

**Is ultraviolet radiation required to obtain adequate vitamin D levels? A protocol for a systematic review to define the optimum method to achieve adequate vitamin D levels whilst minimising the risk of ultraviolet radiation-induced skin cancer**

**Summary**

1. Vitamin D is a prohormone that is critical for calcium homeostasis and skeletal health. Increasingly, it is becoming apparent that deficiency of vitamin D is associated with an increased risk of several forms of cancer, cardiovascular disease, autoimmune diseases, infectious diseases, depression and schizophrenia.
2. Vitamins D2 and D3 are two biologically inert precursors of vitamin D that can be acquired through diet. Vitamin D3 can also be photosynthesised in cell membranes of the skin after exposure to UVB radiation between 290 and 320 nm. However, exposure to UV radiation carries a risk of skin cancer.
3. This study will collate and assess the scientific evidence to establish how serum levels of vitamin D in healthy adults are affected by ultraviolet radiation.
4. The project may allow the development of an evidence-based conclusion as to whether adequate serum vitamin D levels can be attained in people who receive minimal UV radiation thus avoiding an increased risk of skin cancer that results from UV exposure.
5. Subsequently, an intervention to increase levels of vitamin D could be designed and tested. This could ultimately lead to a recommendation for healthcare policy.

## 1. Background

Vitamin D deficiency is increasingly recognised in most age groups of the population of the United Kingdom especially amongst older children and young adults, and in elderly people living in institutions. Women of childbearing age frequently have low vitamin D status and are likely to begin their pregnancies with low stores.(Pehlivan, Hatun et al. 2003; Hollis, Wagner et al. 2004; Hollis 2007) There was thought to be an even greater risk of vitamin D deficiency in certain population subgroups, particularly infants from black and ethnic minority groups but a recent study throws this into question.(Hatun, Ozkan et al. 2005; Dijkstra, van Beek et al. 2007; Andersen, Molgaard et al. 2008; Gordon, Feldman et al. 2008; Prentice and Prentice 2008; Wagner, Greer et al. 2008)

Vitamin D deficiency is classically accepted as a cause of rickets in childhood and osteomalacia in adulthood. However, evidence is accumulating that its deficiency is also linked to many forms of cancer, cardiovascular disease, autoimmune diseases, infectious diseases, depression and schizophrenia.(Gorham, Garland et al. 2005; Hartge, Lim et al. 2006; Berk, Sanders et al. 2007; Giovannucci 2007; Bikle and Bikle 2008; Cantorna 2008; Forman, Curhan et al. 2008; Giovannucci, Liu et al. 2008; Gissel, Rejnmark et al. 2008; Wei, Garland et al. 2008; Lim, Freedman et al. 2009; Tretli, Hernes et al. 2009)

25-hydroxyvitamin D (25(OH)D) is the major circulating metabolite of vitamin D and plasma levels of this metabolite serve as an indicator of vitamin D status. Traditionally a plasma 25(OH)D concentration less than 25nmol/l (10ng/ml)<sup>1</sup> has been regarded an index of suboptimal vitamin D status. However, current research suggests that a level several times higher than this may be beneficial. (Vieth and Vieth 2004; Heaney and Heaney 2005; Whiting, Calvo et al. 2005; Cashman, Hill et al. 2008; Mosekilde and Mosekilde 2008)

Vitamin D can be acquired through UV exposure, diet and dietary supplements.(Burgaz, Akesson et al. 2007) The main source of vitamin D in man is considered to be photosynthesis in the skin following UV radiation exposure but the UV action spectra for vitamin D photosynthesis also induces DNA damage in the skin and thus an increased risk of skin cancer. Other factors complicating the cutaneous synthesis of vitamin D include skin pigmentation, age, season, latitude, melanin concentration, clothing and use of sunscreens. In winter months in the United Kingdom there is not sufficient UV radiation of the appropriate wavelength for the cutaneous photosynthesis of vitamin D, thus body stores and dietary vitamin D are relied upon in order to maintain vitamin D status. (Macdonald, Mavroeidi et al. 2008)

The Dietary Reference Values Committee (Department of Health, 1998), made the assumption that most people aged 4-64 years of age will receive enough vitamin D from exposure of their skin to sunlight. However it suggests that the groups within this age range at high risk of vitamin D deficiency where sunlight exposure is restricted either by clothing, skin pigmentation or institutionalisation, has a recommended vitamin D intake of 10µg/day.

A healthy diet alone does not result in adequate levels of vitamin D. (Rodriguez Sangrador, Beltran De Miguel et al. 2008) Few foods in nature contain vitamin D with the exception of oily fish, and thus in some parts of the world, milk, orange juice, cereals and margarine are fortified with vitamin D. (Calvo, Whiting et al. 2004; Lehtonen-Veromaa, Mottonen et al. 2008)

Vitamin D intake from food and nutrient supplements is expressed in either international units (IU) or micrograms (µg). One IU of vitamin D is defined as the activity of 0.025 µg of cholecalciferol in bioassays with rats and chicks. Thus, the biological activity of 1 µg of vitamin D is 40 IU. The activity of 25(OH)D is 5 times more potent than cholecalciferol; thus, 1 IU = 0.005 µg 25(OH).

Evidence suggests that except for patients with malabsorption as the cause of vitamin D deficiency, dietary supplementation can correct vitamin D insufficiency and deficiency.

## **2. Aims of the project**

The aims of the project include:

- The systematic assessment of scientific evidence relating to the effect of *UV radiation* on vitamin D status
- To identify gaps in the evidence
- To specifically assess whether there is enough evidence that adequate levels of vitamin D can be obtained by dietary supplementation without additional UV radiation exposure
- On this basis it may be possible to design a testable intervention to optimise vitamin D levels and suggest a change in vitamin D guidelines by means of an intervention or an evidence-based recommendation of no change

## **3. Themes for the review**

- Consideration of beneficial and adverse outcomes of current interventions to increase vitamin D
- Consideration of variables affecting vitamin D levels in different population subgroups
- The capacity of the evidence to inform public health policy

## **4. Plan of research**

The main elements include:

- A systematic review of research evidence relating to the mechanisms to attain adequate vitamin D levels
- Close scrutiny of any evidence suggesting that it is possible to attain an adequate vitamin D level without UV radiation exposure in some population subgroups
- Depending on these conclusions, designing an intervention to optimise vitamin D levels without UV exposure which can be tested

### **A. Objectives and Methods for the systematic review work**

#### **1. Objectives**

The questions that will be addressed are as follows:

What is the effect of each of the following on vitamin D status?

- Diet
- Vitamin D supplementation
- Ultraviolet radiation

Is ultraviolet radiation required to achieve adequate vitamin D levels?

Can this information be used to outline public health guidelines on how best our population can attain adequate vitamin D levels whilst minimising risks of skin cancer through ultraviolet radiation?

## **2. Methods**

### **2.1. Criteria for considering selection of studies to include in the review**

Studies will be included if they fulfil criteria based upon the study sample, the independent variables of interest, and the study design.

#### **2.1.1. Sample**

Studies will be limited to healthy adults of any gender or skin type (level of pigmentation and response to UV radiation). Studies focussing solely on post-menopausal women, elderly adults and adults in long-term care will be excluded.

#### **2.1.2 Effect of diet, UV radiation and dietary supplementation (independent variables) on serum vitamin D levels**

Studies that report the relationship between UV radiation (interventional or observational) on serum vitamin D levels in the healthy adult population will be included in the review. Animal studies looking at the effect of these variables will be considered for inclusion.

#### **2.1.3 Outcome**

The single outcome requisite in all studies included in this review is at least a single serum vitamin D measurement of the study participants.

#### **2.1.4 Study design**

Studies with English abstracts will be included which report data on humans and animal studies. Study designs that may be included are:

Cohort

Case-control

Cross-sectional

Experimental - Clinical or controlled trials and, before and after studies

#### **2.1.5 Study settings and timing**

Studies will be included irrespective of their timing and the setting of the studies will not be limited to any geographic location. However, the generalisability of studies to UK populations may vary according to their geographical location. As the setting of the study will be relevant

to the interpretation of its results this setting will be noted as part of the data abstraction and used in the narrative synthesis.

## **2.2 Search strategy for identification of studies**

### **2.2.1 Search strategy**

The search strategy aims to identify studies which describe a relationship between the independent variables and the outcome described which will help to answer the questions posed in the review. The following resources will be searched:

Electronic – Medline, Embase, Cochrane Central Database, Cochrane Database of Systematic Reviews, Cochrane Clinical Trials Registry, Database of Abstracts and Reviews, Google Scholar, Google

Bibliographies of selected papers

Hand searching of retrieved articles, key journals, 'grey' literature and conference proceedings

Consultation with experts in nutrition, dermatology, endocrinology, rheumatology and bone metabolism, and epidemiology

Searches will be continually updated during the course of the review. By publicising the review during its progress and writing to experts, we hope to make contact with other researchers in order to include data from unpublished work in our study and reduce publication bias.

### **2.2.2 Search terms**

Combinations of search terms will be selected to ensure that studies relating serum vitamin D levels to diet, dietary supplementation and UV radiation exposure are retrieved. Search terms representing each outcome and synonymous terms will be used. Articles will then be screened to ensure that only ones relating to UV radiation will be included.

A study design facet within the search terms will not be included as the review requires observational as well as experimental studies and the nomenclature for the former is not standardised.

### **2.2.3 Scoping searches**

Scoping searches were performed between August 2007 and 2008 to assist in the development of a search strategy, with input from an information specialist with expertise in searching.

## **2.3. Methods of the review**

This study will be carried out according to the structure and methods developed by the NHS Centre for Reviews and Dissemination, University of York.

### **2.3.1. Screening of abstracts**

When applying selection criteria, all abstracts will be independently assessed by two independent reviewers and decisions shown to be reproducible. Disagreements will be resolved through consensus and, where necessary, with a third person.

### **2.3.2. Data extraction**

The extraction of data will be carried out by more than one reviewer. Uncertainty will be resolved by the same means as with the screening of abstracts. The data will be entered into an electronic record comprising date of extraction, identification of reviewer, study characteristics, study population characteristics, baseline data, methods of assessment, quality criteria, outcomes, confounding factors, analysis of statistical techniques, adjustment for confounding factors and results.

#### **2.3.2.1 Confounding factors**

The data will be carefully examined for adjustment of the independent variables that could confound or affect their relationship with serum vitamin D levels. The following variables will be considered important potential confounding factors: age, gender, ethnicity, cultural habits, skin type, BMI, occupation, residence in an institution, housebound individuals, country of residence, levels of UV radiation in locality, socio-economic class, sun-bed use, medication, and medical conditions particularly those resulting in malabsorption, bone, kidney and endocrine disorders.

For each study included we will record whether important confounding factors have been measured and whether they were adjusted for in the statistical analysis. This information will be used in the quality assessment.

#### **2.3.2.2 Indicators of inequalities**

Data extraction will include assessment of indicators of inequalities including gender differences, ethnic group, cultural differences, geography and employment status.

### **2.3.3. Study quality assessment**

Study quality assessment will occur at a number of stages in the review:

1. in deciding a threshold for study inclusion in the review
2. assessing methodological data during data extraction
3. during analysis of review findings

Each study will be assessed using a series of questions relating to its methodological quality. The answers to these questions will be used as the basis for a narrative description of the quality of each study, or to compose validity scores to assign a quality level to each study as agreed by the investigators.

### **2.3.4. Synthesis of extracted evidence**

This part of the review will investigate the consistency of effects across the studies included in the review and explore any differences in findings. Descriptive synthesis will be used as

appropriate and this will be determined by the data. We will explore potential for meta-analysis although this may not be possible as the studies will vary in their design and combining them may introduce bias.

### **2.3.5. Formation of advisory group**

This group will advise on the protocol and review outputs of the project. Specialist areas which ideally will be represented in the group include review methodology, qualitative research, epidemiology, statistics, dermatology, human nutrition, public health, endocrinology and bone health.

**Shantini Rice, 2<sup>nd</sup> September 2009**

## **PROTOCOL AMENDMENTS**

7th October 2009

### **2.1.2 Effect of diet, UV radiation and dietary supplementation (independent variables) on serum vitamin D levels**

Studies that report the relationship between either diet, UV radiation and or dietary supplementation (interventional or observational) on serum vitamin D levels in the healthy population will be included in the review. Animal studies looking at the effect of these variables will be considered for inclusion.

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30<sup>th</sup> November 2009

## **Summary**

3. This study will collate and assess the scientific evidence to establish how serum levels of vitamin D are effected by

- a. Diet
- b. Vitamin D supplementation
- c. Ultraviolet radiation



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3. This study will collate and assess the scientific evidence to establish how serum levels of vitamin D in healthy adults are affected by ultraviolet radiation
4. The project may allow the development of an evidence-based conclusion as to whether adequate serum vitamin D levels can be attained in people who receive minimal UV radiation thus avoiding an increased risk of skin cancer that results from UV exposure.

### **Aims of the project**

The aims of the project include:

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- To identify gaps in the evidence
- To specifically assess whether there is enough evidence that adequate levels of vitamin D can be obtained by dietary supplementation without additional UV radiation exposure
- On this basis it may be possible to design a testable intervention to optimise vitamin D levels and suggest a change in vitamin D guidelines by means of an intervention or an evidence-based recommendation of no change
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#### **2.1.1 Sample**

Studies will not be excluded on the basis of the age, gender nor skin type (level of pigmentation and response to UV radiation) of the study participants.

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#### **2.1.1 Sample**

Studies will be limited to healthy adults of any gender or skin type (level of pigmentation and response to UV radiation). Studies focussing solely on post-menopausal women, elderly adults and adults in long-term care will be excluded.

#### **2.2.2 Effect of diet, UV radiation and dietary supplementation (independent variables) on serum vitamin D levels**

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**Shantini Rice, 30<sup>th</sup> November 2009**

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