

## SINGLE MEASUREMENTS OF C-REACTIVE PROTEIN AND DISEASE ACTIVITY SCORES ARE NOT PREDICTORS OF CAROTID ATHEROSCLEROSIS IN RHEUMATOID ARTHRITIS PATIENTS

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### Abstract

**Background:** Although inflammation has a defined role in the pathogenesis of atherosclerosis, the link between rheumatoid arthritis (RA) parameters of disease activity and atherosclerotic findings are not defined.

**Objective:** To investigate the association between subclinical carotid atherosclerosis and clinical/laboratorial parameters of RA systemic inflammatory activity.

**Methods:** Seventy-one RA patients were consecutively selected and compared to 53 healthy controls. Smoking, diabetes and hypertension were excluded, as well as the use of statins or fibrates. B-mode carotid ultrasound was performed in all subjects. CRP, ESR and fibrinogen were determined in both groups. Clinical assessment of RA activity included DAS 28 and SDAI. Correlation between plaques and intima-media thickness (IMT) of common carotid arteries and inflammatory parameters was evaluated.

**Results:** Carotid plaques were more prevalent in RA patients than in controls (14.1% vs. 1.9%,  $p=0.02$ ) and marginally increased IMT was observed ( $0.72 \pm 0.17$  vs.  $0.67 \pm 0.15$ mm,  $p=0.07$ ). RA patients with plaques had older age ( $p=0.001$ ) and increased IMT ( $p<0.001$ ), but low SDAI ( $p=0.025$ ) compared to those without plaques. RA patients with plaques had also longer disease duration, although this difference did not reach statistical significance ( $p=0.06$ ). No significant correlations were found between IMT and ESR ( $p=0.80$ ), CRP ( $p=0.75$ ), fibrinogen ( $p=0.94$ ), HAQ ( $p=0.89$ ) and DAS 28 ( $p=0.13$ ).

**Conclusions:** Carotid atherosclerosis is more frequently detected in RA but its prevalence was not correlated with isolated inflammatory markers measurement or noncumulative activity scores. These findings reinforce the need to evaluate subclinical atherosclerosis in RA patients, and to find predictors of atherosclerotic lesions.

**Keywords:** Rheumatoid Arthritis; Atherosclerosis; Inflammation; C-reactive Protein.

**Abbreviations:** RA: rheumatoid arthritis; CRP: C-reactive protein; DAS 28: disease activity score with 28 joints; SDAI: simplified disease activity index; HAQ: health assessment questionnaire; US: ultrasound; DMARDs: disease-modifying anti-rheumatic drugs

### Resumo

**Introdução:** Embora a inflamação tenha um papel definido na patogênese da aterosclerose, a ligação entre parâmetros de atividade de artrite reumatóide (AR) e achados de aterosclerose não está estabelecida.

**Objetivos:** Investigar a associação entre aterosclerose subclínica de artérias carótidas e parâmetros clínicos e laboratoriais que refletem atividade inflamatória sistêmica na AR.

**Métodos:** 71 pacientes consecutivos com AR foram selecionados e comparados a 53 controles saudáveis. Fumantes, diabéticos e hipertensos foram excluídos, assim como aqueles que estivessem em uso de estatinas ou fibratos. Ultra-som (US) de carótidas foi executado em todos os participantes. PCR, VS e fibrinogênio foram determinados em ambos os grupos. A avaliação da atividade da AR incluiu DAS 28 e índice de atividade da doença sim-

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plificado (SDAI). Testes de correlações foram feitos entre a presença de placas e a espessura da camada íntimo-medial (IMT) com parâmetros de inflamação.

**Resultados:** Placas nas carótidas foram mais prevalentes na AR (14,1% versus 1,9%,  $p=0,02$ ), e a IMT foi discretamente aumentada ( $0,72 \pm 0,17$  contra  $0,67 \pm 0,15$ mm,  $p=0,07$ ). Pacientes com AR e placas apresentavam idade maior ( $p=0,001$ ), IMT aumentada ( $p < 0,001$ ), SDAI menor ( $p=0,025$ ) e duração maior da doença ( $p=0,06$ ). Nenhuma correlação foi encontrada entre IMT e VHS ( $p=0,80$ ), PCR ( $p=0,75$ ), fibrinogênio ( $p=0,94$ ), HAQ ( $p=0,89$ ) e DAS 28 ( $p=0,13$ ).

**Conclusões:** Aterosclerose de carótidas é detectada com maior frequência na AR, mas não se correlaciona com parâmetros inflamatórios isolados. Estes achados reforçam a necessidade de avaliar a presença de aterosclerose subclínica nos pacientes com AR, e encontrar fatores preditivos de lesão aterosclerótica.

**Palavras-chave:** Artrite reumatóide; Aterosclerose; Inflamação; Proteína C reativa.

## Introduction

Although nowadays we have new diagnostic methods and new efficient drugs in Rheumatoid Arthritis (RA), life expectancy is still reduced in 3 to 10 years compared to the normal population.<sup>1-3</sup> Indeed, death rate in severe RA is similar to that found in patients with lymphoma and coronary artery disease.<sup>4</sup> This higher mortality is mainly due to cardiovascular disease, as a consequence of accelerated atherosclerosis found in this disease.<sup>5-13</sup>

Identification of atherosclerosis on its preclinical phases has become a great challenge in normal population, and includes not only the search for new risk factors but also the use of non-invasive diagnostic methods such as carotids ultrasound (US). In RA patients this issue is also a major concern considering that recent studies have showed a higher prevalence of severe coronary artery disease and higher incidence of silent acute myocardial infarction (AMI) and sudden death in this population, which suggests that atherosclerotic disease is later diagnosed in RA.<sup>14,15</sup>

Previous studies in patients without RA pointed out the importance of inflammation in the atherosclerotic process.<sup>16-20</sup> Indeed, some laboratory tests considered markers of systemic inflammation such

as C-reactive protein (CRP) and fibrinogen have showed correlations with the extension of atherosclerotic lesions and cardiovascular and cerebrovascular clinical events.<sup>21-23</sup>

Considering that isolated measurement of CRP or fibrinogen levels in population without RA were predictors of atherosclerotic findings, we decided to analyze if isolated levels of inflammatory parameters and noncumulative activity scores in RA patients are associated with atherosclerosis in US of carotid arteries.

## Patients and Methods

### Study Population

Seventy-one RA patients (according to the ACR criteria)<sup>24</sup> 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 RA patients (81.6%) were taking prednisone (mean dose  $7.6 \pm 3.4$  mg/day), 81.6% methotrexate, 12.7% chloroquine diphosphate, and 14.1% leflunomide. Health Assessment Questionnaire (HAQ)<sup>25</sup>, Disease Activity Score with 28 joints (DAS 28)<sup>26</sup>, and Simplified Disease Activity Index (SDAI)<sup>27</sup> were assessed in RA patients. The study was approved by the local Ethics Committee and informed consent was obtained from all participants.

### Study protocol

**Carotid ultrasound (US):** Common carotid artery US with intima-medial thickness (IMT) measurement and analysis for the presence of plaques was blindly performed by the same examiner in all subjects using a Philips BothelWA, USA, ATL HDI 3000 Ultrasound device, high resolution B-mode with multifrequency 5-12mHz linear transducer. All subjects were examined in a supine position, neck extended, and the chin facing the counter lateral side. Carotids were examined bilaterally in the longitudinal and transversal planes. Average IMT calculation in millimeters was obtained from 3 mea-

surements performed 1 cm below the common carotid bifurcation in a region free of atherosclerotic plaques. IMT was considered normal if below 0.9 mm and plaque was defined if greater than 1.5 mm.<sup>28,29</sup>

**Laboratorial evaluation:** All RA patients and controls were fasting for at least 12 hours at the beginning of the study before blood tests. IgG anti-CCP were detected by ELISA (INOVA Diagnostics, Inc.) and were considered positive if greater than 20 IU.<sup>30</sup> Rheumatoid factor was quantified using nephelometry (Behring 100), with cut-off > 20UI/ml for positive values. CRP levels were determined by standard nephelometry method, plasma fibrinogen was measured by method of Clauss and erythrocyte sedimentation rate (ESR) was evaluated using Westergren method.

**Statistical Analysis:** Statistical analysis was performed with the statistical program SPSS for Windows, version 12.0 (Chicago, Illinois-USA). Results are presented as the mean  $\pm$  standard deviation (SD) or percentage. Comparisons were performed between RA and control groups using Student T test for quantitative variables and chi-square or the exact Fisher test for qualitative variables. Correlations between variables were made by calculating the correlation coefficient through Pearson correlation tests. Statistical significance was set as below 0.05.

## Results

The distribution of age, gender, body mass index (BMI), and family history was similar among RA and control groups, as demonstrated in Table I. As expected, higher levels of ESR ( $p < 0.001$ ), CRP ( $p < 0.001$ ), and fibrinogen ( $p < 0.001$ ) were detected in RA compared to healthy controls (Table I).

RA patients had a mean disease duration of  $9.02 \pm 0.73$  years, and positive RF and anti-CCP antibodies were detected in 59 patients (83%) and 56 (78.9%), respectively. RA group had a mean DAS 28 of  $4.58 \pm 1.04$ , SDAI of  $46.66 \pm 28.74$ , and HAQ of  $1.29 \pm 0.70$ . None of them was in remission according to the ACR criteria. At the time of the study,

**Table I. Demographical and laboratorial characteristics, carotid intima-media thickness (IMT) measurement and prevalence of plaques in RA patients and controls**

	RA (n = 71)	Control (n = 53)	P
Age (years)	48.9 $\pm$ 12.3	45.4 $\pm$ 9.4	0.20
Female [n(%)]	64 (90.1%)	46 (86.1%)	0.56
BMI (Kg/m <sup>2</sup> )	25.7 $\pm$ 4.6	25.6 $\pm$ 4.6	0.69
Family History [n(%)]	36 (51%)	27 (49%)	0.98
ESR (mm 1st/ hour)	32.66 $\pm$ 22.69	16.12 $\pm$ 10.77	<0.001
CRP (mg/l)	18.18 $\pm$ 23.74	4.03 $\pm$ 4.29	<0.001
Fibrinogen (mg/dl)	366.20 $\pm$ 120.28	289.32 $\pm$ 69.95	<0.001
IMT (mm)	0.72 $\pm$ 0.17	0.67 $\pm$ 0.15	0.07
Plaques [n(%)]	10 (14.1 %)	1 (1.9 %)	0.02

Values expressed in mean  $\pm$  standard deviation (SD) or percentage. BMI = body mass index; Family History = acute myocardial infarction, angina or cerebrovascular disease history; ESR = Erythrocyte Sedimentation Rate; CRP = C-Reactive Protein; IMT = intima-media thickness.

**Table II. Correlations between carotid intima-media thickness (IMT) measurement and clinical/laboratorial parameters in Rheumatoid Arthritis patients**

	r coefficient (p)
Age	0.59 (<0.001)
Disease duration	0.13 (0.27)
BMI	0.19 (0.10)
ESR	-0.03 (0.80)
CRP	0.04 (0.75)
Fibrinogen	0.01 (0.94)
Rheumatoid factor	-0.04 (0.72)
Anti-CCP	-0.07 (0.57)
Tender joints count	-0.21 (0.08)
Swollen joints count	0.18 (0.14)
Patient Assessment	0.00 (1.0)
Physician Assessment	-0.01 (0.94)
Pain (VAS)	0.02 (0.85)
DAS 28	-0.18 (0.13)
SDAI	-0.03 (0.77)
HAQ	0.02 (0.89)
Prednisone	-0.04 (0.73)
Methotrexate	-0.21 (0.12)

BMI = body mass index; ESR = Erythrocyte Sedimentation Rate; CRP = C-Reactive Protein; DAS 28 = disease activity score (28 joints analyzed); SDAI = simplified disease activity index; HAQ = Health Assessment Questionnaire; VAS = visual analog scales.

**Table III. Demographical and laboratorial characteristics, carotid intima-media thickness (IMT) measurement and prevalence of plaques in RA patients and controls**

	RA Plaques + (n=10)	RA Plaques - (n=61)	P
Age (years)	60.20 ± 8.78	47.08 ± 11.86	0.001
Disease duration (years)	12.40 ± 6.22	8.47 ± 6.05	0.06
ESR (mm 1st/ hour)	24.10 ± 14.60	34.07 ± 23.54	0.20
CRP (mg/l)	8.64 ± 8.27	19.75 ± 25.08	0.17
Rheumatoid factor	195.10 ± 281.71	308.13 ± 584.46	0.55
Fibrinogen (mg/dl)	326.04 ± 113.56	371.94 ± 121.08	0.32
Tender joints	6.70 ± 3.43	7.75 ± 5.21	0.54
Swollen joints	7.60 ± 3.68	8.57 ± 4.96	0.55
Pain (VAS)*	5.60 ± 1.64	6.00 ± 2.18	0.58
Patient Assessment*	5.70 ± 1.76	5.91 ± 2.25	0.78
Physician Assessment*	6.90 ± 1.45	6.66 ± 1.81	0.69
DAS28	4.24 ± 1.02	4.64 ± 1.05	0.27
SDAI	35.54 ± 12.34	48.50 ± 30.28	0.025
HAQ	1.58 ± 0.52	1.24 ± 0.72	0.17
Prednisone (mg/day)	7.25 ± 2.75	7.72 ± 3.59	0.70
Methotrexate (mg/week)	20.00 ± 5.00	19.09 ± 5.74	0.66
IMT (mm)	0.91 ± 0.18	0.69 ± 0.15	<0.001

BMI = body mass index; ESR = Erythrocyte Sedimentation Rate; CRP = C-Reactive Protein; DAS 28 = disease activity score (28 joints analyzed); SDAI = simplified disease activity index; HAQ = Health Assessment Questionnaire; IMT = intima-media thickness

\*visual analog scales (VAS) - 0 to 10 for pain, patient global assessment and physician global assessment.

58 patients (81.6%) were taking corticosteroids with a mean prednisone dose of  $7.64 \pm 3.45$  mg/d, and 58 patients were using methotrexate (81.6%).

The mean IMT was marginally increased in RA patients versus controls ( $0.72 \pm 0.17$  vs.  $0.67 \pm 0.15$  mm,  $p=0.07$ ) and plaques were also more frequently observed in RA (14.1% vs. 1.9%,  $p=0.02$ ) (Table I). IMT had a significant positive correlation with age in RA patients (Table II). In contrast, IMT did not correlate with BMI, ESR, CRP, fibrinogen levels, titers of Rheumatoid Factor or anti-CCP antibodies. Moreover, it did not correlate with any of the studied scores (DAS 28, SDAI, HAQ) or current therapy (Table II). Rheumatoid nodules were detected in 9 RA patients (12.68%) but IMT measurement did not differ between those with or without them ( $0.65 \pm 0.15$  vs.  $0.73 \pm 0.17$  mm,  $p=0.13$ ).

The comparison between RA patients with ( $n=10$ , 14.1%) and without plaques ( $n=61$ , 85.9%) revealed that the former had significantly older age ( $p=0.001$ ) and a higher mean IMT ( $p<0.001$ ) (Table III). SDAI scores were lower in RA patients with

plaques than in those without ( $p=0.025$ ). There was a trend toward a higher disease duration in RA patients with plaques although it did not reach statistical significance ( $p=0.06$ ). Patients with plaques had similar levels of ESR ( $p=0.20$ ), CRP ( $p=0.17$ ), RF ( $p=0.55$ ), fibrinogen ( $p=0.32$ ), DAS 28 ( $p=0.27$ ) and HAQ ( $p=0.17$ ) compared to those without plaques (Table III).

## Discussion

This study confirmed that atherosclerosis is more prevalent in RA, since we found higher prevalence of carotid plaques and a trend to increased IMT. However, these carotid US findings in RA patients were not predicted by isolated laboratorial parameters such as CRP or single time point disease activity assessment, in contrast to the normal population in which isolated acute phase tests are related to atherosclerotic findings.<sup>21</sup>

To reach these findings the main classic CAD risk factors such as hypertension, diabetes mellitus and smoking were excluded from our studied population, since they independently increase the development of atherosclerosis.<sup>31-33</sup> These strict exclusion criteria allowed us to identify atherosclerosis due to RA itself and its association with the persistent inflammatory process. Indeed, studies on prevalence of atherosclerosis in RA should be carefully analyzed since well-known classic risk factors are usually present. In our study the use of statins and fibrates was not allowed, not only because they interfere with atherosclerotic findings, but due to their possible beneficial effects on rheumatoid inflammatory parameters.<sup>34-36</sup>

Carotid US was chosen in our study since this method can identify early findings of subclinical atherosclerosis which are predictive of future cardiovascular events.<sup>28,37</sup> Interestingly, in the present study IMT measurements were associated with age and there was a trend of thicker IMT in RA compared to healthy subjects. Moreover, a higher prevalence of atherosclerotic plaques was demonstrated

in RA patients than in controls. Although increased IMT has been observed in other RA studies<sup>29,38-42</sup> two recent studies did not find any difference in IMT measurement between RA and controls.<sup>43,44</sup>

Clinical parameters of rheumatoid inflammatory activity such as tender or swollen joints count, pain and global disease assessment were not related with IMT measurement or presence of plaques. RA assessment scores including DAS 28 and HAQ were also not associated with plaques and IMT. In addition, classic laboratorial parameters of inflammation such as CRP, ESR, fibrinogen, and RF levels did not discriminate thicker IMT or a higher prevalence of plaques in RA.

In our RA population, plaques were observed in older patients, with a trend to be detected in those with a longer disease duration suggesting a possible role of chronic RA inflammation and supporting the notion that time of exposition of the endothelium to systemic inflammation can be important to the development of atherosclerosis. On the other hand, no association was observed between IMT or plaques with HAQ scores, which evaluates functional capacity.

Our results reinforce the need for identification of other cardiovascular risk factors in RA that can predict atherosclerotic lesions and reveal the complex relationship between atherosclerosis, rheumatoid arthritis and inflammation.

Also to be considered is the influence of the therapy of RA on atherosclerotic findings and future clinical events. In this regard, we did not find any association of corticosteroid dose with the presence of plaques or IMT which is in accordance with other studies.<sup>40,45</sup> A study in RA demonstrated a decreased cardiovascular mortality with methotrexate,<sup>46</sup> but no association with carotid findings was detected herein regarding its use or dose. Recent studies have found less cardiovascular clinical events or improvement of endothelial dysfunction in RA patients using anti-TNF drugs.<sup>47-51</sup> On the other hand, one recent study showed increased prevalence of carotid plaques in patients treated with TNF blockers, but probably the group with TNF-blocker had more severe disease.<sup>44</sup>

Our study confirms that RA is associated with subclinical atherosclerosis even in the absence of traditional CAD risk factors. This study also shows that the prevalence of atherosclerosis was not related to isolated inflammatory markers measurement.

However, age and disease duration determined a higher risk of having carotid plaques and increa-

sed IMT. These findings reinforce the need to perform tests searching for hidden atherosclerosis, such as non-invasive carotid ultrasound in RA patients.

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29 de Abril a 1 de Maio de 2009