Psoriasis and Metabolic Syndrome

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This article is available from: http://www.jtad.org/2015/2/jtad1592r1.pdf
Keywords: Psoriasis, metabolic syndrome, insulin resistance, obesity, hypertension, dyslipidemia

Abstract

Background: Psoriasis is a chronic inflammatory skin disease characterized by the immune system activation in which the genetic and environmental factors are involved. Metabolic syndrome represents the combination of insulin resistance, obesity, hypertension and dyslipidemia. In recent years, the association between metabolic syndrome and psoriasis has been a focus of interest. Several mechanisms have been accused in the etiologic link between these two disorders. It is crucial for the dermatologist to recognize the relation between psoriasis and metabolic disease as this association may have important clinical implications in the management of psoriasis. Here, we review the most recent data linking psoriasis to metabolic syndrome and discuss the potential underlying mechanisms of this association by the evidence from current literature.

Introduction

Psoriasis is a chronic immune mediated skin disease in which both genetic and environmental factors are complexly involved [1].

In recent years the concept of taking psoriasis as a systemic disease has been increasingly accepted. [2, 3]. Accumulating evidence points to the relationship between psoriasis and the other systemic diseases including cardiovascular diseases, obesity, diabetes, hypertension, metabolic syndrome, nonalcoholic liver disease, anxiety and depression, some malignancies and inflammatory bowel disease [4, 5].

Metabolic syndrome (MetS) is the constellation of risk factors for cardiovascular diseases such as hypertension, central obesity, glucose intolerance and dyslipidemia [6]. The association between psoriasis and MetS has been well established [4]. The discovery that there are differentially expressed genes (DEGs) common in MetS and psoriasis further supported the causal link between these two diseases [7].

The association of immune mediated diseases with metabolic disorders emphasizes the regulatory role of the immune system on the metabolic processes as the disturbance of this regulation results in several comorbidities. The critical question is where and how the cytokine mediated signals and metabolic responses intersect [8].

It is well recognized that the presence of an immune mediated disease such as psoriasis portends a risk for the development other systemic comorbidities. It has been hypothesized that the cytokine network operating locally in psoriatic skin, may affect the distant tissues leading to the development of comorbid conditions encountered during disease [9].

Although the mechanisms underlying the association between psoriasis and MetS have
yet to be determined, inflammatory pathways are suggested to be involved. Also risk factors common for two diseases including smoking, sedentary lifestyle and alcohol abuse has been indicated in this connection [4].

The Clinical Implications of the Association Between Psoriasis and MetS

UAs it is suggested that the individual components of MetS have etiologic role in the development psoriasis, it is compelling to identify and comprehend the relationship between these two conditions. It is thought that the treatment of these comorbidities may remove their negative impact on psoriasis and assist the management of disease.

The drugs for psoriasis may interfere with the concomitant metabolic diseases and oblige the dermatologists to change the treatment option or conversely, they may have beneficial effects on the course of disease [10]. For example, retinoids have negative impact on serum lipid profile and they are indicated to decrease insulin sensitivity [11, 12]. Cyclosporine has been demonstrated to increase triglyceride and cholesterol levels and also increase blood pressure [13, 14]. Pioglitazone, one of the antidiabetic drugs, which has anti-inflammatory effect and increases the insulin sensitivity, has been reported to decrease PASI scores in psoriasis patients [15]. Lipid lowering statins which also have anti-inflammatory actions have been implied to have a positive impact on psoriasis course [16, 17]. Additionally, beta blockers used for hypertension have been shown to exacerbate psoriasis, again indicating the importance of recognizing concomitant diseases in patients [18].

From another perspective, as the chronic psoriatic inflammation has been accused in the development of metabolic complications, it is suggested that the associated morbidity and mortality could be controlled by the proper management of psoriasis [19]. There are studies revealing the beneficial effect of psoriasis treatments on accompanying comorbidities. There is evidence that methotrexate has a cardioprotective role in psoriasis patients, by decreasing the vascular diseases [20, 5]. Although the treatment with TNF-α inhibitors has been associated with weight gain [21], these drugs are reported to improve insulin sensitivity [22, 23] and reduce CRP levels [24].

Finally, the evidence that the metabolic syndrome contributes to the risk of cardiovascular complications, type 2 diabetes and stroke in patients with psoriasis validates the measures regarding the awareness and the prevention of concomitant metabolic disturbances in these patients [25].

In conclusion, the recognition of these comorbidities by the dermatologists and screening the patients for metabolic risks enables the early referral of patients to relevant specialists, allow the selection of appropriate treatment for the patient and also, may even improve the treatment outcomes.

Metabolic Syndrome and Psoriasis

The MetS is an important health problem and defined as the collection of cardiometabolic risk factors including insulin resistance, abdominal obesity, hyperlipidemia and hypertension [6].

Etiology of MetS

The underlying cause of the MetS has yet to be determined but both insulin resistance and obesity are indicated as the major contributors [26]. Genetic susceptibility, physical inactivity, proinflammatory state and hormonal changes also are suggested to have role in the establishment of MetS [6, 26].

Definition Criteria of MetS

Although the diagnostic criteria may vary between different organizations, authorities agree about the fundamental components.

As stated by International Diabetes Federation (IDF), a diagnosis of MetS is made when a person has central obesity (defined as waist circumference for males ≥ 94 cm and females ≥ 80 cm for Europids, Eastern Mediterranean and Middle East (Arab) populations) if BMI is >30kg/m², the existence of central obesity can be concluded.
plus any two of the following four factors: 1) Raised triglycerides ≥ 150 mg/dL or receiving drug therapy for hypertriglyceridemia 2) Reduced high density lipoprotein (HDL) cholesterol <40 mg/dL in males or <50 mg/dL in females or receiving drug therapy for reduced HDL cholesterol 3) Raised blood pressure systolic ≥ 130 mmHg or diastolic ≥ 85 mmHg or receiving drug therapy for hypertension 4) Raised fasting plasma glucose ≥ 100 mg/dL, or previously diagnosed type 2 diabetes [6].

IDF consensus recommended adding novel biochemical markers to MetS criteria including leptin, adiponectin, apolipoprotein B and CRP which are suggested to be etiologically related to MetS [6]. Interestingly, these parameters are also implicated in the psoriasis pathogenesis as discussed below.

**The Epidemiologic Data Regarding the Association Between Psoriasis and MetS**

In a recent study, the prevalence of MetS in U.S. adults has been found to be 22.9% [27]. Among European population, the frequency of MetS has been found to be 24.3% [28].

Accumulating evidence supports the higher frequency of MetS in psoriasis patients [29, 30]. Although the prevalence of MetS among psoriasis patients varies according to the study, Armstrong et al., in their meta-analysis of 12 different observational studies, has found a pooled odds ratio (OR) of 2.26 (95% confidence interval [CI] 1.70-3.01) for MetS among psoriasis patients. They also noticed an association between the psoriasis severity and the frequency of MetS [31].

Although the study by Gisondi et al. confirms the higher frequency of MetS in psoriasis, they have observed no correlation between the severity of psoriasis and the prevalence of MetS. However, authors reported an association between the duration of the disease and the occurrence of MetS. As they found that only hypertriglyceridemia and abdominal obesity were higher in psoriasis patients, one should think that these components may serve as the root of problems in the evolution of MetS in these patients [32].

Zindanci et al. reported that among patients of psoriasis, MetS was more common in women than in men. They also observed that the occurrence of MetS increases after age 40. In their study the prevalence of MetS was not associated with smoking or the severity and duration of psoriasis [33]. Even in the childhood psoriasis the rate of MetS has been found to be increased [34].

Despite the positive association in above studies, there are studies that refuted the link between MetS and psoriasis [35, 36, 37, 38].

**Pathogenesis of the Association Between Psoriasis and MetS**

Although the precise mechanisms of the association between psoriasis and MetS have yet to be elucidated, shared genetic susceptibility, common environmental factors and activation of common signalling pathways, or a combination of these factors has been suggested to be the etiologic components of this association [39].

As psoriasis has an adverse effect on the quality of life, it is frequently associated with depression and stigmatization. This may result in lifestyle changes including smoking, alcohol abuse, reduction in the physical activity and alterations in eating habits which all can contribute to the development of MetS [40, 41, 42].

Obesity, insulin resistance, endothelial dysfunction and oxidative stress which are induced by inflammatory cytokines and various adipokines are suggested as the common mechanisms connecting psoriasis to MetS [43]. Both psoriasis and MetS is characterised by proinflammatory state, hyperuricemia and prothrombotic tendency [2].

Chronic inflammation is indicated to be the causal link between psoriasis and MetS. [41]. Psoriasis is characterized by the activation and the expansion of Th1 and Th17 cells resulting in a complex network of inflammatory cytokines and chemokines expanding in the lesional skin. The mediators which are produced locally, by entering systemic circulation, may exert systemic effects on distant tissues and modulate the metabolic functions including angiogenesis, insulin signalling,
adipogenesis, lipid metabolism and immune cell trafficking. Thus the contribution of psoriatic skin-derived inflammation to the development of obesity, diabetes, thrombosis and atherosclerosis has been proposed.\cite{9, 1}. Recently Davidovici et al. roughly classified molecules from different tissues and organs which are described as risky for cardiovascular disease constructing a model for the complex interplay of mediators between psoriatic skin and distant tissues They also proposed that local inflammation in a skin disease could affect circulating immune cells and, by increasing the adhesion molecule expression, it could result in endothelial cell dysfunction. As hypodermis contains adipose tissue expanding with obesity, they also suggested that psoriatic inflammation bearing enlarged number of macrophages may modify the action of neighbouring tissues such as adipose tissue and lead to metabolic disturbances. Additionally, they mentioned that inflammation either from local psoriasis lesion or obesity could trigger hypertension and coagulation which are well known components of metabolic syndrome\cite{9}. In the study of Suarez- Farinas, some of the proteins upregulated in lesional skin were also found to be overexpressed in the serum of psoriasis patients suggesting that the process starting in the skin may generalize and give rise to comorbid disorders\cite{7}.

Oppositely, inflammatory mediators and hormone like molecules provided by the tissues affected from obesity, diabetes and atherosclerosis may have a role in the development of psoriasis in a genetically susceptible individual or may worsen the already existing psoriatic disease\cite{9}.

In recent years, transcriptome and proteomics studies provided insight into the pathogenesis of psoriasis and led to the better understanding of this linkage by revealing the common signalling pathways operating in psoriasis and MetS. Authors claimed that the sharing of dysregulated pathways as a result of differentially expressed genes (DEGs) may be the common denominator for the development of psoriasis and metabolic disease in the same patient\cite{44}.

Since there is a significant overlap in the mechanisms underlying the causal link between psoriasis and MetS, further studies clarifying their interaction are warranted. Presently, the following section summarizes the recent data concerning the involvement of cytokines, adipokines and other proposed factors in the relation between psoriasis and MetS. But firstly, in order to better comprehend the complex interplay between these factors, the pathogenesis of psoriasis, specifically focusing on the metabolic impacts of the implicated cytokines, is reviewed.

**The Cytokines and Immune Cells Involved in Psoriasis Pathogenesis and Evidence for Their Role in MetS**

Psoriasis is an inflammatory skin disease with a prominent Th1 immune response characterised by an increase in IFN-γ and a decrease in IL-4 levels\cite{45}. In recent years, IL-23, IL-17 and IL-22 has been put to the center of disease pathogenesis and their increased expression in psoriasis has been reported\cite{46, 47, 48, 49}. Also the deficient function of Treg lymphocytes has been recognized in psoriasis\cite{50}.

The current concept of psoriasis is that it is systemic inflammatory disease in which there is a continuous communication between skin-resident dendritic cells (DCs), T cells, infiltrating macrophages and neutrophils, and keratinocytes that is mediated by cytokines and results in the characteristic epidermal changes\cite{51}.

**DCs**

Myeloid DCs have been shown to be the primary stimulators of T cell activation by the secretion of IL-23\cite{52}. T cell activation results in the release of several cytokines including TNF-α, IFN-γ, IL-17, and IL-22 which ultimately ends up with vicious cycle of inflammation that is seen in psoriasis\cite{51}. Together with IL-23, DCs also produce IL-20 and TNF-α which in turn, can trigger the formation of a wide range of proinflammatory cytokines from keratinocytes and other cells operating in psoriatic skin\cite{52, 53}. Upon activation, DCs also produce IL-12. While IL-12 enhances the Th 1 immune response, IL-23 induces the differentiation of lymphocytes into Th17 cells\cite{54, 55}. 


IL-23

In recent years IL-23/Th17 axis has been indicated to have a central role in the pathogenesis of psoriasis [55]. IL-23 is shown to be upregulated in psoriasis lesions and experiments indicate the infiltrating mononuclear cells to be the source of this cytokine [47]. IL-23 strongly activates Th1 immune responses and IFN-γ production [56]. Besides the induction of Th1 cell formation, IL-23, together with IL-12, drives the formation of Th17 and Th22 cells from resident T cells. The induction of Th17 cells is critical in disease pathogenesis as IL-17, which is secreted from Th17 cells, is important for the keratinocyte responses characteristic of psoriasis [55].

Serum IL-23 levels were increased in obese psoriasis patients when compared to normal-weight patients and healthy controls [57]. However, more studies are required to define the exact role of IL-23 in the development of MetS in psoriasis patients.

Th17 cells and IL-17

Several types of cells have been indicated to produce IL-17 in psoriatic lesions including CD4+T cells, CD8+T cells, mast cells and neutrophils [58, 59, 60]. IL-17 has been referred as a key cytokine in the pathogenesis of psoriasis. The serum IL-17 levels correlated with PASI scores in patients [61]. Kryczek et al. demonstrated that Th1 and Th17 act synergistically in psoriasis pathogenesis. They found Th17 cells to be increased in psoriatic skin. IFN-γ which is produced by Th1 cells has been shown to direct myeloid APCs for the induction of IL-17 by secreting IL-1 and IL-23 [58]. The induction of IL-6 production from keratinocytes by IL-17 has been indicated in the exacerbation of psoriatic inflammation [62]. IL-17 induces the production of certain chemokines from keratinocytes that are involved in the recruitment of neutrophils, DCs and T cells into the psoriatic skin [53]. Also the action of IL-17, through CIKS-mediated signalling, in the epidermal changes characteristic of psoriasis has been defined [63].

The association of IL-17 with hypertension and endothelial dysfunction which are well known components of MetS has been demonstrated [64, 65, 66]. Although Madhur et al. suggests a role for IL-17 in the development of MetS [67], others reported conflicting results. Despite the fact that IL-17 levels correlated with blood pressure and glucose in patients, authors observed lower levels of IL-17 in patients with MetS when compared to controls [68]. Th17 and Th22 cells were found to be higher in adipose tissue of insulin resistant obese patients and further studies advocated by the authors to determine the precise role of these cytokines in the development of insulin resistance [69]. Obesity specifically has been demonstrated to increase the Th17 subsets by an IL-6 dependent way and result in more severe disease course in animal models of autoimmune diseases. Whether and how these findings contribute to the association of psoriasis to MetS is not clear yet but warrants investigation [70].

IL-22

In addition to IL-17, Th17 cells are also capable of producing IL-22, which is one of the other cytokines recently recognized in psoriasis pathogenesis [71]. The serum levels of IL-22 correlated with PASI scores together with IL-20 and IL-17 [61]. Nograles et al reported that IL-22 can also be produced by IFN-γ-producing Th1 cells, and a newly described ‘Th22’ cells. IL-22 is demonstrated to down-regulate the genes that are implicated in keratinocyte differentiation and contribute to the establishment of psoriatic phenotype [53]. Additionally, IL-12 promotes the hyperplasia of keratinocytes and the production of proinflammatory mediators from keratinocytes [72]. Angiogenesis, a process critically involved in the establishment of psoriatic inflammation, is indicated to be mediated by IL-22 [73].

Keratinocytes

Keratinocytes are implicated as active contributors to psoriatic inflammation not innocent by-standers. Once activated, they produce abundant cytokines and inflammatory mediators called chemokines. These mediators drive the activation of neutrophils, DCs, Th17 cells and further recruitment of inflammatory cells into lesional skin [53, 74, 75]. Kerati-
nocytes, again appear on the stage by the discovery of CARD14 (caspase recruitment domain family, member 14) mutations in keratinocytes. It has been suggested that triggering factors leading to psoriasis may result in gain-of-function mutations of CARD14 gene. And it is proposed that these mutations may promote the recruitment of immune cells that sustains the inflammatory process in psoriasis [76]. IL-36 is a novel IL-1 family member cytokine that accumulating data implicates its role in psoriasis pathogenesis. The expression of IL-36 in keratinocytes has been demonstrated to be upregulated in psoriatic lesions [77, 78]. The expression of IL-36 is induced by IL-17, TNF-α, IL-22 and IL-36 itself. IL-36 promotes the production of proinflammatory cytokines including TNF-α, IL-6 and IL-8 in keratinocytes [79]. IL-36 has been indicated to be the major controller of IL-23/IL-17/IL-22 pathway and play a key role in psoriatic inflammation [51]. Recently a significant correlation has been observed between the expression of IL-36 and p38 MAPK in psoriatic skin [80]. As will be stated later, p38 MAPK pathway has been indicated to have a role in psoriasis pathogenesis [81, 82]. Since the insulin resistance in keratinocytes is mediated through p38 MAPK, the relationship between IL-36, p38 MAPK pathway and insulin resistance in psoriasis patients is a subject of investigation.

**IL-6**

IL-6 has long been reported to have a pathologic role in psoriasis [83]. It is produced by a wide spectrum of cells including keratinocytes, fibroblasts, endothelial cells, DCs, and macrophages [84, 62]. Evidence indicates that both IL-1 and TNF-α can induce the secretion of IL-6 [62]. Also IL-17 has been demonstrated to increase the production of IL-6 from keratinocytes [85]. Although IL-6 and TGF-β has been demonstrated to promote the differentiation of Th17 cells, the pivotal cells in the pathogenesis of psoriasis, IL-23 was suggested to be essential for gaining the pathologic function of Th17 cells [86]. A recent study showed that the psoriatic phenotype induced by IL-23 is mediated by IL-6 indicating that IL-6 plays a key role in the IL-23/Th17-driven cutaneous inflammation of psoriasis [87]. IL-6 exerts its effect through STAT3 signalling pathway [88] and is reported to be actively involved in the proliferation of keratinocytes in psoriasis [87, 89, 90]. IL-1 also contributes to keratinocyte hyperplasia in psoriatic epidermis [73].

Serum IL-6 levels are found to be positively correlated with obesity and insulin resistance [91]. In other study authors demonstrated that IL-6 levels were inversely correlated to insulin sensitivity whereas they were positively correlated with BMI, blood pressure and triglyceride levels [92]. Serum IL-6 concentrations were found to be significantly elevated and negatively correlated with adiponectin levels in obese psoriasis patients indicating a contributory role for IL-6 in the MetS seen in psoriasis patients [93]. Supportingly, Ra-jappa et al. demonstrated that IL-6 levels, together with leptin, resistin and insulin resistance were increased in psoriasis patients. Also these parameters were found to be positively correlated with disease severity [94]. Other than the relation to insulin resistance, obesity and diabetes, IL-6 has also been etiologically linked to cardiovascular diseases [95].

**IL-8**

IL-8 plays an important role in the neutrophil attraction of psoriatic epidermis [96]. Serum IL-8 levels found to be elevated in psoriasis patients and its level positively correlated with the disease severity [97]. IL-8 is well known to be produced from keratinocytes, however, neutrophils and CD4 + T cells infiltrating skin are also capable of secreting IL-8 [96, 98, 99]. Recently IL-8 has been demonstrated to be secreted from adipocytes and, Kobashi et al. indicated its role in the development of adiponectin resistance in adipocytes [100]. Additionally, Shin et al. suggested a role for IL-8 in the establishment of MetS [101]. However, further studies are required for the confirmation of its role in the link between Mets and psoriasis.

**TNF-α**

Although the macrophages are the major cells responsible for the production of TNF-α, other
immune and non-immune cells including lymphocytes, neuronal cells, fibroblasts, endothelial cells, mast cells and many other cells, even the adipocytes, also can secrete it \[102, 103, 104\]. TNF-α effects the proliferation of many cells, promotes the production of proinflammatory cytokines, increases the synthesis of adhesion molecules and drives the recruitment of leukocytes to the site of inflammation [105]. TNF-α has a pivotal role in the psoriasis pathogenesis. TNF-α levels were found to be increased in psoriasis patients and positively correlated with PASI scores [106]. Primary effect of TNF-α in disease pathogenesis is the regulation of interactions between DCs and antigen specific-T cells that drives the stimulation of T cell responses [107]. Also TNF-α, by the induction of IL-23 production from DCs, results in enhanced Th17 responses which has a key role in cytokine network of psoriasis [108]. By NF-kB signalling, TNF-α induces the hyperplasia of keratinocytes [73]. NF-kB pathway has been reported to play an important role in the establishment of psoriatic epidermis [109]. Visfatin, an adipokine with metabolic actions, is demonstrated to augment the TNF-α induced chemokine expression on psoriatic keratinocytes by NF-kB signalling. This evidence has been suggested play a part in the link between MetS and psoriasis [110]. Chiricozzi et al. found that IL-17 and TNF-α synergistically upregulate some of the genes in keratinocytes that are related to disease pathology [111].

Besides its role in psoriasis, TNF-α, has also been indicated in the development of insulin resistance. Additionally, it was found to be associated with obesity and other related metabolic disturbances [112, 113, 114]. As might be expected, the role of TNF-α, as well as other cytokines in the evolution of MetS was recently mentioned [115]. As the deficient peroxisome proliferator-activated receptor (PPAR) signalling has been indicated both in the pathogenesis of psoriasis and insulin resistance, the evidence of PPAR-γ inhibition by TNF-α raises the possible contribution of this interaction in the association between psoriasis and MetS [116].

T Regulatory Lymphocytes

The proinflammatory state and the increased proliferation of keratinocytes in psoriasis are suggested to partly result from the dysfunctional action of T regulatory lymphocytes (Treg cells) [117, 118]. In psoriasis, Treg cells have been reported to turn into IL-17 producing cells that actively drive the psoriatic inflammation [118]. Decreased and/or dysfunctioned Treg cells have been indicated to disturb other tissues and organs resulting metabolic disturbances [119]. Treg cells have been reported to play a protective role against the development of insulin resistance [120]. Supportingly, obesity is associated with a decrease in Treg cells and resultant adipose tissue inflammation and insulin resistance [121]. Recently it is demonstrated that PPAR-γ mediated signalling drives the accumulation of Treg cells in the adipose tissue preventing insulin resistance [122]. Also insulin, itself, has been reported to diminish the anti-inflammatory action of Treg cells through the inhibition IL-10 secretion [123]. These findings raise the question whether the dysfunctional Treg cells of psoriasis have an impact on the MetS seen in the course of disease.

IL-18

IL-18 is a potent proinflammatory cytokine produced by both immune and non-immune cells. It stimulates the production of IFN-γ synergistically with IL-12 and results in Th1 immune response [124]. IL-18 expression was found to be significantly increased in psoriatic lesions when compared to uninvolved skin and a correlation between its expression and disease severity has been reported [125]. A significant positive correlation between plasma IL-18 levels and PASI score was also reported [126].

IL-18 is also produced by adipocytes [127]. Plasma IL-18 levels were reported to be significantly higher in patients with MetS [128]. The role of IL-18 in the development of MetS has been stressed by several other studies [129, 130, 131]. However, the contribution of IL-18 to the linkage between psoriasis and MetS needs to be clarified.
IL-1 beta (IL-1β)

IL-1β is a proinflammatory cytokine that fosters the expression of T cell chemoattracting chemokines in keratinocytes of psoriatic epidermis [132]. The cross talk between T cells and keratinocytes with the secretion of IL-1β from epithelial cells was suggested to be crucial in the disease pathogenesis [133]. IL-1 has also been implicated in the development of insulin resistance [134]. Whether IL-1β contributes to the pathogenesis of MetS in psoriasis patients is not studied.

Potential Mechanisms, Signalling Pathways, Biochemical Markers and Other Mediators Linking Psoriasis to MetS

I. Obesity

It is well known that obesity is associated with chronic low level of inflammation by the secretion of inflammatory products from adipocytes as well as from non-adipocyte cells [135]. The impairment of adipose tissue metabolism in obesity is proposed to be the basis in the resultant metabolic changes [136]. Although adipocytes produce many inflammatory mediators including interleukin-8 (IL-8), and IL-6, plasminogen activator inhibitor-1 (PAI-1), monocyte chemoattractant protein 1 (MCP-1), vascular endothelial growth factor (VEGF), transforming growth factor-β1 (TGF-β1), tumor necrosis factor-α (TNF-α), IL-1β, IL-10, resistin, C-reactive protein (CRP), and interleukin-1 receptor antagonist (IL-1Ra), majority of the proinflammatory cytokines release in the case of obesity come from non-adipocyte cells [135].

Obesity is known to be associated with the increased risk of many autoimmune disorders and suggested to have role in psoriasis [137]. Obesity has been indicated as a risk factor in the development of psoriasis [138]. Supportingly, several authors suggested that obesity, by providing chronic inflammatory state, may promote the development of psoriasis in susceptible individuals or may predict the intractable course of an existing disease [41, 139, 140]. Recently psoriasis has been described as a novel parameter relating obesity to psoriasis risk [141].

Adipose Tissue as an Active Secretory Organ

Over the past decade, adipose tissue is largely considered as an endocrine tissue that actively produces proinflammatory cytokines and hormone like mediators including TNF-α, IL-6, leptin and other adipocytokines contributing to the development of metabolic disturbances in patients [9, 142, 143]. As the adipose tissue bulk increases with obesity, the level of inflammatory mediators produced from adipose tissue is elevated and give rise to metabolic disturbances [144].

Toussirot et al. recently described adipokines as a causal link between psoriasis and obesity-related complications such as MetS that are seen in patients [145]. Given the suggestion that proinflammatory cytokine load, partly by abnormally secreted adipocytokines, may induce the metabolic syndrome, how this causal interaction can be implemented in the case of psoriasis remains to be clarified [146]. Adipokines were demonstrated to be correlated with Th17 cytokines which supports the link between these molecules and psoriasis [147].

Leptin

Leptin is an adipokine that has a role both in the regulation of food consumption [148], and immunologic responses. Obesity is associated with leptin resistance despite the high levels of circulating leptin [149]. Although leptin is associated with increased insulin sensitivity in animal models [150], as obesity induces both leptin and insulin resistance, increased leptin levels associated with diabetes depending on BMI [151]. Animal models of metabolic syndrome which exhibit mutated leptin receptor, present high levels of lipids, endothelial dysfunction markers such as intercellular adhesion molecule-1 (ICAM-1) and increased PAI-1 as a marker of enhanced prothrombic activity and elevated levels of insulin and oxidized LDL as an indicator of oxidative stress [152]. Additionally leptin has been found to play a role in the development of hypertension [153]. Finally, leptin levels have been suggested to be a risk factor for coronary atherosclerosis [154]. Leptin which is increased with obesity was proven to increase the expression of tissue factor (TF) and cellu-
lar adhesion molecules (CAMs) and suggested to play a role in the connection between obesity and cardiovascular diseases [155]. Other than metabolic effects, leptin has been demonstrated to stimulate Th1 immune responses and angiogenesis [156]. Beyond the systemic effects, the cellular proliferative effect of leptin on skin homeostasis has been mentioned [157]. Leptin has been shown to induce the proliferation of keratinocytes as well as the secretion of proinflammatory cytokines from these cells which is characteristic of psoriatic lesions. Authors observed a marked increase in the expression of leptin in keratinocytes and a positive correlation between PASI scores and leptin levels in obese psoriasis patients [158]. Robati et al. found leptin as well as resistin, triglyceride and cholesterol levels to be increased in psoriasis patients compared to controls. Authors also demonstrated that these parameters were positively correlated with intima-media wall thickness (IMT) of the common carotid artery (CCA) suggesting psoriasis as an independent risk factor for atherosclerotic disease [159]. Although several authors reported the increased level of leptin in psoriatic patients [160, 161, 162, 163], others did not confirm it [164]. Cerman et al. found leptin levels to be correlated with PASI scores and disease duration indicating that this adipokine is implicated in the pathogenesis and chronicity of psoriasis [165]. Leptin is suggested to be involved in the psoriasis pathogenesis by the induction of Th1 immune responses [163]. Moreover, the finding that hyperleptinemia is independent of gender and obesity in psoriasis patients strongly suggests that leptin, on its own, is involved in the development of metabolic syndrome in psoriasis [166].

**Adiponectin**

Adiponectin exerts anti-inflammatory actions by the inhibition of IL-6 and the induction of IL-10 which is mediated in some extent by the inhibition of NF-κB signalling and ERK1/2 activity [167, 168]. It was also demonstrated to exhibit anti-atherogenic and insulin sensitizing properties [171]. Decreased level of adiponectin has been related to metabolic syndrome risk factors whereas leptin levels was positively correlated together with ICAM, monocyte chemoattractant protein-1 (MCP-1), oxidized LDL (oxLDL), TNF-α, IL-6 and hsCRP levels [173]. Serum adiponectin levels were found to be lower in psoriasis patients and the levels negatively correlated with BMI and PASI scores [160].

**Resistin**

Resistin is also an adipokine that has a role in inflammation and insulin resistance [174]. Resistin has been associated with obesity and MetS [175]. We and others demonstrated that resistin levels are elevated in psoriasis patients [176, 177]. Boehncke et al. observed that psoriasis patients showed insulin resistance and suggested a role for resistin in the development of insulin resistance in these patients [177]. The role of resistin in the establishment of MetS in psoriasis needs to be investigated.

**Other Adipokines**

Together with leptin and adiponectin, osteopontin, homocysteine and CRP, all suggested to be involved in the linkage between psoriasis and MetS [178].

Visfatin, an other adipokine, by increasing the chemokine expression on psoriatic keratinocytes through NF-κb pathway, has been demonstrated to be involved in the leukocyte recruitment in psoriasis [110].

**Adhesion molecules**

The increased secretion of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) from visceral fat has been indicated to have a role in the association between obesity and cardiometabolic disturbances [179]. The upregulation of adhesion molecules (ICAM-1 and VCAM-1) in the lesional skin is a characteristic of psoriasis and, by promoting the adhesion of inflammatory cells to the vascular wall, they have been implied as major contributors in the pathogenesis of disease [180]. Ghazizadeh et al. described ICAM-1 and VCAM-1 as common offenders in the establishment of psoriatic and atherosclerotic plaques [181].
Lastly, the linkage between psoriasis and obesity has been reported to be a two-way process that, besides the impact of obesity-induced inflammation on psoriasis, psoriasis is also suggested to predispose obesity. Several mechanisms have been proposed in this association including isolation due to feeling of stigmatization, overeating, increased alcohol consumption and sedentary behaviour [139, 182].

II. Insulin Resistance

It is well known that insulin has not only metabolic effects but also can regulate the proliferation, differentiation and apoptosis of cells in response to mitogenic stimulants [183]. Insulin resistance has been suggested to be central to the pathogenesis of MetS [26]. Chronic low-level inflammation, generated by the adipose tissue-derived mediators, is indicated in the formation of insulin resistance [184]. Certain cytokines, by the activation of insulin receptor substrate (IRS) kinases, can result in the inhibition of insulin signalling, thus, insulin resistance [183]. Both metabolic and inflammatory mediators and also obesity, itself, by the secretion of adipokines and free fatty acids, can drive the insulin resistance through the phosphorylation of IRS [185].

Adipose Tissue Inflammation in the Development of Insulin Resistance

Obesity is associated with the inflammation of adipose tissue that is characterised by the recruitment of inflammatory cells which secrete proinflammatory cytokines [186, 187]. Hypoxia has been proposed to be an inciting etiology of necrosis and macrophage infiltration into adipose tissue that leads to an overproduction of biologically active metabolites [115]. The cytokines and other mediators secreted from inflamed adipose tissue have been suggested to be involved in systemic metabolic effects including insulin resistance [188]. Macrophages, lymphocytes and other innate and adaptive immune cells, even the adipocytes itself, all are reported to have active role in the establishment of the adipose tissue inflammation resulting in the development of insulin resistance [187, 188, 189, 190]. The ratio of T cells in adipose tissue is altered in the case of obesity and, as the number of regulatory T cells (Treg) cells and Th2 cells decreases, the amount of Th1 and CD8 T cells increases [191]. Certain chemokines such as CXCR3 and CCR5 have been implicated in forming the stimulus for the recruitment of immune cells into the adipose tissue [192, 193]. Also lipids that are secreted from adipocytes are suggested to mediate the T cell accumulation in the adipose tissue [194]. Recent researches have put the adipocytes to the center of metabolic syndrome in the sense that several factors such as obesity result in the dysregulation of the expression of adipokines in adipose tissue and eventually give rise to metabolic disturbances. Adipocyte endoplasmic reticulum has been suggested to have a key role in sensing the triggering stimuli and generating the signals that result in the abnormal secretion of adipokines underpinning MetS [195].

After migration to adipose tissue it is necessary for the T cells to be activated in order to maintain the adipose tissue inflammation. Obesity increases the expression of costimulatory molecules such as CD80 and CD86 on adipocytes and, by acting as antigen presenting cells (APCs), adipocytes drive the activation of T cells [196]. Costimulatory signalling is crucial in the T cell activation and mediated by the interaction between CD28 molecule on T cell and CD80/86 (B7) molecule on the APCs. The opposite signal, that promotes the immunosuppressive action of Treg, induced by the binding of CTLA4 (cytotoxic T lymphocyte antigen) on T cell surface to CD80/86 (B7) molecule on the APCs [197, 198]. Costimulatory signalling and the accumulation of macrophages in adipose tissue have been indicated in the development of insulin resistance. CTLA4 mediated message is involved in the maintenance of the anti-inflammatory state of macrophages [199]. The negative signalling through CD80/86 (B7) – CTLA4 binding improves the insulin resistance by the enhancement of Treg cell in the adipose tissue and the reduction of macrophage migration into adipose tissue [200]. Supporting the role of CTLA4 in reversing insulin resistance, the inhibition of costimulatory pathway has been shown to prevent the migration of cells to adipose tissue and recover insulin resistance [201].
The interesting thing is that recently Suarez-Farinas et al. showed that psoriasis patients show increased expression of CTLA4 [7]. As Boehncke et al. demonstrated that psoriasis patients exhibit insulin resistance, the possible involvement of negative feedback mechanisms in this complex relation should be investigated [177].

The significant correlation of insulin resistance with PASI scores supports the role of psoriatic cytokine network in the disturbance of insulin signalling [177]. The role of insulin resistance in the perpetuation of psoriasis plaque has recently been investigated. Buerger et al. emphasized the role of insulin in the differentiation of keratinocytes. IL-1β has been found to be upregulated in psoriasis plaques and, through the induction of insulin resistance, it is suggested to result in the keratinocyte changes characteristic of psoriasis. They showed that IL-1β leads the proliferation but inhibits the differentiation of keratinocytes that happens in psoriasis. Authors also has found evidence that insulin resistance in keratinocytes has been achieved by p38MAPK (mitogen-activated protein kinase), one of the IRS kinases [202]. In recent years, the role of p38MAPK that plays important roles in cell proliferation, differentiation, gene expression, and inflammation has been encouraged in the pathogenesis of psoriasis [81, 82].

Macrophages have been reported to be the central player in the obesity induced inflammation and resultant insulin resistance [203]. The interaction between macrophages (as a part of innate immunity and also one of the principal cells in psoriasis) and the adipocytes (as a part of hypodermis and also white adipose tissue of body) has been implicated in the link between psoriasis and MetS [9]. Also, Treg cells have been recognised as active contributors to the adipose tissue inflammation and systemic metabolic sequelae [122].

Although the exact role of dermal insulin resistance in the link between psoriasis and MetS is not clear, it is suggested to play a part in the development of comorbid conditions encountered in the course of psoriasis [177].

III. Oxidative stress

Oxidative stress has been proposed as an important factor in the establishment of MetS [204]. Impairment in the oxidative metabolism has been reported in psoriasis and suggested to be involved in the disease pathogenesis [205].

Kaur et al. demonstrated that obese psoriasis patients manifest a greater degree of oxidative stress accompanying with lower adiponectin levels when compared to normal-weight psoriasis patients [93]. The decrease in arylesterase levels, an antioxidant enzyme, has been related to MetS in psoriasis patients [206].

IV. Shared Genetic Susceptibility

Psoriasis is a complex disease beyond what happens in the skin that it is characterized by the DEGs which result in the dysregulation of multiple signalling pathways [44]. Attempts to find the underlying reason for the relationship between psoriasis and metabolic syndrome has led the researchers to investigate the possible common genetic background for these two diseases. Several studies reported lists of DEGs in the lesional psoriatic skin. It is noteworthy that Suarez-Farinas et al. observed that the function of DEGs related to psoriasis were associated with endocrine, metabolic, cardiovascular diseases as well as other disorders. Authors noticed that, additional to the previously reported genes, renin and CTLA4 genes, which have metabolic functions, were overexpressed in psoriasis patients [7]. Although Gupta et al. concluded that psoriasis and metabolic syndrome has no genetic correlation in their genome-wide association study [207], others claim that there exists an association [7, 208, 209]. Tian S et al., by meta-analysis of five different studies, demonstrated that 78 genes were commonly upregulated, which are related to metabolic disorders [209]. Also Lu Y et al. revealed that psoriasis patients exhibit particular genes including HLA, FUT2, UBE2L3, SH2B3 which are involved in the development of dyslipidemia, hypertension, and cardiovascular diseases [208].
V. Endothelial Dysfunction and VEGF

Vascular endothelial growth factor (VEGF) expression is increased in the psoriasis plaques and the serum VEGF concentrations correlates with PASI scores [209, 210]. Also, significantly higher serum levels of VEGF were detected in psoriasis patients compared to controls [211]. VEGF is produced by the activated keratinocytes in psoriatic skin [212]. Elevated levels of VEGF, together with decreased nitric oxide (NO) levels, are proposed to be the underlying problem leading to endothelial dysfunction and resultant vascular complications in patients with metabolic syndrome [213]. As the VEGF-driven angiogenesis is a hallmark of both psoriasis and atherosclerosis, it has been suggested as a common offender in the association between two disorders [214]. Adipocytes have been reported to be the source of VEGF as well as with other angiogenic molecules leading to metabolic disturbances in obese patients [215]. Adipose tissue inflammation after high fat diet has been related to endothelial dysfunction and hyperlipidemia [216]. In the light of above mentioned data, it is possible that VEGF may stand somewhere in the bidirectional interaction between psoriasis and MetS.

VI. Hypertension

The contribution of immune system in the development of hypertension has also been described and the role for IL-17 in the pathogenesis has been reported [64, 65, 66]. The significantly enhanced plasma renin activity together with the increased cholesterol, triglycerides and decreased HDL-cholesterol levels was previously reported in psoriatic patients, again, disclosing the relation between psoriasis and metabolic diseases [217]. The demonstration of increased renin expression together with the other cardiovascular and metabolic markers in psoriatic lesions and the dysregulated signalling pathways including atherosclerosis signalling, PPARα, RAR, renin–angiotensin, and leptin signalling which are involved in metabolic and cardiovascular diseases signifies the etiologic link between psoriatic inflammation and MetS [7]. Interestingly, in a recent study, psoriasis has been associated with uncontrolled hypertension depending on the severity of disease indicating the unfavourable impact of the inflammatory burden on the vascular system [218]. Additionally, insulin resistance, which is the key component of MetS, also contributes to the development of hypertension by interfering with the nitric oxide mediated vasodilation [26].

VII. IGF-1

Insulin like growth factor-1 (IGF-1) is a growth hormone, which structurally resembles insulin. Apart from its receptors, it also binds to insulin receptor with low affinity [219]. IGF-1 expression has been found to be increased in psoriatic plaques and suggested to involve in the keratinocyte hyperplasia [220]. In contrast to results from previous reports [221], Friedrich et al. recently revealed that elevated levels of IGF-I portended a risk factor for the development of MetS [222]. Several other studies also implied the complex action of IGF-1 in the development of MetS that both increased and decreased levels of IGF-1 has been associated with insulin resistance [223, 224].

VIII. Dyslipidemia

MetS is characterised by diverse serum lipid abnormalities. Hypertriglyceridermia is the main abnormality partly resulting from insulin resistance. Additionally, elevated levels of low density lipoprotein (LDL) and decreased levels of high density lipoprotein (HDL) are observed in metabolic syndrome patients [225]. Recently, psoriasis has been closely linked to dyslipidemia. Authors noticed an elevation in the cholesterol, triglycerides, HDL and very low density lipoprotein (VLDL) levels when compared to controls, whereas the levels of LDL were similar among two groups. They also observed a decline in HDL levels in parallel with the disease severity and duration [226]. Mallbris et al. showed that psoriasis is associated with serum lipid abnormalities independent from known risk factors for dyslipidemia which strongly suggested that psoriasis is genetically linked to lipid alterations [227]. In the study conducted by Nakhwa et al., as the lipid abnormalities were more
pronounced in hypertensive patients, the contribution of hypertension in the development of dyslipidemia was debated. Also they proposed that long term disease, by the augmented exposure to TNF-α, may disturb the lipid metabolism [226]. Literature about lipid levels in psoriasis patients gave conflicting results. Bajaj et al. found that serum cholesterol, triglyceride and LDL levels were elevated in psoriatrics but the VLDL and HDL levels were not different from controls and suggested that psoriasis is related to hyperlipidemia [228]. In another study, serum triglyceride, cholesterol, LDL and VLDL levels were higher in psoriasis patients while HDL levels was lower than controls, so the authors advocated screening the patients with extended disease for lipid disturbances [229]. A recent study by Al-Asmi et al. demonstrated that serum triglycerides, LDL and VLDL levels were higher in psoriasis patients while HDL levels were decreased when compared to controls [230]. Additionally, in the last years, specific Apolipoprotein E (ApoE) gene polymorphism especially ε2 allele has been linked to psoriasis risk [231, 232]. ApoE is involved in the removal of dietary fat from the plasma and, as the receptor binding activity for ApoE-ε2 carriers is slow, these individuals show poorer clearance of lipids and exhibit hyperlipidemia [233, 234]. Recently ApoE-ε2 allele has also been linked to obesity [235, 236]. Several studies indicated an association of ε4 allele with psoriasis [236, 237]. ApoE-ε4 allele is also associated with dyslipidemia [238]. Al-Harthi et al. found ε4 allele higher in psoriatrics than controls and supported the idea that psoriasis is independently associated with dyslipidemia [231].

In psoriasis, local lipid metabolism disturbances including phospholipids, ceramides, free fatty acids and cholesterol in the skin level has also been reviewed suggesting a complex interaction of molecules between epidermis and the serum resulting in dyslipidemia. Continuing exfoliation in psoriatic skin has been suggested to play a role in the serum lipid abnormalities [239]. In a recent study by He L et al. indicated that psoriatic inflammation itself is playing a role in the disturbance of HDL and LDL function and thus comprising a risk for cardiovascular disease [240].

IX. Prothrombotic Activity

The IDF consensus group recently has called attention to additional variables in defining MetS such as PAI-1 and fibrinogen that are associated with prothrombotic state [6]. Elevated levels of PAI-1 in MetS have been associated with increased prothrombotic activity and cardiovascular diseases [152, 241]. PAI-1 is a protein that inhibits fibrinolysis and involved in atherothrombotic complications. Although it is mainly synthesized by platelets, in obesity, the adipocytes act as an active source of PAI-1 [242]. The abnormal secretory activity of adipose tissue has been suggested to be the underlying mechanism leading to prothrombotic state observed in MetS [243].

Psoriasis, by providing chronic inflammation, has the capacity of effecting platelets, coagulation factors and endothelial cells resulting in homeostatic changes and prothrombotic complications [9]. Conversely, the activated platelets are demonstrated to induce the leukocyte rolling in murine skin and proposed to be the possible drive that sustains psoriatic inflammation [244]. Increased plasma levels of PAI-1 have been detected in psoriasis patients and suggested to have a role in the disease pathogenesis [211]. Recent studies have found that psoriasis patients exhibit platelet activation which is suggested to be partly responsible in the development of atherosclerosis and the levels of platelet activation markers positively correlated with PASI scores [245, 246]. In accordance with these studies, plasma PAI-1 and homocysteine levels were increased in psoriasis patients and the elevation was associated with lipid oxidation suggesting to contribute atherothrombotic complications in these patients [247].

X. PPAR Signalling

PPARs are a group of transcription factors that their activation regulates the expression of several genes involved in metabolic processes and innate immunity. Three types of PPARs identified, namely PPARα, PPARβ and PPARγ. PPARs are indicated to comprise a connection between metabolic disorders and innate immunity. Recently PPARs are indicated to play an important role in the association between psoriasis and MetS [248]. PPARs have been demonstrated to play a role in the keratinocyte
differentiation and the barrier function of the skin [249]. They are also involved in the regulation of lipid metabolism and have anti-inflammatory actions. The two key disturbances in the development of MetS, dysfunction in the fatty acid metabolism and obesity-derived inflammation is closely related to abnormal PPAR signalling [250]. Dysregulated fatty acid metabolism leads to lipid accumulation in non-adipose tissue and, by the impairment of signalling pathways, results in the insulin resistance, which is the key component of MetS [251]. As stated above, proinflammatory cytokine production in obesity inhibits insulin signalling and results in insulin resistance [252]. PPAR signalling has been demonstrated to be the main controller of the accumulation of Treg cells in the adipose tissue, which suppress insulin resistance by inhibiting adipose tissue inflammation [122]. Accumulating evidence support the idea that PPARs have a pivotal role in the development of MetS [250, 253]. As the psoriasis patients exhibit decreased PPARγ staining in the skin, Hegazy et al. proposed that the disordered PPARγ signalling may be one of the underlying abnormality linking psoriasis to MetS [254]. The inhibition of Th17 differentiation of CD4 cells by the PPARγ signalling also substantiates the potential involvement of PPARs in psoriasis pathogenesis [255].

XI. Uric acid
The association between serum uric acid levels and the MetS has been well established and even within the normal range, elevated levels of uric acid has been suggested to be a risk factor for MetS [256, 257]. As a stimulant of systemic inflammation and innate immunity, uric acid has been indicated to have an active etiologic role in the development of MetS [258]. In several studies serum uric acid levels were positively correlated with CRP, IL-6 and TNF-α levels [259, 260]. Also, in patients with MetS, the number of MetS components was found to be in positive correlation with CRP, IL-6, fibrinogen and uric acid levels [261]. Uric acid has capacity to promote TNF-α production from human blood monocytes and synovial cells [262]. Adding to its proinflammatory role, uric acid has been indicated in the induction of L-1β production and Th17 differentiation [263, 264].

Psoriasis patients have increased levels of uric acid and the elevation found to be independent from MetS components in these patients [265]. Kacalak-Rzepka et al., in addition to the high prevalence of MetS in psoriasis patients, found a positive correlation between PASI scores and BMI as well as PASI scores and uric acid levels in these patients [266]. Another study has confirmed the positive correlation of uric acid levels with PASI and BMI although they did not find uric acid levels higher than the controls [267]. The data from above studies and several other authors suggest that hyperuricemia resulting from psoriatic inflammation may play a role in the development of MetS in these patients [268].

XII. C-reactive protein
C-reactive protein (CRP) is an acute phase protein and, by acting as a proinflammatory agent, it has been indicated to have a role in metabolic disturbances [269]. The synthesis of CRP from hepatocytes and/or adipocytes is induced by the IL-6 stimulation [270, 271, 272]. As the adipocyte mass enlarges with obesity, the effect of increasing CRP level in the development of metabolic syndrome in obese psoriatics should be suggested. In a systematic review of 7852 psoriasis patients exploring the evidence of systemic inflammation, the serum levels of CRP together with IL-6, TNF-α, E-selectin and ICAM-1 were found to be elevated in psoriasis patients [273]. Several subsequent studies have demonstrated an elevation in the levels of CRP in psoriasis patients [274, 275, 276].

Although Coimbra et al. found a correlation between PASI sores and CRP levels [275], the others did not confirmed it [274]. As possessing proinflammatory properties, CRP has been indicated as one of the mediators linking the local psoriatic inflammation to systemic metabolic diseases [9]. In the study conducted by Tahashi et al., CRP levels were higher in psoriasis patients with MetS than those without metabolic syndrome suggesting CRP level as a marker for metabolic risk in these patients [274]. Supportingly, another study showed that CRP levels in psoriasis patients correlated with the parameters of atherosclerosis risk [276].
XIII. Ghrelin

Ghrelin is a peptide hormone secreted by endocrine cells in the stomach. It has a role in the weight control, obesity, type 2 diabetes, and MetS \[277\]. Ozdemir et al. found ghrelin levels elevated in psoriasis patients together with leptin, resistin and adiponectin levels \[278\]. However the exact role of ghrelin in the association of MetS with psoriasis needs to be elucidated.

Practical Applications in the Dermatology Setting

There is accumulating data regarding the impact of weight loss in reducing inflammatory cytokine production \[279, 280\]. As it is reported weight loss is associated with better treatment responses in psoriasis \[281\] and patients should be encouraged to lose weight \[140, 282\].

Patients should be advised to stop smoking as it is associated with metabolic complications \[283, 284\].

Exercise has been demonstrated to have beneficial effects on inflammation resulting from metabolic disturbances \[285, 286\]. Therefore, increased exercise is recommended for psoriasis patients \[284\].

Alcohol consumption has been related to psoriasis onset and suggested to be associated with disease severity \[5\]. Thus, the reduction in alcohol consumption is advocated by authors \[284\].

Summary

Understanding the contributory role of MetS components in psoriasis pathogenesis and, the role of psoriatic inflammation in the development of metabolic disturbances provides insight into their complex and uncertain etiology. Additionally, clarifying the relationship between MetS and psoriasis may reveal potential targets that might be of probable utility in the treatment of the underlying disturbances common for both diseases. Also, exploring this association may disclose possible biochemical markers predicting the development of MetS. By this review, we mentioned about possible targets including CTLA4 signalling, PPAR signalling, NF-kB signalling, psoriasis and novel topics such as dermal insulin resistance in the link between psoriasis and MetS. What would be the consequence of targeting these molecules or pathways will be realized by future studies. Although there is no single independent parameter indicating the risk for MetS in psoriasis patients, performing regular blood controls and detecting the psoriasis patients with elevated levels of parameters associated with metabolic risks may enable distinguishing the patients at higher risk.

As a conclusion, psoriasis should not be taken just as a skin disease but rather should be regarded as a whole result of complex interplay between inflammatory mediators and risk factors shared by both immune and metabolic diseases. Dermatologists should be aware of comorbid illnesses, assess the patients for accompanying metabolic disturbances and if suspect from MetS, refer the patient to appropriate specialists.

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