DO INDIVIDUALS WITH AUTOIMMUNE DISEASE HAVE INCREASED RISK OF SUBCLINICAL CAROTID ATHEROSCLEROSIS AND STIFFNESS?

Maria del Mar Vila[1, 2, 3] · Beatriz Remeseiro[4] · Laura Igual[3] · Roberto Elosua[1, 2, 5] · Rafel Ramos[6, 7, 8, 9] · Jose Manuel Valdivielso[10] · Ruth Martí-Lluch[6, 7] · Jaume Marrugat[1, 2] · Maria Grau[2, 11, 12]

[1] CIBER Cardiovascular Diseases, Instituto de Salud Carlos III, Madrid, Spain
[2] IMIM - Institut Hospital del Mar d'Investigacions Mèdiques, Barcelona, Spain
[3] Department of Mathematics and Computer Science, Universitat de Barcelona, Spain
[4] Department of Computer Science, Universidad de Oviedo, Gijón, Spain
[5] School of Medicine, Universitat de Vic – Universitat Central de Catalunya, Vic, Spain
[6] Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol), Girona, Spain
[7] Vascular Health Research Group, Research Unit in Primary Care, Girona, Institut Català de Salut, Spain
[8] Institut d'Investigació Biomèdica de Girona (IdIBGi), Spain
[9] Department of Medical Sciences, School of Medicine, Universitat de Girona, Spain
[10] Unit for Detection and Treatment of Cardiovascular Diseases and Nephrology Unit, Hospital Universitari Arnau de Vilanova, Institut de Recerca Biomèdica (IRB), Lleida, Spain
[11] CIBER Epidemiology and Public Health, Instituto de Salud Carlos III, Madrid, Spain
[12] Serra-Hunter Fellow, Department of Medicine, University of Barcelona, Spain

Correspondence to: María Grau, #143 Casanova St. 08036 Barcelona (Spain); Email: mariagrau@ub.edu

Abstract

To explore the role of chronic inflammation inherent to autoimmune diseases in the development of subclinical atherosclerosis and arterial stiffness, this study recruited two population-based samples of individuals with and without autoimmune disease (ratio 1:5) matched by age, sex, and education level and with a longstanding (≥6 years) diagnosis of autoimmune disease. Common carotid intima media thickness (IMT) and arterial distensibility and compliance were assessed with carotid ultrasound. Multivariable linear and logistic regression models were adjusted for 10-year cardiovascular risk. In total, 546 individuals with and without autoimmune diseases (91 and 455, respectively) were included. The mean age was 66 years (standard deviation 12), and 240 (43.9%) were women. Arterial stiffness did not differ according to the presence of autoimmune diseases. In men, the diagnosis of autoimmune diseases significantly increased common carotid IMT [beta-coefficient (95% confidence interval): 0.058 (0.009; 0.108); p-value=0.022] and the percentage with IMT ≥ 75th percentile [1.012 (0.145; 1.880); p-value=0.022]. Women without autoimmune disease were more likely to have IMT ≥ the 75th percentile [-2.181 (-4.214; -0.149); p-value=0.035], but the analysis of IMT as a continuous variable did not yield significant results. In conclusion, subclinical carotid atherosclerosis, but not arterial stiffness, was more common in men with autoimmune diseases. Women did not show significant differences in any of these carotid features. Sex was an effect modifier in the association between common carotid IMT values and the diagnosis of autoimmune diseases.

Keywords Atherosclerosis; Autoimmune Diseases; Cardiovascular Diseases; Carotid Intima-Media Thickness

Introduction

Cardiovascular diseases are the main cause of death in Western countries [1]. Their common basis is adverse structural and functional changes within vascular walls, specifically atherosclerosis and arteriosclerosis, which tend to coexist, causing progressive, diffuse, and age-related deterioration in all vascular beds [2]. Atherosclerosis is a chronic inflammatory and degenerative process that mainly occurs in large and medium-sized arteries and is morphologically characterized by asymmetric focal thickenings of the innermost layer of the artery, the intima [3]. Arteriosclerosis is degenerative stiffness of the arterial beds, defined as the reduced capability of an artery to expand and contract in response to pressure changes.

The premature arterial degeneration observed in individuals with autoimmune disease may be a consequence of the chronic inflammation inherent to these disorders [4, 5, 6, 7]. Additionally, the cardiovascular risk profile, which is significantly worse in individuals with autoimmune diseases than in the general population [8], is directly associated with both carotid IMT and arterial stiffness values [9, 10]. Most studies that have addressed subclinical atherosclerosis included participants with autoimmune disease, who were usually recruited in hospitals; therefore, they were more likely to have advanced disease stages, which somewhat limited the generalizability of the study results.

The objective of this study was to assess the prevalence of subclinical atherosclerosis (common carotid IMT) and arterial stiffness (distensibility and compliance) in individuals with a longstanding (≥6 years) diagnosis of autoimmune disorders (inflammatory polyarthropathies, systemic connective tissue disorders, inflammatory bowel diseases, and spondylopathies) compared to the general population.

Methods

We carried out a cross-sectional analysis of a population-based sample recruited in Girona Province (northeastern Spain) in 2005 in the context of the REGICOR (REgistre Gironí del COR, or Girona Heart Registry) study. Recruitment details have been described elsewhere [11]. Briefly, participants were randomly selected from the city of Girona (approximately 70,000 inhabitants) and three surrounding rural towns. Inclusion criteria required that participants be free of terminal disease, not institutionalized, aged 45 or older at baseline. and residents of the referral area for at least six months/year (reflecting the stable seasonal presence of a large number of retirees). Participants were contacted by a letter informing them of the aims of the study and the tests to be performed. If they were willing to participate, they were asked to fast for at least 10 hours before their appointment at the health examination site. The participation rate was 73.8%. Participants were reexamined in 2010, and carotid IMT measurements were performed [9]. All participants were duly informed about the study and provided their written consent to participate, and the results of the examination were sent to each of them. The study protocol was approved by the local ethics committee (CEIm-PSMAR 2008/3046/I; 2016/7075/I).

From these data, we selected a sample of exposed individuals diagnosed with autoimmune disease (i.e., inflammatory polyarthropathies, systemic connective tissue disorders, inflammatory bowel diseases, spondylopathies) and nonexposed individuals (no autoimmune diseases). The samples were matched 1:5 by age, sex and education level.

Autoimmune diseases

The diagnosis of autoimmune diseases was obtained from the System for the Development of Research in Primary Care (SIDIAP) database, which includes the anonymized electronic medical records of approximately 80% of the Catalan population [12]. These diagnoses were coded according to the International Classification of Diseases 10th edition (ICD-10) and divided into four groups: (1) inflammatory bowel diseases, (2) inflammatory polyarthropathies, (3) systemic connective tissue disorders, and (4) spondylopathies (Supplementary Table 1).

Measurements

Examinations were performed by a team of trained nurses and interviewers. A precision scale that was easy to calibrate was used to measure weight and height with the participants in their underwear and barefoot. Body mass index was determined as the weight divided by the squared height (kg/m^2). Blood pressure was measured with a periodically calibrated sphygmomanometer (OMRON 711). A cuff appropriate for the upper arm circumference (young, adult, obese) was selected for each participant. Measurements were performed in a seated position after 5 minutes of rest. Two measurements were taken, and the lower value was recorded for the study. Standardized questionnaires were used to collect sociodemographic and lifestyle variables, along with previous history of and treatments for diabetes, hypertension and hypercholesterolemia. Current smoking was defined as active smoking within the preceding year. Blood was drawn after 10-14 h of fasting. Total and high-density lipoprotein (HDL) cholesterol

concentrations were directly measured (Roche Diagnostics, Basel, Switzerland). Low-density lipoprotein (LDL) cholesterol was calculated by the Friedewald equation whenever triglycerides were <3.4 mmol/l (300 mg/dl). The coronary risk in participants aged 35-74 years was calculated by the REGICOR function adapted from the original Framingham function and validated in the Spanish population [13].

Carotid ultrasound

Two trained sonographers performed carotid ultrasound examinations at the follow-up reexamination. An Acuson XP128 ultrasound machine equipped with an L75-10 MHz transducer and extended frequency software was used (Acuson-Siemens, Mountainview, California, United States). The image analyses were performed by expert trained readers with validated software (eTRACK) used in previous studies [14].

Common carotid intima media thickness

B-mode ultrasound images of the common carotid artery segment were obtained in DICOM format with a resolution of 0.043 mm/p. Image files were recorded and sent to the Academic Vascular Image Centre in Amsterdam (AVICA) for analysis (gold standard). Measurements were made in a 1-cm segment in the distal common carotid artery (1 cm proximal to the dilation of the carotid bulb) of both the right and left arteries. Measurements were made every 1 mm in the 1-cm segment, from which the mean values were calculated. Repeatability analysis was performed in 42 participants who were examined by 3 sonographers at 2 different visits. The intraclass correlation coefficients between sonographers and within each sonographer's results for the mean common carotid artery intima media thickness were 0.83 and 0.85, respectively. The

coefficient of variation was 7.3%, and the average maximum within-subject (absolute) difference was 0.098 mm.

A fully automatic deep-learning method able to properly locate the intima media region and then estimate the IMT was used (Supplementary Table 2). This machine-learning procedure is based on convolutional neural networks and was validated using the IMT estimates performed in AVICA as the gold standard [15]. Left and right common carotid IMT values were obtained for each participant, and the mean was considered in the analysis. As a proxy of the presence of atherosclerotic plaques, men and women with common carotid IMT values ≥ the 75th percentile of the population reference values were identified [9, 16].

Arterial stiffness

We obtained the arterial distensibility coefficient and compliance coefficient, defined as the relative and absolute change, respectively, in the cross-sectional area per unit of pressure. During the carotid ultrasound scan, the anterior and posterior walls of the distal right and left common carotid arteries were visualized in B-mode. To obtain the M-mode anterior wall intima-lumen and posterior wall lumen-intima tracings, the sonographer switched from full B-mode to a 1/3 B-mode 2/3 M-mode image of the distal common carotid. The 1/3 B-mode image guides the M-mode. The movement of the arterial walls on the 2/3 M-mode image shows waveforms with double-line patterns of the arterial walls over time. eTRACK software traces the waveforms of the leading edges of the anterior wall intima-lumen and posterior wall lumen-intima interfaces. If the contours of both walls are identified for at least 2 heartbeats, the software can calculate lumen diameter parameters and heart rates. Based on this information, other

outcome parameters (e.g., distensibility and compliance coefficient) were derived using the equations from the Task Force III Summary of Clinical Applications of Arterial Stiffness [17].

Statistical analysis

Continuous variables were summarized as the means (standard deviation) or medians [interquartile range] when they were nonnormally distributed, and categorical variables were summarized as proportions. Effect modification of the relationship of diagnosed autoimmune diseases with subclinical atherosclerosis and arterial stiffness was anticipated a priori [18, 19] and tested with the -2 loglikelihood test of nested models with and without interaction terms. The sample was stratified by sex.

Chi-square, Student's t, and Mann-Whitney U tests were used as appropriate to compare the prevalence of cardiovascular risk factors at baseline in individuals with and without autoimmune diseases and to ascertain arterial distensibility and compliance and the distribution of cardiovascular risk factors by terciles of common carotid IMT values. We fitted linear regression models for men and women, adjusted for the cardiovascular risk factors that significantly modified arterial distensibility and compliance and common carotid IMT. Additionally, a logistic regression was fitted in the case of individuals with a common carotid IMT value ≥ the 75th percentile. To assess the effects of vasodilation factors and anti-inflammatory drugs, we performed a sensitivity analysis excluding current smokers and a multivariable analysis further adjusted for the use of calcium-channel blockers and anti-inflammatory drugs.

The statistical analysis was performed with the R Statistical Package (R Foundation for Statistical Computing, Vienna, Austria; Version 4.0.3).

Results

We included 91 individuals with autoimmune disease and 455 without this diagnosis (n=546). The most common group of autoimmune diseases was inflammatory polyarthropathies in both men (74.0%) and women (51.2%). Systemic connective tissue disorders in women (22.0%) and inflammatory bowel diseases in men (14.0%) were the second most prevalent group of diseases. Men with autoimmune diseases had higher prevalences of hypertension and diabetes, higher LDL cholesterol levels and higher 10-year cardiovascular risk values than those without such diseases. In women, the cardiovascular risk profile did not differ according to the presence of these diseases (Table 1). Biomarkers of subclinical atherosclerosis and arterial stiffness were similar in individuals with and without autoimmune diseases, except for the proportion with IMT ≥ percentile 75, which was significantly lower in the group of women with an autoimmune diagnosis (Table 2).

The 10-year cardiovascular risk was associated, in all instances, with the tercile of common carotid IMT and the distensibility and compliance coefficients (Tables 3, 4 and 5). The risk score used to adjust the multivariate models integrated 8 variables (sex, age, systolic and diastolic blood pressure, total and HDL cholesterol, diabetes, and smoking habit), most of which were significantly correlated with the terciles of subclinical atherosclerosis and arterial stiffness.

The models adjusted for 10-year cardiovascular risk showed that a diagnosis of autoimmune disease in men was associated with a significantly higher mean common carotid IMT values [beta-coefficient (95% confidence interval): 0.058 (0.009; 0.108); p-

value=0.022]. This association was not significant in women [-0.023 (-0.071; 0.025); p-value=0.353]. In addition, the prevalence of common carotid IMT ≥ 75th percentile was higher in men with autoimmune diseases than in those without [1.012 (0.145; 1.880); p-value=0.022]; in contrast, women without autoimmune disease were more likely to have IMT ≥ 75th percentile [-2.181 (-4.214; -0.149); p-value=0.035]. No significant differences were found for arterial stiffness biomarkers (Table 6). Finally, no differences were observed in the sensitivity analysis when current smokers were excluded (Supplementary Table 3) or after further adjustment for the use of calcium-channel blockers or anti-inflammatory drugs (Supplementary Tables 4 and 5).

Discussion

The diagnosis of autoimmune diseases was a risk factor for subclinical atherosclerosis in men in our cohorts of individuals with and without autoimmune diseases matched by age, sex, and education level. Sex acted as an effect modifier in this association: the difference was not significant in women. In contrast, arterial stiffness, as measured by the coefficients of distensibility and compliance, was not increased in individuals with autoimmune diseases.

Autoimmune diseases as a risk factor for subclinical atherosclerosis

Previous studies have shown higher prevalences of subclinical atherosclerosis and clinically overt cardiovascular disease in individuals diagnosed with autoimmune disorders [4, 5, 20, 21, 22, 23]. Thus, immune-mediated inflammation is likely to play a pivotal role in the pathogenesis of atherosclerosis, as it is involved in endothelial dysfunction, plaque rupture and thrombosis [7, 24]. Specifically, for inflammatory joint

diseases, the central event in synovitis and autoimmune atherosclerosis is the accumulation of inflammatory cells and mediators in the synovial tissue and vessel wall, respectively [25]. Therefore, the most recent European League Against Rheumatism guidelines promote the proactive management of cardiovascular risk in individuals with inflammatory polyarthritis and spondylopathies. The primary preventive and therapeutic goal is to control the underlying autoimmune inflammatory process [26]. These recommendations have also been proposed for individuals with systemic lupus erythematosus [27] but could likely be extended to individuals with any systemic connective tissue disorder.

Participant sex modified the effect of autoimmune diseases on IMT

The magnitude of the effect of the diagnosis of autoimmune diseases on subclinical atherosclerosis was higher in men than in women. Indeed, the stratified analysis showed that the effect of exposure to autoimmune diseases on common carotid IMT values remained significant only in men. On the one hand, men participating in our study were older and had a worse cardiovascular risk profile than the women, which could explain the sex-related differences observed in common carotid IMT. This observation concurs with previous studies performed in Spain and in other countries [9, 18, 28, 29]. On the other hand, Freirix et al. described the absence of intima media thickening in women with systemic lupus erythematosus or systemic sclerosis; thus, definite atherosclerosis (plaque detection) frequently occurred without signs of subclinical atherosclerosis (increased IMT) in patients with both autoimmune diseases [30]. This observation could help explain the nonsignificant results found in our study, despite the increased cardiovascular risk traditionally observed in women with autoimmune disease [31].

Arterial stiffness and systemic inflammation

Several studies in the general population revealed an association between inflammatory biomarkers and arterial stiffness [6, 32, 33, 34]. However, our cross-sectional study did not show significant differences in these biomarkers between individuals with and without autoimmune diseases. First, the individuals with autoimmune diseases had varying disease severity because they were selected randomly from a population [11]. Second, most previous studies used carotid-femoral pulse wave velocity, the gold standard for assessing regional arterial stiffness, which is a value usually obtained by tonometry or mechanotransducers [32, 33, 34]. Since we performed an ultrasound analysis, which is commonly used to assess local mechanical properties of arterial walls, the measures used to assess arterial stiffness were carotid distensibility and compliance [35]. Nevertheless, the adjusted coefficients indicated higher resistance to vascular deformation in individuals with autoimmune diseases but did not reach statistical significance.

Limitations

Our study has several limitations. First, the added value of common carotid IMT for cardiovascular risk prediction beyond the classic risk factors remains controversial [36, 37]. In addition, the reproducibility of IMT measures is a controversial issue [38] that we have optimized by adopting the use of a previously validated machine-learning method [39]. The use of carotid ultrasound enabled the detection of arterial stiffness in the carotid wall but did not allow the measurement of carotid-femoral pulse wave velocity, which is the gold standard for assessing this variable. Second, it was beyond

the scope of the objectives of our study to measure blood biomarkers (e.g., systemic inflammation, endothelial dysfunction, prothrombotic state) to explore the potential mechanisms that may accelerate atherosclerosis in patients with autoimmune disease [40]. To avoid misclassification bias, we used the medical diagnosis of autoimmune disease as a robust marker of inflammatory status. Although these diagnoses were extracted from routinely collected data that may reflect underreporting, the SIDIAP database has been validated for research in cardiovascular epidemiology [41] and rheumatic diseases [42]. Indeed, the prevalence of autoimmune diseases found in SIDIAP concurred with the results reported in previous studies based on other datasets [43, 44, 45]. Third, a low prevalence of autoimmune diseases was reflected in our population-based study. Nevertheless, we obtained consistent results from our multivariable analysis adjusted for 10-year cardiovascular risk, which was represented by a composite score with variables that showed significant differences in the bivariate analysis. Indeed, the sensitivity analysis yielded similar results when adjusted for the use of drugs with anti-inflammatory or vasodilation effects (e.g., calcium-channel blockers) and after the exclusion of current smokers. In addition, cigarette smoking has been shown to attenuate endothelium-dependent vasodilation [46]. A priori, this effect might be similar in smokers with and without autoimmune diseases because the sample selection was not based on this variable. Finally, to avoid selection bias, our cohorts were matched by age, sex and education level and did not present significant differences in 10-year cardiovascular risk. Although this approach may reduce the representativeness of the population, the associations found between cardiovascular risk factors and common carotid intima-media thickness concur with those reported in previous studies [9, 29].

Conclusion

Subclinical carotid atherosclerosis, but not stiffness, was more common in men with autoimmune diseases than in the general population. No significant differences were found in women with and without autoimmune diseases in these carotid features. Sex was an effect modifier for the association between the diagnosis of autoimmune diseases and the common carotid IMT values.

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Compliance with ethics standards

Conflicts of interest The authors declare that they have no conflicts of interest.

Ethics approval We declare that our study complies with the principles of the Declaration of Helsinki and that the locally appointed ethics committee has approved the research protocol.

Informed consent Informed consent was obtained from all recruited subjects.

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