Correlation between Diabetic Control and Visual Outcomes of Aflibercept versus Bevacizumab Therapy in Iraqi Patients with Diabetic Macular Edema

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Article Info:

Received 1 Feb 2026
Revised 25 Feb 2026
Accepted 1 Mar 2026
Published 31 Mar 2026
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DOI: https://doi.org/10.32947/ajps.v26i1.1385

Abstract:

Background: Diabetic retinopathy represents a significant burden on the public healthcare system in Iraq. While anti-vascular endothelial growth factor (anti-VEGF) agents have revolutionized management. However, a limited number of studies on the effectiveness of these agents and their comparison in Iraqi patients.

Aim: This study aims to evaluate the clinical outcomes of intravitreal aflibercept compared to bevacizumab in Iraq.

Methods: A prospective study was conducted at the Department of Ophthalmology, Ghazi al-Hariri Surgical Hospital, Baghdad Medical City, from June 2024 to September 2025, involving 120 patients (169 eyes). Participants were stratified into two groups: Group A received aflibercept (n=53), and Group B received bevacizumab (n=67). Baseline pretreatment data and data collected one month after the third anti-VEGF dose were collected. Visual acuity (VA), measured by *LogMar*, and central subfield thickness (CST) are the main clinical outcomes. Baseline pretreatment glycated hemoglobin was recorded, and one month posttreatment.

Results: Both groups demonstrated significant functional and anatomic improvements (p-value < 0.001 in all arms); however, aflibercept showed superior anatomic outcomes (*ΔCST*: 19.51% vs. 14.14%, p-value < 0.001, for IVA and IVB, respectively) and visual gains (*ΔLogMAR*: 0.188 ± 0.126 vs. 0.139 ± 0.120, p-value 0.011, for Group A and Group B, respectively). The anti-VEGF agents were effective independently of the glycemic control.

Conclusion: Aflibercept was clinically superior to bevacizumab.

Keywords: Aflibercept, Bevacizumab, Blood Glucose, Diabetic Retinopathy, Glycated Hemoglobin A, Macular Edema

العلاقة بين ضبط مستوى السكر في الدم ونتائج الرؤية لعلاج أفليبرسبت مقابل بيفاسيزوماب لدى مرضى عراقيين مصابين بالوذمة البقعية السكرية

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الخلاصة:

الخلفية: يُمثل اعتلال الشبكية السكري عبئًا كبيرًا على نظام الرعاية الصحية العامة في العراق. ورغم أن مضادات عامل نمو بطانة الأوعية الدموية (مضادات(VEGF قد أحدثت ثورة في إدارة المرض، إلا أن الآثار الاقتصادية لاختيار العلاج لا تزال مصدر قلق بالغ. ومع ذلك، لا يزال عدد الدراسات التي تتناول فعالية هذه الأدوية ومقارنتها لدى المرضى العراقيين محدودًا.

الهدف: تهدف هذه الدراسة إلى تقييم النتائج السريرية لحقن أفليبرسبت داخل الجسم الزجاجي مقارنةً ببيفاسيزوماب في العراق.

المنهجية: أُجريت دراسة استباقية في قسم طب العيون بمستشفى غازي الحريري الجراحي، مدينة بغداد الطبية، في الفترة من يونيو 2024 إلى سبتمبر 2025، وشملت 120 مريضًا (بإجمالي 169 عينًا). قُسّم المشاركون إلى مجموعتين: المجموعة (أ) تلقت أفليبرسبت (ن = 53)، والمجموعة (ب) تلقت بيفاسيزوماب (ن = 67). جمعت بيانات خط الأساس قبل العلاج، بالإضافة إلى بيانات جمعت بعد شهر واحد من الجرعة الثالثة من مضادات عامل نمو بطانة الأوعية الدموية .(VEGF) يُعد حدة البصر(VA) ، المقاسة بوحدةLogMAR ، وسماكة المنطقة المركزية للشبكية (CST) من أهم النتائج السريرية. سجل مستوى الهيموجلوبين السكري قبل العلاج، وبعد شهر واحد من العلاج.

النتائج: أظهرت المجموعتين تحسناً وظيفياً وتشريحياً ملحوظاً؛ ومع ذلك، أظهر أفليبرسبت نتائج تشريحية أفضل حيث كان مقدار التغيير في سمك منطقة البقعة الصفراء 19.51% مقابل 14.14%، للمجموعتين (أ) و(ب) على التوالي وتحسناً في حدة البصر (التغير في قيمة لوغمار) 0.188 ± 0.126 مقابل 0.139 ± 0.120، للمجموعتين (أ) و(ب) على التوالي. كانت مضادات عامل نمو بطانة الأوعية الدموية فعالة بغض النظر عن مستوى السكر في الدم.

الخلاصة: أظهر أفليبرسبت تفوقًا سريريًا على بيفاسيزوماب.

الكلمات المفتاحية: أفليبرسبت، بيفاسيزوماب، سكر الدم، اعتلال الشبكية السكري، الهيموجلوبين السكري أ، وذمة البقعة الصفر

Introduction:

Diabetes Mellitus (DM) represents a major global health challenge, affecting more than 500 million patients in the world in 2021, a number projected to surge to around 800 million by 2045 [(1)]. Among the chronic complications of DM, diabetic retinopathy stands out as a major cause of severe vision-related disability and even blindness. Within the spectrum of diabetic retinopathy, diabetic maculopathies, particularly diabetic macular edema (DME) [(2)], poses the most significant threat to vision. DME specifically targets the macula, the specialized region in the retina responsible for central, sharp, and color vision, thereby impacting a patient's quality of life (QoL) and ability to perform daily tasks. Intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents have shown promise in the treatment of diabetic macular edema (DME).

A precise understanding of the different vascular endothelial growth factor (VEGF) isoforms is crucial for distinguishing the mechanisms of action of various anti-VEGF agents. The main target of intravitreal anti-VEGF agents is VEGF-A. However, they are not purely selective. Some agents, including aflibercept, a fusion protein that acts as a decoy receptor, also bind other isoforms, including VEGF-B [(3, 4)] and PlGF [(4, 5)]. In addition to this multiple-target property, prolonged duration of

action and high potency suggest a differential metabolic impact. These multiple targets could lead to off-target systemic effects [3]. VEGF-B plays a key role in systemic metabolism and is strongly associated with T2DM, thereby exerting an axial role in glucolipid metabolism [6]. VEGF-B affects insulin secretion and glucose homeostasis [6]. The inhibition of VEGF-B could lead to a more noticeable systemic effect on glucose and lipid metabolism caused by aflibercept than by bevacizumab, which mainly targets VEGF-A [3]. Moreover, despite the high affinity of bevacizumab to VEGF-A, aflibercept has a higher affinity and more prolonged VEGF inhibition [7]. These differences suggest that the choice of a specific anti-VEGF agent may be a pivotal factor in clinical efficacy and safety.

Regarding the intravitreal use of aflibercept and bevacizumab, several studies were published from Iraq. For example, Hussein & Hasan (2018) reviewed the indications for intravitreal bevacizumab injection. They found that diabetic retinopathy complications, mainly DME, are the most common uses of bevacizumab, followed by vitreous hemorrhage, persistent neovascularization of disc (NVD) or neovascularization elsewhere (NVE) in proliferative diabetic retinopathy, and lastly neovascular glaucoma. Other indications include retinal vein occlusion (RVO), such as central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO). Furthermore, other indications include choroidal neovascularization, including neovascular age-related macular degeneration (nAMD) and myopia, central serous chorioretinopathy (CSCR), and circumscribed choroidal hemangioma [8].

Another study by Alkazraji *et al.* (2023) confirmed the effectiveness of aflibercept in AMD [9]. Hussein *et al.* (2023) also affirmed these results in age-related macular degeneration (AMD) [10]. Lastly, Hind A. Mahdi (2024) compared the short-term effect of intravitreal bevacizumab and aflibercept (i.e., the initial three-month doses) in patients with DME and found that aflibercept was superior in improving VA, whereas bevacizumab was more effective in reducing macular thickness [11].

Aims of the study

The study aims to evaluate clinical outcomes after loading initial intravitreal therapies with aflibercept vs. bevacizumab, including functional changes (visual acuity (VA)), anatomical changes (central subfield thickness (CST)), and glycemic control (HbA1c).

Patients and methods:

This is a prospective, single-center, interventional study. The study was conducted at the Department of Ophthalmology, Ghazi Al-Hariri Surgical Hospital, Baghdad Medical City, Baghdad, Iraq, which provides bevacizumab or aflibercept to many ophthalmic patients in Iraq. Pretreatment and one-month posttreatment data were collected from patients' medical records and through face-to-face interviews conducted from June 2024 to September 2025. The study is a registered phase 4 trial on ClinicalTrials.gov (identifier NCT06850571).

A total of 120 patients completed the 3-month study period, out of 412 enrolled. Patients enrolled in this study were adults of both sexes with T2DM. They were diagnosed with diabetic maculopathies according to ETDRS criteria, which include reduced VA (6/9–6/90) and increased CST on OCT (>250 μm), for whom anti-VEGF therapy is recommended. Those patients did not receive IVT (aflibercept or bevacizumab), laser photocoagulation, or surgical intervention (e.g., PPV) in the last 3 months, or intravitreal corticosteroids in the previous 6 months.

Patients excluded from this study include patients with T1DM, patients with T2DM on an insulin-based regimen, patients who had been treated with IVT of an anti-VEGF within the previous 3 months or intravitreal

corticosteroids for 6 months or prior intraocular surgeries or prior macular photodynamic or photocoagulation treatment within 3 months, as ocular surgeries and laser therapies may induce inflammation, leading to edema. Also, patients with uncontrolled hypertension or a history of prior thromboembolic events, as systemic inhibition of VEGF may cause thromboembolic events or even other CV complications. Additionally, patients who have undergone a major surgery within the previous 1 year or are planning a major surgery within the next 6 months, patients with coagulation abnormalities, or current use of an anticoagulant medication. The use of anti-VEGF agents may cause hemorrhagic macular infarction, which is also excluded. Patients with elevated IOP (i.e., 25 mmHg or more) and the presence of vitreous hemorrhage and/or iris neovascularization, patients with chronic kidney disease (CKD), as a patient's condition, may be exacerbated by the use of anti-VEGF agents, pregnant or nursing women, as they are considered exclusion criteria for systemic co-morbidities are all causes or exclusion from the study.

Patients' Grouping

Those patients received either bevacizumab or aflibercept at Ghazi Al-Hariri Surgical Hospital. Patients are divided into 2 groups, which are further divided into 2 subgroups based on the types of medication used and the number of eyes treated. These groups are coded as A1, A2, B1, and B2. The letters "A" or "B" denote "aflibercept" or "bevacizumab," respectively, and the numbers "1" or "2" represent the number of eyes treated per patient. Enrolled patients were divided into 2 main groups according to the type of therapy:

- Group A: patients treated with aflibercept (*Eylea*®, Bayer, available in 4 mg/0.1 ml vial, 2 mg/0.05 ml was administered) for 3 consecutive months.
- Group B: patients treated with bevacizumab (*Avastin*®, Roche, available in 100 mg/4 ml vial, 1.25 mg/0.05 ml was administered).

All patients were evaluated for the study parameters before starting the study (day 0) and after 3 months of treatment. Patients were further divided into subgroups according to the number of treated eyes:

- Group A1: single eye treatment
- Group A2: both eyes treatment
- Group B1: single eye treatment
- Group B2: both eyes treatment

As per the Iraqi guideline, patients received either intravitreal injection of bevacizumab or aflibercept as initial therapy for 3 consecutive months [(12)]. Each patient received 3 monthly doses of either bevacizumab (*Avastin*®, Roche, available in a 100 mg/4 mL vial; 1.25 mg/0.05 mL was injected) or aflibercept (*Eylea*®, Bayer, available in a 2 mg/0.05 mL vial; 2 mg/0.05 mL was injected). The Iraqi Ministry of Health (MoH) supplies these 2 products through the State Company for Drugs and Medical Appliances (KIMADIA), which is responsible for managing contracts with manufacturers or marketing authorization holders. A topical anesthetic was applied [(12)]. Benzocaine eye drops were frequently used in daily practice in the hospital to relieve injection site and ocular pain [(13)]. Pre-injection antiseptic agents (povidone iodine 5%) and post-injection topical antibiotics are used to reduce the risk of injection-related infections. The specialist ophthalmologist was responsible for administering anti-VEGF agents.

Glycated hemoglobin A1c (HbA1c)

Poor glycemic control is a remarkable predictor of poor functional (i.e., visual acuity) and anatomical (i.e., retinal thickness) responses [(14)]. It reflects the glycemic control over the last 3 months [(15)]. According to the American Diabetes Association (ADA), a patient can be considered to be in "good control" if HbA1c is less than 7%, "poor control" if

HbA1c is between 7% and 9%, and "very poor control" if HbA1c is greater than 9%. For older age patients, it is accepted by ADA guidelines to consider a patient in "good control" if the HbA1c level is up to 8% [16, 17].

Ethical Approval

Ethical approval was obtained from the Ethics Committee at the College of Pharmacy/ Mustansiriyah University, with approval number 72 dated June 4, 2024, and reference number 172. Additionally, approval was obtained from the Ministry of Health on February 12, 2024, with reference number 6243. Patients' written consent to participate in this study was obtained after they were informed of the study goals.

Statistical Analysis

Statistical analysis was performed to compare visual outcomes, CST, and glycemic control between the 2 groups. Statistical analysis is based on the number of patients included in the study and the number of eyes treated.

GraphPad Prism version 8.0 and the Statistical Package for the Social Sciences (SPSS 25.0; IBM® SPSS® Statistics 25.0) were used for statistical analysis. A *p-value* less than 0.05 is considered a significant difference.

Statistical analysis was conducted to assess associations, correlations, and the effects of various parameters on the outcome. The values analyzed include baseline pretreatment and posttreatment data. Statistical analysis was performed using the independent t-test for normally distributed variables (i.e., ΔCST) and the Mann-Whitney U test for non-normally distributed variables (i.e., ΔLogMAR).

Results:

This study recruited 412 patients diagnosed with diabetic maculopathies. However, data collection and follow-up were completed for only 120 patients during the 3-month study period. Patients withdrew or were excluded from the study due to many reasons, including lost contact, starting insulin therapy, different health issues, the need for surgical intervention, non-adherence, and voluntary withdrawal from the study. Sociodemographic and clinical data of patients are shown in Table 1.

Table 1: Sociodemographic and clinical data of patients

Patients' group		Group A	Group B	Total	p-value
No. (%)		53 (44.17%)	67 (55.83%)	120 (100%)	
Age		61.47± 10.76	57.94 ±12.96	59.5 ±12.12	0.113
Sex	*Male*	32 (60.38%)	40 (71.15%)	72 (60%)	0.940
	Female	21 (39.62%)	27 (28.85%)	48 (40%)	
BMI (kg/m^2)	*BMI* (mean ± *SD)*	27.3 ± 4.8	27.2 ± 5.3	27.2 ± 5.1	0.915
	Normal BMI (less than 25)	22 (41.5%)	27 (40.3%)	49 (40.8%)	
	Overweight (25 – 30)	13 (24.5%)	21 (31.3%)	34 (28.3%)	
	Obesity class I (>30 – 35)	13 (24.5%)	12 (17.9%)	25 (20.8%)	
	Obesity class II (>35 – 40)	5 (9.5%)	7 (10.4%)	12 (10%)	
Smoking status	*Smokers*	18 (33.96%)	21 (31.34%)	39 (32.5%)	0.890
	Ex-smokers	5 (9.43%)	8 (11.94%)	13 (10.83%)	
	Non-smokers	30 (56.60%)	38 (56.72%)	68 (56.67%)	
Duration of diabetes (years)		13.8 ± 8.5	14.9 ± 3.5	14.4 ± 4.9	0.350
Diagnosis of diabetic maculopathy	*Newly diagnosed (%)*	16 (30.2%)	35 (52.2%)	51 (42.4%)	**< 0.001**
	Previously diagnosed (%) (Duration in months)	37 (69.8%) (19.8 ± 2.1)	32 (47.8%) (17.6 ± 5.7)	69 (57.7%) (18.8 ± 2.8)	
Previously co-existing diseases	*Hypertension*	34 (64.15%)	49 (73.13%)	83 (69.17%)	**0.023**
	Dyslipidemia	21 (39.62%)	28 (41.79%)	49 (40.83%)	0.082
	Other CVDs	14 (26.42%)	17 (25.37%)	31 (25.83%)	0.086
	Other diseases [B]	8 (15.09%)	17 (25.37%)	25 (20.83%)	**0.022**
Surgical history		13 (24.53%)	16 (23.88%)	29 (24.17%)	0.087

Data expressed as N: number, %: percentage
P≥ 0.05 is considered nonsignificant (unpaired T-test)
P< 0.05 is considered significant (unpaired T-test)
A: Fisher's Exact Test was used.
B: Other diseases mentioned by the patients include: persistent allergic rhinitis, asthma, gout, chronic obstructive pulmonary disease (COPD), psoriasis, peptic ulcer, multiple sclerosis, dementia, Alzheimer's disease, benign prostatic hyperplasia (BPH), and unspecified gynecologic diseases, in addition to a patient with a history of thyroidectomy and on thyroxine.

Regarding treatment results, 75 eyes received aflibercept. The statistics for patients who completed the study are listed in Table 2. The mean pretreatment CST was 395 µm, while the mean posttreatment was 318 µm. Additionally, 94 eyes were treated with bevacizumab. The mean pretreatment CST was 373 µm, while the mean posttreatment was 320 µm. Moreover, the mean pretreatment *LogMAR* for patients treated with aflibercept was 0.397, while the mean posttreatment was 0.209. Moreover, the mean pretreatment *LogMAR* for patients treated with bevacizumab was 0.343, while the mean posttreatment was 0.204.

Table 2: Intravitreal agents used and the number of eyes treated

IVT	Total number of patients	Patients with a single eye treated	Patients with both eyes treated	Total number of eyes
Group A	53	31	22	75
Group B	67	40	27	94
Total	**120**	71	49	**169**

Group A: Aflibercept; Group B: Bevacizumab.

Among eyes that achieved a meaningful improvement in VA of 0.2 LogMAR or more, 19 (20.2%) were treated with bevacizumab, whereas the same improvement was observed in 33 (44%) treated with aflibercept. Also, 35 (46.67%) of the eyes treated with aflibercept, including 3 patients with CST less than 250 µm, achieved a reduction of more than 20% in CST, compared with 27 (28.72%) eyes treated with bevacizumab, including 5 patients with CST less than 250 µm. Worsening of CST was reported in 2 eyes (2.67%) treated with aflibercept and 7 eyes (7.45%) treated with bevacizumab. The results for clinical outcomes, classified by degree of improvement, are shown in Table 3.

Table 3: Classification of patients based on clinical improvement

Outcomes	Clinical outcome	Degree of improvement	Group A	Group B	*P-value**
Δ CST*	Worsening	Negative results	2 (2.67%)	7 (7.45%)	0.082
	Weak response	Less than 10%	14 (18.67%)	22 (23.40%)	
	Partial response	10%-20%	24 (32%)	38 (40.43%)	
	Good response	More than 20%	35 (46.67%) [A]	27 (28.72%) [B]	
Δ LogMAR	Limited response	Less than 0.2	42 (56%)	75 (79.8%)	**0.001***
	Good response	More than 0.2	33 (44%)	19 (20.2%)	

Data expressed as N: number, %: percentage
P< 0.05 is considered significant (Chi-square)
Group A: Aflibercept; Group B: Bevacizumab.
A: Including 3 patients with CST less than 250 µm
B: Including 5 patients with CST less than 250 µm

Both treatment groups showed significant improvements in anatomical and functional parameters. Despite nonrandomization and significantly more severe cases in Group A than in Group B, this difference was no longer significant for either parameter. The results for clinical outcomes, by baseline and posttreatment values, are shown in Table 4.

Table 4: Clinical baseline values and posttreatment clinical outcomes

Drug	**Outcomes**	**Mean values**			*P-value**
		Baseline values	**Posttreatment values**	**% Change (mean ± SD)**	
Group A	***ΔCST***	394.63 ± 56.72	317.63 ± 43.43	19.51% (77 µm ± 9.92)	**< 0.001**[A]
	ΔLogMAR	0.397 ± 0.15	0.209 ± 0.13	0.188 ± 0.126	**< 0.001**[C]
Group B	***ΔCST***	373.40 ± 41.43	320.35 ± 46.57	14.14% (53 µm ± 8.75)	**< 0.001**[A]
	ΔLogMAR	0.343 ± 0.12	0.204 ± 0.12	0.139 ± 0.120	**< 0.001**[C]
p-value	***ΔCST***	**0.024**[C]	0.741[B]	**< 0.001**[B]	
	ΔLogMAR	**0.033**[D]	0.834[D]	**0.032**[D]	

Data expressed as N: number, %: percentage
* P< 0.05 is considered significant A: paired T-test, B: unpaired T-test, C: Mann–Whitney U test, D: Wilcoxon Signed-Rank Test Group A: Aflibercept; Group B: Bevacizumab.

Both treatment groups show no significant impact on glycemic control. Despite an apparent improvement in HbA1C control, this effect is minor and may be unrelated to the treatment. Additionally, the p-value at the pretreatment baseline was 0.35, indicating no significant categorical difference in glycemic control between the two groups. However, it was almost identical after the treatment (p-value = 0.93). This means the differences nearly disappear. The results are shown in Table 5. However, it is more important to discuss the exact change in HbA1c, as discussed below.

Table 5: Patient categories according to glycemic control based on pre- and posttreatment HbA1c levels

	Pretreatment			Posttreatment			p-value
	good control	poor control	very poor control	good control	poor control	very poor control	
Group A1	1 (3.2%)	12 (38.7%)	18 (58.1%)	0	17 (54.8%)	14 (45.2%)	0.360
Group A2	1 (4.5%)	7 (31.8%)	14 (63.6%)	1 (4.5%)	9 (40.9%)	12 (54.5%)	
Group A	**2 (3.8%)**	**19 (35.8%)**	**32 (60.4%)**	**1 (1.9%)**	**26 (49.1%)**	**26 (49.1%)**	
Group B1	1 (2.5%)	23 (57.5%)	16 (40%)	1 (2.5%)	23 (57.5%)	16 (40%)	0.841
Group B2	0	9 (33.3%)	18 (66.7%)	1 (3.7%)	9 (33.3%)	17 (63.0%)	
Group B	**1 (1.5%)**	**32 (47.8%)**	**34 (50.7%)**	**2 (3.0%)**	**32 (47.8%)**	**33 (49.2%)**	
p-value	0.350			0.932			
Total	**3 (2.5%)**	**51 (42.5%)**	**66 (55%)**	**3 (2.5%)**	**58 (48.3%)**	**59 (49.2%)**	0.657

Data expressed as N: number, %: percentage
Group A: Aflibercept; Group B: Bevacizumab.
* P< 0.05 is considered significant (Chi-square)
Glycemic control categories: Good control: HbA1c < 7% or <8% for older than 60 years; "Poor control" if HbA1c was between 7% and 9% (8% and 9% for older patients), and "Very poor control" if HbA1c > 9%

The mean HbA1c pretreatment level was non-significantly higher in Group A than in Group B (9.70% vs. 9.30%, respectively, or by SI units: 82.51 mmol/mol vs. 78.14 mmol/mol, respectively, p-value 0.167). There was no significant difference in glycemic control between the two treatment groups. However, the improvement of HbA1c was highly significant in Group A (p-value < 0.001). At the same time, it was not statistically significant in Group B (p-value = 0.065), which was affected by the difference between patient groups treated with a single eye or both eyes, as there was no change in the IVB1 group (p-value = 1.00). The HbA1c test results are shown in Table 6.

Table 6: Patients' glycemic control as measured by pre- and posttreatment HbA1c levels

	Group A1	Group B1	P-value
Pretreatment	9.56 ± 1.60	8.92 ± 1.38	0.088[B]
Posttreatment	8.96 ± 1.11	8.92 ± 1.27	0.896[B]
% change	6.28%	0.0%	
P-value	**0.026**[A]	1.00[A]	
	Group A2	Group B2	P-value
Pretreatment	9.90 ± 1.64	9.86 ± 1.56	0.934[B]
Posttreatment	9.07 ± 1.44	9.38 ± 1.50	0.495[B]
% change	8.38%	4.87%	
P-value	**0.030**[A]	0.150[A]	
	Group A	Group B	P-value
Pretreatment	9.70 ± 1.61	9.30 ± 1.51	0.170[B]
Posttreatment	9.01 ± 1.24	9.10 ± 1.37	0.712[B]
% change	7.11%	2.15%	
P-value	**0.001**[A]	0.251[A]	

Data expressed as N: number, %: percentage
Group A: Aflibercept; Group B: Bevacizumab.
A: P< 0.05 is considered significant (Wilcoxon Signed-Rank Test)
B: P< 0.05 is considered significant (Mann-Whitney U Test)

The baseline demographic and systemic characteristics, including age, HbA1c, and BMI, were well-balanced between the two groups (P > 0.05). However, significant baseline differences were observed in ocular parameters: the Group A had significantly greater CST (p=0.023) and worse VA (p=0.020) than the IVB group, as shown in Table 4.

A highly significant positive correlation between baseline CST and VA (LogMAR) (r = 0.783) was observed in the Pearson correlation analysis of baseline variables, as shown in the heatmap in Figure 1, indicating that increased macular edema is strongly associated with poorer visual outcomes. Additionally, HbA1c showed a moderate positive correlation with both CST and VA (r = 0.386 and 0.342, respectively), highlighting the impact of glycemic control on disease severity. Conversely, BMI did not demonstrate significant correlations with ocular parameters at baseline.

After the 3-month follow-up, there was no statistically significant difference between the aflibercept and bevacizumab groups regarding functional (LogMAR, p=0.965) or anatomical (CST, p=0.758) outcomes, as shown in Table 4. Despite the aflibercept group presenting with significantly worse baseline parameters, both cohorts achieved comparable final visual and anatomical endpoints. Furthermore, no significant differences in HbA1c were observed,

suggesting a comparable systemic safety profile.

Although both treatment groups achieved comparable visual and anatomical endpoints (p>0.05), the analysis of change from baseline revealed a significantly greater magnitude of effect for aflibercept. Despite the aflibercept group having significantly worse baseline CST (p=0.023) and VA (p=0.020), these patients demonstrated a larger reduction in CST (p=0.002) and a greater mean improvement in VA (p=0.009) than the bevacizumab group. Furthermore, the proportion of patients achieving significant vision gain was substantially higher in the aflibercept arm (44.0% vs. 20.2%; p<0.001), as shown in Table 7.

Table 7: Assessment of various parameter changes from baseline

	Group A	**Group B**	**p-value ***
CST	-18.84±9.92	-14.14±8.75	0.002
LogMAR (VA)	-0.19±0.13	-0.14±0.12	0.009
Outcome			<0.001
Vision lost/unchanged	42 (56.0%)	75 (79.8%)	
Vision gain	33 (44.0%)	19 (20.2%)	
HbA1c	-6.45±11.05	-2.28±10.12	0.053
Glycemic control			0.284
Poor	60 (80.0%)	81 (86.2%)	
Good	15 (20.0%)	13 (13.8%)	

Data expressed as N±SD: number ± standard deviation, %: percentage
* P< 0.05 is considered significant (unpaired T-test)
Group A: Aflibercept; Group B: Bevacizumab.
CST: Central subfield thickness, VA: Visual acuity

Additionally, a strong, persistent association between CST and VA (r=0.655) was observed at the final follow-up, supporting the findings regarding the structural-functional relationship. However, a notable divergence was observed regarding metabolic control. While baseline HbA1c correlated significantly with ocular parameters, this relationship weakened considerably at the final visit (HbA1c vs. LogMAR: r=0.042). This suggests that the potent local effect of anti-VEGF therapy may override the systemic influence of glycemic control on macular edema in the short term, allowing for visual and anatomical improvement even in patients with suboptimal HbA1c levels.

Furthermore, the significance of the correlations at the final follow-up was verified (Table 8). The strong structure-function relationship between CST and VA (LogMAR) remained highly significant (p<0.001). Notably, the statistical association between systemic glycemic control and visual function was no longer significant by the end of the treatment period. While HbA1c showed a highly significant correlation with LogMAR at baseline (p<0.001), this relationship became statistically non-significant at the final follow-up (p=0.585), indicating that visual gains were achieved independently of systemic glycemic status. However, a significant association between HbA1c and CST persisted (p=0.013), suggesting that while hyperglycemia may continue to influence anatomical parameters, it no longer influences visual outcome under anti-VEGF therapy.

Table 8: Assessment of the p-value of the correlation between various variables at the last follow-up

	age	CST	LogMAR	HbA1c
BMI	0.490	0.013	0.013	0.919
age		0.076	0.189	0.810
CST			<0.001	0.013
LogMAR				0.585

P< 0.05 is considered significant (paired T-test)
CST: Central subfield thickness

Discussion:

The higher number of male patients than female patients in this study does not reflect the actual male-to-female patient ratio treated in the hospital's ophthalmology department.

An important finding in this study was the low mean age (59.5 ± 12.07 years) of patients treated with intravitreal anti-VEGF agents. This mean age is comparable to that reported by Hussain *et al*. (58.8 years). This study discusses various uses of bevacizumab across all age groups [8]. Also, it is lower than the reported age in many Iraqi studies (68.23 ± 8.5 years by Alkazraji *et al*.) [9], 68.3±8.6 Hussain *et al*. [10], 62.8 years by Mahdi [11] as well as regional and international studies, such as the AURIGA study, with a mean age for treatment-naïve patients of 61.9 ± 10.5 and for previously treated patients of 62.9 ± 9.3 [18]. This reflects the bad glycemic control leading to early DM complications, including diabetic maculopathies.

Analysis of the change from baseline confirmed this superior treatment response. Patients receiving aflibercept achieved a significantly greater reduction in retinal thickness (18.84 vs 14.14 µm, p=0.002) and a larger visual gain (-0.19 vs -0.14 LogMAR, p=0.009) compared to those receiving bevacizumab. This suggests that in eyes with a greater disease burden, aflibercept may exert a more pronounced drying effect, consistent with its higher binding affinity for VEGF-A and its additional inhibition of PlGF [4, 5].

While both agents achieved comparable final endpoints, aflibercept demonstrated a significantly greater effect. Despite a significant baseline difference in disease severity between the two treatment groups, at the end of the study, there were no statistically significant differences between the two groups in final VA (p=0.965) or CST (p=0.758). However, this tie at the finish line masks a critical disparity at the starting line.

Previous non-comparative studies from Iraq regarding the use of anti-VEGF IVT found that diabetic retinopathy was the most common indication for intravitreal bevacizumab [8]. Other studies found that aflibercept was effective in both functional and anatomic outcomes in nAMD [10] and wet age-related macular degeneration (wAMD) [9]. Only a single comparative study, by Hind A. Mahdi, compared aflibercept with bevacizumab in a private hospital. In this study, bevacizumab was more effective for anatomic outcomes (i.e., reducing retinal thickness), whereas aflibercept was more effective for functional outcomes (i.e., improving VA) [19].

Bressler *et al*. reported a strong association between early change in VA and changes in VA at 1 and 3 years, but no significant association between the early CST response and later VA outcomes. In the subgroup in which the early functional response was less than 5 letters at 12 weeks (i.e., 1 month after the third dose), 29% lately improved by 10 or more letters from baseline at 3 years. Whilst among the subgroup that experienced early improvement of 10 or more letters after 3 doses in initial therapy, 72% maintained that improvement at 3 years. This means that suboptimal early

response does not preclude a good outcome with long-term treatment [20].

Moreover, Turski *et al.* found that a single intravitreal dose of bevacizumab resulted in anatomical rather than functional improvement, and that a limited initial reduction in CST with anti-VEGF therapy does not necessarily preclude a subsequent anatomical response with continued treatment. Additionally, with long-term follow-up and continuous therapy, fewer patients may have been classified as non-responders at a later stage [21]. This helps represent the short-term effect of IVT rather than its long-term effectiveness. Furthermore, CST is a reliable quantitative indicator of DME severity. Many studies have considered CST one of the most reliable outcomes for evaluating the efficacy of anti-VEGF therapy for DME. Nevertheless, conflicting results have been reported regarding the predictive value of CST for treatment response [21].

As mentioned above, there was a highly significant positive correlation between HbA1c and VA ($p<0.001$), confirming that poor glycemic control drives the severity of DME. It is well-documented that patients with uncontrolled glycemic levels, longer diabetes duration, and the presence of DME are risk factors for diabetic maculopathies and factors for its severity [16]. In this study, the data reveal that the potent local action of anti-VEGF therapy appears to override the deleterious effects of systemic hyperglycemia on vision in the short term. Essentially, patients who were effectively treated improved their vision regardless of whether their HbA1c remained high or low. The mean HbA1c pretreatment level was higher in Group A than in Group B (9.69% vs. 9.30%, respectively). This difference is due to the ophthalmologist's practice of prescribing aflibercept for more severe cases of diabetic maculopathies rather than bevacizumab. HbA1c levels were decreased in both groups. However, the decrease was significant only in Group A (p-value < 0.0001), whereas it was not in Group B (p-value = 0.065).

Studies found a relationship between anti-VEGF therapy and systemic metabolic health. Patients with poor glycemic control, as indicated by elevated HbA1c levels, have a poor prognosis with anti-VEGF treatment, as poor glycemic control is a strong predictor of poor functional (i.e., VA) and anatomical (i.e., CST) responses [14].

It was interesting that HbA1c was a significant predictor of treatment response in the univariate analysis, but lost significance in the multivariate analysis. That means glycemic control does not independently predict treatment outcome.

Wells *et al.* did not find apparent differences among antivitreal anti-VEGF agents in the treatment of DME. However, at the worst levels of initial VA, aflibercept achieved more vision improvement [22].

Jhaveri *et al.* found that patients started with bevacizumab as initial therapy in severe DME have a high chance of switching to aflibercept for better outcomes. Old age is a predictive factor for being switched [23]. Consistent with this, Hutton *et al.* also found that aflibercept was more effective. However, bevacizumab is recommended as first-line, and the patient can then be switched to aflibercept if needed [24]. Furthermore, Lu et al. found that, in addition to anatomic characteristics and findings by OCT, LDL, serum creatinine, and blood urea are positive predictors for a decrease in CRT [25]. Moreover, Dervis *et al.* found that vitamin D level may be a predictor of anti-VEGF therapy response [26].

Limitations of the study

As this study is a limited-time follow-up, the long-term treatment outcomes of IVT were not recorded. The IVT doses may be changed from monthly dosing to a PRN or T&E regimen. The decision was made by the ophthalmologists for each individual patient. Additionally, data were recorded

for 3 months only as an initial phase of IVT. However, depending on the clinical decision, the initial phase lasted 5 months for some patients. For research purposes, only the results for the first 3 months were recorded. Additionally, participants who complete the study may have better outcomes than the general population, as dropped patients were non-adherent and may experience a lack of IVT benefit, specific ADRs that cause them to skip a dose or discontinue their treatment, or a postponed next dose. Furthermore, one of the main issues in this study was the patient's willingness to respond to the researchers' contacts.

Additionally, a common practice among Iraqi ophthalmologists was beyond doubt; the aflibercept group presented with significantly more severe disease at baseline, characterized by higher CST and worse VA. This practice reaffirmed the non-random allocation of patients to a specific treatment by Iraqi ophthalmologists and thus was considered allocation bias. Although the aflibercept group exhibited more severe disease at baseline, it demonstrated a good treatment response, with anatomical and functional endpoints that were statistically indistinguishable from those of the bevacizumab group.

Furthermore, the clinical decision to use either aflibercept or bevacizumab was based on several factors, including drug availability and the number of patients treated at the hospital. The long waiting list for the treatment forces many patients to pay for it to skip the wait. Furthermore, it may reflect selection bias, as ophthalmologists assign patients with more advanced disease to aflibercept regardless of prior therapy. At the same time, treatment-naïve patients with mild to moderate disease may be assigned to use either aflibercept or bevacizumab. Selection bias may affect the accuracy of the outcome results; however, the results show that aflibercept is clinically superior to bevacizumab. On the other hand, ophthalmologists commit to adhering to clinical guidelines for treatment selection while also managing public and national resources.

Moreover, confounding factors such as dietary modifications, variations in physical activity levels, and concurrent systemic medications for existing comorbidities frequently complicate the interpretation of laboratory test results.

Conclusions

Both aflibercept and bevacizumab are effective therapies for DME by achieving anatomical and functional improvements. Aflibercept demonstrated a superior capacity to reverse severe baseline disease. The passage highlights the role of anti-VEGF therapy in driving improvements in patients, regardless of systemic factors such as glycemic control. It emphasizes the importance of both functional and anatomical outcomes in evaluating treatment response. Anatomical changes are meaningful indicators of visual improvement. In contrast, systemic measures such as HbA1c exert limited influence once therapy is initiated, as anti-VEGF therapy improved the patient's condition regardless of glycemic control.

Finally, and more importantly, the baseline VA is a strong predictor for VA gain from anti-VEGF therapy due to a large margin of response and due to the ceiling effect in the case of mild disease. This may explain the better outcome with aflibercept.

Funding:
The authors did not receive any funds.

Conflict of Interest:
The authors declare there is no conflict of interest.

Acknowledgement:
Thanks to Dr. Luay Salim Rasheed and Dr. Ibrahim Ali Rajab for their efforts and support.

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