Review

From joint to heart: Cardiovascular implications of rheumatoid arthritis

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ABSTRACT

Rheumatoid arthritis is a commonly encountered autoimmune disease and a progressive chronic inflammatory condition that often leads to permanent joint damage. Systemic inflammation in rheumatoid arthritis is linked to various comorbid conditions such as interstitial lung disease, osteoporosis, metabolic syndrome, cardiovascular disease, infections, malignancies, cognitive dysfunction, depression, and fatigue, which can increase morbidity and mortality in rheumatoid arthritis patients. Approximately 36% of patients report worse health and limitations in daily activities, while nearly 30% require more assistance with personal care compared to individuals without rheumatoid arthritis. Epidemiological data from 1990 to 2017 show an incidence of rheumatoid arthritis of 246.6 per 100,000 people aged 33-54 years, with prevalence in women 2-3 times higher. In Southeast Asia, the incidence is 89 per 100,000 in individuals aged 13-22 years, while in Indonesia, it is estimated at around 5-7.5 per 100,000 population. Cardiovascular disease is the primary cause of mortality in rheumatoid arthritis patients, with myocardial infarction being the major contributor. The pathogenesis of rheumatoid arthritis is still complex and involves immunological processes that occur long before joint inflammation symptoms appear, including genetic modifications and environmental factors that lead to deimination and joint disturbances. Cardiovascular manifestations, particularly myocardial infarction, occur due to an atherosclerotic process triggered by rheumatoid antibody complexes. Given the higher cardiovascular risk in rheumatoid arthritis patients, early detection and awareness of these manifestations are crucial for better management.

KEYWORDS: rheumatoid arthritis; cardiovascular disease; pathogenesis; clinical manifestation; complication.

INTRODUCTION

Rheumatoid arthritis is a prevalent autoimmune disorder and a chronic inflammatory disease that progresses over time, frequently resulting in irreversible joint damage. Systemic inflammation in rheumatoid arthritis is associated with a range of comorbidities, including interstitial lung disease, osteoporosis, metabolic syndrome, cardiovascular disease, infections, malignancies, cognitive impairment, depression, and fatigue. These conditions can contribute to increased morbidity and mortality in patients with rheumatoid arthritis.[1] Approximately 36% of patients report worse health conditions and experience limitations in daily activities, with nearly 30% of patients requiring more assistance with personal care compared to individuals without rheumatoid arthritis.[2]

Global epidemiological data from 1990 to 2017 show that the incidence of rheumatoid arthritis is an average of 246.6 per 100,000 people, with the age range of 33 to 54 years.

In women, the prevalence is 2-3 times higher.[3] Epidemiological data in Southeast Asia indicate an incidence of rheumatoid arthritis of an average of 89 per 100,000 in individuals aged 13 to 22 years.[4] In Indonesia, the estimated incidence is around 5-7.5 per 100,000 population.[5] Cardiovascular disease is the primary cause of mortality in rheumatoid arthritis patients. Patients with rheumatoid arthritis face a higher risk, compared to the general population, approximately twice as high, with around 50% of mortality attributed to myocardial infarction.[6]

The pathogenesis of rheumatoid arthritis is not yet fully understood, but some experts have reported that one of the key factors is the immunological process that occurs over years before joint inflammation symptoms appear, referred to as the pre-rheumatoid arthritis phase. Genetic interactions and modifications occur, with environmental factors playing a role in these modifications, leading to deimination and joint disturbances.[7] There are also many other mechanisms believed to contribute to the pathogenesis of rheumatoid arthritis. The pathogenesis of cardiovascular manifestations, particularly related to myocardial infarction, occurs through an atherosclerotic process caused by the deposition of rheumatoid arthritis antibody-antigen complexes.[8] Given the higher risk of cardiovascular disease in rheumatoid arthritis patients, it is important to discuss this to raise awareness and early vigilance regarding the initial symptoms of these manifestations.

The spectrum of extra-articular manifestations in rheumatoid arthritis patients

Rheumatoid arthritis is a widespread autoimmune condition characterized by chronic inflammation and progressive joint damage, often leading to permanent structural impairment. Systemic inflammation in rheumatoid arthritis is connected to multiple comorbidities, such as interstitial lung disease, osteoporosis, metabolic syndrome, cardiovascular disorders, infections, malignancies, cognitive decline, depression, and fatigue. These associated conditions can significantly elevate morbidity and mortality rates among rheumatoid arthritis patients.[1] Approximately 36% of patients report worse health conditions and experience limitations in daily activities, with nearly 30% of patients requiring more assistance with personal care compared to individuals without rheumatoid arthritis.[2]

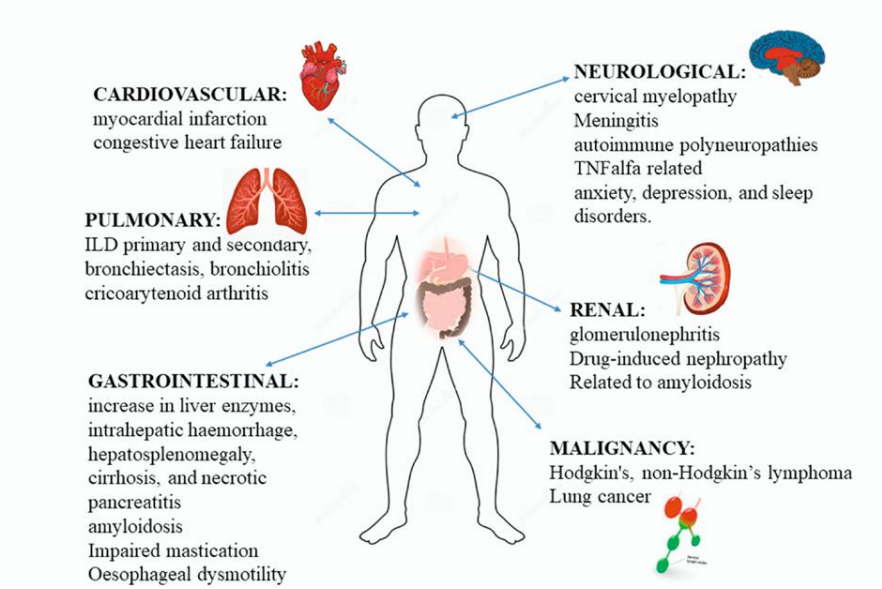

Figure 1. Extra-articular manifestations in rheumatoid arthritis, consisting of cardiovascular involvement as the most common contributor to patient mortality, followed by respiratory system, nervous system, digestive system, renal involvement, and malignancies.

The highest prevalence of rheumatoid arthritis cases occurs in women, approximately 2 to 3 times more than in men. The peak age for diagnosis is around 60 years, and rheumatoid arthritis is the most prevalent condition encountered among chronic inflammatory diseases.[9] Clinically, rheumatoid arthritis varies greatly depending on the phase of the disease, which is divided into the early phase or advanced phase with inadequate therapy. The early phase is characterized by nonspecific symptoms such as flu-like feelings, fatigue, morning stiffness, joint swelling and pain, elevated erythrocyte sedimentation rate (ESR), and increased C-reactive protein. In the advanced phase, with inadequate therapy, complex clinical manifestations occur, including pleural effusion, pulmonary nodules, interstitial lung disease, lymphoma, atherosclerosis, keratoconjunctivitis, vasculitis in small and medium-sized arteries, and hematological abnormalities (thrombocytopenia, eosinophilia, neutropenia, leukopenia, anemia, and rheumatoid nodules).[10]

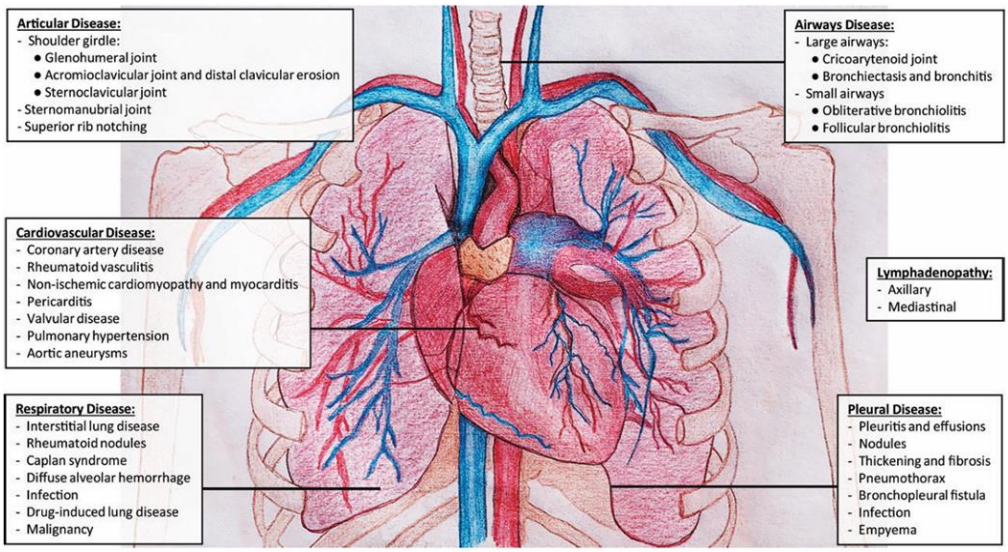

Figure 2. Thoracic manifestations in rheumatoid arthritis patients, including articular disease, cardiovascular disease, respiratory system involvement, lymphadenopathy, and pleural disease.

Extra-articular manifestations in rheumatoid arthritis patients can increase both mortality and morbidity, including rheumatoid nodules, vasculitis, cardiovascular issues, respiratory system, nervous system, digestive system, kidneys, and other hematological diseases, as shown in Figure 1.[8] All patients should generally be screened for risk factors related to extra-articular manifestations to prevent severe complications.[11] In addition to myocardial infarction and congestive heart failure, there are other cardiovascular manifestations specific to rheumatoid arthritis that are part of thoracic manifestations, including coronary artery disease, rheumatoid vasculitis, non-ischemic cardiomyopathy, myocarditis, valve disease, pulmonary hypertension, and aortic aneurysm, as shown in Figure 2.[12] However, to identify these manifestations, clinicians require supporting radiological examinations. In a study of cardiovascular manifestations in rheumatoid arthritis patients with 188 participants, the most common findings were ECG abnormalities (ST segment, QRS complex, PR interval, P and T waves) in approximately 102 patients, pericarditis in 92 patients, valve disorders in 92 patients, cardiomyopathy in 61 patients, mitral regurgitation in 51 patients, aortic regurgitation in 38 patients, and aortic stenosis in 3 patients.[13]

Inflammatory pathways leading to cardiovascular disease in rheumatoid arthritis

The main pathogenesis of rheumatoid arthritis is a complex immunological process. One of the mechanisms is the stimulation of B cells, which also participate in the progression of rheumatoid arthritis by forming immune complexes and complement

activation.[14] There are two autoantibodies in rheumatoid arthritis: anti-citrullinated protein antibodies (ACPAs) and Rheumatoid Factor (RF). When these two autoantibodies are found in a patient, the condition is referred to as seropositive rheumatoid arthritis, which can worsen the disease, including symptoms, joint damage, and increased mortality.[15] However, positive RF is also found in other diseases such as infections, malignancies, and other rheumatic diseases, and can also be found in healthy individuals.[16] ACPA autoantibodies can be detected in the bloodstream of rheumatoid arthritis patients up to 10 years before they show symptoms, making ACPA a useful diagnostic modality in the early phase of the disease.[17] The pathogenesis begins with inflammation induced by autoreactive T cells, such as Th1 or Th17, in the lymph nodes. These autoreactive T cells then activate macrophages and fibroblasts, leading to the production of inflammatory mediators such as Receptor Activator of Nuclear Factor Kappa-B Ligand (RANK-L), interferon (IFN) gamma, interleukin – 17 (IL-17), and Tumor Necrosis Factor (TNF) alpha. Activation of macrophages leads to the release of pro-inflammatory cytokines TNF alpha, IL-1, and IL-6 in the synovium. Autoreactive B cells form ACPA and RF. RANKL then activates fibroblasts, leading to the formation of Matrix Metalloprotease (MMP), osteoclasts, and antibodies, which results in joint damage and bone erosion.[18] This process is illustrated in Figure 3.

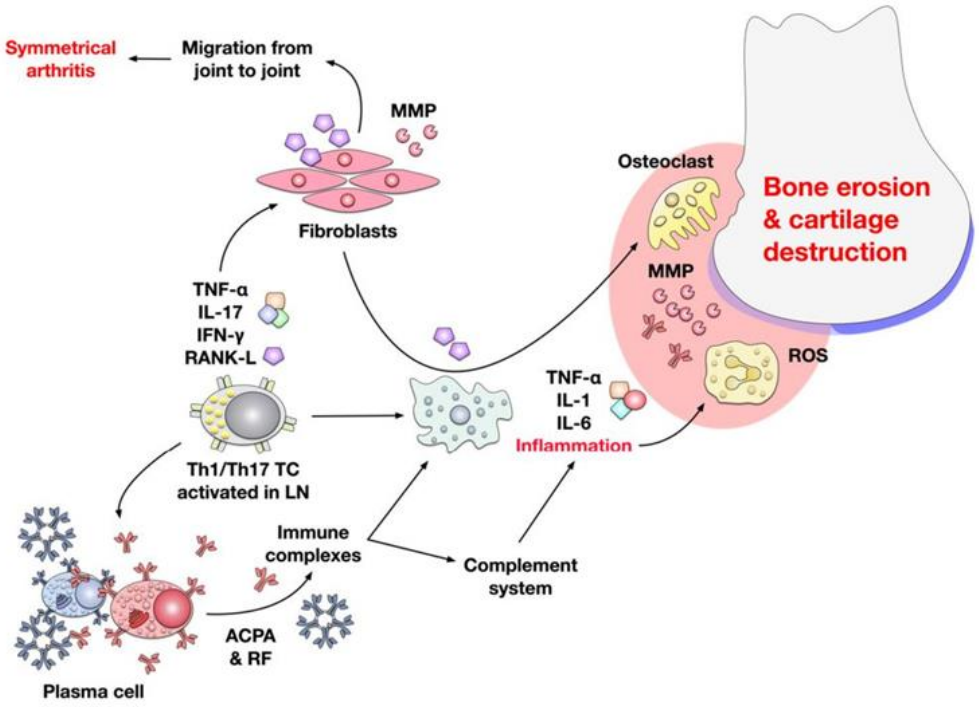

Figure 3. Pathogenesis of rheumatoid arthritis. Bone erosion and cartilage damage occur through various processes: (1) contribution of dendritic cells and inflammation in rheumatoid arthritis, (2) roles of T cells, B cells, macrophages, and fibroblasts in rheumatoid arthritis inflammation, (3) contribution of cytokines to rheumatoid arthritis inflammation, (4) role of B cells and autoantibodies in rheumatoid arthritis, and (5) neovascularization in rheumatoid arthritis.

The pathogenesis of cardiovascular manifestations in rheumatoid arthritis is caused by the formation of atherosclerosis. This occurs through the antigen-antibody complex process in the blood vessels, leading to thrombus formation. The endothelium plays a key role in controlling vascular tone and maintaining homeostasis between the vessel wall and blood cells. Nitric Oxide (NO) plays a crucial role in producing vasoactive substances, which leads to inflammation, endothelial dysfunction, and the formation of atherosclerosis.[19] Endothelial cell activation is mediated by NO, which increases

vascular permeability. Low-Density Lipoprotein Cholesterol (LDL-C) and immune cells such as T lymphocytes and monocytes enter the subendothelial and intimal layers. Here, monocytes transform into macrophages and engulf oxidized LDL-C, turning into foam cells. Macrophages also secrete pro-inflammatory cytokines such as IL-6 and TNF-alpha in the intimal layer. Inflammatory cytokines such as IL-6, TNF-alpha, IL-17, and IL-1 beta contribute to increasing the risk of atherosclerotic plaque rupture because these cytokines enhance the coagulation cascade in the blood vessels.[20] This process is illustrated in Figure 4.

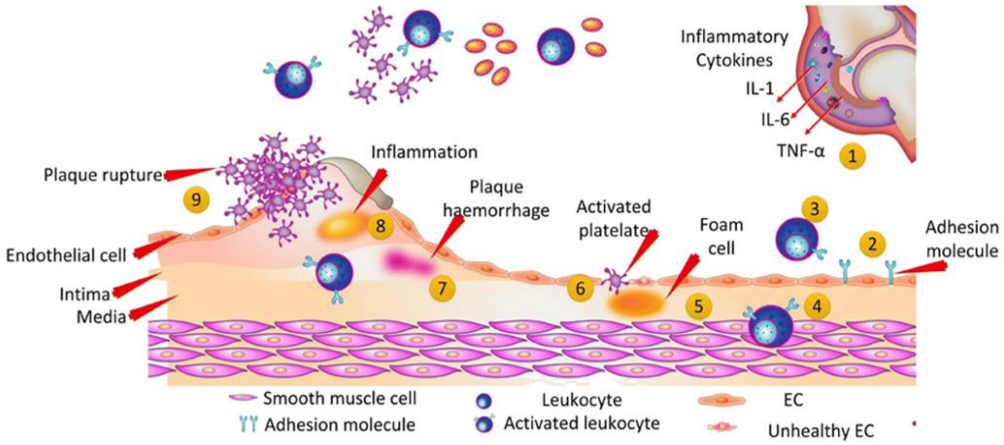

Figure 4. Mechanism of atherosclerosis in rheumatoid arthritis. (1) Begins with pro-inflammatory cytokines IL-1, IL-6, and TNF-alpha, which increase the risk of plaque rupture in atherosclerosis. (2-4) Leukocytes and monocytes adhere to adhesive molecules on the blood vessel surface. (5-6) Foam cells form and activate platelets. (7-8-9) Hemorrhage occurs in the intimal layer, with inflammation further exacerbated by pro-inflammatory cytokines, contributing to an increased risk of atherosclerotic plaque rupture.

CONCLUSION

Rheumatoid arthritis is a prevalent autoimmune disorder and is a progressive chronic inflammatory disease that often causes permanent joint damage. Cardiovascular manifestations include myocardial infarction, rheumatoid vasculitis, non-ischemic cardiomyopathy, congestive heart failure, myocarditis, valve disease, pulmonary hypertension, coronary artery disease, and aortic aneurysm. These manifestations are often discovered accidentally through radiological tests, without specific complaints or physical examinations that are clinically consistent with the patient's condition. The pathogenesis of cardiovascular manifestations is caused by atherosclerosis through the antigen-antibody complex process in the blood vessels. Inflammatory cytokines such as IL-6, TNF-alpha, IL-17, and IL-1 beta contribute to increasing the risk of atherosclerotic plaque rupture because these cytokines enhance the coagulation cascade in the blood vessels.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

None.

CONFLICTS OF INTEREST

We have no conflict of interest

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AUTHOR CONTRIBUTION

Conceptualization: FMR; Data Curation: FMR; Formal Analysis: FMR; Investigation: FMR; Project Administration: FMR; Resources: FMR; Methodology: FMR; Software: FMR; Visualization: FMR; Supervision: SA; Validation: SA; Writing – Original Draft Preparation: FMR; Writing – Review & Editing: SA. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

REFERENCES

1. Wu D, Luo Y, Li T, et al. Systemic complications of rheumatoid arthritis: Focus on pathogenesis and treatment. Front Immunol 2022;13(1):1051082.doi: 10.3389/fimmu.2022.1051082. PMID: 36618407
2. Tanski W, Wojciga J, Jankowska-Polanska B. Association between malnutrition and quality of life in elderly patients with rheumatoid arthritis. Nutrients 2021;13(4):1259.doi: 10.3390/nu13041259. PMID: 33921207
3. Safiri S, Kolahi AA, Hoy D, et al. Global, regional and national burden of rheumatoid arthritis 1990-2017: a systematic analysis of the Global Burden of Disease study 2017. Ann Rheum Dis 2019;78(11):1463-1471.doi: 10.1136/annrheumdis-2019-215920. PMID: 31511227
4. Zou W, Fang Y, Xu D, et al. Increasing global burden of rheumatoid arthritis: an epidemiological analysis from 1990 to 2019. Arch Med Sci 2023;19(4):1037-1048.doi: 10.5114/aoms/162629. PMID: 37560723
5. Darmawan J, Muirden KD, Valkenburg HA, et al. The epidemiology of rheumatoid arthritis in Indonesia. Br J Rheumatol 1993;32(7):537-540.doi: 10.1093/rheumatology/32.7.537. PMID: 8339121
6. Gabriel SE. Cardiovascular morbidity and mortality in rheumatoid arthritis. Am J Med 2008;121(10):S9-14.doi: 10.1016/j.amjmed.2008.06.011. PMID: 18926169
7. Jahid M, Khan KU, Rehan Ul H, et al. Overview of rheumatoid arthritis and scientific understanding of the disease. Mediterr J Rheumatol 2023;34(3):284-291.doi: 10.31138/mjr.20230801.oo. PMID: 37941854
8. Mitrovic J, Hrkac S, Tecer J, et al. Pathogenesis of extraarticular manifestations in rheumatoid arthritis-a comprehensive review. Biomedicines 2023;11(5):1262.doi: 10.3390/biomedicines11051262. PMID: 37238933
9. Collaborators GBDRA. Global, regional, and national burden of rheumatoid arthritis, 1990-2020, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. Lancet Rheumatol 2023;5(10):e594-e610.doi: 10.1016/S2665-9913(23)00211-4. PMID: 37795020
10. Lin YJ, Anzaghe M, Schulke S. Update on the pathomechanism, diagnosis, and treatment options for rheumatoid arthritis. Cells 2020;9(4):880.doi: 10.3390/cells9040880. PMID: 32260219
11. Chen X, Zhang M, Wang T, et al. Influence factors of extra-articular manifestations in rheumatoid arthritis. Open Med (Wars) 2020;15(1):787-795.doi: 10.1515/med-2020-0217. PMID: 33313414
12. Voskuyl AE. The heart and cardiovascular manifestations in rheumatoid arthritis. Rheumatology (Oxford) 2006;45(4):4-7.doi: 10.1093/rheumatology/kel313. PMID: 16980723
13. Shenavar Masooleh I, Zayeni H, Haji-Abbasi A, et al. Cardiac involvement in rheumatoid arthritis: A cross-sectional study in Iran. Indian Heart J 2016;68(3):332-335.doi: 10.1016/j.ihj.2015.08.030. PMID: 27316486
14. Firestein GS, McInnes IB. Immunopathogenesis of rheumatoid arthritis. Immunity 2017;46(2):183-196.doi: 10.1016/j.immuni.2017.02.006. PMID: 28228278
15. Sung WY, Tsai WC. Rethink about the role of rheumatoid factor and anti-citrullinated protein antibody in rheumatoid arthritis. Rheumatol Immunol Res 2021;2(1):19-25.doi: 10.2478/rir-2021-0003. PMID: 36467904
16. Ingegnoli F, Castelli R, Gualtierotti R. Rheumatoid factors: clinical applications. Dis Markers 2013;35(6):727-734.doi: 10.1155/2013/726598. PMID: 24324289
17. Sokolova MV, Schett G, Steffen U. Autoantibodies in rheumatoid arthritis: Historical background and novel findings. Clin Rev Allergy Immunol 2022;63(2):138-151.doi: 10.1007/s12016-021-08890-1. PMID: 34495490
18. Xiang Y, Zhang M, Jiang D, et al. The role of inflammation in autoimmune disease: a therapeutic target. Front Immunol 2023;14(1):1267091.doi: 10.3389/fimmu.2023.1267091. PMID: 37859999
19. Hedar AM, Stradner MH, Roessler A, et al. Autoimmune rheumatic diseases and vascular function: The concept of autoimmune atherosclerosis. J Clin Med 2021;10(19):4427.doi: 10.3390/jcm10194427. PMID: 34640445
20. Moore KJ, Sheedy FJ, Fisher EA. Macrophages in atherosclerosis: a dynamic balance. Nat Rev Immunol 2013;13(10):709-721.doi: 10.1038/nri3520. PMID: 23995626