X linked hypophosphataemia: treatment, height gain, and nephrocalcinosis

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Abstract
The clinical data of 18 patients with X linked hypophosphataemia were analysed retrospectively. The height data were expressed as SD scores. There was no difference in the final height of patients treated with vitamin D (or 1,25-dihydroxyvitamin D) and phosphate for at least two years (n=12) and that of 16 hypophosphataemic family members who had never been treated. The mean final SD score (−2·07) of treated patients, however, was significantly higher than the value before treatment (−2·79), which indicated an average absolute height gain of 4–4·5 cm compared with the expected height values. Six of the treated patients developed ultrasonographically detectable nephrocalcinosis with normal renal function. The daily phosphate intake and excretion of patients with nephrocalcinosis was significantly higher than that of patients with normal renal morphology. There was no difference in the doses of vitamin D between the two groups. The average urinary calcium:creatinine ratio of the two groups was similar to and below the hypercalciuric 0·6 mmol:mmol limit. The group with nephrocalcinosis, however, had a higher incidence of hypercalciuric episodes than the group without nephrocalcinosis (12 in 130 observations compared with six in 334 observations, respectively). The benefits and risks of treatment of patients with X linked hypophosphataemia must be further evaluated. The high dose of phosphate seems to be an important factor in the development of nephrocalcinosis in this group of patients.

Familial hypophosphataemia is a type of hereditary, vitamin D resistant, rickets that is characterised by sustained hypophosphataemia, relative hyperphosphaturia, normocalcaemia, rachitic bone changes, and growth retardation.[1-5] The inheritance is X linked dominant.[3 4] Hypophosphataemia is the result of impaired renal reabsorption and intestinal absorption of phosphate and according to recent data inappropriate low serum concentrations of 1,25-dihydroxyvitamin D (1,25-DHVD) either in absolute terms or compared with the serum phosphate concentration.[5-12] The conventional treatment of X linked hypophosphataemia consists of high doses of vitamin D and oral phosphate supplements. Vitamin D was replaced in recent studies by the active metabolite 1,25-DHVD.[6 7 13] In addition, thiazide diuretics have also been used to reduce urinary losses of phosphorus and calcium.[14]

The value of these treatments has, however, recently been questioned.[15] In addition, serious side effects such as osteomalacia[16] and nephrocalcinosis[17 18] have been reported. Transient hypercalciuria and hypercalcaemia are well known side effects of high doses of vitamin D and potent D vitamin analogues.[18] Calcium, however, is not the only constituent responsible for the growth of crystals in supersaturated urine. High doses of phosphate could also lead to the formation of relatively insoluble salts by at least two mechanisms: firstly, by the formation of calcium phosphate,[19 20] and secondly by provoking enteric hyperoxaluria by intestinal binding of calcium.[21]

The aim of the present study was to analyse the effects of the combined treatment with vitamin D and phosphate on the growth of patients with X linked hypophosphataemia, to find out the incidence of ultrasonographic renal calcification,[18] and to elucidate the role of the treatment in renal calcification.

Patients and methods
Between 1974 and 1989, 18 patients with X linked hypophosphataemia were treated with combined vitamin D (or 1,25-DHVD) and oral phosphate in our clinic.[22] Sixteen adult hypophosphataemic relatives who had not been treated during the growth period served as controls.

All treated patients were diagnosed by the presence of rachitic bone changes, the persistence of hypophosphataemia, relative hyperphosphaturia, normocalcaemia, high alkaline phosphatase activity, and normal serum concentrations of parathyroid hormone.[5 22] X linked dominant inheritance was confirmed by analysis of the pedigrees.

All patients visited our outpatient clinic at regular intervals: infants and young children every three weeks to two months and adolescents and young adults every three to six months depending on the intensity of treatment. Urinary excretion of calcium and phosphate, serum calcium and phosphate concentrations, and creatinine clearance were measured routinely. Calcium, phosphate, and creatinine were estimated by routine laboratory methods.

Hypercalcaemia was defined as a serum calcium concentration of over 2·75 mmol/l. Hypercalciuria was defined as urinary calcium:creatinine ratio above 0·6 mmol:mmol.[23]

All heights were expressed as standard deviations from the mean of the chronological age (SD scores).[15] All patients were recalled for ultrasonographic scanning of their kidneys. The examinations were performed and interpreted by one of us (PFH) without knowledge of the clinical state or details of the treatment.

Statistical analysis was by Student's *t* test for unpaired and paired data, and the χ^2 test.

Results
A total of 464 clinical observations of the 18 patients were considered. The mean age at the start of treatment was 5·8 years (range 5 months

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Table 1   Treatment with phosphate, vitamin D, and 1,25-DHVD in patients with X linked hypophosphataemia at different ages

	Age group (years)							
	0–3 (n=6)		3–14 (n=12)		14–18 (n=15)		>18 (n=11)	
	No of patients	Mean (SD) dose	No of patients	Mean (SD) dose	No of patients	Mean (SD) dose	No of patients	Mean (SD) dose
Phosphate (mg/kg/day)	6	107 (48)	12	74 (30)	15	53 (30)	11	37 (19)
Vitamin D (units/kg/day)	3	1370 (798)	11	902 (405)	13	580 (365)	8	198 (108)
1,25-DHVD (ng/kg/day)	3	35 (6·4)	2	21 (5)	2	5 (0·6)	2	5 (0·3)

– 14·5 years), and at the time of the last visit 15·9 (range 3–24·5) years. The mean treatment time was 8·4 years (range 1–15), and the mean length of treatment during the growth period was 6·8 years (range 1–14).

Patients were usually treated with both oral phosphate supplements and vitamin D (or 1,25-DHVD). The daily doses relative to body weight of vitamin D, 1,25-DHVD, and phosphate were calculated for each patient for each visit to the clinic. Table 1 summarises the average doses calculated from these data for infants, children, adolescents, and adults.

In the age group 3–14 years one patient was changed from vitamin D to 1,25–DHVD, and his vitamin D and 1,25-DHVD doses are therefore both represented in the table. In the age group over 18 years, one patient received phosphate alone (table 1).

GROWTH DATA

The final height (expressed as SD score) of 16 patients with X linked hypophosphataemia who had received no treatment and 12 treated patients who reached their final height at the time of the study are compared in fig 1. There is no significant difference between the two groups (corresponding mean (SD) scores for patients who had received no treatment −2·27 (0·48), and for patients who had been treated −2·07 (0·47).

SD score before treatment and the last recorded score of the 12 patients who were treated for longer than two years and had already reached adulthood at the end of the study are shown in fig 2. The

mean SD score increased from a pretreatment value of −2·79 to −2·07 (p<0·02, Student's t test for paired data). The same significant difference could be noted when the data of all 16 patients treated for longer than two years were compared (p<0·02).

CLINICAL DATA

Six of the 18 patients had abnormally increased echogenicity of the renal pyramids (nephrocalcinosis), and in four there was also acoustic shadowing (fig 3). All six patients received the most intensive treatment during the first two years of observation, which is therefore further analysed. Patients with nephrocalcinosis had significantly higher relative daily doses of phosphate than patients with normal renal ultrasonography (136·4 (30·4) mg/kg/day compared with 69·9 (22·1), p<0·01) (fig 4). There was no statistical difference between the doses of vitamin D and 1,25-DHVD in the two groups (fig 5).

There was no significant difference in the mean (SD) urinary calcium:creatinine ratio of patients with nephrocalcinosis and those with normal renal morphology (0·35 (0·19) and 0·22 (0·16) mmol: mmol, respectively). In contrast children with nephrocalcinosis had significantly higher phosphate:creatinine ratios (21·9 (11·9) and 9·1 (4·8) mmol:mmol, respectively; p<0·01).

The number of hypercalcaemic and hypercalciuric episodes is listed in table 2. One patient in each group had episode(s) of hypercalcaemia, which occurred three times in the patient with nephrocalcinosis. Hypercalciuria was observed at least once in all nephrocalcinotic patients but only in two of the 12 in the group who did not have
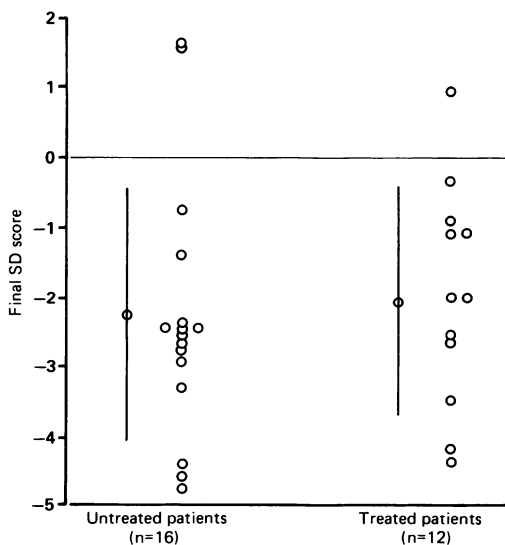

Figure 1   Growth of patients with hypophosphataemic rickets: adult height of 12 patients with X linked hypophosphataemia who were treated continuously and 16 patients who were never treated. The circle and vertical line indicate the mean (SD).
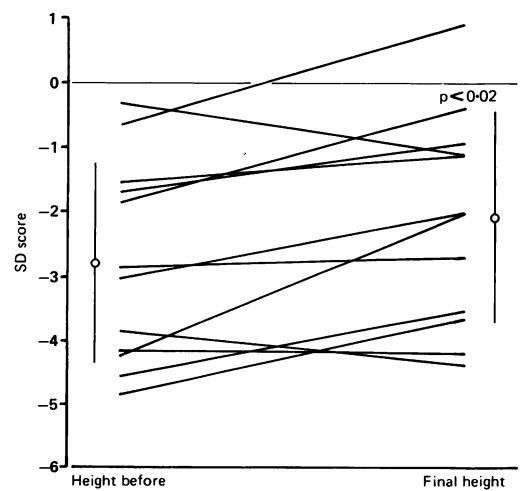

Figure 2   Growth of patients with hypophosphataemic rickets: height before treatment and final height of 12 adult patients with X linked hypophosphataemia who were treated for at least two years. The circle and vertical line indicate the mean (SD).
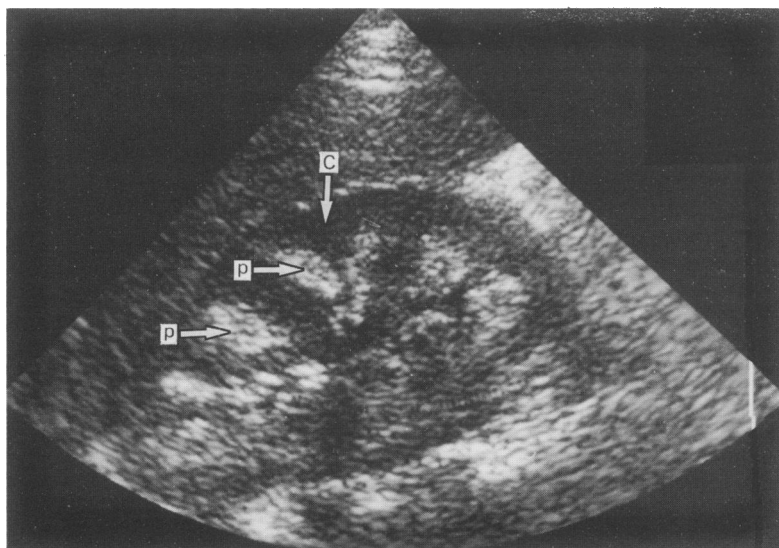
Figure 3 Typical increased echogenicity of renal pyramids in a patient with X linked hypophosphataemia treated with 1,25-DHVD and phosphate. C=cortex; p=renal pyramids.

Figure 5 Daily doses of vitamin D (open triangles) and 1,25-DHVD (open circles) in children with X linked hypophosphataemia during the first two years of treatment.

nephrocalcinosis. Episodes of increased urinary calcium excretion were observed in 9% of the investigations in the nephrocalcinosis group, whereas in the group with normal renal sonography it was detected in only 2% of all periods considered ($\chi^2=13.9$, p<0.01).

There was no significant difference between the urine output (expressed as minute volume) of patients with X linked hypophosphataemia with increased calcium excretion and an age matched control group of 18 healthy children (mean (SD) 0.93 (0.21) compared with 0.83 (0.29) ml/min/1.73m^2 respectively).

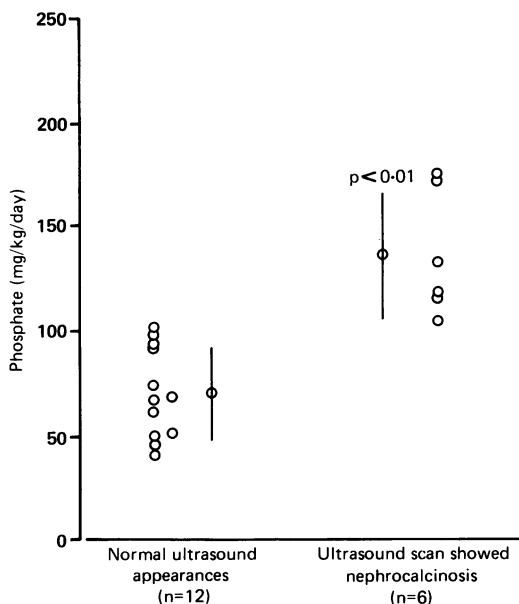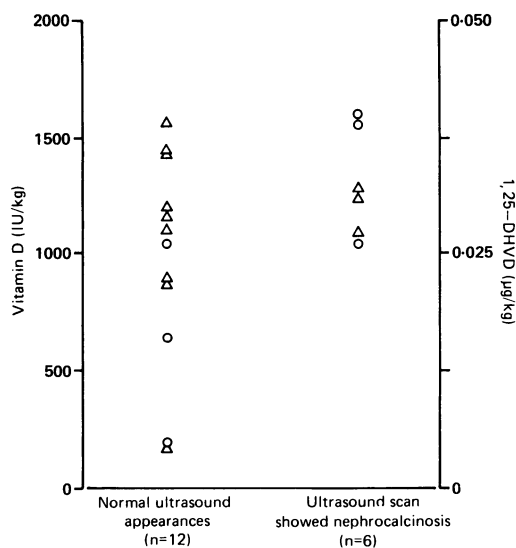Considering all the data, we found no correla-

Figure 4 Daily doses of oral phosphate supplementation in patients with normal ultrasound appearances and those showing nephrocalcinosis. The circles and vertical line indicate the mean (SD).

tion between phosphate dose or urinary phosphate excretion and the change in the SD score in general, and in patients with nephrocalcinosis in particular.

Discussion

There are conflicting data about the benefits of combined vitamin D (or 1,25-DHVD) and phosphate treatment in children with X linked hypophosphataemia. Some authors have not found that the treatment had any positive effect on growth.[15][16] Other reports, based on growth velocity or a smaller number of children, claimed to prove significant improvement in treated patients.[9][10][23][24] The comparison of treated and untreated patients could be biased by the fact that untreated patients might have had a milder form of the disease than treated patients. Indeed in our series two hypophosphataemic family members were only detected by laboratory investigation, because they had normal SD scores and no bone deformities. On the other hand, all treated patients were referred to us because of growth retardation and overt signs of rickets. Thus the evaluation of the final height showed that there was no difference between the average SD scores of treated and untreated adults, but in the treated group there was a significant improvement in the SD scores suggesting that treatment had some positive effect on growth.

In the early stages of nephrocalcinosis radiography often fails to detect calcium deposition. Renal ultrasonography seems to be a more sensitive non-invasive method of diagnosis in such cases. The diagnosis is possible even before detectable functional disturbances occur.[17][18] In the present study six of the 18 patients with X linked hypophosphataemia had ultrasonographically proved nephrocalcinosis with no overt signs of functional renal damage. Our data confirm those of Goodyear et al[18]:11 of their 23 patients with X

Table 2 Hypercalcaemia, hypercalciuria, and ultrasonographic changes in patients with X linked hypophosphataemia

Ultrasonographic pattern	No of patients/episodes of hypercalcaemia	No of patients/episodes of hypercalciuria	Total No of observations
Normal (n=12)	1/1	2/6	334
Showed nephrocalcinosis (n=6)	1/3	6/12	130

linked hypophosphataemia investigated had ultra-sonographically proved nephrocalcinosis with normal renal function.

Analysing the possible causes of calcium deposition in the kidneys, we found a significant difference in the daily phosphate intake and excretion between the nephrocalcinosis group and those with normal renal ultrasonography. The average calcium excretion did not differ between the two groups. The incidence of hypercalciuric episodes was higher in the nephrocalcinosis group, in which all patients had at least one episode of hypercalciuria (table 2). One patient with nephrocalcinosis had episodes of mild hypercalcaemia, while in the group without nephrocalcinosis only one single episode of hypercalcaemia occurred. Goodyear *et al*[18] put forward the hypothesis that increased calcium excretion was thus related to nephrocalcinosis.

In patients with idiopathic renal hypercalciuria the most common finding is recurrent renal stone formation and not nephrocalcinosis. In both the study of Goodyear *et al* and ours no clinical signs of nephrolithiasis were detected. Hypercalciuric patients had, however, constantly increased calcium excretion, whereas in X linked hypophosphataemia hypercalciuria is not a constant state; it was found in only about 10% of the collected urine specimens.

The high phosphate excretion constitutes another important difference between this group of patients and patients with hypercalciuria. Thus in patients with X linked hypophosphataemia the renal collecting ducts are filled continuously and the renal papillae are bathed in a fluid with a high concentration of phosphate. If hypercalciuria then occurs crystallisation will build up.

High phosphate intake may also cause secondary hyperoxaluria. In a recent study we showed a close association between the relative daily dose of phosphate and urinary oxalate excretion in patients with X linked hypophosphataemia.[21] The mechanism could be explained by the binding of calcium in the intestine and consequent hyperabsorption of oxalate.

Urinary calcium excretion of less than even the 0·1 mmol/kg/day limit could contribute to calcification according to the principles of complex equilibria, if other constituents of relatively insoluble calcium salts are present in excess.[19 20]

The spontaneous urine output of patients with X linked hypophosphataemia during periods of hypercalciuria did not differ substantially from that of the control group. This could be taken to indicate the absence of overt hypercalcaemia, but on the other hand absolute excretion of crystalloids is second only to urine volume as the other factor determining urine concentration and saturation. Thus patients with X linked hypophosphataemia—if treated with phosphate and vitamin D analogues—should be encouraged to drink large amounts of fluid and to avoid dehydration. Urinary calcium and phosphate excretion, and the concentration of other potential lithogenic substances should be studied to elucidate further the mechanism of renal calcium deposition in this group of patients.

The lack of correlation between high doses of phosphate and the change in height SD scores means that children receiving higher oral doses of phosphate do not necessarily grow better than patients on lower daily doses of 50–100 mg/kg phosphate. In this group with normal renal ultra-

sonography similar height was achieved without the risk of nephrocalcinosis.

In the light of the data on growth and on the side effects of treatment an even more careful evaluation of the individual data of patients is certainly indicated, but we do not see that the suggested discontinuation of the treatment of patients with X linked hypophosphataemia is justified.[15]

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