EnM
ENDOCRINOLOGY AND METABOLISM

Original Article

Endocrinol Metab 2017;32:451-459
https://doi.org/10.3803/EnM.2017.32.4.451
pISSN 2093-596X · eISSN 2093-5978

Effects of Single Vitamin D_3 Injection (200,000 Units) on Serum Fibroblast Growth Factor 23 and Sclerostin Levels in Subjects with Vitamin D Deficiency

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Background: Vitamin D deficiency remains common in all age groups and affects skeletal and non-skeletal health. Fibroblast growth factor 23 is a bone-derived hormone that regulates phosphate and 1,25-dihydroxyvitamin D homeostasis as a counter regulatory factor. 1,25-Dihydroxyvitamin D stimulates fibroblast growth factor 23 synthesis in bone, while fibroblast growth factor 23 suppresses 1,25-dihydroxyvitamin D production in the kidney. The aim of this study was to evaluate the effects of vitamin D_3 intramuscular injection therapy on serum fibroblast growth factor 23 concentrations, and several other parameters associated with bone metabolism such as sclerostin, dickkopf-1, and parathyroid hormone.

Methods: A total of 34 subjects with vitamin D deficiency (defined by serum 25-hydroxyvitamin D levels below 20 ng/mL) were randomly assigned to either the vitamin D injection group (200,000 units) or placebo treatment group. Serum calcium, phosphate, urine calcium/creatinine, serum 25-hydroxyvitamin D, fibroblast growth factor 23, sclerostin, parathyroid hormone, and dickkopf-1 levels were serially measured after treatment.

Results: Comparing the vitamin D injection group with the placebo group, no significant changes were observed in serum fibroblast growth factor 23, parathyroid hormone, or dickkopf-1 levels. Serum sclerostin concentrations transiently increased at week 4 in the vitamin D group. However, these elevated levels declined later and there were no statistically significant differences as compared with baseline levels.

Conclusion: Serum fibroblast factor 23, sclerostin, parathyroid hormone, and dickkopf-1 levels were not affected significantly by single intramuscular injection of vitamin D_3.

Keywords: Vitamin D3; Injections, intramuscular; Fibroblast growth factor 23; Sclerostin

INTRODUCTION

Vitamin D plays an essential role in bone and mineral metabolism [1]. It is also important in non-skeletal tissues, and its deficiency is closely associated with increased risk of cancers, infections, autoimmune diseases, cardiovascular diseases, and di-

Received: 1 June 2017, **Revised**: 9 August 2017, **Accepted:** 10 October 2017
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abetes mellitus [2-5]. Despite growing public awareness of the multiple health benefits of vitamin D, epidemiological studies have revealed a very high prevalence of vitamin D deficiency worldwide, especially in Asian countries [6,7].

Vitamin D is mainly produced in the skin when directly exposed to sunlight, or obtained from the diet. Active vitamin D maintains calcium and phosphate homeostasis by promoting intestinal absorption for the bone mineralization process [8]. Aside from its role in the endocrine pathway, active vitamin D is known to affect the differentiation and function of bone cells by targeting key genes involved in bone formation and resorption [9]. Oral supplementation with vitamin D and calcium is common practice in the treatment of vitamin D deficiency. In addition to oral supplementation, vitamin D can also be administered by intramuscular injection. Heikinheimo et al. [10] reported that annual intramuscular injection of ergocalciferol vitamin D_2 (150,000 to 300,000 IU) resulted in a significant reduction in the incidence of fractures.

To maintain calcium and phosphate homeostasis, active vitamin D works in combination with two other hormones: fibroblast growth factor 23 (FGF23) and parathyroid hormone (PTH) [11]. 1,25-Dihydroxyvitamin D ($1,25(OH)_2D$) stimulates FGF23 synthesis in bone, while FGF23 suppresses the production of $1,25(OH)_2D$; thus, acting as a counter-regulatory factor [12]. FGF23 levels are reportedly significantly elevated in patients with chronic kidney disease (CKD), who are at increased risk of mortality mainly from cardiovascular disease [13]. CKD-mineral and bone disorder (CKD-MBD) occurs from the early stages of CKD, and there is a strong association between FGF23 and cardiovascular risks, left ventricular hypertrophy, and vascular calcification [13-15]. A study conducted in patients with vitamin D deficiency who were given a high dose vitamin D_2 injection (300,000 IU) combined with usual daily oral supplementations of calcium (1.2 g) and vitamin D_3 (800 IU) reported that high dose vitamin D increased $1,25(OH)_2D$ and FGF23 concentrations [16]. However, there is a paucity of data regarding the effects of single intramuscular injections of 200,000 IU of vitamin D_3.

Sclerostin and dickkopf-1 (DKK1) are two important endogenous Wnt signaling antagonists, mainly produced in bone [17,18]. Sankaralingam et al. [19] reported that bolus intramuscular injection of 300,000 IU of vitamin D combined with oral supplementation of vitamin D and calcium increased sclerostin and DKK1 concentrations. In contrast, another study demonstrated that in patients with vitamin D deficiency who were given a monthly intramuscular injection of 300,000 IU of vitamin D, sclerostin levels decreased considerably after treatment [20].

The aim of our study was to determine the effects of single intramuscular injection of vitamin D_3 at 200,000 IU on circulating concentrations of 25-hydroxyvitamin D (25(OH)D), FGF23, sclerostin, and DKK1 in patients with vitamin D deficiency.

METHODS

Study subjects and design

Thirty-four subjects (five males and 29 females) aged 33.2±7.7 years, diagnosed with vitamin D deficiency at Severance Hospital, Yonsei University College of Medicine and Dongguk University Ilsan Hospital in Korea were recruited in this study. Vitamin D deficiency was diagnosed if serum 25(OH)D concentrations were below 20 ng/mL. Patients who were taking medications that may affect vitamin D metabolism were excluded from the study.

This study was designed as a randomized, double-blinded, and placebo-controlled clinical trial. Subjects were randomly assigned to the experimental group or the placebo group at a 2:1 ratio. All subjects were given either a single intramuscular injection of vitamin D_3 (200,000 IU), or a placebo at the beginning of the study. During this intervention period, consumption of any additional vitamin D supplements and exposure to direct sunlight for more than 10 hours were prohibited. Usual diets were maintained, except diets containing abundant vitamin D.

Laboratory measurements

Fasting blood samples were collected at baseline and weeks 4, 8, 12, and 14 during follow-up visits after vitamin D or placebo injections. Routine biochemical parameters including basic chemistry tests (measuring glucose, calcium, phosphorus, blood urea nitrogen, and creatinine), hematology tests (hemoglobin, hematocrit, and hemoglobin A1c), and urinalyses were conducted via standard methods at each institution, and additional serum samples were stored at –70 for subsequent analyses. Serum 25(OH)D and intact PTH concentrations were measured by electrochemiluminescence immunoassay (ECLIA) (Roche Diagnostics, Mannheim, Germany). The intra- and inter-assay coefficients of variation (CV) for 25(OH)D measurements were 2.2% to 6.8% and 3.4% to 13.1%, respectively. The intra- and inter-assay CV of intact PTH measurements were 1.1% to 2.0% and 2.8% to 3.4%, respectively. Serum FGF23 levels were measured using an intact FGF23 (iFGF23) enzyme-linked immunosorbent assay (ELISA) kit (Millipore Corporation, Billerica, MA, USA). The intra- and inter-assay CV of iFGF23 measure-

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ments were 7.8% to 11.2% and 2.4% to 11.31%, respectively. Sclerostin and DKK1 concentrations were also measured using human sclerostin and DKK-1 ELISA kits (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions. The intra- and inter-assay CV of sclerostin measurements were 1.8% to 2.1% and 8.2% to 10.8%, respectively. The intra- and inter-assay CV of DKK1 measurements were 3.3% to 4.2% and 4.6% to 7.6%, respectively.

Ethics statement

This study protocol was reviewed and approved by the Institutional Review Broad (IRB: 4-2014-0377) at both institutions. Informed consent was submitted by all subjects when they were enrolled.

Statistical analysis

All statistical analyses were performed using GraphPad Prism version 5.01 (GraphPad Software, CA, USA). Results are presented as mean±standard error (SE). Student paired *t* test was used to compare the data from different time points with baseline values when the values were normally distributed, and Wilcoxon signed rank test was used when the data were nonparametric. An analysis of variance (ANOVA) was used to compare different time points between groups. Dunnett's test and Bonferroni correction were performed for the repeated measures test of one-way ANOVA and two-way ANOVA, respectively. A *P* value of <0.05 (95% confidence interval) was considered statistically significant.

Table 1. Demographic and Other Baseline Characteristics of the Study Subjects

Variable	Vitamin D group (*n*=24)	Placebo group (*n*=10)	*P* value
Age, yr	34.20±1.58	30.60±2.35	0.413
Sex, male/female	4/24	1/10	0.882[a]
BMI, kg/m^2	22.74±0.51	21.91±0.47	0.342
Hemoglobin, g/100 mL	12.97±0.38	13.12±0.75	0.845
Hematocrit, %	38.65±0.84	39.07±1.63	0.801
Calcium, mg/dL	9.01±0.06	9.17±0.10	0.165
Phosphate, mg/dL	3.50±0.10	3.70±0.09	0.262
Serum BUN, mg/dL	12.20±0.58	10.57±0.41	0.096
Serum creatinine, mg/dL	0.64±0.03	0.65±0.05	0.784
Cholesterol, mg/dL	185.10±5.73	179.30±9.23	0.590
Glucose, mg/dL	88.90±1.75	87.50±2.17	0.647
HbA1c, %	5.40±0.04	5.26±0.10	0.148
25(OH)D, pg/mL	10.82±0.77	9.14±0.75	0.204
PTH, pg/mL	36.92±2.69	48.35±3.66	0.077
DKK1, pg/mL	3,132±86.88	3,503±492.00	0.268
Sclerostin, pg/mL	185.90±13.53	147.50±6.86	0.085
Urine calcium, mg/dL	9.59±1.58	7.78±2.05	0.597
Urine creatinine, mg/dL	149.80±17.46	154.60±17.40	0.171
Calcium/creatinine ratio	0.066±0.007	0.049±0.016	0.093

Values are expressed as mean±standard error.
BMI, body mass index; BUN, blood urea nitrogen; HbA1c, hemoglobin A1c; 25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone; DKK1, dickkopf-1.
[a]Chi-square test.

RESULTS

Demographic characteristics and changes in routine biochemical parameters following single vitamin D injection

Demographic information and other baseline characteristics of the subjects are shown in Table 1. There were no statistically significant differences between the vitamin D and placebo groups ($P>0.05$). Compared with the placebo group, no statistically significant differences were observed in serum calcium, phosphorus, and the ratio of urine calcium to creatinine at weeks 4, 8, and 12 after vitamin D_3 injection (Fig. 1). Serum 25(OH)D concentrations increased significantly throughout the study ($P<0.001$) after vitamin D_3 injection (Fig. 2A-C). Moreover, there were no significant differences between the two subgroups receiving vitamin D_3 injections which had previously been grouped based on baseline levels of 25(OH)D (Fig. 2D). On the other hand, serum PTH concentrations at weeks 4, 8, and 12 after vitamin D_3 injection in the vitamin D group did not change significantly ($P>0.05$) (Fig. 3A, D). No statistically significant differences were observed in the vitamin D group compared with the placebo group ($P>0.05$) (Fig. 3).

Effects of vitamin D on serum FGF23 concentrations

To determine whether a single injection of vitamin D_3 (200,000 IU) increases circulating FGF23 levels, we measured serum FGF23 concentrations at weeks 4, 8, 12, and 14 after vitamin D_3 treatment. The results showed that no significant difference were observed between vitamin D_3 treatment group and placebo group (Fig. 4A). Similar results were found in the two subgroups (Fig. 4B-D). However, subject 35 (placebo group) showed particularly elevated FGF23 levels throughout the study period including at baseline, even though this was in the placebo group without vitamin D_3 injection.

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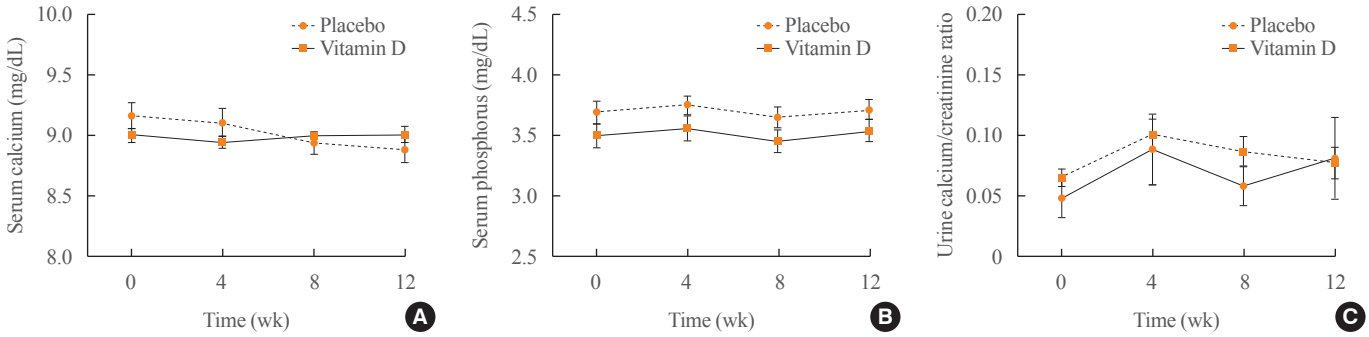

Fig. 1. (A) Serum calcium, (B) phosphorus concentrations, and (C) ratio of urine calcium to creatinine in subjects were measured before and after vitamin D_3 or placebo treatment.

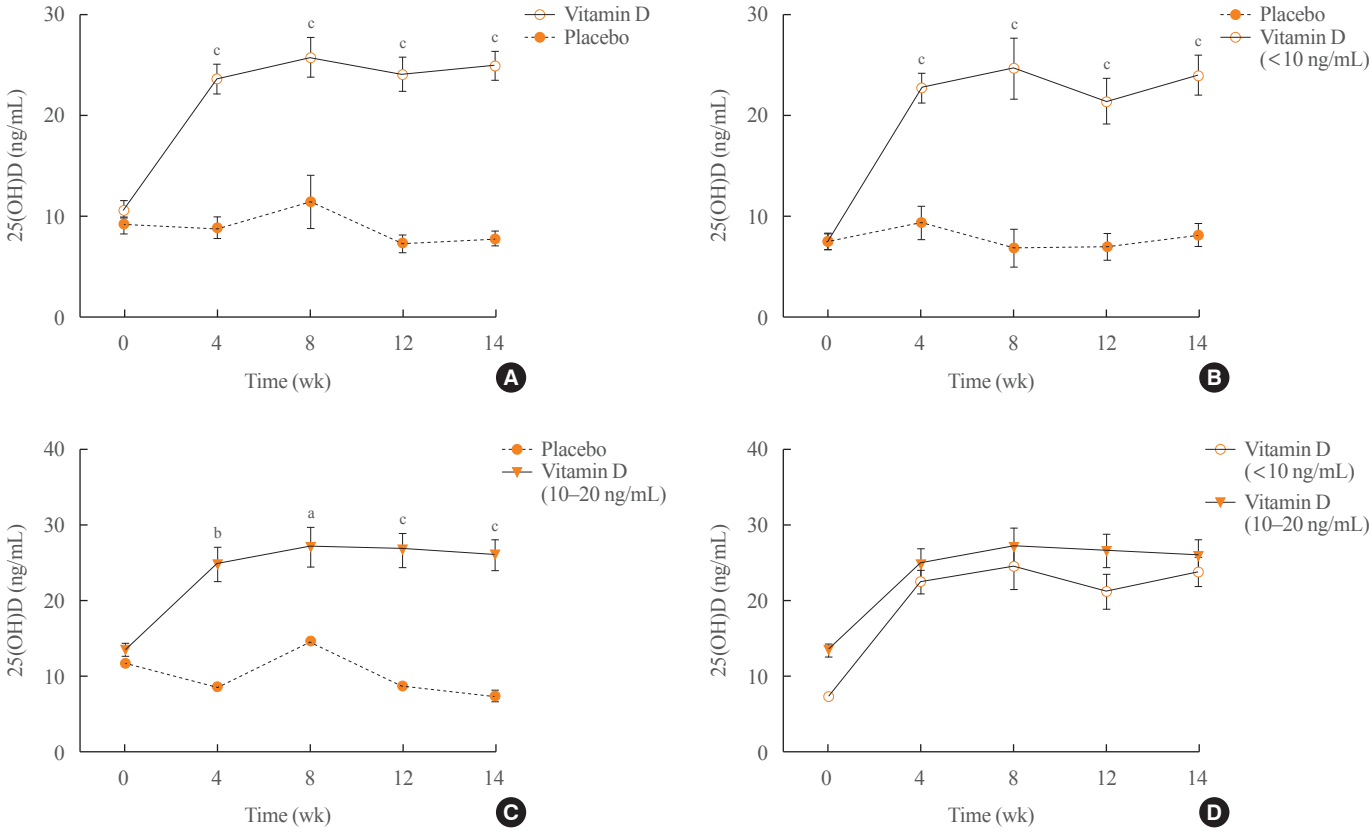

Fig. 2. Serum 25-hydroxyvitamin D (25(OH)D) concentrations were increased at different time points after treatment. (A) All subjects, (B) subjects with baseline 25(OH)D below 10 ng/mL, (C) subjects with baseline levels of 10 to 20 ng/mL, and (D) the vitamin D group. $^{a}P<0.05$; $^{b}P<0.01$; $^{c}P<0.001$.

Changes in sclerostin and DKK1 levels

To evaluate whether vitamin D_3 injection stimulates the expression of Wnt inhibitors, we measured serum sclerostin and DKK1 concentrations after vitamin D_3 injection. In the vitamin D group, serum sclerostin levels were transiently increased at week 4 after vitamin D_3 injection. Comparing the vitamin D group with the placebo group, there were significant differences at weeks 4 and 8 ($P<0.05$) (Fig. 5A). However, the slightly increased levels declined thereafter, and were not significantly different when compared to baseline (Fig. 5A). Moreover, there were no significant differences in sclerostin levels between the two subgroups with vitamin D_3 injection (Fig. 5B). DKK1 levels were not increased in the vitamin D group and there were no significant differences between this and the placebo group (Fig. 5C, D).

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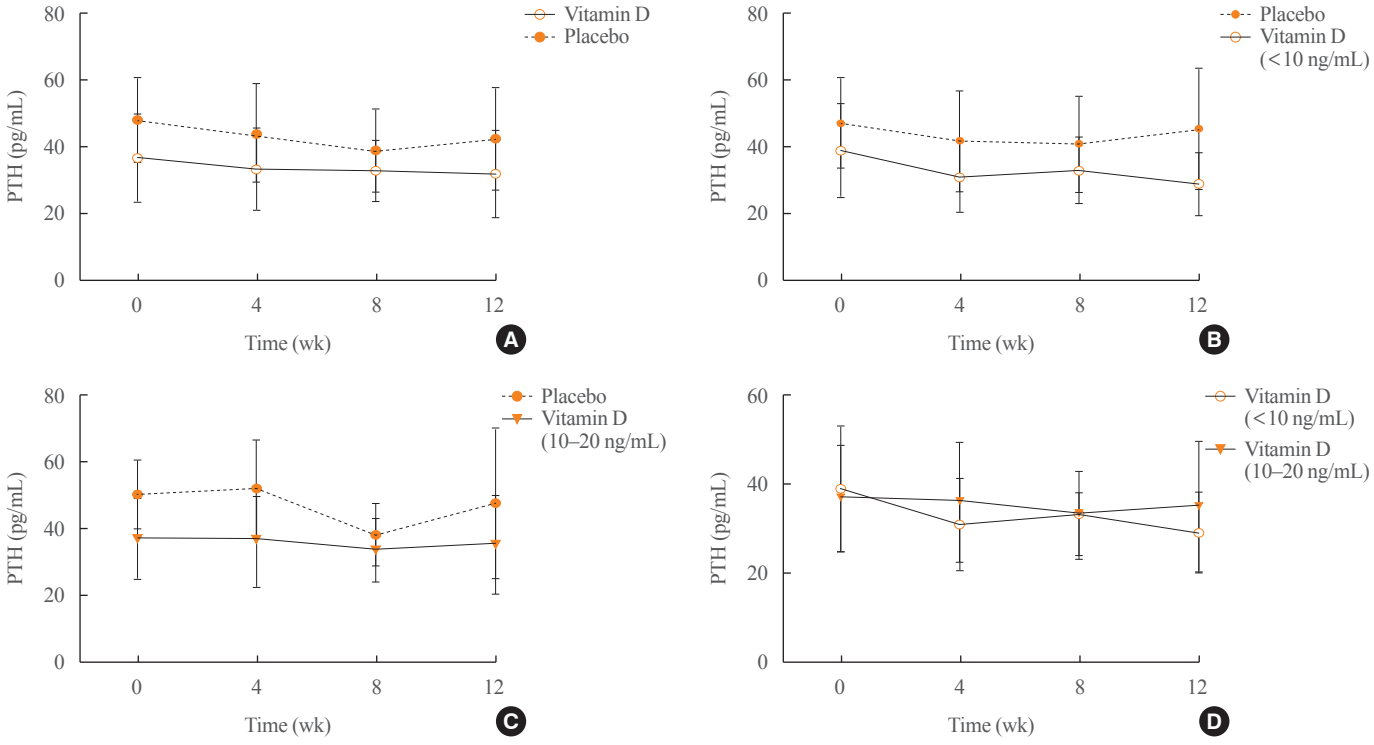

Fig. 3. Serum parathyroid hormone (PTH) levels were detected at the different time points after treatment. The comparison in (A) all subjects, (B) the subjects with less 10 ng/mL of baseline 25-hydroxyvitamin D (25(OH)D), (C) the subjects with 10 to 20 ng/mL of baseline 25(OH)D, and (D) the vitamin D group.

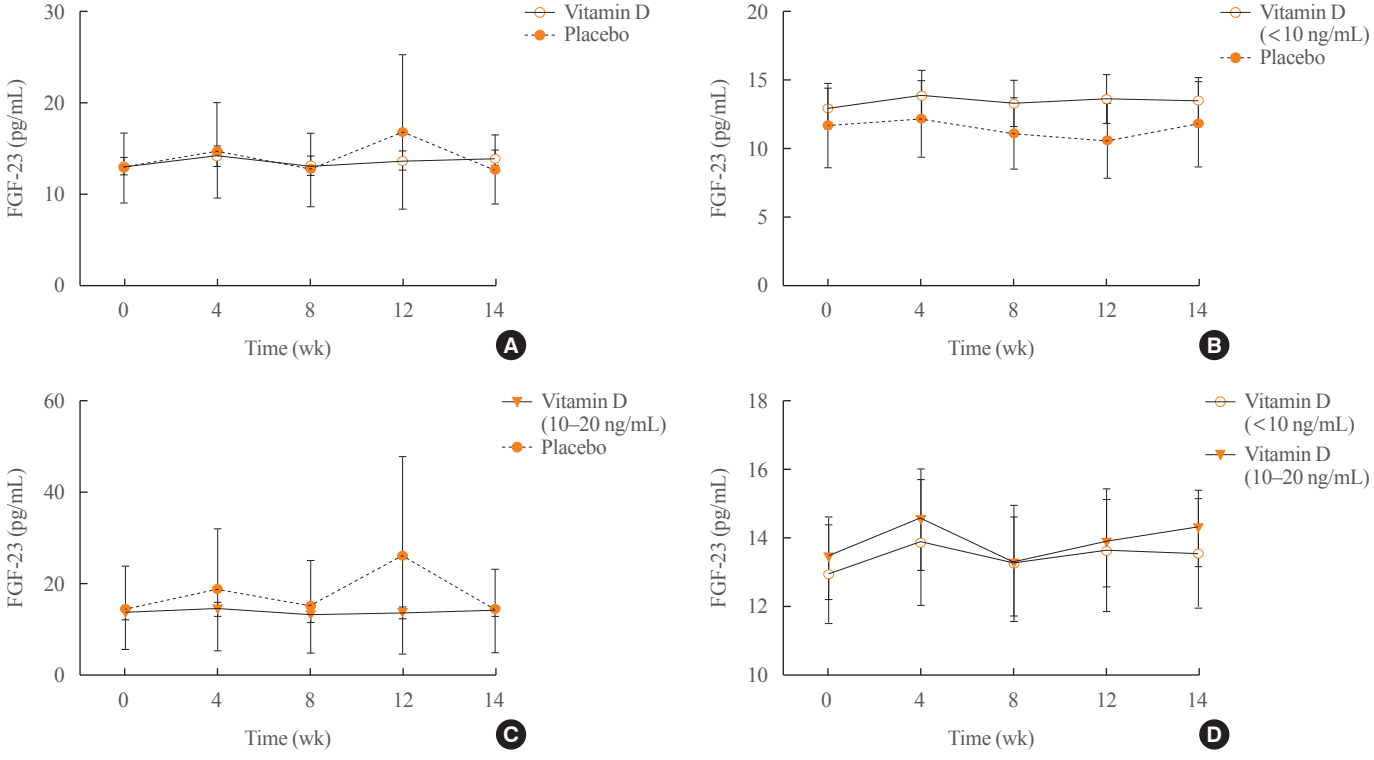

Fig. 4. Serum fibroblast growth factor 23 (FGF23) levels were measured at the indicated times. (A) All subjects, (B) subjects with baseline 25(OH)D below 10 ng/mL, (C) subjects with baseline levels of 10 to 20 ng/mL, and (D) the vitamin D group.

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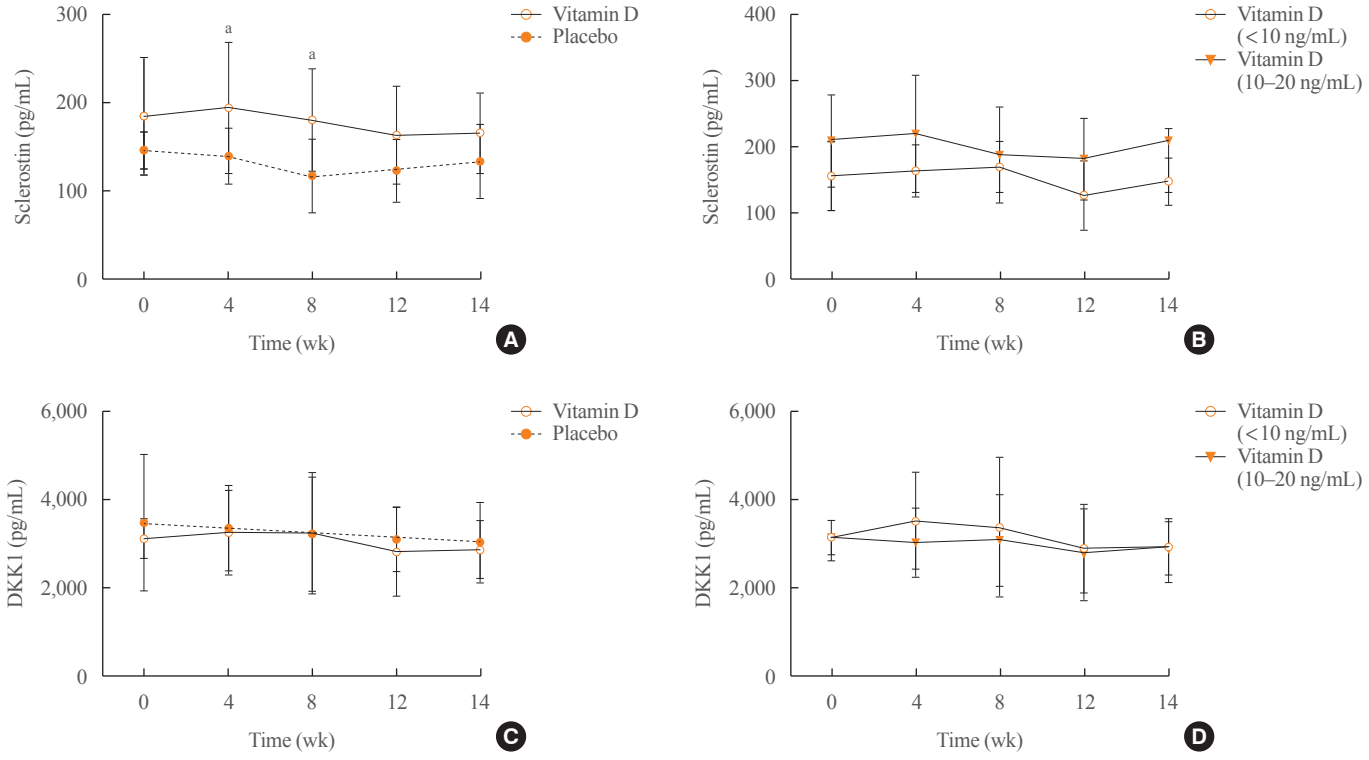

Fig. 5. (A, B) Serum sclerostin and (C, D) dickkopf-1 (DKK1) concentrations were measured at different time points after treatment. Mean±SEM are shown. [a]$P<0.05$ compared to placebo.

DISCUSSION

In the present study, we have shown that serum 25(OH)D levels significantly increased following a single intramuscular injection of vitamin D_3 with 200,000 IU, which is consistent with the report [21]. However, the levels of serum PTH, FGF23, and DKK1 did not change during the 14-week follow-up period after vitamin D_3 injection. Serum sclerostin levels were slightly increased 4 weeks post-treatment but declined thereafter.

Calcium alone, or combined with oral vitamin D, has been suggested as an inexpensive therapeutic method to prevent osteoporotic bone loss and fractures. However, this treatment is less effective if the patients' compliance is poor. Furthermore, therapeutic levels are only reached after a long period. Intramuscular injection of vitamin D alone or in combination with oral supplementation can maintain increased levels of serum 25(OH)D for at least 6 months [22]. Turner et al. [16] reported that intramuscular injection of vitamin D together with oral calcium and vitamin D supplementation, increased $1,25(OH)_2D$ concentrations significantly. Similar findings were also demonstrated recently where 25(OH)D levels were elevated in vitamin D deficient patients who were given a monthly intramuscular injection of 300,000 IU of vitamin D for 3 consecutive months [20]. Our results are consistent with these findings over the 14 weeks following a single vitamin D_3 injection at the dose of 200,000 IU.

Active vitamin D stimulates the production of FGF23 in osteocytes and osteoblasts [23]. Furthermore, increased FGF23 levels reduce expression of 1α-hydroxylase but increase expression of 24-hydroxylase, which converts $1,25(OH)_2D$ to the les biologically active $24,25(OH)_2D$, resulting in decreased $1,25(OH)_2D$ production [12]. FGF23 concentrations were also increased after intramuscular injection of vitamin D (300,000 IU) administered in conjunction with usual daily supplementation of vitamin D and calcium [18]. In contrast, Uzum et al. [24] reported that FGF23 concentrations further declined during vitamin D replacement therapy in vitamin D deficient patients who were treated daily with an oral combination of vitamin D and calcium for 6 weeks. In our study, serum FGF23 levels were not significantly elevated after intramuscular injection of vitamin D_3 (200,000 IU). In contrast with the previous reports, our study did not provide any evidence that single intramuscular injection of vitamin D_3 (200,000 IU) could increase or decrease serum FGF23 levels at all. Participants, medication dosage, and

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treatment methods were all different in the various studies cited. Therefore, serum FGF23 levels may be affected by these factors. In this study, one subject in the placebo group showed high FGF23 concentrations at baseline and after-treatment, and was diagnosed with anemia without other abnormal test parameters. It is known that iron deficiency could elevate C-terminal FGF23 (cFGF23) levels, but not iFGF23 levels [25]. Following intravenous iron repletion, cFGF23 levels fell within 24 hours, whereas iFGF23 did not change significantly. Interestingly, culprit iron formulations could uncouple FGF23 production and cleavage, by decreasing cleavage to a greater extent than production, and thereby increase the serum concentration [26]. We used an iFGF23 detection ELISA kit which only measures iFGF23 and no information was available regarding iron supplementation in the subject. Therefore, the reasons behind the high iFGF23 levels in this subject are still unknown.

Previous reports have shown that the loading dose in vitamin D supplementation influences PTH levels [27]. The sustained increase in serum PTH may affect bone metabolism negatively by increasing bone turnover, and it is expected that decreased PTH levels after vitamin D_3 injection could be beneficial for skeletal bone health. In this study, we did not observe significant changes in serum PTH, calcium, and phosphate levels. The following may explain our findings: firstly, patients did not have secondary hyperparathyroidism at baseline; secondly, short term intramuscular injection of vitamin D_3 at a dose of 200,000 IU may not reveal the PTH suppression effect.

$1,25(OH)_2D$ was reported to increase the expression of low density lipoprotein receptor-related protein 5 (LRP5), a Wnt co-receptor that plays a key role in Wnt signaling and bone formation [9]. Hence, we hypothesized that canonical Wnt signaling could be also regulated after vitamin D injection through up or down regulating Wnt inhibitors, such as DKK1 and sclerostin which bind to LRP5/6 and inhibit bone formation. In the previous study, bisphosphonate and denosumab, both used in the treatment of osteoporosis, have been shown to increase sclerostin levels, and either decrease or have no effect on DKK1 levels [28,29]. The DKK1 response was lower than that of sclerostin, which occurred at 12 months following treatment with denosumab [28]. In our study, a slight increase in sclerostin levels was observed at week 4, and there was no significant change in DKK1 levels after vitamin D_3 injection. These findings are consistent with the previous study where a significant increase in sclerostin was observed after 3 months, but no change was seen in DKK1 after a loading dose of vitamin D injection [19].

The limitations of this study include the fact that only the effects of intramuscular injection of vitamin D_3 (200,000 IU) in subjects with vitamin D deficiency were assessed, while serum 1,25(OH)D and bioavailable 25(OH)D levels were not measured. In addition, FGF23 levels were mostly below the limit of detection of the assay used, and a different assay with better sensitivity should be performed in future. The effects of vitamin D_3 injection on FGF23 should be assessed further in patients with CKD, in whom $1,25(OH)_2D$ replacement thereby for suppression of PTH increases serum FGF23 concentrations significantly.

In conclusion, a single vitamin D_3 injection (200,000 IU) significantly increased serum 25(OH)D concentrations, without affecting serum FGF23, PTH, and DKK1 levels during short term follow up of 14 weeks, and caused only a slight increase in serum sclerostin levels.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

This research was supported by the Brain Korea 21 PLUS Project for Medical Science of Yonsei University, and supported by Kwangdong pharmaceutical company.

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