ECRONICON OPEN ACCESS

EC MICROBIOLOGY
Review Article

Rheumatoid Arthritis and Hypertension: Literature Review of the Last Ten Years

Muhammad Mahmood Akhtar[1]*, Fatima Mohammed Zabani[2], Maryam Awadallah Alkhormani[2], Ali Mohammed Aljafar[3], Mohammed Ahmad Sheikh[4], Rayyanah Abdulkareem Aljohani[4], Saad Abdulrahman Almahbub[5], Yazeed Mohammed Albalawi[5], Fares Bader Alotaibi[6], Bshayer Shaker Zawad[7] and Afnan Hussain Alshaikhali[8]

[1]*Department of Internal Medicine, East Jeddah General Hospital, Jeddah, Saudi Arabia*

[2]*College of Medicine, Batterjee Medical College, Jeddah, Saudi Arabia*

[3]*Department of Nephrology, King Salman Center for Kidney Diseases, Riyadh, Saudi Arabia*

[4]*College of Medicine, Taibah University, Medina, Saudi Arabia*

[5]*College of Medicine, Imam Muhammad ibn Saud Islamic University, Riyadh, Saudi Arabia*

[6]*College of Medicine, Ibn Sina National College, Jeddah, Saudi Arabia*

[7]*College of Medicine, Wroclaw Medical University, Wroclaw, Poland*

[8]*Department of Internal Medicine, King Salman Specialist Hospital, Ha'il, Saudi Arabia*

***Corresponding Author:** Muhammad Mahmood Akhtar, Department of Internal Medicine, East Jeddah General Hospital, Jeddah, Saudi Arabia.

Received: September 08, 2019; **Published:** October 10, 2019

Abstract

Background: Cardiovascular events in rheumatoid arthritis were considered the most common cause of high morbidity and mortality. Controlling the modifiable risk factors for cardiovascular events is considered as one of suggestion to decrease morbidity and mortality. Hypertension was considered one of these factors.

Aim: In this study, we reviewed the recent literature to stand on the incidence and prevalence of hypertension recently after advances in treatment options. Furthermore, we reviewed the literature to find the etiology and consequences of hypertension in rheumatoid arthritis.

Methods: We conducted an electronic database search for suitable studies during, published in the last ten years, in five databases including; Google Scholar, Scopus, Web of Science (ISI), PubMed, and Medline. A manual search of references was done to detect any possible related papers. Two independent reviewers reviewed the resulting papers and reviewed based on our inclusion criteria.

Results: Based on our results, the incidence of hypertension in rheumatoid arthritis was higher than the general population. There is still controversy over the cause of hypertension but generally, it is mainly due to drugs and electrolyte imbalance. Studies implied that inflammatory condition did not increase the risk of hypertension. The risk of cardiovascular events in rheumatoid arthritis was significantly associated with hypertension

Conclusion: Hypertension is one of the most common risk factors for cardiovascular events in rheumatoid arthritis. More attention to the follow-up of the patients should be given.

Keywords: *Rheumatoid Arthritis; Cardiovascular Disease; Hypertension; Morbidity; Mortality*

Introduction

Rheumatoid arthritis is an autoimmune disease that has a deleterious effect on joints [1]. Furthermore, it can affect extraarticular tissues including heart and kidneys [1,2]. The prevalence of rheumatoid arthritis ranges from 0.5 to 1% in European and North American countries [1-6]. However, the incidence in the Asian population was much lower. The disease had very low occurrences in the African population [1-3,7].

The specific etiology of the disease is still vague. It was proved that it had been transmitted in families, but it did not account for the high incidence of the disease [2,8]. Furthermore, the twin study had proved that there was a four-fold increase in its occurrence in monozygotic twins more than dizygotic twins [9]. Other genetic susceptibility factor included HLA DRB alleles. Moreover, it was found that some alleles had a higher risk than other alleles. It was found that HLA DRB1*0404 is a much stronger susceptibility factor than HLA DRB1*0101 [10]. In addition, it was found that patients who have the two alleles were more susceptible to the disease more than those with one allele [9,10].

Environmental factors had been implicated in the etiology of rheumatoid arthritis. Infection and hormonal contraceptive pills have been reported as a protective factor against rheumatoid arthritis. It was found that females taking oral contraceptive pills had less risk for the disease that other females [2,11].

The most common and morbid complications in rheumatoid arthritis are cardiovascular complications [5,12,13]. It was estimated that it is present in 48% of rheumatoid arthritis patients [12]. The mortality rate in those patients was high up to 60% [12]. Based on recent papers, the main reason for cardiovascular risk in rheumatoid arthritis was proinflammatory status [14-17]. Moreover, the basic risk factors including obesity, diabetes, atherosclerosis, and hypertension were also implicated as a cause of high incidence and morbidity [14-16].

Hypertension is one of the modifiable risk factors in rheumatoid arthritis. Furthermore, it relatively has a higher incidence in the general population than rheumatoid arthritis. The factors associated with hypertension in rheumatoid arthritis is not well defined [6,18]. It was reported corticosteroids were associated with a high increase of hypertension incidence in rheumatoid arthritis. The proinflammatory state in rheumatoid arthritis and oxidative stress are attributable factors [6,19,20]. In addition, insulin resistance was reported in those patients. It was also found that homocysteine and leptin were increased in patients with rheumatoid arthritis [7,16]. In contrast, another study found that hypertension in rheumatoid arthritis was not associated with insulin resistance or inflammation but was more associated with BMI, age, and a dose of prednisolone [21-23].

However, this is considered small evidence that was not searched extensively in the past few years. Our aim in this study is to stand on the incidence, etiology, and treatment of hypertension in rheumatoid arthritis.

Methods

We conducted an electronic database search for suitable studies during, published in the last ten years, in five databases including; Google Scholar, Scopus, Web of Science (ISI), PubMed, and Medline. We used the MeSH (Medical Subject Headings) terms for hypertension and rheumatoid arthritis. A manual search was conducted searching the references of the included studies and the related studies in PubMed. We also searched systematic reviews for any relevant papers. We only included human studies assessing the relationship between hypertension and rheumatoid arthritis from 2009. We excluded conference papers, reviews, abstract only papers, and books.

Two reviewers independently reviewed the found papers for fulfilling the inclusion criteria. Then, the qualitative and semiquantitative synthesis of the evidence was performed.

Results

After searching the database, we got 432 study. After the title/abstract screening, 60 studies were included. Only 11 studies fulfilled our inclusion criteria. In total, we had two types of studies; either studies that defines the aetiological causes of hypertension in rheumatoid arthritis [20,24,25], while the other studies reported the prevalence of hypertension in rheumatoid arthritis and its consequences in these patients [6,18,21,22,26-29] (Table 1).

ID	Country	Study design	Purpose	RA patients	Control	Identified cause
Carranza-Leon/2018 [24]	USA	Cross-sectional	Aetiology	116	92	Na, K, and inflammatory markers
Mitrović/2015 [25]	Croatia	Cross-sectional	Aetiology	55	42	Arterial stiffness index and common carotid intima-media thickness
Van Breukelen-vander Stoep/2016 [26]	Netherlands	Cross-sectional	Incidence	327		
Midtbo/2016 [21]	Norway	Cohort	Consequences of hypertension	134	102	
Desai/2016 [20]	USA	Cohort	Aetiology	4822	2400	Tumour Necrosis factor alpha inhibitor
Temiz/2014 [27]	Turkey	Case-control	Consequence of hypertension	77		
Myasoedova/2014 [28]	USA	Cohort	Consequences of hypertension	442	424	
Bartels/2014 [22]	USA	Cohort	Prevalence	201		
Protogerou/2013 [29]	USA	Cohort	Prevalence	214		
Morovic-Vergles/2013 [18]	Germany	Cohort	Prevalence	627		
Serelis/2011 [6]	Canada	Cohort	Consequences	325		

Table 1: *The characteristics of the included studies.*

What is the incidence of hypertension in rheumatoid arthritis?

Five studies reported the incidence of hypertension in rheumatoid patients [18,20,22,26,29]. Bartels., *et al*. had found that the incidence of hypertension in rheumatoid arthritis was 36% compared to 51% without rheumatoid arthritis [22]. Protogerou., *et al*. reported the prevalence of hypertension in rheumatoid arthritis was 44% and it was double the matched population (67% versus 43%). They concluded that 2 out of 5 patients will develop hypertension. Furthermore, only 10% were unaware of hypertension and 29% could not control hypertension [29]. Another study compared hypertension between the high- and low-grade chronic inflammation in rheumatoid arthritis. They found that the prevalence of hypertension did not differ between both grades. However, it was higher in old age and high BMI [18]. Desai., *et al*. found that the incidence of hypertension was 36 per 1000 patients in the TNF-alpha inhibitors group compared to 42 per 1000 persons in the other group [20]. Another study compared the incidence of cardiovascular diseases according to CVRM and EULAR guidelines. The risk of cardiovascular disorders was 52% in CVD risk ⩾20% and according to the EULAR guidelines, 18% had a CVD risk ≥ 20%. They also found that antihypertensive was used in 23 - 25% of the population and only 6% used statins with antihypertensive. However, only 50 - 86% of these patients did not achieve the desired blood pressure [26].

Why does hypertension occur in rheumatic arthritis?

Three studies assessed the etiology of hypertension in rheumatoid arthritis [20,24,25]. Each study assessed specific risk factors. One study assessed the effect of electrolyte balance on the inflammatory status in rheumatic arthritis [24]. In this study, they found that the ratio of Na/K excretion was high in rheumatoid arthritis patients. They found a strong association of this ratio with the incidence of hypertension in rheumatoid arthritis. Furthermore, the low K excretion was correlated with hypertension in these patients. Surprisingly, they were not related to the inflammatory markers assessed in the study. They did not significantly affect VCAM, TNF-alpha, IL-6, CRP and DAS28. They implied this effect is mainly because of the drugs including corticosteroids and coxibs. They also reported that every 1 gm increase of potassium excreted per 24h, there was a 1mmHg decrease in diastolic blood pressure. However, the small sample size and cross-sectional design with lack of follow-up of the patients greatly interfered with the power of the study. Furthermore, the urine sample was collected only once.

The second study in our review assessed arterial stiffness index and carotid intima/media thickness as a cause of hypertension in rheumatoid arthritis patients. In this study, they compared between hypertensive rheumatoid arthritis and normotensive rheumatoid arthritis [25]. They found that the carotid media/intima thickness and arterial stiffness index were significantly higher in rheumatoid patients with hypertension. However, they did not correlate with the inflammatory markers nor the degree of hypertension. This can be attributed to the small sample size and cross-sectional design like the previous study. They inferred from their results that atherosclerosis is much higher in hypertensive rheumatoid patients than normotensive patients. They also implied that a chronic inflammation state is associated with arterial stiffness. They also argued that CRP, ESR, DAS28, and CRP are not an adequate biomarker of inflammation in cross-sectional studies [25].

Desai., *et al*. was the third study to assess the cause of hypertension in rheumatic patients [20]. They assessed the effect of TNF-alpha inhibitor on the blood pressure in rheumatoid patients. Unlike the previous two studies, this study was conducted from 2001 to 2012. They measured the intake monthly and assessed hypertension as a diagnosis and at least one antihypertensive drug was prescribed. They compared between rheumatoid patients taking TNF-alpha inhibitors and rheumatoid patients taking the non-biologic anti-rheumatoid drugs. They found that the incidence of hypertension was 36 per 1000 patients in the TNF-alpha inhibitors group compared to 42 per 1000 persons in the other group. However, they found that there was no reduced risk of hypertension in the tested group. Furthermore, there was no dose-response relationship between drug use and hypertension. They inferred that protective effect of TNF-alpha against the cardiovascular events in rheumatoid arthritis is not mediated through hypertension but through other mechanisms [20].

What are the consequences of hypertension in Rheumatoid arthritis?

Four studies solely assessed the consequences of hypertension [6,21,27,28]. In a large Greek cohort, Serelis., *et al*. concluded that hypertension increased the risk of cardiovascular disorders in rheumatoid arthritis patients. In this study, they reviewed the medical records of patients who had more than two years of follow-up. They found that hypertension was associated with an increase in the inflammatory markers of rheumatoid arthritis. Furthermore, they assessed other risk factors for cardiovascular events in rheumatoid arthritis and it included leflunomide use and high CRP.

Two studies assessed the effect of hypertension on asymptomatic cardiovascular organ damage using echocardiography [21,27]. In one of these studies, left ventricular (LV) geometry and Systemic arterial compliance (SAC) was assessed in both hypertensive and normotensive patients [21]. Left ventricular geometry was abnormal if LV mass index or relative wall thickness was increased. Septal early diastolic tissue velocity < 8 cm/s was an indicator of LV diastolic dysfunction. Stroke volume index/pulse pressure ratio was indicative of systemic arterial compliance. In this study, they found that hypertension was associated with abnormal ventricular geometry, LV diastolic dysfunction, and low arterial compliance. They also found that this effect was not related to the inflammatory condition of the disease [21]. They revealed that hypertension increased the incidence of cardiovascular diseases in three folds. They found that its effect was abundant irrespective of age, diabetes and inflammatory markers [21].

The other study compared between hypertensive and non-hypertensive patients regarding chamber size and wall thickness [27]. They assessed the carotid intima/media thickness and epicardial adipose thickness. However, they found that carotid intima/media thickness and epicardial adipose thickness were significantly higher in hypertensive patients. Furthermore, they found that diastolic function was significantly affected by hypertension in rheumatoid patients. In addition, its effect was independent of other risk factors including old age and diabetes [27].

Another study assessed the long-term effect of hypertension on rheumatic arthritis patients on mortality and cardiovascular events [28]. In this study, they followed the patients for eight years. Out of 442 rheumatoid arthritis patients and during a mean follow-up of seven years, they reported 33 cardiovascular morbidities and 57 mortality. The risk of cardiovascular events per 1mmHg increase in systolic blood pressure was 1.12 (Hazard ratio) while for diastolic blood pressure, it had a higher risk of mortality. The results were the same after controlling for age, dyslipidemia, diabetes, and other risk factors [28].

Conclusion

Based on our results, hypertension is a highly incident in cases of rheumatoid arthritis. It was obvious that it was associated with a high risk of cardiovascular events and it is considered as one of the modifiable risk factors. Its effect on cardiovascular organs was not associated with the inflammatory state of the disease. We recommend that meticulous care should be given for the treatment of cardiovascular events.

Acknowledgements

None.

Conflict of Interest

None.

Bibliography

1. Firestein Gary S. "Evolving Concepts of Rheumatoid Arthritis". *Nature* 423.6937 (2003): 356-361.
2. Silman Alan J and Jacqueline E Pearson. "Epidemiology and Genetics of Rheumatoid Arthritis". *Arthritis Research and Therapy* 4.3 (2002): S265-S272.
3. Gabriel SE. "The Epidemiology of Rheumatoid Arthritis". *Rheumatic Diseases Clinics of North America* 27.2 (2001): 269-281.
4. Riise T., *et al*. "Incidence and Prevalence of Rheumatoid Arthritis in the County of Troms, Northern Norway". *The Journal of Rheumatology* 27.6 (2000): 1386-1389.
5. Assous Noemie., *et al*. "Cardiovascular Disease in Rheumatoid Arthritis: Single-Center Hospital-Based Cohort Study in France". *Joint, Bone, Spine: Revue Du Rhumatisme* 74.1 (2007): 66-72.
6. Serelis J., *et al*. "Cardiovascular Disease Is Related to Hypertension in Patients with Rheumatoid Arthritis: A Greek Cohort Study". *Journal of Rheumatology* 38.2 (2011): 236-241.
7. Solomon A., *et al*. "Risk Factor Profiles for Atherosclerotic Cardiovascular Disease in Black and Other Africans with Established Rheumatoid Arthritis". *Journal of Rheumatology* 37.5 (2010): 953-960.
8. Lawrence JS and J Ball. "Genetic Studies on Rheumatoid Arthritis". *Annals of the Rheumatic Diseases* 17.2 (1958): 160-168.

9. MacGregor AJ., *et al*. "Characterizing the Quantitative Genetic Contribution to Rheumatoid Arthritis Using Data from Twins". *Arthritis and Rheumatism* 43.1 (2000): 30-37.

10. Thomson W., *et al*. "Quantifying the Exact Role of Hla-Drb1 Alleles in Susceptibility to Inflammatory Polyarthritis: Results from a Large, Population-Based Study". *Arthritis and Rheumatism* 42.4 (1999): 757-762.

11. James WH. "Rheumatoid Arthritis, the Contraceptive Pill, and Androgens". *Annals of the Rheumatic Diseases* 52.6 (1993): 470-474.

12. Solomon Daniel H., *et al*. "Cardiovascular Morbidity and Mortality in Women Diagnosed with Rheumatoid Arthritis". *Circulation* 107.9 (2003): 1303-1307.

13. Monk HL., *et al*. "Cardiovascular Screening in Rheumatoid Arthritis: A Cross-Sectional Primary Care Database Study". *BMC Family Practice* 14 (2013): 150.

14. Barra LJ., *et al*. "The Effect of Rheumatoid Arthritis-Associated Autoantibodies on the Incidence of Cardiovascular Events in a Large Inception Cohort of Early Inflammatory Arthritis". *Rheumatology (Oxford)* 56.5 (2017): 768-776.

15. Pappas DA., *et al*. "Prevalence of Cardiovascular Disease and Major Risk Factors in Patients with Rheumatoid Arthritis: A Multinational Cross-Sectional Study". *Clinical Rheumatology* 37.9 (2018): 2331-2340.

16. Avina-Zubieta Juan Antonio., *et al*. "Risk of Incident Cardiovascular Events in Patients with Rheumatoid Arthritis: A Meta-Analysis of Observational Studies". *Annals of the Rheumatic Diseases* 71.9 (2012): 1524-1529.

17. Manavathongchai S., *et al*. "Inflammation and Hypertension in Rheumatoid". *Journal of Rheumatology* 40.11 (2014): 1806-1811.

18. Morovic-Vergles J., *et al*. "Is the Prevalence of Arterial Hypertension in Rheumatoid Arthritis and Osteoarthritis Associated with Disease?" *Rheumatology International* 33.5 (2013): 1185-1192.

19. Panoulas VF., *et al*. "Long-Term Exposure to Medium-Dose Glucocorticoid Therapy Associates with Hypertension in Patients with Rheumatoid Arthritis". *Rheumatology (Oxford, England)* 47.1 (2008): 72-75.

20. Desai RJ., *et al*. "Tumor Necrosis Factor-Alpha Inhibitor Use and the Risk of Incident Hypertension in Patients with Rheumatoid Arthritis". *Epidemiology* 27.3 (2016): 414-422.

21. Midtbo H., *et al*. "The Association of Hypertension with Asymptomatic Cardiovascular Organ Damage in Rheumatoid Arthritis". *Blood Press* 25.5 (2016): 298-304.

22. Bartels CM., *et al*. "Impact of Rheumatoid Arthritis on Receiving a Diagnosis of Hypertension among Patients with Regular Primary Care". *Arthritis Care and Research* 66.9 (2014): 1281-1288.

23. Panoulas VF., *et al*. "Prevalence and Associations of Hypertension and Its Control in Patients with Rheumatoid Arthritis". *Rheumatology (Oxford, England)* 46.9 (2007): 1477-1482.

24. Carranza-Leon D., *et al*. "Association between Urinary Sodium and Potassium Excretion and Blood Pressure and Inflammation in Patients with Rheumatoid Arthritis". *Clinical Rheumatology* 37.4 (2018): 895-900.

25. Mitrovic J., *et al*. "Ambulatory Arterial Stiffness Index and Carotid Intima-Media Thickness in Hypertensive Rheumatoid Patients: A Comparative Cross-Sectional Study". *International Journal of Rheumatic Diseases* 20.12 (2017): 1998-2002.

26. van Breukelen-van der Stoep DF., *et al*. "Marked Underdiagnosis and Undertreatment of Hypertension and Hypercholesterolaemia in Rheumatoid Arthritis". *Rheumatology (Oxford)* 55.7 (2016): 1210-1216.

27. Temiz A., *et al*. "Effect of Hypertension on Echocardiographic Parameters in Rheumatoid Arthritis". *Zeitschrift für Rheumatologie* 73.10 (2014): 934-938.

28. Myasoedova E., *et al*. "Long term Blood Pressure Variability in Patients with Rheumatoid Arthritis and Its Effect on Cardiovascular Events and All-Cause Mortality in Ra: A Population-Based Comparative Cohort Study". *Journal of Rheumatology* 41.8 (2014): 1638-1644.

29. Protogerou AD., *et al*. "Arterial Hypertension Assessed "out-of-Office" in a Contemporary Cohort of Rheumatoid Arthritis Patients Free of Cardiovascular Disease Is Characterized by High Prevalence, Low Awareness, Poor Control and Increased Vascular Damage-Associated "White Coat" Phenomenon". *Arthritis Research and Therapy* 15.5 (2013): R142.

Volume 15 Issue 11 November 2019