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Sodium is Neither a Risk nor a Protective Factor in Urolithiasis?

P. P. Singh, A. K. Pendse, P. Hada, P. C. Nagori, V. Rathore and P. K. Dashora

Department of Biochemistry and Surgery, R.N.T. Medical College, Udaipur, Rajasthan, India

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Summary. The effect of changes in urinary sodium, induced by dietary manipulation in normal subjects (NS) and in stone formers (SF) was studied by observing crytalluria qualitatively and by determining calcium, oxalate and phosphate crystallization quantitatively in an experimental model. In SF the calcium crystallization was significantly higher than in NS at all the three levels of urinary sodium studied. However, no difference was observed in oxalate and phosphate crystallization rates between these two groups. Calcium and oxalate ($p < 0.05$) and oxalate and phosphate ($p < 0.001$) were found to be correlated in NS but were non-significant in SF. The wide changes in the urinary sodium induced by dietary changes did not influence the crystallization rate of calcium, nor of oxalate and phosphate in NS as well as in SF. The results suggested that a sodium intake with lower and upper limits of 124 mg and 6,009 mg respectively did not act as "inhibitor" of crystallization rate nor did it induce hypercalciuria severe enough to pose a "risk" of stone formation. The results did not suggest that a high urinary sodium increases the solubility of calcium phosphate.

Key words: Sodium, Inhibitory activity, Oxalates, Phosphates, Calcium, Calculi.

Introduction

It has been suggested that sodium increases the solubility of calcium in urine by competitive binding to apatite crystals [9]. The concept is that sodium displaces calcium ions not only in solution but also in the solid state, thus increasing the solubility of hydroxyapatite and other similar crystals. Udall et al. [18] demonstrated that none of the 48 lambs given extra salt developed concretions but 29 of the 48 who did not receive extra salt did develop them. Udall et al. also found that urinary sodium was significantly lower in stone forming white subjects as compared to the stone free black population (Bantus) which convinced Modlin [5] that sodium acts as urinary inhibitor of stone. He further lent support to his hypothesis by collecting data from Japan which showed that stone incidence was directly related to salt intake. He showed that the Na/Ca ratio is lower in stone formers.

Robertson et al. [12] initiated the controversial debate on this issue by stating that high Na/Ca ratio in many populations could be due to the increased calcium excretion rather than to the low sodium excretion.

Several other reports have appeared which show a direct relationship between urinary calcium and sodium in animals [19], in normal people [4], and in idiopathic hypercalciuric subjects [8]. Phillips and Cooke [8] studied the urinary excretion of calcium, sodium, potassium and chloride in stone formers and observed a very significant correlation between sodium and calcium. Another noteworthy finding was that there was no significant difference in the excretion of sodium between normal subjects (NS) and stone formers (SF). Recently Silver et al. [13] noted hypercalciuria in 4 stone formers which was corrected by low salt diet thus indirectly implicating sodium as a risk factor.

Sutton and Walker [17] demonstrated a significant positive correlation between urinary Na and Ca, both in NS and SF. They suggested that the risk of hypercalciuria is always more in the presence of high urinary sodium. Rao et al. [11] confirmed these findings and suggested that salt restriction should be advised in subjects who have high urinary sodium (which is always due to high dietary intake) to avoid the risk of hypercalciuria which in turn increases the risk of stone formation.

Thus there are conflicting reports about the role of sodium in urolithiasis but no one has investigated whether urinary sodium increases or decreases "crystallization potential" and crystalluria which should provide better indices of a stone forming episode.

Material and Methods

9 normal subjects (NS) and 32 radiologically confirmed stone formers (SF) were selected for this study 27 patients with upper urinary tract stones (UUTSF) and 5 patients with lower urinary tract stones (LUTSF). To ascertain the effect of dietary sodium, the following regimen was given to both NS and SF.

Diet 1 (DI). Normal hospital diet for two days (average Na intake 3,067.9 mg/day).

Diet 2 (DII). Salt-free diet (the same hospital diet as in DI except that no table salt was added during cooking) with 1 g of calcium (2 tablets of 500 mg calcium Sandoz) after breakfast for two days (average sodium intake 124.4 mg/day).

Diet 3 (DIII). Salt free diet (the same hospital diet as in DI except that no table salt was added during cooking) + 1 g calcium supplementation (after breakfast as stated above) + 15 g of salt added to food items served in breakfast, lunch and dinner. (Average sodium intake 6,009.7 mg per day.)

DII induced low urinary sodium and slightly increased calcium. DIII induced substantial increase in urinary sodium as well as in calcium. During the entire period of study the water intake was kept almost constant.

Each diet was given on two consecutive days. 24 h urine samples were collected only on the second day of the given diet.

The technique used for determination of calcium crystallization was described by Dent and Sutor [1]. This technique was improved by Pandey et al. [7] and subsequently used by them [14] for determining influence of tamarind intake on calcium crystallization rate (Inhibitor assay). We have used the same technique with following modifications.

a. Crystallization rate was measured at 37 °C.

b. Three 3 mm diameter glass fibres were used and 5 ml of 0.2 N HCl was used to wash the rods.

c. The same set of glass fibres were used for all the three samples of one subject.

d. Calcium [2], oxalic acid [3] and inorganic phosphorus [6] content were measured in the washing.

Student "t" test, correlation coefficient (r) and analysis of variance (ANOVA) were applied for statistical evaluation of data.

Results

The urinary crystallization rate of calcium, oxalate and phosphate on DI, DII and DIII in NS and SF is given in Table 1. A statistical comparison of the crystallization rates of these parameters between NS and SF is also given in the same table. There was no statistically significant difference in the phosphate or oxalate crystallization between NS and SF on either of the diets but calcium crystallization was significantly higher in SF on all the three diets. Whether any relationship between calcium and oxalate, calcium and phosphate and oxalate and phosphate was being followed in NS and SF was calculated in Table 2. In NS, calcium and oxalate, oxalate and phosphate correlation was statistically significant whereas calcium and phosphate correlation was insignificant. In SF all these correlations were not significant.

Table 1. Effect of dietary supplementation of calcium and sodium on urinary calcium, oxalate and phosphate crystallization process (inhibitory activity) in normal subjects and stone formers

Parameter	Diet no.	Normal subjects Mean ± SD	Stone formers Mean ± SD	*P*
Calcium (μg)	DI	123.4 ± 107.6	419.7 ± 206.9	< 0.001
	DII	186.8 ± 89.5	474.5 ± 265.4	< 0.01
	DIII	198.6 ± 124.0	454.3 ± 261.1	< 0.01
Oxalate (μg)	DI	154.9 ± 118.9	109.4 ± 114.7	NS
	DII	153.5 ± 69.2	108.6 ± 111.8	NS
	DIII	104.6 ± 34.6	156.8 ± 140.1	NS
Phosphate (μg)	DI	48.4 ± 37.5	94.8 ± 143.3	NS
	DII	47.1 ± 37.0	53.5 ± 66.6	NS
	DIII	34.3 ± 41.6	88.2 ± 143.7	NS

	Average Ca content	Average Na content
DI	470.5 mg	3,067.9 mg
DII	1,512.5 mg	124.4 mg
DIII	1,606.1 mg	6,009.7 mg

Table 2. Correlation between crystallization rates of calcium, oxalate and phosphate in normal subjects and stone formers

Correlation	Normal subjects		Stone formers	
	r	*P*	*r*	*P*
Calcium vs Oxalate	0.4673	p < 0.05	0.1049	NS
Calcium vs Phosphate	−0.0032	NS	−0.0840	NS
Oxalate vs Phosphate	0.8106	p < 0.001	−0.0415	NS

The calcium, oxalate and phosphate crystallization rates during different diets in UUTSF and LUTSF are given in Table 3. There was no significant difference in the crystallization rates of these parameters between the two groups (UUTSF & LUTSF) nor did the urinary changes in sodium and calcium induced by DI, DII, DIII give any discernible pattern. The results of analysis of variance (ANOVA) in NS, UUTSF and LUTSF in respect to calcium, oxalate and phosphate are shown in Tables 4 to 6.

The results in general showed that neither low nor high urinary sodium in the presence of moderately high calcium affected the crystallization rates of calcium, oxalate and phosphate.

Discussion

Several studies have been carried out to examine the calcium oxalate crystal growth in the presence of various compounds [15, 16]. Dent and Sutor [1] compared the crystal growth of calcium oxalate on glass fibres for qualitative comparison to ascertain the inhibitor activity of the urine.

Table 3. Effect of dietary supplementation of calcium and sodium on urinary calcium, oxalate and phosphate crystallisation process (inhibitory activity) in 27 upper and 5 lower urinary tract stone formers

Parameter	Diet no.	Upper urinary tract stone formers (Mean ± SD)	Lower urinary tract stone formers (Mean ± SD)
Calcium (μg)	DI	423.5 ± 203.7	397.9 ± 248.2
	DII	508.9 ± 272.1	279.7 ± 105.3
	DIII	480.2 ± 285.0	376.7 ± 123.6
Oxalate (μg)	DI	114.6 ± 119.0	180.2 ± 246.7
	DII	105.7 ± 104.4	124.1 ± 159.9
	DIII	187.5 ± 164.4	93.5 ± 72.6
Phosphate (μg)	DI	77.7 ± 135.6	142.9 ± 177.7
	DII	49.6 ± 52.9	80.7 ± 121.8
	DIII	95.4 ± 154.6	49.5 ± 49.7

Table 4. Standard error of difference between two means (SED) and critical difference (CD) at 5% and at 1% level of significance for calcium deposition in NS (Gr. I), LUTSF (Gr. II) and UUTSF (Gr. III)

Groups	SED	CD at 5%	CD at 1%
(within Gr. I)	0.1048	NS	NS
(within Gr. II)	0.1406	NS	NS
(within Gr. III)	0.0605	NS	NS
(between I & II)	0.0716	0.1417	NS
(between I & III)	0.0494	0.0978	0.1293
(between II & III)	0.0625	NS	NS

CV = Coefficient of variation (35.71%)

Table 5. Standard error of difference between two means (SED) and critical difference (CD) at 5% and at 1% level of significance for oxalate deposition in NS (Gr. I), LUTSF (Gr. II) & UUTSF (Gr. III)

Groups	SED	CD at 5%	CD at 1%
(within Gr. I)	0.0583	NS	NS
(within Gr. II)	0.0782	NS	NS
(within Gr. III)	0.0336	0.0666	NS
(between I & II)	0.0398	NS	NS
(between I & III)	0.0274	NS	NS
(between II & III)	0.0347	NS	NS

Coefficient of variation (CV) = 93.26%

Note: Since CV is very high conclusions based on these observations are not of much value

Table 6. Standard error of difference between two means (SED) and ciritcal difference at 5% and 1% level of significance for phosphate deposition in NS (Gr. I), LUTSF (Gr. II) and UUTSF (Gr. III)

Groups	SED	CD at 5%	CD at 1%
(within Gr. I)	0.0469	NS	NS
(within Gr. II)	0.0629	NS	NS
(within Gr. III)	0.0270	NS	NS
(between I & II)	0.0320	NS	NS
(between I & III)	0.0221	NS	NS
(between II & III)	0.0279	NS	NS

Coeffecient of variation (CV) = 138.25%

Note: Since CV is very high conclusions based on these observations are not of much value

They also suggested that quantitative measurement of the crystals could also be done by weighing glass fibres before and after the experiment. The present modified technique gave more accurate and reproducible results as a quantitative determination of calcium, oxalate and phosphate was made which excluded the possibility of weighing error.

We have observed that increase in the urinary sodium excretion is accompanied by increased calcium excretion but not by increased calcium oxalate or calcium phosphate crystalluria [10]. We opine that hypercalciuria induced by hypernatriuria should not imply an increased risk of stone formation unless it is shown to enhance crystalluria and calcium crystallization potential. We have, therefore, studied urinary crystalluria and calcium crystallization on glass fibres induced by dietary variations in sodium and calcium.

Our data (Table 1) shows that calcium crystallization on glass fibres was significantly higher in the urine of SF as compared to the NS. As hypercalciuria was not a prominent feature in the NS and the SF, it appeared that factors other than the calcium content of urine are responsible for the enhanced calcium crystallization.

To evaluate the effect of dietary sodium on calcium crystallization in urine in the presence of mild dietary calcium load we placed the subjects on 2 dietary regimen-DII (Calcium and sodium 1,512 mg and 124.1 mg respectively) and DIII (Calcium and sodium 1,606.1 mg and 6,009.7 mg respectively). In NS as well as in SF no significant change in urinary crystallization on either of these diets was observed as compared to the normal diet (DI). The results indicate that neither hypernatriuria nor hyponatriuria, induced by high or low dietary sodium respectively, affected the urinary calcium crystallization. We concluded that sodium has neither an inhibitory nor a promotionary role in calcium crystallization process in the urine.

Urinary oxalate and phosphate crystallization were not significantly different in the NS than SF (Table 1 and 3). Changes in sodium did not bring about significant changes in these crystallization processes between these two groups (Table 1 and 3).

In NS, calcium and oxalate crystallization followed a week correlation while oxalate and phosphate followed a strong correlation. These significant correlations could have

been the result of either their ionic dependence on each other or may have been caused by some other factor altering crystallization behaviour in the same direction. The absence of such correlations in SF is an expression of some abnormality possibly leading to stone formation.

The results of inhibitor assay (calcium, oxalate and phosphate crystallizations) in UUTSF and LUTSF are separately given in Table 3. No significant difference in crystallization potential between these two groups was observed.

The effect of urinary sodium changes on crystallization rate of calcium, oxalate and phosphate within each group i.e. in NS, in UUTSF and in LUTSF; and that among three groups is more precisely explained by analysis of variance presented in Tables 4 to 6.

Table 4 shows the statistical evaluation of the influence of dietary variations in sodium and calcium on urinary calcium crystallization rate in NS, UUTSF and LUTSF. Urinary sodium levels induced by DI and DII did not affect the rate of calcium crystallization suggesting that urinary sodium neither acted as inhibitor nor as promotor of crystallization. This is intuitively explained by the fact that a) it had acted as inhibitor, in which case low sodium and moderately increased calcium in the urine, induced by DII, should have caused increased crystalluria and increased rate of calcium crystallization; and that b) had it acted indirectly as "risk factor" by causing hypercalciuria, then high urinary calcium, induced by DIII should have again given similar results as above.

No significant difference in oxalate or phosphate crystallization was observed due to different diets in NS, UUTSF or LUTSF (Tables 5 and 6). Indirectly these results suggest that sodium variation does not affect the crystallization rate of calcium oxalate or calcium phosphate.

We may emphasize that so far other workers who have ascribed the inhibitory or promotive role to sodium in calcium urolithiasis have done so on the basis of increase or decrease in urinary calcium and sodium and not on the basis of crystalluria nor of crystallization potential of urine which we are convinced is a more reliable index. Our observations based on crystalluria and crystallization studies do not lend support to the hypothesis of inhibitor role of sodium suggested by Modlin [5] nor to the stress laid by Rao et al. [11] in recommending salt restriction for the management of urolithiasis.

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Dr. P. P. Singh
Professor and Head
Department of Biochemistry
R.N.T. Medical College,
Udaipur-313 001
Rajasthan
India