On the ethics of not supplementing low 25-hydroxyvitamin D levels in a controlled study in relapsing remitting multiple sclerosis

Citation for published version (APA):

Smolders, J., Rolf, L., Damoiseaux, J., & Hupperts, R. (2017). On the ethics of not supplementing low 25-hydroxyvitamin D levels in a controlled study in relapsing remitting multiple sclerosis. *Journal of the Neurological Sciences*, 379, 331-331. <https://doi.org/10.1016/j.jns.2017.06.009>

Document status and date:

Published: 15/08/2017

DOI:

[10.1016/j.jns.2017.06.009](https://doi.org/10.1016/j.jns.2017.06.009)

Document Version:

Publisher's PDF, also known as Version of record

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Letter to the Editor

On the ethics of not supplementing low 25-hydroxyvitamin D levels in a controlled study in relapsing remitting multiple sclerosis

We thank Shukla et al. for their critical appraisal of our work. Regarding the first comment: we agree, as already mentioned in the manuscript, that our exploratory study has its limitations and did not reveal major new insights in the role vitamin D₃ may have in the treatment of major depression in multiple sclerosis (MS). Regarding the ethical concerns of Shukla et al., we think there are some important nuances which make our study different from the study discussed by Lo and Grady [1].

First, all participants were treated with a first-line MS disease modifying treatment, Interferon Beta 1a. Second, participants were aware that they could be randomized in a high-dose vitamin D₃ arm for the duration of the trial. Risk-analyses provided confidence about safety, which was further supported by a recent study [2]. In the parental study, SOLAR, detailed safety analyses were performed and supervised by an independent data safety monitoring board, with individual dose-adjustments if toxicity was suspected (NCT01285401). Third, the risk of exposing participants to an adverse disease course of MS by not correcting low 25-hydroxyvitamin D (25(OH)D) levels is uncertain.

The association between 25(OH)D levels and MS outcomes may be driven by a disease modulating effect of vitamin D₃ metabolites [3]. However, a progressing disease severity of MS induces sun-avoiding behavior [4]. Sunlight is not only the main source of vitamin D₃, but has also been argued to have direct disease-modulating effects independent from vitamin D₃ [5]. Additionally, an activated immune system may lower 25(OH)D levels [6]. Although high 25(OH)D levels are associated with favorable MS outcomes in observational studies, it is uncertain whether vitamin D₃ supplements improve these outcomes. From this perspective, it could even be argued to be unethical to advise patients vitamin D₃ supplements with the goal of improving disease outcome. Furthermore, most efficacious 25(OH)D levels to aim for may be above the physiological range. To substantiate such advises, randomized controlled clinical studies with (high doses of) vitamin D₃ should reveal benefit for patients on targeted disease outcomes.

In the study discussed by Lo and Grady [1], a mild anemia was not disclosed to participants, which may hamper the diagnosis of underlying disease. In the case of vitamin D₃, low 25(OH)D levels are frequently found in MS [7] as well as in the general population [4], and its etiology is unlikely to comprise alternative diseases. Patients have their physiological vitamin D₃ exposure from diet and sunlight and were allowed to take 1.000 IU/d vitamin D₃ supplements. As a result of participation in our study, they were actively informed about the possible implications of low 25(OH)D levels in MS.

Although we agree with Shukla et al. that our dataset failed to provide a clear answer to our patients on vitamin D₃ supplementation and the endpoint depressive symptoms in MS, we think our data should encourage investigators to further address this issue. Whether

supplementation of moderate or high amounts of vitamin D₃ improves disease outcomes targeted by patients and clinicians should become clear from clinical trials. If a reproducible positive effect is identified, not supplementing MS patients with low 25(OH)D levels should be reconsidered.

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7 June 2017