

The Effect of Short-Term Low-Energy Ultraviolet B Irradiation on Bone Mineral Density and Bone Turnover Markers in Postmenopausal Women with Osteoporosis: A Randomized Single-Blinded Controlled Clinical Trial

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SUMMARY

Introduction The importance of vitamin D on bone health and osteoporosis was studied by many researchers. The main role of the Vitamin D is to absorb calcium and phosphate and increase bone mineralization. Older people are at an increased risk of the inadequate vitamin D production in the skin because of lower sun exposure and reduced ability of the skin to synthesize vitamin D.

Objective The aim of this clinical trial was to evaluate the efficacy and tolerability of short-term (2 weeks) low energy UVB irradiation in postmenopausal women with osteoporosis using bone mineral density and bone turnover markers.

Methods A three-month, single-blinded, randomized, placebo-controlled clinical trial was conducted at the University hospital in Daegu, Republic of Korea. Fifty-two postmenopausal Korean women (older than 65 years) with osteoporosis were randomly allocated to have either low energy UVB or placebo for 30 minutes a day for two weeks of treatment during winter. Laboratory analysis and physical examination before and 4, 8 and 12 weeks after treatment were carried out and BMD was measured before and 8 and 12 weeks after treatment. The effects of time and treatment interaction between these two groups were evaluated by repeated-measure two-factor analysis, and subgroup analysis was performed to examine UVB effect on the vitamin D insufficient group [serum 25(OH)D₃ concentration <30 ng/mL].

Results In vitamin D insufficient group, the effect of UVB irradiation on vitamin D and bone ALP as well as additional benefit on bone formation was confirmed. The vitamin D insufficient group showed statistically significant increment in serum 25(OH)D₃ compared with the normal group ($p < 0.05$). However, there was no significant difference between two groups in the other bone turnover markers, such as serum calcium, PTH-C, serum osteocalcin, serum CTX and BMD.

Conclusion Low-energy-short-term UVB radiation for postmenopausal women may be of use in vitamin D synthesis. There was a modest benefit in change of bone ALP especially in women with the insufficient vitamin D.

Keywords: low-energy ultraviolet B; osteoporosis; bone mineral density; bone turnover markers

INTRODUCTION

Osteoporosis has emerged as an important metabolic bone disease globally. The percentage of elderly people over 65 years was 3.4 in 1975, 6.8 in 2000 and will be 17% of the world's population by 2050. Based on the population growth, the current incidence of osteoporosis-related fractures in Asia became a significant public health burden [1].

The best treatment option for osteoporosis is prevention by increasing the maximal bone quantity before menopause to decrease the risk of fractures in postmenopausal women [2].

The importance of vitamin D on bone health was studied by many researchers. They suggested vitamin D as a hormone-like material which acts on bone, the intestines and parathyroid.

The main role of the vitamin D is to absorb calcium and phosphate and increase bone mineralisation [3, 4].

Older people are at an increased risk of inadequate vitamin D production in the skin because of diminished sun exposure and reduced ability of the skin to synthesize vitamin D [5]. The resulting vitamin D insufficiency may have negative effects on maintenance of bone mass. There have been many studies showing that calcium and vitamin D supplementation reduces bone loss and has beneficial effect on bone metabolism [6, 7]. Some researchers advocate additional effects of vitamin D in the presence of high calcium intake [8, 9].

Although the role of sun rays has been emphasized by many researchers [3-6], there have been few studies describing the role of ultraviolet

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let light in the elderly population with clinically confirmed osteoporosis in terms of bone mineral density and bone turnover biomarkers in the clinical setting [5, 6]. Furthermore, there are few data on relative effects of ultraviolet B (UVB) in the elderly osteoporotic patients with vitamin D insufficiency [10].

OBJECTIVE

The purpose of this study is to evaluate the efficacy and tolerability of short-term ultraviolet B (UVB) irradiation in the elderly osteoporotic Korean population. This report presents a single-blinded, randomized, placebo-controlled clinical trial of the effects of UVB irradiation on bone mineral density (BMD) and bone turnover markers in postmenopausal women with osteoporosis.

METHODS

Study design

One hundred and ten ambulatory, late postmenopausal (>65 year) women were enrolled in the study. Subjects were excluded who had 1) a history of cancer within the 5 years before the study, 2) a medical disease such as chronic renal failure or Cushing disease, or 3) any condition that might interfere with the evaluation of BMD (e.g., spinal fusion, treatment with systemic steroid, previous fracture of hips or spine). Any participant consuming vitamin D or calcium supplement was excluded. All participants were requested to have BMD study and confirmed osteoporosis based on World Health Organization (WHO) criteria (T-score below -2.5).

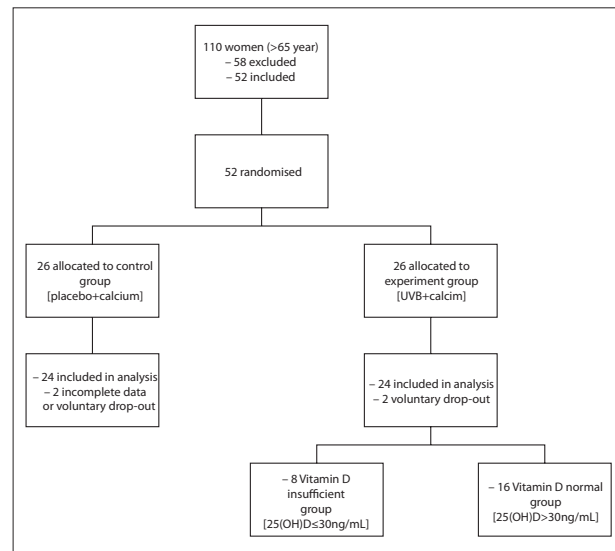
We hypothesized that UVB radiation could affect bone formation. Therefore, bone alkaline phosphatase (ALP) became the primary endpoint in this study. For sample size determination, significance level (α)=0.05, power ($1-\beta$)=0.80 and mean difference of bone ALP between groups was 0.05, SD=0.06 [11] and 10% drop out rate were used. Each group consisted of 26 individuals.

All random codes were generated by the medical statistician using the computer programme, which the other researchers involved in the study were not able to access. Fifty-two subjects were randomly assigned to receive either ultraviolet light lamp or placebo (fluorescent light lamp) (Scheme 1).

The study was approved by the Kyungpook National University Hospital IRB (Institutional Review Board). The informed consent was obtained from all participants before inclusion into the study.

Treatment

The experimental group was exposed to low energy UVB (Senia[®], NB Tech, Korea) at wavelength between 280 and 400 nm on the abdomen and the thigh for 30 minutes a



Scheme 1. A randomization scheme: 52 participants were randomly selected to receive either ultraviolet light lamp or placebo

day for 2 weeks. The control group was exposed to fluorescent lamp in the same setting. The distance between the lamp and abdomen was 100 cm. The of the ultraviolet lamp was 4.0-5.0 $\mu\text{w}/\text{cm}^2$ and it was 0.01 $\mu\text{w}/\text{cm}^2$ for the fluorescent lamp. A serological examination was carried out before treatment and 4, 8, and 12 weeks after treatment between 09 a.m. and 11 a.m. after overnight fasting to control the circadian rhythm. A radiological examination was performed before treatment and 8 and 12 weeks after treatment. All subjects took a calcium tablet daily (Mycal[®], Myungmun, 1000 mg/day) without limitation of food intake or daily activities (for one month) for preventing bone loss during this study.

Biochemical bone markers

Fasting bone specific alkaline phosphate (Bone ALP) and osteocalcin (OC) were measured as bone formation markers. Fasting serum C-terminal telopeptide of type I collagen (CTX) was measured as a bone absorption marker and 25 hydroxyvitamin D [25(OH)D₃], serum calcium, C-terminal parathyroid hormone (PTH-C) and OC were measured as calcium metabolism markers.

Bone ALP was measured by Metra BAP ELISA[®] (QUIDEL, USA; ref 15-41.3 U/L). 25(OH)D₃ was assessed by 25-OH-VitD₃ Ria CT[®] (Biosource, Belgium; ref 7.6-75.0 ng/mL). Serum OC was measured using N-MID osteocalcin ECLIA[®] (Roche Diagnostics, Swiss; ref 14-46 ng/mL). Plasma PTH levels were examined by EIKEN PTH RIA kit[®] (Eiken Chemical Co., Ltd, Japan; ref below 0.6 ng/ml) (the antibody recognizes the portion of PTH-C). Serum calcium was measured on Roche/Hitachi MODULAR System[®] (Roche Diagnostics, USA; ref 8.8-10.2 mg/dl). Serum CTX was determined by Elecsys β -Cross Laps immunoassay[®] (Roche Diagnostics, USA; ref 0.33-0.78 ng/ml). All serum concentrations were measured by regular laboratory method.

Bone mineral density measurements

BMD was estimated using dual energy X-ray absorptiometry (DEXA, Lunar Radiation Corp, Madison, Wisconsin) before, and 8 and 12 weeks after treatment. All lumbar vertebrae and hips were measured.

Statistical analysis

Biochemical markers before treatment and 4, 8, and 12 weeks after treatment, and biomechanical markers before treatment, and 8 and 12 weeks after treatment in each group were analysed with repeated-measure two-factor analysis. All data were referred to as mean \pm standard error (SE).

The statistical package SPSS for Windows ver. 14.0 was used for the analysis. The level of statistical significance was set at p-value less than 0.05.

RESULTS

The demographic and baseline characteristics of the population were shown in Table 1. There were no significant differences between the UVB irradiation group and the control group in baseline characteristics.

Biochemical bone markers

Changes of bone specific ALP (bone ALP): No statistical significance was found in either percentage change or results of the quantitative analysis between two groups ($p>0.05$) (Graph 1A).

Changes of the serum 25 hydroxy-vitamin D₃ [25 (OH) D₃]: At weeks 4 and 8 after the UVB irradiation, the serum level of 25 (OH)D₃ in the UVB group was significantly increased compared with the controls. Particularly, at 4 weeks after the UVB irradiation, the mean(\pm SE) of the UVB group was 1.07 (\pm 0.06)%, which was significantly higher than that of the control group, 0.85 (\pm 0.06)%. There was a statistically significant difference between two groups in the change of the serum 25 (OH)D₃ level from the baseline ($p<0.05$) (Graph 1B).

Changes of the serum calcium level: There was no statistically significant difference between these two groups in values of the serum calcium level ($p>0.05$) (Graph 1C).

Changes of the serum C-terminal PTH (PTH-C) level: There was no statistically significant difference between two groups in changes of the serum PTH-C level over time ($p>0.05$) (Graph 1D).

Changes of the serum osteocalcin (OC) level: There was no statistically significant difference between two groups in changes of the serum OC level over time ($p>0.05$) (Graph 1E).

Changes of the serum C-terminal telopeptide of type I collagen (CTX): There was no statistically significant difference between two groups in change of the serum CTX level over time ($p>0.05$) (Graph 1F).

Bone mineral density

Lumbar vertebrae: There was no statistically significant difference between two groups in terms of percent changes over time ($p>0.05$) (Graph 1G).

Femur: At 8 weeks after the UVB irradiation, the percent change of BMD of the proximal femur in the experimental group was 1.03 (\pm 0.04)%, which was slightly higher than in the controls, 0.97 (\pm 0.04)%. However, there was no statistically significant difference between two groups in percent changes of BMD of the proximal femur over time ($p>0.05$) (Graph 1H).

Subgroup analysis

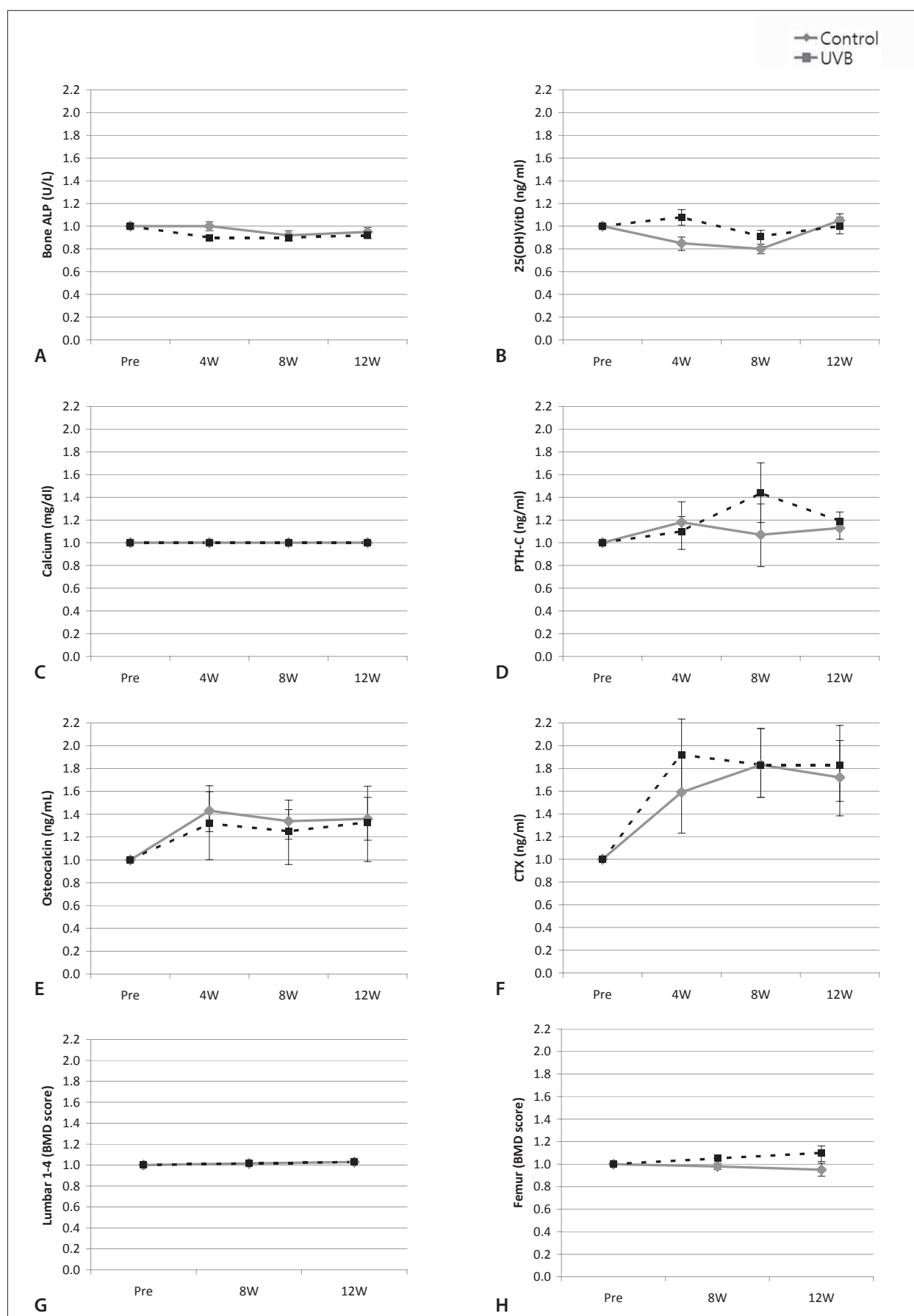
Based on published studies [7, 8], the subjects in the experiment group (UVB group) were divided into two subgroups: if the initial serum 25(OH)D₃ level was below 30 ng/mL, the subject was assigned to the vitamin D insufficient group (n=8); and if the level was above 30 ng/mL, the subject was assigned to the vitamin D normal group (n=16).

Biochemical bone markers: The vitamin D insufficient group showed statistically significant increment in serum levels in the 25(OH)D₃ compared with the vitamin D normal group. Serum 25(OH)D₃ was significantly higher in the insufficient group than in the normal group.

Table 1. Baseline demographic characteristics of the population:

Characteristic	Experimental group	Placebo group
Age (years)	69.20 (3.94)	68.58 (4.43)
Lumbar spine bone mineral density score	-2.39 (0.57)	-2.26 (0.71)
Femur bone mineral density score	-1.22 (0.65)	-1.40 (0.85)
Serum calcium (mg/dL)	9.47 (0.51)	9.44 (0.37)
Bone specific alkaline phosphatase (U/L)	30.21 (11.10)	28.02 (9.42)
C-terminal telopeptide of type I collagen (ng/mL)	0.27 (0.19)	0.31 (0.25)
Hydroxy-vitamin D (ng/mL)	43.83 (20.52)	38.60 (15.55)
Osteocalcin (ng/mL)	13.39 (8.44)	13.68 (5.58)
C-terminal parathyroid hormone (ng/ml)	0.34 (0.14)	0.33 (0.12)

Data are mean (SD) unless otherwise specified. All women were Korean, and the mean age was 68.9 years.



Graphs 1A-H. Percentage changes of biochemical bone markers and bone mineral density between the UVB group and the controls

After the UVB irradiation, 25(OH)D level was significantly higher in the UVB group than that of the control group ($p < 0.05$) (Graph B). However, other bone formation markers did not show any significant difference between two groups ($p > 0.05$).

It was 1.56 (± 0.08)% at 4 weeks in the insufficient group compared to 0.85 (± 0.06)% in the normal group. At 12 weeks, it was 1.41 (± 0.10)% in the insufficient group and it was 0.79 (± 0.07)% in the normal group. There was a statistically significant difference between two groups at 12 weeks ($p < 0.05$) (Graph 2B). The percent change of the serum bone ALP level was 0.99 (± 0.05)% in the vitamin D insufficient group, which was slightly higher than in the normal group, 0.87 (± 0.03)% at 4 weeks after irradiation. Particularly, at 8 weeks, the percent change of bone ALP was higher in the vitamin D deficient group, 0.97 (± 0.06)% than in the normal group, 0.87 (± 0.04)%. The bone ALP was higher in the vitamin D insufficient group than in the normal group, but there was not statistically significant difference between two groups ($p = 0.16$) (Graph 2A). However, other bone formation markers did not show any statistically significant difference between these two groups ($p > 0.05$) (Graphs 2A-H).

BMD study: There was no statistically significant difference in BMD ($p > 0.05$) (Graphs 2G and 2H).

There were no recorded adverse events during the study period.

DISCUSSION

Traditional UVB phototherapy with high intensity of illumination (about 20W) was mainly used for skin disorders such as psoriasis, atopic dermatitis and vitiligo [12, 13]. However, this high-intensity UVB can cause adverse effect such as skin cancer and cataract [14]. This study used low illumination intensity UVB device (2.62W). When the distance between lamp and bed reached 100 cm, it dropped to 4.0-5.0 $\mu\text{W}/\text{cm}^2$, and could result in adverse effect. Recently, Cicarma et al. [15] have reported the effect of low-dose UVB treatment; however, there have been few randomized controlled studies investigating the effect of low energy UVB treatment on patients with the postmenopausal osteoporosis.

One of the most important causes of osteoporosis in the elderly population is vitamin D deficiency, which is essential for normal calcium and bone metabolism [16]. The main source of Vitamin D is sunlight exposure, but a number of factors, such as latitude, season, time of day and use of topical sunscreen influence the cutaneous production of vitamin D [6, 17].

In Korea, despite of the presence of abundant sunlight, Yoon et al. [18] reported potential vitamin D deficiency and its related bone diseases in menopausal women. The percentage of women with serum level of 25(OH)D below 12 ng/ml was 57.2% (out of a total of 276 women). Roy et al. [19] wrote that a number of South Asians had symptoms of vitamin D deficiency; and, in particular, individuals with the values below 15 ng/ml presented with the increased PTH and decreased BMD. Another study reported a correlation between vitamin D, calcium supply and secondary hyperthyroid condition [8, 9, 20]. They reported that serum calcium and phosphate were significantly higher in vitamin D and calcium intake group than in the placebo group.

There are two types of vitamin D production *in vivo*: approximately 10% of vitamin D requirement derives from food intake; more than 90% of vitamin D requirement is from exposure to sunlight [21]. With age, the vitamin D demand is being increased. However, elderly women can produce only one-third of vitamin D as compared to young women [6, 7, 10]. Holick [17] reported that 295-300 nm of the artificial UVB radiation accelerated vitamin D formation in the skin. The advantage of using UVB was to reduce side effects of medication as well as its low cost and easy application.

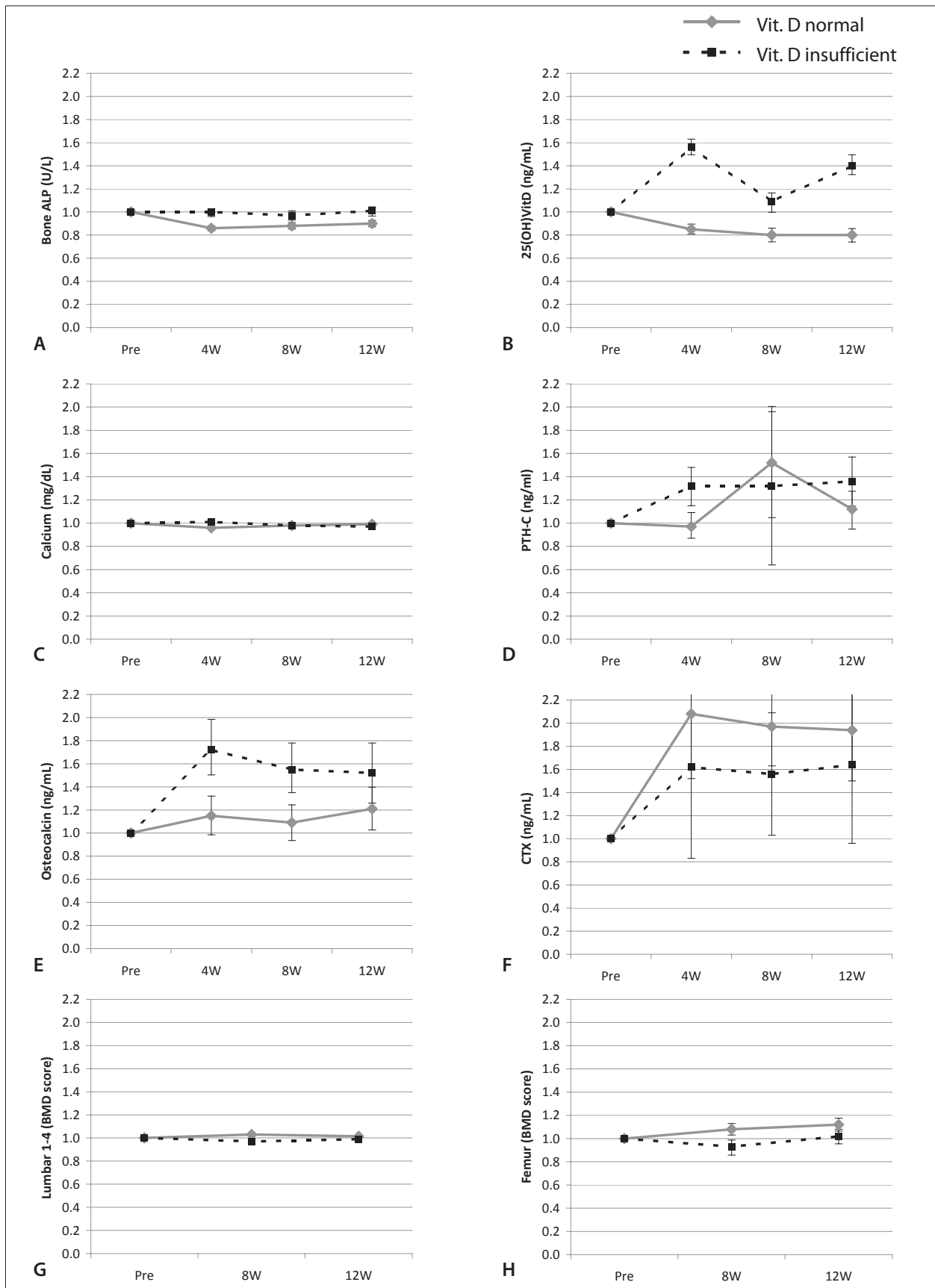
Previous studies reported that exposure of 20% of body to either direct sunlight or tanning bed radiation was effective in increasing the serum vitamin D₃ in both young and old populations [3, 4, 5, 22]. Indeed, Chuck et al. [4] suggested that the use of UVB lamps in nursing homes was the most effective method of maintaining the serum concentration of 25(OH)D.

This study showed the increased serum level of 25(OH)D₃ in the UVB irradiated group compared to the controls, particularly in the vitamin D deficiency subgroup of the UVB irradiated group. Bone ALP and Vitamin D were also increased significantly compared to the control group.

This study analyzed the effect of low energy UVB on bone turnover markers and change of BMD in postmenopausal osteoporotic women for 12 weeks after the treatment period. The bone ALP and other bone formation markers were slightly higher in the experimental group but there was no significant difference during the first four weeks.

When the skin is exposed to UVB with the wavelength between 219 and 315 nm, 7-dehydrocholesterol in the dermal layer is activated and converted to previtamin D₃. Pre-vitamin D₃ then spontaneously isomerizes to cholecalciferol (vitamin D₃) and subsequently it undergoes sequential hydroxylation to calcifediol (25(OH)D₃) in the liver and calcitriol (1,25(OH)₂D₃) in the kidney, which is the major circulating form and the best indicator of vitamin D because of its short half-life [17, 23]. In this study, a sharp increase in 25(OH)D₃ was observed in the experimental group, which was statistically significant. Especially, when the results were compared between the baseline and post-irradiation at 4 weeks using the two-sample t-test, the response was higher in the UVB group (45%) than in the controls (16%).

The PTH secretion was activated by low serum calcium rate, and it appeared that the higher serum PTH rate, the faster bone turnover rate. In a recent study, the PTH-C synthesized in the thyroid yielded five times higher level in circulation than intact PTH. It was cleared predominantly through the kidneys compared to intact PTH, which was cleared through the liver and kidneys [24]. Accordingly, if there were renal problems, PTH-C would be higher in the blood and take part in bone physiological activation [25]. In this study, there was little change in serum PTH-C and calcium over 12 weeks. This could be owing to homeostasis of the calcium as a normal body mechanism, and we expected no side effects from overdose or deficit serum calcium. There were no statistically significant differences in OC, the bone turnover marker, CTX and BMD.



Graphs 2A-H. Percentage changes of biochemical bone markers and bone mineral density between the vitamin D normal group and the vitamin D insufficient group

If the subject's initial serum 25(OH)D level was below 30 ng/mL, the subject was assigned to the vitamin D insufficient group; if the subject's 25(OH)D level was above 30 ng/mL, the subject was assigned to the vitamin D normal group. The 25(OH)D level was significantly higher in vitamin D insufficient group than that of the normal group ($p < 0.05$) (Graph B).

In our study, the treatment group was further divided into two, based on definition of the vitamin D insufficient group as the condition below or equal 30ng/mL vitamin D and the normal group as higher than 30ng/mL vitamin D [3, 4, 26, 27]. However, it is still controversial to define a deficiency of vitamin D. Heaney et al. [9] reported relationship between vitamin D and calcium absorption. They reported that calcium absorption rate was sharply decreased in 50.1 to 86.5 nmol/L range of vitamin D. In another study, the relationship between serum PTH and 25(OH)D required at least 72 nmol/L vitamin D which did not induce secondary hyperthyroidism [28, 29]. According to Lips' study [29], serum PTH level would start to increase when 25(OH)D was between 30 and 78 nmol/L, however, this was also affected by many factors such as serum calcium level. They concluded that the appropriate range for serum 25(OH)D was 50 nmol/L.

The OC is the most important bone specific noncollagen protein and is also called Bone gla protein (BGP). It is dependent on vitamin K, which is stimulated by vitamin D and secreted by osteoblasts. Then, it circulates in the blood or is absorbed into the bone matrix. Therefore, it can be used as the bone turnover index [30]. In this study, the OC increased in post-irradiation weeks 4 and 8 in the vitamin D insufficient group, but there was no significant difference.

A calcium and vitamin D supplement is effective for preventing osteoporosis. Toss et al. [31] reported the role of UVB radiation in vitamin D deficiency groups. They divided elderly people into three groups: 1) the oral vitamin D and calcium intake group, 2) the calcium intake group, and 3) the UVB radiation group. UVB radiation was performed once a week for 3 months. The other groups took 450 IU vitamin D₂ and 420 g calcium. They reported higher serum 25(OH)D in the UVB group and vitamin D and calcium intake group. Bone ALP was decreased in the vitamin D and calcium intake group. They reported that UVB radiation was an effective and safe method for preventing the lack of vitamin D, but it was time-consuming. Meier et al. [32] reported the effects of vitamin D and calcium supply on prevention of bone loss due to seasonal variation in healthy

adults. They showed the increments of BMD and vitamin D in the vitamin D deficient group compared to the controls. However, in this study, we noted little change in BMD in this elderly population.

A limitation of this study is that the effect of UVB was tested without control of the outdoor activities and diet. Further, this clinical trial was conducted over a limited period of two weeks. Comparing to our previous animal pilot study, it has been noted that even two weeks of UVB irradiation is sufficient to find difference in two groups.

CONCLUSION

In summary, UVB radiation (wavelengths between 280 and 400 nm) 30 minutes a day for two weeks added no skeletal benefit in postmenopausal women with osteoporosis during 8 weeks when assessed with BMD. However, vitamin D was increased significantly in subjects in the vitamin D insufficient group. These findings may signify the future application of UVB irradiation for the increase of serum vitamin D in the elderly with vitamin D insufficiency. However, a long-term study in a larger patient group is required to demonstrate clinical significance and confirm this finding.

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Утицај краткотрајног ултраљубичастог Б зрачења ниске енергије на коштану густину и маркере коштанога метаболизма код жена с остеопорозом у постменопаузи: рандомизирана, слепа, клинички контролисана студија

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КРАТАК САДРЖАЈ

Увод Значај витамина Д на густину кости и остеопорозу испитивали су многи истраживачи. Главна улога витамина Д огледа се у апсорпцији калцијума и фосфата и повећању коштане минерализације. Код старих људи је слабија производња витамина Д у кожи због слабе изложености сунцу и смањењу могућности коже за синтезу.

Циљ рада Циљ ове клиничке студије био је да се утврде ефикасност и подношљивост краткотрајног дејства (две недеље) нискоенергетског ултраљубичастог (UVB) зрачења код жена с остеопорозом у постменопаузи мерењем минералне густине кости и маркера коштанога метаболизма.

Методе рада Тромесечна, слепа, рандомизирана, плацебо-контролна клиничка студија урађена је у Универзитетској болници у Дегуу, у Јужној Кореји. Педесет и две жене с постменопаузом остеопорозом (старије од 65 година) насумично су подвргнуте дејству нискоенергетског UVB зрачења или плацебо ефекту у трајању од 30 минута током две недеље, у зимским месецима. Клинички и лабораторијски прегледи рађени су пре излагања зрачењу, а потом четири недеље,

осам и 12 недеља након зрачења. Минерална густина кости мерена је пре, а затим осам и 12 недеље после зрачења.

Резултати Показан је утицај UVB зрачења на витамин Д и ниво коштане алкалне фосфатазе (ALP) код жена са инсуфицијенцијом витамина Д, као и позитивни ефекат на структуру кости. У групи испитаница са инсуфицијенцијом витамина Д уочена је статистички значајна разлика у повећању 25(OH)D₃ у односу на групу која је примала плацебо ($p < 0,5$). Међутим, није било статистички значајне разлике између две групе у погледу других показатеља коштанога метаболизма (Ca, PTH-C, остеокалцин у серуму, серум CTX) и минералну густину кости.

Закључак Краткотрајно излагање нискоенергетском UVB зрачењу жена у постменопаузи које болују од остеопорозе може бити корисно у синтези витамина Д, али је уочено мало побољшање у измени ALP, поготово код жена са инсуфицијенцијом витамина Д.

Кључне речи: нискоенергетско ултраљубичасто зрачење; остеопороза; минерална густина кости; маркер коштанога метаболизма