Annals of Arthritis and Clinical Rheumatology

Short Communication
Published: 17 Dec, 2018

Vitamin D Deficiency and Bone Health in Children

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Short Communication

Vitamin D is a secosteroid hormone that significantly affects bone mass acquisition, by promoting intestinal absorption of calcium and phosphorus thus modulating bone metabolism [1]. Adequate bioavailability of calcium and vitamin D and regular physical activity are main contributors for the acquisition of bone peak, with a key role in increasing bone strength during growth [2]. In the last two decades there has been a huge rising trend in the diagnosis of vitamin D deficiency in pediatric age, with incidence rates of 3.14/100,000 cases in 2000 to 261/100,000 in 2014 and a 15-times increase in the period 2008 to 2014. However, this trend was probably not guided by the clinical implications of low serum 25 (OH) D (the most accurate way to measure vitamin D storage in the body), leading to "Choosing Wisely" Campaigns in North America and Australia that recommended against routine screening of vitamin D status [3]. On the other hand, it should be taken into account increasing prevalence of hypovitaminosis D also in countries with high exposure to UVB irradiation, the main source of vitamin D. Indeed, in a retrospective study, including about 8,000 children and adolescents in the United Arab Emirates, authors reported serum levels of 25 (OH) D <50 nmol/L in 82.5% of cases [4]. Several factors contribute to vitamin D deficiency in children. First, the time they spend outdoor is progressively reducing; in favor of indoor play activities (TV, videogames, indoor sports, etc.). Other common risk factor for low serum 25 (OH) D are non-Caucasian ethnicity with dark skin pigmentation, obesity, inadequate dietary regimens (e.g., vegan diet), reduced sun exposure (due to lifestyle, chronic diseases, hospitalization, disability, cultural/religious reasons, sunscreen use), chronic kidney disease, chronic liver disease, and/or cholestasis, malabsorption syndromes (cystic fibrosis, inflammatory bowel diseases, IBD, and celiac disease), chronic drug use, such as anticonvulsants and systemic corticosteroids [1]. According to the European Academy of Paediatrics (EAP), serum 25 (OH) D should be measured only in the presence of multiple risk factors, and values below 20 ng/ml identifies vitamin D deficiency in children [5].

This condition should be considered also in the perinatal period, particularly during pregnancy, due to its association with poor fetal growth, hypocalcaemia, and musculoskeletal complications, including rickets, characterized by metaphyseal enlargement, bone pain, hypocalcemia and myopathy [6]. Clinical indications for 25 (OH) D measurements during pregnancy are bone pain, hypocalcemia, obesity, non-Caucasian ethnicity with dark skin pigmentation, malabsorption syndromes, alcohol abuse [1]. Major determinants of neonatal serum 25 (OH) D are UV irradiation 6 weeks before birth, accounting for 23% of changes in vitamin D status, and gene polymorphisms, such as rs2282679 and rs12785878, the genes encoding the vitamin D binding protein, and the 7-dehydrocholesterol reductase, an enzyme required for the synthesis of a precursor to 25 (OH) D [7].

Vitamin D deficiency seems to hamper post-natal skeleton response to mechanical load. Animal studies showed that the progeny of mice with hypovitaminosis D has biomechanical alterations and reduced bone strength both during growth and after skeletal maturity, resulting from impaired the anabolic response of the skeleton to mechanical stress, at both the trabecular and cortical sites, which persists even in adulthood [8]. Hypovitaminosis D is also associated with severity of fractures in children. A recent study suggests that the risk of severe fractures (requiring surgery) significantly increases for poor vitamin D status, particularly for serum 25 (OH) D levels <20 ng/ml [9]. Putative mechanisms involved in increased fracture severity in vitamin D deficiency are mineralization defect of the collagen matrix, and both increase of micro-cracks and microcracks with tortuous breaking path in patients with low serum 25 (OH) D [10]. Mounting evidence supports the role of vitamin D in extraskeletal tissues, particularly skeletal muscle. Indeed, this hormone indirectly promotes acquisition of bone mass by enhancing muscle mass and function that are key mechanical stimuli for the development of bone tissue due to the load and tension exerted by the muscle on the skeleton contributing to increase bone strength [1]. The growing

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Received Date: *23 Nov 2018*
Accepted Date: *12 Dec 2018*
Published Date: *17 Dec 2018*

Citation:
Moretti A. Vitamin D Deficiency and Bone Health in Children. Ann Arthritis Clin Rheumatol. 2018; 1(1): 1006.

interest in its extraskeletal effects led to investigate the role of vitamin D in many chronic diseases, also in pediatric population. Several risk factors contribute to hypovitaminosis D in chronic diseases, such as poor UV exposure, impaired absorption of fat-soluble vitamins and other nutritional deficits, chronic use of drugs that interfere with vitamin D metabolism, and pro-inflammatory status [11]. Vitamin D seems to modulate also pain perception in some pediatric conditions, although physiopathological mechanisms are still poor investigated. In a pilot study involving patients affected by sickle cell anemia, a disease characterized by chronic pain caused by ischemia/bone infarcts, adolescents receiving weekly high doses of cholecalciferol (240,000 IU to 600,000 IU) for 6 weeks, showed a negative correlation between serum 25 (OH) D and the number of pain days at 2 months follow-up *vs.* placebo group (r=-0.680, p=0.019) [12]. Although immunomodulatory role of vitamin D has been widely investigated, its effects in patients with Type 1 Diabetes Mellitus (T1DM) are rather controversial. Indeed, neither vitamin D intake nor serum 25 (OH) D levels seem to be associated with autoimmunity or incidence of T1DM1 in children at risk (familiarity), even if an adequate vitamin D status might aid to improve glycemic control [13,14]. Another condition with high prevalence of vitamin D deficiency are IBD, because of several factors, such as malabsorption, poor UV exposure, low levels of physical activity, and chronic immunosuppressants and/or glucocorticoids use. However, only patients with high serum ESR have significantly lower serum 25 (OH) D [15,16]. Cerebral Palsy (CP) is a clinical condition in which the presence of hypovitaminosis D must be carefully investigated for the potential benefits of cholecalciferol supplementation, particularly in terms of bone health, considering that children with CP are highly prone to fragility fractures, particularly at lower limbs (up to 74% of hip fractures). These patients are highly vulnerable to vitamin D deficiency, mainly due to reduced sun exposure and anticonvulsants use. Prevalence of vitamin D deficiency is about 60% in these patients, increasing over 80% in non-ambulatory children [17]. Guidelines about vitamin D supplementation in pediatric population are widely available. Recommended daily allowance for children are 600 IU. According to international recommendations, all infants require cholecalciferol supplementation (400 IU/day) at least up to the 1st year of life (or up to safe exposure to sunlight). Preterm infants should receive 200 IU/day to 400 IU/day of cholecalciferol (400 IU/day to 800 IU/day for birth weight >1,500 g). Patients aged 1 to 18 years require 600 IU/day to 1,000 IU/day in the presence of risk factors for vitamin D deficiency, preferring daily administration. Weekly or monthly regimen (18,000 IU/month to 30,000 IU/month) should be introduced from 5 years of age in case of poor compliance to daily administration. Larger doses of cholecalciferol should be administered to children at high risk of vitamin D deficiency (obesity, malabsorption, chronic treatment with anticonvulsants). In high risk children, doses up to 3 times higher are recommended. In children and adolescents with vitamin D deficiency, treatment duration should be 1 to 3 months with a follow-up after 8 to 12 weeks from start of treatment. Children affected by rickets require highest doses of daily cholecalciferol, for at least 3 months: 2,000 IU in newborns, 3,000 IU to 6,000 IU in 1 to 12 years, 6,000 IU in adolescents. In these patients a combined supplementation of vitamin D and calcium (30 mg/kg/day to 75 mg/kg/day in 3 divided doses, reducing the dose within 1 month) is recommended [1,5]. Vitamin D deficiency continues to be a main topic for both research and clinical practice, even in pediatric population. This condition should be sought and treated for its potential clinical implications, particularly in children with chronic diseases, both in terms of skeletal growth and several extraskeletal effects. Several available guidelines help clinician to define, prevent and treat hypovitaminosis D in infants, children and adolescents in an appropriate manner.

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