Foveal thickness reduction after anti-vascular endothelial growth factor treatment in chronic diabetic macular edema

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Abstract

• AIM: To report foveal thickness reduction in eyes with resolution of macular edema and recovery of a foveal depression after one-year of anti-vascular endothelial growth factor (anti-VEGF) therapy for center-involving diabetic macular edema (DME).

• METHODS: Foveal thickness was assessed with optical coherence tomography to determine the central subfield foveal thickness (CSFT) and macular volume in 42 eyes with DME (CSFT>275 µm). Evaluations also included measurement of best-corrected visual acuity (BCVA), and were performed at baseline, and upon foveal depression recovery achieved after 12 monthly intravitreal injections of either 1.5 mg/0.06 mL bevacizumab (n=21) or 0.5 mg/0.05 mL ranibizumab (n=21). Data was compared to 42 eyes of normally sighted, non-diabetic, healthy individuals with similar age, gender and race distributions.

• RESULTS: Mean baseline BCVA was 0.59±0.04 and 0.32±0.03 logMAR (P<0.001) after treatment and resolution of DME, with all, but 3 eyes, showing BCVA improvement. Mean CSFT before treatment was 422.0±20.0 µm, and after treatment, decreased to 241.6±4.6 µm (P<0.001), which is significantly thinner than CSFT found in control subjects (272.0±3.4 µm; P<0.001). Moreover, in 33/42 DM eyes (79%), CSTF was thinner than the matched control eye. Macular volume showed comparable results, but with lower differences between groups (control: 8.5±0.4 mm³; DME: 8.2±1.0 mm³; P=0.0267).

• CONCLUSION: DME eyes show significantly lower foveal thickness than matched controls after DME resolution achieved with one-year anti-VEGF therapy. Further investigation into the reasons for this presumable retinal atrophy using fluorescein angiography and functional parameters as well as establishing possible predictors is warranted. This finding should be considered during the treatment of DME.

• KEYWORDS: diabetes; macular edema; bevacizumab; ranibizumab; optical coherence tomography; central subfield foveal thickness; diabetic retinopathy

INTRODUCTION

Diabetic retinopathy (DR) is one of the leading causes of blindness in developed countries, and has been reported to account for 5% of blindness worldwide[1]. Although there are many causes of vision loss caused by DR such as proliferative DR with retinal detachment and vitreous hemorrhage, diabetic macular edema (DME) is the leading cause of vision loss in people with diabetes mellitus[2-4].

Pretreatment foveal thickness, determined using optic coherence tomography (OCT) by measuring the central subfield foveal thickness (CSFT), has been reported to be a strong predictor of anatomical and functional outcomes in patients with DME treated with intravitreal anti-vascular endothelial growth factor (anti-VEGF) such as ranibizumab[5-6]. The magnitude of CSFT reduction during the first year, in several treatment regimens, has also been associated with a better visual acuity outcome[7-9]. It is well documented that intravitreal anti-VEGF therapy is related to a reduction in foveal thickness in eyes with center involving DME. While the mean CSFT of non-diabetic individuals is approximately 270 µm regardless of gender, the mean CSFT of diabetic patients with minimal or without retinopathy is reported to range from 250 to 300 µm[10-12].
The aim of the current study is to compare the foveal thickness in eyes after successful treatment of DME with anti-VEGF therapy to the CSFT in eyes of normally sighted, non-diabetic healthy individuals with no known ocular disease. This information may be of great clinical interest for patients with a history of DME treated with anti-VEGF therapy, and may provide insight into whether successful treatment of DME with anti-VEGF results in altered retinal morphology.

SUBJECTS AND METHODS
The study protocol was approved by the Institutional Review Board (IRB) of the Ribeirão Preto School of Medicine, University of São Paulo (the Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto), Brazil. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. Participants were enrolled as part of a previous study cohort.[13] The DME patient population consisted of individuals with mild DR and chronic DME (mean duration of decreased visual acuity due to DME for 38mo).

Inclusion criteria consisted of center-involved DME with central subfield thickness >300 mm on spectral-domain optical coherence tomography (SD-OCT), despite at least one session of macular laser photoocoagulation performed at least 3mo previously, and best-corrected visual acuity (BCVA) measurement between 0.3 logMAR (Snellen equivalent: 20/40) and 1.6 logMAR (Snellen equivalent: 20/800) and a signed informed consent.[13]

Exclusion criteria was occurrence of macular traction as assessed by SD-OCT, proliferative DR in need of panretinal photocoagulation, macular capillary dropout on fluorescein angiography, history of glaucoma, other ocular condition that may affect macular edema or alter visual acuity during the study period and systemic corticosteroid therapy.[13]

The primary outcome measure in the current study was CSFT as measured by SD-OCT (Heidelberg Engineering, Heidelberg, Germany). Macular volume was also reported. Intravitreal injections of either bevacizumab (1.5 mg/0.06 mL; F. Hoffmann-La Roche, Ltd., Switzerland) or ranibizumab (0.5 mg/0.05 mL; Novartis Pharma, Switzerland) for treatment of DME were performed monthly until CSFT was <275 µm for treatment with resolution of the foveal depression within one-year (P<0.001) after treatment and resolution of DME, with all, but 3 eyes, showing BCVA improvement.

The mean CSFT in DME eyes was 422.0±20.0 µm before and 241.6±4.6 µm after treatment with resolution of the DME and recovery of the foveal depression within the study period of one-year (P<0.001). Mean CSFT in control eyes was 272.0±3.4 µm and mean CSFT in DME eyes after anti-VEGF therapy with resolution of DME and foveal depression...
recovery was 30.4±5.7 µm lower to the mean CSFT in control eyes (P<0.001). Of the 42 DME eyes, 33 (79%) had a lower CSFT than the matched control eyes (Figures 1, 2). Total macular volume showed comparable results to CSFT, but with lower differences between groups. Mean control macular volume was 8.5±0.4 mm$^3$ and for DME was 8.2±1.0 mm$^3$ (P=0.0267). Weak, but statistically significant correlation was found between baseline CSFT and total macular volume (r=0.37, P=0.0151), but no correlation was observed between CSFT and macular volume after treatment (r=0.088, P=0.4873).

Analysis of covariance was performed to investigate eventual multivariate correlations between BCVA, CSFT and macular volume measured at baseline, and post-treatment. Baseline BCVA showed significant effect on final BCVA (P<0.001), clearly indicating that patients with good baseline BCVA tend to show better visual acuity after treatment. On the other side, CSFT (P=0.6903) and macular volume (P=0.4874) at baseline, or CSFT (P=0.9856) and macular volume (P=0.1412) after treatment, showed no statistically effect on one-year BCVA. Figure 3 shows analysis leverage residuals for BCVA and CSFT at baseline and after treatment. Moreover, no significant effect was observed for DME classification (diffuse/cystoid) on one-year BCVA (P=0.1054), or CSFT (P=0.2321).

### DISCUSSION

In the present study, CSFT in DME eyes after anti-VEGF treatment, with resolution of DME and complete foveal depression recovery, was found significantly lower than the in CSFT in control eyes of normally sighted non-diabetic healthy individuals with no known ocular disease. Our results are consistent with recent studies, which demonstrated good reproducibility and repeatability of retinal thickness measurements using SD-OCT in healthy and pathological eyes.$^{[14-15]}$

Our reported mean CSFT in normally sighted non-diabetic healthy individuals with no known ocular disease (272.0±3.4 µm)
is comparable to that reported in a previous study by Grover et al\textsuperscript{[12]} who studied normative data for macular thickness, including CSFT (270.2±22.5 µm). Interestingly, a very similar mean CSFT has been reported in eyes with DR without macular edema (270±24 µm)\textsuperscript{[11]}. However, in contrast to the CSFT in non-diabetic healthy individuals, the mean CSFT in our patients with a history of DME treated with anti-VEGF therapy was significantly lower (241.6±4.6 µm).

Recent data from clinical trials such as LUCIDATE and RESTORE, and from the Diabetic Retinopathy Clinical Research (DRCR) network studies, that assessed functional and structural effects of ranibizumab, bevacizumab or aflibercept in eyes with DME all showed a significant reduction of CSFT in DME after anti-VEGF treatment\textsuperscript{[16-18]}. However, data on CSFT after anti-VEGF treatment in these clinical trials always included patients with residual edema and, therefore, cannot be used for the assessment of post-treatment CSFT in DME.

It has been suggested that the leading cause of retinal thinning in the macula of eyes treated previously for DME may be due to focal/grid laser therapy and/or the effects of ischemia\textsuperscript{[19]}. In fact, the current study also showed a significantly decreased CSFT in DME eyes successfully treated with anti-VEGF therapy, and our patient population received at least one session of macular laser photoacogulation at least 3mo prior to the first intravitreal injection. However, a recent study using subthreshold laser treatment as opposed to regular continuous laser even demonstrated a preservation of the photoreceptor layer and CSFT\textsuperscript{[20]}.

We found no significant effect of CSFT or macular volume measured on baseline, during follow-up on one-year CSFT or visual acuity, indicating that the extent of macular thickness found before, during follow-up or after treatment should not be considered alone as a predictor of functional recovery after anti-VEGF treatment, which is certainly multifactorial, depending on cellular organization and function in all retinal layers. Furthermore, the DME classification at baseline (diffuse or cystoid) did not show significant effect on final BCVA or CSFT. This should be carefully interpreted because we did not design this study to investigate the effect of DME classification on macular thickness or visual acuity after treatment, which is certainly explain the larger number of diffuse cases in our sample (33 out of 42).

To our knowledge, and based on a computerized literature search of the MEDLINE database, the present study is the first to demonstrate that CSFT after successful anti-VEGF treatment of DME may be significantly decreased compared to the CSFT in normally sighted eyes. Whether this retinal atrophy may be attributed to the disease time course or intravitreal anti-VEGF therapy or laser therapy remains to be elucidated. Considering the actual scenario, in which intravitreal anti-VEGF therapy represents the current standard of care for DME\textsuperscript{[21]}, further investigation into the reasons for this retinal atrophy using fluoresce in angiography and assessment of central retinal function is warranted.

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Conflicts of Interest: Willmann G, None; Nepomuceno AB, None; Messias K, None; Barroso L, None; Scott IU, None; Messias A, None; Jorge R, None.

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