Fibroblast Growth Factor (FGF)23 in Patients with Acromegaly

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Abstract. Fibroblast growth factor (FGF)23 is a hormone that regulates serum phosphate and 1,25-dihydroxyvitamin D levels. Hyperphosphatemia is sometimes observed in patients with acromegaly while the detailed mechanism of this abnormal phosphate metabolism remains to be elucidated. We have measured FGF23 levels in 18 patients before and after the surgery for acromegaly. Serum GH, IGF-I and phosphate significantly decreased after the surgery. In addition, FGF23 also reduced by the surgery. These results indicate that deficient action of FGF23 is not the cause of deranged phosphate metabolism in patients with acromegaly.

Key words: FGF23, Acromegaly, Hyperphosphatemia, GH, IGF-1

FIBROBLAST growth factor (FGF)23 is the latest member of FGF family and has been shown to work as a hormone that regulates serum phosphate and 1,25-dihydroxyvitamin D levels [1–4]. Actually, excess and deficient actions of FGF23 result in several hypophosphatemic and hyperphosphatemic disorders, respectively [5–12]. For example, familial hyperphosphatemic tumoral calcinosis is associated with reduced serum level of full-length FGF23 [11, 12]. In contrast, FGF23 levels were reported to be high in patients with hyperphosphatemia caused by hypoparathyroidism or chronic renal failure [13–17]. These results suggest that serum FGF23 levels can discriminate the causes of hyperphosphatemia. Hyperphosphatemia caused by deficient action of FGF23 is associated with low FGF23, while hyperphosphatemia derived from other origins results in rather high FGF23 probably by compensatory mechanisms.

There are several endocrine diseases associated with abnormal phosphate levels. Acromegaly is sometimes associated with hyperphosphatemia. Previous studies suggest that high GH or insulin-like growth factor (IGF)-I stimulates proximal tubular phosphate reabsorption, although the detailed mechanism of this regulation of phosphate reabsorption remains to be clarified [18, 19]. Actually, it is not clear whether GH or IGF-I directly modulates phosphate reabsorption or indirectly through the action of some other humoral factors. In this study, we measured FGF23 levels before and after surgery for acromegaly in order to investigate the etiology of derangements of phosphate metabolism in patients with acromegaly.

Material and Methods

We recruited 18 patients with acromegaly operated between August 2004 and July 2005 at Toranomon Hospital. These subjects included 11 male and 7 female patients between 21 and 74 years of age. All the patients showed normal serum creatinine levels. Samples were obtained before and at one week after the operation for acromegaly. Serum FGF23 levels were measured by enzyme-linked immunosorbent assay that
detects only full-length FGF23 (Kainos, Japan). The reference range of FGF23 is 10–50 pg/ml based on FGF23 levels of about 100 healthy adults [7]. Serum phosphate was measured by an autoanalyzer (Hitachi, Tokyo, Japan). Serum growth hormone (GH) and IGF-I levels were assayed by immunoradiometric assay. Tubular maximum transport of phosphate adjusted by glomerular filtrate (TmP/GFR), the index of proximal tubular phosphate reabsorption, was evaluated using a nomogram [20]. This clinical study was approved by institutional review board in Toranomon Hospital, and written informed consent was obtained from all patients. Statistical significance was evaluated by Student’s paired t-test.

**Results**

Serum GH level was clearly elevated in all patients and IGF-I was above the reference range in 17 patients before the surgery. After the operation, GH and IGF-I significantly decreased as shown in Fig. 1. Serum phosphate was above the reference range in 7 of 18 patients before the operation and again significantly decreased after the operation (Fig. 2). TmP/GFR was 4.69 +/- 0.37 mg/dL (mean +/- SD) before the operation and significantly decreased to 4.06 +/- 0.27 mg/dL after the surgery (p<0.05). Serum FGF23 was above the reference range in 6 patients before the operation and significantly decreased after the operation (Fig. 2). There was no significant correlation between basal levels of FGF23 and phosphate in these patient (p = 0.40). Changes in phosphate and FGF23 between pre- and post-operative values did not show significant correlation, either (p = 0.42).

**Discussion**

FGF23 was shown to inhibit proximal tubular phosphate reabsorption by reducing expression levels of type 2a and 2c sodium-phosphate co-transporter [2]. In contrast, because FGF23 knockout mice and patients with hyperphosphatemic tumoral calcinosis caused by deficient action of FGF23 show hyperphosphatemia associated with enhanced phosphate reabsorption, FGF23 seems to be a physiological regulator of phosphate reabsorption and serum phosphate levels [3, 4, 11, 12]. In addition, since FGF23 levels were shown to be high in hyperphosphatemic patients by hypoparathyroidism and chronic renal failure [13–17], and to increase by high phosphate diet [21], it is likely that the expression and serum FGF23 levels are tightly regulated. We have shown here that FGF23 levels decreased after the surgery for acromegaly together with the reduction of serum phosphate, TmP/GFR, IGF-I and GH. In addition, none of these patients showed low FGF23 levels before the surgery. These results suggest that hyperphosphatemia associated with acromegaly is not caused by deficient FGF23 action, although not all patients showed hyperphosphatemia.

FGF23 levels in our patients were not so high as that seen in patients with chronic renal failure [14–17]. The increase of FGF23 in patients with hypoparathyroidism and subjects taking high phosphate diet is not so drastic either, although a different assay for FGF23...
was used in that study [13, 21]. These results suggest that some other confounding factors than hyperphosphatemia alone are responsible for extremely high FGF23 levels in patients with chronic renal failure. Lack of significant correlation between basal levels of phosphate and FGF23, and changes of them may be explained by rather small variations of these parameters and sample size. These results also suggest that FGF23 is not the main determinant of phosphate levels in these patients.

Our study has several limitations. First, the sample size is not large. Second, not all patients showed hyperphosphatemia before the operation. And finally, we collected samples at various time points before the surgery. However, the significant decrease of FGF23 after surgery indicates that the FGF23 level changes in compensation for derangements in phosphate metabolism in patients with acromegaly. Therefore, this study shows that deficient action of FGF23 is not the cause of abnormal phosphate metabolism observed in patients with acromegaly.

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**References**


