Introduction

The skeleton adapts to its mechanical circumstances and thus reduced loading results in fragile bones; indeed, fractures are a common problem in children with cerebral palsy. In these pediatric patients, spontaneous fractures frequently occur at the diaphyses of long bones which consist of cortical bone. Although treatments that improve trabecular bone status are available, there is currently no established method that can be used to limit cortical bone fragility in children with physical disability. Intravenous bisphosphonate, for example, resulted in a marked improvement of areal bone mineral density in the distal femur but its efficacy at the femoral diaphyseal cortex was insignificant, which is consistent with experimental findings in rats. The application of low-magnitude high-frequency mechanical stimuli also produced an improvement in trabecular volumetric bone mineral density in the proximal tibia but did not induce significant beneficial change at the tibial diaphyseal cortex.

Bone is a rich source of vitamin K and accumulating evidence indicates that vitamin K affects bone fragility. Although there have been very few clinical reports investigating the effects of vitamin K therapy on the growing skeleton, we previously found that combined treatment with vitamins D (alfacalcidol) and K (menatetrenone [menaquinone-4]) increased second metacarpal cortical bone mass in children with severe physical disability. As alfalcacidol has been used for the management of bone fragility in children with cerebral palsy for over 10 years in Japan but its effect on the second metacarpal cortical bone mass is limited, we have hypothesized that vitamin K could play a significant role in pediatric skeletal health under conditions with reduced mechanical loading.

Abstract

Fractures frequently occur at cortical bone sites in children with cerebral palsy, but there is no established therapy. We previously found that treatment with vitamins D and K increased cortical bone mass in children with severe physical disability, and have hypothesized that vitamin K could play a significant role in pediatric cortical bones under conditions with reduced mechanical loading. In the present case report, we treated a right hemiplegic ambulant eight-year-old boy with oral vitamin K (15 mg per day) for eight months. Cortical bone geometries at mid-diaphyseal sites in bilateral tibiae were evaluated before and after the treatment. The cross-sectional total, bone and marrow areas of non-hemiplegic tibia increased by 8.8%, 7.4% and 12.0%, respectively, while those of hemiplegic tibia changed by 9.0%, 14.9% and -3.4%, respectively. As a result, the polar moment of inertia, an indicator of the resistance to torsion forces, increased by 13.0% in the non-hemiplegic tibia and by 63.7% in the hemiplegic tibia. Vitamin K may restrict cortical bone fragility, caused by reduced mechanical loading, through its actions at the endosteal bone marrow interface. Further studies are needed to confirm these findings and to clarify the mechanisms involved.

Keywords: Vitamin K, Reduced Mechanical Loading, Cortical Bone, Bone Geometry, Bone Marrow
Methods

An eight-year-old boy had right hemiplegia caused by fetal porencephaly and had been ambulatory occasionally using canes. The hemiplegic ankle joint had shown a slight equinus contracture and the patient had received a right short leg brace; the hemiplegic leg had not been fully weight-bearing. He had received physiotherapy once a week, but had no other disease and had taken no other medication. There was no fracture history. After informed consent was obtained from his parents, we treated the patient with vitamin K (Glakay capsule [15 mg of menatetrenone]; Eisai Co., Ltd., Japan), a drug approved for the treatment of osteoporosis in Japan, for eight months from March to November in 2005 at the Tsuzumigaura Handicapped Children’s Hospital. One vitamin K capsule was given orally within 30 minutes after a meal once a day.

Before and after vitamin K treatment, plain radiography of bilateral legs was performed, and precise axial high-resolution computed tomography (CT) images (0.5-mm slice thickness) at mid-diaphyseal sites in bilateral tibiae were obtained by scanning at 120 kV and 200 mA (Asteion, Toshiba Medical Systems Corporation, Japan) in order to evaluate cortical bone geometry. Considering the different lengths of hemiplegic and non-hemiplegic legs, CT scans of hemiplegic and non-hemiplegic tibiae were separately performed to measure the exact middles of each tibia. CT images were converted to monochromes by Adobe Photoshop software, and the cross-sectional total, bone and marrow areas were measured using ImageJ software (http://rsb.info.nih.gov/ij/). Cross-sectional moment of inertia (CSMI), an indicator of the resistance to bending forces, around anterior-posterior and medial-lateral axes was calculated using Microsoft Visual C++ software, based on the parallel-axis theorem as follows:

\[ \text{CSMI} = \sum_{i=1}^{n} (w h_i^3/12 + w d_i^2), \]

where \( w \) and \( h \) are the width and height of each pixel in the images, respectively, and \( d_i \) is the distance from the neutral axis for pixel number \( i \). The polar moment of inertia (PMI), an indicator of the resistance to torsion forces, was calculated as the sum of the CSMI around the anterior-posterior and medial-lateral axes. The muscle and subcutaneous fat areas were also evaluated.

Results

Prior to treatment with vitamin K, the size of the right hemiplegic tibia was smaller than that of the left non-hemiplegic tibia, and the outer cross-sectional shape of the left tibia was triangular while that of the right tibia was more rounded (Figure 1). The cross-sectional total, bone and marrow areas of the right hemiplegic tibia were only 72.0%, 70.5% and 75.6% of the left non-hemiplegic tibia, respectively. Accordingly, the CSMI around the anterior-posterior and medial-lateral axes in the hemiplegic tibia were 54.7% and 40.8% of those in the non-hemiplegic tibia. The PMI in the hemiplegic tibia was also lower (46.3%) than that in the non-hemiplegic tibia. The lengths of the hemiplegic and non-hemiplegic tibiae were 230 mm and 238 mm, respectively.

Treatment with vitamin K for eight months showed no side effects and the compliance was more than 95%. There were no changes in the physiotherapy from the preceding six months to the end of the study period. The percentage increase in the cross-sectional bone area of the right hemiplegic tibia was twice that observed in the left non-hemiplegic tibia (Table 1). This was mainly the product of a divergence in changes in the area of marrow; with the right hemiplegic marrow area decreasing (by 3.4%), while the left non-hemiplegic marrow area increased (by 12.0%) during the time of treatment. The percentage increases in the right and left total areas were similar. As a result, the percentage increase in the PMI of the hemiplegic tibia was also approximately 5 times higher than in the non-hemiplegic tibia. In contrast, the CSMI around the medial-lateral axis did not show such a change. The percentage increase in the PMI of the hemiplegic tibia was also approximately 5 times higher than in the non-hemiplegic tibia. The lengths of the hemiplegic and non-hemiplegic tibiae were 245 mm and 293 mm, respectively.

<table>
<thead>
<tr>
<th></th>
<th>Right hemiplegic tibia</th>
<th>Left non-hemiplegic tibia</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>before</td>
<td>after</td>
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<tr>
<td>Total area (mm²)</td>
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<td>Bone area (mm²)</td>
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<td>Marrow area (mm²)</td>
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<td>Cross-sectional moment of inertia around an anterior-posterior axis (mm⁴)</td>
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<td>3142</td>
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<td></td>
<td>1680</td>
<td>2048</td>
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<tr>
<td>Polar moment of inertia (mm⁴)</td>
<td>3171</td>
<td>5190</td>
</tr>
</tbody>
</table>

Table 1. Cortical bone geometry at mid-diaphyseal sites in right hemiplegic and left non-hemiplegic tibiae before and after eight-month vitamin K treatment in an eight-year-old boy.
Discussion

In the present case, vitamin K treatment markedly improved cortical bone geometric strength of the hemiplegic tibia. This improvement was associated with periosteal and endocortical bone apposition and resulted mainly from the latter, while an equivalent endocortical change was not observed in the non-hemiplegic tibia. Consistent with our hypothesis, the inner and outer cortical bone apposition observed in the hemiplegic tibia is similar to our previous findings in second metacarpal bones treated with vitamins D and K in children with severe physical disability. Interestingly, the results in the hemiplegic tibia are consistent with recent experimental findings in sciatic neurectomized rats, where vitamin K treatment increased periosteal bone formation and suppressed endocortical bone resorption.

Figure 1. Effects of eight-month vitamin K treatment on right hemiplegic and left non-hemiplegic tibiae in an eight-year-old boy. (A) X-ray photographs of legs. (B) Axial computed tomography images at mid-diaphyseal sites in each tibia. (C) Monochrome images of the tibiae. White spots demarcate position of the centroid.

Furthermore, a previous randomized prospective 12-month trial in hemiplegic adult stroke patients showed that second metacarpal cortical bone mass on the hemiplegic side increased by 4.3% in a vitamin K (45 mg per day)-treated group and decreased by 4.7% in an untreated group while that on the non-hemiplegic side decreased by 0.9% in the vitamin K-treated group and by 2.7% in the untreated group. Thus, vitamin K appears to be especially efficacious for hemiplegic cortical bones in both children and adults.

The mechanisms by which vitamin K improved cortical bone geometric strength of the hemiplegic tibia of our patient remain unclear, but it is possible that vitamin K acts on bone marrow cells because of the marked induction of endocortical bone apposition. Interestingly, reduced mechanical loading has been reported to inhibit osteogenic differentiation and to promote adi-
pogenesis and osteoclastogenesis in bone marrow, and orally administered vitamin K distributes highly in this region. Thus, one possible mechanism is that vitamin K stimulates osteoblastogenesis and inhibits adipogenesis and osteoclastogenesis in bone marrow cells. Notably, previous findings suggest that human bone marrow cells are indeed more sensitive to vitamin K compared with mouse bone marrow cells. On the other hand, periosteal bone expansion during growth is an important factor which acts to strengthen bones, especially in the male, and vitamin K increases 1,25-dihydroxyvitamin D$_3$-induced mineralization by human periosteal osteoblasts in vitro. In the present case, increases in the cross-sectional total areas of hemiplegic and non-hemiplegic tibiae were similar during the time of treatment, suggesting that vitamin K promoted periosteal bone formation under conditions with reduced mechanical loading. As 1,25-dihydroxyvitamin D$_3$ increases the metabolism of vitamin K in human osteoblasts, combination with vitamins D and K rather than vitamin K alone may be more efficacious for the promotion of periosteal bone formation. Finally, as vitamin K also plays specific roles in the nervous system, it remains possible that vitamin K affects bone metabolism by unknown mechanisms through this system. This possibility is strengthened by the apparent difference in the effects of vitamin K treatment in the hemiplegic and non-hemiplegic tibiae.

In conclusion, vitamin K therapy might restrict unloading-induced increases in cortical bone fragility possibly through its actions in bone marrow. This vitamin has a very wide safety range for patients who are not taking warfarin, a vitamin K antagonist, and could be useful for children with physical disability. Our findings agree with the reduced bone mass in children with long-term warfarin therapy; however, vitamin K as well as warfarin have only a weak effect on bone mass in elderly people. Further studies are required to clarify the mechanisms by which vitamin K affects the skeleton in both children and adults.

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References


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