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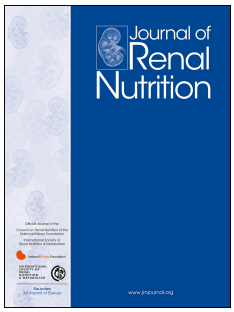

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Association of diet-dependent systemic acid load, renal function, and serum albumin concentration

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One of the authors, Dr. Sebastian, died before the submission of this manuscript was completed. Dr. Sebastian's group was responsible for conducting most of the metabolic balance studies done for in this analysis, and was one of the early pioneers in research on dietary acid loads and their potential pathophysiologic effects.

Association of diet-dependent systemic acid load, renal function, and serum albumin concentration

Abstract

Objective: Inflammation may be present with CKD and diet composition high in protein intake and fats may affect inflammation thereby impacting kidney health. We investigated whether acid load estimated from urine measures is associated with kidney function decline and whether the effect of acid load on an inflammatory marker, serum albumin, is a pathway to this association.

Methods: We studied 188 post-menopausal women in a randomized clinical trial of potassium bicarbonate treatment for up to 36 months. 24-hr urine and arterialized blood collections were done at baseline and at subsequent follow-up visits at 3 months interval. Acid load was estimated from potential renal acid load calculated using urinary measures of chloride, phosphate, sodium, potassium, calcium, and magnesium (UPRAL). Mixed effects model with random-intercept and slope was used to estimate subjects' annual decline rate in creatinine clearance (CrCl), and the association between (i) UPRAL and serum albumin and (ii) serum albumin and CrCl, adjusting for age, body mass index, systolic BP, and glucose. A Cox proportional regression model was used to study the relative hazard (RH) for rapid progression of kidney function decline (defined as loss of ≥5 ml/min CrCl/yr based on the last CrCl in the rolling window) with UPRAL, adjusting for the potential covariates and baseline CrCl.

Results: A 25 mEq/day increase in UPRAL was inversely associated with serum albumin (Adjusted β[95% CI]: -0.02[-0.09;-0.001). During a mean follow-up of 28 months, 19 women (10%) had a rapid decline in kidney function. For each 25 mEq/day increase in UPRAL, the risk

of a rapid decline in CrCl increased by 17% (95% CI: 1.06-1.28). On adjustment for potential confounders, the risk attenuated to 5% (1.02-1.14). Mediation analysis indicated that of the total effect of the association between UPRAL and CrCl, the proportion mediated by serum albumin increased to 0.346 (i.e. 34.6%).

Conclusion: Higher UPRAL was associated with lower serum albumin as well as greater kidney function decline in post-menopausal women. Our findings suggest inflammatory response may exert a modulatory effect on the association of UPRAL and kidney function and might be a potential pathway explaining the effects of systemic acid load on progression of kidney failure.

Introduction

Chronic kidney disease (CKD) is an increasing global public health issue, with an estimated overall prevalence of 8%–16%. More than 1 in 7, that is 15% of US adults or 37 million people, are estimated to have CKD. According to current estimates, CKD is slightly more common in women (14%) than men (12%) and in people aged 65 years or older (38%).[2] The pathophysiological process involved in CKD is characterized by a background of low-grade chronic inflammation.[3] Together with coagulation disorders and neutrophil–endothelium interaction, inflammation is believed to play a role in the genesis of kidney injury, potentially leading to chronically impaired kidney function.[4]

Diet may play a central role in the regulation of chronic inflammation[5] and, possibly, in kidney health. Diet is a major determinant of the acid load that must be excreted by the kidney to maintain acid-base balance.[6] Although contemporary diets in industrialized nations are largely acid-inducing, this may not have been the case throughout the vast majority of human evolution, during which more alkalinizing foods were consumed.[7-9] As a consequence, humans may be poorly adapted to contemporary acid-inducing diets and this may contribute to the pathogenesis of modern epidemics of chronic disease, including kidney disease.[10] Typical Western diets, rich in protein, provide about 1mmol/kg body weight/day of endogenous excretion of H+, mainly due to the high dietary content of sulfur containing amino acids, phosphates and chloride (from table salt)to the metabolism of sulfur rich amino acids (methionine and cysteine). On the other hand, food constituents that are precursors of bases are mostly of plant origin (involves the metabolism of organic anions such as citrate and malate). A modest body of research, including animal studies, observational epidemiology and small clinical trials, has examined the potential role of the dietary acid load in patients with CKD. The evidence largely supports the hypothesis of a

direct relationship between higher dietary acid load and CKD progression, bone loss and sarcopenia.[11-14] The dietary potential renal acid load (PRAL) is an established marker of the diet-dependent proton load and has been used in several studies on different health outcomes in adults.[15,16] PRAL, measured from urinary markers, may be even more reflective of nutrient content compared to estimates of diet intake.[17]

CKD patients with a low serum albumin are also at an increased risk for kidney failure as compared to patients with a normal serum albumin. Hypoalbuminemia is associated with inflammation.[18] Inflammation increases capillary permeability and escape of serum albumin, leading to expansion of the interstitial space and increasing the distribution volume of albumin. The half-life of albumin has been shown to shorten, decreasing total albumin mass.[18] These 2 factors lead to hypoalbuminemia despite increased fractional synthesis rates in plasma. Hypoalbuminemia, therefore, results from and reflects the inflammatory state and is associated with poor quality of life and reduced longevity.[18]

We undertook the retrospective analysis of the potassium bicarbonate supplement intervention trial in postmenopausal women.[19] We hypothesized that a higher diet-dependent systemic acid load is associated with a greater decline in kidney function and that serum albumin, a marker of inflammation, lies in the pathway of this association. Our aim was to investigate to what extent acid load estimated from urine measures is associated with kidney function decline and whether the effect of acid load on an inflammatory marker, serum albumin, is a pathway to this association in the clinical trial conducted for 36 months.

Materials and Methods

The intervention trial using potassium bicarbonate (KHCO3) supplement in otherwise healthy postmenopausal women was a three-year randomized placebo-controlled trial evaluating changes in bone mineral density. The subjects enrolled in this trial had no renal or cardiac disease at baseline.[19] The twenty-four hour urine specimens for determination of creatinine clearance and urine mineral and electrolyte concentration were collected before the subjects were randomized. The subjects were randomized to placebo or KHCO3, either 30, 60, or 90 mmol/d, given in three divided doses with meals. One third of all subjects were randomized to placebo, one third to 60 mmol of potassium, and the remaining one third to either 30 or 90 mmol of potassium. After evaluating the dietary intake, the subjects were given calcium supplements (calcium carbonate) if necessary, to ensure a dietary intake of calcium of at least 1200 mg/d (30 mmol/d). All subjects also received a vitamin D supplement of 400 IU.

All studies were approved by the University Institutional Review Board and followed the Helsinki ethical principles for medical research. Subjects participating in the Clinical Research Center studies signed informed consent documents as specified by the university's Committee on Human Research.

Out of a total of 201 subjects enrolled in this 3-year trial, detailed records were available for 188 women at months 12, 24, and 36 and were included in this analysis. They were followed annually with repeated blood samples and 24-h urine samples for volume, pH, calcium, sodium, potassium, chloride, phosphate, and creatinine. Blood pressures were measured at each visit after the subjects had been sitting quietly for 5-10 minutes. Blood pressures were measured using an automatic cuff (DinaMap@PRO, GE Healthcare Worldwide, Inc., www.gehealthcare.com/). The

anthropometric measurements were also collected for the subjects at the respective follow up visits.

Diet-dependent Acid Load

We estimated diet-dependent acid load (DAL) by net endogenous acid production (NEAP), which results predominantly from the amount of net acid (acid minus base) produced by the metabolic system every day.[20] A methodology developed by Remer et al.[16] was used to calculate estimated NEAP. Estimated NEAP was then used to calculate DAL. Urinary PRAL (UPRAL), which reflects urinary net acid excretion without its organic anion component[21], was calculated as follows:

UPRAL= (Chloride (mmol/day) + sulfate (mmol/day)*2 + phosphate (mmol/day)*1.8) –(sodium (mmol/day)+ potassium (mmol/day)+magnesium (mmol/day)*2 + calcium (mmol/day)*2).

Multiplying by the ionic valences converts the excretions in mmol/d to charge quantities in milliequivalents (mEq/day).[16]

The description of the methods used for measurement of the analytes has been described previously.[14]

Renal function

Creatinine clearance (CrCl) was calculated from the equation, CrCl = (U*V/P*1440), where U is the urinary creatinine concentration in mg/dL, V is the 24-hour urinary volume, and P is the blood creatinine level in mg/dL.[22]

Statistical Analysis

Mean (±SD) estimated Na^+ and K^+ excretion and UPRAL were computed for the entire cohort over the 36-month period.

Mixed effects model with random-intercept and slope was used to estimate subjects' annual decline rate in creatinine clearance (CrCl). We used a mixed effects model to estimate the association between (i) UPRAL and serum albumin and (ii) serum albumin and CrCl, adjusting for age, body mass index, systolic BP, and glucose. A Cox proportional regression model was used to study the relative hazard (RH) for decline in CrCl with UPRAL, adjusting for the potential covariates and baseline CrCl.

We defined rapid progression of kidney function as loss of ≥5 ml CrCl/yr. Based on the findings from the Baltimore Longitudinal Study of Aging[23], a mean decrease in creatinine clearance in normal subjects was noted as less than 1 ml/min/year. An event of rapid progression was based on the last CrCl in the rolling window.

Sensitivity Analysis

Different parameters such as loss of ≥3 ml CrCl/yr was used for sensitivity analysis to validate the consistency of our results.

Decline in renal function estimated by CKD-EPI creatinine equation (2021)

A Cox proportional regression model was used to study the relative hazard (RH) for decline in estimated glomerular function rate (eGFR) with UPRAL, adjusting for the potential covariates and baseline eGFR. GFR was estimated using the CKD-EPI creatinine equation 2021[24] that does not include the term for race. Per KDIGO guidelines[25] 2013, we defined rapid progression as a sustained decline in eGFR of more than 5 ml/min/1.73 m2/year.

Inflammation as a pathway in the association between UPRAL and decline in CrCl

To investigate the link between inflammation and kidney function decline, a mediation model as described by Valeri and Vanderweele was used to test the association between UPRAL and change in CrCl/yr.[26,27] The effects (both direct and indirect effects defined counterfactually) were estimated as hazard ratios using Cox regression. The total effect was computed as the product of the natural direct and indirect effects. The proportion mediated (PM) on the hazard ratio scale is defined as the ratio of the natural indirect effect to the total effect. With hazard ratios used to estimate the natural direct effect (NDE) and the natural indirect effect (NIE), the proportion mediated on the hazard ratio scale is:

$$PM = \frac{NDE(NIE - 1)}{NDE \times NIE - 1}$$

Analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA).

Results

From the 201 postmenopausal women who participated in the potassium bicarbonate trial, 188 women had the complete data available for the analysis from the three follow-up visits over a period of 36 months. Participant characteristics by the treatment group and dose of the treatment are shown in Table 1. There were no significant differences in the baseline characteristics across the different doses of treatment and placebo, except for the 24-hour urinary excretion levels of sodium, potassium, and chloride. The mean age of the subjects was 61.1±7 years. There were 149 Caucasian, 17 Asian, and 4 Hispanic included in the study. At baseline, mean systolic BP and diastolic BP in the treatment group were 132.1±23.4 mmHg and 75.0±13.6 mmHg, respectively and that in the control group were 126.3±24.0 mm Hg and 73.6±11.6 mm Hg,

respectively. Mean CrCl in the treatment group was 85.7 ml/min/year while that in the control group was 85.8 ml/min/year.

Figure 1 shows the change in renal function as measured by CrCl over time in the postmenopausal women who participated in the potassium bicarbonate trial. On removing the participants who were rapid progressors, the mean decrease in creatinine clearance was 0.15 ml/min/year. The slopes of the creatinine clearance vs time fell into a Gaussian distribution around this mean.

Association of UPRAL and rapid progression

During a mean follow-up of 28 months, 19 women (10%) had a rapid decline in kidney function (loss of ≥5 ml CrCl/yr). In unadjusted Cox proportional hazards model, for each 25 mEq/day increase in UPRAL, the risk of a rapid decline in CrCl increased by 17% (95% CI: 1.06-1.28). On adjustment for potential confounders, the risk of a rapid decline in CrCl was attenuated to 5% (95% CI: 1.02-1.10).

Sensitivity Analysis

We found that the association between UPRAL and rapid decline in CrCl was similar by redefining rapid decline as annual decline of >3 ml CrCl/year (relative hazard (RH), 1.08, 95% CI = 1.04–1.14).

Using decline in eGFR as the endpoint, we found that the results were similar to that of our primary analysis (RH [95% CI]: 1.06 [1.01-1.17] in the fully adjusted model).

Mediation Analysis

For each 25 mEq/day increase in UPRAL was related to an 8% (95% CI: 1.02 to 1.14) increased risk of rapid decline in CrCl corresponding to the total effect of UPRAL on rapid decline. We

observe significant direct and indirect effects of UPRAL on rapid decline in CrCl (1.06 [1.00-1.11] and 1.03 [1.01-1.09], respectively) on the hazard ratio scale. An increase of 25 mEq/day increase in UPRAL displays an inverse and significant association with inflammatory status defined by serum albumin in the multivariable model (β [95% CI]: - 0.02 [-0.09, -0.001]; Table 2). Serum albumin is estimated to mediate 34.6% of the effect of UPRAL on rapid decline in CrCl (Table 3).

Discussion

To our knowledge, this is one of the few studies showing an association with diet-dependent systemic acid load measured using urine parameters, inflammatory markers and rapid decline of kidney function in a community elderly women population. In this study, higher UPRAL was associated with both lower serum albumin as well as a more rapid rate of decline of kidney function. These observations provided the rationale for the hypothesis that diet may modify the risk of age-related kidney function decline by affecting the inflammatory status.

The normal age-related rate of renal functional decline is approximately 1 ml/min/year.[28,29] There is little evidence that clearly specify the definition of "rapid CKD progression". The 2002 K/DIGO guideline[30] defined a fast CKD decline as ≥ 4 ml/min/1.73 m2/year; however, the 2012 K/DIGO guideline[25] re-defined the rapid CKD progression as a sustained decline in eGFR of ≥5 ml/min/1.73 m2/year. However, these definitions are arbitrary and lacking in substantial evidence to support these definitions proposed. Our result did not differ much when an annual decline rate of CrCl steeper than 3 ml/year was studied compared to steeper than 5 ml/year. Therefore, an annual CrCl decline rate of 3 ml/year may be specific enough to predict adverse CKD outcomes.

Recent studies have showed that the Western-style diet is a risk factor for impaired kidney function and CKD[31] and in particular that dietary acid load is associated with CKD progression, and base administration slows the rate of progression of CKD.[32]

This has been demonstrated in groups with varying dietary patterns due to race, region, and age group. The Atherosclerosis Risk in Communities (ARIC) study was a community-based observational study of middle-aged adults in the US demonstrating that dietary acid load was associated with incident CKD.[33] In the cross-sectional study of the National Health and Nutrition Examination Survey (NHANES) 1999–2004 in US adults, a higher estimated net endogenous acid production was associated with albuminuria and lower eGFR.[34] In an observational study of adults with CKD, a high dietary acid load was associated with increased risk of ESRD.[35] In this study of 188 postmenopausal elderly women, high UPRAL was independently associated with kidney function decline.

The most striking finding from our study was how serum albumin mediated the association by almost 35%. This inflammatory state, indicated by lower serum albumin levels or hypoalbuminemia, by influencing the association between UPRAL and kidney function decline might be a potential pathway through which diet can affect kidney function. Many studies have shown that a diet high in acid load is associated with an increased incidence of CKD and its progression.[33,34,36] Diet is a common cause of inflammation in the body. One biological explanation for the relationship between dietary acid load and inflammation is that metabolic acidosis can cause tissue damage, which can further initiate inflammatory responses.[37] Animal studies have shown that acidosis caused lung and intestinal damage, stimulated the expression of inflammatory signaling molecules such as induced nitric oxide synthases, increased activities of inflammatory enzymes such as myeloperoxidase, and increased levels of inflammatory cytokines

such as tumor necrosis factor (TNF).[38-40] Dietary acid load contributes to metabolic acidosis if the acid–base balance is not properly adjusted.

The strengths of this study deserve mention. The first strength was the use of multiple 24-hour urine collections updated over time to estimate diet-dependent acid load. Twenty-four hour urine collections provide an objective and quantitative measure of dietary intake on a population level. Other strengths of this study were the prospective design, the use of multiple measured serum creatinine, systolic blood pressure, and glucose levels, the use of a large sample size, and the availability of detailed and updated (midway through the period of follow-up to reduce potential misclassification) information on the exposure and potential confounders. Our findings are subject to the following limitations. Although a broad set of covariates were included in regression models, unmeasured confounding by additional factors could also play a role. Second, the women participants in the placebo group had lower sodium and chloride levels compared to those receiving intervention. Third, our cohort did not include African American women and less than 10% were Asian or Hispanic. Moreover, the present study population primarily consisted of relatively healthy elderly postmenopausal women in good economic state, and thus our findings may not be generalizable to the whole post-menopausal women population and to other racially diverse populations.

In conclusion, we demonstrated an association between diet-dependent acid load measured using urine parameters and kidney function decline in elderly women as well as its association with inflammatory status as defined by serum albumin levels. The consumption of Western-type diets evokes a state of chronic inflammation, which contributes to the development and progression of kidney disease, and these lifestyle-associated pathologies represent a rising public health problem. Our findings raise the possibility of using urinary PRAL as a surrogate for

poor-quality diet associated with kidney function decline. These findings suggest that combining low acid producing diets with treatments that reduce inflammation would improve both metabolic and endothelial functions, especially in those subjects with rapid renal functional decline. Further studies are needed to assess the consistency of these results in clinical trials ultimately to provide dietary prevention of CKD.

Practical Application

Combining low acid producing diets with treatments that reduce inflammation would improve both metabolic and endothelial functions, especially in those subjects with rapid renal functional decline.

Disclosure

The authors have nothing to disclose.

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Table 1: Baseline Characteristics of subjects for each group, treatment and placebo

Characteristic	Dose (mmol) (n=120)			Placebo (n=68)	P Value
	30 (n=35)	60 (n=50)	90 (n=35)		
Age (in years)	62.7 ± 6	61.7 ± 6.8	61.0 ± 6.5	62.4 ± 7.7	0.71
Race/Ethnicity, %					0.07
Caucasian	91.1	93.2	92.7	77.3	
Asian	8.4	3.4	6.2	18.2	
Hispanic	0.5	3.4	1.1	4.6	
Height (in inches)	64.5±2.7	64.4±2.4	63.7±2.9	63.5±2.8	0.14
Weight (in lbs)	146.0±23.2	147.9±27.8	146.8±25.3	143.8±23.7	0.82
Body Mass Index (kg/m^2)	25.1 ± 3.7	24.4 ± 3.6	24.9 ± 3.9	25.4 ± 4.4	0.97
Urine excretion (24 hr)					
Sodium (mEq)	120.8±48.3	135.9±53.7	126.0±48.3	109.3±39.5	0.01
Potassium (mEq)	72.7±25.1	62.7±23.2	69.8±24.1	66.2±19.5	0.03
Calcium (mg)	138.5±60.8	131.5±57.0	141.3±56.8	155.8±77.6	0.25
Magnesium (mg)	94.7±33.6	109.5±40.6	101.8±35.7	95.1±27.9	0.06
Phosphate (mg)	723.3±297.6	728.7±232.1	701.2±221.7	732.9±196.7	0.85
Chloride (mEq)	113.7±46.9	126.7±48.3	111.8±46.1	103.1±39.4	0.02
Creatinine clearance (mL/min)	85.2±21.1	86.4±24.9	84.9±17.9	85.8±18.1	0.97
Blood Pressure (in mmHg)					
Systolic	131.8±23.6	132.1±24.9	132.7±20.6	126.3±24.0	0.44
Diastolic	77.5±10.3	74.4±10.7	73.3±7.9	73.6±11.6	0.49
The body-mass index is the weight in kilograms divided by the square of the height in meters.					

Table 2: Adjusted association between the urinary renal acid load and serum albumin

	β (95% CI)
Unadjusted	-0.04 (-0.01, 0.004)
+Age	-0.03 (-0.08, 0.01)
+BMI	-0.08 (-0.15, -0.01)
+Systolic BP+ Glucose	-0.02 (-0.09, -0.001)

Table 3: Mediation Analysis of the total effect of urinary renal acid load on rapid decline in kidney function, decomposed into natural direct and indirect (mediated) effects, where the hypothesized mediator is serum albumin*

Effect	Estimate (RH)	95% CI	P-value
Natural Direct Effect	1.06	0.96-1.11	0.07
Natural Indirect Effect	1.03	1.01-1.10	0.04
Total Effect	1.08	1.02-1.14	0.03
Proportion Mediated	0.346		

*The proportion of the total effect mediated by serum albumin is 34.6%.

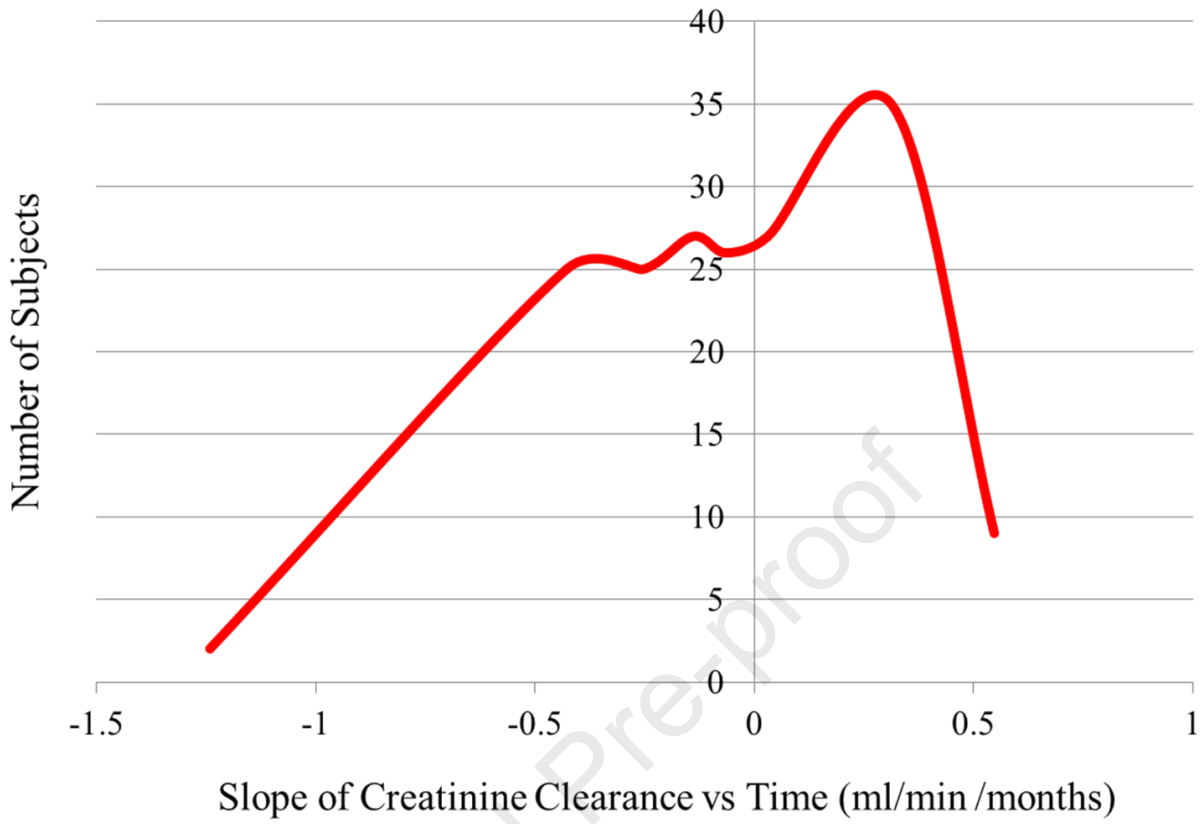

Figure 1. Distribution of regression coefficients of changes in creatinine clearance vs time in months in age-related kidney functional decline

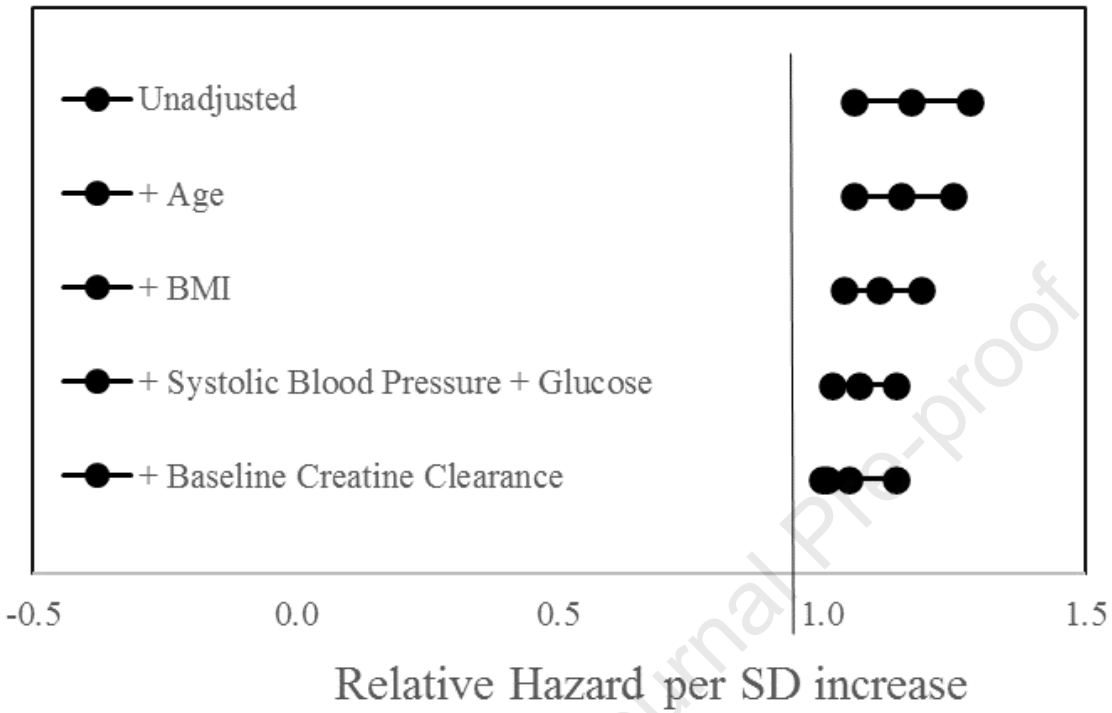

Figure 2. A Cox-proportional model to show the association of urinary renal acid load with rapid decline in Creatinine Clearance (loss of ≥5 ml/min/yr)

Statement of authors' contributions to manuscript

The authors' responsibilities were as follows—TB, AS, LF: designed the research; TB, LF: data curation; TB: analyzed data or performed the statistical analysis; TB, LF: wrote the paper, had primary responsibility for the final content; and all authors: read and approved the final manuscript.