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CLINICAL REPORT

Serum Levels of Parathyroid Hormone and Parathyroid-related Peptide in Psoriasis

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Psoriasis is a common skin disorder that may be triggered by hormonal disturbances, among other factors. Some studies have demonstrated an elevation of serum parathyroid hormone (PTH) levels in psoriasis and several other diseases of keratinization of unknown aetiology. PTH-related peptide (PTH-rp), on the other hand, is a potent inhibitor of epidermal cell growth factor and is not expressed in psoriatic skin. Serum levels of this peptide have not been reported in psoriasis. Immunoassay was used to measure serum PTH and PTH-rp in 22 patients with plaque-type psoriasis before and after treatment with mometasone furoate. Results were compared with a group of 20 healthy, non-psoriatic volunteers. Serum PTH levels were significantly elevated in the psoriatic group compared with the control group ($p=0.001$) and were significantly reduced after treatment ($p=0.01$). A correlation was found between pretreatment serum PTH levels and psoriasis area and severity scores (PASI) ($r=0.42$; $p=0.01$). In contrast, serum PTH-rp levels were not different between psoriatics and controls and were not affected by treatment. These findings indicate that serum PTH concentrations reflect disease activity in patients with psoriasis. ***Key words: psoriasis; parathyroid hormone; parathyroid hormone-related peptide; psoriatic activity.***

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Psoriasis is a skin disease affecting 1.4% of the population in Spain (1). There is strong evidence that T cells play a part in inducing psoriasis in genetically predisposed subjects. In addition, trigger factors such as infections, stress, drugs, injury and hormonal changes are needed to provoke its development. It is well known that psoriasis worsens in life stages accompanied by hormonal disturbance (puberty and menopause) and during pregnancy. In some cases, generalized pustular psoriasis has been associated with hypocalcaemia and hypoparathyroidism (2, 3). We have previously reported on three women with plaque-type psoriasis and correlated increases in severity and extent of the skin lesions with the development of a prolactinoma (4). Furthermore, we have demonstrated a mild but significant hyperprolactinaemia in psoriatic patients compared with a control group and correlated this with psoriasis area and severity scores (PASI) (unpublished observations).

Recently, we have reported the case of a woman with annular pustular psoriasis in which the exacerbations of her skin lesions were always accompanied by elevated serum levels of parathyroid hormone (PTH) and normal levels of calcium (5). (She was successfully treated with oral acitretin.) To our knowledge, there are no other reports of this association. The serum levels of PTH-related peptide (PTH-rp) were always within normal limits.

In 1992, Milstone et al. (6) described elevated serum PTH levels in 15 patients with disorders of keratinization other than psoriasis. These authors also reported a larger group of patients with ichthyosis and concluded that the elevated serum PTH levels are not due to vitamin D ingestion or treatment with retinoids. The significance of these findings remains to be established (7). As in our case, the elevation of PTH serum levels was not secondary to parathyroid adenoma. In 1991, Rico et al. (8), observed that treatment of plaque-type psoriasis with oral calcitriol resulted in elevation of PTH serum levels with normocalcaemia in only 10 Spanish patients, despite the fact that calcitriol classically increases calcium levels and decreases PTH serum levels (9). Other studies on the effects of topical calcitriol (9), calcipotriol (10) and phototherapy (11) on calcium metabolism in psoriatic patients did not show changes in serum PTH. There are no studies on PTH serum levels in psoriatic patients in comparison to healthy subjects.

On the other hand, PTH-rp, a peptide very similar to PTH and responsible for malignant hypercalcaemia, is localized in the granular layer of normal skin but is absent in psoriatic lesions. When cutaneous lesions improved with betamethasone or vitamin D3 analogues, a PTH-rp reactivity was found just above the granular layer (12). These findings substantiate a possible role of PTH-rp as a potent inhibitor of epidermal cell growth. In 1998, Sharpe et al. (13) demonstrated that keratinocytes produce abundant PTH-rp and that this is modulated by 1,25 $(OH)_2$ D3. Based on these findings, Holick et al. (14) have recently shown that a cream

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containing PTH is a safe and effective treatment for psoriasis. There are no reports on the serum levels of PTH-rp in psoriatic patients. In the study reported herein, we measured serum PTH and PTH-rp levels in patients with psoriasis and a healthy control group and studied their correlation with disease activity.

MATERIALS AND METHODS

Patients and healthy controls

Twenty-two patients with plaque-type psoriasis (11 women, 11 men; median age 45.6 years, range 18–83) were studied. At the time of enrolment, none of the patients had received either local or systemic treatment for at least 4 and 8 weeks, respectively. Serum PTH and serum PTH-rp levels were measured before and after a topical treatment with mometasone furoate once a day for 6 weeks. Disease severity was assessed in all the patients by the same dermatologist (M.S.R.).

Twenty healthy, age- and sex-matched volunteers were used as controls (10 women, 10 men; median age 43.8 years, range 18–81).

Exclusion criteria

Patients and controls were excluded from the study if there was evidence of renal, hepatic or thyroid dysfunction and if there was a history of bone lesions or alterations in calcium and phosphorus metabolism. The elderly institutionalized population was also excluded. All patients and controls under treatment with drugs that may contribute to changes in calcium homeostasis were excluded.

PTH and PTH-rp measurements

The serum PTH and PTH-rp concentrations were determined by automatic intact immunoassay (sandwich type) with detection by chemiluminescence. In each case we also measured serum and urine calcium and phosphorus and performed a complete blood analysis to exclude the diseases described above.

Statistical analysis

Statistical analysis was conducted using SPSS for Windows statistical software. All results were expressed as means $\pm$standard deviation (SD) and analysed using Student's t-test. A stepwise multiple regression procedure was followed; p values of <0.05 were regarded as significant.

RESULTS

The serum levels of PTH and PTH-rp in both psoriatic patients and controls are summarized in Table I. Serum PTH was significantly elevated in the psoriatic group compared with controls ($p=0.001$). PTH-rp levels were below detection level (<1.5 pmol/l) in both the psoriatic and control groups.

The response to treatment with mometasone furoate is shown in Table II; a clinical improvement was experienced by all patients (pretreatment PASI 6–42, mean 14.8; post-treatment 2.7–9.4, mean 4.4; $p<0.01$). The serum PTH levels were significantly reduced following treatment ($p=0.01$). Other blood analysis results, including calcium and phosphorus, were always within normal limits.

Table I. *Serum parathyroid hormone (PTH) and PTH-related peptide (PTH-rp) levels in psoriatic patients and healthy controls*

Parameter	Psoriatic patients	Controls
Number of patients	22	20
Serum PTH (pg/ml)	42.3 $\pm$ 1.8	23.4 $\pm$ 9.0*
Serum PTH-rp (pmol/l)	<1.5	<1.5

Serum PTH, normal range=10–65 pg/ml; serum PTH-rp, normal range=0–1.5 pmol/l.
*$p<0.001$.

There was a correlation between pretreatment serum PTH levels and PASI scores (r=0.42, $p=0.01$).

Because the serum PTH elevations observed in our study were always mild and without clinical manifestations of hypercalcaemia, a diagnosis of hyperparathyroidism (hyperplasia, adenoma or carcinoma) was excluded, although neither ultrasound nor computed tomography were performed.

DISCUSSION

PTH (1–34) is a peptide secreted by the parathyroid gland. The release is stimulated by the presence of hypocalcaemia. The main sites of action of PTH in controlling calcium and phosphorus levels are the bone and kidney; its main effect on calcium levels is through mobilization of bone calcium (15). On the other hand, PTH-rp (1–34) is a peptide very similar to PTH. The sequence homology between the 1–34 peptides of PTH and those of PTH-rp indicates that positions 3 and 6 contribute to important determinants of PTH-receptor binding and activation (16). PTH-rp expression occurs in a wide variety of tissues, including the skin. Among its actions, PTH-rp is essential for chondrogenesis in bone and ductal development in the breast and, more importantly, it is responsible for hypercalcaemia in tumours of squamous cell origin (17).

PTH-rp is strongly expressed in the epidermis. The PTH-1 receptor agonists PTH (1–34) and PTH-rp (1–34) inhibited *in vitro* keratinocyte proliferation, induced terminal differentiation and similar to

Table II. *Psoriasis area and severity index (PASI) scores and serum PTH and PTH-rp levels in psoriatic patients before and after treatment (n=22)*

Parameter	Before treatment	After treatment
PASI scores	14.8 $\pm$ 9.2*	4.5 $\pm$ 2.3
Serum PTH (pg/ml)	42.3 $\pm$ 15.8*	28.4 $\pm$ 11.8
Serum PTH-rp (pmol/l)	<1.5	<1.5

*$p<0.01$.

1,25-dihydroxyvitamin D3 it inhibited ^{3}H-thymidine incorporation into the epidermis *in vivo*.

In normal skin PTH-rp is exclusively located in the granular layer. Juhlin et al. (12) have observed that when psoriatic plaques were treated with 1,25 $(OH)_2$D3, PTH-rp expression was restored in psoriatic skin. And Sharpe et al. (13), have shown that keratinocytes produce abundant PTH-rp even though repeated studies failed to detect type 1 PTH/ PTH-rp receptor mRNA in human keratinocytes. These findings substantiate a possible role for PTH-rp as a potent inhibitor of epidermal cell growth. In our study we have not observed decreased levels of PTH-rp in psoriatic patients compared to controls, with no post-treatment modification. However, because PTH-rp action can be exerted in an autocrine and paracrine way, we cannot thereby exclude its influence and further studies should focus on that aspect.

Hyperparathyroidism is a metabolic state resulting from excess levels of PTH; primary hyperparathyroidism is the result of a hyperplasia, adenoma or carcinoma arising in the parathyroid glands; secondary hyperparathyroidism refers to over-activity of the parathyroids secondary to hypocalcaemia; and, finally, pseudohyperparathyroidism refers to a state clinically resembling hyperparathyroidism but which results from production of PTH-rp by a non-endocrine tumour (15). Primary hyperparathyroidism has been associated with several cutaneous diseases: cutaneous T-cell lymphoma (18), melanoma (19) and acquired ichthyosis (20). In each case, a parathyroid adenoma was detected, and hypercalcaemia and raised serum levels of PTH were persistent and then returned to normal after surgical removal of the parathyroid gland. Chronic renal failure is the most common cause of secondary hyperparathyroidism. This cause was excluded in our study. Hypovitaminosis D from lack of sun exposure, which is infrequently observed in our country, cannot be excluded as vitamin D levels were not measured. In pseudohyperparathroidism, laboratory tests revealed normal serum levels of PTH, hypercalcaemia and raised serum levels of PTH-rp. Squamous cell carcinoma of the lung and breast adenocarcinoma are the most common causes of this paraneoplastic syndrome.

In the present study, we detected raised serum PTH levels in psoriatic patients as compared with a control group. The serum levels of PTH in all of our patients were below 100 pg/ml and were significantly reduced after treatment, and there was a correlation between pretreatment serum PTH levels and PASI. In all the cases, serum levels of calcium and phosphorus were within normal limits and based on this finding and on the transitory nature of the serum PTH level elevation, we excluded the diagnosis of hyperparathyroidism. In a previous study (5), we discussed a woman with annular pustular psoriasis who consistently presented elevated serum levels of PTH when her psoriatic condition worsened. Based on our findings, we think that a mild elevation of PTH serum levels may reflect disease activity in psoriasis.

It is of interest that PTH may be an objective alternative to PASI in evaluating the psoriatic disease activity, a finding we have demonstrated with neopterin (21) and prolactin (unpublished observations). Thus, the serum levels of these molecules may be useful for evaluating the efficacy of a treatment.

In contrast to PTH, the serum levels of PTH-rp were always very low in both psoriatic patients and controls and were not affected by the treatment of psoriasis.

The increased serum levels of PTH in some patients with disorders of keratinization (ichthyosis and pityriasis rubra pilaris) described by Milstone et al. (6, 7), are consistent with our findings. In these studies, the authors postulated that a combination of different factors (low vitamin D levels, loss of calcium through the skin and therapy with retinoids) may stimulate secretion of PTH and concluded that the exact significance of this finding remains to be elucidated. In the study by Rico et al. (8), 10 patients with psoriasis presented raised serum PTH levels during treatment with oral calcitriol. Other studies have failed to detect an alteration in PTH serum levels in the course of different treatments (9–11). In the present study, we measured the serum PTH levels in a larger group of patients with psoriasis and in comparison to a control group. The cause of this elevation and decrease after treatment remains unclear. There may be a relationship to the inflammatory response present in psoriasis, but it cannot be excluded that a minimal loss of calcium throughout the skin stimulates PTH synthesis.

It would be of interest to correlate our findings with serum levels of calcium but it was not the aim of our study.

Because PTH accelerates bone turnover and remodelling, one of the most important consequences of the elevated serum PTH levels is the increased risk of osteoporosis. There is some evidence that psoriatic patients treated with retinoids for extended periods developed osteoporosis (22). In addition, reduced bone mineral density, the major risk factor for osteoporosis fracture, has been linked to palmoplantar pustular psoriasis (23) and also to arthropathic psoriasis (24). Other causes of secondary osteoporosis, with hyperprolactinaemia among them (25), may be associated with psoriasis. We have correlated the severity of skin lesions of three women with psoriasis with the development of a prolactinoma (4). Furthermore, significantly elevated serum prolactin levels were observed in another study in a group of psoriatic patients (unpublished observations). On the basis of all of the findings described above, we believe that knowledge of the bone mineral density in

patients with psoriasis is essential, especially in patients suffering the disease long term.

REFERENCES

1. Ferrándiz C, Bordas X, García-Patos V, Puig S, Pujol R, Smandía A. Prevalence of psoriasis in Spain (Epiderma Project: phase I). J Eur Acad Derm Venereol 2001; 15: 20–23.
2. Risum G. Psoriasis exacerbated by hypoparathyroidism with hypocalcemia. Br J Dermatol 1973; 89: 309–312.
3. Kawamura A, Tan Kinoshita M, Suzuki H. Generalized pustular psoriasis with hypoparathyroidism. Eur J Dermatol 1999; 9: 574–576.
4. Sánchez Regaña M, Umbert P. Psoriasis in association with prolactinoma: three cases. Br J Dermatol 2000; 143: 864–867.
5. Sánchez Regaña M, Ojeda R, Umbert P. Elevated serum parathyroid hormone levels in a patient with annular pustular psoriasis. J Eur Acad Dermatol Venereol (In press).
6. Milstone LM, Ellison AF, Insogna KL. Serum parathyroid hormone level is elevated in some patients with disorders of keratinisation. Arch Dermatol 1992; 128: 926–930.
7. Milstone LM, Bale SJ, Insogna KL. Secondary hyperparathyroidism in patients with ichthyosis is not caused by vitamin D deficiency or ingestion of retinoids. Arch Dermatol 1993; 129: 648.
8. Rico H, Robledo A, Crabranes JA, Lopez-Bran E, Hernandez ER. Behavior of calciotropic hormones in psoriasis. Miner Electrolyte Metab 1991; 17: 12–15.
9. Wishart JM. Calcitriol (1alpha, 25-dihydroxyvitamin D3) ointment in psoriasis, a safety tolerance and efficacy multicentre study. Dermatology 1994; 188: 135–139.
10. Gumowski-Sunek D, Rizzoli R, Saurat JH. Effects of topical calcipotriol on calcium metabolism in psoriatic patients: comparison to oral calcitriol. Dermatologica 1991; 183: 275–279.
11. Guilhou JJ, Colette C, Monpoint S, Lancrenon E, Guillot B, Monnier L. Vitamin D metabolism in psoriasis before and after phototherapy. Acta Derm Venereol 1990; 70: 351–354.
12. Juhlin L, Hagforsen E, Juhlin C. Parathyroid hormone related protein is localized in the granular layer of normal skin and in the dermal infiltrates of mycosis fungoides but is absent in psoriatic lesions. Acta Derm Venereol 1992; 72: 81–83.
13. Sharpe GR, Dillon JP, Durham B, Gallagher JA, Fraser WD. Human keratinocytes express transcripts for three isoforms of parathyroid hormone-related protein (PTHrP), but not for the parathyroid hormone/PTHrP receptor: effects of 1,25 (OH)2 vitamin D3. Br J Dermatol 1998; 138: 944–951.
14. Holick MF, Chimeh FN, Ray S. Topical PTH (1–34) is a novel, safe and effective treatment for psoriasis: a randomised self-controlled trial and an open trial. Br J Dermatol 2003; 149: 370–376.
15. Lang PG. The clinical spectrum of parathyroid disease. J Am Acad Dermatol 1981; 5: 733–744.
16. Cohen FE, Strewler GJ, Bradley MS, Carlquist M, Nilsson M, Ericsson M, et al. Analogues of parathyroid hormone modified at positions 3 and 6. J Biol Chem 1991; 266: 1997–2004.
17. Strewler GJ. The physiology of parathyroid hormone-related protein. N Engl J Med 2000; 342: 177–185.
18. Owen CM, Blewitt RW, Harrison PV, Yates VM. Two cases of primary hyperparathyroidism associated with primary cutaneous lymphoma. Br J Dermatol 2000; 142: 120–123.
19. Maerens-Tchokokam B, Bailly N, Collet E, Dalac S, Rat P, Lambert D. Mélanome et hyperparathyroïdie primaire. Ann Dermatol Venereol 1993; 120: 215–217.
20. London RD, Lebwohl M. Acquired ichthyosis and hyperparathyroidism. J Am Acad Dermatol 1989; 21: 801–802.
21. Sánchez Regaña M, Catasús M, Creus L, Umbert P. Serum neopterin as an objective marker of psoriatic disease activity. Acta Derm Venereol 2000; 80: 185–187.
22. DiGiovanna JJ, Sollitto RB, Abangan DL, Steinberg SM, Reynolds JC. Osteoporosis is a toxic effect of long-term etretinate therapy. Arch Dermatol 1995; 131: 1263–1267.
23. Nymann P, Kollerup G, Jemec GB, Grossmann E. Decrease bone mineral density in patients with pustulosis palmaris et plantaris. Dermatology 1996; 192: 307–311.
24. Millard TP, Antoniades L, Evans AV, Smith HR, Spector TD, Barker JN. Bone mineral density of patients with chronic plaque psoriasis. Clin Exp Dermatol 2001; 26: 446–448.
25. Fitzpatrick LA. Secondary causes of osteoporosis. Mayo Clin Proc 2002; 77: 453–468.