PAPERS AND SHORT REPORTS

Renal handling of calcium and sodium in metastatic and non-metastatic malignancy

S R HELLER, D J HOSKING

Abstract

Investigation of the renal handling of calcium and sodium in rehydrated patients with hypercalcaemia associated with malignancy showed enhanced reabsorption of calcium in most cases. This was a feature of both metastatic and non-metastatic malignancy, and in this respect the patients were indistinguishable from patients with primary hyperparathyroidism.

As the increased calcium reabsorption was inversely correlated with the rate of excretion of sodium modest salt loading can be used to inhibit this process. This is an important practical aspect of the treatment of patients with this type of hypercalcaemia.

Introduction

Although the role of the kidney in the pathogenesis of hypercalcaemia of malignancy is well described,^{1,2} much of the emphasis of treatment has centred on reducing bone destruction.³⁻⁶ This may be a missed therapeutic opportunity because most of these patients show increased renal reabsorption of calcium when untreated,^{7,8} and this can be reversed by rehydration and agents such as calcitonin.⁹ It is uncertain, however, whether this increased calcium reabsorption is solely a consequence of the accompanying volume depletion or reflects a non-metastatic effect of the primary tumour on the kidney.¹⁰ This is an important question to resolve because it has profound implications for our understanding of the pathogenesis and treatment of hypercalcaemia associated with malignancy.

We therefore examined the renal handling of calcium in patients with malignancy who were being rehydrated as the initial treatment for hypercalcaemia. The aim of the study was to establish whether enhanced renal calcium reabsorption was purely a feature of non-metastatic disease or a general phenomenon in patients with advanced malignancy.¹⁰ The relation between calcium and sodium

handling by the kidney was also investigated as preliminary studies had suggested that the rate of excretion of sodium was an important variable affecting renal calcium reabsorption under these circumstances.⁷

Patients and methods

The study was based on data from 37 patients with proved malignancy and severe hypercalcaemia (calcium concentrations >3 mmol/l (>12 mg/100 ml)). The patients were divided into those with and without bone metastases on the basis of the results of isotope bone scanning, skeletal radiology, or postmortem examination. Twenty six patients (14 women, 12 men; mean age 58 (range 30-82)) had bone metastases; three had myeloma and one lymphoma, in one the primary tumour was unknown, and the others had tumours of the bronchus (nine), breast (seven), kidney (two), pancreas (one), cervix (one), and gall bladder (one). The 11 patients without detectable bone metastases (four women, seven men; mean age 53 (range 26-75)) had tumours of the kidney (four), breast (two), bronchus (two), oesophagus (one), liver (one), and pancreas (one). Of the 11 patients without skeletal metastases, seven had a normal bone scan and the four others had no sign of bone disease at postmortem examination; eight had evidence of soft tissue (usually hepatic) disease.

All patients except three who were not clinically dehydrated were treated with 3-4 litres of physiological saline for 24-48 hours and then received 2 litres/day until the serum calcium concentration reached a stable minimum value. During this time none of the patients received any drugs known to affect tumour or calcium metabolism.

Biochemical measurements were made at the end of the period of rehydration using standard laboratory techniques. Serum calcium concentration was corrected to a reference serum albumin concentration of 40 g/l using a factor of 0.02 mmol (0.08 mg)/g albumin.¹¹ All measurements of renal handling of sodium and calcium were made either on fasting serum and urine samples or on urine collected between 1500 and 1700 with a midpoint blood sample. Urinary calcium excretion was expressed as excretion/l glomerular filtrate—that is, as urinary calcium (mmol/l) $\times$ serum creatinine (μ mol/l)/urinary creatinine (mmol/l).¹² The notional setting of renal calcium reabsorption (measured as the maximal tubular reabsorption of calcium/glomerular filtration rate (TmCa/GFR)) was calculated using a nomogram.¹³

For comparative purposes 17 patients (mean age 53 (range 25-80)) with primary hyperparathyroidism (subsequently proved at operation) and serum calcium concentrations >3 mmol/l and 25 normal subjects (mean age 44 (range 20-70)) were also studied in the basal state but were not salt loaded. Normal subjects were either laboratory staff or patients attending a metabolic clinic: all had normal calcium concentrations, and none had evidence of current skeletal or renal disease.

Department of Medicine, University Hospital, Nottingham

S R HELLER, MB, MRCP, research fellow

D J HOSKING, MD, FRCP, senior lecturer

Correspondence to: Dr Hosking.

Results

Figure 1 shows biochemical measurements after the completion of rehydration. There was no difference between those with and without skeletal metastases in terms of serum calcium and creatinine concentrations, the setting of renal phosphate reabsorption (maximal tubular reabsorption of phosphate/glomerular filtration rate ($TmPO_4/GFR$)), and variables of bone destruction such as the ratios of urinary calcium to creatinine and of urine hydroxyproline to creatinine concentrations.

FIG 1—Biochemical findings in patients with metastatic (●) and non-metastatic (○) malignancy after rehydration.

Conversion: SI to traditional units—Serum calcium: 1 mmol/l $\approx$ 4 mg/100 ml. Renal phosphate absorption: 1 mmol/l glomerular filtrate $\approx$ 3.1 mg/100 ml. Urinary hydroxyproline: creatinine: 1 μ mol/mmol $\approx$ 1.2 mg/g. Urinary calcium: creatinine: 1 mmol/mmol $\approx$ 350 mg/g. Serum creatinine: 1 μ mol/l $\approx$ 11.3 μ g/100 ml.

Figure 2 shows the relation between urinary calcium excretion and serum calcium concentration after rehydration in the patients with malignant hypercalcaemia and the group with primary hyperparathyroidism. Values obtained in all the patients with hyperparathyroidism and most of those with malignant hypercalcaemia fell to the right of the normal relation, indicating

FIG 2—Relation between serum calcium concentration and excretion of calcium after rehydration in patients with malignant disease (●=metastatic disease, serum creatinine $<150 \mu$ mol/l (<1.7 mg/100 ml); ○=non-metastatic disease, serum creatinine $<150 \mu$ mol/l; ▲=metastatic disease, serum creatinine $\geq 150 \mu$ mol/l; △=non-metastatic disease, serum creatinine $\geq 150 \mu$ mol/l) and in patients with hyperparathyroidism (□=serum creatinine $<150 \mu$ mol/l; ■=serum creatinine $\geq 150 \mu$ mol/l). Hatched area indicates normal relation.

Conversion: SI to traditional units—Calcium excretion: 1 μ mol/l glomerular filtrate $\approx$ 4 μ g/100 ml. Serum calcium: 1 mmol/l $\approx$ 4 mg/100 ml.

that calcium reabsorption was increased. Values lay within the normal range in 14 patients with malignancy (38%), some of whom had metastatic and some non-metastatic disease.

Figure 3 shows the relation between the setting of calcium reabsorption and the rate of excretion of sodium in patients with metastatic and non-metastatic hypercalcaemia. These cross sectional data showed a strong inverse correlation between $\log_{10}$ calcium reabsorption and $\log_{10}$ sodium excretion ($r = -0.79$, $p < 0.001$; $\log_{10}$ calcium reabsorption = $0.374 - (0.127 \times \log_{10}$ sodium excretion)).

FIG 3—Relation between reabsorption of calcium and excretion of sodium after rehydration in patients with malignant hypercalcaemia.

Conversion: SI to traditional units—Calcium reabsorption: 1 mmol/l glomerular filtrate $\approx$ 4 mg/100 ml. Sodium excretion: 1 mmol/l glomerular filtrate = 1 mEq/l.

Figure 4 shows data from the normal subjects and from patients with primary hyperparathyroidism (data on excretion of sodium were unavailable in five patients) in relation to the 95% confidence limits for the group with malignancy. In most patients with malignancy the setting of calcium reabsorption in relation to sodium excretion was higher than that found in normal subjects but indistinguishable from that seen in primary hyperparathyroidism.

There were sufficient data from three patients with carcinoma of the breast for us to study the within patient variation in calcium reabsorption over a range of values of sodium excretion obtained during an extended period of rehydration. The inverse relation shown in the cross sectional study was again observed (fig 5).

Discussion

The prevailing view of hypercalcaemia associated with malignancy is that it is due to an excessive calcium load caused by increased bone destruction that eventually overwhelms the excretory capacity of the kidney.¹¹⁴ In the presence of bone metastases

FIG 4—Relation between reabsorption of calcium and excretion of sodium in normal subjects (●) and patients with hyperparathyroidism (○). Solid line and hatched area indicate mean and 95% confidence limits of the data shown in figure 3.

Conversion: SI to traditional units—Calcium reabsorption: 1 mmol/l glomerular filtrate=4 mg/100 ml. Sodium excretion: 1 mmol/l glomerular filtrate=1 mEq/l.

FIG 5—Relation between reabsorption of calcium and excretion of sodium in three patients (●, ○, △) during four or five days of rehydration.

Conversion: SI to traditional units—Calcium reabsorption: 1 mmol/l glomerular filtrate=4 mg/100 ml. Sodium excretion: 1 mmol/l glomerular filtrate=1 mEq/l.

this is a direct effect of the secondary tumour,¹⁴ while malignancies that have not spread to the skeleton cause hypercalcaemia through circulating tumour products that stimulate osteoclastic bone resorption.¹⁵

That the kidney may also be concerned in the pathogenesis of hypercalcaemia has been increasingly recognised,¹²⁹¹⁶ although several different mechanisms may have a role. Many patients are salt and water depleted at presentation,¹ and this results in a reduction in

the glomerular filtration rate and therefore in the filtered load of calcium. Volume depletion also stimulates proximal tubular reabsorption of sodium, and this limits calcium excretion because the reabsorption of these two cations is closely linked at this site in the nephron.¹⁶¹⁷ The restoration of extracellular fluid volume by infusion of saline rapidly reverses these processes, and the importance of rehydration in the initial treatment of hypercalcaemia is generally acknowledged.⁷¹⁸¹⁹ It was recently shown, however, that even after rehydration many patients continue to show increased calcium reabsorption, and this was attributed to a non-metastatic effect of the primary tumour.¹⁰

Our study confirms that after rehydration the renal setting of calcium reabsorption remains high in most patients with malignant hypercalcaemia and that there seems to be little difference between those with and without bone metastases. Furthermore, the renal handling of calcium in both groups with malignancy is indistinguishable from that of patients with hyperparathyroidism. This is consistent with the view that hypercalcaemia associated with malignancy may be caused by circulating tumour products that have an action on the renal tubule and bone similar to that of parathyroid hormone.²⁰²² Our findings, and those of others,¹⁰ suggest, however, that changes in renal function are not solely a feature of non-metastatic disease but may be a general phenomenon in tumours causing hypercalcaemia. Although currently available techniques for detecting skeletal metastases are fairly insensitive, and therefore non-metastatic hypercalcaemia may tend to be overdiagnosed, this does not diminish the importance of these observations.

The observation that the setting of renal calcium reabsorption is inversely related to the rate of excretion of sodium is of practical importance because it suggests that continued salt loading after dehydration has been corrected has additional value in promoting calcium excretion. This modest degree of salt loading is less complex and requires considerably less monitoring than the forced saline diuresis recommended by some centres.²³²⁴ In theory almost all patients could be made to excrete sufficient sodium to lower calcium reabsorption to a level at which the increased calcium load could be excreted at a normal serum calcium concentration. In practice, however, the degree of salt loading is limited by the risk of cardiac failure in ill or elderly patients.

An interesting observation was that patients with the lowest setting of calcium reabsorption were generally those with the greatest impairment of renal function. As excretion of sodium is derived from the product of the ratio of urinary sodium to creatinine and the serum creatinine concentrations, values will be higher, for a given sodium intake, in patients with renal impairment, and this may account for the low setting of calcium reabsorption. An alternative explanation, and one for which there are supportive animal data, is that the reduced calcium reabsorption is due to the metabolic acidosis of renal failure.²⁵ In the present study, however, we were unable to find a relation between calcium reabsorption and the plasma bicarbonate concentration, although detailed studies of acid base state were not performed.

Our experience of the management of patients with advanced malignancy has left us in no doubt about the value of adequate rehydration and the role of modest salt loading in the early treatment of severe hypercalcaemia. Moreover, the neglect of this aspect of treatment may result in poor responses to other therapeutic agents such as calcitonin (paper in preparation).

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Prospective study of attainment of social class of severely obese subjects in relation to parental social class, intelligence, and education

STIG SONNE-HOLM, THORKILD I A SØRENSEN

Abstract

Cross sectional population studies have shown that subjects who are severely obese are of lower social class than comparable subjects who are not obese. This may be ascribed to lower parental social class, poorer education, and lower intelligence test scores of the obese subjects. In this study based on 242 633 draftees appearing before the draft board in Copenhagen between 1956 and 1977, 1144 extremely overweight men (body mass index ≥ 31 kg/m²) were compared with 2123 young men randomly chosen from the remainder of the population. The two groups were followed up for an average period of 12.5 years, after which time their occupation was obtained from the National Population Register. Social class was derived from a ranking of occupations based on prestige from 0 (unskilled, manual worker) to 7 (for example, judge, professor). Among the obese subjects, only 300 (30%) out of 1006 attained a position above social class 2, compared with 988 (51%) out of 1948 in the control group. At each level of education and intelligence test score, as registered at the draft board, the obese subjects still showed a significantly lower attainment of social class than the controls. Inclusion of parental social class, information which was available for part of the population, did not eliminate the difference in attainment of social class.

The results of this study show that obese subjects not only suffer from a higher risk of somatic diseases but have to live with a social handicap that is independent of parental social class, intelligence, and education.

Introduction

Several studies have shown an inverse relation between obesity and social class, which is seen more strongly in women.^{1,4} A closer analysis of the nature of this relation requires prospective studies of factors related to social class. The social class of adults is positively correlated with parental social class, intelligence, and education.⁵ Several, possibly interacting, mechanisms may exert an influence on the correlation between obesity and social class. Population studies have shown that parents of obese adults have a lower attainment of social class than parents of non-obese adults^{1,6,7} and that obese subjects have lower intelligence, probably because of poorer education, than those who are not obese.^{6,8} It is not known, however, how far the lower attainment of social class of obese subjects may be attributed to lower parental social class, lower intelligence, and poorer education.

In this study we followed prospectively the attainment of social class of the most severely obese young men in a large draftee population and compared this with that of a randomly selected control group, taking into account parental social class, intelligence, and educational level.

Subjects and methods

In Denmark all men are registered with the military authorities at the age of 18. Except for those who volunteer before this age (2%), all are examined by the medical board within the next few years. The study population comprised 242 633 men who had been examined by the board in the metropolitan area of Copenhagen from 1956 to 1977. To describe this population we drew a random 1% sample, numbering 2221 men, which was fewer than the 2426 expected as records were not available for those who were examined and found fit for service from 1958 to 1968 but who in 1969 were living in another region. Those found to be unquestionably unfit for service (86 (4%) out of 2221) did not appear before the board. With few exceptions, the remaining men underwent systematic examination, including measurement of height and weight, intelligence testing, and rating of educational attainment.

We defined extreme overweight as a body mass index—that is, weight/height²—of ≥ 31 kg/m², which is about 45% or more above the old insurance

Obesity Research Group, Department D 105, Herlev University Hospital, DK-2730 Copenhagen, Denmark

STIG SONNE-HOLM, MD, senior registrar
THORKILD I A SØRENSEN, MD, DMS, senior registrar

Correspondence and requests for reprints to: Dr S Sonne-Holm, L E Bruuns vej 27, DK-2920 Copenhagen, Denmark.