Circulating FGF-23 Is Regulated by 1α,25-Dihydroxyvitamin D3 and Phosphorus in Vivo*

Hitoshi Saito‡§, Akira Maeda‡, Shu-ichi Ohtomo‡, Michinori Hirata‡, Kenichiro Kusano‡, Shigeaki Kato‡, Etsuro Ogata‡, Hiroko Segawa**, Ken-ichi Miyamoto**, and Naoshi Fukushima‡

From the ‡Pharmaceutical Research Department II, Chugai Pharmaceutical Co., Ltd., Gotemba, Shizuoka 412-8513, Japan, the §Institute of Molecular and Cellular Biosciences, Tokyo University, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-0032, Japan, the ¶Cancer Institute Hospital, 1-37-1 Kami-ikebukuro, Toshima-ku, Tokyo 170-8455, Japan, and the **Department of Molecular Nutrition, Institute of Health Bioscience, University of Tokushima Graduate School, 3-18-15 Karamoto-cho, Tokushima 770-8503, Japan

Received for publication, August 4, 2004, and in revised form, September 27, 2004
Published, JBC Papers in Press, November 5, 2004, DOI 10.1074/jbc.M408903200

Fibroblast growth factor-23 (FGF-23), a novel phosphate-regulating factor, was elevated in hypophosphatemic patients with X-linked hypophosphatemic rickets/osteomalacia and also in patients with chronic kidney disease. These observations suggested that the pathophysiological importance of FGF-23 on phosphate homeostasis. However, regulation of FGF-23 production is still unclear. We investigated effects of both dietary phosphorus and 1α,25-dihydroxyvitamin D3 (1α,25(OH)2D3) on circulating FGF-23 in vivo. Administration of 1α,25(OH)2D3 dose-dependently increased serum FGF-23 in thyroparathyroidectomized rats without correlating with serum inorganic phosphorus or serum parathyroid hormone. On the other hand, vitamin D receptor null mice had very low serum FGF-23 and did not respond to the 1α,25(OH)2D3 administration. These observations suggested 1α,25(OH)2D3 directly or indirectly regulates circulating FGF-23. Serum FGF-23 had a strong correlation with serum inorganic phosphorus controlled by dietary phosphorus in 5/6 nephrectomized rats. High phosphate diet elicited a 5-fold increase in serum FGF-23 compared with sham-operated rats, whereas serum FGF-23 did not correlate with serum calcium or serum creatinine in 5/6 nephrectomized rats. Administration of 1α,25-dihydroxyvitamin D3 also elicited a severalfold increase in serum FGF-23 in the uremic rats. Taken together, this shows that both serum phosphorus and 1α,25(OH)2D3 regulate circulating FGF-23 independent of each other. Therefore, we proposed there was a feedback loop existing among serum phosphorus, 1α,25(OH)2D3, and FGF-23, in which the novel phosphate-regulating bone-kidney axis integrated with the parathyroid hormone-vitamin D3 axis in regulating phosphate homeostasis.

The parathyroid hormone-vitamin D3 endocrine system, as well as dietary phosphorus, plays an important role in regulating renal and gastrointestinal absorption of phosphate. Recently, emerging evidence suggests that other systemic and/or paracrine/autocrine factors are present in bones for maintaining phosphate homeostasis, such as fibroblast growth factor-23 (FGF-23),1 frizzled-related protein-4 (FRP-4), and matrix extracellular phosphoglycoprotein (MEPE) (1–11). These three factors were highly expressed in tumors isolated from oncogenic osteomalacia patients and reduced phosphate transport in kidney. Among these factors, FGF-23 strongly suppressed 1α,25(OH)2D3 production and elicited hypophosphatemia. Administration of the recombinant FGF-23 protein reduced serum phosphorus without affecting serum calcium, as well as increasing renal phosphorus excretion in mice (12). Mice bearing FGF-23-expressing Chinese hamster ovary cells showed suppressed 25-hydroxyvitamin D3 1α-hydroxylase mRNA expression in the kidney (3). FGF-23 mRNA is expressed in a variety of tissues such as thymus, brain, bone, thyroid/parathyroid gland, and heart (2, 3, 13). Recent studies (13, 14) indicated FGF-23 mRNA as well as FGF-23 protein was elevated in bones from patients with McCune-Albright syndrome and also in bones from HYP mouse, mouse homologue to X-linked hypophosphatemic (XLH) rickets. However, the level of serum FGF-23 in hypophosphatemic patients with XLH is still controversial (15–17). Hyperphosphatemic patients with chronic kidney disease showed significant elevation in circulating FGF-23, which correlated with serum phosphorus and creatinine (16, 18–20), suggesting (a) serum phosphorus was a possible regulator of FGF-23 production or (b) circulating FGF-23 accumulated in chronic renal failure.

The purpose of this study was to evaluate the effects of dietary phosphorus and 1α,25(OH)2D3 on FGF-23 production. Administration of FGF-23 protein or overexpression of Fgf23 gene in rodent suppressed 1α,25(OH)2D3 production by reducing 25-hydroxyvitamin D3 1α-hydroxylase in the proximal tubules (12, 21–23). On the contrary, Fgf23-null mice reported increased circulating 1α,25(OH)2D3 despite hyperphosphatemia, hypercalcemia, and low PTH levels (24). Administration of 1α,25(OH)2D3 increased serum FGF-23 in normal mice (25). These observations suggested mutual regulation between FGF-23 and 1α,25(OH)2D3; however, 1α,25(OH)2D3 administration also increases intestinal phosphate uptake and suppresses PTH. Thus, we used thyroparathyroidectomized rats as well as 5/6 nephrectomized rats fed a diet with various kinds of phosphorus content to examine the direct effect of 1α,25(OH)2D3 administration on serum FGF-23.

1 The abbreviations used are: FGF-23, fibroblast growth factor-23; Pi, phosphate; IP, inorganic phosphorus; TPTX, thyroparathyroidectomy; XLH, X-linked hypophosphatemia; PHEX, phosphate-regulating gene with homologies to endopeptidases on the X chromosome; 1α,25(OH)2D3, 1α,25-dihydroxyvitamin D3; 1α-OHase, 25-hydroxylase; PTH, parathyroid hormone; ELISA, enzyme-linked immunosorbent assay; VDRKO, vitamin D receptor null (−/−).
Dietary phosphate deprivation or loading rapidly induces activation or repression of phosphate absorption in kidney and in intestine, mainly by inducing or suppressing type II sodium-dependent phosphate (Na/Pi) cotransporter expression (26, 27). Therefore, the serum phosphorus level is not susceptible to the change in dietary phosphorus content in normal animals in vivo. We investigated the effects of dietary phosphorus on FGF-23 production in vivo using 5/6 nephrectomized uremic rats, in which the serum phosphorus level can be easily manipulated by dietary phosphorus due to reduced kidney function. We also examined the correlations between serum FGF-23 and (a) serum inorganic phosphorus, (b) serum calcium, (c) serum creatinine, and (d) serum PTH in 5/6 nephrectomized rats.

**EXPERIMENTAL PROCEDURES**

**Normal Rat**—Eight-week-old male Sprague-Dawley rats (CREA Japan, Inc., Shizuoka, Japan) were given either vehicle, 10, 30, 100, or 300 ng of 1α,25(OH)2D3/kg of bodyweight intravenously, three times a week for 2 weeks. Blood samples were obtained from the vena cava under ether anesthesia on day 14. Serum calcium, serum inorganic phosphorus, and serum creatinine were measured as described in the Human FGF-23 ELISA kit (Kinos Inc., Tokyo, Japan).

**Thyroparathyroidectomized (TPTX) Rats and PTH-infused TPTX Rats**—Eight-week-old male Sprague-Dawley rats purchased from Charles River (Tokyo, Japan) were TPTX under ether anesthesia. After confirming hypocalcemia had been induced, rats were divided to two groups, the TPTX group and the TPTX + PTH group. Rats in the TPTX + PTH group were subcutaneously implanted with ALZET® osmotic pumps (model 2ML2, Durect Corp., Cupertino, CA) and administered human PTH-(1–34) at a constant rate of 2.4 μg/day for 14 days.

**RESULTS**

**Effect of 1α,25(OH)2D3 on Serum FGF-23 in Normal Rats**—Intravenous administration of 1α,25(OH)2D3, three times a week for 2 weeks, dose-dependently increased serum FGF-23 (Fig. 1A); however, it also increased serum inorganic phosphorus (Fig. 1B). Therefore, 1α,25(OH)2D3 administration increased both serum FGF-23 and serum phosphorus in normal rats.

**Effects of 1α,25(OH)2D3 on Serum FGF-23 in TPTX Rats**—As shown in Fig. 2, A–C, Thyroparathyroidectomized rats induced hyperphosphatemia, hypocalcemia, and also a slight but signif-

![Fig. 1. Administration of 1α,25-dihydroxyvitamin D3 dose-dependently increased both (A) serum FGF-23 as well as (B) serum inorganic phosphorus in normal rats. Correlation between serum FGF-23 and serum inorganic phosphorus in normal rats (C). Eight-week-old rats were given intravenously either vehicle, 10, 30, 100, or 300 ng/kg 1α,25-dihydroxyvitamin D3 three times a week for 2 weeks. Serum inorganic phosphorus and FGF-23 were determined as described in the text. Each column represents means ± S.E. (n = 4), *p < 0.05, by Dunnett’s t test.](http://www.jbc.org/Downloaded from)
FIG. 2. Effect of 1α,25-dihydroxyvitamin D₃ on serum FGF-23 (A), serum inorganic phosphorus (B), and serum calcium (C) in TPTX rats. TPTX or PTH-infused TPTX rats were given intravenously vehicle (Veh) or 1α,25-dihydroxyvitamin D₃ three times a week for 2 weeks. Serum inorganic phosphorus, calcium, and FGF-23 were determined as described under “Experimental Procedures.” Each column represents mean ± S.E. (n = 4–5). a, statistically significant versus normal; b, versus TPTX vehicle treatment; p < 0.05, by Student’s t test.
icant decrease in serum FGF-23 in comparison with normal rats. Administration of 1α,25(OH)₂D₃ dose-dependently increased serum FGF-23 as well as serum calcium in TPTX rats. Also 1α,25(OH)₂D₃ suppressed serum inorganic phosphorus in TPTX rats. PTH infusion to TPTX rats normalized serum calcium, serum inorganic phosphorus, and serum FGF-23. 1α,25(OH)₂D₃ increased serum FGF-23; however, unlike TPTX rats, no significant change was observed in serum inorganic phosphorus and serum calcium in PTH-infused TPTX rats. These observations suggested that 1α,25(OH)₂D₃ increased serum FGF-23 independent of serum inorganic phosphorus and PTH.

Effect of 1α,25(OH)₂D₃ on Serum FGF-23 in VDRKO Mice—VDRKO mice kept on high calcium (2%) and high phosphorus (1.25%) diets showed considerably low serum FGF-23 (<3 pg/ml, below detection limit) and low serum calcium (5.8 ± 0.6 mg/dl) in comparison with the wild-type littermates (FGF-23, 254 ± 35.6 pg/ml; calcium, 9.5 ± 0.1 mg/dl). 1α,25(OH)₂D₃ administration did not affect either serum FGF-23 (<3 pg/ml, below detection limit) or serum calcium (5.1 ± 0.2 mg/dl).

Effects of Pi-controlled Diets on Serum FGF-23 and Serum Inorganic Phosphorus in 5/6 Nephrectomized Rats—Serum inorganic phosphorus correlated with the dietary phosphorus contents (Fig. 3A) in 5/6 nephrectomized rats. On the contrary, serum calcium correlated with serum phosphorus in a reciprocal fashion (Fig. 3B). The 5/6 nephrectomy induced a significant increase in serum FGF-23 in rats, regardless of the dietary phosphorus contents (Fig. 3C). Serum FGF-23 of sham-operated rats was 305 ± 23 pg/ml. Whereas, serum FGF-23 increased in high, midrange, and low Pi diet groups (5108 ± 989 pg/ml, 1815 ± 200 pg/ml, and 1133 ± 121 pg/ml, respectively). Serum FGF-23 showed a clear correlation with serum phosphorus (Fig. 4A) and a weak inverse correlation with serum calcium (Fig. 4B) in 5/6 nephrectomized rats. However, serum FGF-23 did not correlate with serum creatinine (Fig. 4C).

Effect of 1α,25(OH)₂D₃ on Serum FGF-23 and Serum Inorganic Phosphorus in 5/6 Nephrectomized Rats—Serum FGF-23 in the 5/6 nephrectomized rats on each Pi-controlled diet was augmented significantly by the administration of 1α,25(OH)₂D₃ (Fig. 5). 1α,25(OH)₂D₃ administration also increased serum inorganic phosphorus, serum calcium, and serum creatinine and decreased serum PTH in all diet groups (data not shown). Serum inorganic phosphorus weakly correlated with serum FGF-23 in the nephrectomized rats with or without 1α,25(OH)₂D₃ treatment (Fig. 6A). However, the other three parameters did not have a strong correlation with serum FGF-23 (Fig. 6, B–D).

In normal rats, 30 and 100 ng/kg 1α,25(OH)₂D₃ injection increased serum FGF-23 only by 1.5- and 3-fold, respectively. Whereas, in the 5/6 nephrectomized rats, 50 ng/kg 1α,25(OH)₂D₃ increased serum FGF-23 by 3–9-fold, suggesting that 1α,25(OH)₂D₃ had a more profound effect on increasing serum FGF-23 in rats with chronic renal failure.

DISCUSSION

Shimada et al. reported that a single injection of 1α,25(OH)₂D₃ increased serum FGF-23 and suggested the increase in FGF-23 by 1α,25(OH)₂D₃ was independent of serum inorganic phosphorus (25). We confirmed that intravenous administration of 1α,25(OH)₂D₃ dose-dependently increased serum FGF-23 (Fig. 1A). However, we also observed an increase in serum inorganic phosphorus (Fig. 1B). There was a strong significant correlation between serum FGF-23 and serum phosphorus (Fig. 1C) in the normal rats given 1α,25(OH)₂D₃. Since 1α,25(OH)₂D₃ stimulates intestinal phosphorus uptake and suppresses PTH production, this experiment indicated that 1α,25(OH)₂D₃ increased serum FGF-23 as well.
as serum phosphorus. To evaluate the effect of 1α,25(OH)2D3, apart from serum phosphorus on FGF-23 production, 1α,25(OH)2D3 was administered to thyroparathyroidectomized rats with or without PTH infusion. 1α,25(OH)2D3 also increased serum FGF-23 in thyroparathyroidectomized, and the effect was independent of serum phosphorus (Fig. 2, A–C). The direct effect of 1α,25(OH)2D3 on FGF-23 production was confirmed by the fact that VDRKO mice did not respond to the 1α,25(OH)2D3 administration.

Larsson et al. (18) reported phosphate deprivation and/or phosphate loading to normal subjects did not affect serum FGF-23; however, serum phosphorus weakly correlated with serum FGF-23 in predialysis patients with chronic kidney disease. Recent studies also revealed that serum FGF-23 was elevated in patients with end-stage renal disease (16, 20, 28). In the present study, we investigated the effect of dietary phosphorus on FGF-23 production using 5/6 nephrectomized rats fed the diets with various kinds of phosphorus content. Serum FGF-23 was elevated in uremic rats; however, serum FGF-23 did not clearly correlate with serum creatinine in those rats as was observed in human subjects. Serum phosphorus was well controlled by the dietary phosphorus in 5/6 nephrectomized rats (Fig. 3A). Serum FGF-23 positively correlated with serum phosphorus in those rats (Fig. 3C). In the physiological condition, a high serum phosphorus suppresses 1α,25(OH)2D3 production in kidney. Thus, the elevation of serum FGF-23 induced by a high Pi diet was independent of serum 1α,25(OH)2D3. Moreover, serum FGF-23 was drastically elevated by 1α,25(OH)2D3 administration in 5/6 nephrectomized rats fed with various Pi-controlled diets (Fig. 5). However, serum FGF-23 did not correlate with serum calcium, serum creatinine, or serum PTH in those rats (Fig. 6, B–D). These observations suggested that FGF-23 production was mainly regulated by serum phosphorus and serum 1α,25(OH)2D3.

Recent studies (16, 17) reported that FGF-23 was elevated in some patients with XLH. Serum phosphorus concentrations were negatively correlated with circulating FGF-23 levels in patients with XLH. Moreover, FGF-23 mRNA expression was
enhanced in the calvarial and mandible bones of Hyp-mouse, which is a homologue of human XLH (13). Mutations in PHEX, a phosphate-regulating gene with homology to endopeptidase on the X-chromosome, are responsible for XLH. PHEX mRNA is predominantly expressed in bone and teeth. 1α,25(OH)2D3 decreased PHEX mRNA and PHEX protein in primary osteoblasts derived from newborn mouse calvaria as well as MC3T3-E1 cells, a mouse osteoblastic cell line, in vitro (29). In addition, PHEX mRNA expression in tibial bone was suppressed by 1α,25(OH)2D3 administration in 5/6 nephrectomized rats in vivo (30). It is plausible that administration of 1α,25(OH)2D3 up-regulated circulating FGF-23 levels in 5/6 nephrectomized rats at least partly by down-regulation of PHEX expression in bones.

FGF-23 induces hypophosphatemia by inhibiting both renal and intestinal P1 absorption by suppressing NaPi-IIa and -IIb production (3, 12, 21, 22, 25). FGF-23 also inhibits 1α,25(OH)2D3 production in renal proximal tubules, which results in the reduction of intestinal P1 absorption and PTH secretion. On the contrary, 1α,25(OH)2D3 induced an increase in circulating FGF-23, and also loss of vitamin D signaling in VDRKO mice led to very low serum FGF-23. In 5/6 nephrectomized rats, serum phosphorus controlled by dietary phosphorus content positively correlated with serum FGF-23, suggesting an increase in serum phosphorus induces FGF-23 production. We propose that a feedback loop exists between serum phosphorus, 1α,25(OH)2D3, and FGF-23, in which the novel phosphate-regulating bone-kidney axis would be integrated with the parathyroid hormone-vitamin D3 axis in regulating phosphate homeostasis.

Acknowledgments—We thank Keiko Kuroiwa and Yuko Azabu (Pharmaceutical Research Dept. II, Chugai Pharmaceutical Co., Ltd.) for their technical assistance. We also thank Dr. Paul Langman for his assistance with English usage.

REFERENCES

1. The ADHR Consortium (2000) Nat. Genet. 26, 345–348
2. Yamashita, T., Yoshioka, M., and Its, N. (2000) Biochem. Biophys. Res. Commun. 277, 494–498
3. Shimada, T., Mizutani, S., Muto, T., Yoneya, T., Hino, R., Takeda, S., Takeuchi, Y., Fujita, T., Fukumoto, S., and Yamashita, T. (2001) Proc. Natl. Acad. Sci. U. S. A. 98, 6500–6505
4. Berndt, T., Craig, T. A., Bowe, A. E., Vassiliadis, J., Reczek, D., Finnegan, R., Jan De Beur, S. M., Schiavi, S., and Kumar, R. (2003) J. Clin. Invest. 112, 785–794
5. Rowe, P. S. N., de Zoya, P. A., Vassiliadis, J., Reczek, D., Finnegan, R., Jan De Beur, S. M., Schiavi, S., and Kumar, R. (2002) J. Bone Miner. Metab. 17, 1102–1110
6. Argiro, L. A., Desbarats, M., Glorieux, F. H., and Ecarot, B. (2001) Genomics 74, 342–351
7. Jan De Beur, S. M., Finnegan, R., Vassiliadis, J., Cook, B., Barberion, D., Estes, S., Manavalan, P., Petroziello, J., Madden, S. L., Cho, J. Y., Kumar, R., Levine, M. A., and Schiavi, S. (2002) J. Bone Miner. Metab. 17, 1102–1110
8. White, K. E., Jonsson, K. B., Carn, G., Hampton, G., Spector, T. D., Mannstadt, M., Lorenz-Depiereux, B., Miyauuchi, A., Yang, M., Ljunggren, O., Meitinger, T., Strom, T. M., Juppner, H., and Econs, M. J. (2001) J. Clin. Endocrinol. Metab.

FIG. 6. Correlations between serum FGF-23 and serum inorganic phosphorus (A), serum calcium (B), serum creatinine (C), and serum PTH (D) in 5/6 nephrectomized rats with or without 1α,25-dihydroxyvitamin D3 administration. 5/6 nephrectomized rats fed Pi-controlled diets were given intravenously either vehicle or 50 ng/kg 1α,25-dihydroxyvitamin D3 for 4 weeks. Serum creatinine, serum inorganic phosphorus, and serum FGF-23 were determined as described under “Experimental Procedures.” Open circles represent the data from individual rats.
9. Gowen, L. C., Petersen, D. N., Mansolf, A. L., Qi, H., Stock, J. L., Tkalec, G. T., Simmons, H. A., Crawford, D. T., Chidsey-Frink, K. L., Re, H. Z., McNeish, J. D., and Brown, T. A. (2003) J. Biol. Chem. 278, 1998–2007
10. Quarles, L. D. (2003) Am. J. Physiol. 285, E1–E9
11. Quarles, L. D. (2003) J. Clin. Invest. 112, 642–646
12. Shimada, T., Muto, T., Urakawa, I., Yoneya, T., Yamazaki, Y., Okawa, K., Takeuchi, Y., Fujita, T., Fukumoto, S., and Yamashita, T. (2002) Endocrinology 143, 3179–3182
13. Liu, S., Guo, R., Simpson, L. G., Xian, Z-S., Burnham, C. E., and Quarles, L. D. (2003) J. Biol. Chem. 278, 37419–37426
14. Riminucci, M., Collins, M. T., Fedaeko, N. S., Cherman, N., Corsi, A., White, K. E., Waguespack, S., Gupta, A., Hannon, T., Econs, M. J., Bianco, P., and Robey, P. G. (2003) J. Clin. Invest. 112, 683–692
15. Yamazaki, Y., Okazaki, R., Shibata, M., Hasegawa, Y., Sato, K., Tajima, T., Takeuchi, Y., Fujita, T., Nakahara, K., Yamashita, T., and Fukumoto, S. (2002) J. Clin. Endocrinol. Metab. 87, 4957–4960
16. Webber, T. J., Liu, S., Indridason, O. S., and Quarles, L. D. (2003) J. Bone Miner. Res. 18, 1227–1234
17. Jonsson, K. B., Zahradnik, R., Larsson, T., White, K. E., Sugimoto, T., Imahashi, Y., Yamamoto, T., Hampson, G., Koshiyama, H., Ljunggren, O., Oba, K., Yang, I. M., Miyauuchi, A., Econs, M. J., Lavigne, J., and Juppner, H. (2003) N. Engl. J. Med. 348, 1656–1663
18. Larsson, T., Nisbeth, U., Ljunggren, O., Juppner, H., and Jonsson, K. B. (2003) Kidney Int. 64, 2272–2279
19. Imahashi, Y., Inaba, M., Nakatsu, K., Nagasue, K., Okuno, S., Yoshihara, A., Miura, M., Miyauuchi, A., Kobayashi, K., Miki, T., Shoji, T., Ishimura, K., and Nishizawa, Y. (2004) Kidney Int. 65, 1943–1946
20. Shigematsu, T., Kazama, J. J., Yamashita, T., Fukumoto, S., Hosoya, T., Geeyo, F., Fukagawa, M. (2004) Am. J. Kidney Dis. 44, 250–256
21. Saito, H., Kusano, K., Kinosaki, M., Itc, H., Hirata, M., Segawa, H., Miyamoto, K., and Fukushima, N. (2003) J. Biol. Chem. 278, 2206–2211
22. Bai, X. Y., Mao, D., Goltzman, D., and Karaplis, A. C. (2003) J. Biol. Chem. 278, 8943–8949
23. Shimada, T., Urakawa, I., Yamazaki, Y., Hasegawa, H., Hina, R., Yoneya, T., Takeuchi, Y., Fujita, T., Fukumoto, S., and Yamashita, T. (2004) Biochem. Biophys. Res. Comm. 314, 409–414
24. Shimada, T., Kakitani, M., Yamazaki, Y., Hasegawa, H., Takeuchi, Y., Fujita, T., Fukumoto, S., Tomizuka, K., and Yamashita, T. (2004) J. Clin. Invest. 113, 561–568
25. Shimada, T., Hasegawa, H., Yamazaki, Y., Muto, T., Hina, Y., Takeuchi, Y., Fujita, T., Nakahara, K., Fukumoto, S., and Yamashita, T. (2004) J. Bone Miner. Res. 19, 429–435
26. Katai, K., Miyamoto, K., Kishida, S., Segawa, H., Nii, T., Tanaka, H., Tani, Y., Araki, H., Tatsumi, S., Morita, K., Taketani, Y., Takeda, E. (1999) Biochem. J. 343, 705–714
27. Katai, K., Segawa, H., Haga, H., Morita, K., Araki, H., Tatsumi, S., Taketani, Y., Miyamoto, K., Hisano, S., Fukui, Y., and Takeda, E. (1997) J. Biochem. (Tokyo) 121, 50–55
28. Yoshizawa, T., Handa, Y., Uematsu, Y., Takeda, S., Sekine, K., Yoshihara, Y., Kawakami, T., Arioka, K., Sato, H., Uchiyama, Y., Masushige, S., Fukumizu, A., Matsumoto, T., and Kato, S. (1997) Nat. Genet. 6, 391–396
29. Ecarot, B., and Desbarats, M. (1999) Endocrinology 140, 1192–1199
30. Brewer, A. J., Canaff, L., Hendy, G. F., and Tennenhouse, H. S. (2004) Am. J. Physiol. 286, F739–F748
Circulating FGF-23 Is Regulated by 1α,25-Dihydroxyvitamin D₃ and Phosphorus in Vivo

Hitoshi Saito, Akira Maeda, Shu-ichi Ohtomo, Michinori Hirata, Kenichiro Kusano, Shigeaki Kato, Etsuro Ogata, Hiroko Segawa, Ken-ichi Miyamoto and Naoshi Fukushima

J. Biol. Chem. 2005, 280:2543-2549.
doi: 10.1074/jbc.M408903200 originally published online November 5, 2004

Access the most updated version of this article at doi: 10.1074/jbc.M408903200

Alerts:
• When this article is cited
• When a correction for this article is posted

Click here to choose from all of JBC's e-mail alerts

This article cites 30 references, 6 of which can be accessed free at http://www.jbc.org/content/280/4/2543.full.html#ref-list-1