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Psoriasis and Metabolic Syndrome

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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 underling mechanisms of this association by the evidence form 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 malignencies 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 obligate 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/m^2, 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 Asssociation 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**].

Zindancı 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. [**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 [**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 [**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 [**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 [**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 [**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 [**46, 47, 48, 49**]. Also the deficient function of Treg lymphocytes has been recognized in psoriasis [**50**].

The current concept of psoriasis is that it is systemic inflammatory disease in which there is a continous 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 [**51**].

DCs

Myeloid DCs have been shown to be the primary stimulators of T cell activation by the secretion of IL-23 [**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 [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 [**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 [**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+Tcells, 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 novelly described 'Th22' cells. IL-22 is demonstrated to downregulate 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, *Rajappa* 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 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**]. IIL-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 insulin 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 [**169, 170**] insulin sensitizing properties [**171**]. Decreased level of adiponectin has been related to metabolic syndrome [**172**]. Adiponectin was found to be negatively correlated with 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 demontrated 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 sequeles [**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. Hypertriglyceridemia 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 psoriatics 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 *El 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 psoriatics 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 prothrombic 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 supress insulin resistance by inhibiting adipose tissue inflammation [**122**]. Accumulating evidence support the diea 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 prevelance 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 consequense 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.

References

1. Lowes MA, Bowcock AM, Krueger JG. Pathogenesis and therapy of psoriasis. Nature 2007; 445: 866-873. PMID: 17314973
2. Gerkowicz A, Pietrzak A, Szepietowski JC, Radej S, Chodorowska G. Biochemical markers of psoriasis as a metabolic disease. Folia Histochem Cytobiol 2012; 50: 155-170. PMID: 22763973
3. Reich K. The concept of psoriasis as a systemic inflammation: implications for disease management. J Eur Acad Dermatol Venereol 2012; 26: 3-11. PMID: 22356630
4. Ni C, Chiu MW. Psoriasis and comorbidities: links and risks. Clin Cosmet Investig Dermatol 2014; 7: 119-132. PMID: 24790463
5. Richard MA, Barnetche T, Horreau C, Brenaut E, Pouplard C, Aractingi S, Aubin F, Cribier B, Joly P, Jullien D, Le Maître M, Misery L, Ortonne JP, Paul C. Psoriasis, cardiovascular events, cancer risk and alcohol use: evidence-based recommendations based on systematic review and expert opinion. J Eur Acad Dermatol Venereol 2013; 27: 2-11. PMID: 23845148
6. The IDF consensus worldwide definition of the metabolic syndrome at: http: //www.idf.org/webdata/docs/ IDF_Meta_def_final_pdf.
7. Suarez-Farinas M, Li K, Fuentes-Duculan J, Hayden K, Brodmerkel C, Krueger JG. Expanding the psoriasis disease profile: interrogation of the skin and serum of patients with moderate-to-severe psoriasis. J Invest Dermatol 2012; 132: 2552-2564. PMID: 22763790

8. Hotamisligil GS. Inflammation and metabolic disorders. Nature 2006; 444: 860-867. PMID: 17167474

9. Davidovici BB, Sattar N, Prinz J, Puig L, Emery P, Barker JN, van de Kerkhof P, Ståhle M, Nestle FO, Girolomoni G, Krueger JG. Psoriasis and systemic inflammatory diseases: potential mechanistic links between skin disease and co-morbid conditions. J Invest Dermatol 2010: 130: 1785-1796. PMID: 20445552

10. Ryan C, Menter A. Psoriasis and cardiovascular disorders. G Ital Dermatol Venereol 2012; 147: 179-187. PMID: 22481581

11. Corbetta S, Angioni R, Cattaneo A, Beck-Peccoz P, Spada A. Effects of retinoid therapy on insulin sensitivity, lipid profile and circulating adipocytokines. Eur J Endocrinol 2006; 154: 83-86. PMID: 16381995

12. Ormerod AD, Campalani E, Goodfield MJ. BAD Clinical Standards Unit. British Association of Dermatologists guidelines on the efficacy and use of acitretin in dermatology. Br J Dermatol 2010; 162: 952-963. PMID: 20423353

13. Stiller MJ, Pak GH, Kenny C, Jondreau L, Davis I, Wachsman S, Shupack JL. Elevation of fasting serum lipids in patients treated with low-dose cyclosporine for severe plaque-type psoriasis. An assessment of clinical significance when viewed as a risk factor for cardiovascular disease. J Am Acad Dermatol 1992; 27: 434-438. PMID: 1401280

14. Robert N, Wong GW, Wright JM. Effect of cyclosporine on blood pressure. Cochrane Database Syst Rev 2010; 1: CD007893. PMID: 20091657

15. Malhotra A, Shafiq N, Rajagopalan S, Dogra S, Malhotra S. Thiazolidinediones for plaque psoriasis: a systematic review and meta-analysis. Evid Based Med 2012; 17: 171-176. PMID: 22522793

16. Shirinsky IV, Shirinsky VS. Efficacy of simvastatin in plaque psoriasis: A pilot study. J Am Acad Dermatol 2007; 57: 529-531. PMID: 17707157

17. Rajpara AN, Goldner R, Gaspari A. Psoriasis: can statins play a dual role? Dermatol Online J 2010; 16: 2. PMID: 20178698

18. Waqar S, Sarkar PK. Exacerbation of psoriasis with beta-blocker therapy. CMAJ 2009; 181: 60. PMID: 19581619

19. Farley E, Menter A. Psoriasis: comorbidities and associations. G Ital Dermatol Venereol 2011; 146: 9-15. PMID: 21317853

20. Prodanovich S, Ma F, Taylor JR, Pezon C, Fasihi T, Kirsner RS. Methotrexate reduces incidence of vascular diseases in veterans with psoriasis or rheumatoid arthritis. J Am Acad Dermatol 2005; 52: 262–267. PMID: 15692471

21. Florin V, Cottencin AC, Delaporte E, Staumont-Sallé D. Body weight increment in patients treated with infliximab for plaque psoriasis. J Eur Acad Dermatol Venereol 2013; 27: e186-190. PMID: 22621415

22. Farrokhi F, Taylor HC, McBride NM. Etanercept-induced hypoglycemia and improved glycemic control in a patient with type 2 diabetes. Endocr Pract 2011; 17: 306-307. PMID: 21474422

23. Dominguez H, Storgaard H, Rask-Madsen C, Steffen Hermann T, Ihlemann N, Baunbjerg Nielsen D, et al.. Metabolic and vascular effects of tumor necrosis factor-alpha blockade with etanercept in obese patients with type 2 diabetes. J Vasc Res 2005; 42: 517–525. PMID: 16155368

24. Gonzalez-Juanatey C, Testa A, Garcia-Castelo A, Garcia-Porrua C, Llorca J, Gonzalez-Gay MA. Active but transient improvement of endothelial function in rheumatoid arthritis patients undergoing long-term treatment with anti-tumor necrosis factor alpha antibody. Arthritis Rheum 2004; 51: 447–450. PMID: 15188332

25. Alsufyani MA, Golant AK, Lebwohl M. Psoriasis and the metabolic syndrome. Dermatol Ther 2010; 23: 137-143. PMID: 20415820

26. Gallagher EJ, Leroith D, Karnieli E. Insulin resistance in obesity as the underlying cause for the metabolic syndrome. Mt Sinai J Med 2010; 77: 511-523. PMID: 20960553

27. Beltrán-Sánchez H, Harhay MO, Harhay MM, McElligott S. Prevalence and trends of metabolic syndrome in the adult U.S. population, 1999-2010. J Am Coll Cardiol 2013; 62: 697-703. PMID: 23810877

28. Scuteri A, Laurent S, Cucca F, Cockcroft J, Cunha PG, Mañas LR, Raso FU, Muiesan ML, Ryliškyte L, Rietzschel E, Strait J, Vlachopoulos C, Völzke H, Lakatta EG, Nilsson PM; for the Metabolic Syndrome and Arteries Research (MARE) Consortium. Metabolic syndrome across Europe: different clusters of risk factors. Eur J Prev Cardiol 2014. PMID: 24647805.

29. Sommer DM, Jenisch S, Suchan M, Christophers E, Weichenthal M. Increased prevalence of the metabolic syndrome in patients with moderate to severe psoriasis. Arch Dermatol Res 2006; 298: 321–328. PMID: 17021763

30. Cohen AD, Sherf M, Vidavsky L, Vardy DA, Shapiro J, Meyerovitch J. Association between psoriasis and the metabolic syndrome. A cross-sectional study. Dermatology 2008; 216: 152–155. PMID: 18216477

31. Armstrong AW, Harskamp CT, Armstrong EJ. Psoriasis and metabolic syndrome: a systematic review and meta-analysis of observational studies. J Am Acad Dermatol 2013; 68: 654-662. PMID: 23360868

32. Gisondi P, Tessari G, Conti A, Piaserico S, Schianchi S, Peserico A, Giannetti A, Girolomoni G. Prevalence of metabolic syndrome in patients with psoriasis: a hospital-based case-control study. Br J Dermatol 2007; 157: 68-73. PMID: 17553036

33. Zindancı I, Albayrak O, Kavala M, Kocaturk E, Can B, Sudogan S, Koç M. Prevalence of metabolic syndrome in patients with psoriasis. Scientific World Journal 2012; 2012: 312463. PMID: 22654590

34. Au SC, Goldminz AM, Loo DS, Dumont N, Levine D, Volf E, Michelon M, Wang A, Kim N, Yaniv S, Lizzul PF, Kerensky T, Lopez-Benitez JM, Natter M, Miller L, Pelajo CF, Davis T, Gottlieb AB. Association between pediatric psoriasis and the metabolic syndrome. J Am Acad Dermatol 2012; 66: 1012-1013. PMID: 22583717.

35. Farshchian M, Zamanian A, Farshchian M, Monsef AR, Mahjub H. Serum lipid level in Iranian patients with psoriasis. J Eur Acad Dermatol Venereol 2007; 21: 802–805. PMID: 17567311.

36. Kim GW, Park HJ, Kim HS, Kim SH, Ko HC, Kim BS, et al.. Analysis of cardiovascular risk factors and metabolic syndrome in Korean patients with psoriasis. Ann Dermatol 2012; 24: 11–15. PMID: 22363149.

37. M G G, Talwar A, Kumar B C S, M R, A S N, H B M. A clinical and epidemiological study of psoriasis and its association with various biochemical parameters in newly diagnosed cases. J Clin Diagn Res 2013; 7: 2901-2903. PMID: 24551670

38. Lakshmi S, Nath AK, Udayashankar C. Metabolic syndrome in patients with psoriasis: A comparative study. Indian Dermatol Online J 2014; 5: 132-137. PMID: 24860744

39. Sales R, Torres T. Psoriasis and Metabolic Syndrome. Acta Dermatovenerol Croat 2014; 22: 169-174. PMID: 25230056

40. Hayes J, Koo J. Psoriasis: depression, anxiety, smoking, and drinking habits. Dermatol Ther 2010; 23: 174-180. PMID: 20415825

41. Padhi T, Garima. Metabolic syndrome and skin: psoriasis and beyond. Indian J Dermatol 2013; 58: 299-305. PMID: 23919003

42. Kimball AB, Gladman D, Gelfand JM, Gordon K, Horn EJ, Korman NJ, Korver G, Krueger GG, Strober BE, Lebwohl MG; National Psoriasis Foundation. National Psoriasis Foundation clinical consensus on psoriasis comorbidities and recommendations for screening. J Am Acad Dermatol 2008; 58: 1031-1042. PMID: 18313171

43. Azfar RS, Gelfand JM. Psoriasis and metabolic disease: epidemiology and pathophysiology. Curr Opin Rheumatol 2008; 20: 416-422. PMID: 18525354

44. Suárez-Fariñas M, Lowes MA, Zaba LC, Krueger JG. Evaluation of the psoriasis transcriptome across different studies by gene set enrichment analysis (GSEA). PLoS One 2010; 5: e10247. PMID: 20422035

45. Schlaak JF, Buslau M, Jochum W, Hermann E, Girndt M, Gallati H, Meyer zum Büschenfelde KH, Fleischer B. T cells involved in psoriasis vulgaris belong to the Th1 subset. J Invest Dermatol 1994; 102: 145-149. PMID: 8106745

46. Qu N, Xu M, Mizoguchi I, Furusawa J, Kaneko K, Watanabe K, Mizuguchi J, Itoh M, Kawakami Y, Yoshimoto T. Pivotal roles of T-helper 17-related cytokines, IL-17, IL-22, and IL-23, in inflammatory diseases. Clin Dev Immunol 2013; 2013: 968549. PMID: 23956763

47. Lee E, Trepicchio WL, Oestreicher JL, et al. Increased expression of interleukin 23 p19 and p40 in lesional skin of patients with psoriasis vulgaris. J Exp Med 2004; 199: 125–130. PMID: 14707118

48. Lowes MA, Kikuchi T, Fuentes-Duculan J, et al. Psoriasis vulgaris lesions contain discrete populations of Th1 and Th17 T cells. J Invest Dermatol 2008; 128: 1207–1211. PMID: 18200064

49. Boniface K, Guignouard E, Pedretti N, et al. A role for T cell-derived interleukin 22 in psoriatic skin inflammation.Clin Exp Immunol 2007; 150: 407–415. PMID:17900301

50. Kagen MH, McCormick TS, Cooper KD. Regulatory T cells in psoriasis. Ernst Schering Res Found Workshop 2006; 56: 193-209. PMID: 16329653

51. Tortola L, Rosenwald E, Abel B, Blumberg H, Schäfer M, Coyle AJ, Renauld JC, Werner S, Kisielow J, Kopf M. Psoriasiform dermatitis is driven by IL-36-mediated DC-keratinocyte crosstalk. J Clin Invest 2012; 122: 3965-3976. PMID: 23064362

52. Lowes MA, Suárez-Fariñas M, Krueger JG. Immunology of psoriasis. Annu Rev Immunol 2014; 32: 227-55. PMID: 24655295

53. Nograles KE, Zaba LC, Guttman-Yassky E, Fuentes-Duculan J, Suárez-Fariñas M, Cardinale I, Khatcherian A, Gonzalez J, Pierson KC, White TR, Pensabene C, Coats I, Novitskaya I, Lowes MA, Krueger JG. Th17 cytokines interleukin (IL)-17 and IL-22 modulate distinct inflammatory and keratinocyte-response pathways. Br J Dermatol 2008; 159: 1092-1102. PMID: 18684158

54. Macatonia SE, Hosken NA, Litton M, Vieira P, Hsieh CS, Culpepper JA, Wysocka M, Trinchieri G, Murphy KM, O'Garra A. Dendritic cells produce IL-12 and direct the development of Th1 cells from naive CD4+ T cells. J Immunol 1995; 154: 5071-5079. PMID: 7730613

55. Lowes MA, Russell CB, Martin DA, Towne JE, Krueger JG. The IL-23/T17 pathogenic axis in psoriasis is amplified by keratinocyte responses. Trends Immunol 2013; 34: 174-181. PMID: 23291100

56. Oppmann B, Lesley R, Blom B, et al. Novel p19 protein engages IL-12p40 to form a cytokine, IL-23, with biological activities similar as well as distinct from IL-12. Immunity 2000; 13: 715-725. PMID: 11114383

57. Alobaidi AH, Mothana Z, Najem WS, Alsamarai AM Adiponectin, IL-10, IL-23 and Trace Elements Serum Levels in Patients with Psoriasis. J Am Acad Dermatol 2012; 1: 6-23.

58. Kryczek I, Bruce AT, Gudjonsson JE, Johnston A, Aphale A, Vatan L, Szeliga W, Wang Y, Liu Y, Welling TH, Elder JT, Zou W. Induction of IL-17+ T cell trafficking and development by IFN-gamma: mechanism and pathological relevance in psoriasis. J Immunol 2008; 181: 4733-4741. PMID: 18802076

59. Cai Y, Shen X, Ding C, Qi C, Li K, Li X, Jala VR, Zhang HG, Wang T, Zheng J, Yan J. Pivotal role of dermal IL-17-producing γδ T cells in skin inflammation. Immunity 2011; 35: 596-610. PMID: 21982596

60. Lin AM, Rubin CJ, Khandpur R, Wang JY, Riblett M, Yalavarthi S, Villanueva EC,Shah P, Kaplan MJ, Bruce AT. Mast cells and neutrophils release IL-17 through extracellular trap formation in psoriasis. J Immunol 2011; 187: 490-500. PMID: 21606249

61. Michalak-Stoma A, Bartosińska J, Kowal M, Juszkiewicz-Borowiec M, Gerkowicz A, Chodorowska G. Serum levels of selected Th17 and Th22 cytokines

in psoriatic patients. Dis Markers 2013; 35: 625-631. PMID: 24288431

62. Fujishima S, Watanabe H, Kawaguchi M, Suzuki T, Matsukura S, Homma T, Howell BG, Hizawa N, Mitsuya T, Huang SK, Iijima M. Involvement of IL-17F via the induction of IL-6 in psoriasis. Arch Dermatol Res 2010; 302: 499-505. PMID: 20148256
63. Ha HL, Wang H, Pisitkun P, Kim JC, Tassi I, Tang W, Morasso MI, Udey MC, Siebenlist U. IL-17 drives psoriatic inflammation via distinct, target cell-specific mechanisms. Proc Natl Acad Sci U S A 2014; 111: E3422-431. PMID: 25092341
64. Dhillion P, Wallace K, Herse F, et al. IL-17-mediated oxidative stress is an important stimulator of AT1-AA and hypertension during pregnancy.Am J Physiol Regul Integr Comp Physiol 2012; 303: R353–8. PMID: 22718806
65. Harrison DG. The immune system in hypertension. Trans Am Clin Climatol Assoc 2014; 125: 130-140. PMID: 25125726
66. Nguyen H, Chiasson VL, Chatterjee P, Kopriva SE, Young KJ, Mitchell BM. Interleukin-17 causes Rho-kinase-mediated endothelial dysfunction and hypertension. Cardiovasc Res 2013; 97: 696–704. PMID: 23263331
67. Madhur MS, Funt SA, Li L, Vinh A, Chen W, Lob HE, Iwakura Y, Blinder Y, Rahman A, Quyyumi AA, Harrison DG. Role of interleukin 17 in inflammation, atherosclerosis, and vascular function in apolipoprotein e-deficient mice. Arterioscler Thromb Vasc Biol 2011; 31: 1565-1572. PMID: 21474820
68. Surendar J, Aravindhan V, Rao MM, Ganesan A, Mohan V. Decreased serum interleukin-17 and increased transforming growth factor-β levels in subjects with metabolic syndrome (Chennai Urban Rural Epidemiology Study-95). Metabolism 2011; 60: 586-590. PMID:20667562
69. Fabbrini E, Cella M, McCartney SA, Fuchs A, Abumrad NA, Pietka TA, Chen Z, Finck BN, Han DH, Magkos F, Conte C, Bradley D, Fraterrigo G, Eagon JC, Patterson BW, Colonna M, Klein S. Association between specific adipose tissue CD4+ T-cell populations and insulin resistance in obese individuals. Gastroenterology 2013; 145: 366-374. e1-3. PMID: 23597726
70. Winer S, Paltser G, Chan Y, et al.. Obesity predisposes to Th17 bias. Eur J Immunol 2009; 39: 2629–2635. PMID: 19662632
71. Liang SC, Tan XY, Luxenberg DP, et al. Interleukin (IL)-22 and IL-17 are coexpressed by Th17 cells and cooperatively enhance expression of antimicrobial peptides. J Exp Med 2006; 203: 2271–2279. PMID: 16982811
72. Boniface K, Bernard FX, Garcia M, et al.. IL-22 inhibits epidermal differentiation and induces proinflammatory gene expression and migration of human keratinocytes. J Immunol 2005; 174: 3695–3702. PMID: 15749908
73. Brotas AM, Cunha JM, Lago EH, Machado CC, Carneiro SC. Tumor necrosis factor-alpha and the cytokine network in psoriasis. An Bras Dermatol 2012; 87: 673-681. PMID: 23044557
74. Bromley SK, Mempel TR, Luster AD. Orchestrating the orchestrators: chemokines in control of T cell traffic. Nat Immunol 2008; 9: 970-980. PMID: 18711434
75. Johansen C, Riis JL, Gedebjerg A, Kragballe K, Iversen L. Tumor necrosis factor α-mediated induction of interleukin 17C in human keratinocytes is controlled by nuclear factor κB. J Biol Chem 2011; 286: 25487-25494. PMID: 1628458
76. Jordan CT, Cao L, Roberson ED, Pierson KC, Yang CF, Joyce CE, Ryan C, Duan S, Helms CA, Liu Y, Chen Y, McBride AA, Hwu WL, Wu JY, Chen YT, Menter A,Goldbach-Mansky R, Lowes MA, Bowcock AM. PSORS2 is due to mutations in CARD14. Am J Hum Genet 2012; 90: 784-795. PMID: 22521418
77. Towne JE, Sims JE. IL-36 in psoriasis. Curr Opin Pharmacol 2012; 12: 486-490. PMID: 22398321
78. Johnston A, Xing X, Guzman AM, Riblett M, Loyd CM, Ward NL, Wohn C, Prens EP, Wang F, Maier LE, Kang S, Voorhees JJ, Elder JT, Gudjonsson JE. IL-1F5, -F6, -F8 ,and -F9: a novel IL-1 family signaling system that is active in psoriasis and promotes keratinocyte antimicrobial peptide expression. J Immunol 2011; 186: 2613-2622. PMID: 21242515
79. Carrier Y, Ma HL, Ramon HE, Napierata L, Small C, O'Toole M, Young DA, Fouser LA, Nickerson-Nutter C, Collins M, Dunussi-Joannopoulos K, Medley QG. Inter-regulation of Th17 cytokines and the IL-36 cytokines in vitro and in vivo: implications in psoriasis pathogenesis. J Invest Dermatol 2011; 131: 2428-2437. PMID: 21881584
80. He Q, Chen HX, Li W, Wu Y, Chen SJ, Yue Q, Xiao M, Li JW. IL-36 cytokine expression and its relationship with p38 MAPK and NF-κB pathways in psoriasis vulgaris skin lesions. J Huazhong Univ Sci Technolog Med Sci 2013; 33: 594-599. PMID: 23904383
81. Yu XJ, Li CY, Dai HY, Cai DX, Wang KY, Xu YH, Chen LM, Zhou CL. Expression and localization of the activated mitogen-activated protein kinase in lesional psoriatic skin. Exp Mol Pathol 2007; 83: 413-418. PMID: 17599830
82. Mavropoulos A, Rigopoulou EI, Liaskos C, Bogdanos DP, Sakkas LI. The role of p38 MAPK in the aetiopathogenesis of psoriasis and psoriatic arthritis. Clin Dev Immunol 2013; 2013: 569751. PMID: 24151518
83. Saggini A, Chimenti S, Chiricozzi A. IL-6 as a druggable target in psoriasis: focus on pustular variants. J Immunol Res 2014; 2014: 964069. PMID: 25126586
84. Neuner P, Urbanski A, Trautinger F, Möller A, Kirnbauer R, Kapp A, Schöpf E, Schwarz T, Luger TA. Increased IL-6 production by monocytes and keratinocytes in patients with psoriasis. J Invest Dermatol 1991; 97: 27-33. PMID: 2056189
85. Teunissen MB, Koomen CW, de Waal Malefyt R, Wierenga EA, Bos JD. Interleukin-17 and interferon-gamma synergize in the enhancement of proinflammatory cytokine production by human keratinocytes. J Invest Dermatol 1998; 111: 645-649. PMID: 9764847

86. McGeachy MJ, Bak-Jensen KS, Chen Y, Tato CM, Blumenschein W, McClanahan T, Cua DJ. TGF-beta and IL-6 drive the production of IL-17 and IL-10 by T cells and restrain T(H)-17 cell-mediated pathology. Nat Immunol 2007; 8: 1390-1397. PMID: 17994024

87. Lindroos J, Svensson L, Norsgaard H, Lovato P, Moller K, Hagedorn PH, Olsen GM, Labuda T. IL-23-mediated epidermal hyperplasia is dependent on IL-6. J Invest Dermatol 2011; 131: 1110-1118. PMID: 21289639

88. Goodman WA, Levine AD, Massari JV, Sugiyama H, McCormick TS, Cooper KD. IL-6 signaling in psoriasis prevents immune suppression by regulatory T cells. J Immunol 2009; 183: 3170-3176. PMID: 19648274

89. Sano S, Chan KS, Carbajal S, Clifford J, Peavey M, Kiguchi K, Itami S, Nickoloff BJ, DiGiovanni J. Stat3 links activated keratinocytes and immunocytes required for development of psoriasis in a novel transgenic mouse model. Nat Med 2005; 11: 43-49. PMID: 15592573

90. Honma M, Minami-Hori M, Takahashi H, Iizuka H. Podoplanin expression in wound and hyperproliferative psoriatic epidermis: regulation by TGF-β and STAT-3 activating cytokines, IFN-γ, IL-6, and IL-22. J Dermatol Sci 2012; 65: 134-140. PMID: 22189341

91. De Filippo G, Rendina D, Moccia F, Rocco V, Campanozzi A. Interleukin-6, soluble interleukin-6 receptor/interleukin-6 complex and insulin resistance in obese children and adolescents. J Endocrinol Invest 2014. PMID: 25245339

92. Esteve E, Castro A, López-Bermejo A, Vendrell J, Ricart W, Fernández-Real JM. Serum interleukin-6 correlates with endothelial dysfunction in healthy men independently of insulin sensitivity. Diabetes Care 2007; 30: 939-945. PMID: 17392554

93. Kaur S, Zilmer K, Kairane C, Kals M, Zilmer M. Clear differences in adiponectin level and glutathione redox status revealed in obese and normal-weight patients with psoriasis. Br J Dermatol 2008; 159: 1364-1367. PMID: 18652586

94. Rajappa M, Rathika S, Munisamy M, Chandrashekar L, Thappa DM. Effect of treatment with methotrexate and coal tar on adipokine levels and indices of insulin resistance and sensitivity in patients with psoriasis vulgaris. J Eu Acad Dermatol Venereol 2014 Mar 25. PMID: 24665910

95. Danesh J, Kaptoge S, Mann AG, Sarwar N, Wood A, Angleman SB, Wensley F, Higgins JP, Lennon L, Eiriksdottir G, Rumley A, Whincup PH, Lowe GD, Gudnason V. Long-term interleukin-6 levels and subsequent risk of coronary heart disease: two new prospective studies and a systematic review. PLoS Med 2008; 5: e78. PMID: 18399716

96. Beljaards RC, Van Beek P, Nieboer C, Stoof TJ, Boorsma DM. The expression of interleukin-8 receptor in untreated and treated psoriasis. Arch Dermatol Res 1997; 289: 440-443. PMID: 9266020

97. Arican O, Aral M, Sasmaz S, Ciragil P. Serum levels of TNF-alpha, IFN-gamma, IL-6, IL-8, IL-12, IL-17, and IL-18 in patients with active psoriasis and correlation with disease severity. Mediators Inflamm 2005; 2005: 273-279. PMID: 16258194

98. Duan H, Koga T, Kohda F, Hara H, Urabe K, Furue M. Interleukin-8-positive neutrophils in psoriasis. J Dermatol Sci 2001; 26: 119-124. PMID: 11378328

99. Ferran M, Ferran M, Galván AB, Giménez-Arnau A, Giménez-Arnau A, Pujol RM, Pujol RM, Santamaría-Babi LF, Santamaría-Babi LF. Production of interleukin-8 by circulating CLA+ T cells with skin tropism in patients with psoriasis and in healthy controls. Actas Dermosifiliogr 2010; 101: 151-155. PMID: 20223157

100. Kobashi C, Asamizu S, Ishiki M, Iwata M, Usui I, Yamazaki K, Tobe K, Kobayashi M, Urakaze M. Inhibitory effect of IL-8 on insulin action in human adipocytes via MAP kinase pathway. J Inflamm (Lond) 2009; 6: 25. PMID: 19709445

101. Shin MJ, Lee KH, Chung JH, Park YK, Choi MK, Oh J, Choi JW, Lee SH, Chung N, Kang SM. Circulating IL-8 levels in heart failure patients with and without metabolic syndrome. Clin Chim Acta 2009; 405: 139-142. PMID: 19410569

102. Wajant H, Pfizenmaier K, Scheurich P. Tumor necrosis factor signaling. Cell Death Differ 2003; 10: 45-65. PMID: 12655295

103. Aggarwal BB, Gupta SC, Sung B. Curcumin: an orally bioavailable blocker of TNF and other pro-inflammatory biomarkers. Br J Pharmacol 2013; 169: 1672-1692. PMID: 23425071

104. Sewter CP, Digby JE, Blows F, Prins J, O'Rahilly S. Regulation of tumour necrosis factor-alpha release from human adipose tissue in vitro. J Endocrinol 1999; 163: 33-38. PMID: 10495404

105. Tracey KJ, Vlassara H, Cerami A. Cachectin/tumour necrosis factor. Lancet 1989; 1: 1122-1126. PMID: 2566060

106. Mussi A, Bonifati C, Carducci M, D'Agosto G, Pimpinelli F, D'Urso D, D'Auria L, Fazio M, Ameglio F. Serum TNF-alpha levels correlate with disease severity and are reduced by effective therapy in plaque-type psoriasis. J Biol Regul Homeost Agents 1997; 11: 115-118. PMID: 9498161

107. Summers deLuca L, Gommerman JL. Fine-tuning of dendritic cell biology by the TNF superfamily. Nat Rev Immunol 2012; 12: 339-351. PMID: 22487654

108. Zaba LC, Cardinale I, Gilleaudeau P, Sullivan-Whalen M, Suárez-Fariñas M, Fuentes-Duculan J, Novitskaya I, Khatcherian A, Bluth MJ, Lowes MA, Krueger JG. Amelioration of epidermal hyperplasia by TNF inhibition is associated with reduced Th17 responses. J Exp Med 2007; 204: 3183-3194. PMID: 18039949

109. Goldminz AM, Au SC, Kim N, Gottlieb AB, Lizzul PF. NF-κB: an essential transcription factor in psoriasis. J Dermatol Sci 2013; 69: 89-94. PMID: 23219896

110. Kanda N, Hau CS, Tada Y, Tatsuta A, Sato S, Watanabe S. Visfatin enhances CXCL8, CXCL10, and CCL20 production in human keratinocytes. Endocrinology 2011; 152: 3155-3164. PMID: 21673103

111. Chiricozzi A, Guttman-Yassky E, Suárez-Fariñas M, Nograles KE, Tian S, Cardinale I, Chimenti S, Krueger JG. Integrative responses to IL-17 and TNF-α in human keratinocytes account for key inflammatory

pathogenic circuits in psoriasis. J Invest Dermatol 2011; 131: 677-687. PMID: 21085185

112. Nieto-Vazquez I, Fernández-Veledo S, Krämer DK, Vila-Bedmar R, Garcia-Guerra L, Lorenzo M. Insulin resistance associated to obesity: the link TNF-alpha. Arch Physiol Biochem 2008; 114: 183-194. PMID: 18629684

113. Ruan H, Miles PD, Ladd CM, Ross K, Golub TR, Olefsky JM, Lodish HF. Profiling gene transcription in vivo reveals adipose tissue as an immediate target of tumor necrosis factor-alpha: implications for insulin resistance. Diabetes 2002; 51: 3176-3188. PMID: 12401708

114. Cawthorn WP, Sethi JK. TNF-alpha and adipocyte biology. FEBS Lett 2008; 582: 117-131. PMID: 18037376

115. Kaur J. A comprehensive review on metabolic syndrome. Cardiol Res Pract 2014; 2014: 943162. PMID: 24711954

116. Ye J. Regulation of PPAR gamma function by TNF-alpha. Biochem Biophys Res Commun 2008; 374: 405-408. PMID: 18655773

117. Sugiyama H, Gyulai R, Toichi E, Garaczi E, Shimada S, Stevens SR, McCormick TS, Cooper KD. Dysfunctional blood and target tissue CD4+CD25high regulatory T cells in psoriasis: mechanism underlying unrestrained pathogenic effector T cell proliferation. J Immunol 2005; 174: 164-173. PMID: 15611238

118. Soler DC, McCormick TS. The dark side of regulatory T cells in psoriasis. J Invest Dermatol 2011; 131: 1785-1786. PMID: 21844929

119. Cheng X, Yu X, Ding YJ, Fu QQ, Xie JJ, Tang TT, Yao R, Chen Y, Liao YH. The Th17/Treg imbalance in patients with acute coronary syndrome. Clin Immunol 2008; 127: 89-97. PMID: 18294918

120. Feuerer M, Herrero L, Cipolletta D, Naaz A, Wong J, Nayer A, Lee J, Goldfine AB, Benoist C, Shoelson S, Mathis D. Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. Nat Med 2009; 15: 930-939. PMID: 19633656

121. Wagner NM, Brandhorst G, Czepluch F, Lankeit M, Eberle C, Herzberg S, Faustin V, Riggert J, Oellerich M, Hasenfuss G, Konstantinides S, Schäfer K. Circulating regulatory T cells are reduced in obesity and may identify subjects at increased metabolic and cardiovascular risk. Obesity (Silver Spring) 2013; 21: 461-468. PMID: 23592653

122. Cipolletta D, Feuerer M, Li A, Kamei N, Lee J, Shoelson SE, Benoist C, Mathis D. PPAR-γ is a major driver of the accumulation and phenotype of adipose tissue Treg cells. Nature 2012; 486: 549-553. PMID: 22722857

123. Han JM, Patterson SJ, Speck M, Ehses JA, Levings MK. Insulin inhibits IL-10-mediated regulatory T cell function: implications for obesity. J Immunol 2014; 192: 623-629. PMID: 24323581

124. Nakanishi K, Yoshimoto T, Tsutsui H, Okamura H. Interleukin-18 regulates both Th1 and Th2 responses. Annu Rev Immunol 2001; 19: 423-474. PMID: 11244043

125. Rasmy H, Mikhael N, Ismail S. Interleukin-18 expression and the response to treatment in patients with psoriasis. Arch Med Sci 2011; 7: 713-719. PMID: 22291810

126. Flisiak I, Zaniewski P, Chodynicka B. Plasma TGF-beta1, TIMP-1, MMP-1 and IL-18 as a combined biomarker of psoriasis activity. Biomarkers 2008; 13: 549-556. PMID: 18979644

127. Skurk T, Kolb H, Muller-Scholze S, Rohrig K, Hauner H, Herder C. The proatherogenic cytokine interleukin-18 is secreted by human adipocytes. Eur J Endocrinol 2005; 152: 863-868. PMID: 15941925

128. Van Guilder GP, Hoetzer GL, Greiner JJ, Stauffer BL, Desouza CA. Influence of metabolic syndrome on biomarkers of oxidative stress and inflammation in obese adults. Obesity 2006; 14: 2127–2131. PMID: 17189537

129. Presta I, Andreozzi F, Succurro E, Marini MA, Laratta E, Lauro R. IL-18 gene polymorphism and metabolic syndrome. Nutr Metab Cardiovasc Dis 2009; 19: e5–e6. PMID: 19176284

130. Zirlik A, Abdullah SM, Gerdes N, MacFarlane L, Schonbeck U, Khera A. Interleukin-18, the metabolic syndrome, and subclinical atherosclerosis: results from the Dallas Heart Study. Arterioscler Thromb Vasc Biol 2007; 27: 2043–2049. PMID: 17626902

131. Trøseid M, Seljeflot I, Arnesen H. The role of interleukin-18 in the metabolic syndrome. Cardiovasc Diabetol 2010; 9: 11. PMID: 20331890

132. Sanmiguel JC, Olaru F, Li J, Mohr E, Jensen LE. Interleukin-1 regulates keratinocyte expression of T cell targeting chemokines through interleukin-1 receptor associated kinase-1 (IRAK1) dependent and independent pathways. Cell Signal 2009; 21: 685-694. PMID: 19166933

133. Renne J, Schäfer V, Werfel T, Wittmann M. Interleukin-1 from epithelial cells fosters T cell-dependent skin inflammation. Br J Dermatol 2010; 162: 1198-1205. PMID: 20128791

134. Larsen CM, Faulenbach M, Vaag A, Vølund A, Ehses J, Seifert B, Mandrup-Poulsen T, Donath M. Interleukin-1 receptor antagonist-treatment of patients with type 2 diabetes. Ugeskr Laeger 2007; 169: 3868-3871. PMID: 8031661

135. Fain JN. Release of interleukins and other inflammatory cytokines by human adipose tissue is enhanced in obesity and primarily due to the non-fat cells. Vitam Horm 2006; 74: 443-477. PMID: 17027526

136. Harwood HJ Jr. The adipocyte as an endocrine organ in the regulation of metabolic homeostasis. Neuropharmacology 2012; 63: 57-75. PMID: 22200617

137. Harpsøe MC, Basit S, Andersson M, Nielsen NM, Frisch M, Wohlfahrt J, Nohr EA, Linneberg A, Jess T. Body mass index and risk of autoimmune diseases: a study within the Danish National Birth Cohort. Int J Epidemiol 2014; 43: 843-855. PMID: 24609069

138. Setty AR, Curhan G, Choi HK. Obesity, waist circumference, weight change, and the risk of psoriasis

in women: Nurses' Health Study II. Arch Intern Med 2007; 167: 1670-1675. PMID: 17698691

139. Carrascosa JM, Rocamora V, Fernandez-Torres RM, Jimenez-Puya R, Moreno JC, Coll-Puigserver N, Fonseca E. Obesity and psoriasis: inflammatory nature of obesity, relationship between psoriasis and obesity, and therapeutic implications. Actas Dermosifiliogr 2014; 105: 31-44. PMID: 23177976

140. Hamminga EA, van der Lely AJ, Neumann HA, Thio HB. Chronic inflammation in psoriasis and obesity: implications for therapy. Med Hypotheses 2006; 67: 768-773. PMID: 16781085

141. Salama RH, Al-Shobaili HA, Al Robaee AA, Alzolibani AA. Psoriasin: a novel marker linked obesity with psoriasis. Dis Markers 2013; 34: 33-39. PMID: 23151615

142. Maachi M, Piéroni L, Bruckert E, Jardel C, Fellahi S, Hainque B, Capeau J, Bastard JP. Systemic low-grade inflammation is related to both circulating and adipose tissue TNF-α, leptin and IL-6 levels in obese women. Int J Obes Relat Metab Disord 2004; 28: 993-997. PMID: 15211360

143. Rasouli N, Kern PA. Adipocytokines and the metabolic complications of obesity. J Clin Endocrinol Metab 2008; 93: S64-73. PMID: 18987272

144. Mehta S, Farmer JA. Obesity and inflammation: a new look at an old problem. Curr Atheroscler Rep 2007; 9: 134-138. PMID: 17877922

145. Toussirot E, Aubin F, Dumoulin G. Relationships between Adipose Tissue and Psoriasis, with or without Arthritis. Front Immunol 2014; 5: 368. PMID: 25161652

146. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2005; 365: 1415-1428. PMID: 15836891

147. Nakajima H, Nakajima K, Tarutani M, Sano S. Clear association between serum levels of adipokines and T-helper 17-related cytokines in patients with psoriasis. Clin Exp Dermatol 2013; 38: 66-70. PMID: 23083105

148. Lau DC, Dhillon B, Yan H, Szmitko PE, Verma S. Adipokines: molecular links between obesity and atherosclerosis. Am J Physiol Heart Circ Physiol 2005; 288: 2031-2041. PMID: 15653761

149. Park HK, Ahima RS. Physiology of leptin: energy homeostasis, neuroendocrine function and metabolism. Metabolism 2014 Aug 15. pii: S0026-0495(14)00241-8. PMID: 25199978

150. Sivitz WI, Walsh SA, Morgan DA, Thomas MJ, Haynes WG. Effects of leptin on insulin sensitivity in normal rats. Endocrinology 1997; 138: 3395-3401. PMID: 9231793

151. Bandaru P, Shankar A. Association between plasma leptin levels and diabetes mellitus. Metab Syndr Relat Disord 2011; 9: 19-23. PMID: 20946007

152. Molinar-Toribio E, Pérez-Jiménez J, Ramos-Romero S, Lluís L, Sánchez-Martos V, Taltavull N, Romeu M, Pazos M, Méndez L, Miranda A, Cascante M, Medina I, Torres JL. Cardiovascular disease-related parameters and oxidative stress in SHROB rats, a model for metabolic syndrome. PLoS One 2014; 9: e104637. PMID: 25115868

153. Carlyle M, Jones OB, Kuo JJ, Hall JE. Chronic cardiovascular and renal actions of leptin: role of adrenergic activity. Hypertension 2002; 39: 496–501. PMID: 11882597

154. Wolk R, Berger P, Lennon RJ, Brilakis ES, Johnson BD, Somers VK. Plasma leptin and prognosis in patients with established coronary atherosclerosis. J Am Coll Cardiol 2004; 44: 1819-1824. PMID: 15519013

155. Cirillo P, Angri V, De Rosa S, Calì G, Petrillo G, Maresca F, D'Ascoli GL, Maietta P, Brevetti L, Chiariello M. Pro-atherothrombotic effects of leptin in human coronary endothelial cells. Thromb Haemost 2010; 103: 1065-1075. PMID: 20174754

156. Procaccini C, Jirillo E, Matarese G. Leptin as an immunomodulator. Mol Aspects Med 2012; 33: 35-45. PMID: 22040697

157. Poeggeler B, Schulz C, Pappolla MA, Bodó E, Tiede S, Lehnert H, Paus R. Leptin and the skin: a new frontier. Exp Dermatol 2010; 19: 12-18. PMID: 19601981

158. Xue K, Liu H, Jian Q, Liu B, Zhu D, Zhang M, Gao L, Li C. Leptin induces secretion of pro-inflammatory cytokines by human keratinocytes in vitro—a possible reason for increased severity of psoriasis in patients with a high body mass index. Exp Dermatol 2013; 22: 406-410. PMID: 23711065

159. Robati RM, Partovi-Kia M, Haghighatkhah HR, Younespour S, Abdollahimajd F.Increased serum leptin and resistin levels and increased carotid intima-media wall thickness in patients with psoriasis: Is psoriasis associated with atherosclerosis? J Am Acad Dermatol 2014; 71: 642-648. PMID: 25043845

160. Oh YJ, Lim HK, Choi JH, Lee JW, Kim NI. Serum leptin and adiponectin levels in Korean patients with psoriasis. J Korean Med Sci 2014; 29: 729-734. PMID: 24851032

161. Asha K, Sharma SB, Singal A, Aggarwal A. Association of carotid intima-media thickness with leptin and apoliprotein b/apoliprotein a-I ratio reveals imminent predictors of subclinical atherosclerosis in psoriasis patients. Acta Medica (Hradec Kralove) 2014; 57: 21-27. PMID: 25006659

162. Li RC, Krishnamoorthy P, DerOhannessian S, Doveikis J, Wilcox M, Thomas P, Rader DJ, Reilly MP, Van Voorhees A, Gelfand JM, Mehta NN. Psoriasis is associated with decreased plasma adiponectin levels independently of cardiometabolic risk factors. Clin Exp Dermatol 2014; 39: 19-24. PMID: 24341476

163. Coimbra S, Oliveira H, Reis F, Belo L, Rocha S, Quintanilha A, Figueiredo A, Teixeira F, Castro E, Rocha-Pereira P, Santos-Silva A. Circulating adipokine levels in Portuguese patients with psoriasis vulgaris according to body mass index, severity and therapy. J Eur Acad Dermatol Venereol 2010; 24: 1386-1394. PMID: 20337818

164. Baran A, Flisiak I, Jaroszewicz J, Swiderska M. Serum adiponectin and leptin levels in psoriatic pa-

tients according to topical treatment. J Dermatolog Treat 2014: 1-5. PMID: 24754531

165. Cerman AA, Bozkurt S, Sav A, Tulunay A, Elbaşi MO, Ergun T. Serum leptin levels, skin leptin and leptin receptor expression in psoriasis. Br J Dermatol 2008; 159: 820-826. PMID:18637894

166. Chen YJ, Wu CY, Shen JL, Chu SY, Chen CK, Chang YT, Chen CM. Psoriasis independently associated with hyperleptinemia contributing to metabolic syndrome. Arch Dermatol 2008; 144: 1571-1575. PMID: 19075139

167. Ouchi N, Walsh K. Adiponectin as an anti-inflammatory factor. Clinica Chimica Acta 2007; 380: 24–30. PMID: 17343838

168. Wulster-Radcliffe MC, Ajuwon KM, Wang J, Christian JA, Spurlock ME. Adiponectin differentially regulates cytokines in porcine macrophages. Biochem Biophys Res Commun 2004; 316: 924-929. PMID: 15033490

169. Okamoto Y, Kihara S, Ouchi N, et al.. Adiponectin reduces atherosclerosis in apolipoprotein E-deficient mice. Circulation 2002; 106: 2767–2770. PMID: 12451000

170. Chen H, Montagnani M, Funahashi T, Shimomura I, Quon MJ. Adiponectin stimulates production of nitric oxide in vascular endothelial cells. J Biol Chem 2003; 278: 45021–45026. PMID: 12944390

171. Nawrocki AR, Rajala MW, Tomas E, et al.. Mice lacking adiponectin show decreased hepatic insulin sensitivity and reduced responsiveness to peroxisome proliferator-activated receptor gamma agonists. J Biol Chem 2006; 281: 2654–2660. PMID: 12944390

172. Hulthe J, Hultén LM, Fagerberg B. Low adipocyte-derived plasma protein adiponectin concentrations are associated with the metabolic syndrome and small dense low-density lipoprotein particles: atherosclerosis and insulin resistance study. Metabolism 2003; 52: 1612-1614. PMID: 14669165

173. Bae YJ, Kim SH, Chung JH, Song SW, Kim KS, Kim MK, Kwon O, Choi MS, Sung MK. Evaluation of adiposity-related biomarkers as metabolic syndrome indicators. Clin Nutr Res 2013; 2: 91-99. PMID: 23908975

174. Park HK, Qatanani M, Briggs ER, Ahima RS, Lazar MA. Inflammatory induction of human resistin causes insulin resistance in endotoxemic mice. Diabetes 2011; 60: 775-783. PMID: 21282361

175. Norata GD, Ongari M, Garlaschelli K, Raselli S, Grigore L, Catapano AL. Plasma resistin levels correlate with determinants of the metabolic syndrome. Eur J Endocrinol 2007; 156: 279-284. PMID: 17287419

176. Tatlıcan S, Gülbahar Ö, Eren C, Şimşek KK, Eskioğlu F. Psoriasis hastalarında serum resistin seviyeleri artmıştır ve hastalık şiddeti ile korelasyon göstermektedir. İzmir Eğitim Ve Araştırma Hastanesi Tıp Dergisi 2008; 14: 67-71.

177. Boehncke S, Thaci D, Beschmann H, Ludwig RJ, Ackermann H, Badenhoop K, Boehncke WH. Psoriasis patients show signs of insulin resistance. Br J Dermatol 2007; 157: 1249-1251. PMID: 17916217

178. Takahashi H, Tsuji H, Takahashi I, Hashimoto Y, Ishida-Yamamoto A, Iizuka H. Plasma adiponectin and leptin levels in Japanese patients with psoriasis. Br J Dermatol 2008; 159: 1207–1208. PMID: 18795929

179. Bosanská L, Michalský D, Lacinová Z, Dostálová I, Bártlová M, Haluzíková D, Matoulek M, Kasalický M, Haluzík M. The influence of obesity and different fat depots on adipose tissue gene expression and protein levels of cell adhesion molecules. Physiol Res 2010; 59: 79-88. PMID: 19249917

180. Cabrijan L, Batinac T, Lenkovic M, Gruber F. The distinction between lesional and non-lesional skin in psoriasis vulgaris through expression of adhesion molecules ICAM-1 and VCAM-1. Med Hypotheses 2009; 72: 327–329. PMID: 19022587

181. Ghazizadeh R, Shimizu H, Tosa M, Ghazizadeh M. Pathogenic mechanisms shared between psoriasis and cardiovascular disease. Int J Med Sci 2010; 7: 284-289. PMID: 20827428

182. Zamboni S, Zanetti G, Grosso G, Ambrosio GB, Gozzetti S, Peserico A. Dietary behaviour in psoriatic patients. Acta Derm Venereol Suppl 1989; 146: 182-183. PMID: 2609864

183. Taniguchi CM, Emanuelli B, Kahn CR. Critical nodes in signalling pathways: insights into insulin action. Nat Rev Mol Cell Biol 2006; 7: 85-96. PMID: 16493415

184. Festa A, D'Agostino R Jr, Howard G, Mykkänen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). Circulation 2000; 102: 42-47. PMID: 10880413

185. Boura-Halfon S, Zick Y. Phosphorylation of IRS proteins, insulin action, and insulin resistance. Am J Physiol Endocrinol Metab 2009; 296: E581-91. PMID: 18728222

186. Shu CJ, Benoist C, Mathis D. The immune system's involvement in obesity-driven type 2 diabetes. Semin Immunol 2012; 24: 436-442. PMID: 23333525

187. Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. J Clin Invest 2005; 115: 1111-1119. PMID: 15864338

188. Gerriets VA, MacIver NJ. Role of T cells in malnutrition and obesity. Front Immunol 2014; 5: 379. PMID: 25157251

189. Lumeng CN, Deyoung SM, Bodzin JL, Saltiel AR. Increased inflammatory properties of adipose tissue macrophages recruited during diet-induced obesity. Diabetes 2007; 56: 16-23. PMID: 17192460

190. Huh JY, Park YJ, Ham M, Kim JB. Crosstalk between adipocytes and immune cells in adipose tissue inflammation and metabolic dysregulation in obesity. Mol Cells 2014; 37: 365-371. PMID: 24781408

191. Yang H, Youm YH, Vandanmagsar B, Ravussin A, Gimble JM, Greenway F, Stephens JM, Mynatt RL, Dixit VD. Obesity increases the production of proinflammatory mediators from adipose tissue T cells and compromises TCR repertoire diversity: implications for systemic inflammation and insulin resis-

tance. J Immunol 2010; 185: 1836-1845. PMID: 20581149

192. Rocha VZ, Folco EJ, Ozdemir C, Sheikine Y, Christen T, Sukhova GK, Tang EH, Bittencourt MS, Santos RD, Luster AD, Cohen DE, Libby P. CXCR3 controls T-cell accumulation in fat inflammation. Arterioscler Thromb Vasc Biol 2014; 34: 1374-1381. PMID: 24812325

193. Kitade H, Sawamoto K, Nagashimada M, Inoue H, Yamamoto Y, Sai Y, Takamura T, Yamamoto H, Miyamoto K, Ginsberg HN, Mukaida N, Kaneko S, Ota T. CCR5 plays a critical role in obesity-induced adipose tissue inflammation and insulin resistance by regulating both macrophage recruitment and M1/M2 status. Diabetes 2012; 61: 1680-1690. PMID: 22474027

194. Ioan-Facsinay A, Kwekkeboom JC, Westhoff S, Giera M, Rombouts Y, van Harmelen V, Huizinga TW, Deelder A, Kloppenburg M, Toes RE. Adipocyte-derived lipids modulate CD4+ T-cell function. Eur J Immunol 2013; 43: 1578-1587. PMID: 23504601

195. Tripathi YB, Pandey V. Obesity and endoplasmic reticulum (ER) stresses. Front Immunol 2012; 3: 240. PMID: 22891067

196. Deng T, Lyon CJ, Minze LJ, Lin J, Zou J, Liu JZ, Ren Y, Yin Z, Hamilton DJ,Reardon PR, Sherman V, Wang HY, Phillips KJ, Webb P, Wong ST, Wang RF, Hsueh WA. Class II major histocompatibility complex plays an essential role in obesity-induced adipose inflammation. Cell Metab 2013; 17: 411-422. PMID: 23473035

197. McCoy KD, Le Gros G. The role of CTLA-4 in the regulation of T cell immune responses. Immunol Cell Biol. 1999; 77: 1-10 PMID: 10101680

198. Tai X, Van Laethem F, Pobezinsky L, Guinter T, Sharrow SO, Adams A, Granger L, Kruhlak M, Lindsten T, Thompson CB, Feigenbaum L, Singer A. Basis of CTLA-4 function in regulatory and conventional CD4(+) T cells. Blood 2012; 119: 5155-5163. PMID: 22403258

199. Fujii M, Inoguchi T, Batchuluun B, Sugiyama N, Kobayashi K, Sonoda N, Takayanagi R. CTLA-4Ig immunotherapy of obesity-induced insulin resistance by manipulation of macrophage polarization in adipose tissues. Biochem Biophys Res Commun 2013; 438: 103-109. PMID: 23872146

200. Zhong J, Rao X, Braunstein Z, Taylor A, Narula V, Hazey J, Mikami D, Needleman B, Rutsky J, Sun Q, Deiuliis JA, Satoskar AR, Rajagopalan S. T-cell costimulation protects obesity-induced adipose inflammation and insulin resistance. Diabetes 2014; 63: 1289-1302. PMID: 24222350

201. Ursini F, Mauro D, Naty S, Gagliardi D, Grembiale RD. Improvement in insulin resistance after short-term treatment with abatacept: case report and short review. Clin Rheumatol 2012; 31: 1401-1402. PMID: 22837017

202. Buerger C, Richter B, Woth K, Salgo R, Malisiewicz B, Diehl S, Hardt K, Boehncke S, Boehncke WH. Interleukin-1β interferes with epidermal homeostasis through induction of insulin resistance: implications for psoriasis pathogenesis. J Invest Dermatol 2012; 132: 2206-2214. PMID: 22513786

203. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, Sole J, Nichols A, Ross JS, Tartaglia LA, Chen H. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest 2003; 112: 1821-1830. PMID: 14679177

204. Armutcu F, Ataymen M, Atmaca H, Gurel A Oxidative stress markers, C-reactive protein and heat shock protein 70 levels in subjects with metabolic syndrome. Clin Chem Lab Med 2008; 46: 785–790. PMID: 18601599

205. Wozniak A, Drewa G, Krzyzynska-Maliniowska E, Czajkowski R, Protas-Drozd F, Mila-Kierzenkowska C, Rozwodowska M, Sopońska M, Czarnecka-Zaba E. Oxidant-antioxidant balance in patients with psoriasis. Med Sci Monit 2007; 13: 30-33. PMID: 17179907

206. Usta M, Turan E, Aral H, Inal BB, Gurel MS, Guvenen G. Serum paraoxonase-1 activities and oxidative status in patients with plaque-type psoriasis with/without metabolic syndrome. J Clin Lab Anal 2011; 25: 289-295. PMID: 21786331

207. Gupta Y, Möller S, Zillikens D, Boehncke WH, Ibrahim SM, Ludwig RJ. Genetic control of psoriasis is relatively distinct from that of metabolic syndrome and coronary artery disease. Exp Dermatol 2013; 22: 552-553. PMID: 23879815

208. Lu Y, Chen H, Nikamo P, Qi Low H, Helms C, Seielstad M, Liu J, Bowcock AM, Stahle M, Liao W. Association of cardiovascular and metabolic disease genes with psoriasis. J Invest Dermatol 2013; 133: 836-839. PMID: 23190900

209. Tian S, Krueger JG, Li K, Jabbari A, Brodmerkel C, Lowes MA, Suárez-Fariñas M. Meta-analysis derived (MAD) transcriptome of psoriasis defines the "core" pathogenesis of disease. PLoS One 2012; 7: e44274. PMID: 22957057

210. Nofal A, Al-Makhzangy I, Attwa E, Nassar A, Abdalmoati A. Vascular endothelial growth factor in psoriasis: an indicator of disease severity and control. J Eur Acad Dermatol Venereol 2009; 23: 803-806. PMID: 19309427

211. Nielsen HJ, Christensen IJ, Svendsen MN, Hansen U, Werther K, Brünner N, Petersen LJ, Kristensen JK. Elevated plasma levels of vascular endothelial growth, factor and plasminogen activator inhibitor-1 decrease during improvement of psoriasis. Inflamm Res 2002; 51: 563-567. PMID: 12540021

212. Detmar M, Brown LF, Claffey KP, Yeo KT, Kocher O, Jackman RW, Berse B, Dvorak HF. Overexpression of vascular permeability factor/vascular endothelial growth factor and its receptors in psoriasis. J Exp Med 1994; 180: 1141-1146. PMID: 8064230

213. Kowalski J, Sliwczyńska-Rodziewicz D, Kowalczyk E, Ciećwierz J, Irzmański R, Pawlicki L, Mejer A, Barylski M. Plasma nitric oxide and vascular endothelial growth factor levels in patients with metabolic syndrome and co-existing vascular complications. Pol Merkur Lekarski 2011; 30: 249-252. PMID: 21595168

214. Elias PM, Arbiser J, Brown BE, Rossiter H, Man MQ, Cerimele F, Crumrine D, Gunathilake R, Choi EH, Uchida Y, Tschachler E, Feingold K. Epidermal vas-

cular endothelial growth factor production is required for permeability barrier homeostasis, dermal angiogenesis, and the development of epidermal hyperplasia: Implications for the pathogenesis of psoriasis. Am J Pathol 2008; 173: 689–699. PMID: 18688025

215. Cao Y. Angiogenesis modulates adipogenesis and obesity. J Clin Invest 2007; 117: 2362-2368. PMID: 17786229

216. Wang X, Lin Y, Luo N, Chen Z, Gu M, Wang J, Chen Y. Short-term intensive atorvastatin therapy improves endothelial function partly via attenuating perivascular adipose tissue inflammation through 5-lipoxygenase pathway in hyperlipidemic rabbits. Chin Med J 2014; 127: 2953-2959. PMID: 25131234

217. Ena P, Madeddu P, Glorioso N, Cerimele D, Rappelli A. High prevalence of cardiovascular diseases and enhanced activity of the renin-angiotensin system in psoriatic patients. Acta Cardiol 1985; 40: 199-205. PMID: 3887825

218. Takeshita J, Wang S, Shin DB, Mehta NN, Kimmel SE, Margolis DJ, Troxel AB,Gelfand JM. Effect of Psoriasis Severity on Hypertension Control: Population-Based Study in the United Kingdom. JAMA Dermatol 2014 Oct 15. PMID: 25322196

219. Laron Z. Insulin-like growth factor 1 (IGF-1): a growth hormone. Mol Pathol 2001; 54: 311-316. PMID: 11577173

220. El-Komy M, Amin I, Zidan A, Kadry D, Zeid OA, Shaker O. Insulin-like growth factor-1 in psoriatic plaques treated with PUVA and methotrexate. J Eur Acad Dermatol Venereol 2011; 25: 1288-1294. PMID: 21241374

221. Saydah S, Ballard-Barbash R, Potischman N. Association of metabolic syndrome with insulin-like growth factors among adults in the US. Cancer Causes Control 2009; 20: 1309-1316. PMID: 19415508

222. Friedrich N, Nauck M, Schipf S, Völzke H, Brabant G, Wallaschofski H. Cross-sectional and longitudinal associations between insulin-like growth factor I and metabolic syndrome: a general population study in German adults. Diabetes Metab Res Rev 2013; 29: 452-462. PMID: 23576494

223. Brugts MP, van Duijn CM, Hofland LJ, Witteman JC, Lamberts SW, Janssen JA. Igf-I bioactivity in an elderly population: relation to insulin sensitivity, insulin levels, and the metabolic syndrome. Diabetes 2010; 59: 505-508. PMID: 20103714

224. Friedrich N, Thuesen B, Jørgensen T, Juul A, Spielhagen C, Wallaschofksi H, Linneberg A. The association between IGF-I and insulin resistance: a general population study in Danish adults. Diabetes Care 2012; 35: 768-773. PMID: 22374641

225. Ruotolo G, Howard BV. Dyslipidemia of the metabolic syndrome. Curr Cardiol Rep 2002; 4: 494-500. PMID: 12379172

226. Nakhwa YC, Rashmi R, Basavaraj KH. Dyslipidemia in Psoriasis: A Case Controlled Study. International Scholarly Research Notices 2014; Article ID 729157.

227. Mallbris L, Granath F, Hamsten A, Ståhle M. Psoriasis is associated with lipid abnormalities at the onset of skin disease. J Am Acad Dermatol 2006; 54: 614-621. PMID: 16546581

228. Bajaj DR, Mahesar SM, Devrajani BR, Iqbal MP. Lipid profile in patients with psoriasis presenting at Liaquat University Hospital Hyderabad. J Pak Med Assoc 2009; 59: 512-515. PMID: 19757693

229. Taheri Sarvtin M, Hedayati MT, Shokohi T, HajHeydari Z. Serum lipids and lipoproteins in patients with psoriasis. Arch Iran Med 2014; 17: 343-346. PMID: 24784863

230. El Asmi MA, Zidi W, Mebazaa A, Zayani Y, Ayadi I, Feki M, Ben Osman A, Kaabachi N. Serum lipid level in Tunisian patients with psoriasis. Clin Lab 2014; 60: 1043-1047. PMID: 25016711

231. Al Harthi F, Huraib GB, Zouman A, Arfin M, Tariq M, Al-Asmari A. Apolipoprotein E gene polymorphism and serum lipid profile in Saudi patients with psoriasis. Dis Markers 2014; 2014: 239645. PMID: 24782577

232. Han Y, Liu T, Lu L. Apolipoprotein E gene polymorphism in psoriasis: a meta-analysis. Arch Med Res 2013; 44: 46-53. PMID: 23142524

233. Weintraub MS, Eisenberg S, Breslow JL. Dietary fat clearance in normal subjects is regulated by genetic variation in apolipoprotein E. J Clin Invest 1987; 80: 1571-1577. PMID: 3479440

234. Assmann G, Schmitz G, Menzel HJ, Schulte H. Apolipoprotein E polymorphism and hyperlipidemia. Clin Chem 1984; 30: 641-643. PMID: 6713624

235. Zeljko HM, Škarić-Jurić T, Narančić NS, Tomas Ž, Barešić A, Salihović MP, Starčević B, Janićijević B. E2 allele of the apolipoprotein E gene polymorphism is predictive for obesity status in Roma minority population of Croatia. Lipids Health Dis 2011; 10: 9. PMID: 21244662

236. Coto-Segura P, Coto E, Alvarez V, Morales B, Soto-Sánchez J, Corao AI, Santos-Juanes J. Apolipoprotein epsilon4 allele is associated with psoriasis severity. Arch Dermatol Res 2010; 302: 145-149. PMID: 19911187

237. Campalani E, Allen MH, Fairhurst D, Young HS, Mendonca CO, Burden AD, Griffiths CE, Crook MA, Barker JN, Smith CH. Apolipoprotein E gene polymorphisms are associated with psoriasis but do not determine disease response to acitretin. Br J Dermatol 2006; 154: 345-352. PMID: 16433808

238. Zende PD, Bankar MP, Kamble PS, Momin AA. Apolipoprotein e gene polymorphism and its effect on plasma lipids in arteriosclerosis. J Clin Diagn Res 2013; 7: 2149-2152. PMID: 24298461

239. Pietrzak A, Michalak-Stoma A, Chodorowska G, Szepietowski JC. Lipid disturbances in psoriasis: an update. Mediators Inflamm 2010; 2010. pii: 535612. PMID: 20706605

240. He L, Qin S, Dang L, Song G, Yao S, Yang N, Li Y. Psoriasis decreases the anti-oxidation and anti-inflammation properties of high-density lipoprotein. Biochim Biophys Acta 2014; pii: S1388-1981(14)00186-3. PMID: 25240836

241. Trost S, Pratley R, Sobel B. Impaired fibrinolysis and risk for cardiovascular disease in the metabolic

syndrome and type 2 diabetes. Curr Diab Rep 2006; 6: 47-54. PMID: 16522281

242. Brogren H, Sihlbom C, Wallmark K, Lönn M, Deinum J, Karlsson L, Jern S. Heterogeneous glycosylation patterns of human PAI-1 may reveal its cellular origin. Thromb Res 2008; 122: 271-281. PMID: 18508114

243. Russo I. The prothrombotic tendency in metabolic syndrome: focus on the potential mechanisms involved in impaired haemostasis and fibrinolytic balance. Scientifica 2012; 2012: 525374. PMID: 24278711

244. Ludwig RJ, Schultz JE, Boehncke WH, Podda M, Tandi C, Krombach F, Baatz H, Kaufmann R, von Andrian UH, Zollner TM. Activated, not resting, platelets increase leukocyte rolling in murine skin utilizing a distinct set of adhesion molecules. J Invest Dermatol 2004; 122: 830-836. PMID: 15086572

245. Saleh HM, Attia EA, Onsy AM, Saad AA, Abd Ellah MM. Platelet activation: a link between psoriasis per se and subclinical atherosclerosis--a case-control study. Br J Dermatol 2013; 169: 68-75. PMID: 23448140

246. Takeshita J, Mohler ER, Krishnamoorthy P, Moore J, Rogers WT, Zhang L, Gelfand JM, Mehta NN. Endothelial cell-, platelet-, and monocyte/macrophage-derived microparticles are elevated in psoriasis beyond cardiometabolic risk factors. J Am Heart Assoc 2014; 3: e000507. PMID: 24584739

247. Vanizor Kural B, Orem A, Cimşit G, Uydu HA, Yandi YE, Alver A. Plasma homocysteine and its relationships with atherothrombotic markers in psoriatic patients. Clin Chim Acta 2003; 332: 23-30. PMID: 12763276

248. Lima Ede A, Lima MM, Marques CD, Duarte AL, Pita Ida R, Pita MG. Peroxisome proliferator-activated receptor agonists (PPARs): a promising prospect in the treatment of psoriasis and psoriatic arthritis. An Bras Dermatol 2013; 88: 1029-1035. PMID: 24474126

249. Mao-Qiang M, Fowler AJ, Schmuth M, Lau P, Chang S, Brown BE, Moser AH, Michalik L, Desvergne B, Wahli W, Li M, Metzger D, Chambon PH, Elias PM, Feingold KR. Peroxisome-proliferator-activated receptor (PPAR)-gamma activation stimulates keratinocyte differentiation. J Invest Dermatol 2004; 123: 305-312. PMID: 15245430

250. Wang YX. PPARs: diverse regulators in energy metabolism and metabolic diseases. Cell Res 2010; 20: 124-137. PMID: 20101262

251. Savage DB, Petersen KF, Shulman GI. Disordered lipid metabolism and the pathogenesis of insulin resistance. Physiol Rev 2007; 87: 507–520. PMID: 17429039

252. Schenk S, Saberi M, Olefsky JM. Insulin sensitivity: modulation by nutrients and inflammation. J Clin Invest 2008; 118: 2992–3002. PMID: 18769626

253. Chen L, Jia Z, Yang G. PPARs and Metabolic Syndrome. PPAR Res 2014; 2014: 832606. Mansour M. The roles of peroxisome proliferator-activated receptors in the metabolic syndrome. Prog Mol Biol Transl Sci 2014; 121: 217-266. PMID: 24373239

254. Hegazy RA, Abdel Hay RM, Shaker O, Sayed SS, Abdel Halim DA. Psoriasis and metabolic syndrome: is peroxisome proliferator-activated receptor-γ part of the missing link? Eur J Dermatol 2012; 22: 622-628. PMID: 22853971

255. Klotz L, Burgdorf S, Dani I, Saijo K, Flossdorf J, Hucke S, Alferink J, Nowak N, Beyer M, Mayer G, Langhans B, Klockgether T, Waisman A, Eberl G, Schultze J, Famulok M, Kolanus W, Glass C, Kurts C, Knolle PA. The nuclear receptor PPAR gamma selectively inhibits Th17 differentiation in a T cell-intrinsic fashion and suppresses CNS autoimmunity. J Exp Med 2009; 206: 2079-2078. PMID:19737866

256. Liu M, He Y, Jiang B, Wu L, Yang S, Wang Y, Li X. Association between Serum Uric Acid Level and Metabolic Syndrome and Its Sex Difference in a Chinese Community Elderly Population. Int J Endocrinol 2014; 2014: 754678. PMID: 25136366

257. Lee YJ, Cho S, Kim SR. A Possible Role of Serum Uric Acid as a Marker of Metabolic Syndrome. Intern Med J 2014 Sep 16. PMID: 25228498

258. Billiet L, Doaty S, Katz JD, Velasquez MT. Review of hyperuricemia as new marker for metabolic syndrome. ISRN Rheumatol. 2014 Feb 16; 2014: 852954. PMID: 24693449

259. Bonora E, Targher G, Zenere MB, Saggiani F, Cacciatori V, Tosi F, Travia D, Zenti MG, Branzi P, Santi L, Muggeo M. Relationship of uric acid concentration to cardiovascular risk factors in young men. Role of obesity and central fat distribution. The Verona Young Men Atherosclerosis Risk Factors Study. Int J Obes Relat Metab Disord 1996; 20: 975-980. PMID: 8923153

260. Lyngdoh T, Marques-Vidal P, Paccaud F, Preisig M, Waeber G, Bochud M, Vollenweider P. Elevated serum uric acid is associated with high circulating inflammatory cytokines in the population-based Colaus study. PLoS One 2011; 6: e19901. PMID: 21625475

261. Kirilmaz B, Asgun F, Alioglu E, Ercan E, Tengiz I, Turk U, Saygi S, Ozerkan F. High inflammatory activity related to the number of metabolic syndrome components. J Clin Hypertens 2010; 12: 136-144. PMID: 20167041

262. Giovine FS, Malawista SE, Thornton E, Duff GW. Urate crystals stimulate production of tumor necrosis factor alpha from human blood monocytes and synovial cells. Cytokine mRNA and protein kinetics, and cellular distribution. J Clin Invest 1991; 87: 1375-1381. PMID: 2010550

263. Eleftheriadis T, Pissas G, Karioti A, Antoniadi G, Golfinopoulos S, Liakopoulos V, Mamara A, Speletas M, Koukoulis G, Stefanidis I. Uric acid induces caspase-1 activation, IL-1β secretion and P2X7 receptor dependent proliferation in primary human lymphocytes. Hippokratia 2013; 17: 141-145. PMID: 24376319

264. Conforti-Andreoni C, Spreafico R, Qian HL, Riteau N, Ryffel B, Ricciardi-Castagnoli P, Mortellaro A. Uric acid-driven Th17 differentiation requires inflammasome-derived IL-1 and IL-18. J Immunol 2011; 187: 5842-5850. PMID: 22058415

265. Gisondi P, Targher G, Cagalli A, Girolomoni G. Hyperuricemia in patients with chronic plaque psoriasis. J Am Acad Dermatol 2014; 70: 127-130. PMID: 24183485

266. Kacalak-Rzepka A, Kiedrowicz M, Maleszka R. Analysis of the chosen parameters of metabolic status in patients with psoriasis. Ann Acad Med Stetin 2013; 59: 12-17. PMID: 25026745

267. Kwon HH, Kwon IH, Choi JW, Youn JI. Cross-sectional study on the correlation of serum uric acid with disease severity in Korean patients with psoriasis. Clin Exp Dermatol 2011; 36: 473-478. PMID: 21679368

268. Cassano N, Carbonara M, Panaro M, Vestita M, Vena GA. Role of serum uric acid in conditioning the association of psoriasis with metabolic syndrome. Eur J Dermatol 2011; 21: 808-809. PMID: 21737375

269. Guarner V, Rubio-Ruiz ME. Low-grade systemic inflammation connects aging, metabolic syndrome and cardiovascular disease. Interdiscip Top Gerontol 2015; 40: 99-106. PMID: 2534151

270. Heinrich PC, Castell JV, Andus T. Interleukin-6 and the acute phase response. Biochem J 1990; 265: 621-36. PMID: 1689567

271. Moshage HJ, Roelofs H.M, van Pelt J.F. The effect of interleukin-1, interleukin-6 and its interrelationship on the synthesis of serum amyloid A and C-reactive protein in primary cultures of adult human hepatocytes. Biochem Biophys Res Commun 1988; 155: 112-117. PMID: 3261980

272. Calabro P, Chang DW, Willerson JT, Yeh ET. Release of C-reactive protein in response to inflammatory cytokines by human adipocytes: linking obesity to vascular inflammation. J Am Coll Cardiol 2005; 46: 1112-1113. PMID: 16168299

273. Dowlatshahi EA, van der Voort EA, Arends LR, Nijsten T. Markers of systemic inflammation in psoriasis: a systematic review and meta-analysis. Br J Dermatol 2013; 169: 266-282. PMID: 23550658

274. Takahashi H, Iinuma S, Honma M, Iizuka H. Increased serum C-reactive protein level in Japanese patients of psoriasis with cardio- and cerebrovascular disease. J Dermatol 2014; 41: 981-985. PMID: 25291969

275. Coimbra S, Oliveira H, Reis F, Belo L, Rocha S, Quintanilha A, Figueiredo A, Teixeira F, Castro E, Rocha-Pereira P, Santos-Silva A. C-reactive protein and leucocyte activation in psoriasis vulgaris according to severity and therapy. J Eur Acad Dermatol Venereol 2010; 24: 789-796. PMID: 20002653

276. Alpsoy S, Akyuz A, Erfan G, Akkoyun DC, Topcu B, Guzel S, Kaya S, Kulac M. Atherosclerosis, some serum inflammatory markers in psoriasis. G Ital Dermatol Venereol 2014; 149: 167-175. PMID: 24819636

277. Delporte C. Recent advances in potential clinical application of ghrelin in obesity. J Obes 2012; 2012: 535624. PMID: 22523666

278. Ozdemir M, Yüksel M, Gökbel H, Okudan N, Mevlitoğlu I. Serum leptin,adiponectin, resistin and ghrelin levels in psoriatic patients treated with cyclosporin. J Dermatol 2012; 39: 443-448. PMID: 22300284

279. Samaras K, Viardot A, Botelho NK, Jenkins A, Lord RV. Immune cell-mediated inflammation and the early improvements in glucose metabolism after gastric banding surgery. Diabetologia 2013; 56: 2564-2572. PMID: 24114113

280. Jialal I, Rajamani U. Endotoxemia of Metabolic Syndrome: A Pivotal Mediator of Meta-Inflammation. Metab Syndr Relat Disord 2014 Aug 27. PMID: 25162769

281. Gisondi P, Del Giglio M, Di Francesco V, Zamboni M, Girolomoni G. Weight loss improves the response of obese patients with moderate-to-severe chronic plaque psoriasis to low-dose cyclosporine therapy: a randomized, controlled, investigator-blinded clinical trial. Am J Clin Nutr 2008; 88: 1242-1247. PMID: 18996858

282. Higa-Sansone G, Szomstein S, Soto F, Brasecsco O, Cohen C, Rosenthal RJ. Psoriasis remission after laparoscopic Roux-en-Y gastric bypass for morbid obesity. Obes Surg 2004; 14: 1132-1134. PMID: 15479606

283. Naldi L, Chatenoud L, Linder D, Belloni Fortina A, Peserico A, Virgili AR, Bruni PL, Ingordo V, Lo Scocco G, Solaroli C, Schena D, Barba A, Di Landro A, Pezzarossa E, Arcangeli F, Gianni C, Betti R, Carli P, Farris A, Barabino GF, La Vecchia C. Cigarette smoking, body mass index, and stressful life events as risk factors for psoriasis: results from an Italian case-control study. J Invest Dermatol 2005; 125: 61-67. PMID: 15982303

284. Tablazon IL, Al-Dabagh A, Davis SA, Feldman SR. Risk of cardiovascular disorders in psoriasis patients: current and future. Am J Clin Dermatol 2013; 14: 1-7. PMID: 23329076

285. Mendelson M, Michallet AS, Monneret D, Perrin C, Estève F, Lombard PR, Faure P, Lévy P, Favre-Juvin A, Pépin JL, Wuyam B, Flore P. Impact of exercise training without caloric restriction on inflammation, insulin resistance and visceral fat mass in obese adolescents. Pediatr Obes 2014. PMID: 2508815

286. Kawanishi N, Mizokami T, Yano H, Suzuki K. Exercise attenuates M1 macrophages and CD8+ T cells in the adipose tissue of obese mice. Med Sci Sports Exerc 2013; 45: 1684-1693. PMID: 23954991