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CORRESPONDENCE

Response to 'Comment on: Macular OCT-angiography parameters to predict the clinical stage of nonproliferative diabetic retinopathy: an exploratory analysis'

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To the Editor:

We would like to thank Dr. Chua and Dr. Schmetterer for their interest and relevant comment on our cross-sectional exploratory analysis of the value of optical coherence tomography angiography (OCTA) parameters to predict the clinical stage of non-proliferative diabetic retinopathy (NPDR) [1].

Indeed, several studies have raised awareness to the fact that individual differences in axial length (AL) affect the lateral magnification of OCTA scans and, hence, hamper the accuracy of quantitative measurements made on these images [2]. Dr. Chua and Dr. Schmetterer propose two ways of correcting for this: either (1) computing the vessel density (VD) of the deep capillary plexus (DCP) within an annular region of interest (ROI) that excludes the foveal avascular zone (FAZ) or (2) rescaling of the OCT scans, based on individual AL values. It is relevant to highlight that what is described in the first suggestion is already implemented in our analysis. As described in the "Methods" section, the DCP parafoveal density was defined as "the vessel density (…) within the annular zone of 1- to 3-mm dimeter around the foveal centre (parafoveal density)", which should exclude all (or, at least, most) of the FAZ (as also illustrated in Fig. 2). Unfortunately, image rescaling of the scans in our study (second suggestion) is not possible, because rescaling formulas require the AL value (e.g., refs. [3, 4]) and measurement of AL was not included in our study protocol.

Indeed, the consequence of a larger AL (i.e., of a larger optical path) is that the scanning beam of the OCT effectively scans a larger area of retina and thus, in the OCTA scan, both vessels, and areas without vessels are more compactly displayed. However, the VD, typically calculated as the percentage of pixels above a given grey value threshold ("white" pixels, corresponding to vessels), should not change significantly, as long as the FAZ is not included in the ROI. Accordingly, it was reported that the change in VD calculation after image rescaling is greatest for the area of the scan including the FAZ [5]. Furthermore, within the parafoveal annulus (not including the FAZ), the averaged difference in VD density after rescaling was found to be null, with a 95% confidence interval of ±1% [5]. In our study, the maximal averaged effect size of parafoveal VD in the DCP between ETDRS Level groups is 7.8%; hence, well above the effect magnitude that would be expected purely due to the scaling effect. Nevertheless, we opted to explore this issue further at the level of the statistical analysis.

The distribution of refractive error in the cohort reported in our study is left-skewed, with five statistically outlier observations, pertaining to highly myopic eyes. ETDRS grading of these eyes is as follows: $n = 3$ for Level 20 ETDRS and $n = 2$ for Level 35C ETDRS. The effect of OCT scaling on VD calculation is non-linear and its magnitude was shown to be higher in highly myopic eyes [5]. It

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could be that the calculation of VD in the DCP is overestimated in these eyes and, therefore, it is plausible that these observations could be driving the result supporting the main conclusion of our work, i.e., that sparser VD in the DCP is associated with higher odds of more clinically advanced NPDR. To test this hypothesis, we performed post-hoc sensitivity analyses that we describe below.

When these five observations, outliers for refractive error, are fully excluded from the analysis ($n = 96$), the refractive error (mean ± SD) of the study population according to ETDRS Level group is the following: 0.44 ± 1.82 D, Level 10 ETDRS; 0.48 ± 1.18 D, Level 20 ETDRS; 0.47 ± 1.02 D, Level 35 ETDRS; 0.81 ± 1.00 D, Level 43/47 ETDRS. We observed no significant correlation between refractive error and VD in the DCP ($R^2 = –0.08$, $P = 0.44$). Furthermore, when the multivariate ordered logistic regression (OLR) model is computed with the parameters of the final model reported in our study, DCP parafoveal density is still found to be a predictor of NPDR ETDRS Level (OR = 0.56 (0.33, 0.96), $P = 0.035$). Hence, the finding that DCP parafoveal density is a predictor of NPDR clinical stage does not seem to be driven by the highly myopic observations in the cohort, giving us no justification to exclude them from the analysis. Finally, when refractive error is included as a covariate of the final OLR model in the complete dataset ($n = 101$), refractive error is not a predictor of NPDR ETDRS Level (OR = 0.91 (0.71, 1.17), $P = 0.473$), while DCP parafoveal density still musters at the significance level (OR = 0.55 (0.32, 0.94), $P = 0.030$).

Overall, we feel it safe to conclude that, in our study, refractive error was not a confounder of the association between DCP parafoveal density and NPDR clinical stage. Nonetheless, we agree that AL can be an important confounder of findings drawn from OCT-based quantitative studies and we also emphasize the need to adjust for it, either at the level of image processing or during the statistical analysis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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