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The urinary calcium/creatinine ratio as a measure of urinary calcium excretion

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SYNOPSIS Urine specimens were collected from 26 normal subjects, 10 patients with proven primary hyperparathyroidism, and eight patients with hypercalcaemia due to other causes. After overnight urine concentration, an oral water load was given to induce a diuresis and provide urine specimens with a relatively wide range of creatinine concentration for each subject. In normal subjects the urinary calcium/creatinine ratio was found to be independent of urine concentration. In eight out of 10 patients with primary hyperparathyroidism and in two out of eight patients with hypercalcaemia due to other causes, the urinary calcium/creatinine ratio was found to be high when the creatinine concentration was low, but usually normal when the creatinine concentration was high. The results suggest that if the urinary calcium/creatinine ratio of random urine specimens is used as a 'screening' procedure to detect hypercalciuria the latter cannot be excluded if the urinary creatinine concentration is more than 40 mg per 100 ml.

To estimate the rate of excretion of urinary constituents a 24-hour sample of urine is required and this is not always easy to collect accurately. Nordin (1959) proposed the use of the ratio of the calcium to creatinine concentration in random urine specimens as a convenient index of urinary calcium excretion. In this ratio creatinine serves as a reference standard by virtue of its relatively constant excretion rate throughout the 24 hours. In theory, this should be satisfactory provided that the excretion rate of the substance under study is also relatively constant. Nordin examined random urine specimens from clinically normal subjects and proposed a range above which hypercalciuria might be said to exist. He reported that there was very little difference in the ratio in normal subjects on free diets when compared with those on a low-calcium diet. The use of random urine samples from subjects on a free diet offers considerable advantages over the collection of 24-hour specimens in the 'screening investigation' of patients with disorders of calcium metabolism. Several years of experience have shown that when the calcium/creatinine ratio on random urine samples from hypercalcaemic outpatients was examined repeatedly the ratio was often normal when the urine was concentrated, but high when the urine was dilute. The investigation reported here was undertaken to investigate the validity of a random urine sample as a measure of urinary calcium excretion in normal subjects and in patients with primary hyperparathyroidism and hypercalcaemia due to other causes, and in particular to investigate the effect of variations in urinary concentration on the calcium/creatinine ratio.

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PROCEDURE

A concentration/dilution test was designed to provide urine specimens with a relatively wide range of creatinine concentration for each individual subject. In order to exclude the effect of diet or circadian variation all tests were performed between 0600 and 1200 hours with the subject fasting. From 1800 hours on the evening preceding the study no food or fluids were taken until the completion of the test, other than the water load taken during the test period. Before going to bed on the night preceding the test, the bladder was emptied and the specimen discarded. At 0600, 0700, 0800, and 0900 hours the bladder was emptied and the specimens were collected. After the specimen taken at 0900 hours the subjects drank approximately 1,000 ml of water (slightly warmed to avoid nausea) to induce a diuresis. Further urine specimens were then collected at 1000, 1030, 1100, 1130, and 1200 hours. After the final urine sample a specimen of blood was collected from each subject to give the fasting blood calcium concentration.

PATIENTS

Twenty-six normal subjects were studied, all hospital inpatients who had undergone minor surgical procedures at least eight to 10 days before the study. They were all ambulant and had been on a normal hospital diet for at least three days. None of the subjects had any history of renal stones or other disorder likely to be associated with abnormal calcium metabolism.

The study also included 10 patients with primary hyperparathyroidism and eight patients with hypercalcaemia due to other causes. In those patients with primary hyperparathyroidism the diagnosis was later confirmed by surgical exploration and histological examination of the adenoma.

METHODS

Plasma and urinary calcium concentration was estimated by the Plasmacorinth B (Corinth calcium) AutoAnalyzer method of Wills and Gray (1964). Urinary creatinine concentration was estimated by an alkaline picrate method (Bonsnes and Taussky, 1945).

RESULTS

NORMAL SUBJECTS Two hundred and thirty-one urine specimens were collected from the 26 normal subjects studied, with creatinine concentrations over the range 5 to 394 mg per 100 ml (Table I). The mean fasting plasma calcium concentration was 9·51 mg per 100 ml, with a range of 8·61 to 10·41 mg per 100 ml (mean ± 2 SD). The calcium/creatinine ratios of the urine specimens were average for various values of creatinine concentration. Figure 1 shows the mean ± 2 SD of the ratio for each value of creatinine. If the urinary calcium concentration varied directly with urinary concentration, as measured by creatinine concentration, then the urinary calcium/creatinine ratio should remain constant irrespective of the creatinine concentration. The results obtained in these normal subjects support such a hypothesis. From his data on normal subjects Nordin (1959) proposed a calcium/creatinine ratio of 0·28 as the upper limit of the normal range and at ratios above this value hypercalciuria could be considered to exist. In only one of the normal subjects reported here (M.S.) was a figure above this value recorded. In this subject the urinary calcium/creatinine ratio was 0·29 at a urinary creatinine concentration of 5 mg per 100 ml; in another specimen from the same subject with a creatinine concentration of 6 mg per 100 ml, the calcium/creatinine ratio was 0·28. The analysis of the data on the normal subjects reported here, as shown in Figure 1, shows that the range as deter-

TABLE I

LIMITS OF URINARY CALCIUM/CREATININE RATIOS, CREATININE CONCENTRATIONS, AND FASTING PLASMA CALCIUM CONCENTRATION IN 26 NORMAL SUBJECTS

Subject	*Urinary Creatinine (mg/100 ml)*	*Calcium/ Creatinine Ratios*	*Fasting Plasma Calcium (mg/100 ml)*
R.T.	21-110	0·18-0·21	10·4
M.O.	7-148	0·07-0·18	9·4
G.D.	13-219	0·02-0·07	9·4
W.C.	13-209	0·06-0·15	9·8
C.T.	12-224	0·07-0·12	9·2
H.C.	20-179	0·10-0·24	9·6
P.W.	10-394	0·06-0·10	9·3
M.C.	8-294	0·01-0·04	9·4
C.W.	19-105	0·08-0·22	9·3
I.P.	6-149	0·16-0·26	8·6
J.H.	8-134	0·05-0·12	9·3
J.P.	20-186	0·01-0·06	9·2
J.S.	10-158	0·08-0·15	8·9
C.H.	5-250	0·07-0·11	9·6
G.M.	46-254	0·08-0·19	10·1
B.H.	14-302	0·07-0·16	10·2
W.D.	18-200	0·06-0·17	9·7
B.W.	20-320	0·04-0·12	10·1
M.R.	10-172	0·02-0·09	9·1
R.S.	13-134	0·01-0·05	9·3
M.S.	5- 97	0·13-0·29	9·8
J.J.	14-194	0·17-0·27	9·3
W.M.	10-120	0·17-0·28	10·3
C.R.	23-118	0·15-0·24	9·8
T.Y.	20-388	0·02-0·06	9·3
C.P.	6-112	0·14-0·24	8·9
			Mean 9·51
			Range 8·61-10·41 (mean ± 2 SD)

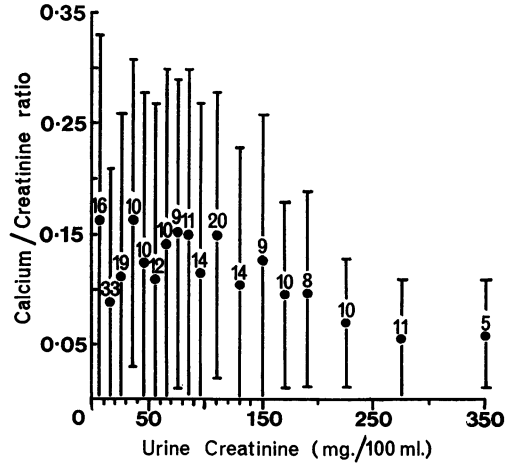

FIG. 1. *Urinary calcium/creatinine ratios for 26 normal subjects (231 urine specimens) shown plotted as the mean ± 2 SD against the creatinine concentration. The number of urine specimens is shown for each value of creatinine concentration.*

mined by mean ± 2 SD exceeds the 0·28 value at urinary creatinine concentrations below 100 mg per 100 ml, and suggests that a value of 0·33 is a more realistic upper limit for the normal range.

HYPERPARATHYROID PATIENTS Ninety-six urine specimens were collected from the 10 patients with primary hyperparathyroidism, with a range of creatinine concentrations from 6 to 202 mg per 100 ml (Table II). In some patients the study was repeated on more than one occasion in an endeavour to obtain a wider range of creatinine concentrations for each patient. Nine of the 10 patients were hypercalcaemic at the time of study. In two patients (D.K. and L.W.) the calcium/creatinine ratios were within the normal limits over the range of urinary creatinine concentrations studied. In the remaining eight patients the ratios were within the normal range at high creatinine concentrations, but increased with falling creatinine concentrations rising into the hypercalciuric range. The complete results for all the patients in this group are shown in Figure 2. In the eight patients with abnormal ratios these were found consistently at a creatinine concentration of less than 40 mg per 100 ml.

TABLE II

LIMITS OF URINARY CALCIUM/CREATININE RATIOS, CREATININE CONCENTRATIONS, AND FASTING PLASMA CALCIUM CONCENTRATION IN 10 SUBJECTS WITH PRIMARY HYPERPARATHYROIDISM

Subject	*Urinary Creatinine (mg/100 ml)*	*Calcium/ Creatinine Ratio*	*Fasting Plasma Calcium (mg/100 ml)*
P.R.	28- 42	0·29-0·35	14·5
N.H.	7- 64	0·21-0·59	12·7
V.L.	21- 44	0·31-0·88	13·8
R.C.	19-200	0·21-1·18	11·8
D.K.	29- 44	0·14-0·27	11·1
M.H.	26- 49	0·34-0·64	10·1
G.M.	22- 37	0·46-1·00	11·1
E.H.	6- 42	0·22-1·47	10·8
L.W.	14-120	0·14-0·29	12·3
D.M.	29-188	0·14-0·28	11·5
		Mean	11·97

OTHER HYPERCALCAEMIC PATIENTS In the eight patients with hypercalcaemia due to causes other than primary hyperparathyroidism (Table III), 62 urine specimens were collected with a range of creatinine concentration from 19 to 161 mg per 100 ml. The complete results for all the patients in this group are shown in Figure 3. In two of the

TABLE III

LIMITS OF URINARY CALCIUM/CREATININE RATIOS, CREATININE CONCENTRATIONS, AND FASTING PLASMA CALCIUM CONCENTRATION IN EIGHT SUBJECTS WITH HYPERCALCAEMIA

Subject	*Diagnosis*	*Urinary Creatinine (mg/100 ml)*	*Calcium/ Creatinine Ratio*	*Fasting Plasma Calcium (mg/100 ml)*
A.B.	Carcinoma bronchus	29- 54	0·36-0·60	14·0
H.F.	Myelomatosis	19-145	0·12-0·18	11·4
R.F.	Hodgkin's disease	26-128	0·09-0·28	12·0
D.F.	Carcinoma bronchus	32-101	0·07-0·13	10·8
L.G.	Calciferol overdose	20- 60	0·12-0·42	14·5
T.D.	Sarcoidosis	67- 91	0·14-0·17	12·5
C.D.	Paget's disease	22-137	0·06-0·23	11·2
H.T.	Hypercalcaemia, ? cause	55-161	0·07-0·17	11·2
			Mean	12·20

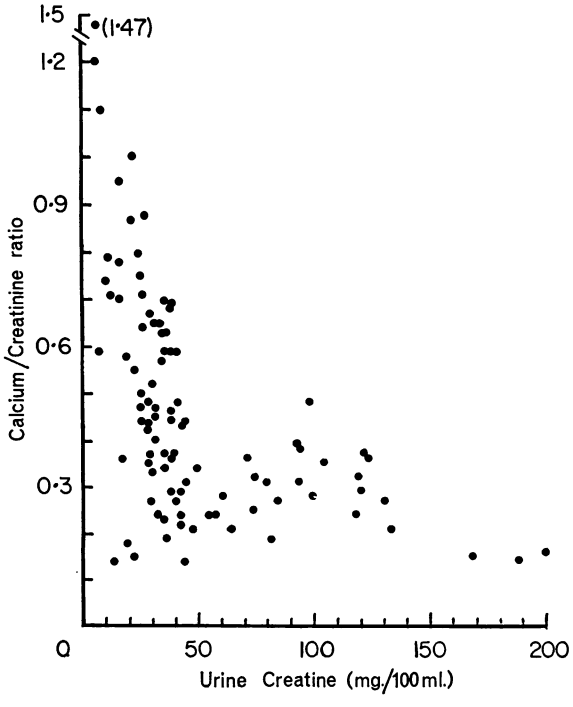

FIG. 2. *Urinary calcium/creatinine ratios in hyperparathyroidism.*

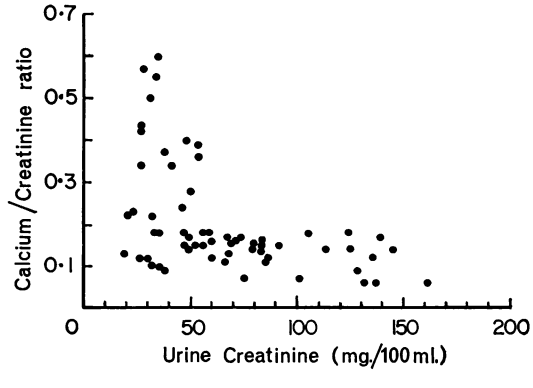

FIG. 3. *Urinary calcium/creatinine ratios due to causes other than primary hyperparathyroidism.*

patients (T.D. and H.T.) urine specimens with a creatinine concentration of less than 40 mg per 100 ml were not obtained. In four patients (H.F., R.F., D.F., and C.D.) the urinary calcium/creatinine ratios were within the normal limits over the range of creatinine concentration studied. In the remaining two patients (A.B. and L.G.) abnormal ratios were recorded and the pattern was similar to that seen in the patients with primary hyperparathyroidism, in that the ratios were higher at low creatinine concentrations than at high creatinine concentrations; again the ratio was abnormal in both at creatinine concentrations of less than 40 mg per 100 ml.

DISCUSSION

The results suggest that if the calcium/creatinine ratio of random urine specimens is used as a 'screening' procedure to detect hypercalciuria in patients suspected of having metabolic bone disease or other abnormalities of calcium metabolism, a normal ratio does not exclude hypercalciuria if the creatinine concentration of the specimen is more than 40 mg per 100 ml.

It is known that parathyroid hormone increases the renal tubular reabsorption of calcium and it would therefore be expected that patients with hyperparathyroidism would be less likely than other hypercalcaemic patients to have hypercalciuria. It is of interest that high urinary calcium/creatinine ratios were found in eight out of the 10 hyperparathyroid patients but in only two out of the eight patients with hypercalcaemia due to other causes.

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