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THE RESPONSE TO 1,25-DIHYDROXYCHOLECALCIFEROL AND TO DIHYDROTACHYSTEROL IN ADULT-ONSET HYPOPHOSPHATAEMIC OSTEOMALACIA

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Summary

The biochemical changes observed in a patient with adult-onset hypophosphataemic osteomalacia after three weeks treatment with 1,25-dihydroxycholecalciferol (1,25-$(OH)_2D_3$) followed by dihydrotachysterol (DHT) are reported. The treatment with 1,25-$(OH)_2D_3$ resulted in restoration of intestinal phosphate absorption to normal with a small rise in plasma phosphate concentration; there was no significant change in tubular reabsorption of phosphate. The tubular reabsorption of bicarbonate, which was initially low, returned almost into the normal range with normalisation of plasma bicarbonate concentration. Aminoaciduria decreased. There were no changes in plasma or urinary calcium but immunoreactive parathyroid hormone (i-PTH) which was initially elevated fell but still remained above the normal range. These changes were maintained after replacing the 1,25-$(OH)_2D_3$ treatment with dihydrotachysterol (DHT).

Introduction

Adult non-familial hypophosphataemic osteomalacia presents clinically with widespread bone pains, myopathy and occasionally with marked loss of height due to vertebral collapse. The biochemical features include persistent hypophosphataemia with a marked decrease in the tubular reabsorption of phosphate, normal plasma and urinary calcium, raised alkaline phosphatase activity, increased urinary excretion of amino acids particularly glycine and in some patients there is a renal glycosuria. The primary defect has not been clearly identified but is considered to be either a failure of phosphate transport or a disturbance in vitamin D metabolism, possibly a defect in renal 1-hydroxyla-

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tion and formation of the active dihydroxy metabolite [1]. The response to the administration of the active dihydroxy metabolite 1,25-$(OH)_2D_3$ in a patient with this rare syndrome has been studied. The studies were repeated after substituting 1,25-$(OH)_2D_3$ with DHT.

Patient and methods

The patient was a 49-year-old woman who had been diagnosed as having this syndrome 5 years earlier. The diagnosis at that time had been based on the history, physical examination, biochemical and bone histology findings. She was on oral treatment with daily doses of calciferol 5 mg, calcium supplement (8 g Ossopan) and disodium hydrogen phosphate 20 g. While on this regimen, she had sustained more than one major fracture involving the femora with exacerbation of her bone pains and muscle weakness.

Before the current study basal measurements were obtained while on her previous treatment regimen (Tables I and II). Intestinal phosphate absorption was assessed using an oral phosphate load [2]. After ammonium chloride loading, the tubular reabsorption for bicarbonate was estimated using oral loads of sodium bicarbonate to avoid volume expansion. (Varghese, Z., Moorhead, J.F. and Wills, M.R., unpublished). Studies were repeated after 3 weeks of oral treatment with 1,25-$(OH)_2D_3$ (1 μg/day) followed with DHT (1 mg/day) for a further 3 weeks. All studies were carried out under standard metabolic conditions.

Results

The substitution of 1,25-$(OH)_2D_3$ for the calciferol in the treatment regimen was associated with improvement symptomatically in muscle weakness and also in some of the biochemical values, all of which were maintained during the treatment with DHT (Table I). The intestinal phosphate absorption profile improved markedly and was within normal limits following the two treatment periods (Fig. 1); there was no change in the tubular reabsorption of phosphate.

TABLE I

BIOCHEMICAL CHANGE WHILE ON TREATMENT WITH CALCIFEROL (BASE LINE), 1,25-DHCC AND DHT

	Plasma			
	Calcium (mmol/l)	Phosphate (mmol/l)	Bicarbonate (mmol/l)	Chloride (mmol/l)
Base line on calciferol	2.63	0.29	20.0	106
On 1,25-DHCC	2.50	0.58	26.0	103
On DHT	2.63	0.65	25.0	103
Normal values	2.42 ± 0.185	1.16 ± 0.28	24—32	95—105

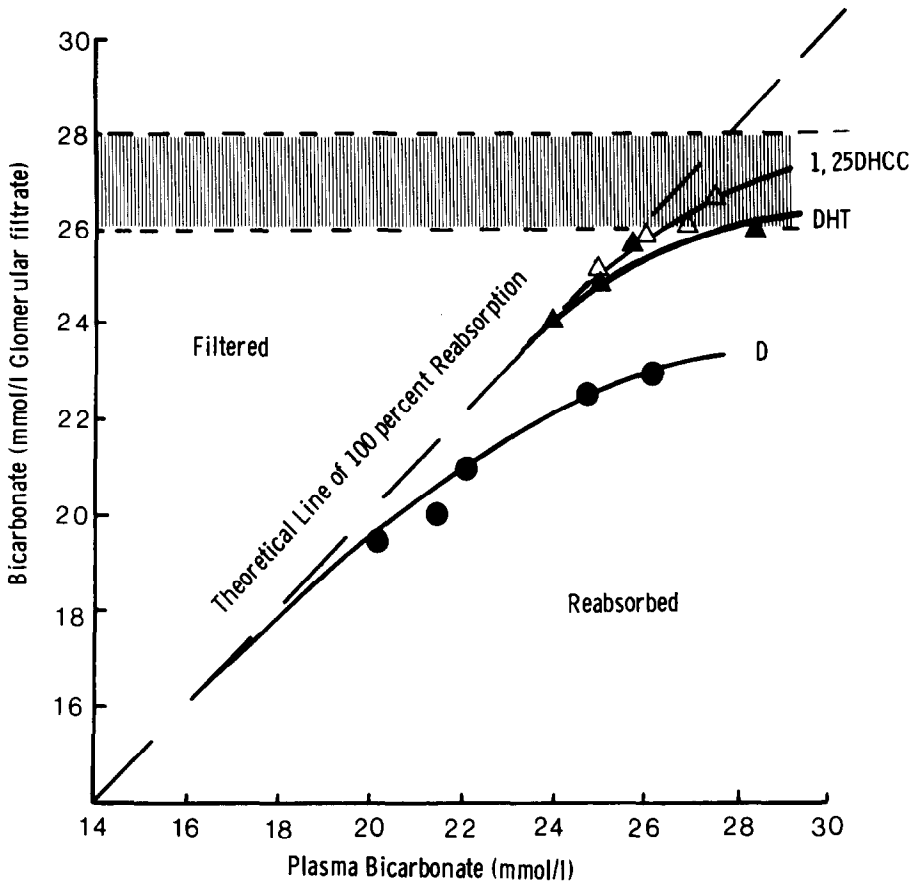

Fig. 2. Maximum tubular reabsorption of bicarbonate while on treatment with calciferol (D_2), 1,25-$(OH)_2D_3$ and DHT. Hatched area represents the normal range.

Urine acidification following oral ammonium chloride was normal throughout the study. The renal tubular reabsorption of bicarbonate was initially reduced and improved following the two treatment periods (Fig. 2). The quantitative plasma amino acid profile was within the normal range throughout the study

Plasma (continued)			Urine		
i-PTH (ng/ml)	25(OH)D_3 (ng/ml)	Alk. K.A. (*I*/dl)	C_{Cr} (ml/min)	C_{PO_4} (ml/min)	% TRP
1.88	198	58	94.3	68.9	27
1.32	79	63	111.7	78.3	30
1.40	62	66	82.8	59.7	28
<9	6—51	3.0—13.0		15	>85

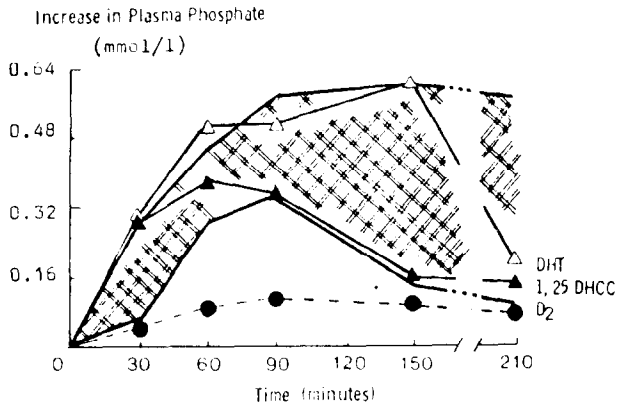

Fig. 1. Phosphate absorption profiles while on treatment with calciferol (D_2), 1,25-$(OH)_2D_3$ and DHT. Hatched area represents the composite absorption profile from 12 normal subjects.

TABLE II

URINE AMINO ACID PROFILE WHILE ON TREATMENT WITH CALCIFEROL, 1,25-DHCC AND DHT

	Threonine	Serine	Glutamine	Glycine	Alanine	Valine
Base line (on calciferol)	452	634	531	10 186	872	190
On 1,25-DHCC	306	520	122	4 108	615	133
On DHT	323	485	246	4 089	334	80
Normal values (μmol/l24 h)	150 ± 40	300 ± 70	100 ± 50	1 000 ± 500	200 ± 100	80 ± 20

period. There was an increased urinary excretion of some amino acids with a reduction towards normal following treatment (Table II).

Discussion

The finding of phosphorous malabsorption in our patient with this rare syndrome is in agreement with the report of Peacock et al. [3]. Both 1,25-$(OH)_2D_3$ and DHT succeeded in correcting this defect in our patient in the doses used, and this was associated with an increase in plasma phosphate concentration. There was, however, no effect on the renal tubular reabsorption of phosphate. Glorieux et al. [4] treated one patient with X-linked hypophosphataemic rickets with 1,25-$(OH)_2D_3$ for a short period with an inadequate response. Peacock et al. [3] used 1α-hydroxy vitamin D-3 in larger doses (up to 6 μg per day) in the treatment of a mixed group of patients with different varieties of hypophosphataemic rickets and reported improvement in intestinal calcium and phosphorus absorption with a progressive rise in plasma concentration and healing of bones. The renal tubular reabsorption of phosphate showed no change in some of their patients while in others it only increased when the bones had almost healed.

In the patient reported here there was an increased plasma level of i-PTH and the presence of mild metabolic acidosis prior to treatment with 1,25-$(OH)_2D_3$. The metabolic acidosis was due to a proximal renal tubular leak of bicarbonate and not to a distal tubular defect. The cause of the hyperparathyroidism in our

patient and its relation to the pathogenesis of the syndrome of hypophosphataemic rickets is debatable. Albright [5] proposed that the primary event in vitamin D resistant rickets was a decreased intestinal absorption of calcium because of resistance to vitamin D. He suggested that the phosphaturia was the result of the secondary hyperparathyroidism. Subsequently other workers as well as Albright have demonstrated hyperplastic changes in the parathyroid glands [6,7] or an elevation in serum i-PTH [8]. It should, however, be stressed that these studies were on patients with the familial type of hypophosphataemic rickets.

Chronic phosphate depletion alone is known to lead to a decrease in renal bicarbonate reabsorption [9,10]. It seems in our patient two factors at least were responsible for the mild acidosis namely the increased circulating levels of parathyroid hormone and chronic phosphate depletion. The correction of the acidosis after three weeks treatment with 1,25-$(OH)_2D_3$ and DHT is of interest. A direct effect of the active metabolites of vitamin D on bicarbonate reabsorption is possible. Siegfried et al. [11] demonstrated that in intact dogs the acute administration of 25-hydroxycholecalciferol resulted in a significant increase in bicarbonate reabsorption but that this did not occur in thyroparathyroidectomized dogs. It is possible that the reduction in i-PTH levels after treatment with 1,25-$(OH)_2D_3$ and DHT also could have contributed to the improvement in the renal bicarbonate reabsorption. A third possible factor could be the improvement in the state of phosphate depletion after the correction of the intestinal absorption defect.

It is known that phosphate regulates the hydroxylation of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol in the normal kidney [12]. In our patient the presence of long-standing hypophosphataemia together with elevated levels of circulating i-PTH and normal renal function should have resulted in production of adequate amounts of 1,25-$(OH)_2D_3$ and normal intestinal absorption of both calcium and phosphorous. The correction of the intestinal defect following 1,25-$(OH)_2D_3$ and DHT administration to our patient suggests that there was an underlying defect in 1α-hydroxylation in the kidney coupled with an intrinsic phosphate leak.

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