Editorial

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Vitamin D in health and disease: the global threat of vitamin D deficient rickets

DOI 10.1515/jpem-2016-0054

Introduction

Nowadays, infectious diseases are less prevalent in many countries around the world and chronic diseases including obesity, diabetes, behavioral problems and nutritional deficiencies are thought to have become the major and eminent health burdens in both the adult and the young population. Among these, vitamin D deficiency poses a major health problem in children and adolescents globally. In fact, even in countries with high sun and specifically high ultraviolet B (UVB) exposure such as Brasil and Australia vitamin D deficiency rickets has become very prevalent. In Australia this has been attributed to the use of sun protecting ointments and changes in life styles that lead to lesser sun exposure especially in children and young people [1]. In populations with dark skin living, for example, in Africa or the Middle East, the prevalence of vitamin D insufficiency with 25-hydroxyvitamin D (25(OH)D) levels ranging between 15 and 20 ng/mL (37.5–50 nmol/L) ranges from 5% to 80%. Risk factors to develop nutritional rickets include traditional dress and avoidance of sunlight exposure, and also multiple dietary factors as a result of specific cultural beliefs in many of the affected countries as nutritional rickets may also be caused by inadequate dietary intake of calcium when, for example, milk and milk products are consumed less or are not available [2]. As a result of vitamin D and/or calcium deficiency severe bone disease, stunted growth and even the emergence of autoimmune disease and alterations of the immune system are being observed in many populations.

Prevention of vitamin D deficiency

Key to the prevention of rickets is ensuring that pregnant women and their infants receive vitamin D supplementation: in the Netherlands the prevalence of vitamin D deficiency at mid gestation was 26%, while in neonates it amounted to 46%. Twenty-one per cent of the mother-infant pairs in the generation R study had persistent vitamin D deficiency (i.e. deficient in maternal and cord samples) and an additional 29% were vitamin D deficient in one of the two samples, either in the mother or the child, only [3]. In this study, persistent vitamin D deficiency was strongly associated with non-European ancestry and spring birth. It is important to note that prevention of vitamin D deficiency can be achieved very easily early in life: for example, infants who receive 400 IU daily can achieve levels of 25-hydroxyvitamin D of >50 nmol/L [2, 4]. However, public health implementation of daily supplementation is more challenging with a need to revisit food fortification strategies to ensure optimal vitamin D status of the population. In addition, it has been proposed that vitamin D supplements given to pregnant women and nursing mothers may be more effective than feeding vitamin D-fortified formula to infants. Healthy life styles ensuring adequate sun exposure are yet another measure to increase vitamin D serum concentrations in whole populations. In this respect, seasonal variations of sun light and hence of sun exposure to the skin are of particular interest in areas in the north and the very south of our globe.

Treatment of vitamin D deficiency

Treatment of nutritional rickets has traditionally been with vitamin D2 or D3. These are often given as a daily oral dose for several weeks until biochemical and radiological evidence of healing has been evidenced. However, other treatment options, for example, applying single or intermittent high doses have also been shown to be effective. It is now recognized that oral calcium either as a dietary supplement or as a natural constituent of foods is also of utmost importance in both preventing, treating and healing nutritional rickets. A recent consensus document on the prevention and management of nutritional rickets has been developed and made available just very recently [4].

Diagnosis and screening strategies for vitamin D deficiency

However, in day-to-day practice, diagnosis and screening strategies for vitamin D deficiency vary greatly. For example, in a study in Melbourne, Victoria, Australia, the 25(OH)D testing patterns and frequency were tested among general practitioners in a major community health service addressing patients aged 18 years and above [5]. Surprisingly, vitamin D testing was strongly related to socio-demographics: The odds of vitamin D testing showed a positive association with age (OR 1.01, 95% CI: 1.00–1.02, $p<0.05$), higher frequency among females compared to males (OR 1.42, 95% CI: 1.18–1.70, $p<0.05$) and more frequent in migrants than non-migrants (OR 2.57, 95% CI: 2.14–3.09, $p<0.05$). Hence, in the adult population, advancing age, being female and being a migrant were associated with an increased likelihood of vitamin D testing [5]. The authors conclude that the development of evidence-based policies and guidelines are needed to manage over-testing of vitamin D in Australia. Studies that include health services from different areas are required to understand vitamin D testing patterns in the medical communities in different countries in all regions.

Current findings on vitamin D deficiency in this issue

In this issue of our journal, a potential effect of 6 months short-term vitamin D supplementation in children with type 1 diabetes is reported [6]. The article by Mishra et al. indicates that indeed vitamin D could play a protective role in autoimmune processes as well as in beta cell survival. Low serum sklerostin levels are present in newborns with vitamin D deficiency. As sklerostin is thought to be one of the many markers of bone turnover, this finding indicates that bone health is impaired in vitamin D deficient states even at a very young age [7]. Antiviral therapy in children infected with HIV might also lead to vitamin D and or calcium deficiency. Aurbipul and co-workers argue that supplementation of both vitamin D and calcium might ameliorate the development or progression of vitamin D and/or calcium deficiency in this patient group [8]. In a letter to our journal Daval rightly points out that there is still a scarcity of data in respect to the efficacy and efficiency of different doses of vitamin D supplementation in children under the conditions of the Indian subcontinent [9]. In another article, Kuchay et al. show that a single monthly dose of cholecalciferol (60,000 IU) may be a safe and cost-effective means to attain and maintain vitamin D sufficiency [10]. Lastly, a study from Denmark, suggests that sufficient vitamin D availability might not only secure good bone health but also to prevent development of type 1 diabetes in Danish boys. This study with a population of 331,623 individuals born in Denmark in the 1980s suggests that early exposure to sunshine and hence to UV light is related to a lower risk to develop diabetes later in life [11].

Scientific dilemma

Very often, appropriate vitamin D reference values for a given population, age and gender are still not available and/or are based upon old assay techniques that may or may not be applicable any more. But even the currently available assays for the determination of 25(OH)D demonstrate a relatively high inter-assay coefficient of variation of approximately 20% as shown in external quality control trials. Whether or not free vitamin D is more meaningful than total vitamin D measurements is also not clear. The importance and clinical relevance of the vitamin D binding protein has not been elucidated so far [12]. It is clear that ethnic differences and genetic differences determine vitamin D binding protein levels and therefore most likely the availability of free vitamin D to tissues [13].

Clinical dilemma

While it is clear that vitamin D sufficiency should be achieved especially in pregnant women, neonates and young infants, many questions still remain as to the diagnosis, prevention, and treatment of nutritional rickets. What are the public health measures that should be undertaken? What are the barriers that prevent affected populations from applying such programs? How do cultural beliefs change over time and hence influence public health measures to reduce vitamin D and/or calcium deficiency? Should there be routine vitamin D testing and screening for vitamin D/calcium deficiency rickets? If yes, at what age and which populations at risk should be tested?

Conclusions

In this issue of our journal we have collected a number of articles related to several aspects of childhood vitamin D deficiency and sufficiency to highlight the importance

of this vitamin for children's health and also to show that pediatric endocrinology has a lot to offer for public health interventions and global wellbeing of the young generations.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
Research funding: None declared.
Employment or leadership: None declared.
Honorarium: None declared.
Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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