THE IMPLICATION OF RHEUMATOID ARTHRITIS ON BLOOD PRESSURE CONTROL

Asso F. Amin *, Raof Merza *, Kosar Muhammed * and Bahra Omer **

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ABSTRACT

Background

Rheumatoid Arthritis associates with excessive morbidity and mortality from cardiovascular events. Hypertension is considered as a major risk factor for development of cardiovascular disease. Insufficient control of blood pressure appears to be more in Rheumatoid arthritis. However, factors influence the control of blood pressure in rheumatoid arthritis is understudied.

Objectives

To determine the control of blood pressure in rheumatoid arthritis versus non rheumatoid arthritis hypertensive subjects by using ambulatory blood pressure measurement and to identify the factors associated with insufficient control of blood pressure in Rheumatoid arthritis patients

Pateints and methods

This is a case control study performed on seventy eight patients, 40 Rheumatoid arthritis hypertensive patient and 38 non-Rheumatoid arthritis hypertensive candidates between September 2012 and March 2013. Participants were between 45 and 85 years. An ambulatory blood pressure measurement was carried out for all patients and an abnormal blood pressure was defined as systolic of more than 140mm Hg and or diastolic of more than 90mm Hg.

Results

Blood pressure control is significantly lower in rheumatoid arthritis hypertensive patients compared to hypertensive non Rheumatoid arthritis control subjects (p-value 0.034). Furthermore, steroid users had more insufficient control of blood pressure compared to non users (p-value 0.028).There was significant association between methotrexate use and better control of hypertension (p-value 0.008).

Conclusion

The present study concludes that blood pressure control is lower in rheumatoid arthritis patients compared with non rheumatoid arthritis subjects; this may be of importance in the context of the increased cardiovascular morbidity and mortality. Those with co morbidity may require closer monitoring and treatment strategies.

Keywords: *Rheumatoid arthritis, Ambulatory blood pressure Measurement*

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* Department of Medicine, School of Medicine Faculty of medical sciences, University of Sulaimani.
Correspondence: delanamin@hotmail.com
** General Medical Teaching Hospital (Shaheed Hemn), Sulaimani Directorate of Health, Sulaimani.

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INTODUCTION

Rheumatoid Arthritis (RA) associates with excessive morbidity and mortality from CVD [1]. Many risk factors such as hypertension, smoking, dyslipidaemia, and insulin resistance are intended to be more prevalent in rheumatoid arthritis [2]. Hypertension is one of the most prevalent and modifiable risk factor resulting in CVD in the general population [3, 4]. Although there were contradictory results from studies on the presence of hypertension in RA ,but the most convincing evidence, came from a large population study involving more than 28000 RA patients, in which the prevalence of hypertension was remarkably higher in RA; 34% Vs 23.4% control [5, 6, 7, 8]. Despite its high prevalence and the impact of its complications, control of hypertension is far from adequate both in general population [8], and in RA [2]. In a recent study the rate of controlled blood pressure was significantly lower at 13.2% in RA than the 21-23% observed in general population [9], with its negative consequences on premature CVD, Peripheral artery disease, and Left Ventricular Hypertrophy [10]. The higher incidence and poor control of blood pressure in rheumatoid arthritis could closely be related to many factors. The connection between systematic inflammations and the prevalence and the control of blood pressure in RA may be one of these explanations [10], although such association is yet to be studied in details [1, 2]. Furthermore, sedentary life, restriction of movement, lack of exercise & obesity, associated with pain and stiffness in these patients may be another explanation [11]. Finally polypharmacy is characteristic of RA [11] and many of these medication can precipitate hypertension. A recent study has shown that both Ibuprofen and Indomethacin have a significant effect on increasing blood pressure compared to placebo [12]. Moreover, the relative risk for causing hypertension was higher for coxibs versus non selective NSAID and placebo, although the risk was not significant [13]. On the other hand, Disease Modified Anti-Rheumatic Drugs has also an impact on blood pressure. Leflunamide is associated with higher blood pressure compared to placebo [14] and cyclosporine should be avoided in hypertensive patients as it raises blood pressure [15].

PATIENT AND METHODS

The present study performed on 78 subjects, 40 patients had RA and hypertension (3 males and 37 females) and 38 hypertensive controls (4 males and 34 females). Participants were between the age of 45 and 85 years. RA patients were selected from patients attending the outpatient clinic (Ali Kamal) of Rheumatology and Rehabilitation in Slemani City and from patients admitted to the General Hospital (Shaheed Hemn)/ department of Rheumatology between September 2012 and March 2013, whom were diagnosed according to the 1987 revised criteria of the American College of Rheumatology [16]. The hypertensive controls were selected from the patients admitted at Sulaimani General Outpatient clinics at the same time. Hypertension was defined by a systolic blood pressure equal and more than 140 mmHg and/or diastolic blood pressure equal and more than 90 mmHg either on treatment or life style modification , according to the British hypertension Society guidelines [17]. To avoid confounding bias ,patients with Diabetes mellitus, classified as a fasting plasma glucose of equal and more than 7 mmol/liter (126 mg/dl) or were taking anti-diabetic medications at the time of the assessment, were excluded [17]. All participants underwent a thorough baseline evaluation including a detailed review of the medical history, physical examination, and contemporary assessments of body mass index, smoking status and duration of hypertension . All hypertensive patients were on one or a combination of anti-hypertensive drugs including thiazide, B-blockers, angiotensin-converting enzyme inhibitors (ACE-I) , angiotensin-II receptor Blockers (ARBs) and calcium channel blockers. In the RA patients the mean duration of disease was 13.8 years. All of them were receiving one or a combination of DMARD as well as steroid and NSAIDs. Oral prednisolone dose was defined as low if less than 7.5 mg/day, medium if between 7.5 and 30mg/ day, and high if more than30 mg/day [18]. Both groups were hypertensive, comparable in age, sex, BMI and number and type of antihypertensive drugs. We used DAS28 (Disease Activity Score 28 joint count) score to evaluate disease activity in patients with rheumatoid arthritis (RA). The level of disease activity can be interpreted as low (DAS28 <3.2), moderate (3DAS28> 3.2 and <5.1), or high (DAS28 > 5.1). A DAS28< 2.6 corresponds to being in remission according to the American Rheumatism Association (ARA) criteria [19] .

Ambulatory Blood Pressure Measurements (ABPM) has to be at least 14 total measurements day time and 7 total measurements at nighttime. The data has to be analyzed and then presented in an overall average, awake time average, night time average, and nighttime dipping [20]. Abnormal ABPM level is controversial, but the normal overall average is when blood pressure is equal or less than 135/85 mmHg [20]. Collected data

were analyzed using ABPM software after being downloaded on the computer.

RESULTS

Table (1) shows that the rheumatoid arthritis (RA) patients and non-RA control subjects were comparable in age, gender, smoking status, BMI and hypertension (HTN) duration.

Table (2) shows that highest percentage of uncontrolled hypertension was reported among RA patients (60.0%), compared with control subjects (37.0%). This association was statistically significant (p-value 0.034).

Table (3) Shows that there was no statistically significant association between uncontrolled hypertension and RF, ESR, CRP and disease duration in RA patients. p-value (0.276, 0.324, 0.280 and 0.888) respectively.

Table 1. Characteristic of the studied groups.

Variable	RA patients (N = 40)	Control subjects (N = 38)
Age (years) Mean+SD	59.6 ± 9.8	59.1 ± 10.4
Gender n (%)		
Male	3(7.5%)	4(10.5%)
Female	37(92.5%)	34(89.5%)
Smoking Status n (%)		
Never smoked	34(85.0%)	33(86.8%)
Ex-smoker	6(15.0%)	5(13.2%)
Current smoker	0(0.0)	0(0.0)
BMI(mean ± SD kg/m2)	27.7 ± 4.8	28 ± 4.3
HTN duration(years)	7.3 ± 7	7.1 ± 6.5

Table 2. The Hypertension state among RA and control group.

Variable	Hypertension		P-value
	Controlled N (%)	Uncontrolled N (%)	
RA Patient	16 (40.0)	24 (60.0)	
Control	24(63.0)	14 (37.0)	0.034
Total	40 (51.3)	38 (48.7)	

Table3. Association of blood pressure control with RF,ESR, and CRP.

Variable	Hypertension		P-value
	Controlled 16 (40.0%)	Uncontrolled 24 (60.0%)	
ESR mm/h			
Abnormal	6(33.3)	12(66.7)	0.324
Normal	10(45.5)	12(54.5)	
CRP			
Positive	7(33.3)	14(66.7)	0.280
Negative	9(47.4)	10(52.6)	
Rheumatoid factor			
Positive	11(45.8)	13(54.2)	0.276
Negative	5(31.2)	11(68.8)	
RA duration (mean ± SD)	13.5 ± 13.1	14 ± 9.3	0.888

Figure 1 shows the percentage of the disease activity in RA patients measured by DAS 28 score; the highest percentage 42.5% had moderate disease activity, while about 5.0% of patients had low disease activity.

Table 4 shows that 75.0% of patients in remission had uncontrolled hypertension compared to 53.8% of patients with high disease activity. There were no statistically significant association between the disease activity and hypertension control in RA patients as p-value was (0.790).

Table 5 shows that there was no statistically significant association between blood pressure control status and the general characteristics (age, gender, smoking status, BMI, family history of HTN and HTN duration) in RA patients p-value (0.201, 0.651, 0.160, 0.704, 0.180 and 0.183) respectively.

Table 6 shows (76.2%) of RA patients who used steroid had uncontrolled hypertension. There is a statistically significant association between steroid use and uncontrolled blood pressure in RA patients with p-value (0.028). On the other hand, 75.0% of patients on NSAIDs had uncontrolled hypertension but this was statistically non significant p- value (0.471).

Table 7 shows that 86.7% of RA patients who did not receive methotrexate had uncontrolled hypertension compared to 44.0% of patients on methotrexate. This was statistically highly significant correlation between methotrexate usage and hypertension control with p-value (0.008). Moreover, there was no statistically significant association between hypertension control status and hydroxychloroquine, sulfasalazine and Leflunamide usage as p-value was (0.436, 0.652 and 0.081) respectively.

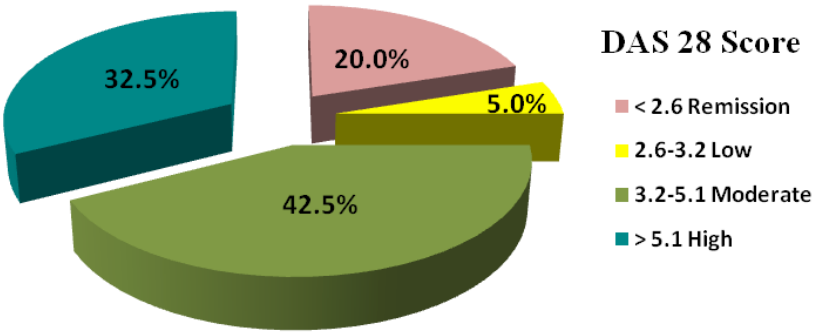

Figure 1. The percentage of the disease activity in RA patients

Table 4. Association between disease activity and blood pressure control.

Disease activity in RA	Hypertension		P-value
	Controlled N (%)	Uncontrolled N (%)	
Remission	2 (25.0)	6 (75.0)	
Low	1 (50.0)	1 (50.0)	
Moderate	7 (41.2)	10 (58.8)	0.790
High	6 (46.2)	7 (53.8)	
Total	16 (40.0)	24 (60.0)	

Table 5. Association between blood pressure control and Patients' general characteristics.

Variable	Hypertension		P-value
	Controlled	Uncontrolled	
Age-years (mean ± SD)	57.2 ± 7.3	61.2 ± 11	0.201
Gender (%) **Male** **Female**	1(33.3%) 15(40.5%)	2(66.7%) 22(59.5%)	0.651
Smoking status **Never smoked** **Ex-smoker** **Current smoker**	12(35.3) 4(66.7) 0(0.0)	22(64.7) 2(33.3) 0(0.0)	0.160
BMI (mean ± SD)	28 ± 4	27.5 ± 5.4	0.04
Family history of HTN (%) **Yes** **No**	13(46.4%) 3(25.0%)	15(53.6%) 9(75.0%)	0.180
HTN years (mean ±SD)	5.4 ± 4.4	8.5 ± 8.3	0.183

Table 6. Association between steroid and NSAID and blood pressure control.

Variable	Hypertension		P-value
	Controlled N (%)	Uncontrolled N (%)	
Steroid use **Yes** **No** **Total**	5(23.8) 11(57.9) 16(40.0)	16(76.2) 8(42.1) 24(60.0)	0.028
NSAIDs use **Yes** **No** **Total**	1(25.0) 15(41.7) 16(40.0)	3(75.0) 21(58.3) 24(60.0)	0.471

Table 7. Association between Blood pressure control and usage of DMARD.

DMARDs Treatment	Hypertension		P-value
	Controlled N (%)	Uncontrolled N (%)	
Methotrexate use			
Yes	14(56.0)	11(44.0)	
No	2(13.3)	13(86.7)	0.008
Total	16(40.0)	24(60.0)	
Hydroxychloroquine use			
Yes	10(45.4)	12(54.6)	
No	6(33.3)	12(66.7)	0.436
Total	16(40.0)	24(60.0)	
Leflunamide use			
Yes	1(12.5)	7(87.5)	
No	15(46.9)	17(53.1) 24(60.0)	0.081
Total	16(40.0)		
Sulfasalazine use			
Yes	15(40.5)	22(59.5)	
No	1(33.3)	2(66.7)	0.652
Total	16(40.0)	24(60.0)	

DISCUSSION

Arthritis and HTN are two of the most common chronic diseases affecting adults in the United States (US) and co-prevalence of HTN and arthritis is considerable. Data from the Third National Health and Nutrition Examination Survey (NHANES III), organized by the National Center for Health Statistics from 1988- 1994, reveals that roughly 30 million people aged equal and more than 35 years have osteoarthritis (OA) or RA and 11.8 million of these use pharmacologic treatment of HTN [21]. Over the past 20 years or so, the correctness of using the traditional RivaRocci sphygmomanometer and Korotkoff's sounds to calculate blood pressure has been queered, and efforts have been made to develop measurements with automated devices [20]. ABPM has been established as a method of first choice in specific indications, for example, white coat hypertension, evaluation of antihypertensive treatment, and circadian patterns of Blood pressure [22].

In this case control study, 90% of both groups were female, 42% between 45-54 years. Inadequate Blood pressure control was remarkable among Hypertensive RA compared to control hypertensive without RA. In RA 60% of patients had abnormal blood pressure compared to 40% having controlled pressure and this is a statically significant finding. This is clearly in agreement with a study done by Panoulas [2] which showed lower control in RA 13.2% compared to general population 21-23%. Increased inflammatory load and higher disease activity has been associated with

worse over all CVD outcome in RA [23], but no directly with hypertension [24]. In this study although higher activity of the disease linked with poorer control of blood pressure, but that was statistically insignificant. However it would be interesting to study this in a bigger prospective cohort study. Furthermore, in this case-control study we have a statistically significant relationship between blood pressure control and steroid usage. 76.2% of steroid users had poor control compared to 23.8% only with optimal blood pressure. In contrast to this, 57.9% of non steroid users had good control and 43.1% had suboptimal control. This finding is compatible with 2 previous studies [1, 2]. This association could possibly be due to the hypertensive effect of steroid rather than choosing patient with higher inflammatory index requiring steroid treatment. In Contrary to this, a study choosing 129 asthmatic and 66 RA patient has revealed no relationship between use of low dose of steroid (defined as less than 20mg/day) and blood pressure increment [25].

Interestingly none of the demographic characteristics of our patients like age, sex, family history of hypertension, and BMI had statistically notable correlation with blood pressure control. This is in contradiction to three previous studies [1, 2, 26].

Finally, we found a highly significant correlation between blood pressure control and methotrexate use. In this study methotrexate had a good effect on achieving optimal blood pressure. However we didn't find any significant association between other DMARDs (Sulfasalazine, Hydroxychloroquine and Leflunamide) with control of blood pressure (P-value 0.652, 0.436 and 0.081) respectively.

Nearly a similar result was concluded by Krause et al. [27] who found that RA patients who had stopped their methotrexate had a greater prevalence of hypertension, coronary heart disease, and heart failure than those continued using the same medication.

In conclusion, the present study aimed to establish factors that may be associated with sub-optimal BP control in patients with RA using ABPM rather than the less reliable home and or office blood pressure measurements. Solid implication of rheumatoid arthritis on blood pressure control was clearly identified. Similarly, using steroid had a significant adverse impact on blood pressure control. This may be of influence in the context of the increased cardiovascular mortality and morbidity. Finally based on the finding of this case-control study, a system for monitoring and better controlling of blood pressure in patients with rheumatoid arthritis should be put in place both in primary and secondary care in order to achieve recommended blood pressure targets. Additionally, related specialist should consider keeping steroid use to minimum especially in hypertensive RA patients and to try to shift to DMARDS as early as possible in the course of the disease, especially those which don't affect blood pressure control adversely.

REFERENCES

1. Panoulas VF, Milionis HJ, Douglas KM . Association of serum uric acid with cardiovascular disease in rheumatoid arthritis. Rheumatology 2007; 46:1466–70.

2. Panoulas V.F, Metsios G.S, Pace A.V, John H, Treharne G.J, Banks M.J, Kitas G.D.Hypertension in rheumatoid arthritis. Rheumatology 2008 ;47:1286-1298.

3. Yusuf S, Hawken S, Ounpuu Sl. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study):Case-control study. Lancet 2004; 364:937–52.

4. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet 2005; 365:217–23.

5. Gonzalez A, Maradit KH, Crowson CS. Do cardiovascular risk factors confer the same risk for cardiovascular outcomes in rheumatoid arthritis patients as in non rheumatoid arthritis patients? Ann Rheum Dis 2008 ;67:64–9.

6. Del.Rincon I, Freeman GL, Haas RW, O'Leary DH, Escalante A. Relative contribution of cardiovascular risk factors and rheumatoid arthritis clinical manifestations to atherosclerosis. Arthritis Rheum 2005; 52:3413–23.

7. Solomon DH, Curhan GC, Rimm EB, Cannuscio CC, Karlson EW. Cardiovascular risk factors in women with and without rheumatoid arthritis. Arthritis Rheum 2004 ; 50:3444-9.

8. Luepker RV, Arnett DK, Jacobs DR . Trends in blood pressure, hypertension control, and stroke mortality: the Minnesota Heart Survey. Am J Med 2006; 119:42–9.

9. Primatesta P, Poulter NR. Improvement in hypertension management in England: results from the health survey for England 2003. Journal Hypertension 2006 ; 24:1187–92.

10. Duprez DA, Somasundaram PE, Sigurdsson G, Hoke L, Florea N, Cohn JN. Relationship between C-reactive protein and arterial stiffness in an asymptomatic population. J Hum Hypertension 2005; 19:515–9.

11. Munneke M, de Jong Z, Zwinderman AH. High intensity exercise or conventional exercise for patients with rheumatoid arthritis? Outcome expectations of patients, rheumatologists, and physiotherapists. Ann Rheum Dis 2004 ;63:804–8.

12. Morrison A, Ramey DR, van Adelsberg J, Watson DJ. Systematic review of trials of the effect of continued use of oral non-selective NSAIDs on blood pressure and hypertension. Curr Med Res Opin 2007 ; 23:2395–404.

13. Franklin SS, Khan SA, Wong ND, Larson MG, Levy D. Is pulse pressure useful in predicting risk for coronary heart Disease? The Framingham Heart Study. Circulation 1999; 100:354–60.

14. Rozman B, Praprotnik S, Logar D et al. Leflunomide and hypertension. Ann Rheum Dis 2002; 61:567–9.

15.Weinblatt ME, Coblyn JS, Fraser PA. Cyclosporin A treatment of refractory rheumatoid arthritis. Arthritis Rheum 1987; 30:11–7.

16. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.

17. Williams B, Poulter NR, Brown MJ. Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004-BHS IV. J Hum Hypertens 2004;18:139–85.

18. Buttgereit F, da Silva JA, Boers M et al. Standardised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology. Ann Rheum Dis 2002;61:718–22.

19. Vangestelam AM, Haagsma CJ, Vanrieil C M: Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. Arthritis Rheum 1998; 41: 1845-50.

20. O'Brien E, Coats A, Owens P, Petrie J, Padheld P, Littler WA. Use and interpretation of ambulatory blood pressure monitoring: recommendations of the British Hypertension Society. BMJ 2000;320:112834.

21. Prospective Studies Collaboration: age specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2006;360:1903–13.

22. Nurmohamed MT. Cardiovascular risk in rheumatoid arthritis. Autoimmun Rev 2009;8:663–7.

23. Kitas GD, Erb N. Tackling Ischemic heart disease in rheumatoid arthritis. Rheumatology 2003;42:607-13.

24. Stevens RJ, Douglas KMJ, Saratzis AN, Kitas GD. Inflammation and atherosclerosis in rheumatoid arthritis. Exp Rev Mol Med 2005; 7:1-24.

25. Jackson SH, Beevers DG,Myers K,.Does long- term low-dose corticosteroid therapy cause hypertension?. Clin Sci(Lond) 1981;61 Suppl 7-381s-3.

26. Stavropoulos-Karlinoglou A, Metsios GS, Koutedakis Y. Redefining overweight and obesity in rheumatoid arthritis patients. Ann Rheum Dis 2007, doi:10.1136/ard.2006.

27. Krause D, Schleusser B, Herborn G, Rau R. Response to methotrexate treatment is associated with reduced mortality in patients with severe rheumatoid arthritis. Arthritis Rheum 2000; 43(1): 14-21.