Sağlık Akademisyenleri Dergisi
http://dergipark.gov.tr/sagakaderg

Sağ Aka Derg, 2021; 8(3): 221-226

Research Article / Araştırma

Fragility fractures in patients hospitalized in the pediatric intensive care unit*

Pediatrik yoğun bakım ünitesinde yatan hastalarda frajilite kırıkları

Gürbüz Akçay[1], Halil Kocamaz[2], Nazan Bayar Şakın[3]

[1]Pamukkale University, School of Medicine Pediatric Intensive Care Unit, gurbuzakcay@hotmail.com, 0000-0002-4682-9258.
[2]Pamukkale University, School of Medicine, Pediatric Gastroenterology Clinic, drkocamaz@hotmail.com, 0000-0002-3366-1695
[3]Pamukkale University, School of Medicine, Pediatric Intensive Care Unit, nazanbayar@gmail.com, 0000-0003-4786-3180

* We presented this work at the 14th International Congress on Quality in Healthcare Accreditation and Patient Safety Congress, Antalya, December 13-16, 2020 as a oral presentation

ABSTRACT

Introduction and Objectives: We aimed to examine the demographic and clinical characteristics of children with Fragility Bone fractures (FF) in our pediatric intensive care unit (PICU) and to evaluate possible risk factors for FF. **Material and methods:** The medical records of patients hospitalized in the PICU in the previous five years were reviewed in terms of their demographic, anatomical, and therapeutic features.**Results:**Seven patients with a total of nine bone fractures were identified. During this period, 807 patients were admitted to the PICU (0.59 fracture cases / 1000 hospitalization days). The median patient age at the time of fracture definition was 5.29±2.82 years (range: 1.39 to 8.43 years). Four patients were diagnosed with congenital quadriplegic cerebral palsy (CP), one with quadriplegia after cerebral venous sinus thrombosis, one with meningomyelocele, and one with spinal muscular atrophy (SMA). Six patients were hospitalized for extended periods. The mean length of hospitalization in patients with bone fractures (73.92 days) was significantly higher than the length of stay of all patients (14.72 days) ($p < 0.001$). Bone fractures were detected between days two and 165 of admission. Bone fractures were in the humerus in one case and the femur in all others. No patients had a weight percentile <5% based on Turkish national data. Based on evaluation of weight for height, one patient had mild protein-energy malnutrition (PEM), one was overweight, one was obese, and the others were normal. All patients were also diagnosed with epilepsy, were fed by nasogastric tube, and experienced prolonged immobility. **Conclusions**: Patients hospitalized in the PICU are at risk for fragility fractures. Rapid evaluation and treatment in terms of fragility bone fractures should be initiated, particularly in the presence of clinical clues during the follow-up of patients with CP. Conditions that cause long-term immobility such as CP and SMA are the principal risk factors.

ÖZ

Giriş ve Amaç:

Çocuk yoğun bakım ünitemizde (ÇYBÜ) Frajil Kemik kırığı (FF) olan çocukların demografik ve klinik özelliklerini incelemeyi ve FF için olası risk faktörlerini değerlendirmeyi amaçladık. **Araç ve yöntemler:** Son beş yıl içinde ÇYBB'de yatan hastaların tıbbi kayıtları demografik, anatomik ve terapötik özellikleri açısından gözden geçirildi. **Bulgular:** Toplam dokuz kemik kırığı olan yedi hasta belirlendi. Bu dönemde 807 hasta ÇYBB'ye kabul edilmişti (0,59 kırık vakası / 1000 hastanede kalış günü). Kırık tanımlandığı sırada ortalama hasta yaşı 5,29 ± 2,82 yıl (aralık: 1,39 ila 8,43 yıl) idi. Dört hasta konjenital kuadriplejik serebral palsi (SP), bir hasta serebral venöz sinüs trombozu sonrası kuadripleji, bir hasta ise meningomiyelosel ve bir hastaya spinal musküler atrofi (SMA) tanısı konmuştu. Altı hasta uzun süre yatmıştı. Kemik kırığı olan hastalarda ortalama hastanede kalış süresi (73.92 gün) tüm hastaların yatış süresinden (14,72 gün) anlamlı olarak daha yüksekti ($p <0,001$). Başvurunun ikinci ve 165. günleri arasında kemik kırıkları tespit edildi. Kemik kırıkları bir vakada humerusta, diğerlerinde femurdaydı. Türkiye ulusal verilerine göre hiçbir hastada ağırlık yüzdesi <% 5 değildi. Boy için kilo değerlendirmesine göre, bir hastada hafif protein-enerji malnütrisyonu(PEM) vardı, biri fazla kilolu, biri obezdi, diğerleri normaldi. Tüm hastalara ayrıca epilepsi teşhisi konmuş, nazogastrik tüple beslenmiş ve uzun süreli immobilite tespit edilmişti. **Sonuçlar:** ÇYBB'de hastaneye yatırılan hastalar kırılganlık kırıkları açısından risk altındadır. Özellikle SP'li hastaların takibinde klinik ipuçları varlığında kırılganlık kemik kırıkları açısından hızlı değerlendirme ve tedaviye başlanmalıdır. CP ve SMA gibi uzun süreli hareketsizliğe neden olan koşullar başlıca risk faktörleridir.

Key Words:
Pediatric Intensive Care Units, Bone fractures, Cerebral Palsy, Spinal Muscular Atrophies of Childhood

Anahtar Kelimeler:
Çocuk Yoğun Bakım Ünitesi, Kemik kırıkları, Serebral Palsi, Çocukluk çağı Spinal Müsküler Atrofileri

Corresponding Author/Sorumlu Yazar:
Pamukkale University, School of Medicine Pediatric Intensive Care Unit, gurbuzakcay@hotmail.com.

Received Date/Gönderme Tarihi:
05.05.2021

Accepted Date/Kabul Tarihi:
19.05.2021

Published Online/Yayımlanma Tarihi:
01.09.2021

INTRODUCTİON

?? Fragility bone fractures have been described as "bone fractures caused by an effect insufficient to break a normal bone" [1]. Spontaneous bone fractures are occasionally observed in intensive care units. Prolonged immobility or immobilization, certain drugs (corticosteroids, anticonvulsants, immunosuppressives, anticoagulants, antiretrovirals, and diuretics) radiation therapy, malnutrition, hyponatremia, and inflammation in hospitalized patients have been reported as risk factors for such bone fractures [2-4].

The purpose of this study was to examine the demographic, clinical, and therapeutic characteristics of children diagnosed with fragility fractures in our pediatric intensive care unit (PICU) over a five-year period and to evaluate potential accompanying risk factors.

METHODS

The study was approved by the local ethics committee (Medical Ethics Committee 12/5/2020 issue 09). The PICU contains nine beds and accepts critical patients aged from one month to 18 years, excluding trauma cases. The records of children hospitalized in the PICU in five years (2015-2019) were retrieved from the hospital information system. The files of those children with bone fractures were then set aside. Radiographs were acquired from the Picture Archiving and Communicating System (PACS). Radiographs with bone fractures were examined. The medical records of each fracture patient were then reviewed for demographic, clinical, and therapeutic details.

Duration of hospitalization ≥14 days (longer than 75% of total hospitalization days) from the time of fracture was defined as extended hospitalization [5]. Prolonged intravenous (IV) loop diuretic use (furosemide ≥7 days), heparinoid intake (≥7 days), prolonged immobility (≥7 days' muscle relaxant use), malnutrition at the time of fracture (<5% weight for age and weight for height), corticosteroid use, and chronic renal failure (CRF) were evaluated [6].

The patients' height and weight percentiles were calculated based on Olcay Neyzi and World Health Organization (WHO) reference values from the Turkish Pediatric Endocrinology and Diabetes Society website [7, 8]. Cerebral palsy (CP) patient percentiles were calculated using the Life Expectancy web site for cases above two years of age, and Kennedy Krieger Institute CP charts for those under two years [9, 10].

At weight for height analysis, >120% was regarded as obesity, 110-120% as overweight, 90-110% as normal (ideal), 80-90% as mild protein-energy malnutrition (PEM), 70-% 80 as moderate PEM, and <70% as severe PEM [11].

Statistical calculations were performed on IBM SPSS version 25 software. The Kolmogorov-Smirnov and Shapiro-Wilk tests were applied to evaluate normality of distribution. The independent sample t-test was used if distribution was normal, and the Mann Whitney U test otherwise. Numerical data was presented as median ± standard deviation. $p < 0.005$ was considered statistically significant.

RESULTS:

Demographic information

Seven patients with a total of nine bone fractures were identified in the five-year data. During this period, 807 patients (total 1036 admission) were admitted to the PICU (0.59 fracture cases per 1000 hospitalization days, 11.15 bone fractures per 1000 patients). The median patient age at the time of fracture definition was 5.29±2.82 years (range: 1.39 to 8.43 years). Age was not normally distributed between the cases with FF and other cases without FF hospitalized in PICU at the same period, according to the Kolmogorov-Smirnov and Shapiro-Wilk tests ($p=0.200$), and the Mann-Whitney U test was therefore used for statistical evaluation.

Four patients were boys, and three were girls. All patients were bed-dependent, four with congenital cerebral palsy, one due to Spinal Muscular Atrophy (SMA), one due to meningomyelocele and congenital hypothyroidism, and one due to a cerebral vascular disease. The median length of stay in the PICU was 71.01 days (between 25.08 and 164.04 days). Five cases were hospitalized for more than 14 days until the day a bone fracture was noticed. The mean length of hospitalization among patients with bone fractures (73.92±49.73 days) was significantly higher than that of all patients (14.72±26.39 days) ($p < 0.001$).

Detection of fracture occurred from the 2nd to 165th days of hospitalization. Bone fractures were suspected on the basis of local swelling during clinical follow-up or painful facial expressions during care and were identified by direct x-ray. Fracture was located in the humerus in one case, the proximal femur in one case, and the distal femur in all the others (Figure 1). The girl with spinal SMA had two bone fractures and had previously received pamidronate therapy. Only one case underwent a dual-energy x-ray absorptiometry (DEXA) scan, with z scores of -3.9 in the right forearm and -5.3 in the lumbar region.

Height data for three cases were unavailable. The weight percentile in one male case was 0.04 (<5%) according to data for Turkey, and the weight percentile for height

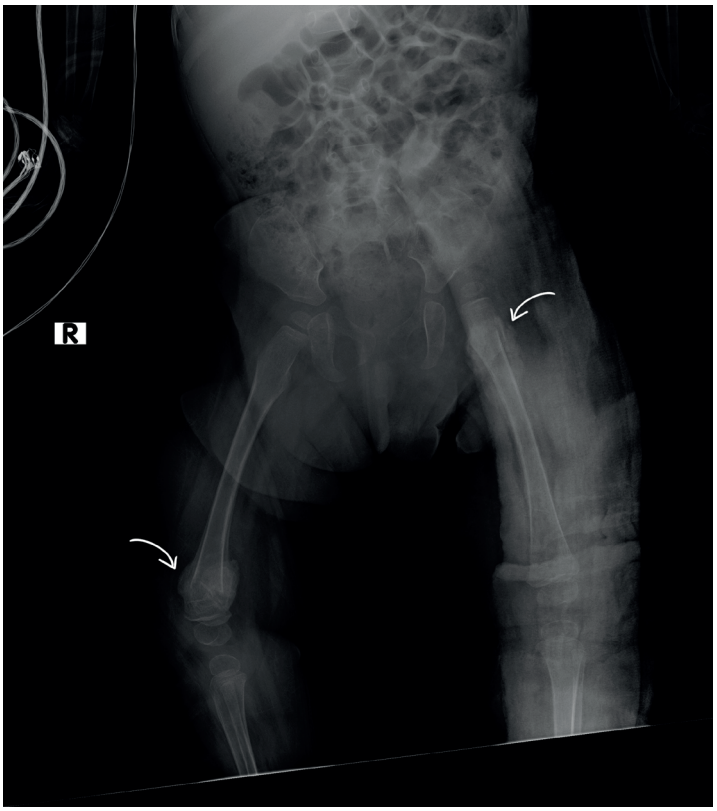

Figure 1. Fractures in the right distal and left proximal femur.

was 100% (normal) according to WHO data. In another male case, although the weight percentile for age based on data for Turkey was 22.9%, the weight for height percentile according to WHO data was 88.12% (80-90; mild protein-energy malnutrition). The patient with congenital hypothyroidism was evaluated as obese (176.66% -obese). Height details for a female patient were unavailable, but her weight for age was 99.89% (normal). The weight for the height of another girl was normal at 107.8%. One male patient had no available height record, and his weight was calculated at 97.72% (normal) according to Turkish country data. No height record was also available for another boy, and his weight was normal at 32.28% based on Turkish country data.

All cases were Level V according to the Gross Motor Function Classification System (GMFCS). Weight percentiles of four patients were 50% based on CP growth charts. One case was evaluated using Kennedy Krieger Institute charts due to being younger than two years old, and a weight percentile >50% was determined. Although the cases' weight percentiles were good, blood albumin levels in five cases and hemoglobin levels in four were below normal values for age.

All cases were diagnosed with epilepsy, were taking multiple antiepileptic drugs, and were fed through nasogastric catheters, and all had prolonged immobility. One patient had a history of long-term heparinoid use. Long-term (>15 days) proton pump inhibitor (PPi) use was detected in two cases and H2 blocker (Ranitidine) use in another two. Short-term furosemide was given in two cases. Five cases were admitted to the PICU with the diagnoses of pneumonia. Four cases had positive blood culture positivity and three had respiratory tract bacteria culture positivity. 25-hydroxy vitamin D levels were low in three cases (<30 µg / L), while calcium was slightly low in one case and adequate in the others [12]. Alkaline phosphatase (ALP) levels were high in one case, low in three, and normal in the others. A significant and noteworthy increase was observed in post-fracture ALP compared to pre-fracture values.

DİSCUSSİON

Seven patients with a total of nine bone fractures were identified over a five-year period (11.15 bone fractures per 1000 patients). The incidence of femoral fracture due to premature osteopenia was reported as 1.08 in 1000 patients in one neonatal intensive care unit [13]. Cheng et al. reported a fracture rate as 1.7 per 1000 patients in a PICU receiving congenital heart disease patients [6]. The patients in that study were aged less than 24 months, while those in the present study were aged up to 8.5 years, and the duration of stay in the

PICU was significantly longer than the clinical average, at 2.7 months. In the present study, the mean length of hospitalization of patients with bone fractures (73.92 days=2.46 months) was significantly greater than that of all patients (14.72 days) ($p < 0.001$). This may suggest that prolonged immobility is the main risk factor for fragility bone fractures.

Fortin et al. reported the presence of a neurological disease in 28.7% of patients with non-traumatic bone fractures. Patients with CP were mostly quadriplegic and spastic [14]. Having CP has been associated with malnutrition alone, and thus with a decrease in bone density and an increased risk of bone fractures [15]. In a community-based cohort study by Henderson et al., Bone mineral density (BMD) was 97% lower in 77% of patients with CP and 97% of those over the age of nine and unable to walk [16]. Studies conducted with Magnetic resonance imaging (MRI) and peripheral quantitative computed tomography (CT) in the lower extremities of patients with CP have also reported disruption of cortical and trabecular structures in the lower extremities [17]. Decreased albumin levels have been reported as a sign of chronic malnutrition in patients with CP. However, these levels can also change in acute inflammatory processes [15]. Patients with SMA also have low mineral density and are prone to bone fractures, regardless of the type and severity [18]. One of the risk factors in children with disabilities is obesity. Families can give their children higher than recommended levels of formula nutrients to help them recover more quickly. Obesity also causes bone fragility in children through a variety of mechanisms [19].

An increased risk of bone fractures has also been reported in children with epilepsy. In addition to mechanical effects occurring during epileptic attacks, osteoporosis caused by antiepileptic drugs also results in a predisposition to bone fractures [20]. Epilepsy and medication are also important risk factors in all patients in the current series.

Cheng et al. reported that fractures were mostly in the humerus, followed by the femur [6]. Fortin et al. reported the femur as the most common site, being observed in 33.3% or non-traumatic childhood bone fractures [14]. Henderson et al. measured BMD from the spine, proximal femur, and distal femur region in children with CP, and observed lower values in the distal femur region. This may explain the high incidence of distal femur fractures in our cases [16].

Bone hemostasis is a complex process involving hormonal, renal, nutritional, and physical components. Parathormone (PTH) and vitamin D are the main active ingredients in this process [21]. Studies conducted in adult intensive care units have associated vitamin D administered in low doses or doses given to normal individuals with impaired osteoblast function [22]. 25-hydroxy vitamin D values were adequate (> 30 µg / L) in four of our cases. However, the level of vitamin D required to prevent bone fractures is unclear [23]. PTH levels were normal in all our patients. All our patients use enteral nutrition solutions containing calories at a ratio of 1:1 or 1:1.5. However, the vitamin D content of these solutions may not be sufficient for a patient's daily needs. Requirements for additional vitamin D support in addition to formula should therefore be evaluated. CRF also impairs bone metabolism [24]. No CRF patient with bone fractures were observed among our patients.

Although pre-fracture ALP values were within normal limits, a significant increase in post-fracture values was associated with the normal process of bone healing [25]. If an increase in ALP values occurs in the PICU, especially in unconscious patients, we recommend that they be investigated for overlooked bone fractures. Long-term use of loop diuretics among other fracture risk factors was not detected in our patients, and two patients received short-term furosemide. Long-term heparin use is also reported to be capable of causing osteoporosis [26].

Cheng et al. reported that long-term heparin was used in 87% of the fracture cases, but that this was not significant compared to the control group. In our study, heparin was used for an extended period in one case due to intracranial thrombosis (enoxaparin 100 u / kg /dose at 12-hour intervals sc for one month).

In terms of corticosteroid use, inhaled budesonide was employed in three cases, and no oral or IV administration was reported in any case. Externally administered corticosteroids suppress the osteoblastic phase of bone metabolism, resulting in a decrease in bone mass and strength. Inhaled corticosteroids are also reported to be capable of causing osteoporosis after long-term use (> 5 years) [27, 28].

Proton pump inhibitors and H2 blockers have been associated with an increased risk of bone fractures in children when used long term [29]. In the present study, long-term PPi use was present in two patients and H2 blocker use in two.

Preventing fragility bone fractures also depends on pre- and post-PICU care. Macro- and micronutrients, energy, protein, and fat ratios should be regulated depending on age and specific disease state. An adequate supply of vitamin C, copper, and zinc is important to the synthesis of matrix proteins such as collagen. Fruit and vegetable consumption has been shown to exhibit a positive effect on bone density. Recommended daily intakes are 70-200

mg / kg / day for calcium and 50-140 mg / kg / day for phosphorus. It is also recommended that blood vitamin D levels be kept above 30 µg / L [12].

Excessive calcium intake should be avoided, as this may lead to hypercalciuria and nephrolithiasis [30]. Bone health can be evaluated by means of history, DEXA, quantitative computed tomography, quantitative ultrasound, and bone biopsy [4]. DEXA screening should only be performed after the age of four years [4].

During patient screening and care, if two or more risk factors are detected, a warning notice should be posted indicating a "risk of fracture" and vitamin D, PTH, calcium, phosphorus, and ALP levels should be measured. Information about fragility should also be provided when a physiotherapy consultation is requested [4].

Physiotherapy should be started early. Dynamic physical therapy applications are reported to be particularly beneficial in increasing BMD in children with CP [30]. Glucocorticoids should be used at the lowest effective dose. Bisphosphonates that inhibit osteoclast functions are commonly used for osteoporosis. They are also recommended for individuals using corticosteroids for more than three months and for immobilized patients [4, 30].

The annual administration of zoledronic acid in children with CP and Rett syndrome has been reported to prevent fragility bone fractures [25].

LIMITATIONS

The main limitations of this study are its retrospective nature, the low number of cases, and that BMD measurements were not performed on all patients. DEXA scan was performed for only one patient in this study. Further multi-center studies on the subject are now needed.

CONCLUSIONS

Fragility bone fractures may occur in PICUs. Conditions that cause long-term immobility such as CP and SMA are the principal risk factors. Bone-sparing nutrition of these patients should be reviewed from the start of hospitalization, and appropriate importance should also be attached at discharge and follow-up.

REFERENCES

1. Organization WH. Guidelines for preclinical evaluation and clinical trials in osteoporosis. World Health Organization; 1998.
2. Xu Q, Pillai SM, Barsony J et al. SUN-371 Hyponatremia Correction Normalizes Bone Mineral Density and Bone Fragility in Rats. Journal of the Endocrine Society 2020; 4: SUN-371.
3. Patel M, Ayus JC, Moritz ML. Fragility fractures and reversible osteopaenia due to chronic hyponatraemia in an adolescent male. BMJ Case Reports CP 2019; 12: e229875.
4. Huh SY, Gordon CM. Fractures in hospitalized children. Metabolism 2013; 62: 315-325.
5. Krell RW, Girotti ME, Dimick JB. Extended length of stay after surgery: complications, inefficient practice, or sick patients? JAMA surgery 2014; 149: 815-820.
6. Cheng HH, Carmona F, McDavitt E et al. Fractures related to metabolic bone disease in children with congenital heart disease. Congenital heart disease 2016; 11: 80-86.
7. Society TPEaD. CHILD METRICS. In: 2020:
8. De Onis M. WHO child growth standards. Geneva: WHO 2006; 1Á336.
9. David Strauss RS, Jordan Brooks. New Growth Charts. In: 2020:
10. Krick J, Murphy-Miller P, Zeger S et al. Pattern of growth in children with cerebral palsy. Journal of the American Dietetic Association 1996; 96: 680-685.
11. Schonfeld-Warden N, Warden CH. Pediatric obesity: an overview of etiology and treatment. Pediatric Clinics of North America 1997; 44: 339-361.
12. Holick MF, Binkley NC, Bischoff-Ferrari HA et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. The Journal of Clinical Endocrinology & Metabolism 2011; 96: 1911-1930.
13. Pektaş MK, Koyuncu H, Kundak AA. Long bone fractures in neonatal intensive care units of Afyonkarahisar: Five-year's experience. Turkish Journal of Obstetrics and Gynecology 2019; 16: 219.
14. Fortin K, Bertocci G, Nicholas JL et al. Long bone fracture characteristics in children with medical conditions linked to bone health. Child Abuse & Neglect 2020; 103: 104396.
15. Jesus AO, Stevenson RD. Optimizing Nutrition and Bone Health in Children with Cerebral Palsy. Physical Medicine and Rehabilitation Clinics 2020; 31: 25-37.
16. Henderson RC, Lark RK, Gurka MJ et al. Bone density and metabolism in children and adolescents with moderate to severe cerebral palsy. Pediatrics 2002; 110: e5-e5.
17. Rehberg M, Azim M, Martakis K et al. Bone microarchitecture assessed by Trabecular Bone Score is independent of mobility level or height in pediatric patients with cerebral palsy. J Bone Miner Res 2020.
18. Wasserman HM, Hornung LN, Stenger PJ et al. Low bone mineral density and fractures are highly prevalent in pediatric patients with spinal muscular atrophy regardless of disease severity. Neuromuscular Disorders 2017; 27: 331-337.
19. Faienza MF, D'Amato G, Chiarito M et al. Mechanisms involved in childhood obesity-related bone fragility. Frontiers in endocrinology 2019; 10: 269.
20. Mohamed N, Makaranka S, Cheema K et al. Bilateral acetabular fractures induced by an epileptic seizure in a paediatric patient: a unique case and its management. BMJ Case Reports CP 2019; 12: e230143.
21. Via MA, Gallagher EJ, Mechanick JI. Bone physiology and therapeutics in chronic critical illness. Annals of the New York Academy of Sciences 2010; 1211: 85-94.
22. Van den Berghe G, Van Roosbroeck D, Vanhove P et al. Bone turnover in prolonged critical illness: effect of vitamin D. The Journal of Clinical Endocrinology & Metabolism 2003; 88: 4623-4632.
23. Contreras JJ, Hiestand B, O'Neill JC et al. Vitamin D deficiency in children with fractures. Pediatric Emergency Care 2014; 30: 777-781.
24. Wesseling K, Bakkaloglu S, Salusky I. Chronic kidney disease mineral and bone disorder in children. Pediatr Nephrol 2008; 23: 195-207.

25. Bowles SA, Kurdy N, Davis AM et al. Serum osteocalcin, total and bone-specific alkaline phosphatase following isolated tibial shaft fracture. Annals of clinical biochemistry 1996; 33: 196-200.
26. Hirsh J, Warkentin TE, Shaughnessy SG et al. Heparin and low-molecular-weight heparin mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. Chest 2001; 119: 64S-94S.
27. Petrisko MA, Skoner JD, Skoner DP. Safety and efficacy of inhaled corticosteroids (ICS) in children with asthma. Journal of Asthma 2008; 45: 1-9.
28. Allen DB. Inhaled Corticosteroids and Endocrine Effects in Childhood. Endocrinology and Metabolism Clinics 2020; 49: 651-665.
29. Wagner K, Wagner S, Susi A et al. Prematurity does not increase early childhood fracture risk. The Journal of pediatrics 2019; 207: 148-153.
30. Mughal MZ. Fractures in children with cerebral palsy. Current osteoporosis reports 2014; 12: 313-318.