



# Increased levels of bone formation and resorption markers in patients with hypophosphatemic rickets

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## CONCLUSIONS

- Biochemical markers of bone resorption, CTX, - formation, P1NP, and inhibitor of osteoblastic bone formation, sclerostin, were increased in XLH compared to controls matched for sex, age and menopausal status, and this irrespective of current treatment
- The finding of higher levels of both bone resorption and - formation markers among the XLH patients in our study was unexpected, as histomorphometric analysis describe XLH as a low bone turnover disease

## Introduction

X-linked hypophosphatemia (XLH) is a rare, inheritable disorder caused by excessive renal phosphate wasting manifesting as rickets in children and osteomalacia in adults. Previous studies of bone metabolism and turnover in XLH using bone biopsies have found a reduced bone remodeling rate and a prolonged bone formation period (1,2). A low bone turnover state has thus been considered a characteristic feature of XLH. Bone turnover may also be assessed using biochemical markers that serve as indicators of the overall skeletal bone formation and resorption activity of osteoblasts and osteoclasts, respectively. Similarly, sclerostin, a protein mainly secreted by osteocytes acting as a potent inhibitor of osteoblasts, can be measured as a marker of osteocytic inhibition of osteoblast bone formation. To what extent these indices are affected in XLH have only been scarcely studied.

## Aim

The aim of this cross-sectional study was to assess bone metabolism, and the potential effects of conventional therapy, using biochemical markers of bone turnover in patients with XLH compared to healthy control subjects.

## Methods

XLH patients aged 18+ years with FGF23 associated hypophosphatemic rickets, either genetically or biochemically confirmed, were included. A disease causing PHEX mutation was found in fifteen patients. In nine patients, all included from the same family, a genome-wide association linkage scan revealed strong evidence of linkage to the PHEX locus on the X-chromosome.

Eleven patients received conventional medical therapy with alfacalcidol and phosphate. For each patient with XLH, three sex- and aged- matched healthy control subjects were included, in addition, female patients were matched with respect to menopausal status. Blood samples were drawn between 8 and 10 am after an overnight fast. The bone resorption marker carboxyterminal cross-linked telopeptide of type 1 collagen (CTX), the bone formation marker N-terminal propeptide of type 1 procollagen (P1NP), and the inhibitor of osteoblastic bone formation, sclerostin were analyzed.

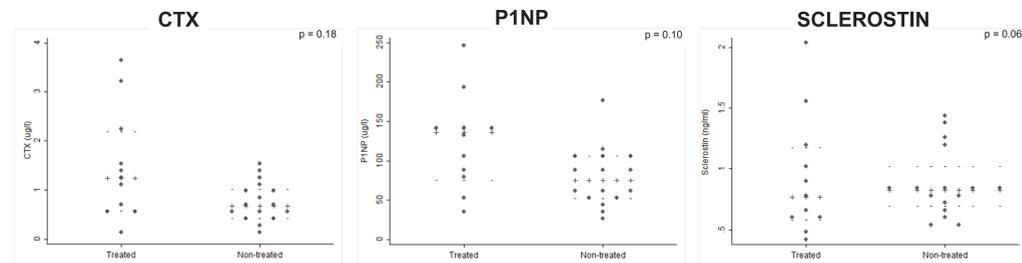
Comparisons between patients with XLH and control subjects were performed using  $\chi^2$  test, student T-test or Wilcoxon's rank-sum test depending on distribution of parameters. To compare values in treated versus non-treated XLH patients a multiple regression analysis was performed controlling for age and sex.

**Table 1: Clinical and antropometric data in XLH and controls**

	All XLH	Currently treated	Currently untreated	Controls
Number	27	11	16	81
Age (years)	47 [24-79]	33 [27-79]	49 [24-72]	48 [24-80]
Sex (female/male)	19/8	7/4	12/4	57/24
Menopausal status (pre-/postmenopausal)	11/8	4/3	7/5	37/20
Genetics				
PHEX mutation	15	9	6	-
X-linked	9	0	9	-
Unknown	3	2	1	-

Median [Range]  
PHEX: phosphate regulating endopeptidase on the X chromosome.

**Figure 1: CTX, P1NP and Sclerostin in treated versus non-treated XLH**



**Table 2: Bone markers in XLH and controls**

	All XLH	Currently treated	Currently untreated	Controls	p-value
Number	27	11	16	81	
CTX (µg/l)	0.81 [0.50-1.34]	1.24 [0.58-2.19] <sup>a</sup>	0.68 [0.43-1.02] <sup>a</sup>	0.48 [0.26-0.71]	<0.001
P1NP (µg/l)	90 [57-136]	136 [75-144] <sup>a</sup>	75 [53-106] <sup>a</sup>	49 [39-65]	<0.001
Sclerostin (ng/ml)	0.81 [0.60-1.18]	0.77 [0.58-1.18] <sup>a</sup>	0.83 [0.70-1.03] <sup>a</sup>	0.54 [0.45-0.69]	<0.001

Mean ± SD or median [IQR]  
CTX: carboxyterminal cross-linked telopeptide of type 1 collagen  
P1NP: N-terminal propeptide of type 1 procollagen  
p-value for comparisons of all HR versus controls and superscript letters for the subgroup comparisons of XLH (treated or non-treated) versus respective controls: a: <0.05 b: p<0.01 c: p<0.001

## Results

- A total of 27 patients with XLH, median age 47 (range 24 – 79 years), of whom 16 were currently untreated, and 81 controls were included in the study (Table 1)
- The resorption marker CTX was higher in XLH patients compared to matched controls (p<0.001) (Table 2)
- CTX remained elevated in XLH when comparing subgroups of treated (p<0.01) and non-treated XLH patients (p<0.05) with their respective controls (Table 2)
- A similar pattern was found for the formation marker P1NP with higher levels in XLH patients compared to matched controls (p<0.001) and in subgroups of treated (p<0.001) and non-treated (p<0.01) XLH patients compared their respective controls (Table 2)
- Sclerostin levels were higher in XLH (p<0.001) and also in subgroups of treated (p<0.01) and non-treated (p<0.01) XLH patients compared to matched controls (Table 2)
- In the age-and sex adjusted multiple regression analysis within the XLH group, there were no statistically significant difference in CTX (p=0.18), P1NP (p=0.10) or sclerostin (p=0.06), when comparing treated vs. non-treated (Figure 1)

