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The Prevalence and Factors Associated with Metabolic Syndrome in Rheumatoid Arthritis Patients

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A B S T R A C T

Background: Rheumatoid arthritis (RA) is an independent risk factor of cardiovascular disease (CVD), causing 30-50% mortality in RA patients. Metabolic syndrome is a combination of metabolic disorders that can be manifested as central obesity, impaired blood pressure, or abnormalities of carbohydrate and lipid metabolism, which is closely associated with CVD in RA patients. The prevalence and factors associated with the incidence of metabolic syndrome in RA patients vary in previous studies. This study aimed to determine the prevalence and factors associated with the incidence of metabolic syndrome in RA patients at Cipto Mangunkusumo National Central General Hospital, Jakarta. **Methods:** A total of 145 RA patients at the Rheumatology Clinic of Cipto Mangunkusumo National Central General Hospital from October to December 2021 were included as research subjects by consecutive sampling method. History taking about the disease and demographic data, physical and anthropometric examination, and laboratory tests were done on the patients. The prevalence of the metabolic syndrome was determined using harmonization criteria. Statistical analysis was performed to determine the association of the variables of age, smoking habit, disease activity, duration of disease, glucocorticoid treatment, and methotrexate treatment with metabolic syndrome in RA patients. **Results:** The prevalence of metabolic syndrome was 19.3% in RA patients with a mean age of 49.8 ± 11.6 years. The variables of gender, age, deformity, physical activity, extraarticular manifestation, smoking habit, disease activity, disease duration, glucocorticoid treatment, and methotrexate treatment were not statistically significant to the incidence of metabolic syndrome in RA patients. **Conclusion:** The prevalence of metabolic syndrome in RA patients in this study was 19.3%, and no variable was associated with the prevalence of metabolic syndrome.

1. Introduction

Rheumatoid arthritis (RA) is a disease that manifests mainly in the joints and can cause deformity and disability. RA as a systemic disease has also been reported to be associated with an increased risk of mortality.[1] A meta-analysis showed that RA is an independent risk factor for cardiovascular disease (CVD) and is associated with the development of the metabolic syndrome.[2] It was reported that RA patients are more likely to have CVD, including coronary artery

disease (CAD), heart failure, or peripheral artery disease, up to 1.5-2 times. In the overall RA population, 30-50% mortality from CVD had also been reported.[3]

Metabolic syndrome is a combination of metabolic disorders characterized by central obesity, impaired glucose and lipid metabolism, and impaired blood pressure regulation which results in accelerating atherosclerosis and increasing cardiovascular events. Insulin resistance, which manifested primarily as a decrease in the effectivity of the insulin hormone to induce the uptake of blood glucose in muscle and liver tissue, is an important key in the pathogenesis of this metabolic syndrome. This insulin resistance was found in a variety of chronic inflammatory diseases, including RA.[4,5] The currently recognized definitions and diagnostic criteria for metabolic syndrome are quite diverse.[6-10] A consensus known as harmonization criteria for the diagnosis of metabolic syndrome has been formed to unify the diagnostic criteria and use an adjusted waist circumference to measure each ethnicity.[6]

Data on the prevalence of metabolic syndrome in RA patients based on studies from various countries vary between 14-63%.[11,12] The cause of this large variation is related to the variations in the characteristics of the research subjects, the criteria used for defining the metabolic syndrome, and the study design.[11] This prevalence data in Indonesia has not been previously reported. Meanwhile, various factors associated with the incidence of metabolic syndrome in RA patients from various studies, including age, smoking habit, disease activity, duration of disease, glucocorticoid treatment, and administration of methotrexate therapy, were reported in a few studies.[4,13,14] Thus, this study aimed to determine the prevalence and these various factors associated with the incidence of metabolic syndrome in RA patients.

2. Methods

The study was a cross-sectional study conducted from October 2021 to December 2021 at Cipto Mangunkusumo National Central General Hospital, Jakarta, Indonesia. The selection of the subjects was a consecutive sampling method. The inclusion criteria were patients that met the RA classification criteria in ACR/EULAR 2010. History taking about the disease and demographic data, physical and anthropometric examination, and laboratory tests were done on each subject to identify the metabolic syndrome criteria according to the harmonization criteria of NCEP-ATP III for the Asian population. Metabolic syndrome was defined when three or more of the five criteria are met: blood glucose levels 100 mg/dL (or diabetes mellitus, or in diabetes mellitus therapy); triglyceride levels 150 mg/dL (or on treatment for hypertriglyceridemia); HDL cholesterol < 40 mg/dL for men or < 50 mg/dL for women (or on low HDL therapy); blood pressure 130/85 mmHg (or on antihypertensive therapy); and central obesity with waist circumference 102 cm in men or 88 cm in women.

All demographics and clinical factors were analyzed by bivariate statistical analysis with a significant p-value of <0.05 and a confidence interval of 95%. All variables with p-value <0.25 would be analyzed with multivariate analysis using the logistic regression method to analyze predictive factors of metabolic syndrome in RA patients. This research received ethical approval with the number KET-911/UN.2F1/ETI/PPM.00.02/2021 from the Medical Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia.

3. Results

A total of 145 RA patients were included in this study. Most of them were women (91.0%), with a mean age of 49.8 ± 11.6 years. Most of the subjects received combination therapy with methotrexate and glucocorticoid (44.8%), with most disease activity achieving the target of treatment was remission or mild disease activity based on DAS 28 ESR (56.5%). Another factor that might be associated with metabolic syndrome was a sedentary physical activity which accounted for 66.9% of the subjects. Complete demographic and clinical data can be seen in table 1.

The prevalence of metabolic syndrome in this study was 19.3% (28 subjects). The results from bivariate

analysis of various clinical and laboratory factors did not find any variable that was statistically associated with the incidence of metabolic syndrome, as described in table 2. A multivariate analysis was performed in this study, although only one variable had a p-value of <0.25. Multivariate analysis using the logistic regression method found that no variable was statistically significant.

Table 1. Subject characteristics.

Variables	Total (%)
Gender (%)	
Female	132 (91.0)
Age [Mean ± Standard deviation], year(s)	49.8 ± 11.6
< 60	113 (77.9)
Treatment (%)	
Methotrexate	52 (35.9)
Glucocorticoid	15 (10.3)
Methotrexate and glucocorticoid combination	65 (44.8)
Other Treatments	13 (9.0)
Sulfasalazine	9 (6.2)
Leflunomide	3 (2.1)
Analgesic	1 (0.7)
Disease duration [Median (Min-Max)], year(s)	3 (0-34)
< 5	89 (61.4)
Deformity (%)	
Yes	12 (8.3)
Extraarticular manifestations (%)	
Yes	27 (18.6)
Menopause (%)	
(n=132, total of female subjects)	
Yes	71 (53.8)
Physical activity (%)	
Sedentary	97 (66.9)
Smoking (%)	
No	135 (93.1)
Mild brinkmann index	10 (6.9)
Heavy brinkmann index	0 (0)
DAS 28 ESR [Median (Min – Max)]	3.080 (0.8-6.5)
Remission-mild	82 (56.6)
Moderate-high	63 (43.4)
Body mass index (%)	
Overweight and obese	76 (52.4)
Underweight and normoweight	69 (47.6)
Metabolic syndrome	
Yes	28 (19.3%)
Criteria of metabolic syndrome	
High waist circumference	73 (50.3)
Hypertension	50 (34.5)
Low HDL	48 (33.1)
High triglyceride	40 (27.6)
High fasting blood glucose	24 (16.5)

Table 2. Factors Associated with metabolic syndrome in RA patients.

Variables	Metabolic syndrome		p-value	OR (CI 95%)
	Yes N (%)	No n (%)		
Gender				
Male	2 (15.4)	11 (84.6)	1.00[b]	0.7 (0.2-3.6)
Female	26 (19.7)	106 (80.3)		
Age				
< 60 Years	19 (16.8)	94 (83.2)	0.24[a]	1.9
≥ 60 Years	9 (28.1)	23 (71.9)		(0.8–4.8)
Deformity				
Yes	1 (8.3)	11 (91.7)	0.462[b]	0.4
No	27 (20.3)	106 (79.7)		(0.1-2.9)
Physical activity				
Sedentary	18 (18.6)	79 (81.4)	0.89[a]	0.8
Active	10 (21.3)	37 (78.7)		(0.4-2.0)
Extraarticular manifestations				
Yes	4 (14.8)	23 (85.2)	0.70[a]	0.7
No	24 (20.3)	94 (79.7)		(0.2-2.2)
Smoking				
No	26 (19.3)	109 (80.7)	1.00[b]	1.0
Yes	2 (20)	8 (80)		(0.2–5.2)
DAS 28 ESR				
Remission-Mild	13 (15.9)	69 (84.1)	0.32[a]	1.6
Moderate-High	15 (23.8)	48 (76.2)		(0.7 – 3.8)
Disease duration				
< 5 years	18 (20.2)	71 (79.8)	0.89[a]	0.8
≥ 5 years	10 (17.9)	46 (82.1)		(0.4–2.0)
Glucocorticoid dosages				
No glucocorticoid	16(24.2)	50(75.8)	0.29[a]	N/A
Low dose	11(16.7)	55(83.2)		
Moderate dose	1(7.7)	12(92.3)		
High dose	0 (0)	0 (0)		
Methotrexate				
No	7 (25)	21 (75)	0.56[b]	1.5
Yes	21 (17.9)	96 (82.1)		(0.6-4.0)

Note: a. Chi-Square; b. Fischer.

4. Discussion

In this study, 28 subjects (19.3%) met the criteria for metabolic syndrome in RA patients based on the harmonization criteria of NCEP-ATP III (for the Asian population). This data was similar to other studies from various countries in both cross-sectional and case-control studies, and the results of those studies were 18.7-20%.[14-19] A meta-analysis by Hallajzadeh et al., collecting data from 70 studies, found that the incidence of metabolic syndrome based on the diagnostic criteria used was slightly higher in RA patients, which was around 30.6% (95% CI 27.9-33.4) with OR 1.4 (0.7-4.1).[20] The wide variation in the prevalence was caused by differences in criteria for metabolic syndrome used and differences in subjects' mean age in various studies. In addition, the characteristics of the research subjects, such as genetic (related to race/ethnicity), culture (activity patterns and eating patterns), and demographic, socioeconomic, clinical, and treatment factors in RA, also played an important role.[20]

The prevalence of metabolic syndrome in RA patients in this study was not significantly different when compared with the general population in

Indonesia (19.3% vs. 21.7%).[21] However, the high mortality rate due to CVD in RA patients provides a strong reason to evaluate various traditional and non-traditional risk factors, including the presence of this metabolic syndrome.[22] One of many aspects that can explain why the prevalence of metabolic syndrome did not increase compared to the normal population is the amount of fat deposit. A study by Giles et al. (2010) showed higher levels of visceral fat areas in male RA patients and subcutaneous fat areas in female RA patients than in controls from the same BMI and waist circumference.[23] Other factors that might also play a role based on several studies were total cholesterol, triglyceride, and LDL cholesterol which tend to decrease in RA patients with more severe disease activity or with rheumatoid cachexia.[24] This phenomenon has known as paradoxical lipids in RA patients because it will increase after DMARD therapy.[25] This paradoxical phenomenon might be caused by the function of protein synthesis in the liver being stimulated to produce acute phase reactant in a highly active inflammatory condition which will decrease lipoprotein production and vice versa.[25]

Association between gender and metabolic syndrome was not statistically significant in this study. A similar result was found in a meta-analysis study by Hallajzadeh (2017), which showed a slightly lower prevalence of metabolic syndrome in male RA patients (31.9%; CI95% 24.4-39.5) compared with female RA patients (33.0%; CI95% 28.1-37.9).[26] It can be concluded that gender did not affect the prevalence of metabolic syndrome as obtained from epidemiological studies in the general population.[27]

Although not statistically significant, this study found that patients aged≥ 60 years old have a higher incidence of metabolic syndrome (28.1 vs. 16.8%) compared to patients in age <60 years. The result of this study was in accordance with a study by Karvounaris et al., which found the role of age in the incidence of metabolic syndrome in RA.[28] There were 135 subjects who did not smoke (93.1%) and 10 subjects who smoked (6.9%). All of them who smoke have a mild Brinkmann index. There was no statistically significant between smoking habit and metabolic syndrome in RA patients (p-value = 1, OR 1.0, 95% CI; 0.2-5.2). This can be caused by a small number of subjects who smoked, and all of them were mild Brinkmann index making the statistical analysis difficult. An existing study by de Oliveira et al. found that a smoking habit with > 400 cigarettes/year was associated with the incidence of metabolic syndrome in RA patients (29% vs. 9%; p value = 0.008).[29] Another study by Zonana-Nanach et al. also found that smoking was closely associated with the incidence of metabolic syndrome (p-value = 0.02) and became a single predictive factor when analyzed with multivariate logistic regression that determined the incidence of metabolic syndrome.[15]

In this study, the prevalence of RA patients with deformity was 8.3%. A study by Dessein et al. (2013) did not find a statistically significant relationship between deformity and metabolic syndrome (p=0.7).[30] Deformity might be severe reflexing inflammation and long disease duration. Besides, deformity in RA patients can be associated with low physical activity and an increased risk of metabolic syndrome. The percentage of sedentary physical activity in this study was 66.9%. However, the association between physical activity and metabolic syndrome was not statistically significant in this study, with the proportion of metabolic syndrome in the sedentary physical activity being lower than in active physical activity (18.6% vs. 21.3%).

The percentage of extraarticular manifestations in this study was 18.62%. The prevalence of metabolic syndrome in subjects with extraarticular manifestations was lower than in subjects without extraarticular manifestations (14.8 vs. 20.3), although not statistically significant. A study by Karvounatis et al. also found that the association between extraarticular manifestation and metabolic syndrome was not statistically significant (p=0.3). Extraarticular manifestation could be considered as an outcome related to disease duration, disease activity, and the degree of inflammation of RA, but it was difficult to determine its association with cardiovascular

events.[31,32]

The results of this study showed a higher incidence of metabolic syndrome in the RA patient group with moderate to high disease activity compared to patients with remission to low disease activity (24.4% vs. 17.3%), although there was no significant association (p = 0.32). Similar results were reported from a case-control study by Sahebari et al. (2011) which found no difference in prevalence between groups of RA patients with DAS28 ESR <3.2 and ≥3.2. In this study, it was stated that determining the degree of RA disease activity by using one kind of scoring criteria was difficult to describe the actual condition of RA disease activity and its relationship to the incidence of metabolic syndrome.[33] This is indeed different from the results of several other studies, such as Dao et al. (2010), which found a significant association with disease activity measured by DAS28 (OR = 1.7; 95% CI 1.3-2.8; p = 0.01). A significant laboratory parameter in this study was the erythrocyte sedimentation rate (OR = 1.5; 95% CI 1.07-3.2; p = 0.04).[34] Another study by Ristic et al. also found that DAS28 ESR ≥ 5.1 was associated with an increase in HOMA-IR in RA patients compared to controls [1.7(1.2–2.5) vs. 1.2(0.8–1.4; p = 0.00].[35] A study by da Cunha et al. (2012) also found that DAS28 disease activity was associated with a greater incidence of metabolic syndrome in RA patients compared with the control group (3.6 ± 1.3 vs. 3.1 ± 1.5; p = 0.01).[36] This difference is most likely due to the different definitions of metabolic syndrome and the difference in the control of factors other than inflammation in RA that also influence the incidence of the metabolic syndrome.

In this study, most subjects have a disease duration of < 5 years (61.4%) with a median of 3 years. The group of patients with disease duration < 5 years has a greater percentage of the incidence of metabolic syndrome (20.2% vs. 17.9%), although the bivariate analysis did not find statistical significance (OR 0.8; 95% CI 0.4-2.0; p = 0.89). Other studies have also failed to find a relationship between disease duration and the incidence of metabolic syndrome.[13,28,36] This might be due to inflammatory conditions or autoimmunity that have occurred since the pre-clinical phase, which vary in duration.

This study obtained different results in the use of glucocorticoids which are thought to play a role in metabolic syndrome. The highest percentage of RA patients with metabolic syndrome was found in the group of patients without glucocorticoids, then the groups with low and moderate doses of glucocorticoids (24.2%, 16.7%, and 7.7%; p = 0.29, respectively). These results may be explained by the mechanism of action of low-dose glucocorticoids that improve lipid profiles (especially elevation of HDL levels) in RA patients. The hypothesis by experts regarding the effect of low-dose glucocorticoids was the activation of lipoprotein lipase and a decrease in the activity of triglyceride lipase in the liver.[33]

Subjects without methotrexate (MTX) treatment has a higher percentage of metabolic syndrome than subjects receiving MTX, although not statistically significant (25% vs. 17.9%; p = 0.56). This was consistent with the study reported by Dao et al. (2010), which found a high incidence of metabolic syndrome in the RA population not receiving MTX treatment (OR = 0.7; 95% CI 0.5-0.9; p = 0.02).[34] Methotrexate has long been known to have an inhibitory effect on the incidence of metabolic syndrome in RA patients. The hypothesis formulated by the experts was that the extracellular adenosine level that is increased by MTX not only has the anti-inflammatory effect by affecting immune cells but also can affect the metabolism and transportation of glucose and lipids in the body. This effect can improve glucose, triglyceride, and HDL profiles in patients. Besides, MTX is also thought to have atheroprotective and anti-inflammatory effects, which resulted in reducing the incidence of CVD.[15] A study from Toms et al. showed a statistical significance of MTX treatment on the incidence of metabolic syndrome in RA patients (46.5% vs. 63.8%; p 0.001) compared with patients who did not receive MTX.[14] A meta-analysis by Baghdadi in 2020 concluded that administration of MTX to RA patients was associated with a lower incidence of type 2 diabetes mellitus (RR 0.48; 95% CI 0.16-1.43), which

was also thought to be directly associated with a lower incidence of the metabolic syndrome.[37]

This study was the first study to obtain the prevalence and factors associated with the incidence of metabolic syndrome in RA patients in Indonesia. The limitation of this study was the research design which was a cross-sectional study. This made this study could not take a clear pattern of cause-and-effect relationships and the contribution of various risk factors. Overall, studied factors have not shown any statistically significant role in the incidence of metabolic syndrome, but there is a tendency to increase the incidence of metabolic syndrome in RA patients with older age, high-moderate disease activity, shorter disease duration, and without glucocorticoid and MTX treatments.

5. Conclusion

The prevalence of metabolic syndrome in RA patients at Cipto Mangunkusumo National Central General Hospital was 19.3%. There were no variables significantly associated with the incidence of metabolic syndrome in RA patients, including gender, age, deformity, extraarticular manifestations, physical activity, smoking, disease activity, disease duration, and glucocorticoid or MTX treatments. Further studies using cohort design are needed to better assess the relationship between various variables in RA patients with the incidence of metabolic syndrome.

6. References:

1. American College of rheumatology/European League against rheumatism collaborative initiative. 2010 rheumatoid arthritis classification criteria. Arthritis and Rheumatism. 2010; 62(9): 2569-81.
2. Robertson J, Peters MJ, McInnes IB, Sattar N. Changes in lipid levels with inflammation and therapy in RA: a maturing paradigm. Nat Rev Rheumatol. 2013; 9(9): 513-23.
3. Crowson CS, Liao KP, Davis JM 3rd, Solomon DH, Matteson EL, et al. Rheumatoid arthritis and cardiovascular disease. Am Heart J. 2013; 166(4): 622-8
4. Ferraz-Amaro I, González-Juanatey C, López-Mejias R, Riancho-Zarrabeitia L, González-Gay MA. Metabolic syndrome in rheumatoid arthritis. Mediators Inflamm. 2013; 1-11.
5. Ferris HA, Kahn CR. New mechanisms of glucocorticoid-induced insulin resistance: make no bones about it. J Clin Invest. 2012; 122(11): 3854-7.
6. Grundy SM et al. Diagnosis and management of the metabolic syndrome, an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. Circulation. 2005; 112: 2735-52.
7. International Diabetes Federation. The IDF consensus worldwide definiton of the metabolic syndrome. IDF. 2006.
8. Beck-Nielsen H. General characteristics of the insulin resistance syndrome: prevalence and heritability. European Group for the study of Insulin Resistance (EGIR). Drugs. 1999; 58 Suppl 1: 7-82.
9. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. 1998; 15(7): 539-53.
10. Bloomgarden ZT. American Association of Clinical Endocrinologists (AACE) consensus conference on the insulin resistance syndrome: 25-26 August 2002, Washington, DC. Diabetes Care. 2003; 26(4): 1297-303.
11. Dessein PH, Woodiwiss AJ, Norton GR, Solomon A. Rheumatoid arthritis is associated with reduced adiposity but not with unfavorable major cardiovascular risk factor profiles and enhanced carotid atherosclerosis in black Africans from a developing population: a cross-sectional study. Arthritis Res Ther. 2013; 15(4): 96.
12. Giles JT, Allison M, Blumenthal RS, et al. Abdominal adiposity in rheumatoid arthritis:

association with cardiometabolic risk factors and disease characteristics. Arthritis Rheum. 2010; 62(11): 3173-82.
13. Kerekes G, Nurmohamed MT, González-Gay MA, et al. Rheumatoid arthritis and metabolic syndrome. Nat Rev Rheumatol. 2014; 10(11): 691-6.
14. Toms TE, Panoulas VF, John H, Douglas KM, Kitas GD. Methotrexate therapy associates with reduced prevalence of the metabolic syndrome in rheumatoid arthritis patients over the age of 60- more than just an anti-inflammatory effect? A cross sectional study. Arthritis Res Ther. 2009; 11(4): 110.
15. Zonana-Nacach A, Santana-Sahagún E, Jiménez-Balderas FJ, Camargo-Coronel A. Prevalence and factors associated with metabolic syndrome in patients with rheumatoid arthritis and systemic lupus erythematosus. J Clin Rheumatol. 2008; 14(2): 74-7.
16. Mok CC, Ko GT, Ho LY, Yu KL, Chan PT, et al. Prevalence of atherosclerotic risk factors and the metabolic syndrome in patients with chronic inflammatory arthritis. Arthritis Care Res (Hoboken). 2011; 63(2): 195-202.
17. Karimi M, Mazloomzadeh S, Kafan S, Amirmoghadami H. The frequency of metabolic syndrome in women with rheumatoid arthritis and in controls. Int J Rheum Dis. 2011; 14(3): 248-54.
18. Lee SG, Kim JM, Lee SH, Kim KH, Kim JH, et al. Is the frequency of metabolic syndrome higher in South Korean women with rheumatoid arthritis than in healthy subjects? Korean J Intern Med. 2013; 28(2): 206-15.
19. Rostom S, Mengat M, Lahlou R, Hari A, Bahiri R, Hajjaj-Hassouni N. Metabolic syndrome in rheumatoid arthritis: case control study. BMC Musculoskelet Disord. 2013; 14: 147.
20. Hallajzadeh J, Safiri S, Mansournia MA, et al. Metabolic syndrome and its components among rheumatoid arthritis patients: A comprehensive updated systematic review and meta-analysis. PLoS One. 2017; 12(3): e0170361.
21. Tahapary DL, Harbuwono DS, Yunir E, Soewondo P. Diagnosing metabolic syndrome in a multi-ethnic country: is an ethnic-specific cut-off point of waist circumference needed? Nutr Diabetes. 2020; 10(1): 19.
22. Soewondo P, Purnamasari D, Oemardi M, Waspadji S, Soegondo S. Prevalence of metabolic syndrome using NCEP/ATP III criteria in Jakarta, Indonesia: the Jakarta primary non-communicable disease risk factors surveillance 2006. Acta Med Indones. 2010; 42(4): 199-203.
23. Giles JT, Allison M, Bingham CO, Scott WM, Bathon JM. Adiponectin is a mediator of the inverse association of adiposity with radiographic damage in rheumatoid arthritis. Arthritis and Rheumatism. September 15, 2009; 61(9): 1248-56.
24. Wolfe F, Michaud K. Effect of body mass index on mortality and clinical status in rheumatoid arthritis. Arthritis Care Res (Hoboken). 2012; 64(10): 1471-9.
25. Abdulsamad T, Al-Zaidi G. Serum lipids in patients with active rheumatoid arthritis and it's relation to drug therapy. J Fac Med Baghdad. 2005; 47(1): 1-5.
26. Hallajzadeh J, Safiri S, Mansournia MA, et al. Metabolic syndrome and its components among rheumatoid arthritis patients: A comprehensive updated systematic review and meta-analysis. PLoS One. 2017; 12(3): e0170361.
27. Adams RJ, Appleton S, Wilson DH, et al. Population comparison of two clinical approaches to the metabolic syndrome: implications of the new International Diabetes Federation consensus definition. Diabetes Care. 2005; 28(11): 2777-9.
28. Karvounaris SA, Sidiropoulos PI, Papadakis JA, Spanakis EK, Bertsias GK, Kritikos HD,

Ganotakis ES, Boumpas DT. Metabolic syndrome is common among middle-to-older aged Mediterranean patients with rheumatoid arthritis and correlates with disease activity: a retrospective, cross-sectional, controlled study. Ann Rheum Dis. 2007; 66(1): 28-33.

29. de Oliveira BM, Medeiros MM, de Cerqueira JV, de Souza Quixadá RT, de Oliveira ÍM. Metabolic syndrome in patients with rheumatoid arthritis followed at a University Hospital in Northeastern Brazil. Rev Bras Reumatol Engl Ed. 2016; 56(2): 117-25.
30. Dessein PH, Woodiwiss AJ, Norton GR, Solomon A. Rheumatoid arthritis is associated with reduced adiposity but not with unfavorable major cardiovascular risk factor profiles and enhanced carotid atherosclerosis in black Africans from a developing population: a cross-sectional study. Arthritis Res Ther. 2013; 15(4): R96.
31. Erickson AR, Cannella AC, Mikuls TR. Clinical features of rheumatoid arthritis. In: Kelley and Firestein's Textbook of Rheumatology. Tenth Edition. Philadelphia: Elsevier, 2017; 1167-86.
32. Karvounaris SA, Sidiropoulos PI, Papadakis JA, Spanakis EK, Bertsias GK, Kritikos HD, Ganotakis ES, Boumpas DT. Metabolic syndrome is common among middle-to-older aged Mediterranean patients with rheumatoid arthritis and correlates with disease activity: a retrospective, cross-sectional, controlled, study. Ann Rheum Dis. 2007; 66(1): 28-33.
33. Sahebari M, Goshayeshi L, Mirfeizi Z, Rezaieyazdi Z, Hatef MR, Ghayour-Mobarhan M, Akhlaghi S, Sahebkar A, Ferns GA. Investigation of the association between metabolic syndrome and disease activity in rheumatoid arthritis. ScientificWorldJournal. 2011; 11: 1195-205.
34. Dao HH, Do QT, Sakamoto J. Increased frequency of metabolic syndrome among Vietnamese women with early rheumatoid arthritis: a cross-sectional study. Arthritis Res Ther. 2010; 12(6): 218.
35. Ristić GG, Subota V, Stanisavljević D. et al. Impact of disease activity on impaired glucose metabolism in patients with rheumatoid arthritis. Arthritis Res Ther. 2021; 95.
36. da Cunha VR, Brenol CV, Brenol JC, et al. Metabolic syndrome prevalence is increased in rheumatoid arthritis patients and is associated with disease activity. Scand J Rheumatol. 2012; 41(3): 186-91.
37. Baghdadi LR. Effect of methotrexate use on the development of type 2 diabetes in rheumatoid arthritis patients: A systematic review and meta-analysis. PLoS One. 2020; 15(7): 1-22.