

CLINICAL REPORT

Women with Palmoplantar Pustulosis Have Disturbed Calcium Homeostasis and a High Prevalence of Diabetes Mellitus and Psychiatric Disorders: A Case-control Study

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Palmoplantar pustulosis is characterized by pustule formation in the acrosyngium. Nearly 50% of palmoplantar pustulosis sera produce immunofluorescence of the palmar papillary endothelium from healthy subjects, but also of the endothelium of normal parathyroid gland. With a case-control design the levels of calcium and parathyroid hormone in serum were measured in 60 women with palmoplantar pustulosis and 154 randomly selected population-based control women. One-third of the controls had been smokers, whereas 95% of the cases were or had been smokers. Mean age-adjusted serum calcium was increased in the patients compared with the controls (2.43 vs 2.36 mmol/l; $p < 0.0001$), whereas the parathyroid hormone concentration was suppressed (23.2 vs 31.1 ng/l; $p < 0.0001$). The plasma levels of parathyroid hormone-related protein were normal in patients but there was a strong expression of this protein in the acrosyngium both in palmoplantar pustulosis and control skin. As even a marginal elevation of serum calcium is associated with an increased risk for diabetes, cardiovascular disease and psychiatric disease, we analysed the risk for these disorders in palmoplantar pustulosis patients compared with that in the control group. Both diabetes mellitus and psychiatric disorders were associated with palmoplantar pustulosis with an odds ratio of 8.7 (95% CI 3.3–22.8) and 5.6 (95% CI 2.2–14.4), respectively. Palmoplantar pustulosis is a complex disease with an increased risk for several non-dermatological disorders. The role of the mildly increased serum calcium for the high risk for diabetes and depression deserves to be studied. *Key words: depression; eccrine sweat gland and ducts; gluten intolerance; parathyroid hormone-related protein; psoriasis; smoking.*

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Palmoplantar pustulosis (PPP) is a chronic skin disease that is considered to be a variant of psoriasis, although it has both clinical and genetic characteristics that differ from those of psoriasis vulgaris (1). PPP is characterized

by pustules, erythema and scaling of the palms and soles and both arthralgia and arthritis are common features. In a recent study, 18% of the patients also displayed psoriasis of the vulgaris type (1). Ninety percent of patients with PPP are women and 95% are smokers at the onset of the disease (2).

It has long been known that among PPP patients there is an increased prevalence of autoimmune thyroid disease, and we have recently also found a high prevalence of coeliac disease (2, 3). Diabetes type 2 also seems to be common in PPP (3) and, in addition, a small Danish study revealed a significant decrease in bone mineral density in patients with PPP (4). Thus, PPP is associated with co-morbidity, but it is not yet known whether the skin disorder and the co-existing diseases have a common pathogenetic background.

In recent studies we observed intense inflammation in the palmar papillary dermis in patients with PPP, and we also noted that the most intense inflammation was concentrated at the acrosyngium (the eccrine sweat duct in the epidermis and stratum corneum) (3, 5). Almost half of the PPP sera in our studies induced immunofluorescence (IF) of the papillary endothelium of palmar skin from healthy subjects. When the palmar skin was taken from a smoker, IF occurred both in the endothelium and the acrosyngium (6). Thus smoking might up-regulate the reactivity to PPP sera, possibly by inducing exposure of more antigens or by changing the surface properties of the acrosyngium. In screening studies with PPP sera on non-dermal tissues, IF of the endothelium was observed in several organs and particularly in the parathyroid glands (7).

In view of these findings, as well as a possible increased risk of osteoporosis (4), serum calcium, parathyroid hormone (PTH) and parathyroid hormone-related protein (PTHrP) levels were measured in women with PPP with the aim of determining whether these patients might have an abnormal calcium homeostasis and parathyroid function compared with matched controls. In addition, the expression of PTHrP in palmar skin and in particular in the eccrine sweat gland and duct was studied. PTHrP consists of 34 amino acids and is produced in the parathyroid gland. Its ectopic

production in tumour cells is a cause of the hypercalcaemia which may be present in malignant disease. Subsequently, data analysis of co-morbidity was carried out by determining the occurrence of diabetes, cardiovascular diseases and psychiatric symptoms in the patients with PPP and controls, as these disorders are known to be more prevalent in individuals with even mildly elevated serum calcium, as reported by Lundgren et al. (8).

MATERIALS AND METHODS

Patients

Sixty consecutive women with PPP (23–76 years old, mean age 55 years) all visiting the dermatology out-patient department at the University Hospital in Uppsala were included in the study which was undertaken in 2001. All patients answered a questionnaire concerning their medical history and medication, smoking habits, sick leave and disability pension. The severity of the PPP varied. Some had 50–100 pustules and erythema and scaling involving the whole plantar surface as well as the palms, whereas others had only a few pustules and mild erythema and scaling.

Four of the patients (smokers) had no lesions at the time of blood sampling, but had shown typical mild–moderate PPP at earlier examination. Eight patients had psoriasis, which was usually mild and localized to the extremities. Two patients were receiving systemic therapy for their PPP (one of them had acitretin 10 mg/day, the other had cyclosporine 1.5 mg/kg body weight per day). Topical treatment of the PPP consisted of emollients and intermittent corticosteroids (irregularly and during a few days when severe flare-ups occurred; no patients received long-term topical corticosteroids) and a few patients were treated intermittently with calcipotriol ointment. None of the patients used calcium and/or vitamin D supplementation. Information about concomitant disease is given in Table I.

Controls

To sufficiently cover the number and age distribution of the cases, control sera for comparison of PTH and calcium were obtained from 154 frequency age-matched women (at least one control per case in each 5-year age group) who were randomly selected from the population register and also participants in two different, previous population-based studies of women examined with dual energy X-ray absorptiometry (DXA) or mammography (9, 10). The former controls ($n=56$) included women with an age range between 23 and 84 years. The remainder of the controls were participants in the Uppsala mammography screening programme which is offered to all women older than 40 years and 80% of this female population participates. To serve as a control in the present study information on weight and height, smoking habits, presence of diabetes, cardiovascular diseases and psychiatric symptoms, and current and former medication had to be available in addition to the calcium, albumin and PTH values. None of the controls received treatment with systemic corticosteroids or vitamin D or calcium.

Blood samples

Total serum calcium, albumin and PTH were measured by routine methods. Calcium was measured by ortho-cresolphthalein dye binding. The coefficient of variation for calcium is 1–4%. Albumin-modified total serum calcium values were

Table I. Some data on the medical history and clinical and laboratory variables of the 60 patients with palmoplantar pustulosis (PPP)

Parameter	n (%)
History of	
Psoriasis vulgaris	8 (13)
Hyperthyroidism	3 (5)
Hypothyroidism	4 (7)
Coeliac disease/increased duodenal intraepithelial lymphocytes	11 (18)
Crohn's disease	0 (0)
Diabetes type 1	2 (3)
Diabetes type 2	15 (25)
Hypertension/cardiovascular disease	18 (30)
Manic-depressive disease	2 (3)
Schizophrenia	1 (2)
Depression	8 (13)
Disability pension	18 (30)
Smoking habits	
Never	3 (5)
Former	10 (17)
Current	47 (78)
Laboratory findings	
IgG antibodies to thyroglobulin and/or thyroperoxidase	12 (20)
IgA antibodies to gliadin (verified coeliac disease included)	11 (18)
IgA antibodies to tissue transglutaminase	4 (7)
Raised HbA1c ($\geq 5.3\%$)	17 (28)
PPP sera producing endothelial immunofluorescence in healthy palmar skin* ($n=59$)	26 (44)
Medication	
Beta-blockers, ACE inhibitors, calcium-channel blockers	18 (30)
Glibenclamide, metformin, repaglinide	8 (13)
Hormone replacement therapy	18 (30)
Antidepressants	9 (15)
Lithium carbonate	1 (2)

*See text.

calculated based on deviation of the serum albumin level from the normal means of women of the same age (11): (uncorrected calcium value + 0.019 (42 $\pm$ measured albumin value)). With this formula Lundgren et al. (9), in a population comprising 5000 women in Uppsala county, found a mean $\pm$ SD calcium value of 2.37 ± 0.09 mmol/l. Intact PTH was measured with the Allegro immunoradiometric sandwich assay (Nichols Institute, San Juan, CA, USA). The coefficient of variation was 6.8%. Values between 10 and 65 ng/l were considered to be within the normal range. The control sera had been analysed earlier than the PPP sera but there had been no change in the analytical procedures for serum calcium and PTH during this interval and the analyses were performed at the same accredited laboratory unit at the University Hospital, Uppsala. There is a continuous rigorous control both with internal and external systems of the analyses in this laboratory.

Serum TSH, thyroxine, HbA1c, and IgG antibodies to thyroglobulin and thyroperoxidase were assayed by routine methods. IgA and IgG antibodies to gliadin (IgA AGA and IgG AGA) were measured with an ELISA method as described previously in detail (12). Patients with IgA AGA ≥ 50 U/l and/or IgG AGA ≥ 12 U/l were considered to have elevated AGA values. In the majority of the patients, IgA antibodies to tissue transglutaminase were also measured using

an ELISA method, and values >6 U/l were regarded as elevated.

PPP sera were screened (dilution 1/100) with respect to their IF-producing effect on endothelium from normal palmar skin from healthy subjects as previously reported (6), and also on sections from normal parathyroid glands (7).

The results indicated increased calcium but decreased PTH levels. PTHrP in plasma was thus also measured and the expression of PTHrP in palmar skin was studied by immunohistochemistry.

PTHrP in plasma from 24 consecutive patients with PPP (the majority were new patients not included in the first group of 60 cases) was measured with a radioimmunoassay as previously reported by Bucht et al. (13). In brief, a synthetic mid-molecular fragment of PTHrP 63–77 was used for antibody production in rabbits, as reference standard and for radio-iodination. The samples were extracted by Sep-PAK C18 cartridge (Waters, Milford, MA, USA). After extraction the detection limit of the assay, based on 2 SD, below maximal binding, was 0.8 ng/l. The intra-assay variation was $<9\%$, and the inter-assay variation was $<15\%$ at all concentrations. Values ≥ 2.9 ng/l are considered elevated.

Skin biopsies – PTHrP expression in palmar skin

Punch biopsy specimens (3 mm in diameter) were taken from normal palmar hypothenar skin (of seven women and one man, non-smokers; and of seven women and one man, all of whom had smoked for many years). Twenty-four specimens from involved palmar PPP skin and eight from non-involved palmar skin in patients with PPP were also obtained. Cryostat sections 6 μ m thick were used. Endogenous peroxidase was blocked with 0.5% H_2O_2 in phosphate-buffered saline for 15 min. The sections were then allowed to react with normal rabbit serum (dilution 1/10) for 10 min to reduce non-specific staining. The polyclonal goat PTHrP (N-19) antibody, dilution 1/50, was incubated for 20 h at 4°C (PTH-rP (N-19): sc-9680, Santa Cruz Biotechnology, Santa Cruz, CA, USA). Biotinylated anti-goat IgG (Vector BA 5000, Vector Lab Inc., Burlingame, CA, USA) diluted 1/200 was used as secondary antibody. Finally the sections were incubated with Vectastain ABC kit. The peroxidase reaction was developed with 3-amino-9-ethylcarbazole. The sections were counter-stained with Mayer's haematoxylin. The staining pattern and staining intensity (0, +, ++, +++) of eccrine sweat glands and ducts and epidermis and the contents of the pustules were evaluated on coded sections by the same observer. Pre-adsorption of the polyclonal PTHrP antibody was carried out at 37°C for 6 h (antibody dilution 1/50 and concentration of the peptide (sc-9680 P) 10 μ g/ml). The pre-adsorbed antibody produced no staining.

Data analysis

The main characteristics of the two variables calcium and PTH are shown by box-and-whisker plots. Both serum calcium, albumin-adjusted calcium and PTH displayed a normal distribution ($p > 0.05$ estimated by a chi-square test, MedCalc®, version 4.3, Belgium) and they were thus analysed in their original form. As gluten intolerance has been reported to influence calcium homeostasis (14) data are presented both for the whole group of patients with PPP and for patients with PPP with or without gluten intolerance.

Smoking status was defined as never, former or current smoking at the time of blood collection. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). Both BMI and age were considered as continuous variables. Separate marker variables were used for each of the

disease groups diabetes mellitus, cardiovascular diseases and psychiatric disorders. The age-adjusted mean total serum calcium and PTH values were calculated with the GLM (general linear models) procedure of the SAS software (SAS Institute, NC, USA) for cases and controls. Additionally, we performed a multivariate analysis including (besides serum calcium and PTH) the potential co-variables age, cigarette smoking (never, former, current), BMI, presence of diabetes mellitus type 1 and type 2, cardiovascular disease and psychiatric disorders. Only results from the age-adjusted model are presented, as the differences between the two models were small. We also used odds ratios (OR) and 95% confidence intervals (CI) computed by unconditional logistic regression as measures of association between PPP and, respectively, smoking status, diabetes mellitus, psychiatric disorders, as well as cardiovascular diseases and BMI. Only the age-adjusted estimates are presented because none of the other co-variables (depending on the examined exposure; smoking, BMI, cardiovascular disease, diabetes mellitus, psychiatric disorders, serum calcium and PTH) influenced the odds ratios more than marginally and they can all also be regarded as either intermediates or not causally associated with the other exposure variables, and therefore these variables should not be considered together in a multivariate model.

The medical ethics committee of Uppsala University approved the study and the patients had given their informed consent.

RESULTS

Clinical characteristics

Some anamnestic, clinical and laboratory data of the patients with PPP are given in Table I. Only one of the 11 patients with gluten intolerance had a previously known coeliac disease; the other 10 were identified after screening for antibodies against gliadin/tissue transglutaminase, which was performed in all patients with PPP. Those who were found to have antibodies were further examined with gastroscopy with duodenal biopsies (unpublished data).

Two patients had had diabetes type 1 since adolescence; one of them also had a previously diagnosed coeliac disease and the other had schizophrenia in addition to severe PPP. Fifteen patients had diabetes type 2 – in all of them with a later onset than the debut of PPP. In seven, a dietary regimen was considered sufficient; eight received oral antidiabetics (Table I).

Two patients had manic-depressive disease. Nine other patients had long-term depressive symptoms including depression, anxiety or insomnia, and one had schizophrenia.

None of the patients had a history of renal disease.

Total serum calcium

As shown in Fig. 1A (crude results) and Table II (age-adjusted results) the mean value for albumin-modified serum calcium in the patients with PPP was highly significantly increased in comparison with that in the controls. The values for unmodified calcium were similar to the modified values (Table II). The mean

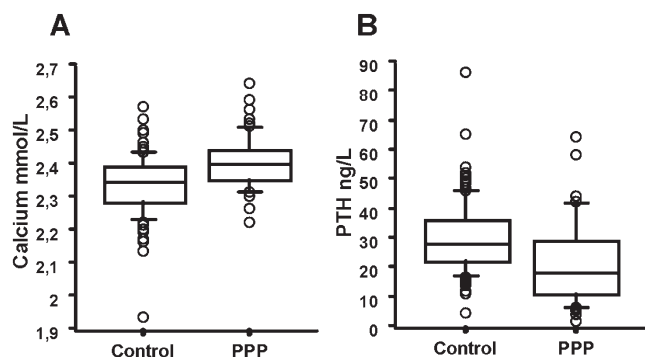


Fig. 1. Serum calcium is elevated (A) and parathyroid hormone decreased (B) in patients with palmoplantar pustulosis (PPP) compared with controls. Box and whisker plots with the 10th, 25th, 50th, 75th, 90th percentiles for calcium (albumin-modified), mmol/L, and parathyroid hormone (PTH), ng/L.

albumin value in the PPP and the control group were the same (43 ± 3 and 43 ± 2 g/l). The difference in calcium values was only minimally changed after further adjustment for smoking status or other conceivable co-variables (data not shown). Furthermore, we observed a three times higher relative risk of PPP with each standard deviation increase in albumin-modified serum calcium (multivariate OR 2.76; 95% CI 1.73–4.39).

Patients with PPP with gluten intolerance had significantly lower unmodified and modified calcium than the patients with PPP with no evidence of gluten intolerance (calcium uncorrected 2.35 ± 0.11 vs 2.44 ± 0.08 mmol/L, $p=0.0005$, unpaired t-test) and albumin-modified calcium 2.36 ± 0.08 vs 2.43 ± 0.07 mmol/L ($p=0.0062$).

It was not possible to analyse the influence of calcipotriol ointment on the calcium values, as few patients used it regularly.

Serum parathyroid hormone

The mean PTH level in the patients with PPP was significantly decreased (Fig. 1B, crude results; Table II, age-adjusted values). The subgroup with gluten intolerance had a similar mean PTH to the other patients with PPP. The risk of being a PPP patient was halved for each standard deviation increase in serum PTH, independent of serum calcium, smoking status, BMI

Table II. Mean age-adjusted* serum calcium (crude and albumin-modified) and parathyroid hormone (PTH) levels with 95% confidence intervals in palmoplantar pustulosis (PPP) patients and controls

	PPP patients $n=60$	Controls $n=154$	p values
Calcium (mmol/L)	2.43 (2.41–2.45)	2.36 (2.34–2.37)	<0.0001
albumin modified	2.42 (2.40–2.45)	2.35 (2.33–2.36)	<0.0001
PTH (ng/L)	23.2 (19.8–26.6)	31.4 (29.3–33.4)	<0.0001

*Age as a continuous variable.

and co-morbidity (age-adjusted OR 0.45; 95% CI 0.30–0.67). Surprisingly, we found no significant correlation ($r=-0.04$, $p=0.53$) between serum calcium and PTH, which is an additional indicator of a disturbed calcium homeostasis. Further, there was no relation between number of pustules and PTH levels or calcium values. The mean PTH value in 14 PPP sera, which produced moderate or strong IF of the palmar endothelium, showed a tendency to be lower than the mean value for the 44 sera giving no or only weak IF (PTH 17.9 ± 11.2 and 27.3 ± 16.9 ng/L respectively, $p=0.05$; Mann-Whitney). The mean calcium value was the same in the sera inducing and not inducing IF.

Parathyroid hormone-related protein in plasma

The concentration of PTHrP did not exceed the upper reference level of 2.9 ng/L in any of the 24 samples from the patients with PPP. The mean value was 1.4 ± 0.5 ng/L (95% CI 1.2–1.6). The mean albumin-modified serum calcium value in these samples was 2.53 ± 0.09 mmol/L. There was no correlation between PTHrP, calcium and PTH values.

PTHrP expression in palmar skin

In all specimens there was strong staining of the eccrine sweat ducts and this was most intense in the ducts in the papillary dermis and in the acrosyringium (Fig. 2A, B). The coils displayed weaker staining than the acrosyringium (Fig. 2C). This pattern was observed both in healthy subjects (smokers as well as non-smokers) and in non-involved and involved PPP skin. The site of the strongest staining corresponds to the final target for the inflammation in PPP, which is the acrosyringium. In specimens with a pustule, the staining of the floor of the pustule and also of some unidentified cells in the vicinity of the pustule was stronger than in any other site, whereas the pustule contents were unstained (Fig. 2D, E). Epidermis was also stained, but more weakly than the eccrine sweat ducts. The epidermal staining was most pronounced in the basal layer. In addition, the papillary endothelium was stained (staining of human dermal endothelial cells was verified on cultured human dermal endothelial cells with IF, results not shown).

PPP, smoking habits and co-morbidity

All but three of the patients with PPP were or had been smokers (95%), whereas only one-third of the controls had ever smoked. Current smoking, compared with never smoking, was associated with a 70 times higher age-adjusted relative risk of having PPP (OR 74.2; 95% CI 20.9–264.2, Table III). Neither in patients nor in controls was there any difference in the mean PTH or calcium value between never or former smokers and current smokers.

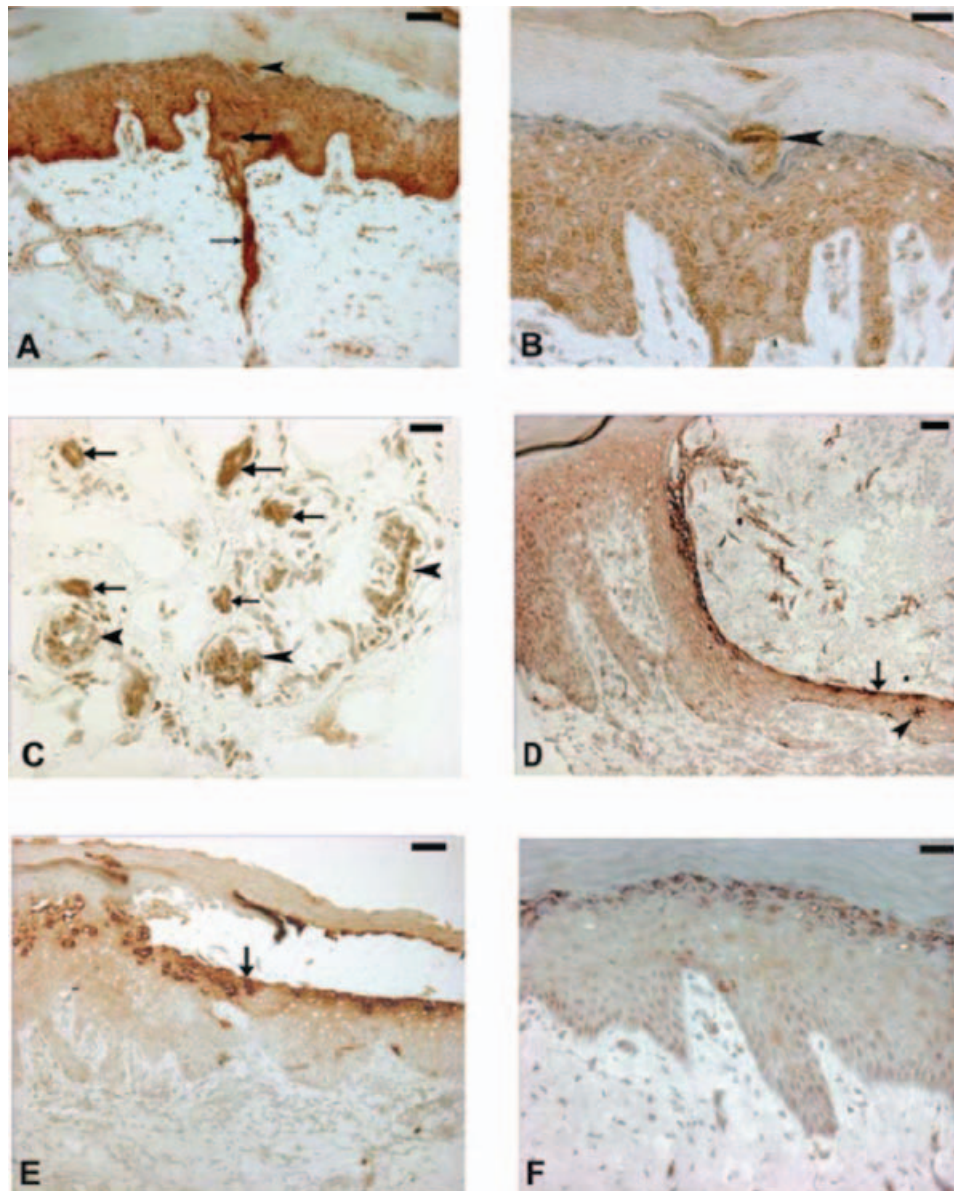


Fig. 2. Expression of parathyroid hormone-related protein (PTHrP) in palmar skin. (A) Strong expression of PTHrP in eccrine duct in papillary dermis (thin arrow), epidermis (thick arrow) and stratum corneum (arrowhead), specimen from non-involved PPP skin. (B) Strong expression of PTHrP in the acrosyringium in the lower part of stratum corneum (arrowhead), specimen from non-involved PPP skin. (C) The eccrine ducts in palmar reticular skin (arrows) are also strongly stained whereas the coil displays a weaker PTHrP expression (arrowheads), specimen from involved PPP skin. (D) Specimen with pustule in the outer part of the acrosyringium and localized to the lowest part of stratum corneum. Note intense staining of the inner lining of the pustule (arrow) and also of some unidentified cells (arrowhead). (E) Specimen with pustule from another patient. Note strong staining of (unidentified) cells in the lower wall of the pustule and also in epidermis (left side of the pustule). (F) Negative control palmar skin (from a healthy person) with pre-adsorbed PTHrP antibody. Scale bar: 50 μ m in A, D and E; 30 μ m in B, C and F.

As already shown in Table I, many of the patients with PPP also had non-dermatological disorders. Diabetes mellitus of any type was associated with an age-adjusted OR of 8.7 (95% CI 3.3–22.8) for PPP (Table III). Fifteen patients had diabetes type 2 and two had diabetes type 1, compared with only seven control individuals with diabetes type 2 and none with diabetes type 1. Exclusion of the two patients with diabetes type 1 resulted only in marginally lower OR. Patients with diabetes type 2 had significantly lower PTH than those

without diabetes (18.1 ± 16.8 vs 24.5 ± 13.0 ng/l, $p=0.05$). Mean age-adjusted BMI in patients with PPP (26.4 kg/m²; 95% CI 25.4–27.5) did not differ from that of the controls (25.8 kg/m²; 95% CI 24.9–26.3). There was also no significant difference in mean BMI values in patients with PPP with and without diabetes mellitus ($p=0.25$).

There was also a substantially increased risk of PPP with psychiatric disorders, mainly depression and anxiety (Table III). The age-adjusted estimate (OR

5.58; 95% CI 2.16–14.40) was attenuated (OR 3.35; 95% CI 1.08–10.30) after further adjustment for smoking status, a variable which in this analysis can be considered as an intermediate. Cardiovascular diseases were no more common among the patients with PPP than among the controls (age-adjusted OR 1.32; 95% CI 0.62–2.79).

DISCUSSION

The results of this study indicate that PPP is associated with a modest but highly significant increase in serum calcium and a significant decrease in the PTH levels in comparison with healthy population-based controls. This finding, which may indicate an abnormal calcium homeostasis, was further strengthened when the subgroup of gluten-intolerant patients with PPP was excluded as they had similar calcium values to the control group and significantly lower mean calcium than the other patients with PPP. Gluten intolerance seems to be more common among patients with PPP (18%; Table I) than in the general population. Thus, in Sweden the prevalence of silent coeliac disease in recent years has been estimated to be less than 1% (14). However, it is not possible in this study to compare the prevalence in the cases and the controls as no screening has been performed in the controls. As coeliac disease has been reported to have a negative influence on intestinal calcium absorption and the calcium homeostasis, this finding seems to be in agreement with previous reports (15).

We have found no studies of any variant of psoriasis in which calcium and PTH levels have been compared with those of healthy subjects. Serum calcium has been measured in clinical trials where topical vitamin D analogues have been used as treatment for psoriasis vulgaris. It is not possible to compare the results of these studies with our results in patients with PPP as no information was given in these studies as to how the calcium values were corrected. Our results indicate that

an abnormal calcium homeostasis can be added to the list of anamnestic, clinical and genetic characteristics of PPP.

The extracellular calcium concentration is normally maintained within a narrow range by the calciotropic hormones PTH and $1,25(\text{OH})_2\text{D}_3$. Alterations in the systemic levels of these hormones or of PTHrP are the major causes of an aberrant extracellular fluid calcium concentration. The most common causes of hypercalcaemia are primary hyperparathyroidism, which was not observed in the present investigation, and malignancy (16). The association between elevated serum calcium and malignancy has been found to be partly attributable to increased levels of circulating PTHrP produced by the tumour cells. Although no increase in the plasma concentrations of PTHrP was found in this study, a rise in calcium levels in PPP due to PTHrP cannot be excluded, as PTHrP is an autocrine-paracrine hormone exerting its effects locally (17) and serum levels might not adequately reflect the local production.

Using immunohistochemistry and in situ hybridisation, keratinocytes (18–20) and endothelial cells (21, 22) have been found to express PTHrP, further cultured endothelial cells have been reported to produce PTHrP (23). In our study we observed that both normal and PPP acrosyngia displayed intense PTHrP staining which was more pronounced than that of the epidermis and endothelium. Furthermore, the floor of the pustule was maximally stained. As palmar and plantar skin have about 600 eccrine glands/cm², compared with 60/cm² in the skin of the back, this might mean that the acrosyngia in palmar-plantar skin could be more important producers of PTHrP than hairy skin.

The inflammation in PPP is exceptionally intense, with – in addition to large numbers of CD4+ T lymphocytes – dense infiltrates of mast cells, many of which are degranulated, and large numbers of neutrophils and eosinophils migrating outwards in the acrosyngium (2, 5). Mast cells contain a number of inflammatory promoters and, in particular TNF- α ,

Table III. Age-adjusted odds ratios with 95% confidence intervals (OR; 95% CIs) for smoking status, diabetes mellitus and psychiatric disorders in patients with pustulosis palmoplantaris (n=60) compared with healthy controls (n=154)

Parameter	Cases	Controls	OR* (95% CI)	p value
Smoking status				
Never smoker	3	103	1.0 (reference)	–
Ever smoker	57	51	36.5 (10.8–123.8)	<0.0001
Current smoker	47	20	74.2 (20.9–264.2)	<0.0001
Former smoker	10	31	10.6 (2.7–41.4)	0.0007
Diabetes mellitus				
No	43	147	1.0 (reference)	–
Yes	17	7	8.7 (3.3–22.8)	<0.0001
Psychiatric disorders				
No	46	146	1.0 (reference)	–
Yes	14	8	5.6 (2.2–14.4)	0.0004

*Age as a continuous variable.

which has been shown to enhance PTHrP- induced hypercalcaemia (24). However, the fact that three of four patients without pustules at the time of blood sampling had calcium levels of 2.60–2.72 mmol/l may indicate other causative factors of elevated serum calcium levels than palmo-plantar inflammation. As our recent findings indicate that 47% of PPP sera also display an endothelial immune reaction in other tissues, in particular in the parathyroid gland (7), there might also be non-dermal mechanisms underlying the increase in serum calcium.

Another inflammatory disease associated with raised serum calcium is sarcoidosis. The probable mechanism causing the raised serum calcium in this disease is overproduction of the active form of vitamin D ($1,25(\text{OH})_2 \text{D}_3$) at sites of granulomatous reactions (25). Admittedly the intense inflammation in PPP has little similarity to sarcoidosis, but this does not rule out the possibility that there might be a disturbance in the function or production of vitamin D in PPP. As no patients used oral calcium and vitamin D supplementation and few used calcipotriol, and only irregularly, for their PPP such factors cannot explain the raised calcium values.

An additional possible mechanism underlying the altered calcium homeostasis in PPP might be an autoimmune reaction in the parathyroid gland. When PPP sera were screened for IF produced on sections from normal parathyroid gland, strong reactivity in the parathyroid gland endothelium (as well as in some hitherto unidentified parathyroid cells) was produced by sera that were also positive in normal palmar papillary endothelium (7).

Interestingly, the PTH level tended to be significantly lower in patients with sera that produced strong IF in the palmar endothelium. It might thus be speculated whether there is a link between an antigen in the palmar and parathyroid gland endothelium. Nothing is known about any inflammatory process in the parathyroid gland in PPP or whether there might be autoantibodies to any component of parathyroid tissue.

It has been shown previously that even marginally elevated calcium levels are associated with an increased risk for diabetes type 2, cardiovascular diseases and psychiatric disorders (7, 26). We now report for the first time a highly increased risk of diabetes type 2 in patients with PPP. An increased predisposition to diabetes in PPP was discussed by Uehara in 1983 (27), but no control group was included. In our study a number of known pathogenetic factors, e.g. serum calcium, smoking status and obesity, which may predispose to diabetes type 2 have been taken into consideration and these variables could not explain the excess risk of diabetes in these patients. Further investigation is needed to identify common pathogenetic mechanisms of PPP and diabetes type 2. In any event, knowledge of this increased risk is important in the clinical work with PPP.

There was also a markedly increased prevalence of various psychiatric symptoms, most commonly depression, among the patients with PPP. Whether this is a consequence of the sometimes disabling skin disease or if it to some extent also might be linked to the abnormal calcium homeostasis is not known. It is noteworthy, however, that depressive symptoms have been reported to be significantly more common even in patients with mild primary hyperparathyroidism compared with healthy subjects (7, 28, 29). Nevertheless, the increased risk of PPP in this study with psychiatric disorders was only marginally influenced after adjustment for serum PTH and calcium.

Our study has some possible limitations. Serum calcium and PTH among controls and cases were measured at different time periods, but the same laboratory setting with continuous internal and external control systems was used for these routine analyses. Recall bias is always a major concern in case-control studies but is not likely to explain the substantial differences observed in prevalence of diabetes mellitus and psychiatric disorders and the possible non-differential misclassification by self-report of these diseases for cases and controls only conservatively biases our estimates. The controls were randomly selected from the population registers of the same county as the cases. Nevertheless, selection bias might be a concern. Although the controls had participated in studies with a population-based setting and a high participation rate, not all eligible controls had participated. As a group, non-participants in any clinical study are less healthy (30), but the differences are of minor order compared with our observed differences.

Further studies are required to understand the mechanisms behind and the relevance of the abnormal calcium homeostasis in PPP. The possible role of vitamin D as a contributory factor needs to be investigated, as well as the role of smoking as a precipitating factor for both the skin lesions and the systemic disease associated with PPP. The results further confirm our recent observations indicating that PPP is a complex systemic disease.

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