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ORIGINAL ARTICLE

Relationships of hyperchloremia with hypertension and proteinuria in patients with chronic kidney disease

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Abstract

Background A few previous clinical studies have shown that chloride (Cl) contributes to the progression and development of hypertension or proteinuria. Therefore, we aimed to determine whether hyperchloremia is associated with hypertension or proteinuria in patients with chronic kidney disease (CKD) and to define the relationships between the reduction in serum Cl concentration associated with CKD treatment and improvements in hypertension and/or proteinuria.

Methods We performed a retrospective observational study of new or referred patients with CKD who had hyperchloremia, moderate proteinuria, renal dysfunction, and hypertension. Patients taking medication for metabolic acidosis or with a history of dialysis were excluded. The participants' systolic and diastolic blood pressure (BP), serum sodium (Na) and Cl concentrations, and urinary protein (UP) concentration were measured at baseline and after 1 month of CKD treatment.

Results Fifty-one patients with CKD were included in the study. Their serum Cl concentration independently correlated with sBP and UP at baseline ($P=0.022$ and $P=0.033$, respectively). After 1 month's CKD treatment, their serum Na and Cl concentrations, sBP, and UP were significantly lower. The change in sBP during the month (ΔsBP) correlated with the change in serum Cl (ΔCl) ($P=0.012$) but not with the change in serum Na. Multivariate analysis showed that ΔsBP was independently associated with ΔCl ($P=0.029$).

Conclusions Hyperchloremia is an independent predictor of hypertension and proteinuria for patients with CKD.

Keywords Chloride · Hyperchloremia · Sodium · Hypertension · Proteinuria · Chronic kidney disease

Introduction

Hypertension is a risk factor for the onset and progression of chronic kidney disease (CKD) [1–3]. It is also present in most patients with CKD, in whom it increases the risks of cardiovascular disease and death [4]. The presence of proteinuria is similarly associated with higher risks of the progression of CKD and death [5]. Furthermore, a recent study showed that patients with CKD and extremely high systolic and diastolic blood pressure (BP) had the highest mortality rates, and similar findings were made in subgroups of patients with high urinary microalbumin/creatinine ratios [6].

Both genetic and environmental factors play significant roles in the development of hypertension. Of the environmental factors that affect BP, salt consumption has been the subject of intense scientific research. Although salt is composed primarily of sodium chloride (NaCl), only sodium (Na) has been thought to be associated with salt-sensitive hypertension. However, in contrast to the effect of NaCl loading, some previous studies have shown that non-chloride sodium salt loading, for example, using sodium bicarbonate ($NaHCO_3$), sodium citrate, or sodium phosphate, is associated with low BP [7–10]. Furthermore, chloride (Cl) loading is associated with progressive renal vasoconstriction and a reduction in glomerular filtration rate (GFR) [11].

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The relationship between dietary salt intake and proteinuria has also been studied in patients with CKD. Dietary salt restriction significantly reduces not only BP but also proteinuria [12]. Although only the Na present in dietary salt has been reported to be associated with proteinuria [13, 14], we have previously shown that in aldosterone-infused rats, the inclusion of NaCl in the drinking water is associated with greater hypertension and proteinuria than the inclusion of $NaHCO_3$ [15], which suggests that Cl contributes to the progression of these defects. However, very few studies, and especially clinical studies, have shown a relationship between Cl and BP or proteinuria. Therefore, to test the hypothesis that Cl has an important role in hypertension and renal damage/proteinuria, we performed a retrospective study of the relationships of hyperchloremia with hypertension and proteinuria in patients with CKD. Specifically, we aimed to define the relationship between the reduction in serum Cl concentration associated with the treatment of CKD and improvements in hypertension and/or proteinuria.

Materials and methods

Study sample

We performed a retrospective observational study of 51 new or referred patients with CKD who were inpatients or outpatients at the Department of Nephrology, Hiroshima University Hospital, Hiroshima, Japan, between 1 April 2011 and 31 March 2019.

The inclusion of patients in the study was based on the following criteria at the time of their initial visit: (1) serum Cl concentration ≥ 105 mEq/L; (2) moderate proteinuria (urinary protein (UP) of 0.15–3.5 g/gCr); (3) renal dysfunction (estimated GFR (eGFR) of 15–90 ml/min/1.73 m^2); and (4) hypertension (clinic sBP ≥ 130 mmHg). We excluded patients who were taking medication for the treatment of metabolic acidosis, such as $NaHCO_3$, and those with a history of dialysis at their initial visit.

The patients underwent routine treatment of their CKD, which comprised lifestyle modification, nutritional education, appropriate consumption of water, and the appropriate use of medication for approximately 1 month. During this treatment period, the patients who demonstrated worsening of their renal function, requiring renal replacement therapy, and those for whom corticosteroid and immunosuppressive treatment for nephritis was started or adjusted were excluded. The patients underwent a further physical examination and laboratory testing approximately 1 month after their initial visit.

This study was approved by the Ethics Committee of Hiroshima University Hospital (approval number E-1752) and was performed in compliance with the principles of the Declaration of Helsinki.

Clinical data

The data were collected from the participants' medical records, and these included age, sex, systolic and diastolic BP, the presence of diabetes mellitus (DM), laboratory data (hemoglobin, albumin, urea nitrogen, creatinine (Cr), eGFR, uric acid, Na, Cl, potassium, total cholesterol (TC), triglyceride, high-density lipoprotein (HDL)-cholesterol, non-HDL-cholesterol, hemoglobin A1c, and UP), the use of medications (antihypertensive agents, diuretics, anti-lipemic agents, medications for metabolic acidosis, corticosteroids, immunosuppressive agents, and other medications for CKD), CKD stage, the primary cause of the CKD, and the length of time between the initial and subsequent visits. Both systolic and diastolic BP were measured in the sitting position using a mercury sphygmomanometer after a 5 min rest. We calculated eGFR using the Modification of Diet in Renal Disease equation ($eGFR = 194 \times Cr^{-1.094} \times age^{-0.287}$, multiplied by 0.739 for women) developed by the Japanese Society of Nephrology. The non-HDL-cholesterol concentration was calculated by subtracting the HDL-cholesterol from the TC concentration. UP was evaluated as a spot urinary protein/creatinine ratio. Patients with DM were identified as those with diabetic kidney disease (DKD) as the primary cause of their CKD. We defined a 1-month period as being between 2 and 6 weeks.

Statistical analysis

Normally distributed continuous data are expressed as median (interquartile range) and categorical data as percentages. Continuous datasets were compared using paired *t* tests. The statistical significance level was set as $P < 0.05$. Univariate and multivariate linear regression analyses were used to identify independent predictors of sBP, UP, the change in sBP, and the change in UP. Data were analyzed using JMP ver. 14 (SAS Institute, Inc., Cary, NC, USA).

Results

A total of 51 patients were enrolled in the study. The principal clinical characteristics of the participants at their first visit are summarized in Table 1. The participants comprised 27 men and 24 women, with a median age of 70 (58–78) years. Thirty-five of the 51 participants (68.6%) were already taking renin–angiotensin system (RAS) inhibitors; and 14 (27.5%) were taking diuretics, including loop, thiazide, and potassium-sparing diuretics. Almost all participants with diuretics (13 participants; 92.9%) were also taking RAS

Table 1 Baseline characteristics of the participants

Characteristics	Value ($n=51$)
Age (years)	70 [58–78]
Male (%)	27 (52.9)
CKD stage (%)	
G2	10 (19.6)
G3a	7 (13.7)
G3b	14 (27.5)
G4	20 (39.2)
Primary disease (%)	
Nephrosclerosis	28 (54.9)
Diabetic kidney disease	11 (21.6)
Nephritis	7 (13.7)
ADPKD	2 (3.9)
Others	3 (5.9)
sBP (mmHg)	140 [134–150]
dBP (mmHg)	70 [60–76]
Hemoglobin (g/dL)	12.2 [10.8–13.5]
Albumin (g/dL)	4.0 [3.7–4.3]
BUN (mg/dL)	25.6 [17.5–32.7]
Cr (mg/dL)	1.5 [1.01–1.82]
eGFR (mL/min/1.73 m^2)	34 [23–51]
Uric acid (mg/dL)	6.3 [5.2–7.6]
Na (mEq/L)	141 [139–142]
K (mEq/L)	4.5 [4.2–4.8]
Cl (mEq/L)	107 [106–109]
Total cholesterol (mg/dL)	197 [174–216]
Triglyceride (mg/dL)	135 [91–201]
HDL-cholesterol (mg/dL)	57 [45–69]
Non-HDL-cholesterol (mg/dL)	138 [118–156]
Hemoglobin A1c (%)	5.9 [5.6–6.3]
UP (g/gCr)	0.83 [0.43–1.87]

Continuous data are summarized as the median [interquartile range] and categorical data as absolute value (percentage)

CKD chronic kidney disease, *ADPKD* autosomal dominant polycystic kidney disease, *sBP* systolic blood pressure, *dBP* diastolic blood pressure, *BUN* blood urea nitrogen, *Cr* creatinine, *eGFR* estimated glomerular filtration rate, *Na* sodium, *K* potassium, *Cl* chloride, *HDL* high-density lipoprotein, *UP* urinary protein

inhibitors. The participants were in stage 4 (20 participants; 39.2%), stage 3b (14 participants; 27.5%), stage 3a (seven participants; 13.7%), or stage 2 (10 participants; 19.6%) CKD. The most frequent nephropathy underlying their CKD was nephrosclerosis (28 participants; 54.9%), followed by DKD (11 participants; 21.6%), nephritis (7 participants; 13.7%), and autosomal dominant polycystic kidney disease (2 participants; 3.9%). The cause in three of the participants (5.9%) was unclear. The median systolic and diastolic BP of the entire sample were 140 (134–150) mmHg and 70 (60–76) mmHg, respectively. The median UP of the entire sample was 0.83 (0.43–1.87) g/gCr. However, the median serum Cl concentration of the entire sample was relatively high because all the participants had high serum Cl concentrations (≥ 105 mEq/L).

Table 2 Relationships between systolic blood pressure and other parameters

	Univariate analysis		Multivariate analysis		*P* value
	R	*P* value	*β*	95% CI	
Age (years)	0.127	0.375	0.054	−0.343 to 0.472	0.751
eGFR (mL/min/1.73 m^2)	−0.141	0.322	−0.051	−0.344 to 0.256	0.769
Na (mEq/L)	0.208	0.144	0.084	−1.587 to 2.843	0.571
Cl (mEq/L)	0.400	0.004	0.353	−0.455 to 5.595	0.022

The results of the univariate and multivariate analyses of sBP are shown in Table 2. sBP significantly correlated with serum Cl concentration at baseline ($P=0.004$), and multivariate analysis also showed an independent association between serum Cl and sBP ($P=0.022$). Similarly, there was a significant association between UP and serum Cl in these analyses ($P=0.002$ and $P=0.033$, respectively) (Table 3).

The characteristics of the participants 1 month after their initial visit are shown in Table 4. The median length of time between the initial and subsequent visits was 28 (21–34) days. The first RAS inhibitor had been started, the dose of RAS inhibitor had increased, the inhibitor had been discontinued, or an alternative RAS inhibitor had been prescribed in 17 participants (33.3%). A thiazide diuretic had been added or the original had been changed to another thiazide diuretic in 20 participants (39.2%). Two participants (3.9%) were newly prescribed $NaHCO_3$. There was no significant change in the CKD stage, although one participant had progressed to stage G5. The serum concentrations of Na and Cl, sBP, UP, and eGFR had significantly decreased from 141 (139–142) to 139 (138–141) mEq/L ($P<0.001$), from 107 (106–109) to 105 (103–108) mEq/L ($P<0.001$), from 140 (134–150) to 124 (120–144) mmHg ($P<0.001$), from 0.83 (0.43–1.87) to 0.76 (0.28–1.28) g/gCr ($P<0.001$), and from 34 (23–51) to 33 (23–46) mL/min/1.73 m^2 ($P<0.001$), respectively.

To identify parameters that may be involved in the reduction in BP with CKD treatment, we analyzed the correlations between the change in sBP (ΔsBP) and the changes in the serum concentrations of Na (ΔNa) and Cl (ΔCl) (Table 5). ΔsBP correlated with ΔCl ($P=0.012$), but not with ΔNa, and multivariate analysis showed that ΔsBP was independently associated with ΔCl ($P=0.029$). The change in UP (ΔUP) did not correlate with ΔCl, but did correlate with the change in eGFR (ΔeGFR) ($P=0.043$) (Table 6), and

Table 3 Relationships between urinary protein and other parameters

	Univariate analysis		Multivariate analysis		*P* value
	R	*P* value	*β*	95% CI	
Systolic BP (mmHg)	0.252	0.075	0.090	−0.012 to 0.022	0.539
eGFR (mL/min/1.73 m^2)	−0.174	0.221	−0.102	−0.019 to 0.009	0.463
Na (mEq/L)	0.184	0.195	0.047	−0.107 to 0.148	0.748
Cl (mEq/L)	0.416	0.002	0.343	0.015–0.327	0.033

eGFR estimated glomerular filtration rate, *Na* sodium, *Cl* chloride, *BP* blood pressure

Table 4 Characteristics of the participants after 1 month of treatment of chronic kidney disease

Characteristics	Baseline Value ($n=51$)	After 1 month Value ($n=51$)	*P* Value
CKD stage (%)			
G2	10 (19.6)	9 (17.6)	
G3a	7 (13.7)	7 (13.7)	
G3b	14 (27.5)	14 (27.5)	
G4	20 (39.2)	20 (39.2)	
G5	0 (0.0)	1 (2.0)	
sBP (mmHg)	140 [134–150]	124 [120–144]	< 0.001
Albumin (g/dL)	4.0 [3.7–4.3]	3.9 [3.6–4.2]	0.145
eGFR (mL/min/1.73 m^2)	34 [23–51]	33 [23–46]	< 0.001
Na (mEq/L)	141 [139–142]	139 [138–141]	< 0.001
Cl (mEq/L)	107 [106–109]	105 [103–108]	< 0.001
UP (g/gCr)	0.83 [0.43–1.87]	0.76 [0.28–1.28]	< 0.001

Missing data: albumin (after 1 month), $n=3$ (5.9%). Continuous data are summarized as the median [interquartile range] and categorical data as absolute value (percentage)

CKD chronic kidney disease, *sBP* systolic blood pressure, *eGFR* estimated glomerular filtration rate, *Na* sodium, *Cl* chloride, *UP* urinary protein

multivariate analysis did not reveal significant associations between ΔUP and any of the clinical parameters.

Discussion

We performed a retrospective observational study of clinical data, focusing on hyperchloremia, collected for 51 Japanese patients with CKD. We found that their serum Cl concentration correlated with their sBP and UP at their initial examination, and that ΔCl correlated with ΔsBP 1 month after the initial visit. These findings imply that hyperchloremia is associated with hypertension and proteinuria in patients with CKD.

The kidneys play a vital role in the control of BP and UP that involves the maintenance of salt and water balance. Dietary salt restriction is well known to reduce both BP and UP; however, the detailed mechanisms whereby each one is reduced by dietary salt restriction remain unclear. There is evidence for the benefits of Na restriction on hypertension [13], proteinuria [16], and arterial stiffness [17] in patients with CKD, but there is also some evidence of a role for Cl in the regulation of BP and UP that indicates it may be even more important than Na.

Dietary salt is the principal source of Cl, and it is lost in sweat and through gastric and renal excretion. A high circulating concentration of Cl, referred to as hyperchloremia, introduces renal vasoconstriction and reduces GFR [11, 18, 19]. Delivery of excess Cl to the macula densa activates tubuloglomerular feedback, which induces afferent arteriolar vasoconstriction, mesangial contraction, and an associated reduction in GFR [20–22], resulting in an increase in systemic arterial BP.

Although no previous clinical studies have shown a direct relationship between hyperchloremia and BP, some have shown that hypochloremia is associated with higher incidences of mortality and cardiovascular disease. For example, Grodin et al. reported that serum Cl concentration is independently and inversely associated with mortality in patients with heart failure [23]. Furthermore, Mandai et al. and Kubota et al. reported that low serum Cl concentration is an independent predictor of death and cardiovascular events in patients with CKD [24, 25], which suggests that

Table 5 Relationships between the change in systolic blood pressure (mmHg/month) and other parameters

	Univariate analysis		Multivariate analysis		*P* value
	r	*P* value	*β*	95% CI	
ΔNa (mEq/L/month)	0.135	0.346	−0.193	−4.704 to 1.440	0.291
ΔCl (mEq/L/month)	0.350	0.012	0.435	0.424–7.278	0.029
Change in RASi			−0.242	−12.923 to 1.952	0.145
Change in thiazide diuretics			0.095	−5.485 to 9.629	0.584

Table 6 Relationships between the change in urinary protein (g/gCr/month) and other parameters

	Univariate analysis		Multivariate analysis		*P* value
	r	*P* value	*β*	95% CI	
ΔsBP (mmHg/month)	0.036	0.803	−0.107	−0.012 to 0.006	0.483
ΔCl (mEq/L/month)	0.253	0.073	0.219	−0.023 to 0.135	0.161
ΔeGFR (mL/min/1.73 m^2/month)	0.285	0.043	0.248	−0.005 to 0.063	0.096
Change in RASi			−0.024	−0.212 to 0.181	0.873

ΔNa change in serum sodium concentration, *ΔCl* change in serum chloride concentration, *RASi* renin–angiotensin system inhibitor, *ΔsBP* change in systolic blood pressure, *ΔeGFR* change in estimated glomerular filtration rate

hypochloremia has effects on blood vessels, but the mechanisms remain unclear.

In our previous study, we showed that aldosterone-infused rats develop more severe hypertension and renal inflammation if they drink water containing NaCl than if they drink water containing $NaHCO_3$ [15]. Conversely, dietary Cl restriction slows the development of hypertension and reduces thiazide-sensitive sodium–chloride cotransporter activation. Moreover, we found that Cl overload is associated with the activation of T lymphocytes, which is involved in the development of both hypertension and renal damage. Furthermore, we found evidence that hyperchloremia causes renal damage, which is indicated by proteinuria, through overactivation of the renin–angiotensin–aldosterone system (RAAS), although a detailed mechanism has not yet been identified.

In the present study, we identified a reduction in serum Cl concentration over a 1-month period. Although the treatment of CKD, such as through a reduction in dietary salt intake, appropriate consumption of water, and the use of diuretics, may have contributed to the reduction in serum Cl concentration, the identity of the most important cause remains unclear. We believe that appropriate water consumption is important for a reduction in serum Cl to be achieved. Cl reabsorption can occur via the sodium–potassium–2 chloride co-transporter (NKCC2) in the thick ascending limb of the loop of Henle, the sodium–chloride co-transporter (NCC) in the distal convoluted tubule, and/or the thiazide-sensitive apical sodium-dependent chloride–bicarbonate exchanger (NDCBE) in the collecting duct [26]. We hypothesize that an amelioration of dehydration through appropriate consumption of water induces a reduction in urinary Cl concentration, leading to an inhibition of Cl reabsorption via a downregulation of one or more of these transporters/exchangers, and reducing serum Cl concentration.

The present study had several limitations. First, the sample size was relatively small because of the use of a number of inclusion and exclusion criteria. Second, because the follow-up period was only 1 month, we do not know what the long-term trends might be: a longer study period may have been required to identify trends with respect to proteinuria. Finally, owing to a lack of clinical data, including the results of blood gas analysis and urinary Na and Cl concentrations, we could not evaluate hyperchloremic metabolic acidosis or the daily NaCl intake. We also could not exclude the presence of secondary hypertension; therefore, it is unclear whether the hypertension of all the participants was secondary to their CKD. Moreover, the measurement of BP alone is insufficient to evaluate CKD treatment; in the future, body fluid volume should be evaluated by measuring body mass and composition.

In conclusion, we have shown that high serum Cl concentration is associated with high sBP and UP. Furthermore, we have shown that sBP decreases when serum Cl concentration decreases, and that these associations are independent of serum Na concentration. However, further clinical studies are required to investigate whether the management of serum Cl concentration would ameliorate hypertension in patients with CKD.

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