Vitrectomy in Diabetic Macular Edema: A Swept-source OCT Angiography Study

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Purpose: The foveal avascular zone (FAZ) has been reported to decrease after anti-VEGF injections in diabetic macular edema (DME) in the long term. This study aimed to present the changes in swept-source OCT angiography after vitrectomy in patients with DME.

Design: Retrospective interventional study.

Participants: Thirty-five eyes were included (mean age: 62 years).

Methods: Patients were followed for 12 months after vitrectomy with internal limiting membrane peeling for DME.

Main Outcome Measures: The following parameters were measured: central retinal thickness (CRT), central choroidal thickness, superficial FAZ, deep FAZ (dFAZ), and vessel density in the superficial and deep retinal layers (dVD).

Results: The CRT and superficial FAZ significantly decreased after surgery (401 μm–338 μm; P < 0.00, 401 μm–293 μm; P < 0.001, respectively). Initial visual acuity (VA) improved from 20/160 (0.97 logarithm of the minimum angle of resolution [LogMAR]) to 20/80 (0.62 LogMAR) (P < 0.001). The vessel density in the superficial retinal layers rate was 42.3% and decreased after surgery, reaching 41.6% at the end of the follow-up. The dVD rate 1 week after surgery was 28.9% and remained stable throughout the observation period. The most important prognostic factors for the final VA were preoperative VA and preoperative CRT, while the dFAZ and dVD at the time of edema resolution also correlated with the final VA.

Conclusions: The superficial FAZ decreases after vitrectomy, which might indicate that vitrectomy has a protective effect on DME, similar to anti-VEGF injections. Prognostic factors for better final functional results are better initial VA and lower CRT before vitrectomy, in addition to a lower dFAZ diameter and a higher dVD at the moment of edema resolution.

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retinal and choroidal vessels. The size of the foveal avascular zone (FAZ) has been shown to be correlated with advancement of diabetic retinopathy. Anti-VEGF treatment, besides its beneficial influence on visual acuity (VA), was also reported to decrease the FAZ in patients treated for DME. This was more significant in the long term, especially at the level of deep retinal layers. Some changes in SS-OCTA parameters have also been discussed in eyes vitrectomized for different indications. Although vitrectomy is not a routine surgery in DME, it not only relieves traction but also increases oxygen concentration and lowers VEGF levels near the fovea. Thus, some changes in SS-OCTA findings might be expected in these eyes.

Recently, vitrectomy with subfoveal balanced salt solution (BSS) was proposed in DME. The suggested mechanisms of action would be decrease of osmotic pressure and viscosity of subfoveal fluid, promoting water transport from the subretinal space to the choroid through the retinal pigment epithelium and washing out cytokines and migratory cells.

Here, we present the results of vitrectomy with subretinal BSS injection in treatment-naive patients and in patients previously treated with anti-VEGF agents. We have also discussed the influence of changes in SS-OCTA images on the final functional outcome.

Methods

This retrospective interventional study was approved by the Local Ethics Committee at Ophthalmic Clinic Jasné Blonia and followed the tenets of the Declaration of Helsinki. All patients signed an informed consent form. We included consecutive diabetic patients (type 1 or 2 diabetes) with confirmed DME on OCT. None of the patients had previously undergone laser photoocoagulation in the macula. Patients who had received anti-VEGF injections earlier were allowed for inclusion in this study if the time since the last injection exceeded >3 months before surgery. These patients had refused further anti-VEGF treatment due to planned pregnancy (4 patients) or financial or logistical reasons. None of them were anti-VEGF nonresponders. A thorough discussion with all patients, informing them about the risks and benefits of such a decision, was performed.

All patients underwent a complete ophthalmic examination before and then 1 week and 1, 3, 6, and 12 months after surgery. Additionally, spectral-domain OCT (Spectralis, Heidelberg Engineering) and SS-OCTA (Triton, Topcon) were performed during each follow-up. The following parameters were measured: CRT, central choroidal thickness (CCT), diameter of the superficial FAZ, deep FAZ (dFAZ), vessel density in the superficial retinal layers, and vessel density in the deep retinal layers (dVD).

The foveal avascular zone was defined as the area around the central fovea with no demarcated vessels seen on SS-OCTA. The FAZ was evaluated using 3 × 3 angiograms. OCT angiography images were automatically segmented at the levels of superficial and deep vasculature, at the avascular zone and choriocapillaris. An experienced examiner monitored all images in course to correct eventual segmentation errors. The FAZ area (mm²) was manually measured, both at the level of superficial capillary plexus and deep capillary plexus. Each en face image was exported into Adobe Photoshop and binarized to obtain automatic threshold selections from gray-level histograms in order to determine the percentage of white and black pixels. Retinal perfusion was calculated by scoring the percentage of white pixels in relation to the number of total pixels, according to published protocols.

Surgery

All patients underwent peribulbar anesthesia. After core vitrectomy, membrane blue was introduced to stain the posterior vitreous (0.06% solution left on the surface of the fovea for 30 s; MembraneBlue-Dual, Dorec). Posterior vitreous detachment was attempted with active suction using a vitrectome. If an epiretinal membrane was present, it was removed. The ILM was stained with membrane blue (45 s) and peeled up to the vascular arcades in all eyes. Subretinal injection of BSS was performed using a 41-gauge needle in the peeled area in all eyes. Air tamponade was subsequently performed. Patients were advised to maintain head-up positioning for 1 hour after surgery and prone positioning until the next day.

Spearman’s rank correlation coefficient (rho Spearman) was used to investigate the strength and direction of dependence between variables. The t test was used to assess the significance of Spearman’s rho. The following classification was used to interpret the strength of Spearman’s rho:

- | r | 0 — no correlation
- 1* 0.0 < | r | ≤ 0.1 — very weak correlation,
- 1* 0.1 < | r | ≤ 0.3 — weak correlation,
- 1* 0.3 < | r | ≤ 0.5 — moderate correlation,
- 1* 0.5 < | r | ≤ 0.7 — strong correlation,
- 1* 0.7 < | r | ≤ 0.9 — very strong correlation,
- 1* | r | > 0.9 — complete correlation.

The following tests were also used for statistical analysis: Shapiro–Wilk test (to evaluate the normality of dependent variables), Levene test (to test the equal variance), analysis of variance (ANOVA) Durbin/Skellings–Mack test, Wilcoxon test, t-Welch test, Mann–Whitney test, and ANOVA with Kruskal–Wallis test; α = 0.05 was considered as statistically significant. The analysis was performed using R statistical package, version 4.0.1.

Results

We included 35 eyes of 35 patients (14 men and 21 women) with a mean age of 62 years (median, 64 years; range, 26–82 years) with either type 1 or type 2 diabetes. Fourteen eyes (6 men and 8 women) had received anti-VEGF injections in the past. Nine patients underwent pan-fundus laser photoocoagulation ≥5 years before surgery.

Spectral-domain OCT was performed in all eyes, and the initial CRT was 546 µm. It gradually decreased to reach statistical significance at week 1 (451 µm; median, 391 µm; P = 0.004). The final CRT was 306 µm (median, 242 µm), which was also significantly lower than the preoperative values (ANOVA Durbin/Skellings–Mack; P < 0.001) (Figure 1A).

The CCT was 266 µm before the surgery. It significantly increased at month 3, reaching 354 µm (P < 0.001) (Fig 2), but normalized at the later time points (257 µm at 12 months after surgery). The mean diameter of the superficial FAZ was 401 µm (standard deviation [SD] = 417.5), which significantly decreased 1 week after surgery (293 µm; SD = 257.6; P < 0.001) (Fig 3). This decrease continued until month 6 (149 µm; SD = 89) and increased again
slightly at month 12 (359 μm). The mean diameter of the dFAZ was 1519 μm (SD = 1479) before surgery and slowly decreased to 317 μm (SD = 376) after 12 months. Statistical significance could not be determined, since the dFAZ was impossible to measure in all eyes with DME before surgery due to the presence of numerous artifacts.

The vessel density in the superficial retinal layers rate was 42.3% before surgery. This value decreased after surgery, reaching 41.6% at the end of the follow-up. The dVD rate 1 week after surgery was 28.9% and remained stable throughout the observation period (Fig 4). The initial VA was 20/160 (0.97 LogMAR), (median, 0.1; ±0.1). Visual acuity slightly decreased 1 week after surgery and slowly improved during the following months. The final VA (12 months after surgery) was 20/80 (0.62 LogMAR) (median, 0.2; ±0.16) and was significantly better than the preoperative VA (ANOVA Durbin/Skillings-Mack; \( \chi^2_{6,0.05} = 25.8; P < 0.001 \) (Table 1 and Fig 1B). Anti-VEGF injections performed before vitrectomy did not significantly influence the results.
Spearman’s rho correlation test was performed to identify factors influencing the final VA. The final outcome was not influenced by the need to administer anti-VEGF injections or the number of anti-VEGF injections performed before surgery. The most important prognostic factors were preoperative VA \((\text{rho} = -0.0604; \ P < 0.001)\), preoperative CRT \((\text{rho} = -0.359; \ P = 0.044)\), and diameter of the dFAZ at the time of edema resolution \((\text{rho} = -0.728; \ P = 0.041)\) (Fig 5).

Vessel density, especially in the deep capillary layers, was impossible to measure in most eyes before surgery due to the presence of macular edema; thus, we analyzed the vessel density in the superficial retinal layers and dVD at the time of resolution of edema, as proposed earlier by Moon et al.\(^{17}\) We noted that at that time point, the final VA was significantly influenced by the dVD \((\text{rho}, 0.826; \ P = 0.022)\) (Fig 6).

Although recurrence of macular edema was not observed in any of the cases during the postoperative follow-up (12 months), long-term data (12–48 months) showed macular edema in 10 cases, mostly in patients (8/10) who were also treated with anti-VEGF injections prior to vitrectomy. These patients required a mean of 2.9 injections (range, 1–6) to stabilize the edema. We used Spearman’s rho correlation to evaluate the factors responsible for the recurrence of macular edema > 12 months after vitrectomy. Among these, high initial CRT \((\text{rho} = 0.346; \ P = 0.042)\), high CRT 12 months after surgery \((\text{rho} = 0.568; \ P = 0.014)\), and low vessel density at the time of resolution of macular edema \((\text{rho} = 0.579; \ P = 0.024)\) were responsible for the occurrence of macular edema.

**Discussion**

Vitrectomy with ILM peeling and subretinal BSS injection results in quick resolution of DME and subsequent improvement in VA. It also reduces the diameter of the superficial FAZ, which might suggest a long-term protective effect of vitrectomy on the fovea in patients with diabetic retinopathy. Better results are expected in patients with better preoperative VA, lower CRT, and smaller dFAZ both before surgery and during the postoperative follow-up. The addition of a subretinal BSS injection may enhance the reduction in CRT, which is already reduced in the first postoperative month, much earlier than that observed in literature reports focusing on vitrectomy with ILM peeling alone.

Diabetic macular edema may occur in approximately 40% of diabetic patients during their lifetime. Currently, the gold standard treatment is regular anti-VEGF injections. Despite the excellent visual gains (7–12 letters) with this treatment,\(^{18}\) the treatment scheme may be difficult to maintain for some patients, either because of the distance to the clinic, time issues, or comorbidities. Another problem is the potential teratogenic effect of anti-VEGF drugs, which limits their use in younger patients planning to start or grow their families. Long-term anti-VEGF treatment is also more expensive than vitrectomy.\(^{19}\) Moreover, 40% to 50% of patients suffer from persistent DME.\(^{20}\)

The Diabetic Retinopathy Clinical Research Study group suggested that an indication for vitrectomy in macular edema might be the coexistence of an epiretinal membrane, vitreomacular traction, or low VA,\(^{21}\) while others have also proposed vitrectomy in cases of treatment-resistant DME.\(^{21}\) Our group previously reported the outcomes of vitrectomy with ILM peeling in patients with treatment-naïve DME and obtained good VA results.\(^{8}\)

Although reduction of CRT was reported in most studies evaluating the role of vitrectomy, the changes in the choroidal tissue are still not well studied. Here, we observed increase of CCT shortly after vitrectomy, which later returned to its original values. We suspect that it might be associated with the fact that removing vitreous decreased...
viscosity of intraretinal fluids, along with increasing the diffusion of molecules around the eye, which in turn increased premacular oxygen concentrations. That might be responsible for a rapid increase of CCT after vitrectomy.

Tachi et al.\textsuperscript{22} reported that half of the patients treated with vitrectomy require approximately 1 year to show an improvement. Since a shorter duration of DME before treatment has been reported to be crucial for preservation of the ellipsoid zone,\textsuperscript{23} it can also be assumed that a long period of time to stabilize the retinal thickness after surgery might be harmful. Subretinal injections of BSS have been proposed to overcome this problem.

Figure 3. Reduction in central retinal thickness in swept-source OCT (B, D, F, H). A correlating decrease was observed in the area of the foveal avascular zone in the superficial retinal vessel layer in swept-source OCT angiography (A, C, E, G). A, B, diabetic macular edema 1 week after surgery. C, D, One week after vitrectomy. E, F, Three months after vitrectomy. G, H, Twelve months after vitrectomy.
Subretinal injections are performed nowadays in subretinal hemorrhages in neovascular age-related macular degeneration and during gene therapy administration. Most surgeons choose to perform paracentral injection to avoid inducing damage to photoreceptors. Takahashi et al.24 have already confirmed that damage to the photoreceptors might depend on the injection pressure; however, even after injections performed at higher pressures, the ellipsoid zone normalized 6 weeks later. Since an earlier study showed that most of the tissue resistance in the retina originates in the ILM,25 a logical approach is to perform ILM removal at the injection site,26 which we also did in the current study.

One of the limitations of vitrectomy is the period until normalization of the retinal thickness. Long-term edema or detachment can cause irreversible vision loss; thus, it seems logical to decrease CRT as soon as possible. To

Figure 4. Vessel density in swept-source OCT angiography. A, Superficial retinal vessel layer. B, Binarization of A in Adobe Photoshop. C, Deep retinal vessel layer. D, Binarization of C in Adobe Photoshop.

Table 1. Long-Term Results After Vitrectomy in Patients With DME

| Factor       | Before  | 1 Week  | 1 Month | 3 Months | 6 Months | 12 Months | Final    |
|--------------|---------|---------|---------|----------|----------|-----------|----------|
| VA (LogMAR)  | 20/160 (0.97) | 20/160 (0.93) | 20/125 (0.76) | 20/100 (0.66) | 20/100 (0.69) | 20/80 (0.64) | 20/80 (0.62) |
| CRT          | 546     | 451     | 335     | 326      | 315      | 292       | 306      |
| MRT          | 574     | 544     | 498     | 471      | 461      | 479       | 494      |

CRT = central retinal thickness; DME = diabetic macular edema; LogMAR = logarithm of the minimum angle of resolution; MRT = maximum retinal thickness; VA = visual acuity.
overcome this problem, intrasurgical subretinal BSS injections have been suggested. Subretinal injections are most often performed to displace submacular hemorrhages, such as those in neovascular age-related macular degeneration. Recently, these injections were also introduced to facilitate gene delivery in retinal dystrophies. More
uncommon indications are foveal hard exudates in diabetes or diffuse DME. This technique has been confirmed to lead to faster resolution of DME when compared to standard vitrectomy. This technique might also be applied in repeated surgery of full thickness macular holes or for subretinal gene therapy.

Several factors have been previously described to be important for persistent VA gain, including photoreceptor integrity or DME-resolved status at 12 months after initiation of treatment. An OCT angiography-based study evaluated earlier factors responsible for good final visual outcome in patients treated with anti-VEGF and steroid injections. They concluded that the dVD and dFAZ at baseline were significant predictors of VA after 12 months of follow-up, which is not surprising since the deep capillary plexus provides approximately 15% of the photoreceptor oxygen supply. Interestingly, we obtained similar results after treatment with vitrectomy and BSS injection. This suggests that both techniques (anti-VEGF injections and vitrectomy) might similarly decrease the level of diabetic retinopathy and provide long-term satisfactory results in DME.

Footnotes and Disclosures

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HUMAN SUBJECTS: Human subjects were included in this study. Retrospective interventional study was approved by the Local Ethics Committee at Ophthalmic Clinic Jasne Blonia. All research adhered to the tenets of the Declaration of Helsinki. All participants provided informed consent.

No animal subjects were used in this study.

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Data acquisition and/or research execution: Nawrocka, Nawrocki
Data analysis and/or interpretation: Nawrocka, Nawrocki.
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Abbreviations and Acronyms:
ANOVA = analysis of variance; BSS = balanced salt solution; CCT = central choroidal thickness; CRT = central retinal thickness; dFAZ = deep FAZ; DME = diabetic macular edema; dVD = vessel density in the deep retinal layers; FAZ = foveal avascular zone; ILM = internal limiting membrane; SD = standard deviation; SS-OCTA = swept-source OCT angiography; VA = visual acuity.

Keywords:
Diabetic macular edema, DME, Swept-source OCT angiography, Vitrectomy, Anti-VEGF injections.

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