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Idiopathic Hypercalciuria and Hyperparathyroidism

PETER ADAMS,* M.R.C.P.; T. M. CHALMERS,* F.R.C.P.; L. F. HILL,† M.R.C.P.; B. McN. TRUSCOTT,‡ F.R.C.S.

British Medical Journal, 1970, 4, 582-585

Summary: With provocative tests of parathyroid activity based on phosphate deprivation and the administration of chlorothiazide 8 out of 19 patients with idiopathic hypercalciuria developed hypercalcaemia. Five of the eight underwent exploration of the neck and four of them had parathyroid adenomas; the fifth patient had "normal" glands but responded satisfactorily to subtotal parathyroidectomy. One patient who failed to develop hypercalcaemia had primary chief cell hyperplasia of the parathyroids.

Introduction

Many patients with calcium-containing renal stones pass excessive quantities of calcium in their urine (Flocks, 1939; Hodgkinson and Pyrah, 1958). A few of these patients have hypercalcaemia and are then usually shown to have primary hyperparathyroidism. The remainder show few biochemical abnormalities other than hypercalciuria. Albright *et al.* (1953) and Henneman *et al.* (1958) recognized a group of such patients, usually men, in whom the hypercalciuria was associated with a tendency to hypophosphataemia; the serum calcium was normal, though in the upper part of the normal range. They called this syndrome idiopathic hypercalciuria and showed that urinary calcium could be reduced with calcium deprivation. Peacock *et al.* (1968) confirmed these observations and suggested that the intestinal absorption of calcium is increased in most patients.

The mechanisms which underlie the increased intestinal absorption of calcium in idiopathic hypercalciuria are unexplained. Peacock *et al.* (1968) suggested that in many cases this is the primary abnormality while others contend that the increased intestinal absorption of calcium is a secondary response to the increased losses of calcium in the urine

(Jackson and Dancaster, 1959; Edwards and Hodgkinson, 1965). The evidence that increased calcium absorption is the primary phenomenon is stronger. Patients with idiopathic hypercalciuria absorb more of an oral calcium load than normal (Peacock *et al.*, 1968), and calcium deprivation does cause a major reduction in urinary calcium in many patients (Henneman *et al.*, 1958; Harrison, 1959; Peacock *et al.*, 1968). The apparent failure of some patients to respond in this way may be related to the severity of the calcium deprivation imposed on them (Peacock *et al.*, 1968).

Patients with idiopathic hypercalciuria may show some of the biochemical abnormalities found in those with primary hyperparathyroidism presenting with renal stone. The urinary calcium is commonly increased in primary hyperparathyroidism, and in both conditions there is a tendency to hypophosphataemia and a reduced renal tubular reabsorption of phosphate (McGeown, 1957). In these respects the two conditions may be indistinguishable. In primary hyperparathyroidism the serum calcium is commonly increased, but even this is not a consistent or universal finding. There are several reports of patients with primary hyperparathyroidism in whom the serum calcium concentration was normal at all times (Yendt and Gagne, 1968; Wills *et al.*, 1969).

That patients with idiopathic hypercalciuria may share abnormalities of calcium and phosphorus metabolism in common with those with primary hyperparathyroidism could suggest that the pathological basis for such abnormalities is the same in both conditions. Albright *et al.* (1953) attributed the changes found in phosphorus metabolism in idiopathic hypercalciuria to parathyroid overactivity. They argued that this was secondary to a tendency to hypocalcaemia caused by excessive urinary loss of calcium, which in turn resulted from a primary abnormality in the renal tubular handling of calcium. This argument is difficult to sustain since in idiopathic hypercalciuria the serum calcium concentration tends toward the upper limit of the normal range (Peacock *et al.*, 1968). Furthermore the renal tubular reabsorption of calcium is generally normal in these patients (Peacock and Nordin, 1968).

* Consultant Physician.

† Formerly Registrar in Medicine.

‡ Consultant Surgeon.

Addenbrooke's Hospital, Cambridge CB2 2QQ.

Requests for reprints should be sent to Dr. T. M. Chalmers.

We have looked for primary hyperparathyroidism in patients with the clinical syndrome of idiopathic hypercalciuria with the aid of provocative tests of parathyroid activity involving phosphate deprivation and the administration of chlorothiazide.

Patients and Methods

Nineteen patients (14 men and 5 women) aged 16 to 66 agreed to take part in the study. All had formed at least one renal stone and in most of them renal stones had been recurrent. None of the patients showed radiological evidence of hyperparathyroidism. None had renal failure.

After preliminary observations, which included serum and urinary calcium estimations, the patients were admitted to hospital for more detailed investigation (Fig. 1). They were first given a ward diet; two 24-hour urine collections were made and fasting blood samples drawn for determination of calcium, inorganic phosphate, and creatinine concentrations. They were then given a diet containing 160 mg. of calcium and 700 mg. of phosphorus for 12 days. On day 4 a further 24-hour urine collection and a fasting blood sample were obtained and the same determinations made. From days 5 to 12 the patients were deprived of phosphorus by means of aluminium hydroxide 60 ml. four times daily after meals; a 24-hour urine collection and a fasting blood sample were obtained on day 8. Chlorothiazide 1 g. twice daily was added on days 9 to 12 and fasting blood samples were obtained on the mornings of days 12 and 13 (Fig. 1). Throughout the study the serum calcium concentrations were corrected for changes in plasma S.G. (Dent, 1962).

Serum calcium was measured by edetic acid titration. Serum and urine inorganic phosphate, serum and urine creatinine, and urine calcium were measured by standard AutoAnalyzer methods (Technicon).

Results

The fasting serum calcium concentrations measured on several occasions were normal in all patients, with a range of 9.8 to 10.7 mg./100 ml.; the maximum serum calcium concentration during the control period is shown in Fig. 2. There was a tendency to hypophosphataemia and in five patients the serum inorganic phosphate concentration was less than normal (Fig. 2). Urinary calcium on a free diet varied from 212 to 655 mg./24 hours (mean 409 mg./24 hours).

The changes in serum calcium after phosphate deprivation and chlorothiazide are shown in Fig. 3. After phosphate deprivation five patients had hypercalcaemia. The addition of chlorothiazide tended to increase the hypercalcaemia in these patients and caused hypercalcaemia to appear in three others. These eight patients were men. The effects of deprivation of calcium and of phosphorus on urinary calcium are shown in Fig. 4. After calcium deprivation urinary calcium decreased and became normal in all patients. There were variable changes after phosphorus deprivation; in 13 patients urine calcium increased.

On the basis of the clinical and biochemical findings we decided to explore the necks of six male patients. Five of these belonged to the group who developed hypercalcaemia; the other did not but he had a family history of primary hyperparathyroidism. Abnormal parathyroid glands were found in five. Three had obvious chief cell parathyroid adenomas (see Table). In a fourth patient the parathyroids were of normal size: a subtotal parathyroidectomy was done and two glands were found to contain small chief cell adenomas (see Table). The histological features of these adenomas are shown in Figs. 5 and 6. The patient without hypercalcaemia had primary chief cell hyperplasia (Adams *et al.*, 1965), which was treated by total parathyroidectomy; a relative suffered from the same condition. One of the patients who developed hypercalcaemia had

normal-sized parathyroid glands; a subtotal parathyroidectomy was done. The glands were considered to be microscopically normal. All six patients have maintained a normal urinary calcium on a free diet for more than a year and none

FIG. 1.—Design of the investigation.

FIG. 2.—Highest serum calcium and lowest serum inorganic phosphate concentrations during the control period. Interrupted lines represent limits of normal range.

FIG. 3.—Changes in serum calcium after phosphate deprivation and chlorothiazide. Interrupted lines represent limits of normal range. Two patients were not given chlorothiazide.

FIG. 4.—Changes in urinary calcium after calcium and phosphate deprivations.

Cases with Parathyroid Adenomas

Case No.	Adenoma	
	Glands	Size (cm.)
1	Left lower	1.1 × 0.6 × 0.6
2	Left lower	0.8 × 0.4 × 0.3
3	Left lower	0.7 × 0.7
4	Left lower	0.5 × 0.4 × 0.4
	Left upper	0.4 × 0.3 × 0.2

FIG. 5.—Case 4. Junction of adenoma (above) and normal parathyroid tissue. (× 60.)

FIG. 6.—Case 3. Large closely packed chief cells in parathyroid adenoma. (× 60.)

FIG. 7.—Biochemical findings in patients who developed hypercalcaemia (●) and those who did not (○). Horizontal bars represent means for each group. Serum calcium and inorganic phosphate concentrations are as shown in Fig. 2.

FIG. 8.—Index of phosphate excretion (Nordin and Bulusu, 1968) in patients who developed hypercalcaemia (●) and those who did not (○). Horizontal bars represent means for each group.

has formed renal stones. The three hypercalcaemic patients not operated on had each formed only a single renal stone and their progress was still being observed.

The patients who developed hypercalcaemia and the patient with proved primary hyperparathyroidism who did not differed from the others (Fig. 7). They had, on average, significantly greater serum calcium concentrations and urinary calcium and significantly lower serum inorganic phosphate concentrations. None of these measurements, however, discriminated sharply between the two groups (Fig. 7). The index of phosphate excretion (Nordin and Bulusu, 1968) was measured once after four days on the low calcium diet; the index was on average greater in the patients with hypercalcaemia, but again discrimination was poor (Fig. 8).

Discussion

Though the syndrome of idiopathic hypercalciuria may include several disorders of calcium metabolism, an increased intestinal absorption of calcium is a feature common to many patients (Peacock and Nordin, 1969). After calcium deprivation the urine calcium is usually reduced to normal (Peacock *et al.*, 1968); an observation we have confirmed in this study.

Henneman *et al.* (1958) commented on the close resemblance between patients with idiopathic hypercalciuria and those with primary hyperparathyroidism presenting with renal stone; but normal parathyroid glands were found in the seven patients of their series in whom the neck was explored. We have shown that at least five patients with the syndrome of idiopathic hypercalciuria had primary hyperparathyroidism. In two patients the parathyroid glands were of normal size: one had chief cell hyperplasia and the other had two small adenomas. Thus the finding of normal-sized parathyroid glands at operation does not exclude the presence of abnormal parathyroid tissue (Adams *et al.*, 1965).

In a sixth patient subtotal parathyroidectomy restored the urinary calcium to normal and prevented further stone formation, though the glands were thought to be microscopically normal. George *et al.* (1965) described similar experiences. Whether such apparently normal glands may in fact be overactive is not known, but this is a possibility which might be further explored when sensitive assay methods for human parathyroid hormone are developed. We assume that in this group of patients the increased intestinal absorption of calcium was related to parathyroid overactivity. There is clinical and experimental evidence that parathyroid hormone stimulates transport of calcium across the gut (Nordin *et al.*, 1968; Robinson *et al.*, 1968).

Since the amount of calcium appearing in the urine is the difference between the amount filtered at the glomerulus and the amount reabsorbed by the renal tubules and since parathyroid hormone is known to promote the renal tubular

reabsorption of calcium (Nordin and Peacock, 1969), the filtered load of calcium must have been increased in these patients. All had normal glomerular filtration rates. Possibly the ultrafilterable fraction of the serum calcium was greater than that inferred from the total serum calcium concentration, or measurement of serum calcium after meals might have shown greater increases than normal; these points will require further study. Patients with idiopathic hypercalcaemia have a greater increase in serum calcium after an oral load of calcium than normal subjects (Peacock *et al.*, 1968).

The detection of parathyroid overactivity in patients with renal stone and normal or marginally raised serum calcium concentrations is difficult in the absence of radiological features of hyperparathyroidism. A variety of tests have been introduced as aids to diagnosis; these have largely been concerned with estimates of the renal tubular reabsorption of phosphate since parathyroid hormone is known to reduce phosphate reabsorption by the renal tubule. Unfortunately these tests have proved of limited value (Strott and Nugent, 1968). Some procedures have been designed to provoke the biochemical abnormalities of primary hyperparathyroidism; these include phosphate deprivation and the administration of thiazide diuretics. Phosphate deprivation is most easily produced by giving a diet low in phosphorus in combination with aluminium hydroxide, which combines with the phosphorus in the diet and inhibits its absorption. In some patients with primary hyperparathyroidism phosphate deprivation causes the serum calcium to increase to unequivocally abnormal levels (Eisenberg, 1968). Though this response has not been described in normal adults, the finding may not be specific to primary hyperparathyroidism. The mechanism by which phosphate deprivation causes hypercalcaemia is unknown but may be related to a reduced amount of calcium incorporated into bone. In some patients phosphate deprivation causes an increase in urinary calcium (Pronove *et al.*, 1961); in the present study changes in urinary calcium after phosphate deprivation did not clearly differentiate the patients with proved primary hyperparathyroidism.

Thiazide diuretics reduce urinary calcium in patients with idiopathic hypercalcaemia without altering the intestinal absorption of calcium (Harrison and Rose, 1968), possibly through increased renal tubular reabsorption of calcium. In normal people thiazides cause small and transient increases in the serum calcium concentration (Seitz and Jaworski, 1964; Smeenk, 1968), an effect which largely results from changes in plasma volume. In some patients with hypercalcaemia, however, contraction of the plasma volume is not the explanation and the ionized fraction of the serum calcium is presumed to be increased (Harrison and Rose, 1968). This may happen through increased renal tubular reabsorption of calcium (Nordin and Peacock, 1969), though there is experimental evidence that thiazide administration may lead to parathyroid overactivity (Pickleman *et al.*, 1969). Van der Sluys Veer *et al.* (1966) reported a persistent increase in serum calcium in patients with primary hyperparathyroidism given chlorthalidone; the abnormal response disappeared after parathyroidectomy. They suggested that this phenomenon might provide a useful aid in diagnosis.

We combined phosphate deprivation with the oral

administration of chlorothiazide and provoked hypercalcaemia in 8 out of 19 patients who had renal stone, hypercalcaemia, and normal serum calcium concentrations. These eight patients were men. Four of the five in whom the neck was explored had parathyroid adenomas. One patient with primary chief cell hyperplasia of the parathyroids (Adams *et al.*, 1965) did not develop hypercalcaemia; this could suggest that other cases of parathyroid disease were overlooked.

The results of this investigation show that some male patients with all the features of idiopathic hypercalcaemia have primary hyperparathyroidism. In comparison with the others the patients with hyperparathyroidism (proved or presumed) had on average higher serum and urinary calcium, lower serum phosphate, and higher phosphate excretion. These differences and the response to provocative tests may or may not reflect two different populations.

We wish to thank Professor H. Lehmann and members of the Section of Biochemistry, John Bonnett Laboratories, Addenbrooke's Hospital, for their assistance; Dr. E. M. Widdowson, Dunn Nutritional Laboratory, Cambridge, for laboratory facilities; and the department of medical illustration, Addenbrooke's Hospital.

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