Vitamin D Metabolism in Psoriasis Before and After Phototherapy

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Epidermis plays a major role in vitamin D synthesis and is a target tissue for 1,25 (OH)2 vitamin D, which could be involved in abnormal proliferation and differentiation of psoriatic keratinocytes. We investigated plasma calcium, phosphorus, alkaline phosphatases, parathyroid hormone, 25 (OH) D, 24,25 (OH)2 D and 1,25 (OH)2 D in 15 control subjects and 20 psoriatic patients before and after 3 weeks of phototherapy (UVB or PUVA). Before irradiation, all parameters were similar in psoriatics and controls, except for serum phosphorus (lower in psoriasis $p < 0.01$). After phototherapy, P rose to normal values in psoriatic patients; 25 (OH) D and 24,25 (OH)2 D were dramatically increased by UVB (but not by PUVA) in psoriatic patients as well as in controls; 1,25 (OH)2 D was unmodified in controls but was significantly increased in psoriasis. Since 1,25 (OH)2 D has been reported to be an effective treatment for psoriasis, the UV-induced increase in 1,25 (OH)2 D could account for the beneficial effect of phototherapy in psoriasis.

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It is well established that skin is responsible for producing vitamin D from 7 dehydrocholesterol on exposure to sunlight. Vitamin D is then hydroxylated in the liver into 25 hydroxyvitamin D (25) (OH) D) and a further hydroxylation occurs in the kidney, leading to 1,25 dihydroxyvitamin D (1,25(OH)2 D) the active metabolite of vitamin D. Recently, cultered keratinocytes were also found to produce 1,25(OH)2 D, indicating that human skin might be an alternative source for this metabolite (1–2).

The receptor for 1,25 (OH)2 D has been found in many tissues, particularly in epidermal and dermal layers of skin (3). Skin may therefore be regarded as both a site of synthesis and a target tissue for 1,25 (OH)2 D (4). The 1,25 (OH)2 D acts not only on calcium homeostasis, but also on cell proliferation and differentiation (4–7). For instance it has been demonstrated that 1,25 (OH)2 D inhibits proliferation of cultured keratinocytes and regulates their terminal differentiation (5).

Hyperproliferation and abnormal differentiation remain the best markers of psoriatic epidermis. In this respect, Smith et al. (8) recently demonstrated that 1,25 (OH)2 D was effective on proliferation and differentiation of psoriatic keratinocytes as it was on normal epidermal cells. These in vitro effects are in agreement with in vivo studies reporting amelioration of psoriasis after vitamin D treatment (9, 10). Moreover, various phototherapies are effective against psoriasis. The exact mechanisms of their beneficial effect are not completely understood, but could involve their impact on vitamin D synthesis. In order to gain further insight into this possible mechanism we were led to study vitamin D metabolism in psoriatic patients before and after phototherapy.

METHODS

Subjects

A total of 35 subjects, 20 patients with psoriasis vulgaris (age range 18–71) and 15 controls (age range 21–41) were included. Most of them had disseminated active lesions. None had been exposed to UV irradiation for at least 3 months and the study was performed between November and February in order to avoid external sun exposure.

Biological examinations

Plasma concentrations of calcium (Ca), phosphorus (P), parathyroid hormone (PTH), 25 (OH) D, 24,25 (OH)2 D and 1,25 (OH)2 D were evaluated before (day 0) and after UV irradiation (day 21). PTH was measured by radioimmunoassy (intact PTH: Nichols Institute, USA); 25 (OH) D was extracted from plasma, purified on silicagel columns and measured by competitive protein-binding assay procedures using normal diluted rat serum as binding protein (11). Plasma 24,25 (OH)2 D and 1,25 (OH)2 D were simultaneously extracted using the Bouillon procedure with slight modifications (12) and separated by high performance liquid chromatography. Plasma 24,25 (OH)2 D was measured using a competitive protein-binding assay procedure similar to that used for 25 (OH) D. Quantitation of 1,25 (OH)2 D was achieved using a non-equilibrium

Table I. *Mean serum levels before and after phototherapy*

		P (mmol/l)		25 OHD (ng/ml)		24–25 $(OH)_2D$ (ng/ml)		1–25 $(OH)_2D$ (pg/ml)	
		Day 0	Day 21	Day 0	Day 21	Day 0	Day 21	Day 0	Day 21
Controls									
UVA	4	1.02±0.10	1.06±0.18	27± 7	22+ 6	2.1±0.8	1.8±0.7	25±10	25±8
UVB	11	1.30±0.25	1.25±0.16	24±13	68+17	2.1±0.9	4.8±1	16± 6	16±6
Total	15	1.22±0.24	1.20±0.18	25±11	55+26	2.1±0.8	4.0±1.7	18± 8	18±8
Psoriatics									
UVA	9	0.95±0.12	1.15±0.33	28±10	27± 7	2 ±0.6	1.8±0.8	19± 7	26±9
UVB	11	1.01±0.15	1.16±0.44	18± 8	54±23	1.2±0.7	3.9±2.5	16± 8	24±7
Total	20	0.98±0.14	1.16±0.40	23±10	42±22	1.5±0.8	3.0±2.1	17± 7	25±8

* $P<0.01$, ** $P<0.05$.

competitive protein-binding assay employing 1,25 (OH)2 D receptor from calf thymus (13) (Incstar Corporation, USA).

Ultraviolet irradiation

Twenty-two subjects (11 psoriatics + 11 controls) were exposed to whole-body UVB irradiation from a Waldman 8000 phototherapy unit (with F 75–85 W Sylvania lamps). The emission spectrum was maximum at 310 nm and total irradiance was 1,28 MW/cm^2. Patients and controls were irradiated three to five times a week, for a 3-week period giving a mean total cumulative dose of 1.40 J/cm^2.

Thirteen subjects (9 psoriatics, 4 controls) were irradiated according to usual PUVA regimen after oral adminitration of 8 MOP (0.6 mg/kg). The measurable energy output below 320 nm was very low. Total irradiance was 6.37 MW/cm^2, whole-body UVA irradiation was repeated three times a week and total cumulative doses were between 22 J/cm^2 and 58 J/cm^2 (mean dose = 41 J/ccm^2).

Statistical analysis

Statustical evaluations were made as appropriate by the Mann-Whitney test for comparison of patients and controls and by the Wilcoxon test for comparison of paired data in the same individuals.

RESULTS

The results are summarized in Table I. Before irradiation (Jo) the serum concentration of P was lower in psoriatic patients ($p<0.01$); Ca, PTH, 25 (OH) D, and 1,25 (OH)2 D levels did not differ statistically between psoriatics and controls, even when cutaneous lesions were disseminated. 24,25 (OH)2 D levels were lower in psoriatics than in normals, but the difference was not statistically significant.

After psoralen + UVA irradiation (J21) a complete clearance of psoriasis was achieved in 2 patients and 7 showed an excellent improvement. Serum P rose significantly to reach basal levels of controls, whereas no change was observed in controls. Serum calcium and PTH levels were similar before and after irradiation. PUVA did not induce any modification of 25 (OH) D and 24,25 (OH)2 D levels in controls and patients. An increase in serum 1,25 (OH)2 D concentration occurred in psoriatics, but again the difference was not significant.

After UVB irradiation (J21) in 2 patients, psoriatic lesions cleared completely, and a marked improvement was observed in the other 9 patients. In psoriatic patients and controls, no changes were found in calcium or PTH levels. Serum P levels rose (as under PUVA therapy) to reach basal of controls. In controls, P levels remained unchanged. An increase in 25 (OH) D and 24,25 (OH)2 D above upper normal contentrations was seen in controls and psoriatic patients. This increase was significant and similar in the two groups.

UVB irradiation did not results in any modifica-

tion of 1,25 (OH)2 D concentrations in controls, but significantly increased the levels in psoriatic patients.

DISCUSSION

This study is the first to demonstrated a previously unknown decrease in P levels in psoriatic patients, not accompained by any modification in Ca or PTH concentrations and returning to normal values under phototherapy. This increase in P levels could be due to the impact of UV-therapy on vitamin D metabolite levels.

Basal 1,25 (OH)2 D levels were similar in psoriatics and controls. Plasma levels of this active metabolite have recently been investigated in psoriatic patients by several investigators, but the results are conflicting. Morimoto et al. observed no significant difference in the mean basal levels of circulating 1,25 (OH)2 D in psoriatics and normal subjects (10), whereas Staberg et al. report that serum concentrations of 1,25 (OH)2 D in patients with disseminated psoriasis were reduced as compared with a control group (14). More recently Smith et al. (8) have studied 14 patients with moderate to extensive psoriasis; all of them had normal serum 1,25 (OH)2 D levels.

On the other hand, basal 25 (OH) D and 24,25 (OH)2 D levels were normal in all studies (8, 13). After UVB irradiation, as expected, we observed a marked increase in these two metabolites in psoriatics and controls. It is now well established that sunlight causes photolysis of 7 dehydrocholesterol to previtamin D, and increases serum 25 (OH) D levels. Only UVB is responsible for the cutaneous synthesis of vitamin D (15) and, in the present work, levels were unchanged during PUVA treatment. Similar results were noted by Mawer et al. (16), Juttman et al. (17) and Staberg et al. (18).

The most striking finding of our study was the increase in serum 1,25 (OH)2 D during UV therapy, occurring only in psoriatic patients and being significant only for UVB therapy. A similar increase during UVB has been reported by Staberg et al. (18) and by Mawer et al. (16). The mechanism of this effect is obscure and several hypotheses could be put forward: for instance phototherapy could induce the production of a skin mediator acting on kidney 1,25 (OH)2 D regulation; on the other hand a direct skin synthesis of 1,25 (OH)2 D could occur in psoriatic skin by UV activation of an epidermal alpha hydroxylase.

The main question to be addressed is whether the beneficial effect of phototherapy in psoriasis could be mediated through this effect on vitamin D3 metabolism. If this were the case most of the antipsoriatic effect of UVB might be due to a direct effect on irradiated skin, since non-exposed areas are not improved by phototherapy. An increase in epidermal 1,25 (OH)2 D could be responsible for the regulation of mitotic activity and differentiation of psoriatic keratinocytes. Further studies are required to study vitamin D3 metabolism in UVB-irradiated psoriatic skin and to determine the possible role of this effect in the clinical efficary of phototherapy.

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