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An Update on the Relationship between Psoriasis and Metabolic Syndrome with Most Recent Search

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Abstract

Background: Psoriasis is a chronic inflammatory skin disease which affects 3% of general population. Metabolic Syndrome (MetS) is the constellation of risk factors including high blood pressure, central obesity, abnormal serum lipids and insulin resistance which increases the cardiovascular complications in that particular patient. The causal association between psoriasis and MetS has gained increasing attention in the last decades. Recent evidence suggests that there is a most probably bidirectional interaction between these two diseases. Common pathophysiology, environmental factors and shared susceptibility genes are the potential mechanisms that underlie this link. The awareness and understanding of the association between psoriasis and MetS is of great importance for both dermatologists and non-dermatologists since the clarification of this connection provides more comprehensive information on their uncertain pathophysiology and enables the identification of novel targets for better treatment options. For dermatologists, psoriasis should be considered as a disease beyond the skin and the patients should be screened for cardiometabolic risks and referred appropriately.

Introduction

Psoriasis is an immune mediated disease th at affects skin and joints. Both genetic and environmental factors are involved in the etiology of the disease. In last years, it is henceforth considered as a systemic inflammatory disease beyond the skin with increased cardiovascular and metabolic morbidity [**1**].

Psoriatic lesion is the result of complex interaction between the immune system and the skin through a wide range of inflammatory mediators including cytokines, chemokines and others (**Figure 1**). Although the exact pathogenesis has not been fully elucidated, the triggering factors induce signals that activate the skin resident dendritic cells (DCs) and keratinocytes (KCs) leading to the infiltration of various types of inflammatory cells to skin resulting in aberrant differentiation and proliferation of KCs. Upon activation, DCs secrete cytokines including interleukin-6 (IL-6), IL-12, tumor necrosis factor-α (TNF-α), and especially the key cytokine, IL-23 leading to the differentiation of T cells into T helper 17 (Th17) cells. Other than IL-23, transforming growth factor (TGF)-β1, IL-6 and IL-1 are all important in the differentiation of Th17 cells. Th17 cells have pivotal role in the psoriasis pathogenes is which secrete proinflammatory mediators including IL-17, IL-21, IL-22 and also TNF-α that are implica-

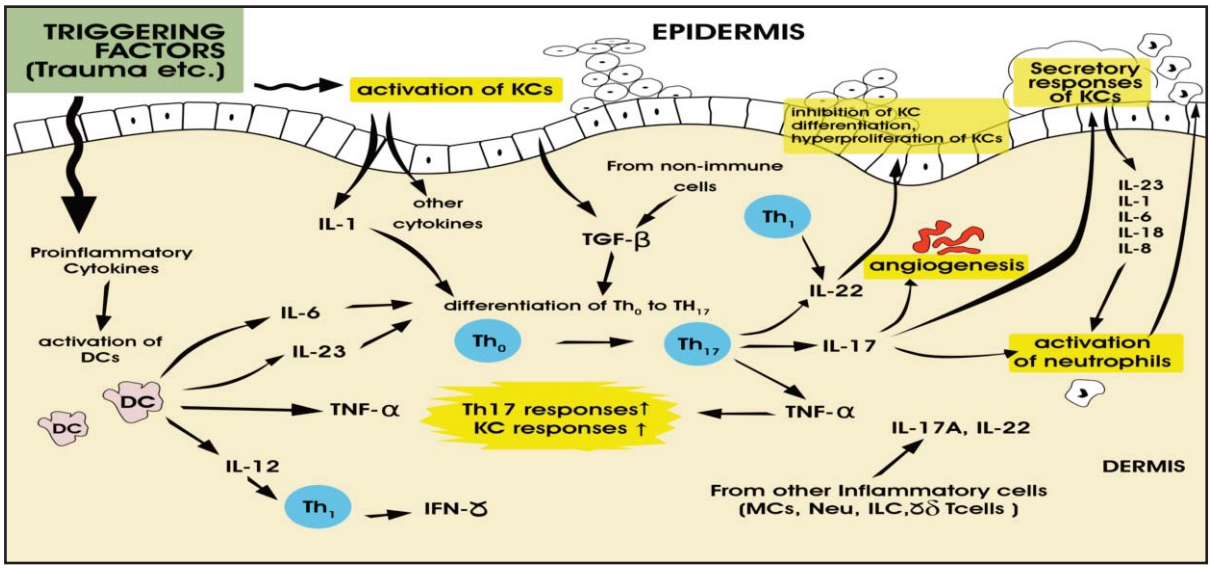

Figure 1. Schematic model of the interplay of cytokines and effector cells in psoriasis pathogenesis (Note: Due to the redundancy and pleiotropic effects of cytokines, the key interactions are depicted in this model)

ted in the perpetuation of psoriatic inflammation. IL-17, may also be secreted from many other cells, promotes neutrophil activation, angiogenesis and secretory responses of KCs. Additionally, IL-22 is important in the inhibition of KC differentiation, hyperproliferation of KCs and angiogenesis. TNF-α is one of key cytokines in psoriasis pathogenesis that induces Th17 cell and KC responses. On the other hand, KCs are actively involved in the inflammatory process. Triggering factors may result in the gain of function mutations in KCs including CARD14 (caspase recruitment domain family, member 14) mutations. Through activation, KCs are able to secrete various mediators including IL-8, IL-23, IL-1 and IL-6 that stimulate many types of inflammatory cells such as neutrophils, DCs and Th17 cells. Psoriatic inflammation is also characterized by an increase in IFN-γ and dysfunction of Treg lymphocytes. Certain HLA haplotypes and gene polymorphisms have been associated with such impairment in the immune response and susceptibility to psoriasis that points the genetic background of the disease [**2, 3**]. Recent studies have highlighted the role of IL-18 in psoriasis as a proinflammatory cytokine that can be secreted from lesional KCs [**4**].

Metabolic Syndrome (MetS) is the clustering of cardiometabolic risk factors including hypertension, central obesity, insulin resistance and dyslipidemia. Although different criteria exist, according to IDF consensus MetS is defined as the presence of central obesity (waist circumference ≥ 94 cm for males and ≥ 80 cm for females for Europids, Eastern Mediterranean and Middle East (Arab) populations) (if body mass index (BMI) is >30 kg/m2, central obesity can be assumed without measuring waist circumference) plus two of the following criteria: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 [**5**].

Studies demonstrated that immune system is actively involved in the development of cardiovascular and metabolic diseases. Dysregulation in inflammatory responses and chronic systemic inflammation have been indicated as the central abnormalities in the pathogenesis of MetS and its components. Especially, the association of obesity with chronic low level inflammation is very well established. Elevation of proinflammatory cytokines and prothrombic factors such as plasminogen activator inhibitor-1 (PAI-1), disturbances in the adipose tissue metabolism and increased oxi-

dative stress are all well known features of MetS [**1, 5, 6**].

Besides, it seems that the individual components of MetS are capable of triggering the development of the others which results in the full formation of MetS. In other words, the impairment in metabolic functions may start one by one and the resultant disturbances may induce the deterioration of the other operating mechanisms. Indeed, hypertriglyceridemia may be induced by insulin resistance and the obesity-induced adipose tissue inflammation may promote endothelial dysfunction and hyperlipidemia through the secretion of proinflammatory molecules and vasoactive substances [**5**].

The pathogenetic relation between psoriasis and MetS has been debated in last decades and subject to studies which provide evidence that these two diseases have common etiopathogenesis. In this short update, we provide an overview of current data on the etiologic link between psoriasis and MetS derived from the most recent researches. We also cover the issues that might have useful implications in the dermatology setting.

Evidence Regarding the Relation between Psoriasis and MetS

The relationship between psoriasis and MetS has been confirmed with several investigations [**7, 8**]. However, studies revealed inconsistent results regarding the relation of MetS to the disease characteristics of psoriasis (severity, duration, age at onset, etc.) [**8, 9**]. Nevertheless, psoriasis has been suggested as an independent risk factor for MetS [**10**].

This view is further strengthened by the fact that MetS accompanies psoriasis even in patients with mild disease or at the beginning of the disease [**7, 11**].

This relationship is obviously complex and most likely bidirectional. That is to say, the local disturbances in psoriatic skin may affect distant tissues resulting in generalized metabolic changes; or, oppositely, the secreted mediators from the tissues where the metabolic disturbances originate may provide a cytokine milieu which predisposes the patient to develop psoriasis or aggravate the established psoriasis. As there is a notable overlap between the pathogenesis of psoriasis and MetS, it is difficult to explain the exact origin of this interaction. It is also possible that once it begins the interaction proceeds in both directions [**3, 4**].

Some authors indicate the insulin resistance as the major link in this connection [**12**]. The insulin signalling and the lipid metabolism are reported as the first metabolic components to be disturbed in the psoriasis setting [**7**]. Other studies found the central obesity as the most common component of MetS together with dyslipidemia in psoriasis patients [**13**].

Finally, studies have already been shown that patients with autoimmune diseases such as diabetes have increased risk of having another autoimmune disease such as psoriasis [**4**].

The Significance of the Relation between Psoriasis and MetS

No matter where this interaction starts, it is crucial to be aware of the relationship between psoriasis and MetS since both diseases have the capacity to complicate the course of the other.

Obesity is reported to negatively affect the course of psoriasis and, weight loss in obese psoriasis patients has a positive impact on response to treatment by lowering the inflammatory burden [**1, 7**]. Whereas some antipsoriatic drugs may worsen the components of MetS (cyclosporine may induce hypertension, retinoids may have negative impact on lipid profile), some drugs used for MetS patients such as statins and beta blockers may aggravate psoriasis. On the other hand, positive metabolic effects may be observed with anti-TNF agents in psoriasis patients as they de crease the overall inflammation [**4, 6**]. Additionally, thiazolidinediones which are used as anti-diabetic agents have been reported to result in the improvement of psoriatic lesions [**1**].

Common Pathogenic Problems to Psoriasis and MetS

Many etiologic factors and pathologic disturbances including triggering environmental

factors, chronic low grade inflammation, signalling pathways that operate, overexpression of certain genes,oxidative stress,hyperuricemia, dyslipidemia, insulin resistance, endothelial dysfunction and prothrombotic tendency are common to psoriasis and MetS [**3, 5, 7**]. Studies revealed that certain differentially expressed genes (DEGs) in psoriasis patients such as renin, CTLA4, CDKALI and PTPN22 genes are related with metabolic and cardiovascular diseases suggestinga shared genetic susceptibility for both conditions [**1, 12, 13**].

Chronic low level inflammation has been suggested as the main pathogenetic background for both psoriasis and MetS. Almost all of the pathologic immune system changes that exist in cardiovascular diseases and MetS can be observed in psoriasis patients [**1**]. Especially, TNF has been regarded as the major common offender in the pathologic cascade of these diseases [**7**]. On the other hand, the pathologic action of adhesion molecules including intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 is common to both psoriatic and atherosclerotic plaques. Additi onally,angiogenesis and endothelial dysfunction through vascular endothelial growth factor (VEGF) are characteristics to both psoriasis and atherosclerosis. The disturbances in the signalling pathways that operate in cardiovascular diseases can also contribute to the psoriasis pathogenesis. Finally, the impairment in insulin signalling and lipid metabolism is also present in psoriasis patients [**1, 4, 6**]

As mentioned above, there is probably a two-way interaction between psoriasis and MetS that is described below.

I. From Psoriasis to MetS

Regarding the theory that psoriatic inflammation promotes the development of MetS, the local disturbances in immune mechanisms has been suggested to be generalized. Overexpressed proteins in the lesional skin have also been found to be upregulated in the serum of psoriasis patients. Correlatively, metabolic disturbances may start at skin level and extend to induce systemic impairments increasing the cardiovascular risks in these patients **(Figure 2**)[**3, 4, 6**].

There is evidence that many of the cytokines and mediators involved in psoriasis pathogenesis have negative metabolic impacts.

Psoriasis - Obesity, Insulin resistance IL-6 has been suggested to be involved in the dysfunctional adipocytokine secretion, insulin resistance and cardiometabolic complications. Additionally, IL-8, which can be secreted from lesional KCs are reported to be involved in the development of insulin resistance and MetS [**3, 4**]. Overexpression of IGF-1 in psoriatic lesions and increased IL-1β in psoriasis patients have both been suggested to be involved in insulin resistance and resultant metabolic disturbances [**3, 4, 14**]. The key cells of psoriatic inflammation, Th17 and Th22 cells are also indicated in the development of insulin resistance and obesity [**4, 15**]. IL-18 that can be secreted from KCs and adipocytes is increased in psoriasis patients and involved in several metabolic complications including obesity, dyslipidemia and insulin resistance [**4**].

Obesity is a very well known trigger for the formation of insulin resistance; however, the insulin resistance even in non-obese psoriasis patients reveals the fact that psoriatic inflammation is directly involved in metabolic complications. The role of psoriatic cytokine network through TNF-α, IL-6, adipokines and other mediators in the disturbance of insulin signalling is further supported by the significant correlation of insulin resistance with PASI scores [**6, 16**].

Peroxisome proliferator-activated receptors (PPARs) are transcription factors which have important roles both in metabolic processes and immunity. Their activation has anti-inflammatory (reduction in production of IL-1, TNF-α and IL-17), anti-atherogenic and insulin sensitizer effects. Abnormal PPAR signalling is associated with obesity induced inflammation and, disturbance in lipid metabolism and insulin signalling. PPARs are also important in KC differentiation [**1**]. In psoriasis patients, the contribution of the decrease in PPARα and γ signalling to the development of MetS has been disputed [**17**].

Psoriasis is characterized by dysfunctional action of Treg cells which is also characteristic for MetS. In normal conditions, Treg cells prevent the development of insulin resis-

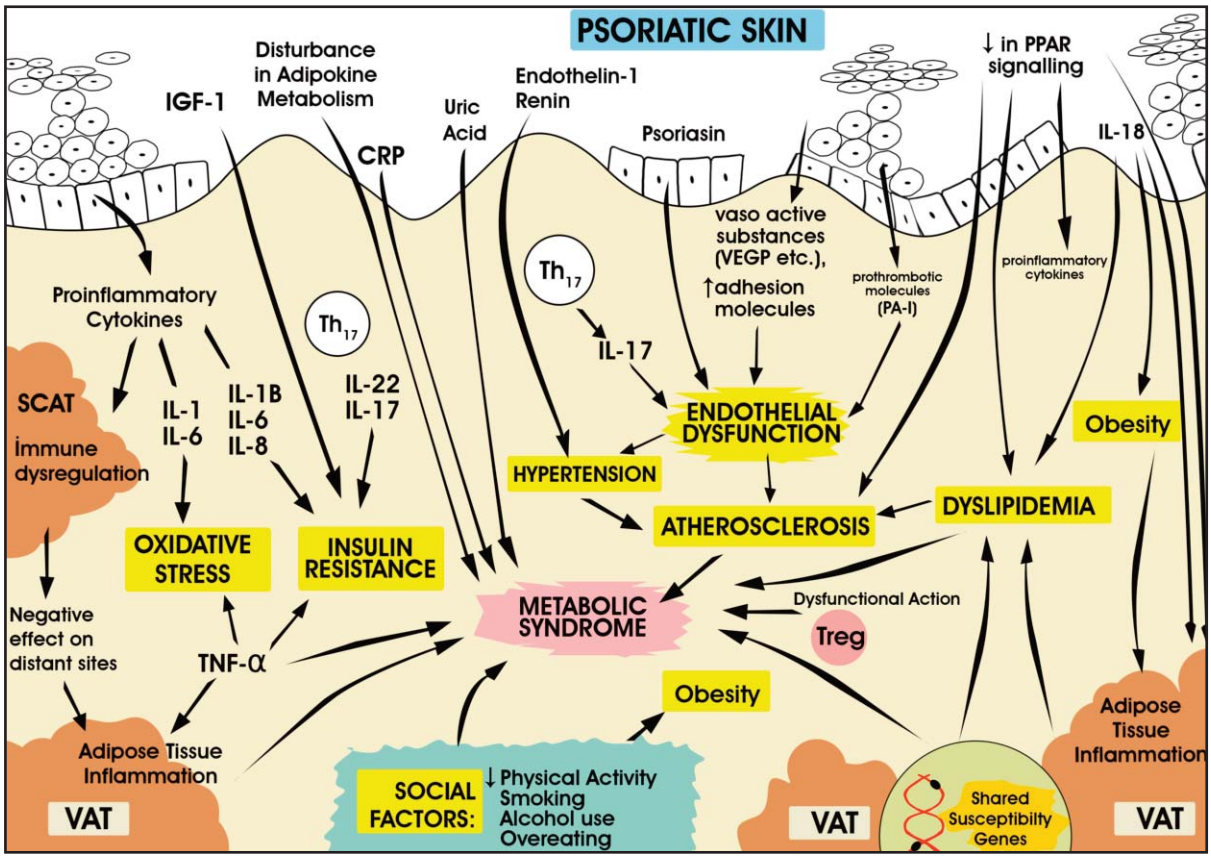

Figure 2. Illustrative representation of the likely contribution of the factors which links psoriasis to MetS.

tance and MetS by anti-inflammatory actions on adipose tissue through PPAR-γ signalling [**18**]. It is suggested that the failure of the inhibitory effects of Treg cells in psoriasis may play part in the development of MetS [**4**].

Other than immune system cells, adipose cells might also participate in the metabolic deterioration observed in psoriasis patients. Dysregulation of immune cell trafficking in lesional skin may disrupt the function of the immune cells in the adipose tissue of distant sites. Macrophages, neutrophils and other immune cells of subcutaneous adipose tissue secrete mediators that may result in dysfunctional action of visceral adipose tissue and result in tendency to obesity, insulin resistance and metabolic diseases in psoriasis patients [**19**]. Indeed, communication between subcutaneous and dermal adipose tissue through psoriatic inflammatory network has been mentioned [**4**].

Interestingly, several studies revealed that the prevalence and incidence of obesity is increased in psoriasis patients. The risk of obesity increases with the severity of psoriatic inflammation [**4, 6**].

Adipokines are substances that can be secreted from various cells including adipocytes and KCs. They have both immunologic and metabolic actions. Whereas some have protective properties (such as adiponectin), the others have negative metabolic impacts including insulin resistance and adipose tissue i nflammation (such as leptin, resistin). Impairment of adipokine signalling in psoriasis is suggested play a major role in increasing the metabolic risks in these patients [**4, 20**].

Psoriasis-Endothelial Dysfunction and Hypertension

Correlating with the severity of psoriatic inflammation, the increase in vasoactive substances including VEGF and adhesion molecules promotes the endothelial dysfunction and vascular complications [**6**].

Disturbance of renin-angiotensin system (increased renin activity) and elevation of endot-

helin-1 in psoriasis patients have been implicated in the development of hypertension [**21**]. Proinflammatory cytokine network of psoriasis also contributes to the atherogenic changes in vascular tissue [**16**]. Higher prevalence of hypertension in psoriasis patients may be partly due to the effect of IL-17 which can result in endothelial dysfunction [**22,23**]. Angiotensinogen which is secreted from adipose tissue and indicated in hypertension may also take role in altered adipokine signalling that further complicates metabolic problems in psoriasis patients [**6**].

Psoriasis - Prothrombotic Activity

Platelet activation and elevation of prothrombotic molecules including PAI-1 through the psoriatic inflammation are well known components of MetS and promote the development of atherosclerosis [**24**].

Other molecules in psoriatic inflammation with metabolic roles

Elevation of serum uric acid levels in psoriasis patients have been suggested as a risk factor for the development of MetS [**25**].

C-reactive protein (CRP) which has proinflammatory effects can be induced by IL-6 and other inflammatory molecules. Elevation of CRP in psoriasis is suggested as a marker for cardiometabolic diseases in these patients [**26**].

An anti-inflammatory molecule ghrelin is found to be decreased in MetS [**5**]. Although the ghrelin levels are higher in psoriasis patients when compared to controls, the decrease in ghrelin levels as the PASI score increases may be related to the loss of protective mechanisms in severe disease [**16**].

Psoriasin is a systemic proinflammatory molecule which is secreted from lesional KCs excessively and involved in the perpetuation of the psoriatic inflammation. This molecule has been demonstrated to play role in angiogenesis, endothelial dysfunction and induction of oxidative stress and other metabolic complications by promoting the formation of advanced glycation end products (AGEs) [**27**].

Non-Immunologic Mechanisms that Link Psoriasis to Mets

Other than all above mentioned immunologic mechanisms, psoriasis may predispose the patient to develop metabolic diseases through alterations in social habits including reduction in the physical activity, smoking, alcohol consumption and overeating [**4, 6**].

II. From MetS to Psoriasis

It has been suggested that each component of MetS may have an etiologic role in the development of psoriasis. Inflammatory mediators and hormone-like molecules secreted by the tissues affected from obesity, diabetes or atherosclerosis may predispose the patient to develop psoriasis in a genetically susceptible individual or may worsen the already existing psoriatic disease (**Figure 3**) [**1**].

Especially, the well-known chronic low level of inflammation associated with obesity is the accused mechanism that connects MetS to psoriasis. In obese patients, the inflammatory mediators produced by both adipose and non-adipose tissues result in the deterioration of adipose tissue metabolism through the activation of macrophages. The eventual inflammatory milieu characterized by increased cytokines including TNF-α, IL-6 and the disturbance of adipokine balance constitutes the fundamental problem for subsequent complications including insulin resistance and other diseases [**3, 4**]. Indeed, obese patients have increased risk for the development of psoriasis in the future [**28**]. The undesired effects of the disturbed adipokine balance (increased leptin, resistin and decreased adiponectin) in patients with MetS on the psoriatic inflammation have been mentioned [**1**]. Vasoactive substances such as VEGF and adipokines such as leptin and visfatin are associated with angiogenesis and KC proliferation which are characteristic for psoriasis [**29**]. In line with these reports, certain adipokines were found to increase Th17 response which is the predominant player in psoriasis pathogenesis [**30**]. Additionally, IL-23 production from the adipose tissue of obese individuals may aggravate preexisting psoriasis or may trigger the development of psoriasis in a susceptible individual [**31**]. On the other hand, obesity is associated with IL-17 overproduction through

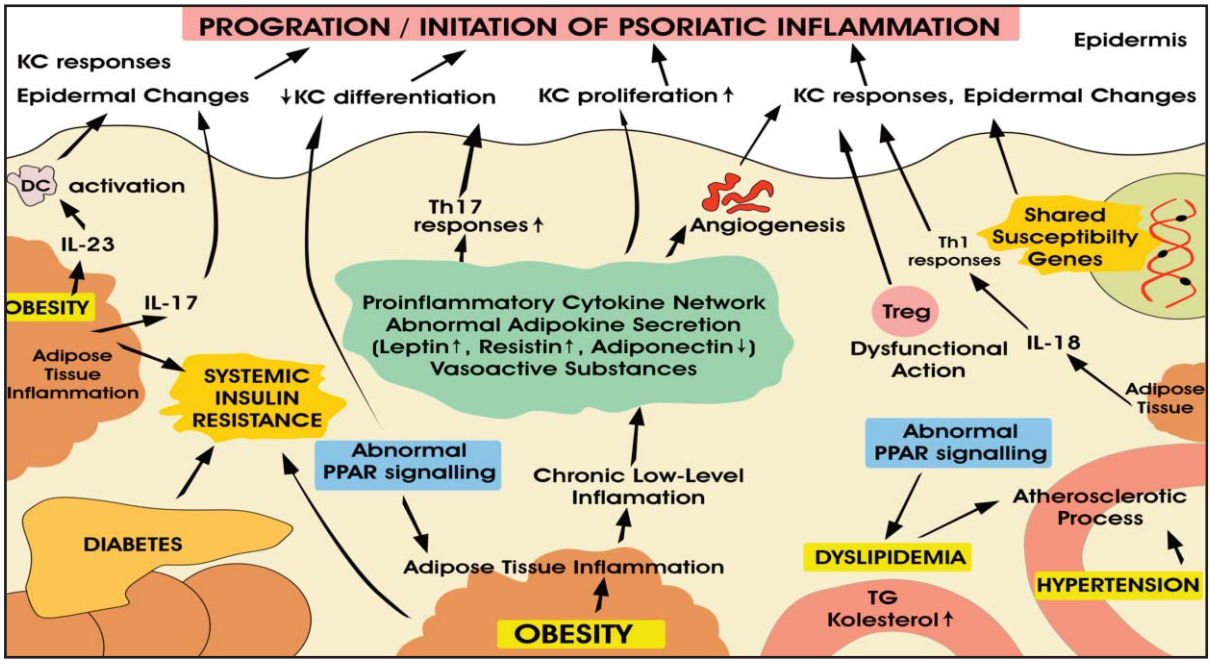

Figure 3. Illustrative representation of the likely contribution of the factors which links MetS to psoriasis.

IL-6 which is the key molecule of psoriatic inflammation [**32**]. The negative impact of de creased Treg cells in obesity on the development of psoriasis may be suggested [**33**]. IL-18 which can be secreted from both KCs and adipocytes is increased in patients with MetS. IL-18 is involved in the enhancement of Th1 responses and has a remarkable role in psoriasis pathogenesis [**34**].

As IL-1β inhibits keratinocyte differentiation through generation of insulin resistance, the possible unfavorable effect of systemic insulin resistance on the keratinocyte maturation may be proposed [**35**]. Supportively, administration of systemic insulin sensitizers such as thiazolidinediones leads to the improvement of psoriasis lesions [**1**].

A few years ago, hyperlipidemia, by activating the inflammatory cascade, has been indicated to increase the risk of psoriasis in patients even not on anti-hyperlipidemics [**36**].

As mentioned above, PPAR signalling has many important roles in both metabolic and inflammatory processes. Altered PPAR signalling has been implicated in the chain of pathologic events including insulin resistance, dyslipidemia and adipose tissue inflammation which are characteristic for MetS. The involvement of PPAR pathway in differentiation of KCs and the improvement of psoriatic lesions by the administration of systemic PPAR agonists raise the possible contribution of defective PPAR signalling in the development of psoriasis in patients with MetS [**1, 17**].

Clinical Implications in Dermatology Setting

From a dermatological perspective, psoriasis should be taken as a systemic inflammatory disease and the patients should be screened for cardiometabolic complications. Early detection of co-morbid diseases and interventions for MetS components not only will result in the reduction of overall morbidity and mortality, but also will likely improve the response to psoriasis treatments. Accordingly, psoriasis patients should be encouraged to increase physical activity, lose weight, minimize alcohol consumption and stop smoking. The use of TNF blockers may reduce metabolic risks to some extent and may be given where indicated. Finally, patients with high metabolic risks should be referred appropriately [**4, 12**].

Conclusion

As a conclusion, recent evidence points to a causal association between psoriasis and

MetS which is most probably bidirectional. Many factors including common pathophysiology, genetic background and environmental factors contribute to this association. Chronic inflammation and the disturbance of physiologic functions through intercellular communication have been suggested as the main mechanism for the link between psoriasis and MetS. The pathogenic process may start either in the setting of psoriasis or in a patient with MetS and then, trigger the development of the other. In other words, no matter where they reside, the continuous communication between immune cells (in skin or visceral tissues) and adipocytes (in subcutaneous tissue or visceral adipose tissue) and their negative impact on the function of each other seems to constitute the basis of this connection.

It is crucial for researchers to be aware of the association between psoriasis and MetS that it provides opportunity to have a more comprehensive knowledge on their complex etiopathogenesis, gives chance for the discovery of novel therapeutic targets and enables clinicians to implement large-scale treatment programs for these patients.

Acknowledgements

The figures of the paper are not taken from any other sources and have been created by the authors themselves.

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