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Effects of low vitamin D status in rickets and type 1 diabetes in children

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Abstract

Purpose – This paper aims to review the metabolism, epidemiology and treatment of vitamin D and calcium insufficiency as well as its relation to rickets and diabetes type 1 during childhood and adolescence.

Design/methodology/approach – The most up-to-date and pertinent studies within the literature are included in this narrative review.

Findings – Vitamin D deficiency is common in developing countries and exists in both childhood and adult life. The great importance of vitamin D is the moderation of calcium (Ca) and phosphorus (P) homeostasis as well as the absorption of Ca. While insufficiency of vitamin D is a significant contributing factor to the risk of rickets in childhood, it is possible that a more marginal deficiency of vitamin D during life span contributes to osteoporosis as well as potentially to the development of various other chronic diseases such as diabetes type 1.

Originality/value – This paper gives a concise, up-to-date overview to nutritionists and dietitians on how vitamin D deficiency may effect rickets and type 1 diabetes.

Keywords Vitamins, Diabetes, Children (age groups), Personal health

Paper type General review

1. Introduction

1.1 Vitamin D metabolism

Vitamin D has two different forms: vitamin D2 which exists in food (plants) and D3 (cholecalciferol) which is produced by the following path: 7-dehydrocholesterol → previtamin D → vitamin D3 in the skin upon ultraviolet B (UVB) sun exposure and at skin temperature. The process of generating vitamin D3 from sun exposure is attenuated by reduced exposure of the skin to sunlight (northern latitudes with decreased direct sun exposure, air pollution, confinement indoors, clothes covering all the skin, broad use of sunscreens, increased skin pigmentation) or in dermatologic conditions such as ichthiosis in which sun inadequately penetrates the epidermis (Thacher *et al.*, 2004). The two vitamin D molecules differ in structure; vitamin D2 has an extra double bond between carbons 22 and 23 and an additional 24-methyl group in comparison to vitamin D3 having been demonstrated to be two to three times more effective than vitamin D2 (Trang *et al.*, 1998; Armas *et al.*, 2004; Houghton and Vieth, 2006). Both forms of the vitamin D diffuse into the circulation and are transported protein-bound to the liver where they are hydroxylated to 25(OH) D3 (calcitriol) and 25(OH) D2. Serum or plasma 25(OH) D3 is the most commonly used and appropriate biochemical marker of vitamin D status (Institute of Medicine, 1997; Fitzpatrick *et al.*, 2000). In the kidney, 25(OH)D3 undergoes a further hydroxylation at the first carbon, catalysed by 1,2-hydroxylase, to form 1,25(OH)2D3 which is the most biologically active form of vitamin D (Fitzpatrick *et al.*, 2000). Although 1,25(OH)2D3 represents the active form of the vitamin, due to a tight regulation of its production as well as a relatively short

Nutrition & Food Science
Vol. 40 No. 5, 2010
pp. 447-455

0034-6659
DOI 10.1108/00346651011076956

half-life (4-6 h), it is not a good indicator of vitamin D status (Institute of Medicine, 1997; Fitzpatrick *et al.*, 2000; Holick, 2003). Serum 25(OH) D3 concentrations is the best indicator of determining adequacy because it represents the combined amounts of vitamin D synthesized in the skin and dietary sources (Haddad and Hahn, 1973). Serum 25(OH) D3 levels are the accepted measure of vitamin D nutritional status (Dietary Reference Intakes, 1997).

2. Prevalence of vitamin D deficiency

In the USA, cases of nutritional rickets have been reported from at least 17 states, with 166 cases reported in the medical literature between 1986 and 2003 (Weisberg *et al.*, 2004). Relatively high rates of subclinical vitamin D deficiencies have been reported in otherwise healthy infants (Gessner *et al.*, 2003; Ziegler *et al.*, 2006; Lee *et al.*, 2007; Gordon *et al.*, 2008), children (Sullivan *et al.*, 2005; Rajakumar *et al.*, 2005) and adolescents (Looker *et al.*, 2002; Gordon *et al.*, 2004) in several American states. A high prevalence of vitamin D deficiency has also been reported in infants, children and adolescents from diverse countries around the world, including the UK (Lawson and Thomas, 1999), France (Guillemant *et al.*, 2001), Greece (Nicolaidou *et al.*, 2006), Lebanon (El-Hajj Fulcihan *et al.*, 2001), Turkey (Pehlivan *et al.*, 2003), China (Du *et al.*, 2001), Finland (Lehtonen *et al.*, 1999; Outila *et al.*, 2001), Canada (Ward *et al.*, 2007; Newhook *et al.*, 2009) and Qatar (Bener *et al.*, 2009). In the research that took place in China, 18 per cent of a total of 42 healthy infants were found with rickets and the fact that not all infants with rickets in this study had low 25(OH)D concentrations suggests two possibilities:

(1) not all rickets are necessarily related to a vitamin D deficiency; or

(2) serum 25(OH)D concentrations is not the best indicator of vitamin D status (Ho *et al.*, 1985).

Among adolescents, reported prevalence rates of vitamin D deficiency have ranged from 0 to 42 per cent, with variation noted secondary to season, latitude and participant race/ethnicity (Tylavsky *et al.*, 2005). Data from national surveys in the UK, the USA and New Zealand show that the prevalence of low vitamin D status is less of a concern for children than for adolescents (Dawson-Hughes *et al.*, 1991; Gregory *et al.*, 2000; Rockell *et al.*, 2005). There are also some suggestion that intakes of vitamin D may be worse in females than in males. For example, Moore *et al.* reported that adolescent males in the USA were the group most likely to consume the adequate intake value for vitamin D, while adolescent females were about half as likely as males of corresponding age to meet their dietary reference intakes (Moore *et al.*, 2004). In addition, Bener *et al.* (2009) recently found a very high incidence of vitamin D deficiency in the young population in Qatar, especially in girls. This deficiency is attributed by the authors as a result from a combination of a limitation in sunlight exposure and a low oral intake of vitamin D. Also, children with renal failure are at risk for vitamin D deficiency. Recently, Ali *et al.* (2009) studied the prevalence in children with vitamin D deficiency over a period of ten years and he found rates from 20 to 75 per cent.

2.1 Rickets

Rickets was a very common disease during the industrialization and had a prevalence of 40-60 per cent in children living in northern Europe (Thacher *et al.*, 2006). Rickets was cured after people were informed about the value of vitamin D in bone conformation and the adequate exposure to sunlight as a prohibitive and therapeutic method. Cod liver oil and fortification of infant formula also helped on this direction.

The problem began to reappear in 1960, especially among breastfed infants and in those infants whose mothers' dress included covering (Chesney, 2002). Over the past 20-30 years, there has been a reemergence of rickets with reports in the UK (Belton, 1986; Pal and Shaw, 2001; Ashraf and Mughal, 2002), Europe (Dagnelie *et al.*, 1990; Bonet *et al.*, 2002; Lopez *et al.*, 2002), North America (Feldman *et al.*, 1990) and Saudi Arabia (Al-Atawi *et al.*, 2009) in a variety of ethnic groups. The resurgence of rickets in North America in the 1990s coincided with skin cancer prevention campaigns (American Academy of Pediatrics, 1999). Other possible reasons for the increasing prevalence of rickets include: breastfeeding without vitamin D supplementation, vegetarian diets (Carvalho *et al.*, 2001), darker-skinned people migrating to countries with less sunlight (Wilton, 1995; Shaw and Pal, 2002; Lopez *et al.*, 2002) and increasing atmospheric pollution (Agarwal *et al.*, 2002).Typically, rickets associated primarily with vitamin D deficiency is presented during the first year of life.

2.2 Vitamin D status and type 1 diabetes mellitus

Type 1 diabetes mellitus (T1DM) is among the most prevalent chronic diseases with onset in childhood, being the second most common chronic disease in children after asthma in the USA. It results from an immune-mediated destruction of pancreatic insulin-producing β-cells, with both genetic and environmental factors playing roles in the aetiology. It is linked about 60 per cent to genes in the human leukocyte antigen (HLA) complex of the major histocompatibility complex (MHC) on chromosome 6p21 (Harris, 2005; Sloka *et al.*, 2008). Non-MHC chromosomal regions are also involved, particularly the regulatory region of the insulin gene and the interleukin-1 receptor type 1 gene. The specific factors that initiate the autoimmune process are not yet well understood, but β-cell destruction often begins during infancy and continues over many months or years (Zipitis and Akobeng, 2008). By the time T1DM is diagnosed, about 80 per cent of the β cells have been destroyed. There is a marked geographic variation in incidence, with a child in Finland being about 400 times more likely than a child in Venezuela to acquire the disease (Zipitis and Akobeng, 2008). The pattern follows a latitudinal gradient that is the inverse of the global distribution of UVB irradiance. It is estimated that currently the incidence is increasing by 3 per cent per year. Furthermore, it is predicted that by 2010 the incidence of T1DM will be 40 per cent higher than it was a decade earlier (Zipitis and Akobeng, 2008).

One of the environmental factors thought to be protective against the development of T1DM is early supplementation with vitamin D. Vitamin D is either produced endogenously, through skin exposure to sunlight or exogenously from ingestion of foods and supplements (Harris, 2005; Zipitis and Akobeng, 2008). T1DM incidence rates are higher in regions that are more distant from the equator, where UVB irradiance is lower, than in those closer to the equator, where UVB irradiance is much higher. Although the importance of vitamin D for preventing rickets and adult bone disease is well established, it is becoming increasingly clear that vitamin D appears to be an immunosuppressive agent, a role that may explain its protective association with autoimmune conditions, including multiple sclerosis and rheumatoid arthritis. Strong evidence of a vitamin D effect on T1DM risk comes from experiments in the non-obese diabetic (NOD) mouse. The NOD mouse experiences disease pathogenesis similar to the human, including autoimmune destruction of β-cells. When 1,25-dihydroxyvitamin D($1,25(OH)_2D$), the active form of the vitamin, was administered to NOD mice in pharmacologic doses, it prevented the development of diabetes. More recently, NOD mice raised in a vitamin D-deficient state were shown to develop diabetes at an earlier age than non-deficient NOD controls (Harris, 2005; Zipitis and Akobeng, 2008; Badenhoop,

2008). The dependence of normal insulin secretion in pancreatic β-cells on vitamin D has been known for several decades. A reduction in vitamin D activity can result in both increased insulin resistance and reduced insulin secretion. Epidemiological data have shown a four- to five-fold higher prevalence of non-insulin-dependent diabetes in dark-skinned Asian immigrants in comparison to British Caucasians, indicating that low vitamin D status may contribute to the pathogenesis of diabetes (Zittermann, 2003).

A recent review including studies from many European countries, particularly the EURODIAB (Mohr *et al.*, 2008), and the Finnish study (Hypponen *et al.*, 2001), concluded that there is evidence from observational studies that vitamin D supplementation in infancy might be protective against the development of T1DM. The EURODIAB study found that children whose mothers consumed vitamin D supplements during pregnancy had a lower risk of type 1 diabetes than those whose mothers did not, and indicated that children being supplemented had a 29 per cent reduction in risk of developing type 1 diabetes compared to their peers who were not being supplemented. The favourable association with vitamin D persisted after adjustment for birthweight, duration of breast feeding, maternal age and study centre (Mohr *et al.*, 2008). A Norwegian study done by Stene *et al.* (2003) looked at the effect of the time of starting supplementation with vitamin D. It appears that those who had cod liver oil, an important source of both vitamin D and the long-chain n-3 fatty acids docosahexaenoic acid and eicosapentaenoic acid in the Norwegian population between 7 and 12 months of age had lower chances of developing T1DM in later life compared to those who were supplemented between zero and six months of age. More recently, significant vitamin D deficiency was found in more than 75 per cent of 128 children with type 1 diabetes (Svoren *et al.*, 2009). Epidemiological studies describing a north-south gradient in incidence rate and an inverse correlation between incidence and mean monthly sunshine hours are also hinting at a possible protective effect of vitamin D (Zittermann, 2003; Mohr *et al.*, 2008). In conclusion, the evidence shows that the vitamin D system plays an important role in T1DM. By interfering with environmental factors, such as sun exposure and subsequent vitamin D levels, there may be an opportunity to prevent some of the cases of T1DM. So, the provision of adequate levels of vitamin D is an important goal for public health (Badenhoop, 2008). Considering the rapid increase in type 1 diabetes incidence among 0-5 year olds and early appearance of islet autoimmunity (IA), maternal intake of certain dietary nutrients during pregnancy including vitamin D through food, may provide sufficient in utero exposure to these nutrients, offering early protection from or promotion of IA in infancy or early childhood (Froncza *et al.*, 2003; Brekke and Ludvigsson, 2007; Mohr *et al.*, 2008).

3. Treatment

Rickets can be treated effectively with vitamin D supplementation. In relation to addressing subclinical vitamin D deficiency and insufficiency, sun exposure and dietary vitamin D intake (including vitamin D fortified foods and supplemental vitamin D use) undoubtedly have important roles. However, the relative importance of these two routes of exposure differs from summer to winter for most people.

If sun exposure is sufficient, very little if any vitamin D is required from the diet during summer (Department of Health, 1998). It is worth remembering, however, that the production of vitamin D in the skin during summer varies with the geographical location, atmospheric conditions, time spent outdoors, clothing and skin pigmentation (Holick, 1995) as well as sunscreen use. According to Holick (1994) approximately 30 min of skin exposure (without sunscreen) of the arms and face to sunlight can provide all the daily

vitamin D needs of the body. When sunlight exposure is limited, dietary intakes of vitamin D, if sufficient, can make a significant contribution to vitamin D status. In particular, at latitudes above 37°N, production of vitamin D3 in winter is virtually zero, because the zenith angle of the sunlight increases in the autumn and winter, and consequently the amount of solar ultraviolet radiation that reaches the Earth's surface is substantially reduced. Therefore, there is an increased reliance on dietary vitamin D for maintaining adequate vitamin D status during winter, and even in summer for those who avidly avoid sunshine exposure. While the US authorities recommend 5 mg vitamin D/day for children and adolescents (aged 1-18 years) (Institute of Medicine, 1997), respectively, in the UK children aged 1-3 years are recommended 7 mg vitamin D/day while there is no dietary recommendation for vitamin D for subjects aged 4-64 years (Department of Health, 1998). This lack of dietary recommendation is on the basis that it is assumed that skin synthesis of vitamin D will generally ensure adequacy which depends on regular exposure to summer sunlight (Department of Health, 1998). If individuals have restricted sunlight exposure, then 10 mg/day is recommended. However, vitamin D is rather sparsely represented in the diet, which might explain the low intakes in children and adolescents during winter, as mentioned earlier. Oily fish such as salmon, mackerel and sardines contain high amounts of vitamin D. Cod liver oil is also an excellent source of vitamin D. Some meats may contain 25(OH) D3. Fortified foods can also be a major contributor to dietary vitamin D2. Vitamin D-fortified foods include some types of margarines, breakfast cereals, infant formulae, fruit juices, chocolates and milks, to name but a few. Use of vitamin D-containing supplements can also make a major contribution to mean daily intake of vitamin D in both adults and children.

While rickets can be prevented with far smaller doses, a level needed to prevent diabetes would require intake, by children aged $\geq$1 year, of approximately 25-50 μg (1,000-2,000 IU)/day of vitamin D3, an intake associated with major reduction in incidence in Norway. Such intake has no known adverse health effects in adults. Children aged $\geq$1 year and who are outdoors in sunlight for a few minutes each day may achieve similar serum levels with smaller oral intake. Pending further research, oral vitamin D intake of infants <1 year old should not exceed 6.25 μg (250 IU)/day. Physicians and nutritionists should advise parents that children $\geq$1 year who live more than approximately 30° from the equator should consume 25-50 μg (1,000-2,000 IU)/day of vitamin D3, especially during winter, to substantially reduce their risk of childhood type 1 diabetes.

4. Conclusions

There is enough evidence that severe deficiency of vitamin D may lead to skeletal and non-skeletal diseases. Both children and adolescents seem to be in high risk of low vitamin D status especially during winter. Increasing foods high in calcium and vitamin D in diet as well as oral supplementation with vitamin D may be necessary for children and adolescents not only in the absence of sun exposure in winter time but also in preventing other diseases such as diabetes type 1. Further research is needed in order to identify the optimal dietary recommendation needed begging from pregnancy in order to prevent vitamin D deficiency.

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