

Article

Impact of Vascular Risk Factors on Longitudinal Changes in Diabetic Macular Edema After Intravitreal Therapy

Carmen Alba-Linero ^{1,2,3,†}, José Coín Ruiz ^{2,4,*,†}, Marta Mérida Luque ², Javier Espíldora-Hernández ^{2,5} and Mario Gutiérrez Bedmar ^{3,6,7} 

¹ Ophthalmology Department, Hospital Universitario Virgen de la Victoria Málaga, 29010 Málaga, Spain

² Ophthalmology Department, Faculty of Medicine, University of Málaga, 29010 Málaga, Spain; martaamerida17@gmail.com

³ Instituto Investigación Biomédica Málaga (IBIMA), 29590 Málaga, Spain

⁴ Ophthalmology Department, Hospital Axarquía Málaga, 29700 Málaga, Spain

⁵ Internal Medicine Department, Hospital Universitario Virgen de la Victoria Málaga, 29010 Málaga, Spain

⁶ Department of Public Health and Psychiatry, Faculty of Medicine, Universidad de Málaga, 29010 Málaga, Spain

⁷ Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Instituto de Salud Carlos III, 28029 Madrid, Spain

* Correspondence: josecoin@gmail.com

† These authors contributed equally to this work.

Abstract

Objectives: The aim of this study was to analyze the association between cardiovascular risk factors such as glycated hemoglobin (HbA1c), low-density lipoprotein cholesterol (LDL-C), hypertension, overweight, and smoking and longitudinal anatomical and functional changes in diabetic macular edema (DME) during intravitreal therapy. **Materials and Methods:** This is a retrospective, observational, descriptive study conducted on a sample of 318 patients with DME associated with some degree of diabetic retinopathy (DR). They were treated with aflibercept, ranibizumab, and/or dexamethasone, assessing anatomical and functional outcomes through visual acuity, retinal thickness, and macular volume. Simultaneously, serum HbA1c and LDL-C levels, blood pressure, body mass index (BMI) and tobacco use were measured at baseline, 6, and 12 months to determine their association with treatment response using linear mixed models. **Results:** Of the variables analyzed in this study, HbA1c and degree of retinopathy were significantly associated with greater retinal thickness over time. Likewise, we found that, compared with aflibercept, dexamethasone intravitreal treatment was associated with greater retinal thickness over time. Concerning visual acuity, we found an inverse relationship with age, tobacco use and degree of retinopathy. Associations between outcomes and the initial intravitreal agent were observed; however, these findings should be interpreted cautiously. **Conclusions:** This study was consistent with previous research suggesting an association between glycemic control and DME response and progression. It also highlighted the importance of degree of retinopathy and intravitreal treatment in diabetic macular edema progression. Treatment-related findings represent exploratory associations and should not be interpreted as evidence of comparative effectiveness.

Keywords: diabetic macular edema; HbA1c; LDL-C; macular thickness; visual acuity



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1. Introduction

Diabetes mellitus (DM) is the most common endocrine disease worldwide. It affects more than 580 million people and its future projections are even more alarming [1].

The condition is characterized by abnormal glucose metabolism, either due to an autoimmune reaction against pancreatic beta cells that causes an absence of insulin (type 1 DM) or due to resistance to it (type 2 DM), with the latter accounting for 92% of the cases [2]. This lack of or resistance to insulin is associated with chronic hyperglycemia. These effects lead to complications at the macrovascular level—including ischemic heart disease, which is the leading cause of morbidity and mortality—and also at the microvascular level, including nephropathy, neuropathy and DR. Among these conditions, DR and DME are the main causes of blindness in the working-age population [3].

DR is classified according to the International Clinical Diabetic Retinopathy (ICDR) Severity Scale [4]. Proliferative DR, typical of advanced stages of the disease, characterized by neovascularization secondary to vascular endothelial growth factor (VEGF) secretion by retinal cells [5], can lead to DME caused by an increase in vascular permeability and inflammatory processes that favor filtration and accumulation of fluid in the macula [6].

In recent decades, the magnitude of the problem has led to numerous investigations involving many advances that, together with technological developments, have made novel tools for diagnosis and monitoring available, such as optical coherence tomography (OCT) or OCT angiography (OCTA) [7]. The multifactorial nature of DR can be observed through these techniques, even before the onset of symptoms, which may allow for preventing visual impairment [8,9]. Likewise, they serve to predict treatment response by measuring the decrease in macular thickness and changes in visual acuity values [10].

The relationship and significance of different variables in the progression of DR have been investigated, with findings that emphasize disease duration as the main risk factor [11]. It is of vital importance to consider glycemic control measured through HbA1c levels, blood pressure figures, lipid levels, ethnicity and other factors [12].

Regarding DR and DME treatment, it is based on laser photocoagulation; intravitreal anti-VEGF injections, which are currently considered gold standard; and intravitreal corticosteroids, which are especially useful in refractory cases [13]. Their development could contribute to improving the quality of life of millions of people [14,15].

Given that DME is a serious and preventable public health problem, this work aims to study the impact of cardiovascular risk factors on DME progression for an integral approach to these patients, promoting educational, preventive, diagnostic, and therapeutic measures that help to avoid these complications, which entail such high costs and a significant healthcare burden.

2. Methods

2.1. Ethical Considerations

This study is a retrospective observational analysis of anonymized clinical data obtained from routine clinical practice. All patients undergoing intravitreal treatment at our institution provided written informed consent allowing the use of their anonymized clinical data for research purposes, in accordance with local ethics committee requirements and data protection regulations. Given the retrospective observational design of the study, it was not registered in a clinical trial registry. No additional procedures beyond standard clinical care were performed.

This study was conducted according to the guidelines of the Declaration of Helsinki and good clinical practice guidelines. Personal data were processed in accordance with Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data. The patients and their samples were registered with an identification number (code) that was assigned in order of inclusion in the study. Personal data were unlinked from clinical and molecular data during the study (Organic Law 3/2018

of 5 December on Personal Data Protection and the Guarantee of Digital Rights and Law 14/2007, of 3 July).

The study protocol was approved by the Provincial Research Ethics Committee of Málaga, which regulates healthcare and biomedical research ethics bodies in Andalucía (study code: 29009).

2.2. Study Design

This is a retrospective observational study based on routinely collected clinical data that aimed to determine the impact of cardiovascular risk factors on the development of DR, specifically DME and its therapeutic response.

2.3. Participants

The study population comprised 318 patients. They were assessed for relevant demographic and clinical characteristics, including sex, age, race, LDL-C values, HbA1c values, hypertension (HT), BMI, tobacco use, degree of retinopathy, and the treatment type and regimen they were receiving. These variables were assessed at three points during follow-up, in consultations at baseline, 6, and 12 months.

2.4. Study Sites

This study was conducted at the Hospital de la Axarquía, in the province of Málaga, Spain, in collaboration with the University of Málaga.

2.5. Inclusion and Exclusion Criteria

The inclusion criteria were patients with type 2 diabetes mellitus who presented with DR associated with DME who were receiving intravitreal treatment and in follow-up at the Hospital de la Axarquía in Málaga Province, Spain. All participants were of legal age and signed the corresponding informed consent form.

Patients who were minors; patients who had significant ocular disease other than DR that could interfere with the evaluation of DME; patients who were unable to complete follow-up visits or required examinations due to logistical or compliance-related reasons; patients who had undergone ocular surgery in the previous six months; those who had a cardiovascular event in the previous six months; and those who refused to sign the informed consent form were excluded.

2.6. Study Variables

Different dependent variables were evaluated in this study, including mean retinal thickness, central retinal thickness, and visual acuity. All measurements at the three scheduled visits—baseline and at 6 and 12 months of follow-up—were obtained using macular OCT imaging performed with a standardized macular cube scan protocol on the Topcon 3D OCT-1 Maestro[®] device (Yamagata, Japan). Central macular thickness (CST) was defined as the mean retinal thickness in the central 1 mm ETDRS subfield. Scans with poor signal quality or relevant motion/segmentation artifacts were excluded.

Visual acuity was recorded in decimal format as part of routine clinical practice and subsequently converted to logarithm of the minimum angle of resolution (logMAR) units for statistical analysis.

As for the patients, non-modifiable factors such as age, sex, and race were taken into account. Similarly, several modifiable factors were evaluated, including overweight (BMI), smoking, degree of retinopathy, previous laser photocoagulation treatment, presence of HT, and LDL-C and HbA1c levels. HbA1c and LDL-C were recorded at baseline, 6 months, and 12 months and included as time-varying covariates in the longitudinal models. Other

systemic variables were treated as baseline characteristics due to the lack of consistent longitudinal data across all visits.

Hypertension was defined as a documented diagnosis and/or current antihypertensive treatment. Smoking status was classified as current smoker versus non-smoker. Overweight was defined as $BMI \geq 25 \text{ kg/m}^2$.

The unit of analysis was the eye. When both eyes of the same patient met inclusion criteria, both were included in the analysis. Descriptive characteristics are reported at the patient level, whereas all inferential analyses were conducted at the eye level.

Progression was operationalized as longitudinal change in OCT thickness and VA across visits.

In regard to the degree of retinopathy, cases were classified according to the International Clinical Diabetic Retinopathy Disease (ICDR) Severity Scale and the findings of the retinography [13].

The DR treatment strategy followed by each patient was taken into account, since there are three distinct approaches. The first is a fixed regimen, in which the time interval between injections is kept constant. The second is the treat-and-extend (T&E) approach, which aims to progressively space out intravitreal injections in order to reduce the number of visits and trips, thus promoting treatment adherence. The third strategy is the PRN (*pro re nata*) regimen, in which injections are administered only when necessary, according to the findings of diagnostic tests.

Treatment type was defined according to the initial intravitreal agent. Treatment switching during follow-up was not explicitly modeled and is acknowledged as a limitation of the study. Detailed information on treatment regimen and the exact number of intravitreal injections during follow-up was not consistently available and therefore could not be included in the analysis.

2.7. Statistical Analysis

Regarding descriptive statistics, numerical variables were expressed as means and standard deviations, and categorical variables as percentages.

Disease progression and treatment response were evaluated based on longitudinal changes in anatomical (mean retinal thickness) and functional (visual acuity) parameters over the 12-month follow-up period. Central macular thickness (CST) was defined as the retinal thickness measured in the central 1 mm ETDRS subfield using spectral-domain OCT.

The data had a hierarchical structure, with repeated measurements (visits) nested within eyes, and eyes nested within patients. To appropriately account for this structure, linear mixed-effect models were fitted. In the primary analysis, a random intercept at the patient level was included to account for intra-individual correlation arising from repeated measurements and the inclusion of both eyes. Thus, eyes were not treated as independent analytical units, but as clustered observations within patients.

In these models, each ophthalmologic variable was considered the dependent variable, and independent variables included follow-up time (in months), age (in years), sex (reference category: male), glycosylated hemoglobin (%), LDL-C (mg/dL), hypertension, tobacco use, overweight, other ocular diseases (dichotomous; reference: no), degree of retinopathy (reference: mild diabetic retinopathy), and type of intravitreal treatment. The primary estimand was defined as the adjusted rate of change over time (slope), expressed as $\mu\text{m/month}$ for retinal thickness and logMAR units/month for visual acuity, derived from the coefficient of time in the mixed-effect models. Therefore, outcomes are interpreted as longitudinal rates of change over time rather than categorical clinical response or progression endpoints.

Parameters were estimated using restricted maximum likelihood (REML). The variance–covariance structure of the random effects was specified as unstructured. Residual errors were assumed to be independent and normally distributed.

As a sensitivity analysis, a more detailed model specification including eye nested within patient as an additional random effect was also explored. For this purpose, a unique eye-within-patient identifier (patient $\times$ eye) was generated in Stata. This specification allows modeling of correlation between repeated measurements within the same eye over time, as well as correlation between fellow eyes from the same patient.

Results were consistent across model specifications; therefore, for reasons of parsimony, the model including a random intercept at the patient level was retained for the primary analyses. The assumptions of the linear mixed models (normality, homoscedasticity, and independence of residuals) were assessed graphically using histograms, P–P and Q–Q plots, and residual-versus-fitted plots. Autocorrelation of residuals was also evaluated. All statistical analyses were performed using Stata 18.0 (StataCorp LLC, College Station, TX, USA). Statistical tests were two-tailed, and $p < 0.05$ was considered statistically significant.

3. Results

Baseline characteristics are presented at the patient level, whereas inferential longitudinal analyses are conducted at the eye level using mixed-effect models.

3.1. Descriptive Results

This subsection reports patient-level descriptive baseline characteristics, with eye-level counts provided where applicable. Retinopathy severity was analyzed per eye; therefore, the total number of observations exceeds the number of patients included in the study.

The study sample comprised 318 patients between 30 and 88 years of age. The mean age was 66 years (SD = 10.85). As for distribution by sex, 205 patients were male (64%, SD = 0.50).

Because some eyes underwent switching or received more than one agent during follow-up, treatment counts are not mutually exclusive and therefore exceed the total number of eyes.

Regarding the clinical conditions of the population analyzed, 263 patients (83%) had hypertension (SD = 0.38) while 205 participants (64%) were overweight, defined as a BMI greater than 25 kg/m² (SD = 0.48). In addition, 119 subjects (37%) were tobacco users at the time of the study (SD = 0.48).

In relation to metabolic parameters, HbA1c values progressively declined throughout follow-up. The initial mean was 8.01% (SD = 1.73). It decreased to 7.77% (SD = 1.43) at 6 months and 7.66% at 12 months (SD = 1.42). LDL-C values also declined. At the baseline assessment, mean LDL-C was 96.91 mg/dL (SD = 37.59). At 6 months, a reduction to 92.81 mg/dL (SD = 28.59) was observed and at one-year of follow-up, levels were 91.80 mg/dL (SD = 32.99).

Visual acuity was assessed in both eyes. Initially, patients had a mean visual acuity of 0.55 (logMarscale) out of a maximum of 0.05 (SD = 0.70). At 6 months, the mean value was 0.49 (SD = 0.60). At the last visit, it was 0.46 (SD = 0.54).

Regarding mean retinal thickness, an initial value of 301.604 μ m (SD = 62.50) was recorded. At 6 months, the average thickness was 286.69 μ m (SD = 110.84). At 12 months, it was 288.52 μ m (SD = 45.67). Likewise, changes in central retinal thickness were found. At the initial evaluation, the average was 320.10 μ m (SD = 103.29). At the second visit, it was 287.67 μ m (SD = 86.83). At the last visit, it was 296.27 μ m (SD = 89.85).

As for the degree of retinopathy, all eyes included in the study were analyzed. At baseline, 98 (15.7%) had mild retinopathy, 353 (56.6%) had moderate retinopathy, 107 (17.2%) had severe retinopathy, 28 (4.5%) had very severe retinopathy, and 38 (6%) had proliferative

retinopathy. After 12 months of treatment, 146 (26.12%) had mild retinopathy, 307 (55%) had moderate retinopathy, 86 (15.38%) had severe retinopathy, 13 (2.3%) had very severe retinopathy, and 7 (1.25%) had proliferative retinopathy. Regarding intravitreal treatment, 125 (27.35%) patients received aflibercept, 262 (57.33%) patients received ranibizumab, and 70 (15.32%) patients received dexamethasone. In terms of treatment regimens, 165 (35.95%) patients followed a fixed regimen, 193 (42.05%) were treated under the treat-and-extend protocol, and 101 (22.00%) received PRN treatment. One hundred and seventeen patients (37%) had previously received laser photocoagulation treatment.

3.2. Analytical Results

All inferential analyses in this subsection were conducted at the eye level, accounting for clustering within patients through mixed-effect models. In the analytical results, longitudinal associations were evaluated using linear mixed-effect models. The variables retinal thickness, central macular thickness, and visual acuity have been considered as dependent variables and were analyzed in relation to the other variables using these models. Results from the alternative model including eye nested within patient were highly consistent with those of the primary model, with no meaningful differences in effect estimates or statistical significance. These results are expressed in Tables 1 and 2.

Table 1. Eye-level mixed-effect model estimates: association between retinal thickness and demographic factors, cardiovascular risk factors, degree of diabetic retinopathy, and treatment used.

Variable	Linear Mixed Model Coefficient (95% CI)	Confidence Interval (95%)	Significance (<i>p</i>)
Age	−0.203	(−0.801, 0.394)	0.504
Glycosylated Hb (HbA1c)	3.677	(0.684, 6.671)	0.016
LDL-C	0.014	(−0.128, 0.156)	0.847
Smoker	−5.147	(−18.646, 8.352)	0.455
BMI	−9.311	(−21.841, 3.221)	0.145
HT	−1.262	(−17.833, 15.308)	0.881
Degree of retinopathy			
Mild	8.979	(−3.731, 21.689)	0.166
Moderate	−39.084	(−124.415, 46.246)	0.369
Severe	29.354	(12.621, 46.086)	0.001
Very severe	17.332	(−10.103, 44.769)	0.216
Proliferative	56.834	(32.148, 81.521)	0.001
Intravitreal treatment			
Ranibizumab vs. aflibercept	4.157	(−9.456, 17.771)	0.549
Dexamethasone vs. aflibercept	18.528	(0.919, 36.138)	0.039

Notes: HbA1c: glycosylated hemoglobin; LDL-C: low-density lipoprotein cholesterol; BMI: body mass index; HT: hypertension.

Table 2. Eye-level mixed-effect model estimates: association between visual acuity and demographic factors, cardiovascular risk factors, degree of diabetic retinopathy, and treatment used.

Variable	Linear Mixed Model Coefficient (95% CI)	Confidence Interval (95%)	Significance (<i>p</i>)
Age	0.018	(−0.12, −0.23)	<0.001
Glycosylated Hb (HbA1c)	−0.014	(−0.042, 0.015)	0.349
LDL-C	0.011	(−0.011, 0.021)	0.045

Table 2. Cont.

Variable	Linear Mixed Model Coefficient (95% CI)	Confidence Interval (95%)	Significance (p)
Smoker	0.206	(0.078, 0.334)	0.002
BMI	−0.056	(−0.02, 0.07) (−0.175, 0.063)	0.354
HT	0.090	(−0.068, 0.249)	0.264
Degree of retinopathy			
Mild	0.167	(0.039, 0.294)	0.010
Moderate	0.110	(−0.768, 0.988)	0.806
Severe	0.547	(0.384, 0.711)	<0.001
Very severe	0.529	(0.264, 0.794)	<0.001
Proliferative	0.823	(0.594, 1.052)	<0.001
Intravitreal treatment			
Ranibizumab vs. aflibercept	−0.077	(−0.206, 0.521)	0.040
Dexamethasone vs. aflibercept	0.066	(−0.101, 0.234)	0.439

Notes: HbA1c: glycosylated hemoglobin; LDL-C: low-density lipoprotein cholesterol; BMI: body mass index; HT: hypertension.

4. Discussion

This study provides a comprehensive real-world analysis of the association between metabolic, systemic, and morphological factors and anatomical and functional outcomes in patients with DR and DME. The findings support the concept that DME represents the final manifestation of a complex interplay of microvascular, inflammatory, and neurodegenerative mechanisms [2,16–18].

In this cohort, poorer glycemic control, as reflected by higher HbA1c levels, was associated with increased retinal thickness, reinforcing the central role of chronic hyperglycemia in the structural progression of DME. Chronic hyperglycemia promotes microvascular instability and blood–retinal barrier breakdown [2,16,17]. The persistence of these alterations despite subsequent metabolic improvement may be explained by the phenomenon of metabolic memory, whereby early glycemic exposure induces long-lasting microvascular damage [19]. Consistent with this, OCT angiography studies have demonstrated that poor glycemic control is associated with early subclinical microvascular alterations preceding clinically evident DR [9,20,21]. In this study, the terms “progression” and “response” refer to model-estimated longitudinal rates of change rather than clinically defined categorical worsening or improvement.

Unmeasured dynamic metabolic parameters may partly explain the lack of association observed for some systemic variables [5,22,23].

While retinal thickness remains a key anatomical marker in the assessment of DME, previous studies have highlighted the complexity of the relationship between anatomical changes and functional outcomes, reflecting the multifactorial nature of visual impairment in these patients [7,8,10,24,25].

The degree of DR showed a clear association with both anatomical and functional deterioration, consistent with prior evidence indicating that progression to advanced stages reflects extensive ischemia, persistent inflammation, and pathological vascular remodeling [3,4]. Features such as IRMA, widespread nonperfusion, and active neovascularization have been identified as independent predictors of poor visual outcomes [4]. In this context, systemic factors have also been implicated in DR progression [11–13].

Several systemic variables did not reach statistical significance. Therapeutic heterogeneity, absence of dynamic metabolic metrics, variability in disease duration, and the presence of pre-existing neurodegenerative damage may limit the predictive value of

isolated systemic markers [5,11,12,22,23]. These factors should be considered when interpreting discrepancies between systemic metabolic control, structural retinal changes, and functional visual outcomes.

With regard to treatment response, the results suggest that an unfavorable metabolic and structural profile may be associated with reduced responsiveness to anti-VEGF therapy, consistent with previous real-world reports [26]. In such scenarios, intravitreal corticosteroids have been proposed as an effective alternative, particularly in chronic or inflammatory phenotypes of DME [14,27]. As treatment classification in this study was based on the initial intravitreal agent and treatment switches were not explicitly modeled, potential attenuation of between-group differences should be acknowledged.

Differences in anatomical outcomes were observed according to the initial intravitreal agent. These findings should be interpreted as exploratory associations rather than comparative efficacy and should therefore be interpreted cautiously, as dexamethasone was more frequently used as rescue therapy or in more advanced disease stages, introducing a potential selection bias that may have limited the observable treatment effect.

Emerging evidence supports a personalized, phenotype-driven approach to DME management [14,28,29]. The growing availability of OCT- and OCTA-based biomarkers may further refine treatment selection and optimize individualized therapeutic decision-making.

The observed improvement in HbA1c and LDL-C during follow-up may reflect closer multidisciplinary monitoring after DME diagnosis and treatment initiation. This observation highlights the value of integrated care models in optimizing both systemic metabolic control and ocular outcomes in patients with DR and DME.

The efficacy of anti-VEGF therapy in DME has been established by pivotal trials such as RISE/RIDE and VIVID/VISTA, supporting their role as first-line therapy [30,31].

5. Limitations and Strengths

The retrospective observational design of this study represents a major limitation and does not allow causal inference. Residual confounding cannot be excluded. Treatment-related findings should be interpreted with caution because treatment allocation was not randomized and clinical decisions may introduce confounding by indication. Therefore, all associations reported here should be interpreted cautiously, and the risk of overinterpretation must be acknowledged.

The limitations of our study also include its single-center nature, sample size limited by the inclusion period, variability and loss to follow-up, therapeutic heterogeneity, and the absence of dynamic metrics such as TIR or quantitative OCTA. However, these limitations are common to other real-world clinical practice studies and do not compromise its relevance. Its main strength lies in the integration of systemic, structural, and functional parameters in a representative cohort, which provides a global view of DME behavior under real-world conditions.

Propensity-based methods were considered; however, treatment heterogeneity, switching, and the longitudinal eye-level structure of the data limited the feasibility of robust propensity score modeling in this cohort. Although a random-intercept model was used in the primary analysis, additional models accounting for eye nested within patient yielded similar results, suggesting that residual intra-individual correlation is unlikely to have influenced the conclusions.

Some estimates showed relatively wide confidence intervals, reflecting a degree of uncertainty and limited precision for certain associations. This may be related to the sample size, the inclusion of multiple covariates, and the hierarchical structure of the data. Therefore, these results should be interpreted with caution, although the overall

patterns and direction of the associations were consistent. Despite this, the consistency of the findings across different model specifications supports the robustness of the results.

A major limitation relates to the absence of detailed treatment exposure data, including the exact number of intravitreal injections and regimen intensity during follow-up. Treatment switching and heterogeneity in treatment strategies may have substantially influenced anatomical and functional outcomes. Therefore, treatment-group comparisons should be interpreted strictly as exploratory associations and not as evidence of comparative effectiveness. Treatment burden may influence both anatomical and functional outcomes and may act as a proxy of disease severity (confounding by indication). Therefore, residual confounding cannot be fully excluded. However, treatment type was included in the models, partially accounting for treatment exposure.

Despite these limitations, the use of longitudinal mixed-effect models allows a robust estimation of temporal changes, making use of all available data and providing clinically meaningful estimates of progression.

Several important systemic and ocular factors that may influence diabetic macular edema outcomes—including duration of diabetes, renal function, lens status, macular ischemia, prior intravitreal exposure, diabetes-related systemic medications, and timing of panretinal photocoagulation—were not consistently available due to the retrospective design and could not be included in the analysis. Therefore, residual confounding and confounding by indication cannot be excluded, particularly in treatment-related comparisons.

The potential influence of these treatments on DME progression should be addressed in future prospective studies.

6. Conclusions

In conclusion, this study was consistent with previous research suggesting an association between glycemic control and DME response and progression. It also highlights the role of age and retinopathy severity in anatomical and functional outcomes during intravitreal therapy. Differences in anatomical outcomes were observed between treatment groups; these comparisons should be interpreted cautiously as exploratory associations, not as evidence of comparative efficacy, given the observational design and potential confounding by indication. However, other cardiovascular risk factors such as LDL-C levels or overweight were not significantly associated with the progression of DME in this sample, although some factors such as tobacco use or advanced age could be associated with changes in final visual acuity as measured in these patients. The future of treatment may benefit from predictive models based on biomarkers and personalized approaches, which could help optimize visual outcomes in patients with DME. These strategies, together with optimal control of systemic risk factors, are aligned with current international recommendations for comprehensive diabetes management [32–34].

These findings represent associations observed in a real-world setting and do not imply causality. Further prospective studies with standardized protocols and comprehensive systemic characterization are warranted.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

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