

Limited Exposure to Ambient Ultraviolet Radiation and 25-Hydroxyvitamin D Levels: A Systematic Review

Running head: Limited UVR exposure and vitamin D levels

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List of abbreviations: 25OHD, 25-hydroxyvitamin D; UVR, ultraviolet radiation

What's already known about this topic?

- Hypovitaminosis D is common worldwide.
- Adequate vitamin D levels are associated with improved health outcomes.
- Vitamin D can be obtained from the diet, through oral supplementation or synthesised in human skin following exposure to ultraviolet radiation (UVR).
- Many authorities advocate that UVR exposure is essential for adequate vitamin D levels.
- UVR exposure can lead to skin cancer development, resulting in approximately 13 million skin cancers worldwide per annum.

What does this study add?

- This study demonstrates that many healthy adults in different population groups across the world can maintain adequate serum vitamin D levels despite negligible UVR exposure for several months of the year.

- Public health campaigns promoting a high vitamin D diet or supplements to healthy adults could positively impact on the burden to the individual and the health service of inadequate vitamin D levels and could avoid negative sequelae of UVR exposure.

Abstract

Background: Vitamin D can be synthesised following exposure to ultraviolet radiation (UVR), ingested in the diet or provided through oral supplementation. The medical literature frequently states that humans obtain most of their vitamin D from sunshine and that UVR exposure is essential to maintain vitamin D levels. Objective: A systematic review was conducted to determine the requirement for UVR in maintaining adequate (>50nmol/L) serum 25-hydroxyvitamin D (25OHD) levels. Method: Studies reporting serum 25OHD during situations of negligible UVR exposure were sought. 41 studies (from a search yielding 42,698 articles) totalling 4,211 healthy adults met the inclusion criteria, providing 56 datasets from different population groups. Results: Over 50% of subjects had >50nmol/L 25OHD in 10 of 19 datasets reporting winter levels in areas with limited UVR. In addition, >50% of subjects had adequate 25OHD levels in 4 of 12 datasets from polar regions during periods of negligible UVR, 1 of 9 datasets documenting clothing-related minimal UVR and 2 of 8 datasets detailing employment-related minimal UVR. Conclusion: The data demonstrate that many adults maintain adequate serum vitamin D levels despite negligible UVR exposure for several months. However, we acknowledge that preceding UVR exposure leading to vitamin D storage and delayed release may account for this maintenance of adequate serum vitamin D levels. There remains a need for further research on whether UVR exposure is required for longer-term maintenance of adequate vitamin D levels.

Introduction

A growing evidence base suggests that adequate levels of vitamin D are associated with superior health outcomes. These include improved bone¹ and cardiovascular health², lower incidence/activity of autoimmune disease^{3,4}, reduced cancer incidence/mortality⁵ and reduced all-cause mortality⁶.

Although vitamin D levels in humans can be increased by dietary intake, dietary supplementation and ultraviolet radiation (UVR) exposure⁷, hypovitaminosis D remains prevalent worldwide^{8,9}. The medical literature frequently states that humans obtain most of their vitamin D from sunshine and that UVR exposure is essential to maintain vitamin D levels^{10,11}.

Consequently, public health guidelines frequently encourage sun exposure for maintenance of adequate vitamin D levels^{12,13}. However, UVR has detrimental effects on human health and the World Health Organisation estimates UVR exposure results in loss of 1.5 million disability-adjusted life years and 60,000 premature deaths worldwide annually, including 200,000 melanomas, 12.8 million non-melanoma skin cancers, and 30% of eight million cataracts¹⁴.

Interventional studies demonstrate that UVR can increase vitamin D in humans, but extrapolating from them to suggest UVR is necessary for adequate vitamin D levels may be erroneous. A recent modelling study reported that 10 – 20 minutes of sun exposure (often advocated by public health statements) is inadequate to significantly boost serum vitamin D levels and that sufficient sun exposure to achieve worthwhile benefit would compromise skin health¹⁵. However, a trial employing artificial UVR three times weekly for six weeks suggested one can achieve adequate serum 25OHD levels from this amount of midday sunshine once individuals (white

Caucasians) expose 35% of their body surface area to sunshine incident vertically on exposed skin¹⁶. Limited data exist for weighing risk/benefit when considering inadequate vitamin D status versus over-exposure to sunlight, and the International Agency for Research on Cancer has argued for more research to address questions about UVR as a means of increasing vitamin D levels¹⁷. With this in mind we sought to address the question: is there evidence to show whether vitamin D levels can be maintained despite extended periods of little or no exposure to sunlight?

Materials and methods

Selection of studies for review

Scoping searches were performed between August 2008 and April 2009 with input from an information specialist to assist in development of the search strategy. Subsequently, following the development of a study protocol (supplementary material), relevant published articles were identified through searches of through Medline (1948 to July 2012), Embase (1980 to July 2012), Cochrane Central Database, Cochrane Systematic Reviews, Cochrane Clinical Trials Registry, Database of Abstracts and Reviews (1986 to July 2012), Health Technology Assessment Database, NHS Economic Evaluation Database (1994 to July 2012), Centre for Research and Dissemination Research in Progress Database, Current Controlled Trials, National Research Registry archive and Cancer Research UK research register. Bibliographies of papers meeting inclusion criteria were used to search for additional relevant publications and recent issues of major journals were hand searched. Given the size of the body of evidence, including effects of age and illness on

circulating vitamin D concentrations, this review focused on healthy adults, with the protocol being altered to reflect this. Only English language articles were included. All searches were continually updated during the course of the review and all references stored in an Endnote database.

For online searches, synonyms of diet, dietary supplementation and ultraviolet radiation were used to create search strings (see supplementary material). A study design facet within the search term was not included, as nomenclature for observation studies is not standardised. Observational studies reporting on the relationship between UVR and serum vitamin D levels in healthy adult populations were included with no exclusions based upon ethnicity, gender or skin type.

Two independent investigators (SAR and MC/LMV/AF) screened titles and abstracts where available from the searches and another author (EH) acted as arbiter where necessary. When there was insufficient information to make an accurate decision about quality or eligibility of an article for inclusion, or numerical data could not be extracted, further information was sought from the author. Papers were excluded where participants were in long-term care, had an intercurrent illness, serum vitamin D was not measured, on drugs that affect vitamin D metabolism, and in the case of duplicate data. We have not listed all excluded studies as they were in excess of 42,000 papers.

Data extraction and study quality assessment

Data extraction was undertaken by two reviewers (SAR and MR/LMV/AF) and entered into an electronic record. Uncertainty was resolved in the same manner as for selection of abstracts. Methodological quality of each study was

assessed through composition of a validity score (see supplementary material) with studies rejected below an agreed score.

Data analysis

Data on serum 25OHD levels from each article were displayed graphically as mean and standard deviation. Where study participants were divided into different groups based on ethnicity or gender, these groups were maintained during data extraction/synthesis processes and labelled as different datasets in graphs. Studies with a mean 25OHD value $>50\text{nmol/l}$ (equivalent to $>20\text{ng/ml}$) were designated as demonstrating that many individuals within the investigated population had adequate 25OHD levels at time of assessment.

Results

A systematic review was conducted according to the structure and methods outlined by the Centre for Reviews and Dissemination (2008) and PRISMA statement¹⁸. To assess whether UVR exposure is necessary to maintain adequate vitamin D levels, we identified and evaluated studies reporting on serum 25OHD in groups of people living in circumstances of absent or negligible UVR to determine whether all healthy adults in these situations have inadequate serum 25OHD.

The search identified 42,695 references, of which 8,489 were duplicates (figure 1). Following screening of title and abstract by two independent reviewers, another 33,905 were excluded, leaving 301 references requiring full text review, with 3 additional papers found on review of reference lists therein. Forty-one studies were included in the final analysis including 11

cross-sectional, 25 observational cohort, 1 interventional cohort, 1 case-control and 3 randomised controlled trials. Each study was represented by one of four categories; (1) seasonal variation in serum 25OHD (studies including wintertime serum 25OHD levels), (2) location-related minimal UVR exposure (studies on participants in polar regions), (3) clothing-related minimal UVR exposure and (4) employment-related minimal UVR exposure.

Seasonal variation in serum vitamin D

Skin synthesis of vitamin D depends on incident UVB radiation and the annual fluence of UVB radiation at 310 nm at 60°, 45° and 30° latitude are 20%, 40% and 65% respectively of the annual fluence at the Equator. The lower solar elevation angle at higher latitudes and higher levels of ozone are thought to account for this variation. Out of 27 datasets (comprising 3,018 individuals between latitudes 22°S and 53°N) from 20 studies¹⁹⁻³⁸, 20 demonstrated mean serum 25OHD levels higher in summer than winter (figure 2). In six datasets, only a wintertime level was measured. There is evidence that ambient UVR in winter is insufficient to generate vitamin D at higher latitudes in nonpolar regions, e.g. no previtamin D3 is produced from November to February inclusive in Boston, USA (42°N), and between October and March in Edmonton, Canada (52°N)³⁹. In 10 datasets, comprising 625 subjects, mean serum 25OHD was adequate (>50nmol/L) during wintertime when UVR during those months would not have acted as a source of serum vitamin D for 19 of the 27 datasets. Although one study reported that black females in Toronto, Canada had mean serum 25OHD levels >50nmol/L in winter and summer²³, four data sets of participants failed to reach an

adequate mean serum 25OHD level in summertime; these comprised non-Hispanic black women and Hispanic women in Galveston, Texas²⁹, black women in Boston²⁰ and a heterogenous group in Paris²⁵.

Location-related minimal UVR exposure

These nine polar region studies included 556 individuals⁴⁰⁻⁴⁸. Mean serum 25OHD remained adequate in four of twelve datasets during the prolonged winter season during which winter UVR does not contribute to serum vitamin D levels (figure 3). Some participants are likely to have maintained serum 25OHD by dietary supplementation; those in Skejvoy consumed a traditional diet comprising regular fish-liver which contains high quantities of vitamin D⁴¹ and the Tromso study ascribed the adequate 25OHD levels to diet, including foods (e.g. margarine) fortified with vitamin D⁴⁰. Two groups of migrant workers from the UK and Australia did not consume vitamin D supplements or a fortified diet, yet all participants in these studies maintained an adequate serum 25OHD level throughout the year^{43,45}.

Clothing-related minimal UVR exposure

Nine datasets in six studies comprised 276 veiled women living between 24°N and 41°N (figure 4)⁴⁹⁻⁵⁴. Eight datasets reported mean 25OHD levels classed as deficient, but one group of 30 veiled women had a mean serum 25OHD of 83 ± 40 nmol/L⁴⁹. Most participants in this latter group led an indoor life in the outskirts of Adana, Turkey with only 33% receiving direct sunlight to uncovered face and distal extremities in the courtyards of their homes.

Employment-related minimal UVR exposure

These six studies contained 361 participants receiving little or no UVR due to their occupational environment (figure 5)⁵⁵⁻⁶⁰. Most had deficient 25OHD levels, but the submariners studied by Duplessis *et al.* had adequate mean serum 25OHD. In that study, some individuals received 400IU of vitamin D supplementation daily and a vitamin D fortified diet. However, >50% of submariners who consumed a fortified diet without additional supplementation also maintained adequate serum 25OHD levels⁵⁸.

Discussion

This systematic review focussed on studies measuring 25OHD in healthy adults exposed to minimal UVR to see whether it is possible for them to maintain serum vitamin D levels without UVR exposure. Many people have higher serum 25OHD in summer than in winter, and this increase during summer months likely relates to skin synthesis of vitamin D following sun exposure. However, the results of this review indicate that many people can maintain adequate serum 25OHD levels in the absence or paucity of sunlight for several months and possibly on a longer-term basis. As adequate levels of vitamin D could be maintained in >50% of participants in 17 of 56 groups amassed from 41 studies, this is a reproducible observation found in population groups in many different parts of the world. Whilst subjects with low dietary vitamin D intake living in areas of high sun-exposure may obtain significant amounts of vitamin D from UVR, the current study suggests that many individuals obtain little or no vitamin D from sunshine for several months of the year.

The vast number of publications on vitamin D makes it difficult to form a valid evidence-based opinion in a short timeframe on whether UVR is necessary for maintenance of adequate vitamin D levels, highlighting a need for this systematic review. Currently, many position statements advocate sun exposure for the maintenance of adequate vitamin D levels, an approach that requires caution given the known negative implications of excessive UV exposure. As the data in figure 2 demonstrate, it is also not sufficient to presume that individuals in sunny environments will necessarily be vitamin D replete in summertime, a finding well and repeatedly supported by other published studies⁶¹⁻⁶⁴.

Whilst there is a generally agreed level of insufficient serum 25OHD (25nmol/L) there is no universally agreed minimum or optimum serum 25OHD level⁶⁵⁻⁶⁹. Having reviewed the literature, we opted for 25OHD levels of adequate (>50nmol/L) and optimal (>75nmol/L) in common with some experts in the field^{68,70-73}. This review concentrated on adequate 25OHD levels and our conclusions relate primarily to this outcome. However the inclusion of lines to indicate both adequate and optimal levels of 25OHD in figures 2 – 5 does allow identification of the studies where individuals reach optimal 25OHD levels.

It is clear that UVR is an important source of vitamin D in many population groups⁷⁴⁻⁷⁶. Whilst some patterns of sunlight exposure have benefits (notably a reduction in lifetime melanoma risk with occupational sun exposure⁷⁷), there is strong evidence that individuals who overexpose themselves to sunlight carry a significantly increased risk of cutaneous carcinogenesis and/or cataract. There is uncertainty about the optimal dietary vitamin D intake and

the acceptable level of exposure to UVB that would permit vitamin D synthesis without increasing UVR-related disease. Although a consensus statement from various societies suggests that suberythemal doses of midday UVR can be helpful in generating vitamin D¹³, suberythemal UVR doses are known to cause a variety of effects in skin, including DNA damage and p53 upregulation^{78,79}.

In order to derive dietary reference values for vitamin D, the dietary requirement for vitamin D when skin-derived vitamin D is very low or negligible needs to be defined. In the UK, there is no dietary reference value for vitamin D for normal adults, which implies no absolute need for a dietary intake and that endogenous production will meet vitamin D requirements. This is unlikely to be correct and indeed in the UK, margarines are fortified with vitamin D by law in an attempt to ensure an intake of vitamin D by the whole population⁸⁰. Recommendations exist for supplementing vitamin D in pregnant women, infants and children up to 5 years of age^{65,81}. Additionally, in population groups who do not take supplements and are not exposed to sunlight during winter months, vitamin D status can become very low during winter and early spring, and it is apparent from the data in figures 2 – 5 that many people are deficient in vitamin D in winter and/or spring despite vitamin D stores from summer exposure^{82,83}. However, a two-compartment model of vitamin D, with summer sun resulting in prolonged tissue storage and subsequent slow release of vitamin D has been postulated by Diffey in 2012⁸⁴ and was proposed as the mechanism for the maintenance of vitamin D during the winter months in the British population. Such a model, where vitamin D is stored in fat, could have implications for those groups studied over the winter

months and for those groups working in locations with little or no UVR presented in this review. Unfortunately, the documentation of individual subject's lifestyle and diet prior to each study is limited and makes the role of these factors difficult to determine from the studies included in this review. As reported in the literature, Figures 2 – 5 illustrate that increasing dietary vitamin D intake through fortification and/or supplementation can increase 25OHD to adequate levels. Studies treating deficient multi-ethnic populations or non-Western immigrants with sunlight exposure, dietary modification or vitamin D supplementation, have documented that fatty fish and vitamin D supplementation are the greatest modifiable contributors to vitamin D sufficiency^{85,86}. Recent interventional studies suggest that the recommended daily vitamin D intake for certain groups set by scientific advisory committees in the UK and USA^{65,73} are reasonable⁸⁷. Cashman *et al.* using mathematical modelling found that it would be possible for 97.5% of “sunshine avoiders” in the UK and Ireland to sustain serum 25OHD >50nmol/L with a dietary intake of 31.0g/day (equivalent to 1,240 IU/day) vitamin D⁸⁸. Whereas some recent studies in post-menopausal women have recorded vitamin D levels, dietary intake and sun-exposure in greater detail than in previous groups^{89,90}, no trial has been conducted in healthy subjects receiving little or no UVR consuming this suggested daily vitamin D intake. Whilst we must consider a role for preceding UVR in the maintenance of adequate vitamin D levels in some of the studies covered in this review, in the study on veiled women from Adana, Turkey⁴⁹ all the women had worn traditional dress covering the whole body except the eyes for at least the previous 3 years (with a mean duration of 8.87 years), yet the mean serum 25OHD was 83 ± 40nmol/L. None of the women

in that study were on vitamin D supplementation and 66.7 % claimed never to be exposed to direct sunlight. In addition, the authors reported that regular food products are not fortified with vitamin D in Turkey, however, individual dietary intake was not documented, the sample size was small and 33% of subjects did “sometimes” expose their face, lower parts of the legs and arms to direct sunlight (20% rarely, 3.3% <1 hour a week, 10% >2 hours a week), all of which may have contributed to their vitamin D results.

A number of studies have looked at associations between vitamin D and skin cancer risk and/or outcome. It has been reported that vitamin D inhibits growth of melanoma cell lines *in vitro*⁹¹ and an inverse correlation has been documented between higher 25OHD levels at time of melanoma diagnosis and Breslow thickness, as well as with risk of relapse and death⁹². Another study which introduced calcium and vitamin D supplementation at the time of non-melanoma skin cancer diagnosis found a reduction in subsequent melanoma incidence⁹³. In addition, vitamin D receptor deficient mice have been reported to exhibit a higher incidence of non-melanoma skin cancer⁹⁴. However, many human studies report inconsistent associations between skin cancer and serum 25OHD levels⁹⁵⁻¹⁰¹, something which may be confounded as a result of elevated serum 25OHD levels arising from high dietary intake/supplementation or alternatively from excessive UVR exposure. In order to promote adequate levels of vitamin D while avoiding the negative sequelae of UVR, public health campaigns encouraging a high vitamin D diet or supplements to healthy adults could positively impact on the health of the individual. Nonetheless, some concerns also exist about long-term fortification and/or supplementation with dietary vitamin D⁸³, thus advocating intake of

foods naturally rich in vitamin D may be more appropriate where diets are low in vitamin D⁴¹.

There were several challenges in this review. The numbers of studies documenting serum 25OHD in relation to natural sun-exposure are limited and as the data within studies is generally pooled from groups of participants rather than individuals, it does not inform on sun exposure and dietary details of each individual. The use of wintertime 25OHD levels is likely to circumvent the risk that subjects are receiving additional, unrecognised sun exposure, but reliance on subjects' retrospective recall is a weakness of this approach. Similarly, the data in studies on clothing or employment-related minimal UVR exposure were reliant on the veracity of participants documenting their limited sun exposure. Various factors influence vitamin D status or responses to UVR, including diet, ethnicity and skin type, and articles often did not comment in detail on these. Exclusion of studies in which subjects were not identified as healthy, were in long-term care, institutionalised or on drugs which could affect vitamin D levels or metabolism means these results cannot be extrapolated to those groups of people. Since the review focussed on healthy adults, further work is needed to clarify whether the results are relevant to other age groups. As there were very few randomised controlled trials and controlled trials on UVR and vitamin D, we also considered evidence from cohort and case-control studies and case series despite their higher potential for bias and this heterogeneity meant that it was not possible to pool the results and conduct a meta-analysis. Additional shortcomings were the size of studies, some being underpowered to detect clinically relevant differences. Despite these shortcomings, the repeated observation

that many people have adequate 25OHD levels during periods of negligible UVR suggests it is possible for a significant proportion of individuals to maintain adequate vitamin D levels, at least for several months, without the necessity of on-going UVR exposure.

This systematic review also had a number of strengths. It was conducted according to rigorous methods^{18,102}. The use of synonyms of search terms and searching widely in databases, registries, published literature plus consultation with experts in the field, minimised risk of publication bias. While the findings of this review provide useful information for evidence-based public health recommendations at the present time, more research is required in the form of prospective clinical trials which accurately record vitamin D intake, its UVR-related synthesis and its storage in the participants throughout the year, in particular in situations of negligible UVR exposure.

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Figure legends

Fig 1. Flow diagram for study selection.

Fig 2. Serum 25OHD (mean +/- SD where documented) in studies which reported on wintertime and/or seasonal variation in vitamin D levels in humans in relation to latitude¹⁹⁻³⁸. In studies where two mean (+/- SD) values are provided (and tied together by a broken line), the winter serum 25OHD is on the left and the summer serum 25OHD is on the right. Studies highlighted by an asterix (*) are those which were conducted at latitudes that experience insufficient UVR for synthesis of vitamin D during winter and in which the mean wintertime 25OHD value is >50nmol/L.

Fig 3. Serum 25OHD (mean +/- SD) in studies which have recorded vitamin D levels in participants residing in polar regions for prolonged periods during the winter season⁴⁰⁻⁴⁸. In studies with two mean (+/- SD) serum 25OHD values (connected by a broken line), the winter and the summer values are on the left and right respectively. Studies denoted with an asterix (*) are those with a mean wintertime 25OHD value >50nmol/L.

Fig 4. Serum 25OHD (mean +/- SD) in studies which measured vitamin D levels in subjects exposed to minimal UVR as a result of clothing attire⁴⁹⁻⁵⁴. A mean serum 25OHD value above adequate levels (>50nmol/L) is seen in the study marked with an asterix (*).

Fig 5. Serum 25OHD (mean +/- SD) in studies which documented vitamin D levels in subjects receiving minimal UVR exposure as a result of certain types of employment⁵⁵⁻⁶⁰. An asterix (*) highlights the groups of participants in which the mean 25OHD value is >50nmol/L.

Supplementary material

Protocol

Search Details

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