

# Predictive factors for treatment in diabetic macular edema

## Facteurs prédictifs du traitement de l'œdème maculaire diabétique

Lotfi Chaabani, Dhouha Nefzi, Mariem Kalou, Ahmed Jaklouti

Ophthalmology department - Kasserine hospital center, University of medicine of Sousse

### ABSTRACT

**Background:** Diabetic macular edema represents the primary cause of blindness in individuals under the age of 50 and in those with diabetes. Treatment success is influenced by numerous factors. Our objective was to identify factors affecting anatomical and functional responses to DME treatment.

**Methods:** This retrospective study included 95 eyes of 54 patients treated for diabetic macular edema in our Ophthalmology Department at the Regional Hospital of Kasserine, Tunisia, between January 2016 and January 2018. Statistical analysis was done in 3 steps: a univariate analysis, then a bivariate analysis and finally, we performed a multivariate analysis with a logistic regression. Analysis was performed using the statistical software "SPSS 20.0".

**Results:** The multivariate analysis selected one principal factor: poor initial acuity as the only predictive factor of poor functional response to treatment with OR=35,763. The independent variables associated with a poor anatomical response to treatment were dyslipidemia (OR = 0.923), diabetic nephropathy (OR = 4.46), and proliferative diabetic retinopathy (OR = 0.063).

**Conclusion:** The treatment of diabetic macular edema is associated with high costs and a variable response from one patient to another, justifying better definition of the predictive factors for treatment. The results of other future studies will probably give answer for this question.

**Keywords:** macular edema, diabetes, Anti-vascular endothelial growth factor, prognosis.

### RÉSUMÉ

**Introduction:** L'œdème maculaire diabétique constitue la première cause de cécité chez les sujets de moins de 50 ans et chez le patient diabétique. Nombreux sont les facteurs qui conditionnent la bonne réponse au traitement. Notre objectif était est de déterminer les facteurs influençant la réponse anatomique et fonctionnelle au traitement dans l'œdème maculaire diabétique.

**Méthodes:** Nous avons mené une étude rétrospective portant sur 95 yeux de 54 patients diabétiques présentant un œdème maculaire diabétique. Nous avons établi dans une première étape une analyse descriptive puis une analyse univariée suivie d'une analyse multivariée par l'utilisation de la technique de la régression logistique. Les analyses ont été réalisées à l'aide du logiciel statistique « SPSS 20.0 ».

**Résultats:** L'étude multivariée a identifié l'acuité visuelle initiale basse (<1/10) comme le seul facteur prédictif d'une mauvaise réponse fonctionnelle au traitement avec un OR=35,763 et la dyslipidémie (OR=0,923), la néphropathie (OR=4.46), la RDP (OR=0.063) comme des variables indépendantes associées à une mauvaise réponse anatomique au traitement

**Conclusion:** Le traitement de l'œdème maculaire diabétique est coûteux avec une réponse variable d'un patient à l'autre. L'identification des facteurs pouvant influencer la réponse au traitement est donc crucial pour minimiser le coût dépensé et améliorer la prise en charge.

**Mots-clés :** diabète, œdème maculaire, pronostic, traitement.

### Correspondance

Lotfi Chaabani

Ophthalmology department - Kasserine hospital center, University of medicine of Sousse

Email: lotfioph@hotmail.com

## INTRODUCTION

Diabetic macular edema (DME) is defined according to the International Classification of the American Academy of Ophthalmology as the presence of any retinal thickening and/or lipid exudate in the posterior pole in patient with diabetic retinopathy [1]. It currently affects nearly 1 in 15 diabetic patients [2]. It is also the primary cause of visual impairment among diabetic patients, with a prevalence ranging from 6 to 10% among diabetic individuals [3].

Laser photocoagulation treatment remains the first-line therapy for focal extra-foveal DME. This treatment is now frequently performed in conjunction with intravitreal injections (IVI) of corticosteroids and/or Anti-Vascular Endothelial Growth Factor (anti-VEGF) agents, which tend to be key elements in the therapeutic approach [4]. Various general and local, functional and morphological factors condition the effectiveness of the treatment.

Our objective was to identify factors affecting anatomical and functional responses to DME treatment.

## METHODS

### Materials

We conducted a retrospective study involving 95 eyes from 54 diabetic patients collected over a period of 2 years, from January 2016 to January 2018.

We included all patients with type I or II diabetes presenting a decrease in visual acuity (VA) secondary to DME affecting the central region, evidenced by Optical coherence tomography (OCT) as a central foveal thickness (CFT) of 205  $\mu\text{m}$  or greater and/or an extrafoveal thickness of 232  $\mu\text{m}$  or greater, with a total follow-up of at least 18 months and previous treatment for DME according to Early Treatment Diabetic Retinopathy Study (ETDRS) criteria.

Patients with a condition that could be responsible for a decrease in central VA other than DME and Patients with a condition causing macular edema other than diabetes were excluded from the study.

### Methods

All patients underwent a complete ophthalmological examination including history taking, comprehensive ophthalmological examination, fundus photography, fluorescein angiography, tomographic examination using OCT.

Therapeutic Scheme was including the treatment of systemic factors, laser treatment for focal and multifocal DME and pharmacological treatment: for IVI of bevacizumab, we used a therapeutic dose of 1.25 mg of bevacizumab.

Patients had a consultation one month after the third IVI to assess their functional and anatomical response. In the case of a functional response, monthly follow-ups were conducted during the first year. In the second year, visits were spaced out in the event of stabilization of VA over two consecutive visits. Injections were discontinued in cases of stabilization of best-corrected visual acuity

(BCVA) or in the absence of functional and anatomical improvement. If no improvement in VA was noted after a series of three injections, continuation of treatment was no longer recommended.

The patient was then followed monthly with a measurement of VA and assessment of the macular edema using SD-OCT. If a new decrease in VA due to DME was observed during a follow-up, treatment was reinstated, and monthly injections were resumed until VA was again stable during three consecutive monthly evaluations.

The IVI of triamcinolone acetonide was administered to pseudophakic patients and those without glaucoma, to patients for whom non-steroidal treatment is not suitable, and as a second-line treatment for patients who were insufficient responders to non-steroidal therapy.

### Factors Influencing the Anatomical and/or Functional Response to Treatment of DME:

A good functional response to treatment in the long term is defined as a gain of at least 10 ETDRS letters (2 lines) at 18 months. A good anatomical response to treatment in the long term is defined as a reduction in CRT of more than 20% at the final examination.

### Data Analysis

Data entry and statistical analysis were performed using the statistical software "SPSS 20.0". Patients characteristics were summarized using descriptive statistics, we performed an analytical study that involved comparing two groups of patients: the good responder's group and the poor responders group, comparison focused on the functional and anatomical outcomes of treatment.

The collected data underwent univariate analysis; however, univariate analysis has several drawbacks as prognostic factors can intertwine, overlap, and interact with one another. These drawbacks are avoided through multivariate study using logistic regression techniques.

## RESULTS

### Descriptive Study

The diagnosis of diabetes was made 4 to 25 years prior to the initiation of DME treatment, with an average of 12.85 years and a standard deviation of 5.96. Diabetic retinopathy was non-proliferative (NPDR) in 19 patients (21%), pre-proliferative in 40 patients (44%), and proliferative (PDR) in 30 patients (33%), of which 25% were of the florid type (7% of patients).

In our study, 83% of patients were treated with retinal pan photocoagulation using laser, of which 11 eyes (25%) were treated during the study, and 33 eyes (75%) had previously received pan photocoagulation before the start of our protocol.

The macular edema had been present for a minimum of 4 months and a maximum of 24 months before the initiation of treatment, with an average duration of 10 months.

The decrease in VA was the most common functional

sign found in 93.7% of patients, with 76.8% presenting metamorphopsia and 12.6% presenting a central scotoma. The average central retinal thickness (CRT) was 427.64  $\mu\text{m}$  with a standard deviation of 100.20  $\mu\text{m}$ . Other associated factors with DME included hard exudates (64% of patients) and lipid exudates (72.6%). According to the therapeutic protocol followed, all our patients received pharmacological treatment for DME. Four point four percent of patients were treated with IVI of bevacizumab and corticosteroids, 3.3% with IVI of corticosteroids alone, and 92.3% with IVI of bevacizumab. 22% of patients received focal treatment for DME.

The follow-up ranged from 18 to 24 months, with an average of  $20.33 \pm 2.65$  months. 20 patients (38 eyes) completed a 24-month follow-up (37.03%).

Subjective functional improvement was reported in 70.9% of treated eyes, with disappearance of visual blurriness in 4 out of 89 eyes (4.5%), disappearance of metamorphopsia in 18 out of 73 eyes (24.7%), and disappearance of the central scotoma in 5 out of 12 eyes (41.7%). For eyes treated with IVI of bevacizumab alone and bevacizumab + corticosteroids, we observed a statistically significant improvement in VA with a good correlation of  $0.6 < r < 0.8$ . For eyes treated with laser focal treatment + IVI of bevacizumab, we noted a statistically significant improvement in VA with an excellent correlation of  $r > 0.8$ . For the 3 eyes treated with corticosteroids, no improvement in VA was observed. Regarding anatomical response, we noted a statistically significant decrease in CRT for eyes treated with IVI of bevacizumab alone ( $r = 0.67$ ). For eyes treated with IVI of bevacizumab + focal laser treatment, we also observed an improvement in CRT with an excellent correlation of  $r > 0.8$ . For the 3 eyes treated with corticosteroids, no improvement was noted, but an increase in CRT was observed. For the 12 eyes followed for DME with centromacular exudates, we noted persistence of exudative maculopathy in 10 eyes (83.33%). For the 61 eyes followed for DME with hard exudates, persistence of hard exudates was observed in 50 eyes (81.9%).

### Analytical study

#### Study of Treatment Response in Multivariate Analysis

Low initial VA ( $<1/10$ ) was the only predictive factor for or a poor functional and anatomical response to DME treatment.

In the multivariate analysis, dyslipidemia, nephropathy, and diabetic retinopathy were independent variables associated with a poor anatomical response to treatment (Table 1).

## DISCUSSION

### General Factors Influencing Treatment Response

The role of age as a prognostic factor for DME is controversial. In our series, a weak correlation was found between patient age, anatomical response ( $r = 0.221$ ) and functional response ( $r = 0.171$ ) to DME treatment.

**Table 1.** Predictive Factors for Poor Functional and Anatomical Response in Multivariate Analysis (Adjusted for Diabetes Imbalance)

| Variable                  | Odds Ratio (OR) | 95% Confidence Interval (CI) | P-value |
|---------------------------|-----------------|------------------------------|---------|
| Low Initial Visual Acuity | 35,763          | 4.035-31,698                 | 0,01    |
| Duration of DME           | 0,922           | 0,844-1,008                  | 0,922   |
| Dyslipidemia              | 0,293           | 0,109-0,816                  | 0,019   |
| Nephropathy               | 4,467           | 1,091-18,286                 | 0,037   |
| Diabetic Retinopathy      | 0,063           | 0,008-0,516                  | 0,010   |
| Diabetes Imbalance        | 1,230           | 0,148-10,205                 | 0,848   |

While some studies indicate that younger age is a favorable factor for visual recovery in patients with DME treated with ranibizumab [5], other studies show no correlation between patient age and functional or anatomical improvement after treatment [6].

In our series, the good functional response to treatment was 58.1% in females and 41.9% in males. We did not observe a statistically significant difference in treatment response, with a P-value of 0.414. Sex did not influence the response to DME treatment in our series. However, in the RISE and RIDE studies, male sex was associated with a better functional response, with final VA greater than 20/40 ( $P < 0.005$ ) [7].

In our series, the good functional response to treatment was 31% in type 1 diabetics and 30.3% in type 2 diabetics. We did not observe a statistically significant difference between the two groups, with a P-value of 0.384. For the anatomical response, a good response to treatment was noted in 76.4% of type 2 diabetic patients and in 20.9% of type 1 diabetics. A statistically non-significant difference was found ( $P = 0.105$ ) between the two groups. Approximately 20% of patients with type 1 diabetes and 30% of patients with type 2 diabetes under treatment develop DME after fifteen years of diabetes [8].

Glycemic control is a major factor influencing the response to DME treatments, in our series, 89.1% of poor functional responders had poor glycemic control, showing a statistically significant difference between the two groups ( $P = 0.007$ ). Using logistic regression, multivariate analysis eliminated interactions between different predictive factors; in this case, it did not show that glycemic control influences functional and anatomical responses to DME treatment independently ( $P = 0.842$ ). In a retrospective study evaluating the benefits of anti-VEGF treatment, patients with glycated hemoglobin (HbA1c) levels below 7% showed greater functional and anatomical improvements compared to those with higher HbA1c levels, without reducing the number of intravitreal injections over 6 months [9].

High diastolic blood pressure has been identified as a risk factor for the occurrence of DME in late-onset diabetics, but not in early-onset diabetics [10]. In our series, poor blood pressure control was observed in 63.4% of poor functional responders and 70% in the group of poor anatomical responders to DME treatment. In univariate analysis, poorly controlled hypertension is considered a predictive factor for poor anatomical response ( $P = 0.098$ ).

A significant association was observed between total hypercholesterolemia and the severity of macular lipid exudates. In our study, dyslipidemia emerged as a predictive factor for poor anatomical response in univariate analysis ( $P = 0.027$ ). Multivariate analysis further confirmed that dyslipidemia is an independent risk factor for poor treatment response, with a  $P$ -value of 0.019 and an odds ratio (OR) of 0.293. These findings are consistent with previous reports in the literature [11].

The severity of renal dysfunction was significantly associated with the occurrence of diabetic macular edema (DME). Our findings demonstrated that a history of nephropathy was more prevalent in the group of poor anatomical and functional responders, with statistically significant differences ( $P = 0.038$  and  $P = 0.037$ , respectively). This observation aligns with the study by Romeo et al., which investigated the relationship between renal microangiopathy and DME [12].

Our study did not identify any cases of sleep apnea syndrome (SAS) among the enrolled patients. However, previous research has established an association between SAS and diabetic macular edema (DME), particularly in type 2 diabetes patients who demonstrate a significantly higher prevalence of SAS compared to the general population [13].

Our study cohort included no pregnant women during the data collection period. Current guidelines provide specific recommendations for ophthalmological follow-up in pregnant diabetic patients, based on the stage of diabetic retinopathy at pregnancy onset. Importantly, anti-VEGF therapies are contraindicated during pregnancy. While intravitreal corticosteroids theoretically have limited systemic absorption, their safety profile in pregnancy remains unestablished, and their use is therefore not recommended [14].

### Local Functional Factors Influencing Treatment Response

In our study, univariate analysis identified DME duration as a predictive factor for poor functional response to treatment. However, multivariate analysis revealed that DME duration was not independently associated with poor functional outcome ( $P = 0.922$ ). Prior to treatment initiation, the mean duration of DME was  $11.43 \pm 5.7$  months (range: 4–24 months). Notably, poor functional responders had a significantly longer mean disease duration compared to good responders (11.7 vs. 10.9 months,  $P = 0.013$ ). Similarly, for anatomical response, poor responders exhibited a longer mean DME duration than good responders (12.47 vs. 9.74 months). These findings align with existing literature demonstrating that shorter DME duration correlates with better visual prognosis following anti-VEGF intravitreal injections [15]. Multivariate analysis in our study identified low baseline visual acuity (VA) as an independent predictor of poor functional response to treatment (OR = 35.76,  $P = 0.01$ ). The mean baseline VA was 0.74 logMAR in good functional responders versus 0.90 logMAR in poor responders, demonstrating a clinically relevant trend ( $P = 0.063$ ). For anatomical response, poor responders had significantly worse baseline VA compared to good responders (0.84

logMAR vs. 0.71 logMAR,  $P = 0.007$ ). These findings are consistent with DRCR.net data showing that patients with baseline VA  $>5/10$  (approximately  $>0.3$  logMAR) achieved significantly better final visual outcomes than those with VA  $\leq 5/10$  [16].

In our study, patients received intravitreal injections (IVI) of either bevacizumab, corticosteroids, or a combination therapy. Among eyes treated with bevacizumab monotherapy, we observed statistically significant improvements in both visual acuity (VA;  $r = 0.69$ ) and central macular thickness (CMT;  $r = 0.67$ ), demonstrating strong treatment correlations. These findings align with prospective randomized trials demonstrating bevacizumab's efficacy in DME. At 12 months, the bevacizumab group achieved a median gain of +8 ETDRS letters versus a -0.5-letter loss in the laser group, requiring a median of 9 IVI compared to 3 laser sessions [8]. Consistent with our results, prior studies have confirmed significant reductions in CMT and VA improvements with bevacizumab [17, 18].

Triamcinolone acetonide, a synthetic glucocorticoid corticosteroid, is used off-label in ophthalmology as a 4 mg (0.1 mL) intravitreal injection (IVI). In our study, the therapeutic effects of triamcinolone were consistent with those reported in the literature. For eyes treated with corticosteroids alone, we observed no improvement in visual acuity (VA). Regarding anatomical response, we found no improvement but rather an increase in central macular thickness (CMT). This worsening of CMT was attributed to the presence of tractional components identified during follow-up in these patients. A literature review indicates that while triamcinolone provides short-term VA improvement in DME, this effect is no longer evident at 6 months [19].

Neither the number of intravitreal injections (IVI) nor their frequency was predictive of treatment response in diabetic macular edema (DME), whether considering anatomical or functional outcomes. In our cohort, the majority of patients (88% of eyes) received bevacizumab therapy. Comparative analysis revealed no statistically significant difference in IVI number between poor and good responders for either anatomical or functional outcomes. These findings align with post hoc analyses from the RESTORE study, where approximately 25% of good responders required  $\leq 6$  IVI during the first treatment year [20]. To date, no reliable predictive factors for treatment response have been established beyond the initial therapeutic response. Indeed, the results of a post hoc analysis of Protocol I (treatment of DME with ranibizumab) have recently been reported, indicating that the functional response obtained after three injections of ranibizumab is highly predictive of final VA [21].

**Focal Laser Treatment:** For many years, laser treatment was the only available option for DME and remained the standard treatment for DME. In our series, for eyes treated with focal laser treatment, we observed a statistically significant reduction in CMT and a functional improvement, with an excellent correlation ( $r = 0.906 > 0.8$ ). The ETDRS study demonstrated that laser treatment reduced the risk of VA loss by 50% at 3 years for eyes with "clinically significant" DME, meaning those threatening or

affecting the center of the macula [22,23].

Recently, the DRCR.Net showed more favorable results for laser treatment than those reported in the ETDRS, with approximately 25% of eyes treated with laser achieving a gain of 2 lines or more after 2 years of follow-up [24].

### Local Morphological Factors

Initial CMT has been described as a predictive factor for treatment response in several studies. In our series, initial CMT did not affect either the anatomical or functional response to treatment. The average initial CMT was 421.4µm for the poor responder group and 440.32µm for the good functional responder group, with a statistically non-significant difference between the two groups ( $P = 0.392$ ). The average initial CMT was 436µm in the poor responder group and 412.7µm in the good anatomical responder group, with a statistically non-significant difference ( $P = 0.28$ ) between the two groups. These findings contrast with DRCR.net data using ranibizumab (with/without laser), which reported 20% poor anatomical responders and 7% non-responders (defined as <10% CMT reduction from baseline) [31].

Vitreomacular interface anomalies: these anomalies are a factor for worse prognosis, especially when there are an obvious tractional component from the posterior hyaloid or an epiretinal membrane associated with a rupture of the internal limiting membrane [7]. In our study, an anomaly of the vitreomacular interface was a predictive factor for poor anatomical response to treatment but did not influence the functional response in our series.

The severity of diabetic retinopathy significantly influences treatment outcomes. Our study demonstrated that proliferative diabetic retinopathy (PDR) predicts poor anatomical response to DME treatment, with 31% of poor responders presenting PDR ( $P=0.054$ ). Multivariate analysis confirmed PDR as an independent predictor of poor anatomical response ( $OR=0.063$ ,  $P=0.010$ ). These findings align with existing literature showing that: visual outcomes after ranibizumab IVI worsen with increasing retinopathy severity [10,25], and macular edema incidence rises significantly with advancing retinopathy stages (WESDR studies,  $P<0.0001$ ).

The prognosis for FDR is very serious, with a high risk of progression to blindness due to tractional retinal detachment and/or neovascular glaucoma, with reported risks ranging from 15% to 70% according to various studies [26]. While our study showed no significant association between florid diabetic retinopathy (FDR) and treatment response (functional  $P=0.506$ /anatomical  $P=0.29$ ), existing literature consistently reports poorer outcomes in FDR cases. This apparent contradiction may stem from several factors. FDR is often associated with extensive macular edema, leading to varying degrees of visual impairment. The presence of DME should not delay the initiation of pan retinal photocoagulation (PRP). In cases of DME associated with severe NPDR or PDR, the ETDRS recommends prioritizing the treatment of DME before performing PRP to prevent worsening the edema due to the PRP procedure. This guideline generally applies, but exceptions exist for cases of FDR [27].

Nonaka et al and McDonald et al suggest that the inflammatory reaction secondary to photocoagulation contributes to the genesis of macular edema. This edema appears to be more frequent when PRP is performed rapidly, and the impacts are intense and numerous [27].

Conversely, in the context of PDR, macular edema seems to be primarily due to the high levels of growth factors, such as VEGF, secreted by ischemic retinal territories.

In our series, 79% of poor functional responders to treatment had received prior PRP, and among the patients who underwent PRP, the majority (68.9%) belonged to the poor anatomical responder group, with a significant difference ( $P = 0.005$ ). A history of PRP constitutes a factor for poor anatomical response in univariate analysis. We compared the gain in VA according to treatment with macular laser and found no statistically significant difference between the two groups ( $P = 0.425$ ).

The initial presence of SRD associated with DME does not influence the therapeutic response to aflibercept. However, the potential gain in VA appears to be significantly greater in patients without SRD at baseline [28]. In our study of 61 eyes followed for DME with SRD, we observed that SRD persisted in 50 eyes (81.9%). SRD resolved in 10 eyes treated with IVI of bevacizumab and in only one eye treated with focal laser treatment. SRD persisted in eyes treated with corticosteroid IVI and in those receiving a combination of corticosteroid and bevacizumab IVI. Of the poor functional responders, 64.1% presented with SRD at examination, with no statistically significant difference between the two groups ( $p = 0.945$ ). Additionally, 55.9% of poor anatomical responders had SRD at the initial examination, and we did not observe a statistically significant difference between the two groups ( $p = 0.227$ ). Thus, in our study, SRD is not a predictive factor for treatment response in DME. This conclusion is supported by post hoc VIVID/VISTA analyses.

## CONCLUSION

This study indicates that patients with lower initial visual acuity, those with PDR, and patients with a history of nephropathy and dyslipidemia potentially have a poor functional and anatomical prognosis for their DME. The results highlight the need for comprehensive patient assessment integrating both ocular and systemic factors to optimize treatment strategies. Future multicenter studies should validate these predictors in diverse populations and explore personalized treatment algorithms incorporating molecular, and advanced imaging biomarkers to further refine prognostic models and improve visual outcomes in DME management.

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