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Cardiovascular risk in patients with selected cutaneous diseases

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Abstract

Introduction and purpose: Cardiovascular diseases are the leading cause of death worldwide. The classic cardiovascular risk factors include age, gender, obesity, diabetes, hypertension, dyslipidemia, smoking and genetic factors. Some dermatological disorders are also potential risk factors for the development of cardiovascular diseases. The aim of the

study is to review recent knowledge on the impact of dermatological diseases on cardiovascular risk.
Description of the state of knowledge: The relationship between skin diseases and cardiovascular risk is influenced by various common dependencies such as: shared pathophysiological basis of disorders, risk factors, presence of a chronic inflammatory process, genetic susceptibility and environmental influences. Increased cardiovascular risk has been reported for several dermatological conditions, including psoriasis, systemic lupus erythematosus, systemic sclerosis, pemphigus, hidradenitis suppurativa, rosacea, atopic dermatitis and many others. Chronic systemic inflammation, typically present in many skin conditions, is a cardiovascular risk factor, because inflammation accelerates atherosclerosis, and furthermore may predispose patients to the development of metabolic syndrome, insulin resistance and diabetes mellitus, thus contributing to the overall increased cardiovascular disease incidence. In patients who are initially metabolically unbalanced, these processes may be even more intense. Cardiovascular disorders, the frequency of which increases in patients with skin diseases, include atherosclerosis, coronary artery disease, ischemic heart disease, cardiac dysfunction, arrhythmias, heart failure, cerebrovascular disease (stroke, TIA) and peripheral arterial disease.
Summary: Many cutaneous disorders, in addition to significantly increasing cardiovascular morbidity and mortality, also reduce the patient's quality of life. The cooperation of dermatologists and cardiologists in the care of patients with dermatological diseases is crucial for the proper treatment of the disease and prevention of cardiovascular complications.

Introduction

Cardiovascular disease (CVD) has been the leading cause of premature mortality worldwide for many years. According to estimates, it is assumed that by 2030 about 23.6 million people will be dying a year because of them. CVD causes 49% of mortality in Europe, and the annual cost of healthcare for CVD in the European Union is approximately EUR 192 billion. CVD is a chronic disease that develops throughout life and is asymptomatic for a long time. They are caused by many factors, such as sex, genes, age, smoking, lack of physical activity, improper diet, hypertension, diabetes, obesity and dyslipidemia [1]. These are common factors that increase cardiovascular risk.

There are a number of dermatological diseases associated to varying degrees with higher cardiovascular risk, sharing features with atherosclerosis. Psoriasis and systemic lupus erythematosus are diseases included in the guidelines for the prevention of cardiovascular diseases. Regarding other diseases, such as scleroderma, sarcoidosis, atopic dermatitis, inverted acne, rosacea and pemphigus, there are also more and more reports about their influence on increasing cardiovascular risk. Chronic inflammatory diseases have been shown to play a particular role in increasing cardiovascular risk. Among such disorders there are many dermatological diseases. [2]

The purpose of this review is to summarize the available information on the cardiovascular risk of selected dermatological diseases in the existing literature.

Psoriasis

Psoriasis is a non-infectious, chronic and systemic inflammatory disease characterized by the formation of specific skin lesions resulting from hyperkeratosis of the epidermis. The mechanism of its formation involves complex pathogenic reactions between the innate and adaptive immune systems. Psoriasis affects about 2% of the population. People suffering from psoriasis have a greater risk of developing many other chronic diseases, including cardiovascular disorders [3].

Several mechanisms may be responsible for the increased incidence of cardiovascular events in psoriasis patients. The presence of generalized inflammation along with metabolic disorders may lead to an increased cardiovascular risk [4].

In psoriasis, there is an increased activation of T lymphocytes, platelets, bone marrow cells and an increase in the level of interferon, tumor necrosis factor alpha (TNFα) and interleukins: IL-6, IL-17, IL-23, which are responsible for the development of atherosclerosis and vasculitis. It is estimated that people with psoriasis increase the risk of cardiovascular disease by up to 50% [5,6].

Additionally, traditional risk factors increase in patients with psoriasis. Patients with diabetes who have additional psoriasis are more likely to develop vascular complications of diabetes than patients with diabetes alone. Hypertension is the next risk factor. It is assumed that with more severe skin disease the likelihood of poorly controlled high blood pressure increases, irrespective of other risk factors. Then obesity is an independent risk factor for psoriasis. In combination with a large mass of abdominal fat, it leads to an increased risk of psoriasis. Smoking is also associated with an increased risk of psoriasis, as well as the severity of existing symptoms. There is also a relationship between the occurrence of psoriasis and depression, which may be important in terms of cardiovascular risk. Depression in patients with psoriasis causes an increased risk of stroke, heart attack and cardiovascular death [3,4].

In a study by Prodanovich et al. In a group of 3,236 patients with psoriasis, a higher incidence of traditional cardiovascular risk factors was observed compared to the control group. Additionally, a relationship between psoriasis and atherosclerosis, and consequently with diseases of the cerebral vessels and peripheral arteries, was noted [7].

In a study by Ahlehoff et al., it was observed that the presence of psoriasis worsened the prognosis of patients who had experienced a myocardial infarction [8].

A study by Mahiques-Santos et al. showed a relationship between the presence of psoriasis and the occurrence of coronary artery disease (CAD) ($p < 0.0029$). The presence of psoriasis increased the likelihood of CAD 1.17 times [9].

Also, studies by Shib et al. On a group of 113,065 patients in Japan showed that psoriasis is an independent risk factor for coronary artery disease [10].

Systemic lupus erythematosus

Lupus erythematosus (LE) is a chronic, autoimmune, inflammatory, multisystem disorder, which clinical manifestations can be restricted to the skin (CLE - cutaneous lupus erythematosus) or may involve many organs (SLE - systemic lupus erythematosus). The clinical picture of this disease is very heterogeneous [11].

SLE is an important risk factor for increased cardiovascular morbidity and mortality. Cardiovascular-related mortality observed in SLE patients is significantly higher than those

prognosed from Framingham 10 year prediction model. [12,15]. Therefore, mortality in SLE is associated with cardiovascular disease on the one hand, but also disease activity and infections on the other. Pathophysiological mechanisms associated with increased CVD incidence relate to pathologic processes like accelerated atherosclerosis, arteritis, vasospasm, thromboembolism and abnormal coronary flow [11,13]. It was noted that patients with SLE develop premature atherosclerosis and vascular injury [13,14,15].

Commonly, SLA patients present traditional cardiovascular risk factors such as diabetes mellitus, hypertension, dyslipidemia, central obesity, insulin resistance, smoking, hyperhomocysteinemia. However, due to the particularly high incidence of cardiovascular events in SLA patients, lupus is now considered an independent risk factor for the development of cardiovascular disease [11,12,13]. Thus, cardiovascular risk in the context of SLA patients can be considered as an increased incidence of traditional cardiovascular risk factors and also lupus specific factors.

The lupus specific factors include accelerated inflammation, overproduction of pro-inflammatory cytokines, endothelial dysfunction, vasospasm, vasculitis, homocysteinemia, oxidative stress, altered fatty acid metabolism in adipocytes, antiphospholipid antibodies, renal disease and proteinuria. Disease related features that contribute to lupus related atherosclerosis also include such variables as demographics, clinical manifestation, psychosocial factors, medications, genetics, immunological mechanisms. All these factors increase the risk of atherosclerosis and thrombosis. [11,13,16,17,20].

The cardiovascular risk in SLA patients is influenced by the chronic organ damage, activity and duration of the disease, the frequency of exacerbations, the type of treatment used, genetic predisposition, psychosocial and environmental factors [11,12,20].

Immunological mechanisms enhancing the atherogenesis process include endothelial insults with deposition of oxidized low-density lipoprotein (oxLDL), presence of anti-phospholipid autoantibodies, overproduction of type I IFNs, and neutrophil extracellular traps (NETs). The inflammatory cascade results from the overproduction of chemokines and proinflammatory cytokines (including MCP-1, IL-8, TNFa and IL-6), adhesion molecules (VCAM-1, ICAM-1, E-selectin) leading to the recruitment of T cells, monocytes and dendritic cells. In a further step monocytes differentiate into macrophages, which phagocyte oxLDL and become foam cells. Inflammatory macrophages are crucial to all stages of the pathogenesis of plaque formation [11,20].

In the study of 498 patients by Manzi s et al., it was noticed that 35-44-year-old women suffering from lupus had a 50 times higher risk of myocardial infarction than healthy individuals. In addition, cardiovascular events occurred more frequently in this group of women in the case of late onset and longer duration of the lupus, early onset of menopause, long steroid therapy and hypercholesterolemia [15].

Over 50% of SLE patients develop heart disease during their lifetime. SLE increases the risk of: coronary artery disease, endocarditis, myocarditis, cardiomyopathy, pericarditis, pericardial effusion and tamponade, cardiac arrhythmias (tachyarrhythmias and bradyarrhythmias), peripheral vascular disease, cerebrovascular accident, venous thromboembolism [13]. Ischemic heart disease in SLE patients occurs at a frequency of 3.8-16%. The risk of myocardial infarction is higher in women. Also the risk of stroke is 2-8x higher in SLE patients [11].

The type of treatment administered to patients also plays a role in their risk. Manzi et al. demonstrated a relationship between the duration of corticotherapy and an increased incidence of myocardial infarction and angina [13]. Whereas Tektonidou et al. showed that higher cumulative doses of steroids intensify carotid plaque formation [18]. Azathioprine will also increase the cardiovascular ratio and formation of carotid plaques. In contrast, drugs with a potentially atheroprotective effect include cyclophosphamide, cyclosporine, hydroxychloroquine and mycophenolate mofetil [19,20]. Antimalarials are commonly used in SLE treatment. These drugs have a beneficial influence on lipid metabolism, lower the risk of metabolic syndrome, reduce the inflammatory processes involved in atherogenesis, reduce plaque formation and carotid/femoral arterial stiffness [11].

In SLE, cardiovascular risk is a fundamental cause of morbidity and mortality in these patients. Due to the complex relationship between cardiovascular risk and SLE, it is so important to monitor and care for cardiovascular health of lupus patients. One of the potential possibilities is control of standard Framingham risk factors (age, total cholesterol, HDL, smoking, systolic blood pressure) but studies have shown that it is not sufficient and requires a more complex approach [12]. As treatment strategies are getting better, mortality associated with disease activity decreases, but cardiovascular and infectious complications remain the main causes of death in lupus patients [17]. Publications on management of cardiovascular disease in patients with systemic lupus erythematosus may be helpful in patient's care [13].

Systemic sclerosis

Systemic sclerosis (SSc) belongs to the group of systemic inflammatory diseases. It is a connective tissue disease, which, depending on its form and severity, may affect the skin and visceral organs to a varying degree [2,21].

Scleroderma heart involvement (SHI) is a very frequent manifestation of the disease and has a significant prognostic value. Heart involvement may be the first sign of disease, although it is often misdiagnosed. Various pathogenic mechanisms typical for this disease, such as microvascular alterations, capillary bed damage, fibrosis secondary to collagen overproduction, possible small artery obliterative disease and complex immune system dysregulation, also occur in the heart causing its damage [2,21].

The main complications associated with cardiac involvement are: right-left ventricular dysfunction (diastolic or systolic), pulmonary hypertension, pericarditis, autonomic dysfunction, rhythm disturbances, conduction defects, angina pectoris, congestive heart failure [2,21,22]. Left ventricular systolic dysfunction is the 'hallmark' of primary systemic sclerosis myocardial involvement. The study by Aguglia G et al. showed that the risk of developing left side diastolic dysfunction is greater in patients with predisposing conditions such as systemic hypertension [22]. Congestive heart failure is rare in the natural course of SSc, but the risk is significantly increased in the presence of other cardiovascular or metabolic disorders [21]. According to the study of Deswal A et al. atherosclerotic coronary artery disease occurs in patients as often as in the general population [23].

Ferri C et al. described dysfunction in the autonomic control of heart activity in patients with scleroderma. In addition, tachycardia, lower circadian, was found to be associated with higher patient mortality risk [24,25].

One of the important causes of sudden cardiac death in patients with scleroderma are supraventricular (the most common conduction disorders) and ventricular arrhythmias (including multiform or coupled extrasystoles and runs of ventricular tachycardia), which result from progressive processes such as myocardial fibrosis, conduction system disease and autonomic cardiac neuropathy. The patients with both skeletal and cardiac muscle involvement had the worst prognosis due to severe cardiac arrhythmias [21,23,24]. Study by Roberts NK et al. showed that in patients with systemic sclerosis, cardiovascular causes (including heart attack, heart failure, and stroke) are responsible for 25% of deaths. Additionally, 26% of deaths result from the vascular complications of the disease - pulmonary hypertension and renal crisis [25].

Intensification of the disease process in patients with systemic sclerosis correlates with the severity of the disease and is a prognostic marker. The extent of skin lesions is an important prognostic factor, because it has been noted by Ferri C et al., that a widespread cutaneous scleroderma correlates with a worse prognosis for patients. The negative prognostic parameters include male gender, diffuse cutaneous involvement, multiple organ damage and serum anti-Sc170 antibodies. Also involvement of one or more visceral organs (mainly lung, heart or kidney) worsens the prognosis. Patients with limited scleroderma have generally better prognosis compared to diffuse variant [21,27].

Multiple studies show that an appropriate treatment of scleroderma-related cardiac disorders improves patients' prognosis and should always be considered when diagnosed.

Pemphigus

Pemphigus is a rare disease characterized by blistering of the skin and mucous membranes. The pathogenesis of the disease is of an autoimmune origin. It is based on the production of IgG autoantibodies against the proteins of desmosomes, which are present in the structures that connect cells. The effect is to alter the integrity of the desmosome and reduce the mechanical stability of the epidermis and mucous membranes. There is acantholysis, blisters and erosions. We can distinguish three types of pemphigus: ordinary, deciduous and paraneoplastic. Pemphigus vulgaris is the most common (70%) and the most severe. In the course of pemphigus, other organs apart from the skin may be affected. Involvement of the kidneys and / or the cardiovascular system is observed in patients with deciduous pemphigus. Antigenic mimicry between cardiomyocytes and the basal membrane zone is considered the most likely cause of heart involvement in this disease. Unfortunately, there is currently a limited amount of research confirming heart involvement in pemphigus [28].

A study by Abreu-Velez et al. Showed heart rhythm abnormalities in patients with endemic pemphigus in the town of El Bagre in Colombia. They had a significantly increased incidence of sinus bradycardia, including the left bundle branch block. Additionally, the immunohistochemical tests showed the presence of antibodies in adjacent junctions in the nodal cells, the cardiac conduction system and His bundle [29].

In a study by Shahidi-Dadras et al., Cardiac function was assessed in patients with pemphigus vulgaris before and after pulse steroid therapy. Using the Global longitudinal strain (GLS) measurement, it was shown that the use of pulse therapy with corticosteroids in pemphigus had a negative effect on the heart function. Patients with pemphigus show autoreactivity to

cardiac epitopes, which may be a predisposition to the occurrence of adverse effects during treatment with steroids [30].
Frustaci et al. Presented a case of a patient with pemphigus cardiomyopathy. The diagnosis was confirmed by myocardial biopsy, which showed a lymphomononuclear infiltrate with cardiomyocyte necrosis. Infiltration of CD45RO + T lymphocytes and overexpression of TLR-4 in cardiomyocytes in the absence of viral genomes indicated inflammation of immune etiology. The evaluation of anti-cardiac antibodies and damage of intercalated disc in the electron microscope image indicate a correlation with pemphigus [28].

Hidradenitis suppurativa

Hidradenitis suppurativa (HS) is a chronic, inflammatory skin disease. The essence of the disease is purulent inflammation of the apocrine sweat glands, which leads to the formation of deeply embedded abscesses, nodules, fistulas and scars in the inguinal and axillary area, around the anus and in the nipple folds. The mechanism of HS formation has not been elucidated, but it is believed that the changes are caused by hyperkeratosis of the hair follicles within the apocrine and sebaceous glands [31]. Recent studies allow to classify HS as a systemic disease associated with several comorbidities. Most often, together with HS, metabolic disorders such as obesity or the metabolic syndrome occur. There are also reports of an increased incidence of autoimmune diseases such as spondyloarthropathies and inflammatory bowel diseases in HS. The relationship between the presence of HS and other systemic diseases may be due to the presence of common inflammatory pathways or genetic factors [32].
In a study conducted by Juhl et al., Which investigated electrocardiographic changes in the course of Hidradenitis suppurativa, it was found that the mean resting heart rate was significantly increased in the group of patients with HS [33].
The study by Egeberg et al. Showed that patients with HS had a significantly increased risk of cardiovascular disorders, and the risk of death was higher in patients with HS than in patients with severe psoriasis [34].
In a cross-sectional study by Miller et al., A significant relationship was found between the occurrence of HS and myocardial infarction ($p = 0.0152$). However, no association was found between stroke or peripheral arterial disease and HS [35].
A study by Alatas et al to determine whether HS influences the amount of epicardial fat thickness (EFT), an independent predictor of severe disease. The study showed that EFT was significantly higher in patients suffering from HS compared to the control group. Moreover, EFT increased with the severity of the disease, and the highest EFT was found in patients with the most severe disease [36].

Rosacea

Rosacea is a progressive inflammatory skin disease with a chronic course, affecting skin mainly of the central face. It occurs equally often in males and females, especially between the ages of 30-50. Typical skin lesions include: nontransient facial erythema with or without edema, inflammatory papules, pustules, telangiectasias and a tendency for facial flushing [37,38,39].

The pathogenesis of the disease is complex and not fully understood but it is believed that genetic factors, dysregulation of the innate and adaptive immune system, neurovascular dysregulation, hypertension, psychogenic factors and environmental factors (UV light, alcohol consumption, microorganisms) are involved. The diagnosis is made on the basis of the patient's clinical picture [37,38,39].

Several studies have shown an increased incidence of cardiovascular events in patients with rosacea, associated with both common pathophysiological processes and the coexistence of risk factors for cardiovascular disease. Increased cardiovascular risk is strongly associated with chronic inflammation associated with rosacea. Significantly elevated C-reactive protein (CRP) levels in these patients indicates that a chronic local skin inflammation induce systemic inflammation [39,41]. Moreover, taking tetracyclines had a protective effect against developing atherosclerosis and reduced the cardiovascular risk due to the anti-inflammatory effect of these drugs [40].

One of the other potential correlations is shown in a study of 100 patients by Hayran Y et al. - they detected the presence of vascular endothelial growth factor (VEGF) + 405C / G polymorphism in patients with rosacea, what is also the risk factor for abnormal coronary microvasculature. There is a correlation between VEGF and inflammation and vascular permeability [39,42].

Chronic inflammatory diseases, including rosacea, generally intensify the processes of atherosclerotic plaque formation. Inflammatory pathways in rosacea and atherosclerosis have connecting points including increased macrophage, mast cell infiltration and abnormal type 1,17 helper T response. These cells overproduce cytokines, induce skin inflammation and generate the development and progression of plaque. Additionally, Th-1 cells further activate macrophages, while Th-17 cells promote intraplaque neoangiogenesis and intraplaque hemorrhage [39,41]. In patients with rosacea level of cathelicidins (LL-37) is significantly elevated. These antimicrobial peptides play an important role in regulating host defense and immunity but also in the pathophysiology of atherosclerosis [39]. Furthermore, excessive gene expression of stratum corneum tryptic enzyme (SCTE), a serine protease, which increases the inflammatory effect of cathelicidin and the formation of atherosclerotic plaques, has also been described in patients, while serine protease inhibitors reduce atherosclerotic processes. [43]

Moreover, upregulation of genes related to alcohol and lipid metabolism has been shown in rosacea patients. A study of 60 participants by Duman et al., found that rosacea patients were significantly more likely to have elevated total cholesterol, LDL-C and CRP levels, a family history of premature cardiovascular disease and a history of smoking and alcohol consumption [39]. There is no association with HDL-C or triglycerides but elevated LDL-C is a risk factor for atherosclerotic cardiovascular disease. This suggests an increased incidence of common risk factors for cardiovascular disease in patients with rosacea. [38,39].

Atopic dermatitis

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease. Its incidence in the US is 11.3-12.7% in adults and 6.9-7.6% in children. The pathophysiology of AD is not fully understood, but numerous studies have shown that skin barrier dysfunction, immune system disorders, and genetic predisposition are largely responsible for the occurrence of AD.

In addition, the defects of key epidermal proteins (filaggrin, transglutaminase, keratin, intracellular proteins) lead to the penetration of pathogens deep into the skin [44]. Patients with AD can suffer from a variety of comorbidities which interact with each other.
In a cross-sectional study conducted by Silverberg et al. On a group of 8217 people, it was observed that AD was associated with a higher risk of, inter alia, heart disease, high blood pressure or diabetes compared to the control group ($p < 0.01$) [45].
Schmidt et al. Conducted a study on 13,126 people with AD and 124,211 people without AD, which aimed to establish the relationship between hospital-diagnosed atopic dermatitis and the onset of atrial fibrillation. Patients with AD had a 20% higher long-term risk of atrial fibrillation compared to the general population, however the absolute risk was low [46].
In a study by Kwa et al. AD was associated with increased cardiovascular and cerebrovascular risk, especially in younger patients. Also, arterial hypertension was more common in AD patients [47].
A meta-analysis of 19 studies by Ascott et al concluded that in AD patients, the risk of a heart attack or a cardiac event was significantly increased. Additionally, the severity of atopic eczema was also associated with a higher risk of cardiovascular complications [48].

Discussion

Many inflammatory and non-inflammatory diseases with cutaneous manifestation have been associated with increased cardiovascular risk. The related pathophysiological processes are complex and multidirectional. Chronic inflammation, metabolic syndrome, and atherogenesis are often described in the context of the correlation between skin diseases and cardiovascular risk.
A particularly high cardiovascular risk is associated with chronic inflammatory dermatological diseases. Inflammatory mechanisms often underlie both cardiovascular and skin disorders, so the risk factors for these two groups are also common. Some dermatological diseases, even with only local skin manifestations, may be associated with chronic, systemic inflammation, which initially asymptomatic, may generate a whole cascade of self-propelling pathological processes.
A group of diseases that are very important for the stratification of cardiovascular risk, are systemic immune-mediated diseases (SIDs), including autoimmune and autoinflammatory diseases. SIDs cover a very wide spectrum of conditions, concerning various organs and structures, in which autoimmune or autoinflammatory processes may predominate to varying degrees. The cardiovascular system is often involved. Basically all heart's structures may be affected. In any case, cardiac involvement is an unfavorable phenomenon and may significantly influence the patient's prognosis. Involvement of the heart may disturb its work and result in: cardiac autoimmunity, electrical disturbance, cardiomyocyte dysfunction and heart failure [2].
The group of SIDs includes many dermatological diseases, including: psoriasis, systemic lupus erythematosus, pemphigus, pemphigoid, scleroderma, acne and acneiform associated diseases, erythema nodosum associated disease, including sarcoidosis, dermatomyositis, polymyositis. Due to the numerous group of diseases that can affect both the skin and the cardiovascular system, it is important to assess the cardiovascular risk in patients with dermatological diseases [2,49,50].

Systemic inflammation is a risk factor for cardiovascular disease as inflammation accelerates atherosclerosis. Atherosclerosis is the underlying process resulting in cardiovascular disorders. In the past, atherogenesis was thought to be the passive deposition of lipid molecules within the walls of blood vessels. Over the years and with the progress of science, knowledge has evolved and today it is known that the process is much more complicated. It involves complex reactions with the participation of the immune system. Therefore, diseases with chronic inflammation may contribute to the intensification of the formation of atherosclerotic plaques. The common pathophysiological relationship results from processes such as: common pathway activation and inflammatory cytokine overexpression, higher prevalence of traditional cardiovascular risk factors and systemic chronic inflammatory state [51,52,53,54].

The primary process in atherogenesis is inflammation, which contributes to both the development of atheroma itself and the eventual rupture of the plaque. Damage and increased permeability of the endothelium result in increased accumulation of modified lipoproteins (oxLDL), which triggers Th-1 cells, monocyte and macrophages to form atherosclerotic plaques [51,52]. Overexpression of pro-inflammatory cytokines (TNFa, IL-1, IFN-y) activates foam cells, which are involved in atherosclerotic plaque formation [51,55]. Th1-cells induce inflammation, secrete IFNγ, increase the influx of inflammatory cells and induce the formation of foam cells. Other T cells are also active in atherosclerotic lesions. Th-17 cells can promote plaque fibrosis [51,53]. In skin diseases such as psoriasis, rosacea, there may be low-grade inflammation, which means a chronic, generalized, subclinical process, which plays a significant role in pathogenesis of atherosclerosis [54,55]. It has been shown that IL-17, which is typical for psoriasis pathogenesis, is associated with the formation of reactive oxygen species, endothelial damage and vascular inflammation [56].

Slowly progressive atherosclerosis may be initially asymptomatic. Accelerated atherosclerosis contributes to the development of arterial cardiovascular diseases, including ischemic heart disease (angina pectoris, myocardial infarction), cerebrovascular disease (stroke, TIA), and peripheral arterial disease [47,51]. Arterial stiffness is a characteristic disorder of patients with atherosclerosis and chronic inflammatory systemic diseases. It contributes to increase in systolic blood pressure and pulse pressure and related complications [58]. Therefore, the factors that increase the accumulation of atherosclerotic plaques contribute to the increased cardiovascular disease incidence and premature mortality [51,57,58].

Patients with metabolic syndrome (MS) are in a group of classical cardiovascular risk factors, including central obesity, hypertension, dyslipidemia (hypertriglyceridemia, decreased HDL cholesterol), and type 2 diabetes/glucose intolerance. Each of these disorders independently contributes to an increase in cardiovascular risk, and their combination in a patient additionally escalates this risk and contributes to more frequent and severe cardiovascular manifestations, and as a result, escalates cardiovascular mortality [59,60]. Evidence for a correlation between visceral obesity, hypertension and atherosclerosis was described as early as 1765 by Joannes Baptista Morgagni. Over the years, further pathophysiological mechanisms linking the components of the metabolic syndrome with cardiovascular diseases have been discovered [61]. Inflammatory process is one of the important linking processes. Metabolic syndrome predisposes individuals to diabetes mellitus or coronary artery disease.

Increased waist circumference, increases in LDL cholesterol and triglycerides, lowered HDL cholesterol, hyperglycemia, and hypertension are common risk factors for coronary heart disease and diabetes. Both of these disorders involve coronary microvascular disease [62,63]. Metabolic syndrome has been associated with cardiovascular conditions including microvascular dysfunction, coronary atherosclerosis and calcification, cardiac dysfunction, myocardial infarction, and heart failure [60].

Many of the diseases discussed in this article are chronic inflammatory diseases. Since systemic inflammation is assumed to promote the development of metabolic syndrome, inflammatory dermatological diseases also increase the risk of cardiovascular diseases and premature death [59]. Inversely, any disorder associated with the loss of metabolic control can cause cutaneous disease [62,63]. Both in the metabolic syndrome and in various skin disorders there are common pathophysiology pathways related to oxidative stress and upregulated inflammatory markers (IL-2, IL-4, IL-6, IL-17, IL-23, TNFa) [62,64]. Lipid disorders in MS lead to the development of insulin resistance, which causes further hormonal changes. This may result in an exacerbation of androgen dependent skin diseases (acne or androgenic alopecia) [62]. The metabolic syndrome may also influence the severity of the course and the frequency of exacerbations of skin conditions. Such a relationship has been noticed, among others, for psoriasis.

The relationship between the metabolic syndrome and dermatological diseases has been described for psoriasis, inflammatory and autoimmune skin disease (systemic lupus erythematosus, pemphigus, lichen planus, atopic dermatitis, seborrheic dermatitis, chronic urticaria), sebaceous and apocrine glands disorders (acne, rosacea, hidradenitis suppurativa, alopecia), cutaneous tumors, miscellaneous skin diseases and skin aging processes [62].

Due to the significant influence of the metabolic syndrome on the cardiovascular risk, as well as the severity of the course of dermatological diseases, it is important to identify patients with components of the metabolic syndrome early. Treatment of these patients allows to restrain the progression of skin disease and its complications, as well as reduce cardiovascular morbidity and mortality.

Conclusion

Correlations between skin diseases and cardiovascular risk are very complex and subject to many variables. Dermatological patients require comprehensive care including the regular assessment of cardiovascular risk, proper treatment of underlying diseases, as well as rapid detection and response to new disorders and complications. Doctors need to pay more attention to identifiable risk factors, especially those related to inflammatory and metabolic disorders, because their proper treatment not only reduces the severity of the skin disease, but also has a positive effect on the cardiovascular risk. The main goals in chronic inflammatory diseases are disease treatment, avoiding exacerbations, achieving remission, controlling inflammation. Referral to a cardiologist for further diagnostic workup and treatment is indicated at any time, if cardiovascular system involvement is suspected based upon clinical and diagnostic findings. This emphasizes the importance of a comprehensive approach to the patient and the importance of effective cooperation of cardiologists and dermatologists in the treatment of systemic skin diseases.

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