Journal of Vascular Diagnostics

Dovepress
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Open Access Full Text Article

SHORT REPORT

Connective tissue diseases and noninvasive evaluation of atherosclerosis

This article was published in the following Dove Press journal:
Journal of Vascular Diagnostics
18 June 2014
Number of times this article has been viewed

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Abstract: Connective tissue diseases (CTDs) are associated with increased risk of cardiovascular disease due to accelerated atherosclerosis. In patients with autoimmune disorders, in addition to traditional risk factors, an immune-mediated inflammatory process of the vasculature seems to contribute to atherogenesis. Several pathogenetic mechanisms have been proposed, including chronic inflammation and immunologic abnormalities, both able to produce vascular damage. Macrovascular atherosclerosis can be noninvasively evaluated by ultrasound measurement of carotid or femoral plaque. Subclinical atherosclerosis can be evaluated by well-established noninvasive techniques which rely on ultrasound detection of carotid intima-media thickness. Flow-mediated vasodilatation and arterial stiffness are considered markers of endothelial dysfunction and subclinical atherosclerosis, respectively, and have been recently found to be impaired early in a wide spectrum of autoimmune diseases. Carotid intima-media thickness turns out to be a leading marker of subclinical atherosclerosis, and many studies recognize its role as a predictor of future vascular events, both in non-CTD individuals and in CTD patients. In rheumatic diseases, flow-mediated dilatation and arterial stiffness prove to be strongly correlated with inflammation, disease damage index, and with subclinical atherosclerosis, although their prognostic role has not yet been conclusively shown. Systemic lupus erythematosus, rheumatoid arthritis, and likely antiphospholipid syndrome are better associated with premature and accelerated atherosclerosis. Inconclusive results were reported in systemic sclerosis.

Keywords: rheumatic disease, subclinical atherosclerosis, arterial stiffness, accelerated atherosclerosis

Introduction

Cardiovascular (CV) morbidity and mortality in patients with connective tissue diseases (CTDs) are higher than in the general population, primarily due to accelerated atherosclerosis.[1] However, the mechanisms of enhanced atherogenesis in this population are not yet well defined. Several studies show that traditional CV risk factors such as smoking, hypertension, or diabetes are not sufficient to explain this phenomenon, leading to the assumption of an effect of other nonconventional risk factors.[2–4] There is growing evidence in favor of persistent inflammation in CTDs, especially in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), leading to premature atherosclerosis and its complications.[5–7] Over time, great emphasis has been placed both on biomarkers of endothelial activation/damage and on noninvasive ultrasound imaging in order to detect early vascular damage and get more accurate risk stratification.

The aim of this review is to summarize aspects of vascular changes found in patients with RA, SLE, antiphospholipid syndrome (APS), and systemic sclerosis (SSc) and,

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when possible, to identify their association with clinically relevant CV events.

A focus on the problem

In several studies, SLE and RA seem to be strongly associated with premature and accelerated atherosclerosis and CV events. Carotid plaques were found with a frequency, ranging between 17% and 65% in SLE patients.[8,9]

Data from a multicenter cohort study suggest that in SLE patients, death due to cardiovascular diseases (CVDs) does not appear to be diminished in recent years, in spite of advances in therapies.[10] SLE patients develop coronary artery disease with a rate from 4 to 8 times higher than normal.[11] Furthermore, younger SLE patients (age under 45 years) have a 52-fold higher risk of myocardial infarction when compared with matched controls.[11]

Many observational studies, summarized in two reviews including about 100,000 RA patients, showed an increased risk of CVD death (ranging from 50% to 60%) when compared with the general population.[12,13] Notably, subsequent exploratory analyses revealed neither any change in standardized mortality ratios of CV mortality over time nor any relation with disease duration at the time of inclusion, despite advances in treatment in recent decades.

Patients with RA or diabetes have the same increased 3-year rate of fatal and nonfatal CV events when compared with the nondiabetic population, suggesting RA as a risk factor with a CV impact similar to that of diabetes; more precisely, patients with RA and those with type 2 diabetes mellitus had the same hazard ratio when compared with the nondiabetic population.[14] A recent study suggested that CV risk factors in patients with RA should be targeted as aggressively as in diabetes patients. CV morbidity and mortality in APS and SSc is unclear. There is no conclusive evidence of premature atherosclerosis in APS,[15] although antiphospholipid antibodies (aPLs) are involved in atherosclerosis pathogenesis.[4,16]

Atherosclerosis and autoimmunity

Accelerated atherosclerosis in CTDs can be attributed to traditional risk factors for atherosclerosis and use of specific drugs, such as corticosteroids, but also might be the result of other autoimmune and inflammatory mechanisms.[15]

In addition to traditional risk factors, nontraditional risk factors may enhance atherogenesis: systemic inflammation, autoantibodies (aPLs, anti-endothelial cells, anti-double stranded DNA, anti-neutrophil cytoplasmic antibodies), heightened lipid oxidation, heat shock proteins, oxidized low-density lipoprotein/beta2 glycoprotein1 complexes, renal impairment, elevated levels of homocysteine, specific medications (especially steroids), exhaustion of endothelial progenitor cells, and antigenic mimicry mechanisms.[2,4,8,15,17,18]

In SLE and APS, accelerated atherosclerosis may be induced directly by proinflammatory and procoagulant activity of aPLs on endothelial cells or indirectly via the inflammatory/immune mechanisms implicated in autoantibody-mediated thrombosis.[16] Inconsistently with this notion, Farzaneh-Far et al,[19] studying 200 SLE patients, found very similar levels of carotid atherosclerosis in aPLs-positive and aPLs-negative patients; moreover, aPLs were not associated with preclinical or clinical atherosclerosis, suggesting that increased cerebrovascular disease in aPLs-positive patients may be better associated with in situ thrombosis or cardiac thromboembolism than with carotid arterial plaque embolization.[19]

Recently, the role of impaired endothelial repair has been highlighted in a study by Rodríguez-Carrio et al,[20] which showed that angiogenic T cells and endothelial progenitor cells were strongly decreased in 101 RA patients when compared to matched healthy controls. In a subsequent regression analysis, adjusted for traditional CV risk factors, disease activity, age at diagnosis, antinuclear antibody positivity, and smoking history were shown to be predictive parameters of greater angiogenic T cell decrease. Finally, a recent review identified type I interferons as predictive biomarkers of endothelial dysfunction in SLE patients.[7]

Therefore, it could be supposed that CTD-related inflammatory and autoimmunity abnormalities, autonomously or synergistically with traditional risk factors, may increase endothelial dysfunction, enhancing atherogenesis.

Methods for noninvasive evaluation of subclinical atherosclerosis

Macrovascular damage and hemodynamic abnormalities can be noninvasively evaluated by ultrasound measurement of carotid or femoral plaque.

Early subclinical atherosclerosis or impaired arterial stiffness, considered markers of vascular remodeling, can be noninvasively evaluated by ultrasound measurement of carotid intima-media thickness (IMT) and carotid-femoral pulse-wave velocity (PWV), respectively.[21–23] Indeed, different methods such as augmentation index (Aix) are also known to evaluate carotid-femoral arterial stiffness.

Carotid-femoral PWV is usually obtained at the right common carotid artery and the right femoral artery; it is a direct measurement and corresponds to the widely accepted

propagative model of the arterial system. Aix explores the retrograde waves proceeding from peripheral arteries, inducing what is called "amplification phenomenon" on aortic walls.[22] This phenomenon also explains the decreased distensibility and increased pulse pressure usually found in an aging vascular system.

Carotid-femoral PWV and Aix are considered both important markers of systemic arterial stiffness and indicators of the resistance encountered by the left ventricle.[24]

Endothelial dysfunction in CTDs can be noninvasively assessed by the flow-mediated vasodilatation (FMV) method.[23] It is based on two-dimensional ultrasound detection of the mean diameter and spectral analysis of blood flow in the humeral artery at baseline and after reactive hyperemia is induced by transient occlusive pressure placed around the proximal third of the arm. This method allows for the evaluation of endothelial-dependent vasodilatation. The evaluation is completed by the measurement of endothelium-independent vasodilatation in response to exogenous nitric oxide.[25]

IMT and connective tissue diseases

Carotid IMT by B-mode ultrasound is the most commonly used method for the detection of subclinical atherosclerosis. A recent systematic review and meta-analysis has shown that carotid IMT can be a useful predictor of future vascular events in otherwise healthy individuals.[21] In particular, it was shown that for an absolute carotid IMT difference of 0.1 mm, the future risk of myocardial infarction increases by 10% to 15%, and the stroke risk increases by 13% to 18%.

In a prospective cohort of patients with SLE, age, cumulative prednisone intake, hypertension, and evidence of antioxidized low-density lipoprotein antibodies were associated with higher IMT.[8] Some authors report that patients with primary and secondary APS had a higher prevalence of carotid plaque or IMT increase, suggesting a potential independent proatherogenic role for aPLs.[16]

Another systematic review and meta-analysis aimed to assess whether RA, SLE, SSc, and other rheumatic diseases are associated with an increased carotid IMT when compared with healthy control subjects.[26] In this work, more than 6,800 subjects were selected from about 1,030 studies. A statistically significant greater mean carotid IMT was observed in patients with any rheumatic disease compared with healthy controls, and similarly, there was increased prevalence of plaques in rheumatic diseases. The absolute mean difference in carotid IMT between case and control groups was 0.061 mm when a random-effects model was applied.

Other investigations provided evidence of increased carotid IMT in RA, and this finding could not be explained by corticosteroid treatment but appeared to be essentially associated with markers of systemic inflammation and disease duration. Of note, higher incidence of vascular events within 5 years is demonstrated in RA patients with increased IMT compared to a similar population without increased IMT.[27]

In RA patients without a history of CV events, carotid ultrasonography, as with IMT and/or carotid plaques, allowed identification of most high/very high CV risk subjects (sensitivity 97.2%) much more reliably than the coronary artery calcification score (sensitivity 24% for a score >100).[28]

Djokovic et al reported average carotid IMT values higher in SLE patients with aPLs present when compared with SLE patients without aPLs, and in multivariate regression analysis, aPLs were significant predictors of carotid IMT changes in SLE patients.[29]

Inconclusive results were reported in SSc when carotid or femoral IMT were compared with matched controls and healthy controls. With regard to macrovascular involvement, many studies recognized distal peripheral artery disease as the most important vascular involvement in SSc.[30]

Arterial stiffness, FMV, and connective tissue diseases

Arterial stiffness via PWV adjusted for patients' age and blood pressure was measured in 46 SLE patients. In this study, abnormalities of PWV were associated with traditional and nontraditional CV risk factors. Furthermore, a significant association was found between PWV and the Systemic Lupus International Collaborative Clinics/American College of Rheumatology (SLICC/ACR) damage index score. Multivariate analysis showed that increased PWV was independently associated with metabolic syndrome and SLICC/ACR damage index score.[31] A recent review[32] evaluated the relationship in SLE patients between arterial stiffness or endothelial dysfunction and traditional or disease-related risk factors (higher organ damage and activity indexes, longer duration of disease, and raised inflammatory biochemical markers). Higher arterial stiffness was found in patients with traditional CV risk factors and in patients with SLE-related risk factors. It is not clear if impaired FMV is associated with SLE-related risk factors. Nevertheless, the authors highlighted how the prognostic roles of both endothelial dysfunction and arterial stiffness have not yet been well established in appropriate studies.[32]

Santos et al used the reactive hyperemia index and Aix (markers of microvascular reactivity and arterial stiffness, respectively) in SLE and RA patients free from CVD and chronic renal dysfunction.[33] In this study, the authors did not find a significant difference in SLE and RA patients when compared with healthy controls.

In SLE patients with secondary APS, increase in inflammatory markers negatively correlated with endothelial-independent vasodilatation, suggesting how secondary APS affects the vascular smooth muscle and not the endothelium.[34]

In SSc, discrepant results were reported in studies evaluating the relationship among endothelial dysfunction and CV risk factors.[30]

Conclusion

Several studies have shown that CTDs are associated with higher rates of CV events; higher rate of CV events without the presence of conventional risk factors increases suspicion that other mechanisms (likely correlated with the underlying disease) are involved in atherogenesis in autoimmune diseases.

CV morbidity and mortality in patients with CTDs reflect complex and dynamic interaction between traditional risk factors (age, hypertension, metabolic syndrome, diabetes, obesity, tobacco smoking, and cholesterol levels) and CTD-related risk factors such as organ damage, activity indexes, disease duration, increased inflammatory biochemical markers, adverse or beneficial effects of treatment. Because conventional risk equations are not sufficiently reliable as a result of these complex interactions, it is particularly difficult to adequately assess CV risk in CTDs patients.

The evaluation of IMT, PWV, Aix, and FMV are proposed as effective methods for noninvasive vascular assessment, especially in early atherogenesis.

Carotid IMT is a leading marker of subclinical atherosclerosis and can be used as a predictor of future vascular events, both in healthy individuals and in CTDs patients. In a number of studies, FMV and arterial stiffness prove to be strongly correlated with inflammation and disease damage index, although their prognostic and predictive value have not yet been conclusively shown. SLE and RA seems to be better associated with premature and accelerated atherosclerosis. Theoretically, primary and secondary APS should be highly related to accelerated atherosclerosis, but it still remains uncertain. Discrepant results were reported when carotid or femoral IMT or endothelial function were measured as surrogate markers of early atherosclerosis in SSc.

New surrogate markers of vascular risk like PWV, Aix, and FMV should be validated for sensitivity, specificity, and predictive value in order to be employed in a more comprehensive screening protocol for CV risk stratification in rheumatic diseases.

Disclosure

The authors report no conflicts of interest in this work.

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