



DOI: 10.14744/eer.2024.72692  
Eur Eye Res 2024;4(3):223–227

EUROPEAN  
**EYE**  
RESEARCH

ORIGINAL ARTICLE

# Effects of blood HbA1c and mean platelet volume levels in diabetic macular edema patients who received dexamethasone implant

 Furkan Alyoruk,  Esra Arican,  Burak Turgut,  Ismail Ersan,  Hakika Erdogan,  Safak Torun

Department of Ophthalmology, Onsekiz Mart University, Canakkale, Türkiye

## Abstract

**Purpose:** The study aimed to investigate the effects of blood glycated hemoglobin (HbA1c) and mean platelet volume (MPV) levels in patients with diabetic macular edema who received a dexamethasone implant (DEXI).

**Methods:** Twenty-two Type 2 diabetic patients with pre-existing HbA1c and MPV measurements before injection were selected for the study. These patients received an intravitreal DEXI injection. Optical coherence tomography images and medical records before and after the injection were evaluated retrospectively.

**Results:** The mean visual acuity level before and after the injection was  $0.21 \pm 0.1$  and  $0.30 \pm 0.09$ , respectively. The median values for patient age, HbA1c, and MPV were 65 years, 7.4, and 10.6, respectively. There was no statistically significant difference in visual acuity levels and foveal macular thickness changes before and after the injection between groups with MPV levels above and below 10.6 ( $p > 0.05$ ). In addition, there was no statistically significant difference in visual acuity changes before and after the injection between patients under and over 65 years of age ( $p > 0.05$ ). There was also no statistically significant difference in foveal macular thickness changes before the injection between patients under and over 65 years of age ( $p > 0.05$ ). However, a statistically significant decrease in central macular thickness was observed after the injection in patients under 65 years of age compared to those over 65 years of age ( $p < 0.05$ ).

**Conclusion:** MPV and HbA1c values have been shown to be markers of inflammation and poor disease control in diabetic patients. Our study indicates that there is no correlation between the response to DEXI injection and MPV or HbA1c values.

**Keywords:** Dexamethasone implant, diabetic retinopathy, hemoglobin, intravitreal injections, mean platelet volume

Diabetic retinopathy (DR) is one of the microvascular complications of diabetes mellitus (DM).<sup>[1,2]</sup> Diabetic macular edema (DME) results from the destruction of the blood-retinal barrier, leading to blood plasma leakage from the small vessels in the macula. DME can occur at any stage of DR and is the most common cause of visual

loss in patients with DR.<sup>[3]</sup> Hyperglycemia, blood pressure, dyslipidemia, and the duration of diabetes are some of the risk factors for the development of DR.<sup>[4]</sup>

Mean platelet volume (MPV) is a marker of platelet activation. Activated platelets have larger volumes than smaller ones and exhibit enhanced adhesion, release,



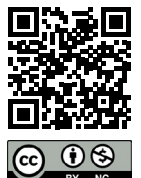
**Cite this article as:** Alyoruk F, Arican E, Turgut B, Ersan I, Erdogan H, Torun S. Effects of blood HbA1c and mean platelet volume levels in diabetic macular edema patients who received dexamethasone implant. *Eur Eye Res* 2024;4(3):223–227.

**Correspondence:** Burak Turgut, M.D. Department of Ophthalmology, Onsekiz Mart University, Canakkale, Türkiye

**E-mail:** burakturgut@comu.edu.tr

**Submitted Date:** 09.01.2024 **Revised Date:** 18.08.2024 **Accepted Date:** 04.09.2024 **Available Online Date:** 29.11.2024

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and agglutination abilities, playing an active role in thrombus formation.<sup>[5]</sup> In the literature, there have been reports regarding DR and platelet indices. MPV has been found to be higher in diabetic patients compared to healthy individuals. In addition, higher MPV values in diabetic patients have been shown to increase the risk of retinopathy development.<sup>[6,7]</sup>

Glycemic control is fundamental to the development of DM. A retrospective study indicated that patients with refractory DME had higher levels of glycated hemoglobin (HbA1c).<sup>[8]</sup>

The aim of this study is to assess the efficacy of dexamethasone implant (DEXI) in patients with high MPV and HbA1c levels. We examined the structural and functional responses of Type 2 diabetic patients with refractory DME in relation to glucose control and inflammation status.

## Materials and Methods

### Study Design and Ethics

This is a retrospective study on the intravitreal injection of a single dose of 0.7 mg intravitreal DEXI in patients with refractory DME who did not respond to anti-vascular endothelial growth factor (VEGF) therapies. These patients were treated at the retina unit of the 18 Mart University Ophthalmology Clinic from December 2022 to October 2023. The study was conducted in full accordance with the Declaration of Helsinki. Informed consent, which detailed the potential side effects of the drug and the application procedure, was obtained from each patient before the intravitreal DEXI application. This study was approved by the clinical research ethics committee of the hospital on Çanakkale 18 Mart University (No: 2023–123).

Among these patients, those who had glycated HbA1C and MPV measurements within the last 3 months before the 0.7 mg intravitreal DEXI (Ozurdex®; Allergan, Inc., Irvine, CA) injection were selected. Patients included in the study were examined with optical coherence tomography (OCT) imaging 1 week before and 1 month after the injection.

The examination records, including slit-lamp examinations, foveal macular thickness measurements obtained through OCT before and after intravitreal injection, and best-corrected visual acuity levels according to the Snellen chart, were evaluated. Patients with pre-existing glycated HbA1c levels, complete blood count values, OCT images (Zeiss Cirrus 5000 HD-OCT, Carl Zeiss Meditec, Dublin, CA, USA), and medical records before and after the injection were included in the study. Patients who missed follow-up

examinations or had ocular surgery within the last 6 months were excluded from the study.

### Injection Procedure

DEXI was administered intravitreally to all patients under sterile operating room conditions. The injection was applied from the inferior temporal quadrant, 3–3.5 mm behind the limbus, through the sclera after the application of 0.5% proparacaine hydrochloride and 5% povidone-iodine to the ocular surface and periocular skin. Patients were prescribed 3% ofloxacin drops to be used 4 times a day for 5 days following the injection. Patients were monitored for injection-related complications after the administration.

### Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) for Windows (version 22.0; SPSS Inc., Chicago, IL, USA) was used for the statistical analysis of the data. Patients were compared according to the median values of the criteria included in the study. The Mann–Whitney U test was used to evaluate differences in macular thickness between the pre-injection and control examinations, with findings considered statistically significant at  $p < 0.05$ . Spearman correlation analysis was used to evaluate the relationships between glycated HbA1c and MPV, pre-injection foveal macular thickness and MPV, and pre-injection foveal macular thickness and glycated HbA1c, with findings considered statistically significant at  $p < 0.05$ .

## Results

A total of 22 patients with 22 eyes were enrolled in our study. Of the participants, 11 (50%) were female and 11 (50%) were male. The mean age of the patients was  $64 \pm 8.4$  years. The right eyes of 12 patients (55%) and the left eyes of 10 patients (45%) were included in the study. The average MPV value was  $10.8 \pm 1.2$ , and the average HbA1c was  $7.7 \pm 1$ . According to the Snellen chart, the mean visual acuity level before the injection was  $0.21 \pm 0.1$ , and the mean visual acuity after the injection was  $0.30 \pm 0.09$ . While no improvement in visual acuity was observed after the injection in 8 of the 22 patients (36.4%), a visual acuity improvement of 20% or more was observed in 5 patients (22.7%).

The median values for age, HbA1c, and MPV were calculated as 65 years, 7.4, and 10.6, respectively. These median values were used as cutoff points, and the patients were divided into two groups based on these values. The groups were compared with each other in terms of foveal macular thickness and best-corrected visual acuity levels before and after the injection (Table 1).

**Table 1.** Patient characteristics

	Mean±SD	Median
Age (year)	64.0±8.4	65
Gender (M/F)	11/11	-
HbA1c	7.7±1.0	7.4
MPV (fl)	10.8±1.2	10.6
Pre-injection CRT (µm)	656±165	602
Post-injection CRT (µm)	320±221	230
Pre-injection BCVA	0.21	0.10
Post-injection BCVA	0.30	0.20

HbA1c: Hemoglobin A1c; MPV: Mean platelet volume; CRT: Central retinal thickness; BCVA: Best corrected visual acuity.

There was no statistically significant difference in visual acuity levels or foveal macular thickness changes before and after the injection between the groups with MPV values above and below 10.6 ( $p>0.05$ ). Similarly, no statistically significant difference was found between the groups with HbA1c levels above and below 7.4 in terms of best-corrected visual acuity levels and foveal macular thickness changes before and after the injection ( $p>0.05$ ). There was also no statistically significant difference in visual acuity changes before and after the injection between patients under and over 65 years of age ( $p>0.05$ ), nor in foveal macular thickness changes before the injection between these age groups ( $p>0.05$ ).

However, a statistically significant decrease in central macular thickness was observed after the injection in patients under 65 years of age compared to those over 65 years ( $p<0.05$ ). The mean value for the under-65 group was  $200\pm109$  microns, whereas for the over-65 group, it was  $438\pm244$  microns. No correlation was found between glycated HbA1c and MPV values. In addition, no correlation was observed between pre-injection foveal macular thickness and MPV or HbA1c values (Tables 2 and 3).

**Table 2.** Comparison of pre- and post-injection values of CRT and BCVA between the groups

	Blood MPV		p	HbA1c		p	Age		p
	Under 10.6	Over 10.6		Under 7.4	Over 7.4		Under 65	Over 65	
	Mean±SD		Mean±SD		Mean±SD				
Pre-injection CRT	652±45	660±58	0.974	627±51	684±50	0.224	667±45	644±56	0.450
Post-injection CRT	252±46	401±83	0.080	295±55	344±79	0.693	201±33	438±74	0.007
Pre-injection BCVA	0.25±0.06	0.17±0.06	0.415	0.24±0.07	0.19±0.06	0.919	0.22±0.07	0.2±0.05	0.892
Post-injection BCVA	0.31±0.07	0.29±0.09	0.690	0.35±0.09	0.25±0.07	0.408	0.32±0.09	0.29±0.06	0.974

HbA1c: Hemoglobin A1c; MPV: Mean platelet volume; CRT: Central retinal thickness; BCVA: Best-corrected visual acuity.

**Table 3.** Cross-tabulation of correlation coefficients between patient variables

	HbA1c	Blood MPV	Pre-injection CRT
Spearman's rho			
HbA1c			
Correlation coefficient	-	-0.065	0.054
Sig. [2-tailed]		0.774	0.810
Blood MPV			
Correlation coefficient	-0.065	-	-0.041
Sig. [2-tailed]	0.774		0.856
Pre-injection CRT			
Correlation coefficient	0.054	-0.041	-
Sig. [2-tailed]	0.810	0.856	

HbA1c: Hemoglobin A1c; MPV: Mean platelet volume; CRT: Central retinal thickness; BCVA: Best-corrected visual acuity.

### Discussion

The most significant cause of vision loss among diabetic patients is DME. The most current treatments for DME include intravitreal anti-VEGF and corticosteroid applications.

Recent studies have demonstrated that Müller cells are among the first to be affected by DME, undergoing apoptosis as the disease progresses.<sup>[9]</sup> Due to the cytotoxic substances secreted by the activated Müller cells, the blood-retina barrier is compromised, leading to glial changes in the retina. A study by Iglicki et al. compared treatment-naive patients with those unresponsive to anti-VEGF therapy. It showed that treatment-naive patients had better anatomical outcomes.<sup>[10]</sup> Although there are only a few studies in the literature, they indicate that naive patients treated with dexamethasone achieve better results.<sup>[11-13]</sup> Early intervention in the inflammatory cascade appears to result in better anatomical and/or functional outcomes. In our study, we included patients

with refractory DME who did not respond to anti-VEGF treatment. A limitation of our study is the lack of precise information on the number of previous injections and the time elapsed since the last injection.

Long-term and refractory DME is known to lead to a decrease in visual acuity due to deterioration in the IS-OS band and the external limiting membrane.<sup>[14]</sup> In addition, macular ischemia has been shown to affect the photoreceptor layer.<sup>[15]</sup> One of the side effects of corticosteroid treatment is cataract development. Studies have shown varying effects of corticosteroid use on lens conditions. For example, a study comparing pseudophakic and phakic eyes treated with intravitreal corticosteroids reported better results in the pseudophakic group.<sup>[16,17]</sup> In our study, the change in visual acuity before and after injection was not statistically significant. We attribute this to the lack of data on the duration of diabetes, the number of previous laser sessions, and the lens conditions of the patients.

High MPV has been associated with prothrombotic processes and impaired hemostasis. A study by Papanas et al. found that MPV was higher in DR patients compared to the healthy group.<sup>[18]</sup> Another study by Citirik et al. found no correlation between MPV and the stages of DR, though MPV was significantly higher in diabetic patients than in the healthy group.<sup>[6]</sup> Some studies have indicated a correlation between glycemic status and MPV in the general population.<sup>[19,20]</sup> However, in our study, no relationship was found between MPV and HbA1c.

There are studies indicating that macular edema is statistically significant in patients with a glycated HbA1c value of eight or above.<sup>[21]</sup> Furthermore, among patients with refractory macular edema, those with higher HbA1c values had a poorer response to intravitreal injections.<sup>[8]</sup> Tetikoğlu et al. found that MPV was higher in diabetic patients with macular edema compared to those without.<sup>[22]</sup> To the best of our knowledge, no study has assessed the relationship between macular edema, MPV values, and response to intravitreal injection based on preexisting MPV values. In our study, we included 22 patients with refractory macular edema and found no relationship between central foveal thickness and MPV. Furthermore, no correlation was found between MPV and the response to intravitreal injections.

In this study, no correlation was found between best corrected visual acuity, central macular thickness, MPV, and glycated HbA1c value at the time of injection in patients with refractory DME who received DEXI. A statistically significant decrease in central macular thickness was observed after

injection in patients under 65 years of age compared to those over 65 years. This result may be associated with a shorter duration of diabetes in the under-65 age group.

The limitations of this study include the small sample size and the lack of data on diabetes duration, medication history, comorbidities, lens condition, and the number of previous laser treatments and intravitreal injections. Future studies could benefit from examining proliferative and non-proliferative diabetes as separate subgroups for more accurate results. There is a need for randomized clinical trials with larger sample sizes and detailed, standardized patient examination records.

## Conclusion

This study found no relationship between MPV and HbA1c, no relationship between central foveal thickness and MPV value, and no correlation between best corrected visual acuity, central macular thickness, MPV, and HbA1c value at the time of injection in patients with refractory DME receiving DEXI. Our study suggests that MPV and HbA1c values do not affect the efficacy of DEXI treatment, which could be interpreted as indicating that inflammation and diabetes severity are not impacted by these parameters. However, further studies with larger patient populations are needed to clarify the effects of HbA1c and MPV levels in patients with refractory DME receiving DEXI.

**Ethics Committee Approval:** This study was approved by the clinical research ethics committee of the hospital on Canakkale 18 Mart University (No: 2023–123).

**Peer-review:** Externally peer-reviewed.

**Authorship Contributions:** Concept: F.A., B.T., E.A., İ.E., H.E., Ş.T.; Design: F.A., B.T., E.A., İ.E., H.E., S.T.; Supervision: F.A., B.T., E.A., İ.E., H.E., S.T.; Resource: B.T., İ.E., H.E.; Materials – B.T., İ.E., H.E.; Data Collection and/or Processing: F.A., E.A.; Analysis and/or Interpretation: F.A.; Literature Search: E.A., S.T.; Writing: F.A., B.T.; Critical Reviews: B.T., S.T.

**Conflict of Interest:** None declared.

**Use of AI for Writing Assistance:** Not declared.

**Financial Disclosure:** The authors declared that this study received no financial support.

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