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REVIEW

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Biochemical markers of psoriasis as a metabolic disease

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Abstract: Psoriasis is a chronic immune mediated inflammatory skin disease with a population prevalence of 2–3%. In recent years, psoriasis has been recognized as a systemic disease associated with metabolic syndrome or its components such as: obesity, insulin resistance, hypertension and atherogenic dyslipidemia. Many bioactive substances have appeared to be related to metabolic syndrome. Based on current literature, we here discuss the possible role of adiponectin, leptin, ghrelin, resistin, inflammatory cytokines, plasminogen activator inhibitor 1, uric acid, C-reactive protein and lipid abnormalities in psoriasis and in metabolic syndrome. *(Folia Histochemica et Cytobiologica 2012, Vol. 50, No. 2, 155–170)*

Key words: psoriasis, metabolic syndrome, adipokines, cytokines, uric acid, CRP, PAI-1

Introduction

Psoriasis is an immune mediated inflammatory skin disease characterized by epidermal hyperproliferation, impaired differentiation of keratinocytes, excessive angiogenesis and immunological dysfunction [1–3]. The immunologic cells engaged in the pathogenesis of psoriasis which have been the focus of attention in recent years include not only lymphocytes Th1, but also Th17, Th22 and regulatory T lymphocytes (Treg). Equally important immunological cells are Langerhans cells and dermal dendritic cells (dDC) (Figure 1). One of the immunological disturbances is the predominance of Th1 response [4–6]. An elevated level of IFN-γ, together with decreased levels of IL-4, fosters the inhibition of Th2 immune response [4, 6]. The leading role in the regulation of immune response in psoriasis is attributed to dendritic cells (DC). A significant increase in the number of dendritic cells which secrete IL-20, IL-23 and TNF-alpha has been observed in patients with psoriasis [7–9]. Activated DC secrete, among others, IL-12, inducing Th-1 immune response and IL-23, which favors the differentiation of naive lymphocytes into Th17 cells [10–12]. Naive T lymphocytes differentiation into Th17 cells depends on the presence of IL-1β, IL-6, IL-21, TGF-β and IL-23 [13, 14]. An increased percentage of Th17 lymphocytes and its cytokines (IL-17a, IL-6) has also been observed in psoriasis [15–21]. Studies conducted by Harper et al. [21] and Norgales et al. [22] revealed the presence of Th 22 lymphocytes in the skin of patients with psoriasis. Differentiation of the Th 22 lymphocytes which produce IL-22 is induced by the presence of IL-6, TNF-alpha, plasmacytoid dendritic cells and Langerhans cells [23–25]. In response to IL-17 and IL-22 stimulation, keratinocytes increase the secretion of IL-8. Furthermore, INF-γ (synthesized by Th1 cells and dendritic cells) together with IL-22, IL-6 and IL-20, enhances the proliferation of keratinocytes [18, 26, 27]. Acti-

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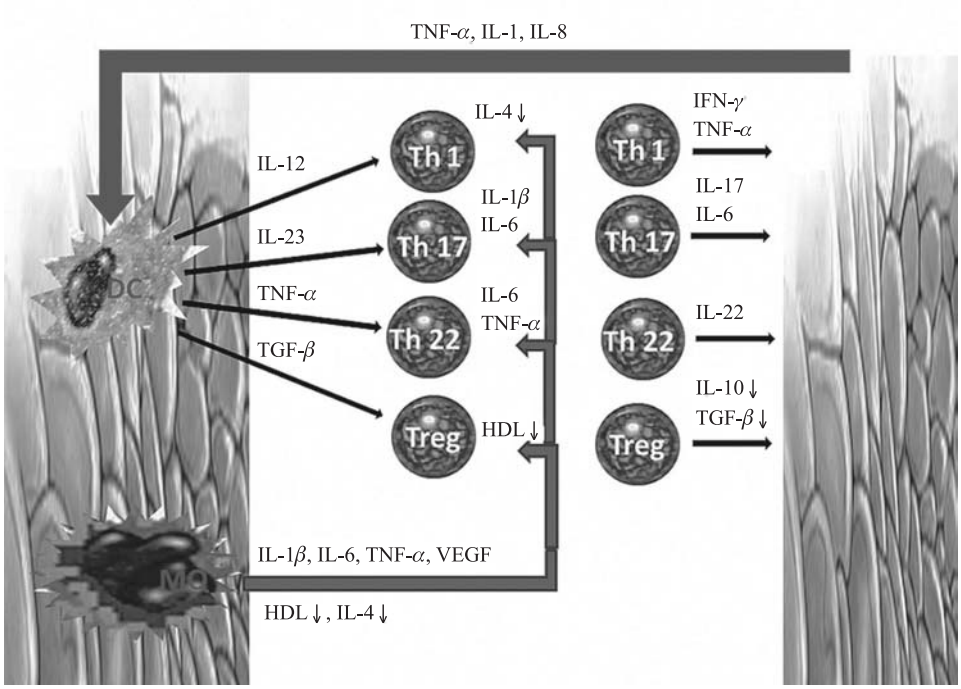

Figure 1. DC — dendritic cells; MQ — macrophages, T — lymphocytes subpopulations (Th1, Th17, Th22, Treg); HDL — high density lipoproteins cholesterol; INF-γ — interferon gamma; TGFâ — transforming growth factor beta; VEGF — vascular endothelial growth factor; TNF-α — tumor necrosis factor alpha and interleukins which are involved in the pathogenesis of psoriasis

vated keratinocytes secrete increased amounts of TNF-alpha, IL-1 and IL-8, enhancing inflammation and activation of dendritic cells. The key role in the inhibition of inflammatory reaction and induction of tolerance to antigen play Treg lymphocytes. Decreased levels of Treg lymphocytes have been demonstrated in Graft-Versus-Host Disease as well as in breast, colon and lung cancer [28–33]. A decreased percentage or impaired function of Treg lymphocytes, observed also in psoriasis, may lead to an increased secretion of proinflammatory cytokines, which subsequently results in enhanced proliferation of keratinocytes [34, 35]. Disturbances in other tissues may occur as a result of dysfunction and changed percentage of Treg and Th1 lymphocytes. Cheng et al. [36] reported that a decreased percentage of Treg lymphocytes and an increased percentage of Th 17 cells in patients with acute coronary syndrome may be one of the potential causes of destabilization of atherosclerotic plaques.

It is estimated that psoriasis affects 120–180 million people worldwide [37]. A growing number of new cases of psoriasis are reported [37, 38]. Recently, psoriasis has been recognized as a systemic disease associated with multiple comorbidities [1, 3]. The lipid disturbances in the course of psoriasis have been analyzed since 1924 [39, 40]. Researchers have focused their attention on comorbidities in psoriasis including: type 2 diabetes, atherosclerosis, hypertension, myocardial infarction, depression and obesity. Hyperuricemia in patients with psoriasis has been noted [1, 3, 41–45]. It seems that metabolic syndrome, for which the coexistence of well-known cardiovascular disease risk factors is characteristic, may be the connection between cardiovascular complications and type 2 diabetes in patients with psoriasis [1].

The first description of a possible coexistence of metabolic disturbances and cardiovascular risk factors was made at the beginning of the 20th century [46]. It was not until the end of that century when the definition and criteria of metabolic syndrome were introduced, being later modified [46].

Guidelines proposed by the International Diabetes Federation (IDF) are the most up-to-date criteria for diagnosing metabolic syndrome [47]. According to the new IDF definition, for a person to be defined as having metabolic syndrome they must have:

1. Central obesity, defined as a waist circumference (of which the values are ethnicity-specific), plus any two of the following factors:

a. Raised triglycerides ≥ 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality,

b. Reduced HDL cholesterol: < 40 mg/dL (1.03 mmol/L) in males, < 50 mg/dL (1.29 mmol/L) in females, or specific treatment for this lipid abnormality,

c. Raised blood pressure (BP): systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg, or treatment for previously diagnosed hypertension,
d. Raised fasting plasma glucose ≥ 100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes.

Comorbidity of metabolic syndrome and psoriasis has been stressed by many researchers. However, the prevalence of metabolic syndrome among patients with psoriasis varies according to the study and the adopted criteria of metabolic syndrome. Sommer et al. [45] reported that metabolic syndrome in patients with psoriasis was at least twice as common as in a control group. The results of this study are consistent with data published by Love et al. [48]. However, in both studies, different criteria of metabolic syndrome were used [45, 48]. Love et al. [48] found the prevalence of metabolic syndrome to be 40% among adult patients with psoriasis and 23% in a control group. In another study performed on 338 patients with plaque psoriasis and 334 patients with other skin diseases, a higher prevalence of metabolic syndrome was observed in the first group (30.1% and 20.6% respectively). Moreover, the prevalence of metabolic syndrome correlated with the duration of psoriasis [44]. Similar results were obtained by Nisa et al. [49] who observed metabolic syndrome in 28% of patients with psoriasis. Mebazaa et al. [50] also observed a higher prevalence of metabolic syndrome in patients with psoriasis than in a control group, although it was not statistically significant. It is worth noting that metabolic syndrome has also been observed in patients with psoriatic arthritis. Raychaudhuri et al. [51] showed that as many as 58% of men and 60% of women with psoriatic arthritis fulfilled the criteria of metabolic syndrome. Additionally, the association between single features of metabolic syndrome and psoriasis has also been investigated [43, 52].

The exact mechanism for the development of metabolic syndrome in patients with psoriasis is yet to be fully understood. Some researchers have suggested that psoriasis predisposes to the development of obesity or hypertension due to a stressful life, reduced physical activity, or greater tobacco and/or alcohol consumption [41].

Currently, it is considered that insulin resistance and abdominal obesity play vital roles in the pathogenesis of metabolic syndrome [46, 47]. The possible comorbidity of psoriasis and obesity has been suggested by many authors. It has been reported that obesity is more common in patients with psoriasis [53, 54]. Naldi et al. [55] demonstrated that the risk of developing psoriasis is related to BMI (body mass index), whereas the risk is higher in obese people.

Nowadays, white fat tissue is considered to be an active endocrine organ which has an effect on many metabolic processes. Fat tissue cells (adipocytes) can produce and secrete numerous bioactive elements known as adipokines including many cytokines, hormones and growth factors [56, 57]. They are involved in preserving homeostasis, regulating the glucose and lipid metabolism and blood pressure. Adipokines also take part in regulating the sensitivity to insulin and they are involved in inflammatory and immune processes [57]. Therefore, taking numerous functions into consideration, adipokines are under constant scrutiny. The contribution of adipokines to metabolic syndrome has also been reported [58].

The IDF has suggested using a so called 'platinum standard' in research studies related to metabolic syndrome which includes additional metabolic criteria such as: leptin, adiponectin, apolipoprotein B (Apo B), low density lipoprotein (LDL), proinflammatory cytokines and C-reactive protein (CRP) levels as well as markers of prothrombotic state [47].

The aim of this study is to review current literature data concerning the biochemical markers of metabolic syndrome in patients with psoriasis.

Adiponectin

Adiponectin is a polypeptide composed of 244 amino acids. It is synthesized mostly by adipocytes [59]. It has been proved that the gene which codes adiponectin (AMP1) is localized on chromosome 3q27. Moreover, it has been found that the locus of proneness to type 2 diabetes is localized on the same chromosome [60]. Adiponectin can occur as an oligomeric complex as well as a high molecular weight adiponectin — HMV which is its most active form [61].

It is recognized that adiponectin has anti-inflammatory properties: it negatively regulates synthesis of TNF-alpha in fat tissue, and inhibits secretion of this cytokine by heart muscle cells. Additionally, adiponectin inhibits production of IL-8, vascular adhesion molecule-1 (VCAM-1), and reactive oxygen species (ROS) in endothelial cells. It also stimulates synthesis of IL-10 [59, 62].

This protein has also a protective antiatherogenic effect which arises through decreasing monocyte adhesion to the endothelium and reducing synthesis of VCAM-1, intercellular adhesion molecule-1 (ICAM-1) and E-selectin [59, 63]. Adiponectin increases the synthesis of nitric oxide in endothelial cells by intensifying the synthesis of mRNA for endothelial nitric oxide synthase (eNOS), subsequently relaxing smooth muscles [59, 63]. *In vitro* studies on cell cultures show

that adiponectin has an anti-apoptotic effect on heart muscle cells and fibroblasts [64]. Therefore, some authors recommend regarding its decreased blood concentration as a risk factor for cardiovascular disease [65].

It is worth noting that low plasma or serum levels of adiponectin have been found in obesity, type 2 diabetes, coronary disease, hypertension and non-alcoholic fatty liver disease in obese patients [59, 66, 67]. It is interesting that in other inflammatory diseases such as lupus erythematosus, cystic fibrosis and type 1 diabetes, circulating levels of adiponectin are elevated [68]. These observations may suggest that adiponectin levels are under the control of other regulatory mechanisms in chronic inflammatory diseases related to obesity [63].

Considering the fact that adiponectin is related to metabolic syndrome [62], which can coexist with psoriasis, it cannot be excluded that this protein plays a role in pathophysiological processes in psoriasis.

Several studies have reported decreased circulating levels of adiponectin in patients with psoriasis compared to a control group [69, 70]. Additionally, researchers have determined that adiponectin concentration levels are negatively correlated with psoriasis severity measured by PASI (Psoriasis Area and Severity Index) as well as with the plasma concentration of TNF-alpha [69]. Shibata et al. [71] demonstrated a significant increase of serum adiponectin concentration in patients with psoriasis and psoriatic arthritis who were treated either with anti-TNF-alpha agents or with narrowband UVB. Moreover, they showed that an increase of adiponectin concentration was associated with a decrease of IL-6 concentration.

Kaur et al. [72] investigated the correlation between adiponectin, body weight and oxidative stress. Obese patients with psoriasis had a significantly higher concentration of IL-6, which additionally was negatively correlated with adiponectin concentration. Only in obese psoriatic patients was the glutathione redox ratio (GHS), which is a marker of oxidative stress, significantly higher, and it correlated negatively with the concentration of adiponectin.

It seems that obesity in psoriatic patients could be connected to decreased protective influence of adiponectin and with enhanced systemic inflammatory process and oxidative stress [72]. Coimbra et al. [73] achieved similar results. They found that the concentration of circulating adiponectin was significantly lower in psoriatic patients with BMI > 30 compared to psoriatic patients with BMI < 25 and to a control group.

The results of this study may point to a correlation between psoriasis and obesity, and its plausible influence on lowering adiponectin concentration, which correlated negatively with BMI [73].

Leptin

Leptin is a polypeptide composed of 166 amino acids of molecular mass 14kDa. It is coded by obesity gene localized on the 7q31 chromosome. [57, 63, 74, 75]. Most of this protein is synthesized in adipocytes, though some minor quantities are found in placenta, ovaries, skeletal muscles, stomach, liver and pituitary gland [60, 72].

The main role of leptin is to regulate food consumption through a neuroendocrine system by reducing appetite [57, 76]. It has also an effect on immunological processes. Moreover, it is involved in wound healing and hair growth [76, 77].

Interestingly, people with leptin deficiency are very obese [63]. On the other hand, obese patients have higher leptin concentration. However, they do not react to higher leptin levels by a decrease in their appetite [76]. Therefore, it is supposed that obese patients are resistant to leptin, just as in type 2 diabetes, where insulin resistance is observed [63, 76, 78]. Furthermore, hyperleptinemia caused by obesity is an important risk factor leading to the development of type 2 diabetes [79].

Hyperleptinemia may lead to the development of atherosclerosis in obese patients [80]. Other authors suggest that leptin is involved in the formation of atheromatous plaques [81]. The suggestion has been made to regard elevated leptin levels as an independent factor indicating future coronary disease and cardiovascular complications [82].

An assumption, based on the articles mentioned above, can be made that leptin is correlated with metabolic syndrome, and moreover it may be involved in the pathophysiology of psoriasis. Wang et al. [74] found higher serum leptin levels in women and men with psoriasis compared to a control group. Higher plasma leptin levels in patients with psoriasis were also noted in a Japanese population [69]. Furthermore, higher leptin concentration was associated with higher PASI, although it was not statistically significant [69]. In another study, significantly elevated serum leptin concentration was found in female patients with psoriasis, whereas male patients with psoriasis showed a trend towards higher values compared to the control groups of the same gender. Furthermore, patients with BMI > > 30 had significantly higher leptin concentration than the groups with lower BMI, as well as the control group. However, it is worth noting that as many as 58% of patients with the highest BMI were women [73]. A study conducted by Johnston et al. [83] on 30 obese patients with plaque psoriasis and a control group (BMI 30.5, 30.8 respectively) did

not prove any statistically important differences in the serum levels of leptin and its soluble receptors compared to the control group. However, the authors proved that there was a significant correlation between BMI, waist circumference and leptin concentration [83]. Therefore, it seems that leptin concentration is related to BMI, and so hyperleptinemia in patients with psoriasis may be correlated with obesity [73].

It has been proposed that leptin, through promoting synthesis of Th1 cytokines and inhibiting synthesis of Th2, might be involved in the pathogenesis of psoriasis [73, 74]. Considering that inflammation mediated by Th1 lymphocytes is one of the factors leading to the development of atherosclerosis and coronary disease [84], it seems that leptin may be a connection between psoriasis and cardiovascular complications [85].

Resistin

Resistin is a polypeptide composed of 108 amino acids of molecular weight 12.5kDa [86]. High cystein content is a characteristic feature of resistin [57]. This adipokine is synthesized mostly by macrophages and monocytes contained in fat tissue [83, 87, 88]. Additionally, resistin is produced in bone marrow, placenta, pancreas, joint fluid, synovial tissue and the peripheral blood [89–92].

There have been suggestions that resistin plays a role in inflammation. It has been proved that proinflammatory cytokines such as TNF-alpha, IL-6, IL-1beta and lipopolysaccharides are able to increase the expression of resistin in peripheral blood mononuclear cells (PBMCs); however, resistin itself is capable of inducing the synthesis of TNF-alpha or IL-12 [63, 93, 94].

It is worth noting that resistin owes its name to the observed influence of this protein on insulin resistance [95]. However, resistin's role in obesity and insulin resistance is not yet fully understood [96]. Mice which were given resistin had a lowered sensitivity to insulin. Another study has reported higher resistin levels in obese mice [97, 98].

Different results were described in a study in which resistin concentration was measured and compared in obese patients, obese patients with type 2 diabetes, and patients with normal body weight. A negative correlation was found between the concentration of resistin and sensitivity to insulin only in the patients with normal body weight [99]. Another study revealed that synthesis of resistin by fat tissue in morbidly obese patients was significantly higher compared to slim people; however, no correlation with BMI was found [100]. Different results observed in humans and mice might suggest that resistin in the human body is synthesized mostly by non-adipose components of fat tissue, which would explain the observed phenomenon [86].

A link between resistin and cardiovascular complications has been emphasized [86]. Significantly elevated serum resistin levels in patients with type 2 diabetes during acute STEMI (acute ST segment elevation myocardial infarction) has been described compared to patients with acute STEMI but without type 2 diabetes, or to a control group [101]. This suggests that resistin may be involved in the pathogenesis of metabolic syndrome.

Elevated resistin levels have been found in patients with psoriasis, and moreover its concentration corresponded with PASI index [73, 83, 85]. It is recognized that obesity is associated with chronic inflammation, which is characterized by elevated proinflammatory cytokine synthesis. Considering this fact, and the ability of resistin to induce synthesis of pro-inflammatory cytokines, it cannot be excluded that resistin is involved in the development of metabolic syndrome observed in patients with psoriasis [73, 85, 102].

Ghrelin

Gherlin is a peptide hormone similar in structure to motilin [103]. It was discovered by Kojima et al. [103] during their search for the natural ligand of a growth hormone secretagogues-receptor (GHS-R). Ghrelin is composed of 28 amino acids. Two forms of ghrelin are distinguished: acylated and unacylated [103–105]. The main source of ghrelin is a mucous membrane of the stomach, but ghrelin is also synthesized in many other organs [106]. Secretion of ghrelin increases when energy balance is negative, which leads to increased appetite and decreased energy expenditure [106].

Recently, it has been suggested that ghrelin takes part in the development of metabolic syndrome [107]. Ghrelin concentration decreases in conditions such as obesity, type 2 diabetes and hypertension [108, 109].

We can find no studies covering the role of ghrelin in psoriasis. However, some authors have suggested that if ghrelin plays a role in the pathogenesis of obesity, which is one of the elements of metabolic syndrome, it can also take part in the pathogenesis of psoriasis [102].

Interleukin-6 (IL-6)

IL-6 is one of the most important inflammatory cytokines. It is synthesized by various cells such as: monocytes, fibroblasts, endothelial cells and adipocytes upon exposure to appropriate stimuli [63, 110].

Particularly interesting is the study conducted by Fujishima et al. [111]. The authors showed that IL-17F was able to induce synthesis of IL-6, both in normal human epidermal keratinocytes (NHEKs) and in mouse skin. It is worth noting that NHEKs expressed much higher amounts of IL-6 after stimulation by IL-17F than by IL-17A or TNF-alpha. The authors suggest that IL-17F may be a crucial cytokine that induces IL-6 expression in NHEKs [112]. IL-6 acts as a chemotactic factor for T cells, thus it stimulates the migration of T cells into the epidermis. IL-6 influences the growth and differentiation of dermal and epidermal cells [112] and is also involved in hematopoiesis [112].

It has been proved that the synthesis of IL-6 in fat tissue and its circulating levels are positively correlated with obesity, inadequate glucose tolerance, and resistance to insulin [113, 114]. Moreover, a reduction of body weight is associated with reduced concentration of this interleukin, as well as reduction of its synthesis in fat tissue [114]. Esteve et al. [115] found that serum IL-6 concentration was negatively correlated with sensitivity to insulin, whereas it showed a positive correlation with BMI, blood pressure values and triglyceride levels. It was also indicated that IL-6 concentration was positively correlated with intima media thickness. Nishida et al. [116] suggested considering serum concentration of IL-6 as a marker of processes which might lead to early arterial alterations in men.

Significantly increased serum levels of IL-6 have been reported in psoriatic patients. [73]. A positive correlation between elevated IL-6 levels and PASI has also been proved [73]. It is worth noting that higher IL-6 levels and its receptor have been observed in psoriatic plaques [117].

It is thought that obesity has a negative influence on the course of psoriasis [118], due to the increased synthesis of leptin, IL-6, TNF-alpha and reduced production of adiponectin by fat tissue [73]. A negative correlation between plasma IL-6 and adiponectin levels in obese patients has been observed [72]. Kaur et al. [72] noted a statistically significant elevation of IL-6 concentration in obese patients with psoriasis compared to a control group. In patients with psoriasis and with normal body weight, the plasma concentration of IL-6 was elevated in relation to the control group, although it was not significant. Johnston et al. [83] came to a similar conclusion. They observed elevated levels of IL-6 in obese patients with psoriasis.

Another study found a positive correlation between plasma concentration of IL-6 and the oxidized LDL-β2-glycoprotein complexes (oxLDL-b2-GPI) in patients with psoriasis [119]. Furthermore, a concentration of oxidized LDL and oxidized LDL-β2-glycoprotein complexes showed a positive correlation with BMI. According to the authors, the correlation between oxLDL-b2-GPI, IL-6 and BMI may suggest a connection between LDL oxidation and inflammation, including the inflammatory process observed in obesity.

Interleukin-8 (IL-8)

IL-8 is a chemokine involved in many pathological processes. The main function of IL-8 is a chemotaxis of neutrophils to a place affected by inflammation. It also induces antibacterial features of neutrophils. Apart from that, IL-8 induces angiogenesis and influences other cells, which take part in inflammatory response including: T lymphocytes, natural killer cells (NK) and basophils, and it is also chemotactic towards keratinocytes [112, 120, 121].

Authors have drawn attention to the fact that IL-8 plays a role in the pathogenesis of type 2 diabetes and of atherosclerosis [122]. Significantly higher circulating levels of IL-8 have been found in patients with heart failure and metabolic syndrome compared to patients with heart failure without metabolic syndrome [123]. It has been proved that proinflammatory cytokines such as TNF-alpha, IL-1 and CRP induce synthesis of IL-8 in human adipocytes [124, 125]. Kobashi et al. [125] stated that IL-8 reduces phosphorylation of AKT by insulin in human adipocytes, which can induce resistance to insulin.

A significantly elevated concentration of IL-8 has been found in patients with acute psoriasis [126]. Another study showed a higher IL-8 plasma concentration in patients with psoriasis, which decreased with the improvement of clinical appearance [127]. In a study performed on a Japanese population, a significant elevation of serum IL-8 levels in patients with psoriasis was found, although a correlation with PASI was not observed [128]. The authors pointed out enhanced local synthesis of mRNA for IL-8 or its receptors in psoriatic plaques [126, 129].

To date, there have been no studies evaluating the correlation between IL-8 levels and the development of metabolic syndrome in patients with psoriasis. However, when the role of this cytokine in the pathogenesis of insulin resistance, type 2 diabetes or atherosclerosis [122, 125, 130] is taken under consideration, it cannot be excluded that elevated circulating levels of IL-8 in patients with psoriasis may contribute to the maintenance of the inflammation, which plays a vital role in the pathogenesis of metabolic syndrome.

Tumor necrosis factor-alpha (TNF-alpha)

TNF-alpha is a proinflammatory cytokine produced by various cells such as: lymphocytes, monocytes/mac-

rophages, mast cells and NK cells [63]. TNF-alpha influences the proliferation, activation or differentiation of many cells [131]. TNF-alpha also increases the synthesis of some proinflammatory cytokines, growth factors and adhesive molecules [112]. Several studies have shown that TNF-alpha may impair insulin signaling in many cells such as liver, adipose tissue or skeletal muscles [132–134]. This cytokine may also lead to insulin resistance through the inhibition of phosphorylation of tyrosine receptor and insulin receptor substrate 1 (IRS-1) [39]. It has been observed that obese mice did not develop insulin resistance if TNF-alpha activity had been blocked [135].

Increased levels of TNF-alpha have been reported in obese patients [136]. A positive correlation between TNF-alpha and BMI has also been reported [137]. Recently, it was reported that elevated plasma levels of TNF-alpha are associated with left ventricular diastolic dysfunction, which is one of the earliest manifestations of left ventricular dysfunction due to diabetes mellitus [138], while administration of TNF-alpha inhibitors leads to an increase of HDL levels [39]. It has been stressed that TNF-alpha is involved in the pathogenesis of metabolic syndrome [1, 46].

TNF-alpha is one of the major cytokines in the pathogenesis of psoriasis. Elevated levels of this cytokine have been reported in many studies in patients with active psoriasis [112, 139]. A positive correlation between serum levels of TNF-alpha and PASI has been noted [112]. It has been shown that TNF-alpha levels negatively correlated with plasma levels of adiponectin, while this cytokine did not show any correlation with leptin levels in patients with psoriasis [69].

In contrast to other adipokines, TNF-alpha is synthesized not only within adipose tissue. Therefore, elevated levels of TNF-alpha, which are observed in the serum of patients with psoriasis, may also result from the severe inflammatory process in psoriasis as well as from the contribution of other cells in the synthesis of this cytokine [63]. It is interesting that several research studies have shown increased body weight in patients with psoriasis after therapy with anti-TNF-alpha agents [140–142].

Interleukin-17 (IL-17)

IL-17 belongs to the cytokines produced by Th 17 cells [143]. This cytokine leads to the mobilization of neutrophils [144], and stimulates secretion of IL-6, IL-8, prostaglandin E2 (PGE2) and granulocyte-macrophage colony-stimulating factor, in fibroblastic, epithelial and endothelial cells [145–147]. IL-17 induces the expression of ICAM 1 on fibroblasts [146] and it enhances the maturation of dendritic cells [147, 148].

Recently, IL-17 has been found to take part in the pathogenesis of multiple sclerosis, inflammatory bowel diseases and rheumatoid arthritis, as well as psoriasis [144].

Elevated levels of IL-17 have been reported in obese patients [149, 150]. However, it has not been elucidated whether IL-17 influences metabolism and leads to the development of obesity, or whether the elevated synthesis of this cytokine results from inflammation observed in the course of obesity [150]. It has also been reported that T cells localized in adipose tissue produce IL-17 [150]. Moreover, this study showed that IL-17 regulates adipogenesis and glucose metabolism [150]. Significantly elevated serum levels of IL-17 have been observed in patients with type 2 diabetes [151].

It has also been shown that patients with acute coronary syndrome have significantly higher levels of IL-17 than patients with stable angina or non-cardiac chest pain [152]. In other studies, elevated plasma or serum levels of IL-17 were also reported in patients with non stable angina or in patients with acute myocardial infarction [153, 154]. It has been suggested that increased levels of IL-17 may be associated with ischemic heart disease [154].

It is interesting that decreased serum levels of IL-17 were observed in patients with metabolic syndrome compared to a control group [155]. It is worth noting that a decline in IL-17 levels was associated with an increase of TGFβ levels [155]. On the other hand, the association between IL-17 and heart disease, hypertension or type 2 diabetes suggests the possible role of this cytokine in the pathogenesis of metabolic syndrome [155].

Nowadays, it is known that IL-17 plays a vital role in the pathogenesis of psoriasis [156]. Fujishima et al. [111] demonstrated that $CD4^+$ T lymphocytes subsets secreted higher amounts of IL-17F in psoriatic lesions than in non-lesional skin. It has also been shown that IL-17F is a strong inducer of IL-6 expression in keratinocytes. Thus, it was suggested that the IL-17F/IL-6 axis might enhance inflammation in psoriatic skin [111]. A positive correlation between elevated serum levels of IL-17 and PASI has been reported [128]. Moreover, biologic agents that inhibit the function of Th 17 cells lead to a decrease of IL-17 production and to an improvement in the clinical condition of patients [157]. However, Nakajima et al. [143] reported no detectable serum levels of IL-17, either in patients with psoriasis or in a control group. So far, there have been no studies which determine the correlation between circulating levels of IL-17 and the occurrence of metabolic syndrome in patients with psoriasis.

Considering the fact that IL-17 is involved in the pathogenesis of psoriasis and atherosclerosis, it has

been suggested that the possible link between psoriasis and one of the metabolic syndrome complications such as myocardial infarction, might be IL-17 [152].

Interleukin-18 (IL-18)

IL-18 exerts its activity on innate immunity but also on Th1 and Th2 driven immune response [158]. Together with IL-12, it triggers the synthesis of INFγ by T helper and T cytotoxic and NK cells. As a result, INFγ leads to a decreased Th2 response and an increased Th1 response [159]. IL-18 has been reported to induce the production of IL-4, IL-13 by basophils, mast cells, T cells and NK cells [158]. Moreover, IL-18 is synthesized by adipocytes and resident macrophages within adipose tissue [160, 161]. Production of this cytokine has also been shown within atherosclerotic plaques [162]. According to some authors, IL-18 may be responsible for the instability of atherosclerotic plaques [163].

In a study of 10,600 European men, significantly increased baseline plasma levels of IL-18 were reported among patients who developed a coronary event during the study compared to those who did not [164]. It was suggested that plasma levels of IL-18 might be considered as an independent predictor of future coronary events [164, 165]. However, Weiss et al. [160] reported that expression levels of IL-18 in adipose tissue were significantly lower in patients with cardiovascular disease compared to those without it.

An elevated concentration of serum IL-18 is associated with an increased risk of the development of type 2 diabetes, both in middle-aged men and women [166]. Hung et al. [167] demonstrated in a large population study that serum levels of IL-18 correlated with IL-6 and C-reactive protein. Moreover, the concentration of IL-18 correlated with waist circumference, triglyceride, blood pressure, and insulin levels, both in men and women. An inverse correlation was observed between IL-18 and HDL levels. According to the authors, IL-18 might be involved in the pathogenesis of metabolic syndrome. Another study reported an association between elevated plasma levels of IL-18 and higher metabolic syndrome prevalence [168].

Increased synthesis of IL-18 has also been reported in psoriasis [158]. Overproduction of IL-18 mRNA levels and IL-18 receptor mRNA was observed within skin lesions in patients with psoriasis compared to a healthy control group [169]. Increased plasma and serum levels of IL-18 were revealed in patients with psoriasis compared to a control group [170–172]. An association between concentration of IL-18 and PASI index has also been reported [171, 173].

To date, there have been no studies evaluating the association between IL-18 levels and metabolic syndrome prevalence in psoriasis. On the other hand, the role of IL-18, both in the pathogenesis of psoriasis and metabolic syndrome, has been reported [112, 158, 167, 169, 174]. Therefore, given the higher prevalence of the components of metabolic syndrome such as hyperlipidemia, hypertension and type 2 diabetes in patients with moderate to severe psoriasis, it might be suspected that IL-18 is involved in the development of metabolic syndrome in patients with psoriasis. However, this hypothesis requires further studies [45].

Interleukin-23 (IL-23)

IL-23 is synthesized by antigen presenting cells, mainly by dendritic cells [175]. It plays a vital role in the type 1 T cells immune response and furthermore it triggers cytotoxicity of lymphocytes $CD8^+$. IL-23 induces development of Th 17 cells which produce IL-17, IL-22 and TNF-alpha [175]. It is considered that IL-23 is a potent stimulus which leads to production of IL-17 [176, 177]. IL-23 has been demonstrated to be a key cytokine in the inflammation in peripheral tissues [178]. Increased concentration in IL-23 has been observed in obese women [149]. Recently, it was reported that IL-23/Th17 pathway is involved in the pathogenesis of psoriasis and numerous inflammatory diseases [179].

The results of studies evaluating the levels of IL-23 in patients with psoriasis are ambiguous. Nakajima et al. [143] demonstrated undetectable serum levels of IL-23, both in patients with psoriasis and in a control group. But Coimbra et al. [127] reported significantly elevated serum levels of IL-23 in patients with psoriasis, which decreased after three weeks of PUVA or NB-UVB therapy.

Monoclonal antibodies derived against IL-12/ /IL-23 have been observed to lead to a decrease of IL-17 levels [152]. Taking into consideration the fact that inhibiting IL-17 in mice leads to a reduction of atherosclerotic plaque size, it is suggested that in humans, a reduction of IL-17 production may inhibit the development of atherosclerosis [152]. Thus it may be suspected that the IL-23/IL-17 cytokine axis is involved in the pathogenesis of cardiovascular disorders. However, precise recognition of its role needs further research.

Interleukin-1 beta (IL-1 beta)

IL-1 beta belongs to the IL-1 family. Due to its proinflammatory properties, ability to induce synthesis of

other cytokines by T cells and to activate neutrophils, monocytes, eosinophils or basophils [112], IL-1 beta is involved in the pathogenesis of a number of autoimmune and inflammatory diseases [180].

Recently, there has been a focus on the link between IL-1 beta and metabolic disorders including metabolic syndrome [181]. Increased expression of IL-1 beta in adipose tissue of obese subjects has been reported [182]. It was revealed that patients with elevated plasma levels of IL-6 and with detectable levels of IL-1 beta had a roughly three-fold higher risk of developing type 2 diabetes than that of a control group. Patients who had only elevated levels of IL-6 and undetectable levels of IL-1 beta did not have an increased risk of type 2 diabetes compared to the control subjects [183]. The authors suggested that interaction between IL-6 and IL-1 beta may be involved in the pathogenesis of type 2 diabetes [183].

Jager et al. [181] demonstrated that IL-1 beta inhibits insulin-induced glucose transport in adipocytes by decreasing an expression of insulin receptor substrate 1 (IRS-1). According to the authors, IL-1 beta, which is produced by adipose tissue-resident macrophages, can impair adipocytes' biology and lead to the development of insulin resistance.

An attempt has been made to evaluate the role of IL-1 beta in the pathogenesis of psoriasis. Elevated levels of IL-1 beta have been reported in supernatants of monocyte cultures obtained from patients with psoriasis [112]. It was also noted that production of IL-1 beta by PBMCs correlated with psoriasis severity [112]. The study conducted by Johnston at al. [83] provided some interesting data. The authors demonstrated that obese patients with psoriasis had significantly higher serum concentration of IL-1 beta compared to the control group. However, no significant changes in the serum levels of IL-1 beta after the course of UVB treatment were noted [83].

Plasminogen activator inhibitor 1 (PAI-1)

PAI-1 is a potent inhibitor of fibrinolysis which interacts both with tissue-type (t-) and urokinase-type (u-) plasminogen activator which leads to inhibition of the conversion of plasminogen to plasmin [184, 185].

PAI-1 is a single chain glycoprotein and belongs to the family of serine protease inhibitors. PAI-1 can be synthesized by a variety of cells including endothelial cells, hepatocytes, smooth muscle cells, adipocytes, and platelets [185].

Recently, it was noted that elevated levels of PAI-1 were related to abdominal obesity, insulin resistance, hypertriglyceridemia, thrombosis and cardiovascular disease [186, 187]. Elevated levels of PAI-1 correlated also with the development of type 2 diabetes [188]. Therefore, a prothrombotic state is implicated in the pathogenesis of metabolic syndrome [47].

Increased plasma levels of PAI-1 have been reported in patients with psoriasis, and the concentration of PAI-1 became lower in the course of the therapy [189]. In another study, elevated PAI-1 levels and reduced levels of t-PA were observed in patients with psoriasis [190]. A positive correlation between elevated levels of homocysteine and PAI-1 has been demonstrated in psoriatic patients [190]. It is worth noting that homocysteine may alter PAI-1 binding to endothelium [190].

These findings are particularly interesting because they stress the presence of fibrinolytic disturbances in psoriasis.

It is considered that PAI-1 is a risk factor for cardiovascular disease and type 2 diabetes [191–195]. Therefore, it cannot be excluded that fibinolytic disturbances observed in psoriasis are involved in the development of cardiovascular complications in these patients.

Uric acid

Recently, it was noted that elevated serum levels of uric acid are associated with factors that contribute to metabolic syndrome, including: hypertriglyceridemia, obesity, hypertension and diabetes [196–199]. An attempt was made to evaluate whether the concentration of uric acid correlated with a single or increased number of elements which contribute to metabolic syndrome. In a large population study, it was demonstrated that increased serum levels of uric acid correlated with hypertriglyceridemia, abnormal waist circumference, high blood pressure and decreased HDL level. After controlling the results with BMI, elevated serum levels of uric acid still showed a correlation with hypertriglyceridemia, increased blood pressure and with decreased HDL levels [200].

Hyperuricemia has also been demonstrated in patients with psoriasis. It is thought that hyperuricemia may result from accelerated epidermal turn-over [201]. Studies conducted in the second half of the 20th century which aimed to determine the relationship between hyperuricemia and psoriasis, produced conflicting results [201].

It has been demonstrated that an elevated serum concentration of uric acid is positively correlated with PASI, BMI and total body surface area compared to a normouricemic group [201]. In another study, an increased concentration of uric acid was found in patients with psoriasis compared to two other groups (patients with skin disorders other than psoriatic lesions,

and a control group). After 12 weeks of therapy, a significant reduction of mean uric acid level was observed in patients with psoriasis. Furthermore, increased concentration of uric acid was accompanied by increased serum level of C-reactive protein. [202]. Hyperuricemia has also been reported in psoriatic arthritis [203].

It has been suggested that serum uric acid should be monitored in patients with psoriasis and metabolic syndrome [200–202]. However, a prospective study is required in order to determine if the prevention or treatment of hyperuricemia may affect the development of metabolic syndrome or the course of psoriasis.

Lipid abnormalities

Different lipid abnormalities are included in the pathogenesis of metabolic syndrome. One of them is an elevated concentration of Apo B. It is recognized that Apo B is responsible for the accumulation of LDL cholesterol within the endothelium; therefore, it is involved in the initiation of atherosclerotic plaques formation. Moreover, increased levels of Apo B are connected to an increased risk of development of atherosclerosis [204]. To date, few studies have demonstrated elevated levels of Apo B in psoriasis [39, 204]. However, there have also been studies which did not reveal any differences in Apo B concentration between patients with psoriasis and the healthy control group [39]. Increased levels of apolipoprotein A1 (Apo A1) have also been reported in patients with psoriasis [205]. It has been shown that an increased concentration of Apo A1 increases the risk of atherosclerosis [206]. Particularly interesting is the study conducted by Wilhelm et al. [207]. They observed that substitution of Apo A-1 to hypercholesterolemic mice lacking high density lipoprotein apolipoprotein A1 (HDL Apo A1) or LDLr(-/-) (low density lipoprotein receptor), apoA-I(-/-) (DKO) resulted in an increased percentage of Treg lymphocytes [207]. Other commonly reported lipid abnormalities in patients with psoriasis include: elevated LDL, total cholesterol and triglyceride levels [205, 208–211] as well as decreased HDL levels [211, 212]. The study published by Tekin et al. [208] indicates that oxidized low-density lipoprotein is accumulated in psoriatic skin lesions.

It is worth noting that, both in psoriasis and atherosclerosis, HDL becomes dysfunctional and has proinflammatory properties [213]. Additionally, $CD209^+/CD163^+$ dermal macrophages which are capable of engulfing oxidized lipids have been identified in psoriatic tissue. Moreover, it has been demonstrated that TPH-1 macrophages stimulated by a component of minimally oxidized LDL express IL-1, 6, 15, 17, 23, VEGF and cathelicidin, all of which are involved in pathogenesis of psoriasis [213]. This study indicated that host lipids and dermal macrophages are involved in the pathogenesis of psoriasis.

It is thought that lipid abnormalities are involved in the pathogenesis of psoriasis. Moreover, they are considered as factors that may lead to increased mortality due to cardiovascular complications. There have been many publications devoted to the role of lipids in psoriasis [39, 204], therefore in this review they will not be discussed in detail.

C-reactive protein (CRP)

A number of studies have demonstrated a link between the concentration of C-reactive protein and cardiovascular disease, BMI, waist to hip ratio, hypertriglyceridemia, increased levels of glucose, abnormal blood pressure, and insulin resistance [214–216].

Several studies have reported a correlation between increased levels of CRP and PASI [73, 217, 218]. Coimbra et al. [219] determined a prevalence of cardiovascular risk factors in patients with psoriasis. They demonstrated significantly higher levels of CRP compared to a control group. Although CRP concentration was reduced after the phototherapy, it still remained higher than in the control group. Considering these results, the authors suggested that in psoriasis there might be an inflammatory process which persists even after the therapy, and may lead to the development of atherogenic changes [219]. A positive correlation between elevated serum levels of high sensitivity of CRP (hs-CRP) and the degree of arterial stiffness in patients with psoriasis was reported in another study [220]. Moreover, increased concentration of hs-CRP seems to be an independent predictor of arterial stiffness. It has been suggested that the inflammatory process in psoriasis, which is characterized by elevated levels of CRP, is connected to increased arterial stiffness and premature development of atherosclerosis. These findings provide further evidence of a link between inflammation and cardiovascular diseases in patients with psoriasis [220]. This study is consistent with the research published by Ludwig et al. [221], which reported an increased prevalence and severity of coronary artery calcification as an indicator for cardiovascular disease in patients with psoriasis.

Conclusions

A large number of recently conducted studies have revealed the link between psoriasis and metabolic syndrome. It is worth noting that both psoriasis and metabolic syndrome are associated with inflammation, characterized by increased proinflammatory cy-

tokines, alteration of adipokine levels, lipid abnormalities, hyperuricemia or a prothrombotic state. Therefore, it is considered that metabolic disturbances may be connected to immunological abnormalities, and that psoriasis may be considered as an immunometabolic disease.

The exact mechanism which could explain the link between psoriasis and metabolic disturbances has not been precisely recognized. Therefore, further studies are needed, designed to estimate the correlation between biochemical markers of metabolic syndrome and psoriasis, as well as to determine which of them could be used to predict the development of metabolic syndrome in patients with psoriasis. This research should cover reference groups selected by age, gender and BMI. The results of such studies could lead to a change of therapeutic strategies and improve psoriasis outcomes.

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