Disease Activity in Spondyloarthropathy: Does it affect Vascular H ealth?

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Abstract

Background: Chronic inflammation in spondyloarthropathy (SpA) is associated with accelerated atherosclerotic cardiovascular disease (CVD). Flow mediated vasodilatation (FMD) and carotid intima-media thickness (cIMT) detects endothelial dysfunction and subclinical atherosclerosis respectively, responsible for atherosclerotic CVD.

Objective: We aimed to examine the association of disease activity in SpA with surrogate markers of CVD, i.e., FMD and cIMT.

Methods: Fifty patients of Axial SpA (Assessment of SpondyloArthritis Society-ASAS 2009 criteria) (<5 years disease duration) and 50 control subjects, matched for age (33.7±8.8 vs. 33.7±8.4 years) and sex, with no CV risk factors were recruited. Ultrasound assessment of FMD of brachial artery and cIMT of both common carotid arteries were performed. Measurements were compared between patients and controls by Student's t test. Association of disease activity in SpA patients with FMD and cIMT, were evaluated by Pearson/Spearman's correlation.

Results: FMD (4.9±1.4 vs. 8.7±1.6 %) and cIMT (0.52±0.04 vs. 0.44±0.11 mm), were impaired in SpA patients than healthy controls (all p<0.05). However, subjects in both the groups had no difference in age and body mass index with similar, within normal range blood pressure and lipid profile.

FMD and cIMT in SpA subjects correlated with disease duration, Bath's Ankylosing Spondylitis Disease Activity Index, Erythrocyte Sedimentation Rate and C-reactive protein (all p<0.05).

Conclusion: We observed that FMD and cIMT were deranged in SpA, and higher disease activity in SpA was associated with impaired FMD and cIMT. However, a larger population with a prospective study-design would further confirm this relationship between SpA disease activity and CVD surrogate markers.

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Introduction

Cardiovascular disease (CVD) is one of the leading causes of death in spondyloarthropathy (SpA),[1] a chronic inflammatory disease of sacroiliac joint and spine. Chronic inflammation, seen in rheumatologic diseases is thought to be involved in accelerated atherosclerosis through endothelial dysfunction.[2-4] Given the inflammatory nature of SpA, atherosclerotic CVD is more prevalent in these patients than healthy subjects.[5] Endothelial dysfunction, forerunner of atherosclerotic CVD, can be detected non-invasively by ultrasonographic analysis of brachial artery-flow mediated vasodilatation (FMD). FMD detects the impaired ability of the artery to dilate in response to a variety of physical and chemical stimuli, as a consequence of reduced nitric oxide bioavailability.[6] On the other hand, carotid intima-media thickness (cIMT) measuring the width of intima and media layers of common carotid artery (CCA) by B-mode ultrasonography, can detect subclinical atherosclerosis.[7] Both FMD and cIMT are early markers of CVD, with high predictive values for future CV mortality.[8,9] In the present cross-sectional study we examined the association of disease activity in Axial SpA patients with surrogate markers of CV health, i.e., FMD and cIMT.

Methods

Study design: This is a cross sectional analysis of individuals with chronic low back pain visiting Rheumatology clinic of Medical College and Hospital, Kolkata from February 2012 to July 2013. The study got clearance from the institutional ethics committee.

Study population

Inclusion criteria

Study group: Fifty patients of newly diagnosed Axial SpA, fulfilling Assessment of SpondyloArthritis Society (ASAS) criteria 2009 for Axial SpA,[10] having disease duration of less than 5 years and, with no prior use of disease modifying anti-rheumatic drugs (DMARDs) as well as use of systemic glucocorticoids ≥10 mg were recruited. The participants were between 18-50 years age as there is higher prevalence of SpA in this age group.[11]

Control group: Similar number of age and sex matched individuals which included healthy persons as well as those with chronic low back pain,

however not fulfilling the ASAS criteria

Exclusion criteria

Those with a body mass index (BMI) <20 kg/m^2 and >35 kg/m^2, diabetes mellitus types 1 and 2, hypothyroidism, treated hypertension or with a systolic blood pressure >140 mm Hg and diastolic >90 mm Hg, history of gestational diabetes, gestational hypertension or pre-eclampsia, and who have smoked (any type) in the past 5 years; additionally, those with history of liver disease, renal disease, Cushing syndrome, active infectious disease and neoplasm, and use of medications at study-entry: those affecting lipid metabolism, oral contraceptives and thyroxine.

Anthropometric measurements

Height (cm) and weight (kg) measurements were performed using standard protocol in light clothing using a balance and wall-mounted stadiometer.

Resting blood pressure assessment

After 10 minutes rest, heart rate and peripheral blood pressure were assessed by oscillometric method in sitting position.[12]

Vascular studies

The participants were in the fasting state and abstained from alcohol, coffee, tobacco and food for a minimum of 12 hours. All vascular measurements, i.e., FMD as well as cIMT assessments were performed by Philips HD 7 ultrasound machine using a 3–12 MHz linear array transducer probe under standardized conditions in a quiet, controlled environment with room temperature at 20-25°C and 55-65 % humidity in the morning. The vascular studies of all participants and subsequent analysis of the stored images were conducted by single experienced examiner to avoid interobserver variation.

FMD Assessment

The FMD assessment was performed on the right arm, in supine position according to existing guideline.[13] Timing of each image frame with respect to the cardiac cycle is determined with simultaneous ECG recording. The brachial artery was scanned longitudinally just above the antecubital crease and a segment with clear anterior and posterior intimal interfaces between the lumen and vessel wall was selected for 2D grayscale imaging. To create a flow stimulus in the brachial artery, a sphygmomanometric (blood pressure) cuff was first placed 1 cm above the antecubital fossa. Blood flow at baseline was estimated by the pulsed Doppler velocity signal obtained from a midartery sample volume.

For FMD evaluation, firstly, the systolic-diameter of the brachial artery was recorded by measuring the distance from the media-adventitia interface of the anterior arterial wall to the posterior arterial wall (basal measurement). Subsequently, hyperemia was induced by inflation of a sphygmomanometer cuff to at least 50 mm Hg above systolic pressure, for 4 minutes, to occlude arterial blood flow. Immediately after cuff deflation, the hyperemic velocity of blood flow was assessed by a mid-artery pulsed Doppler signal. To detect the flow induced change in arterial width, the systolic diameter of the same brachial arterial segment was measured again at 45 seconds following cuff- deflation (post-hyperemia measurement). The averages of 3 measurements from basal as well as post-hyperemia diameters were used for the analysis. FMD was expressed as the relative increase in brachial artery diameter during hyperemia, and calculated as [{(post-hyperemia diameter–basal diameter)/ basal diameter} × 100 %].

cIMT measurement

The cIMT ultrasound scan protocol was according to Mannheim consensus.[14] It required the visualization of the near and far wall of the right and left common carotid artery (CCA) and carotid bifurcation (bulb). Longitudinal images of both CCA were obtained with the head rotated 45 degrees toward the opposite side. Simultaneous ECG tracing was taken and only end diastolic images were captured to compensate for change in cIMT at different phases of cardiac cycle. IMT were calculated by measuring the width of intima and media layers of CCA over a length of 10 mm on the far wall of the artery, 20 mm proximal to the carotid bulb. CCA inter-adventitial and intraluminal diameters were also measured. The maximum value of the cIMT measurements from each side, i.e., right and left CCA was recorded and the average of the maximum readings from 2 sides was calculated for each participant.

Laboratory assessment

Laboratory assessment included measuring erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complete hemogram, fasting lipid profile, fasting blood sugar, urea, creatinine, liver function test, and estimation of human leucocyte antigen-B27 (HLA-B27). Chest x-ray, x-ray and/or magnetic resonance imaging (MRI) of sacro-iliac joint and/or lumbo-sacral spine of the patients were also reviewed. Severity of SpA was measured by Bath's Ankylosing Spondylitis Disease Activity Index (BASDAI).[10] ESR was measured by Westergren method. CRP levels were analyzed with a Cobas Integra system (Roche diagnostics, Switzerland).[15] Serum lipid levels (total cholesterol, high density lipoprotein cholesterol, and triglyceride) were measured using Hitachi 912 analyser (Roche Diagnostic);[16] value of low density lipoprotein cholesterol was calculated using Friedewald's equation. HLA B-27 was estimated by flow-cytometry.

Statistical analyses

Statistical tests were performed with GraphPad Prism 6 software (Version 6.03)[17]. Means and standard deviations were calculated for each parameter. Student's t test was performed to compare parametric variables between case and control groups. Pearson's or Spearman's correlation coefficient was used to examine the association of disease activity and inflammatory markers in SpA with FMD and cIMT. A p-value less than 0.05 was considered as statistically significant.

Results

Participant characteristics

The two groups were similar with respect to age, sex, BMI, BP and lipid profile (Table 1). Sixty percent (n=30) of the SpA patients were positive for HLA-B27 with disease duration of 2.7±1.1 years and BASDAI score of 4.0±0.5. The laboratory parameters, i.e., ESR and CRP, and vascular assessments, i.e., FMD as well as cIMT were significantly higher in SpA patients than the control group. Four SpA patients had carotid plaques compared to none in the control group (Table 1).

Correlation of FMD and cIMT with disease activity and inflammatory markers in SpA patients

FMD and cIMT in SpA subjects correlated significantly with disease

Table 1: Participant characteristics at entry in the study

	SpA patients (n=50)	Control (n=50)	p-value
Age (years)	33.7±8.8	33.7±8.4	0.96
Male/Female	35/15	33/17	1.00
BMI (kg/m^2)	21.3±1.0	21.1±1.0	0.33
SBP (mmHg)	121.0±3.9	119.9±5.5	0.26
DBP (mmHg)	80.3±2.4	80.8±4.3	0.49
Total Cholesterol (mg/dl)	164.0±3.8	162.9±5.1	0.22
LDL-C (mg/dl)	93.6±3.2	92.5±3.6	0.11
HDL-C (mg/dl)	48.9±2.6	47.5±2.6	0.25
TGA (mg/dl)	98.2±10.4	96.4±5.7	0.31
ESR(mm)	32.7±8.6	15.2±3.8	<0.001
CRP(mg/L)	8.5±1.4	3.7±1.0	<0.001
FMD %	4.9±1.4	8.7±1.6	<0.001
cIMT(mm)	0.52±0.04	0.44±0.11	<0.001

Data represented as mean±SD; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BMI: Body mass index; cIMT: Carotid intima-media thickness; CRP: C-reactive protein; DBP: Diastolic blood pressure; ESR: Erythrocyte sedimentation rate; FMD: Flow mediated vasodilatation; HDL: High density lipoprotein; LDL: Low density lipoprotein; SBP: Systolic BP; TGA: Triglyceride

duration, BASDAI, ESR and CRP (Table 2)

Discussion

In this study we found SpA patients had significantly lower FMD and higher cIMT compared to healthy, age and sex matched controls. We also observed FMD and cIMT had significant moderate to strong correlation with disease activity (BASDAI) and markers of inflammation (ESR, CRP) in SpA patients. To date, studies examined FMD and cIMT in SpA patients as well as investigated the association between SpA disease activity and CV markers.

A crosssectional study by Sari et al. [18] observed significantly reduced FMD in 44 patients of Ankylosing spondylitis (AS) (a subgroup of SpA) when compared to healthy control subjects (n=31), however there was no difference of cIMT between the 2 groups nor there was any correlation between FMD and disease activity in AS patients. Nevertheless, another crosssectional study by Bodnar et al.[19] noted both reduced FMD as well as increased cIMT in 43 patients of AS when compared to 40 healthy controls; in this study also there was no correlation between disease activity (BASDAI) as well as inflammatory markers (ESR, CRP) and vascular parameters. Similarly, Mathieu et al.[20] and Gonzalez-Juanatey et al.[21] reported increased cIMT in AS patients compared to healthy individuals, however, disease activity scores as well as ESR and CRP levels did not show any correlation with cIMT in both these studies.

The observation of deranged vascular parameters in AS patients compared to healthy individuals, in the above-mentioned studies[18-21] was similar to our current study. However, in contrast to these reported results,[18-21] interestingly we observed moderate to strong correlations between disease activity and inflammatory markers and, CV markers (FMD and cIMT) in SpA . Our results could explain the role of inflammation in the endothelial dysfunction and subsequent atherosclerotic CVD. The disease activity (BASDAI) and levels of inflammatory markers (ESR or CRP) in our SpA patients was markedly higher in comparison to other published studies,[18-21] this might explain significant association between disease activity and impaired vascular markers in our study, not evident in other studies.

Gonzalez-Juanatey et al.[21] also reported carotid plaque in 19 out of 64 AS patients where as 4 out of 50 SpA patients in our study reported plaques by carotid ultrasound examination. Carotid plaque being the final stage of atherosclerosis, higher disease duration (19.1±11.2 vs. 2.65±1.13 years) reported by Gonzalez-Juanatey et al.[21] in AS patients than our study population might be responsible for this result.

Endothelial dysfunction and subclinical atherosclerosis were also reported in psoriatic arthritis,[22,23] another subgroup of SpA, emphasizing the importance of investigating these surrogate markers (FMD and cIMT) of CVD in the whole disease-spectrum of SpA.

Table 2: Correlation of disease activity with FMD and cIMT in SpA patients

Variables	r_{FMD}	r_{cIMT}
Disease duration	-0.96	0.84
p value	<0.001	<0.001
BASDAI	-0.59	0.46
p value	<0.001	<0.001
ESR	-0.34	0.37
p value	0.01	0.01
CRP	-0.97	0.83
p value	<0.001	<0.001

Pearson/Spearman correlation; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; cIMT: Carotid intima-media thickness; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; FMD: Flow mediated vasodilatation; SpA: Spondyloarthropathy

Several studies investigated changes of FMD and/or cIMT with intervention of anti-tumor necrosis factor (anti-TNF) agents in SpA. Short term (1 month) as well as long term (4.9 years) intervention of anti-TNF agents has been found to either improve or stabilize the disease activity and vascular parameters, suggesting the role of these anti-inflammatory agents in controlling inflammation, thereby improving CV health in SpA.[24,25]

In contrast to the above-mentioned studies, some studies did not observe any significant difference of CV markers between SpA patients and healthy controls.[26-29] Ceccon et al.[28] reported no difference of cIMT between AS patients and healthy subjects; AS patients in this study had a superior metabolic profile than the controls which might have masked the difference of cIMT between the two groups. Although AS patients in comparison to their healthy counterparts had better lipid parameters,[28] Malesci et al.[27] and Divecha et al.[30] observed inflammation driven worse metabolic parameters in SpA patients compared to healthy controls. However, the lipid levels of the SpA patients in our study did not differ from the controls, probably because of small disease duration (2.65±1.13 years).

Our study was limited by small sample size. A larger population would further confirm the association of disease activity in SpA with CVD surrogate markers. Secondly, crosssectional design of our study did not allow us to determine the actual inflammatory or metabolic burden of the SpA patients over time. Similarly, being an observational study, the results were indicative of association of disease activity in SpA

with endothelial dysfunction and sub-clinical atherosclerosis, instead of establishing probable causation. A prospective or interventional study would perhaps shed light on the mechanisms behind these abnormal vascular findings.

Despite these limitations, our study demonstrated endothelial dysfunction and subclinical atherosclerosis in SpA. Further research is needed to clarify the mechanisms involved behind adverse CV outcomes in SpA patients.

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