KEMAS 19 (4) (2024) 596-603

Jurnal Kesehatan Masyarakat

http://journal.unnes.ac.id/nju/index.php/kemas

Rheumatoid Factor, C-Reactive Protein, Erythrocyte Sedimentation Rate Responses on Brisk Walking in Rheumatoid Arthritis Women

Mohammad Arif Ali[1]✉, Dewi Marfu'ah Kurniawati[2], Leo Nacion Santillana[3], Mingming Guo[4], Muhammad Saiful Anam[1], Muhammad Faisal Majid[1], Gustiana Mega Anggita[1], and Azkia Agustina[5]
[1]Faculty of Sports Science, Universitas Negeri Semarang, Indonesia
[2]Department Of Nutrition Science, Faculty Of Medicine, Universitas Diponegoro, Semarang, Indonesia
[3]College Of Education, Mindanao State University-Iligan Institute Of Technology, Iligan, Philippines
[4]College Of Physical Education And Health, East China Normal University, Shanghai, China
[5]Faculty Of Public Health, Universitas Muhammadiyah Semarang, Indonesia,

Article Info

Article History:
Submitted November 2023
Accepted March 2024
Published April 2024

Keywords:
inflammatory parameters; exercise rehabilitation; elderly; degenerative diseases

DOI
https://doi.org/10.15294/kemas.v19i4.48847

Abstract

Modified Physical Exercise Program (MPEP) is necessary for people with rheumatoid arthritis (RA). This study aims to investigate the effects of MPEP on the Rheumatoid Factor (RF), C-Reactive Protein (CRP), and Erythrocyte Sedimentation Rate (ESR); to evaluate the correlation between CRP-ESR. This is a quasi-experimental study. Ten RA women who were recommended by the Dukuhseti PHC have participated. The procedure is ethically approved. The venous blood samples were used to measure the dependent variables. Eight-teen sessions of MPEP were done. A two-tailed paired t-test to elucidate the differences in pre-post data; the bivariate Pearson correlation test for CRP-ESR. The RF increased significantly (pre: 19,40±2,46 and post: 22,40±2,41). CRP increased (pre: 0,30±0,07 and post: 0,37±0,06; p< 0,05). The change in ESR is not significant. There is a strong-positive, significant correlation (r: 0,831) between CRP-ESR. We concluded that MPEP is not able to lower the RA parameters, and there is a positive feedback correlation between CRP-ESR.

Introduction

Each population has a different Rheumatoid Arthritis (RA) prevalence and incidence rate. Women are 2-3 times as likely as men to have RA. In many communities, the prevalence of RA ranges from 0.5 to 1%, which is essentially constant (Safiri *et al*., 2019). Although in Indonesia the precise prevalence of RA is unknown, it is currently predicted that at least 1.3 million Indonesians have the disease (Hidayat *et al*., 2021a). Based on Indonesian Basic Health Research data (Riskesdas), around 7.30% of the population had RA in 2018, declining from 24.7% in 2013, and 6.78% of Central Java residents had RA. As a part of non-communicable disease, several variables such as age, gender, education level, marital status, family history, source of health information, knowledge, and attitude play a role in the prevalence among the community (Prihanti *et al*., 2022).

Nearly 36% of patients reported worsening health, and they were twice as likely to have activity restrictions. Additionally, compared to people without arthritis, patients have a 30% higher likelihood of needing help with personal care (Padjen *et al*., 2020). Rheumatoid factor (RF), which is found in 70–80% of RA patients and is utilized as an RA diagnostic marker, is typically identified in serological tests to determine the presence of RA. To successfully manage the condition and stop further joint deterioration and impairment, early detection, and rapid therapy with disease-modifying anti-rheumatic drugs (DMARDs) are crucial (Padjen *et al*., 2020). To reduce the

✉ Correspondence Address:
Sekaran, Semarang, Central Java, Indonesia 50229
Email: hiarifalikhan@mail.unnes.ac.id

pISSN 1858-1196
eISSN 2355-3596

risk of adverse medication reactions, screening tests must be completed before beginning treatment with conventional synthetic DMARD (csDMARD). C-Reactive Protein (CRP) and erythrocyte sedimentation rate (ESR) are two commonly utilized inflammatory indicators that can be applied to gauge the severity of the condition and the efficacy of treatment.

The primary goal of RA treatment is to control the progression of the illness, particularly to achieve remission, which is characterized by the absence of symptoms and the presence of severe inflammatory signs. Education, medical therapy, and rehabilitation/exercise programs are the three primary aspects of RA treatment (Hidayat *et al*., 2021b). For better treatment outcomes, patients and clinicians must work together to increase adherence to the recommended treatment plan of action. Education significantly improved attitudes, pain, and disability in patients throughout a six-month study with 100 RA patients (Senara *et al*., 2019). The key to controlling the spread of disease is early detection and treatment. Successful treatment during the first six months after starting treatment of the disease can predict how the patient will respond to therapy over the following five years.

Maintaining joint flexibility and muscular strength requires regular exercise and therapy. Other advantages include lowering risk factors for heart disease and bone loss, improving bone density, delaying the development of radiological alterations in small joints, limiting depression, enhancing sleep, lowering the feeling of pain, and improving quality of life. Walking, cycling, and swimming are the suggested forms of exercise. "Start low, go slow" is a good way to begin a workout. It is advised to exercise for 30 minutes each day. The use of orthotics or splints is advised by both the American Pain Society and the American College of Rheumatology, along with aerobic and physical activity that involves flexibility and physical endurance (Verhoeven *et al*., 2016).

Exercise has a strong and beneficial effect on cognitive performance in RA patients. Furthermore, physical exercise is both safe and beneficial in the treatment of chronic inflammatory joint disease, and it is advised as an essential component of these patients' overall care (Azeez *et al*., 2020). In older individuals with stable RA, ten weeks of a high-intensity interval walking program has been linked to reduced disease activity, increased cardiovascular fitness, and enhanced innate immunological functioning, indicating a lower infection risk and inflammatory potential (Bartlett *et al*., 2018). When establishing a PA intervention for patients with RA, it is critical to remember that education from a trained instructor must support program implementation, and it will give favorable effects to effective medicine. This is a recommended strategy to enhance physical activity in people with RA. Determined from the explanation above, the current study aims to investigate the promising effects of a physical exercise program (brisk walking) on biochemical parameters such as Rheumatoid Factor, C-Reactive Protein, and Erythrocyte Sedimentation Rate in women with RA, and to evaluate the correlation between CRP and ESR in individuals with RA.

Method

This is a quasi-experimental study with a group cross-sectional design. The independent variable in this study is the brisk walking program as an exercise therapy, and the dependent variables are RA parameters including Rheumatoid Factor (IU/mL), C-Reactive Protein (mg/dL), and Erythrocyte Sedimentation Rate (mm/h). The target population in this study is all mature women aged 46-64 years in the Alasdowo village with RA and recognized by the Dukuhseti Primary Healthcare Center (PHC), Pati Regency in Central Java. Based on the data, there were found 25 prospective candidates for the subjects in this study. However, only 10 candidates were recommended by the Dukuhseti Primary Healthcare Center.

The Research Procedures have been agreed upon by the institutional health research ethics committee Universitas Negeri Semarang (Number: 323/KEPK/EC/2022). There are five stages (Figure 1) in this study as follows: 1) Preparation stage which includes research permit, focus group discussion with the staff of the Dukuhseti Primary Healthcare Center, subjects agreement (inform consent), and explanation of the research procedure, 2) Pre-

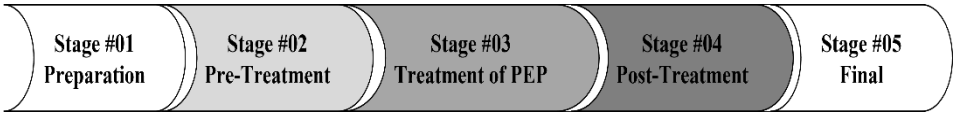

Figure 1. Stages of the current study

treatment stage is a data collection activity (venous blood sampling, 2 days before the first session of brisk walking as MPEP is given to subjects) as the baseline data for RF, CRP, and ESR, 3) Treatment stage is by giving a brisk walking treatment for a total of 18 sessions, about one and a half months, 4) Post-treatment stage is a data collection activity (venous blood sampling, 2 days after the last session of brisk walking exercise given to subjects) as the main data to evaluate the effectiveness of brisk walking program as the exercise treatment, and 5) Final stage including data tabulation, data analysis, data presentation, data interpretation, and writing a report to be published.

The total sessions of the brisk walking program are done 18 times. Subjects performed brisk walking three times a week (every two days) with light intensity (65% of their maximal heart rate). Most RA patients are active at the intensity of very light to light. Exercise at these intensities may reduce disability and disease activity in RA patients and seems to be linked with favorable cardiovascular indicators (Khoja *et al*., 2016). To determine the maximum heart rate, the formula of 220 minus the subjects' age was used. Meanwhile, determine the targeted heart rate for the exercise zone by determining the percentage multiplied by the maximum heart rate. The progressive overload principle was applied in this exercise program by improving the total duration, especially the duration of the main exercise every two weeks of the program. Hence, warming up was given to increase the heart rate, blood flow, and flexibility, and to prevent any risk of injury. On the other hand, cooling down was given as a stress relief, body restoration, regulating the heart rate, reducing the accumulation of blood lactate, and preventing any risk of injury. To check the details about the brisk walking program please see Table 1. Brisk walking was done outside in the public sports facility of Alasdowo Village, Dukuhseti District, Pati Regency, Central Java, Indonesia.

Venous blood drawing was conducted two times at the pre-treatment stage (two days before the first brisk walking program) and the post-treatment stage (two days after the last brisk walking program). Further, the venous blood sample was used to measure the rheumatoid factor (IU/mL), c-reactive protein (mg/dL), and erythrocyte sedimentation rate (mm/h). The procedure for measuring RF, CRP, and ESR refers to the standard operational measurements from the health laboratory of Dukuhseti Primary Healthcare.

The normality and homogeneity tests were carried out as a prerequisite. To determine the effects of brisk walking on changes in rheumatoid parameters such as RF, CRP, and ESR, a paired t-test with two-tailed was used to evaluate the differences in means on endpoints, and the bivariate Pearson correlation test was carried out to estimate the correlation between CRP and ESR. The statistical level of $p< 0,05$ was

Table 1. The Physical Exercise Program (Brisk Walking)

Week (s)	Exercise Structure	Duration (minutes)	Targeted Heart Rate (bpm)	Maximum Heart Rate (bpm)
01st-02nd	Warming up	3'	N.S.	156-174
	Main Exercise	20'	102-113	156-174
	Cooling down	3'	N.S.	156-174
03rd-04th	Warming up	3'	N.S.	156-174
	Main Exercise	25'	102-113	156-174
	Cooling down	3'	N.S.	156-174
05th-06th	Warming up	3'	N.S.	156-174
	Main Exercise	30'	102-113	156-174
	Cooling down	3'	N.S.	156-174

used. Data is presented as the standard error of the mean (SEM). Meanwhile, the presentation in ratio and percentage shows the response of each subject. All data analyses were carried out using IBM SPSS Statistics 26.

Results and Discussion

A total of 25 females with RA were identified in Alasdowo Village, Dukuhseti District, Pati Regency. However, there are only 10 eligible females (aged 46-64 years) who were recommended by the Dukuhseti Primary Healthcare Center. Physical Exercise Program (Brisk Walking) on RA Parameters. The RF (IU/mL) in women with RA increased significantly by Δ 3,00 post-treatment (brisk walking) 22,40±2,41 compared to pre-treatment data 19,40±2,46 as p< 0,05 (Figure 2. A), and the details of individual data are in Figure 2. B showed that 8/10 (80%) of subjects experienced an increase in the RF. The same response also occurred in CRP (mg/dL), it is increased significantly by Δ 0,07 post-treatment 0,37±0,06 compared to pre-treatment 0,30±0,07 (Figure 2. C), and to see the details of everyone's response is in figure 2. D, there are 9/10 (90%) subjects who experienced increased CRP. However, there is no significant change in ESR (mm/h) pre-treatment 31,70±14,43 compared to post-treatment 39,00±11,86 as p> 0,05 (Table 2), and see the detail of individual data in Table 3. There are 6/10 (60%) subjects who showed increased ESR value.

Table 2. Effect of Brisk Walking on ESR (Mean Data)

Variable (s)	Mean±SD	N	Sig. (2-tailed)
ESR Pre-Brisk Walking	31,70±14,43	10	N.S.
ESR Post-Brisk Walking	39,00±11,86	10	
N.S. No Significant as P > 0,05			

Table 3. Effect of Brisk Walking on ESR (Individual Data)

Subject (s)	ESR Pre-Brisk Walking	ESR Post-Brisk Walking
1	35,00	35,00
2	10,00	15,00
3	33,00	33,00
4	18,00	38,00
5	34,00	34,00
6	12,00	42,00
7	48,00	58,00
8	37,00	47,00
9	54,00	52,00
10	36,00	36,00

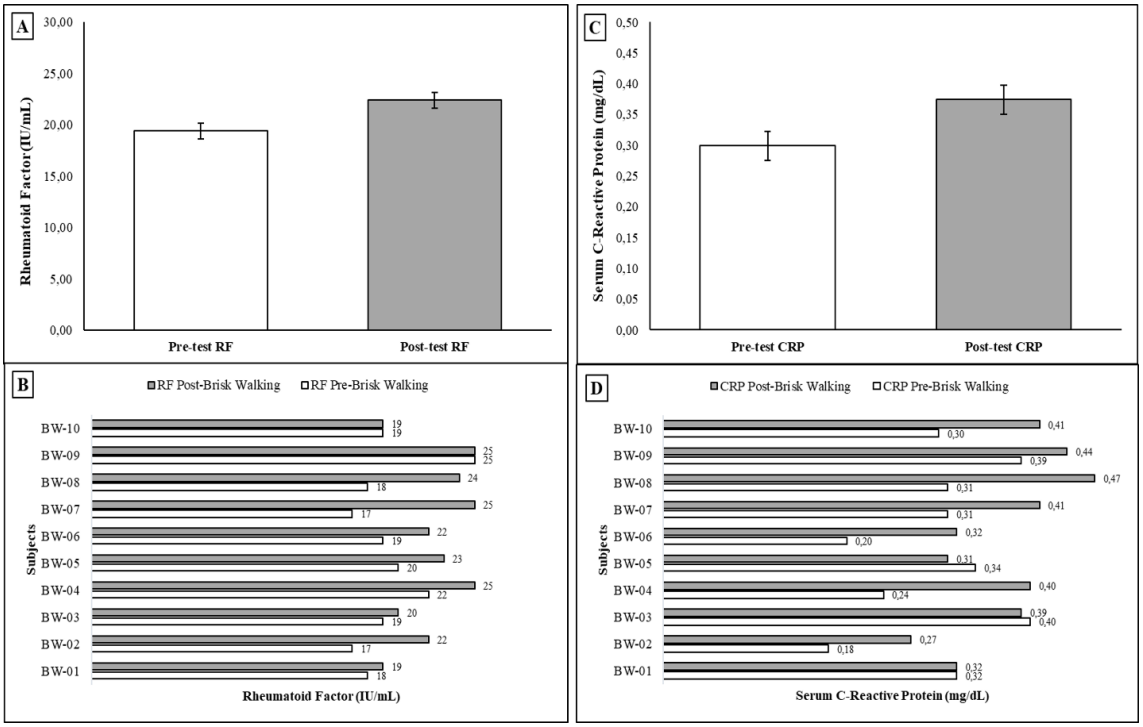

Figure 2. A: Effect of Brisk Walking on RF (Mean Data), B: Effect of Brisk Walking on RF (Individual Data), C: Effect of Brisk Walking on CRP (Mean Data), D: Effect of Brisk Walking on CRP (Individual Data)

Data in Table 4 showed that there is a strong, significant, and positive linear correlation between C-Reactive Protein and Erythrocyte Sedimentation Rate as P < 0,05 and r 0,831. Previous studies also showed that there is a positive linear correlation between these two variables. It is regardless of the age, sex, or duration of RA (Kotulska *et al*., 2015; Lapić *et al*., 2020).

Table 4. The Correlation between CRP and ESR

		CRP	ESR
CRP	Pearson Correlation	1	0,831**
	Sig. (1-tailed)		0,001
	N	10	10
ESR	Pearson Correlation	0,831**	1
	Sig. (1-tailed)	0,001	
	N	10	10

**. Correlation is significant at the 0,01 level (1-tailed)

In this study, we found that a brisk walking program could increase significantly in RF and CRP, but not for ESR. A positive rheumatoid factor (IU/mL), high C-reactive protein (mg/dL), and/or erythrocyte sedimentation rate (mm/h) tests all support RA diagnosis. Most patients with RA have abnormal RF, CRP, and ESR ≥28 (mm/h). This study also confirmed that there is a strong, significant, and positive linear correlation between CRP and ESR. According to a study done by Kotulska, there is a significant correlation between ESR and CRP, and there is no difference in either male or female individuals, or those older than 40 years old (Kotulska *et al*., 2015). The most often used laboratory tests to identify the acute phase response (the bodies quickly strive to reinstate homeostasis post tissue damage, infection, growth of neoplastic, or immunological disruption) and hence diagnosing and observing inflammatory diseases are the ESR and CRP (Bray *et al*., 2016). Furthermore, ESR and CRP have comparable symptomatic accuracy in assessing inflammation, particularly in orthopedic diseases (Lapić *et al*., 2020). ESR's inflammatory response is sluggish and insensitive to mild inflammation. The first spike happens within one to two days of start and is followed by a gradual decline when the inflammation resolves (Markanday, 2015).

The ESR is a simple and popular hematological test that can determine and track the increment of inflammatory activity within the body due to one or more illnesses such as autoimmune disease, infections, or malignancies. It is carried out alongside other tests to detect the existence of elevated inflammatory activity. In RA, the ESR value independently could be used to determine significant increases in symptoms in rheumatic disease, and the elevated rate of ESR in RA patients becomes a signal to have a higher risk (twice) of heart failure compared to individuals without RA (Hashemi *et al*., 2015).

An increase of CRP in the blood concentration has been well acknowledged as a marker of systemic inflammation in RA. Unfortunately, the high level of CRP in RA populations seems to play a primary role in bone destruction, and disease progression such as increased atherogenic consequences, and it is also linked with the danger for other degenerative diseases such as metabolic syndrome, diabetes, cardiovascular disease, pulmonary diseases, and mental disorder such as depression. CRP was found higher in obese patients with positive rheumatic disease compared to patients with low BMI values, and CRP levels in RA were affected by different socio-economic factors (Dessie *et al*., 2021). These factors perhaps become the reason which is related to affordable healthy food both the quantity and the quality of afforded food. Furthermore, the case of high CRP levels found that it is independently related to adiposity in women with RA. CRP and ESR rates are affected by age and sex as non-inflammatory variables in early RA, but BMI seems to become more applicable for the disease's later stages (Siemons *et al*., 2014).

RF is an immune-system protein that can abuse robust tissue in your body. RF degree in the circulatory system is commonly linked with autoimmune disorders such as rheumatic diseases, bacterial infections, lung disease, and other diseases such as aging, malignancy, and periodontal disease. Without immunogenic stimulations, RF is not frequently detected in the blood. They are thought to be a typical response to a range of antigenic stimuli, like bacterial toxins like lipopolysaccharides or

viruses like Epstein-Barr virus (EBV). They produce immunological complexes, which are then phagocytosed by inflammatory cells. The germinal center produces low-affinity, transitory, and polyclonal antibodies. In this regard, their role may be termed protective. The RF in RA, on the other hand, is thought to be produced from germline gene rearrangements and somatic hypermutations. They are monoclonal, show affinity maturation (the formation of antibodies with enhanced avidity to antigens during the process of an immune response), and cause more severe illness at higher titers (Ingegnoli *et al*., 2013).

In the etiology of RA, physical exercise can be a preservative factor. However, the positive benefits and the better improvement in health status can only be seen by the chronic effects of regular physical activity. In general, aerobic exercise is good and safe for RA patients, and it has a certain relieving impact on the condition, such as functional ability improvement, pain alleviation, and increased aerobic capacity (Ye *et al*., 2022). Moreover, people with RA who completed the SARAH exercise program >2 years after randomization, exhibited better hand function compared to baseline data. The opposite was true for the control group. However, the outcomes were no longer statistically different across the groups, which means that the PEP SARAH influence had waned with time. This decrease in hand function relative to earlier follow-up periods correlated with a decrease in self-reported hand exercise performance (Williamson *et al*., 2017).

The acute effect of PEP seems unfavorable. There are no significant differences in the pain sensation, CRP and ESR rate (clinical inflammatory markers), and interleukin 6 and tumor necrosis factor-alpha (inflammatory cytokines) between RA patients and healthy individuals (Balchin *et al*., 2022; Di Giuseppe *et al*., 2015). Moreover, both in patients with RA and healthy subjects, a single session of PEP can effectively lower the serum brain-derived neurotrophic factor levels (it plays a crucial role in the survival of neurons and growth, acts as a neurotransmitter modulator, and participates in neuronal plasticity, which is essential for learning and memory) (Bağlan Yentur *et al*., 2023).

The physical exercise program is a part of three pillars of RA treatment, and to maximize the benefits of a physical exercise program for RA patients, it is necessary to differentiate exercise methods according to the symptoms of RA, and individual needs (Hu *et al*., 2021; Marni & Husna, 2023). Maintenance of a physical exercise program over a lengthy period is difficult for people with developed RA. An excellent quality of life has a positive impact on physical exercise maintenance, but disease-related and unhealthy lifestyle characteristics have a negative impact. Physical exercise programs are multidimensional treatments with several characteristics and behaviors. Hence, any exercise is better than no exercise. When supporting physical exercise maintenance, health providers should include the patient's perspective, preferably through integrated lifestyle treatments (Bremander *et al*., 2020).

Conclusion

The increment of rheumatoid factor, c-reactive protein, and erythrocyte sedimentation rate after eighteen sessions of the brisk walking program with light intensity leads to a conclusion that brisk walking is not able to lower the RA parameters in women with RA. Additionally, there is a strong, significant, and positive linear correlation between c-reactive protein and erythrocyte sedimentation rate. This recent study only focuses on biochemical parameters. However, future studies would be much better the consideration to do assessments of food intake, physical activity, functional movements, drug consumption, socio-economic factors, different sexes, the age categories, as well as qualitative data, and perhaps with different promising exercise programs.

References

Azeez, M., Clancy, C., O'Dwyer, T., Lahiff, C., Wilson, F., & Cunnane, G., 2020. Benefits of Exercise in Patients with Rheumatoid Arthritis: A Randomized Controlled Trial of a Patient-Specific Exercise Programme. *Clinical Rheumatology*, 39(6), pp.1783–1792.

Bağlan Yentur, S., Ercan, Z., Deniz, G., Karataş, A., Gür, M., Alkan, G., & Serdar Koca, S.,

2023. Effects of Acute Aerobic Exercise on Brain-Derived Neurotrophic Factor Level in Rheumatoid Arthritis Patients. *Archives of Rheumatology*, 38(x), pp.i–viii.

Balchin, C., Tan, A.L., Golding, J., Bissell, L.-A., Wilson, O.J., McKenna, J., & Stavropoulos-Kalinoglou, A., 2022. Acute Effects of Exercise on Pain Symptoms, Clinical Inflammatory Markers and Inflammatory Cytokines in People with Rheumatoid Arthritis: A Systematic Literature Review. *Therapeutic Advances in Musculoskeletal Disease*, 14, pp.1759720X221114104.

Bartlett, D.B., Willis, L.H., Slentz, C.A., Hoselton, A., Kelly, L., Huebner, J.L., Kraus, V.B., Moss, J., Muehlbauer, M.J., Spielmann, G., Kraus, W.E., Lord, J.M., & Huffman, K.M., 2018. Ten Weeks of High-Intensity Interval Walk Training is Associated with Reduced Disease Activity and Improved Innate Immune Function in Older Adults with Rheumatoid Arthritis: A Pilot Study. *Arthritis Research & Therapy*, 20(1), pp.127.

Bray, C., Bell, L.N., Liang, H., Haykal, R., Kaiksow, F., Mazza, J.J., & Yale, S.H., 2016. Erythrocyte Sedimentation Rate and C-reactive Protein Measurements and Their Relevance in Clinical Medicine. *WMJ: Official Publication of the State Medical Society of Wisconsin*, 115(6), pp.317–321.

Bremander, A., Malm, K., & Andersson, M.L., 2020. Physical Activity in Established Rheumatoid Arthritis and Variables Associated with Maintenance of Physical Activity Over a Seven-Year Period – A Longitudinal Observational Study. *BMC Rheumatology*, 4(1), pp.53.

Dessie, G., Tadesse, Y., Demelash, B., Genet, S., Malik, T., & Dejenie, T.A., 2021. Evaluation of C-Reactive Protein and Associated Factors Among Patients Suffering from Rheumatoid Arthritis at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. *Open Access Rheumatology: Research and Reviews*, 13, pp.247–255.

Di Giuseppe, D., Bottai, M., Askling, J., & Wolk, A., 2015. Physical Activity and Risk of Rheumatoid Arthritis in Women: A Population-Based Prospective Study. *Arthritis Research and Therapy*, 17(1).

Hashemi, R., Majidi, A., Motamed, H., Amini, A., Najari, F., & Tabatabaey, A., 2015. Erythrocyte Sedimentation Rate Measurement Using as a Rapid Alternative to the Westergren Method. *Emergency*, 3(2), pp.50–53.

Hidayat, R., Bagus, P.P.S., Linda, K.W., Anna, A., Rakhma, Y.H., Endy, A., & Sumariyono., 2021a. Indonesian Rheumatology Association (IRA) Recommendations for Diagnosis and Management of Rheumatoid Arthritis. *Indonesian Journal of Rheumatology*, 13(1), pp.322–443.

Hidayat, R., Bagus, P.P.S., Linda, K.W., Anna, A., Rakhma, Y.H., Endy, A., & Sumariyono., 2021b. Indonesian Rheumatology Association (IRA) Recommendations for Diagnosis and Management of Rheumatoid Arthritis. *Indonesian Journal of Rheumatology*, 13(1), pp.322–443.

Hu, H., Xu, A., Gao, C., Wang, Z., & Wu, X., 2021. The Effect of Physical Exercise on Rheumatoid Arthritis: An Overview of Systematic Reviews and Meta-Analysis. *Journal of Advanced Nursing*, 77(2), pp.506–522.

Ingegnoli, F., Castelli, R., & Gualtierotti, R., 2013. Rheumatoid Factors: Clinical Applications. *Disease Markers*, 2013, pp.727–734.

Khoja, S.S., Almeida, G.J., Wasko, M.C., Terhorst, L., & Piva, S.R., 2016. Association of Light-Intensity Physical Activity with Lower Cardiovascular Disease Risk Burden in Rheumatoid Arthritis. *Arthritis Care & Research*, 68(4), pp.424–431.

Kotulska, A., Kopeć-Mędrek, M., Grosicka, A., Kubicka, M., & Kucharz, E.J., 2015. Correlation between Erythrocyte Sedimentation Rate and C-Reactive Protein Level in Patients with Rheumatic Diseases. *Reumatologia*, 53(5), pp.243–246.

Lapić, I., Padoan, A., Bozzato, D., & Plebani, M., 2020. Erythrocyte Sedimentation Rate and C-Reactive Protein in Acute Inflammation: Meta-Analysis of Diagnostic Accuracy Studies. *American Journal of Clinical Pathology*, 153(1), pp.14–29.

Markanday, A., 2015. Acute Phase Reactants in Infections: Evidence-Based Review and a Guide for Clinicians. *Open Forum Infectious Diseases*, 2(3), pp.ofv098.

Marni., & Husna, P.H., 2023. Physical Domain of Quality of Life in Premenopause and Post Menopause Women in Central of Java. *Kemas*, 19(2), pp.319–332.

Padjen, I., Crnogaj, M.R., & Anić, B., 2020. Conventional Disease-Modifying Agents in Rheumatoid Arthritis - A Review of Their Current Use and Role in Treatment Algorithms. *Reumatologia*, 58(6), pp.390–400.

Prihanti, G.S., Wilyani, D., Isnaini, F., Ailani, A.F., Humaira, A.A., Kurniawan, I.K., Rahayu, K.P., Hadiyanti, L.A., & Santoso, S.R., 2022.

Community Awareness for Screening Non-Communicable Diseases. Kemas, 18(2), pp.181–192.

Safiri, S., Kolahi, A.A., Hoy, D., Smith, E., Bettampadi, D., Mansournia, M.A., Almasi-Hashiani, A., Ashrafi-Asgarabad, A., Moradi-Lakeh, M., Qorbani, M., Collins, G., Woolf, A.D., March, L., & Cross, M., 2019. Global, Regional and National Burden of Rheumatoid Arthritis 19902017: A Systematic Analysis of the Global Burden of Disease Study 2017. *Annals of the Rheumatic Diseases*, 78(11), pp.1463–1471.

Senara, S.H., Abdel Wahed, W.Y., & Mabrouk, S.E., 2019. Importance of Patient Education in Management of Patients with Rheumatoid Arthritis: An Intervention Study. *Egyptian Rheumatology and Rehabilitation*, 46(1), pp.42–47.

Siemons, L., Ten Klooster, P.M., Vonkeman, H.E., Van Riel, P.L.C.M., Glas, C.A.W., & Van de Laar, M.A.F.J., 2014. How Age and Sex Affect the Erythrocyte Sedimentation Rate and C-Reactive Protein in Early Rheumatoid Arthritis. *BMC Musculoskeletal Disorders*, 15(1), pp.368.

Verhoeven, F., Tordi, N., Prati, C., Demougeot, C., Mougin, F., & Wendling, D., 2016. Physical Activity in Patients with Rheumatoid Arthritis. *Joint Bone Spine*, 83(3), pp.265–270.

Williamson, E., McConkey, C., Heine, P., Dosanjh, S., Williams, M., & Lamb, S.E., 2017. Hand Exercises for Patients with Rheumatoid Arthritis: An Extended Follow-Up of the SARAH Randomised Controlled Trial. *BMJ Open*, 7(4), pp.e013121.

Ye, H., Weng, H., Xu, Y., Wang, L., Wang, Q., & Xu, G., 2022. Effectiveness and Safety of Aerobic Exercise for Rheumatoid Arthritis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *BMC Sports Science, Medicine and Rehabilitation*, 14(1), pp.17.