

Gómez de Tejada Romero MJ^{1,2}, Sosa Henríquez M^{2,3}

1 Departamento de Medicina - Universidad de Sevilla (España)

2 Grupo de Investigación en Osteoporosis y Metabolismo Mineral - Instituto Universitario de Investigaciones Biomédicas y Sanitarias - Universidad de Las Palmas de Gran Canaria (España)

3 Unidad Metabólica Ósea - Hospital Universitario Insular - Las Palmas de Gran Canaria (España)

Vitamin D deficiency in childhood

DOI: <http://dx.doi.org/10.4321/S1889-836X2017000200004>

Correspondence: M^a Jesús Gómez de Tejada Romero - Departamento de Medicina (Facultad de Medicina) - Universidad de Sevilla - Avda. Dr. Fedriani, s/n - 41009 Sevilla (Spain)
e-mail: mjgtr@us.es

Introduction

The importance of vitamin D in bone development during childhood has been known since the beginning of the last century. As early as 1554, Theodosius published an observation of rickets taken from an individual, but its relationship to vitamin D was not established until 1917, when McCollum et al. isolated an anti-rickets factor in cod liver oil and suggested the term vitamin D¹.

Since then, the disease has been extensively studied. In addition to the nutritional cause, genetic causes and resistance to vitamin D have been discovered, as well as its relation with hypophosphatemia.

However, in the course of the study of adult osteoporosis, low levels of vitamin D have also been found to endanger the bone, without necessarily reaching levels that produce osteomalacia (the equivalent of rickets in adults). Although this aspect will be discussed more fully elsewhere in this paper, it has been established that vitamin D values below 30 ng/ml may be detrimental to bone metabolism in adults. However, can these limits be applied to the growing individual? In other words, is vitamin D deficiency the same in children as in adults? Throughout this paper, we will discuss various issues regarding hypovitaminosis D in children and adolescents.

Since the cited studies offer values of 25-hydroxy vitamin D in different units (either ng/ml, or nmol/l), to give uniformity to the review all results are shown in ng/ml, after converting them according to the equivalence 1 ng/ml=2.5 nmol/l.

Rickets and vitamin D deficiency

In rickets, bone deformities occur with increased risk of fractures, decreased growth, muscle weakness, delayed motor development, as well as hypo-

calcemia and its consequences (tetany, epilepsy, dilated cardiomyopathy). It is not the only cause, but vitamin D deficiency is one of the most frequent, along with low intake of calcium in the diet.

The prevalence of rickets currently remains high in Africa, Asia and the Middle East, mainly due to nutritional causes, but is increasing in countries where there is no nutritional deficit, such as the United States, Australia, New Zealand, the Netherlands Denmark or the United Kingdom²⁻⁴.

Today, it is generally accepted that with significant vitamin D deficiency (<10 n/ml of 25-hydroxy vitamin D serum) the mineralization alteration characteristic of rickets or osteomalacia, defined as severe vitamin D deficiency, are observed. A study by Ramavat et al. 80% of newborns with rickets studied reported levels of 25-hydroxy vitamin D below 20 ng/ml⁵. It is possible that the disease will occur with levels>10 ng/ml if this is similar to a significant deficit in calcium intake^{6,7}.

However, inadequate levels, though not so low as to produce these diseases, may also be detrimental to bone health. As in adults, low levels of vitamin D may lead to secondary hyperparathyroidism that releases calcium from the bone to maintain calcemia, with consequent effect on bone mass, as shown by several studies^{8,9}. Outila et al. also found an association between vitamin D levels, parathormone (PTH) and bone mineral density (BMD) in adolescent girls¹⁰, as did Cheng et al.¹¹. However, other authors did not find this association in adolescent girls between 16 and 20 years of age^{12,13}. Stein et al., in a study of girls aged 4 to 8 years obtained adequate vitamin D levels, but did not find a positive correlation with BMD, although it did with BMD¹⁴. A recent study with a total of 4,532 children of both sexes aged 0 to 7 years found a correlation between their levels of 25-hydroxy vitamin D and

BMD measured by quantitative ultrasound (QUS) (OR=0.984; 95% CI: 0.977-0.991, $p<0.001$)¹⁵. Another cross-sectional study published in the same year and conducted in Sweden on 120 children aged 8-9 years of both sexes found that 50% of them had levels of 25-hydroxy vitamin D <20 ng/ml, and only 5% had levels above 30 ng/ml. However, 82% had a BMD measured by dual radiological absorptiometry (DXA) with a Z-score >0.0, so that no correlation was found between both parameters, vitamin D and BMD. The authors concluded that the vitamin D deficiency did not affect these children's bone health, although they recognize that the long-term effects should be studied¹⁶. The disparity of results may reflect the lack of uniformity in the populations studied (age, sex) and methods and locations of BMD measurement. However, there is insufficient evidence that, in the absence of rickets, the mere existence of low levels of vitamin D affects BMD, and unless the risk of fracture increases,^{7,17} continued research in this area is required to obtain clearer conclusions and, above all, to see if there can be a later effect in adulthood.

Do we define vitamin D deficiency in children as we do in adults?

According to the recommendations published in 2011 by the Institute of Medicine, serum values >30 ng/ml of 25-hydroxy vitamin D are considered ideal for maintaining calcium homeostasis, and levels between 21 and 29 ng/ml are insufficient, those below 20 ng/ml being deficient¹⁸. These limits are assumed and accepted by much of the scientific community¹⁹. However, these definitions are not without controversy today, even for adults. There are no data from children's populations that can support the levels that are sufficient, insufficient or deficient in children, so data are extrapolated from adult studies³. In 2008, the American Academy of Pediatrics recommended that, among children, serum concentrations of 25-hydroxy vitamin D should be maintained above 20 ng/mL, considering lower numbers as deficient. Although it did not establish the limit between sufficiency and insufficiency, recognizing that this figure is determined on the basis of recommendations made for adults, and that, as at present, there was no consensus on children²⁰.

In a consensus paper by Muns et al., published in 2016, the recommendations on classification of vitamin D status were sufficient for values >20 ng/ml, insufficiency for values between 16-20 ng/ml and deficiency to values <16 ng/ml⁷. These recommendations were based on studies that showed an increase in the incidence of nutritional rickets with values <16 ng/ml²¹⁻²⁶.

Binkley et al. conclude that the basis for these different criteria may be attributed to the lack of standardization of vitamin D measurements, a problem that must be overcome beforehand, and it seems reasonable that the studies focus first on establishing the vitamin D values are associated with rickets or osteomalacia and are identified as severe vitamin D deficiency²⁷.

However, the description of cases of rickets with numbers >30 ng/ml on the one hand, and the fact that most children with <30 ng/ml are asymptomatic, causes researchers to doubt the establishment of this limit as true for diagnosing rickets. As we wrote at the outset, some authors point out that vitamin D deficiency should be considered as important as calcium deficiency in intake, which may justify the previous contradiction⁷.

Prevalence of vitamin D deficiency in childhood and adolescence

Aside from cases of rickets not produced by vitamin D deficiency, nutritional deficiencies and those of genetic cause, rickets would reflect the prevalence of vitamin D deficiency. However, we have already pointed out that not always rickets and vitamin D deficiency levels go together, even though there is no other cause than vitamin D deficiency. Furthermore, a large number of studies in healthy children have shown low levels of 25-hydroxy vitamin D in a high percentage throughout the world and from previous times to date, similar to studies carried out in adults.

It is expected that populations living in areas with limited sunlight or suffering food deficiencies present a high prevalence of vitamin D deficiency. However, the situation goes further. In the large sample (n=6,275) of children and adolescents aged 1 to 21 studied in the US National Health Surveillance Program NHANES (National Health and Nutrition Examination Survey 2001-2004), 9% values <15 ng/ml, and in 61% they were between 15-29 ng/ml²⁸.

In our country, a prevalence of vitamin D deficiency (values <20 ng/ml) was detected in winter in a study of 423 healthy children and adolescents with no nutritional deficiency between 3 and 15 years of age and both sexes and spring of 19.3% and 15.5%, respectively, figures that decreased considerably in summer (3.6%). However, only 24.7% presented values >30 ng/ml in spring²⁹. Another study carried out in Italy (country at a similar latitude to Spain) shows similar results. Vierucci et al. determined serum 25-hydroxy vitamin D in 652 children and adolescents of both sexes aged between 2 and 21 years of age in Tuscany (Northern Italy) and who did not suffer from diseases that could affect the metabolism of vitamin D. The percentage of subjects with values below 20 ng/ml was 45.9%. In addition, 9.5% had levels <10 ng/ml. It is also noteworthy that in summer the mean level of 25-hydroxy vitamin D was 27.1 ng/mL³⁰.

If we go to less favorable latitudes, the results are equally disheartening, as might be expected. We have previously commented on the study conducted in Sweden by Videult et al., who found 25-hydroxy vitamin D levels <20 ng/ml in 50% of the children studied, and only during the months of July to September media levels were higher than this figure, but even then it was <30 ng/ml (24.8 mg/ml)¹⁶. In a study of 376 Finnish children aged 6 to 8 years and both sexes, Soininen et al. repor-

ted mean levels of 25-hydroxy vitamin D of 27.4 ng/ml, below the sufficient level and 19.5% had values <20 ng/ml, with no significant differences between the sexes³¹. In Iceland, Bjarnadottir et al. considered 278 healthy children aged 7 years and both sexes and found that 65.2% had mean levels of 25-hydroxy vitamin D <20 ng/ml. Whereas mean levels in September were 23.95 ng/ml and in November 15.04 ng/ml, a difference that was very significant ($p < 0.001$)³². As a final example, Munasinghe et al. measured 25-hydroxy vitamin D levels in 2,270 Canadian children and adolescents of both sexes (3-18 years). 5.6% had values <12 ng/ml, and only 23.5% showed values 30 mg/ml. Percentages increased and decreased, respectively, in winter (14.6% and 12.3%, respectively)³³.

A large study in China by Zhao et al. reported that 5,571 children aged 1 to 3 years and both sexes showed that 16.1% had levels of 25-hydroxy vitamin D <20 ng/ml, and 38.8% between 20 and 30 ng/ml³⁴.

In the northeastern US, Weng et al. carried out a study in 382 healthy children and adolescents of both sexes and between 3 and 21 years old, published in 2007. The mean levels of 25 (OH) vitamin D were 28 ng/ml, and the percentage of children with levels <30 ng/ml was 55%³⁵. Also in the USA (Pittsburgh), a study of 237 children and adolescents aged 8-18 years of both sexes showed that the mean levels of 25 (OH) vitamin D were 19.4 ng/ml, and that 55.7% had figures <20 ng/ml³⁶.

On the other hand, studies in populations located in more sunny latitudes do not show better results. Bener et al. determined the levels of 25-hydroxy vitamin D in 458 healthy children and adolescents of Qatar (<16 years of age) of both sexes. Of these, 315 (approximately 68.8%) had values lower than 20 ng/ml, without showing differences with respect to sex (153 males/162 females). However, when grouped by age, the group of adolescents (between 11 and 16 years old) showed the highest prevalence of vitamin D deficiency (61.6%), followed by the group of 5 to 10 years (28.9%), being that of children under 5 years of age the lowest prevalence of deficiency (9.5%)². Santos et al. carried out a study in the south of Brazil that included 234 healthy girls and adolescents between the ages of 7 and 18 years. In 36.3% of them 25-hydroxy vitamin D levels were below 20 ng/ml, and 54.3% had values considered insufficient (between 29 and 20 ng/ml). Only 9.4% matched or exceeded 30 ng/ml. In this study, however, they did not find significant differences in 25-hydroxy vitamin D values with regard to age³⁷.

In Mexico, 1,025 children aged 2 to 12 years and both sexes were found by Flores et al. to have a mean level of 37.84 ng/ml, 16% of which had values <20 ng/ml and 39% <30 ng/ml. Bearing in mind the age, children younger than 5 years showed values lower than those of 6 or more years, reaching values <20 ng/ml 20% of these smaller and <30 ng/ml 50% of them³⁸.

Rovner et al., in a review published in 2008 to assess vitamin D deficiency in US children, conclu-

ded that, although vitamin D deficiency was not very common, there was a frequent occurrence of insufficiency³⁹. It should be taken into account that most studies analyzed marked the deficiency limit in serum 25-hydroxy vitamin D values well below 20 ng/ml (15, 12, 11 and even some, 5 ng/ml) currently considered to be deficient, which leads us to believe that the prevalence of deficiency, according to currently accepted criteria, would have been much higher. Recently published, Kraimi and Kremer discuss in another review the widespread presence of vitamin D deficiency worldwide, and especially in a sunny country like Israel, demonstrating that the infant population is also at high risk of vitamin D deficiency⁴⁰. Analyzing studies carried out in Europe, Braegger et al. reported in a review that, even considering the limitations of the observed studies (small sizes, different designs, different definitions of deficiency), a considerable number of children and adolescents in Europe may be expected to have vitamin D deficiency⁴¹.

Without losing sight of the limitation of lack of consensus on vitamin D deficiency and uniformity of 25 (OH) vitamin D determinations, there is widespread recognition that, as in the case of adults, the child population does not have adequate levels of vitamin D. Most researchers agree that poor sun exposure, caused on the one hand by decreased outdoor activity and on the other by measures of prevention of skin cancer, is identified as the main cause of this high prevalence of vitamin D deficiency, aggravated by racial and cultural considerations.

Special mention should be made of the neonatal population. Several authors indicate that newborns are at high risk of vitamin D deficiency, since their inability to produce it during gestation makes their levels dependent on those of the mother. But also after birth the risk can be maintained, since breast milk is not rich in vitamin D⁴². Therefore, vitamin D levels in mothers during gestation and lactation will be transcendent to maintain adequate levels in their children during these periods. However, studies in pregnant women have detected a high prevalence of vitamin D deficiency in these women. ElSORI et al. note that studies in sunny countries such as Ethiopia, India, Kuwait and Qatar found that 80%, 66%, 75% and 48% respectively of pregnant women were vitamin D deficient due to several reasons, including low sun exposure (clothing, staying at home) and predominance of dark skin⁴².

A recently published study conducted in Odense (Norway) analyzed 2,082 umbilical cord blood samples taken during delivery of serum 25 (OH) vitamin D. Of these, 16.7% showed values <10 ng/ml, and in 41.0% the values were between 10 and 20 mg/ml. Considering the criterion of vitamin D deficiency in values <20 ng/ml, 57.7% of the samples showed deficient levels⁴³.

Even in a very recently published study, a relationship has been found between the mother's BMD and the presence of rickets in her children⁴⁴.

It is concluded that, as in adults, the infant population (from infants to adolescents) throughout the world shows a considerable prevalence of vitamin D deficiency, and it seems clear that the causes can be identified as the same in adulthood. We do not know if these low levels of vitamin D may be affecting developing bones, but it seems logical to think that it is not a favorable environment for bone health.

Hypovitaminosis D and other diseases

As in adults, vitamin D deficiency has been associated with various diseases in children and adolescents³. Let us consider here the most relevant.

Obesity and metabolic syndrome

The most studied relationship in this respect is between vitamin D deficiency and obesity, as well as the metabolic syndrome⁴⁰.

In a 2008 study of 127 obese children aged 10 to 16 years to find a relationship between obesity and calciotropic hormones, 74% of the children had serum values of 25-hydroxy vitamin D <30 ng/ml, and 32.3%, <20 ng/ml. But these children also presented a higher body mass index (BMI), greater fat mass, higher intact PTH levels and a lower quantitative insulin sensitivity index (QUICKI) than the group of children with levels >30 ng/ml ($p=0.01$). There was a negative correlation of fat mass with levels of 25-hydroxy vitamin D ($r=-0.40$, $p<0.0001$) and positive with intact PTH ($r=0.46$, $p<0.0001$) without racial or ethnic influences. In addition, 25-hydroxy vitamin D correlated positively with QUICKI ($r=0.24$, $p<0.01$), but negatively with glycosylated hemoglobin, HbA1c ($r=0.23$, $p<0.01$)⁴⁵. Currently, Flores et al., in a study of 2,695 children aged 1 to 11, found that obese or overweight school-age children (<5 years) were at increased risk of vitamin D deficiency compared to children of normal weight (OR=2.23, 95% CI: 1.36-3.66, $p<0.05$)⁴⁶. In our country, Durá-Travé et al. have recently published a study of 546 children of both genders and ages between 3 and 15 years old, in which they observed a high prevalence of hypovitaminosis D (values of 25-hydroxy vitamin D <20 ng/ml) among children with severe obesity (81.1%) and obese (68.2%), whereas it was lower in the group of overweight (55%) and normal weight (58.1%) ($p=0.001$). In addition, children with obesity (simple or severe) had more prevalence of hyperparathyroidism than overweight or normal weight children ($p=0.001$). There was a negative correlation between vitamin D and BMI ($r=0.198$), and positive correlation between PTH and BMI (Z-score) ($r=0.268$)⁴⁷.

This relationship between vitamin D deficiency and obesity has been found in many studies on the prevalence of hypovitaminosis D in children and adolescents^{28,32,33,36}. However, when the population studied had non-obesity criteria the researchers found no correlation between weight and serum levels of 25-hydroxy vitamin D^{16,29,30,35,37}, and even some found that the BMI correlated positively with the values of 25-hydroxy vitamin D^{2,38}.

Vitamin D deficiency associated with obesity is caused by its deposition in adipose tissue, leading

to a decrease in its bioavailability⁴⁸, but it has also been observed that obese children with vitamin D deficiency have lower insulin sensitivity^{44,49}, and increased risk of metabolic syndrome, and therefore, increased cardiovascular risk^{49,50-52}.

Autoimmune diseases

Furthermore, autoimmune diseases have been associated with vitamin D deficiency levels. Because of the immunomodulatory role attributed to vitamin D, diseases such as juvenile idiopathic arthritis (JIA), systemic lupus erythematosus (SLE), and Hashimoto's thyroiditis (HT) and diabetes mellitus type 1 (DM-1) have been studied for possible relations.

Comak et al. studied 47 children with JIA with a mean age of 9.3 ± 3.9 years and both sexes, and found an inverse relationship between 25 (OH) vitamin D levels and disease activity ($p=0.01$, $r=0.37$). Mean JADAS-27 (disease activity calculator) score was significantly higher in patients with levels of 25 (OH) vitamin D <15 ng/ml than those with levels >15 ng/ml ($p=0.003$)⁵³. Stagi et al. compared the vitamin D levels of 152 patients with JIA (16.2 ± 7.4 years) to a control group of similar age and sex ratio. Patients with JIA had values of 25-hydroxy vitamin D significantly lower than those in the control group ($p<0.001$). Among patients, those with the highest activity of their disease had lower numbers than those without active disease ($p<0.005$)⁵⁴.

Dağdeviren-Çakir et al. did not find a link to JIA activity, but found that vitamin D levels were lower in sick ($n=64$) than in healthy subjects ($n=100$): 18.9 ± 11 ng/ml and 18.6 ± 9.2 ng/ml during periods of disease activity and remission respectively, vs 26.7 ± 10.5 ng/ml in healthy children⁵⁵. Similar results were obtained by Garf et al. When they studied 70 children with SLE in front of 40 healthy children⁵⁶, as well as Perracchi et al.⁵⁷. Stagi et al. also found lower levels of vitamin D in children, adolescents and young people with SLE compared with healthy subjects⁵⁸. In a study of 221 children with SLE who participated in the APPLE (Atherosclerosis Prevention in Pediatric Lupus Erythematosus) clinical trial, the authors found that vitamin D deficiency is common among pediatric patients with this disease, and was independently associated to high levels of C-reactive protein, marker for inflammation⁵⁹.

On the other hand, other studies, such as the one carried out by Pelajo et al. in 156 patients with a mean age of 10.6 ± 4.5 years⁶⁰, and de Sousa et al. performed in 50 patients of 13.4 ± 4 years⁶¹, did not show this association. A recently published study obtained the same results⁶².

In a meta-analysis published by Nisar et al. in 2013, there was no clear evidence of a relationship between vitamin D and JIA⁶³.

Finally, a study of 56 children and adolescents with Hashimoto's autoimmune thyroiditis (TH) versus 56 healthy subjects found that the mean level of 25-hydroxy vitamin D was significantly lower than that of the control group (6.48 ± 3.28 vs

13.56±5.08 ng/ml, $p < 0.001$), and that 25 (OH) vitamin D values correlated positively with those of free thyroxine. They conclude that, although low levels of 25 (OH) vitamin D were an independent risk factor for HT, they could not be considered as an independent factor for the progression of HT towards hypothyroidism after adjusting for other confounding factors, such as age, sex and BMI⁶⁴. In another study, the authors determined the levels of 25-hydroxy vitamin D in 90 patients with HT of 12.32±2.87 years of middle age and 79 healthy children and adolescents of the same age (11.85±2, 28 years), observing that the prevalence of deficiency (<20 ng/ml) was higher among HT patients (71.1%) than in healthy children (51.9%) ($p = 0.025$) and that the mean value of 25-hydroxy vitamin D in the patient group was significantly lower than in the control group (16.67±11.⁶⁵ vs 20.99±9.86 ng/ml, $p = 0.001$)⁶⁵. These findings were similar to those found by Sönmezgöz et al.⁶⁶.

Studies to observe the influence of maternal vitamin D deficiency during pregnancy on the risk of DM-1 in children show contradictory findings^{67,68}. A recent study by Sørensen et al. carried out in 113 mothers of diabetic children compared to 220 mothers of healthy children, observed that during pregnancy, levels of the vitamin D transporter protein and 25-hydroxy vitamin D decreased in the 3rd trimester, and that their values tended (without becoming significant) to be lower in the mothers of children with DM-1 compared to controls⁶⁹.

However, a recent study found that the use of multivitamin supplements with vitamin D in pregnant women did not reduce the risk of DM 1 in their offspring⁷⁰, which calls into question the possible effect of vitamin D on infant DM-1.

Mental diseases

Vitamin D deficiency has also been associated in children with mental illness, such as depression⁷¹. Vitamin D is an environmental factor that plays a role in cerebral homeostasis and neurodevelopment, and at a higher level has been suggested to have an impact on the risk of autism. The prevalence of autism in the USA is higher in regions where doses of solar UV radiation are lower⁷². There has also been an increased risk of autism in preterm infants with vitamin D deficiency in mothers during pregnancy, which may act as a risk factor for preterm birth and cause abnormal brain development in the child and an increased risk of alterations in language development^{73,74}.

An interesting study conducted in Sweden by Fernell et al. recruited 58 pairs of siblings, one of whom had autism. From the blood samples taken during the neonatal period for metabolic screening and stored, vitamin D levels were determined. Children with autism had lower vitamin D levels than their siblings, even taking into account Different seasons of the year in which they were born⁷⁵. This relationship between vitamin D deficiency and autism has been explained by several mechanisms^{3,76}.

Hypovitaminosis D in childhood: a real problem?

The importance of vitamin D in musculoskeletal development and in calcium homeostasis is beyond discussion. Rickets are still a health problem in many countries with nutritional deficiencies, but the scarce exposure to the sun that the population of countries without nutritional problems suffers causes the disease to spread to the whole world.

However, much remains to be determined. It is vitally important to define consistently the limits that mark hypovitaminosis D as a situation of deficiency (which would imply an impairment in health) and insufficiency (which would be a risk situation), as well as vitamin D limits considered as healthy, suitable and therefore desirable. More robust and more homogeneous designs are needed to help us achieve this goal.

Even so, it is not arguable that a considerable percentage of the infant population present low vitamin D values, and although its clinical effect is yet to be elucidated, it seems reasonable to conclude that, if maintained over time, they may not only affect bone health but also to promote the appearance of various chronic diseases in adulthood.

Since the main causes of these low levels of vitamin D are easily treatable (adequate sun exposure, high calcium and vitamin D), efforts should be directed at promoting outdoor activities on sunny days and fortifying foods with calcium and vitamin D (especially in countries with low insolation), while supplements should be considered in those individuals or populations at high risk (pregnant, lactating, very little or no sun exposure for geographical, ethnic or cultural reasons)^{3,6,7,19,30,31,40,41}. In this sense, and as an example, there is international consensus among societies and pediatric institutions on supplementing all newborns and children under 1 year of age with 400 IU/day of vitamin D₃ (cholecalciferol) as a preventive measure^{6,7,19,41,77-79}.

Conflict of interest: The authors declare they have no conflict of interest regarding this work.

Bibliography

1. McCollum EV, Simmonds N, Becker JE, Shipley PG. Studies on experimental rickets. XXI. An experimental demonstration of the existence of a vitamin which promotes calcium deposition. *J Biol Chem.* 1922;53:293-312.
2. Bener A, Al-Ali M, Hoffmann GF. Vitamin D deficiency in healthy children in a sunny country: associated factors. *Int J Food Sci Nutr.* 2009;60 Suppl 5:60-70.
3. Ariganjoye R. Pediatric Hypovitaminosis D: Molecular Perspectives and Clinical Implications. *Glob Pediatr Health.* 2017;4:2333794X16685504.
4. Creo AL, Thacher TD, Pettifor JM, Strand MA, Fischer PR. Nutritional rickets around the world: an update. *Paediatr Int Child Health.* 2016 Dec 6:1-15. [Epub ahead of print].
5. Ramavat LG. Vitamin D deficiency rickets at birth in Kuwait. *Indian J Pediatr.* 1999;66(1):37-43.
6. Höglér W. Complications of vitamin D deficiency from the foetus to the infant: One cause, one prevention,

- but who's responsibility? *Best Pract Res Clin Endocrinol Metab.* 2015;29(3):385-98.
7. Munns CF, Shaw N, Kiely M, Specker BL, Thacher TD, Ozono K, et al. Global Consensus Recommendations on prevention and management of nutritional rickets. *Horm Res Paediatr.* 2016; 85(2):83-106.
 8. Tangpricha V, Pearce EN, Chen TC, Holick MF. Vitamin D insufficiency among free-living healthy young adults. *Am J Med.* 2002;112(8):659-62.
 9. Bischoff-Ferrari HA, Dietrich T, Orav EJ, Dawson-Hughes B. Positive association between 25-hydroxy vitamin D levels and bone mineral density: a population-based study of younger and older adults. *Am J Med.* 2004;116:634-9.
 10. Outila TA, Kärkkäinen MU, Lamberg-Allardt CJ. Vitamin D status affects serum parathyroid hormone concentrations during winter in female adolescents: associations with forearm bone mineral density. *Am J Clin Nutr.* 2001;74:206-10.
 11. Cheng S, Tylavsky F, Kroger H, Kärkkäinen M, Lyytikäinen A, Koistinen A, et al. Association of low 25-hydroxyvitamin D concentrations with elevated parathyroid hormone concentrations and low cortical bone density in early pubertal and prepubertal Finnish girls. *Am J Clin Nutr.* 2003;78:485-92.
 12. Kristinsson JO, Valdimarsson O, Sigurdsson G, Franzon L, Olafsson I, Steingrimsdottir L. Serum 25-hydroxyvitamin D levels and bone mineral density in 16-20 years-old girls: lack of association. *J Intern Med.* 1998;243:381-8.
 13. Nakamura K, Nashimoto M, Matsuyama S, Yamamoto M. Low serum concentrations of 25-hydroxyvitamin D in young adult Japanese women: a cross sectional study. *Nutrition.* 2001;17(11-12):921-5.
 14. Stein EM, Laing EM, Hall DB, Hausman DB, Kimlin MG, Johnson MA, et al. Serum 25-hydroxyvitamin D concentrations in girls aged 4-8 y living in the southeastern United States. *Am J Clin Nutr.* 2006;83(1):75-81.
 15. Fu Y, Hu Y, Qin Z, Zhao Y, Yang Z, Li Y, et al. Association of serum 25-hydroxyvitamin D status with bone mineral density in 0-7 year old children. *Oncotarget.* 2016;7(49):80811-9.
 16. Videhult FK, Öhlund I, Hernell O, West CE. Body mass but not vitamin D status is associated with bone mineral content and density in young school children in northern Sweden. *Food Nutr Res.* 2016;60:30045.
 17. Moon RJ, Harvey NC, Davies JH, Cooper C. Vitamin D and skeletal health in infancy and childhood. *Osteoporos Int.* 2014;25(12):2673-84.
 18. IOM (Institute of Medicine). Dietary reference intakes for calcium and vitamin D. Washington DC. The National Academies Press. 2011.
 19. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2011;96(7):1911-30.
 20. Wagner CL, Greer FR; American Academy of Pediatrics Section on Breastfeeding; American Academy of Pediatrics Committee on Nutrition. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. *Pediatrics.* 2008 Nov;122(5):1142-52.
 21. Ward LM, Gaboury I, Ladhani M, Zlotkin S. Vitamin D-deficiency rickets among children in Canada. *CMAJ.* 2007;177:161-6.
 22. Munns CF, Simm PJ, Rodda CP, Garnett SP, Zacharin MR, Ward LM, et al. Incidence of vitamin D deficiency rickets among Australian children: an Australian Paediatric Surveillance Unit study. *Med J Aust.* 2012;196:466-8.
 23. Dawodu A, Agarwal M, Sankaranakutty M, Hardy D, Kochiyil J, Badrinath P. Higher prevalence of vitamin D deficiency in mothers of rachitic than nonrachitic children. *J Pediatr.* 2005;147:109-11.
 24. Specker BL, Ho ML, Oestreich A, Yin TA, Shui QM, Chen XC, et al. Prospective study of vitamin D supplementation and rickets in China. *J Pediatr.* 1992;120:733-9.
 25. Majid Molla A, Badawi MH, al-Yaish S, Sharma P, el-Salam RS, Molla AM. Risk factors for nutritional rickets among children in Kuwait. *Pediatr Int.* 2000;42:280-4.
 26. Molla AM, Al Badawi M, Hammoud MS, Molla AM, Shukkur M, Thalib L, et al. Vitamin D status of mothers and their neonates in Kuwait. *Pediatr Int.* 2005;47:649-52.
 27. Binkley N, Dawson-Hughes B, Durazo-Arvizu R, Thamm M, Tian L, Merkel JM, et al. Vitamin D measurement standardization: The way out of the chaos. *J Steroid Biochem Mol Biol.* 2016;12. pii: S0960-0760(16)30341-7.
 28. Kumar J, Muntner P, Kaskel FJ, Hailpern SM, Melamed ML. Prevalence and associations of 25-hydroxyvitamin D deficiency in US children: NHANES 2001-2004. *Pediatrics* 2009;124(3):e362-70.
 29. Durá-Travé T, Gallinas-Victoriano F, Chueca Guindulain MJ, Berrade-Zubiri S. Deficiencia de vitamina D en escolares y adolescentes con un estado nutricional normal. *Nutr Hosp.* 2015;32:1061-6.
 30. Vierucci F, Del Pistoia M, Fanos M, Gori M, Carlone G, Erba P, et al. Vitamin D status and predictors of hypovitaminosis D in Italian children and adolescents: a cross-sectional study. *Eur J Pediatr.* 2013;172(12):1607-17.
 31. Soininen S, Eloranta AM, Lindi V, Venäläinen T, Zaproudina N, Mahonen A, et al. Determinants of serum 25-hydroxyvitamin D concentration in Finnish children: the Physical Activity and Nutrition in Children (PANIC) study. *Br J Nutr.* 2016;115(6):1080-91.
 32. Bjarnadottir A, Kristjansdottir AG, Hrafnkelsson H, Johannsson E, Magnusson KT, Thorsdottir I. Insufficient autumn vitamin D intake and low vitamin D status in 7-year-old Icelandic children. *Public Health Nutr.* 2015;18(2):208-17.
 33. Munasinghe LL, Yuan Y, Willows ND, Faught EL, Ekwaru JP, Veugelers PJ. Vitamin D deficiency and sufficiency among Canadian children residing at high latitude following the revision of the RDA of vitamin D intake in 2010. *Br J Nutr.* 2017;1:1-9.
 34. Zhao X, Xiao J, Liao X, Cai L, Xu F, Chen D, et al. Vitamin D Status among Young Children Aged 1-3 Years: A Cross-Sectional Study in Wuxi, China. *PLoS One.* 2015;10(10):e0141595.
 35. Weng FL, Shults J, Leonard MB, Stallings VA, Zemel BS. Risk factors for low serum 25-hydroxyvitamin D concentrations in otherwise healthy children and adolescents. *Am J Clin Nutr.* 2007;86(1):150-8.
 36. Rajakumar K, de las Heras J, Chen TC, Lee S, Holick MF, Arslanian SA. Vitamin D status, adiposity, and lipids in black American and Caucasian children. *J Clin Endocrinol Metab.* 2011;96(5):1560-7.
 37. Santos BR, Mascarenhas LP, Satler F, Boguszewski MC, Spritzer PM. Vitamin D deficiency in girls from South Brazil: a cross-sectional study on prevalence and association with vitamin D receptor gene variants. *BMC Pediatr.* 2012;12:62-8.
 38. Flores M, Macias N, Lozada A, Sánchez LM, Díaz E, Barquera S. Serum 25-hydroxyvitamin D levels among Mexican children ages 2 y to 12 y: a national survey. *Nutrition.* 2013;29(5):802-4.
 39. Rovner AJ, O'Brien KO. Hypovitaminosis D among healthy children in the United States: a review of the current evidence. *Arch Pediatr Adolesc Med.* 2008; 162(6):513-9.
 40. Haimi M, Kremer R. Vitamin D deficiency/insufficiency from childhood to adulthood: Insights from a sunny country. *World J Clin Pediatr.* 2017;6(1):1-9.
 41. Braegger C, Campoy C, Colomb V, Decsi T, Domellof M, Fewtrell M, et al. Vitamin D in the healthy European paediatric population. *J Pediatr Gastroenterol Nutr.* 2013;56(6):692-701.
 42. ElSORI DH, Hammoud MS. Vitamin D deficiency in mothers, neonates and children. *J Steroid Biochem Mol Biol.* 2017 Feb 5. [Epub ahead of print].
 43. Lykkedegn S, Beck-Nielsen SS, Sorensen GL, Andersen LB, Fruekilde PB, Nielsen J, et al. Vitamin D supplementation, cord 25-hydroxyvitamin D and birth weight: Findings from the Odense Child Cohort. *Clin Nutr.* 2016 Oct 27. pii: S0261-5614(16)31283-3. [Epub ahead of print].
 44. Hsu J, Fischer FR, Pettifor JM, Thacher TD. The relationship of maternal bone density with nutritional rickets in Nigerian children. *Bone.* 2017;97:216-21.

45. Alemzadeh R, Kichler J, Babar G, Calhoun M. Hypovitaminosis D in obese children and adolescents: relationship with adiposity, insulin sensitivity, ethnicity, and season. *Metabolism*. 2008;57(2):183-91.
46. Flores A, Flores M, Macias N, Hernández-Barrera L, Rivera M, Contreras A, et al. Vitamin D deficiency is common and is associated with overweight in Mexican children aged 1-11 years. *Public Health Nutr*. 2017 Feb 28;1-9. [Epub ahead of print].
47. Durá-Travé T, Gallinas-Victoriano F, Chueca-Guindulain MJ, Berrade-Zubiri S. Prevalence of hypovitaminosis D and associated factors in obese Spanish children. *Nutr Diabetes*. 2017;7(3):e248.
48. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF: Decreased bioavailability of vitamin D in obesity. *Am J Clin Nutr*. 2000;72(3):690-3.
49. Ashraf A, Alvarez J, Saenz K, Gower B, McCormick K, Franklin F. Threshold for effects of vitamin D deficiency on glucose metabolism in obese female African-American adolescents. *J Clin Endocrinol Metab*. 2009;94(9):3200-6.
50. Reis JP, von Muhlen D, Miller ER 3rd, Michos ED, Appel LJ. Vitamin D status and cardiometabolic risk factors in the United States adolescent population. *Pediatrics*. 2009;124(3):e371-9.
51. Johnson MD, Nader NS, Weaver AL, Singh R, Kumar S. Relationships between 25-hydroxyvitamin D levels and plasma glucose and lipid levels in pediatric outpatients. *J Pediatr*. 2010;156(3):444-9.
52. Challa AS, Makariou SE, Siomou EC. The relation of vitamin D status with metabolic syndrome in childhood and adolescence: an update. *J Pediatr Endocrinol Metab*. 2015;28(11-12):1235-45.
53. Çomak E, Doğan ÇS, Uslu-Gökçeoğlu A, Akbaş H, Özdem S, Koyun M, et al. Association between vitamin D deficiency and disease activity in juvenile idiopathic arthritis. *Turk J Pediatr*. 2014;56(6):626-31.
54. Stagi S, Bertini F, Cavalli L, Matucci-Cerinic M, Brandi ML, Falcini F. Determinants of vitamin D levels in children, adolescents, and young adults with juvenile idiopathic arthritis. *J Rheumatol*. 2014;41(9):1884-92.
55. Dağdeviren-Çakır A, Arvas A, Barut K, Gür E, Kasapoğlu Ö. Serum vitamin D levels during activation and remission periods of patients with juvenile idiopathic arthritis and familial Mediterranean fever. *Turk J Pediatr*. 2016;58(2):125-31.
56. Garf KE, Marzouk H, Farag Y, Rasheed L, Garf AE. Vitamin D status in Egyptian patients with juvenile-onset systemic lupus erythematosus. *Rheumatol Int*. 2015;35(9):1535-40.
57. Peracchi OA, Terreri MT, Muneke RV, Len CA, Sarni RO, Lazaretti-Castro M, et al. Low serum concentrations of 25-hydroxyvitamin D in children and adolescents with systemic lupus erythematosus. *Braz J Med Biol Res*. 2014;47(8):721-6.
58. Stagi S, Cavalli L, Bertini F, de Martino M, Cerinic MM, Brandi ML et al. Vitamin D levels in children, adolescents, and young adults with juvenile-onset systemic lupus erythematosus: a cross-sectional study. *Lupus*. 2014;23(10):1059-65.
59. Robinson AB, Tangpricha V, Yow E, Gurion R, McComsey GA, Schanberg LE; APPLE Investigators. Vitamin D deficiency is common and associated with increased C-reactive protein in children and young adults with lupus: an Atherosclerosis Prevention in Pediatric Lupus Erythematosus substudy. *Lupus Sci Med*. 2014;1(1):e000011.
60. Pelajo CF, Lopez-Benitez JM, Kent DM, Price LL, Miller LC, Dawson-Hughes B. 25-hydroxyvitamin D levels and juvenile idiopathic arthritis: is there an association with disease activity? *Rheumatol Int*. 2012;32(12):3923-9.
61. de Sousa Studart SA, Leite AC, Marinho AL, Pinto AC, Rabelo Júnior CN, de Melo Nunes R, et al. Vitamin D levels in juvenile idiopathic arthritis from an equatorial region. *Rheumatol Int*. 2015;35(10):1717-23.
62. Thorsen SU, Pipper CB, Alberdi-Saugstrup M, Nielsen S, Cohen A, Lundqvist M, et al. No association between vitamin D levels around time of birth and later risk of developing oligo- and polyarticular juvenile idiopathic arthritis: a Danish case-cohort study. *Scand J Rheumatol*. 2017;46(2):104-11.
63. Nisar MK, Masood F, Cookson P, Sansome A, Ostör AJ. What do we know about juvenile idiopathic arthritis and vitamin D? A systematic literature review and meta-analysis of current evidence. *Clin Rheumatol*. 2013;32(6):729-34.
64. Metwalley KA, Farghaly HS, Sherief T, Hussein A. Vitamin D status in children and adolescents with autoimmune thyroiditis. *J Endocrinol Invest*. 2016; 39:793-7.
65. Evliyaoglu O, Acar M, Özcan B, Erginöz E, Bucak F, Ercan O, et al. Vitamin D Deficiency and Hashimoto's Thyroiditis in Children and Adolescents: a Critical Vitamin D Level for This Association? *J Clin Res Pediatr Endocrinol*. 2015;7(2):128-33.
66. Sönmezgöz E, Ozer S, Yilmaz R, Önder Y, Bütün I, Bilge S. Hypovitaminosis D in Children with Hashimoto's Thyroiditis. *Rev Med Chil*. 2016;144(5):611-6.
67. Sørensen IM, Joner G, Jenum PA, Eskild A, Torjesen PA, Stene LC. Maternal serum levels of 25-hydroxy-vitamin D during pregnancy and risk of type 1 diabetes in the offspring. *Diabetes*. 2012;61(1):175-8.
68. Miettinen ME, Reinert L, Kinnunen L, et al. Serum 25-hydroxyvitamin D level during early pregnancy and type 1 diabetes risk in the offspring. *Diabetologia*. 2012;55(5):1291-4.
69. Sørensen IM, Joner G, Jenum PA, Eskild A, Brunborg C, Torjesen PA, et al. Vitamin D-binding protein and 25-hydroxyvitamin D during pregnancy in mothers whose children later developed type 1 diabetes. *Diabetes Metab Res Rev*. 2016;32(8):883-90.
70. Granfors M, Augustin H, Ludvigsson J, Brekke HK. No association between use of multivitamin supplement containing vitamin D during pregnancy and risk of Type 1 Diabetes in the child. *Pediatr Diabetes*. 2016;17(7):525-30.
71. Föcker M, Antel J, Ring S, Hahn D, Kanal Ö, Öztürk D, et al. Vitamin D and mental health in children and adolescents. *Eur Child Adolesc Psychiatry*. 2017 Feb 8. [Epub ahead of print].
72. Grant WB, Cannell JJ. Autism prevalence in the United States with respect to solar ultraviolet-B doses: An ecological study. *Dermatoendocrinol*. 2013;5:9-14.
73. Bodnar LM, Plaatt RW, Simhan HN. Early-pregnancy vitamin D deficiency and risk of preterm birth subtypes. *Obstet Gynecol*. 2015;125:439-47.
74. Hanieh S, Ha TT, Simpson JA, Thuy TT, Khuong NC4, Thoang DD, et al. Maternal vitamin D status and infant outcomes in rural Vietnam: a prospective cohort study. *PLoS One*. 2014;9(6):e99005.
75. Fernell E, Bejerot S, Westerlund J, Miniscalco C, Simila H, Eyles D, et al. Autism spectrum disorder and low vitamin D at birth: a sibling control study. *Mol Autism*. 2015;6:3.
76. Cannell JJ, Grant WB. What is the role of vitamin D in autism? *Dermatoendocrinol*. 2013;5:159-204.
77. Grossman Z, Hadjipanayis A, Stiris T, Del Torso S, Mercier JC, Valiulis A, et al. Vitamin D in European children-statement from the European Academy of Paediatrics (EAP). *Eur J Pediatr*. 2017 Apr 12. [Epub ahead of print].
78. Bouillon R. Comparative analysis of nutritional guidelines for vitamin D. *Nat Rev Endocrinol*. 2017 Apr 7 [Epub ahead of print].
79. Siafarikas A, Deichl A, Jahreis G, Pieplow A, Vogel H, Kauf E, et al. Cross-sectional analysis of universal vitamin D supplementation in former East Germany during the first year of life. *J Pediatr Endocrinol Metab*. 2017;30(4):395-404.