Joint Bone Spine 86 (2019) 159–163

Available online at ScienceDirect www.sciencedirect.com

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Review

Vascular involvement in axial spondyloarthropathies

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ARTICLE INFO

Article history:
Accepted 1st March 2018
Available online 19 May 2018

Keywords:
Spondyloarthritis
Artery
Cardiovascular
Vessels
Endothelium
Mortality

ABSTRACT

Ankylosing spondylitis (AS) is a chronic inflammatory joint disease that involves the entheses, causing inflammatory pain and functional impairments. Patients may experience extraarticular manifestations such as uveitis, psoriasis, and inflammatory bowel disease. These, together with the increased risk of cardiovascular disease and osteoporosis and the development of spinal fusion, are the main determinants of adverse disease outcomes. As with many systemic inflammatory diseases, AS is associated with excess cardiovascular mortality due to increased risks of myocardial infarction, stroke, and venous thromboembolism. Studies of markers for subclinical atheroma (endothelial dysfunction, arterial stiffness, and intima-media thickness) have shown earlier onset of arterial disease compared to healthy controls, with the difference being greatest for patients with active AS. The potential vascular effects of drugs used to treat AS have not been established. Few studies have focused on nonsteroidal antiinflammatory drugs and biologics in patients with AS, and their results do not conclusively establish a beneficial or deleterious effect in axial spondyloarthritis. Statins have been found to improve endothelial dysfunction and to decrease mortality. The latest EULAR recommendations on cardiovascular risk management in patients with inflammatory joint disease indicate that statins should be used in compliance with national guidelines.

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1. Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory joint disease responsible not only for pain and functional impairments, but also for extraarticular manifestations and an increased risk of comorbidities. These nonrheumatic symptoms are the main poor prognosis factors and contribute to the excess mortality seen in patients with AS [1,2]. Cardiovascular events are the main causes of excess mortality. Risk increases have been demonstrated for both myocardial infarction and stroke [3].

This article reviews the main vascular changes including signs of subclinical atheroma, venous abnormalities, and inflammatory lesions that contribute to the excess risk of cardiovascular events and death among patients with axial spondyloarthritis (axSpA). We Identified French- and English-language articles on arterial and venous alterations and treatment effects in axSpA by searching PubMed using the following indexing terms: (spondylarthritis OR ankylosing OR spondyloarthritis) AND (vessel OR vascular OR mortality OR atherosclerosis OR cardiovascular diseases [mesh] OR "endothelial dysfunction" OR cardiac OR aorta OR thrombotic venous), with no time limits.

2. Vascular evaluation and prognostic significance

The tools used for vascular assessments in patients with axSpA are not specific of this disease. Most studies focused on early markers of atheroma. The main methods used are described below.

2.1. Methods for evaluating endothelial dysfunction

An imbalance in the production of vasodilating and vasoconstricting factors impairs the vasodilating potential of the endothelium, which is the main marker of endothelial dysfunction.

Flow-mediated dilation (FMD) is the most widely used parameter for assessing endothelial function [4,5]. FMD evaluates the ability of a conductance artery to dilate in response to the lifting of an occlusion. A forearm cuff is inflated for 5 minutes to induce

DOI of original article: https://doi.org/10.1016/j.rhum.2018.03.006.
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https://doi.org/10.1016/j.jbspin.2018.05.003
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hypoxia. The resulting decrease in distal arterial resistance induces hyperemia with shear stress once the cuff is removed. The shear stress is responsible for the production of nitric oxide (NO), which relaxes the vascular smooth muscle, thereby causing the artery to dilate. Arterial diameter is measured by ultrasonography, and the FMD is reported as the percentage change between the largest postocclusion diameter and the preocclusion diameter. This method evaluates macrovascular endothelial function.

Iontophoresis coupled to laser Doppler is a recently introduced method that measures skin microvessel dilation in response to acetylcholine or sodium nitroprusside (an NO donor) delivered by iontophoresis, i.e., by applying a voltage gradient of less than 0.5 mA/cm^2 to the skin.

Peripheral arterial tonometry (PAT) or digital plethysmography assesses changes in fingertip pulsating arterial volume during hyperemia induced by occluding the humeral artery. Major advantages are rapidity and complete independence from the operator. This technique assesses microvascular endothelial function.

Endothelial function biomarkers include ICAM-1, VCAM-1, E selectin, osteoprotegerin, asymmetric dimethylarginine and symmetric dimethylarginine, von Willebrand factor (vWF), circulating endothelial cells, endothelin, and adiponectin. However, none of these markers has been validated in AS and, consequently, none is used in everyday practice [6,7].

2.2. Methods for evaluating arterial rigidity

Pulse wave velocity (PWV) is the speed at which pressure waves travel along the aorta and arterial tree. PWV increases with arterial stiffness.

The augmentation index (AIx) is the ratio of augmentation pressure over pulse pressure and measures the amplitude of the reflected pressure waves, which varies with the degree of peripheral vasoconstriction, internal remodeling of small arteries, and PWV.

2.3. Method for evaluating structural alterations: intima-media thickness (IMT)

Two-dimensional ultrasonography provides reproducible and repeatable measurements of IMT at the common carotid artery. The mean of IMT values at the right and left carotid arteries is the most widely used parameter.

These markers of subclinical atheroma correlate closely with conventional cardiovascular risk factors [8]. IMT, arterial stiffness, and endothelial dysfunction are associated with subsequent cardiovascular events (coronary artery disease and stroke) [9]. They are therefore widely used in patients with chronic inflammatory joint disease to establish risk profiles and to identify antirheumatic drugs with potential preventive effects.

3. Markers of subclinical and established atheroma

3.1. Endothelial function

Our literature search retrieved six studies comparing macrovascular endothelial function assessed by FMD in patients with AS and in age- and sex-matched healthy controls. Among them, four showed alterations in the patients but with no established correlations to disease activity (BASDAI) [10–15]. The single study of peripheral microvascular endothelial function of noncoronary arteries used iontophoresis coupled to laser Doppler in 15 patients with AS and 12 healthy controls [16]. Dilation in response to acetylcholine was markedly diminished in the patients (118% vs. 469% in the controls, $P = 0.02$). These preliminary results deserve careful attention, since endothelium-dependent microvascular dilation is associated with cardiovascular diseases including hypertension, insulin resistance, and obesity in other chronic conditions such as diabetes. They are furthermore consistent with earlier findings of altered coronary microvascular function in patients with AS who had no patent cardiovascular disease [17].

3.2. Arterial stiffness

Higher PWV values indicating increased arterial stiffness in patients with AS compared to healthy controls were found in five of nine studies and increased AIx values in two of four studies. Increased arterial stiffness correlated with scores for disease activity and function [18–24]. In a 5-year study of 85 patients with AS, high baseline values of C-reactive protein (CRP), the erythrocyte sedimentation rate (ESR) and the Ankylosing Spondylitis Disease Activity Score (ASDAS) were associated with the development of arterial stiffness as assessed by the AIx but not by PWV [25].

3.3. Intima-media thickness (IMT) and atheroma plaque

A 2015 metaanalysis evaluated the IMT and presence of atheroma plaque at the carotid arteries in patients with AS and healthy controls [18]. The 11 included studies had a total of 521 AS patients and 445 controls. Mean IMT at the left and right carotid arteries was higher in the patients than in age-matched controls (0.046; 95% confidence interval [95% CI]: 0.015–0.077). Analyses of subgroups defined based on disease activity showed no increase in IMT vs. controls among patients whose mean BASDAI was < 4/10 ($P = 0.1343$). In patients with active AS (BASDAI ≥ 4), in contrast, IMT values were elevated compared to controls (0.097; 95% CI: 0.077–0.117; $P < 0.001$). An analysis of data from five studies showed no difference between patients and controls regarding the presence of carotid artery plaque (relative risk: 1.07; 95% CI: 0.48–2.37). The mean patient age in these studies of about 40 years may explain the very low prevalence of plaque. However, even in this age group, IMT increases consistent with subclinical atheroma were detectable, particularly in patients with active disease.

4. Aortic inflammation

4.1. Inflammation of the ascending aorta

An association of AS with aortitis was first reported in the 1950s [26]. The most common form in AS, and consequently the most extensively studied, is inflammation of the aortic root and ascending aorta. Inflammation of the wall of the ascending aorta causes a gradual increase in diameter, resulting in aortic regurgitation [27], which may be present in 12% of patients with AS [28]. Although usually asymptomatic, inflammation of the ascending aorta is potentially life-threatening. It may antedate the rheumatic manifestations of AS, and the severity of aortic regurgitation does not seem correlated with disease activity [27]. The failing aortic valve exhibits both inflammatory and degenerative histological lesions, with destruction of the elastic tissue by fibrosis [27,29]. Another potential consequence of aortic inflammation is the occurrence of cardiac conduction disturbances due to the development of fibrotic scar tissue within the subaortic interventricular septum. The prevalence of conduction disturbances has been estimated at 3% in patients with less than 15 years of disease duration and 9% in those with longstanding disease [30]. However, reported prevalences vary widely and depend on the detection methods used and time period of analysis. Aseptic aortitis of the descending thoracic aorta or abdominal aorta has been reported more rarely [31]. Pathogenic mechanisms involving similarities between aortic and entheseal antigens may contribute to the development of aortitis:

the inflammation occurs at the aortic root and aortic valve, which are structurally similar to the entheses.

4.2. Association with Takayasu disease

Takayasu disease is characterized by inflammation of the aorta and its branches. The clinical presentation consists in a variable combination of constitutional symptoms (fever, arthralgia, weight loss) related to systemic and arterial inflammation. Ischemic symptoms due to arterial stenoses develop eventually. Two very recent retrospective studies support an association between Takayasu disease and spondyloarthritis. One of these studies evaluated 14 patients with spondyloarthritis (AS, $n = 11$; psoriatic arthritis, $n = 2$, and SAPHO syndrome, $n = 1$) and Takayasu disease [32]. Among them, 3 were HLA-B27-positive. The diagnosis of spondyloarthritis antedated the onset of Takayasu disease in 13 patients. CRP values were consistently high and were ≥ 25 mg/L in 10 (71%) patients. Onset of the arteritis occurred during TNFα antagonist therapy in 3 patients. In 4 other patients, the introduction of a biologic after the onset of arteritis improved the clinical and laboratory markers of vascular disease. Another article reported 3 additional cases of Takayasu arteritis in patents with AS [33]. Thus, although rare, the concomitant occurrence of spondyloarthritis and Takayasu disease does not seem ascribable to chance alone. The main arteries should be examined routinely by palpation and auscultation, and markers of systemic inflammation should be monitored for changes over time.

5. Deep vein thrombosis

Few studies have addressed the occurrence and consequences of deep vein thrombosis in patients with axSpA, contrasting with the large body of work on arterial thromboembolism. In 6448 prospectively studied patients with AS, the risk of deep vein thrombosis was increased by about 50% compared to the general population after adjustment on age and gender (hazard ratio [HR]: 1.53; 95% CI: 1.25–1.87) [34]. A similar risk increase was seen in patients with psoriatic arthritis or undifferentiated spondyloarthritis [34]. The pathophysiological underpinnings of the association are unclear. We studied biological risk factors for venous thromboembolism in 46 patients with AS comparatively to healthy controls [35]. Thrombin generation in the patients correlated with disease activity but was not higher than in the controls [35]. Further research is needed into the increased risk of deep vein thrombosis, which contributes to the excess cardiovascular mortality seen in patients with spondyloarthritis.

6. Consequences of vascular involvement in spondyloarthritis

6.1. Cardiovascular events

An excess risk of cardiovascular disease, including coronary artery events [3], has been demonstrated in several studies of patients with AS [36]. AS is an independent risk factor for early coronary artery bypass grafting [37]. The available metaanalyses support the excess cardiovascular risk. Nevertheless, in some studies the risk of cardiovascular events was not higher than in the general population after adjustment on age and gender [38]. When interpreting study findings, attention should be paid to the study setting, disease duration, disease activity, and whether data were collected before or after the introduction of biologics.

6.2. Mortality

In a 2001 literature review, we found evidence of excess mortality in patients with AS (after exclusion of those given radiation therapy) [2]. However, differences in standardized mortality ratios tended to decline toward nonsignificance in the most recent studies [2]. Our study of death certificates issued in France between 1969 and 2009 confirmed that mortality was higher in patients with AS compared to the general population [1]. Cardiovascular events were the leading cause of death. Causes of excess mortality often reported in the literature include cardiovascular, renal, infectious, and respiratory diseases, as well as traumatic injuries [1,2].

7. Vascular effects of treatments

The impact of treatments on cardiovascular events or mortality has only rarely been assessed, due to the need for prolonged follow-up of young patients who receive a variety of treatments over time. Given the small number of events, studies usually consisted in a retrospective analysis of data from national databases. In 421 patients with AS in the Taiwanese national database, the excess risk of cardiovascular events was chiefly apparent during the first 6 treatment months (OR: 1.41; 95% CI: 1.07–1.86) [39]. Subsequently, the risk tended to decrease with frequent and prolonged nonsteroidal antiinflammatory drug (NSAID) therapy. Another database study compared 21,473 patients with AS to 86,606 age- and gender-matched controls without AS [40]. Vascular mortality was higher in the AS group (HR: 1.36; 95% CI: 1.13–1.65) and decreased with exposure to NSAIDs or statins [40]. A very recent cohort study of patients with AS found a 37% decrease in all-cause mortality among statin users vs. nonusers ($n = 1108$ in each group) after adjustment on a propensity score [41]. The association was independent from age, gender, socioeconomic status, body mass index, existing cardiovascular disease, exposure to other medications, and total cholesterol level [41].

Ten studies have evaluated the effects of treatments on early vascular changes indicating subclinical atheroma (Table 1). Among them, only three were controlled, including two versus a placebo. These studies are recent, with the earliest having been reported in 2009. In all, 321 patients with spondyloarthritis were studied, for 4 to 118 weeks. The focus was endothelial function (5 studies), arterial stiffness (4 studies), and IMT (2 studies). The treatments were TNFα antagonists (7 studies), statins (1 study), spironolactone (1 study), and physical exercise (1 study). Table 1 reports the main findings. Endothelial function, which is the first parameter to deteriorate during the development of atheroma, was restored overall by the various drugs (TNFα antagonists, statins, or spironolactone). The effect was apparent as early as the 4th week and seemed sustained after 24 weeks. In contrast, later stages of subclinical atheroma (reflected by arterial stiffness and IMT) were not sensitive to TNFα antagonist therapy, although they improved with an intensive exercise program. In a placebo-controlled study, PWV improved in the group given golimumab but worsened in the placebo group [47]. This finding should be interpreted in the light of the presence of PWV and ITM alterations in 55% and 40% of studies, respectively, vs. healthy controls, as indicated above (Section 3). In a metaanalysis of data on IMT, a difference vs. healthy controls was found among nonusers of biologics but not among patients taking TNFα antagonists [18].

EULAR recommendations on cardiovascular risk management in patients with inflammatory joint disease indicate that antihypertensive drugs and statins should be used in compliance with national guidelines. Regarding NSAIDs and biologics, the only indication is that appropriate caution should be exercised in certain patients with cardiovascular disease [50].

Table 1
Effect of treatments on markers of subclinical atheroma in patients with spondyloarthritis.

Authors	Year of publication	Diagnosis/number of patients	Placebo/controls	Treatments	Evaluation time point (weeks)	Evaluation criteria	Results
Syngle [42]	2010	AS/12	0	TNFα antagonist	12	FMD	Improvement in FMD
Syngle [14]	2013	AS/20	0	Spironolactone	12	FMD	Improvement in FMD
Garg [43]	2015	AS/32	15	Statin	24	FMD	Improvement in FMD in the statin group
Deyab [44]	2017	AS/20	0	TNFα antagonist	26	PAT	No change in PAT
Van eijk [16]	2009	AS/15	0	Etanercept	4	Iontophoresis	Improvement in microvascular function
Capkin [45]	2012	AS/28	0	TNFα antagonist	24	PWV	No change in PWV
Mathieu [46]	2013	AS/49	0	TNFα antagonist	52	PWV	No change in PWV
Tam [47]	2014	AS/41	21	Golimumab	26	PWV	No change in PWV
Sveaas [48]	2014	axSpA/28	14	Physical exercise	12	PWV	Improvement in PWV
Van sijl [49]	2013	AS/56		TNFα antagonist	118	IMT	No change in IMT
Tam [47]	2014	AS/41	21	Golimumab	26	IMT	No change in IMT

AS: ankylosing spondylitis; axSpA: axial spondyloarthritis; FMD: flow-mediated dilation; PWV: pulse wave velocity; IMT: intima-media thickness; PAT: peripheral arterial tonometry.

Disclosure of interest

The authors declare that they have no competing interest.

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