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Clinical associations between photoreceptor status and visual outcomes in diabetic macular edema

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Aim – to investigate morphological changes and visual acuity response to ranibizumab therapy in patients with different OCT-types of diabetic macular edema (DME) as well as different state of the inner and outer photoreceptor segments (IS and OS) and the outer limiting membrane (OLM); to study relationships between functional and morphological parameters before and after the treatment; to study the effect of glycated hemoglobin levels on morphological parameters and ME duration. **Material and methods**. The study included 113 patients (113 eyes) with DME, who underwent 3 once-monthly intravitreal injections of ranibizumab (the mean patient age, 63.5±2.2 years; men, 51.3%; type 2 diabetes, 81.4%). Basing on the results of OCT, 3 groups were formed: group 1 (40 patients) – intact IS and OS; group 2 (32 patients) – disturbed photoreceptor segments integrity, but intact OLM; group 3 (41 patients) – destruction of both layers. **Results**. Visual acuity at baseline and after the treatment was the highest in group 1 ($p<0.05$). In all groups, most parameters that indicated the state of photoreceptor segments and the OLM improved. Correlation analysis revealed a statistically significant negative correlation between visual acuity at baseline and after the treatment and morphological parameters ($p<0.05$). There was also a direct correlation between the morphometric parameters at baseline and after the treatment ($p<0.05$). The most favorable type of DME in terms of preserving the integrity of photoreceptor segments and the OLM was sponge-like edema, while DME with neuroepithelial detachment and mixed-type DME were prognostically unfavorable. Moreover, the state of photoreceptors and the OLM depended on the duration of ME and the level of glycated hemoglobin. Thus, the integrity of the inner and outer photoreceptor segments as well as the outer limiting membrane can contribute to prognosis for functional outcomes in DME patients that receive antiangiogenic therapy.

***Keywords**: optical coherent tomography, foveolar thickness, ranibizumab, diffuse macular edema, outer photoreceptor segments, outer limiting membrane, inner nuclear layer.*

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Diabetic macular edema (DME) is the leading cause of vision deterioration in patients with diabetes and more than 50% patients suffer loss of more than 20% visual acuity (VA) over 2 years in the absence of adequate glycemic control. The conventional DME treatment (focal laser photocoagulation) doesn't give the intended results in terms of vision improvement, and in some cases is even succeeded by vision acuity decrement in the distant future. A number of studies showed that intravitreal injection of anti-VEGF medications – Ranibizumab, Aflibercept, Bevacizumab – is effective in cases with clinically significant diffuse macular edema (ME), but anatomical resorption of the edema is not always accompanied by significant VA increase [1]. The work of A. Sakamoto et al. demonstrated that central foveal thickness (CFT) of retina does not always correlate with vision improvement and is only one of the factors affecting this most relevant clinical indicator [2].

M. Shimura et al. described three basic structural forms of macular edema and showed the relations between clinical effectiveness of antiangiogenic treatment and structural changes in macular area [3]. Present-day optical coherent tomography (OCT) is used to determine the specifics of structural and morphological changes and to separate different kinds of ME, but it can also help visualize the intraretinal microstructural changes and the condition of inner and outer photoreceptor segments (IS and OS) and outer (external) limiting membrane (OLM) [4].

The correlation of structural changes in the photoreceptor layer and the VA improvement after ME reduction was showed in a number of studies. For example, the continuity of IS/OS visualization line is considered to be a significant prognostic factor for visual function increase in patients with retinal vein occlusion [5], age-related macular degeneration [6], and central serous chorioretinopathy [7].

The correlation between structural changes in the photoreceptor layer and ELM, and visual function in patients with diffuse ME was found in a study by T. Otani et al. [8].

The purpose of this study is to evaluate the changes of VA and morphologic parameters before and after Ranibizumab treatment in patients with different baseline condition of inner and outer photoreceptor segments and ELM, and in relation to the OCT-type of ME; to investigate the correlation between functional and morphological factors before and after the treatment; to examine how glycated hemoglobin level and ME duration affect the morphological parameters.

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Material and methods

The clinical study was housed at Novosibirsk State Regional Hospital. The study population consisted of 113 patients (113 eyes): 58 (51.3%) men and 55 (48.7%) women; 8 patients (8.6%) with type 1 diabetes and 92 patients (81.4%) with type 2 diabetes. Patients' age was 63.5±2.2 years. The mean duration of the disease was 12.02 years.

The inclusion criteria was the presence of clinically significant DME as determined according to ETDRS guidelines, measuring macular thickness in central fovea area by clinical biomicroscopy [8]. Macular area was scanned in vertical and horizontal medians using 5-line raster centered through fovea in red-less colour. Foveal thickness (FT) of the retina was determined automatically by means of OCT (CirrusHD-OCT, HumphreyZeiss, Inc) as mean retinal thickness within 500 µm of the fovea. The integrity of photoreceptor layer was evaluated by the continuity of IS, OS and OLM lines on the grey-scale OCT image. The assessed integrity of those structures was used as the criteria for dividing the patients into tree separate groups: the 1st group included patients with fully visualized layers of inner and outer photoreceptor segments; the 2nd group was characterised by disturbed integrity of outer and/or inner photoreceptor segments and intact OLM; the 3rd group consisted of patients with disrupted photoreceptor layer and OLM (**Fig. 1**).

The disruption of photoreceptor layer segments was determined by absence of hyperreflective line in the image. Therefore, several concepts were introduced in the study: DIL (disrupted IS/OS length) – the length of the disrupted inner and outer photoreceptor segments; DEL (disrupted OLM length) – the length of the disrupted ELM area; DIEL – the length of the disrupted IS/OS and OLM areas. The measurement of DIL, DEL and DIEL was performed manually using Vernier caliper tool in the software. In case of line discontinuity, the separate segments were measured and their sum was used. The measurements were taken by three independent technicians, then compared; if disparities were present, the examination was repeated collectively.

The exclusion criteria were: proliferative diabetic retinopathy, active active neovascularization, laser coagulation and intravitreal drug therapy in past medical history, surgical treatment of the vitreous body, presence of associated ophthalmological diseases such as glaucoma, uveitides etc., or pathology of vitreomacular interface with traction component and vitreomacular adhesion. In patients with DME in both eyes, only the one with most significant changes was considered.

All patients received 3 Ranibizumab injections of 0.05 ml (0.5 mg) four weeks apart. In compliance with routine procedure the injections were carried out in operation room, endovitreally after local epibulbar anesthesia with alcaine (Alcon, U.S.A.) through 27 G needle, 3 mm away from limbus. Baseline and resulting values of visual acuity and foveal thickness were determined during the observation period. The DIL, DEL, DIEL parameters and nuclear layer thickness (NLT) were measured before the treatment and on every attendance.

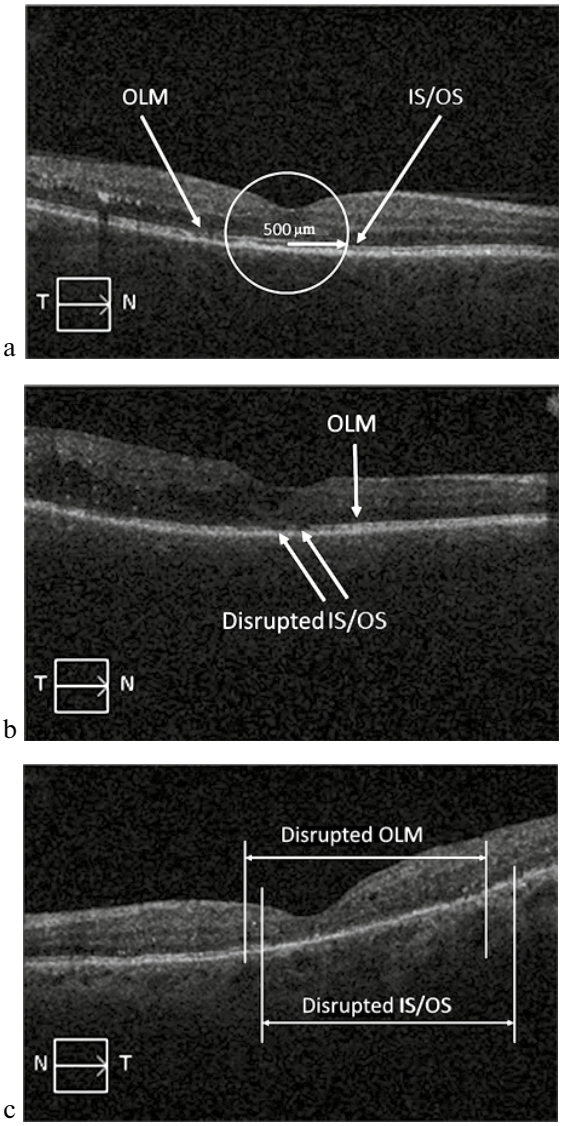

Fig. 1. **Condition of inner and outer photoreceptor segments and outer limiting membrane at 500 µm from fovea center as seen on final capturing after macular edema resorption in 1st (a), 2nd (b) and 3rd (c) groups.**

The data was analysed using Microsoft Office Standard 2007 (Excel 2007) and Statistica 6.0 software. The statistical significance between different groups was evaluated with non-parametric method – Mann-Whitney U-test. Statistical relations were studied by calculating Spearman correlation coefficient (*r*). Statistical assumptions were checked at the critical level of significance of 0.05, i.e. the difference was considered statistically significant at significance level of less than 0.05.

Results and discussion

In the course of the study 113 eyes (113 patients) were examined. All patients were diagnosed with diabetic retinopathy of nonproliferative stage. All patients had baseline glycated hemoglobin levels of 9% and less in the 6 month before the study and throughout the follow-up period. The first, second and the third groups comprised 40, 32 and 41 patients, respectively. The baseline parameters for the groups are present in **Table 1**.

Baseline best corrected visual acuity (BCVA) was significantly ($p<0.05$) the highest in the 1st group (**see Table 1**). After 3 Ranibizumab injections, BCVA in all groups amounted to 0.63±0.16, 0.35±0.11 and 0.16±0.09 respectively and was still significantly ($p<0.05$) higher in the group with intact IS and OS. Hence, after 3 injections the vision improved the most in the 1st group ($p<0.05$) where it increased by 3 lines (mean 0.36 in arbitrary units).

The dynamics of retinal morphologic parameters are presented in **Table 2**. **Figure 2, a-c** shows the dynamics of OCT images in 1st, 2nd and 3rd groups in respect to therapy. Central foveal thickness of the retina was significantly bigger in the 3rd group (488.9±0.11 μm) in comparison to the values in the 1st and 2nd groups ($p<0.05$). The most significant decrease of retinal thickness was achieved in the 3rd group (192.7 μm).

The dynamics of morphological parameters were not accompanied by any significant visual function improvement in the 2nd and 3rd groups. In that regard, the next study phase included the evaluation of photoreceptors and OLM condition.

Specifically, in the 1st group the length of the disrupted inner and outer photoreceptor segments (DIL) prior to treatment was 365±0.221 μm, with disrupted OLM (DEL) – 123.2±0.76 μm, and the DIEL was 203.1±0.1 μm. After 3 Ranibizumab injections, the 1st group showed complete restoration of the photoreceptor layer and OLM ($p<0.05$ for all parameters as compared to the value change in other groups). In the 2nd group, DIL decreased from 743.3±0.318 to 285.2±0.45 μm; DEL decreased from 368.7±0.29 to 148.9±0.34 μm and DIEl – from 657.0±0.33 to 183.2±0.19 μm (the dynamics of the parameters was statistically significant as compared to results in the 3rd group). The most prominent changes were noted in the 3rd group: the disrupted photoreceptors value (DIL) significantly decreased – from 1486±0.22 to 908.6±0.46 μm (by 596.9 μm), the DEL value changed by 614.1 μm (from 1118.4±0.18 to 504.3±010 μm), and DIEL changed by 561.6 μm (from 1232±0.29 to 670.9±0.47 μm); still, the structure wasn't fully restored, so BCVA didn't see any significant improvement as a result.

The correlation analysis showed statistically significant negative correlation between VA before and after treatment, and morphological parameters (**Table 3**). No correlation between baseline VA and retinal thickness was established. Additionally, there was a direct correla-

Table 1. **Baseline parameters of the study groups**

Parameter	Group		
	1st (n=40)	2nd (n=32)	3rd (n=41)
Diabetes duration, years	9.52±2.7	12.24±3.4	14.32±2.9
Patient age, years	62.3±7.7	65.1±2.7	63.2±1.1
HbA1c, %	7.58±0.54	8.2±0.37	8.67±0.45
Visual Acuity, units	0.27±0.15	0.19±0.13	0.09±0.14
Macular edema duration, months	6.3±2.1	9.6±3.2	12.4±2.7

Table 2. **Dynamics of morphologic parameters amid therapy**

Parameter, μm	Group		
	1st	2nd	3rd
Before treatment:			
CFT	456.5 ±0.14	440.1±0.24	488.9±0.11
DIL	365±0.221	743.3±0.18	1486±0.67
DEL	123.2±0.76	368.7±0.29	1118.4±0.18
DIEL	203.0±0.1	657.0 ±0.33	1232.5±0.29
LT	121.3±10.8	112.5±11.5	116.8±10.03
After treatment:			
CFT	273.4±39.66	279.3 ±45.55	296.3±42.93
DIL	0	285.2±0.45	908.6±0.22
DEL	0	148.9 ±0.34	504.3 ±0.10
DIEL	0	183.2 ±0.19	670.9±0.47
NLT	113.5±10.9	104.3±9.5	111.5±16.1

Table 3. **Results of correlation analysis**

Parameter	Spearman coefficient R	p
VA-1&DIL-1	–0.60	0.0001
VA-1&DEL-1	–0.61	0.0001
VA-1&DIEL-1	–0.64	0.0001
DIL-1&DEL-1	0.90	0.0001
DIL-1&DIEL-1	0.86	0.0001
DIL-1&FT-1	0.22	0.02
DEL-1&DIEL-1	0.87	0.0001
DEL-1&FT-1	0.27	0.003
DIEL-1&FT-1	0.20	0.031
VA-2&DIL-2	–0.84	0.0001
VA-2&DEL-2	–0.83	0.0001
VA-2&DIEL-2	–0.86	0.0001
VA-2&FT-2	–0.31	0.0009
DIL-2&DEL-2	0.93	0.0001
DIL-2&DIEL-2	0.93	0.0001
DIL-2&FT-2	0.21	0.025
DEL-2&DIEL-2	0.91	0.0001
DEL-2&FT-2	0.24	0.011
DIEL-2&FT-2	0.25	0.007

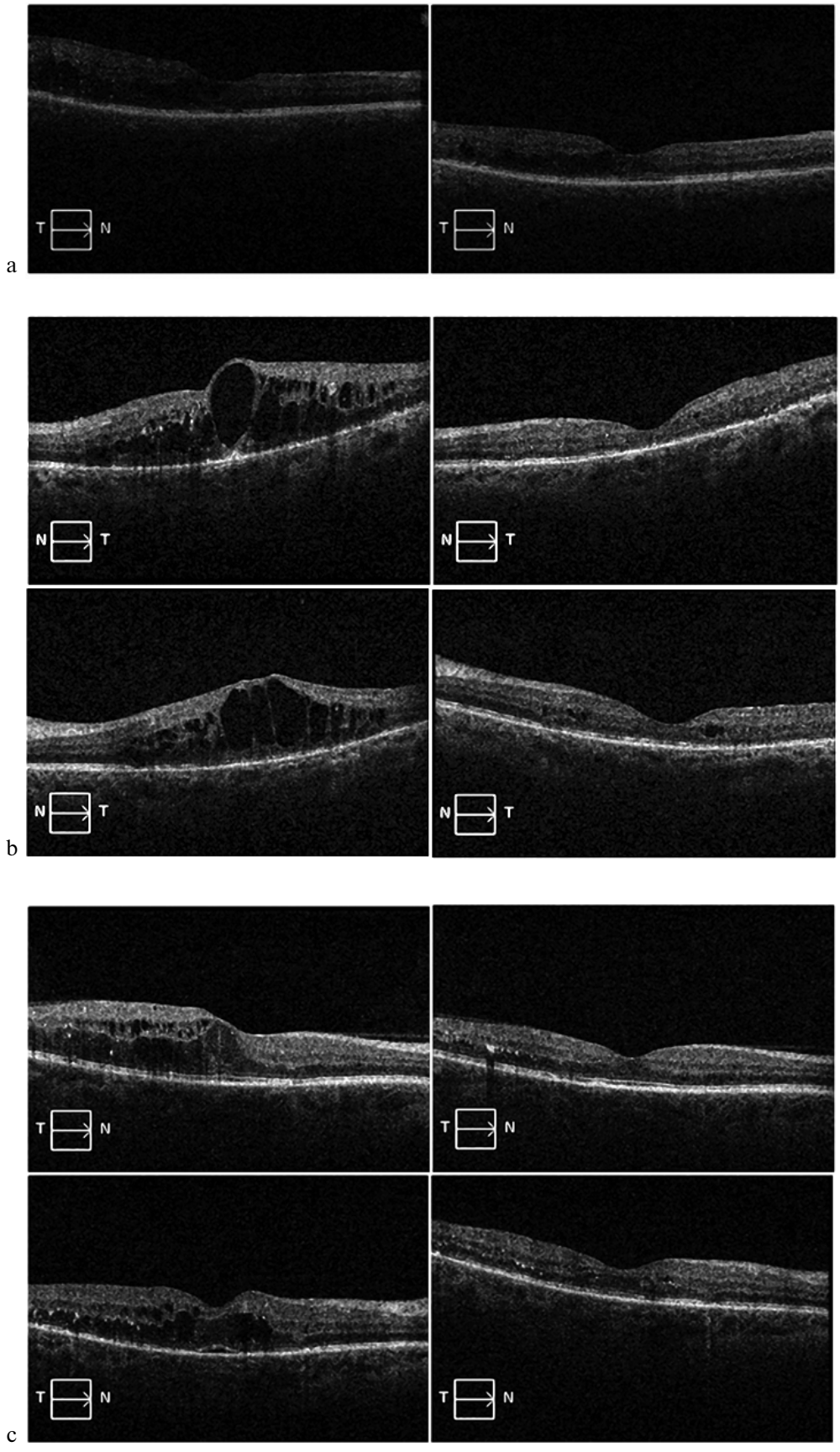

Fig. 2. **Examples of OCT-images dynamics.**

a – in the 1st group (intact IS/OS and OLM); b – in the 2nd group (disruption of IS/OS and intact OLM); c – in the 3rd group (disruption of IS/OS and OLM).

tion between all morphological parameters before and after treatment ($p<0.05$).

The condition of photoreceptor layer and OLM in various OCT-types of ME as classified by T. Otani et al. was also investigated [9].

The baseline DIL in patients with sponge-like DME, cystoid DME, DME with neuroepithelial detachment, and mixed-type DME was respectively 494.3±179.2, 868.6±567.2, 1157.1±566.2, and 1085.4±375.8 μm. Similar pattern was seen for DEL and DIEL parameters, with higher values in patients with mixed-type DME and DME with neuroepithelial detachment, and lower values in cases with cystoid and sponge-like DME.

Consequently, the improvement of morphological parameters, characterized by the central retinal thickness decrease in all groups, was accompanied by BCVA increase in cases where the restoration of inner and outer photoreceptor segments and OLM remained possible. In the patient group with irreversible disruption of photoreceptor layer and/or inner limiting membrane, the increase of BCVA was less significant and statistically unreliable. Additionally, in terms of photoreceptor layer and OLM integrity, the most favourable was sponge-like ME, while ME with neuroepithelial detachment and mixed-type ME were prognostically unfavourable.

Besides the OCT parameters, the study involved the assessment of possible influence of such factors as glycated hemoglobin level and ME duration on the condition of photoreceptor layer and OLM, and consequently on the potential visual function improvement.

The condition of photoreceptors and OLM according to different glycated hemoglobin levels can be seen in **Table 4**.

Specifically, intact photoreceptors and OLM were found in 90.6% of all eyes with HbA1c<7%, in 50% of all eyes with HbA1c level of 7-7.5%, and in zero cases with HbA1c of more than 7.5%. The complete destruction of neurosensory retina and OLM was observed in 64.4% of all patients. Mean central retinal thickness change after 3 Ranibizumab injections was similar in patients with HbA1c levels of 7-7.5% and more than 7.5%, and amounted to 176 and 177 μm respectively, while in patients with HbA1c level of less than 7% retinal thickness decreased in average by 189 μm ($p<0.05$).

Different condition of photoreceptors and OLM was observed in patients depending on the duration of ME existence (**Table 5**). Most patients (86.5%) with ME duration of less than 6 months didn't have changes in photoreceptor layer and OLM, while among patients with ME duration of more than 10 months, in 78.1% the photoreceptor layer and OLM were disrupted.

The effectiveness of anti-angiogenic agents in patients with diffuse ME is well established and the prospective randomized clinical studies RESOLVE, READ-2, RESTORE, DRCR.net have proved that Ranibizumab does indeed lead to improvement of functional and anatomical factors [1]. The effectiveness and safety were studied for various Ranibizumab administration schedules in DME, for example monthly regime in RISE and RIDE studies [12], administration "pro-re-nata" (PRN) in RESTORE and DRCR.net studies [1], and "treat-and-extend" in RETAIN study [25]. In the Ranibizumab therapy group with 3+PRN regime of the RESTORE study, in the course of 1 year 22.6% of patients showed visual function increase by 15 letters, 37.4% - by 10 letters, and 65.2% - by 5 letters and more, while 4.4% suffered visual deterioration [2]. Similar dynamics of VA changes was the motivation to look for reasons of incomplete or negligible visual function increase amid the context of almost complete reduction of edema. In a study by A. Sakamoto et al. visual and functional results of surgical treatment (microinvasive vitrectomy) were shown to be dependant on the integrity of foveal photoreceptors, which directly influences the VA status after ME resorption [14]. Another study by H. Shin et al. supports prognostic value of the integrity of inner and outer photoreceptor segments and OLM [6]. In a study by T. Otani et al. microstructural condition of neurosensory retina was found to correlate with BCVA in patients with DME [15]. Furthermore, in addition to the condition of neurosensory layer after treatment, baseline parameters (before treatment) are also very important [16].

Visual Acuity is still a key indicator of treatment effectiveness from both the point of view of both patients and specialists. According to DRCR.net data (2015), intravitreal injection of various drugs (Ranibizumab and Aflibercept) significantly improves central VA in patients

Table 4. **Condition of photoreceptors and OLM at various glycated hemoglobin levels**

Parameter	HbA1c < 7%	HbA1c 7–7.5%	HbA1c > 7.5%
Number of patients, abs.	32	22	59
Mean level of HbA1c, %	6.5	7.5	7.9
Intact PR and OLM, *n* (%)	29 (90.6)	11 (50)	0
Disrupted PR, intact OLM, *n* (%)	2 (6.3)	9 (40.9)	21 (35.6)
Disrupted PR and OLM, *n* (%)	1 (3.1)	2 (9.1)	38 (64.4)

Note. Here and in Table 5: PR – photoreceptors.

Table 5. **Condition of photoreceptors and OLM at various ME duration**

Parameter	< 6 months	6–10 months	> 10 months
Number of patients, abs.	37	35	41
Mean ME duration, months	4.1	7.5	11.6
Intact PR and OLM, *n* (%)	32 (86.5)	8 (22.9)	0
Disrupted PR, intact OLM, *n* (%)	4 (10.8)	18 (51.4)	9 (21.9)
Disrupted PR and OLM, *n* (%)	1 (2.7)	9 (25.7)	32 (78.1)

with DME, and baseline VA and treatment results directly correlate [17].

Currently, baseline VA can be considered a valid prognostic indicator for vision improvement in patients with such diseases as retinal vein occlusion [18], age-related macular degeneration [19], which is confirmed in this study. In particular this can be seen on the example of the patients of the 3rd group who had low baseline VA (0.09±0.17). Even after full edema resorption seen on OCT imaging, and with statistically significant decrease of central foveal thickness by 60%, but with remaining major disruption of photoreceptor layer and OLM integrity, patients had certain VA improvement – by 0.07 in average, even though this change was not statistically valid. In the 1st group with the highest baseline VA (0.27±0.15) and complete restoration of photoreceptor layer and OLM integrity, BCVA increased to relatively high average values (0.63±0.11). In some studies, no correlation between central retinal thickness and VA in patients with retinal vein occlusion, age-related macular degeneration or DME was found [5, 6, 20]. The present study did not reveal any statistically significant correlation between VA and baseline retinal thickness, however there was a negative correlation between VA and retinal thickness after treatment ($p<0.05$). According to H. Matsumoto et al., outer nuclear layer thickness is a reliable prognostic indicator for visual function improvement [21], but in the present study no statistically reliable correlation between this parameter and BCVA was observed.

This study involved examination of three key parameters in terms of potential prognostic value: the condition of inner and outer photoreceptor segments, and OLM. The integrity of those 3 particular structural layers can be regarded as complementary because anatomical organization of retina suggests close correlation between inner and outer photoreceptor cells and OLM, that represents the apexes of Müller cells. The particular geometric organization of retina ensures its functionality, including the visual cycle. Diffuse macular edema leads to separation of the layers and accumulation of fluid, disruption of metabolic and neurosensory processes. As a result, DME appears to be the disruptive factor initially for microstructural, and subsequently for more serious, irreversible changes (such as the integrity of photoreceptor layer and OLM surface). It can be assumed, that due to anatomical-structural features, the photoreceptor layer can potentially fully recover from initial changes through extension of normally present intercellular space (1st group) and the visual function will improve after treatment. However, in case of more significant edema, the disrupted photoreceptors – even with partially remaining geometric organization via intact OLM (2nd group) – will not fully recover. The destruction of all layers considered in this study (3rd group) prevented any statistically significant improvement of the main clinical factor – VA – even after complete reduction of the edema.

The results of this study also confirm that the least damaged layers are neurosensory retina in cases with sponge-like ME, when, according to OCT data, not only baseline central thickness is lower, but also the structural integrity of the layers is preserved. DME with neuroepithelial detachment is naturally accompanied by major and irreversible changes in photoreceptor layer and OLM.

Furthermore, the role of ME duration was examined, and the findings supported the assumptions about structural compensatory potential of neurosensory retina and duration of pathological process existence. According to high-profile epidemiological studies, the duration of diabetes and the level of metabolic control are prevailing factors for assessment of diabetic retinopathy and ME progression [22-24]. In particular, adequate glycaemic control coupled with lipids level and kidneys function control were proved to be the gold standard for DME treatment [23, 24]. In this regard, glycated hemoglobin levels are considered to have significant influence on the photoreceptors condition and, consequently, on the visual function improvement.

In summary, studying the structural changes in retina using OCT has prognostic value in respect to restoration of both anatomical integrity and visual functions in patients with DME. The integrity of inner and outer photoreceptor segments and outer limiting membrane can contribute to prognosis for functional outcomes in DME patients receiving antiangiogenic treatment.

Conclusions

1. Positive dynamics of morphological condition of retina in response to antiangiogenic treatment was seen in all study groups, but it wasn't always the determining factor for visual and functional outcomes.

2. Functional outcomes of antiangiogenic treatment depended on baseline visual acuity that reflected the condition of photoreceptors and outer limiting membrane.

3. Glycated hemoglobin level and macular edema duration had statistically reliable influence on morphological and functional condition of neurosensory retina.

4. The condition of outer and inner photoreceptor segments is a prognostically valuable parameter in terms of therapeutic response to antiangiogenic treatment.

Author contributions:
Study conception and design — A.F.
Statistical analysis of data — A.F., M.T., G.P.
Drafting of manuscript — A.F., N.C.
Critical revision — A.F., N.C., M.T., I.S., G.P.
The authors declare that there are no conflicts of interest.

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