What are the effects of vitamin D interactions on the developing musculoskeletal system?

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ABSTRACT

Introduction: Vitamin D deficiency is a global public health issue and large health agencies encourage the use of vitamin D supplementation. Vitamin D is an essential hormone which is responsible for both musculoskeletal development and systemic health. The goal of this narrative review was to investigate the following clinical issues: 1) Impact of Vitamin D on the developing musculoskeletal system in the pediatric patient and the growing child's need for nutritional intake or supplementation, 2) Factors important to determine the need for supplementation and appropriate supplementation, 3) Risk for overdose of Vitamin D. **Methods:** Literature search of large search engines. Limits used: age 0-18 years, English language and published in the last 10 years. Key words used 'Vitamin D and pediatric', Vitamin D and development', 'Vitamin D and deficiency', 'Vitamin D and side effects'. **Results:** One Cochrane review, two global epidemiological reviews on nutritional rickets, six guidelines on Vitamin D supplementation, and several articles on vitamin D and musculoskeletal development were identified and considered in the study. The American Academy of Pediatrics and the Canadian Pediatric Society and European guidelines recommended 400 IU/day for infant - adolescent. The US Institute of Medicine and World Health Organization recommended adequate nutritional intake prior to supplementing children 0 —1 and 1—18 years old with 400 and 600 IU/day, respectively. Clinicians must be aware of key points that would significantly affect the correct recommendation and supplementation of Vitamin D. These are history, anthropometric measurements, physical activity levels, dietary habits and sun exposure parameters to achieve optimal musculoskeletal results. **Conclusion:** At present, 400-600IU/day Vitamin D supplementation is the daily recommendation for pediatric population based on the global healthcare agencies. Understanding the great impact of vitamin D on the musculoskeletal system, future work must be done to examine the prophylactic use of vitamin D and its appropriate adapted supplementation.

Introduction

World Health Organization (WHO), US Institute of Medicine (IOM), the Endocrine Society in the USA and the European guidelines acknowledge that vitamin D deficiency is a global public health issue and encourage the use of vitamin D, advising on supplementation and daily recommended dosage. Vitamin D is an essential hormone, which has attracted increasing attention in the last decades. It exists in two forms D3 -cholecalciferol and D2 or ergocalciferol.[1]

Vitamin D is unique as it is both absorbed via dietary intake, in the small intestine by chylomicrons or can be synthesized by an endogenous process.[2] The dual absorption mechanism highlights its importance. Correct absorption is thus subject to adequate nutritional intake. Fatty fish, fish liver oil, and egg yolks are typically good sources of Vitamin D2. Endogenous synthesis is the second way of producing and absorbing pre-vitamin D3.[3]

Sun UV exposure, (290—320 nm) interacts with 7-dehydrocholesterol and is absorbed in the skin. Factors influencing the effectiveness of this process are average skin exposure to sun light, color of skin and latitude of the country.[4] Both versions of Vitamin D (D2 and D3) are inactive until they reach the liver, where the first hydroxylation happens and the following hydroxylation occurs in the kidney. The final product is the bioactive hormone, calcitriol. This is an important hormone as it dictates the homeostasis of several minerals (calcium and phosphate) in the plasma. These minerals and the concentration of parathyroid hormone play a paramount role in the bone metabolism throughout a lifetime.

Well-being of skin, gut, liver, kidney and bone is vital for Vitamin D metabolism. Activated Vitamin D works as a hormone, and its half-life (25(OH)D) is approximately 2—3 weeks.[2] This allows it to be a gene expression regulator, as part of immune function, cell proliferation and differentiation, and cell apoptosis.[2] The most commonly utilized biomarker for vitamin D sufficiency is 25(OH)D and this can be measured in the blood.[3]

The clinical questions asked here were:
1) How does Vitamin D impact the musculoskeletal (MSK) system in the developing pediatric patient and how does this translate into the growing child's need for nutritional intake or supplementation?
2) What are the specific factors that we clinicians need to

consider in order to help parents decide the appropriate supplementation for their child?
3) Is overdose a concern?

Methods
Literature search of large search engines, PubMED, Cochrane library, WHO. Key words used 'Vitamin D and pediatric', Vitamin D and development', 'Vitamin D and deficiency', 'Vitamin D and side effects'.

Inclusion criteria: Articles in English language, Published within the last 10 years, Vitamin D supplementation consideration for healthy pediatric population 0-18 years old. Guidelines from global health agencies.

Exclusion criteria: supplementation for disease specific conditions, articles specific to premature infants. Articles commenting on Vitamin D interaction with other drugs and micronutrients. Excluded articles older than 10 years

Results
One Cochrane review, two global epidemiological reviews on nutritional rickets, six guidelines on Vitamin D supplementation, and several articles on vitamin D and musculoskeletal interaction were identified to answer the three questions reviewed.

1) What is the Vitamin D impact on the musculoskeletal (MSK) system in the developing pediatric patient and how does this translate into the growing child's need for nutritional intake or supplementation?

The American Academy of Pediatrics and the Canadian Pediatric Society, the European guidelines recommended 400 IU/day for infant through adolescent age groups. Whereas IOM and WHO recommended adequate nutritional intake and if this is not met, to supplement children 0—1 and 1—18 years old with 400 and 600 IU/day, respectively.[6] See Table 1.

Homeostasis between vitamin D metabolism and parathyroid hormone ensure an efficient bone mineralization process in early infancy and childhood.[5] Fine balance between calcium and phosphorus concentration in the bloodstream is additionally vital. Randev et al., 2018, explained that correct mineralization in early life safeguards against early osteoporosis in adulthood.[6]

Shore, 20137 identified that infants younger than three months are somewhat protected from Vitamin D deficiency if sufficient placental transfer from the mother has occurred. However, other studies such as Bentley, 2013 expressed their concern as it indicated that maternal calcium

Name of organization	**US IOM**[3]	**WHO**	**Canadian Pediatric Society**[30]	**The Endocrine Society Clinical Practice Guideline**[11]	**American Society of Pediatrics**[31]	**European Guidelines**[32]	**NHS Choices 2012**[12]
Neonates (IU/day)	400	200-400 5 to 10 mcg/ daily	Supplement breast feeding mother 4000IU/ day or 400 infant directly	400	400	400	350-400 8.5-10mcg
Infants (IU/day)	400	200-400 5 to 10 mcg/ daily	800	400	400	400	10mcg
Children (IU/day)	600	Not specified	400-800	600	600	400	10mcg
Adolescent (IU/day)	600	Not specified	200-400	600	600	400	10mcg
NOTES			4000 IU/day vitamin D during pregnancy				

Table 1. Summary of health agency's Vitamin D daily recommendations.

and vitamin D deposits are not sufficient for fully protecting the infant and supplementation is encouraged both during pregnancy and in early infancy.[8] In terms of dosage during pregnancy, 2800 IU /day, had a positive increase in bone mineralization of offspring at both one year and six years after the supplementation.[9]

This highlighted the importance of appropriate dosage and early vitamin D supplementation inpregnancy.[10]

Infancy and childhood is predominantly concerned with longitudinal growth and remodeling of the axial and appendicular skeleton.[11] On average children are expected to grow 5-6 cm and gain 2.5 kg per year until puberty, subject to gender variations. To meet these needs, the UK health department recommends 340-400 IU/day of Vitamin D. The Endocrine Society Clinical Practice Guideline[11] and the IOM support the need of supplementation with 400IU/day in this population.[12] Additionally they recommend at least 15 minutes of uncovered forearm and leg exposure to sunlight between May-September.

Holick et al., 2011, recommended that supplementation of 600—1000 IU/day should be considered if recommended daily sun exposures are not met. If the child is already deficient, they suggested a much higher dosage: 2000 IU/day of vitamin D for at least six weeks or 50,000 IU of vitamin D2 once a week for at least six weeks in an attempt to normalize the blood level of 25(OH)D above 30 ng/ml.

Additional adaptations of this dosage should be based on dietary vitamin D intake and overall bodyweight.[13] Lack of agreement is seen in the statement from the European Academy of Pediatrics (EAP) which still recommends 400 IU/day during the first year of life & 600 IU/day after the first year of life (1—18 years).[14] See Table 1.

The age group 9—18 years old, commonly is faced with rapid growth spurts and increased body mass, increasing the need for dietary calcium and phosphorus to maximize skeletal mineralization and maturation. During puberty, reduction in physical activity is commonly observed in females according to the *WHO Health Behavior in School-age Children* survey[15] and this gender gap increases with age. When exercise is decreased, there is less axial compression to aid bone mineralization. Similarly, if an inactive child enters a highly competitive sport, they might be more vulnerable for fracture if bone mineralization is out of balance.

2) What are the specific factors that clinicians need to consider in order to help parents decide the best supplementation for their child?

Common factors that play a significant role in appropriate supplementation of pediatric cases are: exclusive breast feeding, fortified formula, fortified nutrition in diet, average daily exercise, and daily sun exposure based on their country's latitude, cultural dietary habits, anthropometric measurements and BMI. These factors should be evaluated in the history taking and then combined with any physical findings in the examinations.

Obesity in adolescence is a growing issue.[16] One-third of eleven-year-old children in developed countries, in 2014 were obese.[17] Nutritional choices in adolescence are questionable and it can be very difficult to accurately determine if sufficient vitamin D containing foods are consumed.

Obesity in adolescent children was found to have a faster exponential catalysis of 25(OH)D and parathyroid hormone compared to non-obese peers, especially females,[18] increasing the destruction of bone minerals. This signifies the importance of considering anthropometric measurement of children when supplementing vitamin D and adjust this value according to their BMI.[18]

One of the most commonly associated deficiencies of vitamin D in the pediatric population is nutritional rickets. Rickets was first described in the mid-17th century. Common signs and symptoms of nutritional rickets is insufficient mineralization of bone and cartilage, resulting in bowing of bones, stunted growth, and skeletal malformation.[19] Thus rickets is the result of disruption of appropriate endochondral ossification by not properly mineralizing the osteion.[5] Two global epidemiological reviews on nutritional rickets found that calcium deficiency is also a major component in nutritional rickets particularly in some African, Middle Eastern and Asian countries, despite their dietary lifestyle and sunshine exposure.[20,21]

Rickets typically develops in infants three to 18 months of age, if the problem is due to Vitamin D bioavailability.[22] Rickets due to lack of serum calcium can be seen up to the age of 16.[23] Rickets characteristically has two mechanisms: first, hypocalcaemia due to inappropriate gut absorption leading to reabsorption of calcium from bones (can also lead to seizures or tetany). Secondly, alteration of parathyroid hormone can result in hyperparathyroidism, hypercalcemia, respiratory distress, muscular hypotonia, and skeletal demineralization commonly found in infants.[20]

The most effective diagnosis of rickets is done with the use of biochemical tests and x-rays (disordered mineralization and ossification of the physes of long bones).[23,24]

3) Is overdose a concern?

Supplementation of vitamin D is not completely without potential adverse effects. Some signs and symptoms are weakness, nausea, loss of appetite, headache, abdominal

cramps and diarrhea.[25] However, given that the pediatric population is likely to be deficient, the recommended dosage is very unlikely to cause toxicity.[9,26] Based on the literature, it is understood that although the risk of overdosing of Vitamin D is possible, this is extremely unlikely.

Discussion

The purpose of this review was to improve understanding of the recommendations for Vitamin D supplementation for the growing child's musculoskeletal health, the required dosages, and the factors in individual patients that affect those dosages along with the risk of overdose in order to better serve my patients.

Although the recommendations vary slightly among organizations, consensus occurs in the recommendation of 400 IU/day in the infant and early childhood ages and 600IU/day in adolescent age population.[6] Although these recommendations are fairly straight-forward, the question that we are called to answer as MSK clinicians, is whether these supplementation values are appropriate for the population we treat. For example, most of the pediatric population in developed countries is not likely to have been exclusively breastfed for the recommended time (only 42% globally are breastfed to six months age or more).[27] Further, 144 milion children globally have stunted growth and a further 38.3 million are overweight.[27] Add those to uncertain sun exposure and the risk for poor vitamin D status is high. Additional consideration and adaptation of recommended dosages is essential in obese patients, malabsorption syndromes, or on medications that interact with vitamin D absorption.

Therefore, it is important that we as clinicians take careful nutritional and physical activity histories of the pediatric patient particularly regarding exclusive breast feeding, fortified formula, nutrition and mean time of sunshine exposure, as well as if the family moved from a different location to current geographic latitude. Ideally, vitamin D deficiency is diagnosed based on a blood test via the GP. If access to blood tests is difficult or isn't the best first step, then the current 'over the counter' recommendation of 400 IU daily is indicated.

The WHO, in a position report in 2019, highlighted that not all health care practitioners are on board with supplementation despite exclusive breast feeding and skin pigmentation considerations.[4] The WHO is urging primary health clinicians to be familiar with daily recommended dosages, and to be vigilant in picking up early signs of vitamin D deficiency. Wagner et al in 2008 urged pediatricians and health care professionals to make vitamin D supplements readily available, considering the high likelihood of deficiency. Other authors support this point. Supplementation is now recommended to be initiated within the first few weeks of life and continue throughout childhood.

Fortunately, Vitamin D supplementation provides a cost effective and easy way to tackle nutritional rickets and once again reduce its prevalence in the pediatric population around the world which will help safeguard the next generation against adult conditions such as early osteoporosis.[28] Despite the fortification of food, the standards are variable across the globe. Thus a revision of early supplementation with higher dosage should be investigated. A very small number of articles have been currently available where investigation of 2000-5000IU/ day have been tested. This is a fast changing subject and thus results are subject to updates. We clinicians need to stay aware of this rapidly changing data as it becomes available for the betterment of our patients.

Conclusion

At present, 400-600IU Vitamin D supplementation is the daily recommendation for the pediatric population based on the large healthcare agencies. However, as primary care clinicians, these values must be modified based on the history of each case. Anthropometric measurements, physical activity levels, dietary habits and sun exposure are key points that would significantly affect the correct recommendation and supplementation of Vitamin D. Correct advice can help reduce nutritional rickets in children and safeguard the developing musculoskeletal system.

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