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Effect of vitamin D supplementation on axonal damage in relapsing-remitting multiple sclerosis

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Introduction

- **Background**

The effect of vitamin D supplementation in relapsing-remitting multiple sclerosis (RRMS) is not established[1]. Neurofilament light chain (NfL) is a sensitive biomarker for axonal damage and an inverse relationship has been found between NfL and 25-hydroxy-vitamin D (25(OH)D) levels in RRMS[2].

- **Objectives**

To establish whether high-dose vitamin D supplementation reduces serum levels of NFL.

- **Material and methods**

We analyzed the association between serum levels of NfL and 25(OH)D in a two-year randomized placebo-controlled trial (RCT) of high-dose oral vitamin D3 supplementation (20.000 IU/week) in 68 RRMS patients (NCT00785473)[3]. NfL and 25(OH)D were measured at baseline, week 48 and week 96 with a single molecule assay (Simoa) and mass spectroscopy, respectively[4,5]. Changes in serum NfL over time were analyzed using linear mixed models with follow-up time points, study arm, and the interaction between them as predictors. Log transformed NfL levels were used, and changes are therefore reported as percentages.

Results

Baseline study population characteristics

		Vitamin D group (N; 35)	Placebo group (N; 33)
Females	N	24	24
Age (years)	Mean (SD)	40 (8)	41 (6)
EDSS score	Median (95% CI)	2.5 (2.5-3.5)	2.0 (2.0-3.0)
Disease modifying treatment (DMT)	N	17[a]	17[b]
Disease duration (years)	Mean (SD)	11 (7)	10 (7)
Annual relapse rate[c]	Mean (SD)	0.11 (0.22)	0.15 (0.31)
25-(OH)D (nmol/L)	Mean (SD)	55.6 (29.0)	57.3 (21.8)

[a]16 patients on interferon-β and 1 patient on glatiramer acetate; [b]15 patients on interferon-β, one on glatiramer acetate and one on natalizumab; [c]Determined by relapses leading to hospitalization the last 24 months before the study

Mean (SD) NfL leves during the study (pg/ml)

Patients	Study group	N	Week 0	Week 48	Week 96
All	Vitamin D	35	8.8 (4.3)	8.5 (4.3)	**7.9 (4.1)**
	Placebo	33	10.6 (8.5)	9.7 (7.5)	**10.4 (8.9)[a]**
With DMT at baseline	Vitamin D	17	8.3 (3.9)	8.9 (3.7)	8.1 (4.1)
	Placebo	17	10.5 (9.8)	7.5 (2.5)	7.7 (5.1)
No DMT at baseline	Vitamin D	18	9.2 (4.7)	8.0 (5.0)	**7.5 (4.3)**
	Placebo	16	10.7 (7.9)	11.5 (9.7)	**13.1 (11.0)[a]**

[a]One value missing

Mean (SE) change of NfL levels from baseline (%)

Study group	Week 48	p-value	Week 96	p-value
Vitamin D	-5.2 (8.6)	0.55	**-12.0 (8.6)**	**0.16**
Placebo	-4.1 (8.8)	0.64	**-4.8 (8.9)**	**0.59**
Vitamin D versus placebo	-1.1 (1.2)	0.93	-7.3 (12.4)	0.56

Discussion

- This is to our knowledge the first RCT examining the effect of vitamin D supplementation on serum NfL as a marker of axonal damage in RRMS.
- The main result does not support an effect of vitamin D supplementation on serum NfL levels and is not in line with a previously reported association between high serum 25(OH)D and low CSF NfL levels by Sandberg et al[2].
- The patient populations in these studies differ however, as Sandberg et al.[2] included patients with primary and secondary progressive MS, some of them used DMTs that were not used by the patients in our study, and their vitamin D levels were more variable.
- There was a trend for a beneficial effect of vitamin D supplementation in untreated patients that concurs with our previous findings suggesting an effect of vitamin D on inflammation in untreated RRMS patients[6,7].
- Our study was limited by a relative small size, the patients had a low disease activity and a quite good baseline vitamin D status, and it is possible that daily supplementation of vitamin D is more effective than weekly dosing[8].

Conclusion

- **With a possible exception for patients without disease modifying treatment, weekly oral supplementation with 20.000 IU vitamin D3 seems to have no clear effect on axonal damage in RRMS.**

Literature

[1]Shoemaker TJ, Mowry EM. A review of vitamin D supplementation as disease-modifying therapy. *Mult Scler* 2018;24:6-11; [2]Sandberg L et al. Vitamin D and axonal injury in multiple sclerosis. *Mult Scler* 2015; 22:1027-31; [3]Kampman MT et al. Effect of vitamin D3 supplementation on relapses, disease progression and measures of function in persons with multiple sclerosis: exploratory outcomes from a double-blind randomised controlled trial. *Mult Scler* 2012; 18:1144-51; [4]Gisslen M et al. Plasma Concentration of the Neurofilament Light Protein (NFL) is a Biomarker of CNS Injury in HIV Infection: A Cross-Sectional Study. *EBioMedicine* 2016;3:135-140; [5]Steffensen et al. Can vitamin D supplementation prevent bone loss in persons with MS? A placebo-controlled trial. J Neurol 2011; 258:1624-1631; [6]Loken-Amsrud KI et al. Vitamin D and disease activity in multiple sclerosis before and during interferon-beta treatment. *Neurology* 2012;79:267-273; [7]Røsjø E et al. Vitamin D status and effect of interferon-beta1a treatment on MRI activity and serum inflammation markers in relapsing-remitting multiple sclerosis. *J Neuroimmunol* 2015;280:21-28; Hollis BW et al. Clinical review: The role of the parent compound vitamin D with respect to metabolism and function: Why clinical dose intervals can affect clinical outcomes. *J Clin Endocrinol Metab* 2013;98:4619-4628.