Published in final edited form as:

N Engl J Med. 2011 April 28; 364(17): 1678–1680. doi:10.1056/NEJMc1010928.

Calcitonin Administration in X-Linked Hypophosphatemia

Eva S. Liu, M.D., Thomas O. Carpenter, M.D., Caren M. Gundberg, Ph.D., Christine A. Simpson, M.S., and Karl L. Insogna, M.D.

Yale University School of Medicine, New Haven, CT

Eva S. Liu: eva.s.liu@gmail.com

TO THE EDITOR

In X-linked hypophosphatemia, phosphate wasting results from increased circulating levels of fibroblast growth factor 23 (FGF-23).¹ Administration of calcitonin to a patient with oncogenic osteomalacia caused a drop in serum levels of FGF-23.² We wondered whether calcitonin might have the same effect in patients with X-linked hypophosphatemia.

Serum levels of FGF-23 and indexes of mineral metabolism were measured over 24 hours in seven untreated patients with X-linked hypophosphatemia and in six controls after a single subcutaneous injection of 200 IU of salmon calcitonin administered at noon on the first day of a 2-day admission. Among patients with X-linked hypophosphatemia who received calcitonin, serum levels of FGF-23 dropped from baseline levels (100%) to a mean ($\pm$ SD) of $77 \pm 19\%$ 4 hours after injection, and levels remained below baseline for 16 hours (falling from 66 ± 12 pg per milliliter to 52 ± 20 pg per milliliter, $P < 0.001$) (Fig. 1A). Controls showed no significant change in FGF-23 levels ($P = 0.16$). Thus, the effect of calcitonin on serum levels of FGF-23 was significantly different between groups ($P = 0.01$). Serum levels of 1,25-dihydroxyvitamin D rose similarly in both groups for 21 hours but diverged thereafter ($P = 0.008$) (Fig. 1B). Both groups had slight and similar changes in serum levels of calcium and parathyroid hormone (data not shown). In patients with X-linked hypophosphatemia, serum phosphate levels rose after treatment, reaching a maximum that was $129 \pm 16\%$ of baseline 10 hours after injection (post hoc analysis, $P < 0.001$) (Fig. 1C). Serum levels of phosphate did not change in controls ($P > 0.05$). Overall, there was no significant difference in serum phosphate levels between groups ($P = 0.24$). Post hoc analysis showed no significant change in the tubular maximum for phosphate corrected for glomerular filtration (TmP per GFR) ($P > 0.05$) in the control group or the X-linked hypophosphatemia group at 10 hours (nonfasting) or 21 hours (fasting) after injection (data not shown).

Thus, in patients with X-linked hypophosphatemia, we observed a significant and sustained drop in circulating levels of FGF-23 and an increase in serum levels of phosphorus after the administration of calcitonin. It is possible that there was no effect on TmP per GFR because at 10 hours the calculation was made on the basis of nonfasting values. At 21 hours, although the TmP per GFR was appropriately calculated, on the basis of fasting values, the serum phosphorus level had returned to baseline. The rise in serum levels of 1,25-dihydroxyvitamin D is probably due to the direct stimulatory effect of calcitonin on renal 1α -hydroxylase.³ Recently, Gooi et al. reported that osteocytes express the calcitonin receptor and respond to calcitonin with an increase in sclerostin production.⁴ Since the primary source of FGF-23 is osteocytes, these findings imply that the decline in FGF-23 levels that we observed in patients with X-linked hypophosphatemia was due to the direct

effect of calcitonin on osteocytes in this disease. Our study raises the possibility that calcitonin is a therapeutic option for patients with X-linked hypophosphatemia.

Acknowledgments

Supported by the Yale Bone Center, the Yale Center for X-Linked Hypophosphatemia, and the Yale Center for Clinical Investigation.

References

1. Carpenter, TO.; Drezner, M. Primary disorders of phosphate metabolism. In: Arnold, A., editor. Endotext.org: the endocrine source. South Dartmouth, MA: MDText.com; 2007. (<http://www.endotext.org>.)
2. van Boekel G, Ruinemans-Koerts J, Joosten F, Dijkhuizen P, van Sorge A, de Boer H. Tumor producing fibroblast growth factor 23 localized by two-staged venous sampling. Eur J Endocrinol. 2008; 158:431–7. [PubMed: 18299479]
3. Econs MJ, Lobaugh B, Drezner MK. Normal calcitonin stimulation of serum calcitriol in patients with X-linked hypophosphatemic rickets. J Clin Endocrinol Metab. 1992; 75:408–11. [PubMed: 1639943]
4. Gooi JH, Pompolo S, Karsdal MA, et al. Calcitonin impairs the anabolic effect of PTH in young rats and stimulates expression of sclerostin by osteocytes. Bone. 2010; 46:1486–97. [PubMed: 20188226]

Figure 1. Mean Absolute Changes in Serum Levels of Fibroblast Growth Factor 23, 1,25-Dihydroxyvitamin D, and Phosphorus after Administration of Calcitonin

The mean ($\pm$ SD) of the absolute value plotted as a percentage of baseline for each time point is shown next to that time point in each panel. The values at -2 hours were taken to be the baseline. Calcitonin was administered at time 0. Indexes of mineral metabolism were measured at set time points established in part on the basis of an effort to minimize study subject discomfort and sleep disturbance. Blue squares represent the subjects in the control group (without X-linked hypophosphatemia), and the red triangles subjects with X-linked hypophosphatemia. Panel A shows the percentage change from baseline in serum levels of fibroblast growth factor 23 (FGF-23) measured in picograms per milliliter, Panel B the change from baseline in serum levels of 1,25-dihydroxyvitamin (1,25[OH]₂D) measured in picograms per milliliter, and Panel C the change from baseline in serum levels of phosphorus measured in milligrams per deciliter. Statistical analyses were performed using the absolute values at each time point. Two-way analysis of variance was used to calculate the P values in Panels A and B and post hoc analysis was used to calculate the P value in

Panel C. The normal range for serum levels of FGF-23 is 25 ± 5 pg per milliliter, that for $1,25(\text{OH})_2\text{D}$ is 20 to 60 pg per milliliter, and that for phosphorus is 2.5 to 4.5 mg per deciliter.