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Editorial

Vitamin D and respiratory infections

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Vitamin D is a group of secosteroids involved in a host of functions in the human body. While the role of vitamin D in bone and mineral metabolism has been well studied, its activities on other physiological and pathophysiological processes have been of increasing interest in recent years. Vitamin D, which is photosynthesized in the skin or is derived from nutrition, is metabolized two times, before it mediates its calcemic effects by binding to the nuclear vitamin D receptor (VDR) (St-Arnaud, 2008; Janssens et al., 2009). The first hydroxylation of vitamin D takes place in the human liver on C-25 position by mitochondrial 25-hydroxylase enzyme and the 25-hydoxylated molecule is further hydroxylated at position 1α by the mitochondrial cytochrome P450 enzyme 25-hydroxyvitamin-D-1α-hydroxylase in the proximal tubule of the nephron and converted to the bioactive 1α,25-dihydroxy(1,25-$(OH)_2D_3$). The 1α-hydroxylation of 25-$(OH)D_3$ is upregulated by parathyroid hormone (PTH), calcitonin, low calcium- and phosphate levels as well as by estrogen, prolactin and growth hormone (Kann.,1994). Calcitonin, cortisol, high phosphate levels and 25-$(OH)D_3$ suppress the 25-hydroxy-1α-hydroxylase activity (Zhong et al., 2009). Of the many disorders where vitamin D is believed to play an important role, epidemiological data suggest that several lung diseases, all inflammatory in nature, may be related to activities of vitamin D. Immunomodulatory properties of the steroid hormone are likely to be important in this regard.

Vitamin D, the inflammatory cells and cytokines

Since the report of marked improvement of his patients of tuberculosis by the British physician C.J.B. Williams subsequent to use of cod liver oil (Williams.,1849), many functions of vitamin D have been discovered, that indicate that vitamin D regulates many cellular processes and is potentially involved in the development of many diseases. After the discovery of VDR in virtually every human cells, especially those of the adaptive immune system such as B- and T-lymphocytes (Provvedini, 1983; Provvedini et al., 1986), monocytes and dendritic cells (Eleftheriadis et al., 2009), a number of reports have appeared that indicate immunomodulatory activities of vitamin D. Vitamin D tends to favor a mononuclear phenotype, increasing VDR expression on monocytes and macrophages (Veldmann et al., 2000; Rockett et al., 1986). Circulating vitamin D levels increase the “oxidative burst” potential of macrophages (leading to maturation and production of cytokines) (Cannell et al., 2006), and prevent excessive expression of inflammatory cytokines. Vitamin D also facilitates neutrophil motility and phagocytic function (Lorente et al., 1976). It may also reduce both local and systemic inflammatory responses as a result of modulating cytokine responses and reducing Toll-like receptor (TLR) activation (Jeng et al., 2009), an effect suggested to help sepsis (Plitas et al., 2008). Vitamin D also exerts direct effects on T-cell activation and on the phenotype and function of antigen-presenting cells, especially dendritic cells (Canning et al., 2001). Restricted to myeloic dendritic cells, that express a set of TLRs and cytokines different from plasmacytoic dendritic cells, 1,25-$(OH)_2D_3$ inhibits their maturation and enhances the expression of cytokines like IL-10. Thus 1,25-$(OH)_2D_3$ induces tolerance through the suppression of T_H1 lymphocyte development and the induction of regulatory T cells (Penna and Adorini., 2000). Vitamin 1,25-D_3 inhibits proliferation of T helper 1(Th1) cells, and the attendant production of cytokines like IL-2, tumor necrosis factor α and interferon (IFN), as well as T helper 17 (Th17) cells, skewing cytokine production toward a T helper 2 (Th2) phenotype (Bikle., 2008). Vitamin D also stimulates the expression of potent antimicrobial peptides, such as cathelicidin and human β defensin 2 (Janssens et al 2009), which exist in neutrophils, monocytes, natural killer (NK) cells and epithelial cells lining the respiratory tract (Sawada et al., 2000). VitaminD stimulates the macrophages, lymphocytes and monocytes to increase the expression of antimicrobial peptides, cathelicidin and human beta-defensin- 2 (Cheng et al., 2004; Negri, 2006). Cathelicidin is effective against gram-positive and gram-negative bacteria, fungi and mycobacteria (Janssens et al., 2009). Patients with low levels of vitamin D may be unable to fully express cathelicidin (Sasaki et al., 1991) that might lead to an increased susceptibility to nosocomial infections (St-Arnaud., 2008). Human β-defensin-2 (HBD)-2, another antmicrobial peptide, may have special utility in multidrug resistant microbes from in vitro studies (Penna and Adorni, 2000), although its overall role is

less clearly defined. It exhibits a broad spectrum antimicrobial activity against gram-positive/negative bacteria and fungi (Kochupillai, 2008). It is possible that (HBD)-3 maybe more relevant than (HBD)-2 as shown in the severity of staphylococcal aureus skin infections (Lauridsen et al., 2005). Vitamin D deficiency may also predispose patients to hypocalcemia, which impairs normal lymphocyte and neutrophil function (Kochupillai, 2007).

Vitamin D and Influenza

Respiratory infections have always been known to be commoner during the winter period than during summertime. Influenza epidemics in North America and Europe generally reach peaks during December through March, the months during which ultraviolet-B radiation exposure and serum levels of 25(OH)D are lowest in the population (Grant and Garland., 2008). Insufficient exposure to sun during winter leads to insufficient amounts of vitamin D (Janssens et al., 2010), and might explain the seasonal variation in influenza and other, mostly viral, respiratory infections (Cannell et al., 2006). In the secondary analysis of the Third National Health and Nutrition Examination Survey, Ginde et al. hypothesized an association between vitamin D level and self-reported upper respiratory tract infections (URTI) in 18883 subjects (Ginde et al., 2009). Lower levels of vitamin D were independently associated with recent URTI, the association being about 6 times in asthmatics and twice in those with COPD. Low vitamin D levels in another case control study were found to be associated with severe acute lower respiratory tract infections, with the lowest 25(OH)D levels associated with an 11-times risk of getting infected with influenza (Wayse et al., 2004). In a cohort of 8000 young men serving on an army base, subjects with low vitamin D levels had significantly more days of absence from duty due to respiratory infection than control subjects (Laaksi et al., 2007). In Indian children younger than 5 years, subclinical vitamin D deficiency was a significant risk factor for severe acute lower respiratory tract infections (Wayse et al., 2004). Evidence exists that vitamin D may have a protective role in influenza (Cannell et al., 2006; Urashima et al., 2010) and other viral diseases. Studies dating back to the 1940s have associated a diet poor in vitamin D with susceptibility to experimental influenza viruses in mice (Young et al., 1949). Low vitamin D levels may reduce AMP synthesis, which then is less likely to impede the influenza virus (Cannell et al., 2006). A randomized controlled trial involving Japanese schoolchildren found a relative risk of influenza of 0.36 in those taking 1,200 IU/day compared with those taking 200 IU/day (Urashima et al., 2010). This result was found to be related to influenza type A, with no effect for type B. Sixty thousand IU of vitamin D per week administered for six weeks to 27 children with frequent respiratory infections resulted in a complete disappearance of such infections for the following six months (Rehman, 1994). Aloia and Li-Ng, in a post hoc analysis of their original 3-year randomized controlled interventional trial (Aloia and Li-Neg, 2007), discovered that 104 African American given vitamin D were three times less likely to report cold and flu symptoms than were 104 placebo control subjects ($p < 0.002$). A very low dose (800 IU/d) for two years abolished the seasonality of reported colds and flu, and even a sub-physiological dose of 2,000 IU/d (40% of treated women still had serum 25(OH)D levels of less than 32 ng/mL after 1 year) for an additional year virtually eradicated all reports of upper respiratory tract infections. However, when the same authors gave 2,000 IU/day for four months in the winter, they found no preventative effect, hypothesizing that the dose and length of study was inadequate to show an effect (Li-Ng et al., 2009). This might imply that starting sub-physiological doses of vitamin D in the late fall and winter may be too little and too late.

Vitamin D and other Respiratory Infections

Other respiratory viruses such as respiratory syncytial virus (RSV) and parainfluenza 1 and 2 viruses present with a seasonal pattern too (Fry et al., 2006), although the incidence of RSV seems to relate more to humidity and temperature than to UV radiation exposure (Yusuf et al 2007). Vitamin D appears to decrease the inflammatory response to RSV infections in airway epithelium without jeopardizing viral clearance (Hansdottir et al., 2010).Viral infections also constitute a major cause of recurrent otitis media (Linday et al., 2008). One cannot extrapolate conclusions from studies with the influenza virus to other respiratory viruses like the rhinovirus or the Epstein-Barr virus as a result of differing pathogenetic mechanisms. In tuberculosis, an important scourge of developing world, a recent meta-analysis showed that low serum levels of 25-(OH)D were associated with a higher risk of active tuberculosis with the pooled effect size was 0.68 (Nnoaham and Clarke, 2008). A number of candidate polymorphisms of VDR and vitamin D binding protein (DBP) have been identified that modulate the development of tuberculosis (Leandro et al., 2009). But investigators believe that larger studies are required to determine whether VDR polymorphisms play a role in genetic susceptibility to tuberculosis worldwide (Lewis et al., 2005). Vitamin D was found to help a higher sputum conversion in tuberculosis (Nursyam et al., 2006) and also enhance the ability of participants' whole blood to restrict BCG-lux luminescence after 24 hours in vitro as compared with placebo, but did not affect antigen-stimulated IFN-gamma secretion after 96 hours (Martineau et al., 2007). The authors concluded that supplementation of vitamin D may primarily enhance innate

responses to mycobacterial infection. However, Wejse et al., in their study of 365 tuberculosis patients found that adding 100,000 units of vitamin D at inclusion and again at 5 and 8 months in the 12-month antitubercular treatment period did not result in reduction of TB score or sputum conversion rates amongst the treatment group when compared to the placebo (Wejse et al., 2009). In a 'per protocol analysis' in the 5292 patients from the RECORD trial, designed for vitamin D in secondary prevention of osteoporotic fractures, Avnell and colleagues found a trend towards a benefit of vitamin D, though it was not statistically significant (Avnell et al., 2007).

Taken together, available scientific data seems replete with the evidence of association of vitamin D insufficiency with increased risk and severity of respiratory infections. Evidence to the benefits of the addition of vitamin D to treatment in respiratory infections is slowly accumulating; however, large scale randomized controlled trials need to be undertaken for assessing the efficacy, optimal duration, dosage, and time to intervene before routine recommendations for vitamin D in the treatment of respiratory infections is advocated.

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