even if from a retrospective study, are interesting in terms of visual acuity and the low level of retinal detachment. We are fully aware of the bias a retrospective study presents and we would like to take the opportunity to discuss the different points highlighted by Taubenslag and Kim.[1]

Regarding the significance of the viral loads obtained by quantitative polymerase chain reaction, this certainly does not attest active viral replication; to prove this, retinal biopsy specimens would need to obtained, which is not possible. However, from our point of view, with such significant viral loads (≤1,000 copies/mL) and considering the clearance of aqueous humor, the positive polymerase chain reaction results cannot only correspond to noninfectious viral DNA elimination. This certainly supports the presence of viral activity. In the absence of consensual treatment, the monitoring of viral loads strikes us as an important tool to evaluate therapeutic response and to guide the course of treatment.

As for the implementation of only systemic treatment, the presence of occlusive retinal vasculitides that are common among cases of acute retinal necrosis are responsible for the lower bioavailability at the target site and reduced effectiveness of such drugs. Treatment by intravitreal injection allows for direct administration of the drug at the site of retinal necrosis, even in the presence of arterial occlusion. This is supported by Schoenberger and associates,[2] who report better results in terms of visual acuity and retinal detachment after the combined treatment of both systemic acyclovir and intravitreal injections of foscarnet, rather than systemic therapy alone.

Lastly, we consider viral reactivation inducing retinal necrosis to be a central nervous system manifestation and we therefore treat it as such with an intravenous treatment and not only by oral antiviral medication. Certainly, the cost is higher, but in our experience, we obtain better functional results and less frequent retinal detachment.

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Comment on: Retinal and Corneal Neurodegeneration and Its Association to Systemic Signs of Peripheral Neuropathy in Type 2 Diabetes

EDITOR:

WE READ WITH INTEREST THE STUDY "RETINAL AND corneal neurodegeneration and its association to systemic signs of peripheral neuropathy in type 2 diabetes" by Hafner and associates.[1] The authors have evaluated macular and peripapillary retinal nerve fiber layer in patients with various grades of diabetic retinopathy (DR) using optical coherence tomography (OCT), and have correlated these changes to corneal nerve length/density measured with confocal microscopy, clinical diabetic peripheral neuropathy (DPN) scores, and intraepidermal nerve fiber density (IENFD) measured with skin punch biopsy scores from the leg.

The authors have cited few previous studies that have indicated a strong role for corneal confocal microscopy as a surrogate marker of DPN.[1,2] However, the authors found no or very poor relation between IENFD and corneal neuronal parameters studied. Can this be because of the different nature of the 2 nerves being studied, the corneal nerve being a cranial nerve? In general, DPN is considered a symmetric form of diabetic neuropathy, whereas cranial nerve changes are a reflection of "asymmetric" cranial neuropathy. Other authors have classified DPN separately as a metabolic-microvascular-hypoxic type of neuropathy, while diabetic cranial neuropathy has been classified as inflammatory-immune type.[3]

In the perspective of retinal neuronal degeneration, the process can involve the retina at 3 different junctures: photoreceptors, middle retinal layers, and the inner retinal layers.[4,5] We have previously shown with electroretinogram that retinal neuronal degeneration affects all the layers of the retina at the outset of clinical DR, but as disease advances, middle retinal neuronal layers get more affected.[4] The current study has not used electrophysiology/corneal aesthesiometer to assess the functional nature of ocular neuronal loss, which, as they cite, is agreeably tedious.[1] However, as they have used OCT, middle retinal layers can be assessed at least morphologically and this may add further value to their analysis.

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FUNDING/SUPPORT: NONE. FINANCIAL DISCLOSURES: THE authors have no financial disclosures. All authors attest that they meet the current ICMJE criteria for authorship.

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Reply to Comment on: Retinal and Corneal Neurodegeneration and Its Association to Systemic Signs of Peripheral Neuropathy in Type 2 Diabetes

REPLY

WE WOULD LIKE TO THANK DRS TAKKAR AND TAKKAR FOR their letter and interest in our article.[1]

The authors first comment on our study's finding that even though both corneal and intraepidermal nerve fiber measures decreased in the advanced stages of diabetic retinopathy (DR), there was no statistically significant correlation between them. They suggest that this may be owing to the cranial origin of corneal fibers as opposed to the intraepidermal ones. However, although the corneal fibers derive from the ophthalmic division of the fifth cranial nerve, diabetic cranial neuropathy is known to present as a cranial nerve palsy, mostly either as an oculomotor or facial nerve palsy.[2] The major benefit of using corneal confocal microscopy as a noninvasive technique to detect subclinical small fiber alterations predictive of diabetic peripheral neuropathy (DPN) needs to be emphasized again. Similarly, intraepidermal nerve fiber density, though being invasive, prone to substantial interindividual variability, and specific to the location of biopsy, represents a valuable biomarker of small fiber neuropathy (SFN). Other groups have also found poor correlation of these intraepidermal and corneal signs of neuropathy, where either of them may independently manifest in affected patients, thus promoting a "patchy" pattern of SFN.[3] The precise pathophysiologic mechanisms leading to the different manifestation patterns and the lack of correlation between them are of great scientific interest and definitely merit future investigations prior to selecting one of them as the superior surrogate for DPN.

Further, our study was aimed at defining the extent of inner retinal neurodegeneration in the different stages of DR, and proposes that neurodegenerative changes of the inner retina develop independently of the microvascular alterations defining DR. There is solid evidence that inner retinal neurodegeneration, shown as a selective loss of the retinal nerve fiber layer, ganglion cell layer, and inner plexiform layer thicknesses, plays a pivotal role in the development of diabetic retinal disease.[4] Takkar and Takkar outline that neuronal loss may also affect the "middle retina." Although the "middle retina" is not further defined here, they refer to their previous study,[5] where they used multifocal electroretinography as well as optical coherence tomography (OCT) to evaluate different types of diabetic macular edema (DME). This renders a comparison to our study virtually impossible, as we consciously excluded eyes with DME, as DME represents an entirely different entity of diabetic retinal disease, where the precise segmentation of individual retinal layers in OCT can still be difficult. In particular, it requires meticulous segmentation in order to reveal cases where the presence of intraretinal cysts conceals inner retinal neurodegeneration owing to a consistent central retinal thickness. Whereas Nagesh and associates[5] only assessed the ellipsoid zone and external limiting membrane next to full central macular thickness, they refer to Vujosevic and Midena,[6] who, notably, found an increase rather than decrease in thickness of the inner nuclear and outer plexiform layers in patients with diabetes, which likely represents an activation and hypertrophy of hyperglycemia-susceptible Müller cells rather than neurodegeneration in the "middle retina."

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