Review paper

Cardiovascular risk in patients with plaque psoriasis and psoriatic arthritis without a clinically overt cardiovascular disease: the role of endothelial progenitor cells

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Abstract

Psoriasis is an autoimmune, chronic disease determined by environmental and genetic factors. The occurrence of psoriasis is accompanied by metabolic diseases, cardiovascular diseases (CVD) and depression, disturbances on interpersonal interactions and a tendency towards social isolation. Regardless of the form of psoriasis and the severity of the disease, early arterial lesions are recorded in arterial vessels of patients. Nevertheless, the chance of CVD is higher in the population of patients with severe psoriasis than in patients with mild to moderate psoriasis. The correlation between the presence of atherosclerotic plaque and psoriatic plaque is partially explained by: (1) a similar inflammatory pathway – via the T helper cells, (2) impaired angiogenesis, and (3) endothelial dysfunction. In the considered tests, the diagnostic tools used showed a reduced level of endothelial progenitor cells in the circulation of patients with psoriasis. Endogenous angiopoietin stimulation in patients with psoriasis leads to deterioration of endothelial regeneration, atherosclerosis which secondarily contributes to the progression of heart failure. Clinical and experimental data confirm the potential of immunomodulatory methods to combat both autoimmune and cardiovascular diseases through the use of immunosuppressive drugs. Full understanding of the way in which CVD develops in patients with autoimmune diseases would enable the implementation of targeted cell therapy allowing the quality and life expectancy of patients to be improved. Modern cellular diagnostic tools allow the use of highly specific biomarkers, which in the near future will enable a reduction in morbidity and mortality due to CVD.

Key words: psoriasis, atherosclerotic, cardiovascular diseases, cellular diagnostics, biomarkers.

Introduction

Psoriasis is a genetically determined chronic inflammatory disease triggered by many environmental factors (e.g. trauma, infections, medications, psychological stress) which affects nearly 2% to 4% of the world's population. The most common form of the disease is plaque psoriasis – it accounts for 80% to 90% of all cases [1, 2]. In 75% of cases psoriasis is diagnosed before the age of 40; most often between the age of 16 and 22. During the course of the disease, excessive proliferation, accelerated growth and abnormal maturation of epidermal cells become visible. Sharply demarcated, scaly, erythematous plaques characterize the most common form of psoriasis. The lesions are mainly located on the scalp, elbows and knees, followed by nails, hands, feet and trunk. Psoriatic arthritis is a less common form of psoriasis [2–4]. Three main clinical forms are distinguished, i.e. symmetrical polyarthritis, spondylitis and inflammation of one or more joints with accompanying muscular pain. Approximately 20–30% of patients with plaque psoriasis develop psoriatic arthritis. However, in about 10–15% of cases, psoriatic arthritis occurs before plaque psoriasis. Psoriasis also has a significant impact on patients' quality of life. Currently, the severity of the disease assessment is based on determining the percentage of the body area involved, plaque location and thickness, presence of comorbidities, assessment of the patient's physical and mental condition, and the burden of the pharmacotherapy used [2]. Many clinical scales have been developed to assess the disease severity, the most commonly used are Psoriasis Area and Severity Index (PASI), Dermatology Life Quality Index (DLQI), and Body Surface Area (BSA) [5]. Over the past decade, the perception of psoriasis, as a disease entity that includes only skin dysfunction, has

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changed. A significant influence of ongoing inflammation on the increase in incidence of cardiovascular events was demonstrated [6]. Due to changes in perception of psoriasis and psoriatic arthritis, the question arises if we should consider changes in current treatment of psoriasis and psoriatic arthritis which include the risk of cardiovascular diseases. Additionally, a possible association of type 1 diabetes and obesity have been reported in patients with psoriasis [7]. The pathogenesis of systemic inflammatory diseases has common mechanisms of initiation and progression. Particular attention is paid to the histological similarity of leukocytic infiltration in both psoriatic plaque and atherosclerotic plaque [3]. In addition, chronic inflammation results in the development of insulin resistance, which favours the endothelial dysfunction and increased thickness of the intima-media complex [8]. The currently published clinical and experimental data confirm the therapeutic effectiveness of the immunomodulatory approach through the use of immunosuppressive drugs and targeted therapy in the treatment of both autoimmune and cardiovascular diseases [9].

Common pathways

In the pathogenesis of chronic inflammatory diseases, including psoriasis and atherosclerosis, a number of similarities have been demonstrated. Activation of Th1 and Th17 releases inflammation mediators, i.e. tumour necrosis factor α (TNF-α), interferon γ (IFN-γ) and interleukin: IL-1β, IL-10, IL-17 [3, 10] (Table 1). Together with the activation and hyperproliferation of keratinocytes they trigger the release of detectable circulating apoptotic endothelial cell-derived microparticles (EMPs) of intraepithelial origin. A subset of circulating antigens (CD31 and annexin V) was identified to be a marker of vascular wall dysfunction. In response, the activity of $CD14^+$, $CD45^+$, VEGFR2 $CD309^+$, Tie-2^+ endothelial progenitor cells (EPC) increases as they are responsible for angiogenesis and have regenerative potential. Therefore, these cells may serve as a marker of endothelial dysfunction and reparative capacity [11].

Inflammation and cardiovascular risk

Atherosclerotic plaque formation is induced by the accumulation of low density lipoproteins (LDL) within the artery wall. Oxidised LDLs (ox-LDL) serve as a signal to recruit monocytes, which differentiate to macrophages and convert them into foam cells [3, 9]. The endothelial activation causes overexpression of VCAM-1 and ICAM-1 cell adhesion molecules. In addition, ox-LDLs mobilise for the release of TNF, IL-1β, IL-6 and matrix metalloproteinases (Table 1). In the analysed atherosclerotic masses, the character of T-cell responses, in particular the Th1 subtype, was detected. Regulatory T-cells (Treg) play an important role in maintaining immune homeostasis by preventing autoimmunity. Loss of Treg cell number or a decrease in their response ability leads to atherosclerosis progression. The relationship between the increase in the incidence of cardiovascular events as well as the low level of Treg including the lack of the balance between Treg and T effector has been proven. In addition, positive effects of statins on the increase in the number of Treg lymphocytes were noticed. Experimental and clinical studies have proved the mutual influence of Treg on the metabolism of lipoproteins [12]. In turn, B-lymphocytes are responsible for the release of autoantibodies against oxidised forms of LDL. This action determines the formation of highly inflammatory deposits of immune complexes. In addition, B-lymphocytes present antigens to T-lymphocytes' immunological memory, this promotes the secretion of cytokines and increases the concentration of costimulatory molecules. Ultimately, the consolidation of the presented mechanisms leads to the rebuilding of the atherosclerotic plaque with the accumulation of foam cells, collagen degradation, the erosion of the plaque and the weakening of the fibrous cap structure. The gradually arising unstable phenotype increases the risk of cardiovascular events. In summary, inflammation plays a key role in the progression and destabilisation of patients with atherosclerosis [9]. It is worth noting that individual biomarkers of inflammation, such as interleukin-6, C-reactive protein and metalloproteinases are considered independent prognostic predictors for the course of cardiovascular diseases (CVD) [13]. Currently, immunotherapy is an intensively analysed therapeutic solution dedicated to patients with advanced atherosclerotic lesions. However, due to the need for long-term use of modulation of the immune system, there is a risk of complications associated with immunosuppression. This limits the possibility of the therapy having widespread effects. Nowadays, vaccination-based methods are becoming a realistic therapeutic approach that can be implemented before the disease develops. Strategies that increase Treg, by restoring immune homeostasis, may be a beneficial solution in the treatment of atherosclerosis at various stages of myocardial disease. In addition, specific effector molecules of the immune system can be used as disease modifying agents by promoting the stabilisation of atherosclerotic plaque or improving lipid metabolism [9].

Inflammation, psoriasis and selected autoimmune diseases

The pathogenesis of psoriasis has not been fully explored. The causes of the disease are found in the disruption of complex interactions between keratinocytes, leukocytes as well as dendritic and epithelial cells [1, 3]. An abnormal immune profile in patients with exacerbated psoriasis contributes to the impairment of the inflam-

Table 1. Molecules connecting common pathways in atherosclerosis and psoriasis (based on [8, 10, 15, 17, 27])

Membrane and other molecules		
CD 14	Lipopolysaccharide receptor, monocyte differentiation antigen	Detects antigenic molecules
CD 29	Glycoprotein IIa, β1 integrin, β subunit of fibronectin receptor, β-chain in VLA (CD49)	Participates in inflammation, fibrosis and the apoptosis pathway
CD31	Platelet endothelial cell adhesion molecule	In combination with Annexin V+ is a risk factor for cardiovascular diseases
CD34	Hematopoietic antigen of progenitor cells	Participates in the attachment of hematopoietic stem cells to the extracellular matrix of the bone marrow or directly to stromal cells
CD45	Common leukocytic antigen (LCA), protein tyrosine phosphatase	Regulates the activation of T and B cells mediated by the antigen receptor
CD73	Ecto-5'-nucleotidase	Mediates co-stimulatory signals in the activation of T cells
CD90	Thy-1	Presumably mediates the differentiation of hematopoietic stem cells and mediates the adhesion of white blood cells to activated endothelial cells
CD133	Prominin 1 or AC133	Transmembrane glycoprotein undergoing expression on hematopoietic stem cells and progenitor endothelial cells
Antigen–receptor complex		
KDR	Kinase insert domain receptor (a type III receptor tyrosine kinase)	Can interact with SHC-transforming protein 2, Annexin A5 and SHC-transforming protein 1 (important in the regulation of apoptosis)
VEGF	Vascular endothelial growth factor	Two major pathways of endothelial tyrosine kinase signalling in angiogenesis
Tie 1, 2	Family of tyrosine kinases receptors	
Interleukins and their receptors		
IL-1 (IL-1α, IL-1β)	Interleukin-1 type 1 receptor, Interleukin-1 type 2 receptor	Induces proinflammatory proteins, haematopoiesis, enables differentiation Th17 cells
IL-3(R)	Interleukin-3 + receptor (CD131)	Activates basophils and eosinophils, enables differentiation of dendritic and Langerhans cells Enhances IL-2-induced proliferation and differentiation of B cells
IL-6(R)	Interleukin-6, R (sIL-6R), gp130	Induces acute-phase proteins in hepatocytes Activates leukocytes; participates in T-cell differentiation, activation, and survival Influences B-cell differentiation and production of IgG, IgM, and IgA
IL-10(R)	Interleukin-10, IL-10R1/IL-10R2 complex	Immunosuppressive effect through antigen-presenting cells or direct effects on T-cell subsets Suppression of IgE and induces IgG secretion
IL-12	Interleukin-12Rb1 and IL-12Rb2	Participates in development and maintenance of Th1 cells Activates natural killer cells Supports dendritic cell maturation; induces cytotoxicity
IL-23	Interleukin-12b p40 5 40 kDa, Interleukin-23 p19 5 19 kDa	Stimulates the production of proinflammatory IL17 Enhances T-cell proliferation and promotion of memory T cells Activates natural killer cells; regulates antibody production
T helper cells		
Th1	Type 1 T helper lymphocyte	Secretes γ-interferon, IL-2 and TNF-β, evokes cell-mediated immunity and phagocyte-dependent inflammation
Th17	Type 17 T helper lymphocyte	Multiple inflammatory processes, secretes IL-17A, IL-17F, IL-22, and IL-21
Other mediators		
TNF-α	Tumour necrosis factor α, cachexin	Induces tumour cell apoptosis and cachexia, development of the immune system, protection from pathogens, participates in autoimmune diseases
SCF	Stem cell factor or kit ligand, mast cell growth factor	Promotes progenitor cell survival, accelerates stem cell entry into the cell cycle, chemotactic and chemokinetic factor for stem cells, anchor the hematopoietic cells in the microenvironment, induces progenitor cell adhesion to fibronectin

Table 1. Cont.

Membrane and other molecules		
G-CSF	Granulocyte colony stimulating factor	Stimulates the bone marrow to produce Granulocytes and stem cells, stimulates the survival, proliferation, differentiation, and function of neutrophil precursors and mature neutrophils
TGF-β	Transforming growth factor β	Participates in establishing immunological tolerance, inhibits Th1 and Th2 differentiation from naïve T cells *in vitro*
Adhesion molecules		
VCAM-1	Vascular cell adhesion molecule 1, CD106	Mediates in adherence of inflammatory cells to target cells by binding with the β1-integrin ligand (very late antigen-4) on leukocytes
ICAM-1	Intercellular adhesion molecule 1, CD54	Cell adhesion

matory response. Evidence was sought to link psoriasis to other autoimmune diseases. Hou *et al.* characterized mesenchymal bone marrow stem cells (BMCS) in patients suffering from auto-aggressive diseases [14]. Bone marrow cells secrete molecules that inhibit apoptosis, activate local stem cells of the heart and stimulate angiogenesis [15]. In patients with psoriasis, systemic lupus erythematosus and rheumatoid arthritis BMCS present a reduced proliferative activity, secrete stem cell factor (SCF), granulocyte colony stimulating factor (G-CSF) and IL-6 as well as low levels of TNF-α, IL-1, leukaemia inhibitory factor IL-3 (LIF), hepatocyte growth factor (HGF) and platelet-derived growth factor (PDGF) (Table 1). Mesenchymal stem cells are responsible for immunomodulation, propagation of angiogenesis and CD34+ differentiation and proliferation. Immunomodulatory effects, regulated by TGF-β, VEGF and IL-10, consist of inhibition of T lymphocytes, natural killer cell (NK) overexpression, cell proliferation, modulation of cytokine excretion and the inhibition of dendritic cell maturation. The loss of function performed by BMCS manifests itself in the impairment of the ability to suppress excessively active immune cells. Interestingly, both BMCSs of healthy and sick patients showed a typical fibroblast phenotype – positive for CD29, CD73 and CD90 and negative for CD45, CD34 and HLA-DR (Table 1). In conclusion, the phenotype of the particles including the ability to differentiate and support haematopoiesis were relatively similar in the population of sick and healthy people, however BMCS from patients with psoriasis showed abnormal proliferation, increased apoptosis rate and different gene expression. Hou *et al.* noticed that the compromised immune response suppresses the immunomodulatory and chemotactic function of BMSCs in patients with psoriasis [14]. Liu *et al.* put forward the hypothesis that EPC deficiency in patients with psoriasis leads to the development of atherosclerosis. Four subpopulations of the EPC were estimated by flow cytometry: CD34+ EPC, CD133+ EPC, CD34+ receptor/KDR+ kinase domain EPC and CD133+/KDR+ EPC. Patients with psoriasis have a reduced population of CD34+ EPC compared to healthy individuals. It has also been proven that a reduction in the EPC level in patients with psoriasis promotes the development of atherosclerosis [16]. The determination of particles involved in the immune system and the mechanism of their cooperation in the development of psoriasis and CVD require further elucidation [16, 17].

Cardiovascular risk of patients with psoriasis

A growing body of evidence confirmed a significant effect of psoriasis on the occurrence of CVD [6, 18–20]. In addition, the severity of psoriasis may serve as a prognostic factor in CVD. A higher proportion of myocardial infarction and stroke – including fatalities – was observed in patients with severe psoriasis than in patients with benign forms [19, 20]. According to estimated data collected in the United States, nearly 11,000 psoriasis patients die from cardiovascular causes on an annual basis [18]. The lengthy presence of psoriasis also affects the risk of cardiovascular events. Correlation with age indicates an increase in the risk of CVD in patients who have experienced psoriatic onset during the younger years of their life. This is probably related to prolonging the possible time of atherosclerosis, which is an independent and strong predictor of CVD development. It should also be noted that advanced age is associated with a greater prevalence of type 2 diabetes, arterial hypertension or obesity [7]. This, therefore, requires a multi-factorial analysis of the data on the impact of psoriasis on CVD in the older age group. Recent studies have shown that older patients with psoriasis were more likely to have coronary disease in relation to the general population – this assessment is based on the coronary artery status in coronary angiography of the elderly population [21]. Published meta-analyses reveal beneficial and therapeutic effects of drugs used in moderate to severe cases of psoriasis in order to reduce the risk of CVD. These include methotrexate, TNF-α inhibitors and IL-12/23 inhibitors [9, 22, 23]. Regardless of the severity of disease and age group, patients suffering from psoriasis should be informed about the risk of CVD. The resulting modification of treatment, change of lifestyle and more frequent follow-up visits may cause a reduction

in the mortality attributed to myocardial infarction or stroke in this group of patients. The American Heart Association confirmed that mild and severe psoriasis are associated with an increased risk of myocardial infarction [24]. However recommendations for autoimmune disease by the European Society of Cardiology suggest use of a 1.5 risk multiplier for the CV risk in immune diseases like psoriasis in class IIb level C [25].

Cardiovascular risk assessment in people without clinically overt cardiovascular disease

People suffering from psoriasis, especially in its mild form, are often unaware of the systemic effects of chronic inflammation and the increased risk of CVD. Periodic assessment of the circulatory system determines the prognosis, thereby enabling implementation of early therapeutic steps. Basic check-ups include determination of the plasma lipid and glucose profile, diagnostics dedicated to the assessment of cardiac function (e.g. left ventricle ejection fraction, stroke volume left ventricle) and blood pressure measurement [9]. The tests showed that the platelet to lymphocyte ratio (PLR) value above the reference range is a predictor of total mortality and cardiovascular events. An increased number of platelets correspond to their increased activity, which can lead to a reduction in microcirculation flow. A relationship between a multiday hospital stay and the level of PLR was also observed. Namely, patients presenting increased PLR, showed a higher risk of adverse events than patients with ACS and lower PLR [26]. Molecular biomarkers associated with cardiovascular events and mortality due to CVD have become the subject of intensive research [13]. Results of this research have detected potential biomarkers from plasma measurement of cardiovascular disease and atherosclerosis progression, including those for (1) vascular endothelial growth factor (VEGF); (2) von Willebrand factor (vWf); (3) IL-6; (4) homocysteine and (5) tumour necrosis factor as a weak inducer of apoptosis (TWEAK) [13, 27–29]. The plasma C-reactive protein and N-terminal-pro-brain natriuretic peptide (NT-proBNP) can equally serve as an independent predictor of mortality caused by chronic heart failure [28, 29]. Additionally, CD31 +/Annexin V+ EMP in relation to CD14+ CD309+ cells, added to the NT-proBNP score and clinical data provide a reliable value that distinguishes the kind of heart failure [11]. In conclusion, patients with psoriasis without clinically overt cardiovascular disease should have extended diagnostics performed for myocardial function and progression of atherosclerosis [30]. This information should be convincing for clinicians to start appropriate screening for CVD and oblige physicians to inform their patients about the need for periodic cardiovascular monitoring.

Laboratory methods

The key to understand what intercellular correlations lead to the development of CVD in patients with psoriasis is the mechanism of complex interactions between cells at the level of psoriatic and atherosclerotic plaque [3]. Determining the subtype of particles and the nature of their impact still requires further research. Currently, the assessment of inflammation with classic markers (CRP, leukocytes, ESR) provide insufficient information. Modern and progressively implemented prognostic methods which utilise biomarkers represent a great opportunity in reducing morbidity and mortality due to CVD [13]. This opens a direct route to cellular diagnostics. Stem cells are particles that demonstrate the ability to self-renew, differentiate and reprogram [31]. *In situ* hybridisation (ISH) technology allows the identification, characterisation and location of the stem cell population. In addition, the technique reveals markers for maintaining and regenerating stem cells. An important tool for advanced cellular diagnostics is flow cytometry analysis. It provides information on the expression of cell surface proteins by means of a reliable differentiation of positive and negative cells to a given antigen [32]. Other tools which are helpful in describing the particles include measurement of chromosomal content in cells by means of DNA cytometry or in situ fluorescence hybridisation [31]. Proteomic analysis, using two-dimensional electrophoresis and mass spectrometry, enables the determination of the protein profile in various pathological states. In addition, new cellular methods, based on progenitor cells, allow the regeneration of tissues damaged by the inflammatory process within them. Understanding the role of EPC in chronic inflammation brings hope to understanding the relationship between cardiovascular disease and autoimmune diseases [33]. EPC are circulating cells that have the ability to adhere to the endothelium at sites of hypoxia/ischaemia and participate in the formation of new vessels [34]. Tests performed on the EPC phenotype established CD34+, CD133+ as well as KDR expressions, however, the antigen panel may show a difference for hematopoietic and vascular endothelial subsets [11, 16, 33] (Table 1). Clinical trials were carried out on patients with heart disease, diabetes, peripheral arterial disease and cancer, in which the EPC served as a biomarker or had a beneficial regenerative effect. Perhaps, in the future, EPC will become a therapeutic tool in reducing mortality in general and mortality caused by CVD. The need for a thorough understanding of EPC participation in intercellular interactions may integrate common cardiovascular events with autoimmune diseases.

Conclusions

Patients with psoriasis, regardless of clinical manifestation or severity, are more likely to experience cardiovascular incidents in their lifetime. It is impossible to

precisely estimate the chances of CVD presenting itself. It is impossible to create objective risk stratification results, among others, from the presence of comorbidities and the difference in the age of onset of the first symptoms of psoriasis in the analysed group of subjects. There are high hopes that cellular diagnostics will abolish the existing correlation between cardiovascular diseases and autoimmune diseases [18–20]. Analysis of BMCS, progenitor EPCs and other biomarkers involved in the chronic inflammatory process shed new light on understanding the pathomechanism of both psoriasis and atherosclerosis [14–16]. However, the knowledge gained so far does not answer all the questions. Taking into account the role of angiogenesis in the recovery of ischemic tissue and the availability of the latest cellular diagnostic tools, we will most probably understand the increased risk of cardiovascular events in patients with psoriasis.

Conflict of interest

The authors declare no conflict of interest.

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