# Effects of Calcitriol and Phosphorus Therapy on the Growth of Patients With X-Linked Hypophosphatemia

The growth responses of patients with X-linked hypophosphatemia (XLH) to calcitriol and phosphorus ($PO_4$) therapy in relation to the patients' anthropometric characteristics and/or their pretreatment and posttreatment biochemistries are presented. Twelve consecutive patients whose therapy with calcium (Ca) and $PO_4$ exceeded 1.2 years were studied. The subjects consisted of 4 females and 8 males, whose ages at initiation of treatment ranged from 1.7 to 9.9 years. Diagnosis in each patient was confirmed by the presence of hypophosphatemia, renal phosphate wasting, normocalcemia, and a normal serum parathyroid hormone (PTH) level. Radiologic evidence of rickets was observed in all subjects except 1 patient, and bone biopsy revealed evidence of osteomalacia in all. Retrospective evaluation showed that 6 patients (group 1) presented with a height below the fifth percentile and 6 patients (group 2) presented with a height exceeding the fifteenth percentile. Sexual development and ages of the children in the 2 groups at initiation of treatment were not statistically different, but ages varied from 4.30 ± 0.98 years in group 1 to 7.00 ± 1.92 years in group 2.

Both groups were treated with calcitriol 30 to 65 mg/kg/d administered in a split dose regimen, and K-phos, 20 to 60 mg/kg/d into 4 divided doses during the waking hours. After adjusting the doses over a period of several months, the optimal combination was administered for a term of 1.2 to 8.1 years. The children were followed at 2- to 4-month intervals. At each visit, 24-h urine and creatinine output were determined and serum Ca and $PO_4$ levels were measured. Therapy was adjusted to maintain a midmorning serum phosphorus concentration close to 4.0 to 4.5 mg/dL in youths and 4.5 to 5.0 mg/dL in toddlers, while avoiding hypercalcemia and hypercalciuria, which are reflected by a Ca/creatinine (Cr) ratio of >0.25.

At the initial evaluation, children in group 1 exhibited more severe physical signs; 5 of 6 children had severe bowing of the lower extremities (>5 cm between femoral condyles). This abnormality was present only in 1 of 6 children in group 2 ($P$<0.04). All the children with this finding displayed a marked resolution of the bowing, with reductions of 0 to 2 cm between femoral condyles during the first 2 years of therapy.

Physical manifestations did not correlate with biochemical abnormalities (ie, serum Ca, $PO_4$, Cr levels or Cr clearance). However, the younger children in group 1 tended to have a lower serum $PO_4$ concentration and increased urinary $PO_4$ excretion.

Both groups required comparable doses of calcitriol (51.9 ± 4.4 ng/kg/d in group 1 and 43.8 ± 6.0 ng/kg/d in group 2). In contrast, those in group 1 required significantly more $PO_4$, 47.3 ± 5.1 mg/kg/d vs the group 2 dose of 31.0 ± 4.7 mg/kg/d. In response to therapy, the serum Ca concentration in group 2 increased significantly, but stayed within the normal range. The mean levels were not different from those observed in group 1. The mean urinary Ca excretion in both groups increased during the therapeutic course, but the changes were not significant.

Although serum Cr concentration and Cr clearance in both groups were not significantly different before treatment, urinary Cr clearance declined significantly ($P$<0.03) in children in group 2 and serum Cr increased significantly. Serum $PO_4$ concentration increased in the majority of the patients. Treatment also enhanced the urinary $PO_4$ excretion in both groups. The levels attained during therapy were not different between the 2 groups.

The children in group 1 were shorter than those in group 2. The 6 patients in group 1 presented at a mean height percentile of 1.9 ± 0.6 (z score, -2.2 ± 0.14), whereas those in group 2 presented at a significantly ($P$<0.004) greater mean height percentile of 48.7 ± 8.0 (z score, -0.2 ± 0.8). The short stature in group 1 manifested a decline in the mean height percentile (53.8 ± 12.8; z score, 0.12 ± 0.38) in infancy to that present 3.3 ± 1.1 years later at initiation of therapy. In contrast, group 2 children sustained significantly less growth failure. During therapy, patients in group 1 maintained a low mean height percentile of 2.0 ± 0.9 (z score, -2.3 ± .24), which was not different from that before therapy, and exhibited a growth velocity of (z score) -1.05 ± 0.52. In contrast, children in group 2 significantly ($P$<0.03) increased their mean height percentile to 64.0 ± 9.5 (z score, 0.44 ± 0.25) and exhibited ($P$<0.01) a significantly greater growth velocity (z score, 1.35 ± 0.51).

The authors concluded that the variable growth responses to therapy were not a consequence of the biochemical responses to therapy; that repair of bowing and, presumably, remission of rickets was not related to the variability of growth increment; and that children who were markedly affected with growth retardation at the time of presentation did not significantly increase their growth rate despite improvement in biochemical, radiologic, and other auxologic measures.

Friedman NE, et al. *J Clin Endocrinol Metab* 1993;76(4):839-844.

***Editor's comment:*** *This report attempts to elucidate the factors that determine growth response to treatment in XLH, and concludes that clinical and biochemical control are not the main determinants of the growth response achieved with therapy. However, the authors compare XLH patients with different degrees of severity of the disease. Logically, the more severely affected patients will be the most disadvantaged and least responsive to treatment. Although the authors referred to the radiologic evidence of rickets among all patients studied, they failed to quantitate the differences and degrees among the 2 groups described, before and after therapy. It is likely that those patients with more severe disease continued to show bone abnormalities, even after prolonged therapy, which could contribute to the inadequacy of the growth recovery. Similarly, the bone deformities and bowing, and their contribution to the height deficits, were not quantitated before and after therapy. Upper/lower body segments and arm-span assessments, throughout the treatment period, may shed some light on this question. Furthermore, other factors that are important in determining height need to be addressed (eg, height of the patients' parents).*

*Regardless of the deficits, this paper does point out the need to have a high index of suspicion for XLH so the diagnosis is made early in life and treatment is initiated before bone deformities, rickets, and short stature become evident. Once these signs appear, therapy may not accomplish the desired effects of treatment. An ounce of prevention is worth a pound of cure!*

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