RESEARCH ARTICLE

CORRELATION BETWEEN THE DEGREE OF DISEASE ACTIVITY IN RHEUMATOID ARTHRITIS WITH SERUM URIC ACID IN PATIENTS AT WAHIDIN SUDIROHUSODO HOSPITAL MAKASSAR AND ITS NETWORK

[1,*]AndiKartini Eka Yanti, [1]Faridin, H.P., [2]Syakib Bakri, [2]Hasyim Kasim, [2]Haerani Rasyid, [2]Pendrik Tandean, [2]Fardah Akil, [2]Nu'man As Daud and [3]Arifin Seweng

[1]Rheumatology Division, Hasanuddin University. DR. Wahidin Sudirohusodo Hospital
Perintis Kemerdekaan Rd no. 10, 90245 Makassar, South Sulawesi, Indonesia
[2]Department of Internal Medicine Faculty of Medicine, Hasanuddin University. DR. Wahidin Sudirohusodo
Hospital Perintis Kemerdekaan Rd no. 10, 90245 Makassar, South Sulawesi, Indonesia
[3]Department of Biostatistics Faculty of Public Health, Hasanuddin University. DR. Wahidin Sudirohusodo
Hospital Perintis Kemerdekaan Rd no. 10, 90245 Makassar, South Sulawesi, Indonesia

ARTICLE INFO	ABSTRACT
	Introduction: Rheumatoid arthritis (RA), is a chronic autoimmune disease characterized by progressive joint damage, with very high morbidity and mortality. High level of serum uric acid is associated with a condition of ischemic injury, and aggravate the inflammatory process in RA, it is suggested that uric acid is associated with the degree of disease activity in RA. **Aim:** Determine the correlation between the degree of disease activity in rheumatoid arthritis with level of serum uric acid in patients treated in Wahid in Sudirohusodo hospital Makassar and its network. **Method:** This research is an observational type with cross sectional approach in 57 subjects of rheumatoid arthritis, who were over 18 years old and did not have other autoimmune diseases. The degree of disease activity was assessed based on DAS28-LED instrument. Serum uric acid, serum creatinine, erythrocyte sedimentation rate (ESR) test, using venous blood samples. Sampling is done consecutive sampling and put into the experiment until a certain time so that the number of sample reached. Methods using Multiple and logistic regression to determine the relationship between the degree of rheumatoid arthritis disease activity and serum uric acid levels. **Result:** In this study most were 40-59 years old (43.9%), with the most subjects were females (73%), and most with high degree of disease activity (52.6%). Based on regression and multivariate analysis, male sex was most significantly correlated with uric acid level (p <0,05), there was no significant correlation between degree of disease activity and serum uric acid level. **Conclusion:** There were no significant correlation between the degree of rheumatoid arthritis disease activity and serum uric acid levels, though it may appear that the uric acid levels increased at higher levels of activity. Risk factors most significantly associated with serum uric acid levels is the male gender. Further research is needed with larger sample quantities and longer time, to be able to assess fluctuations in serum acid levels, and to assess other risk factors affecting serum uric acid levels.

INTRODUCTION

Rheumatoid arthritis (RA), is a chronic autoimmune disease characterized by progressive joint damage, with very high morbidity and mortality (Chauhan, 2016 and Mavrogeni, 2013).

Corresponding author: **Andi Kartini Eka Yanti,**
Rheumatology Division, Hasanuddin University. DR. Wahidin Sudirohusodo Hospital, Perintis Kemerdekaan Rd no. 10, 90245 Makassar, South Sulawesi, Indonesia.
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Incident RA is in the age range 30-50 years (Brigss, 2014), and more often in female compared with male, sex hormones is suggested play a role in the progression of this disease (Suarjana, 2014). High disease activity is a bad prognosis, involve many joints and high inflammatory markers, which can be measured using the *Disease Activity Index*28 (DAS28) (Suarjana, 2014). High level of serum uric acid is associated with a condition of ischemic injury, which would aggravate the inflammatory process that occurs, so it is said that uric acid is

Table 1. Characteristic Distribution of Research Subject (n = 57)

Variable		n	%
Gender	Male	15	26,3
	Female	42	73,7
Age	18-39 yo	23	40,4
	40-59 yo	25	43,9
	>=60 yo	9	15,8
Hypertension	Yes	17	29,8
	No	40	70,2
GFR	>atau = 60 mL/min/1,73m^2	46	80,7
	< 60 mL/min/1,73m^2	11	19,3
Serum Uric Acid	High	22	38,5
	Normal	35	61,4
Degree of Disease Acitvity(DAS28)	High	30	52,6
	Moderate/Low	27	47,4

Table 2. Correlation between Degree of Disease Activity (DAS28) with Level of Serum Uric Acid

Degree of Disease Activity		Serum Uric Acid		p
		High	Normal	
High	n	14	16	
	%	46,7%	53,3%	
Low/moderate	n	8	19	0,187
	%	29,6%	70,4%	
Total	n	22	35	
	%	38,6%	61,4%	

associated with inflammatory processes and the degree of disease activity (Ghosh, 2016). Several studies of the coexistence of RA and gout found that uric acid levels increased at a high degree of activity disease in RA, especially in female (Ghosh, 2016). Rabinowic *et al* (2017), that serum uric acid levels are lower in AR compared with non RA. Risk factors that affect, among others, old age, male sex, body mass index (BMI) and hypertension. Coexistence of gout and RA, to date, only about 33 cases have been reported in English literature (Jebakumar, 2013).

MATERIALS AND METHODS

The population of this study was the subjects of Rheumatoid Arthritis treated at Wahid in Sudirohusodo Hospital Makassar and its network, and fulfilled the inclusion criteria, male or female of ages ≥18 years old, diagnosed RA according to ACR EULAR criteria in 2010, and signed informed concent. Subject with other autoimmune diseases are not included in this study. Physical examination and anthropometry were performed at the time of the hospital visit. The degree of disease activity was assessed based on DAS28-LED instrument, serum uric acid, serum creatinine, erythrocyte sedimentation rate (ESR) test, using venous blood samples.

This study evaluated the association between risk factors such as disease activity, age, gender, hypertension, glomerular filtration rate (GFR) on uric acid levels.

Research variable

- Age of the subject using the date of birth listed in the medical record.
- Gender is divided into male and female.
- Hypertension is determined on the basis of the JNC 7 criterion, hypertension, when systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, or taking antihypertensive drugs.

- GFR is calculated based on the CKD-EPI formula, which is calculated by age, gender, serum creatinine, and differentiated between male and female, by using Qx calculate application, divided into: ≥ 60 mL/min/1.73m^2 and < 60 mL/min/1.73m^2
- Hyperuricemia in the presence of elevated serumuric acid levels above the nomal, divided into: males: ≥ 7.0 mg/dl, women ≥ 6.0 mg/dl.[8]

Statistical Analysis

Subject data were described using the mean± standard deviation, simple grouping and percentage. The independent variable is the degree of rheumatoid arthritis disease activity (DAS28), the dependent variable is the serum uric acid levels, and confounding variables including age, sex, hypertension, and GFR. Data analysis was performed using SPSS version 22. The method used was calculation of descriptive statistic (minimum, maximum, mean, standard deviation, and frequency distribution), statistical test using *Pearson's Correlation* test, Anova test, and *independent t-test*. Statistical test results are significant if the value of p <0.05.

RESULTS

Total of 57 RA subject, female 73,7%, most 40-59 years old, 17 subjects of hypertensionand11 subjects decreased GFR. Most subjects with high disease activity (52,6 %) and 22 subjects with hyperuricemia, (Table 1). In this study, since no significant association was found between the degree of disease activity and serum uric acid levels (Table 2), we continued by analyzing the association between risk factors for sex, age, hypertension, GFR with serum uric acid levels. Gender was found to be related significantly to the increase in serum uric acid levels (p<0.05) and hypertension (p <0.05), as shown in Tables 3 and 4. Gender, and hypertension are significantly have correlation with elevated levels of serum uric acid, by Amultivariate analysis using Multiple Logistic Regression found that gender was the only significant variable related touric acid levels (p<0.05), (Table 5).

Table 3. Correlation between Gender and Level of Serum Uric Acid

Gender			Serum Uric Acid		Total	
			High	Normal		p
	Male	n	10	5	15	
		%	66,7%	33,3%	100,0%	
	Female	n	12	30	42	0,009
		%	28,6%	71,4%	100,0%	
Total		n	22	35	57	
		%	38,6%	61,4%	100,0%	

Table 4. Correlation between Hypertension with Level of Serum uric Acid

Hypertension			Serum Uric Acid		p
			High	Normal	
	Yes	n	10	7	
		%	58,8%	41,2%	
	No	n	12	28	0,041
		%	30,0%	70,0%	
Total		n	22	35	
		%	38,6%	61,4%	

Table 5. Multivariate Analysis

Step	Variable	B	Wald	p
Step 1	Gender	1,28	3,15	0,076
	Age	0,50	1,19	0,276
	GFR	0,47	0,33	0,566
	Hypertension	1,11	2,56	0,109
	Disease Activity	0,68	1,21	0,272
Step 2	Gender	1,38	3,92	0,048
	Age	0,45	1,01	0,315
	Hypertension	1,11	2,61	0,106
	Disease Activity	0,66	1,17	0,280
Step 3	Gender	1,28	3,55	0,060
	Hypertension	0,94	2,05	0,152
	Disease Activity	0,63	1,08	0,299
Step 4	Gender	1,39	4,27	0,039
	Hypertension	0,88	1,88	0,170
Step 5	Gender (Male)	1,61	6,22	0,013

DISCUSSION

Total of 57 subject of rheumatoid arthritis patients most were female (73%), 40-59 year-old (43.9%). Dougados, *et al.*[9] reported that most rheumatoid arthritis patients were women (82%). This is associated with the role of sex hormones in the development of this disease (Kuo, 2014). 17 subjects with hypertension (29.8%), were thought to be associated with inflammation in rheumatoid arthritis, resulting in suppression of NO activity, inhibition of vasodilation process, increased angiotensin II, and hypertension (Panoulas, 2008). Manavathongchai, *et al*, (Manavathongchai, 2014), found in 169 RA subjects with an average age of 51.2 - 67 years, there were 90 subjects (53.3%) suffering from hypertension. Subjects who have elevated levels of serum uric acid as many as 22 people (38.5%). Rabinowicks RM dkk (Merdler-Rabinowicz, 2017), found that of 11,540R Asubjects, there were 186 subjects with elevated serum uric acid levels (26.3%). Jebaykumar *et al* (Jebakumar, 2018), reported that813RA patients had only 22 patients with gout, and 6 patients had gout before RA. In contrast to the study by Daniel Kuo *et al* found that of 813 patients with RA compared with 813 patients with nonRA, serum uric acid levels are higher in patients compared with non AR. In this study the proportion of male with elevated uric acid levels was66,7%, whereas in female only28.6%.This result is in accordance with a study by Petsch *et al.* who reported that subjects with rheumatoid arthritis accompanied hyperuricemia, more in male (Petsch, 2016).

The role of estrogen and progesterone that causes kidney clearence of uric acid in female on reproductive age, thus reducing the risk of hyperuricemia and gout in these patients, (Jebakumar, 2013), where in this study, subjects women who have elevated levels of uric acid, is aged over 40 years. The study by Kuo *et al* also found that RA patients with gout were found to be significant in old age. While research by Yu KH *et al*. reported that elevated uric acid levels were more common in the 3rd and 5th decade ages in China. Research by Iseki K, *et al*. found that age and gender were strong factors that had an effect on elevated serum uric acid levels. This is related to the number of causes of elevated serum uric acid levels, including race, diet, alcohol consumption, hormonal and diuretic drug use (Yu, 2003 and Liu, 2015). In this study there was a significant correlation between hypertension and serum uric acid levels that increased 58% (P <0.05). Daniel Kuo *et al.* found that serum uric acid levels in patients with RA, found to be increased in patients with comorbid factors such as hypertension, diabetes mellitus, dyslipidemia and cardiovascular disease. Hyperuricemia can be detected in one-third of patients with essential hypertension. Potential mechanisms on the association between hyperuricemia and hypertensive development are nitricoxide (NO) and renin angiotensin pathways, resulting in decreased excretion of uric acid (Grayson, 2011). Reduced renal blood flow in hypertension results in decreased excretion of uric acid.[19]In addition, the use of anti-hypertensive drugs such as diuretics, β-blockers, ACE-inhibitors, non-losartan angiotensin antagonists,

can increase serum uric acid levels (Choi, 2012). Subjects with GFR <60 mL/min/1.73m^2, hade levated uric acid levels (54.5%), greater than subjects with GFR ≥60mL/min/1.73m^2. Iseki K, *et al* (Iseki, 2001), found that increased serum uric acid is associated with increased serum creatinine, obtained from 6403 subjects in the male subjects (4.1%) compared with female subject (0.8%), decreased of GFR in subjects research, can be caused by hypertension along with other abnormalities which ultimately decreases renal blood flow, leading to decreases the ability of renal excretion (Kang, 2005). Increased uric acid levels were observed in high density of disease activity (46.7%). Ghosh B, *et al*. (Ghosh, 2016), reported a significant association between uric acid levels and the degree of disease activity. The higher the degree of disease activity in RA, resulting in joint damage and serum uric acid secretion (Billiet, 2014).

Conclusion

Gender male is the most significant risk factor associated with elevated levels of serum uric acid in patients with Rheumatoid Arthritis. Further research is needed to assess the risk factors that influence the levels of serum uric in patients with RA, and to monitor the profile of uric acid in patients with RA.

Conflict of Interest

The authors declare there is no conflict of interest regarding the publication of this paper.

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