

Urinary Sodium-To-Potassium Ratio Is A Dual Indicator Of Hypertension And Current Disease Activity In Patients With Rheumatoid Arthritis: A Cross-Sectional Study In The KURAMA Cohort Database

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Abstract

Background: Excessive salt intake is thought to exacerbate both development of hypertension and autoimmune diseases in animal models, but the clinical impact of excessive salt in rheumatoid arthritis (RA) patients is still unknown. We performed a cross-sectional study to clarify the associations between salt load index (urinary sodium-to-potassium ratio (Na/K ratio)), current disease activity and hypertension in an RA population.

Methods: Three hundred thirty-six participants from our cohort database (KURAMA) were enrolled. We used the spot urine Na/K ratio as a simplified index of salt loading, and used the 28-Joint RA Disease Activity Score (DAS28-ESR) as an indicator of current RA disease activity. Using these indicators, we evaluated statistical associations between urinary Na/K ratio, DAS28-ESR and prevalence of hypertension.

Results: Urinary Na/K ratio was positively associated with measured systolic and diastolic blood pressure and also with prevalence of hypertension even after covariate adjustment (OR 1.30, $p < 0.001$). In addition, increased urinary Na/K ratio was significantly and positively correlated with DAS28-ESR in multiple regression analysis (estimate 0.12, $p < 0.001$), as was also the case in gender-separated and prednisolone-separated sub-analyses.

Conclusion: Urinary Na/K ratio was independently associated with current disease activity as well as with prevalence of hypertension in RA patients. Thus, dietary modifications such as salt restriction and potassium supplementation may well attenuate both disease activity and hypertension in RA patients.

Background

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by articular destruction and increased risk of comorbidity and mortality [1]. Over the past decades, clinical outcomes of RA have been dramatically improved by new therapeutics such as biological disease-modifying antirheumatic drugs (bDMARDs) and Janus kinase (JAK) inhibitors [2, 3]. Despite such therapy, some patients continue to exhibit sustained high disease activity, which suggests involvement of unknown genetic or environmental factors.

A number of studies have reported that environmental factors participate in the pathogenesis of RA, including smoking, poor dental care, microbial imbalance and poor dietary habits [4, 5]. Recently, in experimental animal models, excessive salt intake has been implicated in the development of autoimmune diseases (i.e., RA, systemic lupus erythematosus, multiple sclerosis and Crohn's disease) [6, 7]. In addition, excessive salt loading promotes pro-inflammatory responses in RA patients by affecting various types of immune cells [5, 6], and dietary salt presents a dose-dependent risk for the emergence of self-reported RA [8]. However, the clinical association between high salt intake and current disease activity of RA is still unclear.

Previous epidemiological studies have used various methods for estimating daily salt intake, which include Kawasaki's formula and Tanaka's formula [9, 10]. Recently, clinical evidence has emerged suggesting that the urinary sodium-to-potassium (Na/K) ratio is a useful index of dietary salt loading [11, 12]. Urinary Na/K ratio has a stronger correlation with blood pressure (BP) levels than Tanaka's formula, and is used as a simple indicator of hypertension in the general population. However, so far there have been only small-scale studies using the urinary Na/K ratio for evaluation of clinical characteristics in an RA population [13].

In the present study, we used the spot urine Na/K ratio as a simplified index of salt loading, and assessed statistical associations between the urinary Na/K ratio and RA disease activity as well as between the urinary Na/K ratio and hypertension in RA patients.

Methods

Study design and participants

We conducted a cross-sectional study of RA patients who participated in the Kyoto University Rheumatoid Arthritis Management Alliance cohort (KURAMA cohort study) [14, 15]. The cohort was founded in May 2011 on the principle of appropriate control and improved prognosis for RA patients at the Center for Rheumatic Diseases in Kyoto University Hospital. A total of 441 RA outpatients who visited the hospital between May 1 and November 30, 2016 and who fulfilled the 2010 American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) classification were included [16]. Of the 441 participants, we excluded those with the following conditions: unsuccessful measurement of clinical parameters related to this study and lack of a complete dataset of body composition ($n = 70$); those with confounding conditions or treatments such as dialysis, hepatitis, sex-hormone replacement or suppression therapy and psychiatric disorders ($n = 35$) were also excluded. The remaining 336 participants were subjected to the analysis. All study procedures were in accordance with the Declaration Helsinki and were approved by the ethics committee of Kyoto University Graduate School and Faculty of Medicine (Approval number: R0357). In all cases, patient consent was obtained prior to sample and data collection.

Analysis of urine samples

Spot urine samples were collected and stored at -80°C . The concentrations of urinary sodium (Na), potassium (K) and Creatinine (Cre) were measured using Electrolyte Analyzer and enzymatic method, respectively. (LSI Medience Co., Tokyo, Japan). Estimated daily salt intake was calculated using following Tanaka's formula, which includes urinary Na, Cre, body weight, height and age [10]: Daily salt intake: $21.98 \times \{ \text{Na (mEq/l)} \times 24\text{-h Cre excretion} / [\text{Cre (mg/dl)} \times 10] \}^{0.392} \times 0.0585$. 24-h Cre excretion was calculated using following formula: $\text{height (cm)} \times 16.14 + \text{body weight (kg)} \times 14.89 - \text{age} \times 2.04 - 2444.45$.

RA-related factors and other clinical parameters

Disease activity and physical disability of RA was assessed using the following parameters: the 28-Joint RA Disease Activity Score (DAS28-ESR), the health assessment questionnaire-disability index (HAQ) and Steinbrocker's stage and class. The following laboratory data were also evaluated: C-reactive protein (CRP), serum Creatinine (Cre), estimated glomerular filtration (eGFR), rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP antibody), and matrix metalloproteinase-3 (MMP-3). Information on current RA therapeutics including use of methotrexate (MTX), prednisolone (PSL) and biological agents was extracted from the medical records.

Branchial blood pressure was measured after a few minutes rest in the sitting position by automatic digital monitor. Hypertension was defined by antihypertensive medication use, systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg.

Statistical analysis

To analyze tertiles stratified by urinary Na/K level, a Cochran-Armitage trend test for categorical variables and a Jonckheere-Terpstra trend test for continuous variables was performed. To determine the relationship between blood pressure and urinary Na/K, urinary Na/K, SBP and DBP were compared by use of Spearman's rank correlation coefficient. Multivariate analysis was used to assess the association between the prevalence of hypertension and urinary Na/K. Dummy variables were constructed as follows: 0 = without hypertension, 1 = with hypertension, and multivariate logistic analysis was performed with adjustment for variables known to be associated with hypertension, including sex, age and smoking status. To assess the association between RA disease activity and urinary Na/K, multiple linear regression analysis was carried out with adjustment for covariates known to be associated with disease activity including sex, age, RF, anti-CCP antibody, smoking, current therapeutics (use of MTX, PSL and biological agents), eGFR and BMI [17]. Because PSL use and sex difference may be a confounding factors for both disease activity and urinary Na/K, additional multivariate analysis that did not include PSL use or sex difference was performed. Statistical significance was determined by use of JMP 14.0.0 software (SAS Institute Inc., Cary, NC, USA) and SPSS Statistics 26 software (IBM, Armonk, NY, USA); the level of significance was set at $P = 0.05$.

Table 1

Clinical characteristics of study population (n = 336)

Continuous variables are presented as mean (\pm standard deviation) and categorical variables are presented as numbers (%). Data on RA-related parameters are expressed as median (range).

Age, years	61.8 \pm 12.0
Male, n (%)	57 (17.0)
BMI, kg/m ²	22.7 \pm 3.7
Smoking status, n (%)	28 (8.3)
RA-related parameters	
Duration, years	10.6 \pm 9.6
RF, IU/mL	38.5 (0-2833.6)
Anti-CCP antibody, U/mL	50.45 (0.6–3260)
MMP-3, ng/mL	56.8 (18.2-633.6)
CRP, mg/dL	0.1 (0.1–9.6)
DAS28-ESR	2.4 (0.78–7.20)
HAQ score	0.25 (0-2.50)
Stage*	2.38 \pm 1.16
Class*	1.52 \pm 0.60
Laboratory data	
Serum Cre, mg/dL	0.69 \pm 0.20
eGFR, ml/min/1.73m ²	74.6 \pm 18.0
Blood pressure	
SBP (Branchial), mmHg	122.9 \pm 17.4
DBP (Branchial), mmHg	70.5 \pm 11.8
Hypertension, n (%)	110 (32.7)

Abbreviations: BMI Body mass index, RF rheumatoid factor, anti-CCP antibody anti-cyclic citrullinated peptide antibody, MMP-3 matrix metalloproteinase 3, CRP C-reactive protein, DAS28-ESR 28-joint disease activity score using erythrocyte sedimentation, HAQ health assessment questionnaire, Cre creatinine, eGFR estimated glomerular filtration, SBP systolic blood pressure, DBP diastolic blood pressure, Na sodium, K potassium, MTX methotrexate, csDMARD conventional synthetic disease modifying anti-rheumatic drugs, tsDMARD targeted synthetic DMARD, PSL prednisolone.

* Stage and Class: Steinbrocker's classification

Age, years	61.8 ± 12.0
Urinalysis	
Cre, mg/dL	93.9 ± 63.9
Na, mEq/L	102.8 ± 51.7
K, mEq/L	49.9 ± 29.9
Na/K ratio	2.60 ± 1.68
Estimated daily salt intake, g	7.80 ± 2.20
Current RA therapeutics	
MTX use, n (%)	246 (73.2)
Other cs DMARDs use, n (%)	116 (34.5)
Biological agent use, n (%)	174 (51.8)
PSL use, n (%)	70 (20.8)
Abbreviations: BMI Body mass index, RF rheumatoid factor, anti-CCP antibody anti-cyclic citrullinated peptide antibody, MMP-3 matrix metalloproteinase 3, CRP C-reactive protein, DAS28-ESR 28-joint disease activity score using erythrocyte sedimentation, HAQ health assessment questionnaire, Cre creatinine, eGFR estimated glomerular filtration, SBP systolic blood pressure, DBP diastolic blood pressure, Na sodium, K potassium, MTX methotrexate, csDMARD conventional synthetic disease modifying anti-rheumatic drugs, tsDMARD targeted synthetic DMARD, PSL prednisolone.	
* Stage and Class: Steinbrocker's classification	

Results

Characteristics of study participants

The baseline characteristics of the 336 patients with RA are shown in Table 1. The mean age and the average RA duration were 61.8 years and 10.6 years, respectively. Compared to other reports, current RA activity measured by DAS28-ESR was generally low, possibly due to intensive treatments including biologic agents [18]. Indicators of salt intake including urinary Na/K ratio and estimated daily salt intake were similar compared to those in other reports [8, 13]. MTX, biological agent and PSL were used in 73.2%, 51.8%, and 20.8% of RA patients, respectively.

Comparison of characteristics in urinary Na/K ratio tertiles

To clarify the effect of the Na/K ratio on RA-related and hypertension-related factors, RA patients were stratified into tertiles by Na/K ratio, and characteristics were compared among the three groups. As urinary Na/K was increased, the prevalence of hypertension and measured value of blood pressure, both

systolic and diastolic, also increased (Table 2). The current RA disease activity scores including DAS28-ESR and DAS28-CRP also increased significantly as urinary Na/K increased. Age, BMI, eGFR and the percentage of males also increased along with the Na/K ratio. Regarding RA therapeutics, as the urinary Na/K ratio increased, the percentage of MTX use decreased while the percentage of PSL use increased.

Table 2
 Characteristics of RA patients stratified by urinary Na/K ratio

Continuous variables are presented as mean (\pm standard deviation) and categorical variables are presented as numbers (%).

	Tertile 1	Tertile 2	Tertile 3	
urine Na/K ratio	< 1.71		2.94 <	
(N = 336)	<i>n</i> = 112 (33.3%)	<i>n</i> = 112 (33.3%)	<i>n</i> = 112 (33.3%)	P value *
Age, year	60.0 \pm 13.2	62.4 \pm 11.8	63.1 \pm 11.0	0.143
Male sex, n (%)	10 (8.92)	22 (19.64)	25 (22.32)	0.001
Body mass index, kg/m ²	22.0 \pm 3.1	22.6 \pm 3.7	23.4 \pm 4.1	0.011
Smoking habit, n (%)	7 (6.25)	11 (9.82)	10 (8.93)	0.547
Daily salt intake (g/day)	6.09 \pm 1.36	7.67 \pm 1.44	9.66 \pm 2.04	< 0.001
Laboratory data				
Serum Cre, mg/dL	0.69 \pm 0.16	0.72 \pm 0.27	0.66 \pm 0.16	0.081
eGFR, ml/min/1.73m ²	72.9 \pm 18.2	73.0 \pm 18.3	77.8 \pm 17.2	0.010
CRP, mg/dL	0.32 \pm 0.73	0.33 \pm 0.65	0.45 \pm 1.19	0.460
RF, IU/mL	100.3 \pm 302.5	142.5 \pm 279.4	131.4 \pm 289.0	0.246
anti-CCP antibody, U/mL	201.8 \pm 435.8	242.8 \pm 446.3	223.5 \pm 444.2	0.216
MMP-3, ng/mL	73.8 \pm 73.7	93.5 \pm 86.0	96.3 \pm 105.2	0.302
RA disease characteristics				
Disease duration, year	9.66 \pm 9.62	10.91 \pm 9.82	11.16 \pm 9.32	0.117
DAS28-ESR	2.40 \pm 0.83	2.53 \pm 0.96	2.74 \pm 1.08	0.025
DAS28-CRP	1.92 \pm 0.73	2.01 \pm 0.79	2.22 \pm 1.00	0.042
HAQ	0.37 \pm 0.48	0.48 \pm 0.57	0.52 \pm 0.66	0.202
Stage	2.22 \pm 1.14	2.45 \pm 1.14	2.48 \pm 1.19	0.094
Class	1.45 \pm 0.57	1.60 \pm 0.62	1.52 \pm 0.60	0.386
Blood pressure				
SBP (Branchial), mmHg	120.4 \pm 16.5	121.2 \pm 16.4	126.9 \pm 18.5	0.009
DBP (Branchial), mmHg	69.2 \pm 10.5	69.3 \pm 11.3	72.9 \pm 13.1	0.043
Hypertension, <i>n</i> (%)	25 (22.3)	37 (33.0)	48 (42.9)	0.0011

	Tertile 1	Tertile 2	Tertile 3	
Current RA therapeutics				
MTX use, <i>n</i> (%)	90 (80.3)	80 (71.4)	76 (67.9)	0.035
Biological agent use, <i>n</i> (%)	63 (56.3)	55 (49.1)	56 (50.0)	0.386
Prednisolone use, <i>n</i> (%)	17 (15.2)	23 (20.5)	30 (26.8)	0.040

Abbreviations: *RA* rheumatoid arthritis, *Cre* creatinine, *eGFR* estimated glomerular filtration, *RF* rheumatoid factor, *anti-CCP antibody* anti-cyclic citrullinated peptide antibody, *MMP-3* matrix metalloproteinase 3, *DAS28-ESR* 28-joint disease activity score using erythrocyte sedimentation, *CRP* C-reactive protein, *HAQ* health assessment questionnaire, *MTX* methotrexate.

**P*-values are calculated using Cochran-Armitage trend test for categorical variables and Jonckheere-Terpstra trend test for continuous variables

Urinary Na/K ratio is positively associated with measured blood pressure and prevalence of hypertension

Although urinary Na/K ratio is a well-known indicator of blood pressure levels in the general population [11, 12], whether this is true in RA patients is not known. The relationship between urinary Na/K and measured blood pressure was therefore examined in RA patients. A significant positive association between urinary Na/K and systolic blood pressure ($\rho = 0.1516$, $p = 0.0054$) as well as between urinary Na/K and diastolic blood pressure ($\rho = 0.1173$, $p = 0.0316$) was observed. (Fig. 1A and B) Furthermore, the urinary Na/K ratio of RA patients with hypertension was higher than that of RA patients without hypertension (Fig. 1C), and multivariate logistic analysis after adjustment for sex, age and smoking status revealed an independent and positive association between urinary Na/K and prevalence of hypertension in RA patients. (OR 1.30, 95% CI 1.11–1.52, $p < 0.001$) (Table 3) These findings strongly suggest that urinary Na/K is an indicator of hypertension in RA patients as well as in the general population.

Table 3
Multivariate logistic analysis for the factors associated with hypertension

Results of multivariate logistic regression regarding the presence of hypertension in RA patients. We constructed dummy variables as follows: 0 = without hypertension and 1 = with hypertension, and logistic analysis was carried out with potential confounders including age, sex and current smoking status.

variables	OR	95% CI	Pvalue
Age (1 year)	1.10	1.06–1.13	< 0.001
Urinary Na/K ratio (1)	1.30	1.11–1.52	< 0.001
Sex (male = 1, female = 0)	1.97	1.01–3.83	0.046

Abbreviations: *RA* rheumatoid arthritis, *OR* odds ratio

Urinary Na/K ratio is independently associated with current RA disease activity

To determine whether urinary Na/K ratio contributes to current RA disease activity, we performed multiple regression analysis with DAS28-ESR as the dependent variable. After adjustment for covariates known to be related to disease activity, urinary Na/K ratio was found to be independently and positively associated with DAS28-ESR (estimate 0.12, $p < 0.001$) (Table 4). In addition, because use of PSL and sex difference may be a confounding factor affecting both disease activity and urinary Na/K [19], subgroup analysis was performed to account for use of PSL and sex difference. Urinary Na/K ratio remained independently associated with DAS28-ESR in gender-separated analysis (Supplementary Table S1) as well as in PSL-separated analysis (Supplementary Table S2). These results indicate that urinary Na/K ratio is an independent indicator associated with current RA disease activity.

Table 4
Multivariate analysis for independent factors associated with DAS28-ESR

Results of multiple regression analysis adjusted for urinary Na/K and other variables including sex, age, RF, anti-CCP antibody, smoking status, current therapeutics (the use of MTX, PSL and biological agents), eGFR and BMI.

Dependent variables	Independent variables	Estimates	Std. Error	95%CI		p-value
				Lower	Upper	
DAS28-ESR	Sex (male)	-0.58	0.14	-0.85	-0.31	< 0.0001
	Prednisolone (+)	0.48	0.12	0.23	0.72	0.0001
	Urinary Na/K ratio	0.11	0.030	0.048	0.170	0.0004
	age (1 year)	0.015	0.0046	0.0055	0.024	0.0016
	RF (1 IU/mL)	0.00054	0.00019	0.00017	0.00091	0.0042
	Biological agent (+)	-0.23	0.098	-0.42	-0.033	0.021
	Anti-CCP antibody (10 U/mL)	0.0025	0.0012	0.00015	0.0048	0.037
	Abbreviations: <i>DAS28-ESR</i> 28-joint Disease Activity Score using erythrocyte sedimentation rate, <i>anti-CCP antibody</i> anti-cyclic citrullinated peptide antibody, <i>CI</i> confidence interval.					

Discussion

In the present study, we show a statistical correlation between RA disease activity and urinary Na/K ratio as well as between hypertension and urinary Na/K ratio. The Na/K ratio of spot urine was positively associated with systolic and diastolic BP, and was significantly associated with the prevalence of hypertension even after covariate adjustment. In addition, in multivariate analysis including RA related factors, urinary Na/K ratio was independently correlated with current disease activity score (DAS28-ESR). These results indicate that urinary Na/K ratio reflects not only hypertension but also current disease status in RA patients.

Our finding of a statistical association between urinary Na/K ratio and hypertension in RA patients corresponds to previous findings in the general population [11, 12, 19]. Abundant evidence has recently emerged indicating that both excess sodium and potassium deficit participate in the development of hypertension [20–22], and that the combined effect of higher sodium and lower potassium levels on BP is greater than that of either one alone [11, 23]. Similarly, the urinary Na/K ratio has a stronger statistical relationship with BP levels than that of either Na or K secretion alone [11, 24], and also associates with left ventricular hypertrophy and cardiovascular disease [25, 26]. In addition, dietary modifications that can reduce the urinary Na/K ratio are recommended as well-established nutritional therapies for hypertension,

such as salt restriction and increased potassium intake (i.e., a diet rich in fruits and vegetables) [27–29]. Considering these findings together, the urinary Na/K ratio may be useful as an indicator of hypertension in the RA population as it is in the general population; dietary modification strategies that reduce the urinary Na/K ratio in the general population may well benefit RA patients.

We also show a significant correlation between DAS28-ESR and urinary Na/K ratio. Urinary Na/K ratio is a strong indicator of hypertension, and is affected by both dietary salt and potassium as mentioned above. Recently, basic and clinical studies have reported that sodium and potassium are closely related to the immune system and RA development [7, 8, 30]. A high sodium concentration enhances differentiation of potentially pathogenic Th17 cells [31], promotes pro-inflammatory macrophage polarization [32], and reduces anti-inflammatory responses of Treg cells and M2 macrophages [33, 34]. In animal models, mice with collagen-induced arthritis (CIA) on high salt diet show severe joint inflammation that is accelerated by increased Th-17 cell differentiation [35]. In epidemiological studies, dietary sodium has a dose-dependent relationship with the emergence of RA [8], and high salt intake combined with smoking results in increased risk for the appearance of anti-CCP antibodies [36]. In addition, a pilot study has shown that potassium supplementation improves joint pain in RA patients with hypokalemia [37]. Moreover, our group has previously reported that potassium-rich ingredients such as fruits and vegetables are significantly associated with lower RA disease activity [38]. In summary, the urinary Na/K ratio is an independent disease activity marker of RA, and increased Na intake and decreased K intake may contribute to RA pathogenesis.

In multivariate logistic analysis, other variables such as RF, anti-CCP antibody, age, sex and PSL use were also associated with DAS28-ESR. These results are in accordance with previous reports. High titers of RF or anti-CCP antibody are well-known to be unfavorable prognostic factors in RA [39], and female sex is independently associated with increased ESR levels in RA patients [40]. Long-term use of PSL potentially has multiple adverse effects, and is usually limited to patients with few therapeutic options or sustained high disease activity.

The present study combines a large-scale cohort data set with a simplified predictor of hypertension. Among several estimation methods of daily salt intake, sodium excretion of 24-h urinary storage is the most reliable, but is inconvenient for large-scale surveys. The Na/K ratio of spot urine is closely correlated with that of 24-h urine collection [41], and has a stronger association with BP levels than Tanaka's formula [12]. The urinary Na/K ratio is thus a more suitable method for large sample size investigation.

There are several limitations in the present study. Our cross-sectional study does not imply causation, and the long-term effect of urinary Na/K on hypertension and RA disease activity is still unknown. Furthermore, the amount and sensitivity to salt intake differs by background including genetics and dietary habits [28]. In addition, there could be unknown confounding ingredients or nutrients in the diet of our study population. Finally, we did not adjust for certain clinical and lifestyle factors that might affect urinary Na/K ratio such as fasting time and seasonal variation [12].

Conclusions

In summary, this cross-sectional study revealed that the urinary Na/K ratio is significantly associated with RA disease activity as well as prevalence of hypertension. This result raises the possibility that the urinary Na/K ratio is an independent disease activity marker of RA and increased Na intake and decreased K intake contribute to pathogenesis of RA as well as hypertension (Fig. 2). Thus, nutritional strategies that reduce the urinary Na/K ratio such as salt restriction and potassium supplementation may be candidates for attenuating disease activity of RA as well as hypertension.

Abbreviations

RA: rheumatoid arthritis, KURAMA: Kyoto University Rheumatoid Arthritis Management Alliance cohort, Na: sodium, K: potassium, DAS28-ESR: 28-joint disease activity score using erythrocyte sedimentation, BP: blood pressure, HAQ: health assessment questionnaire, CRP C-reactive protein, eGFR estimated glomerular filtration, RF rheumatoid factor, anti-CCP antibody: anti-cyclic citrullinated peptide antibody, MTX: methotrexate, PSL: prednisolone, SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: Body mass index

Declarations

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Competing interests

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Author Contributions

H.M., M.H., and Y.F. are responsible for study conception and design. H.M. and M.K contributed to interpretation of the data, drafted the manuscript, and revised the manuscript. T.Y. contributed to acquisition of the data. M.H. and Y.F contributed to interpretation of the data and revised the manuscript. K.I., N.I., Y.O., M.S., W.Y, R.W., K.M.(Murakami), K.M. (Murata), K.N., M.T., H.I., K.O., S.M., N.I., and A.M. contributed to supervision of the manuscript for intellectual content. All authors have approved the final manuscript for publication and have agreed to be personally accountable for the authors' contributions.

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was conducted according to the Declaration of Helsinki and were approved by the ethics committee of Kyoto University Graduate School and Faculty of Medicine (Approval number: R0357). In all cases, patient consent was obtained prior to sample and data collection

Consent for publication

Not applicable

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Figures

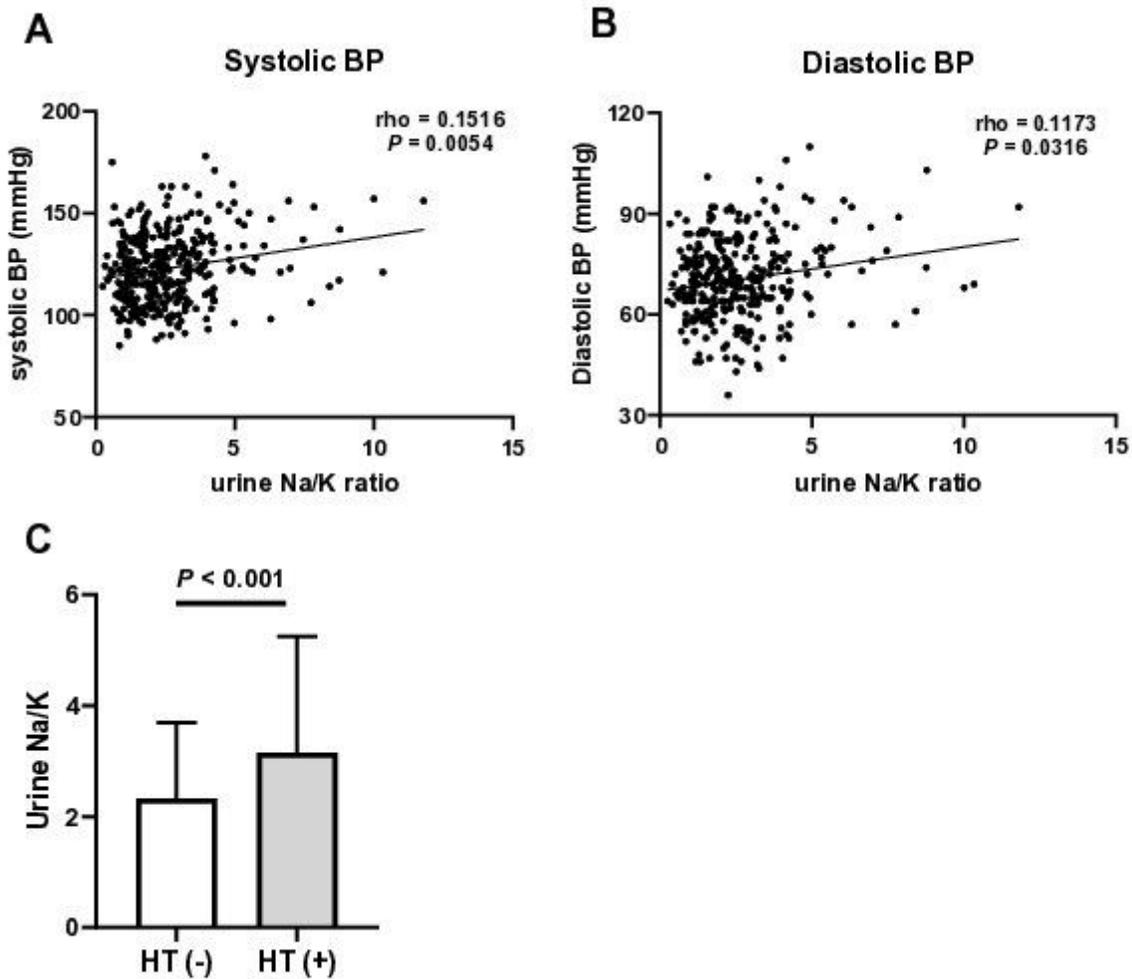


Figure 1

The association between urinary Na/K ratio and blood pressure in RA patients. (A-B) Association between urinary Na/K ratio and systolic blood pressure (A), and between urinary Na/K ratio and diastolic blood pressure (B). (C) Comparison of the spot urine Na/K ratio in the presence or absence of hypertension. P values were obtained from the results of Spearman's rank correlation coefficient (A-B) and unpaired student t-test (C). Abbreviations: HT hypertension, BP blood pressure, RA rheumatoid arthritis

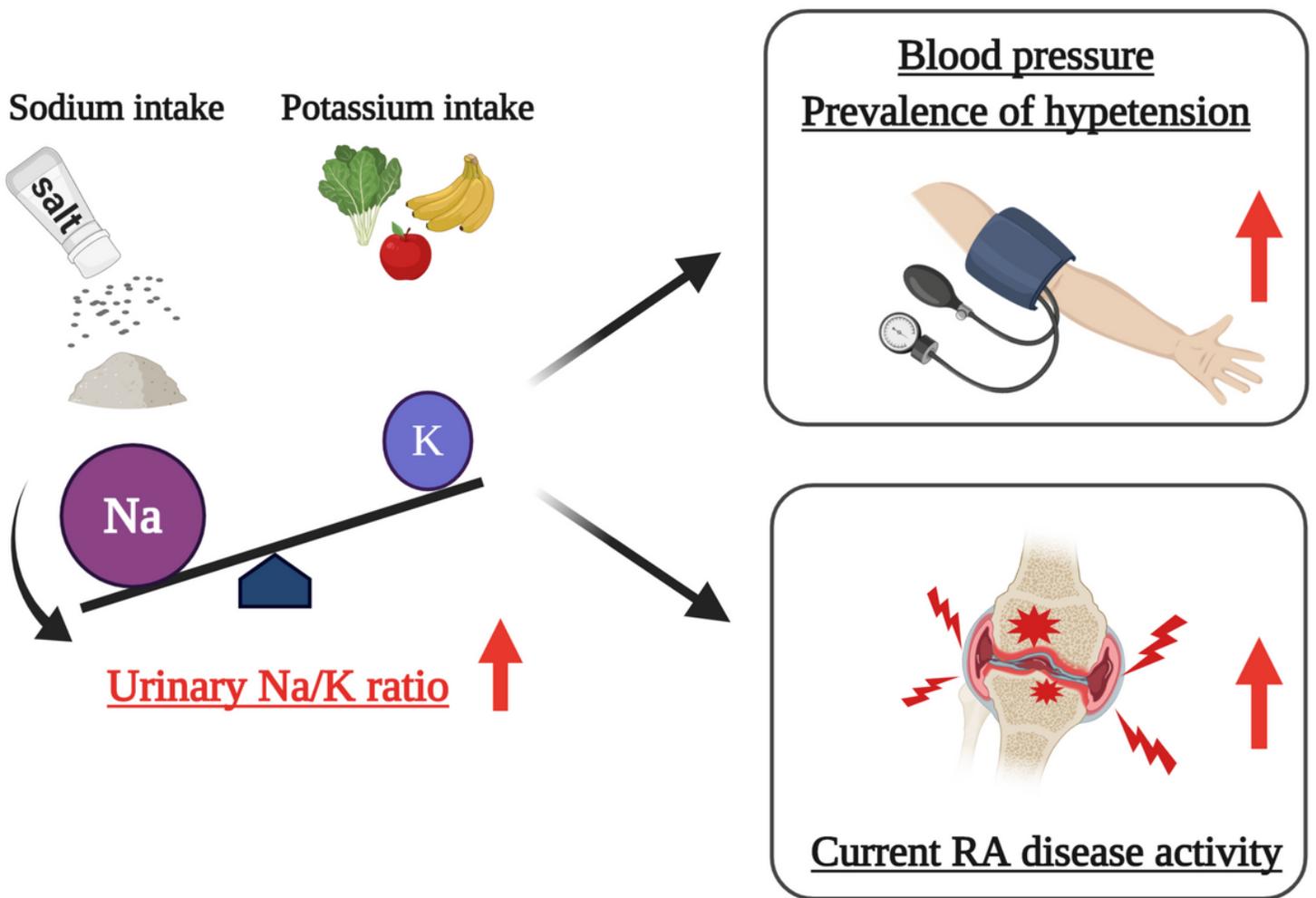


Figure 2

A proposed model of the associations between the urinary Na/K ratio, RA disease activity and hypertension. An increase in urinary Na/K ratio associated not only with an increase in the prevalence of hypertension, but also with an increase in the disease activity of RA. Nutritional interventions that reduce the urinary Na/K ratio such as salt restriction and potassium supplementation could be potential candidates for attenuating disease activity of RA as well as hypertension. Abbreviations: Na sodium, K potassium, RA rheumatoid arthritis

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