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REVIEW ARTICLE

VITAMIN D DEFICIENCY: AN ICEBERG DISEASE

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ABSTRACT

Vitamin D is thought to be important for maintaining normal function of many non skeletal tissues such as muscle (including heart muscle), immune function, and inflammation as well as cell proliferation and differentiation. Studies have shown that it may be useful as adjunctive treatment for tuberculosis, psoriasis, and multiple sclerosis or for the prevention of certain cancers. The consumption of fortified or enriched foods as well as suberythemal sun exposure should be encouraged for people at risk for vitamin D deficiency. The current review focuses on the evidence demonstrating vitamin D deficiency in all age groups.

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INTRODUCTION

Vitamin D deficiency is an iceberg disease which affects all the age groups. It is the most under-diagnosed medical condition in children and adults. This is largely because patients do not typically present with overt clinical signs and symptoms until the deficiency is severe and prolonged. Rickets is considered the tip of iceberg in children while osteomalacia in adults.

Deficiency and manifestations

In children prior to epiphyseal fusion, Vitamin D deficiency results in growth retardation associated with an expansion of growth plate known as rickets (Powers, 2012). In adults, vitamin D deficiency precipitate and exacerbate both osteopenia and osteoporosis and increase the risk of fracture (Holic, 2007). The elderly and nursing home residents are particularly at risk for vitamin D deficiency, since both the efficiency of vitamin D synthesis in skin and absorption of vitamin D from intestine decline with age. A 70 year old has 25% of the 7-dehydrocholesterol that a young adult does and thus has a 75% reduced capacity to make vitamin D3 in the skin (Holic, 1989). Similarly intestinal malabsorption of fats dietary fats leads to vitamin D deficiency. Obesity is associated with vitamin D deficiency, and it is believed to be due to the sequestration of vitamin D by the large body fat pool (Wortsman *et al*., 2000) Medications including antiseizure medications and glucocorticoids and fat malabsorption are also common causes of deficiency (Zhou *et al*., 2006). The hypocalcaemia and hypophosphatemia that accompany vitamin D deficiency result in impaired mineralization of bone matrix proteins, a condition known as osteomalacia (Powers, 2012). The syndrome of osteomalacia in addition to defective bone mineralization is characterized by bone pain, increased bone fragility and fractures (Pearson, 2009).

Epidemiology

Worldwide

Vitamin D deficiency (VDD) is the most common nutritional deficiency worldwide in both children and adults (Hossein-Nezhad, 2013). In the US and Europe, >40% of the adult population >50 years of age is vitamin D-deficient (Zhou and Assem, 2006). Levels of serum 25-hydroxyvitamin D consistent with vitamin D deficiency (<50 nanomol/L) have been reported in 48% of pre-teen white girls, 52% of adolescent Hispanic and black American boys and girls, and 32% of healthy young adults (Gordon, 2004). In Tibet and Mongolia, vitamin D deficiency leading to clinical rickets is described in 60% of infants (Harris, 2001). In the Middle East, a high prevalence of rickets and osteomalacia has been described in Muslim women and their infants, perhaps due to

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increased clothing coverage of the skin (Sedrani, 1986). The practice of *purdah,* whereby all skin is covered and prevented from being exposed to sunlight places those who practice it at high risk of VDD and explains why in the sunniest areas of the world VDD is very common in both children and adults (Fuleihan, 2001). Studies suggest that upwards of 30–50% of children and adults are at risk of vitamin D deficiency (Sato and Iwamoto, 2005).

India

Skin complexion, poor sun exposure, vegetarian food habits and lower intake of vitamin D fortified foods could be attributed to the high prevalence of VDD in India (Goswami R 2008).A high prevalence of hypovitaminosis D (25(OH)D levels <10 ng/mL) was recorded amongst study infants with hypocalcemic seizures (90%), and control infants (41.7%) in a hospital based study (Mehrotra, 2010). A community based study in three different regions of Delhi documented the prevalence of VDD (levels below 14ng/ml) amongst children as 82.9 % and 82% in two regions and 2% in third region (Tiwari and Pulilyel, 2004). A study conducted amongst school girls, reported the prevalence of VDD deficiency as 70% and mean serum 25(OH) D level as less than 12ng/ml (Khadilkar, 2007). In a study the prevalence of VDD in lower socioeconomic strata was higher (97.3%) as compared to upper socioeconomic strata (90.9%) (Marwaha, 2006). In a study conducted amongst adult male and females residing in both rural and urban areas, the prevalence of VDD estimated in urban population was 62% in male subjects and 75% in female subjects, while the prevalence of VDD was slightly lower in rural area as 44% in males and 70% in females. This indicates that the prevalence of VDD was more in females as compared to male subjects in both rural and urban areas (Harinarayan, 2007).

Association with other diseases

Vitamin D receptors have a broad tissue distribution that includes vascular smooth muscle (Merke, 1987), endothelium (Merke, 1989) and cardiomyocytes (Holick MF2006). It is now recognized that VDD increases the risk of many chronic diseases, including cancer, autoimmune diseases, type 2 diabetes, heart disease and hypertension, and infectious diseases (including upper respiratory tract infections and tuberculosis), as well as osteoarthritis (McKenna, 1992). A strong association of VDD with an increased risk of prostate, colon, breast, ovarian, and pancreatic cancers, among many others, has been reported (Toriola, 2007). Several retrospective and prospective studies that evaluated circulating concentrations of 25(OH)D support the concept that vitamin deficiency increases the risk of developing and dying from cancer (Giovannucci, 2006). It has been suggested that adults with 25(OH)D of 50nmol/L who were then followed for upto19years had a 30–50% increased risk of developing colorectal, breast, prostate, and many other cancers (Garland, 1985). A meta-analysis showed that increasing intake of vitamin D to 1000 IU vitamin D3/d would be associated with a decreased risk of colorectal and breast cancer of as much as 50% (Garland, 2006). Men who ingested 400 IU vitamin D/d had a markedly reduced risk of developing several cancers, including those of the pancreas and esophagus and non-Hodgkin lymphoma. Lappe *et al*. 2006, reported that postmenopausal women who received 1100 IU vitamin D3 and 1000 mg Ca daily for 4 years reduced their risk of developing cancer by 60%. It has also been observed that VDD is linked to pre-eclampsia during pregnancy and an increased risk of having a caesarean section (Merewood, 2007). A meta-analysis revealed on the basis of available evidence that there was an association with vitamin D status and several outcomes in children including birth weight and dental caries (Llewellyn, 2010). Vitamin D deficiency has also been linked to an increased incidence of schizophrenia, Parkinson's disease, cognitive dysfunction, and depression, although further research is needed in this regard (Camargo CA Jr 2007). Furthermore, high intake of vitamin D has been shown to decrease the incidence of asthma and wheezing illness (Zerwekh, 2008).

Diagnosis

Assessment of vitamin D status of an individual is best reflected by measurement of circulating vitamin D metabolites. Only two metabolites, namely, 25-hydroxyvitamin D [25(OH) D] and 1,25-dihydroxyvitamin D [1,25(OH)2D], have received the greatest attention in biochemical estimation of vitamin D. Of these, the need for measuring serum 1,25(OH)2D is limited. On the other hand, serum 25(OH)D provides the single best assessment of vitamin D status 25(OH)D as it has a half-life of about 3 weeks, making it the most suitable indicator of vitamin D status (Zerwekh, 1987). A classification given by Lips to define vitamin D status is as follows: mild hypovitaminosis D: 10–20 ng/ml, moderate hypovitaminosis D: 5-10 ng/ml, and severe hypovitaminosis D: less than 5 ng/ml (Levis, 1990).

Prevention of predisposing and risk factors

Major source of vitamin D for most humans comes from exposure of the skin to sunlight typically between 10:00 h and 15:00 h in the spring, summer, and fall (Holick, 2008). An alteration in the zenith angle of the sun caused by a change in latitude, season of the year, or time of day dramatically influences the skin's production of vitamin D_3 (Holick, 2008). Above and below latitudes of approximately 33°, vitamin D_3 synthesis in the skin is very low or absent during most of the winter. Risk factors for vitamin D deficiency and rickets in an infant include breast-feeding without vitamin D supplementation, dark skin pigmentation, and maternal vitamin D deficiency (Shah, 2000). In utero, the fetus is wholly dependent on the mother for vitamin D. The 25(OH)D passes from the placenta into the blood stream of the fetus. Infant can remain Vitamin D sufficient for several weeks after birth, as long as mother was vitamin D sufficient. Human breast milk and unfortified cow's milk have very little vitamin D (Shah M 2000). Thus, infants who are fed only human breast milk are prone to developing vitamin D deficiency, especially during the winter when neither they nor their mothers can obtain vitamin D from sunlight. Recommended adequate intake and RDA for children 0–1 and 1–18 year should be 400 and 600 IU/d, respectively (Pettifor, 1978). In the past, children of all races obtained most of their vitamin D from exposure to sunlight and drinking vitamin D-fortified milk, and therefore, they did not need to take a vitamin D supplement (Weng, 2007). However, children are spending more time indoors now, and when they go outside, they often wear sun protection that limits their ability to make vitamin D in their skin. Children and adolescents are also drinking less vitamin D-fortified milk. Although children between 9-18 years have rapid growth spurt but there is no scientific evidence on increased requirement of vitamin D in this age group (Huh, 2008). Age group 19-50

years is at risk for vitamin D deficiency because of decreased outdoor activities and aggressive sun protection. (Wagner and Greer, 2008 Hence, their requirement is at least 600 IU/d of vitamin D to maximize bone health and muscle function. Men and women older than 51 yr depend on sunlight for most of their vitamin D requirement. It is recommended that all adults aged 50–70 and 70+ yr require at least 600 and 800 IU/d, respectively, of vitamin D to maximize bone health and muscle function.

Daily doses of 600 IU do not prevent vitamin D deficiency in pregnant women (Merewood, 2009). Their daily regimen should at least include a prenatal vitamin containing 400 IU vitamin D with a supplement that contains at least 1000 IU vitamin D. During lactation, the mother needs to increase the efficiency of dietary absorption of calcium to ensure adequate calcium content in her milk. Lactating women should take at least a multivitamin containing 400 IU vitamin D along with at least 1000 IU vitamin D supplement every day. To satisfy the requirements of an infant who is fed only breast milk, the mother requires 4000 to 6000 IU/d to transfer enough vitamin D into her milk (Lee, 2007). Obese adults (BMI $\geq$ 30kg/m^2) when exposed to simulated sunlight or received an oral dose of 50,000 IU of vitamin D_2, they were able to raise their blood levels of vitamin D by no more than 50% compared with non-obese adults. Patients on multiple anticonvulsant medications, glucocorticoids, or AIDS treatment are at increased risk for vitamin D deficiency because these medications increase the catabolism of 25(OH)D. The above groups should be given at least two to three times more vitamin D for their age group to satisfy their body's vitamin D requirement (Holick, 2011).

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