Compared effects of calcium and sodium polystyrene sulfonate on mineral and bone metabolism and volume overload in pre-dialysis patients with hyperkalemia

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Abstract

Background Hyperkalemia is prevalent in end-stage renal disease patients, being involved in life-threatening arrhythmias. Although polystyrene sulfonate (PS) is commonly used for the treatment of hyperkalemia, direct comparison of effects between calcium and sodium PS (CPS and SPS) on mineral and bone metabolism has not yet been studied. *Methods* In a randomized and crossover design, 20 pre-dialysis patients with hyperkalemia (>5 mmol/l) received either oral CPS or SPS therapy for 4 weeks. *Results* After 4 week-treatments, there was no significant difference of changes in serum potassium (K) from the baseline (ΔK) between the two groups. However, SPS significantly decreased serum calcium (Ca) and magnesium (Mg) and increased intact parathyroid hormone (iPTH) values, whereas CPS reduced iPTH. ΔiPTH was inversely correlated with ΔCa and ΔMg (r=-0.53 and r=-0.50, respectively). Furthermore, sodium (Na) and atrial natriuretic peptide (ANP) levels were significantly elevated in patients with SPS, but not with CPS, whereas ΔNa and ΔANP were significantly correlated with each other in all the patients. We also found that ΔNa and Δ(Na to chloride ratio) were positively correlated with ΔHCO_3^-. In artificial colon fluid, CPS increased Ca and decreased Na. Furthermore, SPS more decreased K, Mg, and NH_3. *Conclusion* Compared with SPS, CPS may be safer for the treatment of hyperkalemia in pre-dialysis patients, because it did not induce hyperparathyroidism or volume overload.

Introduction

Hyperkalemia is one of the most common complications in end-stage renal disease patients, and could cause serious electronic abnormality in the heart such as cardiac arrhythmias, thereby being involved in heart failure and sudden death in patients with advanced chronic kidney disease (CKD) [1]. Indeed, it has been reported that higher serum potassium (K) levels are associated with the increased risk of mortality in both CKD and non-CKD patients [2, 3]. Although there is a growing body of evidence that renin-angiotensin system (RAS) inhibitors have protected against the progression of renal disease and its associated organ damage in patients with advanced CKD [4, 5], the therapeutic option may be limited due to considerable side effects, such as hyperkalemia [6, 7]. Therefore, strict management of hyperkalemia is desirable for a wide variety of CKD patients to prevent adverse cardio-renal events [8, 9].

Polystyrene sulfonate (PS), a cation-exchange resin, is the most commonly used drug for the treatment of hyperkalemia [10, 11]. There are two types of PS, calcium (Ca) and sodium (Na) PS (CPS and SPS), which are cross-linked polymers to which reactive sulfonic groups are attached and preloaded with Ca and Na, respectively [12, 13]. Although both types of PS exchange their bound cations for K in the lumen of proximal and distal colon and resultantly reduce serum K levels through the excretion of

K into the stool, as far as we know, there is no head-to-head comparison prospective study of CPS vs. SPS in pre-dialysis CKD patients.

Hypocalcemia and secondary hyperparathyroidism are also prevalent in advanced CKD patients [14, 15], both of which are associated with vascular calcification and osteoporotic bone fracture [16, 17], partly contributing to the increased risk of cardiovascular disease in these patients [18, 19]. Moreover, exposure to Na-containing formulations of medicines has been shown significantly to increase the risk of cardiovascular events in humans compared with standard formulations of those same drugs [20, 21]. Therefore, in this study, we performed an open-labeled, randomized, prospective, and crossover trial to directly compare the effects of CPS and SPS on mineral and bone metabolism, including serum K, Ca, phosphate (P), magnesium (Mg), intact parathyroid hormone (iPTH) and Na levels in 20 pre-dialysis outpatients (estimated glomerular filtration rate (eGFR)<30ml/min/1.73m^2) with hyperkalemia (serum K>5.0mmol/l). We further examined the effects of CPS and SPS on plasma natriuretic peptide (ANP) levels in our patients and investigated whether change of ANP after PS treatments (ΔANP) was correlated with that of ΔNa.

Materials and methods

Patients

A total of 20 pre-dialysis CKD 4-5 outpatients with hyperkalemia (K>5 mmol/l) not treated with PS were enrolled in this study. The patients were followed-up at Kurume University Hospital, Oita Prefectural Hospital, and Munakata Suikokai General Hospital from October 2013 to November 2014. We excluded patients who were already given PSs, who had acute kidney injury. The etiology of renal disease was as follows: diabetic nephropathy (n=6), glomerulonephritis (n=5), nephrosclerosis (n=3), lupus nephritis (n=2), membranous nephropathy (n=1), IgA nephropathy (n=1), and unknown (n=2). More than a half of the patients received RAS inhibitors and Ca blockers for the treatment of hypertension (55 %, 65 %, respectively). No patients received diuretics or phosphate binders during the study period.

Study design

This study was designed as a prospective, open-labeled, randomized, and crossover study (Fig. 1). Twenty hyperkalemic patients were randomly assigned to CPS group (n=10) or SPS group (n=10) by an envelope method. Patients were orally administered CPS (ARGAMATE® 89.29 % GRANULE 5.6 g; powder 5 g) or SPS (KAYEXALATE DRY SYRUP 76%® 6.54 g; powder 5 g) after each meal. After 4 weeks treatment

(period 1), each PS was immediately switched to another PS without washout interval, and followed-up for further 4 weeks (period 2). Blood pressure was measured in the sitting position using an upright standard sphygmomanometer.

Data collection

Before and after the switching to PS, blood was drawn from antecubital veins for determination of serum blood urea nitrogen, creatinine, K, albumin, Ca, P, Mg, Na, ammonia (NH_3), iPTH, and plasma ANP. Urine was collected for evaluation of urinary K and Na excretion levels. Blood and urine chemistries were measured at a commercially available laboratory (SRL Inc., Hachioji, Japan) as described previously [22]. We calculated corrected Ca levels by the following of Ca correction formula (Payne): Ca (mg/dl)+(4-serum albumin(g/dl)) [23]. Venous blood gas was taken to analyze the plasma bicarbonate (HCO_3^-) levels [24].

In vitro study

To investigate the cation-absorption capacity of CPS and SPS, we constructed an artificial colon fluid (ACF) based on the data of human diarrhea as described previously [25]. One gram of CPS or SPS was added into the 50 ml of ACF (n=6, respectively) and

the solution were stirred at room temperature for 120 minutes. After filtration, the concentrations of K, Ca, Na, Mg, and NH_3 in the supernatant were determined.

Statistical analysis

Unless otherwise, data were expressed as mean±SD. Distribution of iPTH is, in general, heavily skewed, therefore, data on iPTH was presented as the median value [interquartile range]. A one-way analysis of variance for repeated measures was used to assess the differences in baseline characteristics. To examine the difference of serum K, Ca, P, Na, chloride (Cl), Mg, iPTH, and ANP levels before and after the treatment with CPS or SPS in the period 1 and period 2, a paired *t*-test was performed. Unpaired t-test was performed in the comparison between CPS (n=20) and SPS (n=15) group. A Wilcoxon rank sum test and a Mann-Whitney U test were used for within group differences and between group differences of serum iPTH, respectively. All statistical analyses were performed by Graph Prism 5.0 for windows (GraphPad Software Inc. La Jolla, CA, USA) except for stepwise multiple regression analysis, which was performed to explore the independent determinants of ΔiPTH using IBM SPSS statistics ver.20 (IBM, Chicago, IL, USA). Statistical significance was defined as $p<0.05$.

Results

Clinical characteristics of the patients

Clinical characteristics of 20 pre-dialysis outpatients with hyperkalemia are shown in Table 1. Overall, 55 % of the patients were women and mean age was 69.7±11.5 years old. Six patients (30 %) had diabetes mellitus. The mean eGFR was 15.9±5.9 ml/min/1.73m^2 and 45 % had an eGFR<15 ml/min/1.73m^2. The mean serum K levels were 5.50±0.51 mmol/l. Nutritional conditions of all subjects were almost normal. There was no significant difference of clinical data between the two groups at baseline. Medications except PS were not changed during the study period. As shown in Fig.1, 5 patients treated with SPS dropped out due to drug-related adverse events, such as edema (3 patients), headache (1 patient), and diarrhea (1 patient).

Effects of CPS and SPS on serum and urinary levels of K

We examined serum K levels before and after the CPS and SPS treatments in period 1 (n=10, respectively). As shown in Table 2, serum K and urinary K corrected for urinary creatinine (Cr) values were significantly decreased by both treatments. The change in serum K and urinary K/Cr from baseline (serum and urinary ΔK) was almost equal between the CPS and SPS group.

Effects of CPS and SPS on other mineral and bone metabolism

We next examined whether CPS or SPS treatment could affect serum Ca, P, Mg, and iPTH levels in our patients. As shown in Table 3, although, serum P levels were not affected by either PS treatment, SPS, but not CPS treatment significantly decreased serum Ca and Mg levels. Furthermore, SPS treatment significantly increased serum iPTH levels, whereas CPS decreased it. In univariate linear regression analysis, ΔCa and ΔMg were positively associated with ΔiPTH values during the period 1 and 2 (n=35, $r=-0.53$, $p<0.001$ and $r=-0.50$, $p<0.01$, respectively) (Figs. 2a and b). Stepwise multiple regression analysis revealed that ΔCa (adjusted $\beta=-0.33$, $p<0.05$), ΔMg (adjusted $\beta=-0.37$, $p<0.01$), and ΔP (adjusted $\beta=0.35$, $p<0.05$) were independent determinants of ΔiPTH values in our patients (Table 4). Multicollinearity in these three values was not recognized.

Effects of CPS and SPS on serum and urinary Na, plasma ANP, and acid-base equilibrium

We further investigated whether the administration of CPS or SPS could affect serum and urinary Na and plasma ANP levels. As shown in Table 5, serum Na levels were

significantly increased by SPS treatment, whereas decreased by CPS. Urinary Na/Cr values were modestly, but not significantly increased by SPS, whereas decreased by CPS (Table 5). Moreover, SPS, but not CPS treatment significantly increased plasma ANP levels. In univariate linear regression analysis, ΔNa was positively associated with ΔANP values during the period 1 and 2 (Fig. 2c). Mean blood pressure and body weight were tended to increase by SPS treatment (95.3±17.5 to 97.5±13.4 mmHg, p=0.14, 54.6±13.1 to 55.0±12.8 kg, p=0.33, respectively). There was a positive correlation between ΔNa and Δbody weight ($p<0.05$, r=0.45, n=20) (Fig. 2d).

It has been reported that SPS induces metabolic alkalosis via the absorption of NH_3 in the colon fluid [26]. So, we next compared the effects of SPS on serum NH_3 and plasma bicarbonate (HCO_3^-) levels with those of CPS (Table 5). SPS, but not CPS treatment significantly increased plasma HCO_3^- and serum Na levels, while serum NH_3 levels were not changed by either PS treatment. As shown in Figs. 3a-c, ΔNa and Δ(Na to Cl ratio) but not ΔNH_3 were positively correlated with ΔHCO_3^- (r=0.75, $p<0.0001$, r=0.84, $p<0.0001$, and r=0.06, p=0.75, respectively).

Effects of CPS or SPS on cation exchange capacity in ACF

As shown in Table 6, K levels in the ACF were significantly decreased by CPS or SPS;

the effect of the latter was larger than that of the former. CPS and SPS had opposite effects on Ca and Na levels in the ACF; CPS increased Ca and decreased Na, and SPS vice versa. Furthermore, SPS treatment more decreased Mg and NH_3.

Discussion

In our human study, although K-decreasing capacity of CPS and SPS was almost equal, serum Ca and Mg levels were significantly decreased by SPS treatment compared with CPS. These findings are consistent with the previous report showing that CPS did not affect serum Ca or Mg levels in patients with chronic renal failure [10]. Furthermore, in this study, SPS treatment significantly increased iPTH levels, whereas CPS decreased it. There was a significant and independent correlation between ΔCa or ΔMg and ΔiPTH values. Since SPS more exchanged their bound Na for K, Mg, Ca, and NH_3 in the ACF, higher cations-exchanging capacity of SPS could be involved in lower serum levels of Ca and Mg, thereby worsening secondary hyperparathyroidism. In addition, although there was no significant difference of serum NH_3 between the two groups, SPS may increase intraluminal pH by absorbing NH_3. Because higher intestinal pH has been reported to inhibit an activity of TRPM6, a major transporter of Mg in the colon [27], which could suppress the absorption of Mg, it might partly contribute to the decrease in

serum Mg levels by SPS.

Parathyroid cells have calcium-sensing receptors (CaRs) on cell-surface, which enable them to respond to changes in extracellular Ca concentration [28, 29]. Although Ca is the main CaR agonist, Mg is also able to activate the CaRs [30]. An increased extracellular Mg has been shown to inhibit PTH secretion by parathyroid cells [31]. Low Ca, low Mg, or high iPTH levels are associated with progression of diabetic kidney disease [32] and cardiovascular mortality in patients with dialysis [33]. So our present findings may raise the safety concern of SPS for the treatment of hyperkalemia in pre-dialysis patients due to its detrimental effects of Ca, Mg, and iPTH [18]. On the other hand, since a meta-analysis revealed that calcium supplements were associated with an increased risk of myocardial infarction [34], Ca load by CPS may also increase the risk of vascular calcification and cardiovascular events in CKD patients. Therefore, excess Ca intake and Ca-based phosphate binders may be avoided in CKD patients, especially those with vascular calcification.

In this study, we also found that serum Na and plasma ANP levels were significantly elevated by the treatment with SPS. Further, ΔNa was positively correlated with ΔANP values during the study (Fig. 2c). The changes in serum Na concentration are determined not only by intestinal Na absorption, but also by water intake. Although we

did not evaluate water intake in our patients, there was a positive correlation between ΔNa and Δbody weight ($p<0.05$, $r=0.45$, $n=20$) (Fig.2d), thus suggesting that the increase of Na level by SPS might be associated with increased extracellular fluid. Recent retrospective study has shown that SPS causes inter-dialytic weight gain and increases blood pressure in dialysis patients in Dialysis Outcomes and Practice Patterns Study [35]. Exposure to sodium-containing formulations of drugs are associated with adverse cardiovascular events in patients compared to sodium-free formulation ones [20]. Therefore, intake of sodium should be strictly controlled in patients who were receiving SPS.

In the present study, although K-exchanging capacity of SPS was higher than that of CPS, serum K-reducing ability of both drugs was nearly the same. It has been reported that K concentration in lower intestine was higher than that in upper one, and the highest in distal colon [36, 37]. SPS has mainly absorbed K, Mg, Ca, and NH_3 in the fluid of upper digestive tract, where K concentration is low. On the other hand, CPS has absorbed K in the distal colon *rather than* upper digestive tract due to the lower cation-exchange capacity, where K concentration is highest. This might be a possible reason for the discrepant results between ACF experiments and pre-dialysis patients.

Treatment of SPS has been reported to increase HCO_3^- levels due to absorption of NH_3

in the digestive tract [26]. Consistent with the previous reports, we found that SPS, but not CPS, dramatically increased plasma HCO_3^- levels. Furthermore, although ΔNH_3 was not associated with ΔHCO_3^- values, ΔNa and Δ(Na to Cl ratio) were positively correlated with ΔHCO_3^-. A close relationship between sodium as well as potassium balance and renal response to a chronic acid load was first reported in 1977 [38]. Further, Lindner et al. have shown that rising serum Na levels could cause a concurrent development of metabolic alkalosis in critically ill patients [39]. Recently Stewart approach is proposed as a new idea of acid-base equilibrium [40, 41].

There are several limitations in this study. First, the sample size was small and the study duration was short. Second, due to the ethical concern, we could not set a washout period in this crossover study. Furthermore, as many as 5 patients were dropped out during the phase of SPS. Impaired capacity of electrolyte excretion by the kidney may affect the present findings.

Conclusion

In summary, although the present study demonstrated that K-reducing capacity of CPS and SPS was almost equal in pre-dialysis CKD patients with hyperkalemia, SPS treatment decreased Ca and Mg levels in association with increase in serum iPTH, Na,

or plasma ANP values, which might lead to hyperparathyroidism and volume overload. Our present findings suggest that CPS might be better than SPS to control hyperkalemia in pre-dialysis patients. Further longitudinal studies are needed to clarify whether CPS treatment could exert more beneficial effects on bone metabolism and cardiovascular events in advanced CKD patients compared with SPS.

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Compliance with ethical standards

Conflict of interest: Dr. Fukami has received honoraria such as lecture fees from Sanwa (Sanwa Kagaku Kenkyusyo). This paper has not been published previously in whole or part.

Human rights: (with IRB approval number) All procedures performed in studies involving human participants were in accordance with the ethical standards of the

institutional ethics committee at which the studies were conducted (Approval No. 13170) and with the 1964 Helsinki Declaration and its later amendments of comparable ethical standards. This trial was registered with the University Hospital Medical Information Network clinical trials database (UMIN 000021955).

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Figure Legends

Fig. 1 Study design. CKD patients were randomized to CPS and SPS groups. After the first 4 weeks of the therapy phase (period 1, n=20), CPS and SPS were immediately switched to another PS, and followed for further 4 weeks (period 2, n=35). CKD, chronic kidney disease; PS, polystyrene sulfonate; CPS, calcium polystyrene sulfonate; SPS, sodium polystyrene sulfonate.

Fig. 2 Pearson's correlation between (a) ΔiPTH and ΔCa, (b) ΔiPTH and ΔMg, (c) ΔANP and ΔNa (n=35, respectively), and (d) Δbody weight and ΔNa (n=20). Δ, changes the values from the baseline or period 1; iPTH, intact parathyroid hormone; Ca, calcium; Mg, magnesium; Na, sodium; ANP, atrial natriuretic peptide.

Fig. 3 Pearson's correlation between (a) ΔHCO_3^- and ΔNa, (b) ΔHCO_3^- and ΔNa to Cl ratio, and (c) ΔHCO_3^- and ΔNH_3 (n=35, respectively). Δ, changes the values from the baseline or period 1; HCO_3^-, bicarbonate; NH_3, ammonia; Na, sodium; Cl, chloride.

Fig. 1

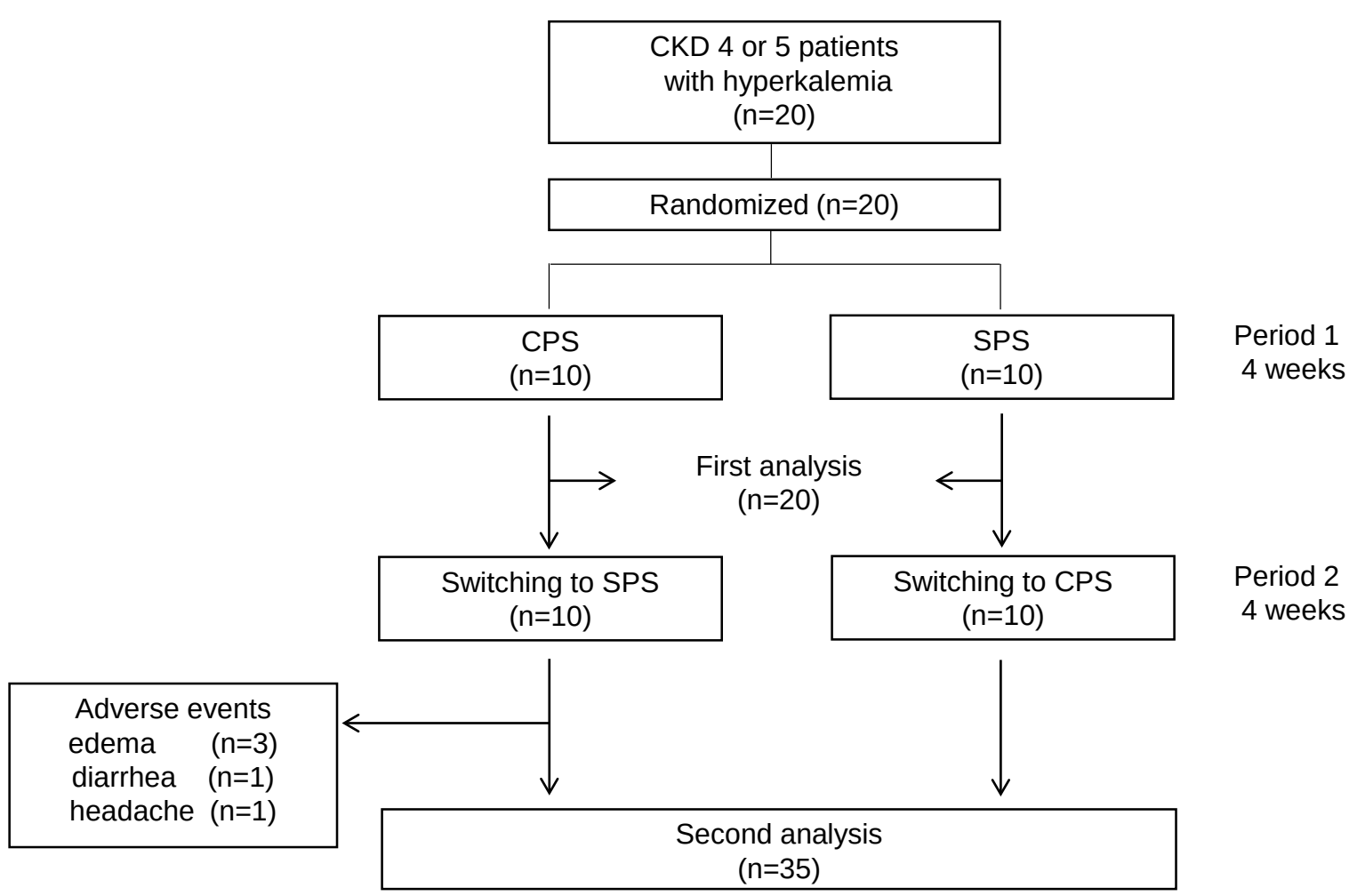
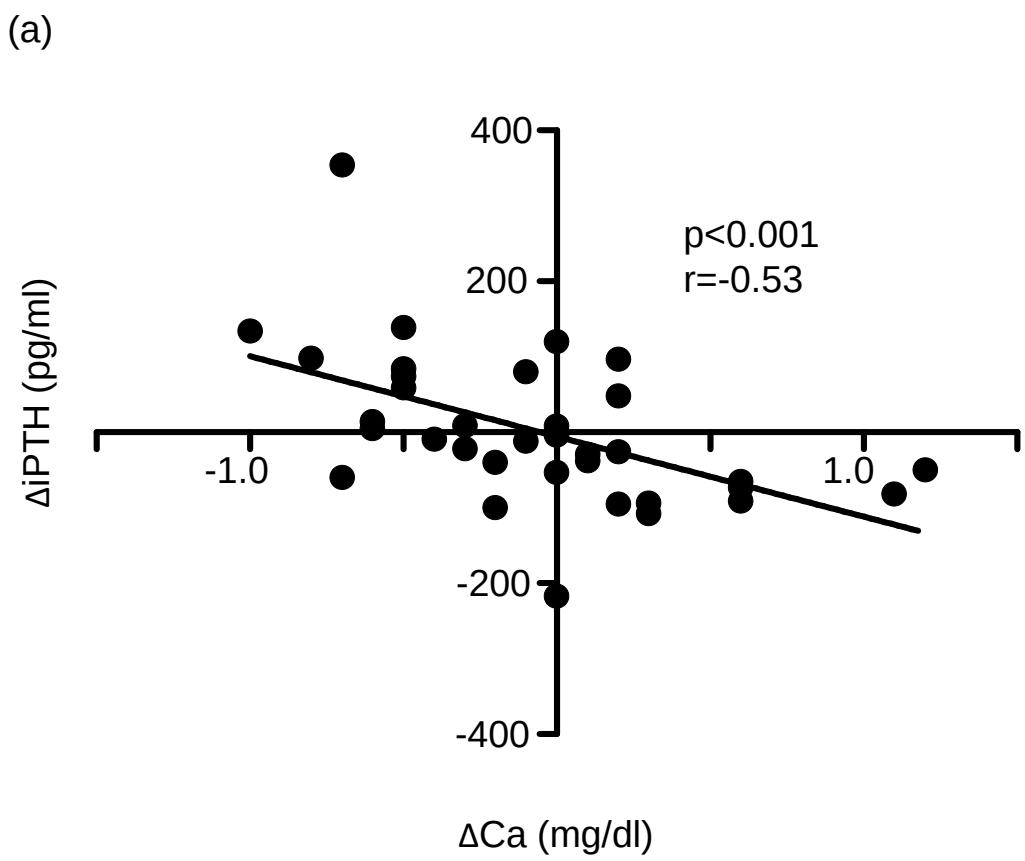
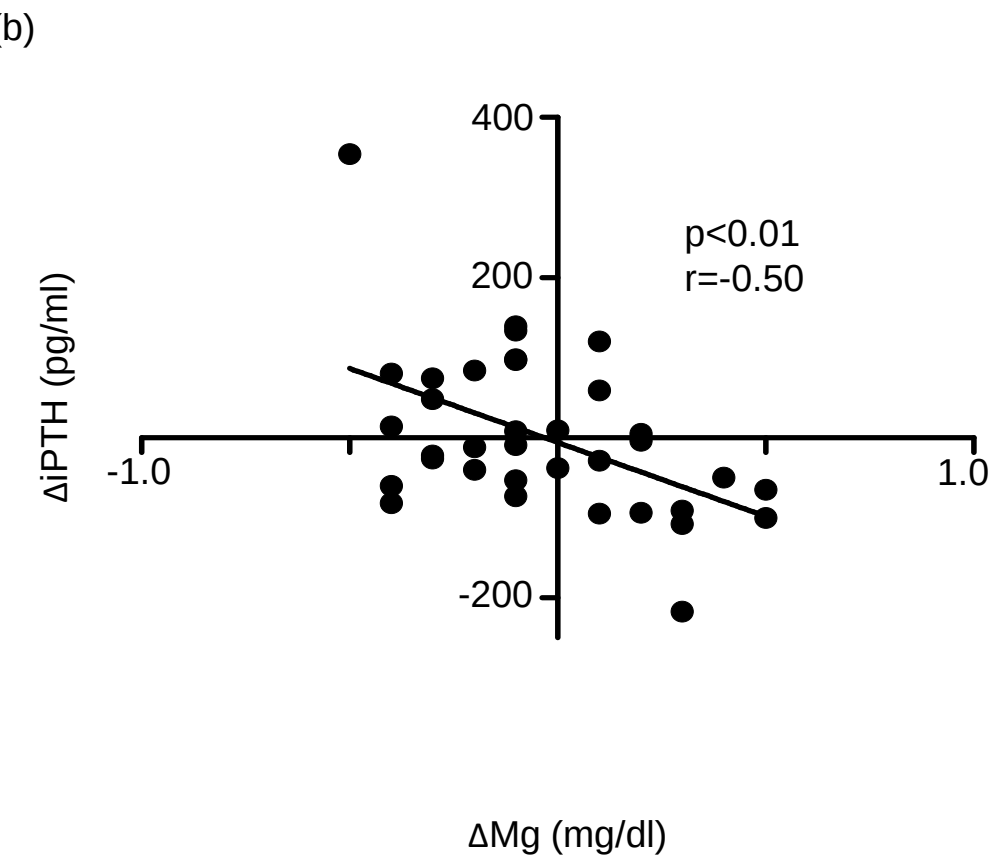
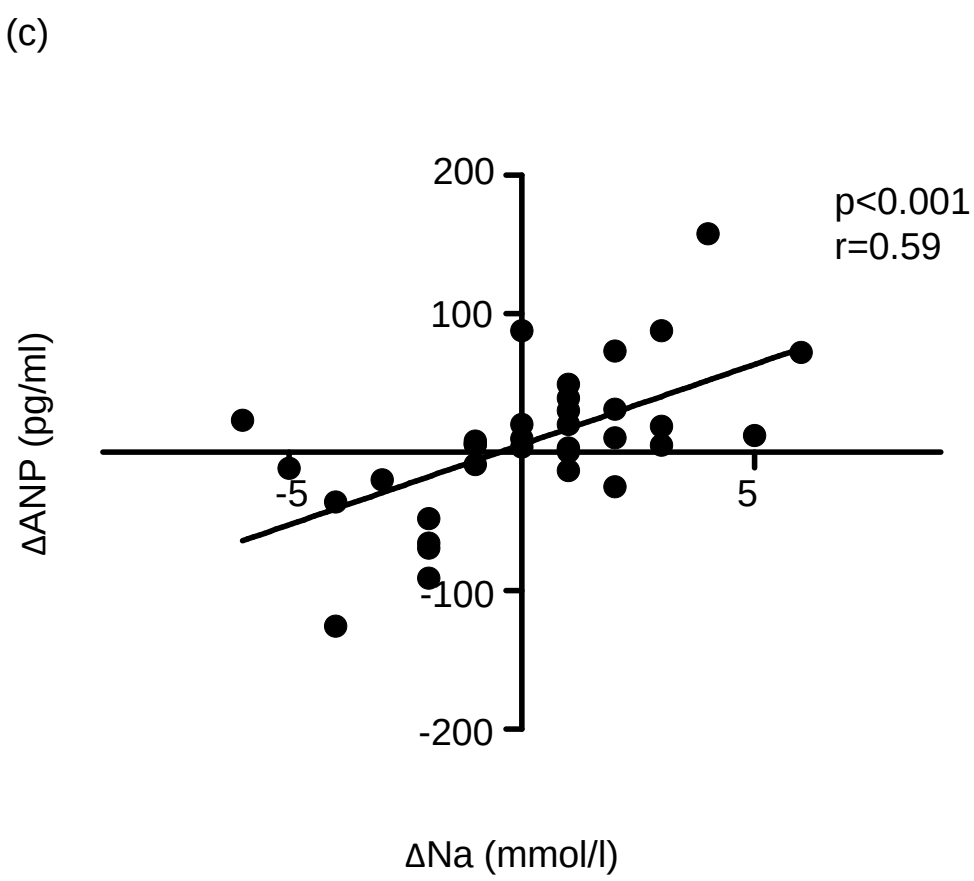

CKD 4 or 5 patients
with hyperkalemia
(n=20)
Randomized (n=20)
CPS
(n=10)
SPS
(n=10)
Period 1
4 weeks
First analysis
(n=20)
Switching to SPS
(n=10)
Switching to CPS
(n=10)
Period 2
4 weeks
Adverse events
edema (n=3)
diarrhea (n=1)
headache (n=1)
Second analysis
(n=35)

Fig. 2


(a)
400
200
-200
-400
-1.0
1.0
p<0.001
r=-0.53
ΔiPTH (pg/ml)
ΔCa (mg/dl)


(b)
400
200
-200
-1.0
1.0
p<0.01
r=-0.50
ΔiPTH (pg/ml)
ΔMg (mg/dl)


(c)
200
100
-100
-200
-5
5
p<0.001
r=0.59
ΔANP (pg/ml)
ΔNa (mmol/l)

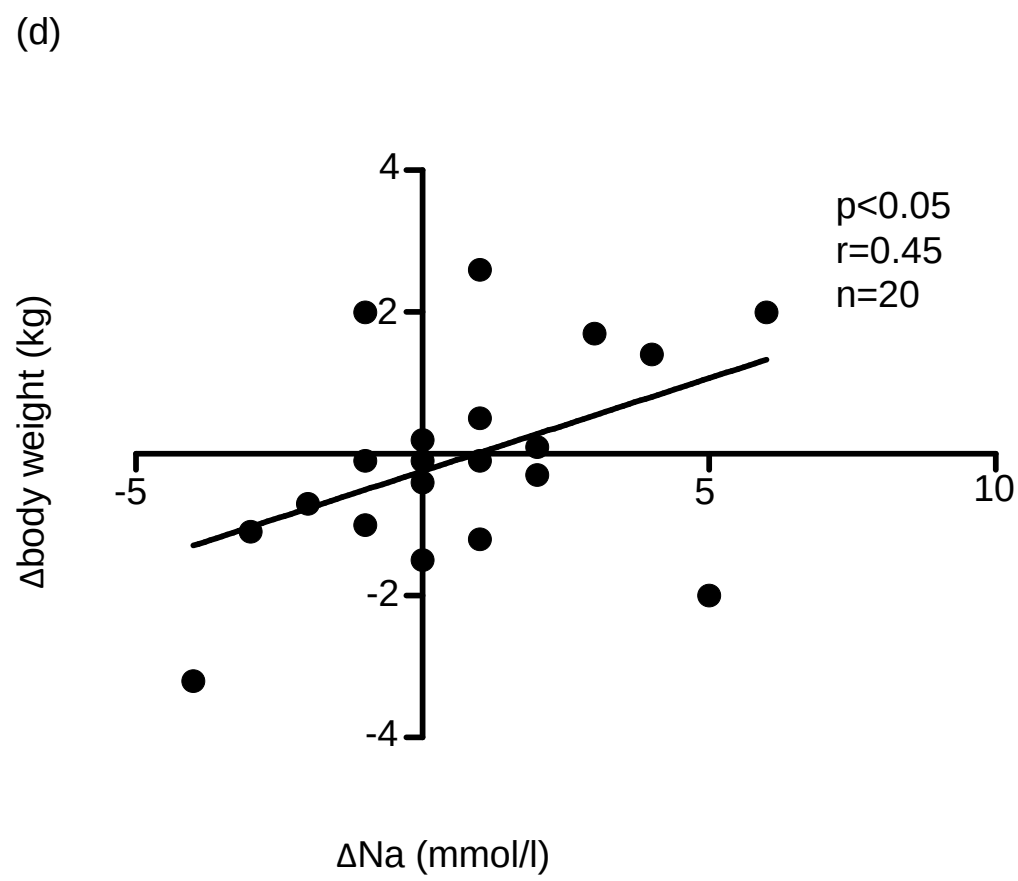
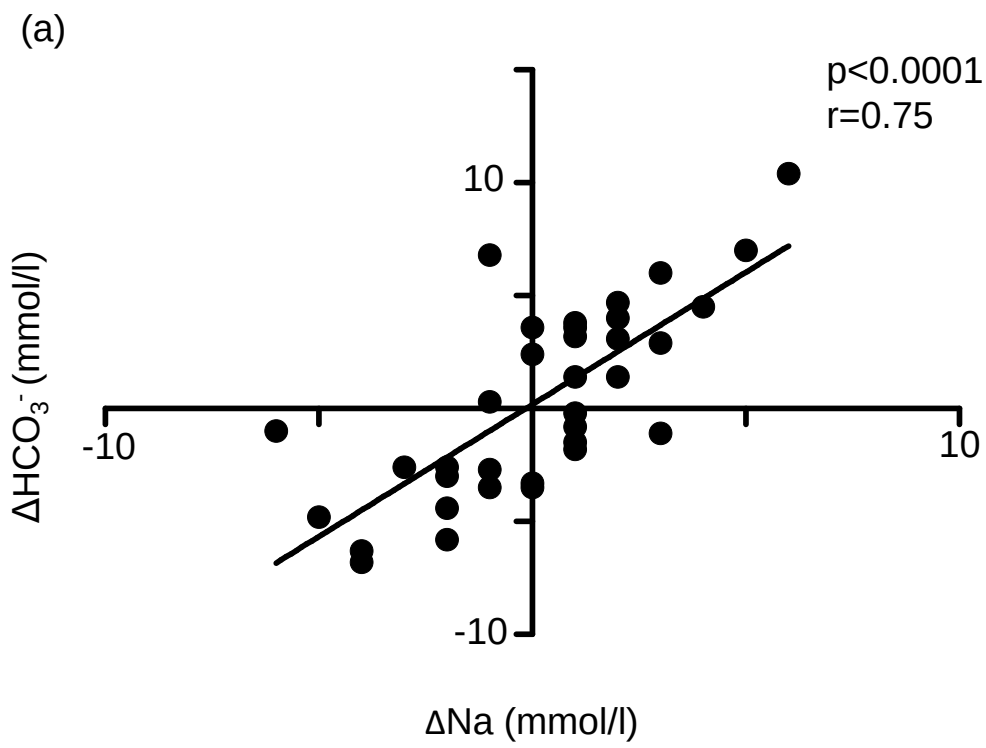
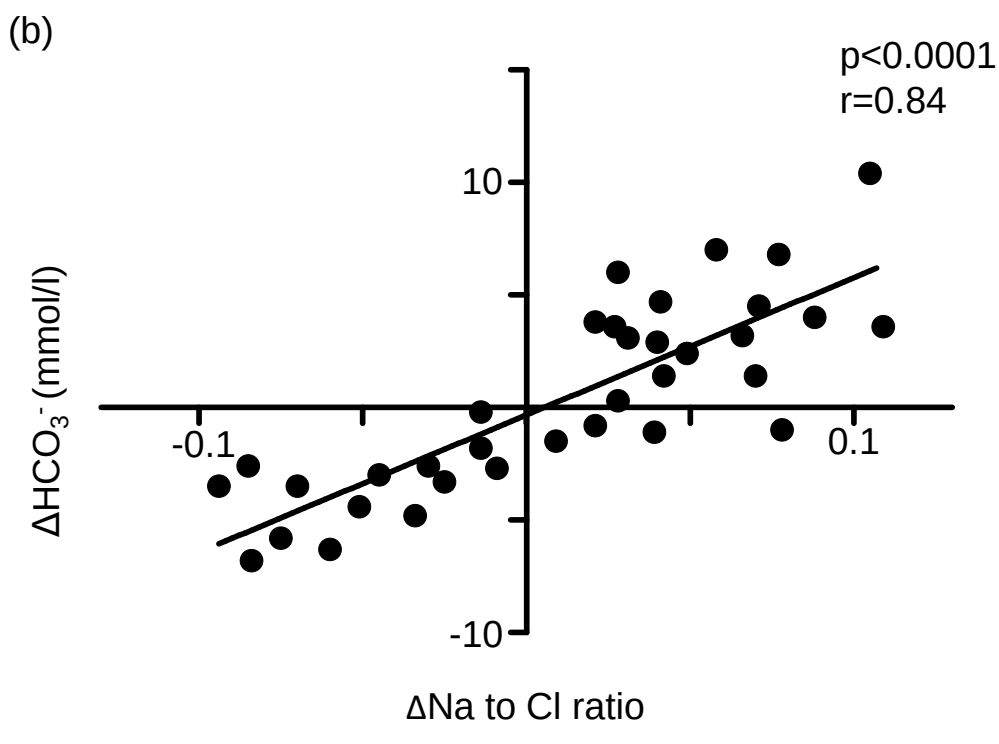

(d)
4
2
-2
-4
-5
5
10
p<0.05
r=0.45
n=20
Δbody weight (kg)
ΔNa (mmol/l)

Fig. 3


(a)
p<0.0001
r=0.75
10
-10
-10
10
ΔHCO3- (mmol/l)
ΔNa (mmol/l)


(b)
p<0.0001
r=0.84
10
-10
-0.1
0.1
ΔHCO3- (mmol/l)
ΔNa to Cl ratio

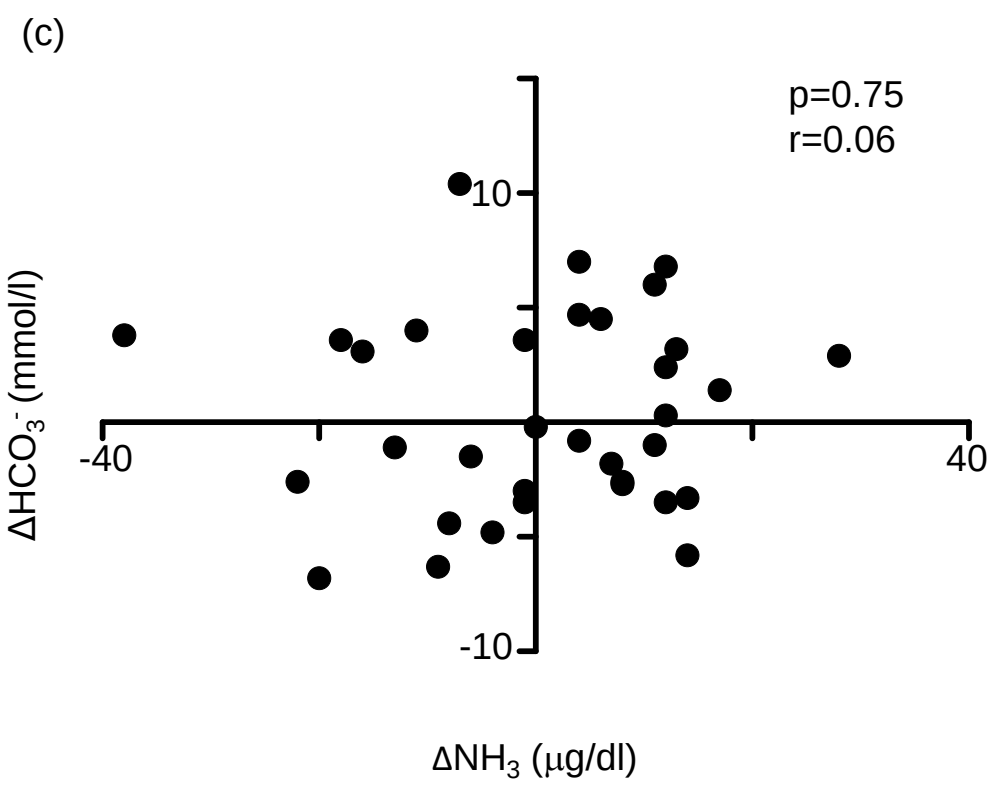

(c)
p=0.75
r=0.06
10
-10
-40
40
ΔHCO3- (mmol/l)
ΔNH3 (μg/dl)

Table 1 Baseline characteristics of the study population

Variables	Total (n=20)	CPS (n=10)	SPS (n=10)	p
Age (years)	69.7±11.5	69.1±12.0	70.2±11.7	0.98
Female No. (%)	11 (55)	6 (60)	5 (50)	0.91
Diabetes No. (%)	6 (30)	4 (40)	2 (20)	0.64
BMI(kg/m^2)	21.9±3.1	21.4±3.0	22.4±3.3	0.78
Body weight (kg)	54.7±12.2	51.9±12.5	57.8±11.8	0.62
Mean BP (mmHg)	91.4±14.0	89.7±14.2	93.2±14.6	0.88
eGFR($ml/min/1.73m^2$)	15.9±5.9	13.0±4.7	18.7±5.7	0.08
Serum Cr (mg/dl)	3.19±1.35	3.79±1.61	2.59±0.68	0.13
Serum BUN (mg/dl)	48.8±16.9	53.8±21.0	45.8±11.2	0.57
Serum albumin (g/dl)	3.97±0.38	3.90±0.44	4.04±0.32	0.72
Serum Na (mmol/l)	140.8±2.1	140.8±2.0	140.8±2.2	0.99
Serum K (mmol/l)	5.50±0.51	5.39±0.49	5.60±0.54	0.66
Serum Cl (mmol/l)	109.6±3.2	109.4±3.2	109.7±3.2	0.98
Serum Ca (mg/dl)	9.11±0.36	9.20±0.29	9.01±0.41	0.51
Serum P (mg/dl)	4.08±0.65	4.03±0.54	4.13±0.76	0.94
Serum Mg (mg/dl)	2.16±0.41	2.19±0.29	2.13±0.53	0.95
Serum NH_3 (μg/dl)	52.3±11.3	54.2±12.0	50.1±10.6	0.74
Plasma ANP (pg/ml)	70.3±68.0	70.8±49.3	69.9±85.7	0.99
Plasma HCO_3^-	21.5±2.9	20.6±2.2	22.4±3.3	0.37
(mmol/l)	1.6±0.8	1.4±0.6	1.8±1.0	0.60
Urinary K/Cr (g/ gCr)	3.2±1.6	3.2±1.8	3.3±1.5	0.99
Urinary Na/Cr (g/ gCr)	154 [106, 253 (147)]	188 [111, 313 (202)]	135 [86, 233(147)]	0.49
Serum iPTH (pg/ml)				
Medications No. (%)	11 (55)	8 (80)	3 (30)	
RAS inhibitors	13 (65)	7 (70)	6 (60)	
Ca-blockers	6 (30)	5 (50)	1 (10)	
α, β-blockers	2 (10)	1 (10)	1 (10)	
Mg oxide	6 (30)	3 (30)	3 (30)	
Sodium bicarbonate				

Categorical and continuous values are expressed as % and mean±SD or median [interquartile range], respectively. A one-way analysis of variance for repeated measures was used to assess the difference of baseline characteristics. CPS, calcium polystyrene sulfonate; SPS, sodium polystyrene sulfonate; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; Cr, creatinine; BUN, blood urea nitrogen; Na, sodium; K, potassium; Cl, chloride; Ca, calcium; P,

phosphate; Mg, magnesium; NH_3, ammonia; ANP; atrial natriuretic peptide; HCO_3^-, bicarbonate; iPTH, intact parathyroid hormone; RAS, renin-angiotensin system.

Table 2 Effects of CPS and SPS treatment on serum and urinary K levels

Serum K (mmol/l)	0week	4weeks	Δserum K (95% C.I.)	p
CPS (n=10)	5.39±0.49	4.14±0.91	-1.25 (-1.90 to -0.60)	p<0.01
SPS (n=10)	5.60±0.54	4.12±0.64	-1.48 (-1.88 to -1.08)	p<0.0001
p	0.37	0.96	0.51	
Urinary K/Cr (g/ gCr)	0week	4weeks	Δurinary K/Cr (95% C.I.)	p
CPS (n=10)	1.39±0.58	0.76±0.25	-0.62 (-0.99 to -0.25)	p<0.01
SPS (n=10)	1.75±0.96	1.01±0.63	-0.73 (-1.34 to -0.13)	p<0.05
p	0.32	0.26	0.72	

K levels were compared only with before and after PS treatment in period 1 (n=10, respectively). Values are expressed as mean±SD. Statistical significance was determined using a paired t-test (within group differences). Statistical significance was determined using an unpaired t-test (between group differences). Δ, change values from the baseline; K, potassium; Cr, creatinine; CPS, calcium polystyrene sulfonate; SPS, sodium polystyrene sulfonate; period 1, after first 4 weeks of therapy phase.

Table 3 Effects of CPS and SPS treatment on mineral and bone metabolism

Serum Ca (mg/dl)	0week	4weeks	ΔCa (95% C.I.)	p
CPS (n=20)	8.96±0.46	9.09±0.52	0.13 (-0.10 to 0.36)	0.26
SPS (n=15)	9.09±0.37	8.77±0.47	-0.33 (-0.54 to -0.11)	p<0.01
p	0.37	0.07	p<0.01	
Serum P (mg/dl)	0week	4weeks	ΔP (95% C.I.)	p
CPS (n=20)	3.96±1.04	3.79±0.73	-0.17 (-0.44 to 0.10)	0.20
SPS (n=15)	3.99±0.69	4.04±1.36	0.04 (-0.55 to 0.64)	0.86
p	0.90	0.48	0.44	
Serum Mg (mg/dl)	0week	4weeks	ΔMg (95% C.I.)	p
CPS (n=20)	2.03±0.46	2.13±0.34	0.11 (-0.01 to 0.22)	0.07
SPS (n=15)	2.17±0.45	1.93±0.48	-0.23 (-0.32 to -0.15)	p<0.001
p	0.37	0.16	p<0.001	
Serum iPTH (pg/ml)	0week	4weeks	ΔiPTH [interquartile range]	p
CPS (n=20)	171 [118, 255 (137)]	122 [71, 224 (153)]	-52 [-93, 3 (96)]	p<0.01
SPS (n=15)	118 [75, 229 (154)]	173 [129, 244(115)]	80 [-22, 120 (142)]	p<0.05
p	0.15	0.08	p<0.001	

Values are expressed as mean±SD. Serum iPTH levels were expressed as median [interquartile range]. Statistical significance was determined using a paired t-test (within group differences) for serum Ca, P, and Mg. A Wilcoxon rank sum test (within group differences) and a Mann-Whitney U test (between group differences) were performed for serum iPTH. Ca, calcium; P, phosphate; Mg, magnesium; iPTH, intact parathyroid hormone; Δ, change values from the baseline or period 1; C.I., confidence internal; CPS, calcium polystyrene sulfonate; SPS, sodium polystyrene sulfonate.

Table 4 Stepwise multiple regression analysis for ΔiPTH in pre-dialysis patients with PS treatment

	Unadjusted (β, p) r^2=0.28	Model 1 (β, p) r^2=0.39	Model 2 (β, p) r^2=0.50
ΔCa	-0.53 (p<0.001)	-0.41 (p<0.01)	-0.33 (p<0.05)
ΔMg		-0.35 (p<0.05)	-0.37 (p<0.01)
ΔP			0.35 (p<0.05)

Stepwise multiple regression analysis was performed for the independent determinants of ΔiPTH (n=35). Pearson's correlation coefficient (r) and the regression line are presented. Multicollinearity was not recognized (tolerance ΔMg=0.86 and ΔP=0.97). β, standardized coefficient; Δ, change values from the baseline (n=20) or period 1 (n=15); iPTH, intact parathyroid hormone; Ca, calcium; Mg, magnesium; P, phosphate; PS, polystyrene sulfonate.

Table 5 Effects of CPS and SPS treatment on sodium loading and acid-base equilibrium

Serum Na (mmol/l)	0week	4weeks	ΔNa (95% C.I.)	p
CPS (n=20)	142±2.7	141±2.8	-1.25 (-2.33 to 0.17)	p<0.05
SPS (n=15)	141±2.0	143±2.7	2.07 (0.99 to 3.14)	p<0.001
p	0.19	p<0.05	p<0.001	
Urinary Na/Cr (g/ gCr)	0week	4weeks	Δurinary Na/Cr (95% C.I.)	p
CPS (n=20)	4.1±3.0	3.0±1.4	-1.1±2.7 (-2.4 to 0.2)	0.09
SPS (n=15)	3.4±1.4	5.0±3.2	1.6±3.5 (-0.3 to 3.5)	0.10
p	0.38	p<0.05	p<0.05	
Serum Cl (mmol/l)	0week	4weeks	ΔCl (95% C.I.)	p
CPS (n=20)	108±3.7	109±4.2	1.00 (-0.86 to 2.86)	0.27
SPS (n=15)	109±3.5	106±4.4	-3.13 (-4.40 to -1.86)	p<0.001
p	0.33	0.06	p<0.01	
Plasma ANP (pg/ml)	0week	4weeks	ΔANP (95% C.I.)	p
CPS (n=20)	93±81	79±68	-14.0 (-36.7 to 8.8)	0.21
SPS (n=15)	80±76	113±92	36.2 (11.1 to 61.2)	p<0.01
p	0.60	0.22	p<0.01	
Serum Na to Cl ratio	0week	4weeks	ΔNa to Cl ratio (95% C.I.)	p
CPS (n=20)	1.32±0.05	1.29±0.04	-0.02 (-0.05 to -0.0)	p<0.05
SPS (n=15)	1.29±0.04	1.35±0.05	0.06 (0.04 to 0.07)	p<0.0001
p	0.11	p<0.001	p<0.0001	
Plasma HCO_3^- (mmol/l)	0week	4weeks	ΔHCO_3^- (95% C.I.)	p
CPS (n=20)	23.4±4.1	20.9±3.6	-2.5 (-3.7 to -1.3)	p<0.001
SPS (n=15)	21.2±3.2	25.9±4.1	4.2 (2.8 to 5.6)	p<0.0001
p	0.07	p<0.001	p<0.0001	
Serum NH_3 (μg/dl)	0week	4weeks	ΔNH_3 (95% C.I.)	p
CPS (n=20)	55±12	54±12	-0.6 (-6.0 to 4.8)	0.82

SPS (n=15)	53±12	54±11	2.4 (-7.1 to 11.9)	0.59
p	0.67	0.97	0.53	

Values are expressed as mean±SD. Statistical significance was determined using a paired t-test (within group differences). Statistical significance was determined using an unpaired t-test (between group differences). The data were in serum, urinary and plasma samples. Δ, change values from the baseline or period 1; C.I., confidence internal; Na, sodium; Cr, creatinine; Cl, chloride; ANP, atrial natriuretic peptide; HCO_3^-, bicarbonate; NH_3, ammonia; CPS, calcium polystyrene sulfonate; SPS, sodium polystyrene sulfonate.

Table 6 Effects of CPS and SPS treatment on K, Ca, Mg, Na, and NH_3 concentrations in ACF

ACF K (mmol/l)	Before	after	ΔK (95% C.I.)	p
CPS (n=6)	8.83±0.08	7.60±0.15	-1.23 (-1.32 to -1.15)	p<0.0001
SPS (n=6)	8.87±0.10	6.80±0.13	-2.07 (-2.24 to -1.90)	p<0.0001
p	0.55	p<0.0001	p<0.0001	
ACF Ca (mg/dl)	Before	after	ΔCa (95% C.I.)	p
CPS (n=6)	19.5±0.19	85.5±2.13	66.0 (63.8 to 68.2)	p<0.0001
SPS (n=6)	19.5±0.23	5.51±0.15	-14.0 (-14.3 to -13.8)	p<0.0001
p	0.69	p<0.0001	p<0.0001	
ACF Mg (mg/dl)	before	after	ΔMg (95% C.I.)	p
CPS (n=6)	11.9±0.47	8.92±0.25	-3.0 (-3.3 to -2.6)	p<0.0001
SPS (n=6)	11.7±0.57	5.57±0.25	-6.1 (-6.5 to -5.7)	p<0.0001
p	0.52	p<0.0001	p<0.0001	
ACF Na (mmol/l)	before	after	ΔNa (95% C.I.)	p
CPS (n=6)	149±2.04	141±3.62	-8.17 (-9.8 to -6.5)	p<0.0001
SPS (n=6)	150±2.58	213±13.8	63.0 (50.3 to 75.7)	p<0.0001
p	0.55	p<0.0001	p<0.0001	
ACF NH_3 (μg/dl)	before	after	ΔNH_3 (95% C.I.)	p
CPS (n=6)	14.0±0.13	12.8±0.17	-1.23 (-1.40 to -1.06)	p<0.0001
SPS (n=6)	14.0±0.16	11.7±0.31	-2.34 (-2.67 to -2.01)	p<0.0001
p	0.67	p<0.0001	p<0.0001	

Values are expressed as mean±SD. Statistical significance was determined using a paired t-test (within group differences). Statistical significance was determined using an unpaired t-test (between group differences). The data were in ACF and ACF plus each polystyrene sulfonates (CPS 1g treatment, n=6 or SPS 1g treatment, n=6). ACF, artificial colon fluid; Δ, change values from the before PS treatment; C.I., confidence internal; K, potassium; Ca, calcium; Mg, magnesium; Na, sodium; NH_3, ammonia; PS, polystyrene sulfonate; CPS, calcium polystyrene sulfonate; SPS, sodium polystyrene sulfonate.