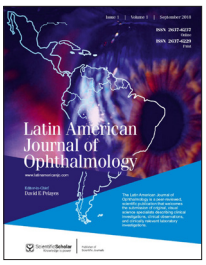
ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

www.latinamericanjo.com

Latin American Journal of Ophthalmology



Review Article *Retina*

The role and efficacy of vitrectomy for the management of refractory diabetic macular edema: Systematic review and meta-analysis

Miguel Angel Quiroz-Reyes[1], Erick Andres Quiroz-Gonzalez[2], Miguel Angel Quiroz-Gonzalez[1], Virgilio Lima-Gomez[3]

[1]Department of Retina, Oftalmologia Integral ABC, [2]Department of Ophthalmology, Ophthalmology Institute, [3]Department of Retina, Hospital Juarez de Mexico, Mexico City, Mexico.

***Corresponding author:**
Miguel Angel Quiroz-Reyes, Department of Retina, Oftalmologia Integral ABC, Mexico City, Mexico.

drquiroz@prodigy.net.mx

Received : 20 May 2023
Accepted : 19 July 2023
Published : 16 August 2023

DOI
10.25259/LAJO_11_2023

Quick Response Code:

ABSTRACT

This study aimed to evaluate the role and efficacy of vitrectomy in the management of chronic diabetic macular edema (DME) refractory to intravitreal anti-vascular endothelial growth factor (anti-VEGF) and corticosteroid treatments. A systematic review and meta-analysis were performed by searching the Embase, Medline, and gray literature. Eight hundred and thirty-nine studies were retrieved and eight were selected (three for quantitative synthesis and five for qualitative synthesis). Visual acuity (VA) and central macular thickness (CMT) were compared between the vitrectomy-treated and control groups (treated with anti-VEGF and intravitreal corticosteroid injection) using the standardized mean difference (SMD) with 95% confidence intervals (CIs) and *P*-values. There was no significant difference in post-operative VA between the vitrectomy-treated and control groups (SMD = −0.31, 95% CI: −0.76, 0.14, $P = 0.18$). However, CMT was significantly lower in the vitrectomy group than in the control group (SMD = −0.31, 95% CI: −0.76, 0.14, $P = 0.18$). In addition, the incidence of post-operative complications was higher in the control groups than that in the vitrectomy group.This systematic review and meta-analysis suggest that vitrectomy may be viable for the management of chronic DME refractory to anti-VEGF and corticosteroid agents. Although there was no significant difference in VA, the CMT was significantly reduced in the vitrectomy group. Moreover, the incidence of post-operative complications was lower in the vitrectomy group than that in the control group. Further studies are needed to confirm these findings and identify patient subgroups that may benefit from vitrectomy.

Keywords: Angiogenesis, Aflibercept, Intravitreal corticosteroids, Dexamethasone, Fluocinolone acetonide, Ranibizumab, Anti-vascular endothelial growth factor, Refractory diabetic macular edema, Triamcinolone acetonide

INTRODUCTION

Diabetic macular edema (DME), a manifestation of diabetic retinopathy (DR), is a major cause of severe visual loss in diabetic patients. Approximately 40% of patients with diabetes mellitus develop DME during their lifetime.[1] The incidence of DME increases with the severity and duration of diabetes. The Wisconsin epidemiologic study of DR found that after 10 years of follow-up, 20% and 14–25% of patients with type 1 and type 2 diabetes, respectively, developed DME.[2] The major pathophysiological cause involves the rupture of the blood-retinal barrier due to elevated vascular endothelial growth factor (VEGF) and pro-inflammatory cytokine

expression. This breakdown leads to hyperpermeability, angiogenesis, and vascular leakage, ultimately resulting in DME.[3] Vascular, neurodegenerative, and inflammatory components have been implicated as causes of DME.[4]

In refractory cases, with the financial burden and treatment complications related to anti-VEGF therapy, there is a general need for repetitive injections to maintain their therapeutic effect due to the prolonged clinical course of DME. In chronic refractory DME, the goal of developing a combination therapy is to prolong the effectiveness of these compounds acting as angiogenesis inhibitors, thus eliminating the need for frequent injections that can have serious side effects along with cost-effectiveness.[5] Optical coherence tomography (OCT) is considered the most important test for diagnosing and monitoring DME progression.[5]

Controlling systemic factors such as hyperglycemia, hypertension, and hyperlipidemia is advantageous for reducing the incidence of retinopathy in patients with type 1 and type 2 diabetes mellitus.[6,7] However, despite these interventions, a significant number of patients still experience vision loss, which has ultimately encouraged the development of pharmacological treatments for DME.[8] The first-line treatment is anti-VEGF agents, such as aflibercept or ranibizumab, whereas corticosteroids, such as dexamethasone or fluocinolone acetonide implants, are only used as second-line treatment.[9]

Patients with refractory macular edema, which is a persistent state of DME that is unresponsive to the current standard of care, including anti-VEGF and intravitreal corticosteroid agents or laser therapy, experience no visual acuity (VA) gain, a reduced anatomical response, and frequent injections therapy.[9-11] The best-known interval between treatment with anti-VEGF and dexamethasone implants has been described for persistent DME in the BEVORDEX trial.[12]

The rate of refractory DME varies among studies, with reported rates ranging from 25% to 64% in eyes with chronic DME. Understanding the prevalence and variability of refractory DME is crucial for identifying appropriate treatment strategies and may also serve as an indication for vitrectomy.[13] New strategies are being explored to manage refractory DME, including newer anti-VEGF agents, and combination therapies such as intravitreal dexamethasone implants combined with navigated 577 nm subthreshold micropulse laser.[4,14,15]

Corticosteroids have become increasingly used in DME management due to the limitations of anti-VEGF treatments.[16] These molecules are powerful non-specific anti-inflammatory agents that inhibit adhesion, leukostasis, and transmigration of leukocytes, downregulation of cytokine and prostaglandin expression, and growth factors, especially VEGF, both *in vivo* and *in vitro*.[17,18] The mechanism of action of corticosteroids in DME treatment is thought to be multifactorial and is considered the most effective against DME when delivered intravitreally.[17,19] According to the DR clinical research (DRCR) Network, randomized controlled trials (RCTs) have shown that peribulbar triamcinolone acetonide is not beneficial in patients with mild DME.[20] Three potent synthetic corticosteroids, triamcinolone acetonide, fluocinolone acetonide, and dexamethasone, have been investigated as intravitreal treatments for DME. The elimination half-life of these agents has been reported to be 2–3 h in the vitreous humor of animal models.[21] Chemicals (such as triamcinolone acetonide) may be slowly dissolved from a crystal structure to enhance the duration of action, or a specialized slow-release device is in development (e.g., dexamethasone and fluocinolone acetonide).[21]

In selected cases, additional therapeutic options include pars plana vitrectomy. Despite not being a routine surgery for patients with DME, vitrectomy not only relieves traction but also raises oxygen levels and lowers VEGF levels close to the fovea.[1]

There are several indications for vitrectomy, including coexisting epiretinal membranes and traction.[13] It has been suggested that diffuse non-tractional DME in patients with subretinal fluid may also benefit from vitrectomy.[23] Although some researchers have confirmed that vitrectomy results in reduced central retinal thickness and favorable anatomical outcomes, others have claimed that it has limited visual improvement. This may be due to several reasons, including the fact that surgeons typically decide to perform vitrectomy in patients with refractory DME, which has been previously reported to be associated with an increased risk of irreversible photoreceptor loss,[1,22] but correlated with continuous and persistent VA gain due to photoreceptors integrity in a significant percentage of patients who showed inner segment/outer segment restoration coexisting with vessel density improvement on long-term evaluations.[1] However, Michalewska *et al*.[23] reported that internal limiting membrane (ILM) peeling in patients with severe diabetic complications, such as tractional retinal detachment or vitreous hemorrhage, reduces the rate of DME in the long-term. With respect to these findings, in 2018, it was reported that patients who underwent surgery for treatment-naïve DME had good functional outcomes with a gain of over one logarithm of the minimum angle of resolution (LogMAR) in 60% of the eyes.[24]

To compare the efficacy and the role of vitrectomy versus anti-VEGF and intravitreal corticosteroid agents in treating refractory DME, we performed a systematic review and meta-analysis to quantify the efficacy and safety of these two treatments.

MATERIAL AND METHODS

Literature search and retrieval

Relevant studies comparing the outcomes of vitrectomy with those of anti-angiogenic and intravitreal corticosteroid agents for DME have been retrieved from various databases. Systematic searches of studies published after January 1, 2010, and before December 11, 2022, were conducted in PubMed, Embase, Cochrane, Medline, and ClinicalTrials.gov. Detailed keywords and search strategies are listed in the supplementary file. The following keywords were applied for the search: ("internal limiting membrane" OR "inner limiting membrane" OR "Internal limiting membrane Peeling" OR "ILM" OR "vitrectomy" OR "vitrectomies") AND ("macular edema" OR "diabetic macular edema" OR "retinopathy" OR "diabetic retinopathy" OR "DME") AND ("bevacizumab" OR "anti-VEGF therapy" OR "Avastin" OR "triamcinolone" OR "randomized controlled trials"). We also searched the reference lists of the studies included in the review for the information on other studies on vitrectomy with anti-angiogenics and intravitreal corticosteroids agents for DME. The last search was conducted on December 11, 2022, and additional searches were performed using Google Scholar to identify the reference lists of the original articles. We did not use any language restrictions in our electronic search.

Data extraction and quality assessment

All retrieved articles were screened by two authors using Covidence.org tools (MAQR and EAQG). The title and abstract of each study were independently screened and studies that satisfied the inclusion criteria were included in the study. The following data were collected from each study: first author, year of publication, sample size, mean age, pre-operative and post-operative best-corrected VA (BCVA), pre-operative and post-operative central macular thickness (CMT), post operative complications, outcomes, and follow-up durations. Disagreements between the two reviewers were resolved by discussion or by a third reviewer (VLG). The methodological index for non-randomized studies scale was used from 0 to 24 to assess non-randomized trials if all selected target studies were non-RCTs.[25] According to the Cochrane Collaboration Reviewers' Handbook,[26] RCTs were assessed as having a "high," or "low," or "unclear" risk of bias. Non-randomized studies with a score ≥18 were considered of high quality.

The inclusion standards

Studies were considered eligible for this review if they met the following criteria: (1) study design: Comparative (clinical) studies that compared the outcomes between patients receiving vitrectomy, anti-VEGF, and intravitreal corticosteroid agents for DME; (2) study objective: Patients diagnosed with DME without age, sex, or race limitations; (3) intervention: Vitrectomy versus anti-VEGF and intravitreal corticosteroid agents; (4) duration of follow-up time: studies with ≥3 months of follow-up periods were considered eligible for vitrectomy, while for anti-VEGF and intravitreal corticosteroid agents 6, 12, and 24 weeks; and (5) outcome evaluation index: BCVA, rate of vision improvement, and CMT changes from baseline after the proposed intervention, rate of CMT reduction, and secondary outcomes reported were complication incidence at the end of follow-up and ocular or systemic adverse effects observed after treatment administration.

The exclusion standards

Studies that were excluded from this systematic review and meta-analysis were as follows: (a) case report studies, non-comparative studies, conference abstracts, letters, editorials, book chapters, news articles, expert opinions, review papers, and reviews lacking original data; (b) studies in which results or patient-relevant clinical parameters were not adequately expressed, making it impossible to extract or calculate the data from the reported data; (c) studies in which patients were followed up for <3 months after vitrectomy or <6 weeks after treatment with anti-VEGF and intravitreal corticosteroid agents; and (4) studies with titles related to vitrectomy and anti-VEGF and intravitreal corticosteroid agents, but the desired findings were not mentioned, and studies with duplicated contents [Supplementary File].

Meta-analysis

The Review Manager software (V.5.3, Cochrane Collaboration, Oxford, UK) was used to conduct the meta-analysis. We assessed the percentage of BCVA improvement, CMT reduction, and complications as the variables of interest. Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated to determine the statistical significance ($P < 0.05$). Although we acknowledge the limited sample size and single-report form of each article, we recognize that the analysis of complications serves as an estimate rather than a direct comparison of the three variables. Heterogeneity was evaluated by calculating the I^2 statistic and performing a Chi-squared test (to assess *P*-value). Heterogeneity was assessed using the Chi-squared test (to assess *P*-value) and computing the I^2 statistic. Based on the detected heterogeneity, we applied a fixed-effects model, random-effects model, and meta-regression for no heterogeneity, low heterogeneity, and high heterogeneity, respectively.

RESULTS

Study selection

In this meta-analysis and systematic review, a comprehensive search was conducted across various databases and other sources (gray literature) to identify potential studies for inclusion. Initially, 883 studies were identified, of which 839 were obtained from database searches and 44 from alternative sources. Duplicates (n = 74) were removed, resulting in a reduced set of 809 unique studies. A subsequent exclusion process was applied, leading to the removal of 391 non-comparative studies and studies lacking treatment interventions for refractory DME. Consequently, a final selection of 418 articles were screened based on their titles and abstracts. Following a thorough assessment of 103 potentially relevant studies, the full texts were downloaded for further screening. Ultimately, eight studies[27-34] were deemed eligible for inclusion in the present study. A detailed Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart depicting the study selection process is shown in [Figure 1].

Characteristics of the studies

This meta-analysis and systematic review aimed to evaluate the role of vitrectomy versus anti-angiogenics agents in the treatment of refractory DME. Eight studies, comprising 203 eyes, were included in this systematic review and meta-analysis. Among them, three studies were deemed eligible for meta-analysis, which exclusively investigated the efficacy of vitrectomy in the treatment of refractory DME. To the best of our knowledge, no comparative study has assessed the efficacy of vitrectomy for refractory DME. Although studies reporting the efficacy of vitrectomy in patients with chronic DME who were unresponsive to intravitreal

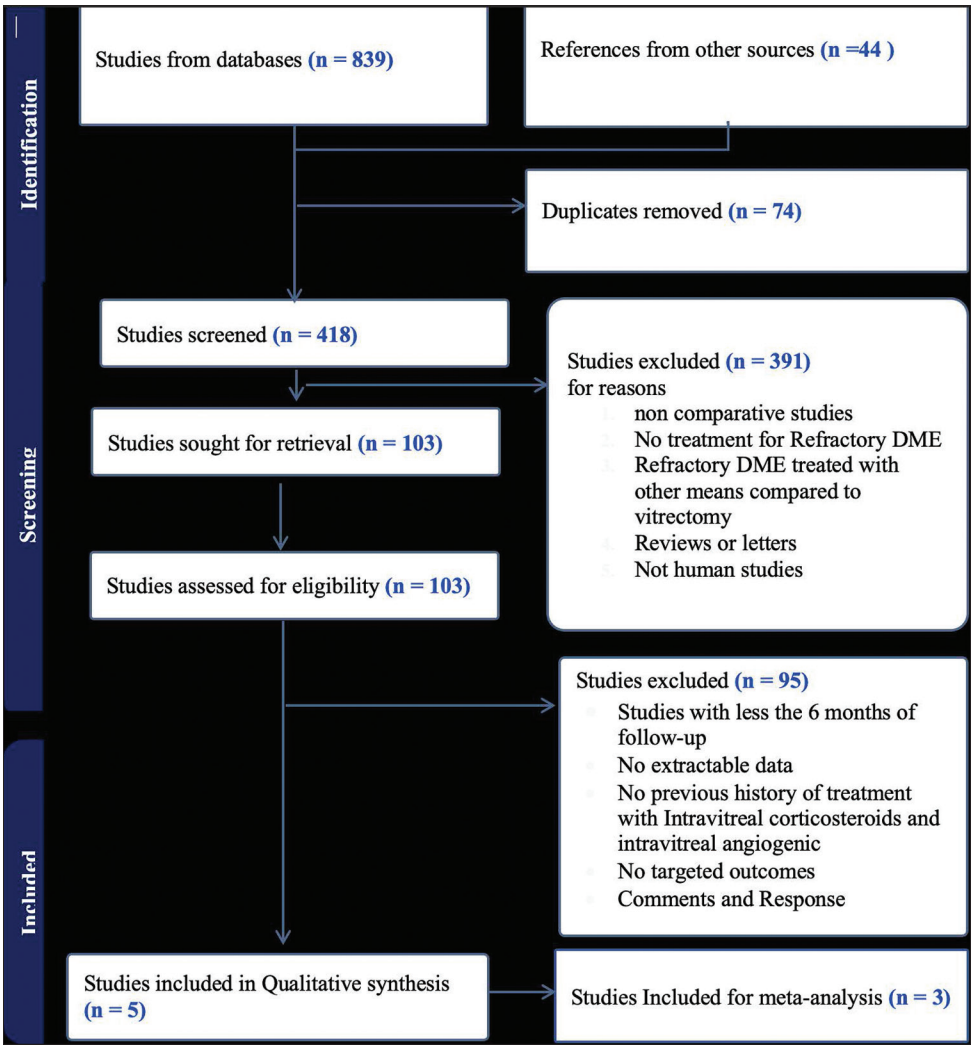


Figure 1: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart shows the sequential extraction and screening of the literature.

corticosteroid injections were not included in the meta-analysis due to a lack of available data, they were subjected to qualitative synthesis. Detailed information regarding the characteristics of the studies[27,29,32-34] that have reported refractory DMT to intravitreal corticosteroid injections is presented in [Tables 1 and 2], respectively. The quality of all the selected studies for quantitative assessment is presented in [Table 3].

Meta-analysis of efficacy

Analysis of the improvement of BCVA

In this study, we analyzed three studies[27,32,33] that evaluated the changes in BCVA in 79 eyes. Pre-operative heterogeneity was not significant among the included studies (I^2 = 0%, P = 0.79), as shown in [Figure 2a], using a fixed-effects model for the meta-analysis. The mean difference (MD) between the pre-operative and post-operative BCVA values in the intravitreal anti-VEGF therapy and vitrectomy groups indicated significant heterogeneity (I^2 = 79%) [Figure 2b]. However, no significant difference was found between the two groups (standardized MD = −0.31, 95% CI: −0.76, 0.14, P = 0.18). A fixed-effects model analysis revealed that the improvement in BCVA was not significantly different; however, there may be some variability in the outcomes between the two groups, for which further research is necessary to determine the significance of these differences.

CMT

Three studies[29-31] assessed the changes in CMT before and after surgical intervention, as shown in [Figures 2c and d]. The studies revealed a consistent decrease in CMT both preoperatively (I^2 = 29% and MD= −58.21, 95% CI: −81.50, −34.92, P < 0.00001) and postoperatively (I^2 = 44% and MD= −62.77, 95% CI: −96.77, −28.78, P = 0.0003). Notably, the heterogeneity across studies was significant, likely due to variations in the treatment criteria for macular edema. The results of the random-effects model analysis did not reveal a significant difference between the effects of intravitreal corticosteroid injections and vitrectomy on the changes in CMT (MD = −49.92, 95% CI: −103.72, 3.88, P = 0.07), as shown in [Figure 2e]. However, vitrectomy was more effective than intravitreal corticosteroid injection, as evidenced by a significant decrease in CMT.

Publication bias and heterogeneity

The present study used Begg's funnel plots to assess the symmetry of mean and risk differences in post-operative BCVA. The results showed satisfactory symmetry, as shown in [Figure 2f].

COMPLICATIONS ASSOCIATED WITH INTRAVITREAL ANTI-VEGF, INTRAVITREAL CORTICOSTEROID, AND VITRECTOMY

This study provides a detailed account of the complications arising from intravitreal anti-angiogenic (IVA) and intravitreal corticosteroid (IVC) injections as well as vitrectomy. The results are presented in [Tables 1 and 2], in which the different types of complications are described. In the IVA and IVC groups, the major complications observed were serious retinal detachment under the fovea, foveal cystoid spaces, and subretinal hemorrhage. No serious complications occurred in the vitrectomy group. However, some studies[28,30-32,34] have indicated that neovascular glaucoma and the progression of lens opacity are common complications of vitrectomy.

DISCUSSION

DME is a major complication of DR that can lead to a significant vision loss.[35-37] Despite advances in the treatment of DME, refractory DME remains difficult to treat. Vitrectomy has been suggested as the treatment option for refractory DME. However, its role remains controversial. This systematic review and meta-analysis aimed to evaluate the role of vitrectomy in the treatment of refractory DME. This study included three non-randomized studies with a total of 203 eyes. The primary outcome measures were VA and CMT measured using OCT. The results of the meta-analysis showed that vitrectomy did not significantly improve the VA in patients with refractory DME. However, there was a significant reduction in CMT after vitrectomy compared with previous treatments with IVA and IVC. The mean reduction in CMT was MD = −62.77, 95% CI: −96.77, −28.78, P = 0.0003.

Our results indicated that vitrectomy could lead to a significant reduction in CMT in patients with refractory DME. Our findings are consistent with those of previous studies,[32] in that vitrectomy helps reduce macular thickness in patients with refractory DME; however, whether VA improves after vitrectomy remains unclear. Several long-term studies have suggested that vitrectomy is beneficial for patients with refractory DME because CMT is reduced, and VA is improved.[36-40] In contrast, in a large prospective study from the DRCR Network, vitrectomy was beneficial in reducing CMT; however, its efficacy in improving VA was limited.[39] However, we did not observe a significant improvement in the VA after vitrectomy. This may be because most of the included studies were non-randomized and had small sample sizes due to the severity and duration of DME, the presence of comorbidities such as DR and macular ischemia, the surgical technique, and the surgeon's experience. Furthermore, the absence of a significant improvement in VA may also be because VA is a subjective measure influenced by factors such as cataracts, macular ischemia, and variability in the testing conditions.

Table 1: Studies included in the meta-analysis.

Study/design	Sex (M/F)	Mean age (years)	No. of eyes	Treatment	Previous treatment	Duration between treatments (months)	Pre-operative CRT (µm)	Post-operative CRT (µm)	Pre-operative VA (LogMAR)	Post-operative VA (LogMAR)	Adverse events after previous treatments	Adverse events after vitrectomy	Follow-up (months)
(Shirakata *et al.*, 2016)[28]	14	66.4±5.3	16	-	Anti-VEGF injections	6.5±4.7 (1–16)	566±193	396±159	0.88±0.57	0.85±0.46	Hypertension, 8 eyes (53.3%);	Three eyes developed neovascular glaucoma	1
Retrospective	8/7	67.6±11.6	15	Vitrectomy	-		566±193	374±143	0.88±0.57	1.01±0.51	Foveal cystoid spaces, 15 eyes (100.0%); Serous retinal detachment under the fovea, 8 eyes (53.3%); Subretinal hemorrhage under the fovea, 3 eyes (20.0%)		21.2±12.9
(Mukai *et al.*, 2021)[30]	19/6	64.6±2.2	27	-	Intravitreal anti-VEGF	21.0±15.0	550±24	415±50	0.49±0.29	0.55±0.33	Nine of the 27 eyes had vitreomacular traction or epiretinal membrane	No serious complications were reported	12
Retrospective			9	Vitrectomy	-		485±35	331±55	0.56±0.12	0.14±0.07			
(Dehghan *et al.* 2010)[31]	6/6	59.6±3.9	12	-	Intravitreal anti-VEGF	7.1 (Range 5–14)	467±107	315±95	1.00±0.80	0.82±0.18	Pseudophakic eyes and mild lens opacity	Progression of diabetic retinopathy from NPDR to PDR with vitreous hemorrhage occurred in 2 eyes; neovascular glaucoma occurred in one eye; Progression in lens opacity occurred in 5 eyes	4.9±1.0
Prospective				Vitrectomy	-	5 (Range, 4–9)	468±107	307±97	0.68±0.31	0.80±0.19			

NPDR: Non-proliferative diabetic retinopathy, BCVA: Best-corrected visual acuity, CMT: Central macular thickness, M: Male, F: Female, PDR: Proliferative diabetic retinopathy, Anti-VEGF: Anti-vascular endothelial growth factor, LogMAR: Logarithm of the minimum angle of resolution, VA: Visual acuity, CRT: Central retinal thickness

Table 2: Studies included for systematic review.

	Shirakata *et al.*[29]	**Hwang *et al.*[32]**	**Kim *et al.*[33]**	**Ghassemi *et al.*[27]**	**Song *et al.*[34]**
Sex (M/F)	14/10	26/13	15/13	5/6	28/23
Study design	Retrospective	Retrospective	Retrospective	Prospective	Retrospective
Mean age (years)	66.4±5.3	57.8±8.2	58.1±12.5	60.33±9.01	59±10
Number of eyes	24	43	28	14	55
Vitrectomy treatment	24	43	26	12	55
Anti-VEGF	24	42	28	12	-
IV corticosteroid treatment	6	4	7	12	27
CRT Improvement after vitrectomy	CRT was significantly reduced at 1 month (P=0.031) after the surgery, and the reduction appeared to have increased with time (P=0.007) at the final visit.	The CMT was 478±122 µm before the surgery, which improved to 314±90 µm 3 years after vitrectomy (P<0.001).	The mean CSTs were 479.9±100.5 µm, and 291.1±72.5 µm before surgery and after vitrectomy, respectively.	The mean CSMT reduced from 559.25±89.65 µm (baseline) to 354.91±76.41 µm (final)	The pre-operative macular thickness 440±130 µm significantly decreased to 306±97 µm post-operatively (P<0.001).
VA improvement after vitrectomy	At the final visit, however, improvement in VA was statistically significant when compared with the baseline VA (P=0.048) but not significant when compared with the pre-operative VA (P=0.078).	Pre-operative VA was 0.526±0.417 (LogMAR), which improved to 0.294±0.374 at 3 years postoperatively (P<0.001).	In the eyes treated with vitrectomy, the mean log MAR BCVA values were 0.47±0.13, and 0.41±0.22 before surgery and after vitrectomy, respectively.	The mean BCVA (logMAR) changed from 0.84±0.32 at baseline to 0.72±0.26 at the last visit	The mean pre-operative BCVA (logMAR) was 0.91±0.40, which improved to 0.72±0.39 postoperatively. The improvement of VA was more than two lines in 27 (49%) eyes.
Adverse events reported before vitrectomy					
Foveal cystoid spaces	21 (87.5%) eyes	N/R	N/R	Significant visual consequences: vitreous loss in combined phaco-vitrectomy procedures, iatrogenic insult to macula or optic nerve, endophthalmitis, significant intraoperative/ early post-operative choroidal effusion/ hemorrhage, significant intraoperative/ early post-operative vitreous cavity hemorrhage, intraoperative/ early post-operative retinal detachment.	N/R
Serous retinal detachment under the fovea	11 (45.8%) eyes	N/R	N/R		N/R
Subretinal hemorrhage under the fovea	10 (41.7%) eyes	N/R	N/R		N/R
Epiretinal membrane	4 (16.7%) eyes	N/R	N/R		32 (58%)
Incomplete perfusion within the macular area	8 (38.1%) eyes	N/R	N/R		N/R
Cataract development	N/R	N/R	N/R		13 (24%)
Presence of hypertension, No. (%)	N/R	19/39 (48.7)	N/R		N/R
Presence of dyslipidemia, No. (%)	N/R	7/39 (17.9)	N/R		N/R

(*Contd...*)

Table 2: (*Continued*).

	Shirakata *et al.*[29]	Hwang *et al.*[32]	Kim *et al.*[33]	Ghassemi *et al.*[27]	Song *et al.*[34]
Adverse events reported after vitrectomy	No serious complications were seen during or after the treatment	Seventeen (40%) eyes experienced a temporary increase in IOP. No other complications were observed during the follow-up period.	7 of 19 eyes (36.8%) were phakic. There were no severe post-operative complications such as retinal detachment, iris neovascularization, or endophthalmitis.	No serious complications were seen during or after the treatment	Deterioration of BCVA was noted in 6 eyes (11%). Two eyes had increased IOP. No eye had complications such as iris neovascularization, and retinal detachments during the follow-up period.
Follow-up (months)	13.8±10.8	36	6	13.5±4.48	8.3±7.0 (6–26)
Comments	CRT was significantly decreased, but there was no significant reduction in VA	Overall, the vitrectomy improved the VA and was considered as the best approach in most of the cases.	The pre-operative CRT was slightly larger in the vitrectomy group, the difference was not significant (P=0.062). The changes in BCVA between the pre-operative and post-operative visit were not significant between the two groups (P=0.790, and P=0.339, respectively).	The vitrectomy treatment did not improve BCVA significantly, despite reducing central macular thickness in eyes with refractory DME.	The mean post-operative VA was significantly better than the pre-operative VA (P<0.001).

CRT: Central retinal thickness, BCVA: Best-corrected visual acuity, LogMAR: Logarithm of the minimum angle of resolution, VA: Visual acuity, IOP: Intraocular pressure

Table 3: MINORS score for assessing the study quality.

MINORS	Mukai *et al.*[30]	Shirakata *et al.*[28]	Dehghan *et al.*[31]
1. A clearly stated aim	2	2	2
2. Inclusion of consecutive patients	2	2	2
3. Prospective collection of data	2	0	0
4. Endpoints appropriately align with the aim of the study	2	2	2
5. Unbiased assessment of the study endpoint	1	1	1
6. Length of the follow-up period appropriately aligns with the aim of the study	2	2	2
7. Loss to follow-up <5%	2	2	2
8. Prospective calculation of the study size	0	0	0
9. An adequate control group	2	2	2
10. Comparative groups	2	1	2
11. Equivalence of baseline characteristics of the groups	2	2	2
12. Adequate statistical analyses	2	2	1
13. MINORS score	20	18	18

MINORS: Methodological index for non-randomized studies

One of the major concerns associated with IVA and IVC is the risk of complications.[41-43] In our study, due to the limitations of the single report form of each article and the limited sample size, we acknowledge that a direct comparison of complications among the three variables was not conducted; rather, the complication analysis was more an estimation than

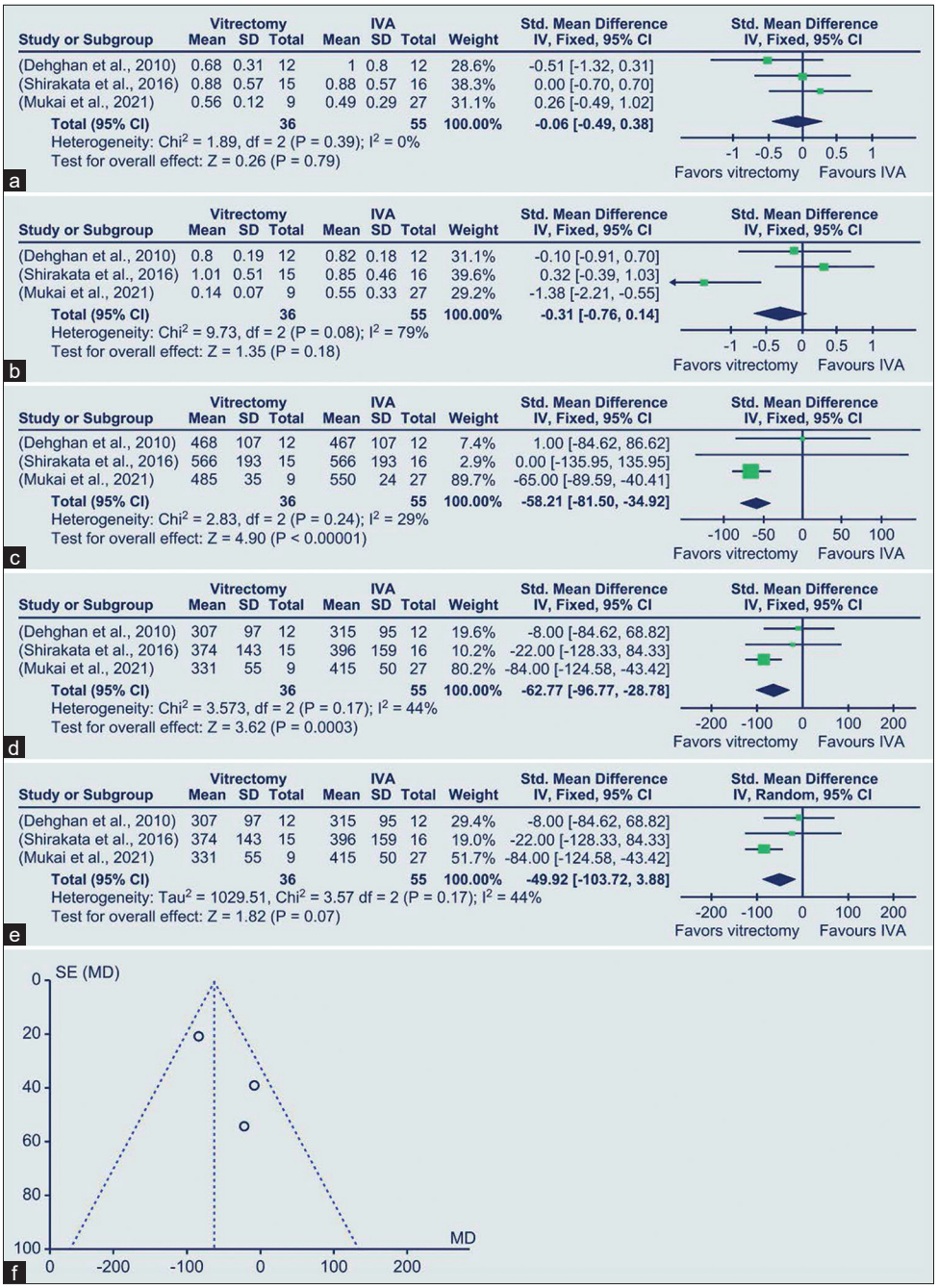


Figure 2: Analysis of the improvement of best-corrected visual acuity (BCVA) and comparison of pre-operative/post-operative central macular thickness (CMT). (a) Comparison of pre-operative BCVA between the two groups. (b) Comparison of post-operative BCVA between the two groups. (c) Comparison of pre-operative CMT between the two groups through a fixed-effects model. (d) Comparison of post-operative CMT between the two groups using a fixed-effects model. (e) Comparison of pre-operative CMT between the two groups using a random effects model. (f) The funnel plot shows that all the studies resided inside the funnel.

a direct analysis. We found that the incidence of complications was higher in the control group than in the vitrectomy group and that the types of complications differed between the two groups. The most common complications in the vitrectomy group were neovascular glaucoma formation and intraocular pressure elevation, which is consistent with previous reports in the literature.[44] In the IVA and IVC groups, multiple complications were reported in the included studies; however,

the major complications were serious retinal detachment under the fovea, foveal cystoid spaces, and subretinal hemorrhage, consistent with previous studies.[45-48] These findings suggest that vitrectomy may be a viable treatment option for refractory DME in cases where other treatments have failed to adequately reduce CMT. The reduction in CMT observed in this meta-analysis may have had a positive impact on long-term visual outcomes because chronic refractory macular edema is a major contributor to vision loss in DME.

Our study has several limitations that need to be considered. First, most of the included studies were non-randomized and had small sample sizes, which limited the strength of our conclusions. Second, it is important to note that the studies included in this meta-analysis had a relatively short follow-up period, ranging from 6 months to 2 years. Therefore, the long-term effects of vitrectomy on visual outcomes and the need for additional treatments require further investigation. Third, the included studies used different vitrectomy techniques, which may have influenced their outcomes. Fourth, the analysis of the complications was more an estimate rather than a direct statistical analysis of the complications as a variable.

CONCLUSION

Vitrectomy appears to be a promising treatment option for refractory DME and significantly reduces the incidence of CMT. However, its role in the improvement of VA remains unclear. Future studies with longer follow-up periods are needed to determine the optimal timing, patient selection criteria, and long-term outcomes of vitrectomy in patients with chronic refractory DME.

Ethical Approval

This study adhered to the tenets of the Declaration of Helsinki and received full approval from the appropriate Research Ethics Committee, Institutional Review Committee, and institutional teaching department (the institutions did not provide reference numbers for the meta-analyses).

Authors contributions

MAQR: Study conception, manuscript writing, dataset interpretation, statistical analysis interpretation, final revision, and conclusions. EAQG: Figure artwork, tables, and material compilation. MAQG: Figure and table construction. VLG: Statistical analysis and final revision. All the authors have approved the manuscript for submission.

Acknowledgments

We express our deep appreciation to the technical staff of the Retina Department at Oftalmologia Integral ABC (Non-profit Medical and Surgical Organization), Mexico City, Mexico, which is affiliated with the Postgraduate Study Division at the National Autonomous University of Mexico.

Institutional review board statement

This study was conducted in the Retina Department of the Oftalmologia Integral ABC Institution, Mexico City, Mexico. The Institutional Review Board approved the study according to the institutional guidelines. No reference numbers were provided for the systematic reviews or meta-analyses at this institution.

Data availability statement

The datasets used in this study are included in the main article. Photographs and figures from this study may be released through a written application to the Photographic Laboratory and Clinical Archives Retina Department at Oftalmologia Integral ABC, Medical and Surgical Assistance Institution (non-profit organization), Av. Paseo de las Palmas 735 suite 303, Lomas de Chapultepec, Mexico City 11000, Mexico, and the corresponding author on request or in the Supplementary File.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Nawrocka ZA, Nawrocki J. Vitrectomy in diabetic macular edema: A swept-source OCT angiography study. Ophthalmol Sci 2022;2:100207.
2. Sorour OA, Levine ES, Baumal CR, Elnahry AG, Braun P, Girgis J, *et al*. Persistent diabetic macular edema: Definition, incidence, biomarkers, and treatment methods. Surv Ophthalmol 2023;68:147-74.
3. Tan GS, Cheung N, Simó R, Cheung GC, Wong TY. Diabetic macular oedema. Lancet Diabetes Endocrinol 2017;5:143-55.
4. Toto L, D'Aloisio R, Quarta A, Libertini D, D'Onofrio G, De Nicola C, *et al*. Intravitreal dexamethasone implant (IDI) Alone and combined with navigated 577 nm Subthreshold micropulse laser (SML) for diabetic macular oedema. J Clin Med 2022;11:5200.
5. Gull A, Niazi FA, Raza A. Intravitrealversus posterior subtenon triamcinolone acetonide in conjunction with intravitreal

bevacizumab for refractory diabetic macular edema. Pak J Ophthalmol 2022;38:186-92.
6. Diabetes Control and Complications Trial Research Group, Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, *et al*. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977-86.
7. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with Type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:837-53.
8. Javey G, Schwartz SG, Flynn HW. Emerging pharmacotherapies for diabetic macular edema. Exp Diabetes Res 2012;2012:548732.
9. Haritoglou C, Maier M, Augustin A. Pathophysiology of diabetic macular edema-A background for current treatment modalities. Exp Rev Ophthalmol 2018;13:273-81.
10. Kuroiwa DA, Malerbi FK, Regatieri CV. New insights in resistant diabetic macular edema. Ophthalmologica 2021;244:485-94.
11. Munk MR, Somfai GM, de Smet MD, Donati G, Menke MN, Garweg JG, *et al*. The role of intravitreal corticosteroids in the treatment of DME: Predictive OCT biomarkers. Int J Mol Sci 2022;23:7585.
12. Mehta H, Fraser-Bell S, Nguyen V, Lim LL, Gillies MC. The interval between treatments of bevacizumab and dexamethasone implants for diabetic macular edema increased over time in the BEVORDEX trial. Ophthalmol Retina 2018;2:231-4.
13. Diabetic Retinopathy Clinical Research Network Writing Committee, Haller JA, Qin H, Apte RS, Beck RR, Bressler NM, *et al*. Vitrectomy outcomes in eyes with diabetic macular edema and vitreomacular traction. Ophthalmology 2010;117:1087-93.e3.
14. Bainbridge J. Refractory diabetic macular edema. J Ophthalmic Vis Res 2010;5:143-4.
15. Stefanini FR, Badaró E, Falabella P, Koss MJ, Eid FM, Maia M. Anti-VEGF for the management of diabetic macular edema. J Immunol Res 2014;2014:632307.
16. Bandello F, Battaglia Parodi M, Tremolada G, Lattanzio R, De Benedetto U, Iacono P. Steroids as part of combination treatment: The future for the management of macular edema? Ophthalmologica 2010;224 Suppl 1:41-5.
17. Schwartz SG, Flynn HW Jr., Scott IU. Intravitreal corticosteroids in the management of diabetic macular edema. Curr Ophthalmol Rep 2013;1:10.1007/s40135-013-0015-3.
18. Antonetti DA, Wolpert EB, DeMaio L, Harhaj NS, Scaduto RC Jr. Hydrocortisone decreases retinal endothelial cell water and solute flux coincident with increased content and decreased phosphorylation of occludin. J Neurochem 2002;80:667-77.
19. Golan S, Loewenstein A. Steroids and the management of macular edema. Ophthalmologica 2010;224 Suppl 1:31-40.
20. Diabetic Retinopathy Clinical Research Network, E Chew, S Strauber, Beck R, Aiello LP, Antoszyk A, *et al*. Randomized trial of peribulbar triamcinolone acetonide with and without focal photocoagulation for mild diabetic macular edema: A pilot study. Ophthalmology 2007;114:1190-6.
21. Edelman JL. Differentiating intraocular glucocorticoids. Ophthalmologica 2010;224 Suppl 1:25-30.
22. Ichiyama Y, Sawada O, Mori T, Fujikawa M, Kawamura H, Ohji M. The effectiveness of vitrectomy for diffuse diabetic macular edema may depend on its preoperative optical coherence tomography pattern. Graefes Arch Clin Exp Ophthalmol 2016;254:1545-51.
23. Michalewska Z, Bednarski M, Michalewski J, Jerzy N. The role of ILM peeling in vitreous surgery for proliferative diabetic retinopathy complications. Ophthalmic Surg Lasers Imaging Retina 2013;44:238-42.
24. Michalewska Z, Stewart MW, Landers MB 3rd, Bednarski M, Adelman RA, Nawrocki J. Vitrectomy in the management of diabetic macular edema in treatment-naïve patients. Can J Ophthalmol 2018;53:402-7.
25. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): Development and validation of a new instrument. ANZ J Surg 2003;73:712-6.
26. Higgins JP, Altman DG. Assessing risk of bias in included studies. In: Cochrane Handbook for Systematic Reviews of Interventions. London: Cochrane Collaboration; 2008. p. 187-241.
27. Ghassemi F, Bazvand F, Roohipoor R, Yaseri M, Hassanpoor N, Zarei M. Outcomes of vitrectomy, membranectomy and internal limiting membrane peeling in patients with refractory diabetic macular edema and non-tractional epiretinal membrane. J Curr Ophthalmol 2016;28:199-205.
28. Shirakata Y, Fujita T, Nakano Y, Shiraga F, Tsujikawa A. Pars plana vitrectomy combined with internal limiting membrane peeling to treat persistent macular edema after anti-vascular endothelial growth factor treatment in cases of ischemic central retinal vein occlusion. Case Rep Ophthalmol 2016;7:1-8.
29. Shirakata Y, Fukuda K, Fujita T, Nakano Y, Nomoto H, Yamaji H, *et al*. Pars plana vitrectomy combined with internal limiting membrane peeling for recurrent macular edema due to branch retinal vein occlusion after antivascular endothelial growth factor treatments. Clin Ophthalmol 2016;10:277-83.
30. Mukai R, Matsumoto H, Akiyama H. Surgical outcomes of vitrectomy for intractable diabetic macular edema. Graefes Arch Clin Exp Ophthalmol 2021;259:363-8.
31. Dehghan MH, Salehipour M, Naghib J, Babaeian M, Karimi S, Yaseri M. Pars plana vitrectomy with internal limiting membrane peeling for refractory diffuse diabetic macular edema. J Ophthalmic Vis Res 2010;5:162-7.
32. Hwang S, Kang SW, Kim KT, Noh H, Kim SJ. Three-year outcomes of vitrectomy combined with intraoperative dexamethasone implantation for non-tractional refractory diabetic macular edema. Sci Rep 2021;11:1292.
33. Kim JH, Kang SW, Ha HS, Kim JR. Vitrectomy combined with intravitreal triamcinolone acetonide injection and macular laser photocoagulation for nontractional diabetic macular edema. Korean J Ophthalmol 2013;27:186-93.
34. Song SJ, Sohn JH, Park KH. Evaluation of the efficacy of vitrectomy for persistent diabetic macular edema and associated factors predicting outcome. Korean J Ophthalmol 2007;21:146-50.
35. Ixcamey M, Palma C. Diabetic macular edema. Dis Mon

2021;67:101138.
36. Hartley KL, Smiddy WE, Flynn HW, Murray TG. Pars plana vitrectomy with internal limiting membrane peeling for diabetic macular edema. Retina 2008;28:410-9.
37. Kumagai K, Furukawa M, Ogino N, Larson E, Iwaki M, Tachi N. Long-term follow-up of vitrectomy for diffuse nontractional diabetic macular edema. Retina 2009;29:464-72.
38. Rosenblatt BJ, Shah GK, Sharma S, Bakal J. Pars plana vitrectomy with internal limiting membranectomy for refractory diabetic macular edema without a taut posterior hyaloid. Graefes Arch Clin Exp Ophthalmol 2005;243:20-5.
39. Flaxel CJ, Edwards AR, Aiello LP, Arrigg PG, Beck RW, Bressler NM, *et al*. Factors associated with visual acuity outcomes after vitrectomy for diabetic macular edema: Diabetic retinopathy clinical research network. Retina 2010;30:1488-95.
40. Kim J, Kang SW, Shin DH, Kim SJ, Cho GE. Macular ischemia and outcome of vitrectomy for diabetic macular edema. Jpn J Ophthalmol 2015;59:295-304.
41. Dugel PU, Bandello F, Loewenstein A. Dexamethasone intravitreal implant in the treatment of diabetic macular edema. Clin Ophthalmol 2015;9:1321-35.
42. Augustin AJ, Schmidt-Erfurth U. Verteporfin therapy combined with intravitreal triamcinolone in all types of choroidal neovascularization due to age-related macular degeneration. Ophthalmology 2006;113:14-22.
43. Kumar B, Gupta SK, Saxena R, Srivastava S. Current trends in the pharmacotherapy of diabetic retinopathy. J Postgrad Med 2012;58:132-9.
44. Pacella F, Agostinelli E, Carlesimo SC, Nebbioso M, Secondi R, Forastiere M, *et al*. Management of anterior chamber dislocation of a dexamethasone intravitreal implant: A case report. J Med Case Rep 2016;10:282.
45. Blumenkranz MS, Haller JA, Kuppermann BD, Williams GA, Ip M, Davis M, *et al*. Correlation of visual acuity and macular thickness measured by optical coherence tomography in patients with persistent macular edema. Retina 2010;30:1090-4.
46. Shikari H, Silva PS, Sun JK. Complications of intravitreal injections in patients with diabetes. Semin Ophthalmol 2014;29:276-89.
47. Adelman RA, Zheng Q, Mayer HR. Persistent ocular hypertension following intravitreal bevacizumab and ranibizumab injections. J Ocul Pharmacol Ther 2010;26:105-10.
48. Jonas JB, Kreissig I, Söfker A, Degenring RF. Intravitreal injection of triamcinolone for diffuse diabetic macular edema. Arch Ophthalmol 2003;121:57-61.

How to cite this article: Quiroz-Reyes MA, Quiroz-Gonzalez EA, Quiroz-Gonzalez MA, Lima-Gomez V. The role and efficacy of vitrectomy for the management of refractory diabetic macular edema: Systematic review and meta-analysis. Lat Am J Ophthalmol 2023:6:12.

SUPPLEMENTARY FILES

Search strategy

Medline

#	Searches	Results
1	Macular edema OR macular edema OR DMO OR diabetic macular edema	16460
2	Diabetic retinopathy OR diabetic maculopathy	39530
3	1 OR 2	49636
4	Intravitreal angiogenic OR anti-VEGF*	9224
5	Ranibizumab OR lucentis OR bevacizumab OR avastin or pegaptanib OR macugen or aflibercept OR vegf trap-eye OR antivascular endothelial growth factor*	28274
6	4 OR 5	32878
7	3 AND 6	5177
8	Steroid* OR corticosteroid* OR intravitreal corticosteroid	464463
9	*(Dexamethasone or fluocinolone or triamcinolone or corticosteroid intravitreal implants or intravitreal dexamethasone drug delivery system or steroid implants or dexamethasone insert or Ozurdex or fluocinolone acetonide insert or Retisert or intravitreal triamcinolone acetonide or Iluvien).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]*	92651
10	8 OR 9	534025
11	3 AND 10	4429
12	Vitrectomy OR Vitreoretinal Surgery OR pars plana vitrectomy	23878
13	*(Vitrectomy or Vitreoretinal Surgery or pars plana vitrectomy or Vitrectom* or vitreoretinal surger*). mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]*	24087
14	12 OR 13	24087
15	3 AND 14	4230
16	7 AND 11 AND 15	158

Embase

#	Searches	Results
1	Macular edema OR macular edema OR DMO OR diabetic macular edema	25329
2	Diabetic retinopathy OR diabetic maculopathy	63716
3	1 OR 2	80675
4	Intravitreal angiogenic OR anti-VEGF*	15929
5	Ranibizumab OR lucentis OR bevacizumab OR avastin or pegaptanib OR macugen or aflibercept OR vegf trap-eye OR antivascular endothelial growth factor*	84609
6	4 OR 5	91737
7	3 AND 6	9780
8	Steroid* OR corticosteroid* OR intravitreal corticosteroid	875643
9	*(Dexamethasone or fluocinolone or triamcinolone or corticosteroid intravitreal implants or intravitreal dexamethasone drug delivery system or steroid implants or dexamethasone insert or Ozurdex or fluocinolone acetonide insert or Retisert or intravitreal triamcinolone acetonide or Iluvien).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]*	237211
10	8 OR 9	1047616
11	3 AND 10	8486
12	Vitrectomy OR vitreoretinal surgery OR pars plana vitrectomy	34884
13	*(Vitrectomy or Vitreoretinal Surgery or pars plana vitrectomy or Vitrectom* or vitreoretinal surger*). mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]*	35064
14	12 OR 13	35064
16	3 AND 14	6987
17	7 AND 11 AND 15	651

CINAHL

Search ID#	Searches	Results
S1	Macular edema OR macular edema OR DMO OR diabetic macular edema	3168
S2	Diabetic retinopathy OR diabetic maculopathy	3168
S3	1 OR 2	3168
S4	Intravitreal angiogenic OR anti-VEGF*	2029
S5	Ranibizumab OR lucentis OR bevacizumab OR avastin or pegaptanib OR macugen or aflibercept OR vegf trap-eye OR antivascular endothelial growth factor*	7,943
S6	4 OR 5	9,142
S7	3 AND 6	963
S8	Steroid* OR corticosteroid* OR intravitreal corticosteroid	73,566
S9	Dexamethasone or fluocinolone or triamcinolone or corticosteroid intravitreal implants or intravitreal dexamethasone drug delivery system or steroid implants or dexamethasone insert or Ozurdex or fluocinolone acetonide insert or Retisert or intravitreal triamcinolone acetonide or Iluvien	12,819
S10	8 OR 9	82,803
S11	3 AND 10	869
S12	Vitrectomy OR vitreoretinal surgery OR pars plana vitrectomy	2,791
S13	Vitrectomy or vitreoretinal surgery or pars plana vitrectomy or vitrectom* or vitreoretinal surger*	2,849
S14	12 OR 13	2,849
S15	3 AND 14	231
S16	7 AND 11 AND 15	30

Gray Literature

Clinical Trials – https://clinicaltrials.gov/(Searched March 18, 2023)

1. (Diabetic macular edema) AND (Vitrectomy) AND (Corticosteroid)
   10 results
2. (Diabetic macular edema) AND (Vitrectomy) AND (Intravitreal angiogenic OR anti-VEGF)
   30 results

1. Conference Proceeding Searches

Conference	Link	Years searched	Search terms	Results/Comments
ARVO	https://arv ojournals. org/index. aspx	01/01/2015 to 03/01/2023	Meeting abstract AND (Diabetic macular edema) AND (Vitrectomy) AND (Intravitreal corticosteroid) AND (Intravitreal angiogenic OR anti-VEGF)	4
AAO All Meetings	https://secure.aao.org/aao/mee tingarchive	"All years available"	Topic: Retina, Vitreous Keywords: "Diabetic macular edema*," "Intravitreal corticosteroid," "Intravitreal angiogenic*," "Vitrectom*"	No relevant abstracts/ presentations found March 18, 2023