Calcitonin Lowers Serum FGF23 Levels in Patients with X-linked Hypophosphatemia

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**Background:** X-Linked hypophosphatemia (XLH) is the most common inherited form of rickets in the United States. Its defining biochemical features are hypophosphatemia due to reduced renal phosphate reabsorption, normocalcemia and paradoxically normal to low-normal circulating levels of 1,25(OH)2 vitamin D3 (1,25(OH)2 D3). XLH patients have rickets as children and osteomalacia as adults. Short stature, tooth root abscesses, and enthesopathy are long-term complications of XLH. The genetic basis for XLH is loss of function mutations in a neutral endopeptidase, PHEX, which leads to increased production of Fibroblast Growth Factor-23 (FGF23). FGF23 directly inhibits renal tubular phosphate reabsorption, and suppresses synthesis of the 25 OH vitamin D-1-alpha-hydroxylase enzyme. XLH is currently treated with an oral regimen of phosphate and 1,25(OH)2 D3. But, this therapy does not lower circulating levels of FGF23 and does not prevent the long term complications of the disease. Previous studies have shown that the administration of salmon calcitonin (CT) to mice as well as patients with XLH leads to the increase in circulating levels of 1,25(OH)2 D3. Whether CT affects circulating levels of FGF23 in XLH is not known.

**Hypothesis:** The administration of CT to XLH patients will decrease circulating FGF23 and thereby improve serum phosphate and 1,25(OH)2 D3 levels.

**Methods:** Seven subjects with XLH and six normal controls were enrolled in this study. Subjects with XLH discontinued all therapy 2 weeks before study. After obtaining baseline values, subjects were administered 200 MRC units of salmon CT intradermally and serial measurements of FGF23, 1,25(OH)2 D3 and indicies of mineral homeostasis were made over the next 24 hrs. Data were analyzed using repeated measures 1-way ANOVA and 2-way ANOVA.

**Results:** In subjects with XLH, CT significantly and rapidly reduced serum FGF23 to a mean value that was 77 ± 7% of baseline by 4 hrs. post injection (66 ± 5 pg/mL → 52 ± 8 pg/mL; p=0.0002). This decrease was sustained for the next 16 hours. In control subjects, FGF23 did not change significantly following treatment (p=0.16). By 2-way ANOVA, the effect of CT on serum FGF23 was significantly different when subjects with XLH and were compared to controls (p=0.01). The decline in FGF23 in subjects with XLH was accompanied by a significant increase in serum 1,25(OH)2 D3 (45 ± 3 pg/mL → 69 ± 5 pg/mL; p=0.0005,). There was a comparable increase in 1,25(OH)2 D3 in control subjects and by 2-way ANOVA the response was not different in the two groups (p=0.15). In XLH patients, there is an increase in serum phosphate and the renal phosphate threshold (Tmp/GFR) following treatment with CT that was maximal at 10 hr post injection (p=0.0003) while normal subjects had a fall in both these parameters first noted at 10 hrs (p=<0.0001). Both groups had comparable and slight declines in serum calcium levels and comparable and slight increases serum PTH.

**Conclusions:** CT administration leads to significant fall in serum levels of FGF23 levels in subjects with XLH but not in normal subjects. These results indicate that CT differentially regulates FGF23 in XLH patients. The rise in 1,25(OH)2 D3 levels in XLH could be due to the known effect of CT to augment proximal renal tubular production of the hormone as well as due to the slight rise in PTH and the fall in FGF23, which normally suppresses 1-alpha-hydroxylase activity. The suppression of FGF23 levels in XLH patients suggests CT may be a promising new therapeutic agent for this disease. Further studies are needed to clarify the cellular mechanisms by CT acts to suppress FGF23 levels but in preliminary data it appears that the effect may be mediated by osteoclasts.