

Low Levels of Renin and High Aldosterone-to-Renin Ratio Among Rheumatoid Patients and Ankylosing Spondylitis Patients: A Prospective Study

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ABSTRACT: **Background:** Patients with rheumatic diseases, such as rheumatoid arthritis (RA) and ankylosing spondylitis (AS), encounter significantly higher rates of cardiovascular morbidity and mortality. The renin-angiotensin-aldosterone system maintains hemodynamic stability through blood pressure regulation. When dysregulated, this system has been implicated in various pathological conditions, including cardiovascular events.

Objectives: To investigate the levels of renin and aldosterone in RA and AS patients.

Methods: Three groups were recruited: patients with RA, patients with AS, and healthy controls. Subjects were excluded if they had a diagnosis of hypertension, hyperaldosteronism, or renal artery stenosis, or were taking drugs that might have affected renin levels. Renin and aldosterone levels were measured using commercially available kits. Data were analyzed using univariate analyses and multivariate regression analyses.

Results: Fifty-one subjects were enrolled in the study: 15 with RA, 4 with AS, and 32 healthy controls. At the univariate analysis, the three groups differed in age ($P = 0.005$), renin levels ($P = 0.013$), and aldosterone-to-renin ratio ($P = 0.019$). At the post-hoc tests, both AS and RA patients differed from controls for renin levels and the aldosterone-to-renin ratio. At the multivariate regression analysis, AS patients had lower renin values than controls (beta standardized regression coefficient -0.323 , $P = 0.022$).

Conclusion: Patients with RA tended to have lower levels of plasma renin compared to healthy subjects. This finding indicates that the renin-angiotensin-aldosterone system might not be directly involved in the process that results in increased cardiovascular events in rheumatoid arthritis.

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KEY WORDS: aldosterone, ankylosing spondylitis (AS), autoimmunity, renin, rheumatoid arthritis (RA)

Rheumatic diseases are chronic diseases characterized by the inflammation of connective tissue [1,2]. Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that is diagnosed in approximately 1%–2% of the world's population and affects women 2 to 3 times more than men [3]. RA is influenced by genetic susceptibility and environmental factors that trigger a cascade of events, resulting in inflammation and subsequent destruction of synovial joints [4,5].

Although the destruction of synovial joints are the hallmark finding in the disease, RA is considered to be part of a systemic disease and is associated with elevated risk of morbidity and mortality [6]. RA patients have a 1.5–2.0-fold increased risk of developing coronary artery disease compared to the general population [7,8].

Ankylosing spondylitis (AS) is an inflammatory arthritis that mainly targets the axial skeleton, which produces characteristic inflammatory back pain, ultimately resulting in structural and functional impairment and debilitation [9,10]. Patients with AS have an increased prevalence of cardiovascular events, such as myocardial infarction [11,12].

In both diseases, the inflammatory process accompanying the disease resembles the intrinsic element of atherogenesis, which includes endothelial dysfunction, atheroma formation, plaque instability, and thrombus formation [13,14].

The renin-angiotensin-aldosterone system (RAAS) is an intricate hormonal system that functions in maintaining hemodynamic stability by regulating blood pressure, water balance, and electrolyte balance. Dysregulation of RAAS has been implicated in various pathological conditions, including hypertension, acute myocardial infarction, and stroke. RAAS has been postulated to initiate vascular inflammation, which subsequently results in oxidant stress and endothelial dysfunction, both early finding in the natural history of atherosclerosis [15].

While systemic inflammation may explain the increased coronary artery disease observed in RA, the mechanism pertinent to cardiovascular disease has yet to be fully explained, and further research is warranted to delineate the method of

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action. In this study, we investigated how the levels of renin and aldosterone vary in patients with RA and AS, compared to healthy controls.

PATIENTS AND METHODS

ETHICS APPROVAL

This study was approved by the ethics committee at Sheba Medical Center, Tel Hashomer, Israel.

STUDY POPULATION

The study group comprised 15 patients with RA, 4 patients with AS, and 32 healthy controls. All enrolled participants were older than 18 years of age, and included both males and females. Subjects with the following diagnoses were excluded: hypertension, cancer, liver cirrhosis, primary hyperaldosteronism, adrenal hyperplasia, renal artery stenosis, and pregnancy, as well as those taking medications that might affect the RAAS (e.g., diuretics, non-steroidal anti-inflammatory drugs, angiotensin-converting-enzyme [ACE] inhibitors, angiotensin II receptor antagonists). Patients with RA and AS were recruited from the Zabudowicz Center for Autoimmune Diseases at Sheba Medical Center. The healthy controls were participants who came to the hospital for routine screening purposes.

SAMPLE COLLECTION

Patients were maintained in the supine position for 30 minutes prior to blood sampling. All subjects were in a euvolemic state when blood sampling was completed. Peripheral blood samples were collected from the antecubital vein through a 21 gauge needle. Four milliliters were added to an EDTA tube for a renin assay, and a similar amount was added for an aldosterone assay. Samples were quickly transferred to the laboratory. Renin was assayed using the LIAISON® direct renin assay kit, and aldosterone was assayed using the LIAISON® ALDOSTERONE kit. Both kits are commercially available and produced by DiaSorin (Italy). The kits use chemiluminescent immunoassay technology for the in vitro quantitative determination of substrate levels in human EDTA-plasma specimens.

STATISTICAL ANALYSIS

Before beginning any statistical processing and analysis, data were visually inspected for potential outliers and normality of data distribution was checked with the Shapiro–Wilk test. Continuous data were computed as mean ± standard deviation. The range of values and median were also reported. Categorical variables were expressed as percentages. Univariate analyses (Fisher's exact test and chi-square test, analysis of variance, and Kruskal–Wallis test) and multivariate regression analyses were conducted to find an association between aldosterone, renin, aldosterone-to-renin ratio, and type of disease. If significance was found with the Kruskal–Wallis test, a post-hoc test was

conducted according to Conover (1999). *P* < 0.05 was considered statistically significant. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 20 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

Our study included an overall sample of 51 subjects. The female-to-male ratio was 43:8 (84.3% female: 15.7% male). The mean age was 47.49 ± 13.62 years, median was 47 (range 19–78) years of age. The average pulse was 70.19 ± 10.68 beats per minute, systolic blood pressure (SBP) was 118.39 ± 12.38, mmHg and diastolic blood pressure (DBP) was 71.33 ± 9.98 mmHg. The mean aldosterone levels were 9.27 ± 4.80 ng/dl, whereas the mean renin levels were 13.45 ± 9.12 ng/dl, and the average aldosterone-to-renin ratio was 1.31 ± 1.91 ng/dl [Table 1].

Among our study population, 15 patients presented with additional co-morbidities. In the control group, seven patients were smokers, and two had a diagnosis of hypothyroidism. In the RA group, two patients were smokers, two had a diagnosis of hypothyroidism, and one patient had a history of uveitis. In the AS group, one patient was a smoker.

The RA group consisted of 15 patients with a mean age of 56.27 ± 13.35 years. Fourteen patients (93.3%) were female, and one patient (6.7%) was male. The AS group included four patients with a mean age of 37.50 ± 9.88 years, with an equal male-to-female ratio. The control group entailed 32 healthy referent adults, with a mean age of 44.63 ± 12.28 years, and included 27 females (84.4%), and 5 males (15.6%), which was the same ratio as the RA and AS groups. Among the three groups, the pulse, SBP, and DBP were within the normal range. No significant difference was shown in the groups in terms of gender, co-morbidities, SBP, DBP, or pulse [Table 2].

Table 1. The demographic data and descriptive statistics for the study population include patients from all three groups (rheumatoid arthritis, ankylosing spondylitis, and controls), N=51

Parameter	Value
Age in years, median (range)	47.49 ± 13.62, 47 (19–78)
Gender	
Female	43 (84.3%)
Male	8 (15.7%)
Co-morbidities	15 (29.4%)
SBP, mmHg, median ± SD (range)	118.39 ± 12.38 (96–147)
DBP, mmHg, median ± SD (range)	71.33 ± 9.98 (46–94)
Pulse, bpm, median ± SD (range)	70.19 ± 10.68 (42–99)
Aldosterone, ng/dl, median ± SD (range)	9.27 ± 4.80, 8.52 (3.07–32.5)
Renin, ng/dl, median ± SD (range)	13.45 ± 9.12, 9.5 (0.9–37.9)
Aldosterone-to-renin ratio, median ± SD (range)	1.31 ± 1.91, 0.74 (0.15–10.39)

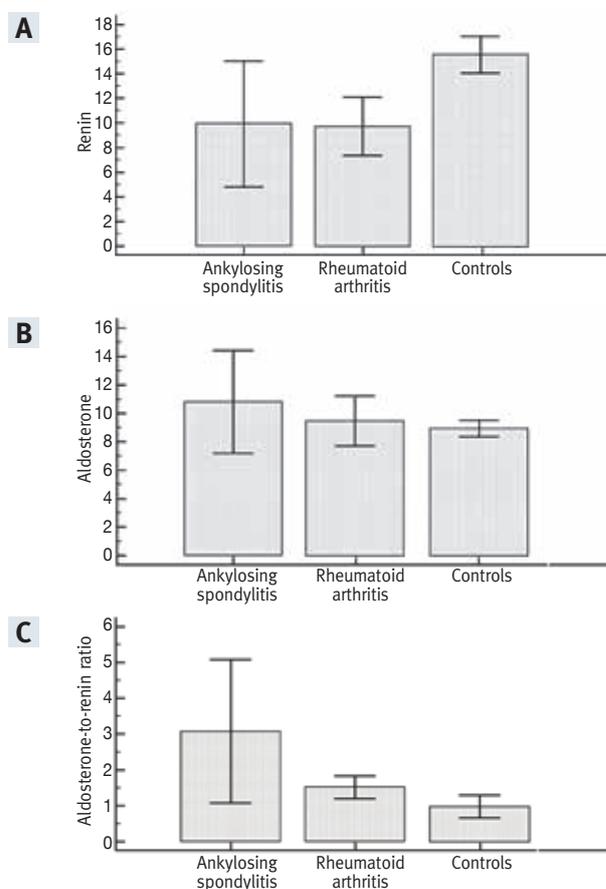
bpm = beats per minute, DBP = blood pressure-diastolic, SBP= blood pressure-systolic, SD = standard deviation

Table 2. Univariate analysis of the three groups of the current study, including statistical analysis of study parameters among the three groups

Parameter	Ankylosing spondylitis (n=4)	Rheumatoid arthritis (n=15)	Controls (n=32)	P value
Age, years	37.50 ± 9.88	56.27 ± 13.35	44.63 ± 12.28	0.005
Gender	2 female (50%) 2 male (50%)	14 female (93.3%) 1 male (6.7%)	27 female (84.4%) 5 male (15.6%)	0.106
Co-morbidities	1 (25%)	5 (33.3%)	9 (28.1%)	0.917
SBP, mmHg	118.75 ± 8.7	121.29 ± 13.0	117.03 ± 12.5	0.575
DBP, mmHg	75.00 ± 4.9	72.57 ± 10.7	70.29 ± 10.1	0.588
Pulse, bpm	76.50 ± 9.1	70.58 ± 8.5	69.23 ± 11.5	0.444
Aldosterone, ng/dl	10.82 ± 7.22	9.49 ± 6.81	8.97 ± 3.27	0.806
Renin, ng/dl	9.93 ± 10.25	9.77 ± 9.19	15.62 ± 8.53	0.013
Aldosterone-to-renin ratio, ng/dl	3.08 ± 3.99	1.52 ± 1.23	0.99 ± 1.76	0.019

bpm = beats per minute, DBP = blood pressure-diastolic, SBP= blood pressure-systolic

Figure 1. Levels of renin, aldosterone, and aldosterone-to-renin ratio in the three subgroups: RA, AS, controls **[A]** Mean renin levels were significantly lower in the RA and AS groups compared to the control group, **[B]** No significant difference in aldosterone levels was observed among the three groups, **[C]** The aldosterone-to-renin ratio was significantly higher in the RA and AS groups compared to the control groups



AS = ankylosing spondylitis, RA = rheumatoid arthritis

Table 3. Multivariate regression analysis of the study population concerning aldosterone, renin, and aldosterone-to-renin ratio.

Ankylosing spondylitis patients had mean renin values lower than controls, and the aldosterone-to-renin ratio was higher in the ankylosing spondylitis group compared to controls

Source	Value	Standard error	T	P value	Lower bound (95%)	Upper bound (95%)
Aldosterone						
Age, years	-0.053	0.245	-0.218	0.829	-0.549	0.442
SBP, mmHg	0.097	0.260	0.371	0.712	-0.431	0.624
DBP, mmHg	-0.094	0.273	-0.345	0.732	-0.646	0.458
Pulse, bpm	-0.054	0.157	-0.341	0.735	-0.372	0.265
Gender, female	0.286	0.166	1.722	0.093	-0.050	0.623
Ankylosing spondylitis	0.194	0.165	1.176	0.247	-0.140	0.528
Rheumatoid arthritis	0.013	0.167	0.080	0.937	-0.324	0.350
No co-morbidities	0.203	0.163	1.248	0.220	-0.127	0.533
Renin						
Age	-0.006	0.201	-0.031	0.976	-0.414	0.402
SBP	-0.394	0.214	-1.838	0.074	-0.828	0.040
DBP	0.126	0.225	0.562	0.577	-0.328	0.581
Pulse	0.097	0.129	0.753	0.456	-0.165	0.360
Gender, female	-0.427	0.137	-3.117	0.003*	-0.704	-0.150
Ankylosing spondylitis	-0.323	0.136	-2.382	0.022*	-0.598	-0.049
Rheumatoid arthritis	-0.260	0.137	-1.899	0.065	-0.538	0.017
No co-morbidities	0.071	0.134	0.526	0.602	-0.201	0.342
Aldosterone-to-renin ratio						
Age	-0.213	0.216	-0.984	0.331	-0.651	0.225
SBP	0.339	0.230	1.472	0.149	-0.127	0.805
DBP	0.023	0.241	0.096	0.924	-0.465	0.511
Pulse	0.157	0.139	1.129	0.266	-0.125	0.438
Gender, female	0.289	0.147	1.970	0.056	-0.008	0.587
Ankylosing spondylitis	0.298	0.146	2.044	0.048*	0.003	0.593
Rheumatoid arthritis	0.088	0.147	0.600	0.552	-0.210	0.386
No co-morbidities	-0.098	0.144	-0.677	0.503	-0.389	0.194

*Statistically significant. P < 0.05

bpm = beats per minute, DBP = blood pressure-diastolic, SBP= blood pressure-systolic

At univariate analysis, mean levels of renin were 9.77 ± 9.19 in the RA group, 9.93 ± 10.25 in the AS group, and 15.62 ± 8.53 among controls (P = 0.013). Mean renin levels were significantly lower in the RA and AS group compared to healthy controls [Figure 1A, Table 2]. Mean aldosterone levels were 9.49 ± 6.81 in the RA group, 10.82 ± 7.22 in the AS group, and 8.97 ± 3.27 among controls (P = 0.806). No statistical significance was documented with aldosterone levels [Figure 1B, Table 2]. In contrast, the aldosterone-to-renin ratio was significantly elevated in both the RA group and AS group when compared to controls (RA 1.52 ± 1.23, AS 3.08 ± 3.99 vs. controls 0.99 ± 1.76, P = 0.019) [Figure 1C, Table 2]. With respect to age, AS

patients and controls were significantly younger than RA patients ($P < 0.005$).

At the multivariate regression analysis, AS patients had mean renin values lower than controls (β standardized regression coefficient -0.323 , $P = 0.022$) [Table 3]. The mean renin levels tended to be lower in females than in males ($\beta -0.427$, $P = 0.003$). Similarly, the aldosterone-to-renin ratio was higher in the AS group compared to controls ($\beta 0.298$, $P = 0.048$). In contrast, among the RA patients, renin levels and the aldosterone-to-renin ratio was not found to be significantly different.

All RA patients were treated with biological therapy at least once. Ten patients (66.6%) were treated with anti-IL-6 (tocilizumab), three (20%) were treated with anti-CD 20 (rituximab), and two (13.3%) received treatment with anti-TNF (infliximab). In addition to biologic therapy, six patients needed additional medications: four (26.7%) were treated with methotrexate, and two (13.3%) were treated with prednisone. In comparison, all patients with AS were treated with infliximab.

DISCUSSION

In this study, we demonstrated lower levels of renin in both the RA and AS patient groups compared to healthy controls. Moreover, the aldosterone-to-renin ratio was higher in the RA and AS groups compared to the healthy subjects.

RA and AS are chronic inflammatory conditions that are associated with higher risk for cardiovascular disease [16]. Both disease entities are characterized by endothelial dysfunction fostering a pro-inflammatory and pro-thrombotic state, which predisposes to the development of atherosclerosis [17].

Abnormalities in the RAAS have been implicated in various conditions, including atherosclerosis. The RAAS has multiple key mediators involved in the inflammatory process. Angiotensin II has been shown to trigger the production of reactive oxygen species in blood vessels, resulting in endothelial dysfunction and lipoprotein peroxidation [15,18,19]. Angiotensin II also promotes vascular smooth muscle proliferation and atherosclerotic lesions through phenotype modulation, which leads to growth factor and extracellular matrix production, and contributes to neointima production [15].

Cobankara and colleagues [20] investigated renin concentrations in the plasma and the synovial fluid of RA patients, osteoarthritis (OA) patients, and healthy controls. Their team found that serum renin levels in RA, OA, and healthy controls were comparable. In contrast, synovial renin concentrations were found to be elevated in RA patients compared to OA patients. These findings have been attributed to possible filtration of renin from the circulation into the synovial fluid, as well as a local generation of renin in RA patients.

Similarly, IZai et al. [21] measured active and inactive levels of renin in RA and OA patients. Active and inactive renin levels were found to be significantly higher in the serum of patients

with RA compared to OA, and similarly, higher levels of renin were documented in synovial fluid of the RA group.

Mavrikakis and co-authors [22] assessed the levels of plasma renin activity in normotensive patients with RA. Plasma renin activity was measured 10 days after discontinuing drugs that affect renin levels. All RA patients were found to have high mean plasma renin activity levels, which positively correlated with rheumatoid factor levels. Furthermore, RA patients with microhematuria had higher renin activity levels compared to patients without microhematuria. The correlation between renin activity, rheumatoid factor, and microhematuria has been suggestive of inflammatory injury involving the juxtaglomerular apparatus.

Due to the postulated inflammatory role of the RAAS, various investigations were set to demonstrate the role of angiotensin converting enzyme inhibitors (ACEIs) in RA animal models. Quinapril, a non-thiol ACEI, demonstrated significant suppression of collagen induced arthritis in an animal model for RA when given prophylactically and therapeutically [23]. Mackenzie and collaborators [24] showed that angiotensin type 1 receptor blockage using losartan significantly decreased the impaired endothelium derived hyperpolarizing factor relaxation in rat models. Such findings highlight angiotensin's involvement in endothelial dysfunction, a key event leading to cardiovascular pathologies.

The lower levels of renin among RA patient might be explained by seepage of renin into the synovial membrane, which is supported by the high levels of renin observed in the synovial fluid [20]. While patients with RA have more cardiovascular events and higher rates of mortality than the general population, the RAAS does not seem to be directly or majorly involved in this process. Endothelial dysfunction in RA patients has been shown to foster a proinflammatory and prothrombotic state that predisposes to the development of atherosclerosis, thus explaining the increased cardiovascular events [25]. To the best of our knowledge, no studies have examined the association between renin and aldosterone levels in AS. Our study is the first to demonstrate a lower level of renin and a high ratio of renin-to-aldosterone levels in patients with AS.

Our study enrolled subjects who were not receiving any medications that could affect RAAS levels, so blood samples were taken in optimal conditions (after resting and in euvoletic states); however, our study is limited by its small sample size.

CONCLUSIONS

RA patients have low serum renin levels, indicating that the RAAS might not be involved in the process that results in increased cardiovascular events in RA. Further research is warranted to better elucidate the pathway that results in the increased morbidity and mortality of RA patients due to cardiovascular events.

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Capsule**Age matters in allergy**

Development of allergy is driven by the type 2 cytokines interleukin-4 (IL-4), IL-5, and IL-13. Type 2 innate lymphoid cells (ILC2s) and T cells can produce these cytokines. **Saglani** and co-authors studied mouse models of allergic airway inflammation and found that the contributions of T cells and ILC2s were dependent on age. T cells were the predominant source of IL-13 in neonatal mice; whereas, ILC2s were mainly

responsible for cytokine production in adult mice. Given that neonates have fewer T cells than adults, the results are contrary to expectations and bring to the fore an unappreciated role of neonatal T cells.

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Eitan Israeli

Capsule**Improving Huntington's disease detection**

Early detection of Huntington's disease (HD) could help the development of therapeutic strategies to block or delay disease progression. **Byrne** and collaborators found that blood and cerebrospinal fluid concentrations of mutant huntingtin (mHTT) and neurofilament light (NfL) proteins correlated with disease severity in HD patients. Alterations in circulating mHTT and NfL

concentrations were among the earliest detectable changes in HD. Thus, concentrations of these proteins in biofluids might be used in combination with other clinical measures to improve the accuracy and efficiency of early HD detection.

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Eitan Israeli