Obesity in psoriasis: leptin and resistin as mediators of cutaneous inflammation

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Summary

Background Obesity is a significant risk factor for psoriasis and body mass index (BMI) correlates with disease severity.
Objectives To investigate the relationship between obesity and psoriasis, focusing on the role of adipokines such as leptin and resistin.
Patients/methods Patients with psoriasis ($n = 30$) were recruited and their BMI, waist circumference and disease severity [Psoriasis Area and Severity Index (PASI)] were recorded. Fasting serum samples were obtained on enrolment and after a course of ultraviolet (UV) B treatment. Age-, sex- and BMI-matched healthy controls were also recruited.
Results On enrolment, serum leptin and soluble leptin receptor levels were not raised compared with the controls. However, resistin, interleukin (IL)-1β, IL-6, and chemokines CCL2, CXCL8 and CXCL9 were all significantly elevated in the patient group and serum resistin correlated with disease severity ($r = 0{\cdot}372$, $P = 0{\cdot}043$). Improvement after UVB treatment was accompanied by decreased serum CXCL8. *In vitro*, both leptin and resistin could induce CXCL8 and tumour necrosis factor-α production by blood monocytes, and leptin could additionally induce IL-1β and IL-1 receptor antagonist production. Leptin also dose dependently increased secretion of the growth factor amphiregulin by *ex vivo*-cultured lesional psoriasis skin.
Conclusions These data support the view that leptin and resistin may be involved in the pathogenesis of psoriasis in overweight individuals, possibly by augmenting the cytokine expression by the inflammatory infiltrate.

Psoriasis is a common inflammatory T-cell-mediated skin disorder, affecting 2–3% of the population,[1] in which the most prominent microscopic abnormality is hyperproliferation and altered differentiation of keratinocytes. While the disease has several distinct yet overlapping phenotypes,[2] by far the most common is chronic plaque psoriasis, which affects about 90% of patients. The aetiology of psoriasis is unknown but the disease is believed to have an autoimmune basis and a strong genetic component.[3] Several HLA alleles are associated with psoriasis, in particular HLA-Cw*0602, which is probably the major genetic determinant of the disease.[4] Despite strong hereditary factors exogenous stimuli such as infection, trauma and stress play an important role in disease manifestation.[5–8]

Obesity has long been associated with and considered detrimental for psoriasis. Henseler and Christophers[9] reported in 1995 that a substantial proportion of psoriasis patients hospitalized for treatment were obese. Patients weighing more than their ideal bodyweight also tend to have worse psoriasis in terms of the proportion of involved skin,[10] and the extent of their psoriasis lesions correlates with body mass index (BMI).[11] In a recent case–control study, Naldi *et al.*[8] found that a moderately increased BMI (26–29) was associated with a slightly increased risk of psoriasis, and clinical obesity (BMI > 29) more than doubled the risk of psoriasis. Further support for a link between these two conditions comes from the observation that obesity is more prevalent in patients with

severe as opposed to mild psoriasis[12] and an increased prevalence of metabolic syndrome in psoriasis patients has recently been reported.[13] Reports also exist of a favourable outcome after 4 weeks on a low-energy (855 kcal daily) diet[14] or resolution of psoriasis after gastric bypass surgery,[15] but such treatment modalities require closer examination and controlled trials. Thus, a causal relationship between obesity and psoriasis has not been fully established as obesity may occur as a consequence of developing psoriasis,[16] although the obese state may well exacerbate the severity of the disease or derive from a common underlying pathophysiology.[17]

White adipose tissue is composed of mature triglyceride-filled adipocytes, along with preadipocytes, endothelial cells, fibroblasts and leucocytes.[18] Expansion of adipose tissue during weight gain leads to the recruitment of macrophages into the adipose tissue[19] and this is probably mediated by adipocyte-derived chemokines such as CCL2 (monocyte chemoattractant protein-1).[20] Macrophages are the chief source of adipose tissue-derived tumour necrosis factor (TNF)-α[21] and are an important component of the nonadipocyte fraction of this tissue, which is also the main source of interleukin (IL)-6 and CXCL8.[22] These cytokines are abundant in psoriasis skin,[23] their levels in suction blister fluids of involved psoriasis skin correlate with disease severity[24] and both have established roles in psoriasis pathogenesis.[25]

Leptin is one of the main adipose-derived cytokines and has been investigated primarily for its role in controlling energy homeostasis by regulating appetite.[26,27] Leptin is also important for cell-mediated immunity and CD4+ T cells are hyporeactive in leptin-deficient mice.[28] Congenital leptin deficiency in humans results in lower frequency of blood CD4+ T cells as well as impaired T-cell proliferation and production of cytokines such as interferon (IFN)-γ,[29] and this hyporesponsiveness can be restored by exogenous leptin.[30] Patients suffering from common variable immunodeficiency have lower serum leptin levels than healthy individuals; however, administration of exogenous leptin could not reverse this deficiency.[31,32] Leptin appears to contribute to T helper (Th) 1 and suppresses Th2 immune responses. *In vitro*, leptin acts on naive T cells, increasing their IL-2 secretion and proliferation, as well as increasing IFN-γ production by memory T cells.[28] Leptin is required for the induction and progression of autoimmune encephalomyelitis in mice,[33] and it was recently shown that leptin inhibits the proliferation of CD4+FoxP3+ regulatory T cells.[34] Thus, elevated leptin levels may lead to enhanced Th1 type immune responses due to diminished regulatory T cell activity. Leptin also increases macrophage activity and their production of IL-1β, IL-6, TNF-α and IL-12.[35,36] Additionally, leptin can alter the morphology of monocyte-derived dendritic cells and increase their production of IL-1β, IL-6, TNF-α and IL-12p70, and priming of naive T cells by leptin-treated dendritic cells resulted in increased Th1 polarization.[37]

Resistin was originally discovered in mouse adipocytes and assigned a key role in the induction of murine insulin resistance.[38] Human adipocytes however do not produce resistin,[39] but resistin is expressed by cells in the stromal compartment of adipose tissue,[21] particularly macrophages.[19] Resistin mRNA is increased in the subcutaneous adipose tissue of obese compared with lean individuals,[40] but there is only a very weak correlation between BMI and serum resistin levels[41] although the proportion of mononuclear leucocytes within adipose tissue correlates well with BMI.[19] Resistin is also expressed by peripheral blood mononuclear cells (PBMC),[42,43] particularly by monocytes[44,45] and is upregulated during their differentiation into macrophages.[44,45] Lipopolysaccharides (LPS) and the inflammatory cytokines IL-1β, IL-6 and TNF-α have all been demonstrated to induce resistin mRNA expression by human PBMCs,[42] and elevated levels of resistin can be induced in the blood of healthy individuals in response to exogenous LPS.[45] Resistin dose dependently stimulates its own production (autocrine effect) and stimulates TNF-α, IL-1β, IL-6 and CXCL8 in PBMCs[43] as well as IL-12 in macrophages.[46] The autocrine effect of resistin and its ability to induce other proinflammatory cytokines that in turn can stimulate more resistin synthesis, suggests a vicious cycle type pathogenic role for resistin.

Although numerous clinical studies have suggested that obesity has an adverse effect on psoriasis,[8–13,16] information is lacking about potential pathophysiological pathways that may be responsible for this association. Here we examine serum adipokine and cytokine levels of patients before and after a course of narrowband 310 nm ultraviolet B (NB-UVB) treatment and compare with BMI-matched nonpsoriatic controls. Further, we investigate how either local or systemic increases in leptin or resistin might trigger or exacerbate psoriasis.

Materials and methods

Recruitment and clinical evaluation of patients and controls

Thirty patients with chronic plaque psoriasis and 29 age-, sex- and BMI-matched controls were recruited to the study. None of the patients were on systemic treatment. On recruitment, weight, height and waist circumference of all individuals in the study were recorded. Disease severity was assessed before and after treatment with the Psoriasis Area and Severity Index (PASI)[47] by the same physician (J.T.S.). All patients completed a questionnaire involving past treatment (medication or visits to the Blue Lagoon) and whether they had noticed a change in their condition after losing or gaining weight. Patients underwent treatment in the Blue Lagoon Dermatological Clinic, which involves regular bathing in the lagoon water combined with NB-UVB irradiation. On completion of treatment, the PASI score, weight and waist measurements were again recorded and a second fasting serum sample taken. All participants gave their informed consent before enrolment. The National Bioethics Committee of Iceland and the Icelandic Data Protection Authority approved the study. A further 16 patients with chronic plaque psoriasis and three healthy control volunteers were recruited for skin biopsy for *ex vivo* skin

culture and immunohistochemistry. Informed consent was obtained from all subjects, under protocols approved by the Institutional Review Board of the University of Michigan.

Measurement of cytokines, adipokines and leptin receptor in serum

Blood was collected from patients and controls after an overnight fast. Serum was isolated after clotting and stored in aliquots at −70 °C until used. Leptin, soluble leptin receptor, adiponectin, resistin, CXCL8 and IL-22 were determined by enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Oxford, U.K.). The cytokines IL-1β, IL-6, IL-10, IL-12p70, CCL2 and CXCL9 were measured using a microsphere-based multiplexed immunoassay (Bio-Plex; Bio-Rad, Sundbyberg, Sweden).

Monocyte cytokine production in stimulated whole blood

Sodium heparin-treated whole blood was collected from healthy volunteers and incubated for 16 h with recombinant human resistin (Santa Cruz Biotechnology, Heidelberg, Germany) or recombinant human leptin (Santa Cruz Biotechnology) in the presence of 10 μg mL^{-1} brefeldin A (Sigma-Aldrich, St. Louis, MO, USA). Cells were first stained for surface CD14 expression (PerCP-CD14, clone MϕP9; BD Biosciences, San Jose, CA, USA), then erythrocytes were lysed (FACS lysing solution, BD Biosciences), lymphocytes fixed and permeabilized (FACS permeabilizing solution; BD Biosciences), and stained intracellularly with fluorescein-isothyocyanate-, phycoerythrin- or allophycocyanin-labelled monoclonal antibodies against IL-1 receptor antagonist (IL-1ra; clone AS17), IL-1β (AS10), CXCL8 (AS14) and TNF-α (6401.1111; BD Biosciences). After washing, cells were analysed using a FACScalibur flow cytometer and Cell Quest Pro software (BD Biosciences).

Ex vivo skin culture

Three psoriatic and three control donors each gave eight 2-mm punch skin biopsies. The biopsies were treated with different concentrations of recombinant leptin (R&D Systems, Minneapolis, MN, U.S.A.) for a total of 5 days in M154 medium (Cascade Biologics, Portland, OR, U.S.A.) when the tissue supernatants were harvested and stored at −70 °C. Amphiregulin was quantified using an ELISA (R&D Systems) according to the manufacturer's instructions. Recombinant human amphiregulin (R&D Systems) was used as the standard, and the blank was unexposed culture medium.

Immunohistochemical staining and automated analysis

Immunohistochemistry was performed with antileptin receptor antibody (R&D Systems) according to the manufacturer's instructions and visualized with 3-amino-9-ethyl-carbazole (BioGenex, San Ramon, CA, U.S.A.), followed by haematoxylin counterstain (Biocare Medical, Concord, CA, U.S.A.). Stained sections were examined by light microscopy, and each stained tissue section was subjected to image capture in its entirety via five digital images taken through the 20 × objective. All images were then analysed using Image Pro software (Image-Pro Plus; Media Cybernetics, Silver Spring, MD, U.S.A.), to capture the area of positive staining for leptin receptor in epidermis vs. dermis. Statistical analysis was performed using a two-tailed unpaired *t*-test assuming equal variances; P values ≤ 0·05 were considered to be significant.

Real-time quantitative polymerase chain reaction

Leptin and leptin receptor expression were validated by quantitative real-time reverse transcriptase-polymerase chain reaction (qRT-PCR). Primers for leptin (cat. no. PPH00581E), leptin receptor (cat. no. PPH00028B) and the housekeeping gene RPLP0 (36B4, cat. no. PPH21138E) were obtained from Superarray Biosciences (Frederick, MD, U.S.A.). The reverse transcription reaction was performed on 0·5 μg of RNA template and cDNA was synthesized using anchored-oligo (dT)18 primers as instructed by the manufacturer (Roche Diagnostics, Mannheim, Germany). qRT-PCR was carried out on the LightCycler 2.0 system (Roche Diagnostics). LightCycler FastStart DNA MasterPLUS SYBR Green I was used for all PCR reactions as instructed by the manufacturer. The reaction profile consisted of an initial denaturation at 95 °C for 15 min followed by 40 cycles of PCR at 95 °C for 10 s (denaturation), 58 °C for 10 s (annealing) and 72 °C for 10 s (extension). The fluorescence emitted was captured at the end of the extension step of each cycle at 530 nm. Results were normalized to the expression of the housekeeping gene 18S ribosomal RNA.

Statistical analyses

Data sets were tested for normality using the Kolmogorov–Smirnov test, and statistical significance determined by Student's t-test, paired t-test (pre- and post-treatment) or Mann–Whitney rank sum tests where appropriate using Sigma Plot version 10 for windows (Systat, Erkrath, Germany.) Data series were also tested for significance with a one-way ANOVA with Dunnett's post-test using GraphPad Prism version 4 for Windows (GraphPad Software, San Diego, CA, U.S.A.).

Results

The study groups

The treatment group comprised 30 patients with chronic plaque psoriasis (14 women and 16 men) and 29 age-, sex- and BMI-matched volunteers (16 women and 13 men) with no skin disease. As shown in Table 1, the patients and controls were very similar regarding age, weight, waist circumference, BMI, fasting serum triglycerides, cholesterol or high-density lipoproteins. The weight and waist circumference of the patients did not change during the treatment. The patients

Table 1 Characteristics of the patient and control study groups. Mean values for each measurement are shown together with minimum and maximum values

	Controls	Patients
Age (years)	47·14	52·87
	22–83	24–77
Height (m)	1·67	1·73
	1·52–1·83	1·54–1·88
Weight (kg)	86·05	90·54
	59·6–143	58·7–125
Waist circumference (cm)	105·61	105·00
	73·6–149	77–129
BMI (kg m^{-2})	30·81	30·51
	22·0–49·5	18·8–39·4
Triglycerides (mmol L^{-1})	1·32	1·57
	0·6–4·6	0·5–4·8
Cholesterol (mmol L^{-1})	5·69	6·01
	3·9–7·8	3·7–8·7
High-density lipoproteins (mmol L^{-1})	1·61	1·51
	1·0–2·6	0·8–2·8

BMI, body mass index.

responded to a questionnaire. While the majority of the patients had not noticed any marked changes in their body weight after the onset of psoriasis, six (20%, two women and four men) reported improvement in their disease following weight loss. Four reported that scaling and erythema lessened after weight loss and worsened following weight gain and the remaining two patients reported that scaling and erythema was decreased following weight loss.

Disease severity

The patients' disease severity was evaluated before and after the treatment using the PASI score. The mean score was 15·33 on enrolment (range 4·9–34·8). As expected, a dramatic decrease in disease severity (PASI) was recorded after the UVB and bathing treatment (mean PASI 3·84, $P < 0·001$).

BMI and waist circumference correlate with serum leptin

The patients and matched controls enrolled in this study had a mean BMI of 30·5 and 30·8 kg m^{-2}, respectively. Among men in the control group, there was a strong positive correlation between serum leptin and BMI ($r = 0·87$, $P < 0·001$), but this was not the case for the female controls ($r = 0·26$, not significant). Interestingly, both male and female patients with psoriasis demonstrated a correlation between BMI and leptin ($r = 0·65$, $P = 0·012$ for women and $r = 0·59$, $P = 0·016$ for men). A very similar relationship existed between waist circumference

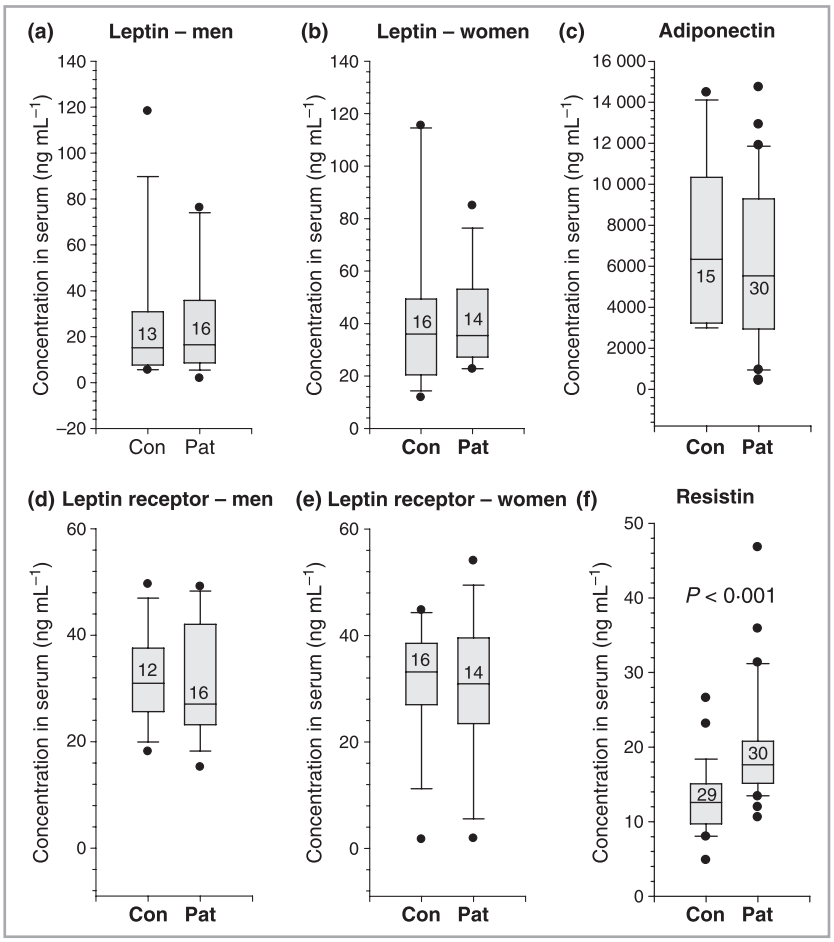

Fig 1. (a–f) Adipokine levels in serum from patients and matched controls. Adipokines were measured by enzyme-linked immunosorbent assay in the serum of patients with psoriasis (Pat) and healthy body mass index-, age- and sex-matched controls (Con) after overnight fast. Leptin, soluble leptin receptor and adiponectin were found not to be elevated in patients compared with matched controls (a–e). Resistin, however, was significantly increased (f). Boxes represent median and interquartile range, whiskers indicate the 10th and 90th percentiles, with values outside this range plotted individually; numbers within boxes indicate the number of individuals tested.

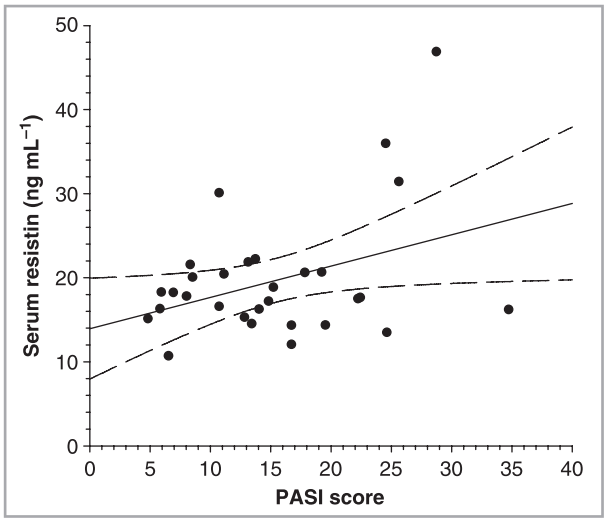

Fig 2. Disease severity (Psoriasis Area and Severity Index, PASI) correlates with patients' serum resistin concentration (n = 30, r = 0·372, P = 0·043). Dashed lines indicate 95% confidence intervals.

and serum leptin in both groups. There was a weak correlation between BMI and disease severity among the men (r = 0·32) but this was not statistically significant and no correlation between the two variables was seen among the women.

Leptin is not elevated in the blood of patients with psoriasis

There were no significant differences in the serum concentrations of leptin, soluble leptin receptor or adiponectin between patients and controls (Fig. 1a–e). As expected, women in both the patient and control groups had significantly higher serum leptin levels than the men (P = 0·017). However, patients' leptin levels were not significantly different from those of the BMI-matched nonpsoriasis controls for either sex (Fig. 1a,b). Serum leptin levels did not correlate with disease severity in either male or female patients.

Serum resistin is elevated in psoriasis and correlated with disease severity

The patients had significantly more resistin in their serum than did the controls (P < 0·001, Fig. 1f) and this correlated with their disease severity (r = 0·372, P = 0·043, Fig. 2).

Serum cytokine levels are altered in psoriasis patients, and responded to NB-UVB therapy

IL-1β, IL-6, CCL2, CXCL8 and CXCL9 were all significantly elevated in the pretreatment serum of the patients compared

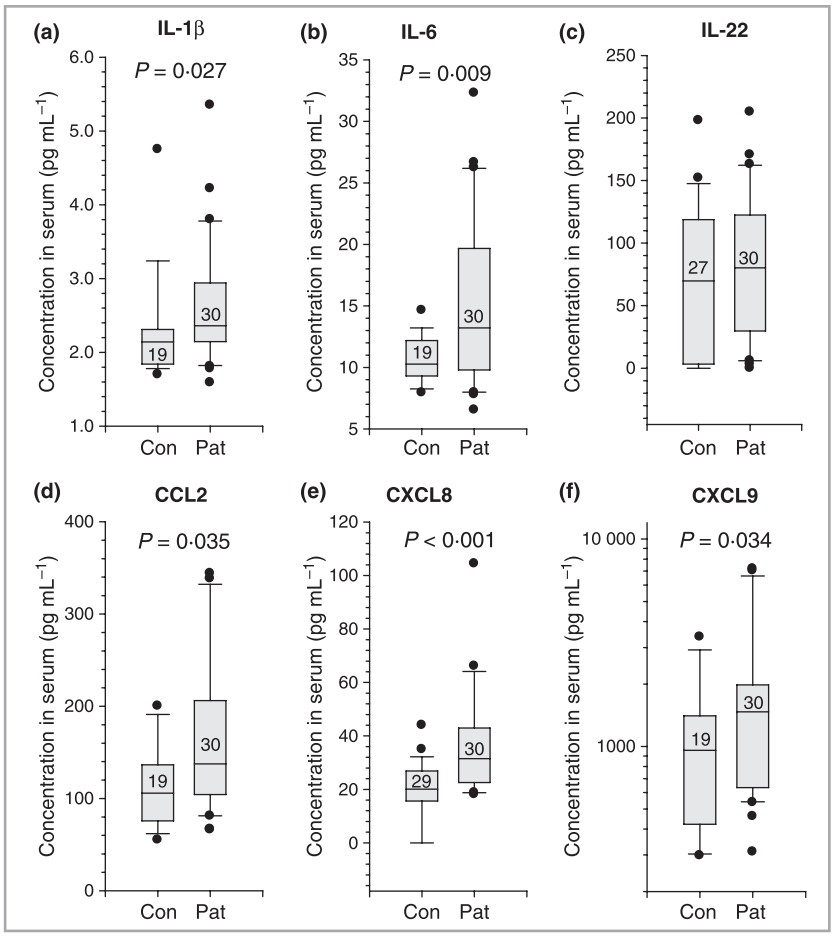

Fig 3. (a–f) Cytokine levels in serum from patients (Pat) and controls (Con). Cytokines were measured in fasting serum by multiplex assay or enzyme-linked immunosorbent assay. Interleukin (IL)-1β, IL-6, CCL2 (MCP-1), CXCL8 (IL-8) and CXCL9 (MIG) were all significantly elevated in patients compared with matched healthy controls. Boxes and whiskers are described in Figure 1.

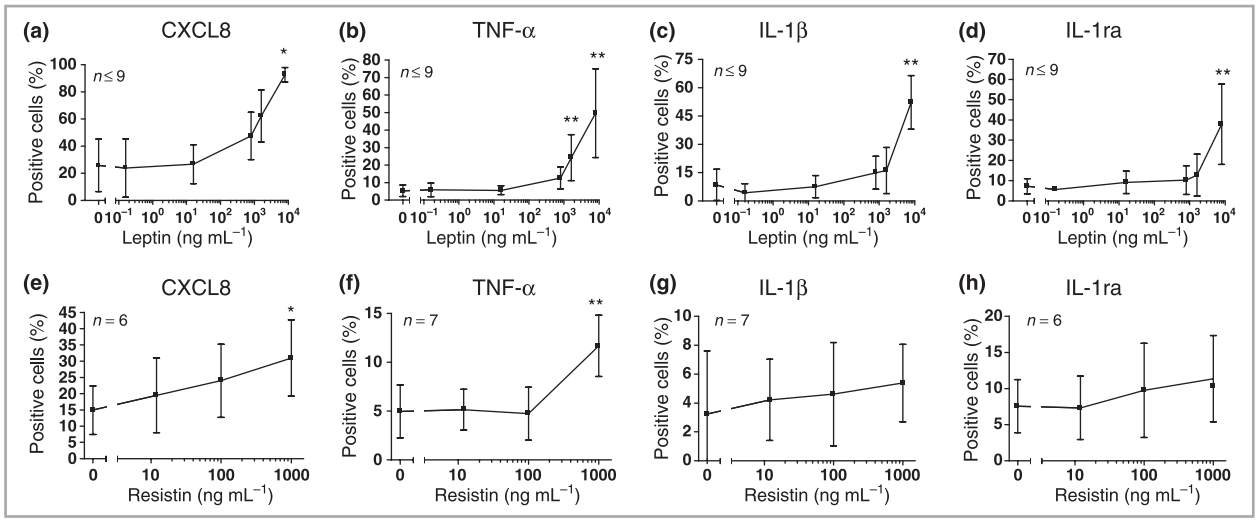

Fig 4. Exogenous leptin (a–d) and resistin (e–h) induce blood monocytes from healthy volunteers to produce proinflammatory cytokines *ex vivo* in a dose-dependent manner. Plots show proportion of cytokine+ CD14+ monocytes detected by intracellular cytokine staining and flow cytometry (mean ± SD). Statistical significance indicated as *P < 0·05, **P < 0·01, by one-way ANOVA with Dunnett's test. TNF, tumour necrosis factor; IL, interleukin; IL-1ra, IL-1 receptor antagonist.

with the controls (Fig. 3); however, no difference was seen in levels of IL-22 (Fig. 3c). Serum IL-10 and IL-12p70 were also increased in the patients (data not shown). Following the treatment, a significant decrease was seen in the serum concentration of both CXCL8 (P = 0·001) and IL-22 (P < 0·001), but no significant changes were observed in serum for IL-1β or IL-6 (data not shown). Although some decrease was observed in resistin levels after treatment this was not significant (P = 0·1).

Leptin and resistin induce proinflammatory cytokine production by monocytes

As serum leptin correlated with the BMI of patients with psoriasis and serum resistin correlated with their disease severity, we chose to examine the effects of leptin and resistin on cytokine production by blood monocytes *ex vivo* using intracellular cytokine staining and flow cytometry. The cytokine content of monocytes after 16 h of incubation with recombinant leptin or resistin is shown in Figure 4. Both leptin and resistin could induce significant amounts of CXCL8 and TNF-α production by the monocytes. In addition, leptin was able to induce the accumulation of IL-1β and IL-1ra in monocytes (Fig. 4c,d).

Leptin-induced amphiregulin expression by *in vitro* cultured skin

As the direct effects of leptin on skin are currently unknown, we exposed biopsies from healthy and plaque psoriasis skin to leptin *in vitro*. Addition of exogenous leptin led to a dose-dependent accumulation of the epidermal growth factor (EGF)-like growth factor amphiregulin in the medium from cultured psoriasis skin,

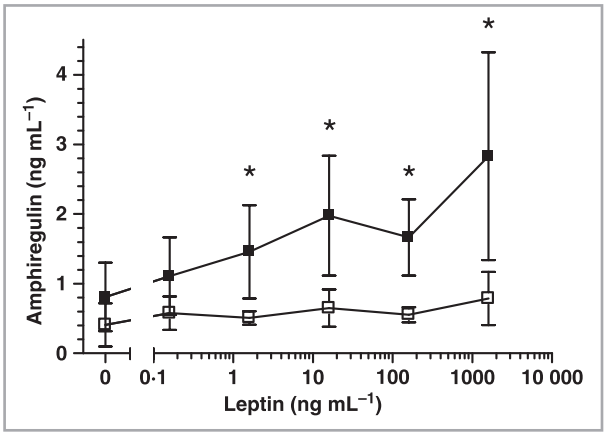

Fig 5. Exogenous leptin induces *in vitro* cultured psoriasis skin to express the growth factor amphiregulin in a dose-dependent manner. Open squares, control skin; filled squares, psoriasis skin, mean (n = 3) ± SD, *P < 0·05, one-tailed *t*-test.

but an increase in amphiregulin was not observed when non-psoriatic control skin was cultured (Fig. 5).

Enhanced expression of leptin receptor was seen in uninvolved psoriasis skin, but was downregulated in lesional epidermis

Because psoriasis skin, but not healthy skin, responded to the addition of exogenous leptin by producing the growth factor amphiregulin, we investigated whether this difference was due to variations in leptin receptor expression. First we examined the leptin and leptin receptor mRNA expression in healthy as well as symptom-free and lesional psoriasis skin

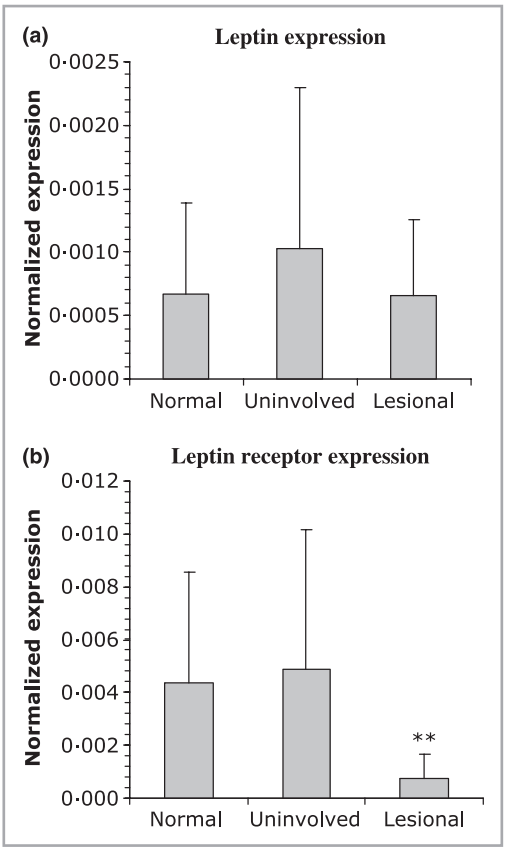

Fig 6. Evaluation of (a) leptin and (b) leptin receptor mRNA expression levels in skin by quantitative real-time reverse transcriptase-polymerase chain reaction. Leptin mRNA levels are of similar magnitude in healthy, symptomless (uninvolved) psoriasis and lesional psoriasis skin. However, leptin receptor mRNA expression is significantly diminished in lesional psoriasis skin compared with both healthy and symptomless skin. Mean ($n = 13$) ± SD, $^{**}P < 0{\cdot}005$, two-tailed *t*-test.

using qRT-PCR (Fig. 6). All three skin phenotypes contained similar amounts of leptin mRNA (Fig. 6a). Lesional psoriasis skin, however, contained significantly ($P < 0{\cdot}005$) less mRNA for leptin receptor than either healthy or symptom-free psoriasis skin (Fig. 6b) and this observation was supported immunohistochemically (Fig. 7). Thus, lesional psoriasis epidermis (Fig. 7c) expressed less leptin receptor than either healthy (Fig. 7a) or uninvolved psoriatic epidermis (Fig. 7b) and this finding was confirmed using computer-assisted image quantification (Fig. 7d). Interestingly, the converse was seen in the dermal compartment, where very little leptin receptor staining was seen in healthy or clinically uninvolved dermis, but some cells within the lesional dermis stained strongly for leptin receptors (Fig. 7c,h).

Discussion

In this study we show that serum resistin is elevated in patients with psoriasis compared with age-, sex- and BMI-matched healthy controls and that resistin correlates with disease severity. This finding confirms a small prospective study assessing the effects of treatment with the oral retinoid acitretin[48] in which increased resistin levels were measured in the blood of patients with psoriasis and compared with age-, sex- and BMI-matched controls; however, that study did not report any correlation between disease severity and serum resistin, probably because only 10 patients were enrolled. However, we and recently others[49] have now shown a positive correlation between psoriasis disease severity and serum resistin levels. There was some decrease in serum resistin after the treatment but this was not significant ($P = 0{\cdot}1$).

We also demonstrate that exogenous resistin can induce monocytes to produce the inflammatory cytokines CXCL8 and TNF-α *in vitro* (Fig. 4e,f) which is in agreement with Bokarewa

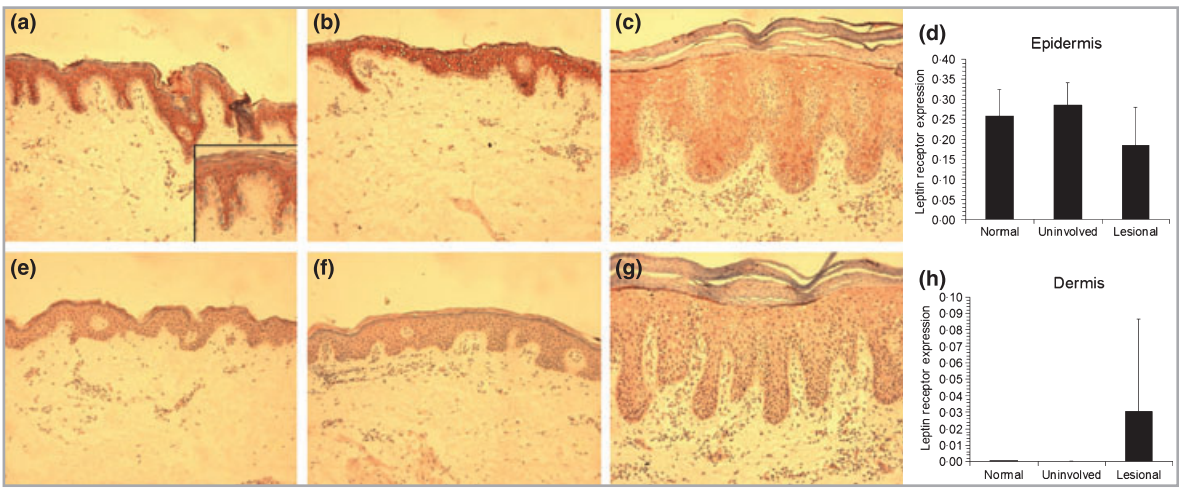

Fig 7. Immunohistochemical evaluation of leptin receptor expression in (a) healthy skin, (b) uninvolved and (c) lesional psoriasis skin. Following immunohistochemical detection of leptin receptor in skin biopsies from three healthy and three psoriatic donors the strength and extent of receptor expression (red staining) was evaluated in the epidermal (d) and dermal (h) compartments using automated analysis with Image Pro software. For comparison isotype control staining is also shown (e–g).

et al.,[43] who showed increases in IL-6 and TNF-α but not IL-1β in the culture medium of PBMC cultures stimulated with 1000 ng mL^{-1} resistin. Resistin has also been shown to increase the expression by human endothelial cells of the vascular cell adhesion molecule-1, CCL2 and endothelin-1.[50] Resistin has furthermore been reported to promote proliferation and migration of cultured endothelial cells and to increase the expression of vascular endothelial growth factor receptors-1 and -2, and matrix metalloproteinases-1 and -2, culminating in *in vitro* angiogenesis.[51] Collectively these various activities of resistin make it an attractive effector molecule in psoriasis.

Like resistin, leptin also induces the production of inflammatory cytokines by monocytes, and in addition to CXCL8 and TNF-α it also markedly induces the production of IL-1β and IL-1ra (Fig. 4a–d). Further, using an *ex vivo* organotypic culture system, we show that exogenously added leptin induces psoriasis skin to produce amphiregulin, an ErbB1-binding member of the EGF family that is known to drive autocrine keratinocyte proliferation in culture,[52] and to promote marked inflammatory hyperplasia when overexpressed in the epidermis of transgenic mice. We also show that leptin receptors are downregulated in lesional psoriasis skin while they are constitutively expressed in healthy and uninvolved psoriatic skin; thus leptin, like IL-23,[53] may induce proinflammatory cytokine production from infiltrating lymphocytes rather than acting directly on the keratinocytes themselves. It is interesting in this context that leptin receptors have been shown to be downregulated during early wound healing, and then strongly expressed by mitotic keratinocytes at the wound edge later in the healing process.[54] Such differential regulation of leptin-driven epidermal proliferation is impaired in Lep^{ob}/Lep^{ob} mice.[55]

CXCL8, a strong neutrophil chemoattractant, is also known to stimulate the proliferation of keratinocytes.[56] We report elevated CXCL8 levels in the serum of patients with psoriasis and that both resistin and leptin can induce the production of CXCL8 by blood monocytes. Given that keratinocytes may both respond to and secrete CXCL8, this chemokine is likely to contribute to the keratinocyte hyperproliferation in psoriasis.

We can now perhaps begin to envision some links between increases in the volume of adipose tissue and severity of psoriasis. Thus, increased adiposity is associated with raised levels of circulating cytokines, including leptin and resistin, which may promote activation of T cells and monocytes, driving both Th1 and Th17 immune responses and at the same time impairing the function of regulatory T cells. High concentrations of leptin may furthermore induce local production of amphiregulin which, together with leptin- and resistin-stimulated production of CXCL8, could help to drive the keratinocyte proliferation which is characteristic for psoriasis.

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