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REVIEW

Vitamin D Deficiency

This clandestine endemic disease is veiled no more

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نقص فيتامين (د)

هذا المرض المتوطّن السّرّي لم يعُد خفيّا

مؤنس مصطفى الششتاوي

الملخص: وفّر العلماء حديثاً مجموعة قوية من البراهين التي قدّمت معلومات جديدة عن التأثير الوقائي لفيتامين «د» على مجموعة واسعة من الحالات المرضية. وتشير هذه الأدلة إلى أنّ فيتامين «د» هو أكثر بكثير من مجرد مادة غذائية لازمة لصحّة العظام بل هو هرمون أساسي ضروري لتنظيم عدد كبير من الوظائف الفسيولوجية. إن وجود تركيز كافي من 25 –هيدروكسي فيتامين «د» في مصل الدم هو أمر ضروري لتحسين صحّة الإنسان. نستعرض في هذا المقال الحالة الراهنة للمعارف العلمية حول وضع فيتامين «د» في جميع أنحاء العالم، ونشير إلى مقالات نُشرت حديثا والتي تناقش بعضا من الجوانب المهمة العامة لفيتامين «د»، بما في ذلك المصادر، الفوائد، والحاجة اليومية لفيتامين «د» الغذائية ونقص تناوله خصوصا في فترة الحمل. وتوفر الدراسة أدلة على أن نقص فيتامين «د» يمكن أن يكون عبئا كبيرا على الصحة العامة في أجزاء كثيرة من العالم، ومعظمها بسبب الحرمان من التعرض لأشعة الشمس. كما نناقش أيضا الجدل الدائر حول التركيز الأمثل لمادة 25 –هيدروكسي فيتامين «د» في مصل الدم، واستطلاع وجهات النظر المختلفة بشأن الكمية المطلوبة من مكملات فيتامين «د» لتحقيق هذا التركيز والحفاظ عليه.

مفتاح الكلمات: نقص فيتامين «د»، 52–هيدروكسي فيتامين «د»، فيتامين «د2» (إرجوكالسيفرول)، فيتامين «د3» (كولكالسيفرول)،أشعة الشمس، عُمان.

ABSTRACT: Recently, scientists have generated a strong body of evidence providing new information about the preventive effect of vitamin D on a broad range of disorders. This evidence suggests that vitamin D is much more than a nutrient needed for bone health; it is an essential hormone required for regulation of a large number of physiological functions. Sufficient concentration of serum 25-hydroxyvitamin D is essential for optimising human health. This article reviews the present state-of-the-art knowledge about vitamin D's status worldwide and refers to recent articles discussing some of the general background of vitamin D, including sources, benefits, deficiencies, and dietary requirements, especially in pregnancy. They offer evidence that vitamin D deficiency could be a major public health burden in many parts of the world, mostly because of sun deprivation. The article also discusses the debate about optimal concentration of circulating serum 25-hydroxyvitamin D, and explores different views on the amount of vitamin D supplementation required to achieve and maintain this concentration.

Keywords: Vitamin D deficiency; 25-hydroxyvitamin D; Vitamin D2 (ergocalciferol); Vitamin D3 (cholecalciferol); Sunlight; Oman.

Vitamin D is not really a vitamin.[1] Vitamin D (which includes both D_2 and D_3) behaves like a hormone and carries out essential biological functions through endocrine, paracrine, and intracrine mechanisms.[2] Vitamin D_2 (ergocalciferol) is a synthetic product produced by irradiation of plant sterols, while vitamin D_3 (cholecalciferol) is a prohormone made in the skin in response to the action of ultraviolet (UV) B irradiation on a cholesterol precursor, 7-dehydrocholesterol.[1,3] When the skin absorbs UVB radiation, the precursor is converted to previtamin D3, which undergoes a thermally induced transformation to vitamin D_3 [Figure 1].[3]

A small part of vitamin D_3 comes from dietary intake, especially fatty fish (e.g. herring, mackerel, sardines, tuna, salmon), eggs, and fortified foods.[4,5] Thus, the major source of vitamin D is sunlight exposure. However, variables such as time of day, season, latitude, clothing, skin pigmentation, and age affect the amount of vitamin D converted in the skin.[3]

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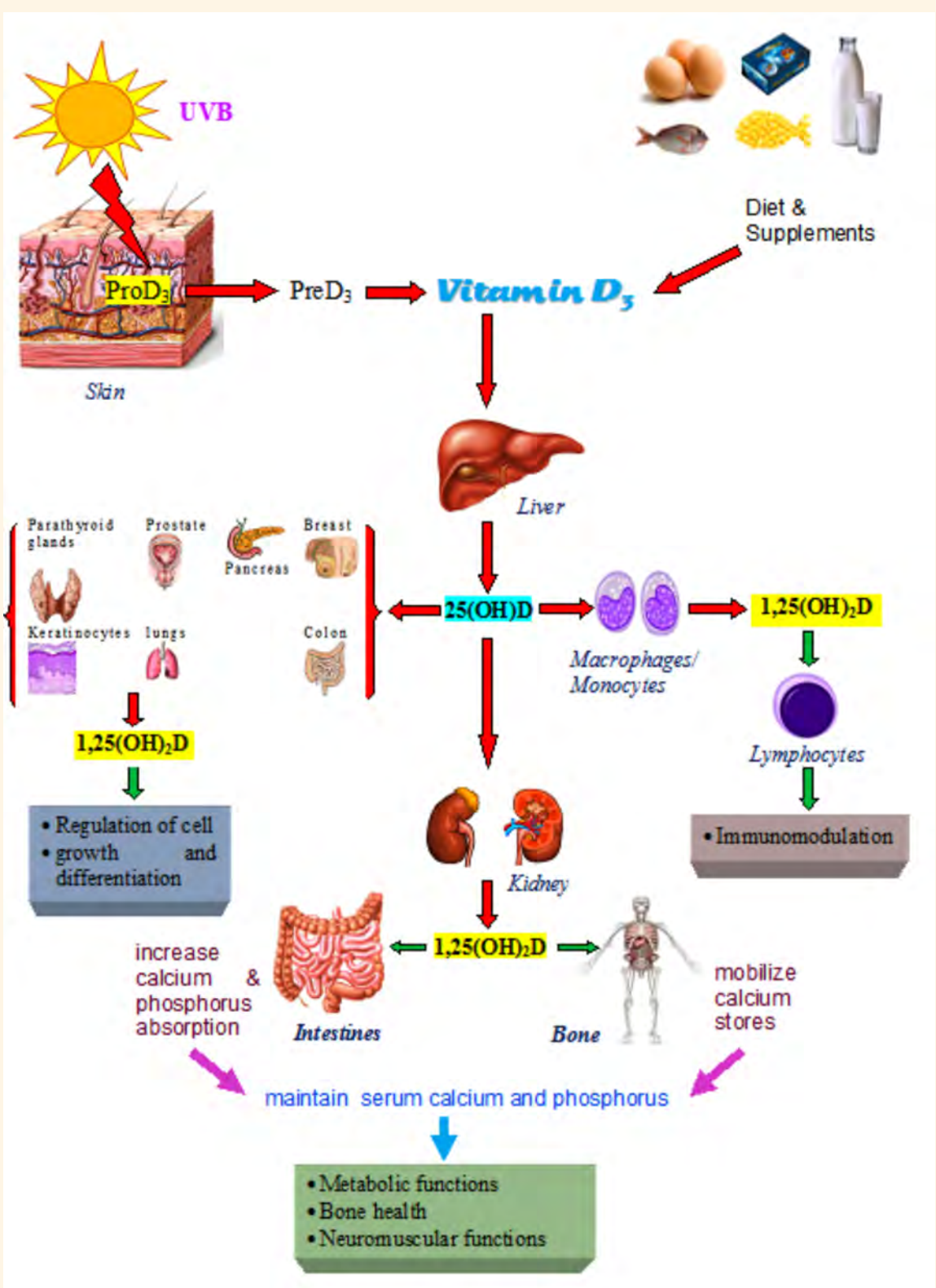

Figure 1: Production, metabolism and functions of vitamin D

Vitamin D, whether absorbed through the skin or consumed, is metabolised in the liver by 25-hydroxylase to 25-hydroxyvitamin D (25(OH) D), a prehormone form.[1,3] In its endocrine action, 25(OH)D is converted by hydroxylation in the kidney to 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), which circulates in the blood as a hormone to regulate mineral and skeletal homeostasis [Figure 1].[3] In addition to the kidney's endocrine production of circulating $1,25(OH)_2D$, vitamin D

also acts through a paracrine-intracrine pathway. In this system, 25(OH)D is converted to $1,25(OH)_2D$ intracellularly by 25(OH)D 1-a-hydroxylases in a variety of end-organ tissues such as the prostate gland, breasts, colon, lungs, and keratinocytes [Figure 1].[6] The conversion of 25(OH)D to $1,25(OH)_2D$ in these tissues appears not to be controlled by calcium, but rather to be directly linked to the substrate availability of 25(OH)D. That is a complex endocrine reaction which begins in the largest organ of the body, the skin.[2]

In contrast to $1,25(OH)_2D$, which has a short half-life of ~4–15 hours, the serum concentration of 25(OH)D has a fairly long circulating half-life of ~15 days,[7] and is considered the best indicator of vitamin D status that can be measured.[8] Serum 25(OH)D reflects vitamin D produced cutaneously and also that obtained from food and supplements.[7–9]

Vitamin D Status around the World

Vitamin D status has been studied on all continents and in most countries throughout the world. In total, approximately 5,060 epidemiological studies have been done according to a PubMed search conducted in February 2012. These studies revealed that vitamin D deficiency was prevalent across all age-groups, geographic regions, and seasons.[10–12]

Despite ample sunshine, vitamin D deficiency is very common in the Middle East (15°–36°N) and African (35°S–37°N) countries.[13,14] The first study to reveal low vitamin D concentrations in people of the Middle East region was conducted by Woodhouse and Norton in 1982 among ethnic Saudi Arabians.[15] Their results were confirmed in 1983, when Sedrani *et al.* recorded a mean 25(OH)D concentration ranging between 10–30 nmol/L (2.496 nmol/L being equivalent to 1 ng/ml) among Saudi university students and the elderly.[16,17] A more recent study that was conducted in the Eastern Province of Saudi Arabia revealed vitamin D deficiency (25(OH)D of ≤50 nmol/L) among 28–37% of 200 randomly selected healthy men.[18] Another study, also conducted in the eastern regions of Saudi Arabia, showed low serum 25(OH)D concentrations among both males and females (25.25 nmol/L and 24.75 nmol/L, respectively) despite the fact that >65% of participants had adequate exposure to sunlight and >90% reported an adequate intake of dairy products.[19]

In Oman, according to the 2004 Ministry of Health survey, out of 298 non-pregnant women of child bearing age, 21.4% were found to be vitamin D deficient (<27.0 nmol/L).[20] Almost half of the women included in the survey (47%) had serum 25(OH)D concentrations below 37.5 nmol/L, while only 10% of them had concentrations above 75 nmol/L.[21] A more recent study tested serum 25(OH)D concentrations in 41 apparently healthy Omani women of childbearing age. The study indicated that all women had serum 25(OH)D concentrations of <50 nmol/L.[22] Another study examined serum 25(OH)D concentrations in 103 healthy Omani pregnant women on their first antenatal visit to the hospital. The study revealed that 33% of cases had 'at risk' concentrations (25(OH)D) <25 nmol/L), and that 65% had serum concentrations of 25(OH)D between 25 and 50 nmol/L, and not one case was found in the optimal range (25(OH)D >75 nmol/L).[23]

Similarly, vitamin D deficiency was found to be highly prevalent in the United Arab Emirates (UAE). Studying the efficacy of daily and monthly supplementation with vitamin D_2 in lactating and nulliparous Emirati women, the results revealed that most women had vitamin D deficiency (25(OH)D ≤ 50 nmol/L at study entry).[24] Also, Dawodu *et al.* investigated the effect of sun exposure at recommended levels on the vitamin D status of eight healthy Arab women of child-bearing age working in the Al Ain district of the UAE. Serum 25-hydroxyvitamin D concentrations were measured pre- and post-intervention. Although vitamin D concentrations remained sub-optimal, median serum 25(OH)D concentrations were significantly higher post-intervention (23.0 nmol/L) than pre-intervention (17.6 nmol/L).[25] A very recent study done by Anouti *et al.* in 2011 investigated a random sample of 208 young Emirati university students in Abu Dhabi, 138 females and 70 males. The mean serum 25(OH)D concentration for female students tested in April was 31.3 ± 12.3 nmol/L, while in October, it was 20.9 ± 14.9 nmol/L.[26] This difference was statistically significant, suggesting that seasonal variation plays an important role in vitamin D status. Female students scored significantly higher than males on the sun avoidance inventory (SAI), indicating that females tend to avoid sun exposure to a greater extent than

males, a possible explanation of the lower vitamin D status.[26]

In Qatar, the mean overall vitamin D concentration among health care professionals working at Hamad Medical Corporation in Doha, was found to be 29.3 nmol/L. Vitamin D concentration was lower in females (25.8 nmol/L) than in males (34.3 nmol/L). A total of 97% of all participants had a mean concentration <75 nmol/L, while 87% had a mean concentration of <50 nmol/L.[27] In another study, vitamin D deficiency was prevalent (68.8%) among young Qatari children below 16 years of age, mostly in the age group 11–16 years (61.6%). Girls were affected more than boys (51.4% versus 48.6%).[28]

Even in north African countries there is a high prevalence of low vitamin D status; 25(OH)D is in the rachitic range. Veiled women, or women wearing *purdahs* (cloth that covers the whole of the body), have a lower vitamin D status than their peers within the same country.[29] Studies in Turkey and Jordan showed also a strong relationship with clothing.[30,31] Serum 25(OH)D levels were highest in women who wore Western clothing, decreasing in traditional women wearing a *hijab* (veil that covers the whole head except the face), and the lowest levels were measured in completely veiled women who wore a *niqab* (additional veil covering the whole face, or all of it except the eyes). Men in these countries have higher concentrations than women. In Iran, a population study that included 1,210 men and women between 20 and 69 years old, showed that the mean serum 25(OH)D was 20.6 nmol/L.[32] In India, among 20 pregnant women in delivery at Sant Parmanand Hospital in Delhi, more than 75% were deficient in 25(OH)D (<50 nmol/L).[33]

Serum 25(OH)D concentrations are not only suboptimal in eastern or southern countries or specific risk groups, but also in adults in many Western countries.[4] For instance, in the Netherlands, a study that assessed the prevalence of vitamin D deficiency in 358 pregnant women of several ethnic backgrounds living in The Hague, recorded that mean serum 25(OH)D concentrations in Turkish women were 15.2 ± 12.1 nmol/L; in Moroccan women 20.1 ± 13.5 nmol/L, and in other non-Western women 26.3 ± 25.9 nmol/L. These concentrations were significantly ($P \leq 0.001$) lower than those in the Western women living in that country (52.7 ± 21.6 nmol/L).[34] In the UK and elsewhere, vitamin D deficiency was found to be common among pregnant women.[35]

Most clinicians believe that vitamin D deficiency has been essentially eliminated in the USA, but recent data indicate that the diagnosis exists in epidemic proportions.[36] Data from the National Health and Nutrition Examination Survey (NHANES) showed that the number of persons with 25(OH)D concentrations below 75 nmol/L nearly doubled between the 1994 and 2004 surveys, each of which extended for several years each.[37] Data from the NHANES III 2004 survey showed that 65–75% of the population had 25(OH) D concentrations of <50 nmol/L.[12] Less than 3% of African-American mothers were vitamin D sufficient, and the mean cord blood concentrations of 25(OH)D in their infants was very low (25 ± 15 nmol/L).[37,38] More recent research from the USA also studied vitamin D concentrations in different ethnic groups, and included 154 African-American, 194 Hispanic, and 146 Caucasian women at <14 weeks of gestation. In logistic regression models, race was the most important risk factor for vitamin D deficiency or insufficiency. African-American women and Hispanic women were more likely to have vitamin D insufficiency and deficiency than Caucasian women.[39] Also, Bodnar *et al*. conducted a study to assess, by race and season, the vitamin D status of pregnant women and their neonates residing in Pittsburgh. The serum 25(OH)D of 200 white and 200 black pregnant women was measured throughout gestation (4–21 weeks), previous to delivery, and in the cord blood of their neonates. The results suggested that black and white pregnant women and their neonates residing in the northern USA were at high risk of vitamin D insufficiency.[40]

Thus, it seems that the world is facing today what is, in fact, a new endemic disease that was, until recently, totally veiled. The actual percentage of vitamin-D-deficient people seems to be far greater than reported, so identifying the reasons for the dramatic increase in vitamin D insufficiency is not an easy task.

Vitamin D Deficiency - Causes and Questions

Declines in 25(OH)D concentrations are usually the result of dietary inadequacy, impaired absorption and use, increased requirements, or increased

excretion.[9] No doubt, the major cause of vitamin D deficiency is inadequate exposure to sunlight.[41–44] The upward trend in body mass index is also accused of causing vitamin D deficiency, and obesity is now added as a major contributory factor to the increasing prevalence of vitamin D insufficiency.[3] Genetic predisposition may also have an effect on vitamin D blood concentrations and it has to be accounted for in the design of preventive measures against vitamin D deficiency.[1,45]

A century since the discovery of its dual origin, many questions have been raised and remain unanswered about vitamin D's concentrations in human beings. For example, why is vitamin D so important? Why should we be concerned about vitamin D deficiency during pregnancy? What concentrations of the vitamin are optimal in adults and children? Do these optimal concentrations vary for the prevention of various disorders or in differing human populations? What amount of supplementation or sunlight exposure is needed to achieve and maintain these concentrations? And how much vitamin D can we really take safely?

Luckily, in the last few years, numerous clinical studies, including crucial randomised controlled trials (RCTs) of vitamin D supplementation were conducted in the search for answers to the above mentioned questions and more. Successful completion of experimental trials was essential to obtain valuable information on the effect of vitamin D in preventing a wide range of disorders, and also for establishing the efficacy and safety of vitamin D supplementation.

Why is Vitamin D so Important?

Vitamin D is much more than a nutrient needed for bone health; it is an essential hormone required for the regulation of a large number of physiological functions. Its receptors were found to be present in nearly every tissue and cell in the body. That is why sufficient concentrations of serum 25(OH)D are essential for optimal functioning of these tissues and cells.[3]

The major function of vitamin D compounds is to enhance the active absorption of ingested calcium (and phosphate). This assists in building bone at younger ages and ensures that, despite obligatory urinary losses, bone does not need to be desorbed to maintain blood calcium concentrations.[1]

Moreover, sufficient concentrations of vitamin D may be important in reducing the occurrence of autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis, diabetes, and some cancers.[46–48,10] Adequate vitamin D may also allow for a normal innate immune response to pathogens, improve cardiovascular function and mortality and increase insulin responsiveness[1,49,50]

A recent work by Grant aimed to estimate the reduction in mortality rates for six geopolitical regions of the world. It was based on an interpretation of the journal literature relating to the effects of solar UVB and vitamin D in reducing the risk of vitamin D-sensitive diseases. Six major diseases that account for more than half of global mortality rates (i.e. cardiovascular disease (CVD), cancer, respiratory infections, respiratory diseases, tuberculosis and diabetes mellitus) were studied in addition to vitamin D-sensitive diseases and conditions that account for 2–3% of global mortality rates such as Alzheimer's disease, falls, meningitis, Parkinson's disease, maternal sepsis, maternal hypertension (pre-eclampsia) and multiple sclerosis. The study showed that increasing serum 25(OH) D concentrations from 54 to 110 nmol/L would reduce the vitamin D-sensitive disease mortality rates by an estimated 20%. The reduction in all-cause mortality rates ranged from 7.6% for African females to 17.3% for European females. Reductions for males were on average 0.6% lower than for females. The estimated increase in life expectancy was 2 years for all six regions.[51]

Why should we be concerned about Vitamin D Deficiency during Pregnancy?

Generally, there are many important health benefits from vitamin D for both mother and fetus. However, new clinical research results over the past decade indicate that appropriate intakes of vitamin D may provide greater health benefits than previously thought, benefits that include not only improved bone health, but other effects as well.[2,52,53] Recent data suggest that $1,25(OH)_2D$ aids implantation and maintains normal pregnancy. It also supports fetal growth through delivery of calcium, controls secretion of multiple placental hormones, and limits

the production of proinflammatory cytokines.[35,54] Maternal nutritional vitamin D status has a good effect on childhood bone mineral accrual and is important also for fetal "imprinting" that may affect neurodevelopment, immune function, and chronic disease susceptibility later in life, as well as soon after birth.[55,56]

Also, maternal vitamin D insufficiency during pregnancy is significantly associated with offspring language impairment. Maternal vitamin D supplementation during pregnancy may reduce the risk of developmental language difficulties among children.[57] Meanwhile, substandard vitamin D intake during pregnancy may lead to decreased birth weight.[58] Moreover, maternal vitamin D deficiency in early pregnancy may be an independent risk factor for preeclampsia[59] and may be associated with increased odds of primary caesarean section.[60] Merewood *et al.* found that 28% of women with serum 25(OH)D concentrations less than or equal to 37.5 nmol/L had a caesarean section, compared with only 14% of women with higher 25(OH)D concentrations (≥37.5 nmol/L).[60]

What is the "Normal" Circulating 25(OH)D Concentration in Human Beings?

Vitamin D deficiency has been historically defined and recently recommended by the Institute of Medicine (IOM), USA, as a 25(OH)D concentration of less than 50 nmol/L. Vitamin D insufficiency has been defined as a 25(OH)D concentration of 50–75 nmol/L.[61] Vitamin D deficiency can be further classified as mild (25–50 nmol/L), moderate (12.5–25.0 nmol/L), and severe (<12.5 nmol/L).[5] However, the preponderance of evidence points to optimal serum 25(OH)D concentrations of at least 80 nmol/L to maximise vitamin D's effect on calcium, bone, and muscle metabolism.[3,50,62] Based on a quick review of the literature for vitamin D during pregnancy, as well as a more detailed review for other diseases, Grant found that serum 25(OH)D concentrations above 75–100 nmol/L are required for good pregnancy outcomes, fetal health, and optimal health in general.[35] Similarly, an international expert panel formulated recommendations on vitamin D for clinical practice, taking into consideration the best recent evidence available based on published literature. The panel reached substantial agreement about the need for vitamin D supplementation in adult patients with, or at risk for fractures, falls, cardiovascular or autoimmune diseases, and cancer. A target range of at least 75 to 100 nmol/L was recommended.[53]

However, one study of a convenience sample of 93 healthy young adults recruited from the University of Hawaii and a Honolulu skateboard shop questioned the frequently suggested serum 25(OH)D sufficiency cutoff of 75 nmol/L. The investigators recruited these prototypic "surfer dudes" (mean age: 24 years; mean body mass index [BMI], in kg/m^2: 23.6). On the basis of a self-reported minimum outdoor sun exposure of 15 hours (mean: 29 hours) per week during the preceding 3 months; 40% reported never using sunscreen, and the group overall reported an average of 22.4 hours per week of unprotected sun exposure. All were clinically tanned. Nevertheless, the group's mean 25(OH)D concentration was 79 nmol/L, and 51% had a concentration below the suggested 75 nmol/L cutoff for sufficiency. The study group was multiracial, but even among the 37 white subjects, the mean value was only 92.8 nmol/L and the highest value was 155 nmol/L.[63]

On the other hand, Luxwolda *et al.* measured the sum of serum 25-hydroxyvitamin D2 and D3 (25(OH)D) concentrations of thirty-five pastoral Maasai (mean age: 34 ± 10 years, 43% male) and twenty-five Hadzabe hunter-gatherers (mean age: 35 ± 12 years, 84% male) living in Tanzania. They had skin type VI, wore a moderate degree of clothing, spent the majority of the day outdoors, but avoided direct exposure to sunlight when possible. The mean serum 25(OH)D concentrations of Maasai and Hadzabe were 119 (range 58–167) and 109 (range 71–171) nmol/L, respectively. These concentrations were not related to age, sex, or BMI.[64] These recent data suggest that a public health goal of ≥75 nmol/L, or even ≥100 nmol/L, for the entire population can be achieved by sun exposure.

How much Vitamin D is required to Optimise Bone and Global Health?

In 2011, the IOM released revised recommendations for the daily intake of vitamin D based on the body's need for skeletal health.[9] The recommended dietary

allowances (RDAs) for vitamin D are 600 IU/d for ages 1–70 years and 800 IU/d for ages 71 years and older, corresponding to a serum 25-hydroxyvitamin D concentration of at least 50 nmol/L. RDAs for vitamin D were based on conditions of minimal sun exposure due to wide variability in vitamin D synthesis from UV light and the risks of skin cancer.[65]

The recommendations of the American Academy of Pediatrics (AAP) are 400 IU/day of vitamin D for exclusively and partially breastfed infants shortly after birth, to be continued until they are weaned and consume ≥1,000 mL/day of vitamin D-fortified formula or whole milk. Similarly, all non-breastfed infants ingesting <1,000 ml/day of vitamin D-fortified formula or milk should receive a vitamin D supplement of 400 IU/day. The AAP also recommends that older children and adolescents who do not obtain 400 IU/day through vitamin D-fortified milk and foods should take a 400 IU vitamin D supplement daily.[66] However, this latter recommendation, issued in November 2008, is less than the Food and Nutrition Board's vitamin D RDA of 600 IU/day for children and adolescents that was issued in November 2010.[67]

All these recommendations have stimulated considerable debate. Many scientists thought that to increase nutritional vitamin D to meaningful concentrations, dietary intakes of ≥2,000 IU/day may be required. In order to calculate the needs of a human body, one should know that sunlight exposure sufficient to result in a mild sunburn for a Caucasian adult in a bathing suit raises the serum 25(OH)D to a concentration comparable to that of a person taking 10,000 to 20,000 IU of vitamin D2 orally; which could be the daily requirement for human beings. [68] Thus, raising the blood concentration of 25(OH)D consistently above 75 nmol/L may require at least 1,000–2,000 IU/day of supplemental vitamin D.[53] Higher concentrations of 2,000 IU/day for children 0–1 years, 4,000 IU/day for children 1–18 years, and 10,000 IU/day for children and adults 19 years and older may be needed to correct vitamin D deficiency.[50]

To end the debate, Bruce Hollis *et al.* have recently conducted a randomised controlled trial, the National Institutes of Health/National Institute of Child Health & Human Development (NIH/NICHD) study, in which women with a singleton pregnancy at 12–16 weeks' gestation received 400, 2,000 or 4,000 IU vitamin D_3 per day until delivery. The relative risk (RR) for achieving ≥80 nmol/L within one month of delivery was significantly different between 2,000 and 400 IU. Circulating 25(OH)D had a direct influence on circulating $1,25(OH)_2$ D concentrations throughout pregnancy with maximal production of $1,25(OH)_2$ D in all strata in the 4,000 IU group. There were no differences between groups on any safety measure. Not a single adverse event was attributed to vitamin D supplementation or circulating 25(OH) D concentrations.[69] Another study by Hollis was conducted in Columbia, South Carolina, USA. The study included diverse groups of women who were randomised to 2,000 or 4,000 IU vitamin D_3/day irrespective of baseline 25(OH)D at <16 weeks' gestation. The aim was to confirm the NIH/NICHD study findings and to prove that no adverse events are associated with vitamin D supplementation.[70] Both of these studies proved that vitamin D supplementation with 4,000 IU vitamin D/day for pregnant women was safe and effective in achieving vitamin D sufficiency in a racially diverse group. In both studies, higher maternal circulating 25(OH)D was associated with a lower risk of co-morbidities of pregnancy.

What are the Possible Effects on Health of High Concentrations of Vitamin D?

According to Heaney, an intake of 1,000 IU vitamin D/day results in an increase of approximately 25 nmol/L in 25(OH)D, although individual responses vary.[71] Accordingly, most international authorities consider a vitamin D intake of 2,000 IU/day as absolutely safe, although literature review revealed that even doses of up to 10,000 IU/day supplemented over several months did not lead to any adverse events.[52]

In 2011, the IOM re-evaluated the potential for high intakes of vitamin D to produce adverse effects and set a safe tolerable upper intake level (UL) for vitamin D of 4,000 IU/day for ages 9 and older and lower for infants (0–6 months: 1,000 IU/day; 6–12 months: 1500 IU/day) and younger children (1–3 years: 2,500 IU/day; 4–8 years: 3,000 IU/day).[9] According to Ross *et al.*, the starting point for the announced UL for vitamin D was 10,000 IU/day.

Given that toxicity is not the appropriate basis for a UL that is intended to reflect long-term chronic intake and to be used for public health purposes, this value was corrected for uncertainty based on chronic disease outcomes and all-cause mortality to 4,000 IU/day.[65] However, Garland and colleagues pointed out that the supplemental dose, ensuring that 97.5% of the population study achieved a serum 25(OH)D of at least 100 nmol/L, was 9,600 IU/day.[72]

It should be mentioned here that sunbathing can produce vitamin D doses equivalent to an oral vitamin D intake of up to 20,000 IU/day and in healthy subjects who spent prolonged periods in a sunny environment, measured 25(OH) D concentrations rarely exceed 250 nmol/L, suggesting that this level may be considered a safe upper limit for serum 25(OH)D levels.[73–75] Furthermore, a benefit-risk assessment of vitamin D supplementation conducted by Bischoff-Ferrari *et al.* reported that hypercalcaemia caused by excess vitamin D in generally healthy adults was observed only if daily intake was >100,000 IU or if the 25(OH) D level exceeded 250 nmol/L.[76] Accordingly, they pointed out that 250 nmol/L should be considered a safe limit, but not as an upper limit to target in clinical practice.[53] Similarly, Hathcock *et al.*, noting the absence of toxicity in clinical trials conducted in healthy adults that used vitamin D doses of ≥10,000 IU, supported the confident selection of this value as the UL.[52]

Conclusion

Over the past two decades, scientists, clinicians and researchers have generated a strong body of evidence to address the problem of vitamin D deficiency and provide advice for correcting its status among all ages, genders and racial/ethnic groups. Many studies, some randomised and some not, have suggested that a population with a higher vitamin D intake would be healthier overall. Accordingly, the following can be recommended

First, vitamin D can be obtained from production by the skin after brief UV exposure. Exposure to bright midday sunlight, rich in UVB wavelengths, is a very efficient way to make vitamin D. Unfortunately, the action spectrum for vitamin D photosynthesis is essentially identical to the spectrum that damages DNA and causes skin cancer.[77,78] The study done by Samanek *et al.* in 2006 illustrates the complexities of calculating UV exposure times and clearly indicates that it is impractical to generate a simple nationally uniform message that prescribes minutes of sun exposure to the general population, given the number of variables that need to be taken into consideration.[79] In response to potential confusion over mixed messages about the risks and benefits of sun exposure, a collaboration of the Cancer Council Australia, the Australian and New Zealand Bone and Mineral Society, Osteoporosis Australia and the Australasian College of Dermatologists gathered Australian experts in Melbourne in December 2006, to review the latest evidence on vitamin D and develop a position statement.[80] Those experts suggested that people should continue to protect themselves from overexposure, especially during peak ultraviolet radiation periods (10 am to 3 pm). For most people, sun protection to prevent skin cancer is required when the UV index is moderate or above (i.e. UV index is 3 or higher). At such times, sensible sun protection behaviour is warranted and is unlikely to put people at risk of vitamin D deficiency. Most people probably achieve adequate vitamin D concentrations through the UVB exposure they receive during typical day-to-day outdoor activities. For example, fair skinned people can achieve adequate vitamin D concentrations (>50 nmol/L) in summer by exposing the face, arms and hands or the equivalent area of skin to a few minutes of sunlight on either side of the peak UV periods on most days of the week. In winter, when UV radiation concentrations are less intense, maintenance of vitamin D concentrations may require 2–3 hours of sunlight exposure to the face, arms and hands or equivalent area of skin over a week.[80]

Second, some groups in the community are at increased risk of vitamin D deficiency. They include naturally dark-skinned people, those who cover their skin for religious or cultural reasons, the elderly, infants of vitamin D deficient mothers, and people who are housebound or are in institutional care.[80] Naturally dark-skinned people (Fitzpatrick skin type 5 and 6) are relatively protected from skin cancer by the pigment in their skin; they could therefore safely increase their sun exposure. Others on this list should discuss their vitamin D status with their medical practitioner as some might benefit from dietary supplementation with vitamin D.[80]

Third, some people are at high risk of skin cancer. They include people who have had skin cancer, have received an organ transplant, or are highly sun sensitive. These people need to have more sun protection, and therefore should discuss their vitamin D requirements with their medical practitioner to determine whether dietary supplementation with vitamin D would be preferable to sun exposure.[80]

Fourth, public education should be provided about the safety of vitamin D supplementation. Individuals with limited sun exposure need to include reliable sources of vitamin D in their diet or take a supplement to achieve recommended concentrations of intake. Needless to say, there is considerable variation in how individuals respond to vitamin D supplementation. The response to treatment varies with season, population, local experience and with the starting concentrations of 25(OH)D. Supplementation without baseline 25(OH)D measurement is recommended for dark-skinned or veiled subjects not exposed much to the sun; individuals with musculoskeletal health problems; cardiovascular disease; autoimmune diseases and cancer; those over 65 years of age, and institutionalised subjects. In these individuals, a dose of 800 IU/day (the standard dose of most RCTs) or its equivalent with an intermittent dosing regimen (i.e. 100,000 IU orally every 3 to 4 months) is recommended.[53,72] All adults who are vitamin D deficient should be treated with 50,000 IU of vitamin D once a week for 8 weeks, or its equivalent of 6,000 IU/day of vitamin D, to achieve a blood concentration of 25(OH)D ≥ 75nmol/L, followed by maintenance therapy of 1,500–2,000 IU /day.[61] Similarly, Pietras *et al.* effectively treated vitamin D deficiency in most patients with 50,000 IU of ergocalciferol weekly for 8 weeks, then continued treatment with 50,000 IU of ergocalciferol every other week for up to 6 years to prevent recurrent vitamin D deficiency.[17]

Fifth, compulsory fortification of some foods (such as milk, infant formula, margarine, and other food products) with vitamin D should be seriously considered. Fortified foods can provide sufficient amounts of vitamin D in the diet. They provide most of the vitamin D in the American diet, and almost all of the USA milk supply is voluntarily fortified with 100 IU/cup. In Canada, milk is fortified by law with 35–40 IU/100 mL, as is margarine at ≥530 IU/100 g. Both the USA and Canada mandate the fortification of infant formula with vitamin D: 40–100 IU/100 kcal in the USA, and 40–80 IU/100 kcal in Canada.[9]

Sixth, in supplements and fortified foods, vitamin D is available in two forms, D_2 (ergocalciferol) and D_3 (cholecalciferol), which differ chemically only in their side-chain structure. However, Vitamin D_3 is approximately 87% more potent in raising and maintaining serum 25(OH)D concentrations and produces 2- to 3-fold greater storage of vitamin D than does vitamin D_2.[81] Accordingly, vitamin D_3 should be the preferred treatment option when correcting vitamin D deficiency through supplementation using an intermittent regimen.[82,83] However, when given as daily doses, vitamin D_2 and D_3 seem to have similar effects on 25(OH)D levels.[84]

Seventh, the use of UVB irradiance may be useful in certain cases. Solar UVB radiation with a wavelength of 290–320 nanometers penetrates uncovered skin and converts cutaneous 7-dehydrocholesterol to previtamin D_3, which in turn becomes vitamin D_3.[9] However, the most commonly used lamps do a poor job of simulating the UVB light intensity of natural sunlight. The only lamps that come close to the intensity of natural sunlight are "sunlamps", which are sometimes used to treat psoriasis.[85] The moderate use of commercial tanning beds that emit 2–6% UVB radiation is also effective.[86,87]

Eighth, in practice, testing for 25(OH) D is recommended after at least 3 months of supplementation (usually 6–12 months).[50] Currently, 25(OH)D measurement is reasonable in groups of people at high risk for vitamin D deficiency and in whom a prompt response to optimisation of vitamin D status is expected.[61] However, serum 25(OH) D assays are expensive, and the need for universal screening has not yet been proven.[3]

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References

1. Mason RS, Sequeira VB, Gordon-Thomson C. Vitamin D: the light side of sunshine. Eur J Clin Nutr 2011 Sep; 65:986–93.
2. Hollis BW, Wagner CL. Nutritional vitamin D status during pregnancy: reasons for concern. CMAJ 2006; 174: 1287–90.
3. Lappe JM. The role of vitamin D in human health: a paradigm shift. J Evid Based Complementary Altern Med 2011; 16:58–72.
4. van Schoor NM, Lips P. Worldwide vitamin D status. Best Pract Res Clin Endocrinol Metab 2011; 25:671–80.
5. Stroud ML, Stilgoe S, Stott VE, Alhabian O, Salman K. Vitamin D: A review. Aust Fam Physician 2008; 37:1002–5.
6. Norman AW. From vitamin D to hormone D: fundamentals of the vitamin D endocrine system essential for good health. Am J Clin Nutr 2008; 88:491–9S.
7. Jones G. Pharmacokinetics of vitamin D toxicity. Am J Clin Nutr 2008; 88:582–6S.
8. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. Nat Rev Endocrinol 2001; 22:477–501.
9. IOM (Institute of Medicine). Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: The National Academies Press, 2011. From: http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D.aspx Accessed: Oct 2011.
10. Garland CF, Gorham ED, Mohr SB, Garland FC. Vitamin D for cancer prevention: Global perspective. Ann Epi 2009; 19:468–83.
11. Holick MF. High prevalence of vitamin D inadequacy and implications for health. Mayo Clin Proc 2006; 81:353–73.
12. Yetley EA. Assessing the vitamin D status of the US population. Am J Clin Nutr 2008; 88:558–64S.
13. El-Rassi R, Baliki G, Fulheihan GEH. Vitamin D status in Middle East and Africa. From: www.iofbonehealth.org/download/osteofound/filemanager/health_professionals/pdf/Vitamin-D-reports/Vitamin_D-MEast_Africa.pdf Accessed: Jan 2012.
14. Alshishtawy MM. To be or not to be exposed to direct sunlight: Vitamin D deficiency in Oman. SQU Med J 2011; 11:196–200.
15. Woodhouse NYJ, Norton WL. Low vitamin D level in Saudi Arabians. King Faisal Spec Hosp Med J 1982; 2:127–31.
16. Sedrani SH, Elidrissy AWTH, El Arabi KM. Sunlight and vitamin D status in normal Saudi subjects. Am J Clin Nutr 1983; 38:129–32.
17. Pietras SM, Obayan BK, Cai MH, Holick MF. Vitamin D2 treatment for vitamin D deficiency and insufficiency for up to 6 years. Arch Intern Med 2009; 169:1806–8.
18. Sadat-Ali M, AlElq A, Al-Turki H, Al-Mulhim F, Al-Ali A. Vitamin D levels in healthy men in eastern Saudi Arabia. Ann Saudi Med 2009; 29:378–82.
19. Elsammak MY, Al-Wossaibi AA, Al-Howeish A, Alsaeed J. High prevalence of vitamin D deficiency in the sunny Eastern region of Saudi Arabia: a hospital-based study. East Mediterr Health J 2011; 17:317–22.
20. Ministry of Health, Oman. Micronutrients Testing, Community Health & Disease Surveillance Newsletter (2008). Muscat: Ministry of Health, 2008. Pp. 12–13.
21. Alasfoor D, Kaur M, Al Kiyumi S, Al Busaidy S, Suleiman AJ, Ruth L, et al. Vitamin D Deficiency: A Public Health Problem in Oman. From: www.micronutrientforum.org/meeting2009/PDFs/Poster%20Presentations/3_Thursday/DKB/TH66_Kaur.pdf Accessed: Apr 2010.
22. Al-Kindi MK. Vitamin D status in healthy Omani women of childbearing age: Study of female staff at the Royal Hospital, Muscat, Oman. SQU Med J 2011; 11:56–61.
23. Al Kalbani M, Elshafie O, Rawahi M, Al Mamari A, Al Zakwani A, Woodhouse N. Vitamin D status in pregnant Omanis: A disturbingly high proportion of patients with low vitamin D stores. SQU Med J 2011; 11:52–5.
24. Saadi HF, Dawodu A, Afandi BO, Zayed R, Benedict S, Nagelkerke N. Efficacy of daily and monthly high dose calciferol in vitamin D deficient nulliparous and lactating women. Am J Clin Nutr 2007; 85:1565–71.
25. Dawodu A, Kochiyil J, Altaye M. Pilot study of sunlight exposure and vitamin D status in Arab women of childbearing age. East Mediterr Health J 2011; 17:570–74.
26. Anouti FAI, Thomas J, Abdel-Wareth L, Rajah J, Grant WB, Haq A. Vitamin D deficiency and sun avoidance among university students at Abu Dhabi, United Arab Emirates. Dermatoendocrinol 2011; 3:1–5.
27. Mahdy S, Al-Emadi SA, Khanjar IA, Hammoudeh MM, Sarakbi HA, Siam AM, et al. Vitamin D status in health care professionals in Qatar. Saudi Med J 2010; 31:74–7.
28. Bener A, Al-Alim, Hoffmann GF. High prevalence of vitamin D deficiency in young children in a highly sunny humid country: A global health problem. Minerva Pediatr 2009; 61:15–22.
29. Prentice A, Schoenmakers I, Jones KS, Jarjou LMA, Goldberg GR. Vitamin D deficiency and its health consequences in Africa. Clinic Rev Bone Miner Metab 2009; 7:94–106.
30. Alagöl F, Shihadeh Y, Boztepe H, Tankol R, Yarman S, Azizlerli H. Sunlight exposure and vitamin D

deficiency in Turkish women. J Endocrinol Invest 2000; 23:173–7.

31. Mishal AA. Effects of different dress styles on vitamin D levels in healthy young Jordanian women. Arch Osteoporos 2001; 12:931–5.

32. Hashemipour S, Larijani B, Adibi H, Javadi E, Sedaghat M, Pajouhi M, et al. Vitamin D deficiency and causative factors in the population of Tehran. BMC Public Health 2004; 4:38.

33. Agarwal N, Arya SC. Vitamin D(3) levels in pregnant women and newborns at a private tertiary care hospital in Delhi, India. Int J Gynaecol Obstet 2011; 113:240–1.

34. van der Meer IM, Karamali NS, Boeke AJP, Lips P, Middelkoop BJC, Verhoeven I, et al. High prevalence of vitamin D deficiency in pregnant non-Western women in The Hague, Netherlands. Am J Clin Nutr 2006; 84:350–3.

35. Grant WB. Importance of vitamin D for pregnant women and developing fetuses. From:www.vitamindassociation.org/eventpdfs/20110517/20110517%20Vitamin%20D%20&%20Obstetrics%20-%20Data%20overview%20-%20Grant.pdf Accessed: Oct 2011.

36. Caplan RH. Vitamin D deficiency in the United States: A reassessment. Gundersen Lutheran Med J 2006; 4:16–21.

37. Ginde AA, Liu MC, Camargo CA, Jr. Demographic differences and trends of vitamin D insufficiency in the US population, 1988-2004. Arch Intern Med 2009; 169:626–32.

38. Greer FR. 25-hydroxyvitamin D: Functional outcomes in infants and young children. Am J Clin Nutr 2008; 88:529–33S.

39. Johnson DD, Wagner CL, Hulsey TC, McNeil RB, Ebeling M, Hollis BW. Vitamin D deficiency and insufficiency is common during pregnancy. Am J Perinatol 2011; 28:7–12.

40. Bodnar LM, Simhan HN, Powers RW, Frank MP, Cooperstein E, Roberts JM. High prevalence of vitamin D insufficiency in black and white pregnant women residing in the northern United States and their neonates. J Nutr 2007; 137:447–52.

41. Holick MF, Chen TC. Vitamin D deficiency: A worldwide problem with health consequences. Am J Clin Nutr 2008; 87:1080–6S.

42. Holick MF, Chen TC, Sauter ER. Vitamin D and skin physiology: A D-lightful story. J Bone Miner Res 2007; 22:V28–33.

43. Moan J, Porojnicu AC, Dahlback A, Setlow RB. Addressing the health benefits and risks, involving vitamin D or skin cancer, of increased sun exposure. Proc Natl Acad Sci USA 2008; 105:668–73.

44. Looker AC, Pfeiffer CM, Lacher DA, Schleicher RL, Picciano MF, Yetley EA. Serum 25-hydroxyvitamin D status of the US population: 1988–1994 compared to 2000–2004. Am J Clin Nutr 2008; 88:1519–27.

45. Baroncelli GI, Bereket A, El Kholy M, Audi L, Cesur Y, Ozkan B, et al. Rickets in the Middle East: Role of environment and genetic predisposition. J Clin Endocrinol Metab 2008; 93:1743–50.

46. Willer CJ, Dyment DA, Sadovnick AD, Rothwell PM, Nurray T, Ebers GC. Timing of birth and risk of multiple sclerosis: Population based study. BMJ 2005; 330:120.

47. Merlino LA, Curtis J, Mikuls TR, Cerhan JR, Criswell LA, Saag KG. Vitamin D intake is inversely associated with rheumatoid arthritis: Results from the Iowa Women's Health Study. Arthritis Rheum 2004; 50:72–7.

48. Hypponen E, Laara E, Reunanen A, Jarvelin MR, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: A birth-cohort study. Lancet 2001; 358:1500–3.

49. Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science 2006; 311:1770–3.

50. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2011; 96:1911–30.

51. Grant WB. An estimate of the global reduction in mortality rates through doubling vitamin D levels. Eur J Clin Nutr 2011; 65:1016–26.

52. Hathcock JN, Shao A, Vieth R, Heaney R. Risk assessment for vitamin D. Am J Clin Nutr 2007; 85:6–18.

53. Souberbielle JC, Body JJ, Lappe JM, Plebani M, Shoenfeld Y, Wang TJ, et al. Vitamin D and musculoskeletal health, cardiovascular disease, autoimmunity and cancer: Recommendations for clinical practice. Autoimmun Rev 2010; 9:709–15.

54. Shin JS, Choi MY, Longtine MS, Nelson DM. Vitamin D effects on pregnancy and the placenta. Placenta 2010; 31:1027–34.

55. Javaid MK, Crozier SR, Harvey NC, Gale CR, Dennison EM, Boucher BJ, et al. Maternal vitamin D status during pregnancy and childhood bone mass at 9 years: A longitudinal study. Lancet 2006; 367:36–43.

56. McGrath J. Does "imprinting" with low prenatal vitamin D contribute to the risk of various adult disorders? Med Hypotheses 2001; 56:367–71.

57. Whitehouse AJO, Holt BJ, Serralha M, Holt PG, Kusel MMH, Hart PH. Maternal serum vitamin D levels during pregnancy and offspring neurocognitive development. Pediatrics 2012; 129:485–93.

58. Mannion CA, Gray-Donald K, Koski KG. Association of low intake of milk and vitamin D during pregnancy with decreased birth weight. CMAJ 2006; 174:1273–

7.

59. Bodnar LM, Catov JM, Simhan HN, Holick MF, Powers RW, Roberts JM. Maternal vitamin D deficiency increases the risk of preeclampsia. J Clin Endocrinol Metab 2007; 92:3517–22.

60. Merewood A, Mehta SD, Chen TC, Bauchner H, Holick MF. Association between vitamin D deficiency and primary caesarean section. J Clin Endocrinol Metab 2009; 94:940–5.

61. The Endocrine Society. The Endocrine Society's Clinical Guidelines: Evaluation, treatment, and prevention of vitamin D deficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2011; 96:1911–30.

62. Vieth R. Why the minimum desirable serum 25-hydroxyvitamin D level should be 75 nmol/L (30 ng/ml). Best Pract Res Clin Endocrinol Metab 2011; 25:681–91.

63. Binkley N, Novotny R, Krueger D, Kawahara T, Daida YG, Lensmeyer G, et al. Low vitamin D status despite abundant sun exposure. J Clin Endocrinol Metab 2007; 92:2130 –5.

64. Luxwolda MF, Kuipers RS, Kema IP, Janneke Dijck-Brouwer DA, Muskiet FA. Traditionally living populations in East Africa have a mean serum 25-hydroxyvitamin D concentration of 115 nmol/L. Br J Nutr 2012; 23:1–5. [Epub ahead of print].

65. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, et al. The 2011 Report on Dietary Reference Intakes for Calcium and Vitamin D from the Institute of Medicine: What clinicians need to know. J Clin Endocrinol Metab 2011; 96:53–8.

66. Wagner CL, Greer FR. American Academy of Pediatrics Section on Breastfeeding; American Academy of Pediatrics Committee on Nutrition. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. Pediatrics 2008; 122:1142–52.

67. Office of Dietary Supplements (ODS). Dietary Supplement Fact Sheet: Vitamin D. From: /ods.od.nih.gov/factsheets/vitamind Accessed: Nov 2011.

68. Holick MF. Vitamin D: The underappreciated D-lightful hormone that is important for skeletal and cellular health. Curr Opin Endocrinol Diabetes 2002; 9:87–98.

69. Hollis BW, Johnson D, Hulsey TC, Ebeling M, Wagner CL. Vitamin D supplementation during pregnancy: Double blind, randomized clinical trial of safety and effectiveness. J Bone Miner Res 2011; 26:2341–57.

70. Hollis BW, Wagner CL. The vitamin D requirement during pregnancy and lactation. From:http://vitamindassociation.org/eventpdfs/20110517/20110517%20Vitamin%20D%20&%20Obstetrics%20-%20Effectiveness%20&%20Safety%20-%20Hollis.pdf Accessed: Jul 2011.

71. Heaney RP. Vitamin D in health and disease. Clin J Am Soc Nephrol 2008; 3:1535–41.

72. Garland CF, French CB, Baggerly LL, Heaney RP. Vitamin D supplement doses and serum 25-hydroxyvitamin D in the range associated with cancer prevention. Anticancer Res 2011; 31:617–22.

73. Barger-Lux MJ, Heaney RP. Effects of above average summer sun exposure on serum 25-hydroxyvitamin D and calcium absorption. J Clin Endocrinol Metab 2002; 87:4952–6.

74. Haddad JG, Chyu KJ. Competitive protein-binding radioassay for 25-hydroxycholecalciferol. J Clin Endocrinol Metab 1971; 33:992–5.

75. Haddock L, Corcino J, Vazques MD. 25(OH)D serum levels in the normal Puerto Rican population and in subjects with tropical sprue and parathyroid disease. P R Health Sci 1982; 1:85–91.

76. Bischoff-Ferrari HA, Shao A, Dawson-Hughes B, Hathcock J, Giovannucci E, Willett WC. Benefit-risk assessment of vitamin D supplementation. Osteoporos Int 2010; 21:1121–32.

77. Wolpowitz D, Gilchrest BA. The vitamin D questions: how much do you need and how should you get it? J Am Acad Dermatol 2006; 54:301–17.

78. El Ghissassi F, Baan R, Straif K, Grosse Y, Secretan B, Bouvard V, et al. A review of human carcinogens – Part D: Radiation. Lancet Oncol 2009; 10:751–2.

79. Samanek AJ, Croager EJ, Gies P, Milne E, Prince R, McMichael AJ, et al. Estimates of beneficial and harmful sun exposure times during the year for major Australian population centres. MJA 2006; 184:338–41.

80. The Australian and New Zealand Bone and Mineral Society, Osteoporosis Australia, the Australian College of Dermatologists and the Cancer Council Australia. Risks and benefits of sun exposure: Position Statement. From: www.cancer.org.au/File/PolicyPublications/PSRisksBenefitsSunExposure03May07.pdf Accessed: Feb 2012.

81. Heaney RP, Recker RR, Grote J, Horst RL, Armas LA. Vitamin D(3) is more potent than vitamin D(2) in humans. J Clin Endocrinol Metab 2011; 96:E447–52.

82. Armas LAG, Hollis BW, Heaney RP. Vitamin D2 is much less effective than vitamin D3 in humans. J Clin Endocrinol Metab 2004; 89:5387–91.

83. Romagnoli E, Mascia ML, Cipriani C, Fassino V, Mazzei F, D'Erasmo E, et al. Short and long-term variations in serum calciotropic hormones after a single very large dose of ergocalciferol (vitamin D2) or cholecalciferol (vitamin D3) in the elderly. J Clin Endocrinol Metab 2008; 93:3015–20.

84. Holick MF, Biancuzzo RM, Chen TC, Klein EK, Young A, Bibuld D, et al. Vitamin D2 is as effective as vitamin D3 in maintaining circulating concentrations of 25-hydroxyvitamin D. J Clin Endocrinol Metab 2008; 93:677–81.

85. Ball JC. A comparison of the UV-B irradiance of low-intensity, full-spectrum lamps with natural sunlight. From: www.anapsid.org/jamesball.html Accessed: Nov 2011.

86. Seppa N. The power of D: Sunshine vitamin's potential health benefits stir up, split scientists. Home 2011; 180:22.

87. Holick MF. Vitamin D deficiency. N Engl J Med 2007; 357:266–81.