

## REVIEW ARTICLE

## Vitamin D deficiency and prevention: Turkish experience

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**ABSTRACT**

A nationwide 'vitamin D prophylaxis augmentation programme' initiated in 2005 in Turkey reduced the prevalence of rickets from 6% in 1998 to 0.1% in 2008 in children under 3 years of age. The programme included free distribution of vitamin D drops to all newborns and infants (0–12 months) visiting primary health stations throughout the country. Free disposal of vitamin D to infants is an effective strategy for preventing vitamin D-deficient rickets.

**INTRODUCTION**

Vitamin D-deficient rickets was recognized as a disease of the growth plate in modern medicine in the late nineteenth and early twentieth centuries among city-dwelling poor children of industrialized countries. The discovery of the central role of vitamin D in the pathophysiology of rickets in 1920s led to the eradication of this disease in developed countries by means of routine vitamin D supplementation to infants and fortification of food such as milk by vitamin D. However, a century later, vitamin D-deficient rickets still seems to be an important public health problem in developing countries, as well as in immigrant and dark-skinned children living in developed countries (1,2). Recent systematic reviews demonstrated that in the last 20 years, rickets has been described from at least 59 countries (1,2). In Turkey, as a fast-changing transitional society, vitamin D-deficient rickets has kept its importance until recently as a common childhood disease and was causing significant morbidity because of pulmonary complications collectively termed as 'Rachitic Pneumopathy' (3).

25(OH) D is the major circulating form of vitamin D, and its levels are the best available indicator of total body

vitamin D status. Serum 25(OH)D levels reflect endogenously synthesized vitamin D and that obtained from the diet. Normal reference values depend on factors such as sunlight exposure, season, latitude, skin pigmentation, age, dietary vitamin D intake and the assay method used (4). There is still an ongoing discussion on the precise definition of vitamin D deficiency and insufficiency in infants. In determining the reference range for 25(OH) D levels, data that are considered include changes in Alkalene

**Key Notes**

- Vitamin D-deficient rickets 'once prevalent in Turkey' is now reduced greatly after a nationwide programme that included free distribution of vitamin D drops to all newborns and infants (0–12 months), visiting primary health stations throughout the country, by primary care doctors and nurses. Free disposal of vitamin D to infants is an effective way of preventing rickets in populations where rickets is prevalent and compliance with supplementation is poor.

Phosphatase (ALP), Parthormone (PTH), bone density and calcium absorption at varying concentrations of 25(OH) D, as well as evidence of rickets. Based on available 'although limited' data, Lawson Wilkins Pediatric Endocrine Society Drug and Therapeutics Committee defined 25(OH) vitamin D level 15–20 ng/mL as vitamin D insufficiency, <15 ng/mL as vitamin D deficiency and <5 ng/mL as severe vitamin D deficiency (5). Rickets or osteomalacia (in adults) is seen in deficiency/severe deficiency situations that have lasted long enough to cause significant bone resorption. Other individual factors that are important in the process of rickets are growth rate of the child, vitamin D receptor activity and PTH secreting capacity of the infant or child.

Global re-emergence of rickets in the last decade resulted in several consequences: increasing number of rickets cases in USA and other industrialized countries led to re-assessment of existing vitamin D recommendation policies for infants (6,7). The importance of vitamin D in adults, especially in women of childbearing age and breastfeeding mothers is now better understood, and the concepts of 'sub-clinical vitamin D deficiency' and 'extraskelatal effects of vitamin D' have become popular areas of research and discussion (8). Studies in vitamin D receptor null mice expanded the current knowledge on skeletal and extraskelatal effects of vitamin D (9).

Vitamin D-deficient rickets has been a common childhood disease in Turkey for decades. There are numerous papers published regarding different aspects of rickets in Turkish children (3,10–20). A study from Eastern Turkey in 1998 reported that 6% of 8631 children under age three had rickets (12). In the recent years, efforts were focused on prevention of rickets. In 2005, vitamin D study group was formed in the Turkish Pediatric Endocrine Society which developed strategies for prevention of rickets and established collaboration with Ministry of Health. As a result of these joint efforts, a nationwide 'vitamin D prophylaxis augmentation programme' was initiated in 2005 with a simple but effective way which included free distribution of vitamin D drops to all newborns and infants (0–12 months) visiting primary health stations throughout the country (21). This was continued until the baby reached 12 months of age. In this article, we summarize our experience regarding vitamin D deficiency/rickets and prevention of vitamin D deficiency in children and mothers, and the effect of above-mentioned vitamin D prophylaxis programme in the light of studies conducted in Turkey.

#### **PROBLEM OF MATERNAL VITAMIN D DEFICIENCY AND ITS EFFECT ON RICKETS IN INFANCY**

It has long been known that vitamin D deficiency is prevalent in women of childbearing age in Turkey. 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 (22–26). Average dietary vitamin D intake of these women was below the Recommended dietary allowance (RDA) (185 IU ± 117/day) (22). Low socioeconomic status,

covered clothing style and low educational level were factors associated with maternal vitamin D deficiency. Bone mineral density revealed osteopenia in 40% of the women with a low vitamin D level (23). All women with osteopenia were from low socioeconomic class and 80% of them had covered dressing style emphasizing the importance of exposure to sunshine for endogenous vitamin D production. Study of 48 premenopausal women showed that serum 25(OH) D levels changed significantly according to type of dressing (25) i.e. those with strict religious dressing had vitamin D levels sixfold and twofolds lower than that of women with Western type of dressing and less strict covered clothing, respectively. Besides clothing style, these women spent less time outdoors because of cultural and lifestyle factors, which contributed to developing vitamin D deficiency.

Babies born to women with vitamin D deficiency have insufficient vitamin D stores and receive less dietary vitamin D because of lower vitamin D levels in the breast milk of the mother. It has been shown that the most important risk factor for low serum 25(OH) D level in the newborn was the maternal level of 25(OH)D lower than 10 ng/mL (OR = 15.2,  $p = 0.002$ ) (23). A recent study showed that vitamin D level is <10 ng/mL in 27% of pregnant sera and 64% of cord blood (26). For these reasons, babies born to vitamin D-deficient women are prone to developing neonatal hypocalcemia/congenital/early rickets, unless vitamin D supplementation is initiated early. Furthermore, in maternal vitamin D deficiency state, supplementation of infant with traditional dose of vitamin D (400 IU/day) may be insufficient to prevent hypocalcemia/rickets. In the light of the above-mentioned observations, vitamin D supplementation in infants should be started early (in the first week of life) and not after 2 weeks of life as it was a common practice in Turkey and other countries for years. In addition, vitamin D supplementation to all pregnant women is of prime importance to prevent both the mother and the offspring from deleterious effects of vitamin D deficiency.

In addition to hypocalcemia, vitamin D deficiency in the neonate or young infant is characterized by low 25(OH) D levels in both infant and mother and it differs from rickets seen in older children by several features; they mostly present with hypocalcemic seizures, their phosphorus level is usually normal or elevated, their PTH and alkaline phosphatase levels can be normal, and radiographic features of rickets are absent (3,13). All of these features in neonatal vitamin D deficiency might lead to misdiagnosis of late-onset neonatal tetany or hypoparathyroidism. In a recent study, Hatun et al. (13) reviewed 42 early infantile rickets cases (age  $60 \pm 19$  days, range 32–112 days). The majority of the cases were exclusively breastfed. Seventy-eight per cent of them presented to the hospital with hypocalcemic seizure, but their serum phosphorus levels were normal in 35% and elevated in 45%, which suggests that they had relative inability to progress from stage I rickets to stage II rickets, i.e. a relative inability to compensate hypocalcemia with bone resorption because of insufficient PTH secretion and/or effect.

**Table 1** Prevalence of rickets under age 3 before and after 'vitamin D prophylaxis augmentation programme' in Erzurum, Turkey

Year	Prevalence of rickets under age 3 (%)	Number of screened children	References
1998	6.1	8631	(12)
2008	0.1	39 133	(29)

Some years ago, hypocalcaemia in infants was precipitated by the high phosphate intake from unmodified cows' milk. Now that more babies are breastfed and infant formulas have low concentrations of phosphate, this cause has almost disappeared and late-onset hypocalcaemia is more likely to indicate poor antenatal vitamin D status than an improper postnatal diet. We suggest that 25(OH) vitamin D level in infant and the mother should be a routine part of evaluation of neonatal hypocalcemia.

#### PREVALENCE OF RICKETS AND THE EFFECT OF VITAMIN D SUPPLEMENTATION AUGMENTATION PROGRAMME IN TURKEY

The prevalence of rickets in 0–3 years children in different parts of Turkey varied between 1.67% and 19.0% in the last 40 years depending on the definition criteria for rickets (3,10–20). Largest among those is the study from Erzurum where 6% of children aged 0–3 years had rickets in 1998 (12). Another recent study in Ankara performed in 2002–2003 reported a prevalence of 6.8% (3). Common finding of all these studies was that children with rickets had inadequate vitamin D intake and had not received vitamin D supplementation. A study investigating the aetiology of rickets in the Middle East identified risk factors for rickets in Turkey as low socioeconomic status, maternal factors and insufficient vitamin D intake, whereas inadequate calcium intake was the major factor responsible for rickets in Egypt (10). In the aforementioned study, only 10% of the rachitic infants from Turkey had received vitamin D prophylaxis, whereas this ratio was 100% in nonrachitic control infants from Turkey (10). These studies demonstrated the scope of the problem and a need for a more effective strategy for prevention of rickets in Turkey. In fact, recommendation of 400 IU/day of vitamin D to all infants starting from 15th day of life until the first birthday of the infant has been a routine practice in Turkish medical system as well as an important chapter in curriculum of medical students and paediatric residents for at least 40 years. However, the widespreadness of rickets among infants in Turkey has pointed to the pitfalls of this strategy. A recent survey among primary care doctors demonstrated that only 85% of paediatricians and 54% of general practitioners recommended vitamin D in the first month of life (27). More importantly, despite this recommendation and written prescription for vitamin D, compliance with this recommendation and maintenance of vitamin D supplementation until 12 months of age is obviously not kept by the majority of the parents.

In 2003, a number of paediatric endocrinologists established the 'vitamin D study group' within the Turkish Paediatric Endocrine Society, to promote research and develop strategies for prevention of rickets in the country. A consensus document was issued on vitamin D deficiency and its prevention in Turkey (28). The Turkish Medical Association facilitated its dissemination to all primary care providers. The consensus document defined two specific goals: (i) attain adequate vitamin D status for the whole population, particularly high-risk groups such as infants, children, adolescents, pregnant and nursing women and (ii) ensure early diagnosis and adequate treatment of rickets and osteomalacia. Proposed public health strategies to achieve these goals were (i) develop a public awareness campaign to establish adequate sunlight exposure, (ii) provide all infants with 400 IU/day of vitamin D supplementation starting at birth, (iii) educate primary care providers in the diagnosis and treatment of nutritional rickets and osteomalacia, (iv) provide vitamin D supplementation to adolescent girls and women at risk and (v) advocate for regulations of mandating vitamin D enrichment of all dairy products. In 2004, the committee appealed to the Ministry of Health of Turkey to assume a leadership role in realising these strategies. In May 2005, the Ministry of Health initiated a 5-year project coordinated by the General Directorate of Maternal Child Health and Family Planning. This project implemented all the proposed strategies. A nationwide campaign of 'vitamin D prophylaxis augmentation programme' was initiated. A curriculum was developed to train healthcare workers. General practitioners who work in the primary care centres were given education on the aims and practices of the programme by local workshops and meetings organized by the Ministry of Health. The most important step of the campaign was the distribution of vitamin D supplements (containing 400 IU in three drops) to every newborn throughout infancy at no financial cost to families by the Ministry of Health through its network of primary care units and maternal-child health centres. As of 2010, a total of 9.194.320 bottles of vitamin D were distributed in 6 years to babies. In addition to this, maintenance of vitamin D until 12 months of age is strictly promoted and questioned in all visits of babies in the health stations for any reason (routine well baby checkups, vaccinations, etc.) by the healthcare workers. This strategy undoubtedly improved access to vitamin D supplementation and compliance. The effectiveness of the programme has been tested by a large study performed also in Erzurum demonstrated that the prevalence rates were decreased from 6.0% in 1998 to 0.1% in 2008 after the vitamin D prophylaxis augmentation campaign (29) (Table 1). Another study performed in 2010 in infants showed that 85% of babies now have sufficient vitamin D levels (>20 ng/mL) (G Yeşiltepe Mutlu, Y Kuşdal, E Özsu, F Çizmeçioğlu, Ş Hatun, unpublished data). However, 27% of 2- to 6-month-old infants and 8% of 6- to 12-month-old infants still have vitamin D insufficiency biochemically (<15 ng/mL) despite receiving vitamin D prophylaxis 400 IU/day (30). These results show that vitamin D prophylaxis augmentation programme has diminished clinical

rickets cases and severe vitamin D deficiencies dramatically in Turkey, but there are still some babies with insufficient vitamin D levels. It is possible that in some infants, a higher dose of vitamin D may be needed because of individual factors [Vitamin D receptor (VDR) polymorphisms? etc.] or alternatively effectiveness of the programme may be suboptimal for certain regions or families and needs further augmentation. A larger nationwide study is now planned to investigate these issues. Nevertheless, the success of this programme is evident as some of our colleagues from medical schools state that 'they cannot find a single case of rickets for teaching purposes anymore'.

Another effective strategy for prevention of vitamin D deficiency could have been fortification of commonly used food products with vitamin D. This strategy is used commonly in the industrialized countries. However, dairy products and cereals are not the main food for 0–1-year-old infants in Turkey which are the most vulnerable population for rickets. Most infants in Turkey are breastfed exclusively up to 4–6 months and continue to receive breast milk during and after the weaning period. Cows' milk is introduced usually after 12 months of age, and processed cereals are not used widely as an infant food in Turkey (most common weaning foods are home-made vegetable and whole grain soups with or without added ground meat and purees made of fresh fruit and home-made plain yogurt). Thus, fortification of food products can be more effective in older age groups but will be less effective in 0–1-year infants in our population. With regard to the cost of this programme to the healthcare system of Turkey, one bottle of vitamin D drop costs 1.26 Turkish Liras (0.78 USD) and contains 50.000 U of vitamin D which provides approximately 4 months of supplementation for an infant. Cost of 1-year supplementation (three bottles of vitamin D) for an infant is 2.5 USD, which is not a high price.

We have chosen daily oral prophylaxis in this programme. It could have been done by single or divided doses of stoss therapy as well, but stoss therapy carries a risk for hypervitaminosis D in some infants (15), and several papers from Turkey demonstrated that iatrogenic hypervitaminosis D is relatively common in Turkey because of misuses of stoss therapy (31–33).

#### **PROBLEM OF HYPERVITAMINOSIS D**

Ironically, hypervitaminosis D is also seen frequently in Turkey. The major reason for hypervitaminosis D is the unnecessary use of high doses of vitamin D. There are two types of vitamin D preparations available in pharmacies in Turkey (a drop form that contains 150 U of vitamin D in one drop and the vial form that contains 300.000 U/mL). Both preparations could be obtained from pharmacies without any prescription. This unnecessary self-use of high-dose (vial form) vitamin D in babies with teething delay and walking delay seems to be the major reason for hypervitaminosis D in Turkey. In a series investigating 27 cases of hypervitaminosis D in 2003–2008 reported leading

symptoms as vomiting (86%), anorexia (57%), weight loss (47%), dehydration (43%), polyuria/polydipsia (38%) and constipation (33%) (31). In the follow-up, 26% of them developed nephrocalcinosis. Oral bisphosphonate has been effectively used in the treatment of hypervitaminosis D in children (32,33).

#### **RECOMMENDATIONS FOR THE FUTURE**

Although vitamin D deficiency is a problem related to all ages, providing free vitamin D to all infants by 'vitamin D prophylaxis augmentation programme' has been an important step towards the solution of this problem in the most vulnerable group. Based on experiences gathered in the initial programme, the next step would be the inclusion of the pregnant and lactating women into this programme considering the widespreadness of vitamin D deficiency in women of childbearing age. Ultimately targeting the whole society, awareness regarding the importance of adequate vitamin D intake will be strengthened and bone health of pregnant women and foetuses will be promoted. The Bone Health Study Group and the Ministry of Health officials have already discussed the details of the upcoming programme for pregnant women. Similar to the infant programme, vitamin D (1200 IU/day) will freely be available to all pregnant women visiting primary healthcare stations throughout the country for routine pregnancy follow-up examinations.

Experience in Turkey obtained from this programme demonstrates that a strategy based on free disposal of vitamin D to infants and perhaps other targeted groups throughout the country by primary care physicians can be effective in the eradication of vitamin D deficiency and related disorders. We hope that this programme can be a model for populations in which vitamin D deficiency is a significant public and child health problem.

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#### **CONFLICT OF INTEREST**

None.

#### **AUTHORS CONTRIBUTION**

All authors listed above had substantial contributions to conception, design and performance of the 'Vitamin D prophylaxis augmentation programme'. All authors had contributed writing and revising of the manuscript and its intellectual content equally and should be regarded as first

authors. The authors approve the final version of the article to be submitted and published, if accepted.

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