Levels of free thyroxine are higher in displaced pediatric supracondylar humerus fractures compared with non-displaced fractures

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Abstract. Relationships between bone metabolic biomarkers and fracture displacement have been reported in the elderly. However, factors related to bone metabolism that predict fracture displacement remain unclear in children. The present study investigated bone metabolic biomarkers associated with the displacement of pediatric supracondylar humerus fractures. A total of 19 patients (7 male and 12 female patients; mean age, 6.3 years) with pediatric supracondylar humerus fractures who underwent surgical treatment at Juntendo University Hospital (Tokyo, Japan) between December 2020 and September 2022 were included. They were divided into two groups according to the Gartland classification: 14 type II patients (6 male and 8 female patients; mean age, 6.3±3.0 years) and 5 type III patients (1 male and 4 female patients; mean age, 6.4±4.0 years). The following bone metabolic biomarkers were examined: 25-hydroxyvitamin D [25(OH)D], intact parathyroid hormone (iPTH), calcium, phosphate, thyroid-stimulating hormone, free triiodothyronine and free thyroxine (FT4). These markers were also compared between the two groups. A total of 16 out of 19 patients (84%) had insufficient serum 25(OH)D levels. Although iPTH levels were elevated, other bone metabolic biomarkers were within normal ranges. When the serum levels of bone metabolic biomarkers were compared, FT4 levels were significantly higher in type III patients than in type II patients (P=0.009). No significant differences were observed in other bone metabolic biomarkers between the two groups. The present results suggest that high FT4 levels are associated with the displacement of pediatric supracondylar humerus fractures.

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Introduction

Bone strength is based on bone mineral density (BMD) and bone quality. Osteoporosis is a skeletal disorder characterized by decreased bone strength with an increased risk of fracture (1). Since BMD is easier to evaluate than bone quality, osteoporosis has been clinically diagnosed using BMD (1). However, the risk of fragility fractures depends not only on BMD, but also on bone quality (2). Bone strength is related to the risk of fracture and fracture displacement. In distal radius fractures, which are fragility fractures, BMD correlates with fracture displacement (3). Moreover, in proximal femur fractures, fracture displacement was found to be greater in patients with bone metabolic biomarker abnormalities, such as vitamin D deficiency (4).

The mechanisms by which BMD and bone metabolic biomarkers affect fracture displacement in pediatric fractures have yet to be elucidated. Previous studies reported that BMD was lower in children with diseases with a high fracture risk, such as rickets and inflammatory bowel disease, than in healthy children (5,6). Furthermore, elevated levels of thyroid hormones in healthy children were found to decrease BMD (7). Therefore, the risk of fractures in children, as in the elderly, may be assessed using BMD and bone metabolic biomarkers. However, factors that predict fracture displacement in pediatric fractures remain unclear.

The present study investigated the bone metabolic biomarkers that are involved in fracture displacement in pediatric supracondylar humeral fractures. Bone metabolic biomarkers were measured using blood samples collected at admission in pediatric patients with supracondylar humerus fractures who underwent surgery at our hospital. Patients were divided into two groups based on the Gartland classification, which considers fracture displacement (8,9). We compared bone metabolic biomarkers between the two groups.

Materials and methods

Patients. This study was approved by the Research Ethics Committee of the Faculty of Medicine, Juntendo University, Tokyo, JAPAN (2-1-1 Hongo, Bunkyo-ku, Tokyo, 113-8421,

Japan; No. E23-0318, Date of Approval: December 11th, 2023). This committee is registered with the Ministry of Health, Labor and Welfare's Research Ethics Review Committee Reporting System in accordance with Japanese ethical guidelines (No. IRB: 21000123). This study was retrospective and approved by the Research Ethics Committee of the Faculty of Medicine, Juntendo University to be conducted with opt-out rather than written consent. According to the ethical guidelines, written informed consent was waved due to the nature of this retrospective study. Instead of the written informed consent, the information of this study and the opt-out opportunity was shown on the hospital website on the internet. All parents of the patients were also given an oral explanation of the opt-out form on the website, allowing them opt-out of this study instead of patients. The patients were subjected to standard clinical practice, including the methods of anesthesia and surgery. The information used in this study already existed by the time the research protocol was created.

Nineteen patients (seven boys and 12 girls, mean age 6.3±3.2 years) with pediatric supracondylar humerus fractures who underwent surgical treatment at Juntendo University Hospital (Tokyo, Japan) between December 2020 and September 2022 were enrolled. None of the patients had underlying diseases related to bone metabolism. All patients were operated on in the supine position under general anesthesia. After the closed reduction of the fracture under fluoroscopic control, percutaneous cross pinning was performed using two Kirschner wires (size: 1.6-1.8 mm depending on the size of the humerus bone). Postoperative immobilization was required for 3 weeks, and the removal of Kirschner wires was performed in the outpatient clinic when callus formation was observed on radiographic images 4 to 6 weeks after surgery.

Blood examinations. Blood examinations were part of the patient's treatment. Blood samples were taken at admission to the hospital to measure the levels of 25-hydroxyvitamin D [25(OH)D] (ng/ml) (25(OH)D: Cat. No. 301AAEZX00048000, Roche Diagnostic, K.K., Tokyo, Japan), intact parathyroid hormone (iPTH) (pg/ml) (iPTH: Cat. No. 21300AMY00492000, Roche Diagnostic, K.K., Tokyo, Japan), calcium (Ca) (mg/dl) (Ca: Cat. No. 13E1X80078000050, KAINOS Laboratories, Inc, Tokyo, Japan), phosphate (P) (mg/dl) (P: Cat. No. 13E1X80078000047, KAINOS Laboratories, Inc, Tokyo, Japan), thyroid-stimulating hormone (TSH) (μlU/ml) (TSH: Cat. No. 13A2X00206000109, Roche Diagnostic, K.K., Tokyo, Japan), free triiodothyronine (FT3) (pg/ml) (FT3: Cat. No. 13A2X00206000146, Roche Diagnostic, K.K., Tokyo, Japan), and free thyroxine (FT4) (ng/dl) (FT4: Cat. No. 13E1X80206000161, Roche Diagnostic, K.K., Tokyo, Japan) as bone metabolic biomarkers. 25(OH)D, iPTH, TSH, FT3 and FT4 levels were assessed using electrochemiluminescence immunoassays (ECLIA). Ca levels were evaluated using the Arsenazo III method. P levels were determined using an enzymatic method. In adults, the fracture displacement of proximal femur fractures was previously shown to be greater in patients with vitamin D deficiency (4). Furthermore, iPTH levels were significantly higher in patients with proximal femur fractures than in the control group (10). Bone growth and metabolism are regulated by trace elements, such as Ca and P; therefore, a deficiency in or an excess of trace elements is a risk factor for osteoporosis (11). Abnormal TSH levels in children have been associated with lower BMD (12). Thyroid hormone maintains skeletal homeostasis by differentiating and regulating chondrocytes, osteoblasts, and osteoclasts (13) A previous study demonstrated that higher FT4 levels were associated with lower BMD (7). Therefore, 25(OH)D, iPTH, Ca, P, TSH, FT3, and FT4 levels were measured as bone metabolic biomarkers in the present study.

Division into groups. Patients were divided into two groups based on the Gartland classification of pediatric supracondylar humerus fractures (8,9): Type II: 14 patients (six boys and eight girls, mean age 6.3±3.0 years) and Type III: five patients (one boy and four girls, mean age 6.4±4.0 years) (8,9). No significant differences were observed in age between the groups ($P>0.05$). Bone metabolic biomarkers examined in blood samples at admission were compared between the groups.

Statistical analysis. Data were expressed as the mean ± standard deviation. GraphPad Prism 7 (GraphPad Software, Inc., La Jolla, CA, USA) was employed for statistical analyses. The Mann-Whitney *U* test was used to calculate the significance of differences in 25(OH)D, iPTH, Ca, P, TSH, FT3, and FT4 levels. $P<0.05$ indicated a significant difference.

Results

25(OH)D, iPTH, Ca, P, TSH, FT3, and FT4 levels in all patients were 21.1±6.8 ng/ml, 91.5±25.1 pg/ml, 9.9±0.4 mg/dl, 4.5±0.4 mg/dl, 1.5±0.7 μlU/ml, 3.9±0.6 pg/ml, and 1.4±0.3 ng/dl, respectively. An adequate 25(OH)D level was previously defined as ≥30 ng/ml (14). In the present study, 25(OH)D levels were sufficient in three patients (32.0, 34.1, and 33.6 ng/ml), but insufficient or deficient in 16 (84% of cases). Although iPTH (normal range 9.0-69.0 pg/ml) levels were elevated (15), the levels of the other bone metabolic biomarkers were within normal ranges (normal ranges Ca: 8.4-10.4 mg/dl, P: 3.4-6.2 mg/dl, TSH: 0.5-5.2 μlU/ml, FT3: 3.1-5.1 pg/ml, and FT4: 1.1-1.6 ng/dl) (16,17).

Bone metabolic biomarkers were compared between Type II and III patients. The results obtained showed that FT4 levels were significantly higher in Type III patients with severe displacement than Type II patients with mild displacement (Type II 1.3±0.2 ng/dl vs. Type III 1.7±0.3 ng/dl, $P=0.009$) (Table I). On the other hand, no significant differences were observed in the levels of other bone metabolic biomarkers between the two groups. The mean levels of bone metabolic biomarkers were as follows: 25(OH)D: 20.7±6.5 ng/ml, iPTH: 33.7±10.9 pg/ml, Ca: 10.0±0.3 mg/dl, P: 4.4±0.4 mg/dl, TSH: 1.6±0.7 μlU/ml, and FT3: 3.8±0.5 pg/ml in Type II patients, and 25(OH)D: 22.5±8.5 ng/ml, iPTH: 44.8±17.5 pg/ml, Ca: 9.7±0.6 mg/dl, P: 4.7±0.5 mg/dl, TSH: 1.2±0.9 μlU/ml, and FT3: 3.9±0.7 pg/ml in Type III patients (Table I).

Discussion

The present results suggest that many children with pediatric supracondylar humerus fractures are deficient in 25(OH)D. Vitamin D is necessary to maintain blood calcium levels by promoting calcium absorption in the intestinal

Table I. Levels of bone metabolic biomarkers [FT4, 25(OH)D, iPTH, Ca, P, TSH and FT3] in the type II and type III classification groups.

Bone metabolic biomarkers	Type II (n=14)	Type III (n=5)	P-value
FT4, ng/ml	1.3±0.2	1.7±0.3	<0.05
25(OH)D, ng/ml	20.7±6.5	22.5±8.5	N.S.
iPTH, pg/ml	33.7±10.9	44.8±17.5	N.S.
Ca, mg/dl	10.0±0.3	9.7±0.6	N.S.
P, mg/dl	4.4±0.4	4.7±0.5	N.S.
TSH, μlU/ml	1.6±0.7	1.2±0.9	N.S.
FT3, pg/ml	3.8±0.5	3.9±0.7	N.S.

FT4, free thyroxine; 25(OH)D, 25-hydroxyvitamin D; iPTH, intact parathyroid hormone; Ca, calcium; P, phosphate; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; N.S., not significant.

tract (18). According to the American Endocrine Society and the American Geriatrics Society, 30 ng/ml of vitamin D is necessary for disease prevention in adults (19,20). However, there is a lack of standardized levels for vitamin D sufficiency in children and its assessment is difficult. The standard value for vitamin D sufficiency in children was previously set at 25(OH)D >30 ng/ml by Holick (21) and >20 ng/ml by Misra *et al* (22). Therefore, further studies are needed to establish a consensus for the standard value for vitamin D sufficiency in children. The American Academy of Pediatric Endocrinology defined vitamin D sufficiency as 25(OH)D ≥30 ng/ml in 2011 to correct these issues and provide a dietary intake standard (14). Based on this criterion, 25(OH)D was insufficient in 84% of patients in the present study. Therefore, children with vitamin D deficiency may be at an increased risk of fracture. The American Academy of Pediatrics stated that vitamin D supplementation is necessary for breastfed infants and for children and adolescents with low intakes of vitamin D-supplemented milk (22). In children with vitamin D deficiency, vitamin D supplementation is a useful means of increasing BMD, which may prevent fractures (23).

In the present study, FT4 levels were significantly higher in Type III patients than in Type II patients with supracondylar humerus fractures. On the other hand, no significant differences were observed in TSH levels between the two groups and TSH was not associated with the extent of fracture displacement in pediatric supracondylar humeral fractures. Thyroid hormones, the synthesis and secretion of which are mainly regulated by TSH, play an important role during childhood by regulating growth, neuropsychological development, and the cardiovascular system (24-27). Bone is also a target organ of thyroid hormones, as demonstrated in a previous study showing that children with congenital hypothyroidism had a short stature, delayed skeletal development, and impaired bone maturation (24). Growth promotion and early maturation of the skeleton have been reported in children with juvenile hyperthyroidism (28,29). The synthesis and secretion of FT4 is regulated by TSH, which also affects BMD (7). These findings suggest that thyroid hormones are important bone metabolic biomarkers in children; however, the mechanisms by which FT4 is regulated by TSH remain unclear. In adults, hyperthyroidism or low TSH levels have been associated with decreased BMD and an increased risk of fracture (26,27,29). On the other hand, the pathology of subclinical hypothyroidism (SH) is defined by a TSH level above the upper limit of the reference range and a serum FT4 level within the reference range (30). Previous studies demonstrated that adult patients with SH had decreased BMD and an increased risk of fractures (31,32). However, Mase *et al* (33) showed that BMD was not reduced in children with idiopathic SH. The lower BMD in adult SH patients may be attributed to SH preventing optimal peak bone mass being reached in adolescence. Further studies are needed on BMD and fracture displacement in children with SH. BMD and bone metabolic biomarkers have not yet been employed to assess the extent of fracture displacement in pediatric fractures.

In children, higher FT4 levels have been associated with lower BMD (7), and FT4 is a relative assessment of BMD. In a study on distal radius fractures in adults, which are fragility fractures, BMD correlated with fracture displacement (3). These findings suggest the involvement of thyroid hormones and TSH in reduced BMD and the risk of fractures in adults and children. In clinical practice, difficulties are associated with measuring BMD in pediatric fracture patients; therefore, an alternative evaluation of BMD is needed. This is the first study to show that a high level of FT4, a relative assessment of BMD, may be associated with the displacement of pediatric supracondylar humeral fractures. Therefore, FT4 levels have potential as an early indicator of fracture severity in pediatric fractures if FT4 has the capacity to function as a biomarker to assess the extent of fracture displacement in other pediatric fractures. Elevated FT4 levels have also been associated with lower BMD in children (7); therefore, a bone health assessment is recommended when FT4 levels are high.

There are several limitations that need to be addressed. A small number of cases was examined. In a case study of 22 patients, Unal *et al* (34) reported that oral bisphosphonates increased BMD in children and adolescents with osteoporosis. However, since Unal *et al* (34) was also limited by difficulties obtaining a large number of pediatric bone metabolism cases, we consider the present study to have value as a clinical study. Furthermore, due to the lack of data from normal children, no comparisons with the fracture group were performed. However, the fracture group did not meet the standard

value for vitamin D sufficiency proposed by the American Association of Pediatric Endocrinologists (14); therefore, despite comparisons with healthy children not being available, the present results suggest that vitamin D insufficiency is a risk factor for fracture. Another limitation is that we were unable to assess BMD in children. BMD is widely assessed as a risk factor for fracture (1), and low BMD has been associated with greater displacement in the elderly (3). In children, low BMD may also lead to greater displacement; however, the measurement of BMD in pediatric fracture patients in clinical practice is difficult. Dual-energy X-ray absorptiometry (DXA) is useful for measuring BMD, but it involves radiation exposure to patients. Children are more susceptible to radiation exposure than adults due to their physical size (35). In addition, according to pediatricians, the use of DXA is not recommended outside of specialist centers due to the need for specialized knowledge (36). Therefore, it is difficult to perform DXA for measuring BMD as a screening test for children. On the other hand, FT4 levels correlated with BMD, they may be used to evaluate relative BMD (7). Moreover, the results of this study suggest that FT4 may be a factor for predicting the amount of fracture displacement in children. Since FT4 can be measured by routine blood examinations, it is expected to become an alternative evaluation of BMD in pediatric fractures. Collectively, the present results indicate that high FT4 levels, a relative assessment of BMD, are associated with the displacement of pediatric supracondylar humeral fractures.

In conclusion, the present study demonstrated that FT4 levels were elevated in displaced pediatric supracondylar humeral fractures.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

NI mainly wrote this manuscript, and was involved in acquisition, analysis and interpretation of data. KN and MI mainly performed the conception and design of the study. SK, TS, YY and KK performed acquisition, analysis and interpretation of data. KN and SK confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Research Ethics Committee of the Faculty of Medicine, Juntendo University (approval no. E23-0318; date of approval: December 11, 2023; Tokyo, Japan). This committee is registered with the Ministry of Health, Labor and Welfare's Research Ethics Review Committee Reporting System in accordance with Japanese ethical guidelines (IRB no. 21000123). The study was retrospective and approved by the Research Ethics Committee of the Faculty of Medicine, Juntendo University to be conducted with opt-out rather than written consent. According to the ethical guidelines, the requirement for written informed consent was waived due to the retrospective nature of the study. Instead of the written informed consent, the information of the study and the opt-out opportunity were shown on the hospital website. All parents of the patients were also given an oral explanation of the opt-out form on the website, allowing them to opt-out of the study instead of patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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