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**Adipocytokines and psoriasis: Insights into mechanisms linking obesity and inflammation to psoriasis**

**Dalamaga M *et al*.** Adipocytokines and psoriasis

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**Abstract**

Psoriasis has been lately seen as a potential systemic inflammatory disease associated with a range of co-morbidities exhibiting an overlapping pathology and presenting a great social health impact such as cardiovascular disease and metabolic diseases, including obesity. Adipose tissue is considered a genuine endocrine organ producing a variety of bioactive adipocytokines, such as leptin, adiponectin, resistin and visfatin, participating in physiological and pathological processes, such as energy balance, insulin sensitivity and resistance, immunity, inflammation, hematopoiesis and angiogenesis. Adipocytokines could serve as a missing link in the association between psoriasis, obesity and metabolic co-morbidities. In chronic inflammatory disease states such as psoriasis, adipocytokines may be implicated in psoriasis onset, progression, severity as well as in the pathogenesis of co-morbidities. Measuring serum adipocytokine levels in the future may be useful in predicting psoriasis severity, progression, treatment outcome and risk of any co-morbidities. Interventions to decrease pro-inflammatory adipocytokine levels could offer preventive and therapeutic options for improving psoriasis severity and protecting against its co-morbidities. Candidate strategic interventions incorporate increased physical activity, weight control and pharmacologic approaches such as metformin. However, the mechanisms underlying the actions of adipocytokines in psoriasis as well as their potential diagnostic, prognostic and/or therapeutic utility require further investigation with larger prospective, longitudinal and mechanistic studies.

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**Key words:** Psoriasis; Adipocytokine; Obesity; Leptin; Adiponectin; Omentin; Resistin; Visfatin

**Core tip:** Adipocytokines could serve as a missing link in the association between psoriasis, obesity and metabolic co-morbidities. In chronic inflammatory disease states such as psoriasis, adipocytokines may be implicated in psoriasis onset, progression, severity as well as in the pathogenesis of co-morbidities. Measuring serum adipocytokine levels in the future may be useful in predicting psoriasis severity, progression, treatment outcome and risk of any co-morbidities. Interventions to decrease pro-inflammatory adipocytokine levels could offer preventive and therapeutic options for improving psoriasis severity and protecting against its co-morbidities. Candidate strategic interventions may incorporate increased physical activity, weight control and pharmacologic approaches such as metformin.

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**PSORIASIS AND ADIPOSE TISSUE**

Psoriasis represents a complex, chronic, systemic, T-cell immune-mediated inflammatory dermatopathy characterized by skin and joint manifestations, and presenting commonly with erythematous, scaly plaques on various surfaces of the body[1,2]. Its prevalence varies approximately from 0.1% to 3% worldwide, with a mean prevalence rate of 1.90% in Western countries and a lower one in Asia[3].

The etiology of psoriasis remains unknown but the disease is believed to result from an interaction between genetic susceptibility and exogenous environmental factors, such as infection, in particular with β-hemolytic streptococci, stress and trauma[1-2,4]. Several human leukocyte antigen (HLA) alleles including HLA-Cw\*0602 are associated with psoriasis with *PSORS1* being the major susceptibility gene mapped next to the HLA-Cw6 antigen[2,5]. Moreover, non-HLA related genes and loci have been identified and associated with psoriasis risk such as interleukin (IL)-12B and IL-23R[2].

Psoriasis has been lately seen as a potential systemic inflammatory disease associated with a range of co-morbidities exhibiting an overlapping pathology and presenting a great social health impact such as cardiovascular disease, metabolic diseases, autoimmune disease, malignancy, chronic obstructive pulmonary disease, sleep apnea and psychiatric disorders[1,2,6,7]. Overweight/obesity, metabolic syndrome (Mets), diabetes mellitus type 2 (t2DM) and dyslipidemia occur at a higher frequency in psoriasis patients than in general population[8]. Mets constitutes a constellation of cardiometabolic risk factors comprising central obesity, impaired glucose tolerance, elevated blood pressure and dyslipidemia[9]. Both psoriasis and Mets share common genetic predisposition; though their exact interplay remains enigmatic. Also, psoriasis and metabolic disorders share common risk factors such as smoking, obesity, physical inactivity and psychological stress[8]. Hence, all these cardio-metabolic risk factors, lifestyle parameters and the underlying chronic systemic psoriatic inflammation may all contribute to an increased risk for cardiovascular disease.

Apart from its fat storage function, adipose tissue constitutes an active endocrine organ secreting several bioactive adipocytokines regulating physiological and pathological processes, such as appetite, insulin sensitivity and resistance, immunity, inflammation, hematopoiesis and angiogenesis[10]. Increased adiposity following weight gain is associated with elevated levels of adipocytokines, comprising leptin, resistin and visfatin, and decreased levels of adiponectin and omentin, that may promote stimulation of monocytes and T cells, leading to both T-helper (Th)1 and Th17 immune responses and impairing the function of T regulatory cells[10-12]. Besides, the etiopathogenesis of Mets is attributed to hyperinsulinemia and insulin resistance mediated by adipocytokines, such as TNF-α, leptin, adiponectin and resistin[11]. It seems that obesity may potentiate the inflammation of psoriasis while, at the same time, it may help the development of Mets. Therefore, adipocytokines may represent a missing link in the association between psoriasis and metabolic co-morbidities, and could be used as potential biomarkers for assessing psoriasis severity, progression, treatment outcome, and risk of co-morbidities.

**ADIPOCYTOKINES AND PSORIASIS**

***Leptin***

Leptin is a 16-kDa, 167-amino acid adipocytokine that is primarily produced in adipose tissue. It is a pleiotropic molecule regulating food intake, appetite, energy expenditure, immunity, inflammation, hematopoiesis, cell differentiation and proliferation[12,13]. Leptin levels are directly proportional to the amount of body fat and fluctuate with acute changes in caloric intake, signaling the amount of energy stored in adipose tissue[12,13]. Although patients with hypoleptinemia and leptin deficiency are obese, common forms of obesity, insulin resistance and metabolic syndrome are accompanied by hyperleptinemia due to leptin resistance[12]. Leptin may be involved in the pathogenesis of psoriasis. It stimulates monocytes and macrophages, enhances the secretion of proinflammatory cytokines tumor necrosis factor-alpha (TNF-α), IL-6, IL-1, and IL-12, and shifts T-cell differentiation to Th1 phenotype[12,14]. Leptin stimulates also keratinocyte proliferation, angiogenesis and expression of adhesion molecules[14]. Despite the small size of epidemiologic studies and the lack of adjustment for body mass index (BMI) in analyses, the majority of studies examining the association between leptin and psoriasis has documented that psoriasis is associated with hyperleptinemia[14-17]. Also, elevated leptin levels characterize psoriatic arthritis and correlate with Psoriatic Arthritis Joint Activity Index[18]. In most studies, leptin correlated with Psoriasis Area Severity Index (PASI) score, representing, therefore, a biomarker of psoriasis severity and chronicity[19]. Indeed, severely affected psoriatic patients exhibit a significant increase in leptin levels compared to moderately affected patients[14]. Furthermore, leptin receptor and leptin expression in skin biopsies were found increased in severe psoriasis[19]. However, a possible association of psoriasis with leptin needs to be analyzed further with larger prospective, longitudinal and mechanistic studies in order to provide further insights into the paracrine and endocrine mechanisms underlying leptin’s role in psoriasis.

***Adiponectin and omentin***

Adiponectin is a 30-kDa, 244-amino-acid protein produced predominantly by white adipose tissue, sharing a homology with TNF-α, collagen VIII, X and complement factor C1q[10,11]. Adiponectin exhibits insulin-sensitizing, anti-inflammatory, anti-atherogenic, cardioprotective and anti-neoplastic effects as well as distinct actions in lipid metabolism[10,11]. The high molecular weight isoform is the biologically active configuration of adiponectin, being related with Mets, insulin resistance and cardiovascular disease[11]. Hypoadiponectinemia is the common pathodenominator of the constellation of risk factors that compose Mets, such as hypertension, dyslipidemia, obesity, hyperglycemia and insulin resistance[11]. In contrast, hyperadiponectinemia is present in chronic inflammatory and autoimmune diseases not related to obesity such as rheumatoid arthritis and inflammatory bowel disease[10]. Adiponectin exhibits powerful anti-inflammatory properties by inhibiting the inflammatory cytokine network and down-regulating TNF-α-induced expression of endothelial adhesion molecules, TNF-α-expression in macrophages and adipose tissue, TNF-α-induced secretion of IL-6 in monocyte cells and keratinocytes *in vitro* as well as TNF-α, IL-6, IL-17, IL-22 and interferon-γ from T-lymphocytes[3,10,14]. Despite the fact that psoriasis is often associated with disease states characterized by hypoadiponectinemia such as Mets and obesity, controversial data exist in the literature regarding the association of adiponectinemia with psoriasis. A decrease, no change and even an increase in adiponectin levels have been reported in psoriasis patients[14,20-22]. Although not all results were adjusted for BMI, some studies have indicated a BMI independent change in adiponectin levels especially after treatment[21] as well as a negative correlation with PASI and pro-inflammatory cytokines such as TNF-α and IL-6[20,22].

Omentin, a newer 40-kDa adipocytokine, secreted mainly by stromal cells in the visceral fat, with similar properties to adiponectin, was found decreased in psoriatic patients in comparison to controls[23].

***Resistin***

Resistin is a 12 kDa cysteine-rich polypeptide which is produced in humans predominantly by stromal macrophages and monocytes of the visceral adipose tissue[24]. Elevated resistin levels are found in obesity and inflammation, and may play a significant role in the pathogenesis of insulin resistance, Mets and t2DM[24-27]. More importantly, resistin acts as a pro-inflammatory factor leading to an increased mRNA expression of twenty chemokines and cytokines including TNF-á, IL-1, IL-6, IL-12, chemokine ligand CXCL8, monocyte chemoattractant protein-1 and resistin itself via the nuclear factor-êÂ (ÍF-êB)[25]. In the majority of studies exploring the association of resistin with psoriasis, hyperrestinemia characterized untreated psoriatic patients and correlated with disease severity and nail psoriasis severity index [14,25-29].

***Visfatin and other adipocytokines***

Visfatin is a 52-kDa pleiotropic adipocytokine secreted by the macrophages of the visceral fat, acting as a cytokine, a growth factor and an enzyme, and playing a significant role in the cellular energy metabolism and in a variety of metabolic and stress responses[30-32]. Despite the conflicting association of visfatin with metabolic and anthropometric parameters, its concentrations are usually elevated in obese individuals, obese children and adolescents, in patients with coronary heart disease, t2DM, Mets and non-alcoholic fatty liver disease as well as in chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease[31-34]. Visfatin enhances the production of IL-1α, ΙL-6, TNF-α, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 through the pro-inflammatory transcription factor NF-κB, and may contribute to the pathogenesis of vascular inflammation of obesity[31,32]. Visfatin may play a significant role in psoriasis pathophysiology. In a small size study, serum visfatin was significantly elevated in psoriasis patients than in healthy controls, correlating positively with disease chronicity and severity[23]. *In vivo*, the visfatin gene expression profile was increased in proriasis while *in vitro* visfatinupregulated TNF-α-induced chemokine ligands: CXCL 8, 10 and CCL20 production and mRNA expression in human keratinocytes[35,36].

Data regarding newer and promising adipocytokines, such as vaspin, retinol-binding protein 4 and chemerin with respect to psoriasis are sparse and controversial [14,37].

The controversy of results in epidemiologic studies examining the association of adipocytokines with psoriasis may be attributed to the (1) retrospective study design; (2) small sample size; (3) non-adjustment of the results for BMI, waist circumference and metabolic parameters as well as for important confounders such as coronary disease; (4) different ethnic groups examined; (5) importance of measuring fasting samples versus non-fasting; and (6) different laboratory assays used.

In conclusion, adipocytokines such as leptin, adiponectin, resistin and visfatin represent key players in many physiologic processes including energy balance, immunity and inflammation. Adipocytokines could serve as a missing link in the association between psoriasis, obesity and metabolic co-morbidities. In chronic inflammatory disease states such as psoriasis, adipocytokines may be implicated in psoriasis onset, progression as well as in the pathogenesis of co-morbidities. Measuring serum adipocytokine levels in the future may be useful in predicting psoriasis severity, treatment success and risk of any co-morbidities. We also speculate that interventions to decrease pro-inflammatory adipocytokine levels could represent a preventive and therapeutic option for improving disease severity and protecting against its co-morbidities. Candidate strategic interventions incorporate increased physical activity[38], weight control and pharmacologic approaches such as metformin[10,11]. However, the mechanisms underlying the actions of adipocytokines in psoriasis as well as their potential diagnostic, prognostic and/or therapeutic utility require further investigation with larger prospective, longitudinal and mechanistic studies.

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