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IMPACT OF TREATMENT OF DIABETIC MACULAR EDEMA ON VISUAL IMPAIRMENT IN PEOPLE WITH TYPE 2 DIABETES MELLITUS: A COMPREHENSIVE SYSTEMATIC REVIEW AND METAAANALYSIST STUDY

[*1]Yovita, [2]Bambang Setiohadji

*[*1]Faculty of Medicine, Maranatha Christian University, Indonesia*
[2]Opthalmology Consultant, Kebonjati General Hospital, Indonesia

Correspondence Author:
viviyovita93@yahoo.com

ABSTRACT

Background: *Diabetic retinopathy (DR) and diabetic macular edema (DME) are among the most significant and disabling chronic complications of diabetes mellitus. DME is an important cause of severe vision loss in type 2 diabetes. Hyperpermeability of retinal blood vessels and subsequent formation of edema and hard exudates are the key clinical features.*

Method*: This systematic review and meta-analysis, conducted following PRISMA guidelines and employing the PICO format, aim to explore about impact of treatment of diabetic macular edema on visual impairment in people with type 2 diabetes mellitus, focusing on treatment, complications, and prognosis. Inclusion criteria encompass diverse study designs (RCTs, observational, quasi-experimental, and case-control studies) investigating impact of treatment of diabetic macular edema on visual impairment in people with type 2 diabetes mellitus among treatment, complications, and prognosis, while exclusion criteria filter out studies lacking relevance to impact of treatment of diabetic macular edema on visual impairment in people with type 2 diabetes mellitus.*

Result*: After conducting three levels of screening, the results of our search in Pubmed get 6 articles, whereas the results of our search on SageJournal get 42 articles, on Lancet 21, and on Scient direct get 60 articles. Records remove before screening are 91, so we get 78 articles for screening. After we screened based on record exclude, we compiled a total of 10 papers. We included four research that met the criteria.*

Conclusion: *There is a particularly robust response to anti-VEGF therapy in both groups when glycemic control is optimized, highlighting the critical importance of communication between the physicians managing the DME and those managing systemic diabetes control. Improving our understanding of the factors that contribute to anti-VEGF response for DME therapy may help to enhance DME treatment outcomes, particularly through the concerted coordinated efforts of the treating retina specialist and the endocrinologist or primary care physician.*

Keywords: *Diabetes mellitus, diabetic macular edema, diabetic retinopathy, vision impairment.*

INTRODUCTION

The aim of this study is to systematically review and conduct a meta-analysis of impact of treatment of diabetic macular edema on visual impairment in people with type 2 diabetes mellitus. By comprehensively synthesizing existing literature, this research seeks to explore the treatment, complications, and prognosis of impact of treatment of diabetic macular edema on visual impairment in people with type 2 diabetes mellitus. Through rigorous evaluation and statistical analysis, the study aims to provide valuable insights into the treatment, complications, and prognosis of impact of treatment of diabetic macular edema on visual impairment in people with type 2 diabetes mellitus. The systematic review and meta-analysis intend to inform healthcare practitioners, researchers, and policymakers about the current state of the treatment, complications, and prognosis of impact of treatment of diabetic macular edema on visual impairment in people with type 2 diabetes mellitus for future research and development in this critical area of public health.

Global estimates suggest that more than 382 million individuals have diabetes mellitus; this number is predicted to increase to 592 million by 2035. In Japan, ~13.5% of the population has either type 2 diabetes or impaired glucose tolerance. High blood glucose weakens the vessels in the eye, which can result in fluid leakage and the development of diabetic macular edema (DME). Epidemiologic studies indicate that 25.4% of those aged ≥30 years with diabetes also developed DME within a 10-year period, despite insulin treatment. DME is a common cause of vision loss that impacts patient quality-of-life (QoL) and carries a major socioeconomic burden. In Japan, visual impairment affects more than 1.64 million individuals and costs ~¥8,785.4 billion (US $72.8 billion), equivalent to 1.7% of Japan's gross domestic product. The indirect costs associated with DME (such as productivity loss and welfare payments) are in the region of ¥1,583.5 billion (US $13.1 billion).[1,2]

Diabetes mellitus is a major public health problem affecting approximately 285 million of people worldwide in 2010. The problem is only increasing with data from the Framingham Heart Study also indicating that the incidence of type 2 diabetes has doubled over the last 30 years. Diabetic retinopathy (DR) and diabetic macular edema (DME) are among the most significant and disabling chronic complications of diabetes mellitus. DME is an important cause of severe vision loss in type 2 diabetes. Hyperpermeability of retinal blood vessels and subsequent formation of edema and hard exudates are the key clinical features. As established in several clinical trials, strict metabolic control still remains the standard care for prevention of DR, which in many cases is only achieved by intense insulin therapy. Regarding DME treatment, anti-vascular endothelial growth factors (anti-VEGF) intravitreal injections with or without laser photocoagulation has become the gold-standard for reducing macular edema and improving visual acuity.[3,4]

Risk of developing VTDR is influenced by diabetes duration and glycemic control. Interventions to increase glycemic control can prevent vision loss. Individuals with diabetes are recommended to receive annual dilated eye examinations for early detection and timely treatment of DR. The preferred treatment for proliferative DR, panretinal laser photocoagulation (ie, scatter laser surgery), reduces the risk of moderate and severe vision loss by 50% in individuals with severe nonproliferative DR or proliferative DR. The standard of care for non–center-involved DME, focal laser photocoagulation surgery, reduces the risk of moderate vision loss by 50% to 70% in patients with macular edema. In the early 2000s, physicians began using intravitreal injections of anti–vascular endothelial growth factor (VEGF) agents (ie, aflibercept, bevacizumab, and ranibizumab) for the treatment of center-involved DME. In the last decade, anti-VEGF injections became the first-line treatment for DME because of their efficacy and ease of administration and are included in the American Academy of Ophthalmology DR Preferred Practice Pattern.[5,6]

METHODS

This systematic review meta analysis was conducted in adherence to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines. Our health care question was defined a priori using the PICO (Population, Intervention, Comparator and Outcomes) format. Population: Individuals at risk of or diagnosed with diabetic macular edema. Intervention: treatment of diabetic macular edema. Comparison: Impact of treatment diabetic macular edema. Outcome: complications and prognosis of treatment of diabetic macular edema.

ELIGIBILITY CRITERIA

For inclusion in this systematic review and meta-analysis on the exploration of impact of treatment of diabetic macular edema on visual impairment in people with type 2 diabetes mellitus, studies with diverse designs will be considered. This encompasses randomized controlled trials (RCTs), observational studies, quasi-experimental designs, and case-control studies. Studies must specifically investigate about impact of treatment of diabetic macular edema on visual impairment in people with type 2 diabetes mellitus, such as treatment, complications, and prognosis of impact of treatment of diabetic macular edema on visual impairment in people with type 2 diabetes mellitus.

The eligible population includes individuals at risk of deiabetic macular edema or those already diagnosed, with no restrictions based on age, gender, or geographical location. Exclusion criteria encompass studies not directly relevant to diabetic macular edema, reviews lacking original data, and studies solely not focusing on impact treatment of diabetic macular edema.

Comparison groups are essential for this analysis, and eligible studies must incorporate a comparison group using the other methods for impact treatment of diabetic macular edema. Excluded are studies without a comparison group or those comparing different of impact of treatment of diabetic macular edema on visual impairment in people with type 2 diabetes mellitus.

Outcome measures of interest include treatment, complications, and prognosis of diabetic macular edema on visual impairment in people with type 2 diabetes mellitus. Studies reporting outcomes unrelated to these measures or not directly addressing the impact of treatment of diabetic macular edema on visual impairment in people with type 2 diabetes mellitus will be excluded. These criteria are designed to ensure the comprehensive inclusion of studies exploring the treatment, complications, and prognosis of diabetic macular edema on visual impairment in people with type 2 diabetes mellitus, facilitating a thorough systematic review and meta-analysis of the current literature.

DATA SOURCES AND SEARCH STRATEGY

In pursuit of exploring impact of treatment of diabetic macular edema on visual impairment in people with type 2 diabetes mellitus, a comprehensive search strategy was deployed. Authors systematically scoured relevant bibliographic databases, including the PubMed, Lancet, Google Scholar, and ScienceDirect. The final search was conducted in February 2024. MeSH terms related to impact of treatment of diabetic macular edema on visual impairment in people with type 2 diabetes mellitus, and articles with relevant terms within the title or abstract were identified ("Type 2 diabetes mellitus"[All Fields] OR "Diabetes mellitus"[MeSH Terms] OR "Complications of diabetes mellitus"[All Fields]) AND ("visual impairment of diabetes mellitus"[MeSH Terms] OR "Treatment of diabetes mellitus"[All Fields] OR "diabetic macular edema"[All Fields] OR "Treatment of diabetic macular edema"[All Fields] OR "complications of treatment diabetic macular edema"[All Fields] OR "Prognosis of diabetic macular edema"[All Fields]) AND ("Risk factor of visual impairment"[MeSH Terms] OR ("mechanism of visual impairment in type 2 diabetes mellitus"[All Fields] AND "Mechanism of diabetic macular edema"[All Fields]) OR "management of diabetic macular edema"[All Fields]).

STUDY SELECTION

Title and abstract screening for eligibility was conducted by two independent investigators. Studies meeting the eligibility criteria were selected, and the full-text articles were obtained and reviewed. Any discrepancies in study selection were resolved through consensus agreement among all authors.

DATA EXTRACTION

Data extraction was performed in duplicate from full-text versions of eligible studies by authors. The data included the total number of events and controls for the treatment, complications, prognosis of diabetic macular edema on visual impairment in people with type 2 diabetes mellitus. Data presented in tabular format were the primary source for extraction.

RISK OF BIAS

The GRADE system was utilized to assess the quality of evidence. The risk of bias was evaluated based on limitations in study design, with RCTs considered high-quality evidence and observational studies as low-quality evidence. Each study underwent scrutiny for limitations, and bias was established across studies for each outcome.

HETEROGENEITY

Heterogeneity was evaluated based on similarity of point estimates, overlap of confidence intervals, and the statistic. Subgroup comparisons were created to explore potential sources of heterogeneity.

EVALUATING THE QUALITY OF EVIDENCE

The GRADE approach was employed to upgrade the quality of evidence, considering factors such as large pooled effects, dose-response relations, and confounders.

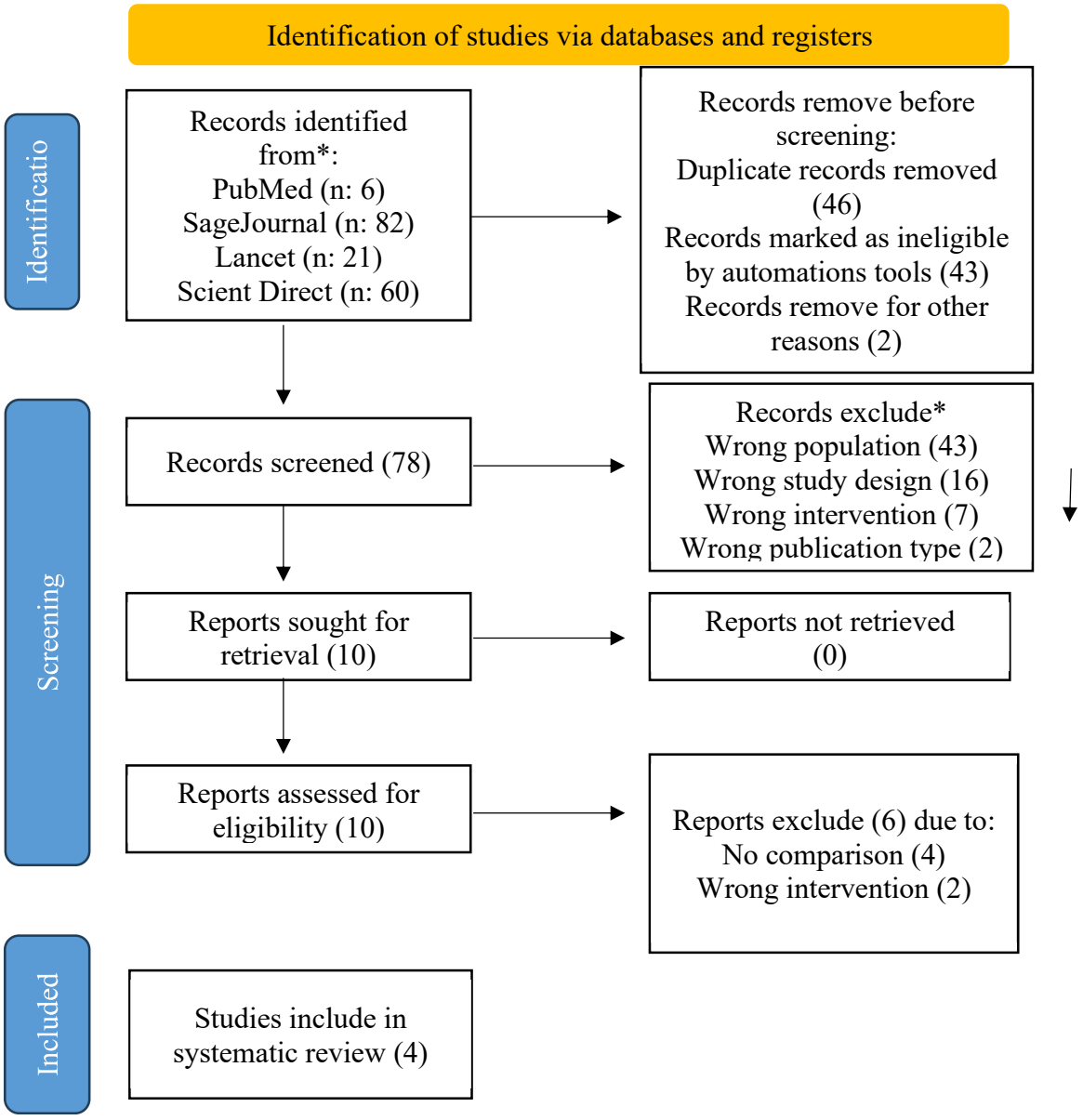

Figure 1. Article search flowchart

RESULT

After conducting three levels of screening, the results of our search in Pubmed get 6 articles, whereas the results of our search on SageJournal get 42 articles, on Lancet 21, and on Scient direct get 60 articles. Records remove before screening are 91, so we get 78 articles for screening. After we screened based on record exclude, we compiled a total of 10 papers. We included four research that met the criteria.

Author	Origin	Method	Sample Size	Outcome	Result
Zirpel, JJ et al., 2020[7]	Switzerland	Patients with newly diagnosed DME were included in this retrospective study if they had received at least three IVTs and a follow-up period≥2 years.	191 patients	The primary outcome measure was the evolution of best-corrected visual acuity (BCVA) over time.	Of 217 eyes (191 patients) with DME, 151 eyes (117 patients) fulflled the inclusion criteria (63 eyes in the frst period, 88 in the second period). Mean follow-up time was 7.9±3.1 (group 1) and

					4.1±1.4 years (group 2; p<0.001).
Massin, P et al., 2020[8]	France	This is a prospective phase 4 observational study. Between December 2013 and April 2015, 84 ophthalmologists enrolled a total of 290 adult patients initiating ranibizumab for visual impairment due to DME and treated them according to their routine practice.	290 patients	The primary outcome (mean change in best-corrected visual acuity [BCVA] after 12 months) was previously reported.	Of the 290 patients enrolled, 187 (64.5%) completed the 36 months of the study (entire cohort). In the entire cohort, 97 patients were treated exclusively with ranibizumab throughout the study, and 90 patients switched to other intravitreal treatments. Mean BCVA was 64.2 (20.1) letters, representing a gain of +4.1 (19.9) letters from baseline to month 36 (M36). CSFT improved over the study, and by M36 had decreased by 127 (138) µm compared to baseline. Over the 36 months of follow-up, patients in the entire cohort paid their ophthalmologists a mean of 30.9 (12.2) visits and had a mean of 7.6 (5.2) any injections. Results for quality of life questionnaires NEI-VFQ25 and HUI-3 remained stable throughout the study. Multivariate analysis on the 145 patients with evaluable BCVA data at M36 found that male gender and milder baseline DME characteristics (BCVA ≥59 and CSFT <500 µm) were predictive factors for achieving a BCVA of ≥70 letters at M36. This study did not find any new safety signals, compared to the known profile of ranibizumab.
Kulkarni, S et al., 2021[9]	India	This retrospective observational study was conducted in nine tertiary eye care centers between January and December 2019. Retrospective chart review of patients with DME who were initiated on treatment and followed up for at least 1 year at 9 tertiary eye care centers during 2016–2017 was performed.	1853 patients	The primary outcome was the proportion of eyes that moved up by one level from baseline VI category (mild/mod/severe VI and blindness) at 1 year.	A total 1853 patients were diagnosed with treatable DME during study period, 1315 patients were treated and 556 patients (1019 eyes) followed up at one year. Although patients achieved significantly better anatomical outcome (central macular thickness of <300µ in 32.3% at baseline compared to 60.7% at 1 year, $P <$ 0.001), visual impairment

					due to DME did not differ from baseline (mild visual impairment in 53.2% at baseline compared to 56% at 1 year, $P = 0.7$). Cystoid type of DME was the most common phenotype (432/1019, 42.4%) followed by spongy type (325, 31.9%) and cystoid plus spongy type (138, 13.5%). Bevacizumab monotherapy was the most common (388/1019, 38.1%) treatment followed by combination therapy (359, 35.2%). Mean number of anti-VEGF injections received per eye in a year was 2.1 (SD ± 0.9).
Kusuhara, S et al., 2022[10]	Japan	This is a real-world clinical study including 1,552 patients with treatment-naïve center-involved DME. The patients were categorized into 4 categories by age at baseline (C1, <55; C2, 55–64; C3, 65–74; and C4, ≥75 years).	1552 patients	To compare the effect of aging, the subjects were divided into 4 categories (C1, <55 years; C2, 55–64 years; C3, 65–74 years; and C4, ≥75 years) based on the age at baseline. The primary outcome was defined as the change in logMAR BCVA from baseline to 2 years after initial treatment. The secondary outcomes were changed in the proportion of logMAR BCVA category (>1.0, >0.3 and ≤1.0, ≤0.3) at 2 years from baseline, change in the proportion of BCVA improvement category defined as the degree of logMAR BCVA difference ('improved' [≤−0.3], 'unchanged' [−0.3 < and <0.3], and 'worsened' [≥0.3]) from baseline to	From baseline to 2 years, the mean changes in logMAR BCVA from baseline to 2 years were −0.01 in C1, −0.06 in C2, −0.07 in C3, and 0.01 in C4 ($P = 0.016$), and the mean changes in CRT were −136.2 µm in C1, −108.8 µm in C2, −100.6 µm in C3, and −89.5 µm in C4 ($P = 0.008$). Treatments applied in the 2 year period exhibited decreasing trends with increasing age category on the number of intravitreal injections of anti-VEGF agents ($P = 0.06$), selecting local corticosteroid injection ($P = 0.031$), vitrectomy ($P < 0.001$), and laser photocoagulation outside the great vascular arcade ($P < 0.001$).

				2 years, the change in CRT from baseline to 2 years, and the number of treatment and the percentage of treated eye in each treatment at the 2 year period.	

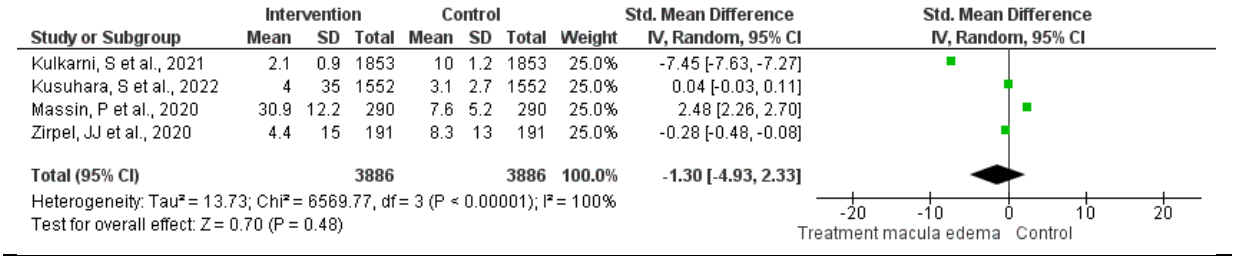

Figure 2. Forest Plot of Related Findings

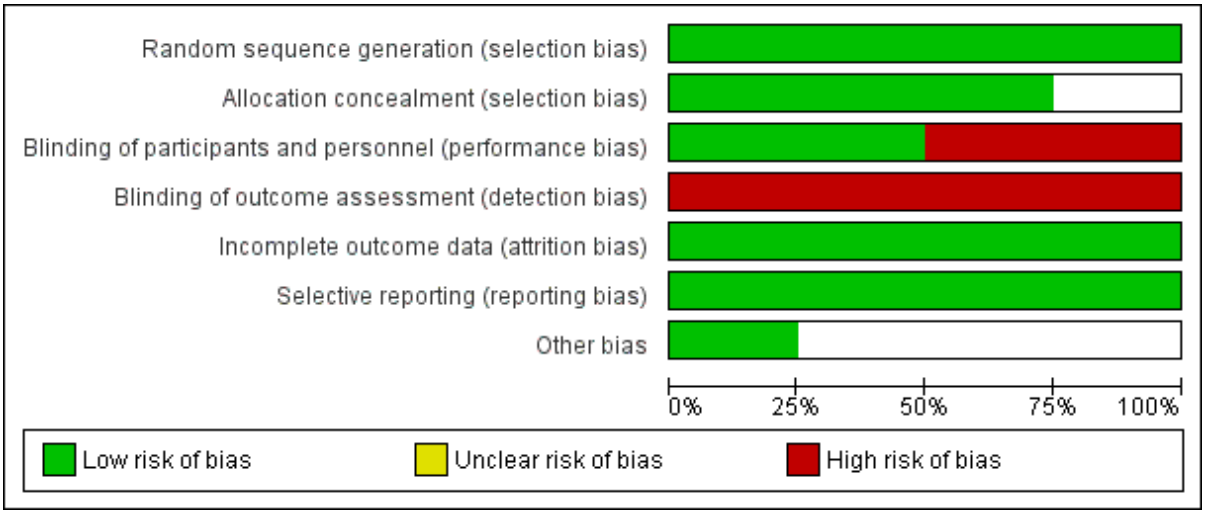

Figure 3. Risk of Bias

DISCUSSION

Both type 1 and type 2 diabetes mellitus are major causes of vision loss. Diabetic retinopathy (DRP) is a general term for vascular changes that occur in the retina that may become sight-threatening and require treatment. Diabetic macular edema (DME) is a result of vascular changes close to the macula leading to swelling of the central retina in the macula and may induce vision loss. Vision loss is the complication of diabetes that affects the person's quality of life the most. Almost every person with type 1 diabetes and more than half of the persons with type 2 diabetes develop some degree of diabetic retinopathy. Many persons with diabetes do not have regular eye examinations, although it is known that early diagnosis and treatment of sight-threatening retinopathy reduce the risk of blindness.[11]

Diabetic retinopathy (DR) is the most common cause of moderate and severe vision loss in working-age adults. Diabetic macular edema (DME) is a major cause of vision loss in DR patients and is characterized by an accumulation of extracellular fluid in the macula due to increased vascular permeability. With intravitreal anti-vascular endothelial growth factor (VEGF) and intravitreal dexamethasone implant treatment, the visual/anatomical prognosis of DME has improved. However, the visual outcomes of DME patients in real-world clinical practice were relatively poorer than those in clinical trials. Loss to follow-up (LTFU) during treatment might be one of the contributing factors that could lead to the poorer visual outcomes of DME patients in real-world practice, compared to those in clinical trials.[12,13]

Regarding treatment adherence in DME patients, about 28.8% of DME patients showed LTFU during anti-VEGF treatment in a previous report. Among these LTFU patients, some returned and received re-treatment for DME. However, there is limited understanding of the visual/anatomical outcomes of re-treatment in LTFU DME patients. Therefore, we aimed to investigate the clinical outcome of DME patients who were lost to follow-up for more than 1 year during the anti-VEGF injection. We also tried to find characteristics of the LTFU patients during treatment.[12,14]

Importantly, most research that assessed the impact of DR and DME on vision-related QoL (VRQoL) have used either the better, or worse affected eye. This is problematic because, although it generally is assumed that the better eye is the predominant determinant of overall visual function, this assumption does not account for the considerable loss of stereopsis, visual fields, and anxiety consequent to having only one seeing eye. Some VRQoL studies on bilateral visual impairment (VI) have demonstrated worsening VRQoL as vision deteriorates in the worse eye despite stable vision in the better eye.[15]

In addition, there is evidence that persons with bilateral DR experience a greater reduction in health-related QoL compared to individuals with unilateral DR. To date, however, we do not have an adequate understanding of how presence or absence of DR and DME in both eyes affects VRQoL. This information may have significant implications for DR and DME management, for instance, in terms of management modality (i.e., active preventative intervention over passive monitoring for those with DR or DME in only one eye) and prioritization (e.g., prioritizing treatment for those with DR or DME in both eyes over those with DR or DME in only one eye).[15]

CONCLUSION

Anti-VEGF therapy for DME is effective and provides similar results in patients taking oral antidiabetic agents or chronic insulin therapy. There is a particularly robust response to anti-VEGF therapy in both groups when glycemic control is optimized, highlighting the critical importance of communication between the physicians managing the DME and those managing systemic diabetes control. Improving our understanding of the factors that contribute to anti-VEGF response for DME therapy may help to enhance DME treatment outcomes, particularly through the concerted coordinated efforts of the treating retina specialist and the endocrinologist or primary care physician.

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