Familial hypocalciuric hypercalcaemia: observations on vitamin D metabolism and parathyroid function

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Abstract. Serum vitamin D metabolites, the renal tubular maximum reabsorptive rate for phosphate (TMP/GFR) nephrogenic cyclic AMP (NcAMP), and CaE (urinary calcium excretion per litre of glomerular filtrate) were measured in 14 adults with familial hypocalciuric hypercalcaemia (FHH). The findings were compared with analyses in 14 patients with surgically proven primary hyperparathyroidism matched for serum calcium, creatinine clearance and vitamin D status (assessed by serum concentrations of 25 hydroxyvitamin D). Vitamin D metabolites were also measured in 16 normocalcaemic relatives of patients with FHH. The serum concentration of 24,25 dihydroxycholecalciferol was appropriate for the prevailing 25 hydroxyvitamin D and no difference was found between groups. The serum concentration of 1,25 dihydroxycholecalciferol was significantly greater in primary hyperparathyroidism (P < 0.0005) compared with patients with FHH and their normocalcaemic relatives. TMP/GFR was reduced in both primary hyperparathyroidism (0.53 ± 0.12 mmol/l GF, mean ± SEM) and FHH (0.86 ± 0.14 mmol/l GF). Patients with primary hyperparathyroidism showed an increase in NcAMP output in the urine (38.5 ± 16 mmol/l GF) which was significantly greater (P < 0.0001) than the normal NcAMP (13.5 ± 9.2 nmol/l GF) found in FHH. CaE was low in FHH indicating increased renal tubular reabsorption of calcium.

It is concluded that there is no abnormality of vitamin D metabolism in FHH comparable with the changes observed in primary hyperparathyroidism. It is suggested that the biochemical abnormalities in FHH cannot be explained solely upon an increased sensitivity of the renal tubules to the effects of endogenous parathyroid hormone.

Foley et al. (1972) first drew attention to a familial form of hypercalcaemia in which, unlike other causes of hypercalcaemia, the urinary excretion of calcium is characteristically low. This condition, - known as familial benign hypercalcaemia or as familial hypocalciuric hypercalcaemia (FHH) (Marx et al. 1977) - is inherited as an autosomal dominant, and closely resembles primary hyperparathyroidism, for which it is commonly mistaken. Clinical experience of FHH is limited, but there is general agreement that with few exceptions the condition is benign. Some patients have presented with acute pancreatitis which has endangered life (Davies et al. 1981). The role of parathyroid hormone in the pathogenesis of FHH is uncertain; immunoassayable parathyroid hormone (iPTH) can often be detected in the serum, sometimes in increased amounts. The parathyroid glands can appear normal at exploration of the neck, but in some patients all the glands are found to be enlarged and hyperplastic (Davies et al. 1981).

The differentiation of FHH from primary hyperparathyroidism is important because surgical treatment is unsatisfactory and seldom indicated (Adams 1982). Unfortunately, no single routine biochemical test clearly distinguishes the individual patient with FHH from one with asymptomatic or uncomplicated primary hyperparathyroidism. The discovery of hypercalcaemia in another member of the family should suggest the diagnosis, but this is not confirmatory, since primary hyperparathyroidism is also sometimes familial (Peters et al. 1966).

Vitamin D, through the actions of its effector metabolite 1,25 dihydroxycholecalciferol (1,25-(OH)2D3) plays a central role in bone and calcium metabolism. The serum concentration of 1,25-
(OH)₂D₃ tends to be increased in primary hyperparathyroidism, and this almost certainly explains the enhanced intestinal absorption of calcium commonly found in this condition. The role of 1,25-(OH)₂D₃ in the pathogenesis of FHH has not been defined. We have measured the serum concentration of 1,25-(OH)₂D₃ and other metabolites of vitamin D in patients with FHH, and compared the findings with those obtained in patients with surgically proven primary hyperparathyroidism.

Patients

Fourteen adults with hypocalciuria and hypercalcaemia and drawn from 4 families (Davies et al. 1981) were assessed in a metabolic unit. The findings were compared with those obtained in 14 patients with surgically proven primary hyperparathyroidism, matched for serum concentrations of calcium and 25 hydroxyvitamin D (25(OH)D) and creatinine clearance. Serum samples were also obtained from 16 adult relatives of the patients with FHH in whom the serum concentrations of calcium and creatinine were normal.

Methods

Serum and urine concentrations of calcium, inorganic phosphate, magnesium and creatinine were measured as previously described (Davies et al. 1977). The renal tubular maximum reabsorption rate for phosphate (TMP/GFR) (Walton & Bijvoet 1975; normal range 0.8—1.35 mmol/l glomerular filtrate), and the urinary excretion of nephrogenic cyclic adenosine monophosphate (NcAMP) (normal range 2.7—23.7 nmol/l glomerular filtrate) were calculated from measurements in fasting samples of urine and serum obtained between 8.00 and 11.00 h. An index of the net tubular reabsorption of calcium was also made on these samples by calculation of the urinary excretion of calcium per litre of glomerular filtrate (Caₑ) (Nordin et al. 1967; normal range 0.0125—0.0375 mmol/l GF). Serum and urine concentrations of cAMP were measured by competitive protein binding assay (Broadus et al. 1977). Serum concentrations of 1,25-(OH)₂D₃ (normal range 40—140 pmol/l) and iPTH (normal range <0.1—0.8 µg/l) were measured by radio-immunoassay (Clemens et al. 1979; Mawer et al. 1975); and the serum concentrations of 25(OH)D (normal range 12.5—60 nmol/l) and 24,25-dihydroxyvitamin D₃ (24,25-(OH)₂D₃) (normal range 1—8 nmol/l) by competitive protein binding assay (Taylor et al. 1978).

![Fig. 1](image_url)

Serum calcium, 24 h urinary calcium and Caₑ in FHH (○), their normal relatives (△) and primary hyperparathyroidism (●). Horizontal bars represent the median for calcium, and the mean for the urine calcium and Caₑ. Hatched areas on the ordinates represent the normal range.
Statistical differences between groups were assessed by Student’s t-test and the Wilcoxon rank sum test where applicable.

Results

The creatinine clearances of patients with FHH (100 ± 22 ml/min) and primary hyperparathyroidism (90 ± 17 ml/min) did not differ significantly ($P = 0.2$). In both groups the distribution of serum calcium was similar ($P = 0.68$) and significantly elevated when compared with the normocalcaemic relatives of the patients with FHH (Fig. 1). The 24 h urinary excretion of calcium was greater in patients with primary hyperparathyroidism and this was associated with a higher CaE and thus a lower renal tubular reabsorption of calcium (Fig. 1). Serum iPTh was detected in all the patients with FHH and in 2 patients was greater than normal; the serum concentration of the group was significantly less than that found in the patients with primary hyperparathyroidism (Fig. 2). The excretion of NcAMP was normal in all but one of the patients with FHH. The mean ($±$ SD) excretion of the group was significantly less than that of the patients with primary hyperparathyroidism, (FHH 13.5 ± 9.2 nmol/l GF, primary hyperparathyroidism 38.5 ± 16 nmol/l GF) (Fig. 2). A significant difference was found in the mean ($±$ SD) serum magnesium (FHH 0.94 ($±$ 0.08) mmol/l; primary hyperparathyroidism 0.85 ($±$ 0.05) mmol/l, $P < 0.003$) serum phosphate (FHH 0.86 ($±$ 0.11) mmol/l vs 0.7 ($±$ 0.1) mmol/l, $P < 0.0005$) and TMP/GFR (FHH 0.86 ($±$ 0.14) mmol/l GF vs. 0.53 ($±$ 0.12) mmol/l GF, $P < 0.0001$).

A considerable variation in the serum concentration of 25(OH)D was found among the patients with FHH, their normocalcaemic relatives, and the patients with primary hyperparathyroidism, but there was no significant difference between the values of the three groups (Fig. 3). The serum concentrations of 1,25-(OH)2D3 were normal in all but one of the patients with FHH, and in all their normocalcaemic relatives; there was no significant difference between the groups. Seven of the patients with primary hyperparathyroidism had elevated serum concentrations of 1,25-(OH)2D3 and as a group the values were significantly greater than those of the patients with FHH and their normal relatives (Fig. 3). This difference was not accounted for by the 3 patients with primary hyperparathyroidism in whom the serum (25(OH)D exceeded 80 nmol/l. When their data are eliminated (serum 1,25-(OH)2D3 106, 118 and 197 pmol/l), there remains a highly significant increase in the
Fig. 3.
Serum 25 hydroxyvitamin D, 1,25-(OH)\textsubscript{2}D\textsubscript{3} and 24,25(OH)\textsubscript{2}D\textsubscript{3} concentrations in FHH (○), their normal relatives (△) and primary hyperparathyroidism (●). Horizontal bars represents the median.

serum concentrations of 1,25-(OH)\textsubscript{2}D\textsubscript{3}. No significant relation was found between the serum concentration of 1,25-(OH)\textsubscript{2}D\textsubscript{3} and the serum concentrations of 25(OH)D and iPTH in the patients with FHH or primary hyperparathyroidism. No correlation was found between serum 1,25-(OH)\textsubscript{2}D\textsubscript{3} and 24 h urinary calcium.

The serum concentration of 24,25-(OH)\textsubscript{2}D\textsubscript{3} was generally appropriate for the prevailing serum concentration of 25(OH)D, and no difference was found between the groups (Fig. 3).

Discussion

The present study has shown that there is no obvious disturbance of vitamin D metabolism in FHH comparable to that found in primary hyperparathyroidism. The serum concentrations of the vitamin D metabolites were normal in both the FHH patients and their normocalcaemic relatives and this suggests that vitamin D metabolism is normal in FHH. Hypercalcaemia in FHH therefore cannot result from an excessive renal synthesis of 1,25-(OH)\textsubscript{2}D\textsubscript{3} with an associated enhancement of calcium absorption from the gut. This distinguishes FHH from primary hyperparathyroidism where the serum concentration of 1,25-(OH)\textsubscript{2}D\textsubscript{3} tends to be increased (Gray et al. 1977) and the associated increased intestinal absorption of calcium is a factor in the genesis of the hypercalcaemia.

It has been suggested that 1,25-(OH)\textsubscript{2}D\textsubscript{3} also increases the reabsorption of calcium in the proximal tubule of the kidney (Kanis et al. 1982). In both FHH and primary hyperparathyroidism there is an enhanced net renal tubular reabsorption of calcium which is much greater in patients with FHH (Marx et al. 1978a; Davies et al. 1981). If 1,25-(OH)\textsubscript{2}D\textsubscript{3} were to be of aetiological importance in this enhanced renal tubular reabsorption of calcium then one might expect greater serum concentrations of 1,25-(OH)\textsubscript{2}D\textsubscript{3} to be found in FHH than in primary hyperparathyroidism, a theoretical finding opposite to that occurring in reality. It seems improbable that vitamin D has any pathogenetic role in the hypercalcaemia of FHH.

In the distal part of the nephron parathyroid hormone promotes calcium absorption through the generation of cAMP, the excretion of which is increased in primary hyperparathyroidism. The urinary excretion of cAMP is commonly normal in
FHH (Broadus et al. 1977; Marx et al. 1978b), although some patients have been found to have increased values (Marx et al. 1980; Heath & Purnell 1980). The present findings agree with these observations; the excretion of nephrogenic cAMP was increased in one patient and normal in the others. Heath & Purnell (1980) assessed the response to acutely induced hypocalcaemia in FHH and primary hyperparathyroidism, and found a significantly greater increment in urinary cAMP (per unit increase in iPTH) in patients with FHH. They also found an increased mean basal excretion of cAMP in FHH. Heath & Purnell (1980) suggested that in FHH the renal tubules were unduly sensitive to the effects of endogenous parathyroid hormone, and that this could account for the enhanced renal tubular reabsorption of calcium. This might be the explanation, but it is difficult to reconcile with the unequivocally normal excretion of nephrogenic cAMP found in many patients (Fig. 2). Moreover, the increased renal tubular re-absorption of calcium persists after total parathyroidectomy when there is unequivocal evidence of hypoparathyroidism (Attie et al. 1980; Davies et al., in press). It therefore seems likely that an increased renal tubular re-absorption of calcium is intrinsic to FHH. Nonetheless, the persistence of normal indices of parathyroid function in the presence of hypercalcaemia, suggests the presence of parathyroid autonomy, and whilst in many patients with FHH the parathyroid glands are normal in size and structure, the glands can be obviously enlarged and hyperplastic (Davies et al. 1981). Thorgeirsson et al. (1981) consider that the parathyroid glands are commonly abnormal in FHH, and have found histological features of hyperplasia in apparently normal sized glands.

Whether FHH is homogenous in terms of parathyroid activity awaits confirmation. The present study adds little to an understanding of the pathogenesis of FHH. However, the absence of any alteration to vitamin D metabolism and the persistence of the increased renal tubular reabsorption of calcium following total parathyroidectomy suggests that the hypercalcaemia in FHH is predominantly due to an intrinsic renal abnormality. Correction of the hypercalcaemia by total parathyroidectomy must arise through a reduced input of calcium from the gut and (or) bone, perhaps by a reduction in the biosynthesis of 1,25-(OH)2D3 induced by hypoparathyroidism (Davies et al., in press).

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References


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