CLINICAL RESEARCH

Renal handling of calcium in hypoparathyroidism

G H NEWMAN, M WADE, D J HOSKING

Abstract

Treatment of hypoparathyroidism usually requires the use of pharmacological doses of parent vitamin D or near physiological amounts of the hydroxylated metabolites, calcitriol or alphacalcidol. Vitamin D intoxication and hypercalcaemia may be a problem but can be minimised by the use of small doses of vitamin D or its metabolites combined with large amounts of oral calcium. The response to treatment can be easily monitored by measuring serum and urinary calcium and creatinine concentrations. This allows the derivation of two simple indices reflecting calcium load presented to the kidney (calcium excretion in mmol/l glomerular filtrate) and renal tubular calcium reabsorption (TmCa/GFR). These can be used to predict the requirement of calcium supplements and also identify those patients at particular risk of hypercalcaemia.

Introduction

The inter-relation between parathyroid hormone and 1α,25 dihydroxycholecalciferol, the principal metabolite of vitamin D, is central to the maintenance of calcium and phosphate homeostasis.[1] Lack of, or end organ resistance to, parathyroid hormone results in a failure of 1α,25 dihydroxycholecalciferol production[2,3] (with a consequent decline in calcium absorption[4,5]), a reduction in renal tubular calcium reabsorption,[6,7] and impairment of the exchange of calcium between bone and extracellular fluid (fig 1).[8,9] Pharmacological amounts of parent vitamin D[10] or near physiological doses of 1α,25 dihydroxycholecalciferol (calcitriol) or alfacalcidol[11,12] will correct the calcium malabsorption and may improve skeletal responsiveness but do not correct the renal leak of calcium.

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To maintain normocalcaemia the obligatory urinary loss has to be balanced by an increase in calcium absorption. This can be achieved either by the use of large doses of vitamin D or by supplementation of the diet with extra calcium, the amount required being inversely proportional to the efficiency of tubular reabsorption. Unfortunately, patients vary in their requirements for vitamin D and calcium, and there is always a risk of overdosage and hypercalcaemia.[13] The two main variables determining the concentration of serum calcium—namely, the load presented to the kidney and the efficiency of tubular reabsorption—can, however, be easily measured in routine clinical practice.

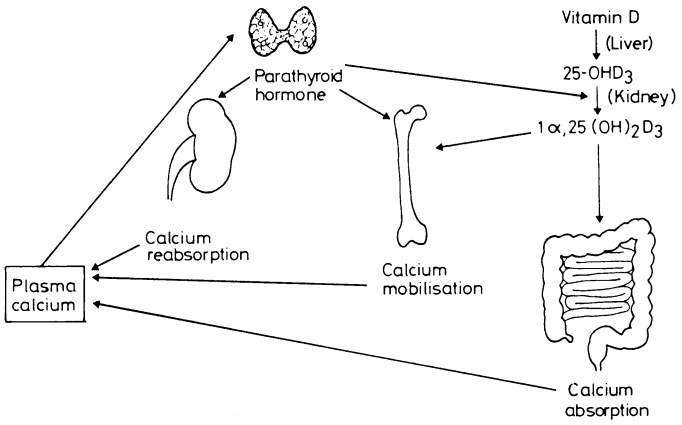

FIG 1—Normal relation between parathyroid hormone and vitamin D in the control of calcium homeostasis. ($25\text{-}OHD_3$=25-hydroxycholecalciferol; 1α, 25 $(OH_2)_3$=1α, 25-dihydroxycholecalciferol).

Patients and methods

The normal adaptive response to changes in calcium intake[14] is lost in hypoparathyroidism with the result that calcium excretion passively follows net intestinal absorption. Under these circumstances serum and urinary measurements may be used as a substitute for direct estimation of calcium absorption, which is otherwise difficult to perform and cannot be easily repeated.

Clinical details and response to treatment in 17 patients with hypoparathyroidism

Case No	Age (years)	Sex	Type of hypoparathyroidism	Pretreatment values: Serum calcium concentration (mmol/l)	Pretreatment values: Serum phosphate concentration (mmol/l)	Pretreatment values: TmCa/GFR (mmol/l)	Treatment	Post-treatment values: Serum calcium concentration (mmol/l)	Post-treatment values: Serum phosphate concentration (mmol/l)	Post-treatment values: TmCa/GFR (mmol/l)
1	76	M	Idiopathic	1·17	1·85	1·20	1α-OHD_3 1 μg	2·28	0·95	1·06
2	62	F	Idiopathic	1·71	1·80	1·38	1α, 25 $(OH)_2$ D_3 0·5 μg	2·24	0·95	1·62
3	44	M	Idiopathic	1·81	1·14	—	1α-OHD_3 1 μg + calcium	2·31	1·40	1·55
4	37	M	Idiopathic	1·78	1·45	1·52	1α, 25 $(OH)_2D_3$ 1 μg + calcium	2·26	0·72	1·62
5	24	F	Idiopathic	1·27	1·29	1·35	1α-OHD_3 1 μg + calcium	2·24	0·95	1·45
6	20	M	Idiopathic	1·18	3·80	1·40	1α-OHD_3 1 μg + calcium	2·23	1·22	1·45
7	76	F	Post-thyroidectomy	1·66	2·20	1·30	1α-OHD_3 1 μg	2·27	1·70	1·55
8	61	F	Post-thyroidectomy	1·42	2·18	1·11	1α-OHD_3 0·5 μg	2·21	1·25	1·43
9	56	F	Post-thyroidectomy	1·76*	1·71	1·30	Vitamin D_2 1·25 mg + calcium	2·22	1·50	1·40
10	43	F	Post-thyroidectomy	1·38	1·44	1·45	1α-OHD_3 1 μg + calcium	2·23	1·56	1·58
11	37	M	Post-thyroidectomy	1·60	1·55	1·40	Vitamin D_2 1·25 mg + calcium	2·10	1·60	1·57
12	61	F	Post-total thyroidectomy	1·78*	1·63	1·20	Vitamin D_2 1·25 mg + calcium	2·22	1·65	1·38
13	59	F	Post-total thyroidectomy	2·06*	1·35	1·30	Vitamin D_2 1·25 mg + calcium	2·23	1·33	1·45
14	33	F	Post-total thyroidectomy	1·53	1·70	1·15	1α,25 $(OH)_2$ D_3 1 μg + calcium	2·25	1·26	1·35
15	64	M	Pseudohypoparathyroidism	1·56	1·20	1·58	Vitamin D_2 1·25 mg	2·36	1·18	1·65
16	36	F	Pseudohypoparathyroidism	1·88	1·44	1·98	1α-OHD_3 0·5 μg + calcium	2·21	1·42	1·87
17	29	M	Pseudohypoparathyroidism	1·25	1·68	1·65	1α-OHD_3 1 μg + calcium	2·23	1·33	1·71

*No pretreatment values available (value shown is the lowest recorded on treatment).
TmCa/GFR = tubular maximum for calcium reabsorption for GFR.

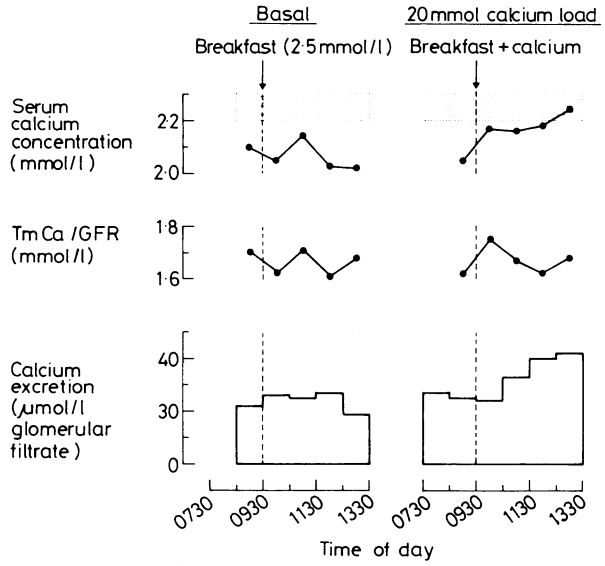

FIG 2—Effect of breakfast and an oral calcium load on the serum calcium, renal tubular calcium reabsorption (TmCa/GFR), and calcium excretion (case 10).

Calcium excretion (μmol/l glomerular filtrate)[15] was measured in 17 patients with hypoparathyroidism either in a metabolic ward or in the outpatient clinic. In each patient vitamin D and calcium supplements were adjusted to achieve a low normal serum calcium concentration and treatment was stable for several months before the beginning of the present study. Calcium excretion was derived from the calculation: urine calcium (mmol/l) multiplied by serum creatinine (μmol/l) divided by urine creatinine (mmol/l). Studies on the metabolic ward were based on hourly urine collections with a midpoint blood sample, while outpatient measurements were made on freshly voided urine and contemporary blood samples. Standard biochemical techniques were used and serum calcium was corrected to a reference serum albumin concentration of 40 g/l.[16]

Using the relation between calcium excretion and serum calcium concentration established for different states of parathyroid function by calcium infusion[15] an estimate of the setting of renal tubular calcium reabsorption (TmCa/GFR) could be derived.[17] This made it possible to assess the separate contributions of load and tubular reabsorption to the maintenance of serum calcium.

Results

The table shows the pretreatment and representative post-treatment values of serum calcium, phosphate, and TmCa/GFR for the 17 patients.

The maintenance of normocalcaemia in hypoparathyroidism depends on a high net intestinal absorption of calcium. This is illustrated in fig 2: breakfast (fruit juice, three slices of toast, honey, margarine, and black coffee) providing 2·5 mmol of calcium was insufficient to raise the serum calcium concentration, and normocalcaemia was achieved only when a 20 mmol supplement (Sandocal 0·8 g) was added. Tubular reabsorption remained constant during both studies but the increase in calcium excretion when calcium supplements were added shows that the restoration of normocalcaemia depended on a high input of calcium from the intestine. This relation is further illustrated by serial measurements of calcium excretion and serum calcium concentration before and hourly for six hours after the standard breakfast supplemented by a 20 mmol calcium load (fig 3). At all

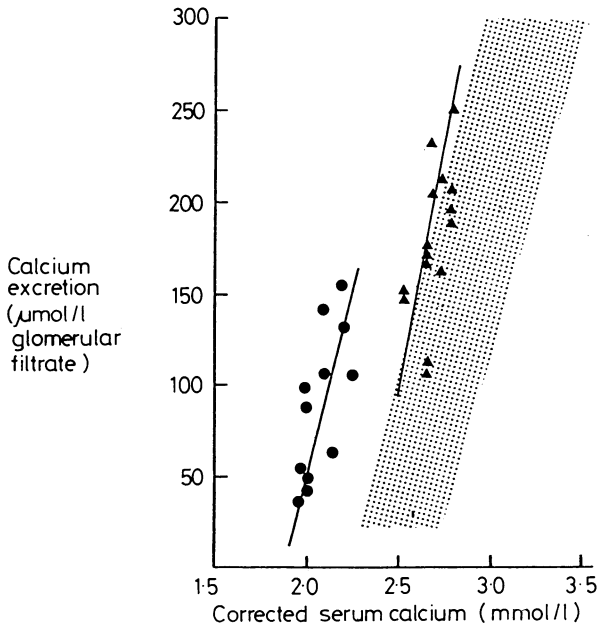

FIG 3—Relation between serum calcium and calcium excretion measured before and hourly for six hours after a 20 mmol calcium load (Ossopan 4·5 g). (Case 14 (●) and case 15 (▲). Hatched area indicates normal range of serum calcium concentration.

times there was a constant relation between these two variables. The slope of the regression line was similar to that seen in normal subjects, and its position was determined by the setting of renal tubular reabsorption; the lower the value of TmCa/GFR the further leftward the displacement.

The slope of the relation between calcium excretion and serum

calcium concentration in patients with hypoparathyroidism was variable and could differ appreciably from that seen in normal subjects (fig 4). The setting of TmCa/GFR also changed with the serum calcium concentration: the less steep the slope of the relation between calcium excretion and serum calcium the greater the increase in renal threshold as serum calcium concentrations rose. Although most patients showed this phenomenon (table) it was not invariable and younger patients and those with pseudohypoparathyroidism seemed to be exceptions.

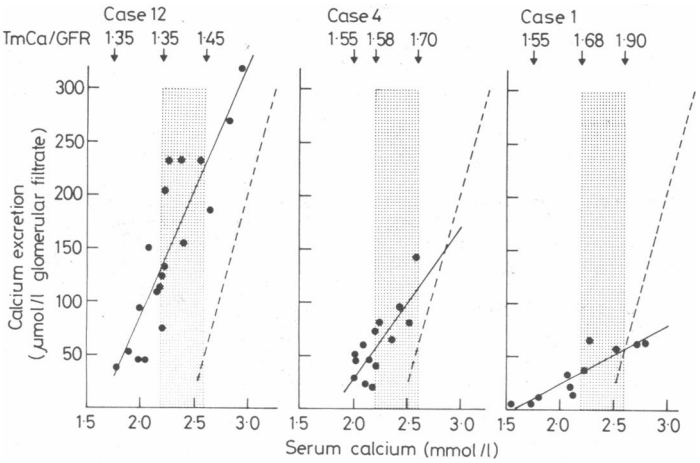

FIG 4—Variation in slope of relations between serum calcium and calcium excretion in cases 1, 4, and 12. Figures and arrows at top indicate different settings of renal tubular reabsorption (TmCa/GFR) at different values of serum calcium. Hatched area indicates normal range of serum calcium. Broken line denotes correlation in normal subjects during calcium infusion.[15]

Discussion

There are two ways in which normocalcaemia may be achieved in patients with hypoparathyroidism.[10 18] The first is to increase the efficiency of intestinal calcium absorption so that the normal diet provides a sufficient calcium load. The disadvantage of this approach is that it requires large amounts of vitamin D with the risk of intoxication,[13] and although the short half life of the newer dihydroxylated metabolites reduces toxicity[19] the risk remains. The second alternative is to use smaller doses of vitamin D to restore intestinal absorption and to increase net absorption by giving large amounts of calcium. This has the advantage that serum calcium is dependent on a high intake of calcium rather than on vitamin D, and should hypercalcaemia develop stopping the calcium intake is immediately corrective. The disadvantage is that patients have to take calcium supplements throughout the day rather than a single dose of vitamin D in the morning.

Irrespective of which alternative is chosen it is essential to monitor the response. In severe hypoparathyroidism the parathyroid hormone 1α,25 dihydroxycholecalciferol system is fixed so that changes in net calcium absorption are reflected by urinary excretion, which can be used as an index of the calcium load presented to the kidney.[20] This has the advantage of convenience and also provides data which illustrate important aspects of renal tubular function.[15] All 17 patients were initially severely hypocalcaemic; half had had some form of thyroid surgery; and, where it was measured (six patients), parathyroid hormone was either undetectable or inappropriately low in the presence of hypocalcaemia. Although 1α,25 dihydroxycholecalciferol concentrations were not estimated the dose of vitamin D or its metabolites was kept constant and changes in calcium load were obtained by manipulating intake. It seems reasonable, therefore, to accept calcium excretion as an indicator of calcium absorption.

By following the relation between calcium excretion and serum calcium concentration after an oral load of calcium the level of calcium excretion required to achieve normocalcaemia may be predicted. It is then a simple matter to adjust the dose or type of preparation to achieve this end. It is important, however, to be aware of the elemental calcium content of the available preparations[10 18]: 20 mmol calcium is provided by 8 × 600 mg tablets of calcium gluconate *BP*, 2 × 400 mg tablets of calcium lactate gluconate (Sandocal), or one 4·5 g scoop of microcrystalline hydroxyapatite (Ossopan). Serial measurements after an oral load will indicate peak and duration of action so that optimum frequency of administration can be found.

It is also possible to identify those patients at risk of developing hypercalcaemia by knowing the level of calcium excretion and the setting of TmCa/GFR. Calcium excretion is directly proportional to net calcium absorption but inversely related to glomerular filtration rate, so that as renal function declines a smaller calcium load is required to achieve normocalcaemia.[21] This is illustrated by data in fig 3. Although both patients were given 20 mmol calcium, a double isotope technique[22] showed that the patient in case 15 absorbed 71% of dietary calcium intake and the patient in case 14 only 56% (this reflects different responses to their current vitamin D medication). The more efficient calcium absorption in the patient in case 15 was amplified by poor renal function, so that calcium excretion reached 250 μmol/l glomerular filtrate compared with 150 μmol/l glomerular filtrate in the patient in case 14. The risk of hypercalcaemia depends on the setting of TmCa/GFR, the lower the value the smaller the risk. Thus the patient in case 15 became hypercalcaemic when calcium excretion exceeded 150 μmol/l glomerular filtrate, while the patient in case 14, with a much lower tubular reabsorption, would not become hypercalcaemic until calcium excretion exceeded 300 μmol/l glomerular filtrate.

The slope of the relation between calcium excretion and serum calcium concentration is also important in determining the risk of hypercalcaemia. This is illustrated in fig 4 where calcium excretion had to increase from 125 μmol/l to 225 μmol/l glomerular filtrate in the patient in case 12 for the serum calcium concentration to rise from 2·2 to 2·6 mmol/l. In contrast, calcium excretion had to increase only from 35 to 55 μmol/l glomerular filtrate in the patient in case 1 to effect the same change in serum calcium; case 4 illustrates an intermediate response.

Thus there are two groups of patients who can be identified as being at risk of vitamin D intoxication and hypercalcaemia. The first are those, like the patient in case 15, who have renal impairment but efficient calcium absorption and relatively high renal tubular reabsorption, so that calcium excretion is readily increased to levels associated with hypercalcaemia. The second group at risk, exemplified by the patient in case 1, are patients in whom the slope relating calcium excretion to serum calcium is so acute that small changes in load are associated with pronounced changes in serum calcium concentration. Both groups are best treated with calcium supplements alone or with very small doses of vitamin D.

The increase in TmCa/GFR as the serum calcium rises appears to be a general phenomenon, though whether this is a consequence of the rise in serum calcium concentration or a response to vitamin D is not clear[23 24]; both mechanisms raise intracellular calcium.[25] The practical implication is that larger amounts of calcium are needed initially when renal tubular reabsorption is low than when normocalcaemia has been achieved and tubular reabsorption is set at a higher level.

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Presence of human papillomavirus DNA sequences in cervical intraepithelial neoplasia

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Abstract

Twenty two patients referred to a district colposcopy clinic because of an abnormal cervical cytology report or a suspicious cervix and found to have a cervical epithelial abnormality were studied. The techniques of cytology, histology, immunohistochemistry, and DNA-DNA hybridisation were used to detect infection by human papillomavirus. Using an indirect immuno-alkaline phosphatase technique human papillomavirus antigen was found in biopsy specimens from six of the 22 patients and DNA of papillomavirus type 6 in biopsy specimens from 13 of these women, including four out of six whose histological diagnosis was cervical intraepithelial neoplasia grade 3. In eight cases where cytological, colposcopical, and histological investigations all indicated the presence of wart virus infection, papillomavirus type 6 DNA was found in seven.

Papillomavirus type 6 DNA was found in more than half of the proved cases of cervical intraepithelial neoplasia. The presence of this viral DNA in women with no cervical abnormality is to be studied.

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Introduction

Until recently infection of the uterine cervix by human papillomavirus was thought to be rare. Reviewing the published reports in 1952 Marsh described 23 cases of papillomatous disease of the cervix, of which only 10 were considered to be condylomata acuminata.[1] In 1954 Raftery and Payne suggested that condyloma of the cervix might not be so uncommon and they found histological evidence of condylomata acuminata in 19 of 587 biopsy specimens from the cervix uteri seen in their department in the years 1949-54.[2] Although Oriel in 1971 described nine cases of exophytic cervical condylomata in 141 women presenting with genital warts,[3] the condition was still thought to be relatively uncommon until two groups working independently in Canada and Finland described cytological changes in cervical smears suggestive of wart virus infection.[4 5] Meisels found evidence of wart virus infection in over 1% of smears from the routinely screened population and suggested that 70% of cases previously diagnosed as mild dysplasia might in fact be reassigned to a wart virus infection category.[6] Describing histological changes consistent with a diagnosis of wart virus infection, Reid found evidence of human papillomavirus infection in over 90% of biopsy specimens from patients with cervical intraepithelial neoplasia and invasive cancer.[7] The apparent increase in the prevalence of cervical wart virus infection is explained by detection of a previously unrecognised "flat wart" lesion, not visible with the naked eye but seen with the increased magnification of colposcopy.[4] On colposcopy, morphological changes other than exophytic condylomata acuminata have been described as evidence of human papil-