TREATMENT OF PRIVATIONAL LATE RICKETS AND OSTEOMALACIA WITH THE VITAMINS D

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INTRODUCTION

A great deal of experimental evidence has led to the view that 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) is the ultimate, active hormonal form of the native vitamin. Early clinical studies suggested that it may provide adequate "replacement" therapy in children (1) and adults (2) with vitamin D deficiency. Not all data are in agreement however. Histiomorphometric analysis has suggested that $1,25(OH)_2D_3$ and 1α-hydroxyvitamin D_3 (1α-OH D_3) do not produce adequate mineralization of osteoid in either vitamin D deficiency (3) or in renal osteodystrophy (4): furthermore doses of $1,25(OH)_2D_3$ as high as 2.5 µg/day did not increase renal tubular phosphate reabsorption in privational disease despite suppression of immuno-reactive parathyroid hormone (iPTH) levels (3). Inadequacy of these responses was judged in comparison with results of treatment with 25-hydroxycholecalciferol (25-OH D_3) and with a combination of $1,25(OH)_2D_3$ and 24,25-dihydroxycholecalciferol ($24,25(OH)_2D_3$). These workers concluded that other vitamin D metabolites had an important part to play in bone mineralization. While $24,25(OH)_2D$ is inactive in most experimental situations certain data have suggested that it may by itself promote both intestinal absorption of radioactive calcium and very transient positive calcium and phosphorus balance in humans (5). Further work is forthcoming to begin to resolve these discrepancies.

Systematic comparison of the vitamins D during metabolic balance studies in healing osteomalacia, perhaps the most direct and quantitative index of response to therapy, has not been reported. One major difficulty is the degree of individual variation in response to any one form of treatment. This, together with the number of patients and length of follow-up required, has meant that we do not even know if there is either a minimal, or an optimal, healing dose of vitamin D. There is also more than one form of effective therapy. Artificial ultra-violet light (UVL), given to the limits of tolerance, produces a brisk rise in plasma 25-OH D levels (6) which was similar to that produced by oral vitamin D in a dose of 250 µg daily but less than that produced by 25-OH D_3 itself in a dose of 40 µg daily (7). Both UVL and 25-OH D_3 rapidly heal the osteomalacia occasionally seen in epileptic patients treated with anticonvulsant drugs, another form of "privational" osteomalacia. "Good" healing is easily recognizable clinically. In order to see first if it was possible to establish quantitative criteria for this unscientific observation and if so, second, to compare the

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effects of the other vitamins D, we have analyzed results during treatment of privational osteomalacia and late rickets (nutritional and anticonvulsant) with oral vitamin D, UVL and 25-OH D_3 on the one hand, and with different doses of $1,25(OH)_2D_3$, 1α-OH D_3 and $24,25(OH)_2D_3$ on the other.

PATIENTS AND METHODS

Although principles and practice of metabolic balance have been established for over 30 years (8), we confined our analysis to patients from 2 centres employing identical balance methods in order to minimise possible technical variation. Successive 3, 4 or 6-day faecal collection periods were separated by an oral carmine marker and measured faecal mineral excretion within these periods was corrected for recovery of an internal marker, taken with each meal, of barium sulphate (studies prior to 1970) or cuprous thiocyanate. Simultaneous calcium and phosphorus balances were always performed, each as an internal check on the other and in order to measure simultaneous changes in renal tubular phosphate reabsorption.

Details of 10 patients with nutritional or anticonvulsant osteomalacia whose results are compared in the present study have already been reported in the literature and are shown in Table 1. Details of 10 further patients, all of Asian origin with nutritional late rickets or osteomalacia are given in Table 2. All presented with symptoms of their condition: hypocalcaemia was recorded in all of them and 9 out of 10 had elevated alkaline phosphatase relative to their age; 9 out of 10 had either rickets or Looser zones on X-ray and osteomalacia was confirmed histologically in the single patient with normal skeletal X-rays. No patient had detectable impairment of renal glomerular function relative to age.

RESULTS

Maximum positive calcium balances, during the period of study, in relation to calcium intake is shown in Tables 1 and 2. All patients in Table 1 had appropriate phosphorus retention (not shown in the table). Results with vitamin D, UVL and 25-OH D_3, on the one hand, and with 1α-OH D_3, $1,25(OH)_2D_3$ and $24,25(OH)_2D_3$ on the other are shown in Fig. 1: data from patients B.P., S.K. and B.D. are represented twice, first after $24,25(OH)_2D_3$ or low-dose 1α-OH D_3 and $1,25(OH)_2D_3$, and second after higher-dose $1,25(OH)_2D_3$. Despite a variable calcium intake all patients receiving vitamin D_2, UVL and 25-OH D_3 showed calcium retention equal to or greater than 40% of intake with values ranging up to a maximum of 82%. The response of 2 patients at more extreme levels of intake (10.3 and 72 mmol/d) suggests that this minimum may hold good over a fairly broad range of physiological calcium intake.

TABLE 1 DETAILS OF PUBLISHED* METABOLIC BALANCE DATA DURING TREATMENT OF NUTRITIONAL OR "ANTI-CONVULSANT" OSTEOMALACIA (OR LATE RICKETS) WITH VITAMIN D_2, UVL AND 25-OH D_3

Treatment	Calcium balance				Reference
Vitamin D_2	Intake (µg/d)	Maximum retention during study µg/d	when noted (d)	retention/intake (%)	
250 µg/d	2880	1150	(weeks)	40%	Case 1, ref. (9)
"	414	169	from 12 days	41%	Case 3, " "
"	1312	1072	" 12 "	82%	Case 4, " "
45 µg/d	1207	592	" 12 "	49%	Case 2, ref. (10)
UVL	1209	550	" 8 "	45%	Case 2, ref. (11)
"	1400	1100	" 8 "	79%	Ref. (12)
"	1300	540	" 8 "	42%	Case 2, ref. (13)
"	900	800	" 16 "	79%	Fig. 3, ref. (6)
25-OH D_3					
40 µg/d	1060	500	" 8 "	47%	Case 1, ref. (14)
10-40 µg/d	980	410	" 12 "	42%	Case 2, " "

* Data collected from the Metabolic Ward, University College Hospital, London, W.1.

TABLE 2 DETAILS OF METABOLIC BALANCE STUDIES DURING TREATMENT OF NUTRITIONAL OSTEOMALACIA (OR LATE RICKETS) WITH 25-OH D_3, $1,25(OH)_2D_3$, 1∝-OH D_3 and $24,25(OH)_2D_3$

Patient Age ♀ Sex	Treatment	Calcium balance (mmol/d)				Phosphorus balance (mmol/d) (simultaneous with max. calcium)
		Intake	Maximum retention mmol/d	when noted	Retention (%) Intake	
R.K. 18 F	1∝-OH D_3, 0.25 - 0.5 µg/d	25.4	4.2	from 8 days	15%	4.9
B.P. 63 M	1∝-OH D_3:0.5 µg/d 8 days, $1,25(OH)_2D_3$: 0.5 µg 4 days, 1.0 µg 4 days, 2.0 µg 4 days	32.9	3.9	" 12 "	12%	- 1.7
			13.2	" 20 "	40%	11.9
K.J. 27 F	$1,25(OH)_2D_3$, 1 µg/d	28.8	15.0	at 6 weeks	52%	11.2
M.M. 28 F	1∝-OH D_3: 2 µg/d	33.7	8.9	from 6 days	27%	5.9
K.G. 39 F	$1,25(OH)_2D_3$: 2 µg/d	29.5	13.1	" 8 "	44%	5.7
B.M. 22 F	$1,25(OH)_2D_3$: 1 µg/d	22.2	12.6	at 2 months	57%	9.2
S.K. 15 F	$24,25(OH)_2D_3$: 5 µg/d, $1,25(OH)_2D_3$: 1 µg/d added on day 10	32.9	2.3	from 6 days	7%	7.3
			14.3	" 12 "	43%	12.6
B.D. 72 M	$24,25(OH)_2D_3$: 2 µg 8 days, 4 µg/d 8 days, 8 µg/d 4 days $1,25(OH)_2D_3$: 2 µg/d substituted day 17	33.3	1.8	from 12 days	5%	- 0.6
			14.7	" 20 "	40%	6.9
P.P. 15 M	25-OH D_3, 40 µg/d	39.5	27.7	from 8 days	71%	16.8
S.P. 17 F	25-OH D_3, 40 µg/d	28.0	20.6	from 8 days	74%	15.2

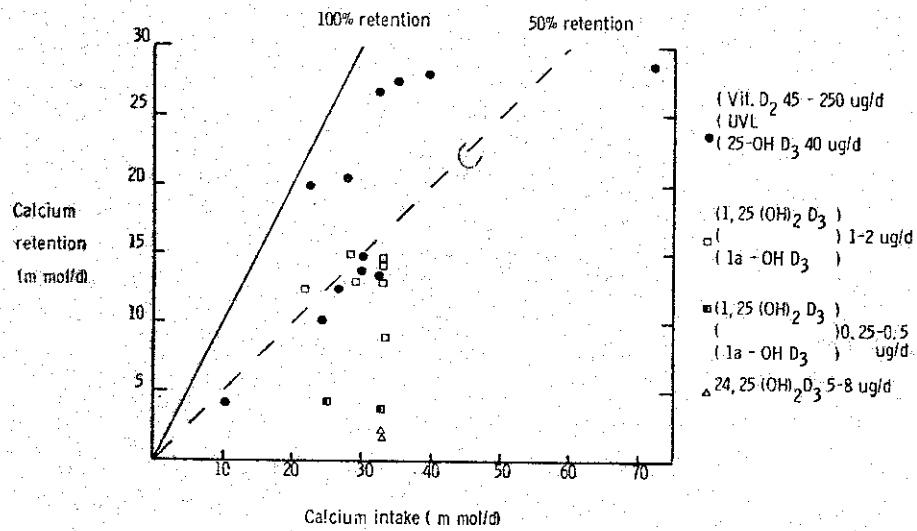

Fig. 1. Relationship between calcium retention and calcium intake during treatment of privational late rickets and osteomalacia with the vitamins D.

1,25$(OH)_2D_3$ and 1∝-OH D_3 in doses below 1 µg daily produced "inadequate" mineral retention according to these criteria: in patient M.M. whose healing on 2 µg daily also appeared inadequate balance was not continued beyond 3 x 3-day treatment periods and her apparently poor mineral retention may conceivably reflect the shorter observation period rather than inadequate treatment.

Treatment with 24,25$(OH)_2D_3$ alone produced no significant improvement (figs. 2 & 3), values for retention being within statistical limits of zero change. Substitution or addition of 1,25$(OH)_2D_3$ produced rapid positive balance.

Figures 4 and 5 show clearly that 1,25$(OH)_2D_3$ alone in a dose of 1 µg daily is sufficient to heal X-ray signs of osteomalacia: it also fully relieved symptoms in these 2 patients. Patient R.K. who received only 0.25 µg daily 1∝-OH D_3 showed little or no change in her Looser zones over 6 weeks, nor improvement in her symptoms.

Comparison of urine calcium excretion in the 2 groups is shown in Fig. 6: urine calcium loss was significantly higher in patients receiving 1∝-OH D_3 and 1,25$(OH)_2D_3$.

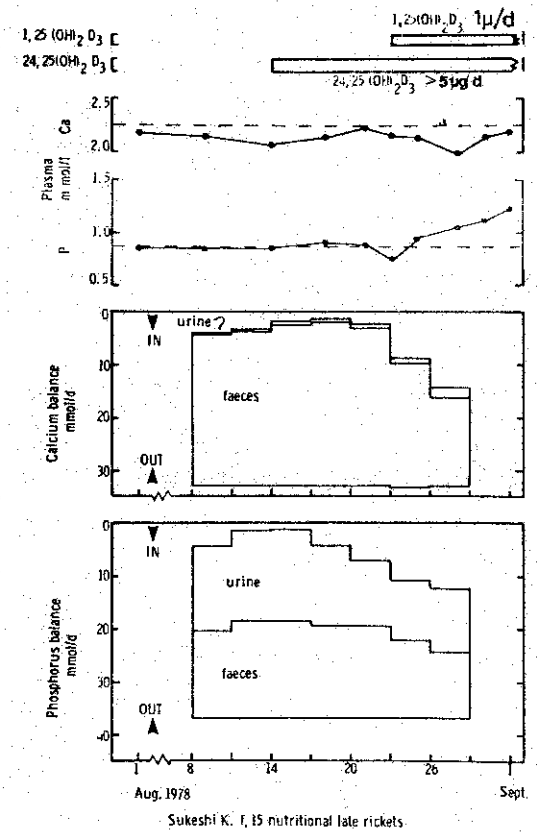

Fig. 2. Metabolic balance during treatment with $24,25(OH)_2$ with subsequent addition of $1,25(OH)_2D_3$. Note the absence of effect of $24,25-(OH)_2D_3$ on calcium retention and the marked persisting hypocalcaemia during early healing with $1,25(OH)_2D_3$. There appears to be a change in P balance on $24,25(OH)_2D_3$ and very rapid calcium retention on starting $1,25(OH)_2D_3$.

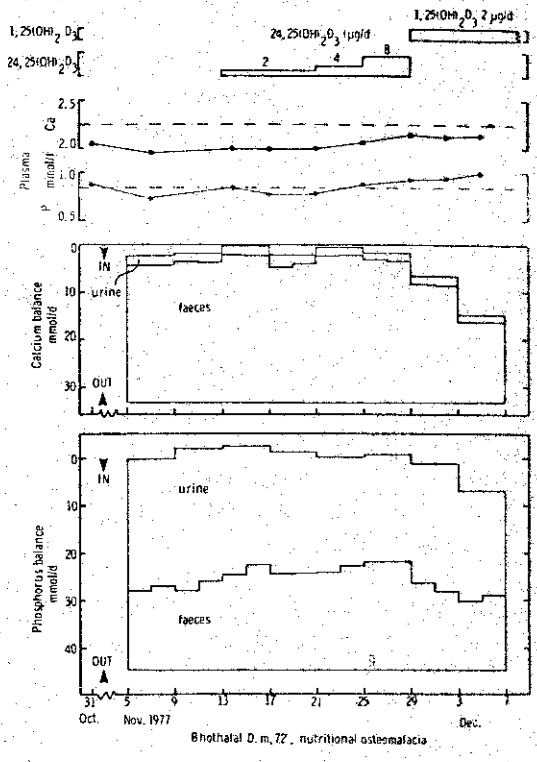

Fig. 3. Metabolic balance during treatment with $24,25(OH)_2D_3$ with later substitution of $1,25(OH)_2D_3$. Note the pattern as in Fig. 2 despite extreme age difference, no effect of $24,25(OH)_2D_3$ on calcium balance but a possible rise in renal phosphorus reabsorption; there is persistent hypocalcaemia despite calcium and phosphorus retention which are notably rapid.

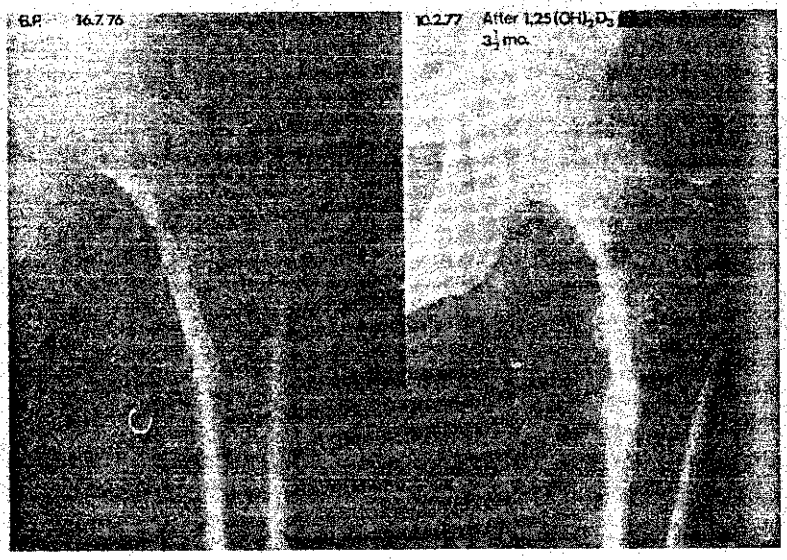

Fig. 4.

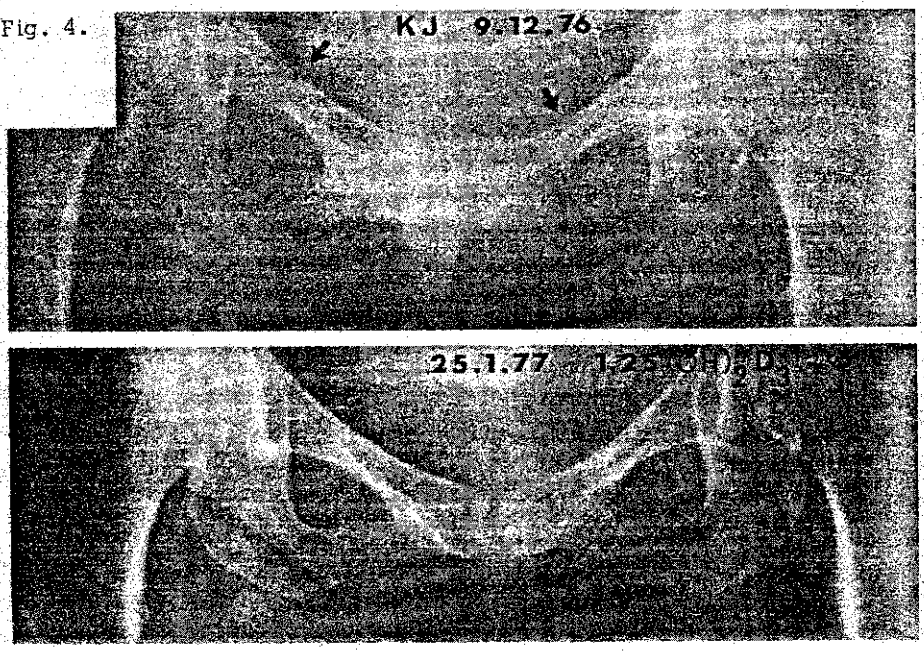

Fig. 5. Radiological healing of Looser zones in 2 patients receiving only 1,25$(OH)_2D_3$ 1 µg daily as supplement to a grossly vitamin D-deficient diet (< 30 i.u. daily).

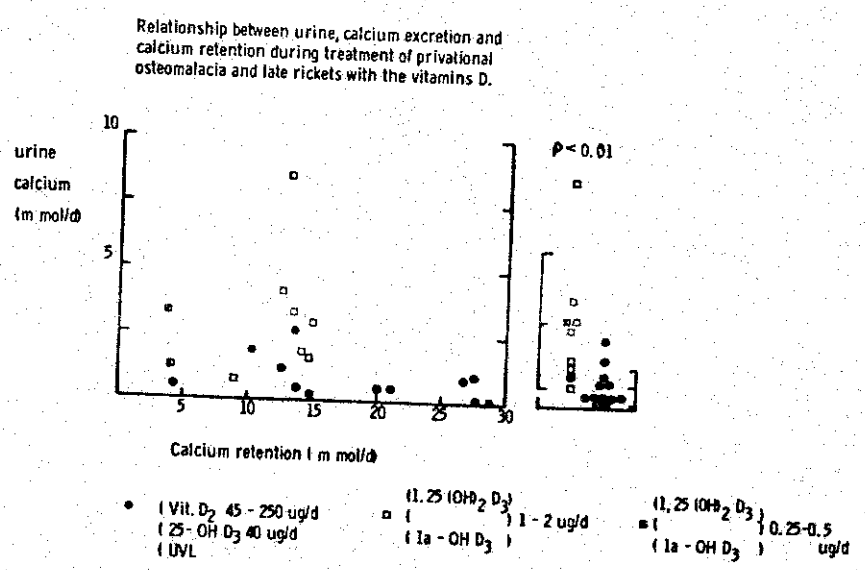

Fig. 6.

A number of other features were apparent from these studies: persistent hypocalcaemia despite good mineral retention occurred in 4 of the 7 patients who responded well to 1∝ -OH D_3 and 1,25$(OH)_2D_3$ (B.P., K.J. - even at 6 weeks -, B.D. and S.K.). Rise in renal tubular phosphate reabsorption, shown by rising plasma phosphorus or falling urine phosphorus (usually but not always both) paralleled quite closely the degree of calcium and phosphorus retention. A small increase in renal phosphorus reabsorption was detectable during 24,25$(OH)_2D_3$ treatment alone in 2 patients (Figs. 2 and 3). A transient rise in alkaline phosphatase was seen in only 2 patients. Simultaneous magnesium balance in one patient (B.P.) showed increasing positive balance associated with falling urine Mg but no other change.

DISCUSSION

The present study shows clearly that 1∝ -OH D_3 and 1,25$(OH)_2D_3$ alone may heal privational osteomalacia in adults, clinically, biochemically and radiologically, in agreement with findings in children (1) but in some

conflict with a recent report in adults (3). However it is noteworthy that very high doses of 1∝-OH D_3 and 1,25$(OH)_2D_3$ in comparison with vitamin D_2, UVL and 25-OH D_3 are required for adequate healing according to the criteria given. It seems correct to describe these doses as "very high" because they have been associated with reports of hypercalcaemia in disorders such as osteoporosis and hypoparathyroidism whereas UVL and vitamin D_2 not in excess of 250 µg daily have never been incriminated in intoxication in the absence of hypersensitivity to the vitamin.

Progressive mineral retention with persisting hypocalcaemia has long been an occasional feature of early healing or of low vitamin D dosage and this was seen in our patients treated with 1∝-OH D_3 and 1,25$(OH)_2D_3$. In other respects, rise in plasma phosphorus, rise in renal tubular phosphate reabsorption, plasma alkaline phosphatase changes (transient rise or rate of fall) and improvement in symptoms, changes all paralleled the early rate of mineral retention. Urine calcium excretion rose above control levels during initial treatment in 6 out of 8 patients treated with 1∝-OH D_3 or 1,25$(OH)_2D_3$, being significantly higher than in those whose treatment provided 25-OH D. However, the "excess" urine calcium was not in most patients sufficient to account for the relative poverty of mineral retention.

Relative to their intoxicating potency, then, 1∝-OH D_3 and 1,25$(OH)_2D_3$ are less effective in the treatment of deficiency disease than vitamin D, UVL and 25-OH D_3 and the possible reasons need to be considered. A requirement for vitamin D metabolite(s) in addition to 1,25$(OH)_2D_3$, perhaps 24,25$(OH)_2D_3$, has been suggested (3-5). Our findings show that 24,25$(OH)_2D_3$ <u>by itself</u>, in doses up to 8 µg daily, plays no detectable part in healing osteomalacia although a small rise in renal tubular phosphate reabsorption deserves further study. Administered 24,25$(OH)_2D_3$ is presumably available for 1∝-hydroxylation to 1,24,25-trihydroxyvitamin D in humans with normal renal function. Our findings conflict with other preliminary balance data (5), but those patients, one with osteogenesis imperfecta and one with hypophosphataemic osteomalacia, were presumably replete with other vitamin D metabolites. Serious consideration must be given to the unphysiological nature of administering once or twice daily a bolus of potent hormone, levels of which normally appear closely regulated within a narrow range. Nevertheless present data do not exclude a role of other vitamin D metabolites in human bone mineralization. The short-term response to 1,25$(OH)_2D_3$ when following treatment with 24,25$(OH)_2D_3$ in patients S.K. and B.D. was rapid and balances were not prolonged sufficiently to exclude ultimate potentiation of the response to 1,25$(OH)_2D_3$. Further studies are in progress to establish whether mineral retention with low doses of 1,25$(OH)_2D_3$ is enhanced by added 24,25$(OH)_2D_3$.

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