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Plasma Calcium Concentration Modifies the Blood Sodium During Hemodialysis: Lessons from Hard Water Syndrome

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Abstract

Introduction. Extracellular sodium (Na^+) concentration is maintained within a tight physiological range due to hormonal control, that mainly modulates thirst, Na^+ and water renal excretion. Extra-renal regulation of Na^+ and water homeostasis is only partially understood. Recently it has been debated whether the osmotically inactive Na^+ storage is fixed or variable.

Methods. In the present study, fourteen End-Stage Renal Disease (ESRD) patients treated by chronic hemodialysis underwent by accident to a sharp increase in plasmatic calcium (Ca^{+2}) levels due to the failure of the water control system, leading to the so-called hard water syndrome. The levels of plasmatic Ca^{+2} after 1 hr of hemodialysis were correlated with urea, Na^+, potassium (K^+) and creatinine levels. Eleven ESRD patients treated with hemodialysis under similar conditions were used as controls.

Results. The hard water syndrome resulted in hypercalcemia, while mean plasma levels of Na^+, K^+ and urea were not different compared to controls. Plasma creatinine levels were slightly but significantly higher that control. A correlation analysis on the measured variables has showed a positive correlation between plasma Ca^{+2} and Na^+ levels (Pearson=0.428, p=0.032), and the absence of any correlation with K^+, creatinine and urea concentration.

Conclusions. Our study suggests that acute changes in plasmatic Ca^{+2} levels may affect Na^+ concentration in the absence of renal function; it is possible that hypercalcemia may trigger Na^+ release from the osmotically inactive storage. These data further support previous observations on the interplay of sodium and calcium at extrarenal sites.

Keywords: calcium, hemodialysis, hard water syndrome, hypercalcemia, natremia

Introduction

The extracellular sodium represents one of the main determinants of plasma osmolarity. A fine regulation of Na^+ plasmatic levels is guaranteed by a strict hormonal control, which mainly acts on the regulation of thirst, Na^+ and water renal reabsorption [1]. Several evidences suggest that a large reservoir of osmotically inactive sodium is represented by the extracellular matrix of bone, skin and muscles [2]. The circumstances under which this reservoir may vary are under active debate. It has been recently suggested that there is a balance between the osmotically active and inactive Na^+ pool; thus, upon slow changes in body fluids, the composition of inactive Na^+ pool changes accordingly. In rats, long-term salt deprivation is accompanied by a decrease in the charge density of skin GAGs, and the consequent mobilization of osmotically inactive Na^+. This finding suggests that the skin and the connective tissues may serve as a Na^+ storage, capable to release Na^+ in response to reduced intake by changing its polyanionic character [3].

In addition, several studies have recently shown that in both humans and animal models, chronic hyponatremia is associated with bone resorption and osteoporosis [4]. One possibility is that chronic hyponatremia may lead to sodium loss from the bones with consequent bone demineralization [5]. It remains unclear how this large Na+ reservoir is regulated. Clearly, since the extracellular proteins can bind both calcium and Na^+, some extrarenal form of interaction between the two ions might exist. For instance, it is well known that many cells express a Na^+- Ca^{+2} Exchanger (NCX), and that there is a perfect coupling between Na^+ and calcium transcellular fluxes based on their extracellular concentrations [6,7].

The exact knowledge of this interplay is important because it may provide an additional mechanism of sodium regulation, independent of the kidney function; in addition, this regulation might have clinical impact particularly in patients undergoing dialysis (who lack

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kidney regulation for extracellular sodium and rely on the dialysis system).

Under physiological conditions, the extrarenal Na^+/Ca^{+2} interplay cannot be easily studied, because of the tight control of the kidney itself of these ions, which masks any extrarenal [8].

On the other hand, in patients with the absence of kidney function, such as in patients under dialysis treatment, the Na^+ and calcium levels are also tightly controlled by the dialysis.

Therefore, it seems impossible in human subjects to test the relation between calcium and sodium levels in the absence of kidney compensation.

Recently, we have had the possibility to study the effects of an extracellular calcium increase on Na^+ levels in subjects undergoing chronic hemodialysis treatment. These subjects underwent by accident to a sharp increase in calcium levels due to a failure in the water control system (Hard Water Syndrome).

These subjects experienced a rapid increase in blood pressure and malaise, and therefore the dialysis process has been interrupted after 1 hr. This unfortunate and irreproducible accident represented also a unique occasion to test the extra-renal effects of calcium on plasma sodium in human subjects without kidney compensation.

The hypothesis is that in presence of a large increase of extracellular calcium, the latter should compete with the Na^+ bound to the extracellular matrix, thus leading to a linear increase of (unbound) plasmatic Na^+.

We also expect that this effect is dampened by the buffering effect of the dialysis process on Na^+ ions; however, a correlation between calcium levels and the Na^+ levels should yet be detected as the rate equilibrium of Na^+ would be slower if a greater amount of Na^+ is mobilized by a larger amount of calcium.

We discuss the findings under the hypothesis of a sodium-calcium interplay at extrarenal sites, which has already received a large support based on animal models (see also the recent review by Sterns) [9].

Materials and methods

Fourteen patients under chronic hemodialysis treatment three times a week for end-stage renal disease (ESRD) have received, by accident, unsoftened tap water in their dialytic process.

Analyses were conducted retrospectively using deidentified patient data; thus this study was deemed exempt from the requirement of ethical approval by the institutional review board. We adhered to the Declaration of Helsinki; informed consent was not required.

The water conductivity in samples derived from tap water reached 483 mS/cm, while the treated water had a mean value of 15 mS/cm. The dialysis treatment was stopped after 60 minutes due to the emergence of severe headache, vomiting, hypertension, tachycardia and nausea, typical for the "Hard Water Syndrome" [10]. Water samples for chemical surveillance were collected from the tubes serving the dialysis: the problem in the water filters was recognized and subsequently solved. All patients subsequently fully recovered from the accident and no patient suffered any health problem due to it.

For comparison, blood samples from 11 patients under regular dialysis were taken 60 minutes after the start of the treatment.

Hemodialysis was delivered using a Fresenius HD machine FX 5800 (Fresenius FMC, Germany) programmed to provide a dialysis flow rate of 500 ml/min at a temperature of 36°C. Standard bicarbonate buffered dialysate concentrate (Fresenius 335) was used to yield a dialysis fluid containing the following concentrations: bicarbonate 32 mmol/L, glucose 5.5 mmol/L, calcium 1.5 mmol/L, K^+ 2.0 mmol/L, Na^+ 142 mmol/L. Blood flow was set in the range 200-360 ml/min.

All patients had arteriovenous fistulas and arterial blood samples were collected from the fistula at the end of the dialysis process. All patients received seleparin 3000-4000U as anticoagulation each dialysis session.

At the end of the 60-min dialysis process, the blood samples were collected to measure plasma sodium, potassium, calcium, urea and creatinine.

Statistical analysis

Multivariate ANOVA was used to verify significant differences between the two groups. Multiple post-hoc was performed to identify significant differences. Correlation analysis between the measured variables was conducted to observe relationships among the serum ions. The rejection value was set at $p<0.05$.

Results

As shown in Table 1, after 1 hr of dialysis treatment, the control and hypercalcemic patients were comparable for urea, K^+ and Na^+ levels. Conversely, in all patients

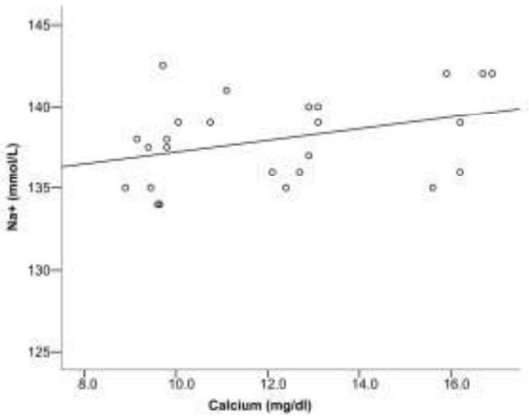

Fig 1. Correlation between calcium (horizontal axis) and sodium levels (vertical axis)

treated with hard water the most remarkable result was the presence of an increase by 45% of blood calcium levels ($p<0.01$, test t for non-paired data). Moreover, hypercalcemic patients also showed a small increase (13%), but statistically significant, of creatinine levels ($p=0.011$, t-test for non-paired data).

A correlation analysis on the measured variables after dialysis is shown in Figure 1. Specifically, calcemia was not correlated with potassium, creatinine and urea levels, whereas a positive correlation was noted with the Na^+ levels (Pearson=0.428, $p=0.032$). Figure 1 also shows the linear regression analysis between calcium and Na^+.

Discussion

The present study shows that, in the absence of renal function, natremia linearly depends on calcium levels. This observation went previously unnoticed because the strength of the relationship was quite weak (for 1 mg/dl of change in calcemia, the natremia changed by only 0.27 mmol/L). Therefore, to observe this relationship two conditions must be met: first, large modifications in the calcemia must occur to induce a quantifiable modification in natremia. This condition was met in our setting when a population of subjects with hard water syndrome was studied. Second, linear correlation methods should be used rather than classification of subjects in two or more calcemic groups. Indeed, even in our settings, if the population was subdivided in only two groups (normal versus high calcium), the power of the test would be insufficient to establish a significant difference in natremia (Table 1).

Table 1. Characteristics of controls and hypercalcemic patients (post-dialysis refers to values after 1 hr)

	Dialysis Controls (mean ±SEM)	Dialysis hypercalcemic (mean ±SEM)	p (t-test for non-paired data)
n	11	14	
Creatinine (mg/dl)	5.2±1.3	5.9±0.3	P=0.058
Urea (mg/dl)	61.9±15	54.6±13.2	NS
Na^+ (mEq/L)	137.23±2.5	138.5±2.6	NS
K^+ (mEq/L)	4.39±0.47	4.29±0.6	NS
Ca^{+2} (mg/dl)	9.66±0.48	14±2	P<<0.01

NS: p> 0.05

The fact that the subjects were ESRD patients under chronic hemodialysis clearly excludes the role of kidney function in the pathogenesis of this phenomenon. However, our observation can be explained by more than one mechanism. The first possibility is that high calcium concentration in the dialysate may affect the dialysis membrane permeability. This hypothesis is unlikely, because the state of hypercalcemia seems not to affect the diffusion of other electrolytes such as potassium, as indicated by the absence of any difference in K^+ plasma levels between patients and controls.

Another possibility is that the increased calcium concentration in the dialysate, leading to an increased osmolality of the dialysis solution, may alter the osmotic gradient, thus producing water and solute removal.

Theoretically, a hypertonic dialysis solution is supposed to diminish the efficiency of water and solute removal. In fact, by the 1980-ties, after the advent of blood pumps and dialyzers with large surface area, the use of hypotonic dialysate solutions (that cause a severe dialysis disequilibrium syndrome) were considered no longer crucial to obtain dialysis salt and water removal, and therefore, dialysate solutions containing more physiological concentration of Na^+ have been used subsequently [11]. However, the increased osmolality of the dialysate caused by the accidental increased calcium content is supposed to diminish urea, water and other solute removal. Interestingly, besides the increased plasmatic calcium levels, and urea, the other measured electrolytes did not differ significantly among patients and controls.

Moreover, we cannot exclude that the elevated amount of extracellular calcium modifies the plasma membrane permeability, leading to a cell loss of Na^+. However, several factors are against this hypothesis:

1) the intracellular amount of sodium is much lower than extracellular fluids, so diffusion or facilitated process is unlikely to occur;
2) as the trend toward an increased plasma concentration is confined to the Na^+, a not-specific and generalized permeability of the plasma membrane is unlikely to happen?

Therefore, we speculate that this phenomenon might be explained by the buffering activity of the extracellular matrix in response to an increased extracellular calcium concentration, leading to release of Na^+ in exchange with calcium (Figure 2).

Major limitations of the study are: (i) the limited sample size (ii) the limited amount of available data (unfortunately, due to the acute setting of the accident, other important hematologic parameters were not measured at the time), (iii) the impossibility to directly measure the amount of osmotically inactive Na^+ before and after the accident. However, given the rarity of the hard water syndrome, this information still retains its validity in human beings.

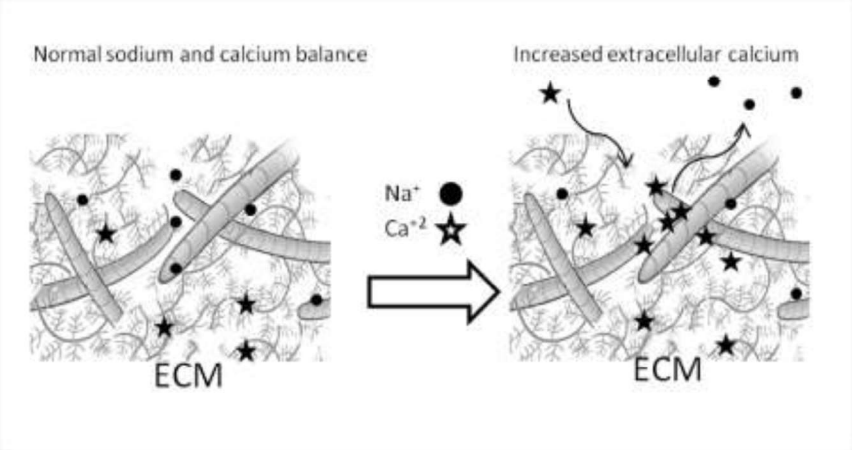

Fig. 2. Schematic representation of sodium/calcium interplay at the level of the extracellular matrix

In fact, the repetition of the study is practically impossible, because it derives from an unfortunate accident during a dialysis treatment. However, the data are of large interest and might foster further studies in the field.

Conclusion

Our data suggest that in the absence of kidney function, an extracellular increase of calcium induced by high calcium levels into the dialysate is accompanied by a trend toward increased plasma Na^+ levels. Speculatively, hypercalcemia might foster sodium release from the extracellular matrix. This might represent an additional form of sodium homeostasis, which does not necessitate kidney intervention. The conclusion of the study has a number of limitations. First, a larger amount of data should be necessary to lend further support to the hypothesis of an extrarenal handling of sodium. However, this is simply impossible, given the incidental nature of our observations, which make them also very precious and rare. Therefore, the observation of a correlation between calcium and sodium in this case is simply a confirmation of the hypothesis of an extrarenal interplay of the two molecules, due to the large extracellular reservoir of sodium [9].

Conflict of interest statement. None declared.

References

1. Pontes RB, Girardi AC, Nishi EE, *et al*. Crosstalk between the renal sympathetic nerve and intrarenal angiotensin II modulates proximal tubular sodium reabsorption. *Exp Physiol* 2015; 100: 502-506.
2. Titze J, Dahlamnn A, Lerchl K, *et al*. Spooky sodium balance. *Kidney Int* 2014; 85: 759-767.
3. Schafflhuber M, Volpi N, Dahlmann A, *et al*. Mobilization of osmotically inactive Na^+ by growth and by dietary salt restriction in rats. *Am J Physiol Renal Physiol* 2007; 292: F1490-F1500.
4. Ayus JC, Negri AL, Kalantar-Zadeh K, Moritz ML. Is chronic hyponatremia a novel risk factor for hip fracture in the elderly? *Nephrol Dial Transplant* 2012; 27: 3725-3731.
5. Titze J, Shakibaei M, Schafflhuber M. Glycosaminoglycan polymerization may enable osmotically inactive Na^+ storage in the skin. *Am J Physiol Hear Circ Physiol* 2004; 287: H203-H208.
6. Molinaro P, Viggiano D, Nistico R *et al*. Na^+-Ca^{+2} Exchanger (NCX3) Knock-Out Mice Display an Impairment in Hippocampal Long-Term Potentiation and Spatial Learning and Memory. *J Neurosci* 2011; 31: 7312-7321.
7. Molinaro P, Cuomo O, Pignataro G, *et al*. Targeted disruption of Na^+/ Ca^{+2} exchanger 3 (NCX3) gene leads to a worsening of ischemic brain damage. *J Neurosci* 2008; 28: 1179-1184.
8. Zacchia M, Capasso G. Parvalbumin: a key protein in early distal tubule NaCl reabsorption. *Nephrol Dial Transplant* 2008; 23: 1109-1111.
9. Stems RH. Disorders of Plasma Sodium-Causes, Consequences, and Correction. *N Engl J Med* 2015; 372: 55-65.
10. Freeman RM, Lawtoon RL, Chamberlain MA. Hard-water syndrome. *New Engl J Med* 1967; 276: 1113-1118.
11. Flanigan MJ. Role of sodium in hemodialysis. *Kidney Int Suppl* 2000; 76: S72-S78.