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Evidence that vitamin D reduces the risk of influenza and pneumonia

William B. Grant, Ph.D.
Sunlight, Nutrition, and Health Research Center (SUNARC)
P.O. Box 641603
San Francisco, CA 94164-1603, USA
www.sunarc.org
wbgrant@infionline.net

Reviewed by:
Adrian Gombart, Adrian <Adrian.Gombart@oregonstate.edu>
James Sabetta <jsabettamd@yahoo.com>

Abstract
There is strong evidence that vitamin D reduces the risk of developing and dying from influenza. The first clue was that influenza incidence rates peak in winter, a time when solar ultraviolet-B doses and, thus, vitamin D production rates, are lowest. Vitamin D strengthens the innate immune system by producing compounds such as cathelicidin and defensins, which have antimicrobial actions. A randomized controlled trial using 1200 IU/d of vitamin D for school children in Japan found a 64% reduction in type A influenza cases compared with controls taking a placebo. The recent H1N1 "swine flu" was type A, and those in groups known to have lower vitamin D levels, such as pregnant women, had much higher rates of hospitalization than others. Vitamin D also reduces the risk of death from influenza by reducing the production of proinflammatory cytokines and fighting the bacteria that lead to pneumonia.

Introduction

That vitamin D might reduce the risk of influenza was proposed by Cannell et al. [2006] based on a consideration of the seasonal variation of influenza infection rate, which peaks in winter, a time when solar ultraviolet-B (UVB) doses are low to absent at high latitudes and serum 25-hydroxyvitamin D [25(OH)D] levels are lowest. Edgar Hope-Simpson [1981] had discussed the global seasonality of influenza activity, recognizing that it was related to the seasonal variation of solar radiation, but ruling out UV rays, which he considered lethal to the virus, since UV doses did not explain the seasonal variations in the tropics.

Exposure to sunlight

The best evidence that solar UVB irradiance, through vitamin D production, reduces the risk of influenza is its seasonality [Cannell et al., 2006]. Even the recent A/H1N1 "swine flu" epidemic, which started in Mexico in April, had peak incidence rates in winter [Ross et al., 2010]. However, variations in absolute humidity levels also contribute to the seasonality since the influenza virus lives longer outside a human or animal body at low humidity levels [Shaman and Kohn, 2009; Shaman et al., 2010]. (Absolute humidity levels are lowest in winter due to low temperatures.) While the annual variation of solar radiation doses has two effects on risk of influenza, it is much easier to control serum 25(OH)D levels.

Vitamin D levels

There are no reports of incidence rates of influenza with respect to serum 25(OH)D levels. However, there are several indirect ways to estimate the dose-response relation. One is to compare wintertime serum 25(OH)D levels to summertime levels since solar UVB is the primary source of vitamin D for most people. Studies in the U.S. and England found that serum 25(OH)D levels increase by about 10-15 ng/mL (25-37 nmol/L) in summer for younger people [Harris and Dawson-Hughes, 1998; Hypponen et al., 2007].

A second is through randomized controlled trials of vitamin D supplementation and incidence of influenza. A study in Long Island involving Black post-menopausal women found a 60% reduction in influenza and common cold cases for those taking 800 IU/d and

90% reduction for those taking 2000 IU/d [Aloia and Li-Ng, 2007]. A second study, involving 334 school children in Japan, half taking 1200 IU/d of vitamin D3, half taking 200 IU/d of vitamin D3, found a relative risk of 0.36 (95% confidence interval, 0.17, 0.79, p=0.006) for the 280 not taking additional vitamin D, i.e., a 64% reduced risk, for type A influenza [Urashima et al., 2010]. Each 1000 IU/d increases serum 25(OH)D levels by 6-10 ng/mL for average sized adults [Heaney et al., 2003]. The population mean values of serum 25(OH)D levels in the U.S. are 16 ng/mL for Black-Americans, 21 ng/mL for Hispanic-Americans, and 26 ng/mL for White-Americans [Ginde et al., 2009]. Thus, it appears that increasing serum 25(OH)D levels to above 35-40 ng/mL provides reasonable protection against type A influenza. A recent prospective cohort study involving healthy adults in Greenwich, CT, USA (latitude 41° N) found a serum concentration of 25(OH)D of 38 ng/mL or higher was associated with a two-fold reduction in the risk of acquiring respiratory viral infections and with a marked reduction in the number of days ill with such infections compared to lower values [Sabetta et al., 2010].

In addition to the well-known seasonality of influenza [Cannell et al., 2006, 2008; Hope-Simpson, 1981], during the recent A/H1N1 "swine flu" epidemic, those at greatest risk of complications following infection were pregnant women [Creanga et al., 2010; Hanslik et al., 2010], Australian Aborigines [La Ruche et al., 2009], and those obese or with diabetes or congestive heart failure [Hanslik et al., 2010]. See, also, the recent review in the New England Journal of Medicine [Writing Committee of the WHO, 2010]. All of these groups have lower serum 25(OH)D levels than that of the average population.

Pneumonia often develops in those who contract influenza [Britten, 1932; Hanslik et al., 2010]. Pneumonia is also frequently found in children with rickets [Banajeh, 2009], who are severely vitamin D deficient.

How does vitamin D work?

The primary epithelial cells generate 1,25-hydroxyvitamin D, which then influences the expression of vitamin D-driven genes that play a major role in host defense through inducing production of cathelicidin and defensins [Hansdottir et al., 2008]. These compounds have antimicrobial and antiendotoxin properties [Mookherjee et al., 2007]. For pneumonia, the roles of vitamin D include reducing the cytokine storm by shifting production from T-helper 1 (Th1) to Th2 cytokines, which generate less inflammation [Ardizzone et al., 2009] and fighting the bacterial pneumonia through induction of cathelicidin and defensins [Liu et al., 2007] as reviewed in Grant and Giovannucci [2009]. The vitamin D-antimicrobial peptide pathway and its role in protection against infection was recently discussed by Gombart [2009].

Preventing influenza and pneumonia with vitamin D

Two randomized controlled trials for vitamin D supplementation and incidence of influenza have been reported, as discussed above. No effect of vitamin D was found for type B influenza [Urashima et al., 2010], which is generally less common than type A influenza. Because vitamin D impacts both the function of the adaptive and innate arms of the immune system, an adequate level of circulating 25(OH)D is essential for allowing a balanced and optimal response by the immune system toward infection. Inadequate levels will likely lead to an imbalanced immune response that is detrimental to the afflicted individual. Vaccination strengthens the body's adaptive immune response, so for optimal protection against influenza, people may want to consider both vitamin D and vaccination.

Treating influenza and pneumonia with vitamin D

There are no published studies of treating those with influenza with vitamin D; however, it is reasonable to expect that if one who develops influenza takes a large dose of vitamin D3 (e.g., 10,000 IU/day), sufficient amounts of cathelicidin and defensins will be induced within a couple of days, strengthening the innate immune system's ability to fight both influenza and pneumonia, the primary risk for death following influenza infection. However, there are no clinical trials to support this suggestion at present. In responding to the viral infection, the body's innate immune system generates proinflammatory cytokines, which have the effect of disrupting the epithelial lining of the lung. This event permits the ever-present bacteria to lead to pneumonia, with death, if it is the result, likely to occur about ten days after the influenza infection [Britten, 1932]. In an ecological study of the case-fatality rate in twelve U.S. communities during the 1918-19 epidemic influenza reported in Britten [1932], it was shown that indices for summertime and wintertime solar UVB explained 46% and 42% of the variance, respectively [Grant and Giovannucci, 2009].

Conclusion

There is strong evidence that vitamin D reduces risk of type A influenza and pneumonia incidence and death. Those wishing to reduce their risk of influenza during the influenza season should consider raising their serum 25(OH)D levels to at least 35-40 ng/mL up to 80 ng/mL, which could take 2000-5000 IU/day of vitamin D3.

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