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, 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. Mean age was 66 years (standard deviation 12), and 240 (43.9%) were women. Arterial stiffness did not differ according to 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 having IMT ≥ percentile 75 [1.012 (0.145; 1.880); p-value=0.022]. Women without autoimmune disease were more likely to have IMT ≥ percentile 75 [-2.181 (-4.214; -0.149); p-value=0.035] but analysis of IMT as a continuous variable did not yield significant results. In conclusion, subclinical carotid atherosclerosis, but not arterial stiffness, was higher 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 change within vascular walls, specifically atherosclerosis and arteriosclerosis – which tend to co-exist, 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 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, 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, usually recruited in-hospital; therefore, they are more likely to have advanced disease stages. This somewhat limits the generalization of 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 longstanding (≥6 years) diagnosis of autoimmune disorders (inflammatory polyarthropathies, systemic connective tissue disorders, inflammatory bowel diseases, and spondylopathies), compared to 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 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 measures were taken [9]. All participants were duly informed and provided their written consent to participate in the study 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 non-exposed 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 in 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 of easy calibration was used for weight and height measurement with participants in underwear and barefoot. Body mass index was determined as weight divided by squared height (kg/m^2). Blood pressure was measured with a periodically calibrated sphygmomanometer (OMRON 711). A cuff adapted to the upper arm perimeter (young, adult, obese) was selected for each participant. Measurements were performed in a seated position after a 5-minute 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 and treatments for diabetes, hypertension and hypercholesterolemia. Current smoking was defined as actively smoking within the preceding year. Blood was withdrawn after 10-14 h of fasting. Total and high-density lipoprotein (HDL) cholesterol concentrations were determined by direct methodology (Roche Diagnostics, Basel, Switzerland). Low-density lipoprotein (LDL) cholesterol was calculated by the Friedewald equation

whenever triglycerides were <3.4mmol/l (300 mg/dl). Coronary risk in participants aged 35-74 years was calculated by the REGICOR function adapted from the original Framingham function and validated for the Spanish population [13].

Carotid ultrasound

Two trained sonographers performed the carotid ultrasound examinations at 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 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 were 0.83 and 0.85, respectively. The coefficient of variation was 7.3% and the maximum within-subject (absolute) difference had an average of 0.098 mm.

A fully automatic deep-learning method able to properly localize 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 were obtained for each participant and the mean considered in the analysis. As a proxy of atherosclerotic plaque presence, men and women with common carotid IMT values ≥ percentile 75 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 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 the double-line patterns of the arterial walls over time. The eTRACK software traces the wave-forms of the leading edges of 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 mean (standard deviation), or median [interquartile range] when their distribution departed from normal, and categorical variables 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-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 common carotid IMT value ≥ percentile 75. To assess the effect of vasodilation factors and anti-inflammatory drugs, we performed sensitivity analysis excluding current smokers and a multivariable analysis further adjusted for calcium-channel blockers and for anti-inflammatory drugs.

Statistical analysis was done 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 prevalence of hypertension and diabetes and higher LDL cholesterol and 10-year cardiovascular risk values, compared to 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 IMT ≥ percentile 75, which was significantly lower in 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 (Table 3, 4 and 5). The risk score used to adjust the multivariate models integrates 8 variables (sex, age, systolic and diastolic blood pressure, total and HDL cholesterol, diabetes, and smoking habit), most of them 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 significantly increased the 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 ≥ percentile 75 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 ≥ percentile 75 [-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 when further adjusted for 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 from our cohorts of individuals with and without autoimmune diseases matched by age, sex, and education level. Sex acted as an effects modifier in this association: the difference was not significant in women. In contrast, arterial stiffness, as measured with 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 prevalence 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, being involved in endothelial dysfunction, plaque rupture and thrombosis [7, 24]. Specifically for inflammatory joint diseases, the central event of 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 guideline promotes a 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 modifies 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 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 developed 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) occurred frequently without signs of subclinical atherosclerosis (increased IMT) in both autoimmune diseases [30]. This observation could help to 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 between individuals with and without autoimmune diseases. First, individuals having autoimmune diseases presented with a wide range of severity because they were selected randomly on a population basis [11]. Second, most previous studies used the carotid-femoral pulse wave velocity, the gold standard for assessing regional arterial stiffness, a value usually obtained by tonometry or mechanotransducers [32, 33, 34]. Since we performed an ultrasound analysis, commonly used to assess local mechanical properties of arterial walls, the measures considered to assess arterial stiffness were carotid distensibility and compliance [35]. Nevertheless, the adjusted coefficients pointed out 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 classical risk factors remains controversial [36, 37]. In addition, the reproducibility of IMT measures is a controversial issue [38] that we have minimized with a previously validated machine-learning procedure [39]. On the other hand, the use of carotid ultrasound revealed the arterial stiffness of the carotid wall but did not allow measurement of carotid-femoral pulse wave velocity, the gold standard for assessing this variable. Second, it was beyond 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 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 previous studies in other datasets [43, 44, 45]. Third, the 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, a composite score with variables that showed significant differences in the bivariate analysis. Indeed, the sensitivity analysis yielded similar results when adjusted by drugs with anti-inflammatory or vasodilation effect (e.g. calcium-channel blockers) and excluding current smokers. In addition, cigarette smoking has shown to attenuate the 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 a selection bias, our cohorts were matched by age, sex and education level and did not present significant differences in the 10-year cardiovascular risk. Although this approach may hamper the population representativeness of the studies, the associations found between cardiovascular risk factors and common carotid intima-media thickness concur with previous studies [9, 29].

Conclusion

Subclinical carotid atherosclerosis, but not stiffness, was higher 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 in the association between the diagnosis of autoimmune diseases and the common carotid IMT values.

Acknowledgments The authors appreciate the System for the Development of Research in Primary Care (SIDIAP) database access, the expert review on autoimmune diseases by Dr. Albert Escola Campabadal, and revision of the English text by Elaine Lilly PhD.

Funding Supported by grants from the Instituto de Salud Carlos III FEDER (CP12/03287, CP17/00012), Health Research Fund (FIS 2003/HERMES PI20471, PI070403, ETES: PI07/90415, FIS11/06765) and Principado de Asturias Regional Government (IDI-2018-000176). Partially supported with European Regional Development Fund funds and grants from Spain's Ministerio de Ciencia, Innovación y Universidades (RTI2018-095232-B-C21) and the Generalitat de Catalunya (2017 SGR 1742).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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

Informed consent The informed consent has been obtained from all the recruited subjects.

References

1. World Health Statistics. Monograph on the Internet. Geneva: World Health Organization; 2011 [cited 2020 May 13]. Available at: https://www.who.int/data/gho/data/themes/topics/noncommunicable-diseases
2. Cavalcante JL, Lima JA, Redheuil A, Al-Mallah MH. Aortic stiffness: current understanding and future directions. J Am Coll Cardiol. 2011;57(14):1511-22. doi: 10.1016/j.jacc.2010.12.017.
3. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med. 2005;352(16):1685-1695. doi:10.1056/NEJMra043430
4. Baena-Díez JM, Garcia-Gil M, Comas-Cufí M, Ramos R, Prieto-Alhambra D, Salvador-González B, et al. Association between chronic immune-mediated inflammatory diseases and cardiovascular risk. Heart. 2018;104(2):119-126. doi:10.1136/heartjnl-2017-311279
5. Dalbeni A, Giollo A, Bevilacqua M, Cioffi G, Tagetti A, Cattazzo F, et al. Traditional cardiovascular risk factors and residual disease activity are associated with atherosclerosis progression in rheumatoid arthritis patients. Hypertens Res. 2020;43(9):922-928. doi: 10.1038/s41440-020-0441-1.
6. Jain S, Khera R, Corrales-Medina VF, Townsend RR, Chirinos JA. "Inflammation and arterial stiffness in humans". Atherosclerosis. 2014;237(2):381-90.
7. Zanoli L, Briet M, Empana JP, Cunha PG, Mäki-Petäjä KM, Protogerou AD, et al. Vascular consequences of inflammation: a position statement from the ESH Working Group on Vascular Structure and Function and the ARTERY Society. J Hypertens. 2020;38(9):1682-1698. doi: 10.1097/HJH.0000000000002508.

8. Agüero F, González-Zobl G, Baena-Díez JM, Dégano IR, Garcia-Gil M, Alzamora MT, et al. Prevalence of lower extremity peripheral arterial disease in individuals with chronic immune mediated inflammatory disorders. Atherosclerosis. 2015;242(1):1-7. doi:10.1016/j.atherosclerosis.2015.06.054

9. Grau M, Subirana I, Agis D, Ramos R, Basagaña X, Martí R, et al. Carotid intima-media thickness in the Spanish population: reference ranges and association with cardiovascular risk factors. Rev Esp Cardiol (Engl Ed). 2012;65(12):1086-1093. doi:10.1016/j.recesp.2012.04.026

10. Martí-Lluch R, Garcia-Gil MDM, Camós L, Comas-Cufí M, Elosua-Bayés M, Blanch J, et al. Differences in cardio-ankle vascular index in a general Mediterranean population depending on the presence or absence of metabolic cardiovascular risk factors. Atherosclerosis. 2017;264:29-35. doi: 10.1016/j.atherosclerosis.2017.07.013.

11. Grau M, Subirana I, Elosua R, Solanas P, Ramos R, Masiá R, et al. Trends in cardiovascular risk factor prevalence (1995-2000-2005) in northeastern Spain. Eur J Cardiovasc Prev Rehabil. 2007;14(5):653-659. doi:10.1097/HJR.0b013e3281764429

12. Bolíbar B, Fina Avilés F, Morros R, Garcia-Gil Mdel M, Hermosilla E, Ramos R, et al. SIDIAP database: electronic clinical records in primary care as a source of information for epidemiologic research. Med Clin (Barc). 2012;138(14):617-621. doi:10.1016/j.medcli.2012.01.020

13. Marrugat J, Subirana I, Comín E, Cabezas C, Vila J, Elosua R, et al. Validity of an adaptation of the Framingham cardiovascular risk function: the VERIFICA

Study. J Epidemiol Community Health. 2007;61(1):40-47. doi:10.1136/jech.2005.038505

14. de Groot E, van Leuven SI, Duivenvoorden R, Meuwese MC, Akdim F, Bots ML, et al. Measurement of carotid intima-media thickness to assess progression and regression of atherosclerosis. Nat Clin Pract Cardiovasc Med. 2008;5(5):280-288. doi:10.1038/ncpcardio1163

15. Vila MDM, Remeseiro B, Grau M, Elosua R, Betriu À, Fernandez-Giraldez E, et al. Semantic segmentation with DenseNets for carotid artery ultrasound plaque segmentation and CIMT estimation. Artif Intell Med. 2020;103:101784. doi:10.1016/j.artmed.2019.101784

16. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, et al. Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. Cerebrovasc Dis. 2012;34(4):290-296. doi:10.1159/000343145

17. Van Bortel LM, Duprez D, Starmans-Kool MJ, Safar ME, Giannattasio C, Cockcroft J, Kaiser DR, Thuillez C. Clinical applications of arterial stiffness, Task Force III: recommendations for user procedures. Am J Hypertens. 2002;15(5):445-52. doi: 10.1016/s0895-7061(01)02326-3.

18. Łoboz-Rudnicka M, Jaroch J, Bociąga Z, Rzyczkowska B, Uchmanowicz I, Polański J, et al. Impact of cardiovascular risk factors on carotid intima-media thickness: sex differences. Clin Interv Aging. 2016;11:721-31. doi: 10.2147/CIA.S103521

19. DuPont JJ, Kenney RM, Patel AR, Jaffe IZ. Sex differences in mechanisms of arterial stiffness. Br J Pharmacol. 2019;176(21):4208-4225. doi: 10.1111/bph.14624.

20. Wang P, Guan SY, Xu SZ, Li HM, Leng RX, Li XP, et al. Increased carotid intima-media thickness in rheumatoid arthritis: an update meta-analysis. Clin Rheumatol. 2016;35(2):315-23. doi: 10.1007/s10067-015-3130-8.

21. Henrot P, Foret J, Barnetche T, Lazaro E, Duffau P, Seneschal J, et al. Assessment of subclinical atherosclerosis in systemic lupus erythematosus: A systematic review and meta-analysis. Joint Bone Spine. 2018;85(2):155-163. doi: 10.1016/j.jbspin.2017.12.009.

22. Wu GC, Leng RX, Lu Q, Fan YG, Wang DG, Ye DQ. Subclinical Atherosclerosis in Patients With Inflammatory Bowel Diseases: A Systematic Review and Meta-Analysis. Angiology. 2017;68(5):447-461. doi: 10.1177/0003319716652031.

23. Bai R, Zhang Y, Liu W, Ma C, Chen X, Yang J, et al. The Relationship of Ankylosing Spondylitis and Subclinical Atherosclerosis: A Systemic Review and Meta-Analysis. Angiology. 2019;70(6):492-500. doi: 10.1177/0003319718814309.

24. Balogh E, Pusztai A, Hamar A, Végh E, Szamosi S, Kerekes G, et al. Autoimmune and angiogenic biomarkers in autoimmune atherosclerosis. Clin Immunol. 2019;199:47-51. doi: 10.1016/j.clim.2018.12.011

25. Szekanecz Z, Kerekes G, Végh E, Kardos Z, Baráth Z, Tamási L, et al. Autoimmune atherosclerosis in 3D: How it develops, how to diagnose and what to do. Autoimmun Rev. 2016;15(7):756-69. doi: 10.1016/j.autrev.2016.03.014

26. Agca R, Heslinga SC, Rollefstad S, Heslinga M, McInnes IB, Peters MJ, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. Ann Rheum Dis. 2017;76(1):17-28. doi: 10.1136/annrheumdis-2016-209775

27. Mosca M, Tani C, Aringer M, Bombardieri S, Boumpas D, Brey R, et al. European League Against Rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies. Ann Rheum Dis. 2010;69(7):1269-74. doi: 10.1136/ard.2009.117200

28. Coll B, Betriu A, Feinstein SB, Valdivielso JM, Zamorano JL, Fernández E. The role of carotid ultrasound in assessing carotid atherosclerosis in individuals at low-to-intermediate cardiovascular risk. Rev Esp Cardiol (Engl Ed). 2013;66(12):929-34. doi: 10.1016/j.rec.2013.05.030

29. Wu TW, Hung CL, Liu CC, Wu YJ, Wang LY, Yeh HI. Associations of Cardiovascular Risk Factors with Carotid Intima-Media Thickness in Middle-Age Adults and Elders. J Atheroscler Thromb. 2017;24(7):677-686. doi: 10.5551/jat.37895

30. Frerix M, Stegbauer J, Kreuter A, Weiner SM. Atherosclerotic plaques occur in absence of intima-media thickening in both systemic sclerosis and systemic lupus erythematosus: a duplexsonography study of carotid and femoral arteries and follow-up for cardiovascular events. Arthritis Res Ther. 2014;16(1):R54. doi: 10.1186/ar4489

31. Kurmann RD, Mankad R. Atherosclerotic Heart Disease in Women With Autoimmune Rheumatologic Inflammatory Conditions. Can J Cardiol. 2018;34(4):381-389. doi: 10.1016/j.cjca.2018.01.015

32. Mendoza-Pinto C, Rojas-Villarraga A, Molano-González N, García-Carrasco M, Munguía-Realpozo P, Etchegaray-Morales I, Morales-Sánchez H, Berra-Romani R, Cervera R. Endothelial dysfunction and arterial stiffness in patients with systemic lupus erythematosus: A systematic review and meta-analysis. Atherosclerosis. 2020;297:55-63. doi: 10.1016/j.atherosclerosis.2020.01.028.

33. Ambrosino P, Tasso M, Lupoli R, Di Minno A, Baldassarre D, Tremoli E, Di Minno MN. Non-invasive assessment of arterial stiffness in patients with rheumatoid arthritis: a systematic review and meta-analysis of literature studies. Ann Med. 2015;47(6):457-67. doi: 10.3109/07853890.2015.1068950.

34. Wang P, Huang L, Xu Q, Xu L, Deng FY, Lei SF. Assessment of Aortic Stiffness in Patients with Rheumatoid Arthritis Using Pulse Wave Velocity: An Update Meta-analysis. Arch Med Res. 2019;50(7):401-412. doi: 10.1016/j.arcmed.2019.10.010.

35. Teixeira R, Vieira MJ, Gonçalves A, Cardim N, Gonçalves L. Ultrasonographic vascular mechanics to assess arterial stiffness: a review. Eur Heart J Cardiovasc Imaging. 2016;17(3):233-46. doi: 10.1093/ehjci/jev287.

36. Katakami N, Mita T, Gosho M, Takahara M, Irie Y, Yasuda T, et al. Clinical Utility of Carotid Ultrasonography in the Prediction of Cardiovascular Events in Patients with Diabetes: A Combined Analysis of Data Obtained in Five Longitudinal Studies. J Atheroscler Thromb. 2018;25(10):1053-1066.

37. Kokubo Y, Watanabe M, Higashiyama A, Nakao YM, Nakamura F, Miyamoto Y. Impact of Intima-Media Thickness Progression in the Common Carotid Arteries on the Risk of Incident Cardiovascular Disease in the Suita Study. J Am Heart Assoc. 2018;7(11):e007720. doi:10.1161/JAHA.117.007720

38. Polak JF, O'Leary DH. Carotid Intima-Media Thickness as Surrogate for and Predictor of CVD. Glob Heart. 2016;11(3):295-312.e3. doi:10.1016/j.gheart.2016.08.006

39. Vila MDM, Remeseiro B, Grau M, Elosua R, Betriu À, Fernandez-Giraldez E, et al. Semantic segmentation with DenseNets for carotid artery ultrasound plaque segmentation and CIMT estimation. Artif Intell Med. 2020;103:101784. doi: 10.1016/j.artmed.2019.101784.

40. Nagy G, Németh N, Buzás EI. Mechanisms of vascular comorbidity in autoimmune diseases. Curr Opin Rheumatol. 2018;30(2):197-206. doi:10.1097/BOR.0000000000000483

41. Ramos R, Balló E, Marrugat J, Elosua R, Sala J, Grau M, et al. Validity for use in research on vascular diseases of the SIDIAP (Information System for the Development of Research in Primary Care): the EMMA study. Rev Esp Cardiol (Engl Ed). 2012;65(1):29-37. doi:10.1016/j.recesp.2011.07.017

42. Fina-Aviles F, Medina-Peralta M, Mendez-Boo L, Hermosilla E, Elorza JM, Garcia-Gil M, et al. The descriptive epidemiology of rheumatoid arthritis in Catalonia: a retrospective study using routinely collected data. Clin Rheumatol. 2016;35(3):751-757. doi:10.1007/s10067-014-2801-1

43. Carmona L, Villaverde V, Hernández-García C, Ballina J, Gabriel R, Laffon A; EPISER Study Group. The prevalence of rheumatoid arthritis in the general

population of Spain. Rheumatology (Oxford). 2002;41(1):88-95. doi:10.1093/rheumatology/41.1.88

44. López P, Mozo L, Gutiérrez C, Suárez A. Epidemiology of systemic lupus erythematosus in a northern Spanish population: gender and age influence on immunological features. Lupus. 2003;12(11):860-865. doi:10.1191/0961203303lu469xx

45. Saro Gismera C, Riestra Menéndez S, Sánchez Fernández R, Milla Crespo A, Lacort Fernández M, Argüelles Fernández G, et al. Epidemiology in inflammatory bowel disease in five areas of Asturias. Spain. An Med Interna. 2003;20(5):232-238.

46. Sarabi M, Lind L. Short-term effects of smoking and nicotine chewing gum on endothelium-dependent vasodilation in young healthy habitual smokers. J Cardiovasc Pharmacol. 2000;35(3):451-6. doi: 10.1097/00005344-200003000-00016.

Table 1. Characteristics of the whole sample and stratified by sex

	Autoimmune diseases					
	Men			Women		
	No *N*=256	Yes *N*=50	*p*-value	No *N*=199	Yes *N*=41	*p*-value
Age (years), mean (SD)	67 (12)	68 (12)	0.813	64 (12)	64 (12)	0.955
Education level, n (%)			0.986			0.949
No studies or primary school	171 (66.8)	34 (68.0)		112 (56.3)	22 (53.7)	
Secondary school	48 (18.8)	9 (18.0)		56 (28.1)	12 (29.3)	
University	37 (14.5)	7 (14.0)		31 (15.6)	7 (17.1)	
Autoimmune diseases, n (%)			--			--
Inflammatory polyarthropathies	--	37 (74.0)		--	21 (51.2)	
Systemic connective tissue disorders	--	3 (6.0)		--	10 (24.4)	
Inflammatory bowel diseases	--	7 (14.0)		--	9 (22.0)	
Spondylopathies	--	3 (6.0)		--	1 (2.4)	
Smoker, n (%)			0.393			0.776
Never	59 (23.0)	17 (34.0)		146 (73.4)	31 (75.6)	
Former	55 (21.5)	8 (16.0)		20 (10.1)	5 (12.2)	
Current	138 (53.9)	25 (50.0)		29 (14.6)	4 (9.8)	
Body mass index, mean (SD)	27.4 (3.5)	28.4 (3.8)	0.104	26.7 (4.3)	27.1 (5.4)	0.693
Systolic blood pressure (mmHg), mean (SD)	138 (20)	142 (21)	0.188	128 (20)	130 (20)	0.675
Diastolic blood pressure (mmHg), mean (SD)	77 (10)	78 (11)	0.546	73 (9)	75 (9)	0.229
Hypertension, n (%)	138 (55.0)	37 (74.0)	0.020	89 (45.9)	19 (46.3)	0.999
Anti-inflammatory treatment, n (%)	12 (4.7)	3 (6.0)	0.719	27 (13.6)	10 (24.4)	0.131
Calcium channel blockers treatment, n (%)	24 (9.4)	9 (18.0)	0.121	4 (2.0)	1 (2.4)	0.999
Total cholesterol (mg/dl), mean (SD)	194 (36)	184 (35)	0.064	212 (37)	210 (33)	0.788
HDL cholesterol (mg/dl), mean (SD)	48 (11)	46 (11)	0.135	57 (11)	58 (10)	0.540
LDL cholesterol (mg/dl), mean (SD)	124 (32)	115 (32)	0.056	136 (32)	133 (27)	0.636
Triglycerides (mg/dl), median [IQR]	97	106	0.417	89	86	0.890

	[69; 127]	[68; 154]		[66; 114]	[68; 115]	
Glycemia (mg/dl), median [IQR]	96 [90; 106]	98 [90; 117]	0.270	92 [85; 100]	87 [83; 96]	0.057
Diabetes, n (%)	65 (26.5)	21 (42.9)	0.034	32 (16.8)	6 (14.6)	0.920
10-year cardiovascular risk (%), median [IQR]	4.9 [2.9; 8.3]	6.6 [4.3; 10.0]	0.038	2.3 [1.5; 4.0]	2.3 [1.7; 3.3]	0.740

HDL: High-density lipoprotein. IQR: interquartile range. LDL: Low-density lipoprotein. SD: standard deviation

Table 2. Subclinical atherosclerosis and arterial stiffness biomarkers by diagnosis of autoimmune diseases

	Autoimmune disease					
	Men			Women		
	No *N*=256	Yes *N*=50	*p*-value	No *N*=199	Yes *N*=41	*p*-value
Atherosclerosis measures						
Common carotid IMT (mm), mean (SD)	0.72 (0.14)	0.75 (0.16)	0.197	0.68 (0.15)	0.65 (0.10)	0.086
Common carotid IMT – percentile 75, n (%)	41 (16.02)	14 (28.00)	0.069	46 (23.12)	3 (7.32)	0.038
Arterial stiffness measures						
Distensibility ($mmHg^{-1}$), mean (SD)	25.99 (9.75)	25.20 (9.65)	0.604	30.53 (11.11)	31.02 (12.63)	0.820
Compliance (cm/mmHg), mean (SD)	0.78 (0.25)	0.77 (0.26)	0.688	0.72 (0.23)	0.75 (0.24)	0.444

IMT: Intima-media thickness. SD: standard deviation

Table 3. Characteristics of the sample by terciles of common carotid intima-media thickness

	Men				Women			
	T1 *N*=102	T2 *N*=102	T3 *N*=102	*p*-value	T1 *N*=80	T2 *N*=80	T3 *N*=80	*p*-value
Common carotid IMT (mm), mean (SD)	0.59 (0.05)	0.70 (0.03)	0.88 (0.11)	<0.001	0.54 (0.04)	0.66 (0.03)	0.83 (0.12)	<0.001
Age (years), mean (SD)	60 (13)	68 (11)	74 (9)	<0.001	55 (11)	66 (10)	72 (9)	<0.001
Education level, n (%)				0.031				<0.001
No studies or primary school	59 (57.8)	66 (64.7)	80 (78.4)		30 (37.5)	48 (60.0)	56 (70.0)	
Secondary school	23 (22.5)	20 (19.6)	14 (13.7)		21 (26.2)	25 (31.2)	22 (27.5)	
University	20 (19.6)	16 (15.7)	8 (7.8)		29 (36.2)	7 (8.8)	2 (2.5)	
Autoimmune diseases	13 (12.7)	21 (20.6)	16 (15.7)	0.310	14 (17.5)	18 (22.5)	9 (11.2)	0.166
Smoker, n (%)	49 (49.0)	57 (57.0)	57 (55.9)	0.469	19 (24.4)	8 (10.1)	6 (7.7)	0.005
Body mass index, mean (SD)	27.7 (3.6)	27.4 (3.9)	27.6 (3.2)	0.788	25.6 (4.7)	27.1 (4.5)	27.7 (4.0)	0.010
Systolic blood pressure (mmHg), mean (SD)	132 (17)	139 (19)	145 (23)	<0.001	117 (16)	130 (19)	138 (19)	<0.001
Diastolic blood pressure (mmHg), mean (SD)	78 (10)	79 (9)	75 (11)	0.009	73 (9)	75 (10)	74 (8)	0.300
Hypertension, n (%)	45 (44.6)	58 (58.0)	72 (72.0)	<0.001	23 (29.9)	34 (43.0)	51 (64.6)	<0.001
Anti-inflammatory treatment, n (%)	5 (4.9)	7 (6.9)	3 (2.9)	0.431	7 (8.8)	15 (18.8)	15 (18.8)	0.129
Calcium channel blockers treatment, n (%)	8 (7.8)	12 (11.8)	13 (12.7)	0.490	2 (2.5)	2 (2.5)	1 (1.3)	0.999
Total cholesterol (mg/dl), mean (SD)	201 (39)	189 (37)	187 (31)	0.008	202 (39)	214 (31)	219 (37)	0.012
HDL cholesterol (mg/dl), mean (SD)	47 (10)	50 (11)	46 (11)	0.037	57 (10)	58 (12)	56 (10)	0.700
LDL cholesterol (mg/dl), mean (SD)	132 (34)	118 (32)	118 (28)	0.003	128 (33)	136 (27)	141 (31)	0.028
Triglycerides (mg/dl), median [IQR]	104 [74; 139]	85 [63; 129]	95 [73; 127]	0.203	77 [56; 107]	89 [68; 123]	92 [78; 121]	0.012
Glycemia (mg/dl), median [IQR]	96 [89; 106]	96 [91; 108]	97 [91; 109]	0.345	88 [83; 95]	93 [86; 101]	92 [88; 102]	0.005
Diabetes, n (%)	19 (19.2)	26 (27.1)	41 (41.4)	0.002	9 (11.7)	13 (16.7)	16 (20.8)	0.312
10-year cardiovascular risk (%), median [IQR]	4.0 [2.6; 6.6]	5.9 [3.3; 8.7]	8.2 [5.1; 12.6]	<0.001	1.5 [0.9; 2.6]	2.9 [1.7; 5.0]	2.9 [2.3; 4.5]	<0.001

IMT: Intima-media thickness. IQR: interquartile range; SD: standard deviation

Table 4. Characteristics of the sample by terciles of arterial distensibility

	Men				Women			
	T1 *N*=98	T2 *N*=98	T3 *N*=97	*p*-value	T1 *N*=80	T2 *N*=80	T3 *N*=79	*p*-value
Arterial distensibility (mmHg-1), mean (SD)	16.5 (3.6)	24.6 (2.3)	36.7 (7.6)	<0.001	19.1 (4.6)	29.2 (3.0)	43.6 (7.4)	<0.001
Age (years), mean (SD)	73 (10)	68 (11)	59 (13)	<0.001	72 (9)	67 (10)	54 (10)	<0.001
Education level, n (%)				0.069				<0.001
No studies or primary school	73 (74.5)	59 (60.2)	63 (64.9)		61 (76.2)	47 (58.8)	26 (32.9)	
Secondary school	18 (18.4)	18 (18.4)	20 (20.6)		14 (17.5)	29 (36.2)	24 (30.4)	
University	7 (7.1)	21 (21.4)	14 (14.4)		5 (6.2)	4 (5.0)	29 (36.7)	
Autoimmune diseases	17 (17.3)	14 (14.3)	17 (17.5)	0.789	15 (18.8)	13 (16.2)	13 (16.5)	0.897
Smoker, n (%)	52 (53.6)	54 (55.7)	47 (49.0)	0.633	5 (6.4)	10 (12.7)	18 (23.4)	0.009
Body mass index, mean (SD)	28.2 (4.0)	27.5 (3.4)	26.9 (3.1)	0.044	28.2 (4.1)	27.4 (4.4)	24.9 (4.4)	<0.001
Systolic blood pressure (mmHg), mean (SD)	149 (23)	137 (14)	128 (16)	<0.001	143 (18)	129 (15)	112 (13)	<0.001
Diastolic blood pressure (mmHg), mean (SD)	77 (11)	79 (9)	77 (10)	0.283	76 (10)	75 (8)	70 (8)	<0.001
Hypertension, n (%)	67 (69.8)	56 (57.7)	42 (44.2)	0.002	59 (76.6)	36 (45.6)	12 (15.4)	<0.001
Anti-inflammatory treatment, n (%)	4 (4.1)	6 (6.1)	4 (4.1)	0.834	18 (22.5)	13 (16.2)	6 (7.6)	0.033
Calcium channel blockers treatment, n (%)	19 (19.4)	4 (4.1)	6 (6.2)	0.001	4 (5.0)	1 (1.2)	0 (0.0)	0.131
Total cholesterol (mg/dl), mean (SD)	186 (33)	188 (37)	200 (38)	0.016	211 (32)	218 (37)	205 (40)	0.073
HDL cholesterol (mg/dl), mean (SD)	47 (11)	48 (12)	48 (10)	0.842	55 (12)	57 (11)	58 (10)	0.326
LDL cholesterol (mg/dl), mean (SD)	117 (30)	118 (32)	131 (34)	0.005	133 (26)	142 (31)	130 (34)	0.041
Triglycerides (mg/dl), median [IQR]	104 [73; 135]	98 [68; 132]	94 [64; 124]	0.464	103 [78; 135]	90 [66; 107]	75 [55; 100]	<0.001
Glycemia (mg/dl), median [IQR]	98 [92; 110]	98 [92; 115]	93 [87; 100]	0.001	97 [89; 107]	91 [85; 97]	87 [81; 93]	<0.001
Diabetes, n (%)	35 (36.8)	29 (30.9)	17 (18.5)	0.019	23 (30.7)	10 (12.8)	5 (6.4)	<0.001
10-year cardiovascular risk (%), median [IQR]	7.3 [4.7; 12.5]	6.3 [4.0; 9.3]	3.6 [2.6; 6.2]	<0.001	4.3 [2.6; 6.0]	2.5 [1.8; 4.5]	1.4 [0.9; 2.3]	<0.001

IQR: interquartile range; SD: standard deviation

Table 5. Characteristics of the sample by terciles of arterial compliance

	Men				Women			
	T1 *N*=98	T2 *N*=98	T3 *N*=97	*p*-value	T1 *N*=81	T2 *N*=81	T3 *N*=77	*p*-value
Arterial compliance (cm/mmHg), mean (SD)	0.55 (0.10)	0.79 (0.07)	1.12 (0.21)	<0.001	0.51 (0.10)	0.74 (0.06)	1.06 (0.16)	<0.001
Age (years), mean (SD)	70 (11)	68 (12)	62 (13)	<0.001	69 (11)	65 (11)	58 (12)	<0.001
Education level, n (%)				0.853				<0.001
No studies or primary school	68 (69.4)	63 (64.3)	64 (66.0)		55 (67.9)	53 (65.4)	26 (33.8)	
Secondary school	16 (16.3)	22 (22.4)	18 (18.6)		23 (28.4)	19 (23.5)	25 (32.5)	
University	14 (14.3)	13 (13.3)	15 (15.5)		3 (3.7)	9 (11.1)	26 (33.8)	
Autoimmune diseases	16 (16.3)	16 (16.3)	16 (16.5)	0.999	15 (18.5)	13 (16.0)	13 (16.9)	0.914
Smoker, n (%)	51 (52.6)	59 (60.8)	43 (44.8)	0.083	7 (8.9)	9 (11.2)	17 (22.7)	0.032
Body mass index, mean (SD)	27.4 (4.0)	28.2 (3.6)	27.0 (3.0)	0.064	27.1 (4.2)	27.1 (4.7)	26.1 (4.4)	0.265
Systolic blood pressure (mmHg), mean (SD)	147 (22)	138 (16)	131 (18)	<0.001	139 (21)	129 (16)	117 (16)	<0.001
Diastolic blood pressure (mmHg), mean (SD)	78 (11)	77 (10)	77 (10)	0.429	76 (9)	74 (8)	72 (9)	0.011
Hypertension, n (%)	64 (67.4)	54 (55.1)	47 (49.5)	0.039	50 (64.1)	35 (43.8)	22 (28.9)	<0.001
Anti-inflammatory treatment, n (%)	5 (5.1)	6 (6.1)	3 (3.1)	0.698	13 (16.0)	17 (21.0)	7 (9.1)	0.116
Calcium channel blockers treatment, n (%)	12 (12.2)	10 (10.2)	7 (7.2)	0.497	3 (3.7)	1 (1.2)	1 (1.3)	0.624
Total cholesterol (mg/dl), mean (SD)	193 (38)	189 (36)	193 (36)	0.683	215 (35)	211 (34)	209 (41)	0.580
HDL cholesterol (mg/dl), mean (SD)	49 (12)	48 (11)	47 (10)	0.627	56 (12)	57 (11)	58 (10)	0.612
LDL cholesterol (mg/dl), mean (SD)	123 (34)	119 (31)	125 (33)	0.369	137 (29)	135 (30)	134 (34)	0.841
Triglycerides (mg/dl), median [IQR]	88 [70; 132]	101 [73; 141]	96 [66; 129]	0.353	95 [75; 133]	90 [68; 110]	75 [57; 99]	0.001
Glycemia (mg/dl), median [IQR]	97 [92; 108]	98 [90; 112]	95 [88; 102]	0.219	96 [88; 107]	91 [84; 100]	88 [83; 95]	<0.001
Diabetes, n (%)	30 (32.6)	30 (30.9)	21 (22.8)	0.292	21 (27.3)	12 (15.4)	5 (6.6)	0.002
10-year cardiovascular risk (%), median [IQR]	7.6 [4.3; 11.4]	6.1 [3.4; 9.2]	3.6 [2.7; 6.2]	<0.001	3.3 [2.1; 5.4]	2.5 [1.6; 4.5]	1.7 [0.9; 2.8]	<0.001

IQR: interquartile range; SD: standard deviation

Table 6. Subclinical atherosclerosis biomarkers by diagnosis of autoimmune diseases

	Autoimmune diseases					
	Men			Women		
	Coefficient	95% confidence interval	*p*-value	Coefficient	95% confidence interval	*p*-value
Atherosclerosis biomarkers						
Common carotid IMT (mm) *	0.058	0.009; 0.108	0.022	-0.023	-0.071; 0.025	0.353
Common carotid IMT – percentile 75†	1.012	0.145; 1.880	0.022	-2.181	-4.214; -0.149	0.035
Arterial stiffness biomarkers						
Arterial distensibility ($mmHg^{-1}$) *	-0.458	-3.988; 3.073	0.800	-0.803	-4.320; 2.714	0.655
Arterial compliance (cm/mmHg) *	-0.025	-0.128; 0.078	0.637	0.008	-0.074; 0.091	0.844

IMT: Intima-media thickness. SD: standard deviation. All models have been adjusted for 10-year cardiovascular risk.
*Linear regression model. †Logistic regression model.