

## **Vitamin D is Now the Most Popular Vitamin**

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(OMNS Jan 17, 2013) There were 3600 publications with vitamin D in the title or abstract in 2012 according to PubMed.gov . This brings the total number of publications on vitamin D listed at PubMed to 33,800 (<http://www.ncbi.nlm.nih.gov/pubmed>). This total compares to 35,100 on vitamin C or ascorbic acid, 21,700 on vitamin E, 19,100 on vitamin A, 17,600 on folate, and 12,000 on vitamin B12. However, since the beginning of 2000, there have been 20,500 publications on vitamin D but only 16,300 publications on vitamin C or ascorbic acid. Thus, vitamin D is the most popular vitamin even though strictly speaking it is not a vitamin. Instead, it is a necessary hormone that can be made in the body through the action of ultraviolet-B (UVB) light. However, it can also be obtained orally through the diet or supplements.

### **Top 16 Vitamin D Papers of 2012**

The following list of top vitamin D papers for 2012 was selected from a search at PubMed.gov at the end of 2012. The list started out with 60 of candidate papers. This list was then sent to a panel of vitamin D researchers and advocates, who added a few more papers, then voted on the entire list. The final list has papers from a variety of health effects. Many other fine papers could not be included due to space limitations.

### **4,000 IU vitamin D3 was of great help during pregnancy**

A topic that generated considerable interest this year was the role of vitamin D during pregnancy. In a pair of papers, researchers from the Medical University of South Carolina discussed the findings and implications of their randomized controlled trial of vitamin D supplementation during pregnancy [Hollis et al., 2012; Wagner et al., 2012]. Over 300 women were enrolled in the study. Women were assigned to take supplements containing 400, 2000, or 4000 IU/d vitamin D3 or a placebo. No adverse effects were found such as hypercalcemia or hypercalcuria. This study found that it took 4000 IU/d to raise serum 25-hydroxyvitamin D [25(OH)D] levels to about 40 ng/ml (To convert to nmol/l, multiple ng/ml by 2.5.), a nearly optimal level of 1,25-dihydroxyvitamin D. 1,25-dihydroxyvitamin D is the active or hormonal metabolite of vitamin D which among other things controls the expression of several hundred genes. (See Hossein-nezhad and Holick [2012] for a summary of the effects of vitamin D on fetal development.) In the study, those taking the higher vitamin D doses had significantly reduced risk of primary Cesarean section delivery and pre-eclampsia. Other adverse pregnancy outcomes occur with vitamin D deficiency such as premature delivery and low birth weight, but too few women were enrolled in this study to find statistically significant results on these conditions.

### **Mounting evidence that vitamin D deficiency is an important risk factor for autism**

A study from Saudi Arabia examined the relation between serum 25(OH)D level and anti-myelin-associated glycoprotein (anti-MAG) auto-antibodies in autistic children near the age of eight years [Mostafa and Al-Ayadhi, 2012]. There was a very strong inverse relation between the two levels ( $r = -0.86$ ,  $p < 0.001$ ). The serum 25(OH)D levels in autistic children averaged 19 ng/ml, while that for

healthy children averaged 33 ng/ml. Both autistic and healthy children had about six hours of sun exposure per week. The reason that MAG is relevant to autistic children is that MAG is a compound that promotes regeneration of young neurons. Anti-MAG auto-antibodies appear to play a role in some autoimmune disorders relating to neurons through attacking cells that maintain a healthy nervous system. Serum anti-MAG auto-antibodies are strongly related to autism measured with the Childhood Autism Rating Scale. This provides very strong evidence that vitamin D deficiency is associated in some way with autism. Whether increasing serum 25(OH)D levels for those with autism reduces the symptoms of autism remains to be determined.

## **Low vitamin D during pregnancy is associated with childhood language impairment**

A study in Perth, Australia measured serum 25(OH)D levels at 18 weeks into pregnancy, and then measured language impairment of the offspring at 5 and 10 years of age. It found that women with serum 25(OH)D levels below 18 ng/ml had children with twice the risk of clinically significant language difficulties compared to those with 25(OH)D levels above 28 ng/ml. Exactly why is not currently known, but there are many possibilities. It is noted that in the United States in the early 2000s, white women of childbearing age had mean 25(OH)D level of 26 ng/ml while black women of childbearing age had mean 25(OH)D level of 14 ng/ml. Both of these levels are low by current standards. As explained below, skin color is directly relevant to serum vitamin D levels produced by exposure to sunlight.

## **Higher vitamin D is associated with lower all-cause mortality rates**

A topic of interest at the other end of life was the relation of mortality rate to serum 25(OH)D levels. A meta-analysis of 11 observational studies and 60,000 individuals found a reduction in risk over about 10 years for highest vs. lowest category of 25(OH)D level of mortality of 29% [Zittermann et al., 2012]. Comparing graded levels of intake, the reduction in risk was 14% for an increase of 5 ng/ml, 23% for an increase of 10 ng/ml, and 39% for an increase of 20 ng/ml in plasma levels of 25(OH)D, starting from a median of ~11 ng/ml. The participants starting with the lowest levels of serum 25(OH)D received the greatest benefits. Those who started with higher serum levels, closer to optimal (30-40 ng/ml), received less benefit from additional vitamin D. This relation between starting serum 25(OH)D levels and health outcome is not surprising because it is similar to many other health studies. Since 25(OH)D levels likely changed over the duration of the studies, and some participants died of unrelated causes, the actual effect of serum 25(OH)D level on mortality rate is greater than these estimates.

## **And less cardiovascular disease**

Cardiovascular disease is an important contributor to mortality rates. A study of 11,000 patients in Kansas was reported. The patients had a mean age of  $58 \pm 15$  years, a body mass index of  $30 \pm 8$  kg/m<sup>2</sup>, and a mean serum 25(OH)D level of  $24 \pm 14$  ng/ml [Vacek et al., 2012]. Serum 25(OH)D levels below 30 ng/ml was significantly associated with several cardiovascular-related diseases, including hypertension, coronary artery disease, cardiomyopathy, and diabetes. After a period of 5.5 years, those with serum 25(OH)D levels below 30 ng/ml had twice the mortality rate of those with higher 25(OH)D levels.

## **And less risk of diabetes mellitus type 2**

In a 2.7-year study of 2000 prediabetics, participants with the highest third of 25(OH)D levels (median, 30.1 ng/ml) had a reduction in risk of 28% for developing diabetes mellitus type 2 compared with participants in the lowest third (median, 12.8 ng/ml) [Pittas, 2012].

## **. . . and less diabetes mellitus type 1 (T1DM)**

An observational study on insulin-dependent diabetes mellitus (T1DM) was based on 1000 U.S. military service personnel who developed this disease between 2002 and 2011 [Gorham et al., 2012]. They had provided blood samples between one and ten years prior to developing T1DM. They were carefully matched with another thousand service personnel who did not develop T1DM. There was a reduction in risk of 78% for developing T1DM for those with serum 25(OH)D levels above 24 ng/ml compared to those with levels below 24 ng/ml. This finding is highly statistically significant and is one of the strongest studies of its type.

## **Fewer bacterial and viral infections**

The effect of vitamin D in reducing risk of infections is a topic of increasing interest. Vitamin D reduces risk of infections primarily by strengthening the innate immune system, primarily by inducing production of cathelicidin, a polypeptide with antimicrobial and antiendotoxin properties. It also shifts production of cytokines, a type of cell signaling molecule, away from proinflammatory ones, and has a number of other actions on both the innate and adaptive immune system [Lang et al., 2012]. While the effects of vitamin D have been found mostly for bacterial infections, some have also been reported for viral infections such as influenza, HIV, and hepatitis C [Lang et al., 2012]. In a supplementation study in Sweden involving 140 patients with frequent respiratory tract infections (RTIs) using 4000 IU/d vitamin D3, those in the supplementation group increased their serum 25(OH)D level to 53 ng/ml while those in the placebo group had levels near 27 ng/ml [Bergman et al., 2012]. Those taking vitamin D3 had a 23% reduction in RTIs and a 50% reduction in the number of days using antibiotics.

## **The benefits of vitamin D in reducing risk of cancer**

One of the important and well-documented effects of vitamin D is reduced risk of cancer and increased survival after cancer diagnosis. There were 400 publications on vitamin D and cancer in 2012 according to PubMed.gov. Evidence from ecological, observational and laboratory studies have identified over 15 types of cancer for which higher solar UVB light and/or serum 25(OH)D levels are associated with reduced risk. Two of the papers are especially noteworthy. One, a study from Norway involving 658 patients with either breast, colon, lung, or lymphoma with serum 25(OH)D levels determined within 90 days of cancer diagnosis were followed for up to nine years [Tretli et al., 2012]. Compared to those with levels <18 ng/ml, those who originally had levels >32 ng/ml had a reduction in risk for dying from cancer of 66%. To a cancer patient, this would be a lifeline.

Another cancer paper reported the results of supplementation with 4000 IU/d vitamin D3 of those with low-grade biopsy-assayed prostate cancer [Marshall et al., 2012]. Forty four patients successfully completed the one-year study. Twenty four of the subjects (55%) showed a decrease in the amount of cancer; five subjects (11%) showed no change; 15 subjects (34%) showed an increase. In comparison, with a historical group of 19 patients, only 4 (21%) had reductions in the

amount of cancer, 3 (16%) showed no changes, and 12 (63%) showed an increase in cancer. Thus optimal vitamin D supplementation appears to be useful for treating those with cancer.

## **Falls and fractures**

The classical role of vitamin D is to regulate calcium and phosphate absorption and metabolism, leading to strong bones. A pooled analysis of 31,000 persons (mean age, 76 years; 91% women) participating in randomized controlled trials of vitamin D supplementation who developed ~1000 incident hip fractures and ~3800 nonvertebral fractures found that those with the highest intake (median 800 IU/d; range 792-2000) had a 30% reduction in risk of hip fracture and a 14% reduced risk of nonvertebral fracture [Bischoff-Ferrari et al., 2012]. The role of vitamin D in neuromuscular control also plays an important role in reducing risk of falls and fractures.

## **Skin pigment adapts slowly to changed ultraviolet environment**

Jablonski and Chaplin have published a series of papers on human skin pigmentation and its relation to solar ultraviolet radiation (UVR) [Jablonski and Chaplin, 2012]. Their primary thesis is that human skin pigmentation has adapted to UVR conditions where a group of people live for 50 generations, or about a thousand years. UVR from mid-day sunlight produces vitamin D, which provides important protection against many diseases, but sunlight also causes skin cancer and destruction of folate. Dark skin protects against free radical production, damage to DNA, cancer, and loss of folate. Thus, dark skin is best in the tropical planes regions while pale skin is best at high latitude regions. Those with skin adapted to UVB between 23° and 46° have the ability to tan, which is an adaptation to seasonal changes in solar UVB doses. However, in recent times, people have moved or traveled to regions where their skin pigmentation is not suited to the local UVR conditions. They discuss three examples: nutritional rickets, multiple sclerosis and melanoma. Their abstract concludes with this observation: "Low UVB levels and vitamin D deficiencies produced by changes in location and lifestyle pose some of the most serious disease risks of the twenty-first century."

## **Vitamin D levels for traditionally living Africans**

A study on traditionally living Africans near the equator provides information on "normal" 25(OH)D levels. A paper was published on serum 25(OH)D levels of the Masai and the Hadzabe living near 4° S in Tanzania [Luxwolda et al., 2012]. They have skin type VI (very dark), wear a moderate amount of clothing, spend the major part of the day outdoors, but avoid direct exposure to sunlight when possible. The mean serum 25(OH)D levels of Maasai and Hadzabe were 48 (range 23-67) ng/ml and 44 (range 28-68) ng/ml, respectively. This finding suggests that serum 25(OH)D levels in the range of 40-50 ng/ml may be optimal for human health, which is generally consistent with observational studies for a number of health outcomes.

Vitamin D is made by exposure to sunlight to a significant degree only when the sun is 45 degrees or more above the horizon. At the latitudes of North America and Europe, this is summer midday sunlight between the hours of 11 a.m. and 3 p.m. In the early morning or late afternoon, light-skinned individuals may tan but they hardly get any vitamin D from sunlight. And in the winter, nobody gets much vitamin D from the sun. This explains the health benefits of taking supplements of vitamin D.

## **Résumé et Conclusion**

Thus, the evidence that serum 25(OH)D levels above 30-40 ng/ml are required for optimal health continues to mount. It takes 1000-4000 IU/d vitamin D3 to reach these levels in the absence of significant UVB exposure. The evidence comes from a variety of studies including observational and laboratory studies and randomized controlled trials (RCTs). While RCTs are required to demonstrate effectiveness and lack of harm for pharmaceutical drugs which, by definition, are artificial compounds, they should not be required for vitamin D since it is a natural compound important for all animal life including humans. In addition, RCTs on vitamin D are difficult to conduct due to other sources of vitamin D and reduced conversion of vitamin D to 25(OH)D level at higher serum levels. It will take five years or more before large-scale RCTs testing vitamin D supplements are completed and reported. The adverse effects of oral intake of up to 4000 IU/d vitamin D3 and serum 25(OH)D levels up to 100 ng/ml are practically non-existent except for those individuals with conditions that may lead to hypercalcemia. Thus, there seems to be little reason to wait for the RCTs before implementing vitamin D policies of higher oral intake and/or moderate UVB exposure and serum 25(OH)D levels. Everyone in North America and Europe should take a supplement of 1000-4000 IU/d of vitamin D in the winter, and those with dark skin or office jobs should take vitamin D all year long. Supplementation with vitamin D is an inexpensive and very effective way to produce huge health benefits.

For further information on vitamin D, the interested reader is directed to these websites: <http://www.Grassrootshealth.net>, <http://www.VitaminDCouncil.org>, and <http://www.VitaminDWiki.com>. Dr. Grant is director of <http://www.sunarc.org>.

Nous exprimons notre gratitude à tous les scientifiques qui ont examiné et contribué à ce document :

Barbara J. Boucher, M.D., Queen Mary University of London, Centre for Diabetes, Blizard Institute, London

John J. Cannell, M.D., Vitamin D Council, San Luis Obispo, CA

Brant Cebulla, Vitamin D Council, San Luis Obispo, CA

Cedric F. Garland, Dr. P.H., professor of Family and Preventive Medicine in the UCSD School of Medicine, and member of the Moores UC San Diego Cancer Center, LaJolla, CA

Afrozul Haq, Ph.D., Institutes of Pediatrics and Laboratory Medicine; Sheikh Khalifa Medical City; Abu Dhabi, United Arab Emirates

Robert P. Heaney, M.D., Osteoporosis Research Center, Creighton University Medical Center, Omaha, NE.

Perry Holman, Vitamin D Society, Canada

Johan E. Moan, M.D., Ph.D., Department of Radiation Biology, The Norwegian Radium Hospital, University of Oslo, Oslo, Norway

Stefan Pilz, M.D., Department of Internal Medicine, Division of Endocrinology and Metabolism, Medical University of Graz, Graz, Austria

Jörg Reichrath, M.D., Ph.D., Department of Dermatology; The Saarland University Hospital; Homburg/Saar, Germany.

And, the Editorial Review Board of the *Orthomolecular Medicine News Service*, listed further below.

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