Fibroblast growth factor 23 production in bone is directly regulated by 1α,25-dihydroxyvitamin D, but not PTH

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Saji F, Shigematsu T, Sakaguchi T, Ohya M, Orita H, Maeda Y, Ooura M, Mima T, Negi S. Fibroblast growth factor 23 (FGF23), which is primarily produced by osteocytes in bone, regulates renal phosphate excretion and 1α,25-dihydroxyvitamin D [1,25(OH)2D3] metabolism. Patients with chronic kidney disease (CKD) have increased levels of circulating FGF23, but the direct effect on circulating FGF23 levels in renal insufficiency is still unclear. To identify the major regulator of FGF23 synthesis in renal insufficiency, we compared the effect of parathyroid hormone (PTH) and 1,25(OH)2D3 on FGF23 synthesis in the calvariae of normal rats with that of uremic rats in vitro. 1,25(OH)2D3 treatment significantly increased the FGF23 concentration in the medium from both groups, but the degree of increase in the uremic group was markedly higher than in the control group. A significant increase in FGF23 mRNA expression occurred as early as 4 h after treatment and reached the maximum within 8 h in the uremic group, whereas in the normal group a significant increase in FGF23 mRNA expression occurred only at 8 h. In addition, the expression of vitamin D receptor (VDR) mRNA in the calvariae of uremic rats was markedly higher than in normal rats. However, in neither group did PTH treatment affect the medium FGF23 concentration or the FGF23 mRNA levels. These results suggest that FGF23 synthesis in bone is regulated by 1,25(OH)2D3 directly, not by PTH, and that increased VDR mRNA expression induced the relatively swift and strong response in the uremic group.

Fibroblast growth factor 23 production in bone is directly regulated by 1α,25-dihydroxyvitamin D, but not PTH. Am J Physiol Renal Physiol 299: F1212–F1217, 2010. First published August 25, 2010; doi:10.1152/ajprenal.00169.2010.—Fibroblast growth factor 23 (FGF23), which is primarily produced by osteocytes in bone, regulates renal phosphate excretion and 1α,25-dihydroxyvitamin D [1,25(OH)2D3] metabolism. Patients with chronic kidney disease (CKD) have increased levels of circulating FGF23, but the direct effect on circulating FGF23 levels in renal insufficiency is still unclear. To identify the major regulator of FGF23 synthesis in renal insufficiency, we compared the effect of parathyroid hormone (PTH) and 1,25(OH)2D3 on FGF23 synthesis in the calvariae of normal rats with that of uremic rats in vitro. 1,25(OH)2D3 treatment significantly increased the FGF23 concentration in the medium from both groups, but the degree of increase in the uremic group was markedly higher than in the control group. A significant increase in FGF23 mRNA expression occurred as early as 4 h after treatment and reached the maximum within 8 h in the uremic group, whereas in the normal group a significant increase in FGF23 mRNA expression was observed only at 8 h. In addition, the expression of vitamin D receptor (VDR) mRNA in the calvariae of uremic rats was markedly higher than in normal rats. However, in neither group did PTH treatment affect the medium FGF23 concentration or the FGF23 mRNA levels. These results suggest that FGF23 synthesis in bone is regulated by 1,25(OH)2D3 directly, not by PTH, and that increased VDR mRNA expression induced the relatively swift and strong response in the uremic group.

chronic kidney disease; phosphate; secondary hyperparathyroidism; vitamin D receptor

REGULATION OF PHOSPHATE HOMEOSTASIS is important in patients with chronic kidney disease (CKD), and secondary hyperparathyroidism (SHPT) is a common complication (36). Hyperphosphatemia, hypocalcemia, and a progressive decline in calcitriol levels stimulate parathyroid hormone (PTH) secretion and thus contribute to the pathogenesis of SHPT (18, 34). Hyperphosphatemic patients with CKD also show a significant increase in the circulating level of fibroblast growth factor 23 (FGF23) (4, 7, 12, 30).

FGF23 is an important regulator of phosphate homeostasis and vitamin D metabolism. An increased circulating level of FGF23 results in both hypophosphatemia, because of renal phosphate wasting, and a low serum 1α,25-dihydroxyvitamin D [1,25(OH)2D3] level, because of decreased expression of renal 1α-hydroxylase and stimlated 24–25 hydroxylase activity (26, 32, 33). FGF23 is primarily produced by osteocytes in bone tissue (14), and we have previously demonstrated that bone contributes to the increased circulating FGF23 levels in uremic rats (28).

The level of circulating FGF23 is regulated by dietary phosphate and the 1,25(OH)2D3 level (15, 27). Recent studies indicate that changes in the serum FGF23 concentration induced by dietary inorganic phosphorus reflect changes in the expression of FGF23 mRNA in bone (20, 21, 24, 25). Understanding the effect of 1,25(OH)2D3 on FGF23 synthesis is important, because vitamin D therapy is often used to treat FGF23-mediated hypophosphatemic disorders, such as X-linked hypophosphatemia (XLH) (37). In fact, others have indicated that active vitamin D therapy is a possible factor in the increased serum FGF23 levels in CKD (22). In addition, a previous study in a mouse model of primary hyperparathyroidism suggested that PTH regulates FGF23 (30). We have confirmed that elevated FGF23 levels in uremic rats decrease after total parathyroidectomy (PTx), consistent with decreased expression of FGF23 in bone (28), and PTx in patients with advanced SHPT and CKD results in a significant reduction in the circulating level of FGF23 (29). These findings suggest that FGF23 is regulated by many factors, including phosphate, 1,25(OH)2D3, and PTH, in CKD. However, the direct regulator of FGF23 synthesis under renal insufficiency conditions is still obscure.

In this study, we hypothesized that regulation of FGF23 synthesis changes between normal and renal insufficiency conditions, and we aimed to identify the dominant regulator of FGF23 synthesis in renal insufficiency. We compared the effect of PTH and 1,25(OH)2D3 on FGF23 synthesis in the calvariae of normal rats and uremic rats in vitro.

MATERIALS AND METHODS

Experimental animals. Six-week-old male Sprague-Dawley rats were purchased from Kiwa Laboratory Animals (Wakaya, Japan) and maintained under specific pathogen-free conditions with a 12:12-h light-dark cycle. The rats then underwent a two-stage 5/6 subtotal nephrectomy to induce renal failure. In the first stage, the left kidney was decapsulated and the approximate upper and lower thirds were removed. The second stage was carried out 1 wk later and consisted of removal of the entire right kidney after the vascular pedicle. Surgical procedures were performed under intraperitoneal pentobarbital sodium anesthesia. The rats were fed a normal diet containing 0.9% phosphorus and 1.12% calcium until 1 wk after the procedure and were then switched to a high-phosphorus diet containing 1.2% phosphorus and 0.4% calcium (Oriental Yeast, Chiba, Japan) for 8 wk (uremic stage). Throughout the experiment, all rats were allowed access to food and drinking water. The animals were killed 8 wk after being placed on the high phosphorus diet, and their calvariae were collected. Age-matched sham-operated rats fed a normal diet were used for comparison. All experimental procedures were approved by the Animal Care and Use Committee of Wakayama Medical University.
Table 1. Body weight and biochemical data of rats from which calvariae were harvested for in vitro treatment with either PTH or 1,25(OH)2D3

<table>
<thead>
<tr>
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<th>PTH Treatment Groups</th>
<th>1,25(OH)2D3 Treatment Groups</th>
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<tr>
<td></td>
<td>Normal</td>
<td>Uremic</td>
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<tr>
<td>Body weight, g</td>
<td>585.1 ± 10.7</td>
<td>380.0 ± 13.5</td>
</tr>
<tr>
<td>P, mg/dl</td>
<td>6.4 ± 0.2</td>
<td>159 ± 1.6*</td>
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<tr>
<td>Ca2+, mmol/l</td>
<td>1.38 ± 0.01</td>
<td>0.94 ± 0.04*</td>
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<tr>
<td>BUN, mg/dl</td>
<td>19.4 ± 1.0</td>
<td>69.2 ± 5.2*</td>
</tr>
<tr>
<td>Cr, mg/dl</td>
<td>0.26 ± 0.02</td>
<td>1.19 ± 0.08*</td>
</tr>
<tr>
<td>Intact PTH, pg/ml</td>
<td>97.4 ± 17.7</td>
<td>8,205.2 ± 1,312.2*</td>
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<tr>
<td>1,25(OH)2D3, pg/ml</td>
<td>175.1 ± 9.3</td>
<td>243.5 ± 34.9</td>
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<tr>
<td>FGF23, pg/ml</td>
<td>466.2 ± 27.5</td>
<td>8,977.4 ± 1,693.7*</td>
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Values are mean ± SE. Normal, n = 12–14/group; uremic, n = 16–23/group. BUN, blood urea nitrogen; Ca2+, plasma ionized calcium; Cr, creatinine; FGF23, fibroblast growth factor 23; P, phosphorus; PTH, parathyroid hormone. *P < 0.01 vs. normal values.

Tissue culture. Part of each calvarium was used to investigate changes in vitamin D receptor (VDR) expression, and the remainder was soaked in ice-cold 0.25 M sucrose solution. The calvariae were halved along the sagittal suture, and each side was weighed. One-half was cut into small pieces to serve as a control for its paired, treated half, which was preincubated overnight in a 35-mm dish with 2.0 ml of medium consisting of DMEM (high glucose) supplemented with 0.25% BSA and antibiotics (100 U penicillin and 100 mg/ml streptomycin) (39). After the preincubation, the medium was removed and replaced with either fresh control medium or medium containing a specific treatment for 48 h: 1) vehicle or 10−7 M PTH (1–34) (Sigma, St. Louis, MO) (1); or 2) vehicle or 10−7 M 1,25(OH)2D3 (Sigma) (11). Cultures were maintained at 37°C in a water-saturated atmosphere containing 5% CO2 and 95% air. The medium and calvarium was collected at 1, 2, 4, 8, 24, and 48 h, and the FGF23 levels were measured. Purified calvarial total RNA underwent real-time PCR for FGF23.

Real-time PCR. Total RNA from each calvarium was purified using TRIzol reagent (Invitrogen, Carlsbad, CA), and cDNA was synthesized using an Omniscript Reverse Transcription kit (Qiagen, Valencia, CA). Real-time quantitative PCR for FGF23 and VDR expressions was performed on an ABI 7700 system (Applied Biosystems) using TaqMan Gene Expression Assays (ID Rn00590709_m1 and Rn00566976_m1, Applied Biosystems). The mRNA levels were normalized to GAPDH mRNA levels (ID Rn09999916_s1, Applied Biosystems).

Measurement of plasma parameters. Blood samples were collected from the carotid artery under anesthesia before death. Plasma phosphorus, blood urea nitrogen (BUN), creatinine, and albumin levels were measured using an automatic analyzer (DRI-CHEM 3500V, Fuji Film, Tokyo, Japan). Plasma ionized calcium (Ca2+) was measured by a portable clinical analyzer (i-stat). Plasma intact PTH and 1,25(OH)2D3 levels were respectively determined using a rat intact PTH ELISA kit (Immutopics) and a radioimmunoassay kit (Thermo, Tokyo, Japan). The plasma and medium FGF23 levels were determined using an appropriate ELISA kit (Kainos Laboratories, Tokyo, Japan).

Statistical analysis. All values are expressed as the means ± SE, and statistical significance was determined using the Mann-Whitney U-test or Wilcoxon rank sum test for the in vitro study. All statistical computations were performed using the Statistical Package for Social Sciences 12.0J for Windows (SPSS, Chicago, IL). P < 0.05 was considered statistically significant.

RESULTS

Body weight and biochemical data. Body weight was significantly lower in the uremic group than in the normal group (Table 1). The plasma concentrations of phosphorus, creatinine, BUN, PTH, and FGF23 were significantly increased in the uremic group compared with the normal group. The plasma Ca2+ level was decreased in the uremic group, but a significant decrease in the plasma 1,25(OH)2D3 level was not observed. No significant differences in these basic parameters of both of

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<th>Normal</th>
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<th>Normal</th>
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<tr>
<td>Body weight</td>
<td>585.1 ± 10.7</td>
<td>380.0 ± 13.5</td>
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<td>359.0 ± 8.0</td>
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<td>P, mg/dl</td>
<td>6.4 ± 0.2</td>
<td>159 ± 1.6*</td>
<td>6.8 ± 0.1</td>
<td>14.4 ± 1.1*</td>
</tr>
<tr>
<td>Ca2+, mmol/l</td>
<td>1.38 ± 0.01</td>
<td>0.94 ± 0.04*</td>
<td>1.38 ± 0.01</td>
<td>1.00 ± 0.03*</td>
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<tr>
<td>BUN, mg/dl</td>
<td>19.4 ± 1.0</td>
<td>69.2 ± 5.2*</td>
<td>19.3 ± 0.5</td>
<td>61.3 ± 4.0*</td>
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<tr>
<td>Cr, mg/dl</td>
<td>0.26 ± 0.02</td>
<td>1.19 ± 0.08*</td>
<td>0.23 ± 0.13</td>
<td>1.00 ± 0.07*</td>
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<tr>
<td>Intact PTH, pg/ml</td>
<td>97.4 ± 17.7</td>
<td>8,205.2 ± 1,312.2*</td>
<td>91.8 ± 10.5</td>
<td>10,766.9 ± 1,312.2*</td>
</tr>
<tr>
<td>1,25(OH)2D3, pg/ml</td>
<td>175.1 ± 9.3</td>
<td>243.5 ± 34.9</td>
<td>211.6 ± 16.4</td>
<td>179.4 ± 17.4</td>
</tr>
<tr>
<td>FGF23, pg/ml</td>
<td>466.2 ± 27.5</td>
<td>8,977.4 ± 1,693.7*</td>
<td>434.3 ± 22.6</td>
<td>8,383.0 ± 1,384.1*</td>
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Statistical analysis performed on an ABI 7700 system (Applied Biosystems) using TaqMan Gene Expression Assays (ID Rn00590709_m1 and Rn00566976_m1, Applied Biosystems). The mRNA levels were normalized to GAPDH mRNA levels (ID Rn09999916_s1, Applied Biosystems).
After treatment. Treatment with 1,25(OH)\(_2\)D\(_3\) significantly changes in FGF23 mRNA expression of the calvariae at 48 h.

In the uremic group, the significant increase was observed within 8 h (Fig. 4B). In the normal group, a significant increase was observed only at 8 h (Fig. 4A). We could not confirm significant differences in FGF23 mRNA expression after PTH treatment in either group (Fig. 5, A and B).

Expression of VDR mRNA in calvariae. To investigate whether the stronger stimulation of FGF23 synthesis by 1,25(OH)\(_2\)D\(_3\) in the uremic group was related to greater expression of VDR mRNA, we examined the expression of VDR mRNA in the calvariae of normal and uremic rats and it was markedly higher in the uremic group (Fig. 6).

DISCUSSION

We performed this study to determine the direct regulator of FGF23 synthesis in bone, and the effect of renal insufficiency on that regulator. We confirmed that 1,25(OH)\(_2\)D\(_3\) treatment of both the normal and uremic group increased the accumulation of FGF23 in the medium. This result is consistent with previous in vivo and in vitro reports (15, 11) and indicates that FGF23 production in bone is regulated directly by 1,25(OH)\(_2\)D\(_3\). Compared with the swift increase in FGF23 concentration at 8 h after treatment in the uremic group, the significant increase in the normal group occurred at 24 h after treatment. In addition, the normal and uremic groups for which the calvariae were used were observed between the PTH and 1,25(OH)\(_2\)D\(_3\) treatment groups.

FGF23 concentration of medium. We observed a significant increase in the FGF23 concentration in the medium with 1,25(OH)\(_2\)D\(_3\) treatment in each group (Fig. 1, A and B). In the uremic group, the significant increase was observed within 8 h after treatment and reached its maximum at 48 h, an approximately ninefold increase compared with vehicle treatment (Fig. 1B). In contrast, the significant increase in the normal group was confirmed at 24 h after treatment, and the maximum was approximately twofold greater at 48 h (Fig. 1A). We did not observe any stimulation by PTH of the medium FGF23 concentration (Fig. 2, A and B). Accumulation of FGF23 in the medium with each vehicle treatment in the uremic group was markedly higher than that in the normal group.

Expression of FGF23 mRNA in calvariae. We investigated changes in FGF23 mRNA expression of the calvariae at 48 h after treatment. Treatment with 1,25(OH)\(_2\)D\(_3\) significantly increased FGF23 mRNA expression compared with vehicle treatment in the uremic group, but in the normal group treated with 1,25(OH)\(_2\)D\(_3\) and in both groups treated with PTH significant changes were not observed (Fig. 3, A and B). Moreover, we examined the time course of the effect of PTH or 1,25(OH)\(_2\)D\(_3\) on the mRNA levels for FGF23 in the calvariae from each group. A significant increase in FGF23 mRNA expression was observed as rapidly as 4 h after 1,25(OH)\(_2\)D\(_3\) treatment and reached the maximum within 8 h in the uremic group (Fig. 4B). In the normal group, a significant increase was observed only at 8 h (Fig. 4A). We could not confirm significant differences in FGF23 mRNA expression after PTH treatment in either group (Fig. 5, A and B).
increase in the FGF23 concentration of the medium in the uremic group was markedly higher than that in the normal group. On the basis of a previous report, these differences might be explained by increased FGF23 synthesis in the bones of uremic rats compared with normal rats (28).

Additionally, we investigated the time course of the effect on FGF23 mRNA expression levels in calvariae by real-time PCR. In the uremic group, the FGF23 mRNA levels were significantly increased at 4 h after 1,25(OH)2D3 treatment and were maintained until the end of the study, consistent with increased accumulation of FGF23 in the medium. The maximum increase was observed at 8 h. On the other hand, the significant increase in FGF23 mRNA expression in the normal group was limited at 8 h, despite increases in the FGF23 concentration of the medium from 24 to 48 h. These discrepancies are predictable, because of the time lag between transcription and translation. Indeed, the increase in FGF23 concentration of the medium at 48 h after treatment was negligible. These data indicate that the response to 1,25(OH)2D3 in the uremic group was stronger than in the normal group.

Next, to determine the cause of the swift and strong response in the uremic group, we examined the expression of VDR mRNA in the calvariae of each group of rats. In its target tissues, 1,25(OH)2D3 exerts most of its biological actions by binding to the VDR. The direct effect of 1,25(OH)2D3 on FGF23 production concurs with the fact that VDR-null mice do not respond to 1,25(OH)2D3 administration (8, 9, 40). In this study, we confirmed that the expression of VDR mRNA in the calvariae of uremic rats was significantly increased compared with normal rats. Our data suggest that increased VDR might induce the relatively swift and strong response in the uremic group, which is an interesting possibility with regard to the relationship between vitamin D therapy and increased serum FGF23 levels in CKD patients. However, a previous report demonstrated a lower density of VDR in parathyroids obtained from patients with CKD (5), which is consistent with our previous study in the same uremic rat model that we used in the present study (31). Therefore, the expression of VDR mRNA in these rats shows a discrepancy between the parathyroid and the calvarium. 1,25(OH)2D3 increases the expression of VDR in the parathyroid, and then decreases PTH gene transcription (23, 35), so it seems that one reason for the reduced number of VDR in parathyroid tissue from patients with CKD is the decreased plasma 1,25(OH)2D3 levels. However, in the present study the plasma 1,25(OH)2D3 levels in the uremic group were not confirmed as significantly different compared with the normal group.

Fig. 4. Time course of the effect of 1,25(OH)2D3 on FGF23 expression in the rat calvarium. Calvariae were treated with vehicle or 10\(^{-7}\) M 1,25(OH)2D3 for 24 h. Expression was assessed by real-time PCR and relative to the levels of the GAPDH control gene. Values are means ± SE. A: normal group (n = 7). B: uremic group (n = 10). *P < 0.05, **P < 0.01 vs. treatment with vehicle.

Fig. 5. Time course of the effect of PTH on FGF23 expression in the rat calvarium. Calvariae were treated with vehicle or 10\(^{-7}\) M PTH for 24 h. Expression was assessed by real-time PCR and relative to the levels of the GAPDH control gene. Values are means ± SE. A: normal group (n = 6). B: uremic group (n = 8).

Fig. 6. Quantitative analysis of vitamin D receptor mRNA levels in the calvariae of normal rats and uremic rats. Expression was assessed by real-time PCR and relative to the levels of the GAPDH control gene. Values are means ± SE. Normal rats, n = 14; uremic rats, n = 23. *P < 0.05 vs. normal rats.
normal group. Our previous study showed that plasma 1,25(OH)2D3 levels increased initially in the uremic model rats because of increased plasma PTH levels and residual renal function, and then decreased to baseline levels, associated with a progressive decline in renal function, at 8 wk, the same time point as in the present study (28). The increased VDR in the calvariae may be induced by the late increase in the plasma 1,25(OH)2D3 levels, and will perhaps decrease ultimately, associated with the decreased plasma 1,25(OH)2D3 levels in renal insufficiency. Perhaps there is a difference between the calvarium and the parathyroid gland in VDR expression under renal insufficiency conditions. Further research is necessary to confirm this.

In contrast, we could not confirm the effect of PTH on FGF23 production in the calvariae from both groups, which suggests that the FGF23 production is not directly regulated by that factor. These observations do not mean that it is not an important regulator of FGF23 production. Indeed, a recent study indicated that PTH-cyclin D1 transgenic (PC2) mice express markedly increased FGF23 levels in bone compared with normal mice (10). No change in the FGF23 production in bone might be explained by loss of the in vivo stimuli required for regulation of FGF23 production. Plasma 1,25(OH)2D3 levels are regulated by PTH, and thus PTH may regulate FGF23 production via 1,25(OH)2D3.

In this study, we examined the effect of PTH and 1,25(OH)2D3 because it is known that their receptors exist in bone. We confirmed the direct effect of 1,25(OH)2D3, and an increase in VDR mRNA levels, in bone. These results support those of previous reports that active vitamin D therapy is a possible factor in the increased serum FGF23 levels in CKD patients (22). However, the circulating 1,25(OH)2D3 levels of patients with CKD are markedly reduced, and several reports suggest that phosphorus levels regulate FGF23 production under CKD conditions (7, 12, 21, 30). In addition, several studies indicate that changes in the serum FGF23 concentration induced by dietary inorganic phosphorus reflect changes in the expression of FGF23 mRNA in bone (20, 21, 24, 25) and that phosphorus and 1,25(OH)2D3 independently regulate FGF23 production (9, 40). Moreover, in a clinical study the elevated serum FGF23 levels in cases of advanced secondary hyperparathyroidism with CKD decreased slowly after PTx (29), consistent with our previous in vivo study (28). These results suggest the existence of another direct factor that is not 1,25(OH)2D3. Indeed, a phosphate-regulating gene with homology to endopeptidases on the X chromosome (PHEX), responsible for XLH, and dentin matrix protein 1 (DMP1), responsible for autosomal recessive hypophosphatemic rickets (ARHR), is known to be a causative factor in increased FGF23 levels, as observed in XLH and ARHR (14, 17). It is known that mutations of ENPP1 also cause ARHR, but the relationship between FGFR23 and ENPP1 is still obscure (13, 19). On the other hand, it is also reported that PHEX expression in bone is increased by chronic renal insufficiency and decreased by 1,25(OH)2D3 administration, and a reduction in PHEX can lead to increased expression of FGF23 mRNA (2, 14, 16). Therefore, there seems to be both direct and indirect mechanisms for the regulation of FGF23 synthesis in bone by 1,25(OH)2D3. However, it remains to be established whether these regulators stimulate FGF23 synthesis via direct effects on osteocyte function or indirectly through alterations in extracellular matrix-related factors. On the basis of these reports, FGF23 synthesis in bone has a complex regulation system. Moreover, we cannot completely disregard that declining renal function in patients with CKD may be a potential explanation for elevated serum FGF23 concentrations as a result of decreased renal clearance. Indeed, a recent study indicated that dialyzed patients with any (even very minimal) urine output have much lower circulating FGF23 levels than do dialysis patients who are completely anuric (38).

In conclusion, the clinical relevance of high FGF23 in CKD is largely unknown, but as recent studies indicate that a high level of FGF23 is an important predictor of the progression of CKD, and a strong predictor of death (3, 6), it is important to understand the regulation system of FGF23 synthesis in patients with CKD. In this study, we demonstrated that 1,25(OH)2D3 increased FGF23 synthesis in the calvariae of rats and that stimulation by 1,25(OH)2D3 was affected more swiftly and strongly in the uremic group. In addition, VDR mRNA levels in the calvariae were increased in the uremic rats. These results suggest that FGF23 synthesis in bone is regulated by 1,25(OH)2D3 directly and that the increase in VDR induced the relatively swift and strong response in the uremic group. However, the existence of another direct regulator of FGF23 expression is predicted and further research is necessary to understand the regulation system of FGF23 in patients with CKD.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

REFERENCES


