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Original article

Auto-antibodies do not influence development of atherosclerotic plaques in rheumatoid arthritis

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Abstract

Background: Many questions remain unanswered about premature atherosclerosis in rheumatoid arthritis (RA). Besides inflammation, some studies have suggested the role of autoantibodies on its pathogenesis.
Objective: The aim of this study was to investigate the presence of antibodies against phospholipids, beta2-glycoprotein1 (beta2-gp1), lipoprotein lipase, and heat shock proteins (Hsp) in RA patients and to evaluate their possible association with subclinical carotid atherosclerosis.
Methods: Seventy-one RA patients and 53 age- and sex-matched controls were selected to perform anticardiolipin antibodies (aCL) (IgG and IgM), anti-beta2-gp1 (IgG, IgM, and IgA), anti-lipoprotein lipase (anti-LPL), anti-Hsp 60, and anti-Hsp 65 by ELISA tests. Intima-medial thickness (IMT) of common carotid and presence of plaques were assessed by high-resolution B-mode ultrasonography. Exclusion criteria were smoking, diabetes, and arterial hypertension. Lipoproteins, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and fibrinogen levels, as well as health assessment questionnaire (HAQ) and disease activity score (DAS) 28 were also evaluated.
Results: Age (48.93 ± 12.31 vs. 45.37 ± 9.37 years; $p = 0.20$) and body mass index (BMI) ($p = 0.69$) were similar in RA and controls, as well as female gender ($p = 0.56$). The mean IMT was similar between RA and controls (0.721 ± 0.16 vs. 0.667 ± 0.14 mm, $p = 0.07$) but the frequency of plaques was higher in RA (14.1% vs. 1.9%; $p = 0.02$). In RA patients, IMT measurements did not differ according to the presence or absence of these antibodies: IgG aCL (0.62 ± 0.64 vs. 0.72 ± 0.17 mm, $p = 0.24$), IgM aCL (0.65 ± 0.79 vs. 0.73 ± 0.17 mm, $p = 0.33$), anti-Hsp 60 (0.78 ± 0.20 vs. 0.71 ± 0.16 mm, $p = 0.27$), anti-Hsp 65 (0.73 ± 0.16 vs. 0.72 ± 0.17 mm, $p = 0.77$), IgG anti-beta2-gp1 (0.73 ± 0.16 vs. 0.71 ± 0.17 mm, $p = 0.72$), and anti-CCP (0.71 ± 0.16 vs. 0.76 ± 0.20 mm, $p = 0.36$). In addition, IMT did not correlate with antibodies titers: IgG aCL ($r = -0.09$, $p = 0.47$), IgM aCL ($r = -0.15$, $p = 0.21$), anti-Hsp 60 ($r = 0.10$, $p = 0.42$), anti-Hsp 65 ($r = 0.05$, $p = 0.69$), IgG anti-beta2-gp1 ($r = -0.07$, $p = 0.57$), IgM anti-beta2-gp1 ($r = -0.05$, $p = 0.69$), IgA anti-beta2-gp1 ($r = 0.03$, $p = 0.79$), and anti-CCP ($r = -0.07$, $p = 0.57$). RA patients with plaques had a significantly higher age compared to those without plaques ($p = 0.001$), as well as higher mean IMT ($p < 0.001$), total cholesterol ($p = 0.001$), and LDL ($p = 0.003$).
Conclusions: In RA a clear association between all autoantibodies studied herein and increased IMT or presence of plaques was not observed. The great prevalence of carotid atherosclerosis in RA was related to age, total and LDL cholesterol, as identified in normal population.
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Keywords: Rheumatoid arthritis; Atherosclerosis; Autoantibody; Antiphospholipid; Anticardiolipin; Anti-beta2-glycoprotein 1; Heat shock protein; Lipoprotein lipase

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1. Introduction

Several diagnostic methods such as carotid ultrasound (US), myocardium perfusion scintillography, and coronary artery angiography showed that rheumatoid arthritis (RA) patients have a high frequency of carotid atherosclerosis, cerebrovascular, ischemic, and coronary disease [1–5]. In fact, a higher risk of cardiovascular events was observed in RA compared to general population [6] and attention should be given to conventional risk factors [6–8]. In normal population, besides the important role of dyslipoproteinemia, systemic arterial hypertension and smoking in the pathogenesis of atherosclerosis, some markers of systemic inflammation such as fibrinogen and C-reactive protein (CRP) have also been implicated to this risk which supports the notion that this process is a consequence of an inflammatory process in artery vessels [9,10]. In this regard, RA itself has been recognized as an independent risk factor due to persistent inflammation [7]. Recent studies have also suggest the role of autoimmunity in the pathogenesis of atherosclerosis due to the detection of antibodies against antigens expressed in the atheroma plaque, such as oxidized LDL (LDLox), heat shock proteins (Hsp 60 and Hsp 65), membrane phospholipids, and beta 2-glycoprotein 1 (beta2-gp1) [11–16]. These antibodies were identified in a higher frequency in RA patients than normal population and than individuals with atherosclerotic events but without this disease [10,17], but their relevance and definitive association in RA atherosclerosis were not completely determined [8]. The aim of the present study is to define if subclinical atherosclerosis in RA may be associated to an autoimmune process. The role of autoantibodies against phospholipids, Hsp, cyclic citrullinated peptide (CCP), beta2-gp1 and lipoprotein lipase (LPL) in RA and its association with the presence of carotid plaques may yield a greater understanding of clinical and therapeutic approach to atherosclerosis in patients with this disease.

2. Methods

2.1. Study population

Seventy-one RA patients (according to the ACR criteria) from the RA outpatient clinic of the Rheumatology Division of Federal University Hospital in Santa Catarina were consecutively included. Fifty three healthy age- and sex-matched subjects from the local community were selected as control group. Exclusion criteria for both groups were smoking (in the last 5 years), diabetes mellitus (DM), hypertension, pregnancy, renal failure, chronic hepatopathy, nephrotic syndrome, and hypothyroidism. All subjects using any lipid-lowering drugs such as statins or fibrates (in the last 3 months) were also excluded. Fifty-eight patients (81.6%) were taking prednisone (mean dose 7.6 ± 3.4 mg/day), 78.9% methotrexate, 12.7% chloroquine diphosphate, and 14.1% leflunomide. Health assessment questionnaire (HAQ) [18], disease activity score with 28 joints (DAS 28) [19], and simplified disease activity index (SDAI) [20] were assessed in RA patients. The study was approved by the local Ethics Committee and informed consent was obtained from all participants.

2.2. Study protocol

2.2.1. Carotid ultrasound (US)

Common carotid artery US with intima-medial thickness (IMT) measurement and analysis for the presence of plaques was blind performed by the same examiner in all subjects using a Philips Bothel WA, USA, ATL HDI 3000 Ultrasound device, high resolution mode B with multifrequency 5–12 MHz linear transducer. All subjects were examined in a supine position, neck extended, and the chin facing the counterlateral side. Carotids were examined bilaterally in the longitudinal and transversal planes. Average IMT calculation in millimeters was obtained from 3 measurements performed 1 cm below the common carotid bifurcation in a region free of atherosclerotic plaques [21]. IMT was considered normal if below 0.9 mm and plaque was defined if greater than 1.5 mm [4].

Laboratorial evaluation: All RA patients and controls were in their usual diet and were fasting for at least 12 h at the beginning of the study. Blood samples were obtained immediately before carotid ultrasound for baseline immunological and biochemical analysis.

2.2.2. Serum immunological analysis

Anticardiolipin antibodies (aCL): Presence of IgG and IgM anticardiolipin antibodies (aCL) were analyzed by enzyme-linked immunosorbent assay as described elsewhere [22]. A positive result was defined as greater than or equal to 3 SD above the mean optical density (OD) for ten normal control sera. Anti-heat shock protein (Hsp) 60 and 65: Antibodies against recombining human Hsp 60 and against *Mycobacterium bovis* Hsp 65 were detected by ELISA (INOVA Diagnostics, Inc., Quanta Lite Hsp 65 and Hsp 60 kits). Optical density equal or higher 0.5 were considered positive as described elsewhere [23]. Anti-beta2-gp1: IgG, IgM, and IgA anti-beta2-gp1 were determined by ELISA (INOVA Diagnostics, Inc.). For IgG and IgM anti-beta2-gpl were considered positive if greater than 20 UI and for IgA anti-beta2-gp1 if greater than 25 UI [24]. Anti-CCP: IgG anti-CCP were detected by ELISA (INOVA Diagnostics, Inc.) and were considered positive if greater than 20 UI [25]. Antibody to lipoprotein lipase (LPL): Anti-LPL reactivity of IgG isotype was measured by ELISA (enzyme-linked immunosorbent assay), as previously described [26]. Briefly, Costar polystyrene plates were coated overnight with commercially available LPL from bovine milk (5 μg/ml) (Sigma Chem Co. St Louis, MO, USA) and then blocked with 15% adult bovine serum in Tris buffered saline (ABS-T) for 1 h at room temperature (RT). Test was performed with serum samples 1/100 diluted in ABS-T incubated for 1 h at RT. Anti-LPL IgG isotype antibodies were determined with alkaline-phosphatase conjugated goat anti-human IgG (Sigma Chem Co. St Louis, MO, USA). The reaction was developed with *p*-nitrophenyl phosphate and optical density (OD) read at 405 nm with a Labsystems Multiskan MS (Helsinki, Finland). Positive results were defined if OD values were $\geq$3SD above

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