Vitamin D as an Early Predictor of Multiple Sclerosis Activity and Progression

Alberto Ascherio, MD, DrPH; Kassandra L. Munger, ScD; Rick White, MSc; Karl Köchert, PhD; Kelly Claire Simon, ScD; Chris H. Polman, MD; Mark S. Freedman, MD; Hans-Peter Hartung, MD; David H. Miller, MD; Xavier Montalbán, MD; Gilles Edan, MD; Frederik Barkhof, MD; Dirk Pleines, MD; Ernst-Wilhelm Radu, MD; Rupert Sandbrink, MD; Ludwig Kappos, MD; Christoph Pohl, MD

IMPORATANCE It remains unclear whether vitamin D insufficiency, which is common in individuals with multiple sclerosis (MS), has an adverse effect on MS outcomes.

OBJECTIVES To determine whether serum concentrations of 25-hydroxyvitamin D (25(OH)D), a marker of vitamin D status, predict disease activity and prognosis in patients with a first event suggestive of MS (clinically isolated syndrome).

DESIGN, SETTING, AND PARTICIPANTS The Betaferon/Betaseron in Newly Emerging multiple sclerosis For Initial Treatment study was a randomized trial originally designed to evaluate the impact of early vs delayed interferon beta-1b treatment in patients with clinically isolated syndrome. Serum 25(OH)D concentrations were measured at baseline and 6, 12, and 24 months. A total of 465 of the 468 patients randomized had at least 1 25(OH)D measurement, and 334 patients had them at both the 6- and 12-month (seasonally asynchronous) measurements. Patients were followed up for 5 years clinically and by magnetic resonance imaging.

MAIN OUTCOMES AND MEASURES New active lesions, increased T2 lesion volume, and brain volume on magnetic resonance imaging, as well as MS relapses and disability (Expanded Disability Status Scale score).

RESULTS Higher 25(OH)D levels predicted reduced MS activity and a slower rate of progression. A 50-nmol/L (20-ng/mL) increment in average serum 25(OH)D levels within the first 12 months predicted a 57% lower rate of new active lesions (P < .001), 57% lower relapse rate (P = .03), 25% lower yearly increase in T2 lesion volume (P < .001), and 0.41% lower yearly loss in brain volume (P = .07) from months 12 to 60. Similar associations were found between 25(OH)D measured up to 12 months and MS activity or progression from months 24 to 60. In analyses using dichotomous 25(OH)D levels, values greater than or equal to 50 nmol/L (20 ng/mL) at up to 12 months predicted lower disability (Expanded Disability Status Scale score, −0.17; P = .004) during the subsequent 4 years.

CONCLUSIONS AND RELEVANCE Among patients with MS mainly treated with interferon beta-1b, low 25(OH)D levels early in the disease course are a strong risk factor for long-term MS activity and progression.
Multiple sclerosis (MS) is a common cause of neurological disability in young adults. Most patients experience bouts of inflammatory demyelination (relapsing-remitting MS) followed years later by treatment-resistant disease progression and brain atrophy. A higher MS risk in individuals with low vitamin D intake or low circulating 25-hydroxyvitamin D (25(OH)D), as well as an inverse correlation between vitamin D status and MS activity, have been reported and suggest that vitamin D is related to the disease process that leads to and perpetuates MS. However, previous clinical studies were conducted among patients with variable disease duration and could not determine whether low vitamin D is a consequence of MS activity or whether vitamin D levels early in the disease course contribute to predict long-term progression and disability. Because the prevalence of vitamin D insufficiency (25(OH)D < 50 nmol/L [20 ng/mL]) is high, supplementation could potentially benefit a large proportion of patients with MS.

Therefore, we aimed to determine whether vitamin D status early in the disease process influenced long-term disease course among participants in the Betaferon/Betaseron in Newly Emerging multiple sclerosis For Initial Treatment (BENEFIT) trial.

Methods

Study Population and Study Design

BENEFIT was originally designed to compare early vs delayed interferon beta-1b (IFNB-1b; Betaseron) treatment in patients with a diagnosis of clinically isolated syndrome (CIS). Between February 2002 and June 2003, patients from 18 European countries, Israel, and Canada were enrolled in 98 centers. Patients presenting with a first episode of neurological dysfunction highly suggestive of MS with a minimum of 2 clinically silent lesions on magnetic resonance imaging (MRI) were randomized in a 1:3 ratio to receive either IFNB-1b, 250 µg, (n = 292) or placebo (n = 176) subcutaneously every other day for 2 years or until a second clinical event occurred and the diagnosis of clinically definite MS (CDMS) could be established. All patients were then eligible to enter a prospectively planned follow-up phase with open-label IFNB-1b up to a maximum of 5 years after randomization. Details of the study results and design have been published elsewhere.

This study was approved by the Harvard School of Public Health institutional review board. Participants in the BENEFIT trial provided written informed consent; our study used de-identified data and biological samples, without direct contact with BENEFIT participants.

Measurement of 25(OH)D

Levels of 25(OH)D were measured in serum samples collected at baseline and 6, 12, and 24 months. Samples were shipped to the central laboratory within 3 days of being drawn and then maintained at ~20°C until further analysis. Only samples with a minimum of 2 mL serum were used for this study, resulting in 465 patients (out of 468 enrolled) with at least 1 25(OH)D measurement, 417 with 2 or more, 396 with 3 or more, and 303 with all 4 measurements. Serum 25(OH)D was measured using an enzyme-linked immunosorbent assay (Immunodiagnostic Systems Inc). The average intra-assay coefficient of variation derived from blind quality control samples was 4.4% and the average interassay coefficient of variation was 11.7%. As expected, serum 25(OH)D levels varied by season (eFigure 1 in Supplement). The baseline level of 25(OH)D was strongly correlated with levels at 12 (Spearman correlation, r = 0.61) and 24 months (r = 0.60) and moderately correlated with the opposite season levels at 6 months (r = 0.30). Because the primary purpose of the study was to estimate the effects of long-term average 25(OH)D levels, seasonal variations were removed as previously described.

Statistical Analyses

Serum 25(OH)D was treated as a time-dependent variable using at each point the average of all previous values. Because the seasonally synchronous baseline, 12-month, and 24-month samples could provide a biased estimate of the year-round vitamin D status, most analyses were restricted to patients who had 25(OH)D measured at both 6 and 12 months. The 12-month level was preferred to the baseline level because the latter had to happen within 60 days after the start of the CIS and thus could have been affected by the acute inflammatory process. To minimize the possibility that lower 25(OH)D levels were a consequence of MS severity rather than its cause, we also related the cumulative average 25(OH)D levels at 12 months with outcomes between 12 and 60 months or between 24 and 60 months (ie, leaving a 1-year lag between 25(OH)D measurement and assessment of MS activity or progression). Three sets of analyses were planned a priori, each with a different specification of serum 25(OH)D levels: (1) continuous to determine the overall linear trend; (2) quintiles to explore the dose response; and (3) categorical with the following predefined intervals: less than 25 nmol/L; 25 to less than 50 nmol/L; 50 to less than 75 nmol/L; and greater than or equal to 75 nmol/L.

Because of sparse data in the extreme groups, these latter categories were collapsed to less than 50 nmol/L vs greater than or equal to 50 nmol/L.

Three outcome categories were analyzed using clinical and MRI assessments: time to a definite diagnosis of MS, MS activity, and MS progression. A specially trained evaluating physician conducted all standardized neurological evaluations and determined the Expanded Disability Status Scale (EDSS) score. Relapses were assessed and defined in accordance with established guidelines. Magnetic resonance images were conducted every 3 months in the first year and then at 18, 24, 36, 48, and 60 months. All MRIs were quality controlled and centrally evaluated by the Image Analysis Center in Amsterdam (lead by F.B.). Definite diagnosis of MS was determined by clinical and MRI criteria (McDonald et al MS [MDMS] criteria) and by purely clinical criteria (modified Poser et al criteria, referred to as CDMS). Activity of MS was assessed as the number of relapses and the number of new active lesions on brain MRI (defined as new T2 lesions, new gadolinium+ lesions or enlarging T2 lesions). Magnetic resonance imaging markers of progression were the percentage change of T2 lesion volume and the percentage change of brain volume. The change in brain...
Table 1. Selected Characteristics of BENEFIT Participants by Average of Baseline, 6-Month, and 12-Month Season-Adjusted 25(OH)D Level

<table>
<thead>
<tr>
<th>Quintiles of 25(OH)D</th>
<th>No. of patients</th>
<th>Average of Baseline, 6-Month, and 12-Month Season-Adjusted 25(OH)D Level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>No. of patients a</td>
<td>93</td>
<td>93</td>
</tr>
<tr>
<td>25(OH)D, median (range), nmol/L</td>
<td>31 (19-36)</td>
<td>40 (36-45)</td>
</tr>
<tr>
<td>Age at recruitment, mean (SD), y</td>
<td>30.4 (7.9)</td>
<td>32.7 (7.3)</td>
</tr>
<tr>
<td>Female, %</td>
<td>69.9</td>
<td>77.4</td>
</tr>
<tr>
<td>Randomized to IFNB-1b, %</td>
<td>65.6</td>
<td>62.4</td>
</tr>
<tr>
<td>Monofocal onset, %</td>
<td>53.8</td>
<td>54.8</td>
</tr>
<tr>
<td>No. of T2 lesions at baseline, median (Q1-Q3)</td>
<td>21 (10-37)</td>
<td>19 (9-45)</td>
</tr>
<tr>
<td>T2 volume at baseline, median (Q1-Q3), mm³</td>
<td>2091 (598.0-5165.0)</td>
<td>1881 (772.0-5184.0)</td>
</tr>
<tr>
<td>Central brain volume at baseline, median (Q1-Q3), cm³</td>
<td>1045 (1026-1072)</td>
<td>1040 (1017-1065)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>25.2 (5.5)</td>
<td>24.2 (4.5)</td>
</tr>
<tr>
<td>Steroids for first clinical event, %</td>
<td>80.6</td>
<td>64.5</td>
</tr>
<tr>
<td>Mean time to last EDSS, d</td>
<td>1558.5</td>
<td>1692.3</td>
</tr>
<tr>
<td>Mean time to last MRI, d</td>
<td>1483.1</td>
<td>1609.7</td>
</tr>
</tbody>
</table>

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BENEFIT, Betaferon/Betaseron in Newly Emerging multiple sclerosis For Initial Treatment; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); EDSS, Expanded Disability Status Scale; IFNB-1b, interferon beta-1b; MRI, magnetic resonance imaging; Q, quintile.

N = 464 patients because 1 patient only had 25(OH)D measures at 24 months.

volume was measured in the Magnetic Resonance Image Analysis Center in Basel (lead by E-W.R.) using the Structural Image Evaluation using Normalization of Atrophy method, focusing on the central cerebral volume. Owing to rigorous criteria with respect to scan quality and brain coverage, approximately 20% of the images were excluded from brain-volume analysis. Considering that the baseline MRI was obtained at a time of acute inflammation (the CIS) with a high probability of partial spontaneous resolution of MRI pathology in the first year after the CIS and considering the possible effect of resolution of edema and cellular infiltrates on atrophy measurements (pseudoatrophy) after initiation of anti-inflammatory MS therapies, the month 12 visit was used as the primary reference point for the analysis of the percentage change in T2 volume and brain volume. Clinically, progression was assessed by changes of the EDSS score over time. Because spontaneous recovery of neurological deficits due to the CIS was expected after the baseline visit the month 6 was used as the primary reference point for analysis of the EDSS score outcome.

McDonald et al MS and CDMS were analyzed using a Cox proportional hazards regression model. Because many conversions occurred during the first 6 months, these results are strongly dependent on 25(OH)D levels measured close to the time of the first clinical event, which may not accurately reflect a patient’s average vitamin D status. Therefore, we also examined the relation between 25(OH)D levels and the rate of conversion to MS using as baseline the 6-month or 12-month visit. Other outcomes, including relapse rate, number of new active MRI lesions, change in T2 lesion volume, percentage brain loss, and change in EDSS score, were analyzed using a generalized mixed-effects model treating the patient as a random effect. The relapse rate was modeled as a binary variable indicating whether a relapse occurred on a given day, the number of new active MRI lesions was modeled as a count variable, and the other outcomes were modeled as continuous variables. The within-subject data were adjusted for any serial correlation that was present.

All the analyses were adjusted for sex, age at baseline, initial group of randomization (IFNB-1b or placebo), baseline T2 lesion score (the logarithm of the number of T2 lesions), and the type of CIS (monofocal vs multifocal). Further adjustments for baseline body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) and use of steroids for the initial clinical event did not materially change the results and were therefore omitted. Because no significant interactions were present between 25(OH)D levels and the type of CIS (monofocal vs multifocal), further adjustments for baseline body mass index and use of steroids for the initial clinical event did not materially change the results and were therefore omitted.

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Results

Patient Characteristics and 25(OH)D

Patients with higher 25(OH)D levels tended to have a younger age, a lower BMI, a lower number of T2 lesions, and a higher brain volume at the CIS but were otherwise similar to those with lower levels (Table 1). Patient characteristics in the subgroup with months 6 and 12 measurements did not differ from these results (eTable 2 in Supplement). The distribution of 25 (OH)D levels by visit and by season is shown in eFigure 1 and eFigure 2 in Supplement.

Conversion to Definite MS

During the 5 years of follow-up, 377 patients (81.3%) converted to MDMS and 216 (46.6%) converted to CDMS. The hazard of conversion decreased with increasing serum 25(OH)D, more strongly after 6 months, and among patients with 25 (OH)D measures at both 6 and 12 months, among whom the hazard of conversion decreased by more than 50% for a 50-nmol/L (20-ng/mL) increase in 25(OH)D (eTable 3 in Supplement). Results by treatment group are in eTable 3 and by quintiles in eFigure 3 in Supplement. Mean serum 25(OH)D levels

Analyses are based on patients with month 6 and month 12 measurements of 25-hydroxyvitamin D. Group comparisons are adjusted for age, sex, treatment, time of follow-up, and T2 lesion score at baseline. The graphs show the probability of conversion to clinically definite multiple sclerosis (CDMS) after 12 months (A); the cumulative number of new active lesions on brain magnetic resonance imaging (B); the percentage change in T2 lesion volume from year 1 to year 5 on brain magnetic resonance imaging (C); and percentage change in brain volume from year 1 to year 5 (D). The error bars indicate the standard error of the mean (SEM).

1b, whereas patients randomized to initial placebo were exposed for a mean of 498 days to placebo and for a mean of 1016 days to IFNB-1b. P values were not corrected for multiple comparisons.
at 12 months contributed to predict subsequent conversions to MDMS (P = .02) and CDMS (P = .05) (Figure 1A).

**MS Activity**

**New Active MRI Lesions**

The rate of occurrence of new active lesions decreased with increasing serum 25(OH)D (Table 2); this inverse association was particularly strong for patients with both 6- and 12-month 25(OH)D measurements, among whom a 50-nmol/L increase in the average 25(OH)D at up to 12 months predicted a 57% lower rate between 12 and 60 months and a 63% lower rate between 24 and 60 months (Table 2). Significant inverse associations were also observed in categorical analyses (dichotomous in Figure 1B; quintiles in Figure 2B). Results by treatment group are in eTable 4 in Supplement.

**Relapses**

On average, patients in BENEFIT experienced 0.2 relapses per year. Overall, the relapse rate decreased by 27% (not significant) for a 50-nmol/L increment in 25(OH)D (Table 2). This association was stronger among patients with 25(OH)D measures at both 6 and 12 months; in this group, a significantly lower relapse rate with increasing serum 25(OH)D was observed after 12 months. No significant associations were found in analyses based on categorical 25(OH)D level (eFigure 4 in Supplement).

**Progression of MS**

**Change of T2 Volume**

Higher levels of 25(OH)D were associated with less T2 lesion volume accumulation over time; the relative decrease in T2 lesion volume for a 50-nmol/L increase in 25(OH)D was 20% per year (P < .001) (Table 3). Restriction to patients with both 6-month and 12-month 25(OH)D measures tended to strengthen the results. Results by treatment group are in eTable 5 in Supplement. Results by dichotomous 25(OH)D are shown in Figure 1C and those by quintiles in Figure 2B.

**Change of Brain Volume**

A 50-nmol/L (20-ang/mL) increase in 25(OH)D was associated with a 0.27% lower rate of brain loss (P = .012) (Table 3). In analyses excluding patients missing the 6- or 12-month 25(OH)D levels, the overall 25(OH)D-related annual difference in brain-volume loss for a 50-nmol/L (20-ang/mL) increase in 25(OH)D was 0.41% (P = .07). Results by treatment group are in eTable 4 (Supplement). In analyses with dichotomous 25(OH)D, the percentage loss in brain volume was lower among patients with 25(OH)D concentrations at 12 months greater than or equal to 50 nmol/L (20 ng/mL) compared with those less than 50 nmol/L (20 ng/mL) (0.34%; P = .005; Figure 1D). Analyses by quintiles revealed an unexpected J-shaped relation (higher brain volume in the lowest quintile; eFigure 5 in Supplement). In this large prospective investigation, we found that average serum 25(OH)D levels in the first 12 months following a CIS strongly predicted MS activity and progression during the subsequent 4 years. By the end of the follow-up at 60 months, those patients with serum 25(OH)D levels were associated with a reduction of 0.16 steps in the average EDSS score (P = .11). Results restricted to patients with measured 6- and 12-month 25(OH)D measures were similar (Table 3). The annualized change in EDSS score was lower among patients with serum 25(OH)D greater than or equal to 50 nmol/L compared with those less than 50 nmol/L (−0.17; P = .004), as well as in patients in the highest quintiles compared with those in the lowest quintile (Figure 2C).

**Discussion**

In this study, the inverse relation of 25(OH)D levels with development of MS, relapses, and MRI measures was observed in a distinct image that the inverse relation of 25(OH)D levels with development of MS, relapses, and MRI measures was observed in a distinct image.
during a 5-year period. Because serum 25(OH)D levels strongly depend on time spent outdoors, which can in turn be affected by MS activity, reverse causation could have explained the cross-sectional or short-term inverse associations between serum 25(OH)D concentrations and MS activity previously reported. The robustness of our results in analyses leaving a 1-year lag time between the last serum 25(OH)D measurement and assessment of MS outcomes provides evidence that low vitamin D was not a consequence of the disease process itself but rather its predictor.
Our study also had some limitations. First, almost all patients in our study were white individuals of European ancestry, thus limiting generalizations to individuals of other races or ethnicities. Second, most participants were eventually treated with IFNB-1b—although uniform treatment is an important advantage, our results may not apply to patients treated with different drugs. Third, although a clear dose response was observed for the most sensitive MRI outcomes, there was no evidence of a ceiling effect, and it is thus possible that the potential benefits of vitamin D are fully reached only at serum 25(OH)D concentrations greater than the still moderate level observed in the highest quintile of participants in BENEFIT (median, 69 nmol/L or 27.6 ng/mL).

The combined results of previous epidemiological studies relating serum 25(OH)D levels to MS risk4–6 and those of the present investigation imply that either serum 25(OH)D levels directly affect the disease process before and after the onset of symptoms or they act as a prognostic marker. The inverse association between vitamin D and MS outcomes could be explained if both were affected by a common factor or confounder. Among healthy individuals, the main predictors of vitamin D insufficiency, which affects about 50% of patients ing already adequate vitamin D levels, our results suggest that genetic effects28,29 are too small to account for the strong inverse associations reported here.34 As in all observational studies, a role of unknown factors cannot be excluded. Results of small double-blind randomized trials have been inconsistent,35–37 but these studies were not powered to determine the efficacy of vitamin D on MS outcomes.

The results of our study reveal a robust prognostic value of vitamin D levels measured early in the MS course and converge with previous epidemiological and biological evidence supporting a protective effect of vitamin D on the disease process underlying MS,38 and thus the importance of correcting vitamin D insufficiency, which affects about 50% of patients with MS in Europe39 and 20% in the United States.11,40 However, further investigations are needed to determine the optimal levels of vitamin D and whether results apply to different races or ethnicities, to patients with the secondary or primary progressive course of MS, or in combination with drugs other than IFNB-1b.

Conclusions
In summary, in this large longitudinal study among patients with CIS randomized to early vs late treatment with IFNB-1b, we found that higher serum 25(OH)D levels robustly predicted a lower degree of MS activity, MRI lesion load, brain atrophy, and clinical progression during the 5 years of follow-up. Although controlled studies currently under way44 may provide more definitive answers as to the therapeutic value of further increasing already adequate vitamin D levels, our results suggest that identification and correction of vitamin D insufficiency has an important role in the early treatment of MS.

**Table 3. Percentage Annual Change in Cerebral T2 Lesion Volume and Brain Volume and Change of EDSS Score for a 50-nmol/L Increment in Serum 25(OH)D**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cumulative Average 25(OH)D Updated to 24 mo</th>
<th>% Change (95% CI)</th>
<th>P Value</th>
<th>Cumulative Average 25(OH)D Updated to 12 mo</th>
<th>% Change (95% CI)</th>
<th>P Value</th>
<th>Cumulative Average 25(OH)D Updated to 12 mo</th>
<th>% Change (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2 lesion volume</td>
<td>12 mo to 60 mo</td>
<td>−20 (−28 to −11)</td>
<td>&lt;.001</td>
<td>12 mo to 60 mo</td>
<td>−25 (−34 to −14)</td>
<td>&lt;.001</td>
<td>12 mo to 60 mo</td>
<td>−27 (−37 to −16)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Brain volume</td>
<td>6 mo to 60 mo</td>
<td>0.27 (0.07 to 0.62)</td>
<td>.12</td>
<td>6 mo to 60 mo</td>
<td>0.41 (−0.03 to 0.85)</td>
<td>.07</td>
<td>6 mo to 60 mo</td>
<td>0.48 (−0.03 to 1.00)</td>
<td>.07</td>
</tr>
<tr>
<td>EDSS score</td>
<td>6 mo to 60 mo</td>
<td>−0.16 (−0.37 to 0.04)</td>
<td>.11</td>
<td>6 mo to 60 mo</td>
<td>−0.18 (−0.44 to 0.09)</td>
<td>.19</td>
<td>6 mo to 60 mo</td>
<td>−0.20 (−0.49 to 0.10)</td>
<td>.19</td>
</tr>
</tbody>
</table>

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; EDSS, Expanded Disability Status Scale.

* All analyses adjusted for age, sex, treatment, time of follow-up, T2 lesion score at baseline, and type of onset.
* N = 434.
* No missing 6-month or 12-month 25(OH)D (n = 332).
Department of Neurology, University Hospital of Bonn, Bonn, Germany (Pohl).

Author Contributions: Dr Ascherio had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Kappos and Pohl contributed equally.

Study concept and design: Ascherio, Munger, Polman, Freedman, Montalban, Pleimes, Sandbrink, Pohl.

Acquisition of data: Ascherio, Polman, Barkhof, Pleimes, Sandbrink, Pohl.

Analysis and interpretation of data: Ascherio, Munger, White, Köchert, Simon, Freedman, Hartung, Miller, Edan, Barkhof, Pleimes, Radi, Sandbrink, Kappos, Pohl.

Drafting of the manuscript: Ascherio.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Ascherio, Munger, White, Köchert, Pleimes.

Obtained funding: Ascherio, Munger, Polman, Sandbrink.

Administrative, technical, and material support: Freedman, Hartung, Pleimes, Kappos.

Study supervision: Ascherio, Polman, Edan, Barkhof, Sandbrink, Kappos.

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