Impact of Etanercept on Vitamin D Status and Vitamin D-binding Protein in Bio-naïve Patients with Psoriasis

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High levels of serum vitamin D-binding protein have been shown previously in patients with psoriasis compared with healthy controls; a possible role in inflammation is implied. The primary objective of this study was to investigate the impact of 24-week etanercept treatment on vitamin D status and vitamin D-binding protein in patients with psoriasis. The secondary aim was to explore whether pre-treatment vitamin D levels could predict the treatment effect. A prospective observational study was performed, including 20 patients with psoriasis and 15 controls. Serum samples were analyzed for, among others, vitamin D metabolites, vitamin D-binding protein and highly sensitive C-reactive protein. Baseline levels of vitamin D-binding protein were higher in patients with self-reported arthropathy than in those without. After 24 weeks' treatment, an improvement in psoriasis was noted, as was a decrease in highly sensitive C-reactive protein. Vitamin D-binding protein decreased in those with self-reported arthropathy. Higher baseline levels of vitamin D were associated with faster and greater improvement in psoriasis. Vitamin D-binding protein may have an inflammatory biomarker role.

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SIGNIFICANCE

Etanercept, a tumour necrosis factor-alpha inhibitor, is an established treatment for psoriasis. In this study, etanercept was found to be effective at reducing both psoriasis severity and vitamin D-binding protein levels. Vitamin D-binding protein may be a new inflammatory serum biomarker in psoriasis. Vitamin D-binding protein levels may be useful as an indicator, both for early detection of psoriatic arthritis and for the treatment effect; this hypothesis warrants further investigation. Vitamin D may have a positive synergy effect with tumour necrosis factor-alpha inhibitor. Further research into vitamin D supplementation during tumour necrosis factor-alpha inhibitor therapy is necessary.

Psoriasis is a chronic, immune-mediated inflammatory disease (1) that affects 2–3% of the world's population and may have a considerable impact on quality of life. Psoriasis is associated with several comorbidities, including arthritis, cardiovascular and gastrointestinal disease, metabolic syndrome, and depression (2). Tumour necrosis factor (TNF)-α inhibitors (TNFis) represent an established and effective treatment option. Etanercept is a soluble, recombinant TNF-α receptor/IgG Fc fusion protein receptor that competitively inhibits the interaction of TNF-α and its cell surface receptors (3).

Vitamin D analogues constitute an established topical treatment for psoriasis, but there is still conflicting evidence regarding the relevance of serum 25(OH)D levels and the benefit of vitamin D supplementation in disease control (4, 5). $1,25(OH)_2D$, the active metabolite of vitamin D and its analogues, may suppress TNF-α expression and Th1-related chemokines and seem to produce an anti-TNF-α effect (6–8). An *in vitro* study of patients with rheumatoid arthritis (RA) found that TNF-α blockade alone could not suppress IL-17A and IL-22, but the combination with $1,25(OH)_2D$ could control human Th17 activity and additively inhibit synovial inflammation (9). This synergic action between $1,25(OH)_2D$ and anti-TNF-α was also seen in other *in vitro* and *in vivo* studies in patients with inflammatory bowel disease (IBD) and RA (10, 11).

Another aspect of the importance of vitamin D in psoriasis is the association of psoriasis with osteopenia and osteoporosis (12).

Vitamin D-binding protein (DBP) is the principal carrier of vitamin D metabolites and regulates the availability of 25(OH)D to target cells (13, 14). The liver is the major source of DBP and its synthesis is stimulated by oestrogens, glucocorticoids, and interleukin 6 (15). Recently, emphasis has been placed on the biological importance of DBP in addition to vitamin D transport, including a possible role in immunomodulation and inflammation (14, 16). DBP may indirectly negatively affect the favourable action of $1,25(OH)_2D$, by binding strongly and restricting access to the pro-hormone 25(OH)D, as shown in monocytes, dendritic cells and T cells (14, 17, 18). Furthermore, DBP is responsible for actions that are independent of vitamin D, such as actin scavenging and tissue neutrophil recruitment, by enhancing the chemotactic activity of complement C5α

and other chemoattractants (e.g. CXCL1) (16). Moreover, deglycosylation of DBP can activate DBP to become a macrophage-activating factor (13, 19). Serum DBP was found to correlate positively with highly sensitive C-reactive protein (hsCRP) in healthy individuals (20).

In a previous study, serum levels of DBP were higher in patients with psoriasis compared with healthy controls (21), and it was suggested that DBP may be a possible biomarker of inflammation.

The primary aim of this study was to investigate the impact of etanercept treatment on vitamin D status, DBP and cardiovascular risk factors (serum lipids, BMI (body mass index) and blood pressure) in patients with psoriasis and to compare the results with those of a healthy control group during a period of 24 weeks. The secondary aim was to investigate whether baseline 25(OH)D levels could predict the clinical response.

MATERIALS AND METHODS

Study design, setting and participants

A prospective, observational study with etanercept (Enbrel®; Pfizer, Puurs, Belgium) in patients with plaque psoriasis during a period of 24 weeks. The study was conducted at the Department of Dermatology at Sahlgrenska University Hospital, Gothenburg, Sweden, between 2013 and 2017. The study was approved by the ethics committee at the University of Gothenburg (reg. number: 089-12). The study followed the principles of the Declaration of Helsinki. Written informed consent was obtained from all subjects.

A total of 20 consecutive bio-naïve Caucasian patients, ≥ 18 years, with moderate-to-severe plaque psoriasis were included in the study. Diagnosis was made clinically by an experienced dermatologist.

Healthy volunteers, without a history of psoriasis, other skin disease or other inflammatory disorder, were included as controls and were matched to the patients with psoriasis with respect to sex, age, and season. Inclusion and exclusion criteria are listed in Table SI[1].

All participants (patients and healthy controls) were examined by a dermatologist at baseline and after 10 and 24 weeks. Only the patients with psoriasis were treated with etanercept, 50 mg, once weekly for 24 weeks. A questionnaire was completed at each visit, including medical history, medication, dietary supplements, sun habits and other lifestyle variables that could affect vitamin D status, DBP and inflammation.

The Psoriasis Area Severity Index (PASI) was used for scoring the severity of psoriasis in the skin.

The Dermatology Life Quality Index (DLQI) was used to measure the impact of the skin disease on the quality of life of the patients with psoriasis.

The visual analogue scale (VAS), applied to the psoriasis group, is a simple method to evaluate self-rated psoriasis activity, ranging from 0–100 mm, where zero means no complaints and 100 the worst complaints. The VAS has previously been used to assess psoriasis severity and has shown good correlation with the PASI and the DLQI (22).

Skin type according to Fitzpatrick (23) was defined at the first visit. Blood pressure, body weight and height were measured and BMI was calculated. BMI ≥ 30 kg/m^2 was classified as obesity.

To minimize the influence of seasonal variation in vitamin D, the participants were divided into those recruited from October to March, when the ultraviolet (UV) index in Gothenburg is < 3 and vitamin D is not produced in the skin, and those recruited from April to September, when the UV index is ≥ 3 and vitamin D production is possible.

To test the hypothesis of vitamin D levels predicting the treatment outcome, the patients were dichotomized into those with serum 25(OH)D ≥ 75 nmol/l (sufficiency) and those with 25(OH)D < 75 nmol/l (insufficiency), as in previous studies (24, 25) and as defined by the Endocrine Society (26).

Blood samples and other analyses

All samples were drawn in the morning. After centrifugation (10 min at 2,300 relative centrifugal force (RCF)) the serum samples were frozen immediately at –80°C. Total 25(OH)D [25(OH)D$_2$ and 25(OH)D$_3$] was analysed with Electro Chemiluminescence Immunoassay (ECLIA) on a Cobas 8000 Roche instrument (Roche Diagnostics Scandinavia AB, Tokyo, Japan) using Elecsys Vitamin D Total II assay. The coefficient of variance (CV) was 12% at 66 nmol/l and 17% at 26 nmol/l. The limit of quantification (LoQ) was 10 nmol/l.

The free 25(OH)D concentration was measured with a 2-step immunosorbent assay (enzyme-linked immunoassay; ELISA) performed on a commercial kit (Future Diagnostics B.V., Wijchen, The Netherlands). To calculate the percentage of free 25(OH)D, the concentration of free 25(OHD) that was initially measured, in pg/ml, was converted to pmol/l using the formula 1 pg/ml=2.496 pmol/l. The percentage of free 25(OH)D was calculated as free 25(OH)D divided by total 25(OH)D. Calculated free 25(OH)D was measured using the equation by Bikle (27), as shown in Appendix S1[1].1,25(OH)$_2$D was analysed with an automated chemiluminescence immunoassay (CLIA) with an IDS-iSYS instrument (IDS, Boldon, UK). The CV was 10% at 80 pmol/l and 15% at 130 pmol/l.

DBP was analysed with a monoclonal ELISA (R&D Systems, Minneapolis, USA). The CV was 9% at the level of 268 µg/ml and LoQ was 1.3 µg/ml.

Table I. Baseline demographic data for the patients with psoriasis treated with etanercept and the healthy controls

	Patients with psoriasis $n = 20$	Healthy controls $n = 15$	*p*-value
Age, years, mean (SD), *n*			
Men	48 (12), 13	50 (9), 10	0.26[a]
Women	56 (15), 7	52 (10), 5	0.64[a]
All	51 (13), 20	51 (9), 15	0.63[a]
Total hours spent outdoors during summer, mean (SD)	5.4 (3.4), 19	3.7 (2.1), 14	0.12[a]
Fish meals/week	1.6 (0.7), 17	1.9 (1.1), 14	0.34[a]
Duration of psoriasis (years)	28 (12), 19		
Skin type, *n* (%)			
II	7 (35)	2 (13)	0.37[b]
III	12 (60)	12 (80)	
IV	1 (5)	1 (7)	
Self-reported arthropathy, *n* (%)	15 (75)	0 (0)	
Current smokers, *n* (%)	8 (40)	1 (7)	
Antidyslipidaemic use, *n* (%)	4 (20)	1 (7)	
Antihypertensive use, *n* (%)	3 (15)	1 (7)	
Antidiabetic use, *n* (%)	1 (5)	0 (0)	
Antidepressant use, *n* (%)	3 (15)	0 (0)	
Painkiller use, *n* (%)	4 (20)	0 (0)	
Hypothyroidism medication, *n* (%)	0 (0)	2 (13)	
Hormonal contraception, *n* (%)	0 (0)	0 (0)	
Aspirin, n (%)	1 (5)	0 (0)	
Obesity (BMI ≥30 kg/m^2), *n* (%)	6 (30)	5 (33)	

[a]Wilcoxon rank sum test. [b]Fisher's exact test.

Serum intact parathyroid hormone (iPTH) was analysed with ECLIA on a Cobas Roche Diagnostics Scandinavia AB. The CV was 7% at the level of 3 pmol/l and 3% at 10 pmol/l.

The serum levels of hsCRP, total cholesterol, triglycerides, creatinine, albumin, calcium, and alkaline phosphatase (ALP) were analysed with standardized laboratory techniques on a Cobas Roche instrument.

Statistical analyses

All data were analysed using R version 3.5.3 (The R Foundation for Statistical Computing, Vienna, Austria). Spearman's test, stratifying with respect to patient, was used for comparing changes within each group. Wilcoxon rank sum test was used for comparison between groups and Wilcoxon signed rank test for changes from baseline to week 10. Spearman's correlation test was used to test for univariate correlations. All tests were 2-sided and $p < 0.05$ was considered statistically significant.

RESULTS

Sociodemographics

Twenty patients with chronic plaque psoriasis and 15 healthy controls were included in the study. There were no significant differences between the 2 groups regarding age, sex, sun habits, fish meals/week and skin type. Demographic data, possible confounding factors for 25(OH)D and DBP levels and co-morbidities are presented in detail in **Table I**.

Three dropouts occurred in the treatment group: 1 due to a side-effect, 1 due to lack of response, and 1 due to lack of compliance. Only 1 dropout occurred in the control group, due to personal reasons.

Table II. Psoriasis disease severity measured with the Psoriasis Area Severity Index (PASI), the Dermatology Life Quality Index (DLQI) and the Visual Analogue Scale (VAS) for the psoriasis group at baseline and after 24 weeks of treatment with etanercept. Comparison between the two groups at baseline (*p*-value; difference between groups at baseline) regarding the studied biochemical variables as well as changes in these variables within each group (*p*-value for trend in time) during the 24-week period

	Patients with psoriasis $n = 20$			Healthy controls $n = 15$			*p*-value; difference at baseline between groups[b]
	Mean (SD)	*n*	*p*-value for trend in time[a]	Mean (SD)	*n*	*p*-value for trend in time[a]	
PASI score							
Baseline	13 (5)	20	< 0.0001				
24 weeks	3 (3)	17					
DLQI							
Baseline	13 (7)	14	0.002				
24 weeks	2 (4)	11					
VAS							
Baseline	7 (3)	20	< 0.0001				
24 weeks	2 (3)	11					
hsCRP (µg/ml)							
Baseline	4.4 (4.0)	20	0.011	2.0 (2.4)	15	0.55	0.010
24 weeks	2.4 (1.8)	17		1.9 (1.6)	12		
DBP (µg/ml)							
Baseline	234 (63)	20	0.003	222 (23)	15	0.083	0.70
24 weeks	202 (39)	17		222 (19)	12		
25(OH)D (nmol/l)							
Baseline	74 (31)	20	0.34	53 (19)	14	0.029	0.018
24 weeks	76 (23)	17		73 (20)	12		
Free 25(OH)D (pmol/l)							
Baseline	11.8 (4.0)	20	0.84	8.0 (2.6)	15	0.006	0.001
24 weeks	11.7 (2.8)	17		10.2 (2.9)	12		
Calculated free 25(OH)D (pmol/l)							
Baseline	24 (11)	20	0.030	17 (6)	14	0.013	0.018
24 weeks	27 (9)	17		24 (6)	12		
Percentage of free 25(OH)D (%)							
Baseline	0.016 (0.003)	20	0.67	0.016 (0.003)	14	0.22	0.23
24 weeks	0.016 (0.004)	17		0.014 (0.002)	12		
1,25(OH)2D (pmol/l)							
Baseline	103 (34)	20	0.68	91 (36)	15	0.088	0.33
24 weeks	96 (20)	17		112 (38)	12		
PTH (pmol/l)							
Baseline	3.8 (1.7)	20	0.027	4.1 (1.6)	14	0.53	0.29
24 weeks	4.5 (2.8)	17		3.4 (1.4)	12		
Albumin (g/l)							
Baseline	40 (2.5)	20	0.47	42 (2.6)	15	0.69	0.007
24 weeks	40 (2.8)	17		42 (2.5)	12		
Calcium (mmol/l)							
Baseline	2.41 (0.10)	20	0.11	2.44 (0.10)	15	0.62	0.35
24 weeks	2.38 (0.10)	17		2.43 (0.03)	12		
Creatinine (µmol/l)							
Baseline	78 (15)	20	0.024	84 (14)	15	0.40	0.22
24 weeks	82 (13)	17		87 (12)	12		
ALP (µkat/l)							
Baseline	1.3 (0.5)	20	0.025	1.3 (0.3)	15	0.30	0.72
24 weeks	1.3 (0.5)	17		1.3 (0.3)	12		

[a]Spearman's test, stratifying with respect to patient. [b]Wilcoxon rank sum test.
hsCRP: highly sensitive C-reactive protein; DBP: vitamin D-binding protein; PTH: parathyroid hormone; ALP: alkaline phosphatase.

Baseline characteristics, biochemistry, and comparison between the 2 groups

Higher total and free 25(OH)D levels were observed in patients with psoriasis compared with healthy controls (**Table II**), even when adjusting for season of recruitment. However, no difference was observed between patients and controls in the concentration of $1,25(OH)_2D$ or iPTH.

Vitamin D insufficiency was found in 55% of the patients with psoriasis and in 73% of the healthy controls. Calculated free 25(OH)D correlated well with directly measured free 25(OH)D in both the patients with psoriasis and the healthy controls (Spearman's correlation coefficient (ρ) = 0.64, $p < 0.002$ and $\rho = 0.91$, $p < 0.001$, respectively).

The levels of DBP were similar in patients with psoriasis and in controls at baseline ($p = 0.63$), but in a subsample analysis it was found that the patients with psoriasis reporting arthropathy ($n = 15$) showed higher DBP levels than those without ($p = 0.044$). HsCRP was higher in patients with psoriasis compared with healthy controls ($p = 0.01$). No correlation between hsCRP and DBP or hsCRP and 25(OH)D was found in either group. Albumin was lower in patients with psoriasis compared with controls ($p = 0.007$).

Changes in patients with psoriasis on etanercept treatment and healthy controls during the 24-week follow-up

All 3 disease severity variables (PASI, DLQI and VAS) improved during etanercept treatment (Table II).

All measured and calculated vitamin D metabolites (total-, free-, percentage of free 25(OH)D and $1,25(OH)_2D$) remained unaltered in patients with psoriasis; however, iPTH increased ($p = 0.027$). At the same time, both total and free 25(OH)D increased in healthy controls where seasonal variation was observed (Table II, **Fig. 1**), while $1,25(OH)_2D$ and iPTH remained unchanged.

HsCRP decreased after 10 weeks of etanercept treatment ($p = 0.013$) and remained low at 24 weeks ($p = 0.011$). Interestingly, DBP levels also decreased after 24 weeks of etanercept treatment ($p = 0.003$). In a subsample analysis it was observed that the decrease in DBP was significant only in the group of patients with reported arthropathy ($p = 0.009$ vs $p = 0.11$ for those without self-reported arthropathy) (**Fig. 2**). In contrast, in the healthy controls, DBP levels and hsCRP remained unaltered throughout the study ($p = 0.083$ and $p = 0.55$, respectively) (Table II). Other factors that could affect DBP levels, such as seasonal variation or sex differences, were not observed. More detailed information about the data for both groups is shown in Tables SII–SIV[1].

Sun habits during the study

Similar sun holiday patterns were observed during the study (total days of sun holiday per individual per group) ($p = 0.39$) between the 2 groups.

Significance of serum 25(OH)D levels at baseline as a predictor of the treatment

At week 10, the reduction in VAS was higher in the group with sufficient 25(OH)D levels ($n = 11$) compared with the group with insufficient levels ($n = 9$) (mean reduction 9.1 vs 5.5, $p = 0.023$). The group with sufficient 25(OH)D levels also showed a trend ($p = 0.092$) towards achieving PASI75 (a 75% reduction or more of PASI) at this time-point, but not the group with insufficient 25(OH)D.
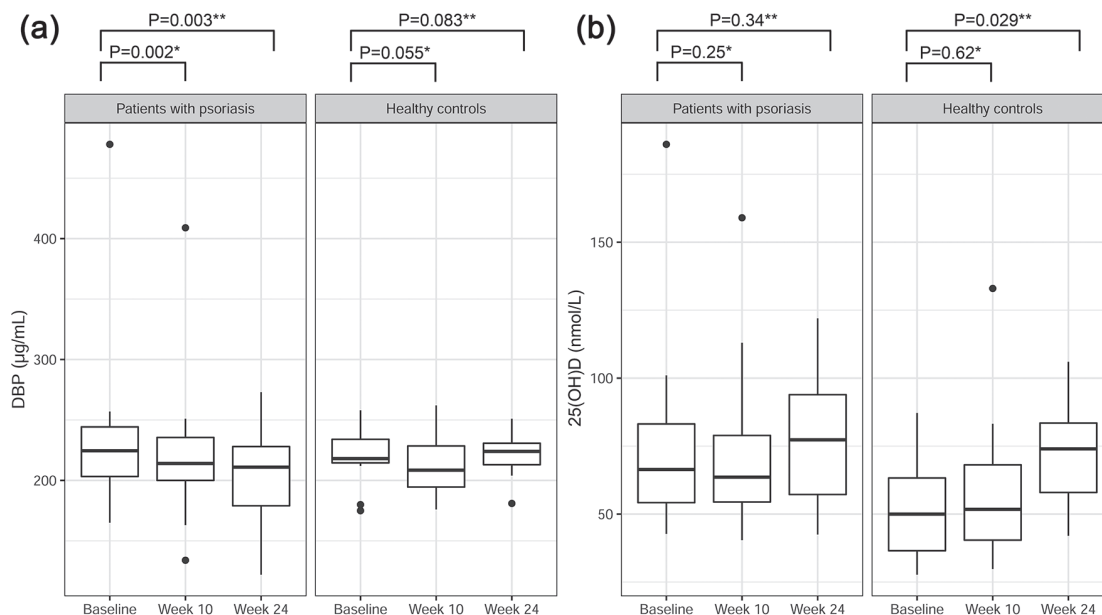
Fig. 1. Boxplots comparing the levels of (a) vitamin D-binding protein (DBP) and (b) total 25(OH)D between patients with psoriasis treated with etanercept and healthy controls. Data are shown for baseline, after 10 weeks and after 24 weeks. *p-value using Wilcoxon signed rank test for changes from baseline to week 10. **p-value using Spearman's test, stratifying with respect to patient, for comparison of changes within each group.
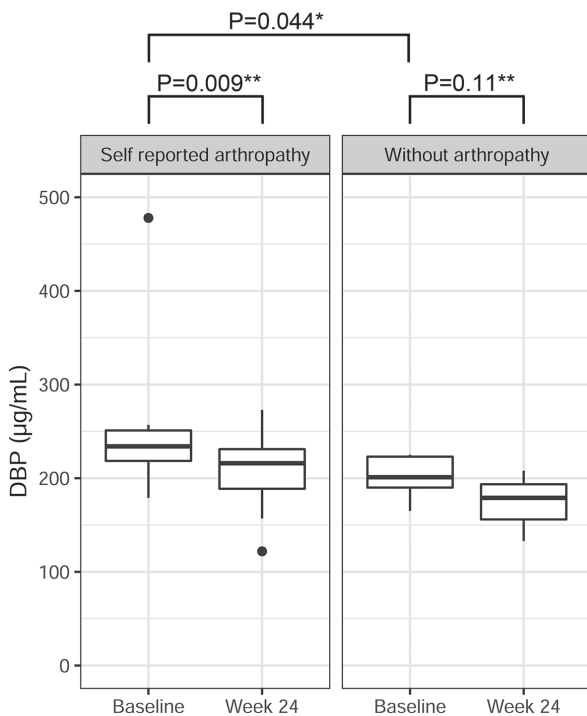
Fig. 2. Boxplots comparing the levels of vitamin D-binding protein (DBP) in the subsamples of patients with psoriasis, with self-reported arthropathy and without arthropathy. Data are shown for baseline and after 24 weeks of etanercept treatment. **p*-value using Wilcoxon signed rank test for comparing DBP levels at baseline between the 2 subgroups. ***p*-value using Spearman's test, stratifying with respect to patient, for comparison of changes within each group.

After 24 weeks of treatment, the patients with sufficient 25(OH)D levels had a greater improvement in their quality of life than those with 25(OH)D insufficiency (mean reduction 19.4 vs 16.9, $p = 0.045$). However, at this time-point, there were no differences between the group with sufficient and the group with insufficient 25(OH)D regarding improvement on the VAS or the PASI75 or reduction in hsCRP.

DISCUSSION

Treatment with etanercept in this psoriasis cohort was effective at reducing PASI and VAS scores and improving quality of life. The inflammation, measured as hsCRP, decreased, but a decrease in DBP was also seen.

Patients with psoriasis had higher levels of total 25(OH)D and free 25(OH)D at baseline compared with healthy controls, and vitamin D levels remained stable throughout the study. On the other hand, both total and free 25(OH)D increased in healthy controls, probably because of summer and normal seasonal variation. The expected seasonal effect and increase in 25(OH)D during the summer was dampened in patients with psoriasis during etanercept treatment, even though sun exposure was similar in the 2 groups during the study. In another study by Welsh et al. (28), serum 25(OH)D in patients with RA remained stable during a 16-week treatment course with TNFis. It remains to be clarified whether a negative impact on the metabolic pathway of vitamin D occurs during TNFi therapy.

BMI increased in the etanercept treatment group but not in the healthy controls. Weight gain during TNFis treatment is a known side-effect (29). In a study by Ganzetti et al. (30) in patients with psoriasis, 25(OH)D decreased after 24 weeks of treatment with TNFis and a significant increase in BMI was noted.

DBP levels were higher in the subsample of patients with self-reported arthropathy compared with those without. Possible confounding factors for DBP, such as female sex, smoking, medication, such as aspirin, and endocrine diseases, such as diabetes and obesity, were not over-represented in the group with arthropathy and could not explain the higher DBP levels (31). DBP levels decreased during the 24 weeks of treatment with etanercept in the patients with psoriasis, but were unaltered in the healthy controls who served as an observation group during the same period. In the subsample analysis among the patients with psoriasis, DBP decreased significantly only in the patients with self-reported arthropathy. High levels of DBP were previously reported in patients with psoriasis compared with healthy controls and were unaffected by ultraviolet B (UVB) phototherapy (21). UVB phototherapy is known not to affect systemic inflammatory and cardiovascular risk markers in psoriasis (32, 33), and TNFis are known to be more potent treatment options. This leads to the theory that DBP may be an inflammatory biomarker for psoriatic arthritis or for the systemic inflammation in psoriasis, which requires further investigation. The reduction in DBP levels observed after 24 weeks of etanercept treatment could be an indicator of a positive treatment effect. To the best of our knowledge, this is the first time the impact of TNFis on DBP levels have been investigated in patients with psoriasis.

High levels of DBP have also been associated with an increased risk of coronary heart disease (34). Psoriasis constitutes an independent risk factor for coronary heart disease and cardiovascular mortality (35, 36). High levels of DBP could predict a risk of relapse in Crohn's disease (37). Should this also be the case in psoriasis, then the decrease in DBP levels should be considered as a beneficial treatment effect.

Serum DBP was found to correlate positively with hsCRP in a Swedish study by Oleröd et al. (20), in which 540 healthy blood donors were tested, and was positively correlated with CRP in a cohort of older men (38). In the current study, no association between DBP and hsCRP was seen, although this may be due to the small sample size.

The decreased DBP levels could be expected to have a positive effect on the concentration of free 25(OH)D, as seen, for example, in patients with cirrhosis, in whom low DBP levels result in higher free 25(OH)D. In the current cohort, baseline DBP levels seem to be within

the normal range, as they are similar to those reported in a study of 450 healthy blood donors from the same region using the same method and the same laboratory (20). The decrease was probably not sufficient to affect the equilibrium between bound and free 25(OH)D.

The increase in serum iPTH levels during TNFi therapy, as found in this study, has been reported previously (39, 40). Inflammation and TNF have a negative impact on the production of PTH, but it is unclear whether the iPTH increase noted during TNFi treatment is dependent on the decreased inflammation or whether it represents a negative influence on the vitamin D pathway. The benefit of vitamin D substitution during TNFi therapy, which could help maintain lower iPTH levels, should be considered in future studies. No significant variation in $1,25(OH)_2D$ was noticed in either group during the entire study, which is in accordance with the strict endocrine regulation of this hormone. $1,25(OH)_2D$ can remain stable even in cases of severe 25(OH)D deficiency. The low serum albumin levels that were found in the patients with psoriasis may be associated with chronic inflammation and cardiovascular risk (41) and have been reported previously (42).

A secondary objective of this study was to examine whether adequate levels of 25(OH)D at the start of the TNFi therapy could have a positive effect on the treatment outcome, as described in patients with IBD (11, 24, 43). The group with sufficient 25(OH)D improved on the VAS more rapidly than their insufficient counterparts, and, after a 24-week treatment course, the sufficient group showed greater improvement in their quality of life. Levels of serum 25(OH)D have previously been found to correlate with health-related quality of life in patients with IBD (44). A study by Zator et al. (24) in patients with IBD could demonstrate that insufficient 25(OH)D at the start of TNFi therapy was associated with earlier cessation of therapy with lack of efficacy being the main reason. In addition, Winter et al. (11) could show that patients with CD, who had normal vitamin D levels at the time of TNFi medication initiation, had 2.64 increased odds of remission at 3 months compared with patients with low vitamin D levels. Given a possible synergic effect between vitamin D and TNFis, and with the knowledge that TNFi treatment alone may negatively affect vitamin D levels (30), it is reasonable to examine the effect of a combination therapy that would secure sufficient vitamin D levels throughout the treatment period in future studies. Vitamin D substitution during TNFi therapy might help to improve the treatment effect and reduce the risk of relapse.

This study has some limitations. The study population was small. The method used for measuring 25(OH)D was not the gold standard method: liquid chromatography-tandem mass spectrometry (LC-MS/MS). However, the method used (Elecsys Vitamin D Total II assay) is certified by the CDC Vitamin D Standardization-Certification Program (CDC VDSCP) and has been validated (45). DBP was measured with a monoclonal ELISA, which has been shown to underestimate DBP levels in individuals of African ancestry, since it does not detect the GC1f-DBP variant. However, all participants, except for 1 Asian individual, were of European ancestry.

Another limitation is that there were no clinical data about the reported arthropathy and the presence of psoriatic arthritis (PsA) was not verified by a rheumatologist. The patients were asked to state whether they experienced any problems from the joints, including both arthralgia and/or morning stiffness. Hence, the self-reported arthropathy might reflect other types of joint problems in addition to PsA. There were no follow-up data either, in order to study the effect of etanercept on the self-reported arthropathy and the possible correlation with the decrease in DBP levels.

A strength of the study was that the control group was matched to the patients with psoriasis with respect to sex, age, and season with similar biochemical analyses performed by the same accredited laboratory.

Etanercept was effective at improving psoriasis disease severity, reducing hsCRP, but also DBP in patients with self-reported arthropathy. DBP might have a role as an inflammatory biomarker in psoriasis. Higher vitamin D levels before initiating TNFi treatment might speed up and strengthen disease improvement, implying a possible synergic action. Further research is needed into vitamin D supplementation during TNFi treatment.

ACKNOWLEDGMENTS

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