Association between urinary sodium excretion and hard outcomes in non-dialysis chronic kidney disease patients

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Abstract

Background: If sodium intake directly affect the progression to renal failure or death in non-dialysis chronic kidney disease (CKD) patients remains uncertain. We evaluated the association between urinary sodium excretion (as a surrogate for sodium intake) with the occurrence of renal failure and death in non-dialytic CKD patients.

Methods: A cohort study of non-dialytic CKD patients, including patients that who have their first visit clinical appointment between October/2006 and November/2010 and followed until March/2017. The inclusion criteria were: at least two 24-hour urinary sodium samples evaluated and aged superior to over 18 years, and the exclusion criteria were: patients who underwent undergoing previous dialysis therapy previously, with in the malignant phase of hypertension, hepatic insufficiency, alcoholics, malignant neoplasms, and implausible biochemical examination values. To measure sodium intake, two 24-hour urinary sodium samples were collected at the first visit appointment and or at maximum six months later. The outcomes were renal failure (onset of renal replacement therapy (RRT)) and death. Multiple Cox regression model was adjusted for age, creatinine clearance, smoking, and proteinuria/creatininuria ratio.

Results: Were screened 292 patients and included 205 patients; during the follow-up period (until 125 months) there were 52 deaths and 37 patients developed renal failure. Considering the first quintile (urinary sodium below 2.51 g/day) as a reference, the second quintile (2.52 and 3.11 g/day) presented an adjusted Hazard Ratio of 0.245 (95% confidence interval: 0.660-0.912; p=0.036). Other quintiles did not present statistically significant association with renal outcome. There were no associations between the quintiles of urinary sodium excretion and death.

Conclusion: Moderate sodium intake was associated with a lower risk of renal failure.

Background

Chronic kidney disease (CKD) affects about 10% of the adult population (1), which is associated with an increased risk of CKD progression and need of renal replacement therapy, as well as increased cardiovascular morbimortality (2-5). The CKD progression is understood as the loss of renal function, regardless the underlying disease and its activity (6).

The treatment aims to attenuate the progression of CKD through interventions on modifiable factors: to increase survival, preparing the patient for a possible renal replacement therapy, and improving the quality of life as well (2). Clinical strategies were directed at controlling blood glucose, arterial hypertension (7), dyslipidemia (8), obesity (9), smoking (10) and lifestyle adjustment. Dietary interventions plays an important role and nutritional support is necessary in all stages of CKD (11), with special attention to the proteins (12) potassium (13), phosphorus (14) and sodium intake (14).

Current guidelines recommend a sodium consumption of 2.0 g/day for the adult population (15-17). The emphasis in this recommendation is due to the its direct relationship with the increase in blood pressure

(18-23). In CKD patients, an excessive sodium intake is also associated with proteinuria (23,24), and in addition to attenuating the antihypertensive and anti-proteinuric effects of drugs acting on the renin-angiotensin system (25).

These mechanisms suggest the relationship between sodium intake with renal outcomes and mortality should be linear. Although several studies have shown a significant association between increased sodium intake with of CKD progression (13,24,26) and patients's mortality (13,26-27), an inverse relationship has been reported by others with at J curve design (28). In view of the heterogeneity of the published results, the purpose of this study was to investigate the association between urinary sodium excretion and outcomes: renal failure and death in non-dialytic CKD patients.

Methods

Patient population and measurements

This is an observational study of non-dialysis CKD patients, were patients had their first clinical appointment between October/2006 and November/2010 and were followed until March/2017. Data collection were carried out from 01/2016 to 01/2018. Sociodemographic characteristics, medical history, lifestyle-related behaviors, and prescribed medications were obtained through the medical records and registered in a standardized form.

Inclusion criteria were: age over 18 years and agreeing two 24-hour urinary sodium assessments during the collection period. The average interval between clinical evaluations was 5.54 months. Patients who received dialysis prior to the laboratory test, in a malignant phase of hypertension, with liver failure, alcoholics and with malignant neoplasm were excluded.

Data collection

In the medical visits, body weight, height, and blood pressure (BP) were measured. Blood samples were taken to obtain serum dosages and 24-hour urine samples were also obtained. Hypertension was defined as an average BP ≥ 140/90 mmHg or self-reported use of antihypertensive drugs. Diabetes mellitus was defined according to the American Diabetes Associations criteria (30). The estimated glomerular filtration rate (eGFR) was calculated according to the CKD-EPI equation (12).

We categorized the patients according to the mean values of urinary sodium excretion. Were categorized into quintiles (n=41) with the respective intervals: 1st quintile: 0.54-2.51 g; 2nd quintile: 2.52-3.11 g, 3rd quintile: 3.12-3.97 g, 4th quintile: 3.98-5.24g and 5th quintile: 5.26-13.80 g. These patients had an average of 3.9±1.7g of urinary sodium excretion.

Outcomes

The primary outcome was defined as initiation of renal replacement therapy (hemodialysis, peritoneal dialysis or transplantation). The secondary outcome was death from any cause and all deaths were

confirmed by the legal certificate. Surviving or of dialysis-free patients at the end of the follow, as well as those transferred from the service or having lost the segment were censored.

Statistical analyses

The results were expressed as mean ± standard deviation for parametric. Median interquartile range non-parametrics or percentage for categorical data. Continuous variables were obtained by calculating the average between the results of the first and second exams. The variables were compared between patients who had or did not have the outcomes. We used the Chi-square test to compare frequencies. Student's "t" test for independent samples for means and the Mann Whitney test for non-parametric data. Patients' survival was analyzed using a multiple proportional risk regression Cox model, considering urinary sodium excretion as a variable of interest and those associated with outcomes, at the level of 0.05 as adjustment variables. For variables collinearity, we choose those with greater clinical significance. For all tests, statistical significance was defined as $p < 0.05$.

Results

An amount of, 292 patients were screened 88 of them were excluded by lack or incomplete two 24-hour urine samples, thus 205 were included. The mean follow-up was 63 months and median 71; the minimum of two months and the maximum of 125 months. The average sodium daily intake of the participants was 3.9 g, which represents about 9.75 g of sodium chloride.

From the average of the two urinary sodium tests, the 205 participants were categorized into quintiles (n=41) with the respective intervals: 1st quintile: 0.54-2.51 g; 2nd quintile: 2.52-3.11 g, 3rd quintile: 3.12-3.97 g, 4th quintile: 3.98-5.24g and 5th quintile: 5.26-13.80 g. These patients had an average of 3.9±1.7g of urinary sodium excretion.

A total of 37 patients (18%) progressed to renal failure. These patients had higher values of baseline serum creatinine, proteinuria, serum phosphorus, proteinuria/creatininuria ratio, parathyroid hormone and proportion of active smokers. Age and eGFR were lower in patients who had the primary outcome (Tables 1 and 2). The intervals of urinary sodium excretion showed marginal statistical differences in relation to the renal outcome (Tables 1 and 2).

Table 1. Demographic and clinical data of patients according to the outcomes renal

	Overall	Outcome		
	(n=205)	With (n=37)	Whitout (n=168)	P *value*
Age (years)	64,8±12,7	55,2±12,4	66,9±15,6	<0,01
Men (%)	53,1	48,6	54,2	0,67
Race (%)				
Black	4,8	5,4	4,8	
Other	0,5	2,7	0	0,40
White	94,7	91,9	92,2	
School graduate (%)				
< Elementary scholl	80,5	73,0	82,2	
First school	7,8	10,8	7,1	0,30
Secondary school	9,8	16,2	8,3	
Higher education	1,9	0	2,4	
Current smoking (%)	11,9	27	8,3	<0,01
Weekly alcohol drinking (%)	4,7	8,1	3,9	0,56
Cause of CKD (%)				
Hypertension	40	32,4	41,7	
Diabetes	17,5	21,6	16,1	0,45
Glomerular	5,9	10,8	5,4	
Other	36,6	35,2	36,8	
Hypertension (%)	97,4	100	96,9	0,64
Diabetes (%)	39,1	37,8	39,5	0,98
CVD (%)	39,5	43,2	38,6	0,74
Dyslipidemia (%)	78,2	75,6	78,8	0,87
Antihypertensives				
Diuretics	81,7	82,6	81,5	0,9
RAS blocker	81,5	89,2	79,8	0,18
Others	26,3	18,9	27,9	0,26
Class antihypertensives (n)	2(2-3)	2(2-3)	2(1-3)	0,42
SBP mean (mm Hg)	134,4±18,1	134,9±16,1	134,3±18,5	0,85
DBP mean (mm Hg)	78,8±10,7	82,1±10,4	78,2±10,7	0,06
BMI (Kg/m2)	25,8±5,3	25,5±3,8	26,2±4,8	0,4

CKD:chronic kidney disease; CVD: cardiovascular disease; RAS blocker: blockers system renin-angiotensin; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index

Table 2. Laboratory data of patients according to the outcomes renal

	Overall	Outcome		
	(n=205)	With (n=37)	Whitout (n=168)	P *value*
Intervals of urinary sodium excretion				
0,54 - 2,51 g	41	18,90%	20,20%	
2,52 - 3,11 g	41	10,80%	22,10%	0,08
3,12 - 3,97 g	41	21,60%	19,60%	
3,98 - 5,24 g	41	35,10%	16,70%	
5,26 - 13,80 g	41	13,60%	21,40%	
Uric acid (mg/dL)	6,9±1,9	6,8±2,0	6,9±1,9	0,59
Serum Calcium (mg/dL)	9,6±0,5	9,5±0,4	9,6±0,5	0,08
Creatinine clearance (mL/min)	26(19-41)	20(16-24)	28(19-42)	<0,01
Urinary creatinine excretion (mg/24H)	913(699-1168)	974(837-1171)	882(670-1165)	0,14
nPNA (g/kg)	0,8±0,2	0,8±0,2	0,8±0,3	0,63
Serum Creatinine (mg/dL)	2,6±1,1	3,5±1,6	2,4±0,9	<0,01
Serum phosphor (mg/dL)	4,1±0,7	4,5±0,9	4,0±0,6	<0,01
CRP (ml/dcl)	0,5(0,2-0,95)	0,5(0,2-1,31)	0,5(0,2-0,9)	0,65
Serum potassium (mEq/L)	4,9±0,5	5,0±0,6	4,8±0,5	0,11
Urinary potassium excretion (mEq/24h)	40,2±17,9	38,0±17,5	40,8±18,0	0,41
Plasma Albumin (g/L)	4,2±0,4	4,2±0,4	4,2±0,4	0,37
Urinary protein excretion (g/24 h)	0,3(0,17-0,6)	0,6(0,4-2,1)	0,3(0,2-0,6)	<0,01
Urinary Protein/creatinine excretion (g/g)	0,4(0,2-0,7)	0,7(0,4-2,1)	0,3(0,2-0,6)	<0,01
PTH (pg/ml)	111(74-160)	134(81-177)	96(62-145)	0,03
Serum sodium (mEq/L)	140,6±3,0	140,1±2,8	140,7±3,0	0,33
Urinary sodim excretion (mEq/24h)	166,3±75,3	166,3±59,3	166,3±78,7	0,12
Urinary sodim excretion (g)	3,9±1,7	3,9±1,4	3,9±1,8	0,12

npna: protein nitrogen; CRP: C-reative protein; PTH: parathyroid hormone

The variables (age, smoking, creatinine clearance, proteinuria/creatininuria ratio) were included in the Cox regression model as adjustament variables. Variables that show collinearity with eGFR were excluded from the model.

The results showed that active smokers and greater proteinuria/creatinine ratio were associated with risk of renal outcome, while higher age and eGFR were associated with lower risk (table 3). The adjusted Hazard Ratio (HR) and confidence interval 95% (CI 95%) showed that patients with urinary sodium excretion between 2.52-3.11 g had a lower risk of renal failure: 0.246 (0.066-0.912) (Table 3).

Table 3. Time-dependent Cox model, according to the outcomes renal

	HR (95% CI)	P *value*
Age (year)	0,956 (0,934-0,79)	<0,00
Smokers		
Never	1	
Active	4,247 (1,687-10,689)	0,02
Inactive	2,408 (1,035-5,602)	0,041
Creatinine clearance (mL/min)	0,941 (0,91-0,973)	<0,001
Urinary Protein/creatinine excretion (g/g)	1,501 (1,179-1,910)	0,001
Intervals of urinary sodium excretion (g)		
0,54 - 2,51	1	
2,52 - 3,11	0,245 (0,066-0,912)	0,036
3,12 - 3,97	0,787 (0,260-2,380)	0,671
3,98 - 5,24	0,770 (0,263-2,260)	0,634
5,26 - 13,80 g	0,741 (0,219- 2,509)	0,630

This result lightly demonstrated a “U” shaped curve (figure 1).

During the follow-up, 52 patients (25%) died. The causes of death included: 23 (44%) due to infectious disease, 18 (35%) cardiovascular diseases (CVD), five (10%) malignancies and six (12%) deaths were due to other causes. Patients who evaluated to death showed statistical differences in the following variables: age, previous CVD, eGFR and creatininuria levels (tables 4 and 5).

Table 4. Demographic and clinical data of patients according to the outcomes death

	Overall	Outcome		
	(n=205)	With (n=52)	Whitout (n=153)	P *value*
Age (years)	64,8±12,7	72±12,3	62,2±15,9	0, 05
Men (%)	53,1	48,1	54,9	0,49
Race (%)				
Blacks	4,8	5,8	4,6	
Asiáticos	0,5	0	0,7	0,78
Whites	94,7	94,2	94,8	
School graduate (%)				
< Elementary scholl	80,5	84,6	79,1	
First school	7,8	5,8	8,5	
Secondary school	9,8	9,6	9,8	0,76
Higher education	1,9	0	2,6	
Current smoking(%)	11,9	18,4	9,7	0,27
Weekly alcohol drinking (%)	4,7	8,2	3,5	0,31
Causes of CKD (%)				
Hypertension	40	36,8	41,9	
Diabetes	17,5	19,7	16,3	0,7
Glomerular	5,9	7,9	4,7	
Other	36,6	35,6	37,1	
Hypertension (%)	97,5	100	96,6	0,19
Diabetes (%)	39,1	48	36,2	0,14
CVD (%)	40	60,4	35,5	<0,001
Dyslipidemia (%)	78,2	76,6	78,8	0,7
Antihypertensives				
Diuretics	81,7	84	80,2	0,59
RAS blocker	81,5	85,5	79,1	0,25
Others	26,3	21,1	29,5	0,1
Class antihypertensives (n)	2(2-3)	2(2-3)	2(2-3)	0,77
SBP mean (mm Hg)	134,4±18,1	130,2±20,4	135,7±17	0,19
DBP mean (mm Hg)	78,8±10,7	74,3±10,6	80,4±10,4	0,71
BMI (Kg/m2)	25,8±5,3	25,0±3,8	26,2±4,8	0,16

CKD: chronic kidney disease; CVD: cardiovascular disease; RAS blocker: blockers system renin-angiotensin; SBP: systolic blood pressure; DBP diastolic blood pressure; BMI: body mass index.

Table 5. Laboratory data of patients according to the outcomes death

	Overall	Outcome		
	(n=205)	With (n=52)	Whitout (n=153)	P *value*
Intervals of urinary sodium excretion				
0,54-2,51 g	41	19,20%	20,30%	
2,52-3,11 g	41	28,80%	17,00%	
3,12-3,97 g	41	21,20%	19,60%	0,37
3,98-5,24 g	41	15,40%	21,60%	
5,26-13,80 g	41	15,40%	21,50%	
Uric acid (mg/dL)	6,9±1,9	6,7±2,3	6,9±1,7	0,15
Serum Calcium (mg/dL)	9,6±0,5	9,6±0,5	9,6±0,5	0,27
Creatinine clearance (mL/min)	26(19-41)	22,4(15-34)	27,1(19-41)	<0,01
Urinary creatinine excretion (mg/24H)	913(699-1168)	815(639-1030)	953(717-1283)	0,01
nPNA (g/kg)	0,8±0,2	0,8±0,2	0,8±0,3	0,25
Serum Creatinine (mg/dL)	2,6±1,1	2,7±1,2	2,5±1,1	0,26
Serum phosphor (mg/dL)	4,1±0,7	4,3±0,8	4,0±0,7	0,15
CRP (ml/dcl)	0,5(0,2-0,95)	0,5(0,3-1,3)	0,5(0,2-0,9)	0,15
Serum potassium (mEq/L)	4,9±0,5	4,9±0,5	4,9±0,5	0,93
Urinary potassium excretion (mEq/24h)	40,2±17,9	37,7±14,8	41,2±18,8	0,18
Plasm Albumin (g/L)	4,2±0,4	4,1±0,4	4,3±0,4	0,19
Urinary protein excretion (g/24h)	0,3(0,17-0,6)	0,3(0,2-0,6)	0,4(0,2-0,7)	0,71
Urinary Protein/creatinine excretion (g/g	0,4(0,2-0,7)	0,3(0,2-0,6)	0,4(0,2-0,8)	0,8
PTH (pg/ml)	111(74-160)	118(70-176)	108(74-152)	0,5
Serim sodium (mEq/L)	140,6±3,0	140,3±2,9	140,8±3,0	0,9
Urinary sodium excretion (mEq/24h)	166,3±75,3	157,7±82,9	169,2±72,8	0,65
Urinary sodium excretion (g)	3,9±1,7	3,7±1,9	3,9±1,7	0,65

npna: protein nitrogen; CRP: C- reative protein; PTH: parathyroid hormone

Cox's risk model, included to the quintiles of urinary sodium excretion, age, eGFR, diastolic BP, diabetes mellitus and previous CVD. The variables diastolic BP and diabetes mellitus, even without statistical significance in the preliminary analyzes, were included in the multiple Cox model (table 6). Finally, only age achieved a statistically significant association with death HR (CI 95%) 1.048 (1.015-1.081), p = 0.003. There was no statistically significant association between quintiles of urinary sodium excretion and death (table 6).

Table 6. Time-dependent Cox model, according to the outcomes death

	HR(95% CI)	P *value*
Age (year)	1,048 (1,015-1,081)	0,003
Creatinine clearance (mL/min)	0,976 (0,948-1,004)	0,092
DBP (mmHg)	0,979 (0,945-1,015)	0,251
Diabetes	1,625 (0,863-3,059)	0,133
CVD	1,371 (0,734-2560)	0,323
Intervals of urinary sodium excretion (g)		
054 - 2,51	1	
2,52 - 3,11	1,917 (0,807 - 4,556)	0,140
3,12 - 3,97	1,107 (0,422 - 2,904)	0,836
3,98 - 5,24	0,095 (0,293 - 3,084)	0,932
5,26 - 13,80	1,158 (0,388 - 3,462)	0,793

DBP: diastolic blood pressure; CVD: cardiovascular disease

Discussion

This study showed that urinary sodium excretion (as a surrogate for sodium intake) between 2.52-3.11 g/day was associated with a lower risk for renal failure in non-dialysis CKD patients when compared with the reference 0.54 – 2.51 g/day. No other sodium excretion range was associated with the renal outcome. Likewise, there was no statistically significant association between quintiles of urinary sodium excretion and death.

Studies that evaluated the association between sodium intake and renal outcome obtained some different results (13,24). In the reanalysis of REIN-2 study, it was reported that only sodium intake greater than 4.59 g/day was associated with a greater risk of CKD progression (24). The same study suggests sodium intake attenuates the antiproteinuric effect of angiotensin converting enzyme inhibitors therapy and is associated with renal failure. However, when adding the proteinuria variable to the model (as performed in this work), there was a loss of significance.

He et al. showed that urinary sodium excretion above 4.47 g was associated with 54% increase risk of CKD progression (13). These mentioned cohort were composed by a high proportion of Black patients, who classically have greater more sodium sensitivity than Whites, differently our cohort.

In the studies cited above, higher sodium intakes were associated with CKD progression in models without the variable proteinuria. In the current study, the association between the second quintile of sodium and renal failure was only obtained after adjustment for proteinuria. This association was independent of protein intake and BP. In experiments addressing proteinuric nephropathies, lower sodium intakes reduced glomerular and tubulointerstitial inflammation, foci of glomerulosclerosis and the pro-

inflammatory TNF-alpha gene (31). In humans, a moderate restriction in sodium intake potentiates the antiproteinuric and antihypertensive effects of renin angiotensin system blockers (25).

Other authors have proposed that daily sodium intakes lower than 2.0 g is associated with vascular endothelial injury and inflammation (32), rennin angiotensin system activation and increased levels of angiotensin II and NADPH oxidase, which can cause reactive oxygen species production (33), and sympathetic system activation (34). Therefore, we could suggest that the sodium intake moderate reduction directly attenuates the CKD progression, but an extreme restriction intake of this ion is not protective. Thus, an efficient strategy for practical recommendations is not prescribe extreme restrictions, that will compromise patients' quality of life. In addition, diets based on excessive animal sources and industrialized foods should be avoid.

An interesting finding of this study was that active smoker had greater risk for progression to dialysis. This result corroborates previous research regarding the progression of CKD in active smokers (36). Experimental data showed that nicotine acts in the proximal tubule causing biosynthesis of pro-fibrotic and pro-inflammatory cytokines, which can accelerate the CKD progression (37), and promotes deregulation of vasoconstrictor and vasodilator mediators, that act in the efferent arteriole (38, 39).

As for the death outcome, Mills et al (26), when reported that patients with established CKD and CVD, presented urinary sodium excretion above 4.54 g/day, which was associated with high risk for CVD (27). In the present study, we did not obtain significant associations between the different quintiles of urinary sodium excretion and death (including cardiovascular causes). When comparing the two studies, Mills' study (26) also contained a higher proportion of Black, hypertensive, obese, smokers and diabetic patients.

Our study should be interpreted taking into account its limitations. First, this is an observational study which does not allow definitive conclusions on the causality of the association between sodium intake and outcomes. Only two 24-hour urine samples may not be enough to estimate the usual sodium intake with precision, but most studies have performed only a single dosage. As for strengths: we used the adjustment of results for proteinuria, considering that this is an important factor in CKD progression. In addition, we performed a 24-hour urine collection, which is considered the gold standard to sodium intake measurement (40), and allowed the establishment of statistically significant associations. Finally, there was no previous Brazilian studies reporting an association between sodium intake with renal disease progression failure and death in non-dialysis CKD patients.

Conclusion

In conclusion, in this longitudinal study, moderate sodium intake was associated with a lower risk of progression to renal failure in patients with established CKD. Further studies are needed confirm the association between sodium intake and outcomes in non-dialysis CKD patients.

Abbreviations

BMI, Body mass index; BP, Blood pressure; CKD, Chronic kidney disease; eGFR, estimated glomerular filtration rate; g, grams; ESRD, End-stage renal disease; RAS, Renin-angiotensin system; RRT, Renal replacement therapy.

Declarations

Ethics approval and consent to participate:

Presentation certificate for ethics approval (CAAE): 29354414.9.0000.5411

Availability of data and materials:

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests:

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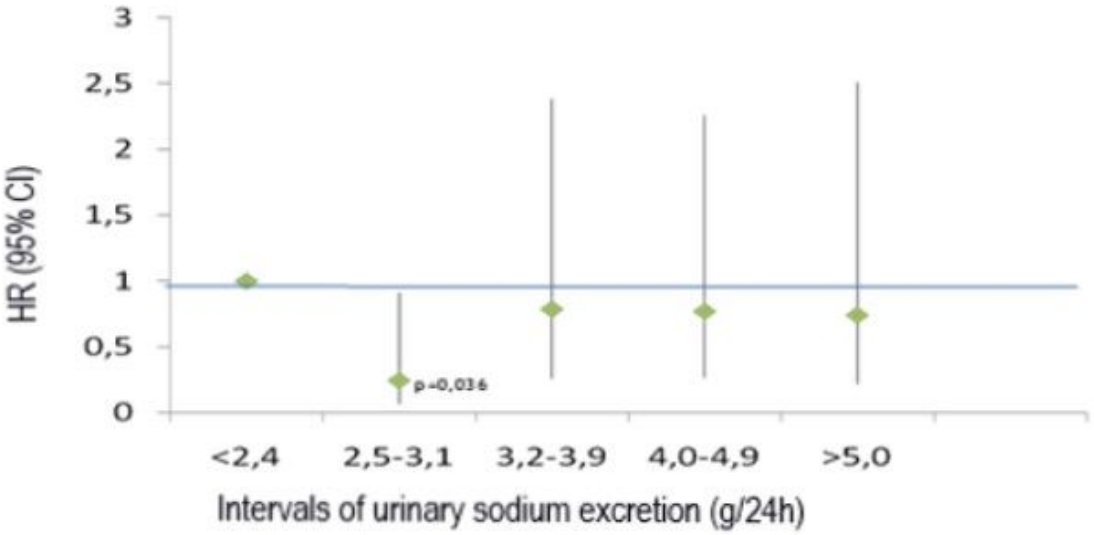
Figures



*Adjusted for age, clearance of creatinine, smoke e proteinuria.

Figure 1

Association between urinary sodium excretion and risk renal failure (Cox Analyze)