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IMMUNE AND METABOLIC RELATIONSHIPS OF PSORIASIS WITH COMORBID CONDITIONS

Psoriasis is a polygenic disease in which chronic inflammation in the skin develops as a result of an interaction between genetic predisposing factors and environmental triggers. The self-sustaining inflammatory response of the skin coexists with autoimmune and autoinflammatory components. From an immunological point of view, psoriasis is characterized by profound changes, including sustained activation of the tumor necrosis factor alpha axis with interleukins 23 and 17 (TNF-α/IL-23/IL-17), as well as high expression of early pro-inflammatory cytokines.

The study of the pathogenesis of psoriasis is still relevant. Numerous studies have established that concomitant ("comorbid") diseases are associated with psoriasis, which may be due to individual links in the pathogenesis of the underlying disease, including through immuno-metabolic disorders.

The purpose of this review was to analyze current data on the relationship between psoriasis and comorbid conditions. The review presents new data on comorbid associations of psoriasis with metabolic syndrome, cardiovascular diseases, intestinal dysbiosis, and other pathologies.

The object of the study was publicly available scientific information, the search for which was carried out in the databases: PubMed, Medline, Scopus, Web of Science, RSCI, without language restrictions. An analysis of the literature data showed that psoriasis should be considered as a systemic inflammatory condition underlying comorbid associations. The pathogenesis of metabolic disorders in psoriasis is associated with constitutionally determined immune hyperreactivity. In turn, the developed metabolic abnormalities increase immune inflammation due to newly formed molecular patterns of dangers (DAMPs). Promising in understanding the causes of the formation of comorbid conditions and diseases in psoriasis is the study of general metabolic parameters, which will expand the understanding of the mechanisms of formation of comorbidity in psoriasis. In addition, this will allow the development of complex pathogenetic therapy, taking into account the correction of violations of metabolic processes in the body of patients. The analysis of scientific information shows that the systemic nature of psoriasis implies a personalized approach to its diagnosis and treatment, taking into account comorbid (comorbid) conditions.

Keywords: psoriasis, metabolic syndrome, cardiovascular disease, psoriatic arthritis, intestinal dysbiosis, metabolic profile.

Introduction. Psoriasis is a chronic inflammatory skin disease that affects 1-2% of the population and has a serious impact on the quality of life of those affected by the disease [15].

Psoriasis results from an interaction between genetic predisposing factors and environmental triggers, leading to a self-sustaining inflammatory skin response in which autoimmune and autoinflammatory components coexist [11, 46]. The condition usually manifests as erythematous, well-defined plaques covered with grayish-white scales, and 30% of affected individuals may develop inflammatory arthritis, psoriatic arthritis (PsA) [39].

The clinical and histological features of psoriatic skin lesions reflect some key mechanisms of the disease, such as hyperproliferation and angioneogenesis. Immunologically, psoriasis is characterized by profound changes involving sustained activation of the tumor necrosis factor alpha axis with interleukins 23 and 17 (TNF-α/IL-23/IL-17) as well as high expression of early proinflammatory cytokines [7, 53]. Numerous studies have shown the prevalence of autoinflammation at the systemic level [14, 31].

Of particular importance are metabolic disorders, which can be independent or induced by primary immune hyperreactivity [38].

Numerous studies have established that associated ("comorbid") diseases are associated with psoriasis, which may be caused by individual links in the pathogenesis of the underlying disease, including through immune and metabolic disorders [3].

According to S.G. Lykova et al. (2020) the concept of "comorbidity" (lat. co - together, morbus - disease) was introduced by A. Feinstein in 1970, putting into this term the idea of the presence of "any distinct additional clinical picture that existed or could arise in the patient during the clinical course of the index (main) disease" [3].

The presence of comorbidity in psoriasis is considered within the framework of the "psoriatic march" concept, which consists in the presence of causal links between dermatosis and pathology of other organs [19].

On this basis, the aim of this review was to analyze the current data on the immune-metabolic relationship of psoriasis with comorbid conditions.

Materials and methods of the study. The object of the study was publicly available scientific information, which was searched in the databases: PubMed, Medline, Scopus, Web of Science, RSCI, without language restrictions. In the process of writing the article the method of analysis and synthesis of information was used.

Results and discussion.

Molecular mechanisms of comorbidity formation in psoriasis. Our analysis of the literature showed that inflammation mediated by type 1 (Th1) T-helper lymphocytes, which is one of the main links in the pathogenesis of psoriasis, is a fundamental factor in the development of obesity, metabolic syndrome, diabetes, atherosclerosis and myocardial infarction [56].

In addition to the abnormal immune cell responses observed in the pathogenesis of psoriasis, recent pathophysiological studies have focused on the activation of the interleukin (IL)-23/IL-17 system, which increases abnormal keratinocyte proliferation and causes psoriasis [56]. Although the exact role of IL-17A in cardiovascular disease is still controversial, accumulation of IL-17-producing cells and elevated IL-17A levels have also been observed in atherosclerotic lesions [10, 17]. According to the literature, the "two plaques, one syndrome" hypothesis

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has been proposed, due to the fact that the molecular mechanisms of these two diseases have striking similarities with T-cell-mediated inflammation [6]. The hypothesis states that psoriasis is a chronic systemic inflammatory disease leading to insulin resistance through suppression of insulin receptors. In addition, decreased expression of insulin receptors in endothelial cells leads to decreased nitric oxide (NO), a vasodilatory agent. This leads to the development of vasoconstriction and increased arterial stiffness. As a result, the cited study reported an increased incidence of myocardial infarctions (MI) and strokes. It has been shown that the use of an insulin stimulator (glucagon-like peptide 1 - GLP-1) can improve the course of psoriasis, emphasizing the effect of insulin resistance in inflammation [38, 45].

According to the literature, elevated levels of the amino acid homocysteine are detected in the blood of psoriasis patients. On the one hand, hyperhomocysteinemia is a sign of unhealthy lifestyle, and together with such risk factors as smoking, dyslipidemia and markers of metabolic syndrome significantly increases the risk of coronary heart disease (CHD) in psoriasis [4]. On the other hand, due to the presence of a large number of dividing cells in the skin in psoriasis, huge amounts of methyl groups are consumed, which may lead to impaired homocysteine metabolism. Also, high levels of homocysteine may indicate vitamin deficiencies (folic acid - B_9, B_6, B_{12}), impaired renal function [1, 22]. At the same time, some medications used in the treatment of psoriasis (methotrexate, methylprednisolone), among others, contribute to an increase in blood homocysteine levels, apparently due to their antimetabolic effect on folic acid.

Numerous studies have confirmed the pathophysiological link between psoriasis and obesity. Adipocytes are known to be the predominant cell type in adipose tissue, secreting important hormones and signaling molecules such as adipokines. At the same time, adipokines can mediate cutaneous inflammation, suggesting a role in the pathogenesis of psoriasis and the development of obesity. In obesity, adipocytes produce increased amounts of proinflammatory adipokines, while the production of this class of anti-inflammatory molecules is reduced. Cytokines characteristic of psoriasis, such as TNF-b, IL-1c, and IL-6, affect adipose tissue by participating in key mechanisms of triglyceride (TG) metabolism and preadipocyte differentiation, including an increased risk of obesity. Secreted adipokines such as leptin, chemerin, retinol-binding protein 4 (RBP4), visfatin, fetuin-A, apelin-36, and lipocalin-2 may enhance the immune response and contribute to immune-mediated disease through their proinflammatory effects; however, adiponectin and omentin show anti-inflammatory effects, but their levels are significantly reduced in obese patients.

In obesity, the hormone leptin plays a key role in the pathogenesis. Numerous studies have demonstrated that plasma leptin levels are elevated in both obese and psoriasis patients, and elevated concentrations correlate positively with body mass index (BMI) and psoriasis area and severity index (PASI) scores, indicating a common important role for leptin in psoriasis and obesity. Indeed, several meta-analyses evaluated circulating concentrations of important adipokines and found that leptin concentrations were significantly higher in patients with psoriasis and without obesity [33, 51], indicating that increased leptin levels in patients with psoriasis may come not only from adipocytes but also from keratinocytes and endothelial cells [26].

It is recognized that obesity is a risk factor for psoriasis, exacerbates existing psoriasis, and that weight reduction can reduce the severity of psoriasis in overweight people [25, 35].

Impaired lipid metabolism is considered an important hallmark in the etiology and pathogenesis of psoriasis. S. Srinivas et al (2019) studied plasma lipid profiles and cardiovascular risk markers in 200 people, among whom 100 patients had psoriasis. The results of the studies revealed a significant increase in lipid profile parameters, cardiovascular risk and atherogenicity index in psoriasis patients compared to the control group [8].

Al Harthi F et al (2014) found that Saudi Arabian psoriasis patients had significantly higher serum cholesterol, triglyceride, and LDL levels compared with controls. The lipid profile results confirm that psoriasis is one of the independent risk factors for hyperlipidemia and emphasize the need for cardiovascular disease screening in patients with psoriasis [9].

In the studies of G. B. Huraib et al (2019) found that106 patients with Saudi Arabian psoriasis vulgaris had significantly elevated body mass index, fasting glucose, total cholesterol, low-density lipoproteins, triglycerides, and C-reactive protein, known markers of cardiovascular disease, compared with controls [30].

In recent years, several studies have shown that nonalcoholic fatty liver disease (NAFLD) is common in patients with psoriasis [37]. The term NAFLD encompasses a wide range of liver lesions, from simple fatty hepatosis to nonalcoholic steatohepatitis (NASH), including various degrees of liver fibrosis, cirrhosis, and even hepatocellular carcinoma [28, 59]. The global prevalence of NAFLD in the general population is estimated at 25% [18], and it is currently one of the leading causes of liver cirrhosis and liver transplantation [32]. NAFLD is now a growing epidemic, partly because of obesity, insulin resistance, and metabolic syndrome [5], but also because of psoriasis [58]. Strikingly, the same comorbidities, especially those associated with metabolic abnormalities that may contribute to hepatic steatosis, have been associated with systemic inflammation in psoriasis. Moreover, specific proinflammatory mediators have been shown to cause a chronic inflammatory state in NAFLD, psoriasis, and the metabolic syndrome [36, 50]. This similarity may indicate a related pathogenesis between psoriasis and NAFLD with potentially increased risk of progressive liver disease [5]. The prevalence of NAFLD in patients with psoriasis is high and is associated with a higher prevalence of metabolic syndrome signs, bacterial translocation, and a higher proinflammatory state.

Clinical manifestations of comorbidity in psoriasis.

Based on the data presented above on the molecular mechanisms of comorbidity formation in psoriasis, the clinical associations are understandable.

There is now accumulating evidence proving comorbid associations of psoriasis with type 2 diabetes mellitus (DM2) [41, 44], the metabolic syndrome and its components: arterial hypertension [23], obesity [34, 35]; cardiovascular disease [40, 43] and other pathologies.

Similar to plaque psoriasis [52, 57], pustular psoriasis is associated with a metabolic syndrome, including hypertension, hyperlipidemia, diabetes, and obesity [13, 49]. A systemic body response has been revealed in psoriasis and psoriatic arthritis patients, which is manifested by unidirectional metabolic disorders and changes in the cellular composition of the blood [2].

Given these observations, there has been a paradigm shift from viewing psoriasis simply as a "skin disease" to a systemic inflammatory condition [27]. Chronic inflammation and genetic determinants appear to underlie comorbid associations.

In recent years, cardiovascular disease has been recognized as an important comorbid condition. Various epidemiological studies have reported a significantly increased risk of serious cardiovascular events such as MI, stroke [40] and venous thromboembolism (VTE) [42] in individuals with psoriasis. Studies by M.J.E. Visser et al (2021) add to the accumulating evidence about the systemic nature of psoriasis and the subsequent risk of associated cardiovascular disease, possibly due to acquired hypercoagulation. Because the processes of inflammation and coagulation are interrelated, persistent systemic inflammation may contribute to the development of a prothrombotic state in psoriasis patients. In this study, the prothrombotic state in patients with psoriasis was characterized by endothelial (elevated sICAM-1 levels) and platelet activation (elevated sP-selectin levels), hypercoagulation (TEG results) and abnormal fibrin deposition (SEM analysis) [47].

Wolska A et al. (2014) found histological similarity between psoriatic and atherosclerotic plaques. Both plaques have increased levels of activated Th1 and T helper lymphocytes type 17 (Th17), which cause inflammation in various tissues [29].

An imbalance of gut microorganisms (dysbiosis) has important functional consequences and is associated with many digestive diseases, as well as with diabetes, obesity, metabolic syndrome, psoriatic arthritis, celiac disease, psychiatric disorders and other diseases [12, 24, 54, 55].

There is ample evidence that intestinal dysbiosis is a possible cause of chronic skin inflammation, particularly psoriasis [16, 20, 21, 48].

Thus, in recent years, the study of the metabolic profile has become increasingly important in the diagnosis of psoriasis as a systemic disease, since certain metabolites can influence the mechanisms of psoriasis formation. Systematic study of metabolic parameters can lead to better understanding of the pathogenesis of psoriasis and eventually to the development of new methods of treatment and diagnostics.

Prospects for therapy of psoriasis with comorbid diseases.

On the basis of the above, new perspectives open up for the treatment of psoriasis in relation to comorbid conditions.

Given the commonality of the pathophysiological processes of psoriasis with comorbid conditions, it becomes possible, on the one hand, to avoid polypragmasy and reduce the toxic load on the body and, on the other hand, to develop maximum targeted therapy in several directions at once. In particular, it has been shown that the use of an insulin stimulator (glucagon-like peptide 1 - GLP-1) can improve the course of psoriasis by emphasizing the effect of insulin resistance in inflammation [38, 45].

There is evidence in the literature that treatment with IL-17A monoclonal antibodies can not only improve psoriatic lesions but also restore impaired lipid metabolism to normal levels in psoriasis patients. Given that impaired regulation of lipid metabolism is considered a critical factor in cardiovascular disease, restoration of lipid metabolites in psoriasis patients indicates that IL-17A monoclonal antibodies may have a potential protective effect against associated cardiovascular disease.

An important direction in the treatment of psoriasis in association with comorbid conditions is lifestyle modification, avoidance of bad habits, and normalization of body weight as significant factors influencing the intensification of systemic inflammation.

It is important to evaluate patients with psoriasis from both a dermatological and a metabolic perspective. The complex interaction of psoriasis with various comorbidities suggests the need for a multidisciplinary approach in the management of psoriasis patients.

Conclusion. Thus, the review of the literature shows that the study of the pathogenesis of psoriasis is still relevant. Currently, there is accumulated data proving comorbid associations of psoriasis with metabolic syndrome, cardiovascular diseases, intestinal dysbiosis and other pathologies. Given these observations, there has been a paradigm shift from viewing psoriasis simply as a "skin disease" to a systemic inflammatory condition. Chronic inflammation and genetic determinants, underlie comorbid associations.

Promising in understanding the causes and diagnosis of psoriasis is a comprehensive study of general metabolic indices and immunoregulatory messengers, which will not only expand our understanding of the mechanisms of psoriasis formation, but also develop a comprehensive pathogenetic therapy with the correction of immune and metabolic disturbances in patients. Analysis of scientific information shows that the systemic nature of psoriasis suggests a personalized approach to its diagnosis and treatment, taking into account comorbid (concomitant) conditions.

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