REVIEW ARTICLE

Diagnosis of early atherosclerotic lesions, and selected atherosclerotic risk factors, in patients with systemic lupus erythematosus

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KEY WORDS

antiphospholipid syndrome, atherosclerosis, imaging study, risk factors, systemic lupus erythematosus

ABSTRACT

Early diagnosis of subclinical atherosclerosis can be established using noninvasive imaging techniques, which enable to assess atherosclerotic lesions at different stages of their development, from endothelial dysfunction, through morphological lesions in the arteries, to advanced atherosclerotic plaques. Given high risk of accelerated development of atherosclerotic lesions in patients with systemic lupus erythematosus (SLE), these techniques should be incorporated in routine diagnostic evaluation in this population. Cardiovascular risk factors in patients with SLE differ significantly from those observed in the general population. Chronic inflammation and the presence of autoantibodies play the key role, while classic risk factors are less important. Subclinical atherosclerotic lesions can be detected in 30% to 40% of the SLE patients. The occurrence of severe symptoms in the cardiovascular and central nervous systems can be caused by such lesions. Recent data indicate that the main causes of death in this patient group represent cardiovascular complications. Early identification of patients in the risk group allows to implement appropriate prophylactic and therapeutic procedures.

Initial reports on the development of early atherosclerotic lesions in patients with systemic lupus erythematosus (SLE) came from autopsy examinations performed by Bulkley and Roberts[1] in 1975. A year later, these observations were confirmed by Urowitz et al.,[2] who developed a 2-model pattern of causes of mortality in this patient group, indicating that the first mortality peak applies to patients with active SLE, concurrent renal involvement, and recurrent infections, who were being treated with high-dose glucocorticosteroids (GCSs). The second mortality peak is observed in patients with inactive SLE, who had been treated with GCSs for many years and had previous myocardial infarction.

These observations are consistent with the new theory regarding the pathogenesis of atherosclerosis and with the "response-to-injury" theory developed by Ross and Glomset in 1973,[3] which showed endothelial damage to be a key initiatior of atherosclerotic lesions. Their hypothesis was complemented in the 1990s. It confirmed the role of immunological and inflammatory factors in the pathogenesis of atherosclerotic lesions at practically every stage of their development,[4] thus enabling the inclusion of inflammatory markers, autoantibodies, as well as infectious agents to the list of risk factors for atherosclerosis. This facilitates understanding of the mechanisms involved in accelerated atherosclerosis in patients with systemic connective tissue diseases, including SLE.[5]

It is now believed that cardiovascular complications, which result from atherosclerotic lesions, are the leading cause of mortality in patients with SLE.[6] The risk of ischemic heart disease is more than 6 times higher in this patient group, and is even 50 times higher in women aged from 35 to 44 years than in the control group.[7] Of note, while clinical symptoms of atherosclerotic coronary vessel disease occur in 6% to 10% of SLE patients, subclinical atherosclerosis can be documented in 30% to 40% of patients.[8] Thus, it is important to detect atherosclerotic lesions in the earliest stages of their development, which allows to implement appropriate preventive and

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therapeutic procedures. Early diagnosis of subclinical atherosclerosis can be established using noninvasive imaging techniques, which enable to assess atherosclerotic lesions at different stages of their development, from endothelial dysfunction, through morphological lesions in the arteries, to advanced atherosclerotic plaques.

Noninvasive diagnostic imaging of atherosclerotic lesions

Assessment of endothelial function The endothelium regulates a series of physiological processes essential for the maintenance of vascular homeostasis, such as vascular tone and permeability, adhesion and aggregation of blood platelets, coagulation and fibrinolysis, leukocyte adhesion, and the release of cytokines, as well as growth factors.[4,9] Endothelial damage occurs in a number of stages. Under the influence of various factors (such as interleukin 1, certain antibodies, and oxidized low-density lipoprotein [oxLDL], among others), stimulation, activation, and subsequent dysfunction of the endothelium occurs, which manifests itself as loss of vascular integrity, increased expression and production of cytokines, adhesion molecules and chemotactins, as well as a change in the endothelial phenotype from anticoagulant to procoagulant.[10,11]

Endothelial dysfunction constitutes the earliest stage in the development of atherosclerotic lesions.[3] It can be described as the impairment of arterial dilatability in response to various stimuli which induce the release of nitric oxide (NO).[12] Techniques designed to assess endothelial function were introduced in the 1990s. The most commonly used method is the measurement of brachial artery reactivity (which is dependent on endothelial function) in response to changes in blood-flow caused by passive congestion (flow-mediated vasodilatation [FMD]).[13] Under normal conditions, changes in blood flow lead to the release of NO and subsequent arterial dilatation through an increase in shear stress acting on the endothelium. At the same time, an endothelium-independent test is performed, in which arterial reactivity in response to nitroglycerin administration (NO-mediated vasodilatation [NMD]) is assessed. The parameter assessed is the change in arterial diameter in comparison to the baseline.[13]

Kiss et al.,[14] who evaluated endothelial function in 61 patients with SLE, showed that FMD was significantly lower in these patients compared with the control group. NMD values, however, were similar in both groups. This may suggest that endothelial reactivity alone was impaired, while reactivity of vascular smooth muscle cells was not affected. The authors indicated that this phenomenon was caused by reduced NO bioavailability resulting from increased oxidative stress in the course of SLE. These observations were confirmed by other researchers.[15,16] In their pioneering study, Hirata et al.[17] also documented vasomotor dysfunction of the coronary arteries in young females with SLE (mean age 29.4 years). By comparing blood flow under conditions of congestion induced by intravenous administration of adenosine triphosphate to the blood flow under basic conditions, the coronary flow velocity reserve (CFVR) was calculated. The study demonstrated that CFVR values were significantly lower in comparison with the control group, thus indicating the presence of subclinical coronary artery disease.

Assessment of vascular elasticity Structural and functional arterial alterations may be demonstrated in the form of reduced vascular elasticity, and they are considered an early stage of atherosclerosis. Measurement of pulse wave velocity (PWV) is the most commonly used approach to assess stiffness of the large arteries. This test entails simultaneous Doppler measurement of blood flow of the carotid and femoral arteries, and PWV is calculated as the quotient of the distance between the two arterial sites examined, and the time required for the pulse wave to cover the distance.[18] Evaluation of aortal wall elasticity in patients with SLE, which is performed through PWV measurement, was the subject of numerous clinical studies.[19,20] They all documented increased aorta stiffness in patients with SLE and its relationship to a higher risk of cardiovascular incidents in the analyzed patient groups. Through applanation tonometry, Bjarnegård et al.[19] evaluated not only aorta elasticity, but also elasticity of peripheral arteries, on the basis of the PWV measurement in the brachial artery. However, they observed significant differences in PWV values between patients with SLE and the control group for the aorta alone. This suggested that this particular measurement should be the method of choice for assessing arterial stiffness in these patients.

Roman et al.[21] also used applanation tonometry to evaluate arterial stiffness. They analyzed patients with SLE and rheumatoid arthritis (RA). They showed that increased arterial stiffness was observed regardless of the presence of atherosclerotic plaques. However, the study demonstrated a significant correlation between arterial stiffness and active inflammation (increase in C-reactive protein and inflammatory cytokines), etc. It suggests a role of other mechanisms, especially inflammatory response, which lead to vascular damage and the subsequent decrease of arterial elasticity in patients with systemic connective tissue diseases.

Recently, there have been reports of a new index that reflects stiffness of the aorta, as well as femoral and tibial arteries, namely the cardio-ankle vascular index (CAVI). Its key advantage over PWV is its independence of blood pressure.[22] The study conducted on females with SLE confirmed its usefulness in the evaluation of early atherosclerotic lesions. In young patients of reproductive age, significantly higher CAVI values were observed compared with the control group.[23] Furthermore, in patients at various stages of atherosclerosis, in whom no systemic connective

tissue disease was documented, there was a significant correlation between CAVI, the presence of atherosclerotic plaques in the carotid and coronary arteries, and the severity of coronary artery disease. This suggests that CAVI can be used to evaluate both arterial wall elasticity and atherosclerotic progression.[24]

High resistance index measurement High resistance index (HRI), measured by color Doppler ultrasonography, is defined as the ratio of peak diastolic reverse flow velocity to peak systolic velocity. This parameter is not associated with cardiac function and changes in blood pressure. This makes it more useful than other indexes used to assess vascular resistance (pulsation index and resistance index, among others). The usefulness of HRI as an index that reflects alterations in vascular resistance was shown in animal models.[25,26] In our own study conducted in 92 patients with SLE, HRI was calculated based on the Doppler spectrum of the popliteal arteries. Significantly lower HRI values were observed in patients with SLE, especially those with coexistent antiphospholipid syndrome (APS), compared with the control group. This indicates that HRI measurement can be used to evaluate early, subclinical lesions in vessels in the course of SLE.[27]

Ankle-brachial index measurement Ankle-brachial index (ABI) measurement enables to identify atherosclerotic lesions in the arteries of the lower extremities. It is calculated as the ratio of systolic pressure measured in the posterior tibial and dorsal arteries of both feet to the systolic pressure in the brachial artery. Measurement is performed using Doppler ultrasonography. In compliance with the European Society of Cardiology (ESC) recommendations, values >0.9 are considered normal,[28] though researchers also accept values of 1.0 as a cut-off point.[29] Clinical studies confirmed the usefulness of ABI in detecting early atherosclerotic lesions in patients with SLE.[29] Furthermore, emphasis is placed on a correlation between pathological ABI values and the risk of cardiovascular complications in patients with systemic connective tissue diseases.[30,31]

Due to its low cost and simplicity, this test is recommended for use in routine diagnostic evaluation to detect asymptomatic atherosclerotic lesions, which reduce the lumen of lower-extremity arteries; moreover, the test is used in the stratification of overall cardiovascular risk.[28]

B-mode ultrasonography This examination is used to measure intima-media thickness (IMT), as well as assessment of the presence of atherosclerotic lesions in the carotid arteries.[32] Due to its simplicity, low cost, safety, and high reliability, IMT measurement is often used in epidemiological studies,[33-35] and also in assessing total cardiovascular risk.[36] Emphasis is put on a correlation between IMT and the development of coronary artery disease[37,38] and cerebrovascular complications.[39-41] These findings were supported by our study on patients with SLE.[42]

The protocol recommended by the ESC includes measurements:

1 in the distal segment of the common carotid artery in both the proximal and distal walls

2 at the common carotid artery bifurcation in the proximal and distal walls

3 in the initial segment of the internal carotid artery in the proximal and distal walls.

In each of the segments, the highest IMT value is chosen. The final IMT value is calculated as the average obtained from all 12 measurements.[28] In compliance with the ESC recommendations, values of IMT above 1.3 mm are considered pathological. However, our own observations[42] and a number of other reports[33-36] indicate a high variability of this parameter in the population and the need to establish a reference range based on the results obtained in the control group. The usefulness of IMT measurement in the evaluation of subclinical atherosclerosis in patients with SLE has been well documented.[42-45] In the course of other systemic connective tissue diseases, IMT also increases. Early atherosclerotic lesions have been reported in patients with RA,[46,47] systemic vasculitis,[48] or APS.[49]

Recent studies have shown that combination of the IMT measurement with high-definition magnetic resonance enables to evaluate the mean wall thickness of the common carotid artery, including the adventitia. Consequently, sensitivity in the detection of focal thickening of the arterial wall is increased, and thereby early-stage atherosclerosis can be assessed more precisely and thoroughly.[50]

Selected risk factors for early atherosclerotic lesions in patients with systemic lupus erythematosus

Coexistence of systemic lupus erythematosus and antiphospholipid syndrome A role of APS and selected antiphospholipid antibodies (aPL) in the pathogenesis of early atherosclerosis has been extensively studied. Štalc et al.[51] demonstrated impaired endothelial function in patients with primary APS. Its manifestations involved significantly reduced FMD values and increased concentrations of intercellular and vascular adhesion molecules.

Similarly, patients with SLE and coexistent APS are significantly more often prone to the development of early atherosclerotic lesions,[52,53] coronary artery disease, and other cardiac complications. We have reported similar findings.[54-56] Among aPL, a crucial role in the pathogenesis of atherosclerosis is attributed to anticardiolipin antibodies (aCL),[57] anti-β_2-glycoprotein I antibodies (anti-β_2GPI), and anti-oxLDL. Le Tonqueze et al.[58] showed in vitro that anti-β_2GPI mediates binding of aCL to endothelial cells leading to their activation, and contributing to thrombosis and thrombocytopenia in patients in whom aCL were present. Furthermore, they documented that β_2GPI may also bind with oxLDL, and thus form highly

immunogenic complexes which, together with immunoglobulin G antibodies directed against them, constitute one of the autoimmune mechanisms that contribute to initiation of atherosclerosis in patients with SLE. The pathogenic significance of anti-oxLDL in the development of atherosclerosis, not only in patients with systemic connective tissue diseases, was also shown in clinical studies.[59,60] On the other hand, however, some researchers failed to demonstrate their role in atherosclerosis[43,44] and, quite the opposite, reported on an inverse correlation between anti-oxLDL concentration and IMT.[61] We have demonstrated that there is no correlation between the presence of anti-β_2GPI and anti-oxLDL, and the development of atherosclerotic lesions in the carotid arteries of patients with SLE.[56]

Antinuclear, antineutrophile cytoplasmic, and antiendothelial cell antibodies Antinuclear antibodies (ANAs), including antibodies directed against selected target antigens, are an important serological marker in the diagnosis of SLE and its monitoring. Proatherogenic activity of anti-double-stranded DNA antibodies (anti-dsDNA) has been emphasized. As shown in vitro, immune complexes consisting of anti-dsDNA, DNA, and LDL enhanced cholesterol accumulation in vascular smooth muscle cells, and demonstrated cytotoxic activity in patients with SLE.[62] Furthermore, individual reports[63] suggested that determination of ANAs may be helpful in the evaluation of the risk of coronary artery disease, also in subjects in whom no systemic connective tissue disease has been diagnosed. This view requires further studies to be confirmed.

Our study confirmed a significant association between antihistone and antinucleosome antibodies and the occurrence of fluid in the pericardium. Antihistone antibodies were significantly more frequently detected in patients with SLE and coexistence of mitral insufficiency.[54] No significant association was found, however, between the ANA presence and IMT in patients with SLE.[42]

Antineutrophil cytoplasmic antibodies (ANCAs) are another important marker, especially in the pathogenesis of inflammatory vascular lesions. In SLE, mainly p-ANCAs are observed and they are linked primarily to vasculitis in the course of lupus nephritis.[64]

Studies performed in patients treated for dyslipidemia and premature atherosclerosis indicated an association between ANCA and peripheral artery atherosclerosis, but did not confirm the role of antibodies against target antigens (myeloperoxidase and proteinase 3).[65,66] However, our study supported a role of p-ANCAs, especially directed against myeloperoxidase, elastase, and cathepsin G, in the pathogenesis of early atherosclerotic lesions (manifested as IMT[42]), coronary artery disease, myocardial infarction, and left ventricular hypokinesis in patients with SLE.[54,55] A probable pathogenic mechanism is linked to ANCA-mediated capacity to directly affect the endothelium together with a prothrombotic tendency associated with ANCA that act as potent platelet agonists.[67-69]

Other antibodies which participate in the pathogenesis of immune/inflammatory damage to the vascular wall are also antiendothelial cell antibodies (AECAs). Numerous clinical observations, including our own research on patients with SLE, confirmed the association between AECAs and peripheral atherosclerosis.[70-72] Research conducted by Wu et al.[73] indicated cross-reactivity of AECAs as well as anti-β_2GPI and anti-oxLDL in patients with SLE. This phenomenon seems to play a significant role in the pathogenesis of many clinical manifestations in the course of SLE, such as thromboembolic complications, vasculitis, or atherosclerosis.

The effect of the therapy used Bulkley and Roberts[1] were the first to emphasize a correlation between GCS therapy and the risk of developing atherosclerotic lesions in patients with SLE. Currently, most investigators share this view.[74,75] Furthermore, Manzi et al.[74] and Doria et al.[43] showed a significant effect of a high, cumulated GCS dosage on the development of subclinical atherosclerosis in patients with SLE. Our study supported this finding.[42] In addition, Petri et al.[76] demonstrated that a decreased GCS dosage is associated with a reduced risk of coronary artery disease.

On the other hand, antimalarial drugs have been shown to have a beneficial effect in SLE. In patients treated with GCS, only 3 months after initiating antimalarial drug therapy, cholesterol decreased compared with the initial values.[77] Moreover, an inverse correlation was observed between hydroxychloroquine therapy and the extent of organ damage, which was evaluated using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.[78]

Summary Accelerated atherosclerosis in patients with SLE constitutes a significant clinical challenge. Particularly important risk factors are related to the disease process and include coexistent APS, autoantibodies, and chronic inflammatory response. A choice of a therapeutic option is also of vital importance. In patients with systemic connective tissue diseases, including SLE, GCS therapy considerably increases the risk of developing premature atherosclerotic lesions. Modification of therapy, especially in patients at risk for developing atherosclerosis, may be crucial for the prevention of cardiovascular and neurological complications.

Atherosclerotic lesions at an initial stage can be detected by means of increasingly sophisticated diagnostic tools. Noninvasive imaging techniques allow to evaluate systemic atherosclerosis, and they should represent an essential component of the diagnostic evaluation of SLE that

is necessary to implement appropriate preventive and therapeutic procedures.

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ARTYKUŁ POGLĄDOWY

Diagnostyka wczesnych zmian miażdżycowych oraz wybrane czynniki ryzyka miażdżycy u chorych na toczeń rumieniowaty układowy

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SŁOWA KLUCZOWE

badania obrazowe, czynniki ryzyka, miażdżyca, toczeń rumieniowaty układowy, zespół antyfosfolipidowy

STRESZCZENIE

Wczesną diagnostykę subklinicznej miażdżycy umożliwiają nieinwazyjne techniki obrazowe, pozwalające na ocenę zmian na różnych etapach ich rozwoju, od upośledzenia funkcji śródbłonka, poprzez zmiany strukturalne naczyń tętniczych, do w pełni uformowanych blaszek miażdżycowych. Ze względu na duże zagrożenie przyspieszonym rozwojem zmian miażdżycowych u chorych na toczeń rumieniowaty układowy (*systemic lupus erythematosus* – SLE), techniki te powinny zostać włączone do rutynowej diagnostyki. Czynniki ryzyka miażdżycy u chorych na SLE istotnie różnią się od czynników ryzyka w populacji ogólnej. Najistotniejszą rolę odgrywają przewlekły stan zapalny i obecność autoprzeciwciał, a tradycyjne czynniki mają mniejsze znaczenie. Obecność subklinicznych zmian miażdżycowych stwierdza się u 30–40% chorych. Są one odpowiedzialne za występowanie poważnych objawów ze strony układu sercowo-naczyniowego i ośrodkowego układu nerwowego. Najnowsze dane wskazują, że główną przyczyną śmiertelności w tej grupie chorych są powikłania sercowo-naczyniowe. Wczesna identyfikacja chorych z grupy ryzyka umożliwia włączenie właściwego postępowania profilaktycznego i terapeutycznego.

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