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ORIGINAL ARTICLE

Significant association among growing pains, vitamin D supplementation, and bone mineral status: results from a pilot cohort study

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Abstract The aim of our study was to analyze the possible relationship between growing pains, vitamin D levels, and bone mineral status. We enrolled 33 children affected by growing pains. Their pain intensity was evaluated through a questionnaire using the Wong–Baker Faces Pain Rating Scale for pain assessment. Serum 25-hydroxyvitamin D (25-OH-D), parathyroid hormone (PTH), and alkaline phosphatase levels were measured as well. A quantitative ultrasound assessment (QUS) was also done, measuring both the amplitude-dependent speed of sound (AD-SOS) and the bone transmission time (BTT), correlating, respectively, with bone density and with cortical thickness. After 3 and 24 months of vitamin D supplementation, we re-evaluated pain intensity and laboratory results. After 24 months we re-assessed QUS parameters. At the beginning of the study the children reported a mean growing pain intensity of 7.5 ± 1.6 SD. The mean values of 25-OH-D and PTH levels were 15.7 ± 6.9 ng/ml and 57.3 ± 27.3 pg/ml, respectively. The AD-SOS *Z* score was −0.53 ± 1.19 SD, and the mean value of the BTT *Z* score was −0.72 ± 0.96 SD. After the first 3 months of vitamin D supplementation we observed an increase in 25-OH-D levels (34.1 ± 17.8, $p < 0.001$) and a reduction in both PTH levels (47.3 ± 30.6, $p = 0.135$) and pain intensity (2.7 ± 2.2, $p < 0.001$). After 24 months we observed a further significant reduction in the pain intensity (3.9 ± 3.4, $p < 0.001$) and in PTH levels (43.7 ± 28.5, $p = 0.004$) and an improvement in the QUS parameters, in particular in BTT *Z* scores ($p = 0.014$). Our study suggests an interesting relationship between growing pains, vitamin D levels and bone mineral status.

Keywords Growing pains · Vitamin D · Parathyroid hormone · Bone mineral status · Quantitative ultrasound assessment

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Introduction

Recurrent lower limb pains, termed growing pains or growth pains, constitute the most frequent cause of musculoskeletal pain in children. Growing pains mostly affect children between the ages of 3 and 12 years, and their prevalence varies from 2.6 % to 49.4 % [1–3]. Growing pains are usually non-articular, almost always bilateral, and often located in the shins, calves, thighs, or popliteal fossa. The pain usually appears late in the day or at night, often awaking the child, with a duration of less than 72 h and without any objective signs of inflammation on physical examination [1]. After the first definition of growing pains by the French physician Duchamp [4], many attempts at better defining this condition have been made, and many researchers have tried to set specific diagnostic criteria [5].

To explain the etiopathogenesis of growing pains, many different theories have been purported [5], but none has ever been confirmed; "growing pains" continue to be diagnosed by exclusion of other factors, and only the symptoms are treated [1].

In the literature, several studies on adults with persistent, non-specific musculoskeletal pain reported that these patients had decreased 25-OH-D levels and that their painful condition improved with vitamin D supplementation [6–12]. It is known that vitamin D deficiency is common [13, 14] also among children [15–17], but few studies have investigated the prevalence of vitamin D deficiency specifically in children suffering from growing pains [18, 19]. Moreover, only one study conducted by Friedland et al. [20] has evaluated bone mineral status in these patients, observing a reduced bone speed of sound (SOS) compared with healthy controls.

Our study is the first that assessed a possible relationship between pain intensity, vitamin D levels, and bone mineral status in children affected by growing pains.

Materials and methods

Patients

We enrolled 33 children, 15 girls and 18 boys, affected by growing pains as defined by Petersen [5]. Their mean ages were 8.1 ± 3.2 years for the boys and 10.0 ± 2.3 years for the girls. Twenty-nine patients (87.9 %) had a BMI between the 5th and 95th sex-specific and age-specific percentiles [on the growth charts of the Center for Disease Control (CDC) and Prevention—http://www.cdc.gov/growthcharts]. Two (5.9 %) had a BMI above the 95th percentile, and 2 (5.9 %) had a BMI below the 5th percentile. The mean BMI value was 16.8 ± 2.8 SD in males and 18.6 ± 4.0 SD in females. Fourteen of the 18 boys (77.8 %) and 5 of the 14 girls (35.7 %) were at a prepubertal stage of sexual development (Table 1).

Inclusion criteria were children or adolescents affected by intermittent pains in both legs (non-articular in location), with no signs of inflammation such as local tenderness or swelling, or movement limitation. Exclusion criteria were history of known bone disease; physical signs (swelling, redness, trauma, reduced joint range, limping) and lab results (blood tests, imaging) of articular diseases; treatment with drugs that could increase bone metabolism (i.e., anticonvulsants, glucocorticoids, highly active antiretroviral therapy, and antirejection medications); a medical condition that would decrease vitamin D; and cognitive impairments which would not enable the child to understand the questionnaire and the pain scale used.

Study design

Our study was designed as a prospective pilot cohort study. The patients first presented to our Pediatric Clinic between January 2010 and May 2010; in May 2010 we decided to end the children's enrollment because the beginning of summer would have produced a bias in the interpretation of vitamin D levels. At first evaluation (T0) all 33 patients enrolled completed a questionnaire where the intensity of their growing pains was rated on a pain evaluation scale. At the same time serum 25-OH-D, PTH, and ALP levels were measured, and a quantitative ultrasound assessment (QUS) of the last four proximal phalanges of the non-dominant hand was performed. After the first 3 months of vitamin D supplementation (T1) we re-evaluated pain intensity and 25-OH-D, PTH, and ALP levels using the same methods used in the initial evaluation. After almost 24 months (T2), when children with levels of 25-OH-D <30 ng/ml continued taking vitamin D supplements, we reassessed pain intensity, lab tests, and QUS evaluations.

Informed written consent was obtained from the parents or guardians of all participating children, and our study followed the medical protocol established by the Declaration of Helsinki.

Table 1 Characteristics of the study population by gender (mean ± standard deviation)

	Total ($n = 33$) Mean ± SD	F ($n = 15$) Mean ± SD	M ($n = 18$) Mean ± SD	p
Age	9.0 ± 2.9	10.0 ± 2.3	8.1 ± 3.2	0.083
Weight (kg)	32.6 ± 13.6	37.8 ± 14.4	28.0 ± 11.4	0.041
Height (m)	1.33 ± 0.18	1.40 ± 0.15	1.26 ± 0.18	0.028
BMI	17.7 ± 3.5	18.6 ± 4.0	16.8 ± 2.8	0.109
Tanner stage P	1.8 ± 1.0	2.2 ± 1.2	1.5 ± 0.6	0.136
Tanner stage T/G	1.8 ± 1.1	2.3 ± 1.3	1.4 ± 0.7	0.052
Tanner stage T/G <2	21 (63.6 %)	7 (35.7 %)	14 (77.8 %)	0.083
Tanner stage T/G ≥2	12 (36.4 %)	8 (64.3 %)	4 (22.2 %)	–
Growing pain intensity (T0)	7.5 ± 1.6	7.7 ± 1.4	7.4 ± 1.8	0.985
25(OH)Vitamin D (ng/ml) (T0)	15.7 ± 6.9	15.2 ± 8.1	16.1 ± 5.9	0.492
PTH (pg/ml) (T0)	57.3 ± 27.3	66.9 ± 26.0	50.3 ± 26.7	0.039
Growing pain intensity (T1)	2.7 ± 2.2	2.7 ± 2.2	2.6 ± 2.3	0.722
25(OH)Vit D (ng/ml) (T1)	34.1 ± 17.8	32.7 ± 16.7	35.5 ± 19.5	0.801
PTH (pg/ml) (T1)	47.3 ± 30.6	69.0 ± 43.4	36.4 ± 14.2	0.223
Growing pain intensity (T2)	3.9 ± 3.4	4.5 ± 2.9	3.6 ± 3.8	0.530
25(OH)Vit D (ng/ml) (T2)	22.7 ± 6.8	24.0 ± 8.2	21.3 ± 5.0	0.487
PTH (pg/ml) (T2)	43.7 ± 28.5	53.4 ± 33.2	30.7 ± 14.7	0.196

The questionnaire

Responses to the questionnaire were collected through semi-structured interviews (a combination of open and closed questions) derived from the literature. The items on the questionnaire regarded age, sex, ethnicity, height, weight, medical history, features of growing pains (pain experiences, frequency, management, and drugs used), family history of growing pains, physical activity, diet (in particular calcium and vitamin D intake), and co-existence of other orthopedic problems.

To assess pain intensity, the questionnaire included a Wong–Baker Faces Pain Rating Scale (WBFPRS), that is, a horizontal line of 6 hand-drawn faces, scored from 0 to 10, that ranged from a smiling face on the left to a crying face on the right (hardly noticeable pain versus strongest conceivable pain). We used this scale because it had adequate psychometric backing in the literature [21].

Laboratory tests

Serum vitamin D levels [measured as 25 hydroxyvitamin D, 25(OH)D] were measured using a chemiluminescent method (LIAISON®25-OH Vitamin D Total, DiaSorin, Saluggia, Italy); serum intact-PTH levels were determined by another chemiluminescent method (LIAISON® 1-84PTH, DiaSorin, Saluggia, Italy), while serum ALP levels were measured with a standardized colorimetric test (ALP2, Roche/Hitachi Cobas c.).

Vitamin D supplements

After the first vitamin D dosage, the patients were divided into 4 categories according to their serum 25-OH-D levels. In increasing order of severity, the 25-OH-D level groups were as follows: normal vitamin D levels (25-OH-D $\geq$30 ng/ml), vitamin D insufficiency (25-OH-D <30 ng/ml, but $\geq$20 ng/ml), vitamin D deficiency (25-OH-D <20 ng/ml) and severe vitamin D deficiency (25-OH-D <10 ng/ml). This classification of 25-OH-D levels was based on data obtained from previous studies [22–24].

During the first 3 months, the patients were given different amounts of cholecalciferol (vitamin D3), according to their 25-OH-D levels: the children with 25-OH-D <10 ng/ml were given 100,000 UI of intramuscular (IM) vitamin D3 once a month; the children with 25-OH-D $\geq$10 but <20 ng/ml were given 100,000 UI orally once a month; the children with 25-OH-D levels $\geq$20 ng/ml but $\leq$30 ng/ml took 25,000 UI orally once a month, and those with 25-OH-D $\geq$30 ng/ml were not treated but just kept under control.

Patients were informed of the consequences and infrequent side effects of vitamin D supplementation [24].

QUS

To assess bone mineral status we performed a QUS with a DMB Sonic 1200 device (IGEA, Carpi, Italy). We considered two parameters: bone transmission time (BTT), which is related to cortical thickness and amplitude-dependent speed of sound (AD-SOS), which better determines mineral density [25, 26].

At each session, the reference speed of the patient's soft tissue was measured by applying the probes to the soft tissue area between the base of the thumb and the index finger. To measure bone density, probes were positioned at the distal metaphysis of the first phalanges in proximity of the condyles. The device automatically calculated the average AD-SOS of the 4 measurements, corrected for the presence of soft tissue and AD-SOS *Z* score.

The phalanx was used to measure bone strength because it is one of the most metabolically active parts of the skeleton, and in this region it is possible to observe small changes in bone turn-over, such as resorption of the trabeculae at epiphyseal and metaphyseal levels and enlargement of the medullary canal [27].

We repeated QUS assessment after 24 months, referring to Mauloni et al. [28], who, considering the sensitiveness of the methodology and the variations expected over time, calculated a minimal interval of 18 months between one measurement and the next to see QUS bone variations.

Statistical analyses

The statistical distributions of continuous variables were described using traditional summary statistics: mean $\pm$ standard deviation (Table 1).

Differences of mean levels for continuous variables (25-OH-D, PTH, pain intensity, AD-SOS, and BTT *Z* scores) were evaluated before and after vitamin D supplementation using a paired samples *t* test. The associations between continuous and discrete variables were assessed using the nonparametric median test. A p value <0.05 was considered statistically significant.

Statistical analysis was performed using Stata 11 (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP.).

Results

At the beginning of the study (T0), the children reported a mean pain intensity of 7.5 $\pm$ 1.6 SD, in particular 7.4 $\pm$ 1.8 SD for boys and 7.7 $\pm$ 1.4 SD for girls.

The mean values of 25-OH-D levels were 15.7 $\pm$ 6.9 mg/dl (16.1 $\pm$ 5.9 mg/dl for boys and 15.2 $\pm$ 8.1 mg/dl for girls), and the mean PTH values were 57.3 $\pm$ 27.3 pg/ml

(50.3 ± 26.73 for boys and 66.9 ± 26.0 for girls) (Table 1). All 33 patients had a serum 25-OH-D level below 40 ng/ml. 31 patients (93.9 %) had 25-OH-D levels below 30 ng/ml, 8 (24.2 %) below 10 ng/ml, 19 (57.6 %) between 10 and 20 ng/ml, and 4 (12.1 %) between 20 and 30 ng/ml. Only 2 children (6.1 %) had 25-OH-D levels above 30 ng/ml, suggesting vitamin D sufficiency.

At the baseline, 20 of the 33 patients (60.6 %) had serum intact-PTH levels higher than 50 pg/ml, and 11 of these 33 (33.3 %) higher than 60 pg/ml. ALP levels were in the normal range for all the patients, with a mean value of 217.7 ± 101.9 UI/l.

Regarding the QUS assessment at T0, 16 of 26 children (61.5 %) and 19 of 26 (73.1 %) had AD-SOS *Z* scores and BTT *Z* scores below the normal mean value of 0, respectively. Six patients (23.1 %) had an AD-SOS Z-score between −1 and −2 SD, and 3 (11.5 %) had scores below −2 SD. Nine patients (34.6 %) had a BTT-*Z* score between −1 and −2 SD, and 2 (7.7 %) had scores below −2 SD. At T0, we observed that children with severe vitamin D deficiency had mean AD-SOS and BTT *Z* scores lower than mean scores of children with higher vitamin D values (Table 2). Moreover, patients with PTH levels below 50 pg/ml had less negative AD-SOS and BTT mean *Z* scores than those with PTH levels above 50 ng/ml (Table 3). However, these differences are not statistically significant.

At T1, after 3 months of vitamin D supplementation, 25-OH-D mean levels increased from 15.7 ± 6.9 to 34.1 ± 17.8 ng/ml ($p < 0.001$), and mean PTH levels decreased from 57.3 ± 27.3 to 47.3 ± 30.6 pg/ml ($p = 0.135$) (Figs. 1, 2). We did not observe any significant difference in ALP mean levels (213.4 ± 88.4 UI/l, $p = 0.350$). Mean pain intensity decreased significantly from a value of 7.5 ± 1.6 SD to a mean value of 2.7 ± 2.2 SD ($p < 0.001$), and in 8 cases (23.5 %) the episodes of

Table 2 AD-SOS and BTT *Z* score mean values (±SD) at T0 in groups of patients according to 25-OH-D levels

	25-OH-D (ng/ml)			*p*
	<10	10–20	20–30	
AD-SOS *Z* score	−0.96 ± 1.13	−0.38 ± 1.28	−0.17 ± 0.81	0.231
BTT *Z* score	−0.66 ± 1.05	−0.73 ± 1.03	−0.77 ± 0.42	0.819

Table 3 AD-SOS *Z* score e BTT Z-score mean values (±SD) at T0 in groups of patients according to PTH levels

	PTH (pg/ml)		*p*
	<50	≥50	
AD-SOS *Z* score	−0.21 ± 1.57	−0.70 ± 1.03	0.136
BTT *Z* score	−0.62 ± 1.24	−0.75 ± 0.88	0.727

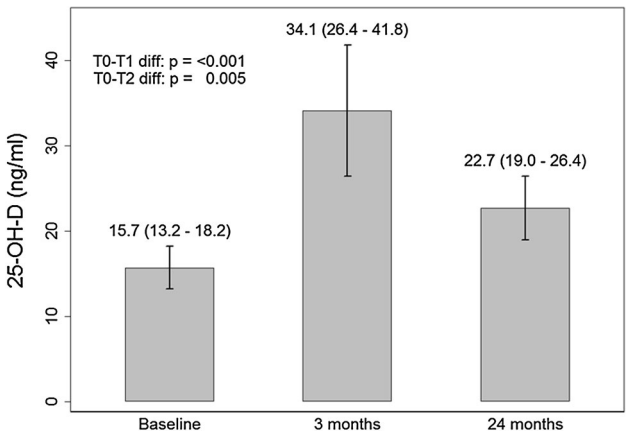

Fig. 1 Vitamin D mean levels in ng/ml (with 95 % confidence intervals) at the baseline, after 3 months, and after 24 months

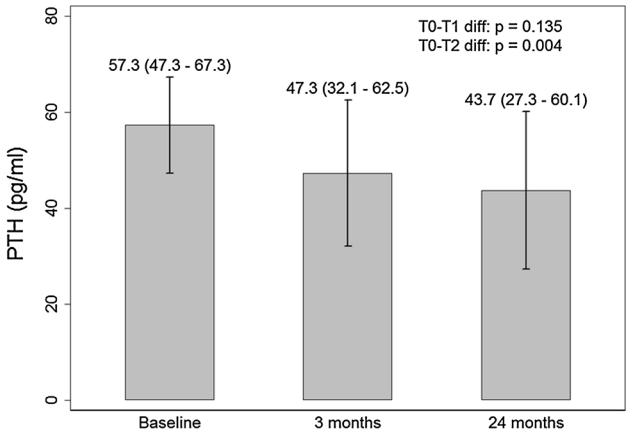

Fig. 2 PTH mean levels in pg/ml (with 95 % confidence intervals) at the baseline, after 3 months, and after 24 months

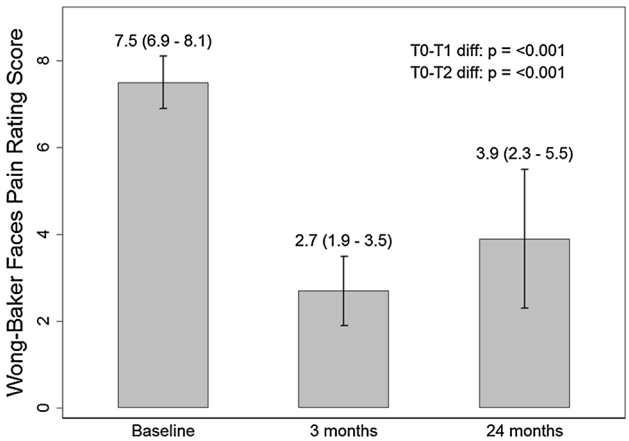

Fig. 3 Mean scores of the Wong–Baker Faces Pain Rating Scale (with 95 % confidence intervals) at the baseline, after 3 months, and after 24 months

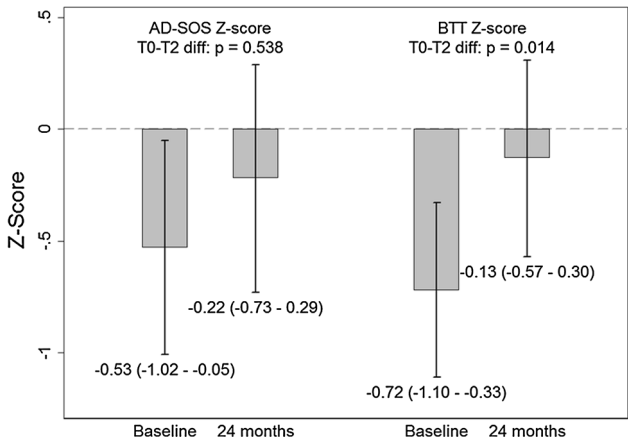

Fig. 4 Values of QUS parameters (AD-SOS and BIT *Z* scores, means with 95 % confidence intervals) at the baseline, after 3 months, and after 24 months

pain disappeared altogether (Fig. 3). An association between the total amount of vitamin D3 taken in the 3 months of treatment and the resulting pain reduction was found ($p = 0.047$).

At T2, after 24 months, the patients maintained vitamin D mean levels higher than they were at T0 ($p = 0.005$), but lower than mean levels at T1 ($p = 0.090$). We observed a further decrease in PTH mean levels. The differences between PTH mean levels at T2 and T0 are statistically significant ($p = 0.004$). At the same time, patients experienced less intense pain than at T0 ($p < 0.001$). Moreover, we noted an improvement in the QUS parameters: AD-SOS *Z* scores grew from -0.53 ± 1.19 SD to -0.22 ± 1.06 SD ($p = 0.538$), and BTT *Z* scores improved from -0.75 ± 0.96 SD to -0.13 ± 0.90 SD ($p = 0.014$) (Fig. 4).

Discussion

Growing pains are the most common form of episodic childhood musculoskeletal pain, concerning both males and females [1].

In 1960 Brenning et al. [5] supposed that "growing pains" were caused by a higher growth velocity rate, and it is known that the most important growth spurt occurs during puberty; nevertheless we observed that our patients were mostly prepubertal; most children did not have a growth velocity greater than their peers without growing pains, and ALP values, which are an expression of osteoblastic activity and growth, were in the normal range in all our patients. Instead, we believe that other factors should be taken into account.

Considering a possible relationship between growing pains and vitamin D levels, we observed that 94 % of our children affected by growing pains had values of vitamin D below the normal range, confirming a previous Pakistani study [19]; the prevalence of hypovitaminosis D observed in these patients seemed to be greater than in healthy children, in which it is reported with a prevalence of 40 %-50 % [15, 18].

A recent study conducted by Friedland et al. [20] described 39 children affected by growing pains, especially in tibial regions, compared with healthy controls in which they observed a reduced bone SOS (hypothesizing a local overuse syndrome; but no studies have evaluated possible relationships between growing pain intensity, vitamin D levels, and QUS assessment). By correlating vitamin D levels and QUS parameters, we observed that patients with 25-OH-D levels below 10 ng/ml had AD-SOS *Z* scores and BTT-*Z* scores lower than children with higher vitamin D values. At the same time we observed an inverse relationship between PTH and AD-SOS and BTT *Z* scores.

Regarding pain intensity, we did not find a correlation between initial 25-OH-D values and the intensity of pain; but pain perception is subjective, and so it may not be helpful to make a comparison between different people and pain sensitiveness; whereas it was interesting to determine a change in pain after vitamin D supplementation in the same individual.

After 3 months of vitamin D supplementation we observed a significant increase in 25-OH-D values ($p < 0.004$) associated with a significant decrease in pain ($p < 0.0001$) and PTH levels. The PTH reduction was not statistically significant, probably because 3 months of vitamin D supplementation are not sufficient to normalize PTH levels. In fact, after 24 months of vitamin D supplementation the reduction in PTH levels became statistically significant, although vitamin D levels at T2 were lower than at T1, probably as a result of a diminishing compliance.

Along with the decrease in PTH levels we observed a clear improvement in QUS parameters, in particular in BTT *Z* scores ($p < 0.01$), which assess cortical bone density; it is probable that increases in vitamin D lead to reduced PTH-mediated cortical bone resorption.

The observed reduction of pain intensity could be attributed to more mineralized cortical bone since it is reported in the literature that skeletal pain could be caused by an altered structure of cortical bone. Specifically, in a state of vitamin D deficiency, through PTH action, osteoblasts continue to deposit a collagen rubbery matrix on both the endosteal and periosteal surfaces of the skeleton; this matrix expands under the periosteal covering and could cause an outward pressure on periosteal sensory pain fibers [12].

Our study is the first that has evaluated a relationship between pain intensity, vitamin D levels, and bone mineral status in young patients affected by growing pains.

In line with our results, we feel that it is helpful to consider vitamin D deficiency in children with

musculoskeletal pains, and that it would be worthwhile to evaluate their bone status with QUS assessment. Further prospective and case–control studies will be necessary to confirm the role of vitamin D supplementation in reducing the incidence of so-called "growing pains".

Conflict of interest We declare no conflict of interest in relation to this paper, and we report no sources of funding.

References

1. Uziel Y, Hashkes PJ (2007) Growing pains in children. Pediatr Rheumatol Online J 5:5
2. Evans AM, Scutter SD (2004) Prevalence of "growing pains" in young children. J Pediatr 145:255–258
3. Kaspiris A, Zafiropoulou C (2009) Growing pains in children: epidemiological analysis in a Mediterranean population. Joint Bone Spine 76:486–490
4. Duchamp M (1823) Maladies de la croissance. In: Memoires de Médecine Practique Paris, Jean-Frederic Lobstein Edited by Levrault FG
5. Al-Khattat A, Campbell J (2000) Recurrent limb pain in childhood ('growing pains'). Foot 10:117–123
6. Ladhani S, Srinivasan L, Buchanan C et al (2004) Presentation of vitamin D deficiency. Arch Dis Child 89:781–784
7. Plotnikoff GA, Quigley JM (2003) Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. Mayo Clin Proc 78:1463–1470
8. Straube S, Derry S, Moore RA et al (2010) Vitamin D for the treatment of chronic painful conditions in adults. Cochrane Database Syst Rev (1):CD007771
9. Gloth FM 3rd, Lindsay JM, Zelesnick LB et al (1991) Can vitamin D deficiency produce an unusual pain syndrome? Arch Intern Med 151:1662–1664
10. Baeke F, Korf H, Overbergh L et al (2011) The vitamin D analog, TX527, promotes a human CD4 + CD25highCD127low regulatory T cell profile and induces a migratory signature specific for homing to sites of inflammation. J Immunol 186:132–142
11. Jones AN, Hansen KE (2009) Recognizing the musculoskeletal manifestations of vitamin D deficiency. J Musculoskelet Med 26:389–396
12. Holick MF, Vitamin D (2003) Deficiency: what a pain it is. Mayo Clin Proc 78:1457–1459
13. Holick MF (2006) Resurrection of vitamin D deficiency and rickets. J Clin Invest 116:2062–2072
14. Holick MF, Vitamin D (2007) Deficiency. N Engl J Med 357:266–281
15. Huh SY, Gordon CM (2008) Vitamin D deficiency in children and adolescents: epidemiology, impact and treatment. Rev Endocr Metab Disord 9:161–170
16. Gordon CM, Feldman HA, Sinclair L et al (2008) Prevalence of vitamin D deficiency among healthy infants and toddlers. Arch Pediatr Adolesc Med 162:505–512
17. El-Hajj Fuleihan G, Nabulsi M, Choucair M et al (2001) Hypovitaminosis D in healthy schoolchildren. Pediatrics 107:e53
18. Pavone V, Lionetti E, Gargano V et al (2011) Growing pains: a study of 30 cases and a review of the literature. J Pediatr Orthop 31:606–609
19. Qamar S, Akbani S, Shamim S et al (2011) Vitamin D levels in children with growing pains. J Coll Physicians Surg Pak 21:284–287
20. Friedland O, Hashkes PJ, Jaber L et al (2005) Decreased bone strength in children with growing pains as measured by quantitative ultrasound. J Rheumatol 32:1354–1357
21. Tomlinson D, von Baeyer CL, Stinson JN et al (2010) A systematic review of faces scales for the self-report of pain intensity in children. Pediatrics 126:1168–1198
22. Misra M, Pacaud D, Petryk A et al (2008) Vitamin D deficiency in children and its management: review of current knowledge and recommendations. Pediatrics 122:398–417
23. Perrine CG, Sharma AJ, Jefferds ME et al (2010) Adherence to vitamin D recommendations among US infants. Pediatrics 125:627–632
24. Holick MF, Binkley NC, Bischoff-Ferrari HA et al (2011) Evaluation, treatment and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 96:1911–1930
25. Cadossi R, de Terlizzi F, Canè V et al (2000) Assessment of bone architecture with ultrasonometry: experimental and clinical experience. Horm Res 54(Suppl 1):9–18
26. Guglielmi G, de Terlizzi F, Scalzo G et al (2010) Cortical thickness and medullary canal dimensions of the bone phalanx are predicted by quantitative ultrasound parameters. J Clin Densitom 13:219–227
27. Baroncelli GI (2008) Quantitative ultrasound methods to assess bone mineral status in children: technical characteristics, performance and clinical application. Pediatr Res 63:220–228
28. Mauloni M, Rovati LC, Cadossi R et al (2000) Monitoring bone effect of transdermal hormone replacement therapy by ultrasound investigation at the phalanx: a four-year follow-up study. Menopause 7:402–412