Author Response: Hyperreflective Intraretinal Foci as an OCT Biomarker of Retinal Inflammation in Diabetic Macular Edema

We would like to convey our gratitude to Midena et al.[1] for their thoughtful letter to the editor and their insightful comment regarding our article.[2] As shown in a previous study by Vujosevic et al.,[3] the reflectivity of hyperreflective foci (HF), as aggregates of retinal microglial cells, might be lower than that of the retinal pigment epithelium (RPE) and could be similar to that of the retinal nerve fiber layer (RNFL). We also agree with the opinion that any investigation of HF regarding optical coherence tomography (OCT) in diabetic eyes should be more precise to avoid inconsistent results because counting HF in diabetic macular edema (DME) could be fairly subjective due to its similarity with other entities, such as hard exudate.

We also first tried to count the number of HF based on a specific threshold, for example, the mean reflectivity of the RNFL, using ImageJ. However, we found that we could not use this threshold as a standard because the relative reflectivity of the RNFL compared to that of the RPE was quite variable even in a single image. In Figure B (inverse image of OCT) in our study,[2] the reflectivity of the RNFL varies according to the horizontal location, while the reflectivity was relatively homogenous in the RPE. In some cases, the RPE band also showed variable reflectivity along its horizontal position, but when we excluded artifact lesions such as low-reflective areas due to shadowing, we could obtain a more reliable standard of threshold for brightness than that of the RNFL. In addition, we suggest that HF, which had higher reflectivity than the RNFL but lower reflectivity than the RPE, should not be excluded. In Figure A in our study,[2] a significant portion of HF in the inner retinal layer showed higher reflectivity than the RNFL (right and left sides of central intraretinal cysts), and although they were not recognized in fundus photography, these HF were small in size and did not show back-shadowing. Therefore, the standard for reflectivity for counting HF was set as the reflectivity "similar" to the mean brightness of the RPE band, and we did not count HF brighter than the reflectivity of the mean RPE band to avoid including dots that were too bright, which might be controversial.

In summary, some HF counted might have been brighter than the mean reflectivity of the RNFL, but when considering the variable reflectivity of the RNFL, we accepted those HF as real HF when they were discrete and well-circumscribed dots, had no shadowing, and did not exist in fundus photography with the largest diameter less than 50 μm.

We agree with Midena, Pilotto, and Bini's opinion[1] that the HF in DME, especially in the inner retina, tend to have lower reflectivity than the RPE, but the exact threshold for counting HF is still difficult to determine in many cases. It is our hope that a more reliable method for counting HF will be developed soon.

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