

Cardiovascular Disease in Ankylosing Spondylitis: Another Extra-Skeletal Feature of a Chronic Inflammatory Disorder?

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Ankylosing spondylitis (AS) is a chronic idiopathic inflammatory disease primarily affecting the skeleton [1]. The hallmark of skeletal involvement is axial disease, which is characterized by inflammation of the sacroiliac joints and spinal structures, such as ligaments, intervertebral discs, zygoapophyseal joints and vertebral bodies [2,3]. The whole process progresses through bone marrow edema, pannus formation, erosive changes of osseous and cartilaginous structures and finally new bone deposition leading to bony ankylosis and syndesmophyte formation [4]. Additional skeletal manifestations may be enthesitis (an almost pathognomonic feature of the spondyloarthritides) and peripheral asymmetric oligoarthritis [2,5].

Apart from musculoskeletal structures, several other tissues and organs may be involved in the course of AS. Indeed, inflammation may affect the uvea, with the occurrence of acute anterior uveitis, the skin, with the appearance of psoriasis, or the gut, which may be inflamed either subclinically or overtly in the form of ulcerative colitis or Crohn's disease [6-8]. It is also established that in a proportion of AS patients, certain parts of the heart and the aorta may be affected [9], possibly as a result of an inflammatory process directed against fibrocartilage present in the central fibrous body of the heart or the arterial wall. Pathologically, inflammation and scarring may be observed in the aortic root, giving rise to aortic regurgitation, whereas involvement of the adjacent heart conduction system may result in various types of conduction abnormalities, up to complete heart block [10,11]. This type of heart involvement seems to be AS-specific both on morphological and genetic grounds. Indeed, a combination of aortic regurgitation and severe conduction abnormalities has been closely associated with HLA B27 positivity, the major genetic marker related to AS [12,13].

Although aortic valve disease and conduction disturbances have been reported in up to 10% and 9% of AS patients respectively [9], their impact on the overall morbidity and mortality of AS remains uncertain. In an electrocardiographic study of 131 AS patients, the most common abnormality was prolonged QRS interval (29.2%), but no cases of high-grade atrioventricular block were identified [14]. Moreover, in an analysis of the causes of death in a cohort of 398 AS patients, the leading cause of death was diseases of the circulatory system accounting for 64 out of 152 or 42.1% of recorded deaths. Compared to the general population, there was a surplus of 11 cardiovascular deaths with a corresponding standardized mortality ratio (SMR) due to cardiovascular causes of 1.2. It should be noted that in that study only 6 deaths (3.9%) were attributed to AS-specific heart disease, which were classified separately from the 64 deaths due to circulatory diseases [15]. Indeed, cardiovascular disease has been confirmed by plenty of other studies to be the most frequent cause of death in AS patients [16], while some authors have asserted that cardiovascular disease may proportionately claim more lives among AS patients than in the general population [17]. Moreover, several studies, employing a wide range of methodologies have demonstrated that AS patients are at significantly greater risk for ischemic heart disease [6,18,19], for myocardial infarction [20], for early coronary revascularization procedures [21], for cerebrovascular disease [18,19], as well as for peripheral vascular disease [18] and heart failure [18,19] (Table 1).

Despite variations in study design and occasionally conflicting results (for example as regards the risk for myocardial infarction), the

overall conclusion drawn from the aforementioned studies is that there seems to be an excess atherosclerotic cardiovascular disease in AS, manifesting as ischemic heart disease, cerebrovascular or peripheral arterial disease. Such a conclusion, though, should not appear irrelevant given the wealth of evidence supporting an increased risk for cardiovascular disease in patients with rheumatoid arthritis (RA) as well [18,22-24]. However, how could such an excess cardiovascular risk in AS be explained? According to the RA paradigm, three potential interpretations might be suggested [25]: that AS treatment has a negative impact on the cardiovascular risk; that classic cardiovascular risk factors are more prevalent in AS patients; or that AS-related systemic inflammation contributes independently to the atherosclerotic process.

For decades, the mainstay of AS treatment have been the non-steroidal anti-inflammatory drugs (NSAIDs), a drug class that has recently been associated with adverse cardiovascular events [26]. However, a study of patients with inflammatory polyarthritis taking NSAIDs failed to demonstrate an elevated rate of cardiovascular deaths

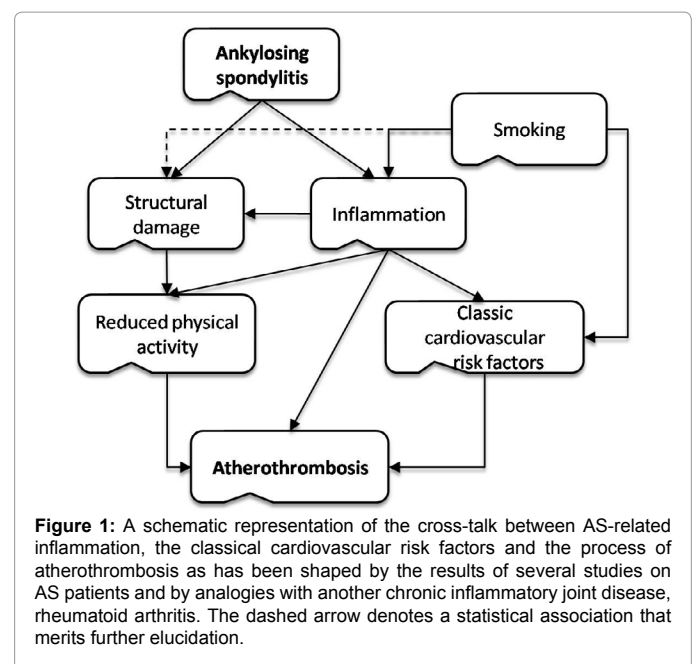


Figure 1: A schematic representation of the cross-talk between AS-related inflammation, the classical cardiovascular risk factors and the process of atherothrombosis as has been shaped by the results of several studies on AS patients and by analogies with another chronic inflammatory joint disease, rheumatoid arthritis. The dashed arrow denotes a statistical association that merits further elucidation.

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Author, Year [Ref]	Study design (Country)	Number of patients	Results
Han, 2006 [18]	Medical database analysis (USA)	1843	Prevalence ratio (lower-upper CI) <ul style="list-style-type: none"> IHD: 1.2 (1-1.5) CHF: 1.8 (1.2-2.6) CVD: 1.7 (1.3-2.3) PVD: 1.6 (1.2-2.2) Hypertension: 1.3 (1.1-1.4) Type 2 DM: 1.2 (1-1.4) Hyperlipidemia: 1.2 (1.1-1.3)
Peters, 2010 [20]	Mail survey (The Netherlands)	383	Odds ratio (95% CI) for MI 3.1 (1.9-5.1)
Szabo, 2011 [19]	Administrative database analysis (Canada)	8616	Standardized prevalence ratios (95% CI) <ul style="list-style-type: none"> IHD: 1.37 (1.31-1.44) CHF: 1.34 (1.26-1.42) CVD: 1.25 (1.15-1.35)
Bremander, 2011 [6]	Prospective cohort (Sweden)	935	Standardized morbidity-rate ratio (95% CI) <ul style="list-style-type: none"> IHD: 2.20 (1.77-2.70) MI: 1.32 (0.81-2.04) Hypertension: 1.98 (1.72-2.28) DM: 1.41 (1.10-1.78) Dyslipidemia: 1.26 (0.89-1.72)

Abbreviations: CI: Confidence Interval; IHD: Ischemic Heart Disease; CHF: Congestive Heart Failure; CVD: Cerebrovascular Disease; PVD: Peripheral Vascular Disease; DM: Diabetes Mellitus; MI: Myocardial Infarction

Table 1: Summary of studies on cardiovascular morbidity in Ankylosing Spondylitis in comparison with the general population.

in this group of patients [27]. Furthermore, a cohort study from Norway showed that mortality of AS patients could be independently predicted by increasing levels of C-reactive protein, delay in AS diagnosis, work disability and, additionally, infrequent use of NSAIDs, suggesting that the risks of NSAID treatment might be offset by the benefits of inflammation suppression [28]. On the other hand, for more than ten years, Tumor Necrosis Factor- α (TNF α) blockers have offered a potent alternative for patients not responding or intolerant to NSAIDs [29]. Due to reports of increased morbidity and mortality in patients with advanced heart failure treated with TNF α antagonists [30], it is advocated that this class of drugs be prescribed with caution to patients with a history of heart failure. Apart from heart failure, though, several studies could not demonstrate an increased risk for cardiovascular disease with the use of TNF α blockers in RA, as well as across other indications [30,31]. On the contrary, in RA patients TNF α blockade has been associated with a reduction of cardiovascular events, an effect that has been attributed at least partly to the suppression of systemic inflammation rather than the modification of classical atherosclerosis risk factors [32-34].

Considerable evidence exists that classical atherosclerosis risk factors are impaired to a greater degree in AS patients compared to non-AS subjects. Regarding lifestyle factors it is possible that AS patients engage in less physical activity due to pain, disability or depression [35]. The issue of smoking in AS deserves special attention owing to several studies that have demonstrated that smoking is associated with higher disease activity, impaired function and worse radiographic damage [36,37]. Interestingly, a couple of recent studies of patients with early axial spondyloarthritis (regardless of fulfillment of the 1984 modified New York criteria for AS [38]) have also demonstrated that smoking status was associated with higher disease activity, poorer function, more severe inflammation on magnetic resonance imaging, as well as worse structural damage and progression [39,40]. Whether smoking is directly implicated in the pathophysiology of AS, as has been suggested for RA [41], remains to be elucidated; however the results of these studies imply that smoking may be twice as harmful to AS patients as non-AS subjects. Not only does it contribute to atherosclerosis and cardiovascular disease *per se*, but also, by enhancing inflammation and promoting structural damage (and consequently disability) limit

physical function and further impair classical atherosclerosis risk factors.

Several other risk factors seem to be impaired in AS as well. Indeed, a meta-analysis has concluded that AS patients have significantly lower levels of the atheroprotective high density lipoprotein (HDL) cholesterol, as well as a higher prevalence of the metabolic syndrome [42]. In some studies, it has been further suggested that both lipid perturbation and the presence of the metabolic syndrome are related to AS disease activity [43,44], while treatment with TNF α blockers seems to suppress insulin resistance, but has little, if any, effect on lipid levels [45,46]. Moreover, blood pressure levels have been found higher in AS patients [43], whereas hypertension and diabetes mellitus have been reported to also be more prevalent in AS compared to control subjects [6,18]. Additionally, a couple of novel atherosclerosis risk factors, such as homocysteine or asymmetric dimethylarginine, have been reported to be disturbed in AS [47,48].

Several cross-sectional studies have investigated the issue of subclinical atherosclerosis in AS, with most evidence stemming from those assessing the carotid intima-media thickness (IMT) as a pertinent marker. A meta-analysis of studies assessing IMT in AS concluded that AS patients have significantly elevated IMT compared to controls [42]. Interestingly, in some reports the IMT correlated not only with classical atherosclerosis risk factors, but also with various measures of AS, such as disease activity, function or metrology [49,50]. Furthermore, effective suppression of the inflammation in spondyloarthritis with anti-rheumatic treatment has been associated with improvements of vascular morphology and function [51,52].

Nevertheless, when interpreting the results of the studies on atherosclerosis and its risk factors in AS, it should be kept in mind that most of them have been cross-sectional, their sample size relatively small and none of them actually addressed prospectively "hard" outcomes, such as clinical cardiovascular disease. Publication bias should also be a concern, since studies failing to report significant results may also fail to reach publication. However, in the era of evidence-based medicine, decision-making ought to take into account the available evidence. Thus, despite the lack of high quality evidence, there seems to be an increased cardiovascular burden in AS patients due both to impaired

classical risk factors, as well as to the inflammatory process itself, as seems to be the case with RA too [25] (Figure 1). Consequently, when managing patients with AS, the cardiovascular system should be screened not only for AS-specific cardiovascular complications, such as aortic insufficiency. Classical cardiovascular risk factors should also be considered given the possibility that cardiovascular disease may be more aggressive in this patient group than the general population and efforts should be undertaken to control these risk factors, as has already been recommended by the European League Against Rheumatism (EULAR) [53]. The treatment of risk factors may involve lifestyle modifications, such as smoking cessation, dietary interventions etc, as well as medical treatment, when appropriate. Importantly, the possible interaction between systemic inflammation and atherosclerosis attaches additional value to the effective control of AS-related inflammation, since it may not only benefit patients in terms of musculoskeletal symptoms and quality of life, but also act as an adjunct to the prevention of cardiovascular disease.

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