

The role of parathyroid hormone in the pathogenesis of skeletal disease in X-linked hypophosphatemic rickets (XLH)

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XLH is the most common heritable form of rickets/osteomalacia in the United States. The disorder is characterized by renal phosphate wasting, rickets and limited growth in childhood. Osteomalacia and fractures occur in adults. At all ages and irrespective of treatment there is a high incidence of secondary hyperparathyroidism.

We hypothesize that elevated PTH levels may significantly contribute to the skeletal disease in XLH. We are presently conducting clinical studies that examine this idea in two ways.

OBSERVATIONAL STUDY

This study provides a detailed characterization of the clinical features of XLH. Skeletal disease burden is assessed through collection and analysis of:

- symptom questionnaires
- height and weight Z scores
- lifetime and annualized number of fractures
- number of osteotomies
- number of dental abscesses
- number and extent of exostoses
- number and extent of calcified entheses (assessed radiographically)
- cardiac echocardiography

The study has been conducted at our Hospital Research Unit with diurnal monitoring of PTH, FGF23 and serum phosphorus levels. Enrollment for the study has been completed and analysis of the available data is underway.

Interim Findings

- 1) Circulating klotho levels differ by age (adults have greater levels than children), but there is no difference in XLH subjects as compared to unaffected control subjects. In contrast FGF23 levels do not differ by age, but XLH subjects clearly have elevated levels in comparison to unaffected controls.
- 2) Treatment with calcitriol and phosphate does not affect circulating klotho levels (Figure 1A), but circulating FGF23 is greater in XLH patients receiving active therapy compared to untreated patients (Figure 1B).

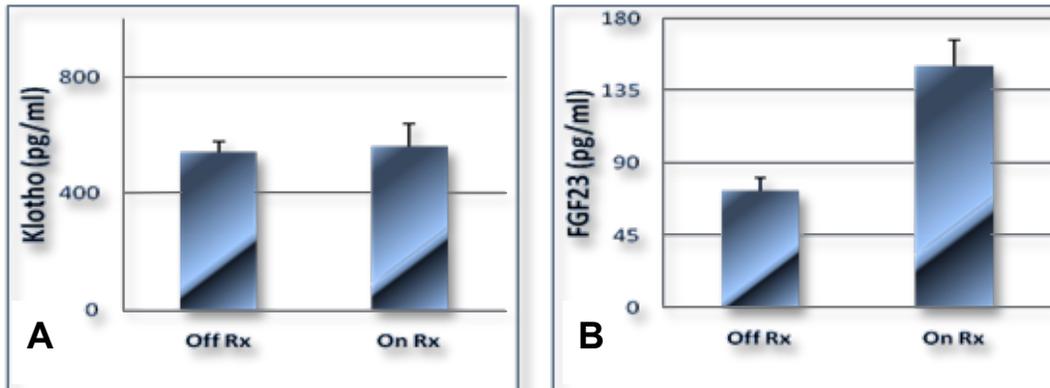


Figure 1. Circulating klotho (A) and FGF23 (B) in untreated (left columns) and treated (right columns) XLH subjects.

- 3) There is no significant circadian variance in circulating FGF23 levels in treated or untreated subjects with XLH or in unaffected controls (Figure 2A), however midnight levels of circulating klotho are low, with similar patterns in XLH and control individuals (Figure 2B).

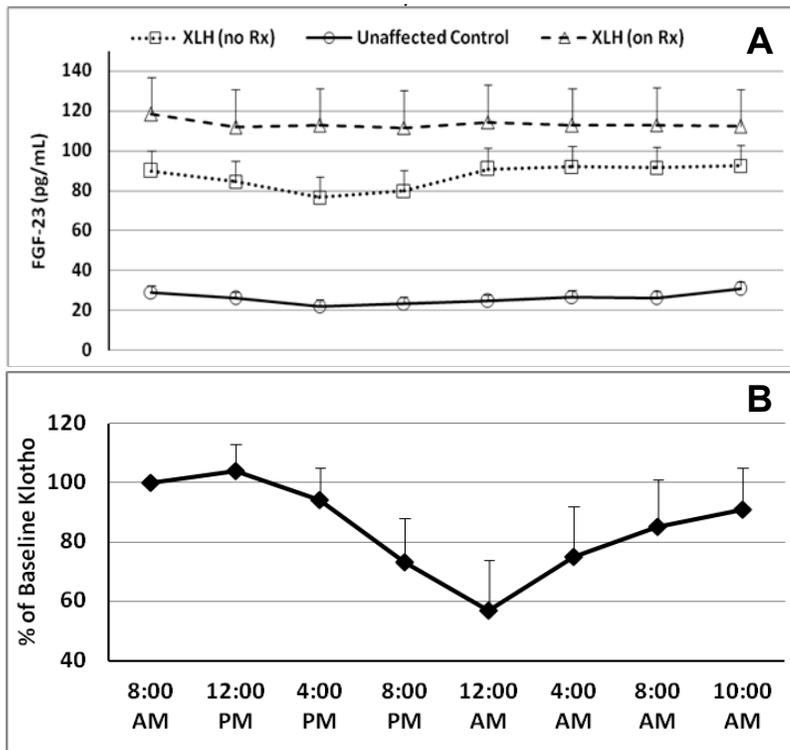


Figure 2.¹ Diurnal pattern of FGF23 (A) or klotho (B). FGF23 levels are shown by disease group, whereas klotho levels are pooled from all groups.

¹ Copyright 2010, The Endocrine Society. This figure first appeared in The Journal of Clinical Endocrinology & Metabolism, 95(11):E352-7, November 2010: "Circulating levels of soluble klotho and FGF23 in X-linked hypophosphatemia: circadian variance, effects of treatment, and relationship to parathyroid status," TO Carpenter, KL Insogna, JH Zhang, B Ellis, S Nieman, C Simpson, E Olear and CM Gundberg.

- 4) PTH and FGF23 are not correlated in control subjects ($P = 0.8$), but are positively correlated in XLH subjects ($P = 0.002$), suggesting that hyperparathyroidism in XLH occurs in part because of a resistance to FGF23's suppressive effect on the parathyroid glands (Figure 3). See: *Carpenter TO, Insogna KL, Zhang JH, Ellis B, Nieman S, Simpson C, Olear E, Gundberg CM; Circulating levels of soluble Klotho and FGF23 in X-linked hypophosphatemia: circadian variance, effects of treatment, and relationship to parathyroid status; J Clin Endocrinol Metab; 95:E352-7, 2010.*

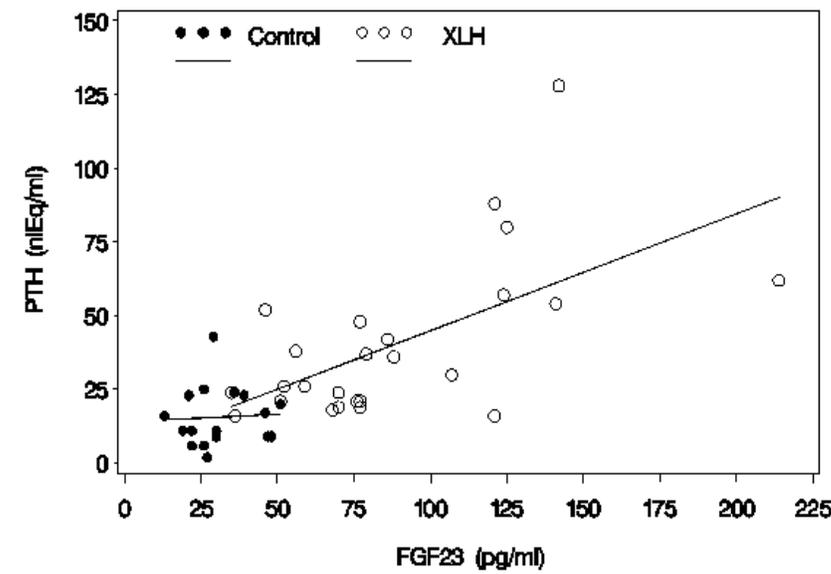


Figure 3. Circulating PTH as relates to circulating FGF23 in XLH subjects and unaffected controls.

INTERVENTIONAL STUDY

Our second study uses paricalcitol to suppress secondary hyperparathyroidism in XLH. We hypothesize that long term correction of secondary hyperparathyroidism in XLH will be accompanied by a reduction in markers of bone turnover and symptomatic improvement in skeletal disease.

Subjects are assessed during a 24-hour stay at the Hospital Research Unit and then are randomized to either paricalcitol (Zemplar®), or placebo. Treatment continues for 12 months, after which a repeat 24-hour evaluation is performed. If successful, this trial will provide proof of concept for the use of paricalcitol in the treatment of XLH.

We are on target to complete this study in 2012. At present we remain blinded to treatment and post-therapy goals.

If you have XLH, and are at least 9 years of age, you may be eligible to participate in this study. To learn more, please send a note to ycxlhinfo@yale.edu.