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Prevalence of lower extremity peripheral arterial disease in individuals with chronic immune mediated inflammatory disorders

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ABSTRACT

Objective: To compare the prevalence of lower extremity peripheral artery disease (PAD) and to assess whether age-associated progression in ankle-brachial index (ABI) differs between individuals with chronic immune-mediated inflammatory diseases (CIID) and the general population.
Methods: Pooled analysis with data from individuals aged 50 years and older with ABI measurements, obtained from population-based cross-sectional studies conducted in Catalonia (Spain). Information on three CIID diagnoses (i.e., inflammatory bowel disease, systemic connective tissue disorders, and inflammatory polyarthropathies and spondylopathies, considered as one entity for purposes of analysis) was obtained from electronic medical records. To ascertain the statistical association between PAD and CIID, logistic regression models were fitted and adjusted for age, sex, and cardiovascular risk factors. We tested the interaction between age and CIID diagnosis for ABI values.
Results: We included 8799 individuals, 312 (3.6%) with CIID. The age-standardized prevalence of PAD was higher in the CIID group (12% vs. 6% in general population, $p = 0.001$), and the model adjusted for age, sex, and cardiovascular risk factors also showed higher risk in individuals with CIID [Odds Ratio (95% confidence interval) = 1.65 (1.15–2.38); $p = 0.007$]. The inflammatory polyarthropathies/spondylopathies diagnosis was significantly associated with PAD in the fully adjusted model [1.80 (1.18–2.75); $p = 0.006$]. The atherosclerotic process was accelerated in individuals with CIID, compared to the general population (p for interaction < 0.001).
Conclusion: In individuals with CIID, age-standardized prevalence of PAD was significantly higher than in the general population and the atherosclerotic process was accelerated. However, only inflammatory polyarthropathies/spondylopathies was associated with significant risk of PAD.

1. Introduction

Inflammation plays a key role in coronary artery disease and other manifestations of atherosclerosis [1]. The premature atherosclerosis observed in chronic immune mediated inflammatory disorders (CIID) may be a consequence of the chronic inflammation inherent to these disorders [2,3]. Due to the long asymptomatic induction period of atherosclerosis, subclinical indicators of lower extremity peripheral artery disease (PAD), such as ankle-brachial index (ABI), can provide early risk detection [4,5]. In addition, pathological ABI is a strong predictor of future cardiovascular events [6].

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PAD is relatively frequent in general population in western countries [7–9] and the prevalence increased an alarming 13.1% from 2000 to 2010 [10]. Several reports have shown higher prevalence of PAD in individuals with CIID (e.g., systemic lupus erythematosus [11], rheumatoid arthritis [12], or inflammatory bowel diseases [13]). However, these studies have a modest sample size, participants have usually been recruited in-hospital, and therefore the patients are more likely to have advanced disease stages. In contrast, a population-based sample that includes individuals in a wide range of disease severity and consistently uses the same non-exposed population would enable a more accurate assessment of the prevalence of PAD associated with CIID.

The objectives of the study were: (1) To determine in individuals aged 50 years and older whether the prevalence of PAD in patients with CIID is higher than in the general population and (2) to assess whether age-associated ABI progression differs between individuals with and without CIID.

2. Methods

2.1. Design and data sources

We carried out a pooled analysis of individual data obtained from two large, population-based, cross-sectional projects that included ABI measures: REGICOR (Girona Heart Registry [Registre Gironí del Cor]) and PERART (Peripheral Artery Disease Study) [7,8]. The REGICOR project is comprised of three cross-sectional studies carried out in 1995, 2000, and 2005 in Girona Province (Catalonia, Northeast Spain), which has a population of approximately 674,000 [14]. For the present analysis, we used data from the 2005 study and from the 2010 follow-up examination of the cohorts recruited in 1995 and 2000 [15]. The PERART study selected a sample from patients attending 28 primary healthcare centers within the metropolitan area of the City of Barcelona and the county of Barcelonès Nord-Maresme between 2006 and 2008. These urban and semi-rural centers cover a population of approximately 600,000 inhabitants [16]. Both studies used similar methodology [17]. All participants were duly informed and signed their consent to participate in the studies, which were approved by the local ethics committees.

The protocol of the present study, which selected REGICOR and PERART participants aged 50 years and older, was approved by the local ethics committee (CEIC-PSMAR).

2.2. Ankle-brachial index measurement

In accordance with current guidelines [6], after 5-min rest we measured systolic blood pressure in the brachial artery in the antecubital fossa in the control arm with a continuous Doppler device, then in the distal calf, using the Doppler probe to determine systolic blood pressure in the supine position at the right and left posterior and anterior tibial arteries. Right and left ABI were calculated as the ratio of the higher of 2 systolic pressures in the lower limbs (posterior and anterior tibial arteries) to the control brachial systolic pressures. The lower of the values obtained was used for analysis. Individuals with ABI $\geq$1.4 were excluded from the evaluation because the possible influence of arterial wall stiffness made it impossible to discard arterial obstruction. PAD was considered when an individual presented with ABI <0.9.

2.3. Chronic immune-mediated inflammatory disorders

The diagnosis of CIID 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 [18]. 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 (Table 1). We considered inflammatory polyarthropathies and spondylopathies as a single group since both pathologies mainly present with joint damage and share the recommendations for cardiovascular risk prevention [19].

2.4. Other measurements

The PERART and REGICOR questionnaires were based on standardized World Health Organization (WHO) surveys [17,20]. Sociodemographic variables and data on tobacco use, history and treatments for hypertension, dyslipidemia, and diabetes and history of cardiovascular disease (e.g. myocardial infarction, angina, stroke, and intermittent claudication) were recorded. Anthropometric measures were collected by physical examination. Claudication was assessed using the Edinburgh questionnaire [21]. Symptomatic PAD was considered when an individual presented with ABI <0.9 and claudication.

Fasting (>10 h) blood samples were analyzed in local laboratories that satisfied external quality-control requirements [8,14]. Triglycerides, glucose, total cholesterol, high density lipoprotein (HDL) cholesterol were measured by standard methods. When triglycerides were <300 mg/dL, low density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula.

Cardiovascular risk in participants with no history of cardiovascular disease was calculated by the Framingham-REGICOR (Girona Heart Registry [Registre Gironí del Cor]) function validated for the Spanish population [22]. In addition, the REASON risk score to select candidates for screening of PAD with ABI was estimated in all participants [23].

2.5. Statistical analysis

Continuous variables were summarized as mean and standard

Table 1
Chronic immune mediated inflammatory disorders diagnoses included in each group.

ICD-10 code	Title
K50–K52	**Noninfective enteritis and colitis**
K50	Crohn disease (regional enteritis)
K51	Ulcerative colitis
K52	Other noninfective gastroenteritis and colitis
M05–M14, L40.5	**Inflammatory polyarthropathies**
M05	Seropositive rheumatoid arthritis
M06	Other rheumatoid arthritis
M07	Psoriatic and enteropathic arthropathies
M08	Juvenile arthritis
M09	Juvenile arthritis in diseases classified elsewhere
M10	Gout
M11	Other crystal arthropathies
M12	Other specific arthropathies
M13	Other arthritis
L40.5	Arthropathic psoriasis
M30–M35, G635	**Systemic connective tissue disorders**
M30	Polyarteritis nodosa and related conditions
M31	Other necrotizing vasculopathies
M32	Systemic lupus erythematosus
M33	Dermatopolymyositis
M34	Systemic sclerosis
M35	Other systemic involvement of connective tissue
G63.5	Polyneuropathy in systemic connective tissue disorders
M45–M46	**Spondylopathies**
M45	Ankylosing spondylitis
M46	Other inflammatory spondylopathies