

Response to "Vitamin D status is negatively correlated with retinal nerve fiber layer thickness in relapsing-remitting MS patients without acute optic neuritis" by Knippenberg et al.

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A total of 10 subjects had a history of ON. Patient characteristics were not significantly different between MS subjects with ON or without ON. The worst performing eye was included in the analysis.

Like Burton et al., we observed a negative correlation between vitamin D status and RNFL thickness at baseline (Figure 1(a)). This correlation was stronger when only subjects without previous ON were analyzed ($r=-0.601$, $p=0.011$). We investigated other outcomes of optic nerve function. Vitamin D status did not correlate with visual acuity, VEP P100 latency, or VEP amplitude (Figure 1(b)–(d), respectively). Stratification for a history of ON did not affect the results (data not shown). Finally, we assessed the correlation between vitamin D status at baseline and the 12-month change of RNFL thickness, VEP P100 latency, and VEP amplitude. We found no correlation between vitamin D status and change of RNFL thickness, change of VEP P100 latency, and change of VEP amplitude (Figure 1(e)–(g), respectively).

Although the negative correlation between 25(OH)D levels and RNFL thickness reported by Burton et al. was hypothesized to be due to inflammation of the optic nerve, we replicated this finding in a cohort without active ON. Therefore, an effect of inflammation is unlikely. Alternatively, a detrimental effect of 25(OH)D on RNFL thickness could be hypothesized but is not supported by the longitudinal data of Burton et al., and by the longitudinal OCT and VEP data in this letter. Providing alternative explanations is challenging. A higher ultraviolet (UV) exposure has been associated with a higher risk of macular degeneration.² Therefore, the lower vitamin D status in patients with a reduced RNFL thickness could be a biomarker for detrimental effects of UV-light exposure on the retina. Nevertheless, although the interpretation of the correlation between vitamin D status and RNFL thickness is uncertain, the beneficial effect of vitamin D status on ON recovery demonstrated by Burton et al. is exciting and warrants further investigation.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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References

1. Burton JM, Eliasziw M, Trufyn J, et al. A prospective cohort study of vitamin D in optic neuritis recovery. *Mult Scler*. Epub ahead of print 1 April 2016. DOI: 10.1177/1352458516642315.
2. Schick T, Ersoy L, Lechanteur YT, et al. History of sunlight exposure is a risk factor for age-related macular degeneration. *Retina* 2016; 36(4): 787–790.

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Dear *Multiple Sclerosis Journal* Editors and Dr Knippenberg and colleagues,

Thank you to Dr Knippenberg and colleagues for your letter.¹ Dr Knippenberg et al. report that in their study of 27 patients with relapsing-remitting multiple

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sclerosis (RRMS) (with or without a history of optic neuritis), 25(OH)D values did negatively correlate with the initial retinal nerve fiber layer (RNFL) thickness measurement, regardless of optic neuritis history. In our prospective longitudinal study of acute optic neuritis of 36 patients, all patients had acute optic neuritis, and so the 25(OH)D measurements we obtained at presentation were temporally associated with all baseline optical coherence tomography (OCT) results including RNFL thickness, which was only elevated in those with a 25(OH)D <80 nmol/L (RNFL of 134.3 vs 95.2 μm in sufficient patients, $p=0.003$). As well, we distinguished groups based on vitamin D status using a threshold 25(OH)D above or below 80 nmol/L, consistent with the biochemical definition of vitamin D sufficiency. The definition of vitamin D sufficiency may vary between different studies and thus could be a factor.

With respect to subsequent ophthalmological measures over time (6 months in our study, 12 months in Knippenberg et al.), we agree that we did not see significant differences in thinning in RNFL at 6 months between our vitamin D cohorts (79.3 vs 76.3 μm in insufficient vs sufficient patients, respectively). However, in vitamin D insufficient patients, we did find evidence of significant neuronal loss in the ganglion cell layer (GCL) on OCT, as well as poorer visual recovery on high-contrast visual acuity testing. In our study, the GCL inter-eye difference, which uses the unaffected eye of the patient as another level of control (unaffected eye value minus affected eye value) differed significantly between vitamin D cohorts. In vitamin D insufficient patients, the GCL inter-eye difference was 14.2 μm , while it was only 4 μm in the sufficient group ($p=0.008$), indicating relatively greater thinning in insufficient patients. The use of the GCL measure is highly practical as it is not impacted by inflammation (as is the RNFL) and correlates with brain atrophy in MS patients.²

Admittedly, both our study and that by Knippenberg et al. are affected by a small sample size. Furthermore, differences in the patient cohorts between studies could be contributing to the different results found by the two studies. Knippenberg et al.'s inclusion of patients without a history of optic neuritis, and those

without acute optic neuritis, may present a challenge in elucidating the apparent impact of vitamin D on retinal structure measurements by OCT, as the timing of vitamin D sufficiency in the context of optic nerve injury itself could be an important variable. Additionally, we did not study ultraviolet (UV) exposure in our patients, so there is the possibility that this variable may be a contributing factor. Both studies have shown some very interesting correlations between OCT measurements of optic nerve integrity and vitamin D status, suggesting that further, larger scale studies of the relationship between vitamin D and optic nerve integrity are warranted.

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References

1. Knippenberg S, Smolders J, van den Maegdenbergh M, Porro G, Damoiseaux J, & Hupperts R. Vitamin D status is negatively correlated with retinal nerve fiber layer thickness in relapsing-remitting MS patients without acute optic neuritis. *Mult Scler*. Epub ahead of print. DOI: 10.1177/1352458516652950
2. Saidha S, Al-Louzi O, Ratchford JN, et al. Optical coherence tomography reflects brain atrophy in multiple sclerosis: A four-year study. *Ann Neurol* 2015; 78: 801–813.

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