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Original article

Effectiveness of vitamin K2 on osteoporosis in adults with cerebral palsy

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Abstract

Background: Osteoporosis can lead to spontaneous fractures in adults with cerebral palsy (CP). Undercarboxylated osteocalcin (ucOC) is a useful marker for vitamin K insufficiency in osteoporosis. The primary objective of this study was to determine the effect of vitamin K2 on bone mineral density (BMD) in adults with CP and vitamin K insufficiency.

Methods: Sixteen adults, median age of 56 years, with CP and osteoporosis in whom the serum ucOC concentration exceeded 4.5 ng/mL were included. All patients received 45 mg of vitamin K2 per day. BMD was measured and presented as a percentage of the young adult mean (%YAM). Serum levels of ucOC and BMD were measured at baseline and after 6 and 12 months.

Results: Serum levels of ucOC decreased from 7.8 ng/mL (range, 4.9–32) at baseline to 3.9 ng/mL (range, 1.9–6.8) after 6 months ($P = 0.001$). BMD increased from 59%YAM (range, 45–67) at baseline to 68%YAM (range, 50–79) after 12 months ($P = 0.003$).

Conclusions: Vitamin K2 had a positive effect on BMD in osteoporotic adults with CP and high serum concentrations of ucOC, and might be useful as a first line treatment for osteoporotic adults with CP and vitamin K insufficiency.

Keywords: Cerebral palsy; Vitamin K2; ucOC; Bone mineral density

1. Introduction

Cerebral palsy (CP) is characterized by motor impairment and can be associated with global physical and mental dysfunction [1]. The life expectancy for adults with CP has increased over the past three to four decades. Many adults with CP are living in institutions for patients with severe motor and intellectual disabilities. In these institutions, patients are exposed to common age-related conditions, such as atherosclerosis, dementias, muscle wasting, osteoarthritis, bone loss, and low-trauma fractures [2]. These problems are likely to occur at a younger age in adults with CP than in adults without CP.

Osteoporosis affects 51% of institutionalized adults with developmental disabilities and 58% of patients with CP, including children [3,4]. Since patients with CP and osteoporosis have a tendency to suffer spontaneous fractures during routine care such as changing clothes [5], constructive treatment for osteoporosis in patients with CP is necessary. There have been some reports regarding treatment for osteoporosis in patients with CP through the use of vitamin D, bisphosphonates and exercise

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therapy [6–10]. However, these treatments have the risk of potentially serious side effects for patients with CP. On the other hand, vitamin K is essential for bone formation and its use is approved as a treatment for osteoporosis in Japan. Tsuji et al. [11] and Tanaka et al. [12] reported that vitamin K2 was effective for the treatment of osteoporosis in Japanese patients with CP. However, both of these reports described its effects only in young populations. In addition, undercarboxylated osteocalcin (ucOC) has been reported to be useful as a marker for vitamin K insufficiency [13]. On the basis of the cut-off values set by Shiraki et al., 4.5 ng/mL ucOC is the cut-off value for predicting vitamin K insufficiency [13].

The primary objective of this study was to determine whether supplementation with vitamin K2 could have a positive effect on osteoporosis in adults with CP who have vitamin K insufficiency as defined by an ucOC level of greater than 4.5 ng/mL.

2. Methods

2.1. Participants and treatment

Thirty-two patients with CP at Orange Gakuen, who had not previously received any treatment for osteoporosis, had a diagnosis of osteoporosis according to Japanese criteria (as shown later). Sixteen of these 32 patients who had ucOC levels that exceeded 4.5 ng/mL were enrolled in the study. Each of the 16 patients received 45 mg of vitamin K2 (Glakay®, Eisai, Tokyo, Japan) per day on consecutive days. For 2 of the 16 patients, bone mineral density (BMD) and biochemical analysis could only be evaluated after 6 months; for the remaining 14 patients, these parameters were evaluated at both 6 and 12 months. The Gross Motor Function Classification System (GMFCS) was used to describe the mobility status in patients with CP. This study was approved by the ethical review board of Orange Gakuen.

2.2. Biochemical analysis

Before supplementation with vitamin K2, serum calcium and albumin concentrations were measured via standard laboratory procedures, and plasma 1,25-dihydroxyvitamin D (1,25 (OH)2 VitD) was determined by radioimmunological assay. Bone-specific alkaline phosphatase (BAP) was also measured using a chemiluminescent enzyme immunoassay. Osteocalcin (OC) was measured with an immunoradiometric assay. Serum levels of ucOC were measured by electrochemiluminescence immunoassay. To assess bone resorption, urinary excreted levels of deoxypyridinoline (uDPD) and type-I collagen cross-linked-N-telopeptide (uNTX) were measured by enzyme immunoassay and enzyme-linked immunosorbent assays, respectively. The results were standardized by the urinary concentration of creatinine. All biochemical analyses were performed by Clinical Pathology Laboratory Corporation (Kagoshima, Japan).

2.3. Bone density measurement and osteoporosis

BMD at the distal one-third of the radius was measured by dual-energy X-ray absorptiometry (DEXA, DCS-600EXV, Hitachi Aloka Medical, Tokyo, Japan). The percentage of the subject's BMD was divided by the BMD of the young adult mean (YAM) (%YAM). Osteoporosis was defined as a BMD of less than 70% of the YAM, according to Japanese criteria for measuring adult density [14]. The Japanese criteria for osteoporosis are almost the same as those of the World Health Organization [14].

2.4. Statistical analysis

Statistical analyses were conducted using SPSS version 17 (SPSS Co., Tokyo, Japan). Data are presented as median values (with ranges in parentheses). The Wilcoxon matched-pairs test and Friedman test were used to assess the significance of changes between biochemical data and BMD at baseline, 6 months, and 12 months. A value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics

The median age of the patients in this study was 56 years (range, 42–69) (Table 1). Three patients were classified as GMFCS level III, 12 patients as level IV and one patient as level V. There was no significant difference in BMD between patients at GMFCS level III (60%YAM; range 47–65) and levels IV/V (58%YAM; (range 45–67) ($p = 0.900$). Thirteen patients had epilepsy and were receiving anticonvulsants. The median serum calcium level was 9.2 mg/dL (range, 8.7–9.8) and the plasma 1,25(OH)2 VitD level was 70.5 pg/mL (range, 42–136); these levels were within the normal ranges for all patients. All patients had a serum albumin concentration greater than 3.0 g/dL.

3.2. Outcomes

Serum ucOC levels decreased from 7.8 ng/mL (range, 4.9–32) at baseline to 3.9 ng/mL (range, 1.9–6.8) at 6 months after treatment ($p = 0.001$). At 12 months after treatment, the level was 4.4 ng/mL (range, 2.4–6.9), which was not significantly different from the concentration at 6 months after treatment (Fig. 1). However, serum OC and serum BAP did not increase

Table 1
Patient characteristics and baseline data.

	No.
Total patients, No	16
Median age (range)	52 (42–69)
Sex	
Male/female	9/7
GMFCS	
III/IV/V	3/12/1
Antiepletic drug	
+/−	13/3
The median of baseline data (range)	
Calcium (mg/dL)	9.2 (8.7–9.8)
Phosphorus (mg/dL)	3.7 (2.4–4.3)
ALP (IU/L)	357 (219–634)
Alb (g/dL)	4.1 (3.3–4.4)
1,25 $(OH)_2D$ (pg/dL)	71 (41–136)
Intact PTH (pg/mL)	29 (13–71)
ucOC (ng/mL)	7.8 (4.9–32)
OC (ng/mL)	6.2 (4.3–13)
BAP (μg/mL)	20 (9.6–41)
uDPD (nmol/mmol·Cr)	11 (6.9–20)
uNTX (nmolBCE/mmol·Cr)	89 (56–196)
BMD (%YAM)	59 (45–67)

GMFCS, Gross Motor Function Classification System; ALP, alkaline phosphatase; ucOC, undercarboxirated osteocalcin; OC, osteocalcin; BAP, bone alkalyphosphatase; uDPD, urinary deoxypyridinoline; uNTX, urinary crosslinked N-telopeptides of type I collagen; BMD, bone mineral density.

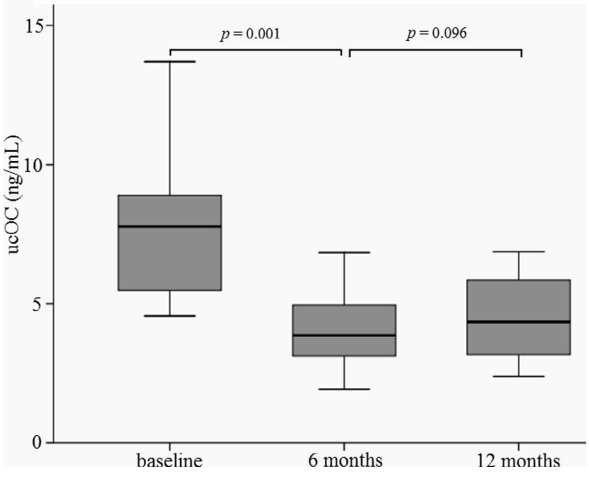

Fig. 1. Changes in undercarboxylated osteocalcin (ucOC) at baseline and at 6 months and 12 months after treatment. Serum ucOC decreased at 6 months after treatment ($p = 0.001$), however, there was no significant difference between ucOC levels at 6 months and 12 months after treatment ($p = 0.096$).

significantly across the 3 time points. Similarly, no significant differences in uDPD and uNTX levels were observed between baseline and 12 months after treatment (Table 2).

BMD tended to increase from 59%YAM (range, 45–67) at baseline to 64%YAM (range, 46–73) at 6 months after treatment ($p = 0.057$), and significantly increased from baseline to 68%YAM (range 50–79) at 12 months after treatment ($p = 0.003$) (Fig. 2). BMD increased in 12 of the 14 patients, and decreased in two patients. There were no discriminating factors to indicate why these two latter patients showed a decrease in BMD, including activity of daily living, use of anticonvulsants or the results of a biochemical analysis.

Table 2
Changing in the bone metabolic data and BMD after vitamin K2, median (range).

	Before	6 months	12 months	*P*
OC	6.2 (4.3–13)	6.8 (5.9–12)	7.7 (4.1–13)	0.328
BAP	20 (9.6–41)	20 (13–35)	19 (7–34)	0.612
uDPD	11 (6.9–20)	10 (6.9–15)	11 (5.8–27)	0.607
uNTX	89 (56–196)	97 (39–382)	95 (57–153)	0.319

OC, osteocalcin; BAP, bone specific alkaline phosphatase; uDPD, urinary deoxypyridinoline; uNTX, urinary crosslinked N-telopeptides of type I collagen.

4. Discussion

OC is a vitamin K-dependent bone-specific protein that is involved in the maintenance of bone quality after it undergoes γ-carboxylation by vitamin K. When levels of vitamin K are insufficient in bone, OC does not undergo complete γ-carboxylation and ucOC is released from osteoblasts into the blood [13]. In the present study, we found that vitamin K2 decreased the serum concentration of ucOC and increased BMD in adults with CP and osteoporosis who had high levels of ucOC at diagnosis. Tsuji et al. [11] reported that BMD was

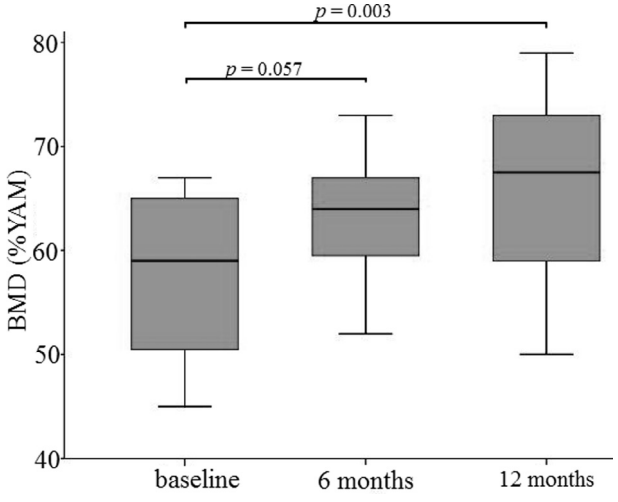

Fig. 2. Changes in bone mineral density (BMD) at baseline and at 6 months and 12 months after treatment. BMD tended to increase from 59%YAM (range, 45–67) at baseline to 64%YAM (range, 46–73) at 6 months after treatment ($p = 0.057$) and significantly increased from baseline to 68%YAM (range 50–79) after 12 months of treatment ($p = 0.003$).

increased in patients with CP and osteoporosis following supplementation with vitamin K2, which is consistent with our results. Conversely, Tanaka et al. [12] reported that there was no change in BMD in patients with CP and osteoporosis, despite increased OC levels. In addition, previous reports have shown that vitamin K2 had no effect on BMD in healthy postmenopausal women or the elderly [15,16]. The difference of effect of vitamin K2 on BMD in each study may be due to the differences in the subjects.

We only treated patients with osteoporosis in whom the ucOC level exceeded 4.5 ng/mL. When ucOC levels exceed 4.5 ng/mL, an osteoporotic patient is considered to be vitamin K deficient [13]. Therefore, it is reasonable that vitamin K2 should have an effect on the BMD in patients with vitamin K insufficiency. While two previous studies examined a Japanese cohort [11,12], neither study investigated the use of serum ucOC levels as a tool for predicting which patients might respond to vitamin K supplementation. In our institution, the number of osteoporotic patients with CP in whom the serum level of ucOC was below 4.5 ng/mL was the same as that in whom the ucOC level exceeded 4.5 ng/mL. Both patients with and without vitamin K insufficiency would likely have participated in these two previous studies. Thus, the difference in the effect of vitamin K2 on BMD may depend on the status of vitamin K insufficiency, which was not determined in previous Japanese studies [11,12], and which was not considered as a therapeutic option in other studies [15,16]. Therefore, the selection of vitamin K2 based on ucOC levels for the treatment of osteoporosis in adults with CP may be good strategy.

Another reason why vitamin K2 had an effect on BMD in our study might be the pathophysiology of osteoporosis in patients with CP. One cause of osteoporosis in patients with CP is considered to be the failure of bone formation due to growth impairment. Intriguingly, Sugiyama et al. [17]. reported that treatment with vitamin K2 improved cortical bone geometric strength of the hemiplegic tibia. In addition, other studies have shown that vitamin K2 ameliorated osteopenia in diffusely affected limbs [18]. Based on these reports and our present study, vitamin K2 should be a more important factor in maintaining the rate of bone formation in patients with CP than in healthy subjects. To clarify this speculation, a prospective study with a larger cohort of patients with CP and basic research regarding vitamin K2 and bone formation will be required.

Various studies on the treatment of osteoporosis have been reported in children and young adults with CP [2]. For instance, some reports have described the effects of vitamin D, bisphosphonates and exercise therapy on BMD in children and young adults with CP [6–10]. In the reports by Tsuji et al. [11] and Tanaka et al. [12], the Japanese subjects were from 14 to 36 years and from 20 to 40 years of age, respectively. On the other hand, the median age of the subjects in our study was 56 years (range 45–67). To our knowledge, the present study is the first to show that vitamin K2 is effective for the treatment of osteoporosis in comparatively elderly adults with CP. Vitamin K2 was chosen for the treatment of osteoporosis for several reasons. First, participants in our study had normal serum vitamin D and calcium concentrations; the administration of vitamin D and calcium would likely have caused kidney stones [19]. Second, a recent review recommended against exercise therapy for osteoporosis [20]. Third, bisphosphonates were only approved as an oral agent when this study commenced; therefore, there was the possibility of esophageal stricture in patients who could not sit for a prolonged period after taking an oral agent. Fourth, vitamin K2 has not been shown to have any major adverse effects. Therefore, vitamin K2 may be a reasonable therapy for osteoporosis in cases of CP and vitamin K insufficiency.

5. Conclusion

In summary, vitamin K2 decreased ucOC levels and increased BMD in adults with osteoporosis, CP and high serum concentrations of ucOC. Vitamin K2 might be useful as a first line treatment for osteoporosis in patients with CP and vitamin K insufficiency.

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