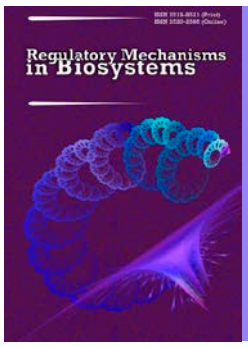

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Serum paraoxonase activity in patients with rheumatoid arthritis, its relationship with the clinical course and cardiovascular compications

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Nowadays low paraoxonase activity is generally recognized as an independent risk factor of cardiovascular diseases involved in pathologic remodeling of the heart and vessels as well as thrombosis in the general population. But the role of paraoxonase activity in RA patients is unknown. Based on the above, the aim of the work was to study serum paraoxonase activity in patients with rheumatoid arthritis, to evaluate its association with clinical course and structural and functional status of the cardiovascular system. 67 patients with RA, 18 males and 49 females were studied. The control group consisted of 25 apparently healthy individuals. Rheumatoid arthritis was diagnosed according to international classification criteria ACR 2012. The indices of total cholesterol (TC), high density lipoprotein cholesterol (HDLC) and triglycerides (TG) in blood serum were determined by standard conventional methods. Low density lipoprotein cholesterol (LDLC) values were calculated by Friedwald formula. Serum paraoxonase activity was measured by spectrophotometric method. High resolution ultrasound and Doppler ultrasonography of the brachial artery were performed to study endothelium function. Sonographic B-mode scanning and pulsed Doppler ultrasound of heart and blood flow spectra were done on ultrasound scanner. Serum paraoxonase activity was found to be about 18.8% lower in the patients with RA than in the control group. Serum paraoxonase activity was shown to decrease proportionally to the increase of the age in RA patients. In the group of patients over 45, the level of the enzyme was 13.0% lower than in the patients over 30. The study established that the increase of systolic and diastolic arterial pressure is associated with decrease of serum paraoxonase activity in RA patients. The patients with RA combined with arterial hypertension had significantly (by 10.9%) lower activity of the studied enzyme than those with no arterial hypertension. However, no significant relationship between paraoxonase activity and duration of the disease, obesity and smoking was revealed. Paraoxonase activity in RA patients was demonstrated to be dependent on lipid levels. The lowest paraoxonase activity was recorded in individuals with the highest levels of TC, LDLC and the lowest HDLC indices. Paraoxonase activity in RA patients is associated not only with atherosclerotic vascular damage (IMT, decreased FMDBA) but also with structural and functional heart status (systolic and diastolic functions, left ventricular myocardial hypertrophy). Decreased serum paraoxonase level is suggested to be the predictor of early development of cardiovascular complications in RA patients.

Keywords: enzyme activity; autoimmune disease; metabolic risk factors; changes of the cardiovascular system

Introduction

Cardiovascular diseases are acknowledged as the leading cause of mortality among patients with rheumatoid arthritis (RA) (Ladak et al., 2017; Meissner et al., 2017; Myasoedova et al., 2017). Framingham risk factors (age, sex, atherogenic lipid levels, history of arterial hypertension, smoking) are considered to have a decisive role in early development of cardiovascular complications. But accelerated atherogenesis cannot be explained exclusively by the action of traditional risk factors in RA patients. Currently much attention is focused on metabolic and immunologic markers which are likely to play one of the key roles in atherogenesis of autoimmune diseases. Recent studies provide convincing evidence that anti-cyclic citrullinated peptide antibodies (anti-CCP), rheumatoid factor IgM, circulating immune complexes, anti-inflammatory cytokines (TNF-alfa, IL-6), Th0/Th1 of T-cells, homocysteine, dyslipidemia, decreased folic acid level, impaired vitamin metabolism as well as disturbances in paraoxonase activity can be involved in the development of cardiovascular diseases in RA (Yang et al., 2015; Batún Garrido et al., 2016; Rodríguez-Carrio et al., 2016; Tocci et al., 2016; Bernardes et al., 2017; Herly et al., 2017). Nowadays low paraoxonase activity is generally recognized as an independent risk factor of cardiovascular diseases involved in pathologic remodeling of the heart and vessels as well as thrombosis in the general population (Kerekes et al., 2008; Tang et al., 2012; Patra et al., 2013; Kovalenko et al., 2014; Wang et al., 2015; Kunutsor et al., 2016). Changes in paraoxonase activity inevitably lead to decreased defense antioxidant function of HDL and increased oxidant stress (Kim et al., 2016; Kulka, 2016). In RA patients the following factors can decrease serum paraoxonase activity: excessive rheumatoid factor, anti-CCP, systemic inflammatory process (El-Banna & Jiman-Fatani, 2014; Shahmohamadnejad et al., 2015). Ethnic and race differences in serum paraoxonase activity have been detected as well (Bounafa et al., 2015; Sayın Kocakap et al., 2015). Despite a large number of studies addressed to cardio-vascular complications in RA, the role of low paraoxonase activity has not been established yet. It should be noted that in the Ukrainian patient population with RA this enzyme activity also has not been studied. The relationship of paraoxonase activity with other metabolic cardiovascular risk factors as well as structural and functional status of the heart has not

been established either. Based on the above, the aim of the work was to study serum paraoxonase activity in patients with rheumatoid arthritis, to evaluate its association with the clinical course and structural and functional status of the cardiovascular system.

Materials and methods

67 patients with RA, 18 males and 49 females were studied. The control group consisted of 25 apparently healthy individuals. Rheumatoid arthritis was diagnosed according to international classification criteria ACR 2012 (Kay & Upchurch, 2012). The analysis of traditional risk factors of atherosclerotic vascular damage was done in RA patients. Body mass index (BMI, kg/m^2) was calculated in all patients with RA. Obesity was estimated in case of BMI > 30. The indices of total cholesterol (TC), high density lipoprotein cholesterol (HDLC) and triglycerides (TG) in blood serum were determined by standard conventional methods. Low density lipoprotein cholesterol (LDLC) values were calculated by Friedwald formula: LDLC = TC – HDLC – 0.45·TG. All detected values were divided into normal, marginally increased and high values of lipid profile according to the Third Report of the National Cholesterol Education Program (2002). High activity of inflammatory process in RA patients was estimated according to increase of ESR, CRP, TNF-α levels and calculated DAS 28 score, Pain index score, Articular index and Edema index score. Serum paraoxonase and arilesterase activity was measured by spectrophotometric method (Connelly et al., 2004). A persistent analytic system was used for the evaluation of serum paraoxonase activity in RA patients and control group. High resolution ultrasound and Doppler ultrasonography of the brachial artery by Celermajer et al. (1992) were performed to study endothelium function. Flow-mediated vasodilation of the brachial artery (FMDBA) was assessed according to changes in its diameter and measured before and after temporary occlusion of the vessel with blood preasure cuff (reactive hyperemia). Location of the brachial artery was associated with visualization of its internal diameter and was measured in the middle third of the shoulder. Sonographic B-mode scanning and pulsed Doppler ultrasound of blood flow spectra were done on ultrasound scanner Sonoline 6000 C (Medisson, Southern Korea) at the 30, 60 and 90th s after cuff decompression. Brachial artery dilation by more than 8% from baseline diameter within 30 s after decompression was considered to be the criteria of adequate endothelial response to ischemia. All measurements of endothelial relaxation were done from 8 to 10 AM.

The thickness of the intima-media complex (IMT) of the common carotid artery (CCA) was determined at the time of B-mode ultrasonography of the carotid artery in diastole 2 cm from bifurcation at maximum magnification. The area of atherosclerotic plaques of the carotid artery (cAP) was measured in all the patients, and the extent of vascular atherosclerotic damage was evaluated (Wendelhag et al., 1993). Echocardiography (EchoCG) was done for 63 patients with RA on ultrasound scanner Sonoline 6000 C (Medisson, Southern Korea) Statistical processing of the obtained results was carried out on a personal computer using the standard statistical programs. The results are presented as the mean ± standard error (x ± SE). All values follow a normal distribution. The average value, standard errors, reliability of the differences were evaluated according to Student's t-criterion. Pearson's correlation coefficient test was used to measure the strength of a linear association between two variables. The statistical significance was determined if P < 0,05.

Results

Serum paraoxonase activity was found to be about 18.8% lower in the patients with RA than in the control group (107.8 mmol/l·h and 132.9 mmol/l·h, respectively) (Table 1). Moreover, according to percentile distribution, serum paraoxonase activity level ranged from 94.5 to 172.6 mmol/l·h in apparently healthy persons, while in the patients with RA it was 80.9–129.4 mmol/l·h. The analysis of traditional risk factors of atherosclerotic vascular damage on the basis of paraoxonase activity in the patients showed no significant differences in the indices of serum paraoxonase activity between males and females, but there was significant decrease of that index with the increase of age (Table 2).

Table 1
Serum paraoxonase activity in RA patients and in the control group

Group	Median	Paraoxonase, mmol/l·h					
		P_5	P_{10}	P_{25}	P_{75}	P_{90}	P_{95}
Control, n = 25	132.9	94.5	118.0	127.9	154.2	161.8	172.6
RA patients, n = 67	107.8	80.9	85.8	89.6	123.3	126.5	129.4

Note: $P_{5, 10, 25, 75, 90, 95}$ – frequency of serum paraoxonase activity occurence (5%, 10%, 25%, 75%, 90%, 95% respectively) below the specified value.

Table 2
Analysis of serum paraoxonase activity depending on traditional risk factors in RA patients (x ± SE)

Index		Paraoxonase, mmol/l·h	
		control group	RA patients
Females, n = 49		108.2 ± 2.51	109.6 ± 2.26
Males, n = 18		105.9 ± 5.38	101.1 ± 4.44
Age	below 30 years, n = 11	113.4 ± 2.71	113.6 ± 2.82
	30–45 years, n = 27	115.7 ± 2.86	113.7 ± 3.54
	>45 years, n = 29	109.2 ± 5.89	99.1 ± 2.68***
Disease duration	<5 years, n = 26	–	109.5 ± 3.65
	5–10 years, n = 18	–	105.8 ± 4.34
	>10 years, n = 23	–	106.0 ± 2.95
With no AH, n = 50		112.6 ± 4.11	110.3 ± 2.34
With AH, n = 17		108.8 ± 3.69	98.2 ± 3.90**
Non-smokers, n = 55		107.0 ± 2.89	107.8 ± 2.37
Smokers, n = 12		102.9 ± 6.31	105.3 ± 5.27
BMI > 30 kg/m^2, n = 57		112.9 ± 2.71	107.4 ± 2.26
BMI < 30 kg/m^2 , n = 10		109.2 ± 7.12	106.9 ± 5.44

Note: * – statistical significance in comparison of examined parameters P < 0.05, ** – P < 0.01, *** – P < 0.001.

In the patients over 45, paraoxonase level was 13% lower than in the patients before 30. A similar tendency was observed in RA combined with arterial hypertension (AH). In such patients paraoxonase activity was decreased nearly 1.12 times. But no significant relationship between paraoxonase activity and duration of the disease, obesity and smoking was revealed. The relationship between paraoxonase activity and lipid metabolism indices (Table 3) was evaluated. For this purpose, all the patients were divided into three groups: those with normal indices, marginally increased and high indices of lipid profile according to the Third Report of the National Cholesterol Education Program (2002). RA patients with high levels of TC, LDLC and low levels of HDLC were found to have significantly lower average paraoxonase level than the individuals with optimal lipid levels. In the patients with high levels of TC and LDLC paraoxonase activity was significantly lower – by 24.0% and 14.5%, respectively, and in those with low levels of HDLC – by 9.4% less than in the patients with optimal levels of those indices. No significant decrease of paraoxonase activity in the patients with hypertriglyceridemia was revealed.

Table 3
Analysis of serum paraoxonase activity depending on lipid level in RA patients (x ± SE)

Indices	Lipid level	Paraoxonase activity, mmol/l·h	
		absolute value	r
TC, mmol/l	optimal, n = 35	115.8 ± 2.47	
	marginally elevated, n = 23	101.4 ± 3.20***	–0.62#
	high, n = 7	88.0 ± 2.91***	
HDLC, mmol/l	normal, n = 24	110.2 ± 3.35	
	subnormal, n = 17	114.0 ± 3.62	0.24
	low, n = 24	99.8 ± 3.38*	
LDLC, mmol/l	normal, n = 39	113.3 ± 2.45	
	marginally elevated, n = 10	101.2 ± 6.58	–0.48#
	high, n = 16	96.8 ± 4.03***	
TG, mmol/l	normal, n = 20	113.2 ± 3.48	
	marginally elevated, n = 20	106.3 ± 4.42	–0.21
	high, n = 25	105.1 ± 2.95	

Note: * – statistical significance in comparison of examined parameters P < 0.05, ** – P < 0.01, *** – P < 0.001, # – strong correlation between the variables.

The relationship between paraoxonase activity and lipid metabolism was further verified by correlation analysis. In RA patients there

was close inverse association between paraoxonase activity and HDLC, and close direct association between paraoxonase activity and LDLC.

The next task was to evaluate the relationship between inflammatory process and enzyme system activity in RA patients (Table 4). The patients with low enzyme activity (≤89.7 mmol/l·h) were found to have higher levels of ESR, CRP and TNF-α by 14–15% than those with relatively normal paraoxonase activity (>89.7 mmol/l·h). A similar tendency was observed in total index of DAS 28 activity, pain index, articular index and edema index (r = 0.30–0.36).

Table 4
The relationship between paraoxonase activity and inflammatory process activity in RA patients (x ± SE)

Indices	Paraoxonase activity		r
	> 89.7 mmol/l·h, n = 48	≤ 89.7 mmol/l·h, n = 19	
ESR, mm/h	34.7 ± 0.30	40.4 ± 0.42***	–0.35#
CRP, mg/l	13.7 ± 0.16	16.4 ± 0.18***	–0.31#
TNF-α, ng/ml	164.7 ± 1.59	195.5 ± 1.78***	–0.33#
DAS_{28}, scores	5.3 ± 0.02	5.9 ± 0.03***	–0.36#
Pain index, scores	29.0 ± 0.41	37.5 ± 0.46***	–0.32#
Articular index, scores	24.9 ± 0.45	32.6 ± 0.48***	–0.38#
Edema index, scores	7.1 ± 0.16	10.1 ± 0.15***	–0.30#

Note: see Table 3.

The thickening of common carotid artery (IMT) walls, decreased FMDBA and severity of atherosclerotic damage in RA patients were revealed to be associated with decreased paraoxonase activity (Table 5). The patients with low paraoxonase level (≤ 89.7 mmol/l·h) had considerably lower FMDBA value (by 16.1%), and considerably larger cIMT (by 23.9%) than those with relatively normal paraoxonase level. Besides, the proportion of patients with decreased FMDBA and increase of IMT was 29.7–32.0% higher in the patients with low paraoxonase level than in those with a relatively normal level. The AP size and the extent of atherosclerotic damage of carotid arteries increased proportionally to paraoxonase activity decrease. Atherosclerotic damage of carotid arteries was revealed in 68.4% of patients with low paraoxonase activity as compared to 4.2% of patients with relatively normal indices of the studied enzyme.

Table 5
The relationship between paraoxonase activity and subclinical manifestations of atherosclerotic vascular damage (FMDBA, IMT, cAP) in RA patients (x ± SE)

Indices	Paraoxonase activity		r
	> 89.7 mmol/l·h, n = 48	≤ 89.7 mmol/l·h, n = 19	
IMT, mm	0.73 ± 0.01	0.96 ± 0.01***	–0.35#
Individuals with cIMT >0.90 mm, n (%)	11 (22.9%)	10 (52.6%)§	–0.31#
FMDBA, %	5.27 ± 0.10	4.42 ± 0.10***	–0.36#
Individuals with FMDBA ≤8.0%, n (%)	20 (41.7%)	14 (73.7%)§	–0.32#
Presence of cAP	2 (4.2%)	13 (68.4%)§	–0.38#
Extent of atherosclerotic CCA damage	0.15 ± 0.02	1.47 ± 0.04***	–

Note: * – statistical significance in comparison of examined parameters P < 0.05, ** – P < 0.01, *** – P <0.001, # – strong correlation between the variables, § – statistical significance in comparison of examined parameters.

The study of structural and functional heart status in RA patients showed its definite relationship with serum paraoxonase activity (Table 6). While the diameter of the aorta and the left atrium was 31.6 ± 0.09 and 36.3 ± 0.33 mm, respectively, in the patients with normal paraoxonase activity, it was 34.9 ± 0.14 and 38.9 ± 0.22 mm, respectively, in the patients with its decreased activity, i.e. it was larger by 9.4% and 6.6%, respectively. In the group of patients with impaired function of the enzyme system, left ventricular posterior wall thickness (LV posterior wall thickness) and intraventricular septum thickness (Septal thickness) appeared to be significantly higher as well. The most evident differences were found in left ventricular mass index: 173.4 ± 2.77 g/m in the patients with normal paraoxonase level, and 259.9 ± 2.57 g/m in those with decreased paraoxonase level (≤ 89.7 mmol/l·h), i.e. higher by 33.3% . In the latter group significant increase in sizes and volumes of the left ventricle were observed: LV diastolic diameter, LV systolic diameter, LV diastolic volume, LV systolic volume, LV mass/height.

Impaired systolic and diastolic functions of the left ventricle were associated with reduced paraoxonase activity in the blood as well. In the patients with low paraoxonase activity the relationship between E/A ratio was by 27% less and ejection fraction – by 16% less than in the patients with normal enzyme activity.

Table 6
Analysis of serum paraoxonase activity depending on structural and functional myocardial changes according to EchoCG findings and in RA patients (x ± SE)

Index	Paraoxonase activity	
	> 89.7 mmol/l·h, n = 43	≤ 89.7 mmol/l·h, n = 18
Aorta, mm	31.6 ± 0.09	34.9 ± 0.14***
LA diameter, mm	36.3 ± 0.33	38.9 ± 0.22***
LV diastolic diameter, mm	47.4 ± 0.27	51.5 ± 0.28**
LV systolic diameter, mm	31.0 ± 0.18	35.9 ± 0.28***
LV posterior wall thickness, mm	9.6 ± 0.09	12.2 ± 0.10***
Septal thickness, mm	10.3 ± 0.08	12.7 ± 0.09***
LV diastolic volume, ml	126.8 ± 1.07	132.6 ± 0.80***
LV systolic volume, ml	46.5 ± 0.77	55.6 ± 1.03***
Ejection fraction, %	62.9 ± 0.35	54.1 ± 0.47***
LV mass/height, g/m	173.4 ± 2.77	259.9 ± 2.57***
E, m/c	64.8 ± 0.82	50.6 ± 0.53***
A, m/c	60.8 ± 0.71	61.9 ± 0.42
E/A ratio	1.14 ± 0.01	0.84 ± 0.01***

Note: see Table 2.

Discussion

The study revealed the Ukrainian patient population with RA to have considerable reduction (by 18.8%) of serum paraoxonase activity as compared to apparently healthy individuals. The data obtained in the study confirmed those presented by other authors (Tanimoto et al., 2003; Isik et al., 2007). Nevertheless, some reports in the modern literature deny the increase of paraoxonase level in RA patients (Hashemi et al., 2010). Serum paraoxonase activity was shown to decrease proportionally to the increase of the age in RA patients. In the group of patients over 45 the level of the enzyme was 13% lower than in the patients over 30. According to reports from the literature, paraoxonase activity in the patients with autoimmune pathology decreases in the process of reproductive aging (Kiss et al., 2007). At the same time, no sex differences in serum paraoxonase levels in RA patients were found.

The study established that the increase of systolic and diastolic arterial pressure is associated with decrease of serum paraoxonase activity in RA patients. The patients with RA combined with AH had significantly (by 10.9%) lower activity of the studied enzyme than those with no AH. However, no significant relationship between paraoxonase activity and duration of the disease, obesity and smoking was revealed. There was only a tendency to decrease of the studied enzyme in the presence of the abovementioned risk factors.

Paraoxonase activity in RA patients was demonstrated to be dependent on lipid levels. The lowest paraoxonase activity was recorded in individuals with the highest levels of TC, LDLC and the lowest HDLC indices. In RA patients with optimal TC level, paraoxonase activity was 24% lower than in those with hypercholesterolemia . Correlation analysis provided additional evidence of the association of enzyme activity with impaired lipid metabolism. Such relationship between paraoxonase activity and lipid metabolism is not surprising as paraoxonase-1 is known to be a part of high density lipoproteins (HDL), it has potent antioxidant properties and protects HDL and LDL against overoxidation under the influence of active oxygen forms (Mkhitarian et al., 2016).

Serum paraoxonase level was found to be associated with increased levels of proinflammatory mediators ESR, CRP and TNF-α, as well as

articular syndrome indices. For instance, in the patients with low paraoxonase activity (≤ 89.7 mmol/l·h) serum levels of proinflammatory mediators were on average 15% higher than in the patients with relatively normal paraoxonase activity (> 89.7 mmol/l·h). The pathogenic role of systemic inflammatory process in impaired function of enzyme systems in RA patients has been previously reported in other studies (Kerekes et al., 2008; Shahmohamadnejad et al., 2015).

The data received in the study suggested low paraoxonase activity to be an adverse factor in progression of structural and functional alterations of the heart and vessels in RA patients. Significant increase of LV mass/height, the diameter of aorta and the left atrium, sizes and volumes of the left ventricle, IMT was recorded in the patients with low paraoxonase level as compared to patients with optimal paraoxonase level. Decrease in systolic and diastolic functions of the cardiac muscle was proportional to the decrease of serum paraoxonase level in RA patients. The area and severity of atherosclerotic damage of CCA had the tendency to increase with the decrease of serum paraoxonase activity. The adverse effect of that risk factor on the clinical course of cardiovascular pathology in RA patients has been previously confirmed in other studies. A low paraoxonase level in RA patients was shown to cause early formation of atherosclerotic vascular damage, to determine the level of FMDBA and IMT (Kerekes et al., 2008; Charles-Schoeman et al., 2013; El-Banna et al., 2014).

Thus, significant decrease of serum paraoxonase level is a common occurrence in RA patients. The concentration of this enzyme decreases proportionally to age, it is associated with arterial hypertension, dyslipidemia and disease activity but is not significantly influenced by the disease duration, obesity or smoking. A close relationship between paraoxonase activity and structural and functional heart status is indicative of potential involvement of this enzyme in the development of atherosclerotic alterations in the vessels.

Conclusions

RA patients have decreased serum paraoxonase activity (by 18%) as compared to apparently healthy individuals. Low paraoxonase activity is associated with age, arterial hypertension, dyslipidemia and disease activity and is not dependent on disease duration, obesity or smoking.

Paraoxonase activity in RA patients is associated not only with atherosclerotic vascular damage (cIMT, decreased FMDBA) but also with structural and functional heart status (systolic and diastolic functions, left ventricular myocardial hypertrophy).

Directions for future research. Further studies can determine the place of paraoxonase among other metabolic and traditional risk factors of cardiovascular complications in RA patients.

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