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Review

Adipokines, psoriasis, systemic inflammation, and endothelial dysfunction

Maeve Lynch, MB BCh BAO, MD, Tomas Ahern, MB BCh BAO, Cheryl M. Sweeney, BA (Mod), PhD, Anna Malara, MSc, PhD, Anne-Marie Tobin, MB BCh BAO, BSc (Pharm), PhD, Donal O'Shea, MB BCh BAO, MD, and Brian Kirby, MB BCh BAO, MD

St. Vincent's University Hospital, Dublin, Ireland

Correspondence
Maeve Lynch, MB BCH BAO, MD
Dermatology Department
St. Vincent's University Hospital
Elm Park, Dublin 4
Ireland
E-mail: lynchmaeve@yahoo.ie

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Abstract

Adipokines are secreted by white adipose tissue, an active endocrine organ, and play a role in the regulation of metabolic functions such as lipid metabolism, inflammation, and vascular homeostasis. Adipokines are secreted in excess in obesity and contribute to the development of associated comorbidities such as metabolic syndrome and atherosclerosis. Psoriasis, a chronic immune-mediated skin disease, is associated with obesity and increased cardiovascular risk. Understanding the role of adipokines in psoriasis may in part explain the association between psoriasis and cardiovascular disease. This review summarizes the data regarding key adipokines in patients with psoriasis and the change in adipokine profiles with psoriasis therapy. Adipokines may be mediators of cutaneous inflammation suggesting a role in the pathophysiology of psoriasis and the development of comorbidities.

Introduction

Psoriasis is a hyperproliferative, immune-mediated inflammatory skin disease. Severe disease is associated with increased cardiovascular morbidity and mortality. The direct mechanisms of the association between increased cardiovascular risk and psoriasis have yet to be elucidated.

Adipokines are cytokines secreted by white adipose tissue (WAT). They play a role in the regulation of metabolic functions such as lipid and glucose metabolism, insulin-mediated processes, inflammation, vascular homeostasis, and coagulation. In obesity, excess adipokines are secreted and contribute to inflammation. Adipokines may have proinflammatory and anti-inflammatory functions. Endothelial dysfunction in obesity is associated with the generation of reactive oxygen species (ROS) and is characterized by reduced production of nitric oxide by endothelial cells. Dysregulated production of adipokines results in the production of ROS and plays a role in endothelial dysfunction. Tumor necrosis factor alpha (TNF-α) is the major regulator of cytokine production in adipose tissue. Levels of the proinflammatory cytokines, interleukin-6 (IL-6), and TNF-α, cytokines in adipose tissue, were correlated with obesity and strongly related to insulin resistance.[1] This imbalance of adipokines may contribute to the development of obesity-linked complications of metabolic syndrome (MS) including psoriasis and increased cardiovascular risk.

Patients with psoriasis are more likely to be obese, and obesity is an independent risk factor for the development of psoriasis.[2,3] The association of obesity with psoriasis could be explained by the role of adipokines, which feature in both

psoriasis and obesity. This review article summarizes the data linking adipokines and psoriasis and the potential role of adipokines in increased cardiovascular risk in psoriasis.

Obesity, Weight Loss, and Psoriasis

The metabolic state of patients with psoriasis may differ from those with other chronic inflammatory diseases. Obesity, defined as body mass index (BMI) in $kg/m^2 > 30$, is highly prevalent in patients with psoriasis. Obesity was reported in 20.7% of patients with severe psoriasis compared with 13.2% of controls.[4] There is a positive correlation between increasing BMI and psoriasis severity as measured by psoriasis area severity index (PASI).[5] Obesity may be a risk factor for the development of psoriasis.[3] Both obesity and psoriasis are associated with systemic inflammation and an increased risk of cardiovascular disease.

In 2006, Hamminga suggested that the treatment of obese patients with psoriasis should be focused on reducing obesity-induced inflammation and may lead to a better clinical outcome by reducing levels of TNF-α, IL-6, leptin, and improving insulin sensitivity.[6] There are reports of patients with severe psoriasis achieving remission after Roux-en-Y gastric bypass (RXYG) and gastrectomy.[7] A possible mechanism for this response is the increase in glucagon-like peptide-1 (GLP-1) levels postoperatively which may exert a direct anti-inflammatory effect on psoriasis and also improve weight loss. This may improve psoriasis indirectly.[8,9]

One study investigated adipokines in 23 nondiabetic morbidly obese patients who had RXYG or laparoscopic sleeve gastrectomy.[10] Leptin levels decreased and adiponectin levels increased postoperatively.

Gisondi investigated the effects of weight loss on 61 patients with moderate-to-severe psoriasis who were obese (BMI > 30).[11] The intervention group was treated with low-dose cyclosporine (2.5 mg/kg/d) and a low-calorie diet and the control group with cyclosporine (2.5 mg/kg/d) alone. A 75% decrease from baseline in PASI (PASI-75) was achieved by 66.7% of patients in the intervention group at 24 weeks and 29% of patients in the control group ($P < 0.001$). The mean weight reduction in body weight was 7 ± 3.5 kg in the intervention group and 0.2 ± 0.9 kg in the control group ($P < 0.001$). The authors suggest that weight loss through a low-calorie diet reduces insulin, leptin, C-reactive protein, and monocyte chemotactic protein-1 (MCP-1) and increases adiponectin concentrations. This may result in a reduction in systemic inflammation that results in improvement of psoriasis.[11] Another study from the same group evaluated psoriasis and weight loss after patients had achieved remission for at least 12 weeks after methotrexate therapy.[12] Forty-two patients were randomly assigned to a hypocaloric diet or free diet for 24 weeks and then followed for a further 12 weeks. There was no significant difference between the two groups in psoriasis remission, despite significant weight loss in obese patients in the intervention group. It is clear that larger studies are required to ascertain the impact of weight loss on psoriasis severity.

Adiponectin is an anti-inflammatory adipokine almost exclusively synthesized by adipocytes. Adiponectin levels are decreased in obese individuals compared to lean individuals. In contrast, adiponectin levels are increased in autoimmune and other chronic inflammatory diseases that are not associated with obesity such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD), and systemic lupus erythematosus (SLE).

Proinflammatory cytokines such as TNF-α and IL-6 inhibit adiponectin production. Adiponectin is reported to be both increased and decreased in patients with psoriasis. There are similar contradictory results in other chronic inflammatory disease states where IL-6 is upregulated, e.g., SLE and RA.

Experimental animal models suggest that adiponectin is important in the pathophysiology of insulin resistance and protects against obesity-linked metabolic dysfunction. Adiponectin suppresses TNF-α, IL-6, and IFN-γ production and has antiatherogenic activity. Low adiponectin levels are a risk factor for endothelial dysfunction. Adiponectin increases the production of nitric oxide (NO) in endothelial cells by the activation of phosphatidylinositol-3 kinase/Akt signaling pathway.[13] These data may explain the role of adiponectin in endothelial dysfunction and increased cardiovascular mortality. Adiponectin receptors are expressed in normal human keratinocytes as well as in monocytic THP-1 cells (human acute monocytic leukemia cell line).

Several studies have demonstrated that plasma levels of adiponectin were reduced in patients with psoriasis.[14–26] Adiponectin has been negatively correlated with PASI ($r = -0.34$, $P < 0.05$)[17,19] and TNF-α levels ($r = -0.64$, $P < 0.01$).[14] A positive correlation between adiponectin and interleukin-22 (IL-22) has been shown.[27] Interleukin-22 is a cytokine produced by Th17 cells which is increased in psoriasis.

A correlation between obesity and reduced adiponectin levels has been shown.[28] Another study in contrast did not find significant differences in the serum concentration of adiponectin in obese psoriasis patients (mean BMI 30.5) compared to controls.[29] An additional study of 204 patients with psoriasis showed that serum adiponectin levels were inversely correlated with BMI ($r_s = -0.30$, $P < 0.001$) and positively correlated with disease duration ($r_s = 0.18$, $P < 0.018$) but not to PASI.[30]

A study compared the prevalence of the MS and related biomarkers in 155 patients with psoriasis without arthritis and 203 patients with psoriatic arthritis (PsA).[31] Adiponectin was significantly associated with PsA ($P = 0.005$), the use of anti TNF-α therapy ($P = 0.03$), and active joint count ($P = 0.001$) suggesting a role in joint inflammation.[31]

The effect of treatment on adiponectin levels has been investigated (Fig. 1). TNF-α blockade therapy in two studies of patients with RA and PsA treated with adalimumab and onercept, respectively, did not demonstrate a change in adiponectin

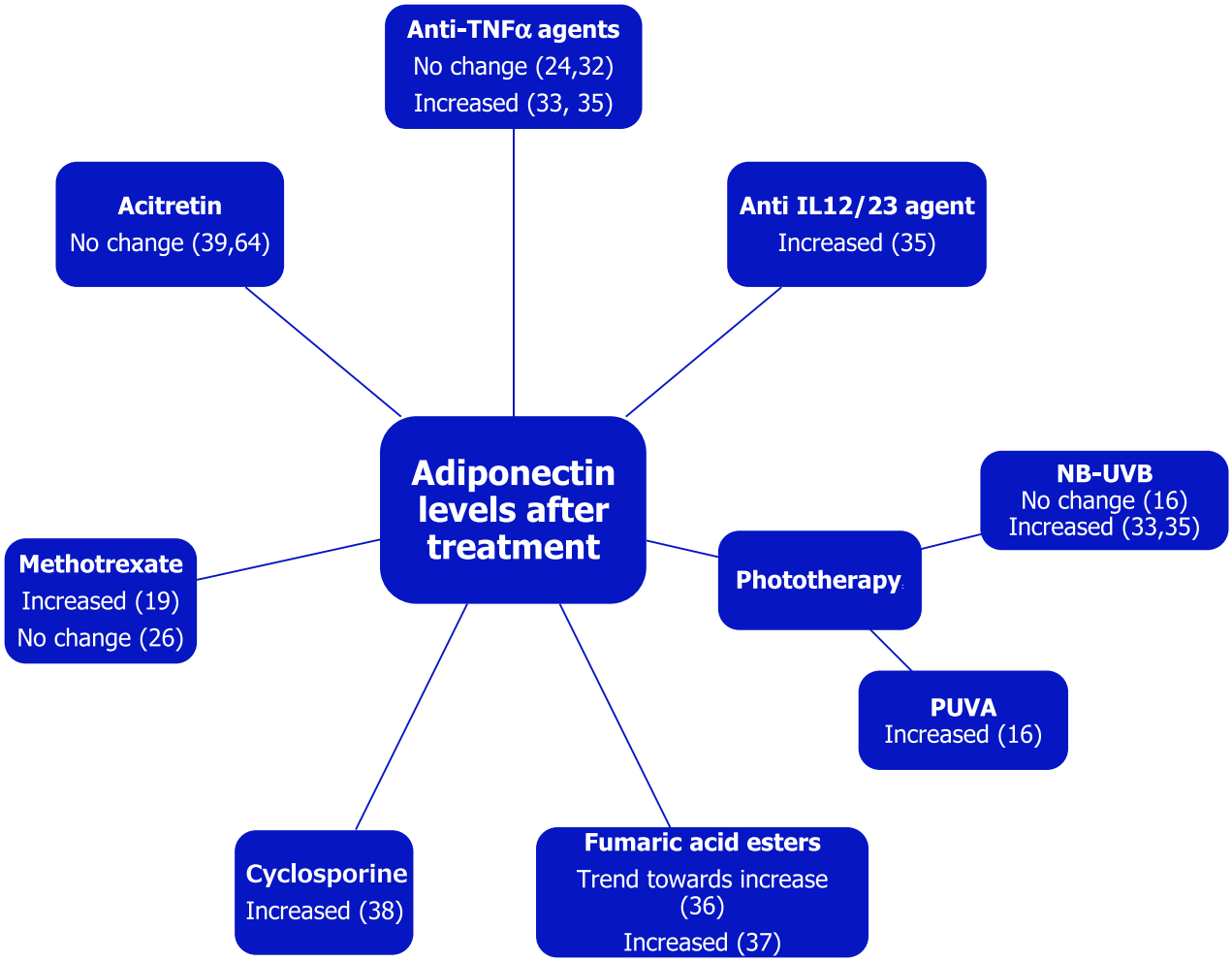

Figure 1 Adiponectin levels after treatment

levels before and after treatment, despite reductions in inflammatory activity.[32] Similarly, a lack of change in adiponectin levels with anti-TNF-α agents has been observed in another study of 47 psoriasis patients.[24]

A different study in psoriasis patients demonstrated a rise in adiponectin levels in 17 patients after a course of psoralen ultraviolet-A (PUVA) chemotherapy and not with topical therapy or NB-UVB phototherapy.[16] A study evaluating 14 psoriasis patients treated with anti-TNF agents and NB-UVB therapies demonstrated a significant increase in serum adiponectin levels and reduction in IL-6 levels after treatment.[33] The study discussed the possibility that IL-6 production suppresses adiponectin production in patients with psoriasis. In contrast, a study evaluating Goeckerman therapy (crude coal tar ointment and ultraviolet radiation) in psoriasis demonstrated a significant decrease in adiponectin levels after treatment.[34] Another study of 37 psoriasis patients demonstrated a significant increase in adiponectin levels after 24 weeks but not after 12 weeks, of treatment with either adalimumab, infliximab, ustekinumab, or NB-UVB phototherapy.[35]

A small study by Boehncke *et al.* followed 13 patients receiving fumaric acid esters prospectively for 24 weeks. Ten completed the study. Adiponectin showed a trend toward increased serum levels during therapy.[36] Another study of 27 psoriasis patients demonstrated a significant rise in adiponectin levels with fumaric acid ester treatment after 16 weeks.[37]

The effect of cyclosporine treatment in patients with psoriasis on adipokine levels has also been analyzed.[38] Twenty-six patients with psoriasis and 26 BMI-matched healthy controls were treated with cyclosporine and assessed for 6 months, after which cyclosporine treatment levels of adiponectin and resistin increased significantly.[38] In another study, there was no significant change in adiponectin levels after 3 months of acitretin treatment.[39] Rajappa investigated 60 patients with psoriasis and 60 healthy controls.[19] Patients with psoriasis treated with methotrexate or coal tar for 12 weeks demonstrated significantly

higher adiponectin levels from baseline. A lack of change in adiponectin levels after methotrexate treatment has also been reported.[26]

In vitro adiponectin exerts anti-inflammatory effects both in THP-1 cells and keratinocytes. High molecular weight (HMW) adiponectin is suggested to be a more sensitive marker for obesity and disease severity in psoriasis. In contrast to several previous studies a study by Nakajima of 30 patients with psoriasis and 30 controls did not show a difference in adiponectin levels between the two groups.[40] High molecular weight adiponectin levels were significantly lower in patients with psoriasis ($P = 0.001$) and negatively correlated with PASI ($r = -0.3$). In addition, serum levels of HMW adiponectin negatively correlated with BMI in patients with psoriasis ($r = -0.27$). A slightly negative correlation was found between serum HMW adiponectin levels and IL-6 levels.

In contrast to the results of the previous study by Nakajima *et al.,*[40] a study of 79 patients with psoriasis demonstrated significantly higher HMW adiponectin in the psoriasis group in comparison with the control group.[41]

A different study by Nakajima sought to evaluate the relationship between adipokines and Th-17-related cytokines, as both are altered in patients with psoriasis.[27] High molecular weight adiponectin levels were significantly decreased in 30 psoriasis patients compared with controls. There was a strong positive correlation between adiponectin and IL-22 levels as discussed previously ($r = 0.60$, $P < 0.01$). The authors propose that this relationship between adipokines and Th-17-related cytokines is involved in the pathogenesis of psoriasis.

Kaur investigated 60 patients with psoriasis and found that adiponectin was negatively correlated with BMI. Leptin, oxLDL, and oxLDL-β(2)-GPI levels were positively correlated with BMI.[42] High levels of adiponectin were strongly associated with higher levels of TNF-α and high-density lipoprotein cholesterol and lower triglycerides suggesting that adipokines may be one of the mechanisms behind the close association between CVD and psoriasis.

The anti-inflammatory adipokine, adiponectin, is decreased in obesity and upregulated in chronic inflammatory diseases not associated with obesity, including RA and SLE. Patients with psoriasis are more likely to be obese, but studies evaluating adiponectin levels have demonstrated contradictory results. Adiponectin levels have been found to be decreased, unchanged, and increased in various studies of patients with psoriasis. The majority of studies have shown a rise in adiponectin after psoriasis treatment. Many studies have not controlled for BMI, psoriasis severity, and the presence of PsA, which may explain the variability in results obtained. The measurement of HMW versus total adiponectin may also account for differing results.

Patients with psoriasis often have diseases associated with decreased adiponectin levels, and further research into the possible mechanisms of increasing adiponectin levels are reasonable. Low adiponectin levels are associated with endothelial dysfunction. Elevated adiponectin levels could suppress inflammation and immune responses of psoriasis. Lower adiponectin levels in psoriasis could contribute to the development of concomitant diseases such as the MS or cardiovascular diseases independently as well as synergistically with obesity.

Leptin is a proinflammatory adipokine which regulates feeding behavior through the central nervous system. Mice that lack leptin show hyperphagia, obesity, and insulin resistance. These changes are reversed by the administration of leptin. Leptin is effective at improving metabolic dysfunction in patients with lipodystrophy or congenital leptin deficiency. Resistance to leptin occurs, however, where obese individuals have high levels of leptin without the expected anorexic responses. It is expressed primarily in the hypothalamus but also in various tissues including peripheral blood mononuclear cells, endothelial cells, fibroblasts, and basal keratinocytes.

Leptin has many effects including keratinocyte proliferation, the expression of adhesion molecules, and angiogenesis. Functional leptin receptors are expressed on endothelial cells, and leptin upregulates mediators of vascular inflammation including TNF-α and IL-6. Leptin-induced endothelial dysfunction is thought to be mediated by the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway. Leptin increases the formation of ROS associated with reduced NO production and endothelial dysfunction. Leptin increases the production of the TH1-type cytokines IL-2 and IFN-γ and suppresses the production of the TH2-type cytokine IL-4 by T cells or mononuclear cells. As psoriasis is an inflammatory disease with a preponderance of TH1 cytokines, leptin has been suggested to play a role in its pathogenesis.[29]

Several studies have demonstrated elevated serum leptin levels in patients with psoriasis compared to controls.[14,17,19,24,27,34,40,43–50] The serum leptin levels in patients with psoriasis has demonstrated a positive correlation with BMI[25,29,41-43,45,] and PASI[19,26,49,51] in several studies but not with PASI in other studies.[41,43,48] A positive correlation with waist circumference in psoriasis patients and controls has been shown.[29,41] Another study by Nakajima demonstrated significantly elevated leptin levels in psoriasis patients and a nonsignificant positive correlation with IL-6, a proinflammatory cytokine ($r = 0.32$, $P = 0.12$).[27] A study comparing patients with psoriasis only to those with PsA demonstrated higher leptin levels in women with PsA ($P = 0.04$).[31] One study in contrast demonstrated lower leptin levels in psoriasis patients compared to controls,[18] although this study did not control for BMI. Leptin levels were not different between psoriasis patients and controls in another study[26]

Injured keratinocytes express leptin receptors and show similar behavior to hyperproliferative psoriatic keratinocytes, with activation of the STAT3 pathway in both situations. Leptin levels are increased in models of wound healing where leptin stimulates angiogenesis. Psoriasis is analogous to accelerated wound healing, and leptin may play a role in psoriasis

pathogenesis via similar pathways involved in wound healing. Leptin has been shown to increase the proliferation and secretion of proinflammatory cytokines in vitro.[51]

In a study evaluating 30 patients with psoriasis,[29] leptin induced the production of proinflammatory cytokines CXCL8 (known to stimulate keratinocyte proliferation) and TNF-α by monocytes and the accumulation of IL-1β and IL-1ra in monocytes. Enhanced expression of leptin receptors were seen in uninvolved skin of patients with psoriasis but was downregulated in lesional epidermis. The authors suggest that leptin may induce proinflammatory cytokine production from infiltrating lymphocytes rather than acting directly on keratinocytes.

An additional study investigated 36 patients with psoriasis prior to and after bath-psoralen UVA (PUVA) or NB-UVB.[52] Phototherapy did not induce any remarkable change in leptin levels but significantly decreased serum resistin levels.[52] Patients were not controlled for gender. The lack of change in leptin levels is interesting. One potential explanation could be that the timepoint at which leptin was measured after phototherapy may be too early to see a reduction in leptin levels, although this was not true for resistin levels in this study. Another explanation could be that while psoriasis has cleared with phototherapy at a clinical level, there may continue to be subclinical inflammation, which may account for the persistently elevated leptin levels. In one study, disease-gene activation in the leptin pathway improved by only 56% in 11 patients with psoriasis who responded to treatment with etanercept after 3 months.[53] This supports the hypothesis that even when clinically resolved, psoriasis plaques demonstrate subclinical inflammation.[53] The authors propose that as leptin disease-gene expression improved only partially despite clearance of psoriasis, this may explain the persistence in risk for obesity and metabolic syndrome in these patients.

One study evaluated psoriasis patients treated with methotrexate or coal tar and demonstrated a significant reduction in leptin levels after 12 weeks of methotrexate treatment ($P < 0.0001$).[19] In contrast a lack of change in leptin levels was observed in 35 psoriasis patients after methotrexate treatment.[26] Another study evaluated 47 patients treated with infliximab, adalimumab, ustekinumab, or NB-UVB in addition to topical therapies and found a significant decrease in leptin levels after 24 weeks ($P < 0.05$) but not after 12 weeks.[35] Similarly, a decrease in leptin levels after 24 weeks of treatment with anti-TNF agents has been observed.[24] In a study involving 29 patients with psoriasis, after 6 months of treatment with adalimumab there was no change in leptin levels observed.[54] Treatment with acitretin for 3 months did not result in a significant change in leptin levels in one study of 34 patients with psoriasis.[39]

Chen analyzed 77 Taiwanese patients with psoriasis and 81 controls and showed that on multivariate analysis, psoriasis was an independent risk factor for hyperleptinemia (OR 4.57; CI 1.47–14.23, $P = 0.009$).[45] Higher serum leptin levels were seen in patients with psoriasis and obesity ($P = 0.002$) and the MS ($P = 0.003$).[45]

Cerman studied 43 patients with psoriasis, 10 patients with other skin diseases and 10 healthy controls, all with a normal BMI.[49] The authors showed that serum leptin concentration was significantly higher in patients with severe psoriasis compared with those with mild or moderate disease, diseased controls, or healthy controls. Tissue leptin and leptin receptor expression showed an increased expression only in patients with severe psoriasis ($P < 0.05$). A positive correlation of serum leptin levels, tissue leptin, and tissue leptin receptor expression was shown with disease duration ($P < 0.01$). The authors concluded that leptin may serve as a marker of severity in psoriasis and may contribute to chronicity of disease. They suggest that leptin antagonists as an adjuvant therapy in obese patients with psoriasis may be an issue for further research.[49]

A study involving 79 patients with psoriasis and 80 healthy controls showed that the mean values of HMW adiponectin and visfatin were significantly higher in psoriasis patients, and the mean value of retinol-binding protein 4 (RBP4) was significantly lower in this group.[41] Leptin levels surprisingly did not demonstrate a significant difference between the patients with psoriasis and the control group. A significant correlation with PASI was not found for any of the adipokines. The authors suggest that the increased levels of adiponectin and reduced levels of RBP4 could be protective against vascular and metabolic disease in patients with psoriasis. In contrast, the increased levels of visfatin, a proinflammatory cytokine, could contribute to the increased risk of CVD in psoriasis.[41]

In one study of 109 patients with psoriasis and 125 healthy controls, the frequencies of a common polymorphism in the promoter of the human leptin gene (G-2548A, Ch7q31.3) were compared.[55] No evidence of association between the G-2548A variant of the leptin gene and psoriasis was found.[55] The same authors studied 65 patients with psoriasis and 64 healthy controls. They did not find any association between G2548A leptin gene polymorphic differences and leptin levels, although they report that the number of participants was too small to make a precise conclusion.[56]

In a study involving 94 patients with psoriasis and 100 healthy controls, the relationship between the G-2548A polymorphism of the leptin gene and the clinical features of the patients were analyzed.[57] There was a significant difference between the GA, AA, and GG frequencies in patients and controls and in patients with and without the metabolic syndrome. Serum leptin levels were significantly higher in patients compared to controls ($P < 0.001$) and among the different leptin genotypes in the patients' group. The authors conclude that the leptin gene G-2548A polymorphism could be a predictor for higher plasma leptin and increased risk of psoriasis and could be used as a marker for psoriasis-related comorbidity risk.[57] This is interesting, however, a locus for psoriasis has not been found on chromosome 7 in genome wide association scans.[58]

Table 1 Adiponectin levels in psoriasis studies

Study (reference)	Adiponectin, change in psoriasis	Controlled for BMI	Controlled for PASI	Controlled for PsA	Technique
Takahisha *et al.*[14] 122 PsO patients; Topical therapy, NB-UVB, etretinate, cyclosporine (CSP)	↓ in PsO vs. controls, Negative correlation with PASI, Negative correlation with TNF-α	No	Yes	No	ELISA, Biosource, Camarillo, CA, USA
Coimbra *et al.*[15] 56 PsO patients 37 controls	↓ in PsO vs. controls, Trend towards lower levels in those with moderate and severe disease vs. mild disease	Yes	Yes	No	ELISA, R&D Systems, Minneapolis, MN, USA
Kaur *et al.*[28] 10 normal weight PsO patients, 12 obese PsO patients;	↓ in obesity, ↑ in PsO vs. normal weight controls, Normal in obese PsO patients, ↑ in normal weight PsO patients × 2 vs. controls	Yes	No	No	Quantitative sandwich enzyme immunoassay R&D systems, Minneapolis, MN, USA
Johnston *et al.*[29] 30 PsO patients; Pre & Post NB-UVB	No difference in PsO vs. controls	Yes	Yes	No	ELISA, R&D Systems, Oxford, UK
Laws *et al.*[30] 204 PsO patients	Inversely correlated with BMI, Positive correlation with disease duration, No correlation with PASI	Yes	Yes	No	ELISA
Eder *et al.*[31] 203 PsA patients, 155 PsO patients	↑ in PsA vs. PsO	Yes	Yes	Yes	ELISA, R&D Systems, Minneapolis, MN, USA and Invitrogen
Peters *et al.*[32] 2 studies; PsA – 126 patients pre & postonercept; RA – 171 patients pre & postadalimumab, 16 weeks	Higher in females, No significant change pre and posttreatment in PsA, No change in RA	No	No	Yes	R&D Systems, Oxon, UK
Coimbra *et al.*[16] 10 PsO patients – topical therapy; 17 PsO patients – NB-UVB; 17 PsO patients – PUVA	↓ in PsO vs. controls, ↑ posttreatment only with PUVA – still lower than controls	Yes	Yes	No	ELISA, R&D Systems, Minneapolis, MN, USA
Shibata *et al.*[33] 8 PsO patients, 6 PsA patients; 8 received infliximab treatment; 6 received NB-UVB; Levels measured pre and posttreatment at 4, 8 weeks	↑ posttreatment, No difference between adiponectin change and type of treatment, IL6 ↓ posttreatment	No	No	No	ELISA, R&D Systems, Minneapolis, MN, USA
Boehncke *et al.*[36] 13 PsO patients; FAE treatment × 24 weeks	Trend toward ↑ levels posttreatment	No	No	No	ELISA, R&D Systems Minneapolis, MN, USA
Ozdemir *et al.*[38] 26 PsO patients, 26 BMI matched controls; CSP treatment	↑ pre treatment in PsO vs. controls (not significant), ↑ posttreatment in PsO (significant)	Yes	Yes	No	ELISA, AssayMax Human Adiponectin ELISA kit, Assay Pro

Table 1 Continued

Study (reference)	Adiponectin, change in psoriasis	Controlled for BMI	Controlled for PASI	Controlled for PsA	Technique
Nakajima *et al.*[40] 30 PsO patients, 30 controls	No difference between PsO and controls, HMW adiponectin ↓ in PsO Negative correlation with PASI and BMI, Negative correlation with BMI in controls also, Negative correlation between HMW adiponectin & IL-6, Positive correlation between total adiponectin and IL-6	Yes	Yes	No	ELISA, R&D Systems, MN, USA
Nakajima *et al.*[27] 30 PsO patients, 30 controls	HMW adiponectin ↓ PsO, Positive correlation between IL-22 and adiponectin	No	No	No	ELISA, Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan
Kaur *et al.*[42] 60 PsO patients	Negative correlation with BMI, high levels associated with higher TNF-α, HDL, and lower triglycerides	Yes	Yes	No	Quantitative sandwich enzyme immunoassay, R&D systems, Minneapolis, MN, USA
Gerdes *et al.*[41] 79 PsO patients, 80 controls	Total levels – no difference between PsO and controls, HMW adiponectin ↑ in PsO despite overweight, Negative correlation with WHR and BMI, No correlation with PASI	Yes	Yes	No	ELISA, Alpco Diagnostics, Salem, NH, USA
Corbetta *et al.*[64] 10 male PsO patients, 10 controls; Acitretin treatment	No difference between PsO and controls, No change on acitretin, No correlation with BMI	Yes	Yes	No	ELISA, R&D B-bridge International, San Jose, CA, USA
Oh *et al.*[17] 24 PsO patients, 15 controls	↓ in PsO vs. controls, Negative correlation with BMI and PASI	Yes	Yes	Yes	ELISA, R&D Systems, MN, USA
Baran *et al.*[18] 49 PsO patients, 16 controls; Topical therapy	↓ in PsO vs. controls, No change with topical therapy	No	Yes	No	ELISA, R&D Systems, MN, USA
Rajappa *et al.*[19] 60 PsO and PsA patients, 60 controls; Coal tar or methotrexate treatment	↓ in PsO vs. controls, Negative correlation with PASI Significant change with topical/systemic therapies	Yes	Yes	Yes	ELISA, Diagnostic Biochem Canada
Akcali *et al.*[20] 50 PsO patients, 40 controls	↓ in PsO vs. controls	No	No	No	ELISA, Zen-Bio, NC, USA
Li *et al.*[21] 122 PsO patients, 134 controls	↓ in PsO vs. controls	Yes	Yes, treatment type recorded, not PASI	No	ELISA, Linco Research, MO, USA
Karadag *et al.*[39] 34 PsO patients, 34 controls; Acitretin treatment	↑ in PsO vs. controls, No change with treatment	Yes	No	No	ELISA, Boster Biological Technology, Immunoleader
Kadry *et al.*[22] 35 PsO patients, 35 controls	↓ in PsO vs. controls, Inverse association with BMI and metabolic syndrome	Yes	Yes	No	ELISA, R&D Systems, MN, USA

Table 1 Continued

Study (reference)	Adiponectin, change in psoriasis	Controlled for BMI	Controlled for PASI	Controlled for PsA	Technique
Takahashi *et al.*[35] 37 PsO patients; Ustekinumab, infliximab, adalimumab, NB-UVB	↑ after treatment at 24 weeks	No	No	No	ELISA, R&D systems, Oxon, UK
Warnecke *et al.*[23] 100 PsO patients	↓ in PsO vs. controls	Yes	No	Yes	Not recorded

BMI, body mass index; PASI, psoriasis area severity index; PsO, psoriasis; PsA, psoriatic arthritis; ELISA, enzyme-linked immunosorbent assay; NB-UVB, narrowband UVB phototherapy; PUVA, psoralen UVA phototherapy; TNF-α, tumor necrosis factor alpha; PsC, psoriasis without psoriatic arthritis; RA, rheumatoid arthritis; FAE, fumaric acid esters; CSP, cyclosporine; MTX, methotrexate; HMW, high molecular weight; IL-6, interleukin 6; HDL; high-density lipoprotein; WHR, waist hip circumference ratio; IL-22, interleukin-22.

This suggests this finding may be spurious and may represent a type 1 statistical error or a false-positive result.

A study with 50 psoriasis patients and 10 healthy controls evaluated serum leptin levels, lipid profiles, and carotid intima-media thickness (IMT).[46] Patients with psoriasis showed significantly higher leptin levels and IMT than controls. The mean IMT of the four vessels examined correlated positively with patients' mean ages, disease duration, BMI, and PASI. The mean IMT also correlated positively with the mean systolic blood pressure, diastolic blood pressure, leptin levels, LDL levels, and triglyceride levels. The authors concluded that psoriasis is an independent risk factor for subclinical atherosclerosis and that cardiovascular impairment is influenced mainly by disease severity, serum triglyceride levels, and serum leptin levels.[46] Two other studies demonstrated similar findings of increased IMT and leptin levels in psoriasis patients[47] and a positive correlation between IMT and serum leptin in psoriasis patients.[47,59]

Resistin is a proinflammatory adipokine that has been shown to induce insulin resistance in mice and mice lacking resistin have low fasting blood glucose levels. Resistin deficiency in mice that lack leptin (*ob/ob* mice) leads to increased obesity, but these mice have improved glucose tolerance and insulin sensitivity. In humans, resistin is mainly produced by macrophages and monocytes residing in adipose tissue and in peripheral blood monocytes and is not detectable in adipocytes. Transcription of the resistin gene is induced by TNF-α, interleukin-1 (IL-1), and IL-6, and resistin itself promotes the expression of TNF and IL-6 by mononuclear cells, thus enhancing its own activity by a positive feedback mechanism. In addition, resistin counters the anti-inflammatory effects of adiponectin on vascular endothelial cells by promoting the expression of vascular cell adhesion molecule 1, intercellular adhesion molecule 1, and pentraxin 3 in these cells enhancing leukocyte adhesion.

Resistin has been proposed as a potential link between obesity and diabetes although no correlation between resistin, adiposity, and insulin resistance could be identified.[60] Resistin has been shown to be a marker for cardiovascular risk, and a reduction in risk might be in part related to reduced resistin level.[61,62] Resistin may be more closely linked to inflammation and resulting atherosclerosis than to obesity and insulin resistance.

Several studies demonstrated that resistin levels were elevated in patients with psoriasis compared with healthy controls[16,19,24,26,27,29,40,63–66] and correlated with disease severity.[16,19,29,65,67] A correlation between resistin levels and BMI has been shown in one study.[26] Not all studies have controlled the results for BMI or waist hip circumference ratio (WHR) to demonstrate whether the resistin level was independent of obesity.

The PASI was significantly associated ($r = 0.32$, $P < 0.05$) with serum resistin levels in 39 patients with psoriasis. There was also a significant correlation in the psoriasis group between PASI and insulin secretion ($r = 0.36$, $P < 0.05$) (measured at $t = 30$ mins of OGTT).[67] Serum resistin levels were not correlated with PASI or BMI in patients with psoriasis in a study by Nakajima, although resistin levels positively correlated with waist circumference.[40] Resistin correlated with TNF-α, a proinflammatory cytokine upregulated in psoriasis ($r = 0.45$, $P = 0.02$).[27] One study demonstrated increased IMT and resistin levels in psoriasis patients[47] and a positive correlation between IMT and serum resistin. Resistin induced significant amounts of CXCL8 and TNF-α production by monocytes making it an attractive potential effector molecule in psoriasis. There was some decrease in resistin levels after treatment with NB-UVB, but this was not significant.[29] Treatment with infliximab in a study of 40 psoriasis patients resulted in a significant reduction in resistin, chemerin, and CRP levels ($P < 0.01$).[63]

A Portuguese study demonstrated that after therapy for psoriasis including topical, NB-UVB, and PUVA, levels of resistin were significantly reduced.[16] Another study evaluated 47 patients treated with infliximab, adalimumab, ustekinumab, or NB-UVB in addition to topical therapies and found a significant decrease in resistin levels after 24 weeks ($P < 0.05$) but not after 12 weeks.[35] In contrast two studies in psoriasis patients demonstrated a lack of change in resistin levels after treatment with anti-TNF-α agents.[24,54]

Phototherapy significantly reduced resistin levels in 36 patients with psoriasis at the end of their treatment course, as

Table 2 Leptin levels in psoriasis studies

Study	Leptin, change in psoriasis	Controlled for BMI	Controlled for PASI	Controlled for PsA	Technique
Eder *et al.*[31] 203 PsA patients, 155 PsO patients; Fasting	↑ in women in PsA vs. PsO	Yes	Yes	Yes	ELISA, R&D Systems, Minneapolis, MN, USA and Invitrogen
Nakajima *et al.*[27] 30 PsO patients, 30 controls; Fasting	↑ in PsO	No	No	No	ELISA, B-Bridge International Inc., Mountain View, CA, USA
Romani *et al.*[44] 50 PsO patients, 50 controls Fasting	↑ in PsO vs. controls, ↓ in leptin after NB-UVB in patients with MS	Yes	Yes	Yes	ELISA, Assaypro, St Charles, MO, USA
Cerman *et al.*[49] 43 patients with PsO, 10 diseased controls, 10 healthy controls; Fasting; All normal BMI; No control for sex	↑ serum leptin levels, ↑ tissue leptin, ↑ leptin receptor expression in severe PsO vs. mild-moderate PsO patients or controls. Serum levels: positive correlation with PASI, Serum levels, tissue leptin and leptin receptor: positive correlation with disease duration	No	Yes	No	Immunometric sandwich enzyme-linked immunosorbant assay (ELISA), Diagnostic Systems Lab, Webster, TX, USA
Kawashima *et al.*[52] 36 PsO patients; No control for sex; Fasting	Positive correlation with BMI, No change in leptin levels postbath PUVA or NB-UVB, Significant ↓ in resistin	Yes	Yes	No	ELISA, R&D Systems, Minneapolis, MN, USA
Chen *et al.*[45] 77 PsO patients, 81 controls; Controlled for sex; Fasting state not recorded	↑ in PsO, Positive correlation with BMI, Female sex and obesity associated with ↑ leptin in psoriasis	Yes	Physician Global Assessment recorded, not PASI	Yes	ELISA, R&D Systems, Oxon, England
Enany *et al.*[46] 50 PsO patients, 10 healthy controls; Fasting; Not controlled for sex	↑ in PsO and higher carotid IMT	Yes	Yes	No	ELISA, Diagnostic System Lab, USA
Wang *et al.*[43] 144 PsO patients, 54 healthy controls; Male/Female examined separately; Fasting state not recorded	↑ in PsO, Positive correlation with BMI, No correlation with PASI	Yes	Yes	Yes	Not recorded in article
Johnston *et al.*[29] 30 PsO patients; Fasting; Pre & Post NB-UVB; Controlled for sex	No difference in PsO vs. controls, Leptin induced proinflammatory cytokines by monocytes and amphiregulin expression, Enhanced expression of leptin receptor in uninvolved skin but ↓ in lesional epidermis	Yes	Yes	No	ELISA, R&D Systems, Oxford, UK
Coimbra *et al.*[16] 10 topical therapy, 17 NB-UVB, 17 PUVA; Nonfasting; Controlled for sex	↑ in PsO vs. controls, No change posttreatment	Yes	Yes	No	ELISA, R&D Systems Minneapolis, MN, USA

Table 2 Continued

Study	Leptin, change in psoriasis	Controlled for BMI	Controlled for PASI	Controlled for PsA	Technique
Takahashi *et al.*[14] 122 PsO patients; Topical therapy, NB-UVB, etrinate, CSP; Fasting state not recorded; Not controlled for sex	↑ in PsO vs. controls, Correlation with PASI (not significant)	No	Yes	No	ELISA, Biosource, Camarillo, CA, USA
Nakajima *et al.*[40] 30 PsO patients, 30 controls; Fasting; Not controlled for sex	↑ in PsO vs. controls, Positive correlation with waist circumference	Yes	Yes	No	ELISA R&D Systems, MN, USA
Gerdes *et al.*[41] 79 PsO patients, 80 controls; Controlled for sex; Fasting state not recorded	No difference between PsO and controls, Correlated with BMI	Yes	Yes	No	ELISA, Alpco Diagnostics, Salem, NH, USA
Kaur *et al.*[42] 60 PsO patients; Fasting; Controlled for sex	Positive correlation with BMI, Associated with hsCRP, oxLDL and triglyceride levels	Yes	Yes	No	Quantitative sandwich enzyme immunoassay, R&D systems
Ozdemir *et al.*[38] 26 PsO patients, 26 BMI matched controls; CSP treatment; Fasting; Controlled for sex	↑ pre treatment vs. controls (not significant)	Yes	Yes	No	ELISA, AssayMax Human Leptin ELISA kit, Assay Pro
Robati *et al.*[47] 60 PsO patients, 60 controls; Fasting; Not controlled for sex	↑ in PsO vs. controls Positive correlation with mean intima-media wall thickness of common carotid artery	Yes	Yes	No	ELISA, Biovendor Research & Diagnostic Products
Asha K *et al.*[59] 80 PsO patients, 80 controls; Fasting; Not controlled for sex	Positive correlation with mean intima-media wall thickness of common carotid artery	No	Yes	No	ELISA, Biovendor
Oh YJ *et al.*[17] 24 PsO patients, 15 controls; Fasting; Controlled for sex	↑ in PsO vs. controls	Yes	Yes	Yes	ELISA, R&D Systems, MN, USA
Baran A *et al.*[18] 49 PsO patients, 16 controls; Topical therapy	↓ in PsO vs. controls ↑ after topical therapy	No	Yes	No	ELISA, R&D Systems, MN, USA
Rajappa *et al.*[19] 60 PsO and PsA patients, 60 controls; Coal tar or methotrexate treatment; Fasting; Not controlled for sex	↑ in PsO vs. controls ↓ posttreatment after 12 weeks	Yes	Yes	Yes	ELISA, Diagnostic Biochem Canada
Karadag AS *et al.*[39] 34 PsO patients, 34 controls; Acitretin treatment; Fasting; Not controlled for sex	Leptin decreased after treatment compared to controls	Yes	No	No	ELISA, Boster Biological Technology, Immunoleader

Table 2 Continued

Study	Leptin, change in psoriasis	Controlled for BMI	Controlled for PASI	Controlled for PsA	Technique
Xue K *et al.*[51] 99 PsO patients; Fasting; Controlled for sex	Positive correlation with PASI in overweight or obese males ↑ secretion of proinflammatory cytokines by keratinocytes *in vitro*	Yes	Yes	No	R&D Systems, MN, USA
Takahashi *et al.*[35] 37 PsO patients; Ustekinumab, infliximab, adalimumab, NB-UVB; Not controlled for sex; Fasting state not recorded	↓ posttreatment after 24 weeks	No	No	No	ELISA, R&D systems, Oxon, UK
Aly DG *et al.*[48] 40 PsO patients, 20 patients with skin disease, 20 controls; Fasting Controlled for sex	↑ in nonobese PsO patients vs. controls No correlation with PASI	Yes	Yes	No	ELISA, DRG® ELISA EIA-2395, New Jersey

BMI, body mass index; PASI, psoriasis area severity index; PsA, psoriatic arthritis; PsO, psoriasis; ELISA, enzyme-linked immunosorbent assay; PUVA, psoralen UVA phototherapy; NB-UVB, narrowband UVB phototherapy; MS, metabolic syndrome; IMT, intima-media thickness; FAE, fumaric acid esters; CSP, cyclosporine; MTX, methotrexate; hsCRP, high sensitivity C reactive protein; oxLDL, oxidized low-density lipoprotein.

discussed previously.[52] Treatment with topical therapies, etretinate or cyclosporine resulted in a significant decrease in resistin levels in 62 psoriasis patients ($P < 0.05$).[65] Another study demonstrated a significant decrease in resistin levels after 12 weeks of treatment with methotrexate or coal tar.[19] In a study of 10 male patients with psoriasis and 10 healthy controls, serum resistin levels were higher than observed in control subjects and normalized after 1 month of actitretin treatment.[64] This reduction was maintained at 3 months. The transient impairment in insulin sensitivity in this study was not associated with an increase in resistin levels seeming to exclude a role for resistin in insulin resistance.[64] A study of three patients with psoriasis, using microdialysis to examine the micromilieu of psoriatic plaques, demonstrated a decrease in resistin concentration in lesional skin after 12 weeks of treatment with fumaric acid esters.[68] Methotrexate treatment did not effect a change in resistin levels in 35 psoriasis patients.[26] A study with 23 male patients with moderate-to-severe psoriasis evaluated hormonal status, in particular sex hormone-binding globulin (SHBG), as an indicator for insulin resistance in patients receiving systemic therapy.[69] PASI-50 was achieved in 19 of the 23 patients. Statistically significant correlations between the PASI and fasting insulin on the one hand, and SHBG on the other hand, were present before but not after effective therapy. Leptin had a significant influence on SHBG ($P = 0.03$), as did resistin at baseline in those who responded to therapy ($P < 0.001$). The measurements of hs-CRP, PASI, leptin, and resistin all improved after therapy, thus losing their influence on SHBG. The authors suggest that SHBG improvement, as well as the decrease in serum resistin levels, likely reflects a state of reduced cardiovascular risk in patients receiving continuous systemic therapy.[69]

Retinol-binding protein 4 (RBP4) is secreted by hepatocytes, adipocytes, and macrophages. It transports retinol (vitamin A) and is involved in the regulation of glucose homeostasis in type 2 diabetes. Retinol-binding protein-4 is produced by visceral adipocytes in states of obesity and insulin resistance. Increased RBP4 levels are associated with cardiovascular risk factors such as BMI, WHR, serum triglycerides, and systolic blood pressure. Retinol-binding protein-4 levels are inversely associated with plasma high-density lipoprotein. A pathogenic role for RBP4 in cardiovascular disease and obesity has therefore been proposed.[70]

RBP4 levels were decreased in 79 patients with psoriasis compared to controls in one study.[41] Patients were controlled for BMI, WHR, and psoriasis severity. RBP4 levels were increased at baseline in a study of patients with moderate-to-severe psoriasis compared to controls and correlated with PASI.[44]

In a study discussed previously, evaluating the association between adipokines and Th-17-related cytokines, a strong negative association was found between RBP-4 and IL-6 in 30 patients with psoriasis.[27] The authors suggest that RBP-4 expression may be downregulated when proinflammatory mediators are increased.[27] Treatment with acitretin significantly reduced RBP-4 levels in psoriasis patients ($P < 0.0001$).[39]

Other adipokines that may be involved in psoriasis pathogenesis include *visfatin, chemerin,* and *omentin*. Visfatin is a proinflammatory cytokine that upregulates the production of IL-6, interleukin-1 beta (IL-1β), and TNF-α in human monocytes. In addition, visfatin shows insulin-like effects by binding to insulin receptors. Ten patients with severe psoriasis (<60% body surface area) had gene profile expression of peripheral blood mononuclear cells analyzed before and after treatment.[71] Gene expression of visfatin was strongly upregulated in the diseased

state. Visfatin has been demonstrated to enhance the production of antimicrobial peptides in human keratinocytes and their orthologs in murine imiquimod-treated skin, mimicking psoriasis.[72] Antimicrobial peptide expression is enhanced in psoriatic lesions and may result in disease development, suggesting a role for visfatin in the development of psoriasis. Visfatin was higher in 40 patients with psoriasis than controls in one study, although the difference was not significant and surprisingly increased after 12 months of treatment with infliximab.[63] One proposed theory is that at higher concentrations visfatin may induce the expression of anti-inflammatory cytokines such as IL-10 and IL-1 receptor antagonist.[63]

Chemerin is a chemotactic protein involved in the recruitment of plasmacytoid dendritic cells in the early stages of psoriasis development. It is mainly released by dermal fibroblasts. Chemerin was significantly elevated in the patients with psoriasis as previously discussed and correlated with CRP ($r = 0.4$, $P = 0.01$) and resistin ($r = 0.3$, $P = 0.01$).[63] Chemerin levels were higher in patients with psoriatic arthritis than patients without arthritis ($P = 0.01$).[63] A significant reduction in chemerin was observed after 2 months of infliximab treatment ($P < 0.01$).[63]

Omentin is a protein secreted from visceral adipose tissue. It increases insulin sensitivity in human adipocytes. Decreased omentin levels have been shown to be associated with obesity and insulin resistance. Omentin may play a role in comorbidities associated with obesity.[73] Higher levels of visfatin and lower levels of omentin-1 were demonstrated in 46 patients with psoriasis compared to 42 healthy controls.[74] Visfatin levels positively correlated with disease severity and duration.[74]

Conclusion

Adiponectin, an anti-inflammatory and antiatherogenic adipokine that is reduced in obesity, has demonstrated a contradictory pattern in patients with psoriasis (Table 1). Levels of adiponectin have been reported to be reduced, unchanged, and

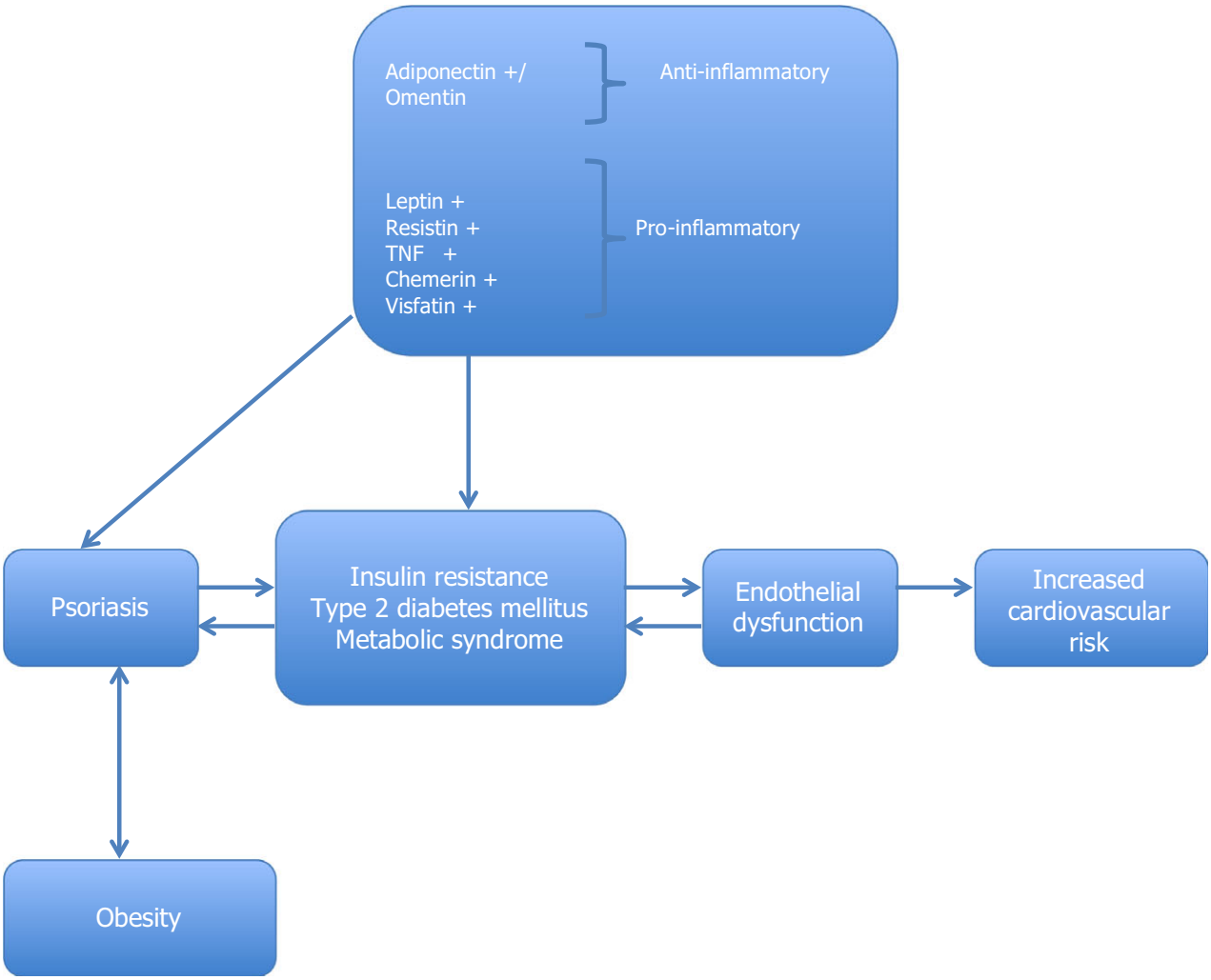

Figure 2 Adipokines, psoriasis, and increased cardiovascular risk

increased in patients with psoriasis. The disparity in adiponectin levels measured in patients with psoriasis in these studies may be due to the fact that not all studies controlled for BMI, psoriasis severity, or the presence of psoriatic arthritis. The variability in study results may reflect different immunoassay techniques and the measurement of adiponectin levels at different timepoints in the disease. Continuous systemic therapy for psoriasis therapy has resulted in increased levels of adiponectin in some studies (Fig. 1). Elevated adiponectin levels may suppress inflammation and reverse metabolic dysfunction. A prospective controlled study of patients with psoriasis, measuring adiponectin at different timepoints, before, during, and after systemic therapy, is needed.

The proinflammatory adipokines, leptin (Table 2) and resistin, have been shown to be elevated in patients with psoriasis in many studies. A correlation with disease severity has been shown. Resistin levels are significantly reduced in most studies of patients with psoriasis after treatment.

Patients with psoriasis are at risk of obesity and obesity-related diseases. Adipokines are dysregulated in patients with psoriasis, both as a consequence of and independently of obesity. Adipokines may provide a link between the state of

Table 3 Selected adipokines and possible effects on psoriasis

Adipokine	Role of adipokine	Effects on psoriasis
Adiponectin	Anti-inflammatory	HMW adiponectin inversely correlates with psoriasis severity
	Antiatherogenic	Contradictory adiponectin level results in psoriasis patients
	Protects against obesity-linked metabolic dysfunction in mouse models	Majority of studies show increase in adiponectin levels with psoriasis therapy associated with metabolic syndrome and CVD
		?Elevated adiponectin suppresses inflammation and immune responses of psoriasis
Leptin	Proinflammatory	Increased in psoriasis
	Regulates feeding behavior through the CNS	Increases Th-1 type cytokines and decreases Th-2 type cytokines – ?role in pathogenesis of psoriasis
	Affects keratinocyte proliferation, expression of adhesion molecules, and angiogenesis	
Resistin	Proinflammatory cytokine	Increased in psoriasis
	Induces insulin resistance in mice	Correlates with disease severity
		Decreased in most studies after psoriasis treatment
		Possibly involved in the metabolic syndrome
Retinol binding protein-4	Transfers retinol	Decreased in psoriasis compared to controls surprisingly not known
	Plays a major role in insulin resistance	
Visfatin	Proinflammatory cytokine	Enhances production of antimicrobial peptides in human keratinocytes mimicking psoriasis
	Binds to insulin receptors	
		Visfatin gene upregulated in patients with psoriasis
Chemerin	Chemotactic protein	Involved in the recruitment of plasmacytoid dendritic cells in the early stage of psoriasis
	Released by dermal fibroblasts	
Omentin	Increases insulin sensitivity in human adipocytes	Lower levels of omentin-1 in psoriasis patients compared to controls
	Anti-inflammatory	Increased after treatment
		Risk factor for insulin resistance
Apelin	Angiogenesis, blood pressure regulation	Higher levels in psoriasis
		Not known
IL-6	Pro and anti-inflammatory	Increased in psoriasis
		Positive correlation with PASI
		Risk factor for CVD and diabetes
TNF-α	Proinflammatory	Increased in psoriasis
		Positive correlation with PASI
		Development of metabolic syndrome and vascular diseases
MCP-1	Proinflammatory	Increased in psoriasis
		Decreased in lesional psoriasis after therapy
		Associated with cardiometabolic disease
PAI-1	Inhibitor of fibrinolysis	Increased in psoriasis
		Lower with therapy
		Risk factor for CVD and T2DM

HMW, high molecular weight; CVD, cardiovascular disease; CNS, central nervous system; IL-6, interleukin-6; TNF-α, tumor necrosis factor alpha; PASI, psoriasis area and severity index; MCP-1, monocyte chemoattractant protein-1; PAI-1, plasminogen activator inhibitor-1; T2DM, type 2 diabetes mellitus.

inflammation and endothelial dysfunction in patients with psoriasis (Fig. 2; Table 3).

In addition to dysregulated adipokines, other mechanisms have been proposed to link psoriasis with the MS and increased cardiovascular risk. Vitamin D is an immune modulator implicated in keratinocyte turnover. The hormonally active form of vitamin D, 1-α, 25 hydroxyvitamin D3 (calcitriol), acts through the vitamin D receptor (VDR) on keratinocytes.[75] The VDR binds to and activates transcription of genes leading to antiproliferative and prodifferentiative effects on keratinocytes. Calcitriol has been shown to play an important role in psoriasis due to its ability to modulate innate and adaptive immunity.[75] It is thought that through these mechanisms topical vitamin D is effective in psoriasis.[76] Recent evidence suggests that vitamin D may play a role in improving the MS. Vitamin D has been shown to be sequestered in adipose tissue in MS with reduced circulating levels.[77] Low vitamin D has been linked with insulin resistance, the MS,[78] and an increased incidence of cardiovascular events.[79] Vitamin D has been shown to have anti-inflammatory effects.[80] Systemic oral vitamin D has been suggested to play a role in both treating psoriasis and reducing the risk of cardiovascular disease and large-scale long-term clinical trials to evaluate this have been recommended.[81]

Continuous therapy of patients with psoriasis has been shown to improve the dysregulated adipokine profile associated with their increased cardiovascular risk. Further research is required into the role of adipokines in patients with psoriasis and their psoriasis-related comorbidities in particular CVD. Examining adipokines in a well-phenotyped population with psoriasis, controlling for endocrinological factors, is important to further our understanding of the disease. Adipokines may be mediators of cutaneous inflammation suggesting a role in the pathophysiology of psoriasis and the development of comorbidities.

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