Cardiovascular Disease in Patients with Ankylosing Spondylitis from the Rheumatology Outpatient Clinic of the UFMS-affiliated Hospital

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Abstract

Background: Cardiovascular diseases are a major cause of morbidity and mortality today. Despite its wide distribution, it presents particularly prevalent in certain groups of individuals, particularly when exposed to a higher degree of inflammation, giving increased cardiovascular risk. Rheumatic diseases expose their holders to this increased cardiovascular risk condition; however only recently have been associated with spondyloarthritis, particularly ankylosing spondylitis (AS). For being a classically autoimmune disease related to HLA histocompatibility system, AS may present phenotypic variations in different ethnic groups with possible diverse cardiovascular consequences.

Objectives: To estimate the prevalence of cardiovascular disease (CVD) and the cardiovascular risk profile, correlating the time since diagnosis and activity of ankylosing spondylitis (AS) in patients from the rheumatology outpatient clinic of the UFMS-affiliated hospital.

Methods: Of 55 patients with AS, 42 were selected consecutively and compared to a control group (CG) in a cross-sectional study. Patients with diabetes, indigenous background and pregnant women were excluded. Quantitative variables were assessed by use of Student t test, while qualitative variables, by chi-square test. The patients underwent electrocardiography, echocardiography and carotid Doppler examination, measurement of serum lipid levels and inflammatory markers, and were stratified according to global cardiovascular risk. The AS activity and impairment were evaluated by use of the BASMI, BASDAI, BASFI and ASDAS.

Results: Mean age, 42.87 ± 12.37 years; time since AS diagnosis, 10.76 ± 8.74 years. There was no difference in cardiovascular risk stratification between the groups, most of the patients being at high or moderate risk (AS: 64.3%, and CG: 52%, p = 0.134). The prevalence of manifest CVD (2%) showed no difference between the groups, except for right bundle-branch block (AS: 14%, and CG: 2%, p = 0.027). The prevalence of subclinical CVD showed no difference between the groups, except for higher carotid medial-intimal thickness (CIMT) in the AS group (AS: 1.82 ± 2.63, and CG: 0.67 ± 0.16, p = 0.018). There was no correlation between AS activity or inflammatory markers and CVD, but with time since AS diagnosis and CIMT (p = 0.039, r = 0.328).

Conclusions: Prevalence of CVD and risk factors was similar in the groups. Subclinical atherosclerosis degree was higher in the AS group, related to the time since diagnosis, but was independent of the cardiovascular risk factors or inflammation. Most patients with AS are at high cardiovascular risk. (Int J Cardiovasc Sci. 2019;32(1)10-18)

Keywords: Cardiovascular Diseases; Risk Factors; Cross-Sectional Studies; Spondylitis, Ankylosing / complications; Spondylitis, Ankylosing / diagnosis.

Introduction

Cardiovascular diseases (CVD) are currently a major cause of morbidity and mortality. Recent data from the World Health Organization have shown that 30% of the total of deaths worldwide in past decades result from CVD, approximately 17 million individuals.[1,2] The traditional risk factors for CVD, such as diabetes,

metabolic syndrome, dyslipidemia, hypertension, smoking and family history, have been well established as predictors of cardiovascular events, and measures for their control and monitoring are recommended to reduce and fight CVD.[3]

However, in certain clinical conditions, such as rheumatic diseases, the traditional risk factors do not seem to contribute to the total incidence of CVD.[4] Despite the well described higher incidence of CVD in rheumatic diseases, especially rheumatoid arthritis, systemic sclerosis, systemic vasculitis, antiphospholipid syndrome and systemic lupus erythematosus, it was only recently that the association of CVD and ankylosing spondylitis (AS) gained attention.[5,6]

The greater mortality of individuals with AS compared to that of the general population seems to be related to CVD.[7,8] Early atherosclerosis has been reported in association with chronic inflammation and with AS.[9] Some studies have shown that CVD and their traditional risk factors are more prevalent in patients with AS,[10,11] which is still controversial when interpreting inflammation as the major responsible for the higher cardiovascular impairment.

Despite the international publications, Brazilian studies correlating CVD and AS are scarce and more recent, especially those assessing their various presentation forms (clinically manifest or subclinical CVD).[12-14]

The characteristic racial miscegenation of the Brazilian population increases the interest for such studies, because it can lead to differences in the prevalence of CVD in that population, considering the association between AS and the HLA system.

This study was aimed at estimating the prevalence of CVD in individuals with AS from the Spondyloarthritis Outpatient Clinic of the Rheumatology Service of the Mato Grosso do Sul Federal University hospital (HU-UFMS), in addition to correlating the traditional risk factors and the inflammatory process of CVD.

Patients and methods

This is a quantitative descriptive study carried out from March to October 2015 with individuals with AS selected by convenience and consecutively from the patients regularly cared for at the Spondyloarthritis Outpatient Clinic of the Rheumatology Service of the HU-UFMS, which has records of 170 patients diagnosed with spondyloarthritis (psoriatic arthritis, AS, reactive arthritis, and enteropathic arthritis). Of those 170 patients,

55 were diagnosed with AS. A control group (CG) was formed by convenience sampling with employees of the UFMS without rheumatic disease and was similar to the AS group regarding age and sex. The inclusion and exclusion criteria allowed the selection of 42 individuals for the AS group and 50 for the CG.

Before data collection, all individuals provided written informed consent, duly registered in the Ethics Committee in Research of the UFMS (CAAE: 34043614.8.0000.0021).

Individuals with the following characteristics were excluded: diabetes, indigenous background, hypothyroidism or neoplasia, illiteracy, and pregnant women. All participants were screened for CVD and cardiovascular risk factors.

All individuals underwent cardiology clinical examination, laboratory tests, electrocardiography, echocardiography and carotid doppler examination on the same day, and within 20 days from the initial interview, which collected data from medical history and AS. The laboratory tests, performed after a 10-12-hour fasting, comprised the following measurements: total cholesterol and fractions, glycemia, glycated hemoglobin, uric acid, microalbuminuria, erythrocyte sedimentation rate (ESR), high-sensitivity C-reactive protein (hs-CRP) and interleukin 6 (IL-6).

The criteria to assess cardiovascular risk according to the V Brazilian Guideline on Dyslipidemia and Atherosclerosis Prevention comprised the presence of dyslipidemia, metabolic syndrome, arterial hypertension, current smoking, family history of early CVD, cardiac hypertrophy, and elevated levels of glycated hemoglobin, uric acid and hs-CRP.[15]

Cardiovascular disease was classified as clinically manifest or subclinical. Individuals with manifest CVD were those with history of myocardial infarction, stroke, coronary artery bypass graft surgery (CABG), peripheral revascularization surgery or procedure (PRV), or peripheral obstructive arterial disease (POAD), echocardiographic evidence of segmental, systolic, diastolic (over grade I) or hypertrophic cardiomyopathy, arrhythmias or bundle-branch and atrioventricular blocks on the electrocardiogram, and presence of carotid plaque obstruction > 50% of the lumen on Doppler.

Subclinical CVD was identified by an ankle-brachial index (ABI) < 0.9 or > 1.3, a carotid intima-media thickness (CIMT) >1 mm, but without significant plaque obstruction (> 50%) or microalbuminuria > 30 mg/g.[3]

Disease activity was assessed by using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score (ASDAS). The ASDAS-CRP and ASDAS-ESR indices16 were calculated after blood collection, using the information obtained when assessing the Bath Ankylosing Spondylitis Metrology Index (BASMI) and the Bath Ankylosing Spondylitis Functional Index (BASFI). In addition, the disease activity indices were correlated with the serum levels of IL-6, hs-CRP and uric acid, and compared to the occurrence of clinically manifest or subclinical CVD.

The AS group individuals were also assessed regarding the occurrence of CVD up to the age of 40 years and after 40 years.

Statistical analysis[17]

The results referring to the quantitative variables are presented as mean ± standard deviation, while the results of the categorical variables are presented as relative frequency followed by absolute frequency. The quantitative variables were compared between individuals with and without spondyloarthritis by use of parametric Student t test for independent samples (nonpaired) because most of the samples were normally distributed (Shapiro-Wilk test; p > 0.05). Student t test was used to compare quantitative variables between age groups. The association between the qualitative variables and the presence or absence of spondyloarthritis was assessed by use of chi-square test, which was also used to assess the association between the qualitative variables and the patients' age groups. The linear correlation between some quantitative variables was assessed by use of Pearson's linear correlation test. The results of the other variables were presented as descriptive statistics or tables and graphs. The SPSS statistical program, version 22.0, was used for statistical analysis, considering a 5% significance level.

Results

General characteristics

There was no significant difference between individuals with or without AS regarding age, sex, skin color, educational level, weight, height, blood pressure and body mass index (Table 1).

Risk factors for cardiovascular disease

Table 2 shows the results regarding the cardiovascular risk factors in the two groups. There was no significant

Table 1 - Sociodemographic and physical data of the individuals with and without spondyloarthritis assessed in this study

Variables	Spondyloarthritis		p value
	No	Yes	
Age	40.60 ± 1.79	45.57 ± 1.78	0.054
Sex			
Female	28.0 (14)	23.8 (10)	0.648
Male	72.0 (36)	76.2 (32)	
Skin color			
White	73.5 (36)	76.2 (32)	0.766
Non-white	26.5 (13)	23.8 (10)	
No information	1	0	
Educational level			
Secondary education	71.4 (35)	83.3 (35)	0.179
Higher education	28.6 (14)	16.7 (7)	
No information	1	0	
Weight	79.99 ± 2.68	74.80 ± 2.70	0.179
Height	167.60 ± 1.54	164.74 ± 1.34	0.172
SBP	125.08 ± 1.77	129.05 ± 1.90	0.130
DBP	81.56 ± 1.12	84.86 ± 1.46	0.072
Abdominal circumference	92.28 ± 1.86	93.07 ± 2.22	0.783

SBP: systolic blood pressure; DBP: diastolic blood pressure. The results are expressed as mean ± standard error of the mean or relative frequency (absolute frequency). P value in the Student t test (quantitative variables) or the chi-square test (qualitative variables).

difference between the groups regarding the variables family history, smoking habit, alcoholism, abdominal circumference, systemic arterial hypertension, total cholesterol, HDL-cholesterol, triglycerides, glycated hemoglobin, hs-CRP, microalbuminuria, metabolic syndrome, and IL-6. The LDL-cholesterol levels in the AS group, however, were higher than those in the CG (p = 0.012). The uric acid levels in the AS group were lower than those in the CG (p = 0.019).

All individuals were stratified into low, intermediate and high cardiovascular risk. Despite the higher frequency of high cardiovascular risk in the AS group, the difference was not significant; thus, there was no

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Table 2 - Cardiovascular risk factors of the individuals with and without spondyloarthritis assessed in this study

Variables	Spondyloarthritis		p value
	No	**Yes**	
Family history			
No	76.0 (38)	73.2 (30)	0.757
Yes	24.0 (12)	26.8 (11)	
No information	0	1	
Smoking			
No	90.0 (45)	92.9 (39)	0.628
Yes	10.0 (5)	7.1 (3)	
Alcoholism			
No	60.0 (30)	71.4 (30)	0.252
Yes	40.0 (20)	28.6 (12)	
BMI	27.99 ± 0.76	27.33 ± 0.90	0.575
SAH			
No	64.0 (32)	57.1 (24)	0.502
Yes	36.0 (18)	42.9 (18)	
Total cholesterol	170.60 ± 5.36	180.67 ± 6.66	0.237
HDL	43.13 ± 2,45	45.81 ± 2.18	0.420
LDL	88.87 ± 6.36	110.79 ± 5.65	0.012
Triglycerides	137.58 ± 14.19	123.40 ± 11.76	0.455
Glycated hemoglobin	6.65 ± 1.41	5.59 ± 0.08	0.484
Uric acid	6.02 ± 0.26	5.22 ± 0.20	0.019
hs-CRP	2.35 ± 0.31	16.10 ± 8.88	0.130
Microalbuminuria	3.87 ± 0.95	8.31 ± 2.04	0.053
Metabolic syndrome			
No	62.0 (31)	69.0 (29)	0.480
Yes	38.0 (19)	31.0 (13)	
Interleukin-6	4.62 ± 0.48	4.84 ± 0.80	0.806

BMI: body mass index; SAH: systemic arterial hypertension; hs-CRP: high-sensitivity C-reactive protein. The results are expressed as mean ± standard error of the mean or relative frequency (absolute frequency). P value in the Student t test (quantitative variables) or the chi-square test (qualitative variables).

association between the presence or absence of AS and the cardiovascular risk classification.

To assess the cardiovascular risk of well-controlled patients, and thus with lower inflammation level, the global cardiovascular risk was calculated separately in patients with ASDAS-CRP < 2 and low disease activity level, but no significant statistical difference was found between the CG and the AS group patients with that characteristic.

Manifest cardiovascular disease

Most individuals assessed in this study had no clinically manifest CVD, with prevalence between 2% and 26%, and valvular dysfunctions were the most frequent change, although all of them were mild. The percentage of individuals with right bundle-branch block was higher in the AS group than in the CG. The following variables showed no association with the presence or absence of AS: stroke, acute myocardial infarction, CABG, angioplasty, PRV / POAD, presence of carotid plaques and other findings on echocardiogram and electrocardiogram. None of the individuals in the CG and AS group showed significant carotid obstruction (plaque obstruction ≥ 50% of the lumen) (Table 3).

Subclinical cardiovascular disease

None of the individuals achieved the cutoff values for the occurrence of microalbuminuria (> 30 mg/g) or altered ABI (< 0.9 and > 1.3); in addition, the mean values of ABI and microalbuminuria were similar in both groups. Carotid plaques without significant obstruction (< 50% of the lumen) were slightly more frequent in the AS group [CG: 12.2% (n = 6); AS: 21.4% (n = 9)], but with no significant statistical difference (p = 0.239). However, as shown in Figure 1, CIMT was higher in the AS group (p = 0.018), and the cutoff value to determine altered CIMT (> 1 mm) was more often observed in the AS group [CG: 2.3 (n = 1); AS: 24.2 (n = 8)] (p = 0.003). This difference was observed when individuals with carotid plaques were excluded. Considering only the individuals with carotid plaques, no significant difference regarding CIMT was observed between the groups (CG: 0.78 ± 0.13; AS: 1.45 ± 2.12) (p = 0.464).

Ankylosing spondylitis activity and specific data

Most individuals were HLA positive (64.3%, n = 27) and had exclusive (33.3%, n = 14) or predominantly (61.9%, n = 26) axial clinical manifestations and extra-

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Table 3 - Results regarding manifest cardiovascular disease of the individuals with and without spondyloarthritis assessed in this study

Variables	Spondyloarthritis		p value
	No	Yes	
Stroke			
No	98.0 (49)	97.6 (41)	0.901
Yes	2.0 (1)	2.4 (1)	
AMI			
No	98.0 (49)	97.6 (41)	0.901
Yes	2.0 (1)	2.4 (1)	
CABG, angioplasty, or PRV / POAD			
No	98.0 (49)	100.0 (42)	0.357
Yes	2.0 (1)	0.0 (0)	
ECHO			
Normal	76.0 (38)	61.9 (26)	0.143
Valvular dysfunction	20.0 (10)	26.2 (11)	0.481
Aortic ectasia	6.0 (3)	14.3 (6)	0.183
Hypertrophy	4.0 (2)	4.8 (2)	0.858
Diastolic dysfunction	2.0 (1)	0.0 (0)	0.357
Chamber dilatation	0.0 (0)	4.8 (2)	0.119
Ejection fraction	0.0 (0)	0.0 (0)	-
Segmental change	0.0 (0)	0.0 (0)	-
ECG			
Normal	86.0 (43)	69.0 (29)	0.050
Right bundle-branch block	2.0 (1)	16.7 (7)	0.013
Ventricular repolarization change	8.0 (4)	2.4 (1)	0.236
Left hemiblock	2.0 (1)	4.8 (2)	0.458
Ventricular overload	2.0 (1)	7.1 (3)	0.228
Inactive area	0.0 (0)	2.4 (1)	0.273
Atrial fibrillation	0.0 (0)	0.0 (0)	-
Left bundle-branch block	0.0 (0)	0.0 (0)	-
Atrioventricular block	0.0 (0)	0.0 (0)	-

AMI: acute myocardial infarction; CABG: coronary artery bypass graft surgery; PRV: peripheral revascularization surgery or procedure; POAD: peripheral obstructive arterial disease; ECHO: echocardiography; ECG: electrocardiography. The results are expressed as relative frequency (absolute frequency). P value in the chi-square test.

articular symptoms (54.8%, n = 23), enthesitis being the most frequent (69.6%, n = 16).

Time since diagnosis ranged from 2 to 34 years (mean of 10.76 ± 8.74 years). The time since symptom onset ranged from 3 to 47 years (mean of 19.36 ± 11.02 years). The AS activity grade and impairment were: BASDAI = 2.84 ± 2.04, BASFI = 3.77 ± 2.82, BASMI = 4.59 ± 2.17, ASDAS-CRP = 2.17 ± 1.10 and ASDAS-ESR = 1.77 ± 0.81.
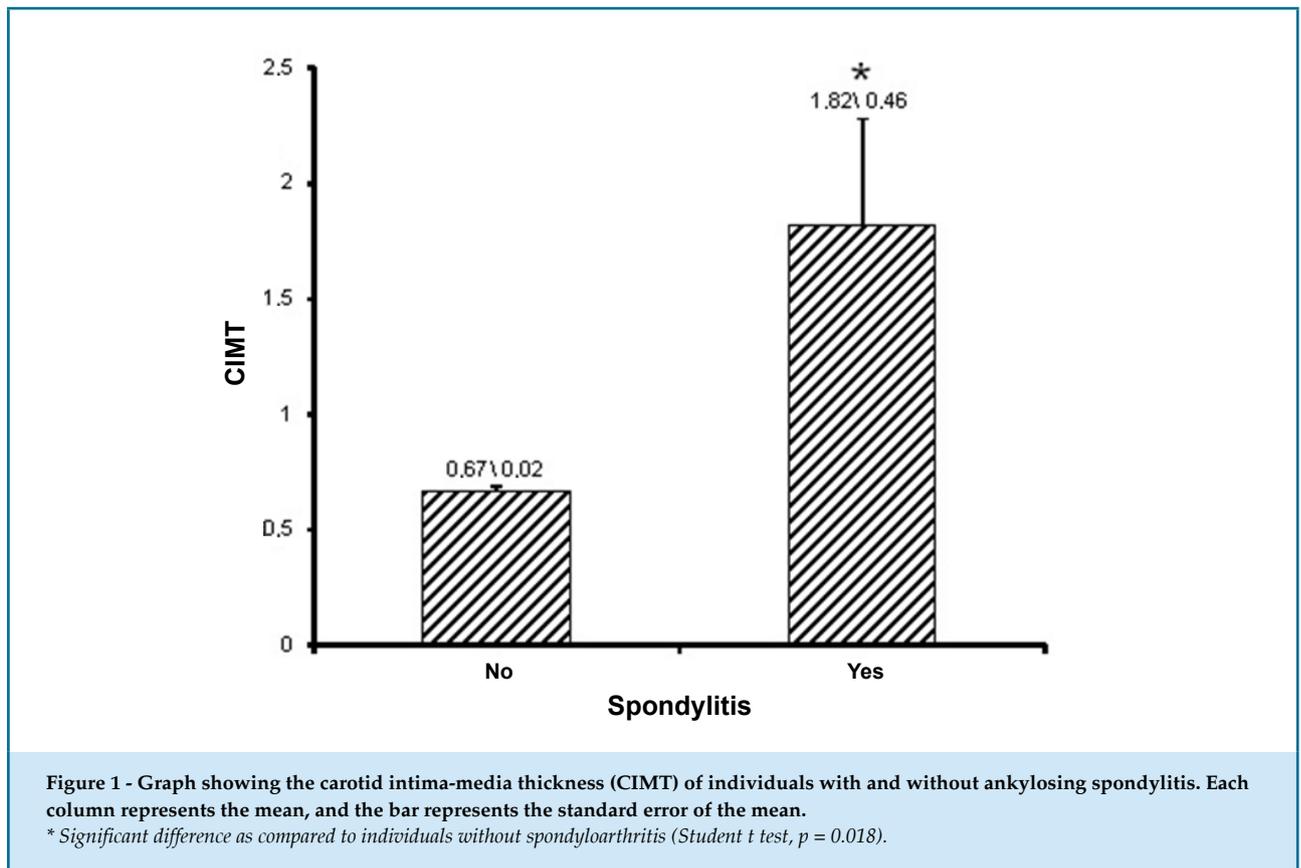
The hs-CRP and IL-6 levels were analyzed in both groups as one of the inflammation markers. The IL-6 showed no statistically significant difference (CG: 4.62 ± 3.41, AS: 4.84 ± 5.20; p = 0.806). Although more elevated in the AS group, the hs-CRP levels showed no significant difference as compared to those in the CG (CG: 2.35 ± 2.21, AS: 16.10 ± 56.85; p = 0.130).

There was moderate and positive significant linear correlation between the hs-CRP values obtained and those of ASDAS-CRP (Pearson, p < 0.001; r = 0.657), in addition to a positive significant, although weak, linear correlation between the hs-CRP values obtained and those of ASDAS-ESR (p = 0.007; r = 0.418). On the other hand, there was no significant linear correlation between the other inflammation markers and the disease activity indices assessed in this study (p-value between 0.177 and 0.875).

There was no linear correlation between the values obtained in ASDAS-CRP and the CIMT measures (p = 0.932, r = -0.014). In addition, there was no linear correlation between the values of hs-CRP and CIMT (p = 0.625, r = -0.079) or between time since diagnosis and CIMT (p = 0.152, r = -0.225). The lack of statistical significance in the linear correlation between CIMT and ASDAS-CRP, hs-CRP and time since diagnosis persisted even when individuals with and without plaque were separated.

In addition, the AS group patients were assessed according to age group (up to 40 years and over 40 years). There was no significant association between age group and manifest CVD. Regarding subclinical CVD, however, the percentage of patients older than 40 years with carotid plaques was significantly higher than that of those under 40 years. Microalbuminuria, ABI and CIMT showed no statistically significant difference according to age group (Table 4).

There was no linear correlation between time since diagnosis and CIMT in the age group under 40 years (p = 0.688, r = -0.130). However, there was a significant positive correlation between time since diagnosis and CIMT in individuals older than 40 years (p = 0.049,

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Figure 1 - Graph showing the carotid intima-media thickness (CIMT) of individuals with and without ankylosing spondylitis. Each column represents the mean, and the bar represents the standard error of the mean.
* Significant difference as compared to individuals without spondyloarthritis (Student t test, p = 0.018).

r = -0.362). Among individuals with AS older than 40 years and no carotid plaque, the correlation between time since diagnosis and CIMT was also positive (Figure 2).

Medications

In the AS group, 34 patients (81%) used immune biologics, 26 (61.9%) used nonsteroidal anti-inflammatory drugs, 13 (31%) were on immunosuppressant drugs (methotrexate/sulfasalazine), and only 4 (9.5%) were using corticosteroids. There was no significant statistical difference between the CG and the AS group regarding the use of statin, angiotensin-converting-enzyme inhibitor/angiotensin-receptor-blocker, beta-blocker, calcium-channel blockers, and acetylsalicylic acid.

Discussion

The higher frequency of cardiovascular impairment in rheumatic diseases, whose major background is chronic inflammation, explains the higher cardiovascular morbidity and mortality of those patients.[18] However, the role of inflammation in the occurrence of CVD remains controversial in AS.

Although the prevalence of cardiovascular impairment in AS is not high,[12] there is consensus that the mortality rate of those patients is higher than that of the general population, mainly due to higher cardiovascular mortality.[7,8] In addition, the more accurate definition of the weight of each factor involved, such as chronic inflammation, traditional cardiovascular risk factors and genetics, still lacks. The cyclic characteristic of AS throughout life, the time of exposure to disease, the effect of treatment, and the variety of exposure to cardiovascular risk factors can interfere with the CVD occurrence in that population, hindering the better understanding of the correlation between AS and heart diseases.

Unlike rheumatoid arthritis, whose cardiovascular risk score is higher,[9] publications on AS are controversial. Some authors have explained the higher prevalence of subclinical atherosclerotic disease, such as a higher CIMT, in patients with AS because of the higher exposure to cardiovascular risk factors,[7] while others, have reported that the cardiovascular impairment was independent of the presence of the traditional risk factors for CVD.[19]

In our study, both groups were similarly exposed to the traditional risk factors for CVD, except for mean

Table 4 - Results regarding subclinical cardiovascular disease of the individuals up to 40 years of age and those older than 40 years assessed in this study

Variables	Age group		p value
	≤ 40 years	> 40 years	
Ankle-brachial index	1.11 ± 0.05	1.06 ± 0.02	0.375
Microalbuminuria	15.04 ± 6.35	5.62 ± 1.10	0.170
CIMT (excluding those with plaques)	1.97 ± 0.88	1.73 ± 0.53	0.811
Carotid plaque			
No	100.0 (12)	70.0 (21)	0.032
Yes	0.0 (0)	30.0 (9)	
CIMT (only those with plaques)	-	1.45 ± 0.71	-
Ankle-brachial index			
Not altered	75.0 (9)	93.3 (28)	0.097
Altered (< 0.9 or > 1.3)	25.0 (3)	6.7 (2)	
CIMT (excluding those with plaques) cutoff value			
Not altered (< 1 mm)	83.3 (10)	71.4 (15)	0.443
Altered (> 1 mm)	16.7 (2)	28.6 (6)	

CIMT: carotid intima-media thickness. The results are expressed as mean ± standard error of the mean or relative frequency (absolute frequency). P value in the Student t test (quantitative variables) or the chi-square test (qualitative variables).

LDL-cholesterol, higher in the AS group, which can be related to the use of immune biologics[20,21] or only to a more cautious diet in the CG.

No difference in the prevalence of manifest and subclinical CVD was found between the groups; however, most individuals were classified as intermediate and high risk. Considering that most individuals in both groups were young, the prevalence of risk factors for CVD at an early age is clear, which is especially relevant in patients with rheumatic diseases.

Excluding the limitations of a non-blinded study, the higher mean values of CIMT in the AS group indicate higher subclinical atherosclerosis. Despite the lack of consensus in the literature,[14,22] we believe that such finding reflects early subclinical atherosclerosis in a population with traditional risk factors for CVD similar to those of the general population, being an independent marker of risk. The presence of carotid plaques and the positive correlation between CIMT and the time since diagnosis of AS in individuals older than 40 years reinforces that hypothesis.

In addition, it is worth noting the considerably higher mean value of hs-CRP of the AS group individuals, indicating their higher cardiovascular risk. Furthermore, a good part of those with well-controlled rheumatic disease and low inflammation (ASDAS < 2) were at high cardiovascular risk and out of the recommended LDL-cholesterol target (< 70 mg/dL).

We do not know any Brazilian study using this cardiovascular risk stratification approach for those patients, but it is worth noting that some researchers have sought cardiovascular risk markers specific for AS,[23] according to the recommendations established for rheumatoid arthritis and systemic lupus erythematosus.[9]
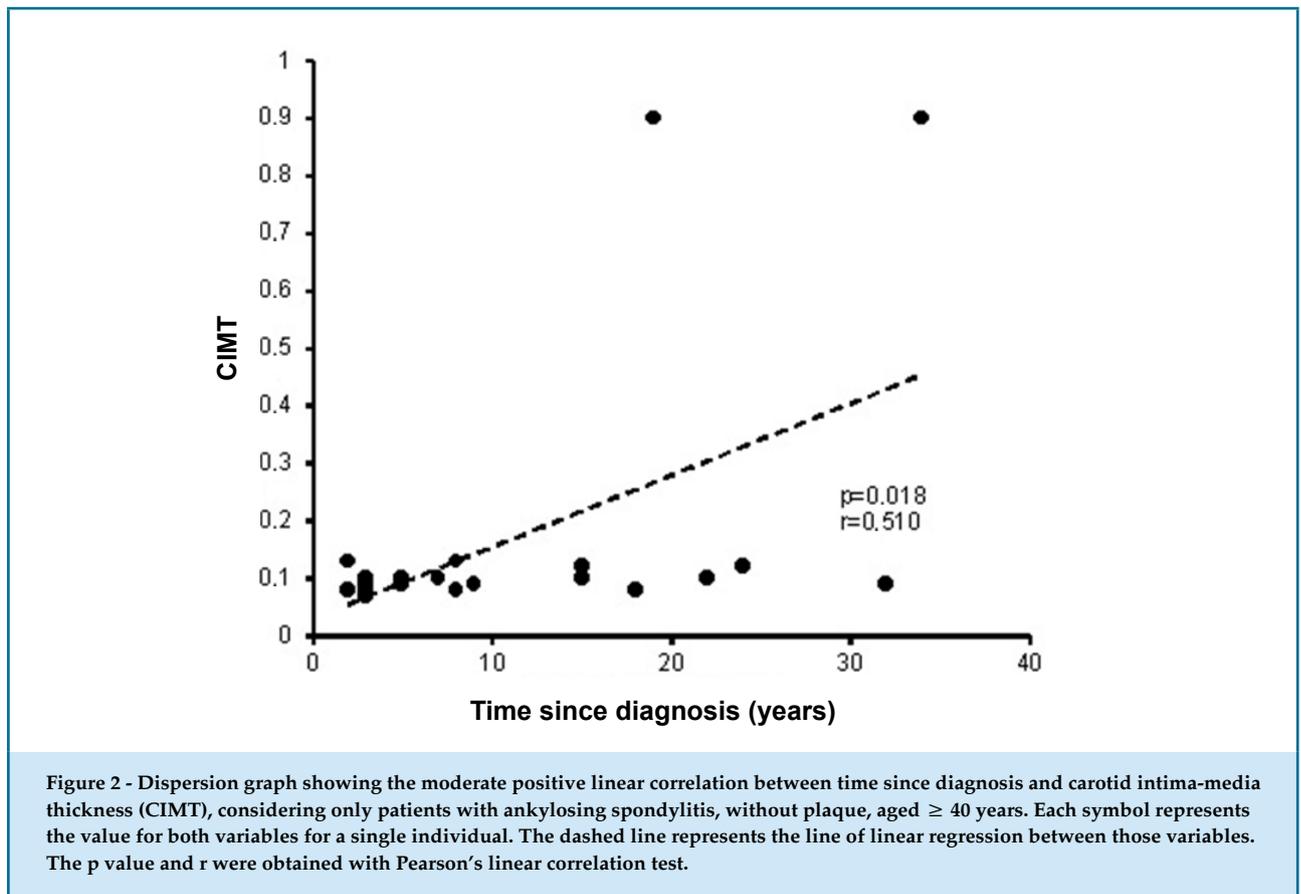
The lack of correlation between markers of inflammation, activity and disease impairment in the AS group can be partially explained by the low mean age of the patients or the use of immune biologics in 80% of them. By being a cross-sectional study might have contributed to that, although other authors have found no correlation between inflammation and early atherosclerosis when cardiovascular risk factors were excluded.[13,21]

Conclusions

There is no difference in the prevalence of manifest CVD in patients with AS as compared to that of the CG. However, subclinical CVD is more prevalent in AS patients when assessed by use of CIMT, has no relation to the AS activity, but to the time since AS diagnosis and to more advanced ages. Most patients with AS are not only at higher cardiovascular risk, even when clinically controlled, but their CVD prevention is inadequate as well.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Universidade Federal do Mato Grosso do Sul* under the protocol number CAAE: 34043614.8.0000.0021. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Figure 2 - Dispersion graph showing the moderate positive linear correlation between time since diagnosis and carotid intima-media thickness (CIMT), considering only patients with ankylosing spondylitis, without plaque, aged ≥ 40 years. Each symbol represents the value for both variables for a single individual. The dashed line represents the line of linear regression between those variables. The p value and r were obtained with Pearson's linear correlation test.

Author contributions

Conception and design of the research: Silva Junior DG. Acquisition of data: Silva Junior DG. Analysis and interpretation of the data: Silva Junior DG. Statistical analysis: Silva Junior DG. Writing of the manuscript: Silva Junior DG. Critical revision of the manuscript for intellectual content: Silva Junior DG, Costa IP.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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