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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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Diabetic macular edema (DME) is the main cause of vision loss in diabetic patients,[1] and about 40% of patients with diabetes mellitus develop DME during their lifetime. Due to the growing number of patients with diabetes mellitus, DME is expected to become an even more acute medical problem over the coming decades.

Although anti-VEGF injections remain the gold standard treatment for DME, several indications for vitrectomy exist, such as coexisting epiretinal membrane or traction.[2] Recalcitrant edema, which was earlier reported in 25% to 64%[3] of eyes, may also be an indication for vitrectomy. One recent study suggested that patients with subretinal fluid in diffuse DME might also benefit from vitrectomy.[4] Anti-VEGF injections must be repeated on a regular basis in most patients,[5] which might be difficult due to factors such as travel limitations or comorbidities in some cases. Decreased compliance is usually associated with lower visual gains. Also of importance is the fact that in some countries, access to continuous anti-VEGF injections is limited due to financial constraints.[6] Moreover, anti-VEGF injections might be teratogenic and should be avoided in patients of child-bearing age.

Although vitrectomy yields good anatomic outcomes (reduced central retinal thickness [CRT]), the visual gains after the procedure were reported to be limited in some studies.[2] One of the factors responsible for this might be the fact that surgeons usually decide to perform vitrectomy in long-standing, usually treatment-resistant cases, and persistent DME was previously reported to usually be associated with an increased risk of irreversible photoreceptor loss. However, we proved several years ago that internal limiting membrane (ILM) peeling performed in severe complications of diabetes, as vitreous hemorrhage or tractional retinal detachment, reduces the rate of DME in the long term.[7] Our group had earlier presented good functional outcomes in patients operated on for treatment-naïve DME, with a gain of over 1 logarithm of the minimum angle of resolution (LogMAR) line in 60% of the eye.[8]

Swept-source OCT angiography (SS-OCTA) is a novel technique that enables noninvasive visualization of the

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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.[9] Anti-VEGF treatment, besides its beneficial influence on visual acuity (VA), was also reported to decrease the FAZ in patients treated for DME.[10] This was more significant in the long term, especially at the level of deep retinal layers.[11] Some changes in SS-OCTA parameters have also been discussed in eyes vitrectomized for different indications.[12] 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.[13] 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.[14]

Here, we present the results of vitrectomy with subretinal BSS injection in treatment-naïve 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 Jasne 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 photocoagulation 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 (mm^2) 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.[15]

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, Dorc). 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.[16] 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:

1* $|r| = 0$—no correlation
1* $0.0 < |r| \leq 0.1$—very weak correlation,
1* $0.1 < |r| \leq 0.3$—weak correlation,
1* $0.3 < |r| \leq 0.5$—moderate correlation,
1* $0.5 < |r| \leq 0.7$—strong correlation,
1* $0.7 < |r| \leq 0.9$—very strong correlation,
1* $0.9 < |r| \leq 1.0$—almost perfect correlation,
1* $|r| = 1$—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) Duribn/Skillings−Mack test, Wilcoxon test, t-Welch test, Mann−Whitney test, and ANOVA with Kruskal−Wallis test; $\alpha = 0.05$ was considered as statistically significant. The analysis was performed using R statistical package, version 4.01.

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 photocoagulation ≥ 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 Duribn/Skillings−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

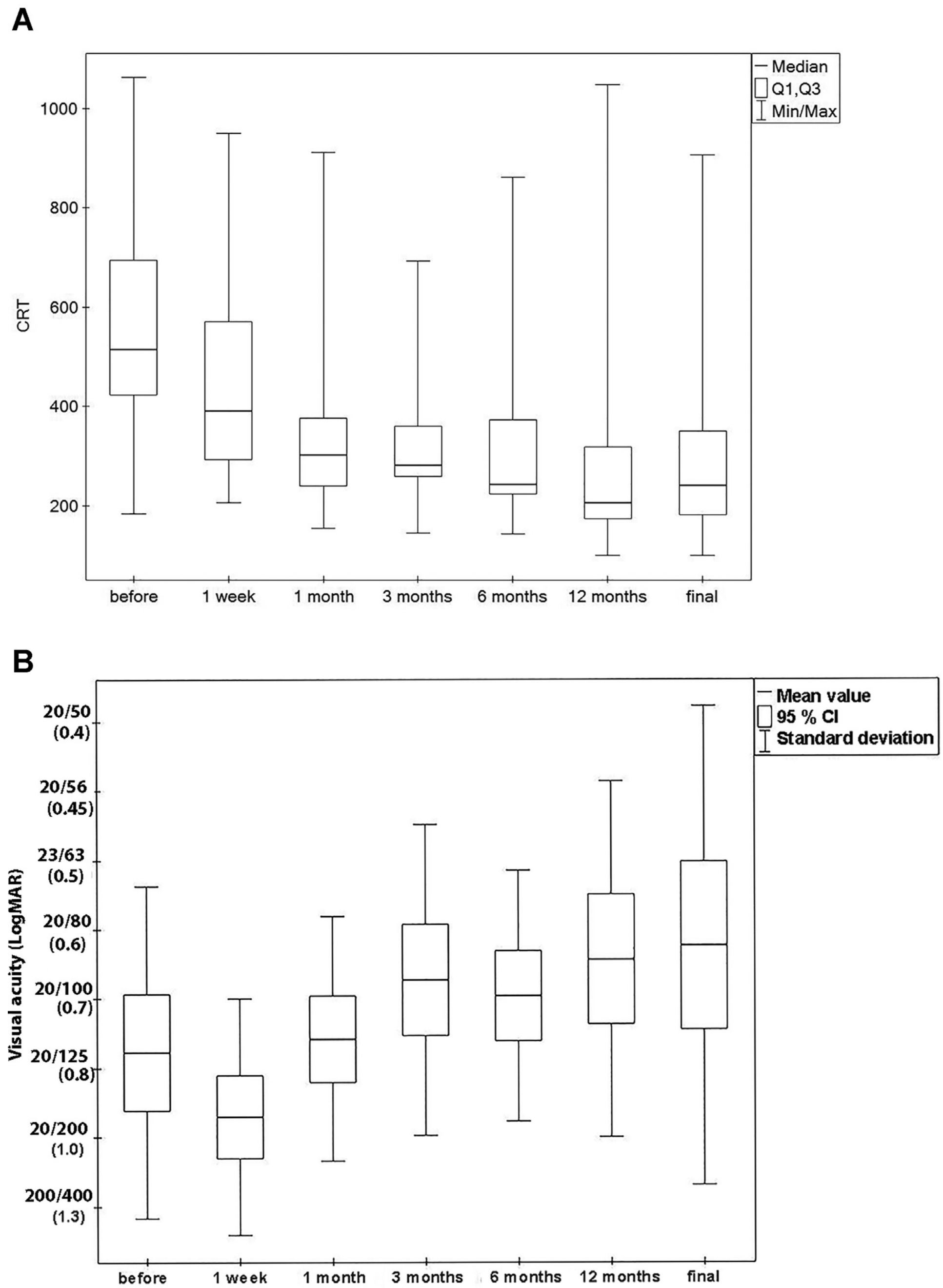

Figure 1. **A,** Changes in central retinal thickness (CRT) after vitrectomy for diabetic macular edema. **B,** Changes in visual acuity in time after vitrectomy for diabetic macular edema. CI = confidence interval; LogMAR = logarithm of the minimum angle of resolution.

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 Duribn/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.

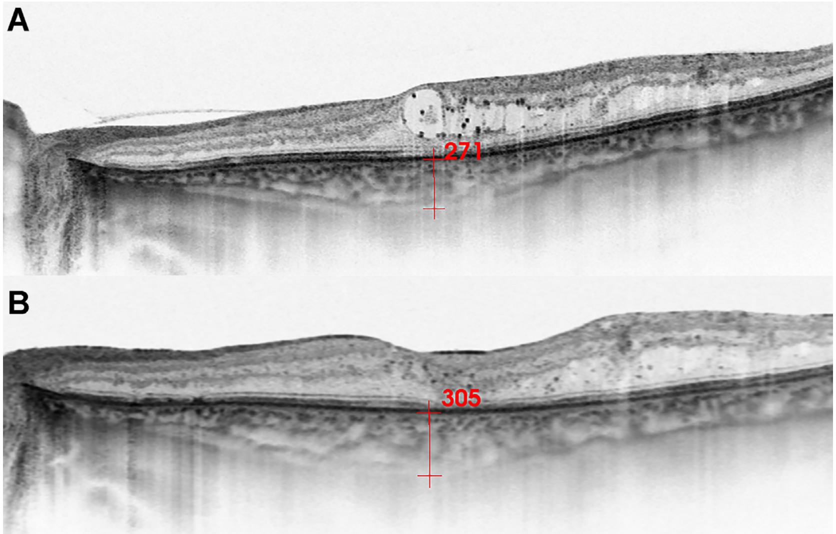

Figure 2. A 65-year-old woman with diabetic macular edema before (**A**) and 1 week after vitrectomy (**B**). Swept-source OCT shows a reduction in central retinal thickness. An increase in central choroidal thickness (red numbers) was noted.

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 (rho = −0.0604; $P < 0.001$), preoperative CRT (rho = −0.359; $P = 0.044$), and diameter of the dFAZ at the time of edema resolution (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 (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 (rho = 0.346; $P = 0.042$), high CRT 12 months after surgery (rho = 0.568; $P = 0.014$), and low vessel density at the time of resolution of macular edema (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,[2] 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

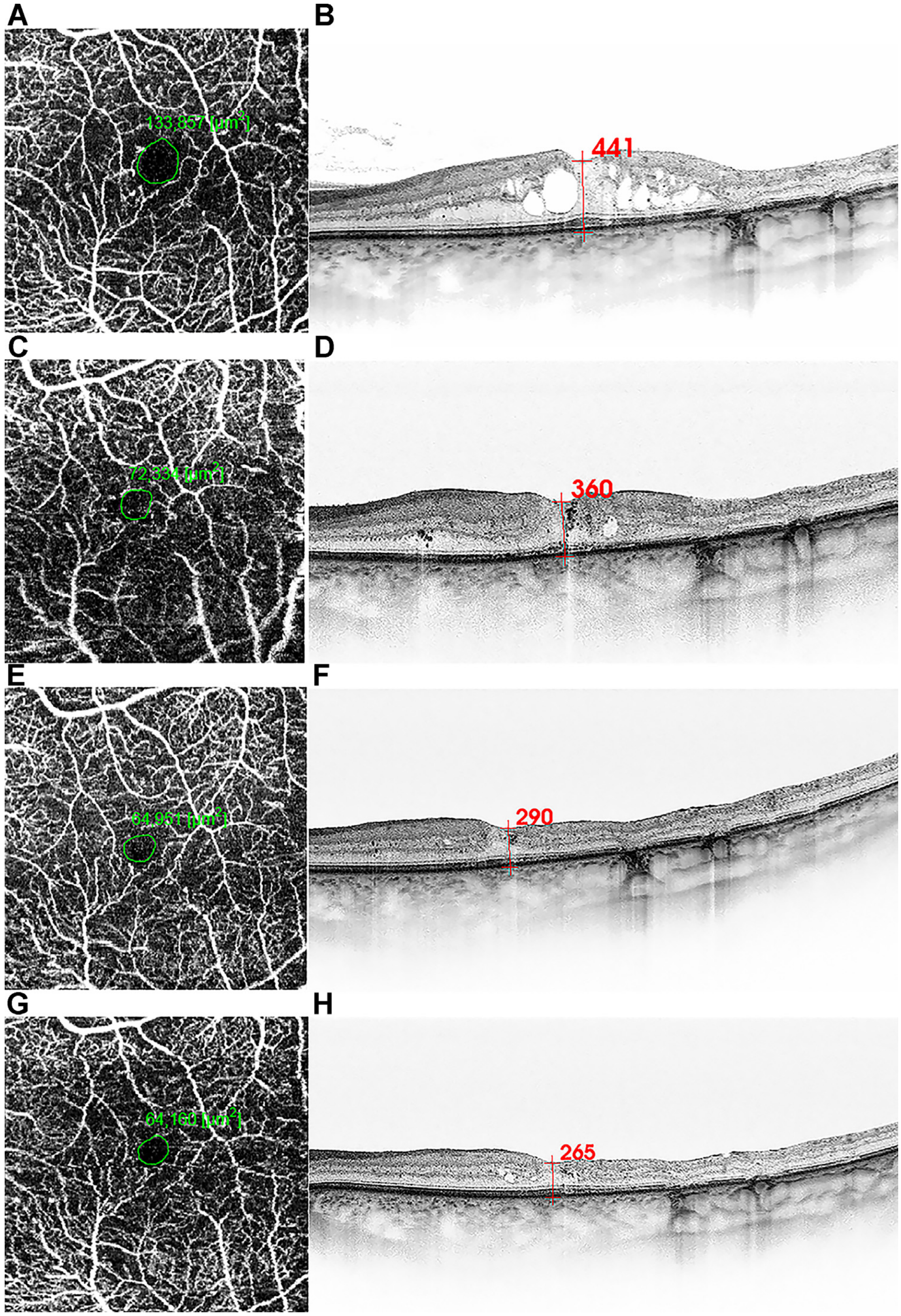

Figure 3. Reduction in central retinal thickness in swept-source OCT (**B**, **D**, **F**, **H**). A correlating decrease was observed in the area of the foveal avascular zone in the superficial retinal vessel layer in swept-source OCT angiography (**A**, **C**, **E**, **G**). **A, B,** diabetic macular edema 1 week after surgery. **C, D,** One week after vitrectomy. **E, F,** Three months after vitrectomy. **G, H,** Twelve months after vitrectomy.

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[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,[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.

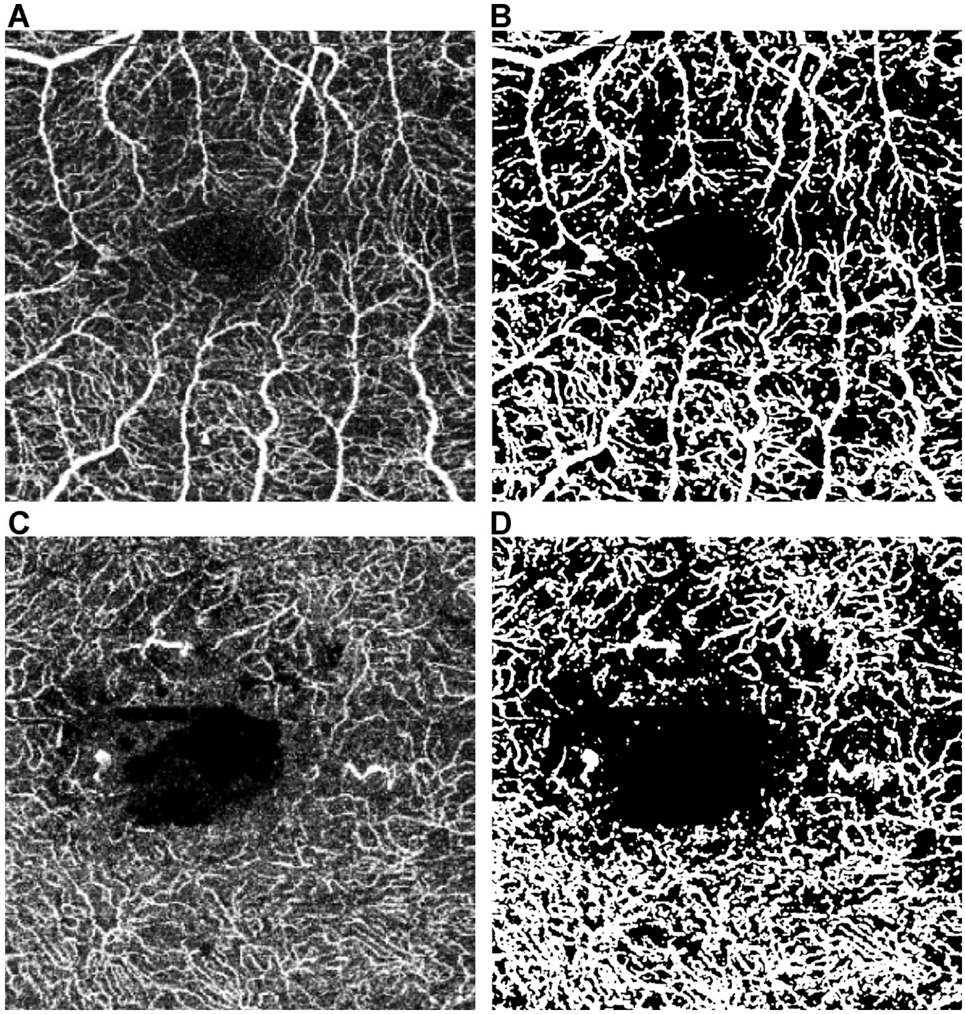

Figure 4. Vessel density in swept-source OCT angiography. **A,** Superficial retinal vessel layer. **B,** Binarization of **A** in Adobe Photoshop. **C,** Deep retinal vessel layer. **D,** Binarization of **C** in Adobe Photoshop.

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

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.

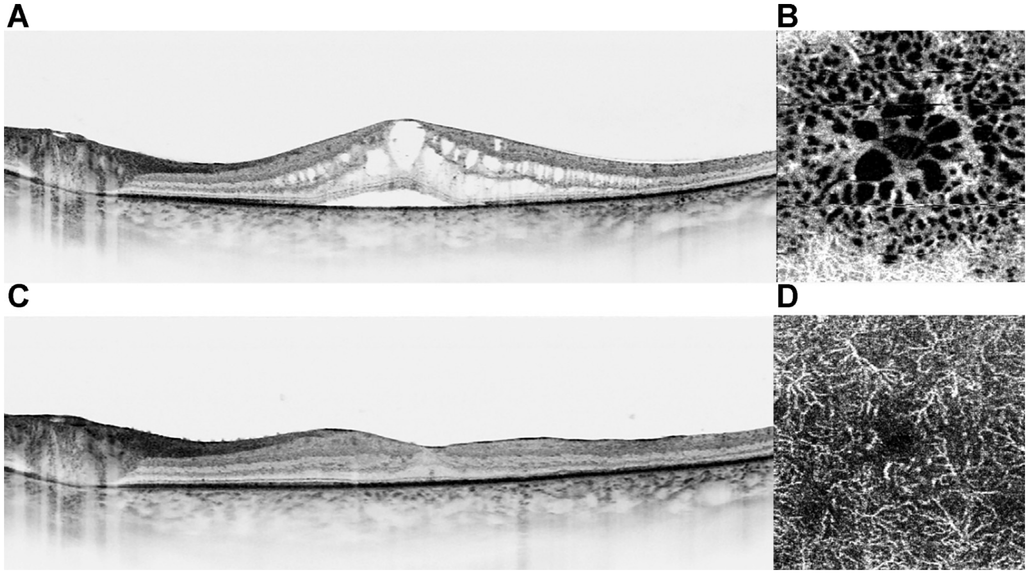

Figure 5. The foveal avascular zone in the deep retinal vessel layer might be difficult to estimate in the presence of diabetic macular edema. Its diameter at the moment of resolution is a prognostic factor for final visual acuity. **A,** Swept-source OCT shows diabetic macular edema. **B,** Swept-source OCT shows resolution of diabetic macular edema after vitrectomy. **C,** A central artifact obscuring the deep retinal vessel layer in swept-source OCT. **D,** Deep retinal vessel layer in swept-source OCT angiography after edema resolution. Measurement of the diameter of the foveal avascular zone is possible.

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.[27] Recently, these injections were also introduced to facilitate gene delivery in retinal dystrophies.[28] More

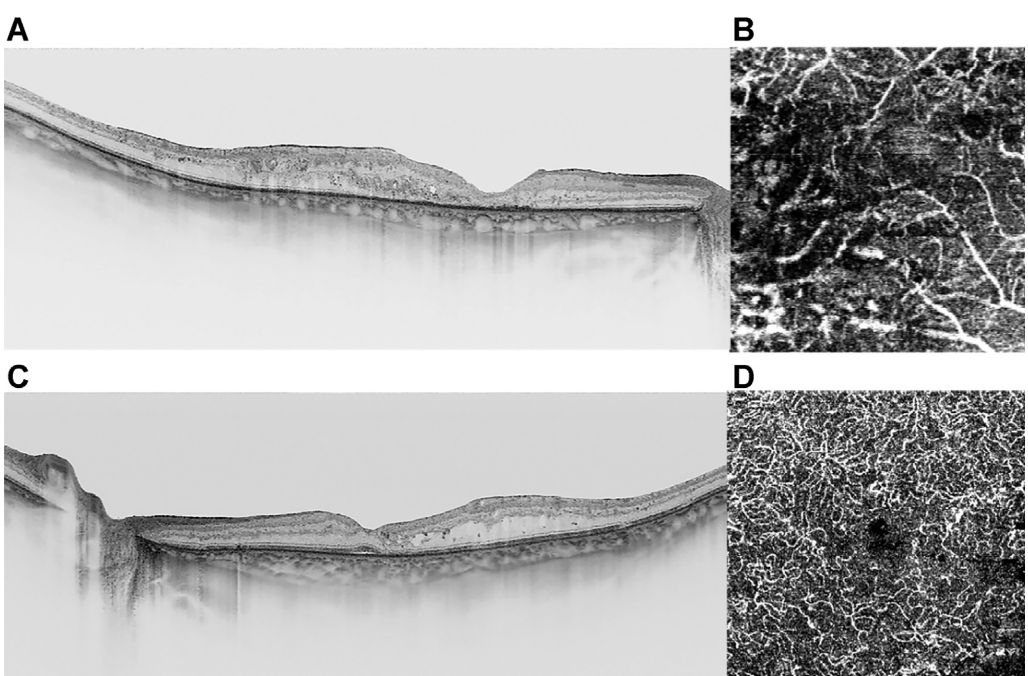

Figure 6. **A,** Swept-source OCT performed after vitrectomy in a 64-year-old woman. The foveal contour is regular. Photoreceptor defects are visible. **B,** Low vessel density in the deep retinal vascular layer in swept-source OCT angiography. The final visual acuity is 20/400 (1.3 logarithm of the minimum angle of resolution [LogMAR]). **C,** Swept-source OCT performed after vitrectomy in a 65-year-old woman. The foveal contour is regular. Subfoveal photoreceptor defects seem to be preserved. **D,** A normal vessel density in the deep retinal vascular layer in swept-source OCT angiography. The final visual acuity is 20/40 (0.3 LogMAR).

uncommon indications are foveal hard exudates in diabetes[29] 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.[30]

Several factors have been previously described to be important for persistent VA gain, including photoreceptor integrity[31] or DME-resolved status at 12 months after initiation of treatment.[17] 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,[17] which is not surprising since the deep capillary plexus provides approximately 15% of the photoreceptor oxygen supply.[32] 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.

Conclusions

Recurrence of macular edema after vitrectomy was earlier reported to be approximately 15%.[7] In the current study, while we did not observe any such cases during the 12-month observation period, a recurrence rate of approximately 28% was observed over the later time points. These patients were treated with a single anti-VEGF injection. Recurrences were observed more often in patients with a lower vessel density, when the macular edema had resolved.

The CRT significantly decreased as soon as 1 week after vitrectomy and slowly continued to decrease during the observation period. Visual acuity improvement (5 EDTRS letters) correlated with normalization of the foveal contour. Better initial VA, lower CRT, and lower dFAZ are prognostic factors for a good final visual outcome after vitrectomy with subretinal injection of BSS. Decreased dVD at month 6 was another good prognostic factor for the final visual outcome.

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.

Author Contributions:

Research design: Nawrocka, Nawrocki

Data acquisition and/or research execution: Nawrocka, Nawrocki

Data analysis and/or interpretation: Nawrocka, Nawrocki.

Obtained funding: N/A

Manuscript preparation: Nawrocka, Nawrocki

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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