatment, it was 0.90±0.17 at the 1-month, 0.81±0.24, at 3-month, and 0.77±0.26 at the last visit examinations and the differences were significant when compared with baseline values (for each, Po0.001). The mean oedema map values significantly decreased by 33.3% at the last visit examination when compared with preinjection values (Po0.001). Mild anterior chamber inflammation was observed in four eyes (13.3%), which resolved in a

week with topical corticosteroid. No other injection-or drug-related complications were observed.[68]

2-A Study was done in Department of Ophthalmology, Hallym University College of Medicine, Hallym University Sacred Heart Hospital, Anyang, Korea

Result: All patients completed 3 months of follow-up with a mean follow-up period of 5.26±2.39 months. The mean BCVA at baseline was 0.73±0.36 logMAR, which significantly improved to 0.63±0.41 (p=0.02), 0.58±0.36 (p=0.003), and 0.61±0.40

logMAR (p=0.006) at 1week, 1month, and 3months. Final BCVA analysis demonstrated that 15 eyes (50%) remained stable and 12(40%) improved ≥2 lines on BCVA. The mean central retinal thickness was 498.96±123.99µm at baseline and decreased to 359.06±105.97(p<0.001), 334.40±121.76 (p<0.001), 421.40±192.76µm (p=0.035) at 1 week, 1 month, and 3 months. No ocular toxicity or adverse effects were observed.[69]

3-A Study was done in America in 2009 to study " Primary intervitreal bevacizumab for diffuse diabetic macular edema: the Pan-American Collaborative Retina Study Group at 24 months "

Result: The mean age of the patients was 59.4±11.1 years. The mean number of IVB injections per eye was 5.8 (range, 1–15 injections). In the 1.25-mg group at 1 month, BCVA improved from 20/150 (0.88 logarithm of the minimum angle of resolution [logMAR] units) to 20/107, 0.76 logMAR units (P<0.0001). The mean BCVA at 24 months was 20/75 (0.57 logMAR units; P<0.0001). Similar BCVA changes were observed in the 2.5-mg group: at 1 month, BCVA improved from 20/168 (0.92 logMAR units) to 20/118 (0.78 logMAR units; P = 0.02). The mean BCVA at 24 months was 20/114 (0.76 logMAR units; P<0.0001). In the 1.25-mg group, the mean central macular thickness (CMT) decreased from 466.5±145.2 µm at baseline to 332.2±129.6 µm at 1 month and 286.6±81.5 µm at 24 months (P<0.0001).[70]

4-Study was done in America in 2008 to study " Effects of a Single Intravitreal Bevacizumab (Avastin) Injection as Treatment of Diabetic Macular Edema"

Result: Best-corrected visual acuity improved in 8 eyes (24.2%), remained stable in 15 eyes (45.5%), and decreased in 10 eyes (30.3%). Mean CMT at baseline was 560 +/- 147 µm and decreased to a mean of 464 +/- 208 µm. The CMT remained unchanged in 11 eyes (33.4%). No systemic or ocular adverse events were observed.[71]

5-A Study was done in India in 2007 to study " Intravitreal bevacizumab (Avastin) treatment of diffuse diabetic macular edema in an Indian population"

Result: All the patients received two injections of bevacizumab at an interval of six weeks per eye. No adverse events were observed, including endophthalmitis, inflammation and increased intraocular pressure or thromboembolic events in any patient. The mean baseline acuity was 20/494 (log Mar=1.338+/-0.455) and the mean

acuity at three months following the second intravitreal injection was 20/295 (log Mar=1.094+/-0.254), a difference that was highly significant (P =0.008). The mean central macular thickness at baseline was 492 microm which decreased to 369 microm (P =0.001) at the end of six months.(72)

6-Study was done in pakistan in 2018 to study " Role of Intravitreal Bevacizumab (Avastin) in Diffuse Diabetic Macular Edema"

Results: 50 eyes of 29 patients between 35 and 75 years of age (mean 49.28±8.16 years) were given Intravitreal injection of Bevacizumab. The Base line VA & central macular thickness mean were noted, significant increase in VA & decrease in macular thickness after 3 months of 3 rd administration of injection Avastin was confirmed by OCT. Two way ANOVA was used to analyze the data.(73)

7-Department of Ophthalmology, PSG Institute of Medical Sciences and Research in India on patients with CNV secondary to angioid streaks which found a statistically significant decrease in the CRT from 324.40 μm at baseline to 265.53 μm at the final visit and improved or stabilized VA in 73.33% of the eyes.(74)

Chapter 3: Materials and Methods

3.1 Study setting

The setting for this study was the archive files of diabetic macular edema patients who had intravitreal bevacizumab injections in Magrabi Eye Hospital, Sana'a, Yemen.

3.2 Study Design

This is a retrospective, Analytical study was conducted between June 2022 and December 2022 at Magrabi eye hospital, in Sana'a, Yemen

3.3 Study population

Study population is macular edema patients who underwent intravitreal bevacizumab injections in Magrabi Eye Hospital 2020-2021

3.4 Inclusion criteria

Patients with the history of macular edema in association with diabetes maletus admitted in the retinal unit in Magrabi Eye Hospital, Sana’a, Yemen and need medical intervention regardless of age.

3.5 Exclusion criteria

Hemorrhagic retinopathy

Retinopathy caused by hypertension

Retinal vien occlusion

Age related macular degeneration

And Any other macular edema not caused by diabetes mellitus

3.6 Sample size & Methods

It's all files of diabetic macular edema patients who treated with intravitreal bevacizumab injections in between January 2020 and December 2022 at Magrabi eye hospital in Sana'a Capital City of Yemen.

3.7 Statistical analysis

The data was analyzed using statistical software (SPSS, version 25.0, SPSS Inc, Chicago, Illinois, USA).

The paired t-test was used for comparison of preoperative and postoperative VA, BCVA and central retinal thickness. For all statistical tests, a p value < 0.05 was considered statistically significant.

3.8 Ethical Considerations

Approval was obtained from 21September University of Medical and Applied Sciences (21UMAS), from community medicine department in 21September University of Medical and Applied Sciences (21UMAS) and from Magrabi eye hospital. The study was conducted under the current ethical guidelines for retrospective studies. The study was taken from Magrabi eye hospital archive files and the researchers undertake to maintain the personal data as strictly confidential and to use anonymised data to the extent feasible

CHAPTER 4 : Result

The results of the study are summarized in table No.(1)

Table No. (1) showing the distribution of participants' characteristics for injections to improve visual acuity and macular oedema thickness;

Variable	characteristics	Fre	%
Gender	Male	**129**	**52.7**
	Female	**116**	**47.3**
AGE	20-40	**8**	**3.3**
	40-60	**154**	**62.9**
	more than 60	**83**	**33.9**
Length of Diabetes years	1 -10 years	**136**	**55.5**
	10-20years	**103**	**42.0**
	more than 20	**6**	**2.4**
Injected Eye	OD Right eye	**119**	**48.6**
	OS left eye	**126**	**51.4**
Length of Follow up/month	once month	**52**	**21.2**
	Two month	**44**	**18.0**
	Three month	**41**	**16.7**
	Four month	**28**	**11.4**
	Five month	**22**	**9.0**
	Sixth month	**58**	**23.7**
OCT Outcomes	**Improved**	**184**	**75.5**
	Not improved	**16**	**6.5**
	worse	**44**	**18.0**
Visual Acuity Outcomes	**Improved**	**135**	**55.1**
	Not improved	**110**	**44.9**
BCVA Outcomes	**Improved**	**176**	**71.8**
	Not improved	**69**	**28.2**
Hx of other Chronic diseases	Non	**195**	**79.6**
	HTN	**44**	**18.0**
	Cataract	**4**	**1.6**
	CVA	**2**	**.8**

Result: Through the results of the table above, it was found that the study sample consisted of (245), of whom (52.7%) were Males and (47.3%) were Females. (62.9%), (33.9%) and (3.3) for the age groups of (40-60) years, (>60) years and (1-10) years respectfully. The results also showed through the Length of Diabetes per years that the percentage (55.5%) for the category (1- 10) years, with a rate of (42.0%) for the category of (10-20) years, and a rate of (2.4%) for the category over (20) years. Also, the results of injections to the eye showed that the Left eye reached (51.4%), while the Right eye reached (48.6%).

The Length of Follow up was (21.2%) in the first month, (18.0%) in the second month, (16.7%) in the third month, (11.4%) in the fourth month, (9.0%) in the fifth month and (23.7%) in the sixth month. OCT Outcomes results were improved by (75.5%), while the patients that not improved and had worsen was (6.5%) and (18.0) respectively. The Visual Acuity outcomes revealed that (55.1%) of patients are improved, and (44.9%) not improved. While the BCVA Outcomes revealed that (71.8%) of patients are improved, and (28.2%) not improved. The results also showed that the Hx of other chronic diseases was non by (79.6%) and high blood pressure by (18.0%), while cataract was (1.6%) and CVA was (0.8%).

Demographic data:

1. Age:

Table No. (2) shows the frequencies and percentages of the research sample in relation to the age variable;

Age years	Frequency	Percentage
20-40	8	3.3
40-60	154	62.9
more than 60	83	33.9

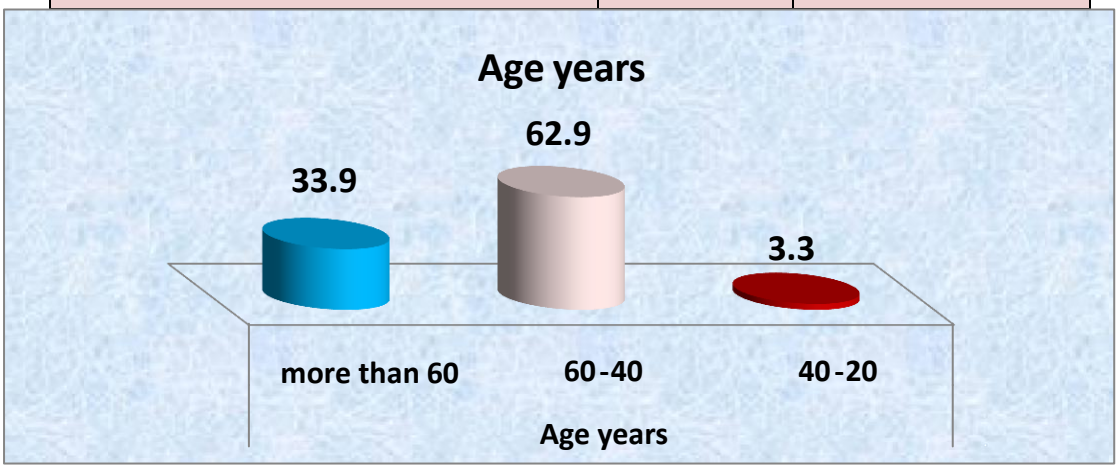

Figure No. 1

It was shown through the table and the figure above that the age group with the highest proportion (40-60) amounted to (62.9%) Followed by the age group over (60) years with a rate of (33.9%) and the age group (20-40) with a rate of (3.3%).

2. Sex:

Table No. (3) shows the frequencies and percentages of the sex variable.

Gender	Frequency	Percentage
male	**129**	**52.7**

female	**116**	**47.3**

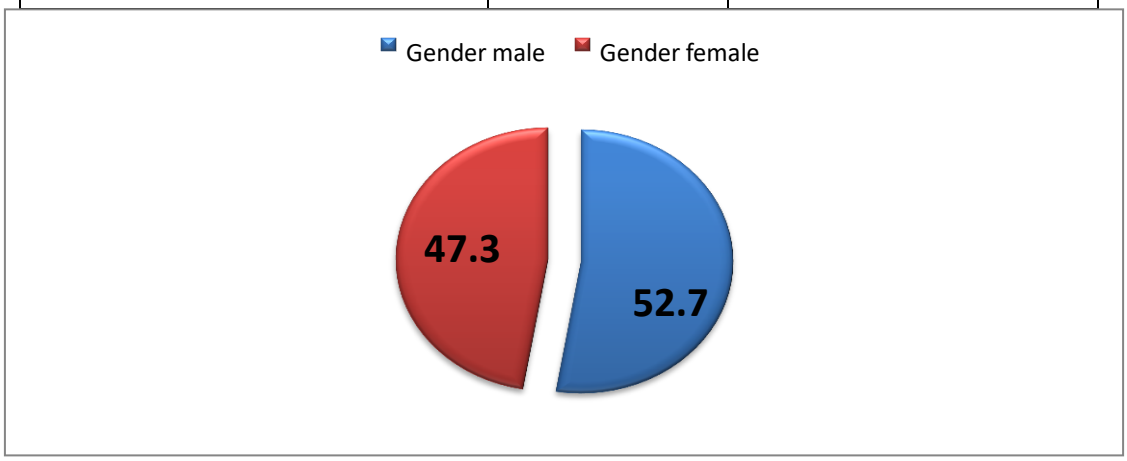

Figure No. 2

It was shown through the above table and figure that the number of males is the largest, amounting to (52.2%), while the percentage of females amounted to (47.3%).

3. Length of Diabetes years:

Table No. (4) shows the frequencies and percentages for Length of Diabetes years;

Length of Diabetes years	Frequency	Percentage
1-10 years	136	55.5
10-20 years	103	42.0
more than 20	6	2.4

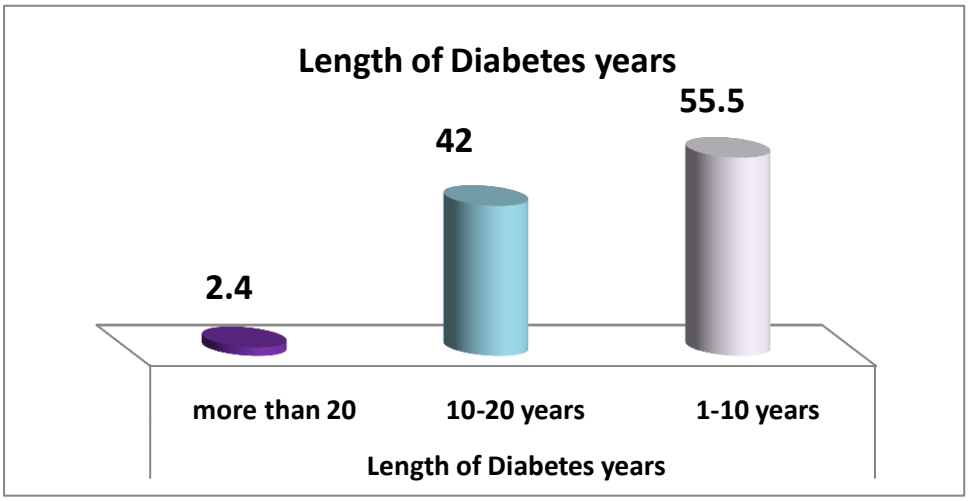

Figure No. 3

The results also showed through Length of Diabetes per years that the percentage (55.5%) for category (1- 10) years old, with a rate of (42%) for the category of (10-20)years, and a rate of (2.4%) for the category over(20) years.

4. Injected eye:

Table No. (5) shows the frequencies and percentages of the number of eye injections.

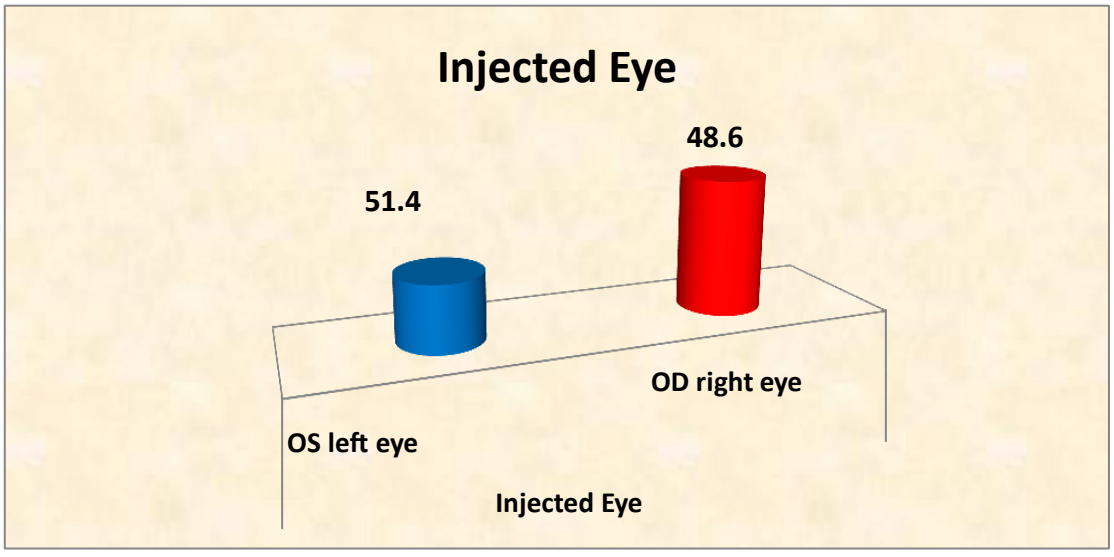

Figure No. 4

Injected Eye	Frequency	Percentage

OS left eye	126	51.4
OD right eye	119	48.6

It was shown through the above table and figure that the number of times of injections to the left eye was the highest percentage (51.4%), while the percentage of injections to the right eye was (48.6%).

5. Length of Follow up/month

Table No. (6) shows the Length of Follow up per month;

Length of ollow up month		
	Frequency	Percent
1.0	52	21.2
2.0	44	18.0
3.0	41	16.7
4.0	28	11.4
5.0	22	9.0
6.0	58	23.7
Total	245	100.0

6. OCT Outcomes:

Table and Figure No. (7) showing the frequencies and percentages of OCT Outcomes.

OCT Outcomes	Frequency	Percentage
Improved	185	75.5
no improved	16	6.5
Worse	44	18.0

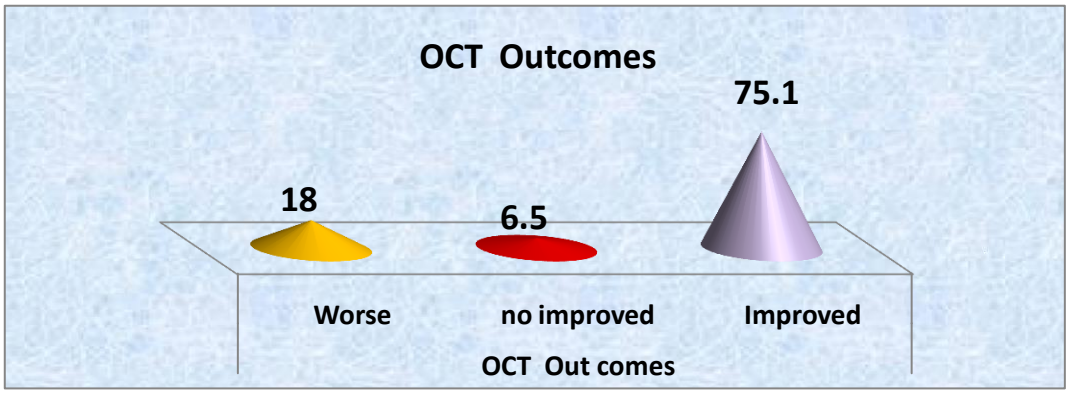

Figure No. 5

It was shown through the table and the figure above that the improvement of vision amounted to (75.5%), while those who did not improve vision by (6.5%), and the worse by (18%).

Table No. (8) shows the difference test between two related samples OCT before injection – OCT after injection;

		Paired Differences					t	df	p:value
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	OCT before injection – OCT after injection	63.37	148.9	9.51	44.63	82.12	6.660	245	.000

The results of testing two related samples showed that there is a significant difference between the two variables, as the probability value (0.00) indicated that it is less than the significance level (0.05), which indicates that there is a difference between OCT before injection – OCT after injection.

7. Visual Acuity Outcomes:

8. BCV Outcomes:

Table No. (9) showing the differences between Outcomes - BCV Outcomes (improved - non improved).

			BCVA outcomes		Total	x2	p. value
			improved	non improved			
Visual acuity Outcomes	improved	fre	124	11	135		.000
		%	91.9%	8.1%	100.0%	60.381[a]	
	non improved	Count	51	59	110		
		% total	46.7%	53.3%	100.0%		
Total		fre	176	69	245		
		%	71.8%	28.2%	100.0%		
		% of Total	71.8%	28.2%	100.0%		

Table No. (10) showing the Paired Differences between Visual acuity Outcomes - BCV Outcomes (improved - non improved).

		Paired Differences					t	df	p. value
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Visual acuity Outcomes – BCVA outcomes	.1639	.4777	.0306	.1037	.2242	5.361	245	.000

Through the results of the table above, it was found that there are statistically significant differences between Visual acuity Outcomes - BCV Outcomes (improved - non improved), as indicated by the value of (.000) = p, which is less than the level of significance (0.05).

Table No. (11) showing the differences test between Baseline VA and VA at last visit.

			VA at last visit				Total	p:value
Baseline VA	mild	Fre	mild	moderate	Sever	profound low vision		
		%	75.90%	15.50%	0.00%	8.60%	100.00%	0.00
	moderate	Fre	27	18	8	12	65	
		%	41.50%	27.70%	12.30%	18.50%	100.00%	
	sever	fre	4	15	3	10	32	
		%	12.50%	46.90%	9.40%	31.30%	100.00%	
	profound low vision	fre	5	9	12	64	90	
		%	5.60%	10.00%	13.30%	71.10%	100.00%	

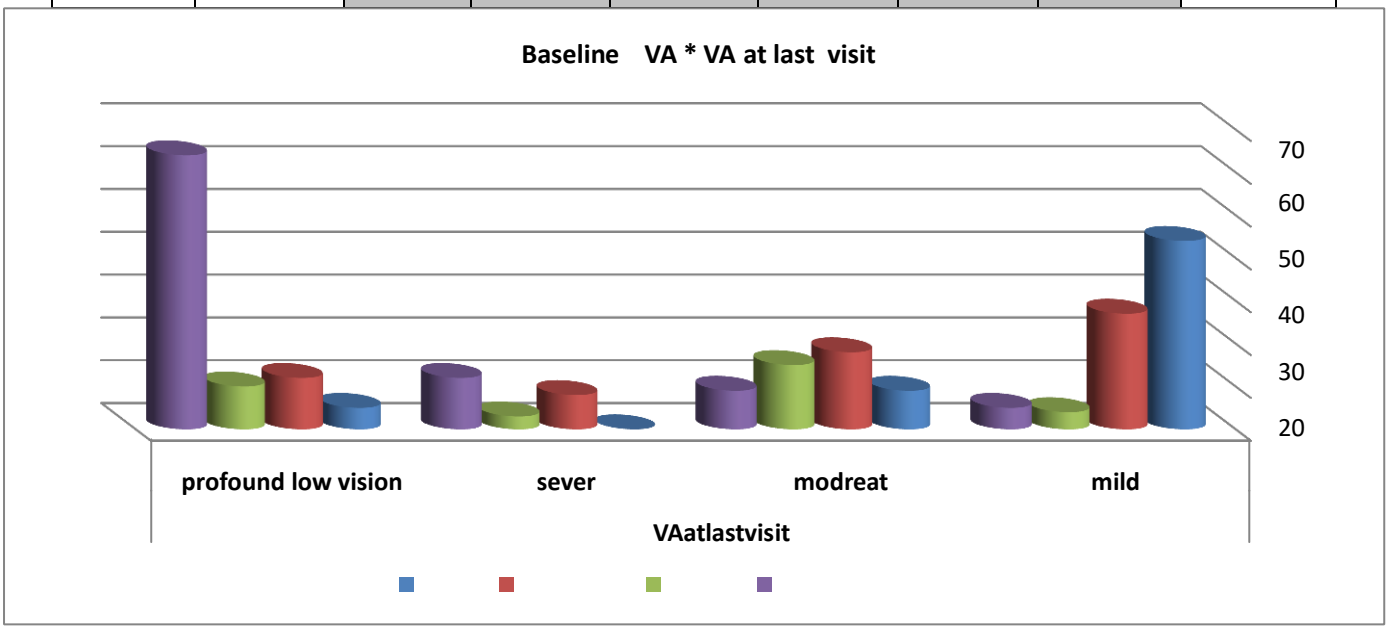

Figure No. 6

The results of the table and the figure above showed that there are significant differences between the two variables, as the probability value (0.00) showed that it is less than the significance level (0.05), which indicates that there is a difference between the Baseline VA and VA at last visit.

Table No. (12) shows the difference test between Baseline VA – BCVA.

			Baseline VA				Total	
			mild	modreat	sever	profound low vision		p:value
BCVA	mild	fre	50	47	13	21	131	.000
		%	38.2%	35.9%	9.9%	16.0%	100.0%	
	moderate	fre	4	4	14	14	36	
		%	11.1%	11.1%	38.9%	38.9%	100.0%	
	sever	fre	1	7	3	12	23	
		%	4.3%	30.4%	13.0%	52.2%	100.0%	
	profound low vision	fre	3	7	2	43	55	
		%	5.5%	12.7%	3.6%	78.2%	100.0%	

The results of the table above and figure below showed that there are significant differences between the two variables, as the probability value (0.00) showed that it is less than the significance level (0.05), which indicates that there is a difference between Baseline VA and BCVA.

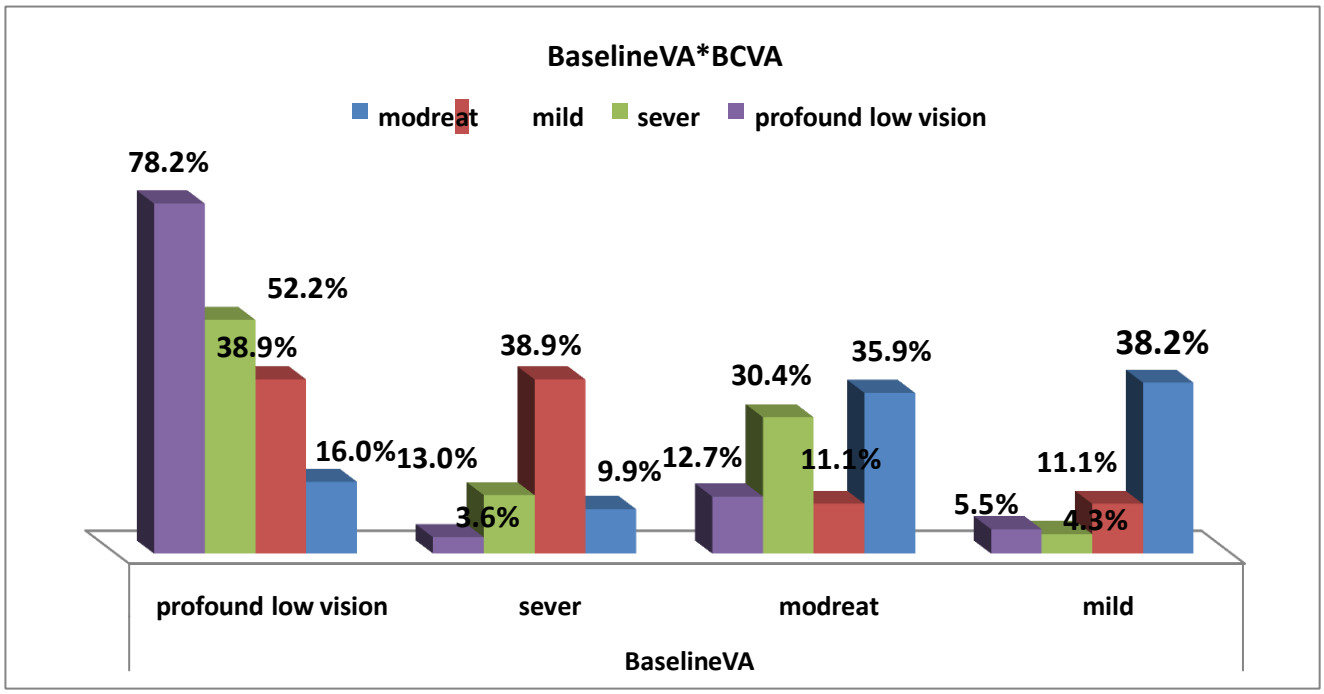

Figure No. 7

Table (13) shows the difference test between VA at last visit and BCVA.

			VA at last visit				Total	p:value
			mild	moderate	sever	profound low vision		
BCVA	mild	fre	74	35	9	13	131	.000
		%	56.5%	26.7%	6.9%	9.9%	100.0%	
	moderate	fre	5	13	10	8	36	
		%	13.9%	36.1%	27.8%	22.2%	100.0%	
	sever	fre	1	1	4	17	23	
		%	4.3%	4.3%	17.4%	73.9%	100.0%	
	profound low vision	fre	0	2	0	53	55	
		%	0.0%	3.6%	0.0%	96.4%	100.0%	

The results of the above table showed that there are significant differences between the two variables, as the probability value (0.00) showed that it is less than the significance level (0.05), which indicates that there is a difference between the last visit BCVA.

9. Hx of other Chronic diseases:

Table (14) showing the frequencies and percentages of OCT Outcomes.

Hx of other Chronic diseases	Frequency	Percentage
HTN	**44**	**18.0**
NON	**195**	**79.6**
CVA	**2**	**.8**
Cataract	**4**	**1.6**

It was shown through the above table and figure that the incidence of Non (79.6%), while chronic diseases such as high blood pressure (18%) and CVA (.8%), while glaucoma was (1.6%).

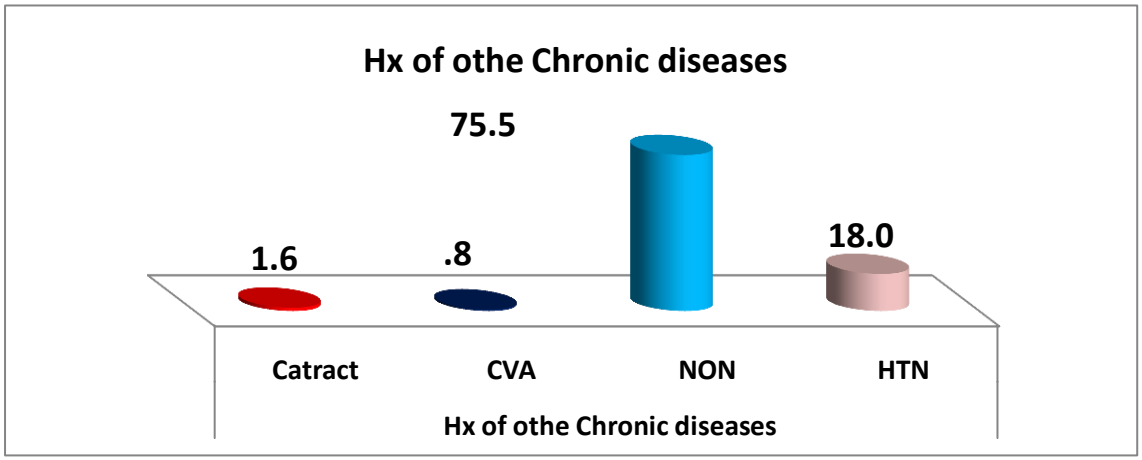

Figure No. 8

CHAPTER 5 : Discussion

Diabetic macular edema is one of the leading causes of avoidable blindness in diabetic adults. However; in Yemen there are a multiple issues including low

economic status and low health care status, in addition to poor education status of the patients.

Our study was conducted to evaluate the efficacy of intravitreal injection Bevacizumab in patients with diabetic macular edema in term of detect the improvement of visual acuity, macular edema and central retinal thickness according to the ophthalmological parameters[Optical Coherence Tomography (OCT), Visual Acuity (VA) and Best-Corrected Visual Acuity (BCVA)]. The data were collected from the medical records of the patients at Magrabi eye hospital, Sana'a, Yemen. The study sample was consisted of (n:245) eyes of 173 patients. The data analysis was performed on the cleaned datasets using SPSS Software (SPSS inc., Chicago.II.USA, version 25.0). The results of this retrospective study establish that treatment with intravitreal Bevacizumab injections provided clinically and statistically significant improvement in OCT parameters and visual acuity (VA) in patients with macular oedema secondary to diabetic retinopathy. Our study found that the study sample consisted of (245) eyes, of whom (52.7%) were Males and (47.3%) were Females. (62.9%), (33.9%) and (3.3) for the age groups of (4060) years, (>60) years and (1-10) years respectfully. It also found that the Length of Diabetes per years in those patients was the percentage (55.5%) for the category (1- 10) years, with a rate of (42.0%) for the category of (10-20) years, and a rate of (2.4%) for the category over (20) years.

The Length of Follow up of the patients before and after treatment was (21.2%) in the first month, (18.0%) in the second month, (16.7%) in the third month, (11.4%) in the fourth month, (9.0%) in the fifth month and (23.7%) in the sixth month.

In our analysis, the mean average change in BCVA post intravitreal

Bevacizumab injections was 0.16, which mean that BCVA improved by (71.8%), while (28.2%) not improved. The average reduction in CRT is 148.9 microns, which mean that OCT outcomes improved by (75.5%), while (24.5%)

not improved. Also Visual Acuity outcomes post intravitreal Bevacizumab injections revealed that (55.1%) of eyes are improved, while (44.9%) not improved.

Importantly, it is observed that in (20.4%) of cases a significant decrease in CRT was noted without a significant improvement in vision. This lack of improvement in visual acuity could be owing to other concomitant ocular diseases such as Hypertension, cataract, glaucoma, macular ischemia.

Similarly, BCVA and anatomic CRT improvements with Bevacizumab treatment in our set up were comparable to an interventional retrospective case series conducted at the Department of Ophthalmology, PSG Institute of Medical Sciences and Research in India on patients with CNV secondary to angioid streaks which found a statistically significant decrease in the CRT from 324.40 µm at baseline to 265.53 µm at the final visit and improved or stabilized BCVA in 73.33% of the eyes.[73]

Another study comparing with our study was done in America in 2008 to study " Effects of a Single Intravitreal Bevacizumab (Avastin) Injection as Treatment of Diabetic Macular Edema" The Result Best-corrected visual acuity improved in 8 eyes (24.2%), remained stable in 15 eyes (45.5%), and decreased in 10 eyes (30.3%). Mean CMT at baseline was 560 +/- 147 µm and decreased to a mean of 464 +/- 208 µm. The CMT remained unchanged in 11 eyes (33.4%). No systemic or ocular adverse events were observed.[71]

5.1 Strength and Limitations of the study

Even though this study had several strengths, including fundus examinations performed by skilled ophthalmologists and the use of optical coherence

tomography were two of them. It's also the first study to look into the scope of macular edema in Yemen and the factors that contribute to it. Another aspect of this study was the huge sample size and number of independent factors.

Using a retrospective study design, average fasting blood sugar was another drawback in this study area due to a lack of HbAlc facilities.

CHAPTER 6 : Conclusion And Recommendation

The present study concluded that research work showed that Bevacizumab significantly improved visual acuity and anatomical morphology in Magrabi

eye hospital, Sana'a, Yemen patients with visual impairment due to macular edema secondary to diabetic retinopathy. However, the important issues that mentioned in this study related to pre and post injection decreases the chance of improvement. Therefore, We recommend the following:

1-further researchers to continue our effort to cover others eye's hospitals to evaluate efficacy of intravitreal bevacizumab injection.

2-Educate the patients about disease and the consequences in case of Poor glycemic control, Irregular follow up of patients pre and post intravitreal bevacizumab inection and having been ill for more than ten years.

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Questionnaires

1-	Patient name:			
2-	Sex	M, F (……...)		
3-	Age	20-40 (……)	40-60 (……)	More Than 60 (……)
4-	Stage of disease	Early ( )	Late ( )	
6-	OCT	Before ( )	After ( )	
7-	BCVA	Before (…….)	After (……..)	
8-	Complication			

Work plane with time table

ACTIVITIES	JUL 2022	AUG 2022	SEP 2022	OCT 2022	Nove 2022	Dec 2022
Filed visit& Preparation of research proposal						
Discussion of research proposal						
Approval of final proposal by department						
Data collection						

Analyze data and display result						
Writing the final report of the thesis						
Print and publish the thesis						

مستشفيات ومراكز مغربي

MAGRABI HOSPITALS & CENTERS

٢٠٢٢/١٠/٢٤م

المحترم المدير التنفيذي

الأستاذ/ عطا طاهر

تحية طيبة وبعد

الموضوع/استخراج ملفات من الأرشيف

اتقدم اليكم بأطيب تحية وبالإشارة للموضوع أعلاه ارجو منكم التوجيه باستخراج ملفات من الأرشيف لبعض حالاتي ليتم تعريف طلاب الجامعة عليها، مع العلم بأننا سنحتاج الملفات داخل المستشفى فقط وبحضوري شخصياً مع الطلاب.

د.نبيل طارش

رئيس قسم الشبكية والجسم الزجاجي