Subclinical atherosclerosis in ankylosing spondylitis: is there a role for inflammation?

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Article info

Abstract

Objectives: To evaluate the prevalence of subclinical atherosclerosis in patients with ankylosing spondylitis (AS) in comparison to controls with similar cardiovascular risk factors.

Methods: Forty-two consecutive patients with AS and 42 controls matched for age (43.3 ± 11.7 vs. 43.7 ± 11.3, P = 0.89), gender, smoking, diabetes mellitus and arterial hypertension were enrolled. Participants were excluded if a personal cardiovascular disease (CV) history was present. A questionnaire recording demographic data, medical and medication history was fulfilled. Blood pressure, abdominal circumference, height and weight were measured. Lipid profile was determined in a 12-hour fastened blood sample. Ultrasound analysis of the common carotid artery was performed by one blind observer. The distance between the lumen-intima interface and the leading edge of the media-adventitia interface (IMT) was measured and participants were also evaluated for the presence of plaques.

Results: The comparative analysis of demographic and cardiovascular risk factors between AS patients and controls did not reveal statistically significant differences. Also, no significant differences between groups were observed for TC, HDL-C, T-C/HDL-C, LDL-C, triglycerides, or dyslipidemia frequency. IMT measures were not different in AS and controls (0.62 ± 0.09 vs. 0.61 ± 0.09, P = 0.39) as well as plaques frequencies (19% vs. 17%, P = 0.78).

Conclusions: Subclinical atherosclerosis assessed through carotid ultrasound imaging was not more prevalent in the AS group when compared to controls with similar cardiovascular risks. Our observations may imply that CV risk factors may have more influence on the CV system than AS itself. These findings should be confirmed in a larger population with a prospective study design.

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Atherosclerose subclínica em pacientes com espondilite anquilosante: há um papel para a inflação?

**Resumo**

**Objetivos:** Avaliar a prevalência de aterosclerose subclínica em pacientes com espondilite anquilosante (EA) em comparação com controles com fatores de risco cardiovasculares similares.

**Métodos:** Foram recrutados 42 pacientes consecutivos com EA e 42 controles equiparados para idade (43,3 ± 11,7 vs. 43,7 ± 11,3, P = 0,89), gênero, tabagismo, diabetes mellitus e hipertensão arterial. Qualquer participante seria excluído se estivesse presente uma história pessoal de doença cardiovascular (CV). Foi preenchido um questionário registrando dados demográficos e histórias médica e de medicação. Foram determinados: pressão arterial, circunferência abdominal, altura e peso. O perfil lipídico foi determinado em uma amostra de sangue com 12 horas em jejum. Foi realizada uma análise ultrassonográfica da artéria carótida comum por um observador desconhecedor da pesquisa. Foi medida a distância entre a interface lúmen-intima e a borda de ataque da interface média-adventícia (EIM) e os participantes também foram avaliados para presença de placas.

**Resultados:** A análise comparativa dos fatores de risco demográficos e cardiovasculares entre pacientes com EA e controles não revelou diferenças estatisticamente significativas. Também não foram observadas diferenças significativas entre grupos para TC, HDL-C, T-C/HDL-C, triglicerídeos ou frequência de dislipidemia. As medidas de EIM não foram diferentes em EA e controles (0,62 ± 0,09 vs. 0,61 ± 0,09, P = 0,39) e nem as frequências de placas (19% vs. 17%, P = 0,78).

**Conclusões:** A aterosclerose subclínica avaliada por meio de imagens ultrassonográficas da carótida não foi mais prevalente no grupo EA, em comparação com os controles com riscos cardiovasculares similares. Nossas observações podem implicar que os fatores de risco CV podem ter mais influência no sistema CV versus a própria EA. Esses achados devem ser confirmados em uma população maior, por meio de um estudo prospectivo.

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**Introduction**

Ankylosing spondylitis (AS) is a chronic, inflammatory rheumatic disease. Its musculoskeletal manifestations include both inflammation and structural damage. Characteristic extra-articular manifestations include aortitis, cardiac conduction defects, pulmonary fibrosis and inflammatory bowel disease indicating that AS is a systemic disease.

AS is known primarily for causing a lifetime of pain, impaired physical function, work disability, and decreased quality of life, rather than for shortening life itself. However, patients with AS also experience premature mortality. The standardized mortality rates (SMR) associated with AS are approximately 50% higher than in the general population. The four non-inception cohort studies published to date quote SMRs of 1.33, 1.54 and 1.87.

Increased mortality is largely attributable to cardiovascular diseases (CV). A recent large population based study has shown more ischemic heart disease (prevalence ratio 1.2), peripheral vascular disease (ratio 1.6), atherosclerosis (ratio 1.5), congestive heart failure (1.8) and more cardiovascular risk factors (prevalence ratios between 1.3 and 1.7) in AS patients compared to healthy controls.

It is unclear whether the increased cardiovascular risk of AS patients could be explained by traditional cardiovascular risk factors alone. In fact, there is increasing evidence that the underlying inflammatory process in chronic inflammatory conditions resembles the chronic inflammatory processes that contribute to various stages of atherothrombosis, from early atheroma formation to plaque instability and thrombus formation. However, it is unknown whether AS patients without CV disease risk factors show early signs of large artery damage compared to controls, and if so, what the determinants of such large-vessel abnormalities are. This knowledge could prove useful for development of risk stratification, intervention strategies and for a better disease understanding.

High-resolution ultrasonography can be used to measure the intima-media thickness (IMT) as well as vascular elasticity of the carotid artery. An increased carotid IMT reflects the atherosclerotic burden and predicts the development of (clinically apparent) CV disease in the general population. Hence, this study was designed to determine whether signs of subclinical atherosclerosis are more prominent in a sample of AS patients compared to controls without the disease but with similar cardiovascular risks. Other studies assessing IMT in AS patients and controls have been published but results were contradictory and will be discussed further.

**Methods**

Study population: forty-two consecutive patients with AS attending the outpatient clinic of the University Hospital of the
Federal University of Santa Catarina, Brazil. All patients fulfilled the modified New York diagnostic criteria for AS. Forty-two volunteers (hospital staff or patients who attended the General Clinic for the University employees) matched for age, sex, smoking (current or in the last five years), diabetes mellitus and systemic arterial hypertension served as controls. All participants gave written informed consent and the institutional ethics committees of the University Hospital approved the study protocol.

Patients and controls were excluded if a personal CV disease history was present (myocardial infarction, percutaneous transluminal coronary angioplasty, surgery for ischemic heart disease, stroke, transient ischemic attack, carotid endarterectomy, peripheral arterial reconstructive surgery, or limb amputation).

Patients and controls were examined by a research physician. A questionnaire recording demographic data, medical and medication history was fulfilled. Blood pressure, abdominal circumference, height and weight were measured. Body mass index (BMI) was calculated as the ratio of weight and height squared. We considered the patient/control as diabetic if they referred hypoglycemic drug use or in the presence of at least two glycemic tests higher than 126 mg/dL. We considered the patient/control as hypertensive if they referred antihypertensive drugs use or a systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg measured in two different occasions. We considered the patient/control as dyslipidemic if they referred hypolipemiants drugs use or if they presented at least one of the following: LDL-C (low density lipoprotein) > 130 mg/dL; triglycerides > 150 mg/dL; HDL-C (high-density lipoprotein) < 40 mg/dL.

Laboratory variables were determined in a 12-hour fasted blood sample and included: TC (total cholesterol), HDL-C, LDL-C, triglycerides (all analyzed by enzymatic techniques); C-reactive protein (CRP by nephelometry method), and erythrocyte sedimentation rate (ESR by Westergreen method).

Arterial measurements were conducted in a quiet room after 15 minutes of rest, with the subjects in supine position. Ultrasound analysis of the common carotid artery (bilaterally) was performed by a cardiologist who were unaware of the participants’ clinical or laboratory characteristics. Measurements were performed using a B mode high resolution ultrasound ATL HDI 3000 (Phillips Bothel, WA, USA) with a 5-12MHz linear probe. The distance between the lumen-intima interface and the leading edge of the media-adventitia interface of the far wall corresponds with IMT. After localization of the common carotid artery, cross-sectional measurements were performed 10 mm proximal from the carotid bulb. Sites with mural atherosclerotic plaque were excluded while measuring. Three measurements were performed at each side. A mean of each side (right or left) was calculated and finally the mean of both sides (mean) was achieved. We defined plaques as focal widening of the vessel wall of 50% relative to adjacent segments with protrusion into the lumen or a IMT > 1.5 mm.

The distribution of each continuous variable was examined graphically and statistically for normality. Numerical data are summarized as the mean and standard deviation (SD). Variables not normally distributed were compared using the Wilcoxon nonparametric test for differences. Variables normally distributed were compared using students’ t-tests. Categorical data among groups were compared by the chi-square or the Fischer exact test statistics when appropriate. Some results were evaluated according to the established normal values and were subsequently ranked as elevated or depressed. A statistical significance was set at P < 0.05. All statistical analyses were performed using NCSS software.

Results

Comparative analysis of demographic and cardiovascular risk factors between AS patients and controls did not reveal statistically significant differences as demonstrated in table 1. AS mean age was 43.3 ± 11.7 years-old and the mean time of disease duration was 15.9 years.

Also, no significant differences between groups were observed for TC, HDL-C, T-C/HDL-C, LDL-C, triglycerides, or dyslipidemia frequency as showed in table 2. AS patients had a significant elevation in CRP (38.1% vs. 14.3%, P = 0.01), but not in the ESR.

In table 3 we demonstrate medications use in both groups. 31% against 11.9% of AS patients were on hypolipemiants (P = 0.03). Anti-TNF was used in 66.6% of all AS patients.

There was no difference in IMT measures in AS and controls (0.62 ± 0.09 vs. 0.61 ± 0.09, P = 0.39). Also no difference was observed in the frequency of plaques (table 4).
Indeed, many of the traditional risk factors for cardiovascular disease are present in the AS versus the general population, including a higher incidence of hypertension, elevated lipids, increased fibrinogen and CRP levels, and poorer physical activity levels. BMI and total cholesterol and triglycerides have been positively correlated with IMT and/or arterial stiffness.23

In accordance with our findings, Choe et al. found that carotid IMT and parameters related with arterial elastic properties in young AS patients without clinically evident cardiovascular risk factors were not different from those of sex- and age-matched healthy controls. Serum levels of TNF-α, IL-6, and MCP-1 did not reflect the degree of carotid subclinical atherosclerosis.15 In addition, recently, Capkin et al. evaluated a total of 67 AS patients, and age, sex, body mass index (BMI) smoking status, lipid profiles and blood pressure-matched healthy control subjects (n = 34). They also found no difference in IMT-C between groups. Our study has some limitations. No disease activity index was analyzed. However, the isolated disease activity measure would not allow drawing any conclusions about the inflammatory burden possibly associated with atherosclerosis. Also, 66.6% of patients were on anti-TNF treatment. A sub-analysis comparing AS patients suggested that the group on anti-TNF treatment (n = 28) was not different from the group treated with non-biologic drugs (n = 14) when it comes to the IMT, however, they had numerically less plaques (10.7% vs. 35.7%, P = 0.09). Although this study was not designed to assign for this exact issue, our finding raises the question about the anti-TNF playing a part to a better cardiovascular outcome. Studies on ischemic heart disease related mortality and morbidity following anti-TNF therapy have shown mixed results. Ferrante et al.22 observed a significant decrease of carotid IMT in anti-TNF-treated RA patients after two years but not in the group treated with methotrexate alone, although significant improvements were seen in measures of disease activity, CRP and fibrinogen levels with both type of treatments. It is thought though that anti-TNF treatment has the potential not only to reduce inflammation but also to modify traditional cardiovascular risk factors and endothelial dysfunction in RA.23,24 Additionally, one third of the AS patients were more frequently on hypolipemiant (31% vs. 11.9%), although dyslipidemia (as defined by this study) was not more prevalent in AS patients. However, it well known that statins’s vascular improvement is independent of statins’ cholesterol-lowering actions, fact that has been associated with their anti-inflammatory and immunomodulatory properties.25 Similarly to the anti-TNF treatment, because of the study design we cannot be conclusive about statins contribution for a possible better cardiovascular outcome on these AS cases.

In conclusion, our observations are in agreement with the findings of others and may imply that CV risk factors have more influence on the CV system than AS itself. However, we could not be conclusive because of the anti-TNF and hypolipemiant use. These findings should be confirmed in a larger population with a prospective study design. Further research concerning the pathogenesis of increased cardiovascular risk in AS patients should be high priority, as many risk factors are likely to be modifiable.

### Table 3 – Medications use in AS and controls.

<table>
<thead>
<tr>
<th>Medications</th>
<th>AS (n = 42)</th>
<th>Controls (n = 42)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoid, n (%)</td>
<td>8 (19)</td>
<td>22 (52.3)</td>
<td></td>
</tr>
<tr>
<td>NSAID, n (%)</td>
<td>22 (52.3)</td>
<td>22 (52.3)</td>
<td></td>
</tr>
<tr>
<td>Sulfasalazine, n (%)</td>
<td>6 (14.3)</td>
<td>6 (14.3)</td>
<td></td>
</tr>
<tr>
<td>Methotrexate, n (%)</td>
<td>5 (11.9)</td>
<td>5 (11.9)</td>
<td></td>
</tr>
<tr>
<td>Anti-TNF, n (%)</td>
<td>28 (66.6)</td>
<td>28 (66.6)</td>
<td></td>
</tr>
<tr>
<td>Hypolipemianta, n (%)</td>
<td>13 (31.0)</td>
<td>5 (11.9)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

AS, ankylosing spondylitis; NSAID, non-steroidal anti-inflammatory drugs.

*aAll hypolipemiants used were from the statins group

### Table 4 – Carotid ultrasound in AS and controls.

<table>
<thead>
<tr>
<th>IMT (mm) ± SD</th>
<th>AS (n = 42)</th>
<th>Controls (n = 42)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaques, n (%)</td>
<td>8 (19.0)</td>
<td>7 (17.0)</td>
<td>0.78</td>
</tr>
</tbody>
</table>

AS, ankylosing spondylitis; SD, standard deviation.

### Discussion

Given that inflammation has increasingly been acknowledged as the reason rheumatic patients bear elevated CV risk,20 we selected a study population of AS patients matched for five major CV risk factors in order to better assign for this issue.

Our study revealed that CV risk among AS patients as indicated by IMT is not different from controls without the disease. On the opposite, Peters at al found a greater IMT in AS patients in comparison with controls.13 However, the authors also found a high CV risk factor profile in patients with AS, and some of these risk factors (lipids and BMI) were associated with a greater carotid IMT and increased arterial stiffness. No association between large-vessel properties and higher Bath AS indices or CRP values were found. Also, Mathieu et al.14 found significantly increased IMT in the AS group compared with healthy controls. However, after adjustment for confounding factors, only an underlying trend towards increased IMT was present. IMT was positively correlated with tobacco use and blood pressure but not correlated with CRP level or mSASS. In the AS group, IMT was correlated with traditional risk factors, such as smoking and systolic blood pressure.

Although the cross-sectional study design does not permit a good estimate of the cumulative inflammatory burden and the small series of patients are associated with a low statistical power, their results suggest that an adverse CV risk profile may cause, at least partly, the greater IMT found by them and there is no sufficient evidence to support a role of biological inflammation.

Gonzalez et al., recruited 64 AS patients and 64 matched controls with no cardiovascular morbidity. Patients with AS exhibited greater carotid IMT than did matched controls (mean ± SD, 0.74 ± 0.21 mm vs. 0.67 ± 0.14 mm; P = 0.01; differences of means, 0.07; 95% confidence interval [CI], 0.016-0.139). In this case, although the best predictors for carotid plaques in patients with AS were erythrocyte sedimentation rate (ESR) at time of disease diagnosis (odds ratio [OR], 1.18; 95% CI, 1.04-1.33; P = 0.01) and duration of disease (OR, 1.39; 95% CI, 1.01-1.92; P = 0.05); there was no significant correlation between carotid IMT and either ESR or C-reactive protein.13
Confl icts of interest

The authors declare no confl icts of interest.

REFERENCES