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Importance of dietary sodium in the hypercalciuria syndrome

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Importance of dietary sodium in the hypercalciuria syndrome. Daily urinary calcium excretion in renal stone-forming subjects is shown to vary directly with moderate changes in dietary sodium intake. The changes produced are sufficient to alter the basic diagnostic classification from 'hypercalciuric' to 'normocalciuric' because dietary sodium is reduced from 200 to 80 mM/day. Similar changes were observed in fasting morning 'spot' urine samples, resulting in alteration of diagnostic subclassification between so-called 'absorptive' and 'renal' categories, in the absence of demonstrable change in parathyroid function. Diagnostic and therapeutic studies in stone-forming subjects require control of both dietary calcium and dietary sodium if misinterpretations are to be avoided. Habitual high sodium intake may be an etiological factor in the generation of excessive excretion of calcium, sodium, and phosphate — the hypercalciuria syndrome.

Importance du sodium alimentaire dans le syndrome d'hypercalciurie. Il est montré que l'excrétion urinaire journalière de calcium chez les sujets atteints de lithiaseurinaire varie directement avec des modifications modérées de l'apport alimentaire en sodium. Les modifications produites sont suffisantes pour altérer la classification diagnostique de base entre 'hypercalciuriques' et 'normocalciuriques' lorsque le sodium alimentaire est réduit de 200 à 80 mM/jour. Des modifications identiques ont été observées sur des échantillons d'urine ponctuels le matin à jeûn, altérant la sous-classification diagnostique entre les catégories dites 'absorptives' et 'rénales' en l'absence de changement démontrable de la fonction parathyroïdienne. Les études diagnostiques et thérapeutiques chez des sujets lithiasiques demandent le contrôle à la fois du calcium et du sodium alimentaires si on veut éviter des erreurs d'interprétation. Un apport habituel en sodium élevé pourrait être un facteur étiologique dans l'apparition d'une excrétion excessive de calcium, sodium et phosphate — le syndrome d'hypercalciurie.

Renal stone disease is commonly due to hypercalciuria, which may be assessed either from 24-hr urinary collections or from the fasting 'spot' morning urine [1]. Results may sometimes be variable, however, and a number of collections are usually necessary before the pattern is clear. It is generally accepted that dietary calcium should be moderately restricted before recording urinary calcium, but there is a lack of unanimity on the question of dietary sodium adjustment during this time. Kleeman et al [2] demonstrated marked changes in urine calcium in normal subjects following large alterations in sodium intake from 20 to 425 mEq/day. Lemann, Adams, and Gray [3] recently concluded, however, that dietary sodium manipulation within more usual limits resulted in relatively small changes in urinary calcium.

Many past observations in the physiological literature have shown a close relationship between urinary calcium and sodium excretion [4–7]. However, recent clinical studies have laid little emphasis on the possible effect of changes in urinary sodium on tubular reabsorption of calcium [3, 8]. Preliminary data in three subjects studied by us suggested that important changes in urinary calcium resulted from a short-term reduction in dietary sodium from 200 to 60 mEq daily [1]. Since such a change might occur easily with normal day-to-day dietary sodium variation, it seemed desirable to study the question further in a larger group and over a longer period of time. If an important effect of dietary sodium variation could be shown, and if it were present within the limits of customary sodium intake, an answer might be forthcoming to the vexing problem of seemingly random discrepancies in daily urinary calcium measurements. In addition, careful standardization of dietary sodium would become necessary before assigning stone-forming subjects to various diagnostic categories. Finally, long-term patient management might be improved by stricter adherence to a low sodium as well as to a calcium-restricted diet.

Method

Fourteen male and four female stone-forming subjects were studied. Each showed hypercalciuria according to the criteria of Hodgkinson and Pyrah [9] with mean value in excess of 300 mg/day in the male or 250 mg/day in the female in a number of preliminary random collections as an out-patient on unrestricted diet. Seventeen patients were classified as 'idiopathic hypercalciuria,' and one male had Klinefelter syndrome with mild osteoporosis.

The protocol was carried out on an ambulatory basis in each subject as follows:

Dietary calcium was restricted moderately in the range 500 to 700 mg/day by elimination of cheese intake, and restriction of milk to one-half pint. Dietary sodium was adjusted to 80 mEq daily by elimination of processed meats or fish, sauces, canned vegetables, and salt at table. Bread intake was restricted to 180 g daily. In the case of two subjects, estimated dietary sodium was rather lower than 80 mEq: It was 40 mEq in one subject and 54 mEq in the other. A 24-hr urine sample collection was carried out on day 7 of this regime, and on completion the following morning, a fasting 2-hr 'spot' urine sample was collected from 7 to 9 A.M. with a serum sample taken during that interval. Subsequently, the same diet was continued for a

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Table 1. The effect of alteration in dietary sodium on serum and urinary constituents in 18 subjects with hypercalciuria and renal stone disease

	Low Na diet		High Na diet		
	Mean	SD	*Mean*	SD	*P*
Serum					
Total Ca, *mg/dl*	9.80	0.34	9.68	0.36	<0.05
Ionized Ca, *mg/dl*	4.90	0.19	4.82	0.18	<0.2
Phosphate, *mg/dl*	3.12	0.48	2.97	0.44	<0.01
Sodium, *mEq/liter*	141	2.2	141	2.2	NS
iPTH, *ng/ml*	0.09	0.085	0.108	0.085	NS
24-Hr urine					
Volume, *ml/day*	1829	791	1846	652	NS
Ca, *mg/day*	278	76	384	91	<0.001
Na, *mEq/day*	73	33	177	49	<0.001
C_{Cr}, *ml/min*	110	19	118	23	<0.02
2-Hr 'spot' urine					
Na, *mEq/min*	0.043	0.032	0.133	0.068	<0.001
Ca, *mg/min*	0.138	0.045	0.178	0.061	<0.01
Ca, *mg/dl GF*	0.136	0.044	0.175	0.051	<0.001
Ca/Cr, *mg/min*	0.132	0.043	0.175	0.057	<0.001
Ca filtered ionized, %	2.78	0.88	3.61	1.01	<0.001
C_{Cr}, *ml/min*	103	17	103	18	NS
TRP, %	89.6	3.8	88.6	3.2	<0.2
T_MPO_4/GF	3.11	0.59	2.84	0.47	<0.02
cAMP, *mm/dl GF*	4.23	1.64	5.79	3.56	NS

further 7 days with the addition of oral sodium chloride 120 mEq/day, calculated to bring total sodium intake to 200 mEq daily. A 24-hr urine sample collection was again made on day 14 together with a fasting 'spot' urine and serum samples on the following morning. Throughout the study each subject received careful dietary instructions from the dietitian on the metabolic floor and in the day-care ward. Urine samples were collected in chemically clean plastic bottles for 24-hr samples and acidified before analysis (10 ml concentration HCl/liter urine).

Statistical calculations were performed using analysis of variance and Student's *t* test for paired observations. The 95% limit of probability was accepted as significant.

Measurements of serum sodium, serum total, and ionized calcium, inorganic phosphate, creatinine and in some cases immuno-reactive parathyroid hormone (iPTH) were also recorded on the final day of each dietary period [10, 11]. These measurements were combined with the morning 'spot' urine measurements to express urinary calcium per deciliter of glomerular filtrate and 'percent filtered ionized calcium' in addition to simple urinary calcium/creatinine ratio. The expression 'percent filtered ionized calcium' is an approximation which ignores the contribution of the small component of complexed nonprotein-bound serum calcium to urinary calcium. cAMP excretion was also measured [12, 13] on the 'spot' urine samples from ten patients (Table 1), using Kit TRK 432 from the Radiochemical Centre, Amersham, England. Normal values for urinary cAMP in our laboratory are 3.6 ± 1.4 nmoles/dl GF ($N = 9$). Total serum and urinary calcium and sodium were measured by atomic absorption spectroscopy using an IL instrument. Values for total calcium derived from 41 normal subjects were 9.0 to 10.6 mg/dl (±2 SD) or 8.6 to 11.0 mg/dl (±3 SD). Serum ionized calcium measurements were performed with the Orion flow through electrode Model 92-10. Normal values from 24 healthy subjects were 4.1 to 5.3 mg% (±2 SD) and 3.8 to 5.6 mg% (±3 SD). Serum iPTH values were measured by radioimmunoassay using a C terminal specific antiserum Chicken 9, developed by Dr. E. Slatopolsky (Barnes Hospital, St. Louis, Missouri) and kindly donated by him. Using this antiserum, circulating PTH was detectable in 97% of normal subjects (range, 0 to 0.33 ng/ml), and values were elevated in 49 of 51 subjects with proven primary hyperparathyroidism [11].

Results

Daily urinary sodium excretion at the end of each of the 2 weeks of study was reasonably consistent with the prescribed intake of that week at 73 ± 33 and 177 ± 49 mEq (Fig. 1 and Table 1). Corresponding values for fasting 'spot' urine sodium were 0.043 and 0.133 μEq/min.

Daily urinary calcium had decreased to 278 ± 76 following low sodium intake, rising to 384 ± 91 mg/day on high sodium diet ($P < 0.001$). Significant changes in serum ionized calcium or sodium were not evident, and serum total calcium showed a small decrease on high sodium intake. Nine of 18 subjects studied had reduced urinary calcium to less than 300 mg/day and had therefore fallen into the normocalciuric range of Hodgkinson and Pyrah [9], following seven days of low sodium diet. An additional four were less than 320 mg/day (Fig. 1). Of the five subjects with urine calcium persisting above 320 mg, two showed coincident urinary sodium unexpectedly high in relation to their recommended dietary sodium allowance, at 126 and 154 mEq compared to 73 ± 33 mEq/24 hr for the group as a whole. Poor dietary compliance, therefore, may be suspected in these subjects. One subject only showed a slight decrease in urine calcium following high sodium diet, but a marked decrease in C_{Cr} from 91 to 77 ml/min probably reflects an incomplete urine collection at that time.

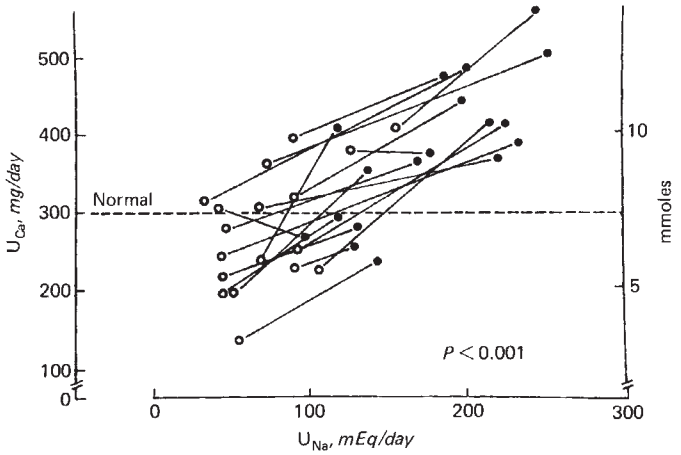

Fig. 1. *Twenty-four hour urinary calcium in relation to urinary sodium on low sodium intake* (open symbols) *and high sodium intake* (closed symbols) *in idiopathic hypercalciuria.* The *dashed line* represents the upper limit of normal for males as described by Hogkinson and Pyrah [9].

Seventeen subjects satisfactorily completed the fasting morning 2-hr 'spot' urine sample collections at the end of each of the 2 weeks of study. One subject had 'spot' urine collection on a low sodium diet only. On high sodium intake, urine calcium was expressed as mg/dl. GF was raised in 15 of 17 patients (Fig. 2) when compared to values for nine control subjects studied in this department [1]. The three subjects with normal urine calcium (mg/dl GF) at this stage also had 24-hr urine calcium values of less than 300 mg/24 hr. The data of Pak et al [8] indicate an upper limit of 0.11 mg/dl GF for normal 'spot' urine calcium on a 400 mg Ca intake, and by chance, this limit agrees closely with the 0.121 mg/dl GF which was the +1 SD of our recently published normal subjects [1]. Using this limit as an arbitrary dividing line between 'renal' and 'absorptive' hypercalciuria (Fig. 2), 15 of 17 patients on the 200 mEq diet would be classified as having 'renal' hypercalciuria. However, six had fallen into the 'absorptive' grouping following seven days of 80 mEq of sodium.

A similar pattern was seen when using the simpler urinary calcium/creatinine ratio as well as urinary calcium 'percent filtered ionized calcium'. In all methods of expression a highly significant decrease in urinary calcium accompanied decreased urinary sodium on the low sodium intake.

Serum iPTH values measured in ten subjects were normal in six, and in the undetectable range in four, without significant change between the first and second weeks of study. Urinary cAMP values (Table 1) were rather higher than our normal controls (3.6 ± 1.4 nmoles/dl GF) and also exceeded the normal range of 3.74 ± 1.3 nmoles/dl quoted by Pak et al [8]. They did not change significantly with changing sodium intake.

Serum inorganic phosphate fell slightly but significantly ($P < 0.01$) on the higher sodium regime, and this was accompanied by a lowering of the tubular phosphate reabsorptive threshold (T_MPO_4/GF) ($P < 0.02$) [9].

Discussion

The results show that 24-hr urinary excretion of calcium is affected significantly by change in dietary sodium intake in the range, 80 to 200 mEq. Our data support those of Kleeman et al [2] with the additional information that important changes in urinary calcium can result from relatively minor dietary sodium adjustments. The pattern in Figure 1 indicates that most of those subjects previously shown to be hypercalciuric on multiple random collections were confirmed as such following a week of 200 mEq sodium intake but were converted to apparent normocalciuria during the 80 mEq sodium regime. Such misleadingly low values for urinary calcium may also result when concomitant urinary sodium is lowered by other circumstances such as physical exertion, severe sweating or the postoperative state. The latter seems particularly important since diagnostic studies in the busy hospital setting may often be carried out in the immediate aftermath of stone removal. Renal stone subjects, therefore, must be studied during a steady state with sodium intake of not less than 200 mEq before hypercalciuria can be confirmed validly or excluded.

Our findings were surprising in view of the recent conclusions of Lemann, Adams, and Gray [3] that urinary calcium may be expected to alter by a mere 24 mg/100 mEq increment in urinary sodium. McCarron et al [14] have also recorded an increase of only 65 mg in urinary calcium as urinary sodium was raised from 18 to 249 mEq, though this figure may be biased by a very short intervening time of 3 days. Both studies were carried out in normal subjects. Our data in Table 1 suggest a mean figure of 97 mg increase in daily urinary calcium when urinary sodium increases by 100 mEq. It appears that the hypercalciuric subject may be essentially different from normal in respect to the slope of a regression of urinary calcium on urinary sodium, analogous to the differing slopes of urinary calcium versus dietary calcium as reviewed by Lemann, Adams, and Gray [3]. Both the absolute levels and the degree of change in dietary sodium in the current study appear well within the range expected during normal day-to-day dietary alterations. Such variation, therefore, may be an important factor in the known and troublesome swings in urinary calcium commonly encountered during ambulatory diagnostic studies.

Pak et al [8] have been careful to specify a recommended fixed dietary sodium intake of 100 mEq during the 'restricted' phase of their recent studies. However, we would note that the recorded urinary sodium excretion was frequently in excess of this and also quite variable between groups. Perhaps this was fortunate, since 100 mEq if adhered to is dangerously close to our 80-mEq regime, which successfully disguised underlying hypercalciuria in many of our subjects. It is of interest to examine closely the data of Pak et al [8] in the light of our present conclusions. In particular, the essential difference between their 'absorptive type 1' and 'absorptive type 2' groupings is that daily urinary calcium was above 200 mg in type 1 and below 200 mg in type 2 when on a 400 mg Ca and 100 mEq Na diet. However, dietary compliance on their ambulatory protocol was clearly variable, to the extent that urinary sodium was 133 ± 63 in their type 1 group and 92 ± 45 in type 2. On the basis of our current data, obtained on a very slightly different diet, we would suggest that the lower urinary calcium in their 'type 2' may be explained simply on the basis of the lower urinary sodium in that group. Also, we note further that their 'renal' grouping, that is, subjects with the highest fasting urinary calcium, showed the highest urinary sodium at 141 ± 66. Differences in urinary sodium therefore may be at the root of these rather arbitrary diagnostic classifications.

Pak et al [8] suggested that the hypothetical 'renal' and 'absorptive' categorization of hypercalciuria is supported by

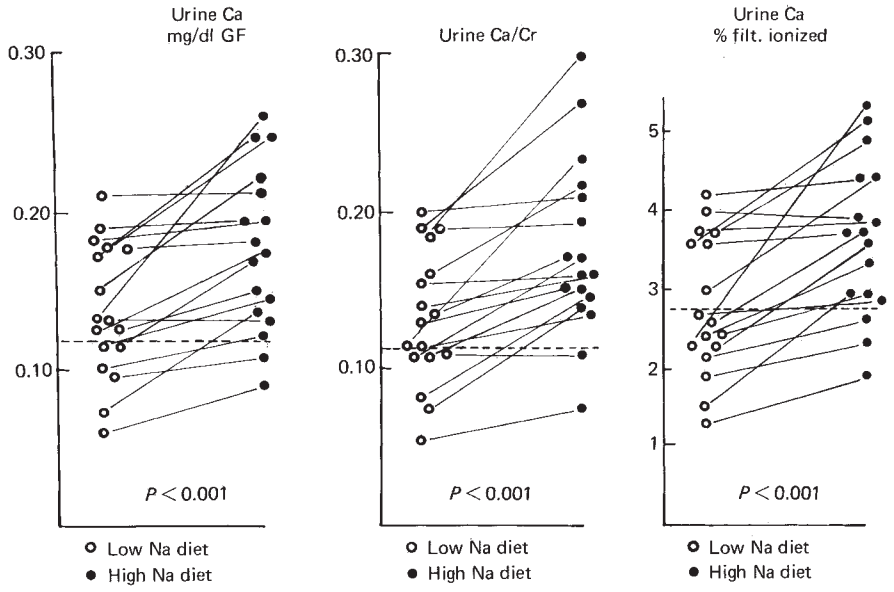

Fig. 2. *Two-hour morning urine calcium, expressed per deciliter glomerular filtrate, as calcium to creatinine ratio, and as percent filtered ionized calcium following low and high sodium intake.* The *dashed line* represents upper limit of normal (one SD) in control subjects [1].

independent evidence in that the 'renal' group shows elevation of either serum iPTH or urinary cAMP whereas the 'absorptive' cases do not. In our experience, however, subjects with an apparently 'renal' pattern of morning hypercalciuria show serum iPTH within normal limits provided that marginal or 'normocalcemic' hyperparathyroidism has been excluded [1, 10, 15]. Ten subjects of the present series confirm this experience. Urinary cAMP was elevated slightly but did not differ between 'absorptive' or 'renal' subjects in this study. It is evident that some subjects changed from one apparent category of hypercalciuria to the other during sodium manipulation without any significant alteration in either serum iPTH or urinary cAMP. The results confirm our earlier view [15] that there is no real benefit in persisting with the arbitrary 'renal' versus 'absorptive' subdivisions of hypercalciuria.

If restriction of dietary sodium to 80 mEq daily for 1 week results in reduction of hypercalciuria to normal levels, it may be asked fairly if maintenance of such a diet would continue to control urinary calcium for longer periods. If so, a potentially valuable mode of therapy may result, analogous to the successful control achieved by Porter et al [16] in the particular circumstances of hypoparathyroidism where a low salt diet was combined with chlorthalidone therapy to reduce urinary calcium and maintain serum calcium levels. An added advantage would be the possibility of maintaining normocalciuria without the need for additional thiazide therapy, with its attendant hazards of hypercalciuria, glucose intolerance, and increased renal phosphate loss. Sodium restriction may provide a more complete mode of treatment in the syndrome by reversing the tubular leak of both calcium *and* phosphate. Patient compliance is obviously a crucial factor here, but an immediate and convenient check is provided by the simultaneous estimate of urinary sodium as well as calcium in each collection as shown in this study.

Since the effect of dietary sodium change persists to the following morning after at least 8 to 10 hr of fasting, it appears independent of recent intestinal sodium absorption. 'Spot' urine sodium was also higher at this time suggesting that extracellular fluid volume or 'third factor' signals may be important regulatory factors governing both sodium and calcium excretion in the fasting state. In support of this possibility is the slight increase in creatinine clearance found in the 24-hr samples, though not seen in the short 'spot' collections. A number of earlier observations by other investigators confirm the concurrence of urinary sodium and calcium excretion under a variety of experimental conditions [4–7]. The 'third factor' signal governing the observed alterations in tubular function may be an increased circulating level of natriuretic factor, such as an inhibitor of renal sodium-potassium dependent ATPase [17]. Tubular phosphate reabsorption and serum phosphate have been shown previously to fall following extracellular volume expansion in normal man [18]. The concurrence of falling tubular reabsorption of both calcium and phosphate together with mild hypophosphatemia is reminiscent of the two main features of idiopathic hypercalciuria syndrome as described by Henneman et al [19]. The present data indicate that both are at least partly dependent on sodium intake in hypercalciuria.

The intriguing possibility therefore arises that the idiopathic hypercalciuria syndrome may be provoked by high sodium intake. Habitual dietary sodium intake has not been formally assessed in these subjects prior to study, but we have been struck by the number who have admitted to being unusually fond of salt and for whom the advised 80-mEq intake appeared at first to be an unattainable target. For the future we would suggest that a careful dietary assessment of sodium intake be made *prior* to any dietary manipulation with its consequent increase in patient awareness. In addition, urinary sodium as well as calcium should be measured in random ambulatory collections at home, because urinary sodium accurately reflects intake in the steady state. By both means it should be possible to assess in a larger number of subjects whether or not habitual high sodium intake may be a significant factor in the generation of the hypercalciuria syndrome.

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