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Ultraviolet B activated $1,25(OH)_2D$ affects the level of fibroblast growth factor-23 in human

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Abstract. Fibroblast growth factor 23 (FGF-23) is known as a phosphaturic factor regulating phosphate homeostasis. Several studies suggest that dietary phosphate, serum phosphate and 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] are candidate regulators of FGF-23. While the human studies, which modulated the dietary or serum phosphate showed in rather controversial results, manipulation of the active vitamin D definitely affected FGF-23 in animals. This study was conducted to elucidate the relationship between active vitamin D directly stimulated by ultraviolet B (UVB) exposure and FGF-23 level in human. Ten healthy young adults were recruited to get the UVB exposure thrice a week at sub-minimal erythemal dose with gradual increment by 10% only for 4 weeks. Serum calcium, phosphate, mineral-related hormones and bone turnover markers were analyzed before and after the UVB exposure every 4 week for 12 whole weeks. Twenty five-hydroxyvitamin D [25(OH)D] increased by 115% (19.8 ng/mL to 40.5 ng/mL, $p < 0.001$) after 4 weeks of UVB exposure. While $1,25(OH)_2D$ increased by 75% (49.9 pg/mL to 64.4 pg/mL, $p < 0.001$) then both level decreased after 4 weeks of withdrawal. C-telopeptide peaked at 2nd week then decreased, while osteocalcin increased gradually. FGF-23 started to increase from the 4th week of UVB exposure then significantly at the 4th week after withdrawal of UVB (27.8 pg/mL to 41.4 pg/mL, $p < 0.05$). UVB exposure effectively increased $1,25(OH)_2D$ with delayed stimulatory effect on FGF-23. This result could support the regulatory loop of $1,25(OH)_2D$ and FGF-23 in human, FGF-23 regulation by $1,25(OH)_2D$.

Key words: Fibroblast growth factor 23, Ultraviolet B, Vitamin D

INORGANIC PHOSPHORUS (Pi) is crucial component for diverse processing and signaling of cells. Fibroblast growth factor 23 (FGF-23), a novel member of the FGF family, has recently been identified as a novel phosphaturic agent regulating phosphate homeostasis [1-3]. FGF-23 acts negatively on the sodium-dependent Pi cotransporter, NaPi2a and 1α-hydroxylase, leading to reduced levels of 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] with a resultant decrease in renal phosphate reabsorption [4]. The expression of FGF-23 is up-regulated by $1,25(OH)_2D$ in mice model [5-7]. Whereas, the supportive data which clearly showed the possible stimulatory effects of $1,25(OH)_2D$ on FGF-23 secretion in human is insufficient.

External ultraviolet-B (UVB) radiation can activate vitamin D system in human. UVB irradiation thrice per week induces comparable serum level of vitamin D to oral supplement in the elderly [8]. In the present study, we examined whether the active vitamin D stimulated by UVB exposure could influence the FGF-23 level in healthy human, and could conclude that the increased $1,25(OH)_2D$ affects FGF-23 secretion in human.

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Subjects and Methods

Subjects

The study subjects were 10 healthy Korean volunteers. All subjects gave written informed consent to the study, which was approved by the institutional review board at

Yonsei University. None had any acute or chronic diseases, and none were taking any medication. During the study period, from December 2006 to March 2007, all subjects were instructed to consume a nutritionally balanced diet without any supplementary medication.

UVB exposure

The subjects received whole body UVB irradiation three times per week during 4 weeks (total 12 times) using broadband UVB lamps (Light Sources FS72 T12 UVB HO, Philips, Amsterdam, Netherlands) in a standard phototherapy unit. Radiance of the light was measured by UVB detector (UVB 500C, National Biological Corporation, Beachwood, USA). We checked each minimal erythemal dose (MED) of subjects individually. Irradiation was started with dose of 70% of MED of each subject, and the duration of exposure was increased by 10% in every following irradiation up to sub-MED doses. Exposure time varied from 20 to 50 seconds and total energy varied from 20 to 50 mJ/cm^2.

Blood sampling and measurements

Biological measurements were done at once with blood collected and frozen during the study period. The levels of serum calcium (Ca) and Pi were measured using standard methods. Twenty five-hydroxyvitamin D [25(OH)D] was measured by radioimmunoassay (RIA; INCSTAR Corp., Stillwater, MN, USA); the intra-assay coefficient of variation (CV) was < 12.5% and the interassay CV was < 11.0%. Plasma 1,25$(OH)_2$D levels were also measured by RIA (Diasorin Inc., Stillwater, MN, USA); the intra-assay CV was < 7.7% and the interassay CV was < 11.1%. The serum intact PTH level was determined using the Nichols Bio-Intact assay (Nichols Institute, San Clemente, CA, USA); the intra-assay CV was < 2.7% and the inter-assay CV was < 3.5%. Serum osteocalcin was measured by RIA (CIS-Bio International, Gif-sur-Yvette, France). Serum C-terminal cross-linked telopeptide of type I collagen (CTx) was measured by enzyme chemiluminescence immunoassay (Elecsys β-CrossLaps; Roche Diagnostics, Mannheim, Germany); the intra-assay CV was < 5.9%, and the interassay CV was < 5.8%. Plasma FGF-23 was measured with a two-site enzyme-linked immunosorbent assay (ELISA) sensitive to the human FGF-23 C-terminus and N-terminus (Immunotopics Inc, San Clemente, CA,USA), and the intra-assay CV was < 4.4%, and the interassay CV was < 6.5%. All measurements used in this analysis were performed at the baseline visit. And then, same tests were repeated after 2, 4, 8 and 12 weeks later. Nutritional status of the subjects was assessed by questionnaire at the baseline visit. Daily calcium, phosphorus and vitamin D intake was calculated according to Korean version of Food Frequency Questionnaire.

Adverse effects of UVB exposure

Adverse effects by UVB exposure including burn, erythema, itching sensation and hyperpigmentation were monitored during and after the UVB exposures. Itching sensation was evaluated by visual analogue scales (VAS) (0=none to 10=extreme).

Statistical analysis

Analyses were conducted with SPSS 13.0 for Windows (SPSS, Inc., Chicago, USA). Wilcoxon signed ranks test was used to evaluate the changes of each scale between baseline and those obtained after irradiation. p values < 0.05 were considered to indicate statistical significance.

Results

Baseline characteristics

Table 1 showed the baseline characteristics of study participants. The mean age of the 10 subjects (7 men and 3 women) was 27.9 years (range: 23-38). Mean body mass index was 23.2 kg/m^2. Calculated daily intakes of each nutrient were shown as Table 1. Each mean 25(OH)D and 1,25$(OH)_2$D at baseline were 19.8 ± 10.9 ng/mL and 49.5 ± 14.6 pg/mL. Nine of ten subjects fell under 'vitamin D insufficient group', *i.e.*, 25(OH)D under 30 ng/mL.

Changes in vitamin D metabolites and FGF-23

The changes of serum parameters including vitamin D metabolites, PTH, FGF-23, Ca, Pi and bone turnover markers were provided in Table 2 and Fig. 1A. After 2

Table 1 Baseline nutritional characteristics of enrolled subjects

	Mean	Range
Age (yr)	27.9	23-38
BMI (kg/m^2)	23.2	20.9-26.0
Weekly sun exposure (h)	4.4	1.0-10.0
Daily calcium intake (mg)	788	444-1505
Daily phosphorus intake (mg)	1773.5	1175-2320
Daily vitamin D intake (mcg)	69.5	20.0-185.0

Table 2 Levels of serum parameters including Ca, Pi, vitamin D metabolites, PTH, FGF-23 and bone turnover markers in each time points after UVB exposure

	Baseline	2nd week	4th week	8th week	12th week
25(OH)D, ng/mL	19.8 ± 10.9	33.4 ± 8.8*	40.5 ± 11.1*	31.7 ± 10.5*	28.4 ± 12.7*
$1,25(OH)_2D$, pg/mL	49.9 ± 14.6	63.3 ± 13.4*	82.6 ± 26.5*	60.2 ± 13.9	62.5 ± 25.6
PTH, pg/mL	32.0 ± 11.5	30.2 ± 10.9	35.1 ± 11.6	36.3 ± 12.8	34.5 ± 9.2
FGF-23, pg/mL	27.8 ± 14.0	34.4 ± 20.9	37.5 ± 18.7	41.4 ± 11.5*	47.1 ± 25.3†
Ca, mg/dL	9.9 ± 0.2	9.7 ± 0.3	9.7 ± 0.3	9.6 ± 0.4	9.5 ± 0.3
Pi, mg/dL	3.8 ± 0.6	4.0 ± 0.6	4.0 ± 0.4	3.8 ± 0.5	3.7 ± 0.6
CTx, ng/mL	0.270 ± 0.197	0.400 ± 0.210*	0.397 ± 0.232*	0.333 ± 0.168	0.315 ± 0.195
Osteocalcin, ng/mL	6.7 ± 3.3	7.9 ± 3.0	7.5 ± 3.4	7.8 ± 3.0	13.1 ± 6.0*

25(OH)D, 25-hydroxyvitamin D; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; PTH, parathyroid hormone; FGF-23, fibroblast growth factor-23; Ca, Calcium; Pi, inorganic phosphorus; CTx, serum C-terminal cross-linked telopeptide of type I collagen
Data are mean ± SDs. *$p < 0.05$ *vs*. baseline levels, †$p = 0.09$ *vs*. baseline level

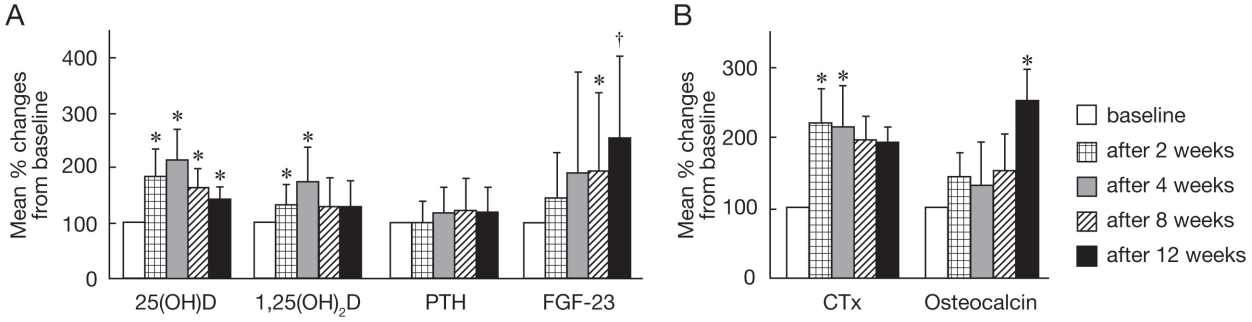

Fig. 1 Percent changes compared to baseline in the vitamin D metabolite, PTH, FGF-23 (A) and bone turnover markers (B)
Sub-MED UVB were done only during the first 4 weeks. 25(OH)D, 25-hydroxyvitamin D; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; PTH, parathyroid hormone; FGF-23, Fibroblast growth factor 23; CTx, C-telopeptide. *$p < 0.05$ *vs*. baseline †$p = 0.09$ *vs*. baseline

weeks of UVB exposure, statistically significant changes of serum 25(OH)D and $1,25(OH)_2D$ were noticed (19.8 ng/mL to 33.4 ng/mL, and 49.5 pg/mL to 63.3 pg/mL, $p < 0.05$ respectively). After 4 weeks, 25(OH)D increased by 115% (19.8 ng/mL to 40.5 ng/mL, $p < 0.05$), while $1,25(OH)_2D$ increased by 75% (49.9 pg/mL to 82.6 pg/mL, $p < 0.05$). After 4 weeks of UVB withdrawal, at 8th week of study period, both parameters decreased to 31.7 ng/mL and 60.2 pg/mL, respectively. However, no significant changes in Ca, Pi or PTH were noticed during the study period. FGF-23 gradually increased after the exposure to UVB, and significant increase was detected at 4th weeks after withdrawal of UVB by 194% (27.8 pg/mL to 41.4 pg/mL, $p < 0.05$). FGF-23 further increased after 8 weeks of UVB withdrawal (27.8 pg/mL to 47.1 pg/mL, $p = 0.09$).

Effects on bone remodeling

CTx rose about 220% higher as early as 2nd week of UVB exposure and then decreased, while osteocalcin increased up to 250% later on at the last 12th weeks (Table 2 and Fig 1B).

Adverse effects of UVB exposure

Six of the subjects had itching sensation during the UVB exposure with VAS score ranging 1 to 7 (mean VAS score = 4.33). Itching sensation disappeared after 20 days of exposure. Seven subjects showed temporary hyperpigmentation of the skin as the result of tanning, which disappeared within 12 to 60 days.

Discussion

FGF-23 is one of major phosphate-regulating hormone, therefore information about how FGF-23 regulation occurs is important for understanding homeostasis of phosphate and human physiology. There have been several *in vivo* or *in vitro* reports which supported a possible role of $1,25(OH)_2D$ in the regulation of FGF-23 production, whereas few human

studies showing the relation between the $1,25(OH)_2D$ and FGF-23 [9-12]. To our knowledge, this is the first study to show that $1,25(OH)_2D$ activated by UVB affects the plasma FGF-23 levels in human. Two findings are notable associated with the physiology of FGF-23. First, $1,25(OH)_2D$, which was increased by UVB, gradually stimulated synthesis of FGF-23 without affecting serum calcium or phosphate level. Second, the delayed increase of FGF-23 together with osteocalcin suggests that some time lapse exists to fully activate the osteoblasts or osteocytes coupled to active osteoclasts stimulated by active vitamin D [13].

Currently known factors affecting FGF-23 are dietary phosphate, serum phosphate and calcitriol [14]. However, there are controversies among the studies dealing with the effect of dietary phosphate on circulating FGF-23 [15-18]. Previous report on the gonadal steroid withdrawal on FGF-23 was negative even though there was a clear increment of serum phosphate within 4 weeks of starting GnRH analog. The increase of serum phosphate was due to the acutely elevated bone turnover since the testosterone and estrogen went down to very low level [14]. On the contrary, in the situation of chronically stimulated bone remodeling such as in Graves' disease resulted in hyperphosphatemia with appropriate diminution of FGF-23 level [19]. Therefore, to see any changes in the tightly regulated FGF-23, we needed to choose UVB to stimulate the levels of vitamin D metabolites without any changes in gastrointestinal environment. It was unexpected to have such a high increases in $1,25(OH)_2D$, since it is known that skin blocks itself of any further excessive synthesis of $1,25(OH)_2D$ by UVB. According to Adams *et al*., vitamin D deficient subjects are prone to over-exaggerated response to UVB, probably resulting from previously chronically stimulated PTH and 1-α hydroxylase [20]. The prevalence of vitamin D insufficiency was almost 90% in our study group, which was a very unique finding in Korean young healthy population in a recent 4th Korea National Health and Nutrition Examination Survey (KNHANES Ⅳ) [21]

Collins *et al*. reported that administration of calcitriol showed stimulatory effect on the FGF-23 production [22]. Also in this study, we could also observe later significant increase in serum FGF-23 level following the UVB stimulated elevation of $1,25(OH)_2D$ level. Even though there was a time gap between the up-regulation of $1,25(OH)_2D$ and FGF-23, these serial changes could support that the possible regulatory role of $1,25(OH)_2D$ in FGF-23 production from bone. Since the delayed changes of serum FGF-23 level happened in parallel with increase of serum osteocalcin. The time-lapse of late increment of FGF-23 and osteocalcin indicates that the subsequently coupled osteoblasts to activated osteoclasts induced by $1,25(OH)_2D$ might have contributed to the time differences [9, 13]. Meanwhile, the levels of $1,25(OH)_2D$ declined to the baseline levels in time points of 8th and 12th week when the level of FGF-23 peaked. As one of feedback mechanism, FGF-23 has inhibitory action on 1-alpha hydroxylase to prevent further production of $1,25(OH)_2D$, so these recovery pattern in $1,25(OH)_2D$ levels might also have been caused by increased FGF-23 levels [23].

Regarding the levels of Ca, Pi and PTH, we could not observe any significant changes. Even though the physiologic contribution of FGF-23 is important in Ca and Pi homeostasis, those minerals are also tightly regulated by other hormone, including PTH, in kidney-intestine-bone axis in human. Therefore, the acute and transient changes of PTH might have occurred, and the subsequent adaptation of mineral metabolism could already have been accomplished at 2nd week of our first analysis. This might be a possible mechanism of stationary trends in the levels of Ca, Pi and PTH, and this phenomenon was similarly observed in other studies [22, 24, 25] . Consequently, what we see here could be the delayed and final response of bone itself, and bone turnover markers, CTx and osteocalcin, were increased after UVB exposure. The $1,25(OH)_2D$ has both catabolic and anabolic actions in bone mineral homeostasis targeting intestine or bone, and harmony of these bi-directional actions is crucial for maintaining the physiologic levels of calcium and phosphate levels [26, 27]. These changes observed in bone turnover markers might contribute to maintain mineral homeostasis in a reasonable range with FGF-23 being the negative regulator of calcitriol even in the clinical setting as in the rodent model [7]. However, whether the changes of bone turnover markers affected bone quantity and quality is unknown.

There are several limitations in this study. The sample size was small. Additionally urinary excretion of Ca and Pi was not measured, despite these parameters might be quite informative for investigating biological significance of stimulated FGF-23 production. FGF-23 has been known that it diminishes renal expression of NaPi2a and increases urinary Pi excretion [24, 28]. We suggested that urinary excretion of Pi in these study

subjects might have been also affected, but we could not conclude without corresponding results. Furthermore, we measured the serum parameters with time intervals of 2 or 4 weeks, so we could not conclude whether transient changes of these assessed markers were happened or not during the initial 2 weeks of UVB exposure. Another limitation is the lack of a control group which did not receive UVB exposure. However, it has been shown in a previous study that FGF-23 level stays quite stable under physiologic condition without any specific stimuli [29].

In conclusion, we showed that $1,25(OH)_2D$ effectively stimulated by 4 weeks of sub-MED UVB exposure was associated with delayed increase of FGF-23 level and this result could clearly support that FGF-23 in human physiology might be significantly related to changes in the $1,25(OH)_2D$ levels, over the rapidly controlled Ca, Pi and PTH axis.

Disclosure of Financial Conflicts of Interest

The authors disclose that they have no competing interests in this work.

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