

Changes in Serum Level of Vascular Endothelial Growth Factor before and after Intravitreal Injection of AntiVEGF for Diabetic Macular Edema

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Abstract:

Background: Diabetic macular edema (DME), a frequent etiology of vision impairment in individuals with diabetes, is linked to increased levels of vascular endothelial growth factor (VEGF). Anti-VEGF therapy, such as intravitreal ranibizumab (Lucentis), is a standard treatment to reduce retinal edema and improve vision. Aim: The present investigation aims to assess intravitreal ranibizumab impacts on serum VEGF levels in DME. **Methods:** This quasi-experimental study included 50 eyes with DME from patients at the Ophthalmology Clinic, Benha University Hospitals. Blood samples were obtained prior to and one month following the intravitreal injection of ranibizumab. VEGF levels were measured using an enzyme-linked immunosorbent assay kit. Data were analyzed using the Statistical Package for the Social Sciences, with statistical significance defined as $p < 0.05$. **Results:** The median serum VEGF level before injection was 24.77 (range: 11.75–169.59), which significantly decreased to 18.34 (range: 0.076–135.98) post-injection ($p < 0.001$). No significant correlations were found between pre- and post-injection VEGF levels and demographic factors (age, diabetes duration). However, males had higher pre-injection VEGF levels than females ($p = 0.027$). The median percentage change in VEGF levels was greater in males (-33.3%) compared to females (-6.7%), however, this difference did not reach statistical significance ($p = 0.113$). **Conclusions:** Intravitreal ranibizumab significantly diminishes serum VEGF levels in patients with DME. Although the reduction was more pronounced in males, gender did not significantly influence the overall treatment outcome.

Keywords: Diabetic Macular Edema, Vascular Endothelial Growth Factor, Ranibizumab, Intravitreal Injection, Diabetes Mellitus.

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Introduction

Diabetes mellitus (DM) is an escalating global health concern, with projections estimating it will affect 592 million people by 2035, driven by increased prevalence of prediabetes and DM ^[1]. Diabetic retinopathy (DR) is a major adverse event of DM, with risk factors including disease duration, poor glycemic control, and hypertension ^[2]. Diabetic macular edema (DME), a frequent cause of vision loss in working-age adults, can develop at any stage of DR. It has a prevalence of 3.8% among individuals over the age of 40, with higher rates observed in African Americans compared to Asians ^[3-5]. DME results from retinal microvascular damage due to high glucose levels, leading to macular thickening, ischemia, and fluid leakage, which distorts retinal architecture and diminishes visual acuity ^[6, 7].

Hypoxia due to microvascular disease in diabetic eyes triggers the release of vascular endothelial growth factor (VEGF), increasing vascular permeability and causing retinal edema ^[8]. Elevated VEGF levels are observed in vitreous samples from DME patients, and VEGF introduction in primate eyes induces similar DR changes, including microaneurysm formation ^[9]. VEGF, a growth factor family member produced by hypoxic cells, promotes vasculogenesis and angiogenesis by binding to VEGF receptors, particularly VEGFR2 on vascular endothelial cells, triggering signaling cascades that impact gene expression and cell behavior ^[10, 11]. VEGF-A, specifically, disrupts endothelial cell junctions and promotes neovascularization, resulting in retinal and macular edema in diabetic eye disease ^[12, 13].

Over three decades of research since the first Early Treatment DR Study highlighted the central role of VEGF in chorioretinal vascular diseases, including DME, leading to the development of effective VEGF-binding drugs that reduce DME and improve vision, revolutionizing

DME treatment ^[14]. Anti-VEGF agents such as Pegaptanib (Macugen®), Ranibizumab (Lucentis®), and Bevacizumab (Avastin®) target VEGF to prevent blood-retinal barrier breakdown in DME. Pegaptanib, an anti-VEGF aptamer, received FDA approval in 2004 for neovascular age-related macular degeneration (AMD) ^[15], while Bevacizumab was FDA-approved for colon cancer the same year ^[16]. Ranibizumab, a second-generation anti-VEGF monoclonal antibody, was FDA-approved in 2006 for ocular use ^[10]. Ranibizumab (Lucentis, Genentech/Roche) was specifically engineered to treat neovascular AMD by modifying a murine monoclonal antibody fragment targeting VEGF-A. Its fragment antigen binding (Fab) was humanized and optimized for retinal penetration, unlike full-length antibodies, allowing it to inhibit all VEGF isoforms effectively. In primate studies, ranibizumab reduced choroidal neovascularization and vascular leakage, leading to FDA approval for AMD in 2006 and subsequent use for DME ^[17]. Another anti-VEGF agent, aflibercept (Eylea; Regeneron/Bayer), targets all VEGF-A forms and placental growth factor ^[18]. Systemic side effects of intravenous bevacizumab, like hypertension and proteinuria, raise concerns about reduced systemic VEGF following anti-VEGF treatments, although intravitreal injections produce low systemic drug levels. Current data does not confirm an increased systemic side-effect risk from intravitreal anti-VEGF therapy ^[19, 20].

This investigation aims to detect level of serum VEGF before and after one month of intravitreal injection of ranibizumab (lucentis) in DME patients.

Patients and methods

Design and population

The quasi experimental study was conducted on 50 eyes with DME the patients were selected from out Patient ophthalmology clinic of Benha university

hospitals from June 2023 to June 2024. The study was done after being approved by the Research Ethics Committee, Faculty of Medicine, Benha University (Approval Code: MS 2-6-2023). An informed consent was obtained from the patients. Each patient was informed about the purpose of the study and assigned a unique confidential code number to ensure anonymity.

Eligibility

The study included patients of both sexes and all ages with DME, presenting with visual impairment and no history or presence of other ocular conditions that could contribute to vision loss, such as AMD. Inclusion also required the presence of fovea-involving macular edema, defined as a central subfield macular thickness of $\geq 300 \mu\text{m}$.

Participants were excluded if they had a history of prior anti-VEGF injections, retinal photocoagulation in the study eye within three months prior to the initial injection, previous local steroid treatment, or a history of cerebrovascular accidents or myocardial infarction. Additional exclusions included systemic diseases requiring medications that could affect study outcomes, poorly controlled diabetes ($\text{HbA1c} > 12.0\%$), or any other condition deemed by the investigators to compromise eligibility.

Procedures

A thorough and systematic approach was undertaken for each participant enrolled in the study. Initially, a comprehensive medical and ocular history was obtained. The medical history encompassed detailed information regarding the duration of DM, the mode and effectiveness of its management, any prior therapeutic interventions, and an assessment of glycemic control parameters. In parallel, the ocular history focused on documenting the onset, duration, and progression of DME symptoms, as well as any previous ophthalmic treatments, such as anti-vascular endothelial growth factor (anti-VEGF) therapy or retinal

photocoagulation. Additionally, any coexisting ocular pathologies, including but not limited to glaucoma, were also recorded.

A general clinical examination was conducted to evaluate the overall systemic health status of the participants. This included measurement of recent glycated hemoglobin (HbA1c) levels and blood glucose concentrations. Any systemic abnormalities or comorbid conditions that could potentially influence ocular health or treatment response were noted. A focused physical examination further aimed to identify systemic diseases or abnormalities that could have a direct or indirect impact on the patient's visual status. When necessary, laboratory investigations were ordered to confirm or monitor systemic parameters, especially those related to glycemic control.

Venous blood samples were collected from each participant at two time points: prior to the intravitreal injection of the anti-VEGF agent and again four weeks post-injection. For accurate measurement of VEGF levels, blood samples were drawn into tubes pre-treated with a combination of Citrate, Theophylline, Adenosine, and Dipyridamole (CTAD), which serve to preserve platelet integrity and inhibit their activation. This step was crucial to minimize the artificial release of VEGF and other cytokines from activated platelets. The collected samples were centrifuged at 3,000 revolutions per minute (rpm) for 20 minutes within one hour of collection. The resultant plasma was then carefully aliquoted and stored at -20°C until further analysis.

Quantification of plasma VEGF levels was performed using a standardized enzyme-linked immunosorbent assay (ELISA) kit, strictly adhering to the manufacturer's protocol. The procedure involved the use of microtiter plates pre-coated with monoclonal antibodies specific to human VEGF. Plasma samples were added to the wells, allowing VEGF present in the samples to bind to the immobilized

antibodies. Subsequently, biotinylated secondary antibodies specific to VEGF were introduced, forming a sandwich complex. This was followed by the addition of Streptavidin-Horseradish Peroxidase (HRP), which binds to the biotinylated antibodies. After a period of incubation, unbound components were washed away, and a chromogenic substrate was added to initiate a colorimetric reaction. The intensity of the color produced, which is directly proportional to the amount of VEGF in the sample, was measured spectrophotometrically at a wavelength of 450 nanometers following the addition of an acidic stop solution to terminate the reaction.

Treatment and follow-up

Each patient received an intravitreal injection of ranibizumab (commercially known as Lucentis) under strict aseptic conditions within the confines of a sterile operating theater. Prior to the procedure, pharmacological dilation of the pupil was achieved using 1% tropicamide eye drops. Topical anesthesia was administered using 0.4% Benoxinate hydrochloride to ensure patient comfort. The ocular surface and surrounding area were disinfected using 5% povidone-iodine solution, and the eye was draped appropriately. A sterile eyelid speculum was then used to maintain adequate exposure.

A single intravitreal injection consisting of 0.5 mg (0.1 ml) of ranibizumab was administered through the pars plana, specifically targeting the superotemporal quadrant, approximately 4 mm posterior to the limbus, using a 28-gauge needle. To minimize post-injection reflux, the syringe was withdrawn carefully while simultaneously applying a cotton-tipped applicator to the injection site. Upon completion of the injection, the eyelid speculum was removed, and an antibiotic-steroid combination ointment was applied to the treated eye. A sterile patch was then placed over the eye. Patients were subsequently prescribed topical moxifloxacin eye drops (5 mg/ml) to be

used four times daily for five consecutive days as prophylaxis against infection.

Throughout the study duration, patients were advised to maintain regular follow-up visits with their primary care physician or internist for optimal management of systemic health parameters, including blood glucose, lipid profile, and blood pressure. One month following the intravitreal injection, patients returned for follow-up assessment, during which a second blood sample was collected to evaluate changes in circulating VEGF levels.

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Statistical methods

Data management and statistical analysis were done using SPSS version 28 (IBM, Armonk, New York, United States). Quantitative data were assessed for normality using the Shapiro-Wilk test and direct data visualization methods. According to normality, quantitative data were summarized as means and standard deviations or medians and ranges. Categorical data were summarized as numbers and percentages. VEGF values were compared before and after treatment using the Wilcoxon signed ranks test, and they were compared according to gender, treatment modality, and diabetes duration using the Mann-Whitney U test. Correlations were done using Spearman's correlation. All statistical tests were two-sided. P values less than 0.05 were considered significant.

Results

The study population had a mean age of 57 years (SD=9), with females representing 60% (n=30) and males 40% (n=20). The mean duration of diabetes was 15 years (SD=6). Most participants (86%, n=43) were on insulin therapy, while 14% (n=7) were managed with oral medications.

Table 1

The median VEGF level prior to injection was 24.77 (range: 11.75 - 169.59), which significantly decreased following the injection to a median of 18.34 (range:

0.076 - 135.98). The reduction in VEGF levels was statistically significant, with a p-value of <0.001. **Table 2**

Correlation analysis of pre-injection VEGF levels with demographic factors showed no significant relationship with age ($r = -0.097$, $p = 0.504$) or duration of diabetes ($r = -0.09$, $p = 0.536$). Post-injection analysis also found no significant correlations, with age showing a weak inverse trend ($r = -0.243$, $p = 0.089$) and duration of diabetes showing a very weak, non-significant correlation ($r = -0.082$, $p = 0.571$). **Table 3**

Analysis of VEGF levels by gender revealed that pre-injection VEGF levels were significantly higher in males (median = 32.63) compared to females (median = 15.39, $p = 0.027$), but post-injection VEGF levels did not differ significantly (males: median = 21.655, females: median = 16.835, $p = 0.239$). The median percentage

change in VEGF levels was greater in males (-33.3%) compared to females (-6.7%), but this difference was not statistically significant ($p = 0.113$). Regarding treatment modality, pre- and post-injection VEGF levels were similar between the oral treatment and insulin groups, with no significant differences (pre-injection $p = 1.0$, post-injection $p = 0.784$). The median percentage change in VEGF levels was -36.61% in the oral group and -11.23% in the insulin group, with no significant difference ($p = 1.0$). Similarly, no significant differences in pre- and post-injection VEGF levels were found between those with ≤ 10 years or > 10 years of diabetes (pre-injection $p = 0.834$, post-injection $p = 0.873$), and the median percentage change in VEGF levels was not significantly different between the two groups (-23.35% vs. -10.49%, $p = 0.772$). **Table 4**

Table 1: Demographic characteristics and diabetes characteristics of the studied patients

Demographics	Age (years)	Mean \pm SD	57 \pm 9
	Sex		
	Males	n (%)	20 (40.0)
	Females	n (%)	30 (60.0)
	Duration of diabetes (years)	Mean \pm SD	15 \pm 6
Diabetes characteristics	Treatment		
	Oral	n (%)	7 (14.0)
	Insulin	n (%)	43 (86)

n: number of patients, SD: standard deviation, %: percentage.

Table 2: Serum Level of Vascular Endothelial Growth Factor pre and post-injection

VEGF	Median (range)	P-value
Pre injection	24.77 (11.75 - 169.59)	<0.001*
Post injection	18.34 (0.076 - 135.98)	

*Significant P-value; VEGF: Vascular Endothelial Growth Factor

Table 3: Correlation between VEGF post and pre injection, and other parameters

	VEGF pre injection		VEGF post injection	
	r	P	r	P
Age (years)	-0.097	0.504	-0.243	0.089
Duration of diabetes (years)	-0.09	0.536	-0.082	0.571

r: Correlation coefficient

Table 4: VEGF before and after injection according to gender, treatment type, and diabetes duration

VEGF	Gender		P-value
	Males (n = 20)	Females (n = 30)	
Pre injection	32.63 (11.75 - 169.59)	15.39 (11.77 - 167.09)	0.027*
Post injection	21.66 (12.2 - 135.98)	16.84 (0.076 - 101.2)	0.239
% change	-33.3 (-90.58 - 110.78)	-6.7 (-99.35 - 88.94)	0.113
	Treatment		P-value
	Oral (n = 7)	Insulin (n = 43)	
Pre injection	22.89 (13.87 - 167.09)	26.64 (11.75 - 169.59)	1.0
Post injection	18.54 (12.85 - 44.45)	18.21 (0.076 - 135.98)	0.784
% change	-36.61 (-73.4 - 88.94)	-11.23 (-99.35 - 110.78)	1.0
	Diabetes duration		P-value
	≤10 years	> 10 years	
Pre injection	23.43 (12.63 - 152.75)	26.11 (11.75 - 169.59)	0.834
Post injection	18.54 (12.68 - 135.98)	17.94 (0.076 - 101.2)	0.873
% change	-23.35 (-69.48 - 88.94)	-10.49 (-99.35 - 110.78)	0.772

VEGF: Vascular Endothelial Growth Factor, data in table was presented as median (rang).

Discussion

DME, a frequent etiology of vision impairment in individuals with diabetes, is linked to increased levels of VEGF^[21]. Anti-VEGF therapy, such as intravitreal ranibizumab (Lucentis), is a standard treatment to reduce retinal edema and improve vision.

The study included 50 patients diagnosed with DME to evaluate changes in serum VEGF levels before and one month after receiving a 0.5 mg (0.1 cc) intravitreal injection of Ranibizumab (Lucentis). The participants had a mean age of 57 years (SD = 9), with females representing 60% of the sample (n = 30) and males making up 40% (n = 20).

In this investigation, no significant relationship was found between age or duration of diabetes and changes in VEGF levels. Although the median percentage change in VEGF levels after the injection was greater in males compared to females, this difference was not statistically significant. Furthermore, no notable differences were detected between the group treated with insulin and the group treated with oral medication.

Our study found a statistically significant reduction in VEGF level indicating decrease in serum VEGF after injection of lucentis after one month as we found The median VEGF level prior to injection was 24.77 (range: 11.75 - 169.59), which significantly decreased following the injection to a median of 18.34 (range: 0.076 - 135.98). The reduction in VEGF levels was statistically significant, with a p-value of <0.001.

The research conducted by Avery et al.^[20] aimed to assess the systemic pharmacokinetics of ranibizumab in patients diagnosed with DME. Their findings revealed the smallest reduction in plasma levels of VEGF among the various treatments assessed. In contrast, a study by Zehetner et al.^[22] evaluated plasma VEGF concentrations before and after intravitreal injection of ranibizumab in a cohort of 10 patients with DME. However, their results did not demonstrate any significant reduction in VEGF levels following the treatment.

On the other hand, the investigation by Matsuyama et al.^[23] focused on plasma VEGF levels in patients suffering from proliferative DR, comparing measurements before and after the administration of intravitreal bevacizumab.

Their results showed a significant reduction in VEGF levels, indicating the effectiveness of bevacizumab in managing the condition. Similarly, Hirano et al.^[24] conducted a study involving 42 patients with DME who received intravitreal injections of three different anti-VEGF agents: bevacizumab, aflibercept, and ranibizumab. The study found that both bevacizumab and aflibercept led to significant reductions in plasma VEGF levels, while no such decrease was observed in patients treated with ranibizumab.

The discrepancy between our study and previous research may stem from various factors, including differences in sample size and the complexity of measuring VEGF levels in the bloodstream. While different studies report similar relative results, the absolute VEGF concentrations vary significantly due to several factors, including the role of platelets, which contain high concentrations of VEGF. Plasma VEGF levels can also differ depending on the anticoagulants used to prevent platelet activation^[25].

Despite the variations in absolute VEGF levels, a common finding is that bevacizumab lowers systemic VEGF levels more significantly than ranibizumab, as noted by Zehetner et al.^[22]. This observed difference in outcomes is likely due to the distinct systemic half-lives of the drugs. Bevacizumab and aflibercept both contain an Fc fragment that binds to endothelial cell receptors, which facilitates recycling and thereby extends their systemic half-life. In contrast, ranibizumab lacks this Fc fragment, resulting in a significantly shorter intrinsic systemic half-life.

However, despite the valuable insights provided by our findings, the current study does have several limitations. One of the primary limitations is the relatively small sample size, which may reduce the generalizability of the results. Additionally, the recruitment of patients from a single center could introduce bias

and limit the external validity of the study. Another important limitation is the short follow-up period of only six months, which may not be sufficient to fully capture the long-term effects and potential complications associated with the treatments. A longer follow-up duration would be beneficial to provide a more comprehensive evaluation of the outcomes and to monitor for any delayed adverse effects or complications.

Conclusions

Our study showed that significant reduction in VEGF level indicating decrease in serum VEGF after single intravitreal injection of lucentis after one month for the treatment of DME

Data Availability

All data are included in this article

Conflict of interest

All authors have no conflicts of interest that are directly relevant to the content of this review

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