HHS Public Access

Author manuscript

*Clin Rheumatol*. Author manuscript; available in PMC 2019 April 01.

Published in final edited form as:

*Clin Rheumatol*. 2018 April ; 37(4): 895–900. doi:10.1007/s10067-017-3935-8.

# Association between Urinary Sodium and Potassium Excretion and Blood Pressure and Inflammation in Patients with Rheumatoid Arthritis

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## Abstract

**Objective—**Hypertension is highly prevalent in patients with rheumatoid arthritis (RA). In other populations, high sodium ($Na^+$) and low potassium ($K^+$) intake are associated with an increased risk of hypertension, and in animal models a high salt intake exacerbated arthritis. Patients with RA have many comorbidities associated with salt-sensitivity, but their salt intake and its relationship to blood pressure and inflammation is unknown.

**Methods—**Using the Kawasaki formula, $Na^+$ and $K^+$ urinary excretion (reflecting intake) was estimated in 166 patients with RA and 92 controls, frequency matched for age, sex, and race. Inflammatory markers and disease activity were measured in RA patients. We tested the associations between blood pressure and $Na^+$ and $K^+$ excretion.

**Results—**Estimated 24 hour $Na^+$ excretion was similarly high in both RA (median [IQR] 5.1 g, [3.9 g–6.6 g]) and controls (4.9 g, [4.0 g–6.5 g]), p=0.9; despite higher rates of hypertension in RA (54% vs. 39%, p=0.03). The $Na^+$:$K^+$ excretion ratio was significantly higher in RA (2.0 [1.6–2.4]) vs. 1.7 [1.5–2.1]), p=0.02] compared to controls. In RA, a lower $K^+$ excretion was inversely correlated with diastolic blood pressure (adjusted-β= -1.79, p=0.04). There was no significant association between $Na^+$ or $K^+$ excretion and inflammatory markers.

**Conclusions—**Despite a similar $Na^+$ excretion, patients with RA had higher rates of hypertension than controls, a finding compatible with increased salt sensitivity. Patients with RA had a lower $Na^+$:$K^+$ excretion ratio than controls, and lower $K^+$ excretion was associated with higher diastolic blood pressure in RA.

### Keywords

rheumatoid arthritis; hypertension; sodium; potassium

Hypertension is a modifiable risk factor for cardiovascular disease (CVD) and is highly prevalent among patients with RA compared with the general population.(1) The relative

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Conflict of Interest: none

risk of CVD in RA patients with hypertension has been reported to be as high as 4.3 compared to those with normal blood pressure.(2) This increased risk of CVD mediated by hypertension in RA is particularly important because the risk of CVD is significantly higher in patients with RA compared to the general population.(3, 4) However, the underlying determinants of hypertension in patients with RA remain poorly defined.(5)

High sodium ($Na^+$) intake is associated with both the risk of hypertension (6) and CVD mortality in the general population.(7-9) The 8$^{th}$ edition of the Dietary Guidelines for Americans, released by the U.S. Department of Health and Human Services in 2015 recommends a daily $Na^+$ intake of less than 2,300 mg, compared to the average daily consumption by the American population of 3,440 mg per day.(10) The current daily intake of $Na^+$ is also considered high by the American Heart Association which has made reduction of $Na^+$ intake in the general population a priority.

The potential benefits of decreasing $Na^+$ intake continue to be debated although a study using data on sodium consumption from 66 countries estimated that 1.65 million deaths from cardiovascular events that occurred in 2010 alone were attributed to a $Na^+$ consumption above the reference level of 2.0 g per day.(11) The effects of reducing $Na^+$ intake in hypertension are clear; for example, a large multi-center cohort study among persons with and without hypertension showed that reducing $Na^+$ intake from 142 mmol/day to 107 mmol/day) for 30 days decreased systolic blood pressure (SBP) by 2.1 mmHg. A further decrease in $Na^+$ consumption to 65 mmol/day caused an additional reduction in SPB of 4.6 mm Hg.(6, 12)

In addition to $Na^+$ intake, the intake of potassium ($K^+$) and the Na+/K+ ratio are also associated with the risk of developing CVD.(7, 8) In a large multicenter cross-sectional study, $K^+$ excretion was inversely associated with SBP,(13) and the combined effect of high $Na^+$ and low $K^+$ intake, measured by an increase in the $Na^+$:$K^+$ excretion ratio, was associated with an increase in both SBP and DBP.(13)

Patients with RA have many clinical features associated with increased salt sensitivity including an increased prevalence of metabolic syndrome,(14) vascular stiffness,(15) insulin resistance,(16) central obesity,(17) and endothelial dysfunction.(18, 19) Furthermore, recent findings in animals implicate salt in autoimmunity and inflammation. A high salt diet augmented inflammation markedly in an experimental autoimmune encephalomyelitis (EAE) model of autoimmunity.(20, 21) In keeping with the concept that salt may exacerbate autoimmunity, a low salt diet ameliorated clinical and histological features of arthritis in a murine model.(22) However, little is known about the association between $Na^+$ and $K^+$ intake and blood pressure and the relationship between $Na^+$ intake and inflammation in patients with RA. Therefore, the aims of this study were: (1) to examine the hypothesis that urinary $Na^+$ and $K^+$ excretion differed in patients with RA compared to control subjects, and (2) that urinary $Na^+$ and $K^+$ are related to blood pressure and markers of inflammation among RA patients.

## Materials and Methods

We studied 166 patients with RA and 92 controls without an autoimmune disease from a cross-sectional study performed at Vanderbilt University Medical Center from a cohort assembled to evaluate cardiovascular risk factors in RA. (23, 24) As described previously, patients with RA were recruited from rheumatology clinics in Nashville TN if they met the following inclusion criteria: fulfillment of the 1987 American College of Rheumatology classification criteria for RA,(25) age 18 years or older. Control subjects were volunteers without RA or inflammatory diseases. RA patients and control subjects were frequency-matched on age, sex, and race. Vanderbilt's Institutional Review Board reviewed and approved this study (IRB approval #000567).

RA patients and control subjects underwent a standard medical interview. Information about demographic characteristics, cardiovascular risk factors, disease duration, physical activity, medication use, and smoking habits was obtained by conducting a standardized interview, physical examination, and laboratory testing. Additional information was extracted from the electronic medical records. Height and weight were measured for body mass index (BMI) calculations and the presence of metabolic syndrome (14), using the modified World Health Organization (WHO) criteria was determined.(26) Briefly, subjects were classified as having metabolic syndrome if they had insulin resistance (homeostasis model assessment index in the upper quartile), impaired fasting glucose (≥6.1 mmol/L), or diabetes with at least 2 of the following criteria: central obesity, dyslipidemia and high blood pressure.

First morning midstream urine samples were collected and stored at a temperature of - 80° C. For analysis, urine samples were thawed, centrifuged at 5000 rpm at 4°C for 5 minutes, and 100 μl of supernatant transferred to new Eppendorf tubes. The concentrations of urinary $Na^+$ and $K^+$ were measured by flame photometry using an EFOX 5053 Electrolyte Analyzer from Eppendorf ®. The estimation of 24 hour $Na^+$ and $K^+$ excretion was performed using the Kawasaki formula. The Kawasaki formula incorporates age, sex, height, weight, and the creatinine to $Na^+$ and $K^+$ concentrations of a spot urine sample.(27, 28) Additionally, RA patients had blood samples drawn after an overnight fast to measure markers of inflammation. C-reactive protein (CRP) was measured by the hospital laboratory or by enzyme-linked immunosorbent assay (ELISA; Millipore, St. Charles, MO). Interleukin-6 (IL-6), vascular cell adhesion molecule-1 (VCAM-1), tumor necrosis factor (TNF-α), and insulin concentrations were measured by Multiplex ELISA (LincoPlex Multiplex Immunoassay kit, Millipore). The homeostasis model assessment (HOMA) index was used to determine insulin sensitivity ([fasting glucose (mmoles/liter) x fasting insulin (μU/ml)]/ 22.5), which was in turn used to determine insulin resistance, a diagnostic criteria for metabolic syndrome, which is associated with CVD in RA patients.(14)

Blood pressure was measured while patients were seated comfortably. The average of two measurements 5 minutes apart was considered as the blood pressure of study subjects. Hypertension was defined as the use of anti-hypertensive medications or SBP of ≥ 140 mmHg or DBP of ≥ 90 mmHg.

Informed consent was given by all patients and controls prior to data and sample collection. The study protocol was approved by the Vanderbilt University Medical Center's institutional review board.

## Statistical Analysis

Categorical and continuous variables were compared using Fisher's exact test and Wilcoxon's test, respectively. Spearman correlations were used to test the association between estimated 24 hour $Na^+$ and $K^+$ excretion and blood pressure in RA patients and controls, and estimated 24 hour $Na^+$ and $K^+$ excretion and inflammatory markers in RA patients. Multivariate linear regressions were modeled to assess the association between systolic and diastolic blood pressures and $Na^+$ and $K^+$ excretion and their ratio, adjusting for sex, age, and race. All statistical analyses were performed using Stata Version 13.0 (StataCorp, College Station, TX). Two-sided p-values of <0.05 were considered statistically significant.

## Results

The characteristics of this cohort have been described previously. (14, 23, 29) Patients with RA (n=166) and control subjects (n=92) had similar median (interquartile range) age of 54 (45 - 63) vs. 53 (45 - 60) years, respectively, p =0.43], were predominantly female (68.7% vs. 63.0%, p=0.41) and Caucasian (88.6% vs. 84.8%, p=0.44). Baseline characteristics that differed significantly among RA and control groups included insulin resistance (51.9 % vs 17.8 %, p <0.001), metabolic syndrome (37.1% vs 21.8%, p=0.02), smoking (23.5% vs 8.7%, p=0.004), prevalence of hypertension (54.0% vs. 39.0%, p=0.03) and SBP [134 (119 to 146) mmHg vs. 129 (115 - 137) mmHg, p =0.05) (Table 1).

The estimated median 24 hour $Na^+$ excretion was 5.1 (IQR = 3.9 - 6.6) and 4.9 (4.0 - 6.5) g/day, (p = 0.9) and for $K^+$ was 2.5 (2.1 - 3.2) and 2.7 (2.2 - 3.8) g/day, p=0.08 in RA patients and control subjects, respectively. The estimated urinary $Na^+$:$K^+$ ratio was higher in patients with RA than in controls (2.0 [1.6 - 2.4] vs. 1.7 [1.5 - 2.1], p-value = 0.02). There was no statistically significant difference in $Na^+$, $K^+$ or their ratio in either RA patients or controls with and without hypertension or metabolic syndrome (all p-values >0.05).

There was no significant association between the estimated $Na^+$ and $K^+$ excretion and SBP among RA patients; however, the estimated $K^+$ intake was inversely correlated with DBP [β coefficient (95% CI) = − 1.79 (− 3.46 to − 0.13), p-value = 0.04] after adjustment for age, sex and race (Table 2). Neither $Na^+$ nor $K^+$ intake was significantly associated with DAS28 or markers of inflammation, including VCAM-1, CRP, IL-6, IL-10 and TNF-α (all p-values >0.05). (Table 3)

## Discussion

This study has several novel findings. First, the estimated 24 hour $Na^+$ was high but did not differ in RA and controls despite a greater prevalence of hypertension in RA. Second, the mean estimated 24 hour $Na^+$:$K^+$ excretion ratio was higher among RA patients compared to

control subjects. Third, among RA patients, the estimated 24-hour $K^+$ excretion ratio was inversely associated with diastolic blood pressure (DBP).

The median estimated daily $Na^+$ intake was approximately 5,500 mg in both groups and this is higher than the average intake of US adults.(30) This high intake has adverse cardiovascular effects and the American Heart Association and the Institute of Medicine recommend an intake of less than 1,500 mg (31) and 2300 mg (32) of $Na^+$, respectively, putting these patients at an increased risk for hypertension, cardiovascular events, and death.

We have previously reported in this cohort of RA patients that hypertension was more prevalent than in controls and this observation is concordant with the findings of others.(5, 7, 33) The finding that $Na^+$ excretion did not differ among patients with RA and controls is interesting because it suggests that patients with RA may represent a salt-sensitive population. Salt sensitivity is characterized by an increase in blood pressure caused by salt loading and a decrease of blood pressure following salt depletion. Salt sensitivity, which affects about half of the hypertensive population (34), has been associated with metabolic syndrome(35) and endothelial dysfunction,(36) but its association with RA has yet to be studied.

A greater $Na^+$:$K^+$ ratio is a risk factor of hypertension in the general population,(13) and was higher in RA patients compared to control subjects. The higher $Na^+$:$K^+$ ratio likely reflects dietary intake but it is likely affected by medications commonly used for RA such as NSAIDs, coxibs and glucocorticoids(33, 37). Also, 24-hour $K^+$ excretion and DBP were inversely correlated. Similar findings were observed in the general population.(13, 38) The linear regression model indicated that for every 1 gram increase in 24-hour $K^+$ excretion, there was a 1.79 mmHg decrease in DBP. Despite being a modest decrease in DBP, previously published meta-analyses have shown that even small changes in diastolic blood pressure of 10 and even 5 mmHg can substantially modify the risk of cardiovascular death by as much as two fold.(39, 40) This is important because low $K^+$ intake is a modifiable risk factor of hypertension and it means that increasing $K^+$ intake may reduce the risk of hypertension among RA patients.

In addition to the vascular effects of $Na^+$, pre-clinical studies have demonstrated that a high salt diet promotes inflammation and manifestations of autoimmune diseases.(20, 21, 41) Recent work in mice showed that high salt concentrations activate the immune system, particularly Th17 cells, resulting in production of IL-17 and other pro-inflammatory cytokines.(20) Moreover, clinical inflammation was markedly augmented by a high salt diet in an experimental autoimmune encephalomyelitis (EAE) model of autoimmunity.(20, 21) Additionally, in studies presented in abstract,(22) a low salt diet ameliorated clinical and histological features of arthritis in a murine model. Also, recent epidemiologic studies suggest a relationship between high $Na^+$ intake and risk for RA.(42, 43) Despite these pre-clinical and epidemiologic findings, we did not find a statistically significant association between estimated $Na^+$ and $K^+$ excretion and inflammation markers among patients with RA. However, just as sensitivity of blood pressure to the same $Na^+$ intake varies, so too may the inflammatory response.

The study had some limitations. The cross-sectional design, with urine collected on only one occasion, limits our ability to identify a temporal relationship between $Na^+$ and $K^+$ excretion and blood pressure. Second, the sample size was relatively small and thus, we cannot exclude small changes or weak correlations between $Na^+$ and $K^+$ and blood pressure or inflammatory markers.

In conclusion, despite a similar $Na^+$ excretion, patients with RA had higher rates of hypertension than controls, a finding compatible with increased salt sensitivity. Patients with RA had a lower $Na^+$:$K^+$ excretion ratio than controls, and lower $K^+$ excretion was associated with higher diastolic blood pressure in RA. Future intervention studies are needed to fully understand the effects of $Na^+$ and $K^+$ intake on hypertension in this patient population.

## Acknowledgments

**Financial Support:** Supported by grants from: Alpha Omicron Pi (Stein), Arthritis Foundation Clinical to Research Transition Award (Stein), P60-AR-056116 (Stein), K23AR064768 (Chung), Rheumatology Research Foundation K-supplement (Chung), T32 GM07569 (Stein), and CTSA awards No. UL1TR000445 and UL1RR024975 from the National Center for Advancing Translational Sciences. Its contents are solely the responsibility of the authors and do not necessarily represent official views of the National Institutes of Health.

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## Table 1

Characteristics of patients with rheumatoid arthritis (RA) and control subjects

| Characteristics | RA patients (n=166) | Control (n=92) | P-value* |
|---|---|---|---|
| Age (years) | 54 (45 – 63) | 53 (45 - 60) | 0.43 |
| Female sex – n (%) | 114 (68.7) | 58 (63.0) | 0.41 |
| Race – White (%) | 147 (88.6) | 78 (84.8) | 0.44 |
| Education level | | | |
| High school or less – n (%) | 80 (48.5) | 26 (28.3) | 0.002 |
| College level or more – n (%) | 85 (51.5) | 66 (71.7) | 0.002 |
| Body mass index – kg/m$^2$ | 28.4 (24.0 – 33.2) | 27.0 (24.5 – 31.2) | 0.43 |
| Weight – kg | 79.0 (70.2 – 91.2) | 76.5 (69 - 92.4) | 0.56 |
| Height – m | 1.7 (1.6 -1.8) | 1.7 (1.6-1.8) | 0.74 |
| Currently smoking | 39 (23.5) | 8 (8.7) | 0.004 |
| Insulin resistance – HOMA-IR index$ | 84 (51.9) | 16 (17.8) | <0.001 |
| Metabolic syndrome – n (%)$ | 59 (37.1) | 19 (21.8) | 0.02 |
| Diabetes mellitus – n (%) | 19 (11.4) | 4 (4.3) | 0.07 |
| Serum creatinine – mg/dl | 0.8 (0.7-0.9) | 0.8 (0.7 - 0.9) | 0.62 |
| GFR – ml/min per 1.73 m$^2$ | 87.3 (73.7 – 102.7) | 84.8 (76.3 – 94.3) | 0.40 |
| Duration of disease - years | 3.5 (2 – 18) | N/A | N/A |
| DAS28 score | 3.9 (2.6-4.8) | N/A | N/A |
| Hypertension (%) | 54.0 | 39.0 | 0.03 |
| Systolic blood pressure (mm Hg) | 134 (119 – 146) | 129 (115 – 137) | 0.05 |
| Diastolic blood pressure (mm Hg) | 75 (68 – 82) | 72 (68 – 78) | 0.08 |
| Anti-hypertensive use (%) | 38.6 | 26.4 | 0.06 |
| Diuretic use (%) | 30 (18.1%) | 9 (9.8%) | |
| Non steroidal anti inflammatory drugs use (%) | 51 (30.7) | 9 (9.9) | |
| Estimated 24 hour urinary Na (grams), median (IQR) | 5.1 (3.9 – 6.6) | 4.9 (4.1 – 6.5) | 0.9 |
| Estimated 24 hour urinary potassium (grams), median (IQR) | 2.5 (2.1-3.2) | 2.7 (2.3 – 3.8) | 0.08 |
| Estimated 24 hour urinary Na:K ratio | 2.0 (1.6 – 2.4) | 1.7 (1.5 -2.1) | 0.02 |

Continuous variables are presented as median (interquartile range)

$ Data to calculate the HOMA (Homeostasis Model Assessment) index was available in 160 patients with RA and 90 control subjects. A HOMA index of >2.114 was used as a cut-off point of insulin resistance.[17]

Data to calculate the metabolic syndrome was available in 159 patients with RA and 87 control subjects

* P-values represent the comparison between RA patients and controls by Mann-Whitney test and Fisher's exact test, as appropriate.

** 1 mmol sodium = 23 mg sodium

**Table 2**

Relationship between $Na^+$ and $K^+$ excretion and $Na^+$: $K^+$ excretion ratio and systolic and diastolic blood pressure in patients with RA

| Parameters | 24 h $Na^+$ excretion Adjusted β (95% CI) | P- value | 24 h $K^+$ excretion Adjusted β (95% CI) | P-value | $Na^+$: $K^+$ ratio Adjusted β (95% CI) | P- value |
|---|---|---|---|---|---|---|
| Systolic Blood Pressure | −0.02 (−1.09 to 1.04) | 0.97 | −0.48 (−3.32 to 2.36) | 0.74 | 2.0 (−2.3 to 6.3) | 0.36 |
| Diastolic Blood Pressure | −0.28 (−0.92 to 0.35) | 0. 38 | **−1.79 (−3.46 to −0.13)** | 0.04 | 2.1 (−0.4 to 4.7) | 0.10 |

$Na^+$, estimated 24 hour urinary sodium excretion (grams); $K^+$, estimated urinary potassium excretion (grams), $Na^+$:$K^+$ ratio excretion ratio.

*Linear regression was performed adjusting for age, sex, and race

## Table 3

Association of disease activity score and inflammatory markers with estimated 24 hour urinary $Na^+$, $K^+$, and $Na^+$: $K^+$ ratio in patients with rheumatoid arthritis

| Parameters | $Na^+$ (grams) | $K^+$ (grams) | $Na^+$:$K^+$ excretion ratio |
|---|---|---|---|
| **VCAM-1** | rho= 0.01 | rho= -0.03 | rho= 0.06 |
| | p= 0.88 | p= 0.67 | p= 0.46 |
| **CRP** | rho= −0.1 | rho= −0.11 | rho= −0.05 |
| | p= 0.17 | p= 0.16 | p= 0.54 |
| **IL-6** | rho= −0.04 | rho= −0.10 | rho= 0.01 |
| | p= 0.56 | p= 0.19 | p= 0.91 |
| **TNF-α** | rho= -0.09 | rho= 0.01 | rho= −0.11 |
| | p= 0.27 | p= 0.90 | p= 0.14 |
| **DAS28** | rho= −0.007 | rho= 0.009 | rho= 0.009 |
| | p= 0.93 | p= 0.91 | p= 0.91 |

VCAM 1: Vascular Cell Adhesion Molecule-1, CRP: C-reactive protein, IL-6: interleukin-6, TNF-α: tumor necrosis factor alpha, DAS28: Disease Activity Score 28, n=161.

Correlation analysis was performed using Spearman Correlation. P value of <0.05 were considered statistically significant.