URINARY EXCRETION OF CALCIUM AND CREATININE IN RELATION TO AGE AND BODY WEIGHT IN NORMAL SUBJECTS AND PATIENTS WITH RENAL CALCULUS

L. BULUSU, A. HODGKINSON, B. E. C. NORDIN AND M. PEACOCK

M.R.C. Mineral Metabolism Unit, The General Infirmary, Leeds

(Received 28 October 1969)

SUMMARY

1. Variations with age in body weight, urine volume and calcium and creatinine excretion were determined in 246 normal subjects and 305 patients with calcium-containing renal stones.

2. Body weight, urine volume and creatinine excretion increased with age to a maximum in the third decade in both male and female controls and stone-formers. Thereafter body weight and urine volume did not change appreciably but creatinine excretion decreased.

3. In normal subjects the daily excretion of calcium and calcium concentration increased in the first two decades and remained relatively constant thereafter until the eighth decade when they decreased. The calcium/creatinine ratio was high in the first decade and fell during the second and third decades. Thereafter it remained relatively constant in men until the eighth decade when it fell. In women, however, there was a second rise in the fifth and sixth decades. The calcium/body weight ratio remained relatively constant with age until the eighth decade, when it fell.

4. Patients with renal calculus showed similar variations in calcium excretion with age. The mean values, however they were expressed, were higher than those in normal subjects of the same age and sex.

5. The daily excretion of calcium was higher in men than women, whether normal subjects or stone-formers. This difference was abolished when calcium excretion was related to body weight and reversed when excretion was related to creatinine.

6. Comparison of the present data with previous data from the same population indicated that the mean daily excretion of calcium by both normal subjects and patients with renal calculi has increased during the last decade.

7. The significance of these observations in relation to calcium homeostasis and renal calculus formation is discussed.

Correspondence: Dr A. Hodgkinson, M.R.C. Mineral Metabolism Unit, The General Infirmary, Leeds LS1 3EX.
The urinary excretion of calcium may be expressed in a variety of ways depending on the information which is required. Excretion is commonly expressed in mg/24 hr and Nordin (1959) has shown that a calcium/creatinine ratio can be usefully employed in random and 24 hr urine collections. But these expressions do not adequately take into account the dependence of calcium excretion on dietary intake and body weight, and in nutritional studies, therefore, it is advantageous to express both calcium excretion and dietary calcium in mg/kg body weight day⁻¹ (Knapp, 1947). Similarly, the effect of glomerular filtration rate on calcium excretion can be reduced by expressing calcium output in mg/100 ml glomerular filtrate (Nordin, Hodgkinson & Peacock, 1967). On the other hand, in the context of renal stone formation, it may be more meaningful to express urinary calcium as a concentration since the precipitation of calcium salts is presumably a function of calcium concentration rather than total output.

Information on the normal relationships between age, body weight, urine volume and calcium and creatinine excretion is limited. These relationships have, therefore, been examined in normal men and women and in patients with renal stone disease and the results are presented in this paper.

**METHODS**

Observations were made on 336 normal subjects aged 3–89 years and 319 patients with renal calcium stone disease of the idiopathic type whose ages covered a similar range (Table 1). The normal subjects were members of staff and their families and medical outpatients with minor disorders unrelated to calcium or bone metabolism. The social class distributions of the patients and controls were similar since both groups were drawn predominantly from the middle classes and from workers in sedentary occupations (Blacklock, 1965; R. W. E. Williams, unpublished observations). One 24-hr urine sample was collected at home from each subject.
while they were on a free diet. The urine specimens were collected in plastic containers to which had been added 1 ml of 20% w/v chlorhexidine dihydrochloride (Hibitane).

Samples of each urine specimen were boiled with one part of concentrated nitric acid to 25 parts of urine for 5 min in order to dissolve any calcium precipitate which was present (Fales, 1964). Calcium was determined by automatic colorimetry using Cresolphthalein Complexone. Magnesium interference was suppressed by the addition of 8-hydroxyquinoline (Technicon AutoAnalyzer Method N-3b). Creatinine was also determined by automatic colorimetry (Technicon AutoAnalyzer Method N-11b).

RESULTS

Changes with age in body weight, urine volume and urine creatinine

Body weight, urinary volume and creatinine excretion increased with age to a maximum value in the third decade in both male and female stone-formers and controls. Thereafter body weight and urine volume did not change with age. Urinary creatinine excretion, however, gradually decreased with age in males and was significantly reduced from the maximum level by the eighth decade. A similar though less well defined pattern occurred in women (Fig. 1a and b).

Fig. 1. Variations with age in the mean daily excretion of creatinine by (a) males and (b) females. Open circles denote normal subjects and solid circles denote patients with renal calculus. The vertical lines denote ±1 SEM.
Comparison of the mean daily urine volume, creatinine excretion and body weight

The mean values in adult men and women, controls and stone-formers, are compared in Table 2. The body weight and creatinine output were significantly higher in males than females in both controls and stone-formers, but only in men with stone disease was the urine volume significantly higher than in women. Men with stone disease had significantly higher outputs of creatinine and urine and they were significantly heavier than the male controls. There was no significant difference between the women with stone disease and their controls in body weight or creatinine output but, like the males, they tended to have an increased urine volume compared to the controls. Table 2 also shows that the variance of these parameters was similar in both sexes and both groups and the greatest variance was in daily urine volume.

Changes with age in daily calcium output, calcium concentration, calcium/creatinine ratio and calcium/body weight ratio

The daily urinary calcium output increased in the first two decades. Thereafter it remained relatively constant until the eighth decade when it was significantly reduced in patients with renal stone disease and control subjects, both male and female (Fig. 2a and b). Calcium concentration rose slightly over the first two decades and remained fairly constant during adult life until the eighth decade when there was a fall in concentration, except in the male patients with renal stone disease (Fig. 3a and b).
The calcium/creatinine ratio was high in the first decade and fell over the second and third decades. Thereafter the ratio did not alter significantly in men but in women there was an apparent rise during the fifth and sixth decades in normals and in the sixth decade in stone-formers. This rise was statistically significant at the 5% level if a comparison was made between normal women in the sixth decade and those aged 20–39 years or between female stone-formers in the sixth decade and those aged 20–29 years. Other comparisons within these groups, however, failed to yield statistically significant differences. There was a fall in calcium/creatinine ratio in the eighth decade in both groups, male and female (Fig. 4a and b).

The calcium/body weight ratio remained relatively constant with age till the eighth decade when it fell, but this fall was only significant in the patients with renal stone disease (Fig. 5a and b). Female patients with renal stone disease were exceptional in that they had a high calcium/body weight ratio in the second decade. This was due mainly to an exceptionally high calcium excretion rather than to a low body weight.
Comparison of the mean daily calcium excretion, concentration, calcium/creatinine ratio and calcium/body weight ratio

The mean calcium values in adult men and women, controls and stone-formers, are compared in Table 3. The mean daily calcium output was significantly higher in men than women but there was no significant difference in the calcium/body weight ratios. The male stone-formers had a higher calcium concentration than the female stone-formers, but there was no difference in concentration between the normal males and females. The sex difference was reversed when excretion was expressed as a calcium/creatinine ratio and the difference was statistically significant in the normal subjects.

![Fig. 3. Variations with age in the 24 hr urine calcium concentration of (a) males and (b) females. Open circles denote normal subjects and solid circles denote patients with renal calculus. The vertical lines denote ±1 SEM.](image)

When the patients with stone disease were compared with controls, then urinary calcium, however it was expressed, was significantly higher in the stone-forming group with only one exception—calcium concentration did not differ significantly between normal and stone-forming women. Table 3 also shows that the variance of the calcium excretion data was similar however it was expressed, although there was a tendency for calcium concentration to vary more than other parameters.
Distribution of urinary calcium values

Fig. 6a and b shows the distribution of values for the daily excretion of calcium in 104 normal males and 217 males with renal stone disease and in 142 normal females and eighty-eight females with renal stone disease. Fig. 6c and d shows the frequency distribution of the calcium/creatinine ratios in these same subjects. All these distributions showed a significant positive skewness (Snedecor & Cochran, 1967), except that of daily calcium output by normal men.

DISCUSSION

The rise and subsequent fall in creatinine excretion with age presumably reflects the changes in lean body mass which occur during growth and ageing (Muldowney, Crooks & Bluhm, 1957; Widdowson & Dickerson, 1964). Body weight also rose in the first two decades but then remained constant so that there was a continuous fall in the creatinine/body weight ratio of adults with increasing age. This could mean that the loss of muscle tissue in later life is offset
by a gain of fat. Since calcium excretion seems unlikely to be related to the fat of an individual, a calcium/creatinine rather than a calcium/body weight ratio would appear to be more physiological and may be preferable to the excretion in mg/24 hr.

Male stone-formers were heavier and had significantly higher outputs of creatinine than male controls (Table 2). Blacklock (1965) reported a similar weight difference between male stone-formers and normal men in the Royal Navy. Since the hypercalciuria of stone-formers is generally due to increased calcium absorption (Peacock, Hodgkinson & Nordin, 1967) the possibility suggests itself that large men absorb more calcium than small men because their intestinal absorbing surface is greater.

![Figure 5](image)

**Fig. 5.** Variations with age in the 24 hr urine calcium/body weight ratio in (a) males and (b) females. Open circles denote normal subjects and solid circles denote patients with renal calculus. The vertical lines denote ±1 SEM.

However it is expressed, the frequency distribution of calcium excretion tends to be positively skewed in both normals and stone-formers, thus confirming the earlier observations of Knapp (1947) and Hodgkinson & Pyrah (1958). We cannot say whether this is due to the frequency distribution of calcium intake or calcium absorption but it is true of many biological variables besides calcium excretion.

Previous reports have indicated that calcium excretion tends to fall with age (Cottet & Vittu, 1955; Cottet, Vittu & Canarelli, 1962). This was confirmed in the present study although
the fall was significant only in the eighth decade and was most obvious when calcium excretion was expressed in mg/24 hr. This fall in calcium excretion in old age could well be due to a reduced absorption of calcium (Avioli, McDonald & Lee, 1965).

Examination of our data shows that from the purely statistical point of view there is nothing to choose between the four ways in which we have expressed calcium output. The dispersion of the data is similar whether they are expressed in mg/24 hr, mg/ml, mg/kg or as a calcium/creatinine ratio (Table 3). However, the differences between the sexes and between the stone-formers and controls were affected by the mode of presentation. Thus the hypercalciuria of the male stone-formers is more apparent when expressed as total calcium output than when expressed as a calcium concentration because their urine volume tends to be high. The most likely explanation of this observation is that patients with stone disease are often advised to increase their fluid intake.

When the sexes are compared, calcium output in mg/24 hr is significantly greater in men than women in both groups. Calcium concentration is higher in men than in women in the stone-formers only. Calcium output in mg/kg is not different in the two sexes. However, the mean calcium/creatinine ratio is higher in women than men in both groups, suggesting that women excrete more calcium than men for a given lean body mass.
A previous survey in Leeds revealed a mean calcium excretion of 178 mg/day by normal men and 140 mg/day by normal women (Hodgkinson & Pyrah, 1958). The present values are appreciably higher (219 mg and 186 mg/day respectively) (Table 3) while still higher values were reported recently from London (Watson & Dale, 1966). Similarly the daily calcium excretion in stone-formers has increased from a value of 260 to 338 mg in males and from 200 to 241 mg in females. These increases probably reflect changes in dietary habits with improvement in the standard of living. For example, there is evidence that the average dietary calcium intake in the Leeds area has increased from about 800 mg/day to 1000 mg/day in the last decade (Hodgkinson & Pyrah, 1958; Peacock & Nordin, unpublished results). Other dietary factors may also be contributing such as an increase in salt intake (Phillips & Cooke, 1967), an increase in meat intake (Thomas et al., 1959) and an increase in carbohydrate intake (Lemann, Piering & Lennon, 1969), all of which are known to cause an increase in calcium excretion. If increased calcium excretion is a factor in the cause of stone disease then this rise in calcium excretion would be expected to coincide with a rise in the incidence of renal stone disease of the calcium oxalate-phosphate type. The studies by Andersen (1968) support this view since he has demonstrated an increase in the incidence of renal stone disease in Western countries over the last 50 years.
Urine calcium and creatinine

The occurrence of an increased excretion of calcium in patients with renal calculus is well recognized (Flocks, 1939) but its significance as a causative factor in stone formation remains a subject of debate (Boyce & King, 1959; Malm, 1963; Modlin, 1967). We believe that although hypercalciuria is not the cause of stone disease, individuals with a high urine calcium are at greater risk than those with a normal excretion and more liable to precipitate calcium salts in the urinary tract (Nordin et al., 1969). The present study confirms that calcium excretion is higher in patients with renal stone disease than in controls of the same age and sex and this difference is apparent however the calcium excretion is expressed. These results support the view that increased calcium excretion, or more specifically, an increased calcium oxalate or calcium phosphate activity product (Robertson, Peacock & Nordin, 1968) is a contributing factor in crystalluria (Robertson, Peacock & Nordin, 1969) and stone formation.

REFERENCES

L. Bulusu et al.


