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Letter to the Editor

The value of choroidal thickness in diabetic macular oedema is contradictory

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Editor,

The choroidal thickness (CT) or the subfoveal choroidal thickness (SFCT) have been indicated as prognostic factors for the treatment of diabetic macular oedema (DMO), including in recent works (Mathis et al. 2020; Endo et al. 2020). Authors usually engage the decrease in CT and the decrease in central retinal thickness (CRT) under the action of anti-vascular endothelial growth factor (VEGF) agents, in a cause–effect relationship. Therefore, it is common to see the conclusion that the CT is a marker of DMO outcome. One has to consider that the VEGF action through its receptors 1 and 2 may be independent in the retina and in the choroid and acting in different cell types, including pericytes (Fig. 1), Müller cells (MC) and the fenestrated pores of the choriocapillaris (Daruich et al. 2018). The association of VEGF-dependent thinning of the retina and thinning of the choroid may be appealing, but they may be just two independent actions of the anti-VEGF agents and not necessarily being correlated one another. Drying of the retina is mainly dependent on MC at the retinal level, and of the presence of pores in the fenestrated endothelium of the choriocapillaris at the retinal pigment epithelium (RPE) level. However, while anti-VEGF agents thin the choroid, they reduce the number of pores at the choriocapillaris in a transient way, as demonstrated by electron microscopy studies (Shimomura et al. 2009).

In a prospective work, we found that the anti-VEGF thinning of the choroid has no prognostic value for the treatment of DMO, when we stratify patients by outcome. Choroidal thickness (CT) decrease was just an indicator of anti-VEGF side effect on the choroid and the time curves of CRT and SFCT did not overlap (Campos et al. 2018).

In the report of Endo *et al.*, if CT increase in DMO was to be dependent on the level of VEGF, as stated by the authors, it is hard to explain why eyes of patients with proliferative diabetic retinopathy had lower CT, despite having higher CRT, than patients with non-proliferative diabetic retinopathy. On the other hand, VEGF levels depend on systemic treatment of diabetes, but the authors did not find that systemic treatment of diabetes significantly changed CT (Endo et al. 2020).

In the work of Mathis et al. (2020), there was a relation of CT increase with the anti-VEGFs' subsiding effect on the choroid, but it was not clear that monitoring CT would be more useful to detect recurrence than monitoring CRT. It is possible that an anti-VEGFs' waning effect on the choroid does not imply a need for another treatment if the CRT remains stable, that is, changes

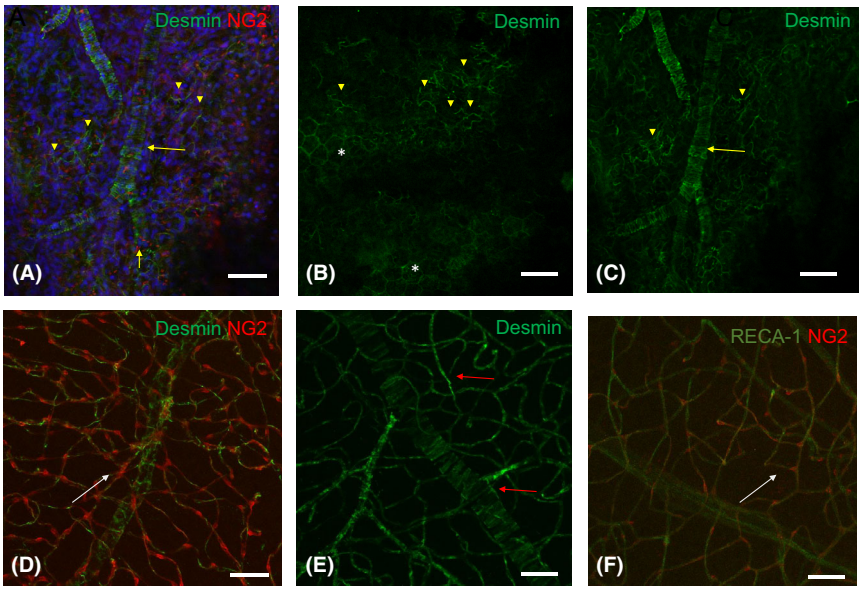

Fig. 1. Pericytes and perivascular mural cells in the choriocapillaris, middle choroid and retina of a 16-week Wistar rat show distinct morphological distribution. (A) Perivascular mural cells immunostained by desmin wrap around choroidal vessels (yellow arrows), while they assume a linear or stellate configuration at the choriocapillaris (arrowheads), corresponding to a scanty non-circumferential distribution of pericytes. NG2 staining of choroidal pericytes shows a sparse distribution. (B) Linear immunostaining of pericytes by desmin (arrowheads) near the hexagonal RPE cells' plane (asterisks) shows a scanty non-circumferential distribution. (C) Distinct morphology of mural cells immunostained by desmin wrapping around choroidal vessels (yellow arrow), while pericytes show a linear morphology and scanty non-circumferential distribution at the choriocapillaris level (arrowheads). (D) NG2 immunostaining of pericytes in the retina displays a perivascular location, even at the retinal capillary network (white arrow). (E) Pericytes and mural cells immunostained with desmin wrap around retinal vessels (red arrows). (F) Retinal vessels immunostained with RECA-1 (rat endothelial cell antibody 1) and pericytes immunostaining with NG2 prove that the location of pericytes in the retinal vessels is always perivascular (white arrow). Scale bar: 50 μm. 10× Full size: *x*: 850.19 μm, *y*: 850.19 μm.

in CT do not necessarily forecast a DMO recurrence and a need for an additional injection (Mathis et al. 2020). Furthermore, it is to be expected that the choroid thickens as the anti-VEGF effect subsides, because CT decreases as a side effect of anti-VEGF administration (Campos et al. 2018). It would be interesting if the authors would have mentioned the time elapsed from the latest injection before inclusion. Of course, the lack of data on the baseline CT before starting the treatment was also a shortcoming, since unilateral DMO implies that fellow eyes may not be alike.

In conclusion, CT as a surrogate of choroidal inflammation in diabetes, of choroidal flux or of DMO outcome is still under dispute. The value of CT thickening as an indicator of recurrence as the anti-VEGF effect wanes needs further comparison with treated patients that have no recurrence after the anti-VEGF effect subsided. It is debatable whether CT has any advantage over CRT as an indicator of DMO recurrence.

References

Campos A, Campos EJ, do Carmo A, Patrício M, Castro de Sousa JP, Ambrósio AF & Silva R (2018): Choroidal thickness changes stratified by outcome in real-world treatment of diabetic macular edema. Graefes Arch Clin Exp Ophthalmol **256**: 1857–1865.

Daruich A, Matet A, Moulin A et al. (2018): Mechanisms of macular edema: Beyond the surface. Prog Retin Eye Res **63**: 20–68.

Endo H, Kase S, Takahashi M et al. (2020): Relationship between diabetic macular edema and choroidal layer thickness. PLoS One **15**: e0226630.

Mathis T, Mendes M, Dot C et al. (2020): Increased choroidal thickness: a new indicator for monitoring diabetic macular oedema recurrence. Acta Ophthalmol. https://doi.org/10.1111/aos.14447.

Shimomura Y, Hirata A, Ishikawa S & Okinami S (2009): Changes in choriocapillaris fenestration of rat eyes after intravitreal bevacizumab injection. Graefes Arch Clin Exp Ophthalmol **247**: 1089–1094.

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