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Review

Use of Vitamin D in Children and Adults: Frequently Asked Questions

Short title: Use of Vitamin D in Children

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What is already known on this topic?

In recent years, the increase in interest and use of vitamin D has been attributed mainly to the effects of vitamin D on the extra-skeletal effects and confusion about normal reference values for serum 25-OHD. Global Consensus Recommendations on Prevention and Management of Nutritional Rickets recommends 30 nmol/L (12 ng/ml) as a cut-off level for vitamin D deficiency □ Deficiency.

What this study adds?

This study adds a new perspective and attitude towards unnecessary vitamin D testing and high dose vitamin D supplementation.

Abstract

In recent years, the increase in interest and use of vitamin D has been attributed mainly to the effects of vitamin D on the extra-skeletal effects and confusion about normal reference values for serum 25-OHD. However, The Institute of Medicine (IOM), which determines daily intake of nutrients, vitamins and minerals in the United States, emphasizes that there is no additional benefit of having a 25OHD level above 20 ng/ml in terms of PTH suppression, calcium absorption and "fall risk". Taking into consideration that there has not been a significant increase in vitamin D deficiency and related conditions in Turkey over the past 5 years, it is not hard to suppose that this increase is due to declarations of doctors who have shown vitamin D as a "panacea" in media platforms. This paper aims to answer some frequently asked questions such as the threshold values recommended for the evaluation of vitamin D status, the clinical indications for measuring 25OHD and suggestions on the use of lifelong vitamin D starting from pregnancy.

Introduction

Over the last 10 years a spike in interest in vitamin D deficiency and its effect not only on extra-skeletal tissues but also on general human health has been observed in Turkey and all over the world.

Recently published research based on data of 711718 children in the UK showed that the frequency of diagnosis of vitamin D deficiency increased from 3.14 / 100.000 in 2000 to 261 / 100.000 in 2014 and a 15-fold increase was declared after the impact of the population increase adjustment (1). However,

reliable institutions and researchers have expressed that we are not confronting a vitamin D deficiency pandemic, instead this rise is related to diagnostic behaviours of physicians (other health care professionals) as well as to the increase in the demand for vitamin D examination in routine follow-up (1,2).

Severe vitamin D deficiency may result in hypocalcemic seizures, hypocalcemic cardiomyopathy in infancy. Therefore, we suggest that 25(OH) vitamin D level in infant and the mother should be a routine part of evaluation of infantile hypocalcemia. It also should be noted that the regulation and action of PTH can be disturbed with vitamin D deficiency, particularly in infancy. The elevated PTH levels associated with hypocalcemia and normal or high phosphate indicate an element of end-organ resistance to PTH, mimicking PHP (3). Studies performed in the last decade detected severe vitamin D deficiency (<10 ng/mL) in 46–80% of pregnant women and nursing mothers in different regions of Turkey. Low socioeconomic status, covered clothing style and low educational level and spending less time outdoors because of cultural and lifestyle factors are factors associated with maternal and perinatal vitamin D deficiency (4-8). There is no doubt that the only way of preventing vitamin D deficiency and its complications is vitamin D supplementation.

Besides, a national data demonstrating increase in frequency of vitamin D deficiency over time does not exist in Turkey. Nonetheless, the serum 25OHD levels of 110774 individuals which were taken between January 2011 to December 2016 (measured by using the LC-MS / MS method in a reliable laboratory serving the whole country) revealed no significant difference over time (9). Surprisingly, data obtained from “Intercontinental Marketing Services Health” (IMS Health) showed that in 2012, 2,280,626 boxes of vitamin D (300,000 units of D vitamins) were sold in Turkey, which rose to 8,376,319 in the first 8 months of 2016. According to the same data, in 2015, only 925,734 of 8,754,753 boxes of vitamin D (almost one in ten) were sold with a prescription.

Taking into consideration that there has not been an increase in vitamin D deficiency related conditions in Turkey during the recent years, it is not hard to suppose that this increase is due to declarations of doctors who have shown vitamin D as a “panacea” in media platforms. The Turkish National Pediatric Endocrinology and Diabetes Society was forced to make a statement about the harm that these physicians might cause and has drawn attention to false information on vitamin D (10). This paper aims to answer some frequently asked questions such as the threshold values recommended for the evaluation of vitamin D status and suggestions on the use of lifelong vitamin D starting from pregnancy.

What is the reason for the increasing interest in vitamin D in recent years? What are the normal threshold values for vitamin D?

In recent years, the increase in interest and intake of vitamin D has been attributed mainly to the effects of vitamin D on the extra-skeletal effects and confusion about normal reference values for serum 25-OHD, in particular The American Endocrine Society’s recommendation proposing at least 30 ng/ml for lower range of serum 25OHD level (11).

The Institute of Medicine (IOM), which determines daily intake of nutrients, vitamins and minerals in the United States, emphasizes that there is no additional benefit of having a 25OHD level above 20 ng/ml in terms of PTH suppression, calcium absorption and “fall risk”. In several reports it was stated that skeletal effects of vitamin D plateau when the 25OHD level is between 12-16 ng/ml and 25OHD levels below 20 ng/ml should not be accepted as ‘deficiency’ in all cases. The IOM remarks ‘it is false to specify 25-OHD > 30 ng/mL as the “desired” threshold and there is no need to supplement high doses of vitamin D for obese individuals’ (12, 13). Recently, members of the IOM D Vitamin Committee addressed supplementing vitamin D and recommend 400 units per day in the first year of life, 600 units in the first 70 years of age, and 800 units of vitamin D after age of 70 years. They noted that it is possible to achieve serum vitamin D levels of 16-20 ng/mL in 97.5% of the general population.

In this report the authors highlighted the misinterpretation of a value of 20 ng/ml 25OHD as a threshold value for bone health given that 97.5% of the general population actually have a 25OHD level as equal to or below 20 ng/mL (2). This misconception may result in the threshold value to increase up to 50 ng / ml, which means that the upper limit (4000 units of vitamin D per day) will become normal practice, which is also risky.

It should not be forgotten that inadequate dietary calcium intake is as important as vitamin D to the development of rickets/osteomalacia. IOM’s recommendation for daily calcium intake is 700-1300 mg for children, 1000-1200 mg for adults (12).

How important are extra-skeletal effects of vitamin D? Is there a need to define a different threshold of 25OHD level for those effects ?

In addition to the intestine which is the main site of active vitamin D (calcitriol) effects, several tissues such as breast, bone marrow, nerve cells, and the immune system have vitamin D receptors and it is proposed that calcitriol plays a role in the functions of 230 different genes (14). Recently, attention has focused on the extra-skeletal effects of calcitriol and numerous studies establishing a relationship between calcitriol and many diseases (especially cancer) have almost "invaded" medical journals. The vast majority of this research is made up of correlational studies and fails to meet the cause and effect relation criteria.

Some researchers in The United States, claim that severe forms of vitamin D deficiency result in bone diseases such as rickets, but milder deficiency of vitamin D causes a predisposition to diseases of extra-skeletal tissues (15). Those publications have caused concern in the community by highlighting the 'risks' associated with 25OHD levels below 30 ng/ml and they have encouraged healthy people to check vitamin D levels and intake high-doses of vitamin D (15).

However, data from vitamin D receptor knocked-out animal studies indicated the effects of calcitriol on extra-skeletal tissues were not significant, yet entirely confirmed its effects on calcium absorption and indirect effects through calcium supply to bone texture (16). Besides, a research carried out in human with hereditary vitamin D resistant rickets showed that calcium absorption was highly dependent on vitamin D from infancy until the end of puberty, however HVDRR patients have normal plasma renin activity, without any indications of hypertension or gross heart abnormalities, such as reduced contractility or hypertrophy, at least until the age of 37 years (17).

The IOM remarked that the outcomes of studies that relate the level of vitamin D to non-skeletal problems such as cancer, cardiovascular disease, diabetes and auto-immune diseases are not consistent with each other and do not require establishing a different 25-OHD threshold or a higher intake of vitamin D to prevent these diseases (12,13).

From a clinical point of view, an increase in problems expected from extra-skeletal effects of vitamin D deficiency in countries/regions/groups where vitamin D deficiency is frequent has not been reported. For instance, there are no reports of a high frequency of type 1 diabetes among children who had rickets. The relationship between vitamin D deficiency and the occurrence of type 1 diabetes has almost been a "cliché" and this information is often regarded as correct because it has been repeated for many years. Recent research in Finland has shown that there is no association between antibody positivity regarding Type 1 diabetes, the development of clinical Type 1 diabetes and serum 25OHD levels (18).

In conclusion, studies on the effects of vitamin D on extra-skeletal effects do not provide coherent data and the recommendation for 25OHD level to be at least 30 ng/ml to obtain those effects is not valid.

Does Total 25-OH D show the whole truth? Is it necessary to supplement a high dose of vitamin D to obese children and adolescents?

Approximately 80% of Total 25-OHD is transported with Vitamin D Binding Protein (VDBP), which has a half-life of 1-2 days. It is known that VDBP is a negative acute phase reactant and in cases such as sepsis, the synthesis in the liver decreases and therefore the total 25-OHD is found to be low (19).

In a research it was shown that total 25-OHD levels in black women in the United States were associated with low VDBP, so that black women and white women were similar in terms of "bioavailable" D vitamin levels (20). Similarly, in another study, despite the low level of total 25-OHD in obese children, the bioavailable D vitamin level was determined to be normal and there was a negative correlation between insulin resistance and VDBP (21). Research from Turkey revealed no relationship between of insulin resistance parameters and vitamin D levels in obese children (22).

It is well known that 25-OHD levels are generally low in obese people, however it is recovered with weight loss and vitamin D requirements are not different from non-obese people (13).

On the basis of these observations, there is no need to routinely monitor the serum vitamin D level in obese subjects and it is not required to prescribe vitamin D at doses higher than 400 IU per day to enhance the low levels of 25-OHD levels.

Is routine Vitamin D testing and/or intake of vitamin D ampoules necessary for healthy people?

Overall, when vitamin D deficiency is severe (serum 25-OHD level ≤ 12 ng/mL) bone metabolism deteriorates and diseases known as rickets in children and osteomalacia occur in adults (23).

In Turkey, a nationwide 'vitamin D prophylaxis augmentation programme' was initiated in 2005 using a simple but effective method which included free distribution of vitamin D drops to all new-borns and

infants (0–12 months) visiting primary healthcare stations throughout the country. This programme has reduced clinical rickets cases and severe vitamin D deficiencies dramatically in Turkey (24). There is absolutely no need to test vitamin D levels in routine follow-up and to prescribe high doses of vitamin D because of low vitamin D levels in infancy and childhood. Indeed, the Global Consensus clearly states that testing is not indicated in asymptomatic individuals. Instead, all infants from birth, all pregnant women and all ethnic/cultural risk groups require supplementation (23). Nevertheless, the frequency of serum 25 OH D testing has increased approximately 2.60 times in the ages of 0-18 years and 32% in the age of 18 years between 2011-2016 (4).

Adults with osteomalacia might suffer from widespread bone pain and muscle weakness, particularly in the vertebrae when vitamin D level drops to 12 ng/mL or less. Therefore, neither a routinely vitamin D testing in healthy, asymptomatic subjects over 40 years of age, nor prescription/intake high dose vitamin D for levels of vitamin D below 20 ng/mL is required. Because serum level of vitamin D is only a biochemical parameter, it is necessary to test serum alkaline phosphatase (ALP) and parathyroid hormone (PTH) levels together with clinical/radiological findings to diagnose the disease.

Has the definition of vitamin D deficiency changed? Who should have been treated with high dose vitamin D ? Is testing only serum 25-OHD enough for decision ?

Thresholds used for vitamin D deficiency differ in children and adults, but many physicians tend to interpret values below 20 ng/mL as deficiency.

In children, the laboratory 25OHD threshold for vitamin D deficiency is 12 ng/ml and 12-20 ng/ml for insufficiency. Serum 25OHD values above 20 ng/ml are accepted as vitamin D sufficiency (23) (table 1). However, in The Endocrine Society's 2011 guidelines, a 25OHD level below 20 ng/mL is defined as deficiency and a level between 20-30 ng/mL is defined as insufficiency (11). This recommendation has been leading physicians to administer high dose vitamin D treatment and it is outdated in relation to musculoskeletal effects of vitamin D. A similar recommendation exists in the guidelines of The Association of Adult Endocrinology and Metabolism in Turkey and administering "vitamin D stoss therapy" is recommended if the serum 25-OHD level is <20 ng/ml (25). Despite those recommendations, as it mentioned before, the IOM members consider that an intake of 400 IU/day of vitamin D is adequate in order to ensure a serum vitamin D level between 16 and 20 ng/ml (12). Additionally, in a CDC report analysing vitamin D status in the US, the threshold serum 25OHD level was taken as 12 ng/ml as a definition of vitamin D deficiency and it was determined that levels above 50 ng/ml are 'possibly harmful' (26). Furthermore, it is essential to confirm an elevation of serum ALP and/or PTH before administration of vitamin D in the treatment dose. Treatment dose is determined as a peroral single dose of 50.000 IU vitamin D for children aged 3-12 months, 150.000 IU for 12 months-12 years and 300.000 IU for >12 years in The European Society for Pediatric Endocrinology's Global Consensus Recommendations on Prevention and Management of Nutritional Rickets (23). As mentioned above, vitamin D stoss therapy (a single high dose vitamin D) or 2,000-6,000 IU/day vitamin D administration based only on serum vitamin D level is not advisable.

Seasonal variations of 25OHD level also should be taken into consideration while vitamin D status is being assessed. A seasonal decline in serum 25OHD levels has been well documented from summer to winter in two large scaled studies from different regions of Turkey as well (27,28).

What is the lifelong daily maintenance dose of vitamin D ? Is vitamin D supplementation needed during pregnancy?

Lifelong daily vitamin D requirements are regularly updated by the IOM in the United States. These updates include the amount that meets at least 97.5% of the target population (Recommended Dietary Allowance (RDA)) - and the maximum amount that can be taken per day without any risk (Upper Intake Level (UL)). The last update made in 2011 specified the RDA for vitamin D is 400 IU/day in the first year of life (UL is 1000 IU/day for infants >6 month-old, 1500 IU/day for infants 6 months -1 year) and 600 IU/day for individuals between 1 and 71 years (UL is 2500 IU/day for children between 1 and 3 years, 3000 IU/day for children between 4 and 8 years and 4000 IU/day for individuals >8 years) and 800 IU for individuals >71 years (7). Global consensus report has recommended that 400 IU of vitamin D be given orally to all infants until 1 year of age (23). The IOM's recommended dose for supplementing vitamin D in pregnancy is 600 IU/day (UL: 4000 IU). D-vitamin supplementation during pregnancy is primarily required for the prevention of late hypocalcemia in the new-born period. In countries where maternal vitamin D deficiency is common, such as our own, a dose of 1200 IU/day or more is recommended (29).

400 IU/day vitamin D for new-borns (from the first day of life) and 1200 IU/day vitamin D for women since third month of pregnancy and lactation is recommended through the national program for the prevention of vitamin D deficiency in Turkey (30, 31).

It is considered that supplementation of vitamin D in the form of oral drops until at least the first year of life, preferably up to 3 years, is sufficient.

Sunlight exposure, 30 minutes per week with only diaper and at least 2 hours per week when they are fully clothed is also substantial for babies after 6 months to have a vitamin D level at 11 ng/ml, however the duration of sunlight exposure that is necessary for infants and children to maintain vitamin D levels at 50 nmol/L (20 ng/mL) in children remains to be determined. In the meantime, it is necessary to keep in mind that sunscreens and glasses reduce the synthesis of vitamin D more than 90% (32, 33).

What are the main incorrect attitudes regarding use of vitamin D in children?

In Turkey, vitamin D deficiency rickets was a common problem in the first two years of life for many years. Those infants had signs such as delayed walking and teething. Because of this relationship, some families, pharmacists and sometimes physicians had a tendency to make toddlers drink vitamin D ampoules with the idea of "earlier walking" and "earlier teething".

However, supplementing a baby with higher doses of vitamin D than required has no effect on early walking and teething. Beyond that, it may result in permanent damage by causing "vitamin D intoxication" and calcium deposits in the kidneys.

Another misconception related to vitamin D is the administration of high dose D vitamin to children with bowed legs without thorough examination. Vitamin D deficiency rickets is a cause for bowed legs, but it is not the only reason. The aetiology of leg bowing includes physiologic bowing and genetic skeletal disorders. Thus, the children with bowed legs should not be randomly given high dose vitamin D, and these cases should definitely be examined by a pediatric endocrinologist.

Finally, some physicians in Turkey discontinue supplementing vitamin D in the first few months by indicating that their fontanelles were "small". This is another incorrect approach. Indeed, closure of the fontanelles is delayed in the case of vitamin D deficiency, but normal even high doses of vitamin D is not associated with early closure or smallness of the fontanelles.

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Table 1. Classification of vitamin D status, based on serum 25OHD levels (22)

Vitamin D status	Serum 25 OHD levels (nmol/L)
Sufficiency	>50 (20 ng/ml)
Insufficiency	30-50 (12-20 ng/ml)
Deficiency	<30 (12 ng/ml)
Recommended upper limit	250 (100 ng/ml)
Toxicity	>250 (100ng/ml) + hypercalcemia, hypercalciuria and suppressed PTH