ORIGINAL ARTICLE

Serum levels of folate, 25-hydroxyvitamin D3 and cobalamin during UVB phototherapy: findings in a large prospective trial

B. Weber,[1,*] R. Marculescu,[2] S. Radakovic,[1] A. Tanew[1]

[1]Department of Dermatology, Medical University of Vienna, Vienna, Austria
[2]Department of Laboratory Medicine, Medical University of Vienna, Vienna, Austria
*Correspondence: B. Weber. E-mail: benedikt.weber@meduniwien.ac.at

Abstract

Background Narrowband UVB phototherapy (NB-UVB) is a mainstay in the treatment of numerous inflammatory dermatoses. Whereas, a wealth of studies has shown that NB-UVB treatment increases 25-hydroxyvitamin D3 (25(OH)D) levels, only sparse and controversial data exist on its effect on serum folate and cobalamin.

Objectives To determine whether exposure to NB-UVB alters serum folate or cobalamin levels.

Methods A single-centre, prospective, open observational study on 101 patients subjected to NB-UVB phototherapy between late fall and early spring. Serum folate, 25(OH)D and cobalamin levels were measured after 0, 12, 24 and 36 NB-UVB exposures.

Results After 12 NB-UVB exposures a significant decrease of mean serum folate (−1.0 nmol/L; $P = 0.03$) and cobalamin (−14.5 pmol/L, $P = 0.03$) levels was observed whereas serum levels of 25(OH)D showed a significant increase (35.4 nmol/L, $P < 0.0001$).

Conclusions A standard course of NB-UVB induces a small but significant decrease of serum folate and cobalamin levels.

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Conflicts of interest

The authors declare no conflicts of interest.

Funding source

None.

Introduction

Phototherapy is a mainstay in the treatment of numerous inflammatory dermatoses including psoriasis, mycosis fungoides, vitiligo and atopic dermatitis.[1–4] Other than PUVA (psoralen plus UVA), UVB phototherapy does not require the administration of a photosensitizer making it an easy-to-perform and versatile therapeutic approach with a favourable side-effect profile. In particular, UVB phototherapy is a safe treatment option for patients with relative or absolute contraindications to systemic treatments such as pregnant women, patients with severe kidney or liver disease or patients with cancer.[5] In the 1980s, UVB phototherapy has been improved by the development of narrowband UVB (NB-UVB) therapy, which combines therapeutic effectiveness comparable to PUVA with a lower carcinogenic risk.[6,7]

Several studies have demonstrated an increase in 25-hydroxyvitamin D3 (25(OH)D) in response to repeated exposure to NB-UVB.[8–10] The potential of UVB phototherapy to affect serum folate levels is, however, a rarely addressed issue.[11] It is of particular interest to women of childbearing age as birth defects including neural tube defects (NTD), cardiac defects and facial clefting have all been associated with folate deficiency.[11–14] In addition, folate deficiency may increase the risk of colorectal cancer and influence serum homocysteine levels, which is thought to be a risk factor for cardiovascular disease, depression and dementia.[13,15–17] Photodegradation of folate *in vitro* after exposure to simulated sunlight has been documented[18] and reduced folate levels have been reported in patients treated with extracorporeal photopheresis.[19] On the other hand, data on the effects of NB-UVB on serum folate levels are controversial.

Clinical trials registration information: The study was registered in the public clinical trials database (Clinical Trials.gov-identifier: NCT03246308).

While two studies reported a potential effect of UVB on serum folate levels,[20,21] several other studies did not reveal any changes due to UVB exposure.[22–25] However, all of these studies were relatively small and included only 5–52 patients.[11,15,20–24] In addition, all but one of these studies evaluated patients with only up to 20 NB-UVB exposures. Almost no data are available on the effects of NB-UVB treatment on serum levels of cobalamin (vitamin B12), which is known to metabolically interact with folate.

The objective of the present prospective study was to assess folate, cobalamin (vitamin B12) and 25(OH)D (vitamin D) serum levels during NB-UVB phototherapy in a large patient cohort with at least 12 and up to 36 NB-UVB exposures.

Methods

Patients

All patients assigned to NB-UVB phototherapy at our Phototherapy Unit between September 2017 and May 2018 were invited to participate in the study. Approval from the institutional ethics committee (EK-1462/2017) was obtained, and patients provided written consent. The following exclusion criteria were applied: age <18 years, the intake of drugs that interfere with folate metabolism or an underlying disease with abnormal folate metabolism (e.g. thalassaemia), inability to attend regularly for treatment or regular sunbed use and pregnancy at the onset of phototherapy. Blood samples were taken before phototherapy as well as after 12, 24 and 36 exposures of NB-UVB. The following parameters were determined: folate, 25-hydroxyvitamin D (25(OH)D) and vitamin B12 (cobalamin). The study was registered in the public clinical trials database (ClinicalTrials.gov-identifier: NCT03246308).

Blood sample analysis

All analyses were performed at the Department of Laboratory Medicine, Medical University of Vienna, with IVD-certified and ISO-15189 accredited methods. Serum folate and cobalamin levels were measured using Cobas-8000 electro-chemiluminescence immunoassays (ECLIA) on Cobas-e602 analyzers (Roche Diagnostics, Rotkreuz, Switzerland). 25(OH)D values were determined using Liaison XL chemiluminescence immunoassays (CLIA; DiaSorin, Saluggia, Italy).

Phototherapy

NB-UVB was administered using a Waldmann UV-7002 cabinet (Herbert Waldmann GmbH&Co. KG, Villingen-Schwenningen, Germany) 2–3 times per week. The irradiance was measured with an integrated radiometer and was on average 10.5 mW/cm^2. The initial NB-UVB dose was chosen according to the patients skin phototype and ranged between 0.3 and 0.6 J/cm^2.[26] Dose increments of 10–20% were performed at each visit in the absence of treatment-induced erythema up to a maximum exposure dose of 3.0 J/cm^2.

Statistical analysis

SPSS software (SPSS-24; SPPS-Inc., Chicago, IL, USA) and Excel-2016 macOS-software (Microsoft Corp., Redmond, WA, USA) were used to analyse the results. Imputation of missing values was performed if required prior to the statistical analysis. For comparison of laboratory values either a paired *t*-test or a Mann–Whitney *U*-test was used. P values ≤ 0.05 were considered statistically significant.

Results

In total, 125 patients met the inclusion criteria and were enrolled into the study. Twenty-two patients stopped NB-UVB therapy before completing 12 exposures or missed the second blood test and were excluded from analysis. The data from two patients were not evaluable since the blood sample clotted prior to analysis. The remaining 101 patients had at least 12 NB-UVB exposures. Forty-six patients (45.5%) had received 24 exposures and seven patients (6.9%) 36 exposures (Fig. 1). The patients' characteristics and indications for phototherapy are shown in Table 1. The most frequent indications for NB-UVB phototherapy were psoriasis vulgaris, eczema and vitiligo. None of the patients reported excessive alcohol consumption.

Folate levels during the course of phototherapy did not follow a consistent pattern. About two-thirds of the patients (63.4%) showed a decrease of serum folate levels after 12 exposures of NB-UVB phototherapy, while one-third (36.6%) had an increase. In patients with prolonged NB-UVB treatment, 60.9% showed a decrease after 24 exposures and 71.4% after 36 exposures, respectively (Fig. 2a–d). 17% of all patients already had abnormal folate serum levels (<9.53 nmol/L) at baseline and in only 6% of the patients, a change from normal to abnormal values was observed during the course of NB-UVB phototherapy.

Overall, there was a slight decrease in serum folate levels that correlated with the number of NB-UVB treatments. After 12 exposures, the median decrease was −0.8 nmol/L (mean: −1.0 nmol/L), after 24 exposures −1.5 nmol/L (mean: −0.9) and after 36 exposures −2.2 nmol/L (mean: −2.5; Fig. 2a–d).

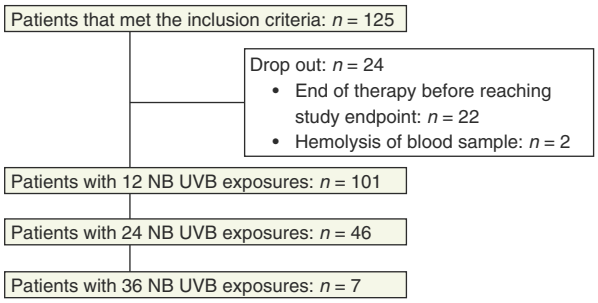

Figure 1 Patient recruitment.

Table 1 Summary of patient characteristics and indications for phototherapy (absolute numbers and percentage)

Patient characteristics	Number of patients (%)
Gender	
Male	57 (56.4)
Female	44 (43.6)
Mean age (years ± SD)	49.7 (±18.08)
Smoking	27 (26.8)
Skin phototype	
II	13 (12.9)
III	82 (81.2)
IV	5 (5.0)
VI	1 (1.0)
Topical vitamin D therapy	7 (6.9)
Systemic vitamin D therapy	6 (5.9)
Daily use of topical sun protection	2 (2.0)
Vegetarian food only	3 (3.0)
Medical indication for phototherapy	
Psoriasis vulgaris	34 (33.7)
Eczema (atopic, nummular)	18 (17.8)
Vitiligo	19 (18.8)
Others	30 (29.7)

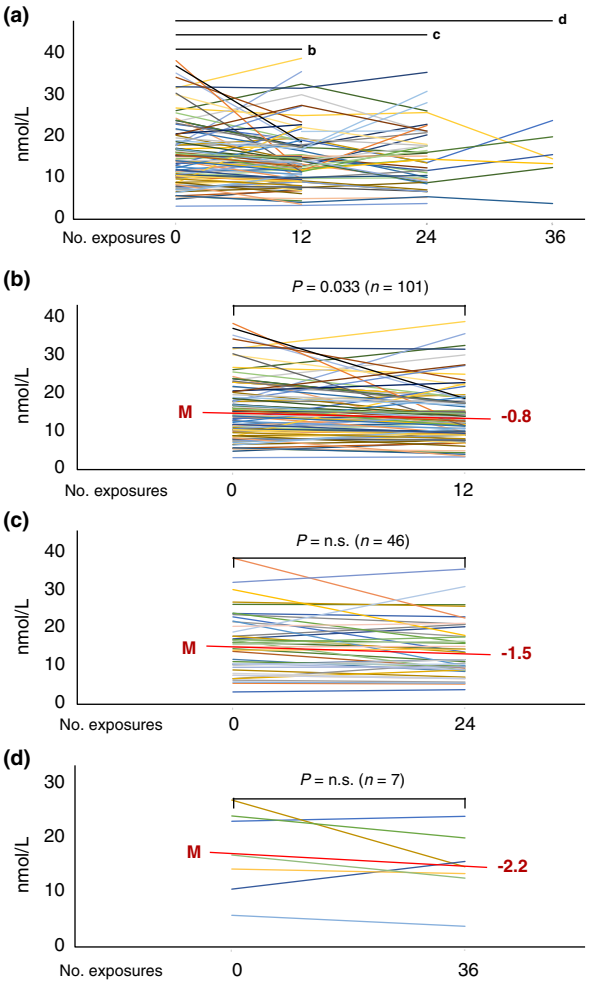

Figure 2 Serum folate levels over the entire course of phototherapy (a), after 12 (b), 24 (c) and 36 (d) exposures of NB-UVB (M = median; n.s. not significant).

While the decrease of serum folate levels after 12 exposures was statistically significant ($P = 0.033$), no significant changes were observed between baseline and 24 ($P = 0.187$) or 36 exposures ($P = 0.266$). Since the median folate reduction increased further with prolonged treatment, the lack of statistical significance for the later time points is likely due to the lower number of evaluable patients.

In 79% of all patients, the difference between folate levels at baseline and the end of phototherapy was less than ±5.0 nmol/L (Fig. 3a). We therefore independently analysed those patients whose changes in serum folate levels exceeded the ±5 nmol/L range after 12, 24 and 36 exposures ($n = 20$; Fig. 3a–c). Interestingly, in patients with a decrease of serum folate levels of >5 nmol/L after 12 exposures the median baseline folate level (28.9 ± 6.4 nmol/L) was significantly higher than in all patients together (15.4 ± 7.8; $P < 0.001$) or in patients with an increase of serum folate of more than +5 nmol/L (17.7 ± 5.9 nmol/L; $P = 0.002$). These results indicate that patients with high serum folate levels at initiation of NB-UVB phototherapy are more prone to major serum folate changes than patients with low baseline levels.

Interestingly, alterations in folate levels also seemed to depend on the type of skin disorder treated. While in patients suffering from psoriasis vulgaris or eczema, more than two-thirds showed a decrease of serum folate levels of >5 nmol/L during phototherapy, the same was true for only about one-third of vitiligo patients (Fig. 3d). In contrast, an increase in folate levels was detected in 63% of patients with vitiligo as opposed to only 31% of patients with psoriasis and 27% of patients with eczema, respectively. This difference in change of folate levels between vitiligo and psoriasis or eczema patients after 12 NB-UVB exposures was significant ($P = 0.021$).

In line with previous reports, the 25(OH)D serum levels significantly increased during NB-UVB phototherapy. The median increase was 29.9 nmol/L (mean: 35.4 nmol/L; $P < 0.0001$) after 12 exposures, 45.3 nmol/L (mean: 50.3 nmol/L; $P < 0.0001$) after 24 exposures and 37.6 nmol/L (mean: 44.5 nmol/L; $P = 0.001$) after 36 exposures. Patients with psoriasis and eczema yielded a higher increase of 25(OH)D serum levels (+44.4 and +45.1 nmol/L, respectively) than patients with vitiligo (+18.1 nmol/L), but the difference lacked statistical significance ($P = 0.12$; Fig. 4).

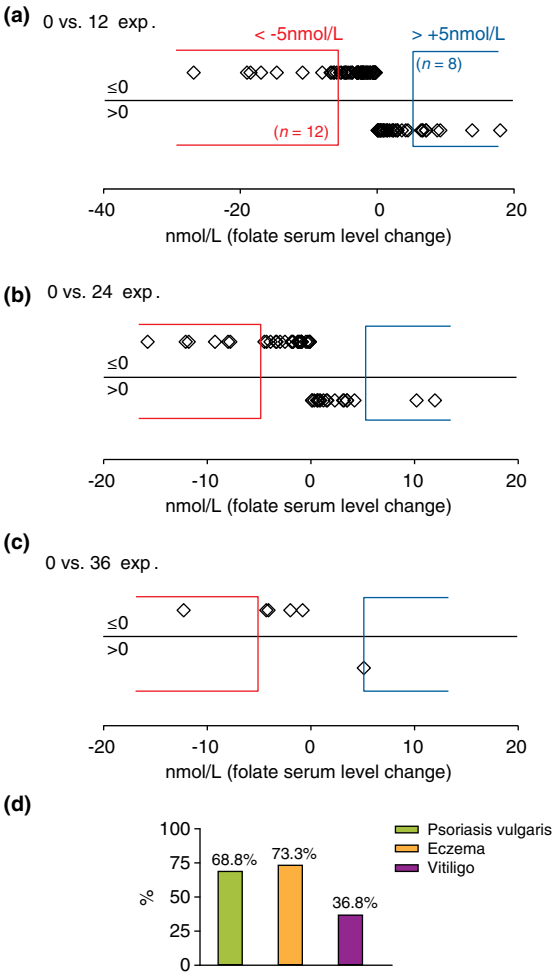

Figure 3 (a–c) Serum folate level changes in nmol/L after 12 (a), 24 (b) and 36 (c) NB-UVB exposures. (d) Percentages of patients with a decrease of serum folate levels among different dermatoses.

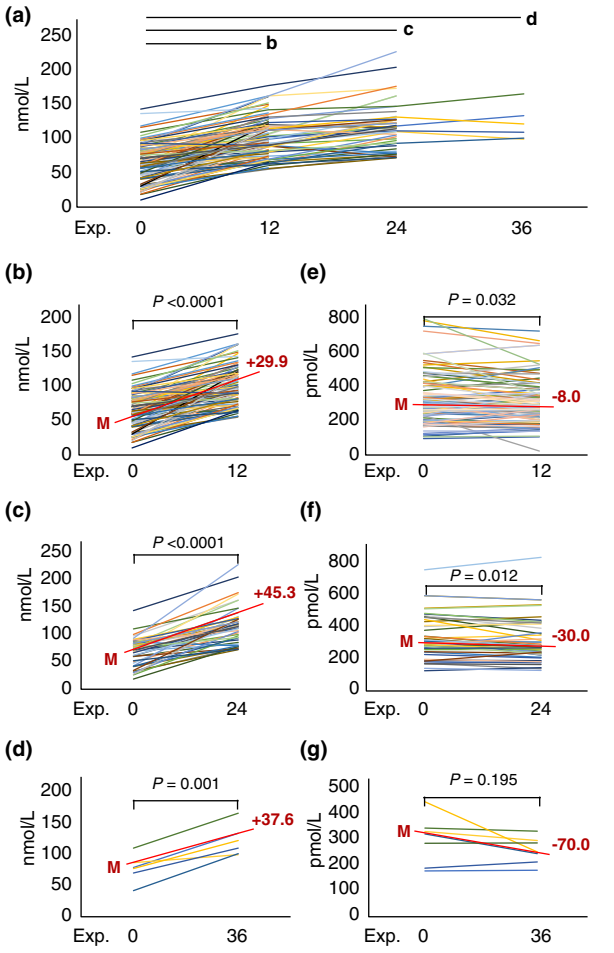

Figure 4 25(OH)D levels over the entire course of therapy (a), after 12 (b), 24 (c) and 36 (d) exposures of NB-UVB phototherapy (M = median). Serum cobalamin levels after 12 (e), 24 (f) and 36 (g) exposures of NB-UVB phototherapy (M = median).

The effect of NB-UVB on cobalamin levels was both significant and progressive. The median cobalamin serum level changed by −8 pmol/L (mean: −14.5 pmol/L, $P = 0.032$) after 12 exposures, −30 pmol/L (mean: 17.1 pmol/L, $P = 0.012$) after 24 exposures and −70 pmol/L (mean: 42.0 pmol/L, $P = 0.195$) after 36 exposures. Changes in serum folate and cobalamin levels followed the same trends. In patients experiencing a decrease of serum folate after 12 NB-UVB exposures, cobalamin was also decreased by a mean of −25.3 ± 69.6 pmol/L whereas an increase in serum folate levels was paralleled by a mean increase in cobalamin (+6.7 ± 57.1 pmol/L).

Discussion

Folate, also known as vitamin B9, is an essential nutrient required for amino acid metabolism and DNA synthesis via facilitating the transfer of one-carbon groups in biosynthetic reactions. Humans cannot synthesize folate *de novo* and therefore depend on sufficient folate uptake by diet. Besides intake via folic acid supplementation, naturally occurring folate is found primarily in the form of 5-methyltetrahydrofolate in leafy dark-green vegetables, liver and fortified foods such as bread and cereal.[11,15] Absorption takes place in the small intestine. The enzymes involved in this process may be inhibited by gastrointestinal disorders, alcohol and various drugs (e.g. anticonvulsants) resulting in decreased bioavailability.[11] Folate deficiency results in impaired cell replication, which may manifest as macrocytic anaemia. In addition, an increasing body of evidence suggests that deficient folate levels are associated with a higher risk for colorectal cancer[16] and hyperhomocysteinemia, the latter being a risk factor for cardiovascular disease.[17] In pregnancy,

decreased folate levels may cause congenital abnormalities such as neural tube defects (NTD), cardiac defects and facial clefting.[12,14,27] The risk for deficiency is enhanced by increased folate requirements during pregnancy and lactation.[11] Current WHO guidelines therefore recommended that women who intend to become pregnant should take folic acid supplementation to reduce the risk for congenital defects.[27]

A rarely addressed issue relates to folate inactivation by UV exposure, which has been suggested by several *in vitro* studies. The action spectrum for folate degradation spans from UVC to UVA with maximum degradation around 270 nm.[11,28–31] The issue of UV-induced folate photolysis is of particular interest in pregnant women undergoing UV phototherapy given the increased risk for congenital malformations. A mathematical model suggested a relationship between UV exposure and the incidence of NTD thereby explaining the impact of season and latitude.[32] In addition, a small case series described three healthy young women who had exposed themselves to sunbeds during early gestation and gave birth to newborns with NTD.[33] The impact of UV irradiation on serum folate has been investigated in several studies. A decrease in folate levels was found after extracorporeal photopheresis,[19] whereas no significant changes were observed after UVA phototherapy.[34] The data for UVB phototherapy are also controversial. While two studies reported a potential effect of NB-UVB on serum folate levels,[20,21] others failed to detect significant changes after NB-UVB treatment.[15,22–24] All the above-mentioned studies, however, were limited by small sample sizes (5–52 patients) and a limited number of UVB exposures.[11,15,22–25]

We therefore in this prospective study assessed folate, vitamin B12 (cobalamin) and vitamin D (25(OH)D) serum levels in a large cohort of patients receiving between 12 and 36 exposures to NB-UVB. A slight but steady decline in median folate levels was found with increasing length of treatment. However, these changes were statistically significant only after 12 but not after 24 or 36 NB-UVB exposures, which may be due to the lower number of evaluable patients at the later time points. Our results corroborate the assumption that therapeutic NB-UVB irradiation may induce a decrease of serum folate levels as early as after 12 exposures, an effect that may have been missed in previous studies due to the low number of analysed patients and the lack of statistical power. The magnitude of this effect also appears to depend on the cumulative NB-UVB dose as it is positively correlated with the number of NB-UVB treatments. In addition, a much higher decrease of folate (and increase in 25(OH)D) was found in patients with psoriasis or eczema who require a more aggressive UV dosimetry as compared to patients with vitiligo where lower UV exposure doses are used. Accordingly, two previous studies extending over a longer treatment period (up to 36 exposures) showed a decrease in folate levels[20,21] whereas all studies of shorter treatment duration (up to 20 exposures) failed to detect changes in folate levels.[15,22,23] One study on 52 vitiligo patients, however, did not find a reduction in folate after 80 NB-UVB sessions.[24] Additional factors such as genetic polymorphisms may have contributed to the disparate changes of folate levels in response to NB-UVB phototherapy. Unfortunately, our study design did not allow for a further in-depth analysis of this interesting issue.

It is important to put the clinical bearing of our findings into right perspective. The overall effect of NB-UVB phototherapy on serum folate levels was small and only amounted to a median of −0.8 nmol/L (mean −1.0 nmol/L) after 12 treatments. Almost, 80% of the patients yielded changes in folate levels of less than ±5.0 nmol/L and 17% of patients already had abnormal folate levels before initiating NB-UVB. Thus, a clinically significant decrease in serum folate values attributable to NB-UVB phototherapy only occurred in 6% of all patients. Further on, our investigation revealed substantial differences between different skin diseases in NB-UVB-induced alterations of serum folate levels. 75% of all patients with a major (>5 nmol/L) decrease of serum folate levels suffered from psoriasis vulgaris while 50% of the patients with a substantial increase (>5 nmol/L) had vitiligo. It is recognized that patients with widespread psoriasis may be deficient in folate,[35] presumably due to an increased skin cell turnover, which in turn may contribute to an increased risk for cardiovascular disease.[36] Thus, an inherent tendency towards low folate serum levels may predispose psoriasis patients to overt folate deficiency during NB-UVB treatment. However, one study on 35 psoriasis patients failed to detect statistically significant changes in serum folate levels during NB-UVB phototherapy.[15]

We also investigated vitamin B12 (cobalamin) levels during NB-UVB phototherapy given its metabolic interaction with folic acid. Cobalamin, the active form of vitamin B12, has a major role in human folate metabolism via regenerating tetrahydrofolate from *N*-methyl tetrahydrofolate.[37] In addition, both folate and cobalamin are critical for the production of tetrahydrofolate, a key metabolite in DNA synthesis and fetal growth.[38] A recent investigation on 23 evaluable healthy females revealed an insignificant drop in serum cobalamin concentration from 300 to 260 pmol/L after the first UV exposure and no additional decline after further exposures.[39] As with serum folate levels, we found a progressive and statistically significant albeit small decrease of serum cobalamin levels during NB-UVB phototherapy. As mentioned for serum folate levels, the clinical significance is again questionable given the rather low mean deviations from baseline of −14.5 pmol/L after 12 exposures and −17.1 pmol/L after 24 exposures.

One limitation of our study is the fact that it was not possible to completely rule out any effect of external factors (e.g.

differences in dietary habits or accidental sun exposure) on our findings. In addition, we did not assess the impact of genetic factors on NB-UVB-induced changes in vitamin levels. Finally, since our trial did not include pregnant women the obtained results are not representative for this particular patient population.

In summary, the present prospective study provides evidence that NB-UVB phototherapy may lower serum folate to abnormal levels in a minority of patients after as few as 12 exposures. With respect to the overall low changes from baseline values and the fact that despite decades of clinical use there are no reports on severe UVB-induced folate or cobalamin deficiencies we do not recommend repeated measurements of these vitamins during a course NB-UVB phototherapy. However, as data on pregnant women are not available, the general recommendation of folic acid supplementation for women wishing to become pregnant should specifically be re-emphasized in this patient group before initiating NB-UVB phototherapy.

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