

Impact of Inflammation on the Onset and Severity of Vascular Disease in Patients with Ankylosing Spondylitis

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ABSTRACT Ankylosing spondylitis associates an increase in morbidity and mortality from cardiovascular disease, existing a defined relationship between cardiovascular diseases and ankylosing spondylitis. Recent studies reported impairment of endothelial function, suggesting that atherosclerosis (ATS) induced by systemic chronic inflammation and altered lipid profile could be responsible of cardiovascular mortality increase. We assessed the role of inflammation in the induction and severity of vascular disease in patients with ankylosing spondylitis. We included 73 patients with no other vascular risk factors and assessed subclinical ATS at common carotid artery, the involvement of aorta, aortic valvular regurgitation and the correlation of these pathological changes with inflammatory status. 21 of the 73 patients (29%) showed different types and degrees of vascular disease which was correlated with pro-inflammatory markers, disease activity and the time from diagnosis. The chronic inflammatory status and other common risk factors are involved in the increase of cardiovascular risk in these patients.

KEY WORDS ankylosing spondylitis, atherosclerosis, inflammation, endothelial dysfunction, vascular disease

Introduction

Ankylosing spondylitis associates an increase in morbidity and mortality from cardiovascular disease, existing a defined relationship between cardiovascular diseases and ankylosing spondylitis whose significance hasn't yet been assessed. The chronic inflammatory status along with other traditional risk factors are responsible for the fact that the cardiovascular risk is getting to these patients (1).

The most frequent aims of the inflammation are the sacroiliac articulations, the peripheral articulations' synovia, the vertebral bodies along with the intervertebral discs and the entheses. The tissues' inflammation and infiltration of T cells (CD4+ predominates over CD8+), B cells (CD20+ and macrophages CD68+) and the overexpression TNFalpha and TGFbeta is present and can affect other organs, like the gastrointestinal tract and the eyes (2). The chronic inflammatory status in patients with spondylitis may imply different structures of the heart leading to an *increase in mortality from cardiovascular disease with almost 20-40%. Disease of the aorta's emergence, with its increased thickness, rigidity and dilatation, of the aortic valves and guidance faluts* are the most common. Besides, *pericarditis, cardiomyopathy and disease of the mitral valve* can also appear (3-5). The prevalence of subclinical, valvular and aortic root disease has been estimated at

approximately 82% of the patients with ankylosing spondylitis who have been explored through transesophageal echocardiogram (6,7). The inflammation present at the level of the aorta determines a marked fibroblastic repair response, adventitial increased thickness and retractile scars at the level of adventitia, focal destructions of the media elastic tissue, intimal proliferation and the vasa vasorum are reduced and present perivascular lymphoplasmocitary infiltration. This process extends towards the aortic ring and produces basal increased thickness and cusps retraction. The adventitial scars extend up to under the aortic valve's base, forcing a more important increased thickness behind the aortic valves' cusps commissures and forming a commissural fibrous eminence. Thus, the aortic failure is due to the cut and increased thickness of the aortic valves' cusps, the circulation of cusps towards the fibrous eminences and aortic root dilatation. The fibrosis extension towards aortic-mitral joint makes a subvalvular fibrous crest or subaortic protuberance.

Valvular regurgitation has been observed at approximately 50% of the patients. Also, it has been proved that the aortic root and aortic valves diseases are progressive, leading to cardiovascular morbidity (8). In prosthetic patients, after valve

replacement, the valves' histologic examination has shown signs of active inflammation.

Heart failure in patients with ankylosing spondylitis is due especially to *left ventricular dysfunction*, many studies (9–11) referring to disease of the *diastolic function* in these patients.

Recent studies dedicated to vascular pathology have evidenced **alteration of the endothelial function**, suggesting that atherosclerotic modifications caused by chronic systemic inflammation and by atherogenic lipid profile as well as by disturbances of the T-helper lymphocyte subsets could be involved in the increased cardiovascular mortality (12–14). The healthy effects of the statin treatment with improvement of the inflammatory circulating mediators and the atherogenic lipid profile plea for new therapeutic options for patients with spondylitis (15).

Inflammation is well known for its role in the onset and progression of atherosclerosis. Studies made on animal models as well as clinical ones show that hyperlipidemia leads to endothelial activation with infiltration and seize of the low-density lipoproteins (LDL) in arterial intima. An inflammatory response is set up with the increase of adhesion molecules expression and attracting leukocytes on the activated endothelium. The monocytes migrate in the vessel's wall, with gap in macrophages, which will modify LDL and stir a cytokine synthesis burst. This will attract more inflammatory cells, including T cells. Activated T cells become the source of the proinflammatory cytokine synthesis and will control the lesional inflammatory reactions through negative feedback mechanisms, like the secretion of anti-inflammatory cytokines by the regulatory T cells (16,17).

C reactive protein (CRP) represents an inflammatory non-specific marker issued by the liver under the influence of some inflammatory stimuli like a variety of interleukins among some inflammatory diseases or after an acute coronary syndrome. Recent data suggest that CRP is produced by neat muscular cells under the influence of some local stimuli (TNF α or IL-6). Moreover, there has been proved the role of CRP over the expression of adhesion molecules which attract circulating monocytes and its action as ligand for a promotor of atherogenesis-LOX-1 (lectin-like oxidized LDL receptor-1) and on animal models (transgenic mice) the CRP overexpression was associated with increase of the ATS risk.

There are two types of CRP tests: one of them presents a measurable area which includes values

obtained in patients with infectious or inflammatory processes (generally, 3–200 mg/L) and the other one can detect lower CRP levels (analytical sensibility around 0.1 mg/L) for estimating the risk of cardiac events. For this reason, the second test is named CRP with high sensibility (CRP ultrasensitive; "high-sensitive" CRP).

Initial values and interpretation of the results:

Decision intervals for estimating cardiovascular are established according to CDC/AHA recommendations:

- low risk: < 1mg/L
- moderate risk: 1- 3 mg/L
- increased risk: > 3 mg/L

Obiectives: estimation of the role of inflammation in the onset and severity of vascular disease in patients with ankylosing spondylitis.

Material and method: The study had prospective character, which took place over a period of four years, in the Medical Rheumatology Clinic I of the Emergency County Clinical Hospital in Craiova. Biological and immunological investigations were done in the Laboratory of the Emergency County Clinical Hospital in Craiova, mainly the Immunology Laboratory of UMF Craiova and those for estimating the progression and extraarticular disease, in the professional clinics within the same hospital (Cardiology, Radiology Clinics).

All the patients have signed the informed consent and have had the UMF Ethic board's approval.

The calendar of explorations of the patients within the study has consisted of an initial complete examination when being included in the batch which implied an estimation regarding the opportunity of being included in the study and a complete estimation 12 months after being included in the study.

- *The study* has been of *prospective* type over 4 years by allowing a batch of 73 patients with akylosing spondylitis that have met the diagnostic modified New York criteria (1984):

- Clinical - low lumbar pain and stiffness of > 3 months improved by exercises and not influenced by repose; limiting the lumbar column mobility in sagital and frontal plane; decreasing the expansion of thoracic cavity in comparison with the; corrected normal values

- Radiologic - bilateral > gr.2 or unilateral >gr. 3 sacroiliitis

Admission criteria:

- Patients who meet the diagnostic criteria
- IMC in normal limits

- Do not present associated cardiovascular or renal pathology
- Naive patients for antiTNFalpha and DMARDs therapy

Rule-out criteria:

- RAA history
- Lues history
- Arterial hypertension
- Sugar diabetes
- Overweight/obesity
- Sedentarism
- Smoking

Design of the study implied: registering the patients with SA, evolution duration of the disease, type of articular disease (axial or peripheral), progression of the disease, activity (BASDAI), mobility (BASFI) and severity signs, therapeutic protocol, standard EKG and HOLTER, echographic cardiac and vascular examination (including Doppler).

After performing the anamnesis, with accent on the family history for seronegative spondyloarthropathies and cardiovascular risk factors, assessing the anterior therapeutic protocol (AINS, disease-modifying antirheumatic drugs, Leflunomid, biological therapy), the physical examination was performed completely, biological explorations (HLG, acute-phase reactants: VSH, fibrinogen, hs-CRP, glycemia, complete lipid profile, creatinine, uric acid).

Also, for all the patients, there were performed standard radiologic examination-sacroiliac articulations and dorso-lumbar joint, lumbar, thoracic, cervical vertebral column, standard EKG, echocardiographic examination (2D + Doppler): estimating the aorta's dimensions at the level of the ring, sinus of Valsalva, at the level of the ascending aorta, echographic examination (2D + Doppler) at the level of the carotid arteries: intima-media index, presence, severity (stenosis degree) and morphology of ATS plates.

Subclinical atherosclerosis has been evaluated at the level of the common carotid through the thickness of intima-media index (IMT) on echographic images obtained in B-mode by using a 10 MHz transducer. Measurement of the intima-media complex was performed at the level of the posterior walls of the common carotid artery. Thickness of linar echo was measured which represents the intima and the anechogenic area between intima and adventitia which represents the media. For each artery there was performed the media of five measurements done at equal intervals through all the length of the artery. Subclinical atherosclerosis has been considered at IMT values bigger than 0.9mm. The IMT average

value on the right common carotid artery was 0.947mm and on the left common carotid artery was 0.923mm.

Independent variables (factors followed in the study) are represented by:

- IMT value
- Presence of atheroma plates at the level of carotid arteries
- Carotid stenosis degree
- Dimensions and echographic aspect of the aorta
- Aspect of the valves and aortic valvular regurgitation

Statistical processing

Collecting the data was done for each patient during the time of registration in the study, clinical data about the evolution of the disease, paraclinical ratings considered according to the first protocol. These data were entered in an Excel database (from the Microsoft package) which is compatible with all the statistical interpretation programs I will be using when analysing the collected information. Filling the data will be done on entry and on the 12 months reevaluation.

Significant processing was made by the aid of SPSS 18 statistical soft SPSS 18 using descriptive statistical modules, correlation tests and liniar regression. The results were considered statistically significant at $p < 0,05$ and highly significant at $p < 0,01$.

Results

Demographic characteristics of the batch

The batch comprised 73 patients, 58 males (79,45%) and 15 females (20,55%) (Chart 1).

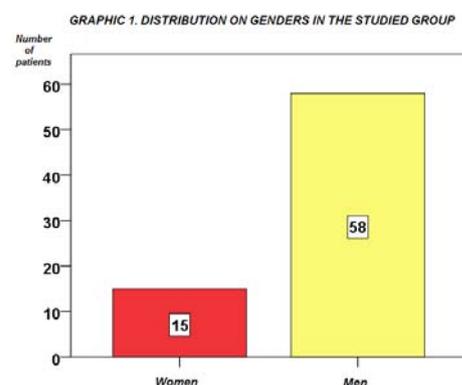


Chart 1. Distribution of sexes for the studied batch

Average age of the studied batch was of 41,4 years (DS=8,4315) with the minimal age of 24 and the maximal age of 64 (Chart 2).

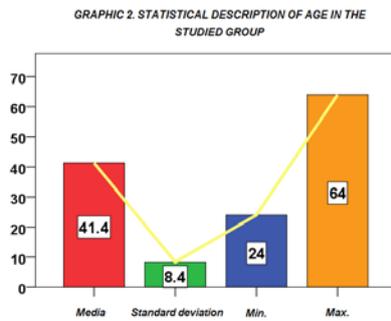


Chart 2. Age descriptive statistics for the studied batch

Origin environment was rural for 22 patients (20,14%) and urban for 51 of them (69,86%).

Average duration of disease evolution was 14 years, with limits between 6 and 27 years.

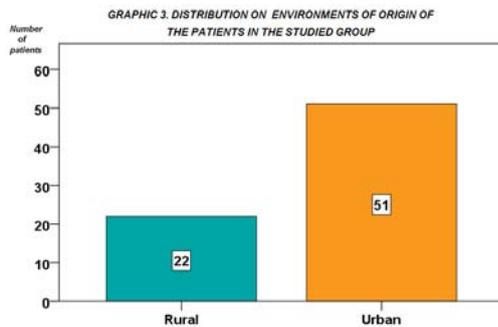


Chart 3. Distribution of origin environments of the patients in the studied batch

Distribution of patients in the rated batch according to the disease degree was the following: stage I – 26 patients (36%), stage II – 21 patients (29%), stage III – 17 patients (23%) and stage IV – 9 patients (12%).

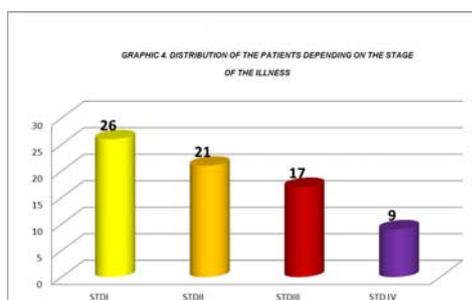


Chart 4. Distribution of patients according to the disease stage

HsCRP values for the patients in the studied batch have had the following representation:

Of the 73 patients, 21 patients (29%) presented various types and vascular disease degrees and they were correlated with the inflammatory markers.

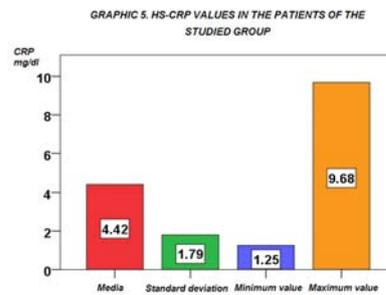


Chart 5. HsCRP values for the patients in the studied batch

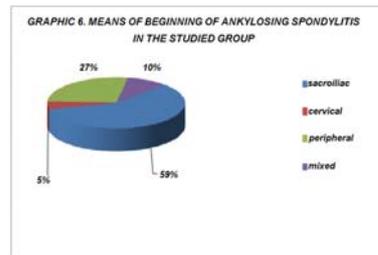


Chart 6. Onset forms of ankylosing spondylitis in the studied batch

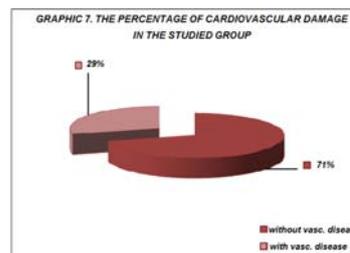


Chart 7. Rates of cardiovascular disease in the studied batch

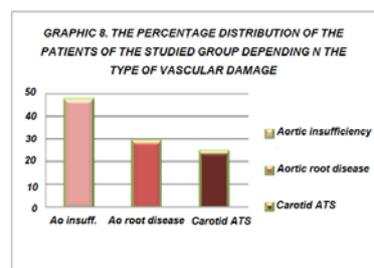


Chart 8. Percentage distribution of the patients in the studied batch according to the type of vascular disease

Distribution of the patients in the studied batch according to the type of vascular disease was the following:

- 10 patients presented a degree of aortic regurgitation (7 patients with II-nd degree, 3 patients with III-rd degree)
- 6 patients presented increased dimension of the ascending aorta (over 30 mm)
- for 5 patients atheroma plates were highlighted at the level of the internal carotid arteries with 6mm and 8mm dimensions, which reduce the vascular lumen with 30% and 45%
- IMT was increased for all the patients with hs-CRP>5mg/l and BASDAI over 8.

The degree of aortic regurgitation was correlated with the seric levels of hs-CRP, BASDAI and duration of disease evolution.

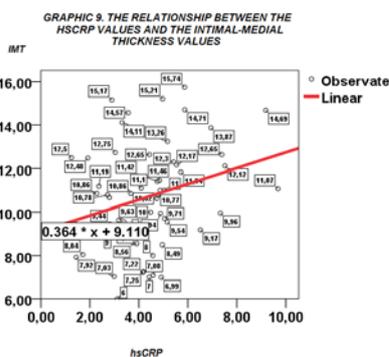


Chart 9. Relation between hsCRP values and intima-media index values

It was noticed that the patients who presented increased dimensions of the proximal aorta and those who presented atheroma plates at the level of the internal carotid arteries over the normal values have had a disease history of more than 12 years, IV-th disease stage and the inflammatory markers very much increased.

There were also positive correlations between IMT and hs-CRP, duration of disease evolution and activity indices of the disease.

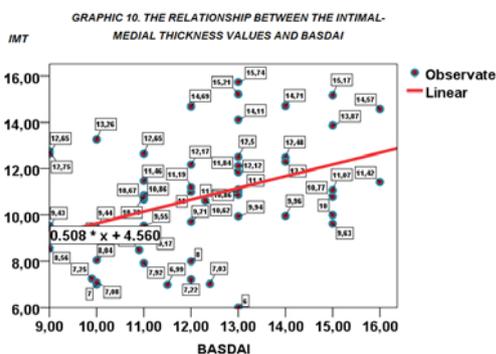


Chart 10. Relation between intima-media index and BASDAI values

It was also noticed that the circulating inflammatory mediators like *hs-CRP* lead to early

endothelial dysfunction, all the patients with hs-CRP>5mg/l having increased IMT.

Arguments:

Chronic inflammation and immune disequilibriums noticed for immune-mediated diseases are considered to be involved in accelerated atherosclerosis and the comparative studies have shown a bigger prevalence rate of atherosclerosis for the patients with spondylitis in comparison with controlled subjects (18).

Systematic histological studies of vascular modifications in patients with SA are sporadic and describe the presence of inflammation, with vasa vasorum increased thickness, intimal proliferation and adventitial cicatrization, vascular structural modifications which lead to aortic failure and significant increased thickness of the vascular wall (19).

A form of early detection of endothelial function alteration, as opening event in atherosclerosis sequences, is quantifying the relation carotid intima-media (IMT) and flow-mediated dilatation (FA) at the level of the brachial artery in order to prove the endothelial function alteration, considered an important early event for the onset of atherosclerosis (20) and the conclusion of the study was that IMT was positively correlated with age and severity of the disease in patients with ankylosing spondylitis, what suggests that patients with more severe disease have a more severe intimal increased thickness or atherosclerotic modifications at the level of the vascular wall (21).

The presence of anomalies of the aortic root and aortic valves in patients with ankylosing spondylitis are well known and recent studies suggest the hypothesis of endothelial and microvascular coronary function alteration, showing that vascular pathology could be involved in the increase of the cardiovascular mortality rate. Potential mechanisms for the burst of cardiovascular complications include a chronic inflammatory condition, with increased seric levels of the cytokines and acute-phase reactants and a more atherogenic lipid profile. Susceptibility for the onset of the disease and of a proinflammatory phenotype of the circulating cells in patients with ankylosing spondylitis is given by the association with the HLA-B27 histocompatibility antigen and variations of some inflammatory genes like the complex of IL-1, TNFalpha genes, as well as the transforming growth factor (TGF beta) (22).

Conclusions

Cardiovascular disease prevalence in the studied batch is at approximately 29%

It was correlated with seric levels of inflammatory markers, with disease activity questionnaires, with duration of disease evolution.

Patients with ankylosing spondylitis present subclinical atherosclerosis. They present accentuated endothelial dysfunction and modified carotid intima-media index.

The healthy effects of the statin treatment on the circulating inflammatory mediators and atherogenic lipid profiles support the new therapeutic options for patients with spondylitis.

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