Comparison of 25-OH vitamin D levels between children with upper and those with lower extremity fractures: A prospective case-control study

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Abstract

Objective: The aims of this study were (1) to compare 25-OH vitamin D levels between children with upper and those with lower extremity fractures and (2) to determine whether 25-OH D insufficiency prevalence is increased compared to healthy controls.

Methods: This is a prospective case–control study for 12 months. The study was conducted with children aged 5-18 years, including 60 children with non-displaced, impaction type upper extremity and lower extremity fractures resulting from low-energy trauma. In addition, 60 healthy children were included as controls. In all participants, risk factors for low bone mineral density were assessed and serum 25(OH)D levels were measured. Vitamin D levels were compared among groups.

Results: Vitamin D deficiency (25-OH D <20) was 14.8 times (OR= 95% CI= 5.61 - 39.8) and 2.9 times (OR= 95% CI= 1.46-5.75) higher in patients with upper and lower extremity fractures, respectively. In the upper extremity fracture group, serum 25(OH)D level was considered deficient (25-OH D level<20 ng/mL) in 91.6% (54/59) and the fracture risk is higher in upper extremity fractures than in lower extremity fractures. In children with fractures, routine vitamin D evaluation should be considered.

Introduction

It is unclear why slight trauma causes fracture in some healthy individuals. Though it is known that prior fracture increases the risk of additional fractures, it has not been fully elucidated which children are at risk for multiple childhood fractures12 and there is no scale to predict which demographic, medical, and social factors identify the risk for fracture in a child.

Vitamin D plays an important role in the homeostasis of several metabolic processes, including the calcium absorption and preservation essential for the nervous system, teeth, and bones.3 Vitamin D deficiency has been linked to diabetes mellitus, cardiovascular diseases, immune system disorders, and bone mineralization defects in adulthood.44 In pediatric populations, hypovitaminosis D is associated with rickets, obesity, sickle cell disease, childhood malignancies, chronic inflammatory disorders, and insufficient bone growth.5,6 Besides the well-known association with rickets, vitamin D deficiency is also linked to hip and knee osteoarthritis, distal radius fracture, and articular infirmities.7 These bone and joint conditions have led to increasing interest in the relationship between vitamin D and orthopedic disorders.10 Previous studies have mostly focused on the association between vitamin D levels and fracture in elder individuals.11,12 The first studies in this field focused particularly on victims of child abuse and concluded that vitamin D deficiency was unlikely to have contributed to the fractures.13-15

Some case–control studies have correlated low vitamin D levels with increased fracture risk; however, there are also case–control studies that were unable to confirm this relationship.1,10,16-19

Some studies conducted without a control group found a high rate of vitamin D deficiency in fracture patients, and vitamin D supplements were recommended.20,21 The threshold 25-hydroxyvitamin D(25(OH)D) concentration for deficiency is 20 ng/mL; however, there is debate on threshold concentration for insufficiency, with numbers ranging from 20 to 29 ng/mL.22

The current literature contains few reports comparing the relationship between vitamin D level and blood mineral level in non-displaced, impaction-type upper and lower extremity fractures.
This study compares 25(OH)D insufficiency in children with upper and lower extremity fractures and determines whether 25(OH)D insufficiency prevalence is increased compared to healthy controls.

**Materials and Methods**

**Study design and setting**

This is a prospective case–control study. Subjects were recruited from the orthopedic emergency department of a public hospital serving as a tertiary referral and level I trauma center for a multicounty catchment area. The study was approved by the local ethics committee (approval number 2020/604.02). All participants and/or their parents gave informed consent.

**Study population**

The study population included 180 children (aged 5-18 years) comprised of 120 patients (60 with upper extremity and 60 with lower extremity fractures) and 60 healthy controls. The patient group was recruited from an orthopedics emergency outpatient clinic and included children with a simple fracture at the upper or lower extremity. The study included patients treated conservatively; no patients in the study received surgical treatment. The controls were recruited from a pediatrics outpatient clinic and included children presenting in a random manner for routine pediatric assessment by a blind clinician or who were diagnosed with upper respiratory tract infection or otitis media.

The study excluded non-ambulatory children, malnourished children, and children on steroid or anticonvulsant medications; children with osteogenesis imperfecta, rickets, or other bone disorders; children with diabetes mellitus, kidney disease, cystic fibrosis, malabsorption, or chronic gastrointestinal illnesses; children on any medications determined to affect vitamin D levels; and children with any other chronic illness that may affect nutrition and/or vitamin D levels. In the patient group, those with pathological fractures or those with level I or II trauma were excluded. Patients with fractures caused by high-energy mechanisms (motor vehicle accidents, fall from >10 feet) were also excluded. Anteroposterior and lateral radiographs were obtained from children demonstrating pain and swelling at the traumatized extremity.

**Data collection**

We collected data for all children presenting with simple fractures at the upper or lower extremity between January and December 2020. Data were collected through face-to-face interviews with patients and/or legal guardian regarding race/ethnicity, medical and fracture history, mechanism of injury (for patients), medications, daily intake of milk, soda, and daily use of vitamin supplements. Age, fracture site, sex, and weight were obtained from the patient’s chart at the time of enrollment.

**Laboratory evaluations**

Peripheral venous blood samples were collected from all participants and 25(OH)D, phosphorus (P), calcium (Ca), magnesium (Mg), and alkaline phosphatase (ALP) levels were studied. An immunochromiluminometric assay was used to measure 25(OH)D levels. A colorimetric method was used to measure phosphorus and calcium levels and a kinetic method was used to measure ALP level.

**Study variables and definitions**

Vitamin D deficiency was defined as 25(OH)D level <20 ng/mL, while vitamin D insufficiency was defined as serum 25(OH)D level ≥20 ng/mL and <30 ng/mL. Serum 25(OH)D level ≥30 ng/mL was considered normal. About.com Pediatrics Growth Chart Percentiles Calculator provided bodyweight percentiles (http://pediatrics.about.com/cs/growthcharts2/a/percentiles.htm).

**Statistical analysis**

All statistical analyses were performed using Statistical Package for Social Science software version 16.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics are summarized as the mean, standard deviation, median, and frequency distribution. Shapiro–Wilk test was used to assess normal distribution of variables. Student’s t-test was used to compare variables in 2 independent groups. The Kruskal–Wallis test was used to compare more than 2 groups. Average differences in vitamin D between groups were determined using post hoc tests.

The risk of fracture in the presence of vitamin D deficiency was determined by risk analysis with the odds ratio (OR) test for those with a low vitamin D value of 20 ng/mL, patients with 20 ng/mL and above, and the control group. A P-value ≤0.05 was considered significant. The data obtained were converted into tables and graphics using Microsoft Office Excel program.

**Results**

The study population included 60 children with upper extremity fracture, 60 children with lower extremity fracture, and 60 healthy controls. In both upper and lower extremities, fracture pattern was limited to non-displaced, impaction-type fractures. Table 1 presents fracture types and localizations. The mean age was comparable among upper extremity fracture (9.4 ± 3.5 years), lower extremity fracture (10.7 ± 3.9), and control groups (8.7 ± 2.6 years) (P = .34). No significant difference was observed in the demographic characteristics of participants regarding physical activity level and breastfeeding. Table 2 presents the demographic characteristics of participants.

The history of neonatal vitamin D use was not statistically significant between the study and control groups (P = .831). In the patient group, the risk of fracture in the presence of vitamin D deficiency was determined by risk analysis with the odds ratio (OR) test for those with a low vitamin D value of 20 ng/mL, patients with 20 ng/mL and above, and the control group. A P-value ≤0.05 was considered significant. The data obtained were converted into tables and graphics using Microsoft Office Excel program.

**Table 1. Fracture types and localizations**

| Fracture Type | Transverse | Oblique | Spiral | Total |
|--------------|------------|---------|--------|-------|
| Clavicle     | 0 (0)      | 3 (25)  | 0 (0)  | 3 (25) |
| Humerus      | 1 (0.8)    | 8 (67)  | 2 (17) | 11 (9.2) |
| Forearm      |            |         |        |       |
| Radius only  | 2 (1.7)    | 26 (21.7) | 3 (25) | 31 (25.8) |
| Radius and ulna | 3 (2.5) | 8 (67)  | 4 (33) | 15 (12.5) |
| Femur        | 1 (0.8)    | 9 (75)  | 2 (17) | 12 (10) |
| Tibia        | 2 (1.7)    | 12 (10) | 8 (67) | 22 (18.3) |
| Fibula       | 0 (0%)     | 8 (67)  | 4 (33) | 12 (10) |
| Foot         | 1 (0.8)    | 10 (83) | 3 (25) | 14 (11.7) |
| Total        | 9 (7.5)    | 85 (70.8) | 26 (21.7) | 120 (100) |
Table 2. Demographics and patient characteristics of the patient and control

| Groups | Upper Limb (n = 60) | Lower Limb (n = 60) | Control (n = 60) | P** |
|--------|---------------------|---------------------|------------------|-----|
| Age (years) | 9.4 ± 1.5 | 10.7 ± 3.9 | 8.7 ± 2.6 | 0.34 |
| Gender (% male) | 42/60 (70) | 43/60 (71) | 42/60 (70) | 0.97 |
| Weight (kg) | 39.9 ± 14.9 | 42.3 ± 19 | 37.5 ± 15.6 | 0.21 |
| Height (cm) | 136 ± 18.3 | 142 ± 21.9 | 133.2 ± 163 | 0.05 |
| BMI | 20.3 ± 3.5 | 19.4 ± 3.6 | 20.6 ± 2.3 | 0.171 |
| Neonatal vitamin D | 88.3 (n = 53) | 90 (n = 54) | 91.7 (n = 55) | 0.831 |

BMI, body mass index.

**P < 0.05 is considered as significant.

Table 3. Blood parameters of the patient and control groups

| Groups | Upper Limb (n = 60) | Lower Limb (n = 60) | Control (n = 60) | P** |
|--------|---------------------|---------------------|------------------|-----|
| Ca (mg/dL) (Mean ± SD) | 9.75 ± 0.4 | 9.73 ± 0.5 | 9.6 ± 0.3 | 0.337 |
| Mg (mg/dL) (Mean ± SD) | 2 ± 0.2 | 2.1 ± 0.4 | 2 ± 0.2 | 0.24 |
| P (mg/dL) (Mean ± SD) | 4.8 ± 0.5 | 4.9 ± 0.6 | 4.9 ± 1 | 0.41 |
| ALP (IU/L) (Mean ± SD) | 264 ± 47 | 260 ± 56 | 252 ± 31 | 0.401 |
| 25(OH)D (ng/mL) (Mean ± SD) | 12.1 ± 5 | 15.3 ± 4 | 26.7 ± 6 | 0.000** |

Ca, calcium; Mg, magnesium; P, phosphorus; ALP, alkaline phosphatase; SD, standard deviation.

**P < 0.05 is considered as significant.

there was no child with a history of the previous fracture. The index fracture was the first fracture in all patients. Mean body mass index (BMI) was comparable among groups (P = .19). There were no obese patients (BMI >30 or BMI percentile >85%) in the study population. Table 3 summarizes the blood parameter results.

It was found that mean vitamin D level [25(OH)D] was significantly lower in the patient group compared to healthy controls (13.7 ± 5 ng/mL vs. 26.7 ± 7 ng/mL, t (12.588) = 88.026, P = .000) (Figure 1). Again, there was significant difference in mean vitamin D level [25(OH)D] between upper and lower extremity fracture groups [12.1 ± 5 ng/mL vs. 15.3 ± 4 ng/mL, t (3.651) = 144.6, P = .000]. Table 4 presents rates of vitamin D deficiency or insufficiency in the patient and control groups.

Low vitamin D level was associated with a higher risk for upper extremity (P = .000). Vitamin D deficiency (25(OH)D <20) was 14.8 times (OR: 95% CI: 5.61-39.8) and 2.9 times (OR: 95% CI: 5.61-39.8) higher in patients with upper and lower extremity fractures, respectively. No significant difference was detected in the remaining blood parameters between patient and control groups. Vitamin D replacement therapy (200 IU/kg) was prescribed to the children with vitamin D deficiency or insufficiency in both patient and control groups. Increased daily milk consumption and sun exposure in all patients with fractures are recommended.

Discussion

Our study is one of the rare ones in the literature comparing vitamin D levels in patients with upper and lower extremity fractures. Our data present a cross-sectional analysis of vitamin D and fracture risk in an urban, cosmopolitan population encompassing all ethnicities. Vitamin D is required for calcium homeostasis and bone remodeling. Only a limited number of studies on the role of vitamin D in pediatric fractures have reported insufficient vitamin D levels in the majority of patients. Recent studies suggest that malnutrition, poor sunlight exposure, physical inactivity, pigmentation, and genetics can lead to decreased bone mineral density. In children, vitamin D deficiency is linked to rickets, low bone mineralization, and increased risk for fracture. Vitamin D requirements are met by nutrition in less than half of children belonging to low socioeconomic status populations. In addition, storing of vitamin D is low in infants born in such populations as these infants absorb extremely low amounts of vitamin D when breast-fed. The daily intake of milk and dairy products was low in our study population.

Approximately 50% of all children experience a fracture during childhood. Upper extremity fractures are among the most common.

Figure 1. a, b. 25(OH)D level of groups (a). Boxplot graphics (b).
injuries and may be considered a marker of poor bone health. There is growing evidence associating such fractures with future osteoporosis.26

Although lower extremity fractures lead to higher morbidity and mortality compared to upper extremity fractures, they are less commonly seen.27 The fracture risk is increased 1.6-fold in obese children when compared to normal-weight children.27 In our study, no significant difference was detected among groups regarding body weight. This may be due to variations in socioeconomic level and nutritional habits.

The literature reports more pronounced vitamin D deficiency in children with fractures.16,19,20,26 In agreement, we found that it was more likely to have low serum 25(OH)D level in the fracture cohort compared to healthy controls. Serum 25(OH)D levels were deficient in 100 (83%) and insufficient in 20 (17%); sufficient serum 25(OH)D levels were present in no patient. These ranges are much worse compared to ones in the study by James et al28 investigating upper extremity fractures.

A previous study showed no significant difference in serum 25(OH)D levels between children with lower extremity fracture and upper extremity fracture. Authors have reported higher rates of vitamin D insufficiency in children in all groups.10 Minkowitz et al11 demonstrated that pediatric fracture was not associated with serum 25(OH)D levels but found children with lower serum 25(OH)D levels to be at higher risk for severe fractures. In contrast, we found a significant difference in vitamin D level between our fracture patient and healthy control groups: vitamin D deficiency was found to be rare in the control group while vitamin D deficiency or insufficiency was detected in all patients with fractures. Again, lower vitamin D level was found to be associated with upper extremity fractures.

Our study has some limitations. First, we did not included mean weekly sunlight exposure and bone mineral density (BMD) Z scores in the analysis. Second, we did not exclude children with attention-deficit hyperactivity disorder.

Our study has some unique features. In the literature, studies on vitamin D levels in patients with fractures were conducted in children aged 6-12 and 3-10 years.32,33 Our study includes a wider range, with patients from 5 to 15 years of age.

Our study demonstrated that vitamin D deficiency was more prevalent in patients with upper and lower extremity fractures compared to healthy controls; our study also reported higher rates than previously reported rates. In addition, in comparing upper and lower extremities, our study showed that lower vitamin D level was associated with upper extremity fractures. Additional studies are needed to further elucidate such a relationship.

Ethics Committee Approval: Ethics committee approval was obtained from the Local Ethics Committee of Mardin State Hospital (2020/694-02)

Informed Consent: Informed consent was obtained all participants and/or their parents.

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