



# Psoriasis and insulin resistance: a review

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## Abstract

Psoriasis is a T-cell mediated inflammatory disease of the skin and joints. It has been linked to obesity and to the metabolic syndrome. It is now recognized that psoriasis is also associated with insulin resistance, diabetes and atherogenesis. This appears to be due to the adipokines and mediators of inflammation which are common to these conditions. In this review, we sought to demonstrate the increasing evidence that these conditions are associated and to review the potential pathogenesis and mechanisms.

**Keywords:** Psoriasis, insulin resistance, cytokines, adipokines, type 2 diabetes mellitus, endothelial dysfunction

## Introduction

### Psoriasis

Psoriasis is a chronic T-cell type 1 (Th-1) mediated inflammatory disease of the skin with prevalence of 2% [1]. Psoriatic arthritis may be present in up to 20% of patients with skin disease [1]. The improvement of psoriasis when treated with ciclosporin was the first indication that psoriasis was a T-cell mediated disease [2-4]. Later studies demonstrated the infiltrate in psoriatic plaques to be composed of Th1 cells, producing Th1 cytokines (for example TNF-alpha). The improvement of psoriasis in response to anti-TNF therapies supported the hypothesis that psoriasis is a Th1-mediated disease [4-8]. More recently a novel class of T helper lymphocytes, described as Th17 lymphocytes expressing IL-17 and Th17 cytokines (for example IL-17 and IL-22) were found to be expressed in psoriatic lesions, indicating that these cells also play a role in the pathogenesis of psoriasis [9-11].

In recent years, more has been learned about psoriasis and its disease associations, and physicians now recognise that psoriasis is a disease that affects much more than just the skin. Patients with moderate or severe psoriasis have increased rates of obesity (defined as a body mass index greater than 30) [12,13], but additionally psoriasis has also been linked to the metabolic syndrome. This cluster of pathophysiological states and cardiovascular risk factors which includes abdominal obesity (as well as impaired glucose regulation, hypertriglyceridaemia, reduced high-density lipoprotein, and hypertension) [14-18] affects 25% of the US population and predisposes to the development of cardiovascular disease and type 2 diabetes [18]. Indeed, patients with psoriasis are at risk of cardiovascular events at a younger age [19-21] than their counterparts unaffected by the disease. As might be deduced from these disease associations, there is now a growing body of evidence that insulin resistance is also

more prevalent in patients with psoriasis [22,23].

### Insulin resistance

Insulin resistance is the phenomenon where glucose absorption by cells stimulated by insulin is reduced [24]. In response to this, beta cells in the pancreas are stimulated to secrete more insulin, leading to abnormally elevated levels of insulin. This eventually induces beta-cell failure, which may lead to the development of type 2 diabetes. Thus insulin resistance may be a pre-emptive stage in the pathogenesis of type 2 diabetes. Insulin resistance can be assessed in patients by several means. Firstly, the hyperinsulinaemic-euglycaemic clamp quantifies exogenous glucose required for a euglycaemic state, but it is an invasive and expensive method of assessing insulin resistance [25]. The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) is instead a mathematical formula to calculate insulin resistance:

$$\text{Insulin resistance} = \frac{\text{fasting insulin (mIU/L)} \times \text{fasting glucose (mmol/l)}}{22.5}$$

An index of 2.5 indicates insulin resistance [25]. An alternative practical means is the oral glucose tolerance test (OGTT). During this test, patients consume 75g of glucose and blood glucose and insulin levels are measured at 0 minutes, 30 minutes, 60 minutes, and 120 minutes [25]. These methods can thus be used effectively to assess patients with psoriasis for insulin resistance and are invaluable to this research.

## Review

### Insulin resistance in patient with psoriasis

Boehncke et al., noted that the severity of psoriasis, as measured by the Psoriasis Area and Severity Index PASI (an objective measure of the severity of a patient's psoriasis) correlated with

insulin resistance, as determined by the OGTT and HOMA-IR [22]. Other studies have also supported this finding. In an observational study of 65,449 patients, Brauchli et al., found that patients who had psoriasis for more than two years, were at a significantly increased risk of developing diabetes, and therefore insulin resistance [23]. Ucak et al., found that patients with psoriasis were more insulin resistant than healthy controls, as measured by HOMA-IR [26]. Karadag et al., found significantly elevated fasting levels of insulin and insulin resistance as calculated by HOMA-IR in patients with psoriasis when compared to controls [27]. Interestingly, Boehncke et al., also found that cytokine-induced insulin resistance may contribute to epidermal dysfunction and therefore the development of psoriasis [28].

The National Psoriasis Foundation now recommend that fasting blood glucose levels be evaluated at least every 5 years or every 2 years (if risk factors are present) in patients with psoriasis, with a target level of <100mg/dl [29,30].

Not only is the association between psoriasis and the development of insulin resistance now being recognized, the consequences of insulin resistance in such patients are also apparent. Downstream of the insulin receptor, a signaling protein, IRS-1, normally acts to induce glucose uptake in fat cells and vasodilator production in endothelial cells [25]. With decreased sensitivity to insulin, levels of IRS-1 fall [25]. The effects of this may be endothelial dysfunction, predisposing to paradoxical arterial vasoconstriction and therefore earlier atherogenesis. Evidence for this hypothesis is that patients with lower IRS-1 levels are noted to have a thicker intima media in the carotid arterial bulb [33]. Additionally, patients with psoriasis and insulin resistance, as calculated by HOMA-IR, appear to have higher levels of endothelin-1 and impaired flow-mediated vessel dilation [27]. Carotid atheroma plaque is also observed more frequently in patients with psoriasis than with controls [32].

### Pathogenesis

But what exactly is the pathogenesis of insulin resistance and all its downstream effects in psoriasis? The answer to this question seems to be a complex interplay between adipokines and cytokines associated with psoriasis.

In obese patients, adipose tissue macrophages constitute 40% of adipose tissue and produce various adipokines which can influence glucose metabolism. Therefore visceral adipose tissue may act as an endocrine organ and play a role in the development of the metabolic syndrome and type 2 diabetes [33]. It may contribute to the development of insulin resistance in patients with psoriasis by secreting such adipokines as resistin, adiponectin and leptin.

Resistin and leptin are polypeptides that may contribute to insulin resistance in psoriasis. Resistin is a polypeptide synthesized by monocytes and macrophages in fat tissue, capable of promoting synthesis of TNF-alpha [34], which is involved in the pathogenesis of psoriasis. A link between

resistin and insulin resistance has been demonstrated, although not yet fully elucidated. Mice given resistin have a lower sensitivity to insulin and obese patients, in whom insulin levels are elevated, also have higher levels of resistin, than thin people [34,35]. A link between resistin and psoriasis has also been demonstrated - Boehncke et al., showed that psoriasis severity and PASI scores are associated with elevated levels of resistin, and indeed, levels of resistin fall with phototherapy, which is commonly used to treat psoriasis [28]. Leptin, a polypeptide also produced by adipocytes, acts as a neuropeptide to reduce appetite and therefore regulate food consumption. Leptin deficiency is a pathological cause of obesity, however, in patients who are obese due to excess food consumption and insufficient exertion, leptin levels are high, and this hyperleptinaemia is a risk factor for type 2 diabetes [36]. Additionally, there is evidence to support the hypothesis that leptin may contribute to insulin resistance in patients with psoriasis. Patients with psoriasis have higher leptin levels when compared to controls [34,37,38]. It is also postulated that leptin may in fact contribute to the development of psoriasis by promoting Th1 cytokine synthesis [39].

As mentioned, adipocytes in visceral tissue also produce adiponectin, a polypeptide that has both anti-inflammatory and anti-atherogenic effects [40]. However, both patients with type 2 diabetes and psoriasis have lower levels of adiponectin than controls, and interestingly, adiponectin levels are negatively correlated with both disease severity, as indicated by PASI scores, and plasma concentration of TNF-alpha [41,42].

While there does appear to be a link between the adipokines produced by fat tissue and insulin resistance in diabetes, it does not explain entirely the association between psoriasis and diabetes, independent of obesity. It is now thought that the inflammatory molecules associated with psoriasis may not only antagonise the effects of insulin, but also contribute to the downstream effects of insulin resistance. Inflammatory mediators additionally contribute to the development of atherosclerotic plaque and continuing inflammation may also result in atherosclerotic plaque rupture and therefore lead to thrombo-embolic events [25]. Examples of such mediators are interleukins 6, 8, 17 and 18; TNF-alpha and plasminogen-activator-inhibitor 1.

TNF-alpha is a pro-inflammatory cytokine produced by various cells that influences the production of other cytokines as well as the proliferation and activation of cells involved in inflammation. The key role of TNF-alpha in psoriasis has been demonstrated by the fact that levels are elevated in patients with psoriasis and correlate with disease severity. Major breakthroughs in the treatment of psoriasis came with the development of TNF-alpha inhibitors, which are now commonly used to treat severe or resistant disease. But TNF-alpha may also contribute to the development of insulin resistance in patients with psoriasis. This is suggested by the fact that obese individuals also have higher levels of TNF-

alpha, which fall with weight loss. Additionally, injection of TNF-alpha into healthy mice results in insulin resistance [43]. It is thought that the mechanism may be by reducing tyrosine kinase activity of the insulin receptor.

As mentioned IL 6, 8, 17 and 18 may also contribute to the development of insulin resistance. Interleukin-6 is a pro-inflammatory cytokine, levels of which are significantly increased particularly in obese patients with psoriasis and increase with disease severity [39]. While it certainly plays a role in the pathogenesis of skin disease, higher levels of IL-6 are also positively correlated with poor glucose tolerance, blood pressure and levels of triglycerides, suggesting a role in the development of insulin resistance and the metabolic syndrome [44,45]. Interleukin 1-beta, also a pro-inflammatory cytokine, may act in conjunction with IL-6. Patients with higher levels of both IL-6 and -1-beta are at increased risk of diabetes compared with patients with elevated IL-6 only. This may be because IL-1-beta antagonises insulin-mediated glucose uptake by adipocytes. Similarly, IL-17 and IL-18, other pro-inflammatory cytokines are increased in patients with psoriasis. Both are also found at higher levels in type 2 diabetes and therefore may be related to the development of insulin resistance [46,18,48,49]. Interleukin-8, a chemokine, may inhibit the action of insulin through MAP kinase. Levels of this chemokine are also elevated in psoriasis and fall with successful treatment [47].

Several other inflammatory mediators may also play a role. Plasminogen-activator-inhibitor 1 (PAI-1) is a serine protease inhibitor considered a risk factor for the development of diabetes. Elevated levels of PAI-1 correlate with insulin resistance. Levels of this glycoprotein are also noted to be elevated in patients with psoriasis and decrease with successful treatment [50,51]. Similarly, serum lipocalin-2 levels, also related to insulin resistance, are significantly higher in patients with psoriasis [52]. It is thought that the development of islet amyloid in the pancreas may contribute to the pathogenesis of type 2 diabetes and serum amyloid A may be elevated in patients with psoriasis, particularly in those with psoriatic arthropathy [53,54].

Further evidence supporting the role of both adipokines and inflammatory mediators in the development of insulin resistance in patients with psoriasis comes from evolving therapies for type 2 diabetes and for psoriasis. The glucagon-like-peptide-1 receptor agonists exenatide and liraglutide are used to achieve glycaemic control in diabetes. They act as agonists at the glucagon-like-1 peptide receptor and this action has the effect of lowering glucose levels. More recently they were noted to improve itching and PASI scores in three obese patients with psoriasis and type 2 diabetes after 6 weeks of therapy. This appears to be due to their additional anti-inflammatory effect, as treatment with these agents resulted in a reduction in the number of natural killer cells in psoriatic plaques and an increase in the number in circulation [55,56]. This anti-inflammatory action may improve insulin

resistance, which may also account for their successful use in the treatment of type 2 diabetes.

## Conclusion

As knowledge of psoriasis expands, it is evident that it is in fact a systemic disease rather than one limited to the skin. It is very important that clinicians are aware of the risk of insulin resistance in patients with psoriasis. This is a particular risk in those patients with severe or long-standing disease. Regular monitoring for the development of impaired glucose tolerance and diabetes and its complications is required in these patients. It is also important to bear this association in mind when selecting treatments for such patients. There is much further research warranted to clarify the exact pathogenesis of this link and to perhaps establish further therapies for patients who have both diabetes and psoriasis.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

Authors' contributions	RF	MS	MC	AMT
Research concept and design	✓	✓	✓	✓
Collection and/or assembly of data	✓	--	--	--
Data analysis and interpretation	✓	--	--	--
Writing the article	✓	--	--	--
Critical revision of the article	✓	--	--	✓
Final approval of article	✓	--	--	✓
Statistical analysis	--	--	--	--

## Publication history

EIC: Geoffrey Burnstock, University College London, UK.

Received: 05-Oct-2013 Revised: 24-Jan-2014

Accepted: 26-Feb-2014 Published: 11-Mar-2014

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**invariant natural killer T cells: lessons from obesity, diabetes and psoriasis.** *Diabetologia.* 2011; **54**:2745-54. | [Article](#) | [PubMed Abstract](#) | [PubMed Full Text](#)

**Citation:**

Fitzgerald R, Sadlier M, Connolly M and Tobin AM. **Psoriasis and insulin resistance: a review.** *J Diab Res Clin Met.* 2014; **3**:3.  
<http://dx.doi.org/10.7243/2050-0866-3-3>