Review

Atherosclerosis and cardiovascular disease in the spondyloarthritides, particularly ankylosing spondylitis and psoriatic arthritis

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ABSTRACT

The spondyloarthritides (SpA) are a group of idiopathic inflammatory diseases affecting the axial and/or peripheral skeleton. Recent evidence points towards an increased mortality and morbidity due to cardiovascular disease, especially within the two major forms of SpA, ankylosing spondylitis and psoriatic arthritis. Several studies have identified alterations of the lipid profile, insulin sensitivity and other metabolic cardiovascular risk factors in SpA patients. An array of vascular morphologic and functional abnormalities has also been reported in these diseases, supporting the hypothesis of accelerated atherosclerosis in SpA. Inflammation appears to be a major player, involved both in the impairment of the classic cardiovascular risk factors, as well as directly in the process of endothelial injury, dysfunction and ultimately atherosclerosis. Multiple studies in rheumatoid arthritis have suggested that effective suppression of inflammation with synthetic disease-modifying anti-rheumatic drugs or with biologics may also exert favourable effects in the cardiovascular risk. Although such evidence is currently lacking for SpA, there is little doubt that physicians caring for patients with SpA should aim at controlling both inflammation and traditional cardiovascular risk factors. Such an integrated approach is expected to benefit patients in multiple levels.

Introduction

The term spondyloarthritis (SpA) encompasses a group of idiopathic inflammatory diseases with diverse clinical features on a common template. Their features include the type of musculoskeletal involvement (axial disease and/or peripheral arthritis predominantly affecting the large joints of the lower limbs, enthesitis, dactylitis), a common genetic background (frequent recurrence within families, raised prevalence of HLA B27 antigen) and a -more or less- shared array of extra-articular features: skin disease (psoriasis, keratodermia blennorrhagica), ocular disease (acute anterior uveitis), gastrointestinal disease (Crohn's disease, ulcerative colitis) etc (1-6). These features apart from distinguishing each particular type of SpA (ankylosing spondylitis [AS], psoriatic arthritis [PsA], reactive arthritis, enteropathic arthritis, undifferentiated SpA, pre- or non-radiographic axial SpA and relevant categories of juvenile idiopathic arthritis, such as enthesitis-related arthritis and juvenile PsA) constitute evidence that SpA is a systemic inflammatory disease, not merely confined to skeletal structures.

In parallel, ample evidence has accrued that another chronic arthritis, rheumatoid arthritis (RA), produces detrimental effects on metabolism and the cardiovascular system. It has been shown that RA patients have quantitative and qualitative perturbations in serum lipids and lipoproteins (7); that vascular function and morphology are impaired in RA patients to a greater degree than non-RA controls (8); and that RA patients suffer from greater cardiovascular morbidity and mortality than the general population (9, 10). Recently, RA has been paralleled to diabetes mellitus in terms of cardiovascular burden (11, 12) and the European League Against Rheumatism has issued recommendations for the management of the cardiovascular risk in patients with RA (13).

In the following sections, an approach to the issue of cardiovascular disease in SpA will be attempted by reviewing the evidence concerning the SpA two major subsets: AS and PsA. Other forms of SpA will not be discussed, either due

Table I. Studies reporting mortality rates due to all causes and due to cardiovascular diseases in ankylosing spondylitis patients in comparison with the general population.

Author, year (ref.)	Period of observation	Number of patients	x-ray exposure	SMR due to all causes	SMR due to CVD	Percentage of deaths due to CVD
Brown, 1965 (14)	1935-1960	14554	Yes	1.8	1.3	26.9%
Smith, 1977 (15)	1935-1965	1021	No	1.6	1.4	40%
Radford, 1977 (16)	1935-1968	836	No	1.6	1.4	41.1%
Kaprove, 1980 (17)	1947-1976	76 62	Yes No	2.62 1.33	3.27 1.22	50% 40%
Khan, 1981 (18)	1934-1975	56	No	1.32		45%
Smith, 1982 (19)	1935-1970	14111	Yes	1.7	1.3	33.9%
Darby, 1987 (20)	1935-1983	14106	Yes	1.46	1.2	39%
Lehtinen, 1993 (21)	1961-NA	398	No	1.5	1.2	42.1%
Bakland, 2005 (22)	1960-NA	534	No	Males 0.2 Females 0.1		
Bakland, 2011 (23)	1977-2009	677	No	Males 1.63 Females 1.38		40.2%

SMR: standardised mortality ratio; CVD: cardiovascular disease; NA: not available.

to their rarity and consequently lack of relevant evidence (reactive arthritis, juvenile SpA) or due to peculiarities of each individual form. For instance, the presence of overt inflammatory bowel disease in enteropathic arthritis often raises nutritional issues and/or infectious complications that would preclude observations on metabolism from being generalisable to the whole SpA group. Besides, non-radiographic axial SpA has only recently been proposed as a distinct SpA entity (3), while there is obviously no consensus as to what constitutes undifferentiated SpA (more than a merely exclusion diagnosis).

Epidemiology

Cardiovascular mortality and morbidity in AS

Several studies have reported on mortality and causes of death in patients with AS (14-23). The majority of studies attribute to AS patients greater mortality rates, in terms of standardised mortality ratio (SMR), compared to the general population (Table I). Excluding estimates which take into account the survival of patients treated with radiation therapy (which has been associated with an increased mortality due to malignancies), SMRs are still higher for AS patients in almost all studies. On the other hand, although non-steroidal anti-inflammatory drugs (NSAIDs) have been the mainstay of AS treatment for decades, it is difficult to assess their potential contribution to the increase of mortality in AS, particularly given their broad array of adverse events, including cardiovascular ones. However, in a recent study, risk factors for increased mortality in AS were high C-reactive protein (CRP) levels, delay in diagnosis and infrequent use of NSAIDs. This probably reflects, at least in part, the cumulative detrimental effects of inflammation, which may outweigh the risks of drug treatment (23).

Focusing on the causes of death among AS patients, cardiovascular disease is ranked top across all studies, usually followed by malignant disease. Compared to the general population, SMRs due to cardiovascular causes are also higher in AS patients. Yet, some causes of cardiovascular death (*e.g.* conduction disturbances, aortic disease, cardiomyopathy) may be direct manifestations of AS itself (24). However, no study makes a clear distinction between cardiovascular death directly related to AS or not. Thus, it is uncertain whether the excess cardiovascular mortality observed in AS patients should be ascribed solely to AS-specific cardiac disorders or also to a concomitant excess of common cardiovascular disease related to atherosclerosis. Of note, in the study by Lehtinen, all deaths deemed directly due to the AS process itself (including cardiovascular ones) were classified separately as "diseases of locomotor system". Nonetheless, there remained a surplus of 11 cardiovascular deaths not explained by AS, corresponding to a SMR for circulatory diseases of 1.2 (21).

Moreover, several papers have been published reporting a higher cardiovascular morbidity in AS patients relative to the general population. Han et al, based on a large medical database, which included 1843 AS and 3066 PsA patients, reported that subjects with AS had more often a concomitant diagnosis of cerebrovascular disease, ischaemic heart disease, congestive heart failure, peripheral vascular disease, dyslipidemia and arterial hypertension than controls. The respective prevalence ratios (lower-upper limit of confidence interval [CI]) for AS patients compared to controls were 1.8 (1.2–2.6) for congestive heart failure, 1.7 (1.3–2.3) for cerebrovascular disease, 1.6 (1.2–2.2) for peripheral vascular disease, 1.3 (1.1–1.4) for hypertension, 1.2 (1.1–1.3) for hyperlipidaemia and 1.2 (1–1.5) for ischaemic heart disease (25). In another medical database analysis, which included 8616 AS patients, AS was also associated with a significantly elevated risk for cardiovascular disease with standardised prevalence ratios (95% CI) equal to 1.37 (1.31–1.44) for ischaemic heart disease, 1.34 (1.26–1.42) for congestive heart failure and 1.25 (1.15–1.35) for cerebrovascular disease (26). In a small retrospective study, Sukenik *et al*. found that the overall prevalence of cardiovascular complications of AS was 42.5%, while ischaemic heart disease was reported for 7 (17.5%) patients, four of whom had no other cardiac manifestation. Of note, among 40 control subjects, the prevalence of ischaemic heart disease was 12.5% (27). Further, in a survey of AS patients, the prevalence of myocardial infarction was estimated to 4.4% and the adjusted odds ratio (95% CI) in relation with the general population was 3.1 (1.9–5.1) (28). Finally, in a recent cohort study comprising 935 AS patients, the standardised morbidity-rate ratio, calculated on data of the local population, was significantly increased for ischaemic heart disease (2.20, 95% CI 1.77–2.70), hypertension (1.98,

95% CI 1.72–2.28) and diabetes mellitus (1.41, 95% CI 1.10–1.78). However, the ratio for myocardial infarction was not elevated (29). Nevertheless, SpA has been shown to be an independent predictor of early coronary artery by-pass grafting, stronger even than traditional cardiovascular risk factors (30). Taking all the above together, there seems to be a raised prevalence of cardiovascular disease in AS patients, which probably contributes to an increased mortality.

Cardiovascular mortality and morbidity in PsA

Estimating the risk for cardiovascular disease in PsA may be a more complicated task due to the presence of psoriasis and the potential cardiovascular burden that isolated skin disease confers to patients. Indeed, severe psoriasis has been associated with an increased overall mortality than the general population with a hazard ratio (HR) as high as 1.5 (95% CI 1.3–1.8) (31), as well as an increased cardiovascular mortality with a corresponding SMR up to 1.52 (95% CI 1.44–1.60) (32). Further, psoriasis has been shown to be an independent risk factor for myocardial infarction (33). The situation becomes more complex when taking into account the diversity of classification criteria for PsA that have been applied in studies during the last decades (34); and finally the "grey zone" between psoriasis and PsA, wherein a patient with apparently skin-limited disease is found to have subclinical musculoskeletal involvement as detected with modern sensitive methods, such as magnetic resonance imaging and musculoskeletal ultrasound (35). Given the above, as well as differences in the design of epidemiologic studies (36-39), data on mortality of PsA patients have been conflicting (Table II). Hence, while Shbeeb (36) and Buckley (39) refute an increased mortality in PsA, two studies from the Toronto clinic support a raised death rate, with a propensity, though, to decrease over calendar time (37-38).

A number of studies have also addressed cardiovascular morbidity in PsA patients. In the aforementioned study by Han *et al*., PsA patients were reported to have more often cerebrovascular disease, ischaemic heart disease, congestive heart failure, peripheral vascular disease, dyslipidemia, type 2 diabetes mellitus and arterial hypertension than controls. The prevalence ratios (lower-upper limit of CI) for PsA patients compared to controls were 1.3 (1.1–1.7) for cerebrovascular disease, 1.3 (1.1–1.5) for ischaemic heart disease, 1.5 (1.1–2) for congestive heart failure, 1.6 (1.2–2) for peripheral vascular disease, 1.3 (1.2–1.4) for hypertension, 1.2 (1.1–1.3) for hyperlipidaemia and 1.5 (1.4–1.7) for diabetes [25]. In a prospective study of PsA patients followed over 8.3 years on average, the standardised prevalence ratio was significantly elevated for angina (1.97, 95% CI 1.24–3.12), myocardial infarction (2.57, 95% CI 1.73–3.8) and hypertension (1.9, 95% CI 1.59–2.27), but not for congestive heart failure and cerebrovascular accidents. Moreover, in regression analysis, severe psoriasis [as assessed by Psoriasis Area and Severity Index (PASI) score], along with diabetes and high triglyceride levels, was associated with an increased risk for the first cardiovascular event (40). In a cross sectional study comparing PsA with RA patients in terms of non-fatal cardiovascular disease, the authors estimated the prevalence of such cardiovascular events to 10% in PsA patients, which was not different from the respective prevalence in RA patients (12.4%) (41).

Finally, a couple of recent studies have addressed the issue of co-morbidities in PsA in comparison to psoriasis. The first was a nationwide Danish study that concluded that the risk for cardiovascular disease or cardiovascular death in patients with PsA was similar to that of severe psoriasis and was comparable to the risks conferred by diabetes mellitus (42). However, a Canadian cohort study found an increased prevalence of cardiovascular disease (as well as of hypertension, hyperlipidemia, diabetes and obesity) in PsA patients compared to psoriasis patients. Yet, after adjusting for age, sex, psoriasis duration, medication, PASI and other factors, only hypertension was still statistically more prevalent in PsA than psoriatic subjects (43). Overall, PsA seems to confer an increased cardiovascular risk, although it appears difficult to estimate the extent to which skin or articular disease independently contribute to this excess risk.

Disentangling the links between chronic synovial inflammation and atherosclerosis

As several studies in RA and other rheumatic disorders have shown, the

Table II. Studies reporting mortality rates due to all causes and due to cardiovascular diseases in psoriatic arthritis patients in comparison with the general population

Author, year (ref)	Period of observation	Number of patients	SMR due to all causes	SMR due to CVD	Percentage of deaths due to CVD
Shbeeb, 2000 (36)	1982–1992	66	Survival not different to the general population		
Wong, 1997 (37)	1978–1994	428	1.62 (95% CI 1.21–2.12)	1.33 (95% CI 7.72–21.53)	36.2%
Ali, 2007 (38)	1978–2004	680	1.36 (95% CI 1.12–1.64)		24.5%
Buckley, 2010 (39)	1985–NA	453	0.82 (95% CI 0.58–1.13)		38%
Ahlehoff, 2011 (42)	1997–2006	607	1.74 (95% CI 1.32–2.30)*	1.84 (95% CI 1.11–3.06)*	

SMR: standardised mortality ratio; CVD: cardiovascular disease; CI: confidence interval; NA: not available; * rate ratio.

excess cardiovascular morbidity and mortality seen in those patients seems to be multifactorial. Arthritis patients may engage in less physical activity due to pain and/or disability (44). Physicians may be unwilling to prescribe drugs for cardiovascular disease prevention in patients who already use NSAIDs, disease-modifying anti-rheumatic drugs (DMARDs) or biologics (45, 46). Finally, chronic inflammation may itself pave the way to cardiovascular disease either directly, as an independent risk factor, or indirectly by impairing established atherosclerosis risk factors.

Indeed, inflammation, through the actions of various inflammatory mediators, such as tumour necrosis factor (TNF)-α, interleukin (IL) -1 and IL-6, may affect metabolism and the cardiovascular system in several ways (47). Both quantitative and qualitative lipid and lipoprotein alterations are observed. There is a decrease in overall, high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol levels (48), with a proportionately greater decrease in the atheroprotective HDL levels resulting in a less favourable atherogenic index (7, 49); triglycerides are often reported to rise in inflammation (48). Apolipoprotein levels are disturbed (7), while lipid particle composition is impaired enhancing further the effects of a pro-atherogenic lipid profile (50). Levels of oxidised LDL rise (7, 50), while HDL particles are depleted of apolipoprotein A which is replaced with serum amyloid A (SAA) (50). This impairs the ability of HDL particles to stabilise the enzyme paraoxonase 1 that protects LDL from oxidation. Additional compositional alterations of the HDL particle are also responsible for impaired anti-oxidant and reverse cholesterol transport capacity of HDL and thus for a significantly less efficient atheroprotective HDL function (51-53).

It has been known for decades that systemic inflammation may enhance insulin resistance through the actions of TNF-α (54), while anti-TNF-α treatment of patients with rheumatic diseases has resulted in improvement of insulin sensitivity (55). Moreover, hyperinsulinemia is a key component of the metabolic syndrome and plays a role in hypertension, conditions that ultimately associate with cardiovascular disease (56). Systemic inflammation may also induce adipokines, such as leptin, resistin and visfatin, and suppress others, such as adiponectin, with unfavourable effects on metabolism and cardiovascular risk (57, 58). Homocysteine, an independent cardiovascular risk factor, has also been shown to correlate with inflammatory markers (59). Furthermore, systemic inflammation induces endothelial dysfunction, with upregulation of adhesion molecules and altered vasodilatory and anti-coagulant properties (60-62). Finally, elevations of coagulation factors, such as tissue factor, fibrinogen, and thrombocytosis are well-known sequelae of acute phase response (47, 63).

In summary, mediators that are produced and operate at sites of inflammation, such as the synovium in chronic arthritis, exert also an array of systemic effects. At the liver, they induce acute phase reactants, such as CRP, SAA and coagulation factors, skew lipid metabolism promoting triglyceride production and impairing the HDL/LDL balance and composition. In adipose tissue and muscles insulin resistance is enhanced. The endothelium sustains injury due to the altered lipid profile, becomes activated with the corroboration of circulating cytokines and attracts inflammatory cells that engage in promoting and perpetuating vascular inflammation. The whole process results in atheroma formation, while the associated pro-coagulant state eventually heightens the risk of thrombosis on unstable inflamed arterial plaques and of acute cardiovascular events (Fig. 1). In the following sections available evidence on metabolic risk factors and vascular dysfunction/alterations in AS and PsA will be reviewed.

Metabolic perturbations in the spondyloarthritides

Ankylosing spondylitis

Aside from the large database analysis performed by Han *et al*., which showed that AS patients were more often diagnosed with hyperlipidaemia, compared to non-AS subjects (25), several studies (though most of them with a limited number of participants) have reported comparisons of the lipidemic profile of AS patients with controls with variable results (64-78). However, in a recent meta-analysis on cardiovascular profile of AS patients, it was estimated that, across all studies combined, AS patients had significantly lower levels of total cholesterol, HDL-cholesterol and triglycerides compared to controls, but no difference in LDL-cholesterol and the atherogenic index (79). Furthermore, some studies have shown that lipid levels in AS patients correlated with several clinical and/or laboratory markers of inflammation (73, 80) and that differences in lipid levels between patients and controls disappeared after adjustment for inflammatory markers (64). Diabetes mellitus was not more prevalent among AS subjects in the analysis by Han (25), while serum glucose levels in AS patients across several studies included in a meta-analysis were comparable to those of the control group (79). In contrast, Bremander *et al*. found an increased prevalence of diabetes mellitus in their AS cohort compared to the general population (29). Consequently, the association of AS with diabetes remains controversial. Furthermore, two studies have reported a higher prevalence of the metabolic syndrome in AS patients compared to controls (66, 73). Both also showed that AS patients had significantly higher blood pressure, although in the meta-analysis previously mentioned no components of the metabolic syndrome other than HDL-cholesterol were found significantly impaired in AS patients compared to controls (79). In contrast, a third study could not prove a higher prevalence of the metabolic syndrome in AS (81).

Hyperhomocysteinaemia (defined as a homocysteine level >15 μmol/L) was reported in one study to be significantly more prevalent in AS patients than the control group, while its presence correlated with worse function and higher erythrocyte sedimentation rate (ESR) (82). In another cross-sectional study, AS patients had also significantly higher levels of homocysteine compared to controls. In that study, homocysteine

levels were higher in those on sulphasalazine with or without methotrexate compared to those on NSAIDs only. However, homocysteine levels did not correlate with disease activity status (83). Finally, asymmetric dimethylarginine (ADMA), an inhibitor of nitric oxide (NO) synthase, has been found significantly elevated in 3 cross-sectional studies of AS patients. Plasma/serum ADMA levels were correlated with the presence of AS, measures of skeletal mobility, ESR and high-sensitivity CRP (72, 75, 84). Although this might have implications as regards vascular function, no correlations of ADMA levels with indices of vascular morphology and function could be demonstrated (75, 84). Interestingly, in a recent study in RA patients no association was also found between ADMA levels and parameters of micro- and macrovascular function, despite the fact that the patients had significantly higher ADMA levels than controls (85). Clearly, the potential links between chronic arthritis, ADMA levels and vascular dysfunction needs further elucidation.

Psoriatic arthritis

In the study by Han, PsA patients had been assigned the diagnosis of hyperlipidaemia and diabetes mellitus more often than controls (25). Besides, several studies have also investigated the lipid profile in PsA (Table III) (86-91). The most consistent finding across them is a significantly lower HDL cholesterol level compared to control subjects. Nevertheless, while one study did not find additional differences in the lipid profile of PsA patients (other than lower HDL and HDL_3 subfraction levels), when focusing on patients with active disease, a fall of the total and LDL cholesterol in comparison to the control group could also be demonstrated. Moreover, LDL production in PsA was skewed towards the more atherogenic LDL_3 subfraction (86). In another study, HDL- cholesterol and apolipoprotein AI (ApoAI) levels inversely correlated with CRP, whereas the total cholesterol/HDL-cholesterol and ApoB/ApoAI ratios positively correlated with CRP (89).

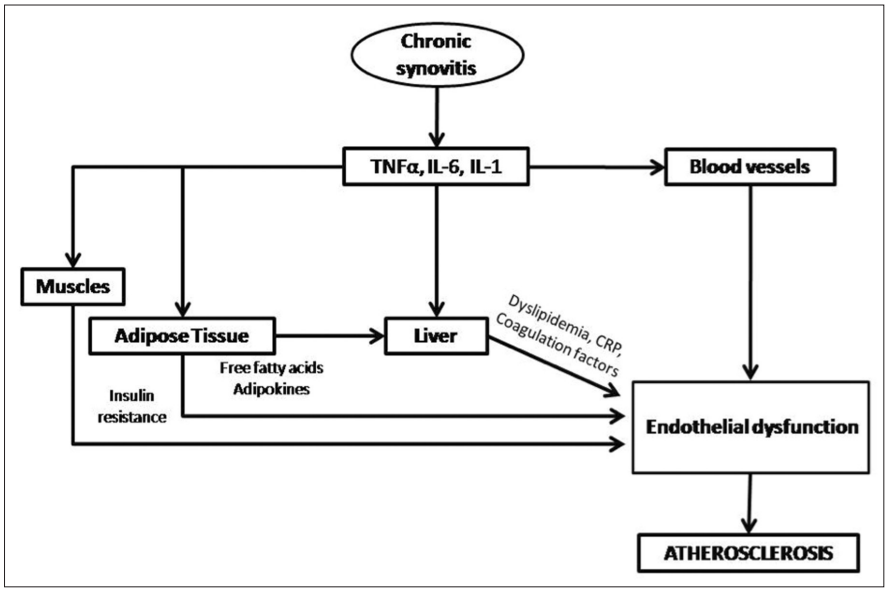

Fig. 1. A simplified scheme showing the complex effects of inflammatory mediators released at the sites of synovitis on metabolic processes and vascular function and integrity. Pro-inflammatory cytokines induce insulin resistance at peripheral tissues (muscles, fatty tissue) with the repercussions associated with the resulting metabolic syndrome. Increased lipolysis at the adipose tissue, as well as direct effects on liver function result in dyslipidaemia. Altered lipoprotein levels and composition, adipokines and coagulation factors along with inflammatory cytokines elicit endothelial activation and dysfunction triggering and contributing to an accelerated atherosclerotic process.
TNF-α: tumour necrosis factor-α; IL: interleukin; CRP: C-reactive protein.

Table III. Summary of studies comparing lipid levels of psoriatic arthritis patients with those of control subjects (up/down arrows correspond to statistically significant differences relative to controls, horizontal arrows indicate no significant differences).

Author, year (ref)	Number of PsA patients	Number of controls	Chol	HDL-C	LDL-C	Trg	Chol/HDL
Jones, 2000 (86)	50	50	↔	↓	↔	↔	↔
Kimhi, 2007 (87)	47 (older than controls)	100	↑	↓	↑	↑	NA
Gonzalez-Juanatey, 2007 (88)	59	59	↔	↔	↔	↔	NA
Tam, 2008 (89)	102	82	↓	↔	↓	↔	↓
Eder, 2008 (90)	40	40	↔	↓	↔	↔	NA
Atzeni, 2011 (91)	22	35	↔	NA	NA	↔	NA

PsA: psoriatic arthritis; Chol: total cholesterol; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; Trg: triglycerides; NA: not available.

Three studies have also reported on the prevalence of the metabolic syndrome in PsA. One of them found no difference in the prevalence of the metabolic syndrome in the PsA group, although hypertension and diabetes mellitus were more prevalent in PsA patients, even after adjustment for body mass index (89). In a retrospective study of PsA patients, the prevalence of the metabolic syndrome was 58.1%, while the proportion reported for the Third National Health and Nutrition Examination Survey (NHANES III) population was 35.2% (92). Finally, a third study showed that the metabolic syndrome was significantly more prevalent in PsA patients than healthy controls with an odds ratio of 2.68 (95% CI 1.60–4.50). Compared to the healthy subjects, PsA patients had greater waist circumference, while compared to RA and AS patients, they had a higher adjusted odds ratio to have central obesity, impaired fasting glucose, hypertriglyceridaemia and low HDL cholesterol (81). As for ADMA levels, in one cross sectional study they were found significantly elevated in PsA subjects than controls and they correlated inversely with coronary flow reserve. However, no correlation was noted between ADMA levels and

carotid intima-media thickness (IMT), Disease Activity Score for 28 Joints or PASI (91). In conclusion, several metabolic disturbances appear to be present in PsA patients, some of them showing some association with the presence of inflammation.

Pre-clinical atherosclerosis in the spondyloarthritides

Several non-invasive methods have been developed in order to detect early morphological or functional changes of the vasculature and ultimately to predict the future occurrence of clinical cardiovascular disease. Ultrasound-assessed carotid IMT is an established method (93), while others are the measurement of the endothelium-dependent vasodilatation, arterial pulse wave analysis and velocity, coronary flow reserve (for coronary arteries) etc. Plenty of studies have assessed preclinical atherosclerosis in AS (65, 66, 68-71, 74-78, 94) and PsA (87, 88, 90, 91, 95-98). Most of them have revealed morphological and/or functional disturbances and demonstrated correlations between the abnormality detected and the presence/duration of SpA, various measures of disease activity, function or metrology and a range of laboratory parameters. Particularly for carotid IMT, across 10 studies comparing AS patients with controls, five of them concluded that AS patients had statistically greater carotid IMT (71, 74, 76-78). Further, a meta-analysis of 6 studies on this topic supported the same conclusion (79). In the case of PsA, across 7 studies assessing carotid IMT, six showed that PsA patients had significantly elevated IMT compared to controls (87, 88, 90, 96-98). Although most of the above-mentioned studies have been cross-sectional with relatively small sample sizes (ranging between 40 and 82 patients with the exception of the study by Di Minno (98), which included 224 PsA patients), they certainly provide some evidence of a faster atherosclerotic process in SpA patients which also seems to be related with the SpA process itself.

Conclusions and prospects

Considerable epidemiological evidence suggests that AS and PsA are associated with increased cardiovascular morbidity and mortality. Potential links between SpA and cardiovascular risk have also been put forward by plenty of studies. However, most of these studies have been cross-sectional with limited size and not powered or designed to address "hard" outcomes, such as cardiovascular events, in relation with the disease status. On the other hand, advances in Rheumatology during the last decades have increased awareness of SpA. It is, thus, likely that earlier studies had included patients with more severe disease, which conferred a heavier burden on their health status and overall survival. This is best illustrated in the study by Ali *et al*. who observed a gradual decline in mortality rates as they focused sequentially from remotely to more recently recruited subjects in their cohort of PsA patients (38). An alternative explanation could be that the more aggressive management of the latter patients' disease might have favourably affected their general health and survival as well. Finally, a last point to consider, when dealing with studies of patients with rheumatic diseases spanning several decades, is that patients may not be comparable across studies due to variations in classification criteria applied. This, again, is best exemplified in the PsA paradigm, but also holds true for AS and for the whole concept of SpA in general (3).

On the other hand, evidence from RA, deriving mainly from registries and from meta-analyses, is convincing that effective control of rheumatoid inflammation, irrespective of the drug(s) used, has beneficial effects on the cardiovascular prognosis of these patients (99-104). Particularly for TNF-α blockers, the associated cardiovascular risk reduction in RA seems to be related to the suppression of inflammation rather than to a mere effect on the classical cardiovascular risk factors, such as lipid levels, which TNF-α blockers appear to affect fairly modestly (105,106).

In the spondyloarthritides, several papers have reported various changes in the lipid profile (68, 94, 107-112) or insulin sensitivity of patients receiving anti-rheumatic therapy (113). Others have also attested improvements in the vascular morphology and function (94, 114, 115). However, until large prospective long-term studies confirm whether effective suppression of inflammation contributes to a reduction of the emerging excess cardiovascular risk borne by those patients, the whole issue should not remain a theoretical one. As has been stressed by several national and multinational rheumatological associations, SpA patients do need early and effective anti-rheumatic treatment to comfort their musculoskeletal symptoms, (116-119). However, assessing for classical cardiovascular risk factors should not be overshadowed by those symptoms and treatment of the risk factors according to published recommendations not withheld on the excuse of concomitant anti-rheumatic therapies (13). Perhaps, cardiovascular disease in SpA patients should practically be regarded by the rheumatologist as another "extra-skeletal manifestation" rather than as "someone else's job".

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