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Prevalence of Asymptomatic Arterial Hypertension and Its Correlation with Inflammatory Activity in Early Rheumatoid Arthritis

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Abstract

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BACKGROUND: Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that worsens during the course of the disease and can cause disability. Early RA refers to the onset of symptoms within the past 3 months. In RA, increased levels of mediators of inflammation may cause arterial stiffness consequently leading to arterial hypertension.

AIM: The aim of this cross-sectional study was to assess the prevalence of asymptomatic arterial hypertension in early RA patients as well as the correlation with parameters of inflammation.

METHODS: One hundred and seventy-nine early RA patients diagnosed in agreement with ACR/EULAR (American College of Rheumatology/ European League against Rheumatism) 2010 criteria were consecutively included in the study. CRP (C-reactive protein) and anti CCP (Antibodies to cyclic citrullinated peptides) serum levels, WBC (white blood cells) count and ESR (Erythrocyte sedimentation rate), likewise DAS-28 (28-joint disease activity score) were determined in all included patients. Parametric tests were used to compare the characteristics of the groups and to test the correlation of the variables.

RESULTS: Statistical data analysis revealed that a majority of the patients were females (n = 141; 78.7%); the mean age at RA onset was 49.13 ± 12.13 years. Overall prevalence of hypertension was 44.13 % (n = 79). In comparison with the normotensive patients, the hypertensive patients were older and had significantly higher values of CRP, ESR, anti-CCP and DAS-28. A highly significant positive correlation between all the study parameters and systolic and diastolic blood pressure was observed.

CONCLUSION: Presence of significantly higher values of CRP, ESR, anti-CCP and DAS-28 in hypertensive patients indicate that inflammation is associated with an increased risk of hypertension. In this context, early screening for arterial hypertension and adequate therapeutic measures should be considered in early RA patients.

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease characterized by joint and multiple organ systems involvement that worsens during the course of the disease and can cause disability [1, 2]. Early RA is defined as the onset of symptoms of joint (typically polyarticular) pain, stiffness or swelling within the past 3 months [3, 4].

Increased risk for adverse outcomes in patients with RA that can partially be attributed to cardiovascular (CV) disease has been reported by several studies [5-9]. In RA, increased levels of mediators of inflammation may cause arterial stiffness

and increase peripheral resistance, consequently leading to arterial hypertension, thus providing a potential link between inflammation and arterial hypertension in RA [10-14]; in addition, physical inactivity, medications used in RA and co-morbidities may contribute to blood pressure increments [15, 16].

Early treatment of RA may minimize the impact of RA associated factors in arterial hypertension development and thus may improve short- and long-term outcome of RA [4, 17].

To date, there is limited information available about the prevalence of arterial hypertension in early RA patients. Thus, the main objective of the present cross-sectional study was to assess the prevalence of arterial hypertension in early RA patients. In addition,

the correlation of clinical and laboratory parameters of inflammation with systolic and diastolic arterial blood pressure was assessed.

Material and Methods

One hundred and seventy-nine early RA patients diagnosed in agreement with ACR/EULAR 2010 criteria [18] were consecutively included in this cross-sectional study. The study was conducted in the Rheumatology department at the University Clinical Center of Kosovo, between April 2013 and May 2016.

Blood pressure (BP) measurements were performed by the physician with the patient sitting in a chair for at least ten minutes. Mean values of three BP measurements obtained five minutes apart were recorded. Arterial hypertension was defined as systolic BP equal to or greater than 140 mmHg, and/or diastolic BP equal to or greater than 90 mmHg. According to the BP values, the patients were categorized into two groups: hypertensive patients (n = 79) and normotensive patients (n = 100).

Venous blood samples were collected after an overnight fasting period of 10-12 hours. White blood cells (WBC) count and C-reactive protein (CRP) concentration measurements were performed at the main hospital laboratory, while auto antibodies to cyclic citrullinated peptides (anti-CCP) were measured by a licensed private laboratory. Enzyme-linked immunosorbent assay (ELISA) kits were used to measure CRP and anti-CCP concentrations. Westergren erythrocyte sedimentation rate (ESR) was expressed as millimeters in one hour (mm/h),

The Disease Activity Score-28 (DAS-28), an index containing a 28-joint count for tenderness, swelling, inflammation (CRP or ESR) and visual analogue scale (VAS) was used to describe the severity of RA [19].

Local ethical committee approved the study protocol prior to the initiation of the study and all the participants gave written informed consent.

The study variables were evaluated for the normality of the distribution using the Kolmogorov-Smirnov test. As the variables were normally distributed, independent samples t-test was performed to compare the characteristics of the groups while Pearson's correlation test was performed to test the correlation between the study variables. Data are presented as mean \pm standard deviation (S.D.) or proportions, as appropriate. A p value less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 16.0 software (SPSS Inc., Chicago, USA).

Results

The demographic and laboratory characteristics of hypertensive and normotensive early RA patients are summarized in Table 1. Data analysis revealed that 141 (78.7%) patients were females while 38 (21.3%) patients were males; the mean age at RA onset was 49.13 ± 12.13 years (range, 25-80). The prevalence of hypertension in this sample of patients was 44.13 % (n = 79). The patients with early RA were categorized into two groups according to BP values. Comparison of the means \pm SD of hypertensive patients vs. normotensive patients with independent samples t-test demonstrated significantly higher values of CRP, ESR, anti-CCP and DAS-28 in hypertensive patients ($p < 0.001$). In comparison with the normotensive patients, the hypertensive patients were older ($p = 0.005$); however, there were no significant differences between the groups in gender ($p = 0.714$), place of residence ($p = 0.095$) or WBC count.

Table 1: Demographic and laboratory characteristics of the patients with early rheumatoid arthritis

	All (n = 179)	Hypertensive patients (n = 79)	Normotensive patients (n = 100)	p value
Age (years)	49.13 \pm 12.13	52.03 \pm 12.16	46.85 \pm 11.67	$p = 0.005$
Gender (F/M)	141/38	61/18	80/20	$p = 0.714$
Place of residence (Village/City)	100/79	50/29	50/50	$p = 0.095$
CRP (mg/dl)	37.87 \pm 35.71	56.79 \pm 41.46	22.92 \pm 20.66	$P < 0.001$
ESR (mm/h)	39.76 \pm 25.97	51.91 \pm 28.91	30.17 \pm 18.54	$P < 0.001$
Anti-CCP (U/dml)	207.49 \pm 165.99	303.95 \pm 167.65	131.30 \pm 117.76	$P < 0.001$
DAS-28	5.43 \pm 1.12	6.19 \pm 0.99	4.82 \pm 0.79	$P < 0.001$
WBC	8.81 \pm 3.57	9.21 \pm 3.74	8.49 \pm 3.41	$p = 0.186$

CRP = C-reactive protein; ESR = Erythrocyte sedimentation rate; Anti-CCP = Antibodies to cyclic citrullinated peptides; DAS-28 = 28-joint disease activity score; WBC white blood cells.

When all the early RA patients were considered, as presented in Table 2, a highly significant positive correlation between all the study parameters and systolic and diastolic blood pressure was observed ($p < 0.01$).

Table 2: Pearson's correlation analysis between clinical and laboratory parameters and arterial blood pressure in patients with early rheumatoid arthritis categorized according to presence or absence of arterial hypertension (r)

	All study subjects (179)		Hypertensive patients (n = 79)		Normotensive patients (n = 100)	
	Systolic AP (mm/Hg)	Diastolic AP (mm/Hg)	Systolic AP (mm/Hg)	Diastolic AP (mm/Hg)	Systolic AP (mm/Hg)	Diastolic AP (mm/Hg)
Age (years)	0.303**	0.272**	0.176	0.125	0.279**	0.243*
CRP (mg/dl)	0.498**	0.490**	0.288*	0.268*	0.135	0.065
ESR (mm/h)	0.481**	0.505**	0.317**	0.388**	0.218*	0.176
Anti-CCP (U/dml)	0.493**	0.473**	0.174	0.231*	0.095	-0.107
DAS-28	0.695**	0.698**	0.474**	0.578**	0.380**	0.223*
WBC	0.204**	0.212**	0.223*	0.283*	0.208*	0.152

* $p < 0.05$; ** $p < 0.01$; AP = Arterial pressure; CRP = C-reactive protein; ESR = Erythrocyte sedimentation rate; Anti-CCP = Antibodies to cyclic citrullinated peptides; DAS-28 = 28-joint disease activity score; WBC white blood cells.

When the participants were classified into two groups based on blood pressure (Table 2), the Pearson's correlation analysis demonstrated significant positive correlation of ESR, CRP, WBC values and DAS-28 with systolic blood pressure in hypertensive patients, while anti-CCP values were in a significant positive correlation only with diastolic blood pressure. Pearson's correlation analysis indicated significant positive correlation between ESR, WBC count and DAS-28 with systolic blood pressure in normotensive patients. It is noteworthy, that age was positively correlated to blood pressure only in normotensive patients.

Discussion

This cross-sectional study showed the prevalence of arterial hypertension to be 44.13%: 43.26% in women and 47.36% in men with RA. The main findings of the present study were significantly higher levels of surrogate markers of inflammation and higher DAS-28 scores among the hypertensive compared to normotensive early RA patients; in addition, all the study variables were significantly correlated with both systolic and diastolic blood pressure.

Several studies showed increased risk for CVD and increased morbidity and mortality in RA patients compared to non-RA patients [5-9]. An association between the inflammation, atherosclerosis and hypertension in RA and non-RA populations is observed in several prior studies [10-14, 22]. A recent study of Innala *et al.* [20] reported considerable comorbidity, especially arterial hypertension, among early RA patients at the time of the disease onset, emphasizing the importance of inflammation in the occurrence of comorbidities. In this context is a Greek cohort study of Serelis *et al.* [21] who concluded that hypertension is an important risk factor for CVD development among RA patients and highlight the importance of strict control of hypertension in RA patients. Similarly, Panoulas *et al.* [22] reported increased prevalence of arterial hypertension in RA patients; in addition, authors, reported that hypertension is underdiagnosed and undertreated, especially in older RA patients.

Our findings are partially in agreement with the findings of the Karvounaris *et al.* [24] and Karakoç *et al.* [25] in observing a significant correlation between blood pressure values and the DAS-28 score. Another recently published study of Hamamoto *et al.* [26] reported an association between RA disease activity and increments of nocturnal blood pressure.

Nevertheless, our findings are in disagreement with the findings of Panoulas *et al.* [21]

and Manavathongchai *et al.* [27] who failed to find a significant association between generalized systemic inflammation, as measured by CRP, ESR and DAS-28 score, and arterial hypertension in RA patients; however, the latter study reported that the most likely pathogenic mechanisms of hypertension in RA involve fat and vascular homeostasis.

A limitation of the current study is the fact that we didn't account for medications used to treat RA (particularly NSAIDs and glucocorticoids) that might affect blood pressure. Nevertheless, there are studies that did not find an association of medications use and arterial hypertension in RA patients [21, 26]. The lack of a control group without RA for comparison purposes is another limitation of our study.

In conclusion, despite relatively low prevalence of hypertension in this study sample, presence of significantly higher values of CRP, ESR, anti-CCP and DAS-28 in hypertensive patients indicate that inflammation is associated with an increased risk of hypertension. Early RA patients should be screened for arterial hypertension and appropriate early treatment of hypertension alongside with early treatment of RA should be considered in order to improve the overall outcome in RA.

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