Short communication

High levels of serum vitamin D-binding protein in patients with psoriasis: A case-control study and effects of ultraviolet B phototherapy

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ABSTRACT

The role of vitamin D in psoriasis remains contradictory despite the fact that vitamin D analogues constitute an established treatment for psoriasis. It has been proposed that the ability of vitamin D to exert anti-inflammatory effects might not depend solely on the concentration of serum 25(OH)D but also on the concentration of vitamin D-binding protein (DBP). High concentrations of DBP might diminish vitamin D’s biologic action. The aims of this study were (i) to analyze the serum levels of DBP, total and calculated free 25(OH)D in patients with psoriasis and compare the results with healthy controls and (ii) to study the effect of ultraviolet B (UVB) phototherapy on DBP levels. Caucasian subjects (n = 68) with active plaque psoriasis were compared with a population-based sample of men and women (n = 105), matched for age and sex. Season of enrollment was taken into consideration. The patients were also studied before and after UVB phototherapy. The severity of the disease was calculated as Psoriasis Area Severity Index (PASI). DBP, free 25(OH)D index and total 25(OH)D were higher in patients with psoriasis compared with controls (P < 0.004, P = 0.045 and P < 0.0001, respectively). DBP did not change after phototherapy, whereas 25(OH)D increased and intact parathyroid hormone (iPTH) decreased (P < 0.001 for both). Psoriasis improved and PASI decreased after phototherapy (P < 0.004, P = 0.045 and P < 0.0001, respectively). There was no correlation between DBP and 25(OH)D or between DBP and PASI. Measurement of DBP is recommended when evaluating vitamin D status in patients with psoriasis. High DBP levels in psoriasis imply a disturbed vitamin D pathway that warrants further investigation. Direct measurement of free 25(OH)D, instead of total 25(OH)D that circumvents abnormally high levels of DBP, could be considered.

1. Introduction

The role of vitamin D in psoriasis remains contradictory despite the fact that vitamin D analogues constitute established treatment for psoriasis [1]. Vitamin D exerts antiproliferative, prodifferentiative and anti-inflammatory actions in psoriatic skin [1,2]. However, studies correlating vitamin D status with disease severity and treatment outcomes are conflicting [3]. Vitamin D exerts its immunomodulatory effect via tissue-specific, locally produced 1,25(OH)D in an autocrine and paracrine manner on the condition that 25(OH)D is directly available for cellular uptake [4,5].

Vitamin D-binding protein (DBP), the major carrier of vitamin D metabolites, regulates the availability of 25(OH)D to target cells and the subsequent conversion into 1,25(OH)2D [2]. Around 85 % of total 25(OH)D circulates bound with high affinity on DBP and ~15 % on the low affinity carrier, albumin. Only <0.1% of 25(OH)D circulates as free and is capable of passively entering the cells and yielding biologic action (the free hormone hypothesis) [2,4,6].

In clinical conditions where serum DBP levels are affected, the equilibrium between protein-bound 25(OH)D and free 25(OH)D changes [7]. In pregnancy, higher concentrations of DBP result in lower
concentrations of free 25(OH)D and in cirrhosis, vice versa [7]. Furthermore, in vitro studies have shown that higher DBP concentrations diminish the beneficial effects of 1,25(OH)₂D in monocytes, dendritic cells and T-cells by restricting the access to 25(OH)D [4,5,8].

Therefore, it has been proposed that the ability of vitamin D to exert immunomodulatory effects might not depend solely on the concentration of 25(OH)D but also on the concentration of DBP [4].

The primary hypothesis of this case-control study was that DBP levels would be higher in patients with psoriasis compared to population-based healthy controls due to the systemic inflammation in psoriasis. High levels of DBP were found in other systemic inflammatory diseases that are known comorbidities of psoriasis (cardiovascular disease, inflammatory bowel disease, chronic periodontitis) [9-11]. The secondary hypothesis was that DBP levels would decrease after UVB phototherapy since UVB phototherapy has a known good effect on skin inflammation.

2. Materials and methods

2.1. Patients and controls

Caucasian subjects, n = 68, with active plaque psoriasis were examined before and after UVB phototherapy (two to three times /week for 8–12 weeks) and described in detail earlier [12]. All of the patients had previously been treated with UVB phototherapy, but not within two months prior to their inclusion in the study. None had vitamin D supplements or was allowed to use local vitamin D analogues during the study. No oral psoriasis treatments were used during the present study, but the patients could use, if they wished, local steroids.

A random sample of men and women (n = 1615), all Caucasians, from the World Health Organization (WHO), MONItoring of trends and determinants for CArdiovascular disease (MONICA) project in Gothenburg, Sweden, was used for comparison. Hormones and DBP were analyzed in every 4th subject (n = 410). A randomly selected subsample was matched to the patients with respect to sex and age (n = 105). Calcium/vitamin D supplementation was used by only two of the controls.

Season of enrolment was taken into consideration.

2.2. Laboratory analyses

Serum samples for DBP, total 25(OH)D [25(OH)D₂ and 25(OH)D₃] and intact parathyroid hormone (iPTH) were obtained at baseline and after the last dose of radiation. For the patients with psoriasis, serum samples were also analyzed for albumin before and after phototherapy. Analysis of DBP was performed with a monoclonal ELISA (R&D Systems, USA).

25(OH)D was measured using the 125I RIA (radioimmunoassay), (Diasorin, Stillwater, MN, USA).

2.3. Measuring psoriasis severity

The severity of the disease was calculated as Psoriasis Area Severity Index (PASI) which is a quantitative rating score. PASI takes into consideration the body surface area affected as well as the plaque appearance (erythema, induration and scaling). PASI score ranges from 0 (no disease) to 72 (maximal disease). A score higher than 10 indicates severe disease.

2.4. Statistical analyses

Simple descriptive statistics and univariate Spearman’s correlations were performed. Fisher’s exact test and Wilcoxon’s rank sum test were used for two sample tests and Wilcoxon’s signed rank test was used for paired tests.

2.5. Calculation of free 25(OH)D, bioavailable 25(OH)D and free 25 (OH)D index

Calculated free and bioavailable 25(OH)D for the psoriasis group were measured using the following equations by Bikle, [13]:

Calculated free 25(OH)D = \[
\frac{\text{Total 25(OH)D}}{1 + (6 \times 10^3 \times \text{[Albumin]}) + (7 \times 10^3 \times \text{[DBP]})}
\]

Bioavailable 25(OH)D = (6 x 10^3 x [Albumin]) - 1) x calculated free 25(OH)D

Where:

- affinity constant of DBP for 25(OH)D = \(7 \times 10^3\text{M}^{-1}\)
- affinity constant of albumin for 25(OH)D = \(6 \times 10^3\text{M}^{-1}\)

\([\text{DBP}] = \text{serum DBP concentration in g/L}\)
\([\text{Albumin}] = \text{serum albumin concentration in g/L}\)

Free 25(OH)D index was calculated by the formula

\[
\frac{\text{Total 25(OH)D ng/mL}}{\text{DBP µg/mL}}
\]

2.6. Ethical considerations

The study was approved by the Ethics Committee at the University of Gothenburg (Dnr 025–06 and Dnr 088–06) and the Swedish National Data Inspection Board. Declarations of Helsinki protocols were followed. Written informed consent was obtained from all subjects.

3. Results

DBP and total 25(OH)D were higher in patients with psoriasis compared with controls (Table 1, Fig. 1 and Fig. 2). Calculated free 25(OH)D in the patients with psoriasis correlated well with the free 25(OH)D index. Therefore, comparative statistics between patients and controls (Table 1, Fig. 1 and Fig. 2). Calculated free 25(OH)D index was higher in patients with psoriasis compared with healthy controls (P = 0.045) (Table 1). The difference between the two groups using free 25(OH)D index compared to total 25(OH)D was lower (P = 0.045 vs P < 0.0001) (Table 1). There was no sex difference or seasonal variation in DBP in any group.

DBP did not change after phototherapy whereas 25(OH)D increased and PASI as well as iPTH decreased (Table 2). The improvement in PASI score was irrespective of the baseline levels of DBP and 25(OH)D. There was no correlation between DBP and 25(OH)D ( Spearman’s correlation coefficient (\(\rho\)) = 0.0073, P = 0.55). No correlation was found between DBP and PASI (\(\rho\)=-0.062, P = 0.63).

Neither the albumin calculated nor the free index 25(OH)D correlated with PASI (\(\rho\) = 0.069, P = 0.59 and \(\rho\) = 0.068, P = 0.60, respectively).

4. Discussion

DBP levels were higher in patients with psoriasis compared to healthy controls. Possible confounders such as medication (i.e., hormonal contraceptives and aspirin use), smoking or other comorbidity [14,15] were not found in the psoriasis group and cannot explain this difference in the DBP levels. DBP is mainly produced in the liver and besides estrogens, proinflammatory cytokines, like interleukin-6, have been shown to stimulate DBP production [7]. High levels of DBP have been reported in other inflammatory disorders which are also known comorbidities of psoriasis. In patients with Crohn’s disease, which shares a common pathogenesis and similar inflammatory response with psoriasis, high levels of DBP were associated with the risk of disease flare [9]. High DBP levels were also found in periodontitis [10] and associated with an increased risk of coronary heart disease [11]. The above studies emphasized DBP’s role in the inflammatory process, i.e.
actin-scavenging in tissue damage, macrophage activation, enhanced neutrophil chemotaxis and an indirect negative effect on both the innate and adaptive immune system by inhibiting vitamin D’s actions. Furthermore, in previous studies, DBP was found to positively correlate with C-reactive protein [16, 17].

The patients with psoriasis within the present study have had their diagnosis for many years (mean duration 29.5 ± 15.3 years) and all of them had previously been treated with either narrowband or broadband UVB phototherapy, but not within two months prior to their inclusion in the study. This could possibly contribute to the higher 25(OH)D levels in the patients with psoriasis compared to the healthy controls. The high DBP levels might also partially contribute to the high 25(OH)D levels.

Table 1

Demographic data, vitamin D-binding protein (DBP), serum 25(OH)D, free 25(OH)D index and intact parathyroid hormone (iPTH) in patients with psoriasis before ultraviolet B (UVB) phototherapy (baseline) compared with population-based controls from the World Health Organization, MONItoring of trends and determinants for Cardiovascular disease (WHO MONICA) study Gothenburg, Sweden. SD = Standard Deviation. CI = Confidence Interval. P-value is given for patients versus controls. Number (%) is given.

| Variable | Psoriasis Baseline | WHO MONICA |
|----------|--------------------|-------------|
| Sex      | Men                | Women       | Men                | Women       |
|          | 51 (75 %)          | 17 (25 %)   | 78 (74 %)          | 27 (26 %)   |
| Age (years) | Min Median Max Mean SD | n | Min Median Max Mean SD | n |
|          | 26, 55.5, 85, 54.4, 15.7, 68 | 65 | 39, 58, 77, 57.8, 10.8, 105 |
| Duration of psoriasis (years) | Min Median Max Mean SD | n | Min Median Median Max Mean SD | n |
|          | 6, 25, 72, 29.5, 15.3, 61 |
| Use of medication | | | | |
| Antihypertensive use | 6 / 68 (9%) | 22 / 105 (21 %) |
| Antidiabetic use | 2 / 68 (3%) | 14 / 105 (13 %) |
| Antidepressant use | 3 / 68 (4%) | 2 / 105 (2%) |
| Painkiller use | 0 / 68 (0%) | 13 / 105 (12 %) |
| Medication for hypothyroidism | 5 / 68 (7%) | 9 / 105 (9%) |
| Hormonal contraception | 0 / 68 (0%) | 0 / 105 (0%) |
| Aspirin use | 3 / 68 (4%) | 10 / 105 (10 %) |
| Smoking | | | | |
| Current smoker | 10 / 68 (15 %) | 12 / 105 (11 %) |
| Ex-smoker | 30 / 68 (44 %) | 43 / 105 (41 %) |
| Never smoked | 28 / 68 (41 %) | 48 / 105 (46 %) |
| Missing data | 0 / 68 (0%) | 2 / 105 (2%) |
| Included winter (November-March) | 50 / 68 (74 %) | 68 / 105 (65 %) |
| Serum DBP (µg/mL) | Min Median Max Mean SD | n | Min Median Max Mean SD | n |
|          | 121, 305, 1007, 350, 181, 68, 87, 262 | 68 | 121, 305, 1007, 350, 181, 68, 87, 262 |
| Serum 25(OH)D (ng/mL) | Min Median Max Mean SD | n | Min Median Max Mean SD | n |
|          | 12.5, 33.55, 81.5, 36.0, 14.0, 68, 5.7, 21.9, 60.4, 24.3, 10.7, 105 | 68 | 12.5, 33.55, 81.5, 36.0, 14.0, 68, 5.7, 21.9, 60.4, 24.3, 10.7, 105 |
| Free 25(OH)D index | Min Median Max Mean SD | n | Min Median Max Mean SD | n |
|          | 0.03, 0.11, 0.36, 0.13, 0.08, 68, 0.01, 0.09, 0.42, 0.11, 0.07, 105 |
| Serum iPTH (ng/L) | Min Median Max Mean SD | n | Min Median Max Mean SD | n |
|          | 5.4, 30, 82, 33, 17, 68, 18, 45, 106, 46, 16, 104 |

Fig. 1. Vitamin D-binding protein (DBP) in the patients with psoriasis before and after phototherapy treatment and in comparison, with the healthy individuals from the World Health Organization, MONItoring of trends and determinants for Cardiovascular disease (WHO MONICA) cohort.

Fig. 2. Serum total 25(OH)D in the patients with psoriasis before and after phototherapy treatment and in comparison, with the healthy individuals from the World Health Organization, MONItoring of trends and determinants for Cardiovascular disease (WHO MONICA) cohort.
since DBP could bind more 25(OH)D.

UVB phototherapy had a good effect on skin inflammation, causing regression of the psoriatic lesions (reduction of PASI), but DBP was unaffected. UVB phototherapy does not affect systemic inflammatory markers in psoriasis as shown before [18,19]. The finding of a stable DBP during UVB treatment and no correlation of DBP with 25(OH)D speaks in favor of DBP being a marker of systemic inflammation rather than related to 25(OH)D per se, as reported previously [2,6,20].

One limitation is that a monoclonal ELISA was used for measuring DBP instead of using the polyclonal ELISA. This can lead to falsely low DBP concentration in individuals of African origin where the GC1f-DBP isoform is more common [6]. However, this can be overcome since the population studied consisted of Caucasians and none was of African origin. Another limitation is that anthropometric data were missing in the patients as high body weight is inversely correlated to 25(OH)D and might, even though it is conflicting, affect the levels of DBP [21].

In the last years, there has been a resurgence of interest in DBP: how DBP affects vitamin D’s metabolism and actions but even about its role in inflammation and association to different diseases [2,4,6]. DBP facilitates the internalization of DBP-bound 25(OH)D in cells expressing the megalin-cubulin receptor (e.g. renal cells, mammary cells and placenta). However, in the majority of other cells and tissues, including the immune cells and skin, megalin-cubulin receptor is not expressed. Instead, it is the unbound-free fraction that is available for diffusion through the lipid layer of the cell membrane. Therefore, measurement of total 25(OH)D (bound and free fraction) might not always accurately represent the amount of 25(OH)D that is capable of exerting biologic activity [4]. In order to investigate the impact of the high DBP levels on free and bioavailable 25(OH)D simple calculations using validated formulas were performed. The difference in the level of total 25(OH)D found at baseline between patients with psoriasis and healthy controls decreased when comparing the free 25(OH)D index. A new commercial method has been developed for the direct measurement of the free fraction of 25(OH)D. Studies have shown that the levels of directly measured free 25(OH)D are lower than the levels of calculated free 25(OH)D [22]. Current algorithms to calculate free 25(OH)D may not be accurate [22] since they use invariant association constants which might not be valid [23]. Furthermore, in a recent study, directly measured free 25(OH)D in patients with psoriasis was significantly lower compared to healthy controls, while the level of total 25(OH)D was similar between the two groups [24]. However, DBP was not measured in this study.

High DBP levels in psoriasis patients implies a disturbed vitamin D pathway that warrants further investigation. DBP may restrict, instead of facilitate, vitamin D’s availability to the target cells and tissues by binding it with very high affinity [4,5,6]. This could impair the positive immunomodulatory effects of vitamin D in psoriasis despite a seemingly normal vitamin D status.

If high DBP levels in psoriasis patients are confirmed in future studies, then DBP could be used as a new disease biomarker similar to the use in Crohn’s and coronary heart disease [9,11]. Furthermore, it would be interesting to study the effect potent systemic treatment in psoriasis would have on DBP. In another study, free 25(OH)D rather than total 25(OH)D was associated with an increased risk of cardiovascular mortality [25].

5. Conclusion

In conclusion, measurement of DBP could be valuable when evaluating vitamin D status in patients with psoriasis. Furthermore, direct measurement of free 25(OH)D, instead of total 25(OH)D that circumvents abnormally high levels of DBP, could be considered, since free 25(OH)D might more accurately reflect the biologic activity of vitamin D in psoriasis.

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Declaration of Competing Interest

None.

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