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REVIEW ARTICLE

Vitamin D deficiency in childhood: an opportunity for prevention

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Abstract The prevalence of vitamin D deficiency in the pediatric population has increased in recent years and continues to be underdiagnosed and undertreated. According to data from the "ENSANUT 2006" (National Health and Nutrition Survey), the prevalence of vitamin D deficiency in Mexico was 16% in children aged 2-12 years. Vitamin D plays a critical role in the formation and bone homeostasis and consequently on growth. Its deficiency is clearly associated with diseases such as rickets and osteomalacia, and it has been linked to other diseases such as obesity, metabolic syndrome, diabetes, cancer, respiratory infections and immune system disease. Specific risk groups have been described in the medical literature for vitamin D deficiency in which supplementation may offer a benefit. Currently, there is still controversy in defining the serum levels of proficiency and dose supplementation. In Mexico, the daily suggested intake of vitamin D is 5.6 μg (224 IU), which is significantly lower than the recommendations in the U.S. and Europe (i.e., between 400 and 1000 IU/day).

An increase in vitamin D deficiency has been reported in recent years. There is no consensus regarding the sufficiency levels of vitamin D. Cut-off values vary from 20–30 ng/ml. Therefore, the objective of this review was to provide an overview of the problem in the pediatric population and to describe the groups at risk, as well as to analyze the current recommendations for vitamin D supplementation.

Vitamin D deficiency was considered rare in Mexico according to the National Institute of Medical Science and Nutrition Salvador Zubirán. Lack of evidence did not help to establish the international recommended daily intake. Currently, vitamin D deficiency must be recognized

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as a health problem, worthy of attention and action. We suggest that prospective studies are carried out in our country where the relationship between serum vitamin D deficiency and poor bone mineralization will be established.

PALABRAS CLAVE
Deficiencia de vitamina D;
Pediatría;
Adolescentes;
Ingesta diaria recomendada;
Ingesta diaria sugerida

Deficiencia de vitamina D en la edad pediátrica. Una oportunidad de prevención

Resumen La prevalencia de deficiencia de vitamina D en la población pediátrica ha incrementado en los últimos años y se considera que continúa subdiagnosticada y subtratada. De acuerdo con datos de la Encuesta Nacional de Salud y Nutrición 2006, en México se ha estimado una prevalencia del 16% en niños de2a 12 años. La vitamina D desempeña un papel fundamental en la formación y homeostasis del hueso, y consecuentemente en el crecimiento. Su deficiencia se asocia con enfermedades como raquitismo y osteomalacia, y se ha relacionado con otros padecimientos, como obesidad, síndrome metabólico, diabetes, cáncer, infecciones de vías respiratorias y problemas del sistema inmune. En la literatura se han descrito grupos específicos de riesgo para deficiencia de vitamina D en los que el suplemento pudiera ofrecer un beneficio. Actualmente aún hay controversia en definir los niveles séricos de suficiencia, así como la dosis de suplemento. En México, la ingesta diaria sugerida de vitamina D es de 5.6 µg/día (224 UI), que resulta significativamente menor a las recomendaciones en los Estados Unidos y Europa (entre 400 y 1000 UI). Debido al aumento en la deficiencia de vitamina D en los últimos años ya la falta de consenso con respecto a los niveles de suficiencia de vitamina D (ya que los valores de corte varían de 20 a 30 ng/ml considerados por la asociación de endocrinología), el objetivo de esta revisión fue proporcionar un panorama general del problema en la población pediátrica, así como describir aquellos grupos en riesgo y analizar las recomendaciones vigentes para el suplemento de vitamina D.
La deficiencia de vitamina D se ha considerado rara en México, y la falta de evidencia no ha permitido establecer las recomendaciones de ingesta diaria, de acuerdo con el Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. Sin embargo, hoy debe reconocerse como un problema de salud, meritorio de atención y acción. Sugerimos que se lleven a cabo estudios prospectivos en nuestro país, donde se establezca la relacion entre la deficiencia sérica de vitamina D y la pobre mineralizacion ósea.

1. Introduction

In recent years a growing interest has been reported in the metabolism and physiology of vitamin D. In addition to being an essential micronutrient, it is considered a prohormone involved in bone homeostasis. Various studies have been published worldwide where an increase in the prevalence of vitamin D deficiency is documented (defined as serum values ≤20 ng/ml or 50 nmol/l) from 10 to 41.6% in population studies.[1] However, this condition continues to be underdiagnosed and without treatment. For this reason, the need for national guidelines on its supplementation as well as monitoring of serum levels of vitamin D in the vulnerable population has increased. The objective of this review was to identify the pediatric age groups at risk for presenting vitamin D deficiency as well as the consequences of such deficit on health.

2. Pathophysiology

Vitamin D comprises a group of prohormones identified from the discovery of the anti-rickets effect of cod liver oil from the 20th century.[2] Vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) are the two main biologically inert precursors.[3,4] Vitamin D3 forms from the exposure of 7-dehydrocholesterol on the skin from solar UVB rays (UVB 290-320 nm) and is converted into previtamin D3. In a heat-dependent process previtamin D3 is transformed to vitamin D. On the other hand, vitamin D2 is derived from plants and is exogenously produced from ergosterol and enters into the circulation through diet.[2] In our bodies, both precursors (D2 and D3) experience a first hydroxylation in the liver to be converted into 25-hydroxyvitamin D [25(OH)D], a metabolite that is measured in blood to determine the serum levels of vitamin D. 25(OH)D requires

a second hydroxylation at the level of the kidney to be converted into 1,25-dihydroxyvitamin D [1,25(OH)2D] calcitriol, the active metabolite of this vitamin.[5]

Vitamin D plays a fundamental role in maintaining serum levels of calcium and phosphorus. Without this vitamin only 10 to 15% of the ingested calcium in the diet would be absorbed and ~60% of the phosphorus. For this reason, vitamin D has a great effect on bone formation and maintenance.[6,7]

In the year 2010, the Committee from the Institute of Medicine (IOM) updated the recommendations for vitamin D intake in the general population, both the upper limit of toxicity [to maintain the vitamin D serum levels <50 ng/ml (125 nmol/l)] as the definition of deficiency [from 20 ng/ml (40 nmol/l) for the requirements from 97.5% of the healthy population]. It is recommended to maintain serum levels of vitamin D >20 ng/ml to optimize peak bone mass, prevent bone loss and reduce the risk of fractures due to osteoporosis.[8,9]

3. Nutritional requirements for healthy children

The IOM report provides recommendations for vitamin D intake for healthy children including the recommendation for children >1 year of 600 IU/day with the goal of achieving serum concentrations of 25-hydroxyvitamin D of 50 nmol/l. It has been recognized that the serum concentration of 25(OH)D in healthy children is most identified as a marker of exposure to vitamin D than as a value to which specific health benefits can be attributed. There is controversy regarding the daily recommendation of 600 IU/day; i.e., if this value satisfies the needs of all healthy children, especially for healthy children who are at risk of having serum values of <50 nmol/l. The guide was based on a minimal sun exposure, noting that sunscreen is widely used in children. In particular, the Guide on the nutritional intake of 600 IU/day includes African-American, Latino or children with dark skin pigmentation.[1]

According to ESPGHAN (The European Society of Pediatric Gastroenterology, Hepatology and Nutrition), infants <1 year of age should receive oral supplementation of 400 IU/day under the supervision of a health professional. Children and adolescents should continue with a healthy lifestyle and diet rich in vitamin D. However, children considered to be at risk for deficiency, those with dark skin, those who receive sun exposure, as well as children who are obese, should receive oral supplementation. ESPGHAN considers serum levels of vitamin D >50 nmol/l to be sufficient and values <25 nmol/l classifies them with severe deficiency.[10]

In Mexico, the suggested daily intake of vitamin D is found in the Official Mexican NORM NOM-051-SCFI/SSA1-2010, "General specifications for labeling non-alcoholic pre-packaged food and drink – Commercial and health information."[11] This norm suggests a daily intake of 5.6 µg (224 IU) of vitamin D based on the recommendations from the National Institute of Medical and Nutritional Sciences Salvador Zubirán (INCMNSZ), which is significantly less than those recommended in the U.S. and Europe, i.e., between 400 and 1000 IU/day. This recommendation is based on the report issued by the INCMNSZ in 2007 where it is noted that "there are no studies that demonstrate the need for adding vitamin D to foods in the Mexican population. In Mexico, there are only isolated cases of rickets seen and the calcium deficiency is not considered to be a public health problem; therefore, there are no programs available to combat it."[12] New recommendations in the country have not been issued and there are no formal studies that document the average vitamin D intake in Mexican children.

4. Vitamin D deficiency

Vitamin D deficiency is associated with rickets in children and osteomalacia in adults. Nutritional rickets is a preventable disease. Its main characteristic is the lack of calcium in the bones, which affects children during growth. This disease is characterized by deformities of the long bones and widening of the wrists and costochondral joints; in newborns it cases a delay in closure of the fontanels and craniotabes as well as hypotonia with seizures and heart failure.[13,14]

Although the prevalence of rickets has decreased significantly with dietary supplements, it is now recognized that this disease has re-emerged in several countries, mainly among groups with little exposure to UVB rays, infants of mothers with low serum levels of vitamin D during pregnancy, and those fed exclusively breast milk.[14]

An adequate intake of vitamin D and calcium during infancy reduces the risk of a poor mineralization of the skeleton, loss of bone strength, and reduction of the peak mineral mass at the end of the puberty, as well as osteoporosis.[15] In the decade of 2000, scientific interest in the relationship between vitamin D deficit and chronic skeletal diseases increased, such as infections, autoimmune diseases (multiple sclerosis, rheumatoid arthritis), breast, ovarian, prostate, colon and rectal cancer, as well as type 2 diabetes mellitus, cardiovascular and metabolic diseases. However, a causal relationship has not been able to be established. In the UMBRELLA meta-analysis published in 2014, evidence was based on a systematic review from reviews and meta-analysis of observational studies and clinical trials that evaluate the association between the concentrations of vitamin D and a large range of diseases. An association of vitamin D concentrations with birth weight, the presence of dental caries in children, maternal concentrations of vitamin D, term pregnancy and concentrations of parathyroid hormones (PTH) was reported in chronic renal disease in patients who require dialysis. In contrast to other studies, these findings place into question the efficacy of vitamin D as the only measure for the prevention of osteoporosis and falls. This review points out the lack of meta-analysis in relation to autoimmune diseases as well as randomized clinical trials on vitamin D supplementation in cancer, cognition and infectious diseases.[16] Some prospective studies suggest that vitamin D supplements consumed during infancy could reduce the incidence of these diseases.[17]

Few studies have been published in Mexico on the prevalence of vitamin D deficiency. In the few reports, serum measurements of this vitamin have been per-

formed with different methods. Within these studies in the Mexican population it is important to comment on the multicentric study conducted in 2008 in four representative centers of Mexico City with 117 healthy children 3-8 years of age who had the concentration of vitamin D levels measured by radioimmunoassay. An overall average of 59.12 ± 12.82 nmol/l was reported; 25% of the children had deficiency and 63% insufficiency. Likewise, the National Institute of Public Health in Mexico analyzed data from 1025 children from 2 to 12 years of age who participated in the 2006 ENSANUT and whose vitamin D levels were determined by ELISA with an average serum concentration of 25(OH)D3 of 94.6 ± 47 nmol/l. Pre-school children had a greater prevalence of vitamin D deficiency (24.6%) compared with school-age children (10.2%). Of the total sample, 16% had vitamin D deficiency (25(OH) D3 <50 nmol/l); 23% of the children presented insufficiency (25(OH)D3 between 50 and 75 nmol/l).[18] Finally, in another investigation in Mexico, in 261 boys and girls from 5–14 years of age, the median concentration of 25(OH)D was 26.13 ng/ml and for PTH was 25 pg/ml. The prevalence of 25(OH)D (<20 ng/ml) deficiency was 10% (n=26), for insufficiency (20-29 ng/ml) it was 60.9% (n=159) and for sufficiency (>30 ng/ml) of 29.1%. On analyzing the possible risk factors for vitamin D deficiency, no significant relationship was found with the use of sunblock, sun exposure and skin phototype.

5. Groups vulnerable to vitamin D deficiency

5.1. Preterm newborns

The fetus receives the greatest intake of minerals to the skeleton during the last trimester of pregnancy. According to studies performed by Widdowson et al. in cadavers, it is known that calcium accretion in the uterus during the third trimester varies from 100-130 mg/kg/day and reaches maximum accretion between 32 and 36 weeks of gestation (WG).[19] Because of this, preterm newborns (<37 WG) have low mineral reserves, which added to low weight (<2250 g) and to associated diseases, increasing the risk of suffering from mineral deficiency and leading to disorders of bone metabolism. The risk of not reaching adequate development compared with reference growth tables is high.[20] It has been reported that adults with a history of prematurity have a lower bone density compared with controls without this history.[21] Levels of vitamin D in the mother are determinant in the mineralization of the fetus. According to the review by Garza et al. there is evidence on the association between maternal concentrations of vitamin D (25(OH)D) and bone mass of the newborn. Mothers with vitamin D deficiency during the last trimester of pregnancy had products with a lower bone mineral content with respect to those products of mothers with "full" levels of vitamin D (mean 1.04 kg ± 0.16 vs. 1.16 kg ± 0.17, $p = 0.002$). This association between low concentrations of 25(OH)D of the mother and bone mineral accretion in infancy persists up to 9 years of age.[22]

There are no population studies on the prevalence of rickets in preterm newborns. Approximately 10-20% of newborns hospitalized for low weight (<1000 g) have radiographic signs of rickets (metaphyseal changes) despite the nutritional practices carried out.[23] This frequency is much lower in comparison with the 50% incidence previously described for this population prior to milk fortification and the routine use of formulas with a high mineral content for premature babies.[24]

Recommendations from the IOM only refer to supplements in eutrophic children to prevent vitamin D deficiency-associated rickets (400 IU/day). Special populations, such as premature newborns, were not taken into consideration. Premature babies have unique mineral bone requirements, which cannot be considered similar to those of term newborns. Guidelines from the U.S. limit their recommendations to the term newborn; therefore, the ESPGAHN described enteral nutritional recommendations for preterm babies. The ESPGHAN recommends an intake of 800-1000 IU/day for premature babies with the goal of improving serum concentrations of 25(OH)D and plasma concentrations of 1,25(OH)2D and thereby the rates of calcium absorption. The recommendation is the same for premature infants fed breast milk as for those fed with formula milk.[25]

According to the findings published by Abrams in 2013, routine management of preterm infants, particularly those of low weight (<1800–2000 g), must include human milk fortified with minerals or formulas designed for preterm newborns. Routine evaluation of the bone mineral status by biochemical methods *is indicated for low weight infants* (<1500 g). Such tests should be carried out 4–5 weeks after birth. When the infants reach a weight of >1500 g and can tolerate total enteral feeding, they should be supplemented with vitamin D from 400 IU/day up to a maximum of 1000 IU/day.[26]

5.2. Infants fed exclusively breast milk

A resurgence of rickets has been currently reported in those infants fed with breast milk. Babies who are fed exclusively breast milk and do not receive vitamin D supplements and adequate sun exposure are at risk of developing vitamin D deficiency or rickets.[13] Rickets due to vitamin D deficiency occurs with greater frequency in infants with dark skin fed with breast milk, children of mothers who are vitamin D deficient and exclusively fed breast milk.[27-29] Preliminary studies suggest that infants fed breast milk and children of mothers who take high doses of vitamin D_3 supplements can attain levels of circulating vitamin 25(OH)D similar to those infants who receive oral supplementation with vitamin D_3.[30] The vitamin D content in human milk depends on the maternal status of vitamin D. A woman who is breastfeeding and receives a supplement of 400 IU/day of vitamin D will have milk with a vitamin D content of 25-78 IU/l.[13]

The recommendation to prevent infantile rickets, both in Europe as well as in the U.S., is supplementation with vitamin D at 400 IU/day, which is equivalent to a tablespoon of cod liver oil. Infants fed exclusively or partially with breast milk should receive a vitamin D supplementation of 400 IU/day beginning from the first days of life. This supplement should continue up to the time that the infant is weaned and consumes <1 l/day of fortified fomula with vitamin D or whole milk. Whole milk should be

not given before 12 months of age. For children between 12 months and 2 years of age with overweight or obesity or with family history of obesity, dyslipidemia or cardiovascular disease, the use of low-fat milk is recommended.[13]

5.3. Obesity

It has been reported that obese persons have lower serum concentrations of 25(OH)D.[31,32] Although different studies have shown that the skin levels of 7-dehydrocholesterol (vitamin D precursor) are similar in obese and non-obese subjects,[33] it is thought that subcutaneous fat (vitamin D reservoir) sequesters synthesized vitamin D in the skin, which translates into less release of vitamin D from the skin into the circulation in obese as well as non-obese subjects.[34] Obese and overweight children and adults have demonstrated vitamin D deficiency. In Mexico, Elizondo et al. determined the prevalence of vitamin D deficiency and its association with obesity and lifestyle in school-age children from six public schools in Monterrey, Mexico.[35] This study reported an insufficiency in 61.2% (21-29 ng/ml) and deficiency in 20.2% (<20 ng/ml) of a sample of 198 subjects. When the sample was stratified by body mass index (BMI) (presence or absence of obesity), a significant difference was found in the concentrations of 25(OH)D among the groups: obese patients had lower concentrations (23.05 ± 5.396 ng/ml) with respect to non-obese subjects (26.39 ± 6.066 ng/ml), with a mean difference of 3.34 (95% CI 1.73–4.95 p = 0.001).

In obese children, circulating levels of 25(OH)D may be low although body reserves are not deficient. Up to this point, clinical trials have not demonstrated a specific clinical benefit from the ingestion of doses of vitamin D above the daily recommendations for healthy children.[36]

In studies where moderate weight loss is achieved, an increase has been found in circulating serum levels of 25(OH)D, despite maintaining a stable intake of vitamin D; this increase has been proportional to the weight loss. There is no evidence of any effect on bone health or other health conditions from a vitamin D intake above the suggested requirements in obese persons.[37]

6. Diseases involving alterations in vitamin D metabolism

6.1. Chronic renal insufficiency

Among the alterations resulting from chronic kidney disease (CKD) is a lower activity of 1-α-hydroxylase, which leads to a decrease in the production of calcitriol, resulting in a decrease of intestinal absorption of calcium and renal excretion of phosphate, with consequent hypocalcemia and hyperphosphatemia. Hypocalcemia reduces activity of the receptors sensitive to calcium in the parathyroid gland and stimulates PTH secretion. PTH, in response to low serum levels of calcium and elevated phosphate levels, increases tubular absorption of calcium and secretion of phosphate and, in this manner, stimulates the renal enzyme 1-α-hydroxylase to produce 1,25(OH)2D. However, patients with CKD are not able to produce adequate amounts of 1,25(OH)2D. Also, these patients may have nutritional deficiencies due to an inadequate intake secondary to uremic hypoxia and because of the dietary restriction to which they are subjected, which produces an inadequate amount of substrates for the conversion of the calcitriol.[38] This observation indicates the need for vigilance of vitamin D deficiency in patients with compromise of renal function, regardless of the regular replacement with calcitriol. Current guidelines from the Kidney Disease Outcomes Quality Initiative suggest measuring levels of 25(OH)D if serum PTH levels are above the expected range for stage II CKD and above, as an attempt to delay secondary hyperthyroidism and its effects.[39]

Children with renal insufficiency have an elevated risk of presenting alterations in bone development due to renal osteodystrophy with concomitant vitamin D deficiency. The levels of vitamin D deficiency in this disease reach a prevalence of up to 75% (levels of 25(OH)D <37.5 nmol/l) in this population.[40] Similarly, the prevalence of hyperthyroidism in CKD is high as well as the significant relationship between the levels of PTH and 25(OH)D, independent of calcitriol levels. Optimizing vitamin D levels could provide an additional benefit for preventing or improving hypothyroidism in patients with early CKD and is important as part of adjuvant treatment in children with CKD.[41-43]

Multiple clinical practice guidelines have been recently published about vitamin D supplementation in children and adults with CKD. The most recent guidelines emphasize the lack of results that support supplementation in CKD and recommend correction of vitamin D deficiency using the same strategies as for the general population. Observational studies in patients with CKD have associated vitamin D deficiency with mortality, insulin resistance, anemia, inflammation and progression of renal disease.[44-46]

6.2. Cancer

Development of curative therapies for pediatric oncological diseases has generated a growing population of surviving children at risk for impaired bone metabolism because cancer treatment can interfere with the attainment of peak bone mass and potentially predispose the premature onset of osteopenia and osteoporosis or more serious complications. Bone mineral deficiencies have been reported after oncological treatment and represent a morbidity that can be reduced or prevented through lifestyle changes and timely diagnosis when it is suspected as cancer sequelae (such as hypogonadism).[47]

The etiology of the deficit in bone mineral density (BMD) in pediatric patients with cancer is multifactorial and includes direct and indirect effects of cancer and its treatment resulting in bone loss, decrease in bone growth and decrease of the mineral deposit. Malignant infiltration and some chemotherapeutic agents such as methotrexate and glucocorticoids could directly interfere with mineral metabolism, reducing mineral bone accretion during treatment.[47-49] Inadequate nutrition and physical inactivity (result of cancer and treatment), as well as some secondary side effects of treatment such as hypothalamus-pituitary endocrinopathies and primary hypogonadism, could also cause BMD deficit.

The adverse side effects of chemotherapeutic agents on bone metabolism have been described. Alkylating agents could contribute to the BMD deficit and deterioration of gonadal function. Similarly, radiation could result in osteopenia, causing alterations of the hypothalamus-pituitary axis or gonadal dysfunction. Finally, mineral deficit in survivors treated with hematopoietic cell transplantation could result from the treatments described as well as total body radiation or medications used for maintenance of grafts and prevent complications such as graft vs. host disease or treatment for endocrinopathies. Likewise, genetic predisposition such as being Caucasian and lifestyle may confer an additional risk to the patient. Genetic factors are not modifiable. However, lifestyle, for example low mobility secondary to a surgical intervention or low ingestion of calcium and vitamin D could have a negative impact on bone modulation and in achieving peak bone mass. Because of these factors, patients may benefit from calcium and vitamin D ingestion based on daily recommendations.[50]

In studies that have used dual x-ray absorption, reduction in BMD has been shown during treatment of the disease.[51] Longitudinal studies of bone mineral content in acute lymphoblastic leukemia (ALL) survivors in the pediatric age group (without having received skull radiation) suggest that treatment of ALL does not result in harmful effects on bone development. However, lack of complete normalization of the trabecular and cortical BMD indicates that these patients require a vitamin D-sufficient supplement. Children with ALL, during and shortly after treatment, have a risk six times greater of vertebral fractures compared with controls.[52] Still uncertain is the benefit of vitamin D supplementation during chemotherapy, specifically calcitriol, because a modest deterioration of the cytotoxicity of dexamethasone as well as the induction of apoptosis in pre-ALL human cells has been reported.[53]

6.3. Fat malabsorption

Vitamin D is a fat-soluble vitamin that requires the presence of dietary fats in the intestine for its absorption. This is the reason why vitamin D deficiency has been documented in some pathological conditions associated with fat malabsorption such as Crohn's disease, cystic fibrosis (CF), celiac disease, or intestinal or partial gastric resection. Patients with CF suffer from an exocrine pancreatic insufficiency, which results in malabsorption of fat-soluble vitamins including vitamin D. Patients with CF absorb <50% of the normal vitamin D, depending on the degree of exocrine impairment.[54]

6.4. Inflammatory intestinal disease

Inflammatory intestinal diseases (IID) including Crohn's disease and ulcerative colitis are multifactorial diseases characterized by inflammation of the intestine, nutrient malabsorption and bone demineralization. *In vivo* studies done in animal models indicate that 1,25(OH)2D plays a role in the physiology of experimentally induced forms of IID. The development of IID has been shown to be able to be inhibited with this active form of vitamin D.[55] Some current studies have involved the manipulation of aberrant innate immunity of intestinal microbiota as an initiator of the damage of the adaptive immunity associated with Crohn's disease.[56] It is proposed that the effect of vitamin D in this disease may involve both pathways, activation of innate immunity along with suppression of adaptive immunity and the associated inflammation. It has been recognized for 5 years that bone demineralization, including osteopenia and osteoporosis, has been a clinically meaningful outcome of the disease in patients.[57,58] Multiple studies report a prevalence >30% of low levels of 25(OH)D in patients with IID.[59,60] In a controlled clinical trial the safety and efficacy of vitamin D replacement in patients with IID (5-21 years of age) and serum levels of 25(OH)D <50 nmol/l was analyzed. This study compared oral doses of 2000 IU daily of vitamin D_3 and doses of 50,000 IU of vitamin D_2 weekly for 6 weeks and found that the dose of 2000 IU daily for 6 weeks best elevated serum levels of 25(OH)D.[60]

6.5. Asthma

Insufficiency and deficiency of vitamin D is common in children with asthma. Many of the risk factors that have been associated with hypovitaminosis D (such as Afro-American ethnicity and obesity) are similarly associated with asthma. Brehm et al. reported a prevalence of 35% serum levels of 25(OH)D <75 nmol/l in a sample of 1024 children with persistent moderate asthma; likewise, it was associated with a higher risk of requiring hospitalization or for presenting to emergency services in these children.[61]

Vitamin D supplementation has been studied as a measure of asthma control and risk of acute respiratory infections (ARI). In a study by Majak et al., patients who received 500 IU of cholecalciferol per day for 6 months had a lower risk of exacerbation of asthma triggered by a respiratory tract infection. These results indicate the beneficial effect of vitamin D supplementation in children with vitamin D deficiency with asthma and ARI.[62]

6.6. Nutritional disorders

Various clinical entities are grouped among eating disorders such as anorexia nervosa, bulimia nervosa, eating disorders due to alcoholism, and other unspecified disorders. Eating disorders place adolescents and young adults at risk of harm to their bone health. Low BMD seen in those who suffer from eating disorders is caused by failure of accretion of peak bone mass during adolescence as well as bone loss during the first years of adult life.[63,64] Patients with eating disorders and bone mass loss could be asymptomatic or have bone pain and have a high incidence of fractures. Adolescents with eating disorders are more likely to suffer stress fractures, kyphoscoliosis, decrease in stature, or growth failure.[65] Bone loss in eating disorders is commonly irreversible and treatment modalities are limited. Bone loss in these disorders could occur during the first 12 months at the beginning of the disease.[66]

There are many mechanisms that influence BMD decrease of subjects with eating disorders including a low caloric intake and malnutrition with serum growth factor

levels similar to insulin (IGF-1); low body weight and a small reserve of adipose tissue with low leptin levels and high levels of YY peptide; deterioration of thyroid function, hypogonadism with decrease in sex hormone levels and high levels of circulating cortisol.[67] Eating restriction combined with exercise in healthy women has adverse effects on bone formation and reabsorption.[68]

The greatest bone mass accumulation in females occurs between 11 and 14 years of age. Environmental factors with the most influence on the accumulation of bone mass in adolescents are estrogen levels, exercise, body weight and nutrition. All these factors come together in adolescents with eating disorders, excessive thinness and amenorrhea.[69] Alteration of these factors and disruption of the normal physiological processes for bone acquisition can result in a lower than expected bone mass. Body weight, adjusted for height and influenced by genetics and environmental factors, is the variable which, in an isolated manner, most influences bone mass.[69] Excessive thinness during adolescence leads to low bone mass during adulthood and lower bone reserves at the beginning of menopause with a low BMD and greater risk of fractures.[70,71]

Minerals such as calcium, phosphorus, magnesium and vitamin D are essential nutrients for bone mineralization. Calcium metabolism is abnormal in patients with eating disorders. Bio-availability of vitamin D in subjects with anorexia nervosa is similar in normal-weight subjects and may not be different when given vitamin D.[72]

The effectiveness of calcium and vitamin D supplementation for increasing BMD in anorexia nervosa has not been demonstrated.[73] However, it is advisable to optimize calcium and vitamin D intake. Vitamin D deficiency may exacerbate deterioration of bone metabolism in anorexia.[74] The IOM recommends 1300 mg/day of calcium with a limit of 3000 mg, and vitamin D_3 600 IU/day with a limit of 4000 IU for ages 9-18 years.

7. Treatment and status of vitamin D

7.1. Intensive therapy

A high prevalence (40-69%) of low vitamin D concentrations (<50 nmol/l) has been observed in critically ill children admitted to intensive care services. A greater deficiency has been observed in older children with dark skin. Significantly reduced vitamin D levels have been found in patients with severe disease at the time of their hospital admission. Hypocalcemia, use of catecholamines and administration of volume boluses has been frequently associated with decrease in the circulating levels of vitamin D. The greater the severity and longer stay in intensive care units, the greater the likelihood of having vitamin D deficiency.

There is no consensus or guidelines for vitamin D supplementation in these patients. Therefore, further research and a study protocol is required on the supplement in intensive therapy units. It has been observed that those children who received supplement with vitamin D or who ingested formulas supplemented with vitamin D showed higher levels of concentration of 25(OH)D.[75-77]

7.2. Use of antiepileptic drugs

Long-term use of antiepileptic drugs used to treat seizures and bipolar disorder such as phenobarbital, phenytoin and carbamazepine, as well as the antibiotic rifampicin, can cause osteomalacia.[78,80] This harmful adverse reaction is initiated through the induction of the catabolism of 1,25(OH)2D.

7.3. Chronic use of steroids

Steroids exert their effect on bone through multiple pathways including a decrease in osteoblastic activity, increasing bone resorption, interfering with the growth hormone -IGF-1 axis, reducing muscle strength and altering the calcium balance at the level of the intestine and kidney.[81] Children and adolescents who are exposed to high doses of steroids (dose equivalent to 900 mg/m^2 of prednisone) are at greater risk of lower bone density and at the conclusion of treatment will not be possible to recover normal values.[48] Thus, use of more powerful glucocorticoids such as dexamethasone has been associated with a high incidence of BMD deficit and fractures.[82]

8. Monitoring of the supplement with vitamin D

Despite supplementation with 400 IU/day, children with vitamin D deficiency can continue to have this deficiency because they may require higher doses of vitamin D to maintain normal levels. Circulating vitamin D levels should be determined in these children with laboratory tests (serum concentrations of 25(OH)D, concentrations of PTH and determination of bone status). If supplementation with vitamin D is begun, serum levels should be followed every 3 months until normal levels are reached. Bone mineral status and PTH levels may be monitored every 6 months until they normalize.

Childhood and adolescence are critical periods for the development of a healthy skeleton; however, during these stages there are many comorbidities including vitamin D deficiency. It is important for clinicians to recognize that there are populations where a universal supplement should be recommended such as the population of newborn, preterm infants and children fed exclusively on breast milk.

An increase in vitamin D deficiency has recently been reported. There is no consensus with respect to sufficient levels of vitamin D. In addition, cut-off values vary from 20–30 ng/ml. Dietary intake recommendations in the international literature have values listed between 400 and 1,000 IU, depending on the age group.

Vitamin D deficiency has been considered rare in Mexico. Lack of evidence did not allow establishing the recommended daily intake according to the considerations of the National Institute of Medical Sciences and Nutrition Salvador Zubirán. Today, however, vitamin D deficiency must be recognized as a health problem, worthy of attention and action. It is suggested that prospective studies be carried out in Mexico where the relationship between serum vitamin D deficiency and poor bone mineralization has been established.

Conflict of interest

The authors declare no conflict of interest.

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