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Lower serum vitamin D levels are associated with a higher relapse risk in multiple sclerosis

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ABSTRACT

Objective: There is increasing evidence that vitamin D can be protective against the development of multiple sclerosis (MS), but it may also be beneficial for the clinical course of the disease. Our objective was to prospectively investigate if 25-hydroxy-vitamin D (25-OH-D) levels are associated with exacerbation risk in MS in a study with frequent serum measurements.

Methods: This was a prospective longitudinal study in 73 patients with relapsing-remitting MS. Blood samples for 25-OH-D measurements were taken every 8 weeks. Associations between 25-OH-D levels and exacerbation rates were assessed using Poisson regression (generalized estimating equations) with the individual serum levels as time-dependent variable.

Results: During follow-up (mean 1.7 years), 58 patients experienced a total of 139 exacerbations. Monthly moving averages of 25-OH-D levels were categorized into low (<50 nmol/L), medium (50–100 nmol/L), and high (>100 nmol/L) levels. Exacerbation risk decreased significantly with higher serum vitamin D levels: respective relative exacerbation rates for the medium and high-level category as compared to the low-level category were 0.7 and 0.5 (p value for trend: $p = 0.007$). The association between 25-OH-D concentrations and exacerbation rate was log linear without a threshold. With each doubling of the serum 25-OH-D concentration the exacerbation rate decreased by 27% (95% confidence interval 8%–42%, $p = 0.008$).

Conclusions: Our finding that higher vitamin D levels are associated with decreased exacerbation risk in relapsing-remitting MS suggests a beneficial effect of vitamin D on disease course in MS. However, the possibility of reverse causality cannot be ruled out completely. Randomized intervention studies are therefore needed to investigate the effect of vitamin D supplementation in MS. *Neurology*® 2012;79:261–266

GLOSSARY

25-OH-D = 25-hydroxy-vitamin D; **CI** = confidence interval; **EDSS** = Expanded Disability Status Scale; **MS** = multiple sclerosis.

Multiple sclerosis (MS) is a chronic disease of the CNS that starts in most patients with a relapsing-remitting disease course. The etiology of MS is multifactorial. Both genetic susceptibility and environmental exposure contribute to the pathogenesis.¹ One of the environmental factors associated with the development of MS is vitamin D.²

Vitamin D is a group of fat-soluble prehormones, related to steroid hormones. It can be absorbed from food, but in the human body the main source for vitamin D is the production in the skin under influence of UVB light. Although the active metabolite of vitamin D is 1,25-dihydroxy-vitamin D (1,25-diOH-D), or calcitriol,³ the metabolite best reflecting the vitamin D status of the patient is 25-hydroxy-vitamin D (25-OH-D), or calcidiol.⁴

A protective effect of vitamin D on the onset of MS is supported by many studies in epidemiology as well as in basic and clinical science,^{5–10} but recent evidence suggests that vitamin D might also influence the clinical course of the disease. Several studies report lower

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serum 25-OH-D concentrations during exacerbations then during remission.^{11–13} So far, only one prospective study was conducted to investigate the association between serum 25-OH-D concentrations and exacerbation rate.¹⁴ In that study, higher serum 25-OH-D concentrations were found to be associated with a lower hazard for exacerbation. However, calculations were based on only 2 measurements of serum 25-OH-D concentrations per person per year. Because serum 25-OH-D concentrations are known to be fluctuating with season, more frequent sampling would allow for a more accurate estimation of vitamin D levels. The aim of this study is therefore to investigate the association between serum 25-OH-D concentrations and disease course in relapsing-remitting MS prospectively with serum measurements every 8 weeks.

METHODS Standard protocol approvals, registrations, and patient consents. Data and samples were collected in the Rotterdam Study on Exacerbations in Multiple Sclerosis, a longitudinal prospective study in patients with relapsing-remitting MS.¹⁵ Patients were included sequentially during an inclusion period of 1.7 years in 1997–1999. Serum 25-OH-D measurements were performed in 2010. At the time of recruitment and data collection, written informed consent was obtained from all patients. The Medical Ethical Committee of the Erasmus MC approved the study protocol.

Patients. Patients aged 18–55 years could be included in the study if they had clinically definite MS with a relapsing-remitting disease course. Patients were excluded from participation if they suffered from other serious diseases.

Definitions. All patients fulfilled the McDonald criteria for the diagnosis of MS.¹⁶ Exacerbation was defined as a worsening of existing symptoms or the appearance of new symptoms lasting for more than 24 hours, after a period of more than 30 days of improvement or stability, confirmed by neurologic examination.¹⁷ A temporary neurologic deterioration associated with fever was not considered as an exacerbation.

Because infection is a known risk factor for exacerbations in MS, the at-risk period around infection was used as a covariate in this study.¹⁵ Infection was defined as the appearance of coryza, sore throat, flu-like feeling, myalgia, fever, diarrhea, or a urinary infection lasting >24 hours. The at-risk period for infection was defined as the period of 2 weeks before until 5 weeks after the onset of a clinical infection, as described previously.¹⁸

Visits, samples, and measurement of exacerbations. All patients visited the outpatient clinic of the Erasmus Medical Centre University Hospital regularly every 8 weeks. On every visit, samples for 25-OH-D measurements were taken and disability was measured using the Kurtzke Expanded Disability Status Scale (EDSS).¹⁹ Furthermore, patients were instructed to contact the study center when they experienced symptoms of infection or neurologic impairment. In case of a suspected infec-

tion or exacerbation, an additional visit to the outpatient clinic was arranged within 3 days, to confirm the infection or exacerbation. Serum samples were stored at -80°C until serum 25-OH-D measurement, performed in 2010.

Measurement of 25-OH-vitamin D. Concentrations of 25-OH-D have been determined by a RIA method (DiaSorin, USA) using an extraction method. The interassay variation coefficient at a concentration of 62 and 109 nmol/L is 11.6% and 10.3%, respectively. The intra-assay variation coefficient at the levels is 5.7% and 6.6%, respectively. Only serum samples taken at the regular 8-weekly visits were used for 25-OH-D measurements; samples taken during exacerbation visits were not evaluated.

Statistical analysis. Graphical display of individual serum 25-OH-D concentrations vs calendar time indicated a sinusoidal pattern. Therefore a sinusoidal model was used to describe the 25-OH-D concentrations along calendar time:

$$\text{Log}_{10}(\text{concentration}) = a + b \sin(2\pi[t + c]).$$

In this formula the parameter a represents the mean logarithmically transformed concentration, b represents the amplitude, c denotes the phase of the sinusoidal curve, and t represents the day of the year the blood sample was taken. Concentrations were transformed logarithmically in order to get approximately normal distributions.

Nonlinear regression was used to estimate the parameters in the regression model and the parameters a and b were allowed to differ from patient to patient, i.e., individual's levels and amplitudes were taken as random effects in the regression model. SAS software (PROC NL MIXED; SAS Institute Inc., Cary, NC) was used in the calculations.

To assess the association between individual serum 25-OH-D concentrations and the incidence rate of exacerbations, the follow-up time for each patient, which covered a maximum period of 2.3 years, was split into intervals of 1 week each. For each of these intervals the number of exacerbations was determined. The individual exacerbation rate was assumed to depend on the geometric mean serum 25-OH-D concentration during the previous 4 weeks. To obtain the latter mean level, for each individual the 4-weekly levels between measurements were determined using interpolated values. In case a planned sample was missing for a patient, and his last as well as the next observation occurred more than 4 weeks earlier, respectively later, than the date at which patients were estimated to have their maximal or minimal value in view of the sinusoidal pattern, this interpolation was not done and interpolated values were set missing. This was done to avoid weekly estimates of the concentration that were likely to be either too low or too high in view of the sinusoidal pattern. During the period of 4 weeks following an exacerbation, the individual was not considered at risk for another exacerbation. A priori it was decided to categorize the geometric mean serum levels of the 4 preceding weeks into a low level (<50 nmol/L), a medium level (50–100 nmol/L), and a high level (>100 nmol/L). The relationship between serum 25-OH-D concentrations and the incidence rate of exacerbations was assessed using Poisson regression models with the geometric mean individual serum levels as a time-dependent variable. Generalized estimating equations with an exchangeable covariance matrix for the subsequent study weeks were used in the calculations (SAS PROC GENMOD). The effect of other factors including gender, age, EDSS, number of exacerbations before study entry, and use of interferon- β during the study was also estimated using a multivariable generalized linear model with a log-link function.

Table 1 Characteristics of patients at baseline

Variable (n = 73)	Mean (range) or %	SD
Age, y	39.4 (19-55)	9.1
Disease duration, y	5.2 (0-25)	4.1
Disability (EDSS) ^a	2.5 (0-6.0)	1.6
Exacerbations in previous 2 years	2.2 (1-8)	1.3
Gender, F/M	77/23	
Interferon use, N/Y	82/18	

Abbreviation: EDSS = Expanded Disability Status Scale.

^a EDSS is a method for quantifying disability in multiple sclerosis, ranging from 0.0 (normal neurologic examination) to 10.0 (death due to multiple sclerosis).

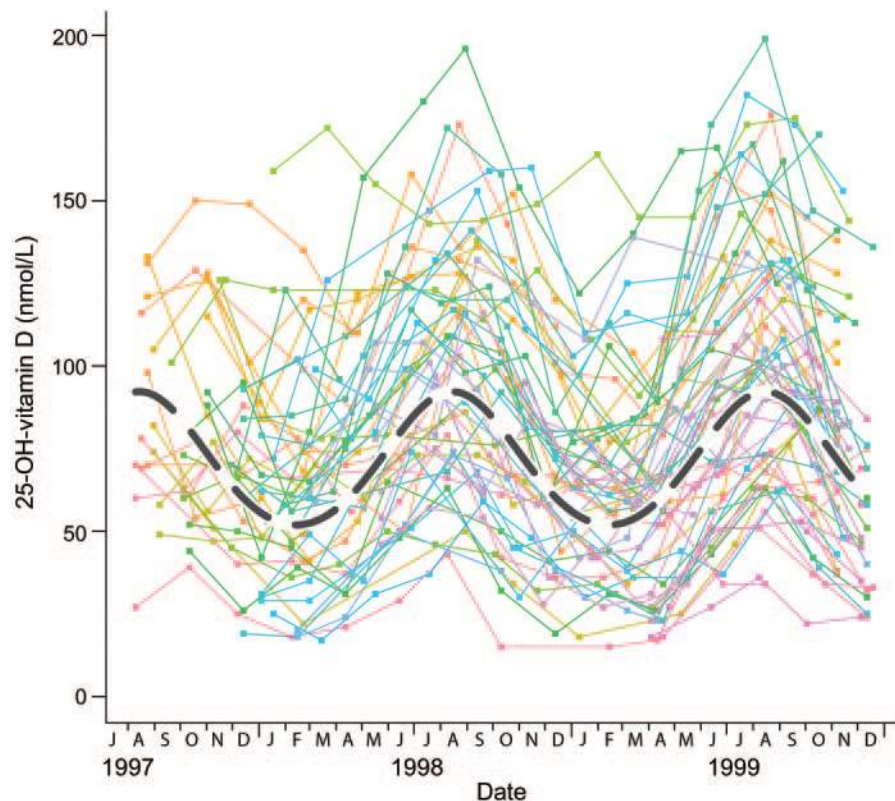
To evaluate whether the occurrence of exacerbations after entry into study affected the dropout rate, Cox regression was used with the cumulative number of exacerbations as a time-dependent variable. $p = 0.05$ (2-Sided) was considered the limit of significance in all analyses.

RESULTS Patient characteristics. A total of 73 patients were included in this study. Mean follow-up time of all patients was 1.7 years (range 0.4–2.3). Nine patients had dropped out of the study before intended completion date (1 patient because of par-

ticipation in another study; for the 8 other patients no reason was known). All patients were Dutch Caucasians; baseline characteristics of included patients are shown in table 1. In addition to the 13 patients who used interferon- β at study entry, 15 patients started to use interferon- β during follow-up; 28 patients used interferon- β at some point during on average 56 weeks. Vitamin supplements were not widely used among the patients: 5 patients used vitamin B complex and 2 used multivitamin pills not containing vitamin D. One patient took calcium supplements; it was unknown if those contained vitamin D.

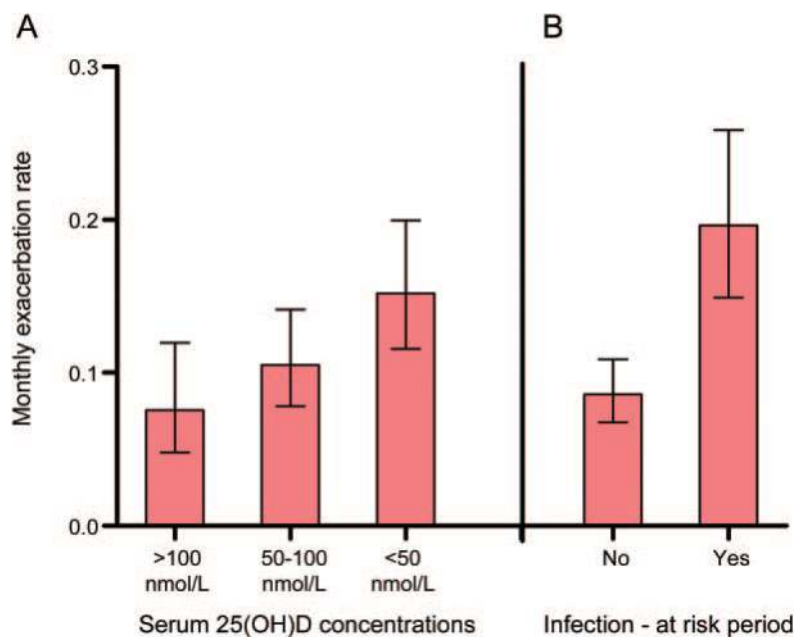
A total of 58 patients experienced a total of 139 exacerbations during this study. Median time from inclusion to first exacerbation was 20 weeks. Thirty-three patients had more than 1 exacerbation; the average exacerbation rate was 1.2 per year (range 0–6.2 per year). Three patients experienced a sixth exacerbation during follow-up.

Serum 25-OH-D concentrations. Serum 25-OH-D concentrations showed a seasonal sinusoidal fluctuation (figure 1). Serum concentrations were high in summer and low in winter, with peak levels in mid

Figure 1 Fluctuation of 25-hydroxy-vitamin D (25-OH-D) levels

The 25-OH-D concentrations per patient vs date of blood sampling. Data of individual patients are connected by straight lines. The dotted curve represents the overall fitted sinusoidal curve. Estimates (\pm standard error) of the parameters of the model $\text{Log}_{10}(\text{concentration}) = a + b \sin(2\pi[t + c])$ are $a = 1.837 \pm 0.022$, $b = 0.125 \pm 0.009$, and $c = -0.367 \pm 0.006$.

Figure 2 Monthly exacerbation rates for the different groups



(A) Monthly exacerbation rates for the different groups of serum 25-hydroxy-vitamin D (25-OH-D) concentrations, and (B) for at-risk period for infections. Error bars denote 95% confidence intervals. Serum 25-OH-D concentrations: p (trend) = 0.007; infections $p < 0.001$.

August and nadirs in mid February. The fitted sinusoidal curve resulted in a geometric mean 25-OH-D concentration of 69 nmol/L. There was a considerable variation in mean levels between patients (coefficient of variation 41%).

Association between serum 25-OH-D concentrations and exacerbation risk. Exacerbation rates were found to decrease with increasing levels of serum 25-OH-D concentrations (figure 2A). For the low (<50 nmol/L), medium (50–100 nmol/L), and high (>100 nmol/L) category the monthly exacerbation rates were 0.15 (95% confidence interval [CI] 0.12–0.20), 0.10 (95% CI 0.08–0.14), and 0.07 (95% CI 0.05–0.12), respectively. The risk of an exacerbation

was significantly increased in the group with low serum 25-OH-D concentrations (<50 nmol/L) compared to the group with high serum concentrations (>100 nmol/L). Rate ratios for the low and medium group were 2.0 and 1.4, respectively (p for trend = 0.007).

In univariate analysis it was also found that infections were associated with the risk of an exacerbation. The exacerbation rate within an at-risk period was 2.1-fold increased (95% CI 1.6–2.8, $p < 0.001$, figure 2B). Simultaneous evaluation of categories of levels of serum 25-OH-vitamin and infections showed that both factors were related to the exacerbation rate (table 2). Also the effect of one factor did not depend on the other (interaction: $p = 0.18$).

Other characteristics (gender, age, EDSS, use of interferon- β , and number of exacerbations in the 2-year period before entry into the study) were not significantly associated with the exacerbation rates. This applied in univariate (all $p > 0.18$) as well as multivariable analysis (all $p > 0.17$). In particular, the effect of vitamin D on exacerbations was not modified by interferon use ($p = 0.78$ for the interaction effect).

No significant differences among the 4 seasons were found regarding exacerbation rates, in univariate, or in multivariate analysis.

Analyzing logarithmically transformed serum 25-OH-D concentrations on a continuous scale showed that a doubling of serum 25-OH-D concentrations caused a decrease of the exacerbation rate by 27% (95% CI 8%–42%, $p = 0.008$) (adjusted for the effect of infections). Adding quadratic and cubic terms of the linear predictor, i.e., log(serum concentration), did not significantly improve the fit of the model, indicating the linearity of the association and the absence of a threshold.

Analyzing the 9 dropouts it was found that the dropout rate did not significantly correlate with the cumulative number of exacerbations during the study (Cox regression: $p = 0.29$), nor with any baseline characteristic.

Table 2 Association between exacerbation rate and serum 25-OH-D concentrations and infection according to multivariable analysis

	Relative exacerbation rate	95% Confidence interval	p Value
ARP infection			
Yes	2.3	1.7-3.1	<0.001
No	1 (reference)	—	
Vitamin D level			
Low (<50 nmol/L)	1.9	1.1-3.2	0.013 ^a
Medium (50-100 nmol/L)	1.4	0.8-2.2	0.235 ^a
High (>100 nmol/L)	1 (reference)	—	

Abbreviation: 25-OH-D = 25-hydroxy-vitamin D; ARP infection = at risk period for infection. ^a p Value for trend: 0.012.

DISCUSSION In the present study we show that lower 25-OH-D levels are significantly associated with a higher exacerbation risk in patients with relapsing-remitting MS. In the category of low 25-OH-D levels, the risk for an exacerbation was 2 times higher than in the category of high levels. This association was log linear without a threshold effect; a doubling of serum 25-OH-D concentrations lowered the exacerbation risk by 27%. Adjustment for potential confounders, including infection, gender, disability (EDSS), and use of immunomodulatory therapy, did not alter this association. In particular,

although in experimental autoimmune encephalomyelitis the effect of vitamin D is found to be stronger in female mice,¹⁰ we did not find an influence of gender on the association between 25-OH-D and exacerbations in this study.

The key strength of this study is the frequent measurement of serum 25-OH-D concentrations. So far, only one prospective study has been performed to investigate the association between serum 25-OH-D concentrations and disease course in patients with relapsing-remitting MS with more than 1 serum measurement.¹⁴ In that study, a significant association between 25-OH-D levels and exacerbation risk was found, but this was based on only 2 serum measurements per patient per year. It is well known that vitamin D levels fluctuate with season. Also, there is great interindividual variation of the mean vitamin D level and the amplitude of the seasonal fluctuation (also shown in our data). This makes extrapolating data from only 1 or 2 measurements per year using sinusoidal models very imprecise. With the present study, the suggested association between 25-OH-D levels and exacerbation risk can now be confirmed with much more accurate data on vitamin D levels. Furthermore, we included infection as a confounder and provide more frequently measured information on disability.

An additional strength of this study is the infrequent use of interferon- β among the patients. This allowed us to study the sole effect of vitamin D. Although some studies suggest an additional beneficial effect of vitamin D in interferon- β users,^{20,21} we did not find an additional effect of interferon- β treatment in this study. The fact that the association between vitamin D and exacerbation risk held in patients who used interferon- β might suggest that the effect of vitamin D is additive to the effect of interferon- β . However, this study was not set up to measure such an additive effect.

Our study was limited by the lack of information on the amount of sunshine the patients had during this study. We do not expect sun exposure and subsequent cutaneous vitamin D production to differ much among patients, as all patients were Caucasians from the Rotterdam region, but sun exposure is a potential confounder that we could not adjust for.

Although we found a strong seasonal fluctuation of vitamin D levels, the association between clinical disease activity and season was not significant in this study. Several other studies describe seasonality of MS disease activity, mostly with higher activity in spring. What we show here is an association between vitamin D and exacerbation risk that persists through all seasons. In this respect it should be noted that vitamin D and some other UV-mediated immune

processes can act separately on the immune system, as recently described.^{22,23}

In studies on vitamin D and disease course in MS, there is often the issue of reverse causality: the possibility that the higher relapse rate is not caused by lower vitamin D levels, but that the low vitamin D levels are caused by increased disability that prevents patients from spending time outdoors. In this study, 2 facts argue against such a phenomenon. First, for every week the influence of the vitamin D levels during the preceding 4 weeks on exacerbations was calculated. Secondly, adjustment for disability (EDSS) did not alter the inverse association between 25-OH-D levels and exacerbation risk. Furthermore, only the serum samples taken at the regular 8-weekly visits were used in the sinusoidal model, and samples taken during exacerbation visits were not evaluated.

The biological plausibility for a protective role of vitamin D on the disease course of MS has been given in many experimental settings. Different cells of the immune system, including macrophages and activated T lymphocytes²⁴ and B lymphocytes,²⁵ contain vitamin D receptors. 1,25-(OH)₂ D has been shown to inhibit the production of inflammatory cytokines in vitro²⁶ and to promote the development of regulatory T lymphocytes.^{27,28} Furthermore, a correlation between serum 25-OH-D concentrations and a more anti-inflammatory Th1/Th2 ratio has been found.²⁰ Also in other autoimmune diseases, such as rheumatoid arthritis, type 1 diabetes, and systemic lupus erythematosus, evidence for a protective role of vitamin D is growing.²⁹ However, in these ailments prospective studies are scarce.

To evaluate if the association between vitamin D levels and exacerbations in MS could be causal, Hill's criteria of causation can be used.³⁰ Hill's criteria are as follows: 1) strength of the association, 2) consistency of the association, 3) temporality, i.e., does the exposure precede the disease (this is the issue of reverse causality), 4) biological gradient, or dose-response curve, 5) plausibility of the causation, and 6) experiment: have there been experiments to investigate if a change in exposure alters disease frequency. In the present study, we found a moderately strong association (criterion 1), which was linear (criterion 4). Our findings are consistent with previous research and are biologically plausible (criteria 2 and 5). Despite arguments provided above, the theoretic possibility of reverse causality (criterion 3) cannot be ruled out completely. Therefore clinical intervention trials are needed to further investigate the relationship between vitamin D supplementation and disease course in MS.

In this prospective cohort study we have demonstrated that lower serum vitamin D levels are associ-

ated with increased exacerbation risk in patients with relapsing-remitting MS; for each doubling of the serum 25-OH-D concentration the relapse risk in MS decreases by 27%.

Vitamin D has the advantages of being cheap, safe, and easy to administer, and could therefore be a valuable addition to the existing treatment opportunities in MS.

AUTHOR CONTRIBUTIONS

R.Q.H., D.B., and T.F.R. designed the study. D.B. was responsible for sample collection. Y.B.D.R. was responsible for sample analysis. W.C.H. performed statistical analyses. T.F.R., W.C.H., and R.Q.H. interpreted the data. T.F.R. drafted the manuscript. All authors critically revised the manuscript and approved the decision to submit for publication. R.Q.H. is guarantor.

DISCLOSURE

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