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COMORBID CONDITIONS IN PSORIASIS

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Psoriasis is a chronic dermatosis of a multifactorial nature with a dominant role in the development of genetic factors, characterized by hyperproliferation of epidermal cells, impaired keratinization, and inflammation in the dermis. Currently, its prevalence in the population is from 0.1 to 7%, and among people hospitalized in dermatological hospitals – from 25 to 40%.

In the scientific literature, the issue of considering psoriasis as a systemic disease is widely discussed, which includes damage not only to the skin, but also to other organs and systems.

Thus, the indicated problems of combined pathology are relevant, require further in-depth study and search for evidence-based solutions that will improve the quality of medical care for patients with both psoriasis alone and its combined course.

Keywords: *psoriasis, comorbidity, combined pathology, cardiovascular diseases, endocrine pathology, gout, inflammatory bowel diseases.*

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Introduction

Psoriasis is a chronic proliferative and inflammatory condition of the skin, which characterized by erythematous plaques covered with silvery or white scales, commonly over the scalp, and extensors of extremity, particularly over knees, elbows, and lumbosacral region [1].

Psoriasis affects 1.5-3% of the population in Europe and North America, but it less common in Africa and Japan. In Belarus psoriasis affects about 4% the population.

Several factors trigger psoriasis, including genetic variants, infection (Streptococcal tonsillitis), wound, obesity, stress, and drugs (lithium, interleukin II, interferon, beta-blockers, anti-malarial, non-steroidal anti-inflammatory drugs), alcohol and smoking and also ultraviolet radiation.

Psoriasis can be considered as a multifactorial disorder, influenced by both genetic and environmental factors. Its genetic basis has long been established through twin studies and familial clustering. Human leukocyte antigens (HLA) types usually associated with psoriasis are HLA-B13, -B37, -B57, and, specifically, HLA-Cw6, which is a candidate upon functional involvement. The association of psoriasis in relation with the HLA-Cw6 allele has been shown in many studies. Recent genome-broad association studies have identified a large number of other genes associated to psoriasis. All most all of these genes regulate the innate as well as adaptive immune system. These discoveries indicate that a dysregulated immune system may play a major role in the process of pathogenesis of psoriasis. [2, 3].

Early upstream events in psoriasis involve the innate immune activation of skin resident keratinocytes or fibroblasts or recruited plasmacytoid dendritic cells (pDCs) or neutrophils. Cytokines derived from these innate immune cells promote myeloid dendritic cell maturation, with consequent Th17. T cell development and the beginning of the adaptive immune phase. T cell infiltrate promotes inflammatory amplification of innate immune cells, leading to the formation of an autoimmune self-amplifying loop that drives pathogenic hyperproliferation of keratinocytes and manifestations of psoriasis (figure 1) [4].

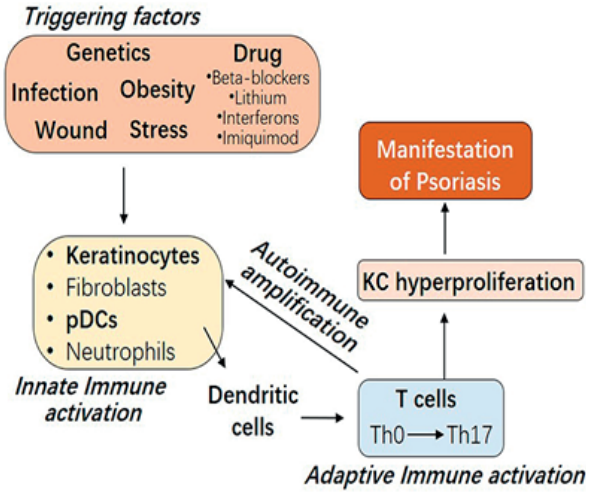

Figure 1. – Causes of psoriasis [4]
Рисунок 1. – Причины псориаза [4]

It is possible to identify various subtypes of psoriasis but the plaque type is the most common and presents on the trunk, extremities, and scalp. Psoriasis has no permanent cure and the disease waxes and wanes with flareups.

Generally, Plaque psoriasis comes up as erythematous plaques with silvery scales most commonly over extensors of extremities and it is the most common type of psoriasis which affects 85% to 90% of patients [5].

Guttate psoriasis has another name as eruptive psoriasis is commonly seen in children after an upper respiratory tract infection with the streptococcal organism. It presents with erythematous and scaly raindrop-shaped lesions usually seen over the trunk and back. It is the type of psoriasis having the most accurate prognosis.

Pustular psoriasis is characterized with small non-infectious lesions with puss with erythema

surrounding it. Localized and generalized forms are recognized in this scenario. Generalized pustular psoriasis is associated with hypocalcemia and presents with sterile pustules on an erythematous plaque involving the whole body.

Erythrodermic psoriasis is one of the widespread inflammations in the form of erythema and exfoliation of the skin covering more than 90% of the body area. It has such symptoms like pain, severe itching and swelling. It comes as the result of an exacerbation of unstable plaque psoriasis, following the abrupt elimination of systemic steroids. Absence in barrier functions of the skin, disturbance in basal metabolic rate, and raised cutaneous circulation in turn affecting the heart with cardiac failure can be pointed out as complications of erythroderma [6, 7].

Inverse psoriasis has another clinical name as flexural psoriasis or intertriginous psoriasis. It is clinically present as smooth, erythematous, and sharply demarcated patches affecting intertriginous areas like groins, armpits, intergluteal region, and inframammary region. In certain cases, the skin will appear moist, macerated, and may contain fissures that might be malodorous, pruritic, or both.

Seborrheic psoriasis is a form of psoriasis which usually causes red plaques along with greasy scales. It significantly affects areas with elevated sebum production such as forehead, nasolabial folds, sternum, retro-auricular folds and scalp.

Psoriatic arthritis is a type of chronic inflammatory arthritis which influences on 30% of patients who have psoriasis. It commonly occurs in relation with skin and nail psoriasis. In most of the cases it takes part in painful inflammation of the joints as well as connective tissue commonly affecting the joints of the fingers and toes. It results in to formation of sausages shaped swelling of the fingers and toes which is called dactylitis. Psoriatic arthritis can also affect the hips, knees, and spine presenting as spondylitis and sacroiliac joints with sacroiliitis.

Nail alterations in psoriasis are found as pitting, oil spots, subungual hyperkeratosis, nail dystrophy, and anchyloses [8].

Ocular features: psoriasis has an impact on the eyelid, conjunctiva, and cornea which lead to trichiasis, ectropion, conjunctivitis, and corneal dryness [9].

The most frequent eye feature is blepharitis which leads to cicatricial ectropion, madrasas, and trichiasis. In certain cases, anterior uveitis may be seen too.

Fissured tongue is the most usual discovery of oral psoriasis and has been noted to occur in 6.5% to 20% of people with psoriasis with skin conditions [10].

Many patients with psoriasis develop depression as the quality of life is poor.

Psoriasis is a chronic inflammatory systemic disease. Evidence shows an association of psoriasis with arthritis, depression, inflammatory bowel disease and cardiovascular diseases. Recently, several other comorbid conditions have been proposed as related to the chronic inflammatory status of psoriasis [11].

The hypothesis of a causative role of psoriasis in its cardiovascular and metabolic comorbidities is based on pathophysiologic concepts establishing a link between chronic inflammation in psoriasis, endothelial dysfunction, formation of atherosclerotic plaques, and the different compounds of metabolic syndrome [12].

As dermatologists are the primary health-care providers for psoriasis, adequate knowledge of comorbidities helps in choosing the appropriate therapy as well as timely intervention [13]. Important comorbidities are psoriatic arthritis, metabolic syndrome, Crohn's disease, depression, and cancer (figure 2) [14].

Inflammatory bowel disease (Crohn's disease, ulcerative colitis) and psoriasis

Inflammatory bowel disease, i.e., Crohn's disease and ulcerative colitis, arise due to unsuitable immune response upon commensal microorganisms in individuals with genetic predispositions. A review of literature represented three potential epidemiologic links between Inflammatory bowel disease and psoriasis [15].

Several researches done across the world claims that individuals with Inflammatory bowel disease and their associates are predisposed to the progression of psoriatic lesions to a significantly larger extent than subjects from the general population, and the incidence of psoriasis in the previous group can be even up to fivefold greater [16].

On the other hand, in the case of psoriasis the inverse phenomenon has been recognized, i.e., higher incidence of inflammatory bowel disease in psoriatic. Available evidence implies that the risk of Crohn's disease and ulcerative colitis during the course of psoriasis is greater than twofold and nearly two times higher than in the general population, respectively, also after exclusion of patients who are treated by anti-tumor necrosis factor (TNF) agents [17].

Moreover, some studies have shown that in spite of the lack of clinical abnormalities, psoriatic patients may come up with microscopic evidence of intestinal inflammation and elevated levels of perinuclear anti-neutrophil cytoplasmic antibodies (pANCA), i.e., the features of a latent inflammatory bowel disease [18].

The above-mentioned associations could be at least partially explained by a common genetic background of psoriasis and inflammatory bowel disease. Several areas of chromosomes 16, 6, 4 and 3 were found to contain common genetic markers of psoriasis and inflammatory bowel disease. Aside from the main histocompatibility complex components, also a few other genes, specifically those encoding interleukin 23 receptor and interleukin 12B were implicated in the pathogenesis of both psoriasis and inflammatory bowel disease. Furthermore, both diseases share some common inflammatory pathways: Both diseases are Th1-mediated inflammatory disorders associated with enhanced synthesis of cytokines, TNF-alpha and interferon gamma [19, 20].

Celiac disease in psoriasis

Celiac disease can be considered as an autoimmune condition triggered by ingestion of gluten in genetically predisposed individuals. The

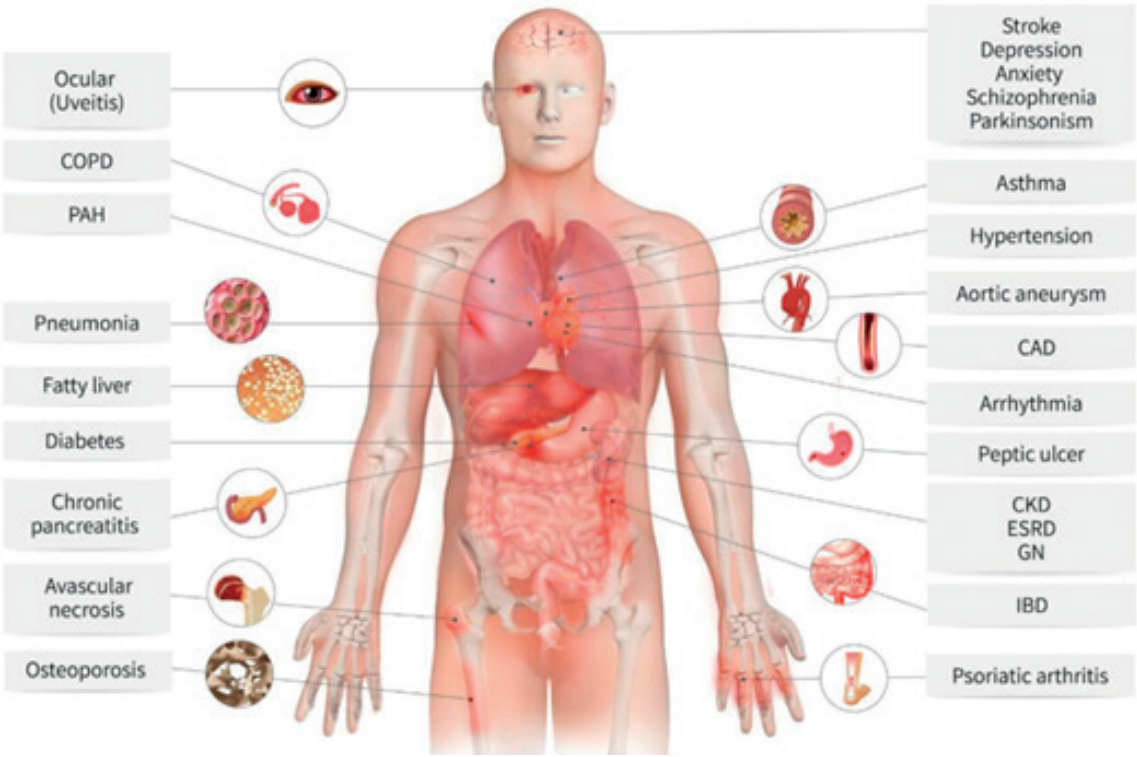

Figure 2. – Comorbidity of psoriasis. CAD – coronary artery disease; CKD – chronic kidney disease; COPD – chronic obstructive pulmonary disease; ESRD – end-stage renal disease; GN – glomerulonephritis; IBD – inflammatory bowel disease; PAH – pulmonary arterial hypertension [14]

Рисунок 2. – Коморбидность псориаза. ИБС – ишемическая болезнь сердца; ХБП – хроническая болезнь почек; ХОБЛ – хроническая обструктивная болезнь легких; ЭСРД – терминальная стадия почечной недостаточности; ГН – гломерулонефрит; ВЗК – воспалительное заболевание кишечника; ЛАГ – легочная артериальная гипертензия [14]

entity of celiac disease – specific antibodies were also reported in subjects with psoriasis and other autoimmune and inflammatory conditions like systemic lupus erythematosus, rheumatoid arthritis and Sjogren's syndrome [21].

Specifically, the level of these antibodies was shown to correlate with the severity of psoriasis. Except this serological evidence, also epidemiologic links between psoriasis and celiac disease have been documented.

On the other hand, large nationwide study demonstrated that subjects with celiac disease are at increased risk of psoriasis both before and after the diagnosis of gluten intolerance [22].

The association between celiac disease and psoriasis can be sorted out by several mechanisms. First, lack of absorption is associated with celiac disease might predispose to vitamin D deficiency; also, gluten-free diet used in the treatment of celiac disease is often deficient, regarding in this vitamin [23].

Second, although celiac disease is typically associated with Th2 response, also Th1 and Th17 cells, i.e., the lymphocyte subpopulations involved in the development of psoriasis, play an important role in the pathogenesis of this condition. Third, also a common genetic background may describe the link between psoriasis and celiac disease. The fourth implicated mechanism may be associated with an increase in the intestinal permeability, a characteristic feature of celiac disease that has been also found in some psoriasis [24, 25].

Non alchoholic fatty liver disease in psoriasis

Non-alcoholic fatty liver disease can be pointed out as a heterogeneous condition including both relatively benign simple fatty liver and severe non-alcoholic steatohepatitis. Non-alcoholic fatty liver disease is diagnosed in 20-30% of individuals from the general population, and represents an established cardiovascular risk factor and a very usual manifestation of the metabolic syndrome also usually coexists with insulin resistance [26].

The enteropathogenic link between psoriasis and non-alcoholic fatty liver disease is not straightforward, as recently both these entities have been increasingly recognized as systemic conditions. Some pro-inflammatory cytokines synthesized by lymphocytes and keratinocytes in psoriatic skin, including interleukin-6, interleukin-17 and TNF-alpha, may contribute to systemic insulin resistance, a common feature of non-alcoholic fatty liver disease [27, 28].

Cardiovascular complications in relation with psoriasis

Certain studies have also investigated the context between the severity of psoriasis and the risk of cardiovascular complications [29].

Previous studies have shown that mortality rates are increased in psoriasis patients compared to healthy controls, and the life expectancy of patients with moderate to severe psoriasis is decreased by approximately 5 years, mainly due to cardiovascular comorbidities. Furthermore, the

presence of cardiovascular comorbidities in patients elevated economic and healthcare burden are greatly associated with arising psoriasis cases [30].

A significant number of epidemiological studies conducted in various countries have shown that psoriasis is significantly related with the increased prevalence of cardiovascular diseases. A large-scale population-based epidemiological study performed in the UK using the General Practice Research Database represented that the risk of myocardial infarction is increased in patients with psoriasis. Moreover, there was a close relationship between the risk of myocardial infarction and psoriasis disease severity [31].

Moreover, patients with psoriasis were shown to have an increased risk of developing cerebrovascular disease (stroke), which correlates with the severity of psoriasis disease. A meta-analysis done recently has found that the risk of stroke (expressed in terms of the hazard ratio) was 1.10 and 1.38 for mild and severe psoriasis, respectively, and the risk of myocardial infarction (expressed in terms of the hazard ratio) was 1.20 and 1.70 for mild and severe psoriasis, respectively [32].

Atheroclerosis in psoriasis

Several studies have attempted to determine the causal relationship between psoriasis and cardiovascular disease. Atherosclerosis plays major role in pathological change preceding the development of myocardial infarction and stroke. Patients with psoriasis have been found to have increased arterial stiffness compared to healthy controls, and there is a positive correlation between arterial stiffness and psoriasis disease duration. In addition, it has been shown that improvement of psoriasis skin disease can lead to a reduction of aortic vascular inflammation [33].

Coronary artery atherosclerosis is a crucial risk factor for ischemic heart disease. Several studies have found that patients with psoriasis have in raised prevalence and severity of coronary artery calcification and atherosclerosis (measured by cardiac computed tomography, coronary computed tomography angiography, or coronary angiography) compared to healthy controls. On the other hand, a subsiding in psoriasis disease severity has been found to be associated with a development in coronary atherosclerosis. The progression of coronary atherosclerosis in psoriasis patients may be partially associated to collapsed cholesterol efflux capacity from macrophages [34].

Atherosclerosis of the carotid artery is taken into account as a risk factor for the development of cerebrovascular disease. Using carotid artery ultrasound, many studies have demonstrated that patients with psoriasis have higher carotid intima-media thickness compared to healthy controls, indicating carotid atherosclerosis. The severity of skin disease has been found to correlate with carotid intima-media thickness values [35].

Hypertension in psoriasis

Several studies have shown significant contexts between psoriasis and the prevalence of hypertension. A meta-analysis found elevated the entity of hypertension in psoriasis patients, with odds ratios of 1.30 for mild psoriasis and 1.49 for severe psoriasis. Patients with psoriasis were also found to have greater risk of uncontrolled high blood pressure, and the risk associates with the severity of psoriasis [36].

In addition, the presence of hypertension may increase the risk of incident psoriasis. In the Nurses' Health Study involving 77,728 women, patients with hypertension were found to have a greater risk of developing psoriasis. This may be associated with the use of beta- blockers to treat hypertension [37].

Gout in relation with psoriasis

The major outcome of this study was the presence of gout in the psoriasis and non-psoriasis cohorts. Gout was considered as the entity of minimum three outpatient claims or one inpatient claim based on the ICD- 9-CM code 274. Both groups were followed until the onset of gout, withdrawal from the national insurance system, or December 31, 2013, whichever occurred initially. Since the context between gout and psoriasis may be confounded by multiple concurrent diseases, we recognized the illustrated comorbidities considering the ICD-9-CM diagnostic codes: hypertension (401–405), hyperlipidemia (272.0–272.4), diabetes mellitus (250.x), obesity (278.0), chronic liver disease (571), chronic renal disease (585), chronic obstructive pulmonary disease ([COPD] 491, 492, 496), and autoimmune disease (710.x, 714.x, 720.x). Diffuse diseases of the connective tissue (710.x), rheumatoid arthritis and other inflammatory polyarthritis (714.x), and ankylosing spondylitis and other inflammatory spondylopathies (720.x) were considered as autoimmune diseases. These comorbidities were taken into account if they were diagnosed one year before the entry date. Moreover, nonsteroidal anti-inflammatory drugs usage was considered when they had been used for ≥ 30 days [38].

Endocrine complications in psoriasis

The hormones make a great impact on the severity of psoriasis clinical manifestations. This fact is indicated by the disease frequency peaks during puberty and menopause, besides the peaks around the age of 30 and 50 years. Hence, the hormonal variances, major alterations and the hormonal diseases could represent risk, triggering or modulating factors in the evolution of psoriasis [39].

Sex hormones in psoriasis

Estrogens particularly affect the immune responses, modulating the development and activation of immune cells, via the influence and control exerted upon the expression of different cytokines [40].

In vitro and in vivo studies demonstrated the anti-inflammatory effects of estrogens: they drop down the neutrophil's blood level and keratinocytes production of some macrophage-attracting cytokines, and they elevate the production of interleukin-10 by B lymphocytes and dendritic cells. Those estrogens influence may also reduce the psoriatic inflammation. Other influences of estrogens is the reduction of matrix metalloproteinase activity

in fibroblasts, which drops down the destruction of extracellular matrix and the release of factors that aid growth, another pathogenic psoriatic link [41].

The effects of estrogen are differently modulated by estrogens receptor-α (ER-α) and β (ER-β). Among negative effects of estrogens in psoriasis, some should be mentioned: the reduction of apoptosis and the stimulation of proliferation at keratinocyte level, the stimulation of growth factors production in macrophages, keratinocytes and fibroblasts, which could stimulate the development of neovascularization, a pathogenic way in psoriasis. At the same time, Progesterone, which is a usually indicated drug, can precipitate some forms of psoriasis [42].

Pregnancy

Extremely high levels of hormonal and immunological changes occur during pregnancy, as maternal adaptations to the developing fetus [43].

The evolution of psoriasis is variable during pregnancy. At mid pregnancy (around 30th week of gestation), the patients' psoriatic symptoms can diminish (in >50%) or worsening (in >20%). A comprehensible explanation could be that at this moment, there is an immunity moves from Th2 to Th1, mainly due to the increased levels of estrogen, progesterone and cortisol [44].

Other chronic immune diseases Th1-driven were shown to progress during pregnancy, such as multiple sclerosis and rheumatoid arthritis. Therefore, it was proclaimed that the increased hormone levels improve the psoriatic symptoms [45].

Menopause

During menopause, the estrogen level drops down and a low-grade inflammation may appear, meaning that menopause may aggravate the psoriasis evolution. This fact is in concordance with the observation that after menopause the chance of having chronic inflammatory diseases in women became closer or greater than the incidence in males [46].

Androgens

Androgen receptors express the epidermis, dermis and hair follicle and the associated sebaceous glands androgen receptors, and the skin is an important androgen target. Androgen hormones affect the homeostasis of the epidermal barrier, the development and of the hair and the sebaceous gland. They also antagonize the macrophage's production of vascular endothelial growth factor, which can elongate the inflammation and the wound healing. The adrenal androgens decrease in chronic inflammatory diseases and the therapies based on androgen can aggravate/exacerbate psoriasis [47].

Stress hormones and exercises

Both endocrine and immune reactions are highly influenced by stress. The hypothalamic-pituitary-suprarenal axis modulates the stress hormones, cortisol and epinephrine, which are antagonists and have important effects on immune system [48].

Immune cells (macrophages, lymphocytes T and B) express beta-adrenergic receptor and epinephrine induces multiple but dual immune responses: triggers macrophages responses through increasing secretion of cytokines TNF-α, interleukin-1, interleukin-10, and regulates the level of T- and B-lymphocyte function. Also, it has been proposed that an acute activation of the sympathetic nervous system attenuates the innate immune response [49].

The immunomodulation in stress takes place at intersections in signaling cascade at various levels: for example, stress signals in immune response are modulated via the key Nuclear Factor-kappa and the epinephrine stimulation of β2-adrenergic receptors, expressed on immune cells, interact with the Nuclear Factor-kappa signaling cascade [50].

Thus, the indicated problems of combined pathology are relevant, require further in-depth study and search for evidence-based solutions that will improve the quality of medical care for patients with both psoriasis alone and its combined course.

Further study will lead to a change in understanding of the key approaches to the diagnosis and treatment of comorbidity. Due to the frequent association of psoriasis with lesions of other organs and systems, an interdisciplinary approach should be sought, with coordination between dermatologists and other specialists, which will lead to improved standards for the diagnosis and treatment of patients suffering from this pathology. In this regard, the problem of psoriasis and associated diseases is relevant and requires further study in this direction.

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КОМОРБИДНЫЕ СОСТОЯНИЯ ПРИ ПСОРИАЗЕ

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Псориаз – хронический дерматоз многофакторного характера с доминирующей ролью в развитии генетических факторов, характеризующийся гиперпролиферацией клеток эпидермиса, нарушением ороговения, воспалением в дерме. В настоящее время распространенность данного дерматоза среди населения составляет от 0,1 до 7%, а среди людей, госпитализированных в дерматологические стационары – от 25 до 40%.

В научной литературе широко обсуждается вопрос рассмотрения псориаза как системного заболевания, которое включает повреждение не только кожи, но и других органов и систем.

Таким образом, указанные проблемы сочетанной патологии актуальны, требуют дальнейшего углубленного изучения и поиска доказательных решений, которые позволят повысить качество медицинской помощи пациентам как только с псориазом, так и с его комбинированным течением.

Ключевые слова: *псориаз, сопутствующие заболевания, комбинированная патология, сердечно-сосудистые заболевания, эндокринная патология, подагра, воспалительные заболевания кишечника.*

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