25-hydroxy vitamin D and ischaemia-modified albumin levels in psoriasis and their association with disease severity

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ABSTRACT

Psoriasis is a T-helper-1 (Th1)/Th17-mediated chronic inflammatory skin disease, characterised by hyperproliferation of keratinocytes. Psoriasis and cardiovascular disease share similar pathogenic mechanisms such as vascular endothelial cell dysfunction, oxidative stress and metabolic syndrome. 25-hydroxy vitamin D is an immune-regulatory hormone, with the ability to reduce cellular proliferation in psoriasis. Ischaemia-modified albumin (IMA) is a marker of oxidative stress. This study examined 25-hydroxy vitamin D, IMA and high-sensitivity C-reactive protein (hs-CRP) levels in patients with psoriasis, in comparison with healthy controls and their possible association with disease severity. A total of 43 cases of psoriasis and 43 controls were included in this cross-sectional study, and severity grading was performed according to psoriasis area severity index (PASI) scoring. Serum 25-hydroxy vitamin D, IMA and hs-CRP were evaluated in all study subjects. In psoriasis, 25-hydroxy vitamin D showed a significant decline, while hs-CRP and IMA levels were significantly elevated, as compared with controls. Serum 25-hydroxy vitamin D showed a significant negative correlation with PASI score. hs-CRP and IMA showed a significant positive correlation with PASI score. Significant negative correlation was observed between 25-hydroxy vitamin D and hs-CRP; 25-hydroxy vitamin D and IMA levels in psoriasis. The results indicate that psoriasis is associated with significantly lowered 25-hydroxy vitamin D levels, along with increased systemic inflammation and oxidative stress, especially in severe disease. Thus, vitamin D supplementation might reduce systemic inflammation and oxidative stress and help in delaying the pathogenesis of co-morbidities associated with psoriasis.

KEY WORDS: Inflammation.
Oxidative stress.
Psoriasis Area Severity Index.
Psoriasis.
Vitamin D

Introduction

Psoriasis, a T-helper-1 (Th1)/Th17-mediated chronic inflammatory skin disease, is no longer considered a disease confined to the skin, rather a systemic disease associated with cardiovascular co-morbidities. Recent studies show that atherosclerosis, the forerunner of cardiovascular diseases, is also T-helper-1 (Th1)/Th17-mediated.[1] In addition, psoriasis and cardiovascular diseases share other common pathogenic mechanisms such as vascular endothelial cell dysfunction, oxidative stress, systemic inflammation and metabolic syndrome.[2]

25-hydroxy vitamin D is an immune-regulatory hormone with beneficial effects on inflammatory diseases mediated by Th1/Th17 cells, such as psoriasis.[3,4] It reduces cellular proliferation, decreasing the turnover of skin cells in psoriasis. In addition, vitamin D deficiency has been reported as a risk factor for metabolic syndrome and cardiovascular disease. Thus, vitamin D deficiency is implicated as one of the pathogenetic mechanisms involved in co-morbidities in psoriasis.

Cutaneous inflammation in psoriasis is perpetuated by release of cytokines, interleukin-6 and tumour necrosis factor-α (TNFα) that trigger the synthesis of C-reactive protein (CRP) by the liver. C-reactive protein appears to down-regulate activation of neutrophils and chemotactic responses, reducing endothelial adhesion and therefore neutrophil migration to tissues.[5,6] In addition, cutaneous inflammation leads to release of other inflammatory cytokines resulting in systemic inflammation.

Ischaemia-modified albumin (IMA) is a marker of oxidative stress, with increased IMA levels in hypoxia and tissue damage due to free radicals. Oxidative stress is an important forerunner of systemic inflammation that occurs in psoriasis, and hence IMA can be used as a marker to assess oxidative stress in psoriasis.[7] Although only a few studies have evaluated the circulating levels of hs-CRP, IMA and vitamin D in psoriasis, most are inconclusive and are conflicting. Hence, this study aims to assess the levels of 25-hydroxy vitamin D, IMA and hs-CRP in patients with psoriasis, in comparison with healthy controls, and their possible association with disease severity.

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Table 1. Comparison of baseline characteristics between cases ($n=43$) and controls ($n=43$).

	Cases Mean±SD	Controls Mean±SD	*P* value (Unpaired *t*-test)
Age (years)	44.6±12.0	43.9±11.2	0.80
Gender (M:F)	33:10	33:10	–
BMI (kg/m^2)	23.7±3.5	22.8±1.9	0.15
W/H ratio	0.9±0.03	0.9±0.05	0.40
Daily vitamin D intake (IU)	319.5±211.0	314.9±231.8	0.79*
Weekly sunlight exposure (hours)	33.7±19.2	32.7±18.5	0.840*

*Mann Whitney U test

Materials and methods

This was a hospital-based cross-sectional study involving two groups – cases and controls. A total of 43 patients with psoriasis were recruited, attending the Psoriasis Clinic at a tertiary care centre in Puducherry, South India; 43 age- and gender-matched healthy volunteers acted as controls. Ethical approval was obtained from JIPMER Human Ethics Committee (IEC/SC/2012/4/105). The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and written informed consent was obtained from all study subjects. All study participants were recruited in the winter season to avoid seasonal variations in vitamin D levels.

Sample size estimation

Sample size was estimated from serum 25-hydroxy vitamin D values. Mean level of 25-hydroxy vitamin D among healthy Indians is 13.5±6.9 ng/mL.[8] Previous studies in Italy on the mean level of serum 25-hydroxy vitamin D among psoriatics found a magnitude of difference compared to normal controls to be 45%.[4] However, we assumed a more conservative margin of difference in calculating sample size (30%). In order to detect this difference with 80% power at 5% level of significance, the minimum sample size required for the study was estimated as 43 in each group (cases and controls). This was calculated using the PS Power and Sample Size Program version 3.0.43 software.

Study population and work-up

Subjects on any systemic medication that might influence 25-hydroxy vitamin D, including bisphosphonates, systemic corticosteroids, 25-hydroxy vitamin D and calcium supplementation, or those with malignancy, diabetes mellitus, any infectious or inflammatory disease, hepatic and renal disease, cardiovascular disease and pregnancy were excluded from the study. Psoriasis was diagnosed using the International Psoriasis Council Consensus Classification,[9] and disease severity was assessed using psoriasis area severity index (PASI) scoring.[10]

Assay of study parameters

Blood (5 mL) was drawn from all subjects in a fasting state. Routine parameters such as fasting glucose, lipid profile, uric acid, total protein and albumin were estimated immediately using an Olympus AU400 automated clinical chemistry analyser. Serum levels of 25-hydroxy vitamin D (Diasource Immunoassays, Belgium) and high-sensitivity CRP (hs-CRP; Diagnostics Biochem Canada) levels were estimated using commercially available enzyme immunosorbent assay (ELISA) kits. High-sensitivity CRP was estimated instead of CRP, as low levels are more accurately estimated using the hs-CRP kit, and these levels gain importance in assessing the cardiovascular risk more precisely. Serum levels of IMA were estimated using the spectrophotometric method of Bar-Or *et al*.[11]

Statistical analysis

Statistical analysis was performed using IBM SPSS statistics version 20 for Windows. Baseline characteristics of all study subjects were analysed using descriptive statistics. The normality of continuous data was assessed by the Kolmogrov–Smirnov test. The data were described as mean±standard deviation (SD). Comparison of the various parameters between cases and controls was performed by independent Student's *t*-test for parametric data and Mann–Whitney U-test for non-parametric data. The levels of the various biochemical parameters were correlated with PASI using Pearson correlation and the correlation between the various study parameters was analysed using Spearman rank correlation. To assess the effects of confounders, a multivariate linear regression analysis was performed with 25-hydroxy vitamin D as the dependent variable. Analysis was carried out at the 5% level of significance and $P<0.05$ was considered statistically significant.

Results

Forty-three patients with psoriasis and 43 healthy controls were included in the study. The mean duration of psoriasis was 49.65±48 months. All patients had chronic plaque psoriasis and 13 patients with psoriasis had co-existent psoriatic arthritis. Mean PASI was 15.20±8.61. The baseline characteristics between cases and controls were comparable (Table 1). The baseline routine parameters between cases and controls were comparable, except for significantly higher serum levels of total cholesterol, low-density lipoprotein (LDL) cholesterol and lower levels of albumin among cases, when compared to controls (Table 2).

All study participants had Fitzpatrick skin type V and were residents of Puducherry or adjacent areas, to avoid geographic differences in sun exposure and vitamin D levels. All study participants were recruited in the winter season to avoid seasonal variations in vitamin D levels.

Serum 25-hydroxy vitamin D levels are significantly lower in cases when compared to controls. hs-CRP and IMA are

Table 2. Comparison of routine parameters between cases (n=43) and controls (n=43).

	Cases Mean±SD	Controls Mean±SD	*P* value (Unpaired *t*-test)
Fasting glucose (mg/dL)	87.1±18.6	85.9±13.6	0.75
Uric acid (mg/dL)	4.9±1.7	4.5±1.3	0.20
Total cholesterol (mg/dL)	158.1±36.0	142.9±21.4	0.02
LDL cholesterol (mg/dL)	98.6±34.4	84.0±23.5	0.02
VLDL cholesterol (mg/dL)	25.4±9.3	22.8±5.1	0.12
HDL cholesterol (mg/dL)	34.1±6.6	36.0±6.6	0.20
TG (mg/dL)	127.0±46.7	114.2±25.3	0.12
Total protein (g/dL)	7.4±1.0	7.5±0.4	0.24
Albumin (g/dL)	4.0±0.1	4.3±0.2	<0.0001

significantly higher in patients with psoriasis than in the control group (Table 3). Psoriasis severity, as assessed by PASI, correlated positively with hs-CRP and IMA and negatively correlated with serum levels of 25-hydroxy vitamin D. (Figs. 1–3). Serum levels of 25-hydroxy vitamin D correlated negatively with hs-CRP (r=–0.398, P≤0.001) and IMA (r=–0.461, P=0.001) by Spearman correlation. Serum levels of hs-CRP correlated positively with IMA (r=0.438, P≤0.0001) by Pearson correlation.

To assess the effects of confounders on the study parameters, a multivariate linear regression analysis was performed with vitamin D as the dependent variable. It was observed that psoriasis was an independent risk factor (P=0.002), after adjusting for age, gender, body mass index (BMI), total cholesterol, LDL cholesterol, vitamin D dietary intake and sunlight exposure.

Discussion

Psoriasis, a chronic immune-mediated inflammatory cutaneous disorder, is reported to be associated with a higher prevalence of cardiovascular risk factors. Psoriasis-related chronic inflammation is the major instigator of metabolic syndrome and subclinical atherosclerosis found in these patients.[1,3]

Systemic inflammation plays a central role in the pathogenesis of co-morbidities associated with psoriasis.[12–15] Coimbra *et al*.[16] reported significantly higher levels of hs-CRP which correlated positively and significantly with PASI as well as with total leucocytes, with neutrophils and their activation products (elastase and lactoferrin) as well as with the specific inhibitor of elastase, α1-antitrypsin, in patients with psoriasis. They identified that CRP could be used as a powerful and sensitive marker to evaluate psoriasis severity, as it is not based on a visual evaluation of the lesions, as occurs with PASI. Rocha-Pereira *et al*.[17] reported significantly higher values of hs-CRP in active psoriasis than in inactive psoriasis and a control group. Although some studies have not observed an association, this could be attributed to inter-observer differences in recording PASI, non-homogeneity of the cases, and difference between hs-CRP and CRP. However, in the present study, we observed a significantly higher level of hs-CRP in patients with psoriasis when compared to controls with a significant positive correlation with disease severity (PASI).

Psoriatic patients are exposed to diverse endogenous and exogenous sources of oxidative stress. This may be attributed to the chronic nature, recurrence and co-morbidities of the disease and the therapy instituted. Although an increase in IMA has been reported in hyperlipidaemia, obesity and metabolic syndrome, which are also co-morbidities associated with psoriasis, the mechanism for this increase is not fully known.

Ozdemir *et al*.[7] reported a significant increase in IMA levels in patients with psoriasis in comparison to healthy controls. However, they observed no significant correlation between IMA and PASI. We observed a similar finding with significantly higher levels of IMA in psoriatics correlating with disease severity (PASI). Ischaemia-modified albumin is considered a biomarker for myocardial and skeletal muscle ischaemia, hence its elevation in psoriasis suggest utility in assessing the cardiovascular risk in these patients.[18–20]

Substantial evidence suggests that vitamin D plays a pivotal role in modulating dendritic cell function and regulating keratinocyte and T-cell proliferation. Vitamin D is considered an immune regulatory hormone with beneficial effects on inflammatory diseases mediated by Th1/Th17 cells, such as coronary artery disease and psoriasis. Vitamin D decreases Th1/Th17 cells and increases Th2/T-reg cells, thus skewing the pro-inflammatory state to an anti-inflammatory state.[3]

Table 3. Comparison of study parameters between cases (n=43) and controls (n=43).

	Cases Mean±SD	Controls Mean±SD	*P* value (Mann Whitney U test)
25-hydroxy vitamin D (ng/mL)	13.3±6.9	22.4±18.4	0.004
hs-CRP (mg/L)	4.7±3.0	2.8±2.3	0.002
IMA (ABSU)	1.3±0.2	1.0±0.3	<0.0001

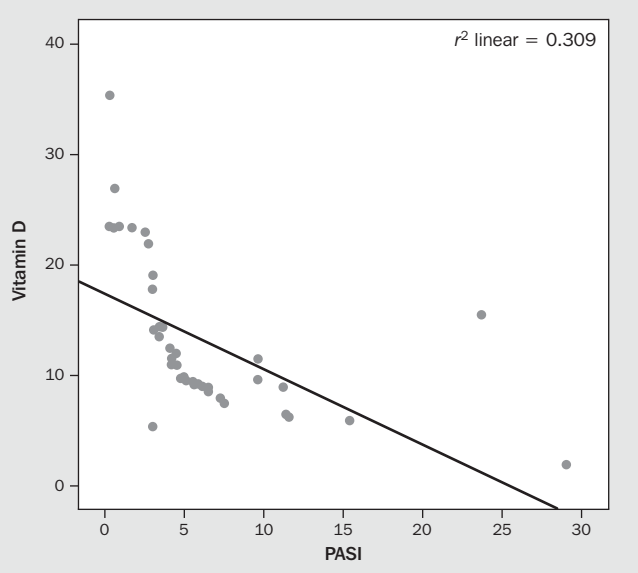

Fig. 1. Correlation of 25-hydroxy vitamin D with disease severity (PASI) (r=–0.71, P≤0.0001)

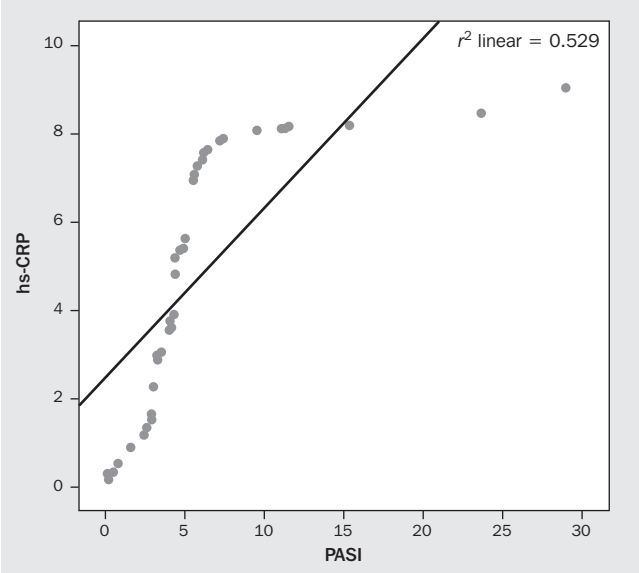

Fig. 2. Correlation of hs-CRP with disease severity (PASI) (r=0.89, P≤0.0001).

In a study conducted by Molina *et al.*,[2] they observed that serum levels of 25-hydroxy vitamin D were significantly lower in psoriatic patients than in controls, which negatively correlated with BMI and CRP. In addition, they reported that psoriatic patients with a BMI ≥27 kg/m^2 were found to have a greater risk of 25-hydroxy vitamin D insufficiency, than that of healthy controls. In another study by Molina *et al.*[21] in psoriatic patients, it was observed that serum 25-hydroxyvitamin D levels inversely correlated with fasting glucose, total cholesterol, LDL and triglyceride levels.

Previous studies have explored the interplay between vitamin D levels and systemic inflammation and oxidative stress. Vitamin D plays a major role in maintaining the redox potential of the cell. Its antioxidative effect was found to be mediated partly through inhibition of inflammatory responses such as suppressing immune cell infiltration by attenuating cytokine production or reducing the inducible nitric oxide synthase (iNOS) in macrophages and astrocytes to reduce free radical formation from nitric oxide derivatives.[22,23] Vitamin D has recently emerged as a negative phase reactant, levels of which decrease with progressive inflammation. Hence, assessment of vitamin D levels gains particular importance in psoriasis as low levels of vitamin D has also been identified recently to be a marker of cardiovascular disease.[24]

In the present study we observed that 35/43 patients had deficient vitamin D in comparison to 24/43 controls. Multivariate linear regression analysis performed with vitamin D as the dependent variable showed that psoriasis was an independent risk factor (P=0.002), after adjusting for age, gender, BMI, total cholesterol, LDL cholesterol, vitamin D dietary intake and sunlight exposure. The results of this study were consistent with that of previous studies[2,4,21] in demonstrating significantly lower levels of 25-hydroxy vitamin D in psoriatics. In addition, we demonstrated a significant negative correlation of 25-hydroxy vitamin D levels with PASI, hs-CRP and IMA.

Whether a cause or consequence of psoriatic inflammatory progression, vitamin D deficiency in psoriasis remains a debate. However, vitamin D exerts a prominent effect on the immunoregulatory cells of the skin and its deficiency is associated with impairment of immunoregulatory cell suppressor activity, thus perpetuating the vicious cycle of cutaneous inflammation, leading to systemic inflammation, increased oxidative stress, insulin resistance and finally cardiovascular disease.[25]

In conclusion, we observed significant systemic inflammation, oxidative stress and lowered 25-hydroxy vitamin D levels in patients with psoriasis. Moreover, there was a significant positive correlation of lowered 25-hydroxy vitamin D with the inflammatory and oxidative stress parameters. As these markers were found to correlate with PASI, it might be possible for the clinician to use them to monitor therapeutic response. Lower vitamin D has been found to be associated with cardiovascular disease, which may be alleviated by supplementation, which in turn might reduce systemic inflammation and oxidative stress, thus

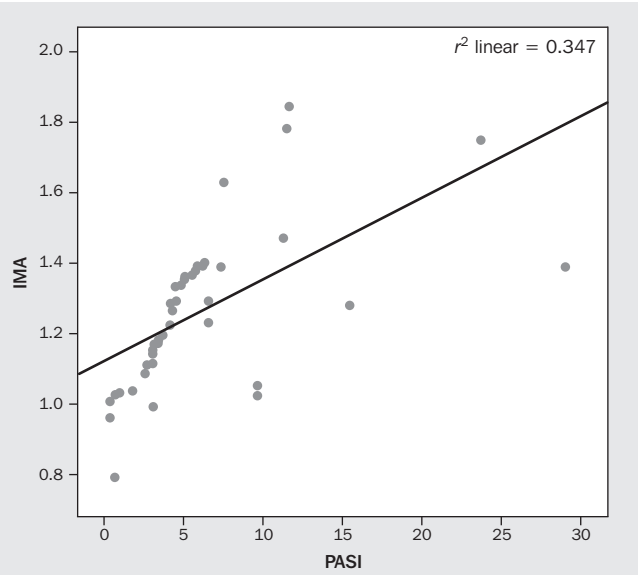

Fig. 3. Correlation between IMA and disease severity (PASI) (r=0.71, P≤0.0001).

delaying the pathogenesis of co-morbidities associated with psoriasis.

The limitations of this study were a relatively small sample size, and the fact that the effects of anti-psoriatic treatment and vitamin D supplementation were not studied. Clearly, further studies of a larger population are needed to assess effects on psoriasis severity.

What is already known?

- Psoriasis is a Th1/Th17-mediated chronic inflammatory primary disease of skin.
- Psoriatic patients are at increased risk for cardiovascular disease.
- Psoriasis is associated with systemic inflammation and increased oxidative stress.

What does this study add?

- Psoriasis is associated with lower vitamin D levels.
- The vitamin D deficiency seen in psoriasis is associated with systemic inflammation and increased oxidative stress.
- Vitamin D supplementation may reduce progression of psoriasis and its co-morbidities. □

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