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Correlation between Visual Acuity and Optical Coherence Tomography-Measured Retinal Thickness in Diabetic Macular Edema

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ABSTRACT

Background and Objective: Diabetic macular edema (DME) is one of the common complications of diabetes which significantly accounts for preventable visual impairment and blindness. Central macular thickness (CMT) is a feature found in DME patients. This study aims to determine the relationship between optical coherence tomography (OCT)-measured CMT and visual acuity (VA) in patients with DME before and after intravitreal injection of bevacizumab.

Methods: This cross-sectional study was conducted on 100 patients with diabetic macular edema with involvement of both eyes referred to the Ophthalmology Department of Rouhani Hospital in Babol who underwent intravitreal injection of Bevacizumab. VA (measured by Snellen chart), CMT (measured by OCT), clinical and paraclinical factors (including the duration of diabetes, glycosylated hemoglobin (HbA_{1c}), fasting blood sugar (FBS), hypertension, and smoking history data) were evaluated and compared among all patients just before and 45 days after Bevacizumab injection.

Findings: Before the injection of Bevacizumab in 200 eyes, the mean value of VA (letter score) and mean value of CMT (µm) were 36.83±12.73 and 425.48±85.18 µm, respectively ($p<0.001$, 95% CI=12.5 – 17.5 and 95% CI=-71.5 – -55.5, respectively). 45 days after Bevacizumab injection, the mean value of absolute VA changes was 15.24±10.16, and the mean value of absolute CMT changes was -67.83±43.08 µm (coefficient=-0.18, 95% CI=-0.39 – 0.05).

Conclusion: Although VA was correlated moderately with CMT and the polynomial regression model enhanced the predictive ability, it remains fully obvious that CMT and clinical factors could play an essential role as VA surrogates.

Keywords: *Diabetic Retinopathy, Bevacizumab, Visual Acuity*.

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Introduction

Despite tremendous advances in the screening, diagnosis, and treatment of eye diseases, diabetic retinopathy remains a significant cause of preventable visual impairment and blindness in working-age adults (1-4). Diabetic macular edema (DME) is a common complication of diabetes mellitus defined by abnormal growth of retinal capillaries, dilation, and permeability of blood vessels. Eventually, blood-retinal barrier destruction leads to fluid leakage from extracellular space resulting in disruption of cellular function (5-7). A complex and vague mechanism provoked by a high glucose concentration in the blood leads to the development of further diabetic-related retinal dysfunction (2). The genetic and epigenetic alteration, oxidative stress and inflammatory factors, advanced glycosylation end products, and vascular endothelial growth factors (VEGF) are implicated mechanisms involved in DME (2, 5, 8).

As a mediator involved in DME, VEGF demonstrates the importance of prescribing Anti-VEGF as a potential option against progressive retinal neovascularization (9-11). VEGF expression could be enhanced following retinal hypoxia and maladaptive inflammatory response, resulting in retinal permeability and angiogenesis, which trigger macular edema and proliferative diabetic retinopathy, respectively (1). Ongoing clinical trials have shown the effect of Bevacizumab intravitreal injection on improving visual acuity (VA) in eyes with DME (12-14).

Retinal thickness and severity of macular edema are quantitatively measured in high resolution and cross-sectional imaging by a non-invasive optical coherence tomography (OCT) (13). Thus, OCT allows ophthalmologists to clearly understand retinal events before macular edema develops as a prognostic tool and as follow-up equipment (15-17). Furthermore, since the new diagnostic tools require retinal evaluation in the early detection of macular degeneration, once an apparent relationship is found, OCT-measured central macular thickness (CMT) could be considered as a surrogate for visual acuity to evaluate visual function more quickly and efficiently. Therefore, the present study was conducted to determine the relationship between OCT-measured CMT and VA in patients with DME before and after Bevacizumab intravitreal injection.

Methods

After being approved by the ethics committee of Babol University of Medical Sciences with the code IR.MUBABOL.HRI.REC.1400.224, this cross-sectional study was conducted among 100 patients with DME who visited the Ophthalmology Department of Ayat Allah Rouhani Hospital in Babol from September 2015 to March 2020 and received bevacizumab.

The diagnosis of DME was based on OCT (18). An ophthalmology specialist obtained OCT images after 30 min pupil dilation using ZEISS Cirrus HD-OCT 5000. Also, CMT and VA were measured just before and 45 days after Bevacizumab injection. Patients with diabetic retinopathy for at least ten years with all VA ranges in the best-corrected Snellen chart and at least 300 µm of CMT were included. Furthermore, the associated clinical/paraclinical data (i.e., duration of diabetes, HbA1c, FBS, hypertension, and smoking history data) were recorded based on the patient's history. Patients with other congenital or acquired eye abnormalities, history of photocoagulation, cataract extraction, glaucoma, corneal, lenticular, and vitreous pathology, renal failure or dialysis, and macular edema were excluded.

Data were imported into R (version 4.0.3) (19), and all further analysis and plotting were performed in this programming environment using "eye", "dplyr", "ggpubr", "ggplot2", "psychometric", and "hrbrthemes" packages. First, Snellen scores were converted to ETDRS letter scores (20). Then, the normality of data was examined by histogram plot, Q-Q plot, and Kolmogorov-Smirnov test. Spearman's

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correlation coefficient, Mann-Whitney U test, and Wilcoxon signed-rank test were utilized since the data did not follow the normal distribution. The false discovery rate was controlled by Bonferroni correction, and $p<0.05$ was considered statistically significant.

Results

Of the 100 studied patients, 43 were men and 57 were women with a mean age of 63.2±9.71 years (Table 1). Before the injection of Bevacizumab in 200 enrolled eyes, the mean value of VA and mean value of CMT (µm) were 36.83±12.73 and 425.48±85.18, respectively. After Bevacizumab intervention, the mean value of VA (letter score) and mean value of CMT (µm) were 52.07±16.77 and 357.65±62.93, respectively. Both VA ($p<0.001$, 95% CI=12.5 – 17.5) and CMT (p-value<0.001, 95% CI=-71.5 – -55.5) improved significantly after injection. The correlation between baseline VA and OCT-measured CMT showed that the coefficient score was -0.83 (95% CI=-0.89 – -0.74), and the slope of the data-fitted regression line was -0.116. The coefficient score in the correlation between VA and CMT after treatment was -0.81 (95% CI=-0.88 – -0.72), and the slope was 18.7 (95% CI=14.1 – 23.2) (Figure 1).

Table 1. Demographic and Clinical Characteristics

Parameters	Values
Total patients (both eyes involved), (Number)	100
Gender, (Number)	
Male	43
Female	57
Age (yrs), Mean±SD	63.2±9.71
Duration of diabetes (yrs), Mean±SD	19.3±5.61
HbA_{1c}(%), Mean±SD	9.91±1.18
Visual acuity, n(%)	
20/100 or better	46(23%)
20/160	46(23%)
20/200	66(33%)
20/400 or worse	42(21%)
Mean±SD	0.12975±0.0941 (~between 20/630 & 20/80)
OCT Thickness Central Subfield (µm), n(%)	
<375 (µm)	50(25%)
375 – 399 (µm)	53(26.5 %)
400 – 424 (µm)	26(13%)
≥425 (µm)	71(35.5%)
Mean±SD	425.48±85.18
Current insulin therapy, n(%)	44(44%)
Current non-Insulin therapy, n(%)	78(78%)
Hypertension, n(%)	77(77%)
Hyperglyceridemia, n(%)	90(90%)
Fasting blood sugar(mg/dl), Mean±SD	202.38±35.73
Proliferative diabetic retinopathy	50(50%)
Smoking, n(%)	25(25%)
NA*, n(%)	10(10%)

*NA= Not Available

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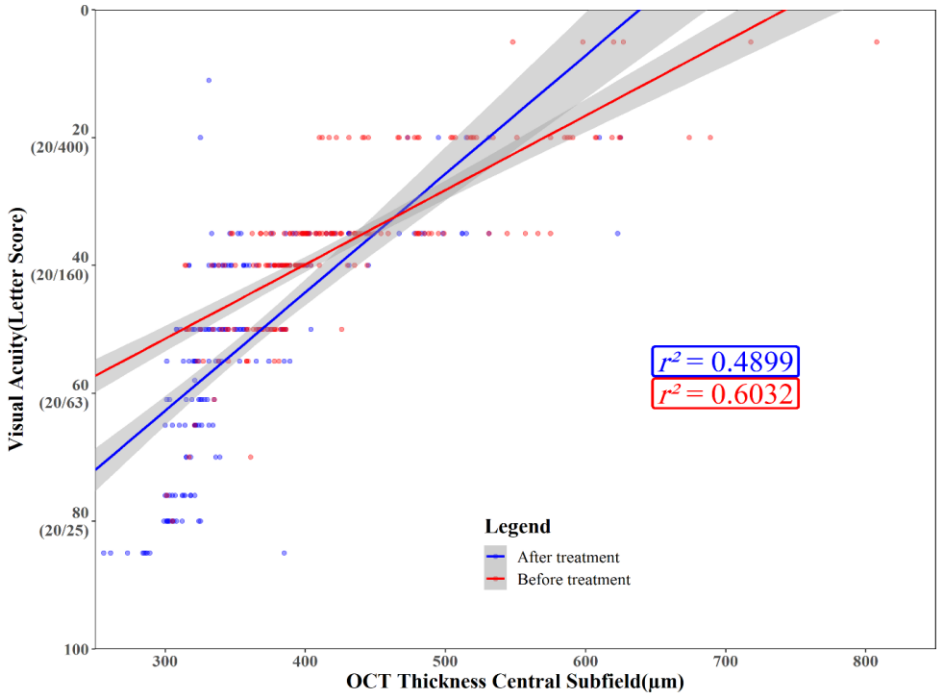

Figure 1. Scatter plot of VA and OCT-measured CMT before and after treatment. **Linear regression models are shown with the 95% confidence interval as gray areas.**

45 days after Bevacizumab injection, the mean value of VA changes was 15.24±10.16, and the mean value of CMT changes was -67.83±43.08. Spearman's correlation coefficient of absolute changes was -0.18 (95% CI=-0.39 – 0.05), which indicates a lack of a significant correlation between CMT and VA absolute changes, while the mild correlation of relative changes between VA and CMT with a correlation of -0.32 (95% CI=-0.52 – -0.10) and slope of 1.66 (95% CI=0.18 – 3.14) was seen (Figure 2).

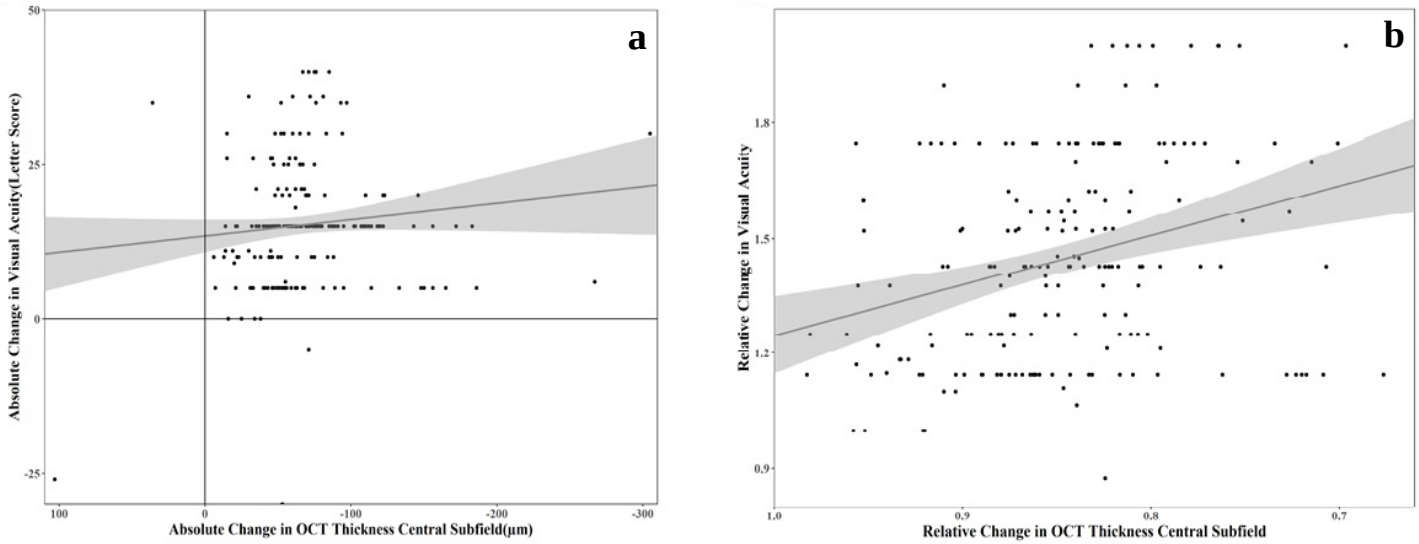

Figure 2. A scatter plot and best-fitted regression line of VA changes and OCT-measured CMT changes. a) absolute changes, b) relative changes. **95% confidence intervals are highlighted as a gray area.**

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Also, pairwise analysis of age, duration of diabetes, FBS, and HbA_{1c} show various significant correlations with VA and CMT (Table 2).

Table 2. The relationship between other characteristics and factors

Factor and Association	p-value	Correlation coefficient or difference of medians*	95% CI of a correlation coefficient or difference of medians
Age			
Duration of diabetes	<0.001	0.44	0.13 – 0.67
Duration of diabetes			
VA-before	0.022	-0.24	-0.45 – -0.01
VA-after	<0.01	-0.28	-0.48 – -0.05
CMT-before	<0.05	0.24	0.01 – 0.45
CMT-after	<0.05	0.27	0.02 – 0.46
HbA_{1c}	<0.01	0.38	0.07 – 0.63
Fasting blood sugar			
VA-before	<0.001	-0.44	-0.61 – -0.23
VA-after	<0.001	-0.43	-0.61 – -0.23
CMT-before	<0.001	0.37	0.16 – 0.56
CMT-after	<0.001	0.36	0.13 – 0.54
HBA1C	<0.001	0.80	0.65 – 0.89
HbA_{1c}			
VA-before	<0.001	-0.52	-0.67 – -0.33
VA-after	<0.001	-0.44	-0.61 – -0.23
CMT-before	<0.001	0.37	0.16 – 0.56
CMT-after	<0.001	0.36	0.13 – 0.54
Retinopathy			
FBS	<0.01	22.00	3.00 – 43
HbA_{1c}	<0.001	1.10	0.40 – 1.80
VA-before	<0.001	-10.00	-15.00 – -5.00
VA-after	<0.001	-15.00	-25.00 – -10.00
CMT-before	<0.001	49.00	22.00 – 90.00
CMT-after	<0.001	38.00	15.00 – 65.00
VA-changes	<0.001	-5.00	-10 – -0.01

*Correlation coefficient refers to the linear model, and the difference of medians refers to Mann-Whitney U test.

Discussion

In this study, VA and CMT improved significantly. Like the baseline correlation, moderate correlation with a slight decrease was observed after the treatment, which is similar to the previous study (21). It has been proven that DME is implicated in the loss of VA and early recognition, ensuring effective treatment and reducing temporary complications remain to be further investigated. With the advent of OCT, high resolution and quantitative cross-sectional retinal assessment became possible and allowed clinicians to detect pathological events before any destructive visual outcome and monitor confirmed DME (15).

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Several studies have demonstrated an average correlation between VA and macular thickness ranging from 0.26 to 0.79. According to these findings, baseline VA was correlated with OCT-measured CMT in this study. Alasil et al. showed that OCT-measured CMT, subretinal fluid volume, and photoreceptor outer segment thickness are significantly correlated with VA in DME patients. They introduce the photoreceptor outer segment thickness as an important predictor of function and VA in DME patients (22). Consistent with our study, Blumenkranz et al. showed that OCT-measured CMT was significantly correlated with VA. In this study, patients with DME received dexamethasone, which was significantly associated with reduced CMT after 90 days of treatment. They suggest that dexamethasone therapy is significantly associated with increasing the VA and reducing OCT-measured CMT (23). In the study of Bressler et al. on 652 DME patients, it was demonstrated that changes in OCT-measured CMT are associated with a small proportion of VA following Bevacizumab therapy and Bevacizumab therapy is not a surrogate for changes in visual acuity (24).

Diabetic Retinopathy Clinical Research Network found a significant relationship between VA and CMT before and after focal laser therapy in patients with DME in a study on 251 eyes. In addition, they suggest OCT-measured CMT as an essential tool in clinical evaluation, but it is not a reliable surrogate for VA in DME patients (21). Goebel et al. demonstrated that OCT is a suitable tool for CMT measurement in DME patients. Also, OCT can diagnose sight-threatening macular edema with good reliability and reproducibility (25). Also, Islam et al. showed a significant correlation between OCT-measured CMT and VA in DME patients, but VA and CMT cannot be used interchangeably in clinics (26). In a clinical study, Shen et al. showed that IS/OS junction and ELM integrity are correlated with VA in DME patients (27).

Univariate analysis shows a significant correlation between baseline VA and duration of diabetes, FBS and HbA_{1c}. This indicates that DME patients with a shorter duration of diabetes and lower levels of FBS and HbA_{1c} have higher VA. Moreover, age was not correlated with VA and CMT (before or after Bevacizumab injection), while Ach et al. found that younger patients with lower CMT at baseline show a significantly better response to treatment (28). Moreover, Daien et al. found that early injection of Bevacizumab in young patients lead to significant VA improvements (29). Similar to our study, Islam et al. also did not find any association between age and VA and CMT (26).

One of the limitations of this study was the reporting of qualitative characteristics instead of quantitative characteristics and that most of the patients in this study were elderly and had suffered from diabetes for at least a decade. For instance, based on raw data, patients were divided into smoker and non-smoker, without specifying how many years and how many packs per day a patient smoked (pack per year). Indeed, stronger correlations and more accurate VA estimates can be achieved if we have more clinical information.

Based on the results of this study, baseline VA was moderately correlated with CMT in a simple linear model, and this correlation was enhanced by utilizing polynomial regression. Conversely, other factors did not show enough significance to promote the regression model and predictive ability, so approaching VA via its surrogates remains fully obvious. We need more clinical data to make more accurate decisions. In fact, our findings introduce bevacizumab as a powerful treatment in reducing OCT-measured CMT and increasing VA.

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