Original Paper

Assessing Endothelial Dysfunction in Patients with Ankylosing Spondylitis

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ABSTRACT: The objectives proposed were the evaluation of the endothelial dysfunction by ultrasonographic with examination in patients with (AS), the evaluation of the lipid profile of these patients and the identification of some correlations with certain clinical and biological parameters. Material and method: The study has a prospective nature, type case-control, and took place in the Rheumatology Clinic of Emergency County Hospital Craiova and was performed on 140 patients, who were divided in two groups, patients from the population of patients suffering from ankylosing spondylitis and non-inflammatory rheumatic affections assisted in the same period of the research. Study design involved: patients' with AS registration, duration of the disease, type of joint damage (axial or peripheral), progression of the disease, activity indices (BASDAI), mobility (BASFI) and severity, therapeutic protocol, complete physical examination, ESR, hs-CRP, level of the glucose in the blood, creatinine, uric acid, complete lipid profile, bonejoint radiological examination, ultrasound examination (2D+Doppler) of the carotid arteries. Results and discussions: endothelial dysfunction was more important in patients with AS and was significantly associated with the inflammatory status-especially with hs-CRP, age, duration and severity of the disease. Results of the study show that patients suffering from AS are included in a high risk class due to the chronic inflammatory status and to the pro-atherogenic lipid profile, mutually reinforcing variables. Conclusions: Patients with AS have a pro-atherogenic status and early atherosclerotic lesions.

KEYWORDS: *AS, inflammation, atherosclerosis*

Introduction

Recent studies show the precocity of the atherosclerotic injuries in patients with chronic inflammatory pains, the inflammatory status, the atherogenic lipid profile and the immunological abnormalities play an important role in the alteration of endothelial function, these have a significant impact over the cardiovascular mortality [1,2,3]. There are proves that patients with ankylosing spondylitis have a higher risk of early atherosclerosis in comparison with control subjects. These are supported by histological studies on vascular changes in patients with AS, which describe the presence of the inflammation, with the thickening of vasa vasorum, intimal proliferation and adventiceale scarring, vascular structural changes that lead to a significant thickening of the vascular wall [4]. Chronic inflammation and immune imbalances observed in the immune mediated diseases are considered to be involved in the accelerating atherosclerosis [5].

A way of early detection of the alteration of the endothelial function, like the inaugural event in the sequences of atherosclerosis is the intima-media index quantification of the carotid arteries (IMT) [6], and the research revealed a correlation between IMT age and severity of the disease in patients with ankylosing spondylitis, which suggests that patients with active disease present a more important intimal thickening or atherosclerotic changes of the vascular wall [7].

The proposed objectives were based on the endothelial dysfunction evaluation, on the degree of atherosclerosis by ultrasound examination in patients with ankylosing spondylitis, evaluation of the lipid profile of these patients and correlation with the inflammatory status.

Material and method

The study has a prospective nature, type case-control, and took place in the Rheumatology Clinic of Emergency County Hospital Craiova and was performed on 140 patients, who were divided in two groups, patients from the population of patients suffering from ankylosing spondylitis and

non-inflammatory rheumatic affections assisted in the Rheumatology Clinic in the same period of the research, by the same medical staff over the whole duration of the study. In the study were included patients who have the modified New York diagnostic criteria (1984). Patients with antecedents of arterial hypertension, diabetes mellitus, cardiovascular or renal affections associated, overweight/obesity, sedentary, smokers were excluded. All the patients sign the informed consent, and the study had the agreement of the Ethics Committee of UMF Craiova.

Study design involved: patients' with AS registration, duration of the disease, type of joint damage (axial or peripheral), progression of the disease, activity indices (BASDAI), mobility (BASFI) and severity, therapeutic protocol, level of glucose in the blood, creatinine, uric acid, complete lipid profile- total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, atherogenic index.

From the biological explorations, a special importance has the inflammatory syndrome and the lipid profile, emphasizing the evaluations of hsCRP because is better correlated with the risk of vascular damage.

There were also carried out of all the patients a bonejoint radiologic examination, ultrasound examination (2D+Doppler) of the carotid arteries: intima-media index, presence severity (degree of stenosis) and morphology of the atherosclerosis plaque.

Subclinical atherosclerosis was evaluated at the commune carotid artery by the thickness of the intima-media index (IMT) on the ultrasound images obtained in B-mode by using a 10 MHz transducer. Measuring the intima-media complex was made at the rear wall of the commune carotid artery. The thickness of the linear echo, which represents the intima and the anechoic area situated between the intima and the adventitia that represents the media, was measured. For each artery was calculated the average of five measurements realized at equal intervals on the whole length of the artery. Subclinical atherosclerosis was considered at values of IMT higher than 0.9mm.

Statistical analysis - Data base was managed with **Excel** program form Microsoft Office package, and statistical analysis was managed with **MedCalc** and **Epi Info 2000** statistic programs.

Statistical indicators - from the central tendency indicators were analyzed the **arithmetic mean, mode, median,** and as data scattering indicators were analyzed **standard deviation, standard error** of the mean and 95% trust interval of the mean.

Statistical tests utilized: Square Test Chi, Exact Test Fisher, ANOVA test. For the positive tests ANOVA Student-Newman-Keuls test was applied for comparisons between subgroups.

The results are expressed as average values+/-standard deviation (SD) or as median if the data were not normally scattered.

Linear regression was utilized for describing the relation between two variables and for expressing predictions of one's value depending on the other. The coefficient of determination r^2, F ratio and p value, whose statistical signification was accepted for values under 0.05 were expressed. The regression right Was presented by Scatter diagrams, utilizing also the 95% trust interval for this.

Results

Clinical and biological evaluation of the subjects included in the study aimed the highlighting of the homogeneity of the two groups of patients, both in terms of clinical and biological parameters, which match the inclusion criteria in the study. From the biological parameters, the values of biochemical determinations, which would represent metabolic risk factors were comparable for both investigated groups (Table 1).

Total cholesterol values, triglycerides, uric acid are comparable for the two groups are situated in normal limits, explained by exclusion criteria. Another thing that draws our attention is the difference between the two groups in what the serum values of HDL cholesterol are concerned (35,49±6,67 in patients with AS, in comparison to 45,69±6,61 at the control group, $p<0,001$) and the atherogenic index (5,54±1,19 in patients with AS, in comparison to 3,91±0,93 at the control group, $p<0,991$), which includes the patients with AS in a high risk class, in comparison with the control subjects.

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Table 1. Clinical and biological parameters compared at the two groups

PARAMETER	GROUP WITH AS(N=70)	CONTROL GROUP(N=70)	P Value
Duration of the disease	17,23±9,39	-	-
IMC	23,45±1,11	22,4±1,46	<0,001
TAS	119,36± 12,45	119,17± 12,87	0,931
TAD	73,35±8,11	73,5±7,95	0,916
Total cholesterol	189,8±19,11	175,04±13,76	< 0,001
HDLcholesterol	35,49±6,67	45,69±6,61	< 0,001
Atherogenic index	5,54±1,19	3,91±0,93	< 0,001
Triglycerides	130,8±13,68	132,92±20,82	0,479
Uric acid	3,39±0,83	3,01±0,54	0,002

(results are presented as mean M ± standard deviation SD)

For the evaluation of the disease's activity the most important indicators which allowed establishing the activity degree – ESR, hsCRP, BASDAI were utilized (Table 2).

Table 2. Inflammatory status in comparison at the two groups

PARAMETER	DIFFERENTIAL GROUPS		P value
	AS (n=70)	C (n=70)	
ESR	34,41±13,71	8,56±2,74	<0,001
hs- CRP	8,07±3,72	0,38±0,12	<0,001
BASDAI	6,85±1,59	-	-

(results are presented as mean M ± standard deviation SD)

The average value of the ESR was 4 times bigger at the AS group (Mean=34,41mm; DS=13,71; IC95% 31,14-37,68; limits 13-60), in comparison with the control group (Mean=8,56mm; DS=2,74; IC95% 7,93-9,23; limits 4-16): the differences between the two means were highly statistically significant (Anova F ratio=238,78; p<0,001) (figure 1). For the cases group the average value of hsCRP was 8,08 (DS=3,73; IC95% 7,189 - 8,968; limits 1-16), and for the control group 0,38 (DS=0,12; IC95% 0,27-0,49; limits 0-1,6), the differences beeing highly statistically significant (p,0,001) (Fig.1).

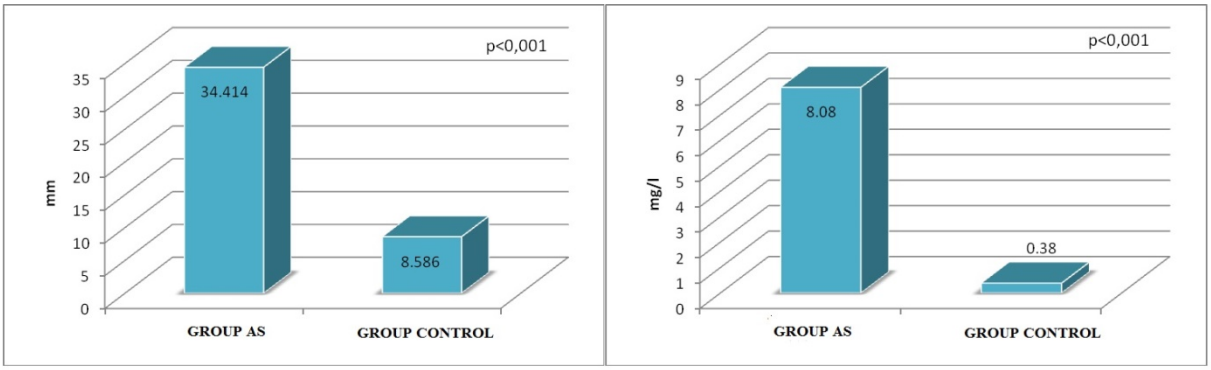


Fig.1. Average value of ESR at 1 h (mm) and hs CRP at the AS group in comparison with the control group

HsCRP represented a more sensitive parameter for predicting BASDAI (correlation coefficient r=0,57; ic95% 0,39-0,71; p,0,001; linear regression r^2=0,34; p<0,001) in comparison with ESR (r=0,327) (Fig.2).

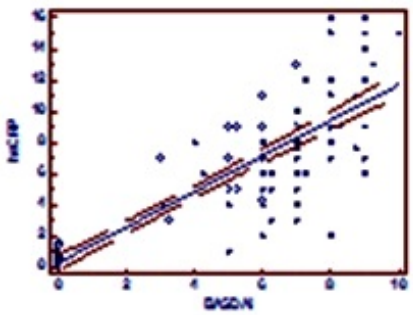


Fig.2. Linear regression between hsCRP and BASDAI

Appreciation of endothelial dysfunction as an inaugural event in the atherosclerotic sequences by IMT quantification at the carotid arteries

Cases with ankylosing spondylitis presented in a proportion of 34,29% (24 cases) values over the IMT limit considered in the study, and in the control group only 4 cases exceeded this value (5,71%).

In the AS group, the risk of identifying an IMT value over the normal limits was 8 times higher in comparison with the control group (RR=8,6; 2,79-26,47; p<0,001).

A statistically significant influence of the inflammatory status was found: the inflammatory status was represented in the study by ESR (r=0,47, IC95% 0,27-0,64, p<0,0001), serum levels of hsCRP (r=0,56, IC95% 0,37-0,7, p<0,0001) and the assessment of disease activity score BASDAI (r=0,42, IC95% 0,21-0,6, p=0,004) over the augmentation of infraclinical risk of atherosclerosis, ultrasound quantified by IMT measurement at the carotide arteries (Fig. 3).

Linear regression was utilized to capture the correlation measure between the IMT's intermediate level (average of the values at the right and left common carotid arteries) and the inflammation markers utilized (figure 3). All three inflammation markers presented significant values (p<0,001) of the correlation coefficient r^2, its value being higher for hsCRP (r^2=0,318) in comparison with ESR (r^2=0,23) and BASDAI score (r^2=0,184). Correlation research in the control group dind not allow establishing a significant bound between inflammation indicators and IMT for hsCRP (p=0,915) and ESR (p=0,914).

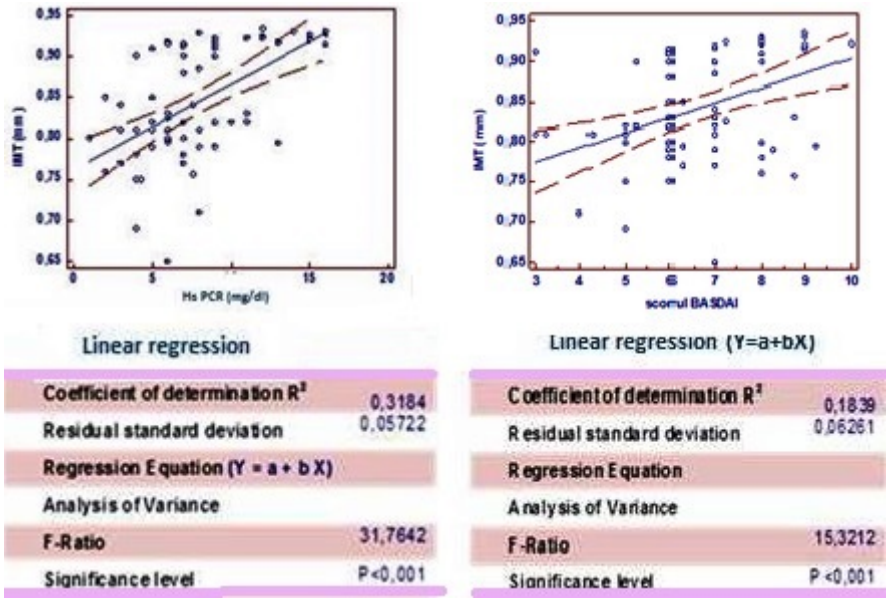


Fig.3. Scatter diagram and regression line of IMT and hsCRP (left) and BASDAI (right) values for AS group

A statistically significant influence of age was observed (r=0,54, IC95% 0,35-0,69, p<0,0001), duration of the disease (r=0,39, IC95% 0,17-0,57, p=0,008) and the severity of

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disease evaluation score BASFI (r=0,41, IC95% 0,19-0,59, p=0,0004), over the growing risk of developing infraclinical alatherosclerosis, ultrasound quantified by IMT measurement (Fig.4).

	Age	Duration of the disease	BASFI
Correlation coefficient r	0,54	0,39	0,41
Significance level	P<0,0001	P=0,008	P=0,0004
95% Confidence interval for r	0,35 to 0,69	0,17 to 0,57	0,19 to 0,59

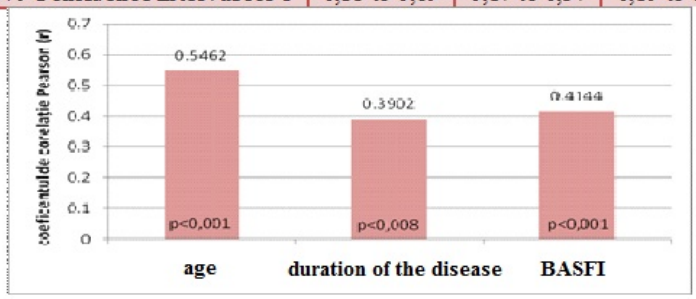


Fig.4. Endothelial dysfunction correlation with age, duration of the disease and BASFI score

Accelerated atherosclerosis reflection by ultrasound objectifying of the atheroma plaque at the carotid arteries

One of the important evaluated parameters which reflects the accelerated atherosclerosis of the patients with AS was ultrasound objectifying of the atheroma plaque at the carotid arteries, the incidence of the atheroma plaques in cases with AS being 4,29%. The risk of carotid atherosclerosis in cases with ankylosing spondylitis was 6 times higher than the control group (OR=6,09; IC95% 1,67 - 22,12; p<0,006).

The incidence of atherosclerotic vascular damage was higher in cases with AS (37,14%), in this group vasculare damage was present at 26 cases.

In the control group, only 5 cases presented atherosclerotic vascular damage, the incidence for the control group being 7,14%; the risk of vascular damage of this disease is 6 times higher in comparison with the other group (OR=7,68; IC95% 2,74-21,53; p<0,001).

Table 3. Comparison of the main clinical and biological parameters on patients with AS which have atherosclerotic vascular damage and on those without vascular damage

	Without vascular damage	With vascular damage	p
Age(years)	38,04±10,22	49,69±9,06	< 0,001
Duration of the disease(years)	13,68±8,05	23,23±8,52	< 0,001
ESR - 1H(mm)	29±11,88	43,57±11,72	< 0,001
hsCRP	6,51±2,57	10,73±3,91	< 0,001
BASDAI (0-12)	6,25±1,37	7,894±1,41	< 0,001
BASFI(0-100)	41±11,41	56,46±14,22	< 0,001
Total cholesterol(mg/dl)	186,31±16,57	195,69±21,86	0,047
TG(mg/dl)	130,61±12,21	131,11±16,14	0,883(NS)
HDL-cholesterol	37,45± 7,16	32,15±3,99	0,003
LDL-col(mg/dl)	122,74±17,67	137,31±23,54	0,004

(results are presented as mean M ± standard deviation SD)

In Table 3 is presented the comparison of the main clinical and biological parameters previous analyzed in patients with AS, who present atherosclerotic vascular damage and in those without vascular affection (Table 3).

Discussions

Augmentation of morbidity and mortality by cardiovascular disease was described in patients with ankylosing spondylitis, chronic inflammatory status among other traditional risk

factors being responsible for escalating the cardiovascular risk in these patients [8, 9].

Susceptibility to both disease and proinflammatory phenotype of circulating cells occurrence in patients with AS is linked to the association with the histocompatibility antigen HLA-B27 and certain inflammatory genes such as IL-1 genes complex, alpha TNF and also transforming growth factor (TGF beta) [10].

Profile of the patients with accelerated atherosclerosis

The presence of endothelial dysfunction as an inaugural event in the atherosclerosis' sequences, early detected by the quantification of the intimate-media index at the common carotid arteries was proved at 34,29% of the AS cases in comparison with only 5,71% in the control group.

A statistically significant influence of the inflammatory status was noted; the inflammatory status was represented in the study by ESR (r=0,47, IC95% 0,27-0,64, p<0,0001), serum levels of hsCRP (r=0,56, IC95% 0,37-0,7, p<0,0001) and BASDAI score (r=0,42, IC95% 0,21-0,6, p=0,004) over the augmentation of infraclinical risk of developing atherosclerosis, ultrasound quantified by IMT measurement.

A significant impact of the patients' age was found (r=0,54, IC95% 0,35-0,69, p<0,0001), duration of the disease (r=0,39, IC95% 0,17-0,57, p=0,008) and BASFI score (r=0,41, IC95% 0,19-0,59, p=0,0004) over escalation the risk of endothelial dysfunction.

Highlighting by vascular ultrasound the already established vascular damage, represented by the atheroma plaques at the carotid arteries, proved an incidence of 21,43% in patients with AS, in comparison with the control group, where the incidence was 4,29%.

The risk of carotid atherosclerosis in cases with ankylosing spondylitis was 6 times higher than the control group (OR=6,09; 1,67 - 22,12; p<0,006).

Endothelial dysfunction was described in association with many cardiovascular risk factors, such as active and passive smoking, arterial hypertension, hypercholesterolemia, obesity and diabetes mellitus type 2 [11].

By excluding criteria, we tried to eliminate any risk factors for the vascular atherosclerotic damage, respectively, smoking, arterial hypertension, obesity, dyslipidemia, diabetes mellitus. Referring to the metabolic profile of the patients included in the study, total cholesterol values, triglycerides, uric acid, were comparable for the two groups, being in normal limits. But a difference between the two groups was observed in what the serum values of HDL cholesterol (35,49 ± 6,67 in patients with AS, in comparison to 45,69 ± 6,61 in the control group, p<0,001) and atherogenic index (5,54 ± 1,19 in patients with AS in comparison to 3.91 ± 0.93 in the control group, p<0,001) are concerned, that includes the patients with AS on a higher risk step, in comparison to control patients.

High levels of LDL cholesterol and low level of high density lipoproteins (HLD-cholesterol) are associated with an increasing cardiovascular morbidity and mortality. There are studies that had evaluated the lipid profile in patients with AS, but the results are controversial.

So either a change in the serum levels of LDL and HDL cholesterol was not found or a decreasing of serum levels of LDL and HDL cholesterol was observed, resulted from a slight rise of the fraction total cholesterol/HDL cholesterol [12]. An augmentation of this fraction is, in general, considered proatherogenic. In our research, biological parameters which reflect the inflammatory process recorded, regardless of the group, higher limits than the physiological limits, according to the activity degree of the disease. HsCRP represented a more sensitive parameter for predicting BASDAI (correlation coefficient r=0,57; rIC95% 0,39-0,71; p<0,001; linear regression r^2=0,43; p<0,001) comparable with ESR (r=0,327).

There are proves that the inflammation only can deteriorate the lipid profiles, and the increasing disease's activity in patients with modified spondylitis was associated with the decreasing of the serum levels of lipids, but with a lipid profile more atherogenic, like the decreasing of HDL's concentration two times more than total cholesterol [13].

Similar to our research's results, Mathieu S and his contributors [14] noted a significant augmentation of IMT in patients with AS in comparison to healthy subjects included in the control group, But IMT was positively correlated with the smoking status, fraction waist/hip (waist-to-hip ratio WHR), arterial tension and was not correlated with serum levels of CRP.

Gonzalez-Juanatey C et al studied subclinical macrovascular atherosclerotic disease was present in patients with ankylosing spondylitis (AS) without clinical history of cardiovascular disease. The study was performed using high-resolution B-mode ultrasound.Patients with AS exhibited greater

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carotid IMT than did matched controls (mean +/- SD, 0.74 +/- 0.21 mm vs. 0.67 +/- 0.14 mm; p = 0.01; differences of means, 0.077; 95% confidence interval, 0.016-0.139). Carotid plaques were more commonly observed in patients with AS than in controls (19 [29.7%] vs. 6 [9.4%], respectively; p = 0.03). The best predictors for carotid plaques in patients with AS were erythrocyte sedimentation rate (ESR) at time of disease diagnosis (odds ratio [OR], 1.18; 95% confidence intervals [CI], 1.04-1.33; p = 0.01) and duration of disease (OR, 1.39; 95% CI, 1.01-1.92; p = 0.05). In contrast, there was no significant correlation between carotid IMT and either ESR or C-reactive protein in this study. Results of the present study show that patients with AS without clinically evident cardiovascular disease have a high prevalence of subclinical macrovascular disease in the form of increased carotid IMT and carotid plaques compared to matched controls[15].

Similarly, Peters MJ et al showed that AS was associated with subclinical atherosclerosis and arterial stiffness, supporting epidemiological evidence of an increased CV risk in these patients. Whether these differences are due to AS or to a higher prevalence of CV risk factors in patients with AS remains to be determined[16].

In contrast to our findings, Sari and his contributors (1) in a recent study of the degree of atherosclerosis and endothelial dysfunction in patients with AS, utilizing ultrasound techniques – the intima-media index at the common carotid arteries (IMT) and the dilatation mediated by the flow in the brachial arteries (FMD), did not emphasize statistically significant differences of IMT in the common carotid arteries between patients with AS and control subjects, but FMD was significantly lower in patients with AS. The average IMT at the commune carotid arteries was positively correlated with age and BASMI score. Yet, smoking status, gender, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, CRP, ESR, BASFI and BASDAI were not correlated with IMT. The study showed that endothelial function in patients with AS is deteriorated in comparison to healthy subjects included in the control group. By ultrasound measurement of IMT, the authors did not detect significant differences between patients with AS and control subjects, but the average age of the patients included in the study was 37 years (+/- 11 years). Another study including older patients, with a longer duration of the disease would have higher chances to find significant differences between IMT in patients with AS and control subjects. The most significant limitation of this study was the small number of patients and the low statistical power, more extensive studies being necessary for confirming these modifications [1].

In patients with cardiovascular affections, high proatherogenic serum levels of cholesterol, are efficiently treated with statins. In addition, statins are well known for their strong anti-inflammatory effects [17]. Recent studies showed the beneficial effects of statins over the activity of the disease in patients with AS, improving pain scores, serum levels of CRP and total cholesterol [18, 19].

Conclusions

Presence of the endothelial dysfunction as an inaugural event in the atherosclerosis sequences, precocious detected by quantification of the intima-media index at the common carotid arteries and atherosclerosis (atheroma plaque) was more important in patients with AS.

Inflammatory status – especially hsCRP, age, duration and severity of the disease have a statistically significant impact for defining the risk.

Results of the study show that patients with AS are included in a higher risk class due to the chronic inflammatory status and to the lipid proatherogenic profile, variables that are mutually reinforcing.

By complex intervention on the lipid profile and the on the inflammation patients may benefit of the reduction of the cardiovascular risk by preventing accelerate atherosclerosis.

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