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REVIEW ARTICLE

Photoprotection and vitamin D: a review

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SUMMARY

Background

The topic of vitamin D is at the forefront of discussions due to evidence suggesting its role in extra-skeletal health. It is already established that vitamin D plays a key role in skeletal health in young and elderly adults. This vitamin is obtained mainly through sunlight; various factors such as skin pigmentation and seasons affect cutaneous synthesis. Debates about the effects of sunscreen use on cutaneous synthesis of vitamin D have arisen in recent years.

Results

An updated review of the literature emphasizes that adequate levels of vitamin D are needed to prevent osteoporosis, falls and fractures in the elderly population. Emerging data also point to its role in cardiovascular disease, autoimmune conditions and cancers. Normal usage of sunscreen by adults has not shown to decrease cutaneous synthesis of vitamin D. Recommended Daily Allowance for vitamin D, released in 2010, was based on studies examining skeletal effects of this vitamin.

Conclusion

Oral intake with vitamin D-enriched foods or vitamin D supplements is recommended over prolonged ultraviolet exposure to maintain proper serum levels. Patients should not be discouraged from normal usage of sunscreens due to their well-established photoprotective effects.

Photodermatol Photoimmunol Photomed 2014; ••: ••–••

In addition to the well-established effects of vitamin D on bone health, numerous studies have shown the association of vitamin D with extra-skeletal conditions, such as cardiovascular disease and several cancers (1). Since sun exposure is one of only three ways of obtaining vitamin D, a debate has ensued about the consequences of photoprotection, such as sun avoidance, the use of photoprotective clothing and hats, and the application of sunscreens, on serum 25-hydroxyvitamin-D (25(OH)D) levels. Serum levels of 25(OH)D reflect vitamin D status. The following review focuses on the recent evidence on the association between extra-skeletal benefits and serum 25(OH)D levels, the impact of photoprotection, and recommendations for managing vitamin D insufficiency and deficiency.

ROLE OF VITAMIN D

The benefits of vitamin D in skeletal health have been well-established in literature. Optimization of bone mass

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from infancy until adolescence forms the foundation for primary prevention of osteoporosis. In a survey of children with vitamin D deficiency, defined as serum 25(OH)D concentrations < 50 nmol/l, 71% of these children displayed rachitic changes on radiographic studies (2, 3). Additionally, vitamin D deficiency in adolescence can trigger osteoporosis and pathologic fractures in late adulthood. In fact, supplementation of vitamin D in the elderly decreases the risk of falls and fractures. A more recent meta-analysis by Bischoff-Ferrari *et al.* (4) included a large set of double-blind, randomized controlled trials of vitamin D supplementation in persons greater than 65 years of age. This analysis suggested that a median dose of 800 International Units (IU) of vitamin D decreases the risk of hip fractures by 30% and the risk of any non-vertebral fractures by 14% in patients over 65 years of age. These studies are just a few in the myriad of investigations that have validated the benefits of appropriate vitamin D levels on bone health (4–6).

The possibility of extra-skeletal effects of vitamin D was initially based on the discovery of vitamin D receptor (VDR) in tissues such as the skin, placenta, pancreas, breast, prostate and colon cancer cells. Laboratory studies with animal models indicate the active form of vitamin D, 1,25-dihydroxyvitamin D_3 (1,25 $(OH)_2D_3$), plays a diverse role in cancer progression, cardiovascular health, the innate immune system and autoimmune conditions. Other studies with cancer mouse models have demonstrated the efficacy of 1,25 $(OH)_2D_3$ in reducing the severity of prostate cancer and in inhibiting tumor activity in colorectal cancers. The importance of vitamin D has been outlined in immune regulation with the discovery of vitamin D receptors on immune system cells. The active metabolite of vitamin D, 1,25$(OH)_2D_3$, plays an immunogenic role in down-regulating TH_1 immune responses, lowering proliferation of activated B cells, and promoting regulatory T cells (7–10). This finding is particularly relevant in patients with autoimmune diseases such as lupus erythematosus, as photoprotection is necessary to prevent exacerbations of disease; avoidance of sun exposure in these patients could potentially be a double-edged sword as it leads to lower 25(OH)D levels if not supplemented (11).

Contradictory opinions persist regarding the extra-skeletal effects of vitamin D. According to a report released by the Institute of Medicine (IOM) in 2010, evidence for the role of vitamin D in extra-skeletal functions was inconsistent, and as such, insufficient to make public health recommendations (12). Controversy also exists concerning what levels of serum 25(OH)D qualify as sufficient or deficient. According to the IOM, serum levels of 25(OH)D of 20 ng/ml (~50 nmol/l) fulfill the requirements of 97.5% of the population in North America; levels greater than 50 ng/ml (~125 nmol/l) were potentially related to adverse effects such as hypercalcemia, hypercalciuria, and soft tissue calcification to name a few. The levels stated above are used by most laboratories now as reference ranges for 25(OH)D (12, 13). Corroboration of the upper cut-off value of 50 ng/ml for 25(OH)D was provided in a cohort study conducted by de Boer *et al.* in 2012. This study demonstrated that the threshold 25(OH)D concentrations approaching 50 nmol/l in the springtime correlated with a potential risk for adverse clinical outcomes, measured as hip fracture, myocardial infarction, cancer and death. This study used season-specific thresholds for 25(OH)D and supported IOM's cut-off values (14).

In contrast, Holick *et al.* (15), writing for the Endocrine Society, recommended a higher cut-off value at 30–100 ng/ml (equal to 75–250 nmol/l) of 25(OH)D concentration in the serum; this recommendation was based on systemic reviews performed by the Task Force, appointed by the Endocrine Society. This rebuttal centered on studies that demonstrated a minimal circulating level of 25(OH)D of 30 ng/ml to maintain normal skeletal health. Additionally, this report included studies that demonstrated increased intestinal calcium absorption with increased 25(OH)D levels (15).

In conclusion, although the IOM recommendations for adequate vitamin D levels are now widely used, a full consensus has not been reached regarding adequate levels of vitamin D.

SOURCES OF VITAMIN D

The name vitamin D is a misnomer as it is not a vitamin but a fat-soluble, steroid hormone which can be procured through dietary sources, vitamin supplements and from sunlight exposure. Cutaneous formation of vitamin D after sunlight exposure is the most recognized source of this vitamin, thus labeling it as the 'sunshine' vitamin.

The action spectrum of cutaneous vitamin D synthesis is in the ultraviolet B (UVB) portion of sunlight, specifically, at a wavelength of 300 ± 5 nm. Upon such exposure, the precursor 7-dehydrocholesterol (7-DHC) in the plasma membranes of keratinocytes and fibroblasts is converted to previtamin D_3. Approximately 65% of 7-DHC is found in the upper layers of the epidermis, whereas 95% of previtamin D3 is produced in the basal and suprabasal layers of the epidermis. Previtamin D3 is then converted to vitamin D3 via a thermal, non-enzymatic process in the plasma membrane. With additional exposure to UVB, previtamin D3 can also be non-enzymatically converted to

Photodermatol Photoimmunol Photomed 2014; ••: ••–••

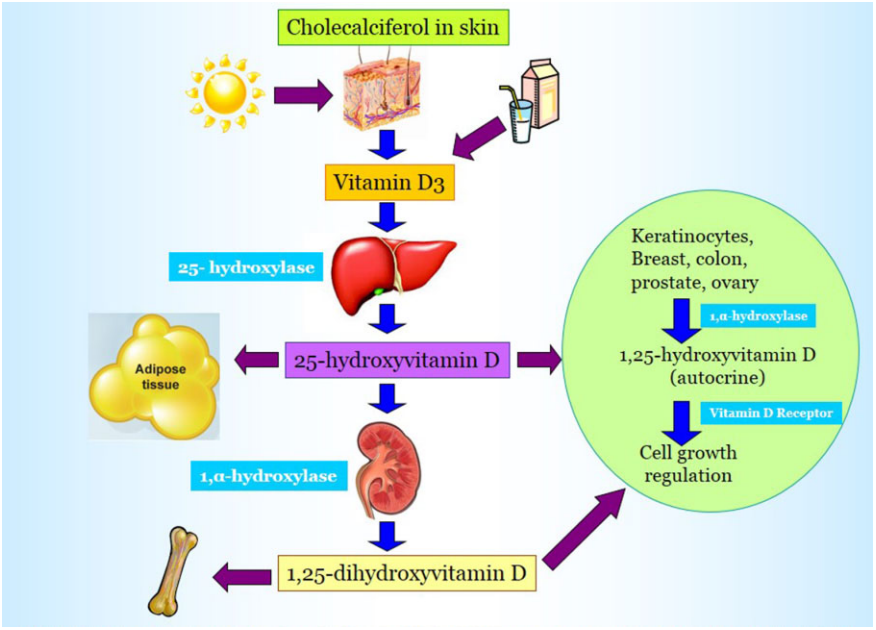

Fig. 1. Synthesis of vitamin D and the skeletal and extra-skeletal effects of vitamin D (16–19).

the inactive products, lumisterol and tachysterol. Photoconversion of previtamin D3 to the inactive products regulates production of vitamin D3 to prevent vitamin D intoxication with prolonged sun exposure. The thermal product vitamin D3, also known as cholecalciferol, is released from keratinocytes' plasma membrane and is bound by vitamin D binding protein in the plasma. It is then transported to the liver, and converted by 25-hydroxylase to 25(OH)D, the major circulating vitamin D metabolite. Levels of this metabolite are measured in patients to determine vitamin D status. 25(OH)D is further hydroxylated in the kidney by 1-α-hydroxylase to form the secosteroid hormone 1,25 $(OH)_2D_3$. This metabolite is the active form that regulates calcium homeostasis and other autocrine functions (5, 7, 8, 16–20). Of note, laboratory studies show other sites of conversion of 25(OH)D to 1,25 $(OH)_2D_3$ in keratinocytes, bone, placenta, prostate cells, macrophages, T-lymphocytes, and dendritic cells. (See Fig. 1 for pathway of vitamin D synthesis)

Cutaneous production of vitamin D_3 is influenced by numerous factors including skin pigmentation, photoprotection, time of day, season, latitude, altitude and even air pollution. An increase in the angle of the sun, that occurs in the wintertime, early mornings and late afternoons, results in better absorption of UVB photons in the ozone layer. This explains why vitamin D_3 synthesis occurs mainly between 10am and 3pm in the northern and southern regions of the world. Additionally, in the winter months, regions above or below 33 degrees latitude (this latitude crosses the southern tip of the United States, Iraq and Pakistan), there is insufficient ambient UVB to result in adequate epidermal production of vitamin D_3. Likewise, people residing in urban cities, such as Los Angeles, California and Mexico City, Mexico, are at a disadvantage as high nitrogen dioxide and ozone levels absorb significant UVB photons (21–24).

Vitamin D can also be obtained exogenously though dietary intake. Unfortunately, only a few foods naturally contain adequate levels of vitamin D_3, and these include cod liver oil, and fatty fish such as sword fish, salmon and tuna. Vitamin D_3 fortified milk and orange juice provide another food source for vitamin D (see Table 1). Vitamin D supplementation represents the third and final source of vitamin D. It is available as over-the-counter preparations in the United States; these are predominantly in the form of vitamin D_3. The prescription form in the United States is available as 50 000 IU ergocalciferol or vitamin D_2 (6, 7).

Ingested vitamin is incorporated into chylomicrons, which then enter the blood stream and become bound to vitamin D-binding proteins (VBPs) and lipoproteins. Both vitamin D_2 and D_3 are converted to the active metabolite by the pathway described above (25–28). A recent meta-analysis of randomized clinical trials on the effect of vitamin D_2 vs. D_3 in elevating serum 25(OH)D levels concluded that vitamin D_3 supplementation more effectively raises serum 25(OH)D concentrations (29). This supports the common practice on fortification and supplementation, which are achieved mainly through vitamin D_3.

Table 1 Food sources of vitamin D. Data from the National Institutes of Health Office of Dietary Supplements (61)

Food Source	Vitamin D, International Units (IU)
Cod liver oil (1 tbsp)	1360
Swordfish, cooked (3oz)	566
Sockeye salmon, cooked (3oz)	447
Tuna fish, canned (3oz)	154
Orange juice, vitamin D-fortified (1 cup)	137
Milk, vitamin D-fortified (1 cup)	115–124
Yogurt, vitamin D-fortified (6oz)	80
Cheese, Swiss (1oz)	6

MOLECULAR EFFECTS OF VITAMIN D

The active metabolite of vitamin D, 1,25 $(OH)_2D_3$, performs its functions mainly by acting as a regulator of gene transcription through a nuclear vitamin D receptor (VDR) and retinoic acid X receptor (RXR). The heterodimeric complex, formed by 1,25 $(OH)_2D_3$, VDR and RXR, binds to specific nucleic acid sequences in the DNA known as vitamin D response elements. Binding of other transcription elements to this complex subsequently results in either up-regulation or down-regulation of genetic activity. An estimated 60 human cell types express the vitamin D receptor, with an estimated 200 to 2000 genes forming the vitamin D response elements. Many organs and cell types including the brain, vascular smooth muscle, prostate, breast and macrophages not only contain VDR but also convert 25(OH)D to 1,25 $(OH)_2D_3$. The genes responsive to vitamin D influence biologic processes such as inhibition of cellular proliferation, apoptosis, inhibition of angiogenesis, insulin production, regulation of renin production, and production of bactericidal proteins. These genes are also involved in over 80 pathways linked to cancer, autoimmune diseases, cardiovascular health and bone health (1, 5, 7, 16–18). A recent study reported that improvement in serum 25(OH)D concentration in subjects with vitamin D deficiency (mean concentration of 25(OH)D < 20 ng/ml) or vitamin D insufficiency (mean concentration of 25(OH)D < 30 ngm/ml) resulted in a 1.5-fold alteration in genetic expression of about 291 genes (30).

Remarkably, other analogues of vitamin D have been shown to affect cell differentiation and apoptosis. A study conducted by Slominski *et al.* (31) demonstrated that an analogue called 20-hydroxyvitamin D_2, through the vitamin D receptor, inhibited DNA synthesis in keratinocytes and melanoma cells in-vitro (31). Likewise, another study, performed by the same author, discusses a novel pathway in the skin that predominantly produces 20-hydroxyvitamin D_3, which is metabolized to biologically active but non-calcemic derivatives. These derivatives also show anti-proliferative and anti-carcinogenic properties (32).

VITAMIN D LEVELS IN INDOOR WORKERS

Individuals at risk for vitamin D insufficiency include those with low sunlight exposure such as the elderly, home-bound individuals and even young adults with predominantly indoor exposure. A prospective study was conducted in a hospital community that measured vitamin D and calcium intakes and serum 25(OH)D and PTH concentrations in 35 internal medicine residents. In the fall season, 26% of the residents had serum concentrations of 25(OH)D < 20 ng/ml, and in the springtime, 47% had insufficient levels of less than 20 ng/ml. Medical residents were deemed to be at risk for hypovitaminosis D (defined as 25(OH)D levels < 20 ng/ml) particularly during the winter months (33). Another investigation was conducted in Australia of indoor workers that included 129 office workers in the summer and 175 workers in the winter. These researchers demonstrated that 14% of the participants had insufficient vitamin D levels in the summer compared to 51% in the winter (insufficient levels measured as 25(OH)D <50 nmol/l). Based on results from the questionnaire performed in this inquiry, high 25(OH)D levels in the summer correlated with increased time spent outdoors in non-peak UV periods, whereas in the wintertime, high levels were associated with vitamin D supplementation (34).

PHOTOPROTECTION AND VITAMIN D LEVELS

Patients with photosensitive disorders, who practice rigorous photoprotection, tend to maintain lower 25(OH)D levels. Typically, these patients avoid the sun, which can restrict vitamin D photosynthesis. A study of 52 patients with biopsy-proven cutaneous lupus erythematosus demonstrated low values of 25(OH)D < 25 nmol/l in 3.8% of the patients and concentrations less than 75 nmol/l in 65.4% of the patients. These levels were lower in sun avoiders and daily sunscreen users (35). A cohort of 201 patients with erythropoietic protoporphyria was studied in the United Kingdom, and the authors found 63% of the patients had levels of 25(OH)D less than 50 nmol/l. This insufficiency was inversely associated with the time (in minutes) to onset of symptoms following sunlight

exposure (36). Another retrospective investigation of 165 patients with photosensitivity residing in northern latitudes determined that blood collection in the winter, strict photoprotection and onset of symptoms within an hour of sunlight exposure were predictors of low vitamin D levels, defined as 25(OH)D < 50 nmol/l. Use of vitamin D supplement was associated with higher vitamin D levels approaching 50 nmol/l, even in patients who strictly avoided sunlight (37).

Studies have been conducted on the role of sunscreen application and vitamin D status. One of the first studies in 1988 consisted of a comparison of 20 fair-skinned individuals, with a history of skin cancer, applying para-aminobenzoic acid (PABA) sunscreen on all exposed body parts and 20 controls with no sunscreen use. These subjects were exposed to similar amounts of sunlight over summertime, and serum 25(OH)D levels were then measured. The study found the average serum level of 25(OH)D was significantly lower in the sunscreen user group compared to the control group; the measured levels of 25(OH)D in the PABA user group were still within normal range (38). However, this study had limitations as the baseline concentration of 25(OH)D was not measured prior to the usage of sunscreens, nor did the investigators note the amount of PABA sunscreen applied by the patients. These limitations make it difficult to determine the change in serum levels of vitamin D in these patients. Matsuoko *et al.* (1990) performed another study in which SPF 15 sunscreen was applied to different areas of individuals with skin phototype III an hour prior to whole-body UVB radiation of less than one minimal erythema dose. Serum $25(OHD_3$ levels were measured before and 24 h after exposure. The investigators found that whole-body coverage prevented vitamin D_3 synthesis, whereas a significant rise in vitamin D_3 occurred if more than 19% of total body surface area was free of sunscreen (39). Similarly, Holick (22) commented that daily application of sunscreen with SPF 8 on all sun-exposed body parts reduced cutaneous vitamin D production, measured as serum levels of 25(OH)D, by 90% (40).

A more recent randomized control trial by Faurschou *et al.* (41) included 37 healthy volunteers that were randomized to different thickness layers of SPF 8 sunscreen: 0.5 mg/cm^2, 1 mg/cm^2, 1.5 mg/cm^2 or 2 mg/cm^2. Participants were then irradiated with a fixed UVB dose of 3 standard erythema doses 20 min after sunscreen application, repeated four times with a 2–3 day interval. Blood samples for 25(OH)D measurements were drawn before the first irradiation and three days after the last dose. They found that vitamin D production increases exponentially when thinner sunscreen layers than recommended are applied (< 2 mg/cm^2) and proposed a re-evaluation of sun-protection strategies (41).

Even though the evidence based on controlled studies in mostly laboratory settings suggests that sunscreen suppresses vitamin D synthesis, larger-scale studies, in which subjects were asked to apply suncreens as they normally would, do not demonstrate these findings. In 1995, Marks *et al.* conducted a randomized, double-blind, controlled trial involving 113 Australian subjects; half of these patients applied SPF 17 sunscreen and the other half used placebo cream. Patients were instructed to apply either cream to the head and neck, forearms and dorsal hands at least once in the morning and to re-apply the cream if sweating or washing the product off during the day. Both groups wore sun badges to ensure equal amounts of sun exposure. Serum levels of 25(OH)D and 1,25 $(OH)_2D_3$ were measured before and after completion of the study period. The concentration of 25(OH)D rose similarly in each group; however, the level of 1,25 $(OH)_2D_3$ rose only in the control group. This difference could not be explained by the investigators. They noted that these levels were still in the upper half of the reference range in both groups during the entire study. Thus, the trial concluded that regular sunscreen use does not decrease vitamin D production in subjects exposed to sufficient amounts of sun (42).

Another study in Barcelona followed 24 elderly patients who applied sunscreen SPF 15 daily and 19 controls for a period of two years. Both serum 25(OH)D and 1,25 $(OH)_2D_3$ levels as well as parathyroid hormone and bone markers were measured at various intervals throughout the study. Serum concentrations of 1,25 $(OH)_2D_3$ and bone markers did not differ between the groups. Serum levels of 25(OH)D decreased in the winter by 31–35% in the control group and by 17–40% in the sunscreen group. In the summer, serum 25(OH)D levels increased slightly more in the control group than in the sunscreen group. This difference was not significantly large due to speculation that sunscreens are not applied adequately by patients. The same group of researchers followed 10 sunscreen users and 18 controls over two years and evaluated bone mass with dual X-ray absorptiometry in two summers and two winters during the duration of the study. These authors concluded that patients' typical use of sunscreen did not increase the risk of osteoporosis in their study population (43, 44).

Technically, sunscreens do not completely hinder cutaneous absorption of UVR but permit a calculated fraction of UVB photons to penetrate the skin, equaling to 1/SPF. For example, a sunscreen with SPF 30 allows 1/30 or 3.3% of UVR to be transmitted through the skin. Additionally, sunscreens are rarely applied at the tested level of

Fig. 2. Risk factors for vitamin D deficiency (6, 53).

protection, 2 mg/cm^2, as most individuals tend to apply 0.5 mg/cm^2. An applied sunscreen of SPF 16 is reduced to SPF 2 at a concentration of 0.5 mg/cm^2. Based on review of published results, Norval *et al.* concluded that sunscreens can significantly reduce the production of vitamin D under strict photoprotection, but their normal usage does not result in vitamin D insufficiency, most likely due to inadequate application (< 2 mg/cm^2) by the average users (45, 46).

Other recent investigations support the conclusion that normal usage of sunscreens does not decrease serum 25(OH)D levels. Linos *et al.* extrapolated data from NHANES 2003–2006 questionnaires regarding sun protection and concluded that frequent sunscreen use is not associated with low 25(OH)D levels in white individuals (47). However, white subjects who practiced photo-protective behaviors such as seeking shade or wearing long sleeves did have lower 25(OH)D levels and would be at risk for vitamin D deficiency. Since sun avoidance, long sleeves and shade clearly provide less UVR exposure than the use sunscreens alone, the odds of multiple sunburns are significantly lower in individuals practicing such behaviors (48). Another small study in an Australian subtropical community showed no correlation between sunscreen use and vitamin D status; however, persons who tended to seek shade, when spending less than 50% of daytime outdoors, had lower vitamin D levels than those who did not prefer shade (62.5 vs 68.8 nmol/l respectively, $P = 0.01$) (49).

SKIN TYPES AND VITAMIN D LEVELS

Constitutive skin pigmentation also affects serum vitamin D levels. An examination of different racial groups in the United States found lower levels of 25(OH)D in Mexican-Americans and African-Americans compared to Caucasians of the same age groups (50). An investigation in 1991 reported a relationship between skin pigmentation and vitamin D_3 formation. After a fixed dose of UVB radiation, serum vitamin D_3 levels were significantly higher in white and Asian populations than in black and East-Indian groups (51). Nevertheless, serum 1,25 $(OH)_2D_3$ levels were similar in all groups, irrespective of skin pigmentation. A more recent cohort performed in Ontario, Canada, measured serum 25(OH)D levels in several skin types in the wintertime. They reported that while low vitamin concentrations were common during the wintertime in young adults, a higher percentage of East Asians and South Asians had 25(OH)D levels less than 40 nmol/l than their European counterparts (52).

VITAMIN D SUPPLEMENTATION

Population groups at risk of vitamin D deficiency include: older adults, breast-fed infants, individuals with limited sun exposure due to climate, or rigorous photoprotection or full coverage of skin with opaque clothing, dark-skinned individuals, and persons suffering from malabsorption syndromes or obesity (6). Another common cause of

vitamin D deficiency is medication use, such as anticonvulsants or glucocorticoids, which can increase catabolism of vitamin D (53). (see Fig. 2 regarding risk factors for vitamin D deficiency].

Supplementation of vitamin D can be obtained through sunlight exposure, irradiation with UVB radiation, vitamin D supplements or intake of vitamin D-enriched foods. A randomized control trial of 211 non-Western immigrants in the Netherlands with vitamin D deficiency (baseline 25(OH)D was 22.5 ± 11 nmol/l) compared supplementation of vitamin D 800 IU/day or 100 000 IU every 3 months to advised sunlight exposure of 30 min per day between March and September. Patients responded more significantly to vitamin D supplementation than to recommended sunlight exposure (53 nmol/l with 800 IU/day, 50.5 nmol/l with 100 000 IU/3 months, 29.1 nmol/l with sunlight) (54). These authors concluded that vitamin D supplementation is more effective in treating vitamin D deficiency in non-western immigrants than sunlight exposure.

Other investigations illustrate more contradictory data when comparing the efficacy of narrowband UVB (NB-UVB) exposure to oral intake of vitamin D in increasing serum 25(OH)D levels. Bogh *et al.* investigated the treatment of vitamin D deficiency with NB-UVB compared to supplementation with oral vitamin D_3 1600 IU and calcium 1000 mg. In their study, full body NB-UVB, three times per week, more effectively raised vitamin D levels than oral supplementation (from 19.2 to 75 nmol/l and from 23.3 to 60.6 nmol/l, respectively in the NB-UVB and supplementation groups) (55).

Similar conclusions were drawn in another investigation with 67 healthy subjects whose 25(OH)D concentrations measured less than 75 nmol/l. These volunteers were randomized to either 12 NB-UVB exposures with a mean cumulative dose of approximately 48 standard erythema doses or to 20 μg (~800 IU/d) of oral cholecalciferol (vitamin D3) daily for 4 weeks. After 12 NB-UVB exposures given during a 4 week period, the mean concentration of 25(OH)D increased by 41.0 nmol/l vs. 20.2 nmol/l increase in the cholecalciferol group. The difference in response was significant at two weeks, four weeks and two months after treatment course. These authors concluded that a short course of NB-UVB effectively increases vitamin D balance in the wintertime with evidence of response two months after the course (56).

Even though the above proof-of-concept studies show the relative efficacy of NB-UVB in improving vitamin D status, the authors did not supervise oral intake of vitamin D supplementation, which raises the concern for compliance. Additionally, the limitation of resources (time and cost) to perform these treatments makes them less advisable for patients with low vitamin D levels. Since vitamin D supplementation and vitamin D-rich foods are available in ample quantities, these can be easily obtained from nutritional stores if necessary.

RECOMMENDATIONS FOR VITAMIN D SUPPLEMENTATION

Recommendations from the Institute of Medicine (IOM) regarding vitamin D supplementation were based on available scientific evidence supporting a role of vitamin D and calcium in skeletal health. IOM also assumed minimal or no sun exposure when forming these guidelines for dietary requirements. Information regarding the extra-skeletal outcomes, such as cancer, cardiovascular diseases, diabetes mellitus and autoimmune conditions were considered inconsistent to amend nutritional requirements. The 2010 guidelines established Recommended Dietary Allowances (RDAs) of vitamin D for different age groups: 400 IU for ages < 1 year, 600 IU for ages 1–70, including pregnant and lactating women, and 800 IU for ages > 71. Furthermore, IOM concluded that a serum 25(OH)D level of at least 20 ng/ml (50 nmol/l) would meet the requirements of at least 97.5% of the population in North America (13), hence should be considered adequate. The RDA values for infants were confirmed in a randomized controlled trial of 132 healthy infants at one month of age. These participants were assigned to receive vitamin D3 of 400 IU/d, 800 IU/d, 1200 IU/d or 1600 IU/d. These investigators concluded all dosages used, including the 400 IU/d, established 25(OH)D concentrations of 50 nmol/l or greater in 97% of the infants at 3 months and sustained these effects in 98% of the infants at 12 months; higher doses of 1600 IU/d increased 25(OH)D concentrations to levels that trigger hypercalcemia (57).

The recommendations determined by the IOM were authenticated in a meeting held in Europe in 2011, hosting the leading experts on vitamin D. These experts recognized the importance of combined vitamin D and calcium supplementation in reducing fracture risk in the elderly population. Thus, adults > 65 years of age are recommended to meet an RDA of 800 IU/day, which is best achieved with supplementation (58). Likewise, the U.S. Preventive Services Task Force (USPSTF) in 2013 recommends similar supplementation with 800 IU of vitamin D in community-dwelling asymptomatic adults > 65 years of age without a history of fractures; however, they do not endorse daily supplementation with vitamin D < 400 IU and calcium < 1000 mg for primary prevention of fractures in post-menopausal, non-institutionalized females. In

premenopausal women and in men, evidence is lacking to verify the effect of vitamin D and calcium supplementation on the incidence of fractures (59).

CONCLUSION

A large body of investigations establishes that vitamin D plays a role beyond just bone health and produces multiple bodily effects. Longitudinal studies, however, do not associate vitamin D deficiency with an increased overall mortality or other extra-skeletal effects (60). Thus, recommendations for dietary requirements of vitamin D are based on skeletal benefits that are established in young adulthood and in the elderly. To treat vitamin D deficiency in at-risk population groups, oral supplementation is recommended over sunlight exposure or even NB-UVB radiation. The former can be obtained easily and inexpensively, while intensity of sunlight can be affected by multiple variables, and NB-UVB exposure is costly. Sunscreens applied at recommended concentrations of 2 gm/cm^2 reduces vitamin D synthesis. However, in the practical in-use setting, sunscreen application does not lead to decreased vitamin D levels. However, other sun-protective methods such as sun avoidance, seeking shade or wearing long sleeves, and darker skin pigmentation can result in insufficient serum vitamin D levels; hence, vitamin D supplement should be considered for these at-risk groups.

REFERENCES

1. Hossein-nezhad A, Holick MF. Vitamin D for health: a global perspective. *Mayo Clin Proc* 2013; **88**: 720–755.
2. Koo W, Walyat N. Vitamin D and skeletal growth and development. *Curr Osteoporos Rep* 2013; **11**: 188–193.
3. Bone health and osteoporosis. A report of the Surgeon General U.S. Department of Health and Human Services. Available at: http://www.surgeongeneral.gov/library/reports/bonehealth/full_report.pdf. Accessed 8 August 2013.
4. Bischoff-Ferrari HA, Willett WC, Orav EJ *et al.* A pooled analysis of vitamin D dose requirements for fracture prevention. *N Engl J Med* 2012; **367**: 40–49.
5. LoPiccolo MC, Lim HW. Vitamin D in health and disease. *Photodermatol Photoimmunol Photomed* 2010; **26**: 224–229.
6. Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation. *JAMA* 2005; **293**: 2257–2264.
7. Vanchinathan V, Lim HW. A dermatologist's perspective on vitamin D. *Mayo Clin Proc* 2012; **87**: 372–380.
8. Reddy KK, Gilchrest BA. What is all this commotion about vitamin D? *J Invest Dermatol* 2010; **130**: 321–326.
9. Christakos S, Hewison M, Gardner DG *et al.* Vitamin D: beyond bone. *Ann N Y Acad Sci* 2013; **1287**: 45–58.
10. Singh A, Kamen DL. Potential benefits of vitamin D for patients with systemic lupus erythematosus. *Dermatoendocrinol* 2012; **4**: 146–151.
11. Mok CC. Vitamin D and systemic lupus erythematosus: an update. *Expert Rev Clin Immunol* 2013; **9**: 453–456.
12. Institutes of Medicine. *Dietary reference intakes: vitamins*. Washington DC: Institute of Medicine, 2001. Available at: http://www.iom.edu/Home/Global/News%20Announcements/~/media/Files/Activity%20Files/Nutrition/DRIs/DRI_Vitamins.ashx. Accessed 8 July 2013.
13. Ross AC, Manson JE, Abrams SA *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**: 53–58.
14. de Boer IH, Levin G, Robinson-Cohen C. Serum 25-hydroxyvitamin D concentration and risk for major clinical disease events in a community-based population of older adults: a cohort study. *Ann Intern Med* 2012; **156**: 627–634.
15. Holick MF, Binkley NC, Bischoff-Ferrari HA *et al.* Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2011; **96**: 1911–1930.
16. Holick MF, MacLaughlin JA, Clark MB *et al.* Photosynthesis of previtamin D3 in human skin and the physiologic consequences. *Science* 1980; **210**: 203–205.
17. Lehmann B, Meurer M. Vitamin D metabolism. *Dermatol Ther* 2010; **12**: 2–12.
18. Bikle DD. Vitamin D metabolism and function in the skin. *Mol Cell Endocrinol* 2011; **347**: 80–89.
19. Shahriari M, Kerr PE, Slade K, Grant-Kels JE. Vitamin D and the skin. *Clin Dermatol* 2010; **28**: 663–668.
20. Webb AR, de Costa BR, Holick MF. Sunlight regulates the cutaneous production of vitamin D3 by causing its photodegradation. *J Clin Endocrinol Metab* 1989; **68**: 882–887.
21. Diehl JW, Chiu MW. Effects of ambient sunlight and photoprotection on vitamin D status. *Dermatol Ther* 2010; **23**: 48–60.
22. Holick MF. Environmental factors that influence the cutaneous production of vitamin D. *Am J Clin Nutr* 1995; **61**: 638S–645S.
23. Webb AR. Who, what, where and when-influences on cutaneous vitamin D synthesis. *Prog Biophys Mol Biol* 2006; **92**: 17–25.
24. Engelsen O, Brustad M, Aksnes L, Lund E. Daily duration of vitamin D synthesis in human skin with relation to latitude, total ozone, altitude, ground cover, aerosols and cloud thickness. *Photochem Photobiol* 2005; **81**: 1287–1290.
25. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am J Clin Nutr* 2008; **87**: 1080S–1086S.
26. Sage RJ, Lim HW. Therapeutic Hotline: recommendations on photoprotection and vitamin D. *Dermatol Ther* 2010; **23**: 82–85.
27. McCullough ML, Robertson AS, Rodriguez C *et al.* Calcium, vitamin D, dairy products, and risk of colorectal cancer in the cancer prevention study II nutrition cohort (United States). *Cancer Causes Control* 2003; **14**: 1–12.
28. Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2007; **167**: 1730–1737.
29. Tripkovic L, Lambert H, Hart K *et al.* Comparison of vitamin D2 and vitamin

D3 supplementation in raising serum 25-hydroxyvitamin D status: a systemic review and meta-analysis. *Am J Clin Nutr* 2012; **95**: 1357–1364.
30. Hossein-nehzad A, Spira A, Holick MF. Influence of vitamin D status and vitamin D3 supplementation on genome wide expression of white blood cells: a randomized double-blind clinical trial. *PLoS ONE* 2013; **8**: e58725.
31. Slominski AT, Kim TK, Janjetovic Z *et al*. 20-Hydroxyvitamin D2 is a noncalcemic analog of vitamin D with potent antiproliferative and prodifferentiation activities in normal and malignant cells. *Am J Physiol Cell Physiol* 2011; **300**: C526–C541.
32. Slominski AT, Zmijewski MA, Semak I *et al*. Cytochromes P450 and skin cancer: role of local endocrine pathways. *Anticancer Agents Med Chem* 2013 [Epub ahead of print].
33. Haney EM, Stadler D, Bliziotes MM. Vitamin D insufficiency in internal medicine residents. *Calcif Tissue Int* 2005; **76**: 11–16.
34. Vu LH, Whiteman DC, van der Pols JC, Kimlin MG, Neale RE. Serum vitamin D levels in office workers in a subtropical climate. *Photochem Photobiol* 2011; **87**: 714–720.
35. Cusack C, Danby C, Fallon JC. Photoprotective behavior and sunscreen use: impact on vitamin D levels in cutaneous lupus erythematosus. *Photodermatol Photoimmunol Photomed* 2008; **24**: 260–267.
36. Holme SA, Ansley AV, Badminton MN, Elder GH. Serum 25-hydroxyvitamin D in erythropoietic protoporphyria. *Br J Dermatol* 2008; **159**: 211–213.
37. Reid SM, Robinson M, Kerr AC, Ibbotson SH. Prevalence and predictors of low vitamin D status in patients referred to a tertiary photodiagnostic service: a retrospective study. *Photodermatol Photoimmunol Photomed* 2012; **28**: 91–96.
38. Matsuoko LY, Wortsman J, Hanifan N, Holick MF. Chronic sunscreen use decreases circulating concentrations of 25-hydroxyvitamin D. A preliminary study. *Arch Dermatol* 1988; **124**: 1802–1804.
39. Matsuoka LY, Wortsman J, Hollis BW. Use of topical sunscreen for the evaluation of regional synthesis of vitamin D3. *J Am Acad Dermatol* 1990; **22**: 772–775.
40. Holick MF, Matsuoka LY, Wortsman J. Regular use of sunscreen on vitamin D levels. *Arch Dermatol* 1995; **131**: 1337–1339.
41. Faurschou A, Beyer DM, Schmedes A, Bogh MK, Philipsen PA, Wulf HC. The relation between sunscreen layer thickness and vitamin D production after ultraviolet B exposure: a randomized clinical trial. *Br J Dermatol* 2012; **167**: 391–395.
42. Marks R, Foley PA, Jolley D, Knight KR, Harrison J, Thompson SC. The effect of regular sunscreen use on vitamin D levels in an Australian population: results of a randomized controlled trial. *Arch Dermatol* 1995; **131**: 415–421.
43. Farrerons J, Barnadas M, Rodriguez J *et al*. Clinically prescribed sunscreen (sun protection factor 15) does not decrease serum vitamin D concentrations sufficiently either to induce changes in parathyroid function or in metabolic markers. *Br J Dermatol* 1998; **139**: 422–427.
44. Farrerons J, Barnadas M, Lopez-Navidad A *et al*. Sunscreen and risk of osteoporosis in the elderly: a two-year follow-up. *Dermatology* 2001; **202**: 27–30.
45. Norval M, Wulf HC. Does chronic sunscreen use reduce vitamin D production to insufficient levels? *Br J Dermatol* 2009; **161**: 732–736.
46. Faurschou A, Wulf HC. The relation between sun protection factor and amount of sunscreen applied *in vivo*. *Br J Dermatol* 2007; **156**: 716–719.
47. Linos E, Keiser E, Kanzler M *et al*. Sun protective behaviors and vitamin D levels in the US population: NHANES 2003–2006. *Cancer Causes Control* 2012; **23**: 133–140.
48. Linos E, Keiser E, Fu T, Colditz G, Chen S, Tang JY. Hat, shade, long sleeves or sunscreen? Rethinking US sun protection messages based on their relative effectiveness. *Cancer Causes Control* 2011; **22**: 1067–1071.
49. Jayaratne N, Russell A, van der Pols JC. Sun protection and vitamin D status in an Australian subtropical community. *Prev Med* 2012; **55**: 146–150.
50. Bischoff-Ferrari HA, Dietrich T, Orav EJ, Dawson-Hughes B. Positive association between 25-hydroxyvitamin D levels and bone mineral density: a population-based study of younger and older adults. *Am J Med* 2004; **116**: 634–639.
51. Matsuoka LY, Wortsman J, Haddad JG, Kolm P, Hollis BW. Racial pigmentation and the cutaneous synthesis of vitamin D. *Arch Dermatol* 1991; **127**: 1155–1228.
52. Gozdzik A, Barta JL, Wu H *et al*. Low wintertime vitamin D levels in a sample of healthy young adults of diverse ancestry living in the Toronto area: associations with vitamin D intake and skin pigmentation. *BMC Public Health* 2008; **8**: 336.
53. Bordelon P, Ghetu MV, Langan RC. Recognition and management of vitamin D deficiency. *Am Fam Physician* 2009; **80**: 841–846.
54. Wicherts IS, Boeke AJP, van der Meer IM, van Schoor NM, Knol DL, Lips P. Sunlight exposure or vitamin D supplementation for vitamin d-deficient non-western immigrants: a randomized clinical trial. *Osteoporos Int* 2011; **22**: 873–882.
55. Bogh MKB, Gullstrand J, Svensson A, Ljunggren B, Dorkhan M. Narrowband ultraviolet B three times per week is more effective in treating vitamin D deficiency than 1600 IU oral vitamin D3 per day: a randomized clinical trial. *Br J Dermatol* 2012; **167**: 625–630.
56. Ala-Houhala MJ, Vahavihu K, Kautiainen H *et al*. Comparison of narrowband ultraviolet B exposure and oral vitamin D substitution on serum 25-hydroxyvitamin D concentration. *Br J Dermatol* 2012; **167**: 160–164.
57. Gallo S, Comeau K, Vanstone C *et al*. Effect of different dosages of oral vitamin D supplementation on vitamin D status in healthy, breastfed infants. A randomized trial. *JAMA* 2013; **309**: 1785–1792.
58. Brouwer-Brolsma EM, Bischoff-Ferrari HA, Bouillon R *et al*. Vitamin D: do we get enough? A discussion between vitamin D experts in order to make a step towards the harmonisation of dietary reference intakes for vitamin D across Europe. *Osteoporos Int* 2013; **24**: 1567–1577.
59. Moyer VA, U.S. Preventive Services Task Force. Vitamin D and calcium supplementation to prevent fractures in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2013; **158**: 691–696.
60. Skaaby T, Husemoen LL, Pisinger C *et al*. Vitamin D status and cause-specific mortality: a general population study. *PLoS ONE* 2012; **7**: e52423.
61. National Institutes of Health Office of Dietary Supplements. Dietary supplement fact sheet: vitamin D. National Institutes of Health Office of Dietary Supplements 2010. Available at: http://dietary-supplements.info.nih.gov/factsheets/vitamind.asp#h3. Accessed 31 July 2011.