



Scientific Advisory Committee on Nutrition

Paper for discussion: Draft scope for vitamin D review

Agenda Item: 2

Please see paper attached for discussion. The Committee is asked to note that this paper does not represent Terms of Reference for a further review of vitamin D, and is simply a paper to initiate discussion about the about the scope of the review. The overall approach to the review and draft Terms of Reference will be considered following the Committee's discussion.

DRAFT

Draft Scope for further review of vitamin D

INTRODUCTION

1. SACN last considered the evidence on vitamin D in its 2007 position statement '*Update on Vitamin D*' (Scientific Advisory Committee on Nutrition, 2007). This was not a systematic review of the relationship between vitamin D status and health, but provided an update to assess whether there was sufficient accumulating evidence to support the need for a full review of vitamin D requirements. At the time, the Committee concluded that there was insufficient evidence to warrant a full risk assessment.
2. However, further research on vitamin D has been published since the 2007 position statement and it is now considered appropriate for the Committee to consider a full risk assessment for vitamin D.

BACKGROUND

Current Position

3. SACN's update in 2007 highlighted that a significant proportion of the UK population have low vitamin D status (based on a plasma 25-hydroxy vitamin D (25(OH)D) concentration below 25nmol/L), which increases their risk of vitamin D deficiency. They also highlighted that risk of deficiency is a concern during pregnancy and breastfeeding, for young children, black and ethnic minority groups, people aged 65 years and over, and others at risk of inadequate sunshine exposure. At the time, SACN reiterated the existing Dietary Reference Values (DRVs) set by COMA in 1991 and concluded that further risk assessment and consideration of these would only be warranted when definitive evidence becomes available.
4. The update also highlighted the necessity for a better understanding of the following issues in relation to vitamin D:
 - The length and intensity of sunlight exposure necessary to balance maintenance of vitamin D status with the risk of developing skin cancer
 - The effects of adiposity on circulating 25(OH)D concentration and its implications for vitamin D requirements
5. In addition, the Committee concluded that standardisation of laboratory methodologies for measurement of plasma 25(OH)D concentration and identification of markers of functional outcome in different age and vulnerable groups was required. This would enable more robust assessment of the relationships between plasma 25(OH)D concentration and health outcomes and allow better characterisation of threshold concentrations indicative of adequate population status.

Developments since the 2007 update

6. Since its publication in 2007, SACN's position statement has been presented by Members and the Secretariat at various meetings, workshops and seminars on vitamin D. It has also been used to inform government advice on vitamin D. An information leaflet for health professionals, based on SACN's position statement, was produced by the Department of Health for England to inform them about vitamin D deficiency. A similar leaflet was also recently launched by the Scottish Government.
7. The following sections outline further developments since publication of the SACN 2007 position statement, which have led to the consideration of a further review.

FSA-funded research on vitamin D and research workshop

8. Results are now available from three studies commissioned by the Food Standards Agency (FSA) to provide evidence for relative contributions of dietary vitamin D intake, and vitamin D synthesised by skin exposure to sunlight, to vitamin D status (as mentioned in the SACN 2007 position statement). Results from these studies will help to inform a further review.
 - **N05062: 15 month longitudinal study of dietary and sunlight influences on vitamin D status in a well-characterized population of postmenopausal women at 57°N.** A longitudinal study of women to determine whether diet and summer sunlight exposure maintain vitamin D status (fasting 25(OH)D levels) at northerly British latitudes (57° N, Aberdeen), and whether vitamin D status is associated with markers of bone resorption, muscle strength and falls (Mavroei et al., 2010).
 - **N05063: Dietary requirements for vitamin D: An investigation of the relative significance of dietary intake and sunlight on vitamin D status in young and elderly adults.** This randomised controlled trial (RCT) assessed the effect of vitamin D supplementation on vitamin D status. Subjects in two age groups (20-40years, n=238; 64+years, n=225) were randomised to receive 0, 5, 10 or 15 micrograms/day of vitamin D3 throughout 22 weeks in winter (Cashman et al., 2008 & 2009; Cashman 2009).
 - **N05064: Interaction between diet and sunlight exposure on vitamin D status and functional markers of bone health in premenopausal and postmenopausal Caucasian and Asian women in Southern England.** This longitudinal study assessed the effect of diet and sunlight exposure on vitamin D status and markers of bone health. The subjects were Caucasian and Asian, pre- and postmenopausal women living in southern England (51° N, Surrey). This study followed the same study design as the Aberdeen study and so results could be compared for different latitudes (Mavroei et al., 2010).
9. In November 2009, FSA convened a workshop of international scientific experts (including some SACN members) to review the findings of these projects (Ashwell et al., 2010).

10. The Food Standards Agency (FSA) also commissioned two projects to provide evidence on the relation between vitamin D status and markers of cardiovascular, metabolic and bone health.

- **N05079: Effect of 1 year vitamin D intervention on risk of cardiovascular disease: a randomized controlled trial at 57°N.** An RCT of women aged 60-70 years who are supplemented for one year with either placebo, 10 µg/day or 25 µg/day vitamin D (n= 3 x 100). Blood samples will be taken every two months to measure markers of CVD risk (fasting glucose, insulin, free fatty acids, blood lipids, hsCRP, ICAM, IL6). The final report will be available toward the end of 2011.
- **N05081: Vitamin D status and associated health outcomes: towards an evidence basis for defining vitamin D status sufficient to reduce risk of chronic disease.** Blood samples arising from an RCT (FSA project N05063) of 240 younger (20-40 years) and 240 older adults (65+ years) will be analysed for markers of bone turnover, cardiovascular health and metabolic health, as well as vitamin D receptor genotype and vitamin D binding protein phenotype. The project's results for bone markers have been published (Seamans et al., 2010). The final project report will be available by December 2010.

FSA Workshop on methodologies for measuring 25-hydroxyvitamin D

11. Following SACN's recommendation in 2007, FSA commissioned a review of analytical methods for measuring plasma 25(OH)D, in order to recommend the most appropriate and secure method for measuring vitamin D status in the UK National Diet and Nutrition Survey (NDNS) and other national surveys (de la Hunty et al., 2010). Following a desk review of the available methods, an expert workshop was held in November 2009, attended by international scientists and methodologists. The recommendation from the workshop was that the LC-MS/MS (Liquid Chromatography-Mass Spectrometry) method should be the preferred method for future NDNS and other national survey work. Furthermore, a detailed specification for the method should be drawn up in close liaison with Centres for Disease Control and Prevention (CDC), who are already using the method in National Health and Nutrition Examination Survey (NHANES).

International Association for Research on Cancer (IARC) report on Vitamin D and Cancer

12. In 2008, the International Association for Research on Cancer (IARC) published a report on *Vitamin D and Cancer* (IARC, 2008). A group of international experts had systematically reviewed the epidemiological literature on vitamin D and cancer and performed a meta-analysis on observational studies of vitamin D status and risk of colorectal, breast and prostate cancers and of colorectal adenomas. They concluded that an increased risk of colorectal cancer and colorectal adenoma is associated with serum 25(OH)D concentrations below 40 nmol/L. They recommended that existing vitamin D requirements should only change once results from randomised trials,

including analysis of the health impact of vitamin D supplementation according to a baseline serum 25(OH)D level are available.

Other published research

13. Several studies on vitamin D and chronic disease have been published since 2007. For example, an initial search identified several systematic and narrative reviews published on vitamin D and cardiovascular disease, cancer and type 1 and type 2 diabetes, and some meta-analyses and randomised controlled trials are also available.

Institute of Medicine (IOM) review

14. The Institute of Medicine (IOM) is currently reviewing the current data and assessing the need to update as appropriate the US Dietary Reference Intakes (DRIs) for vitamin D and calcium. Their report is due to be published in October/November 2010. A systematic review on vitamin D, calcium and health outcomes has been completed to inform this process; the report was published in 2009 (Chung et al., 2009).

Other activity

15. There has been a great deal of media attention and public discussion around vitamin D, and a number of workshops and seminars set up to discuss the current issues and challenges concerning vitamin D and health. In addition to the FSA workshops, these have included seminars/workshops hosted by Cancer Research UK, National Heart Forum and a Rank Prize funded Forum on Vitamin D.

16. There has also been considerable activity on vitamin D in Scotland. For example, in September and November 2009 SACN was asked to comment on a Scottish Parliament Public Petition calling on the Scottish Parliament to urge the Scottish Government to look at guidelines on vitamin D supplementation for children and pregnant women, and to run a vitamin D awareness campaign (petition PE1259). SACN's response reflected its 2007 position statement.

Vitamin D status in the UK

17. The 2007 position statement noted the lack of national data on vitamin D status, particularly for certain population subgroups, which makes it difficult to obtain reliable estimates of the prevalence of low vitamin D status in the UK population. The Committee highlighted the need for further national surveys of vitamin D status in order to fully quantify the problem in the UK and to monitor prevalence into the future.

18. New information is now (or will soon be) available on vitamin D status in the UK from a number of sources which can be used to inform a review, including:

- NDNS Rolling Programme (Years 1 and 2) (expected Summer 2011)

- Health Survey for England (expected December 2011)
- Diet and Nutrition Survey of Infants and Young Children (DNSIYC) (expected September 2012)
- FSA funded research on vitamin D

19. Additional information on use of vitamin D supplements during pregnancy and breastfeeding will be available from the 2010 Infant Feeding Survey.

PROPOSED SCOPE FOR THE REVIEW

20. An initial list of potential topics that could be covered in the review is outlined below (Table 1). This is currently divided into four areas, but does not necessarily represent the order in which the review should be undertaken.

21. Initial guidance is being sought on the areas of work to be covered to allow terms of reference to be drawn, and to allow further discussion about the overall approach.

Table 1 – Potential topics to be covered in the review

<p>a) Develop Dietary Reference Values (DRVs) for the UK</p> <p>i) Criterion on which to base the DRVs (based on minimal sunshine exposure?):</p> <ul style="list-style-type: none"> • Biochemical criteria for adequate vitamin D status • Suitable functional markers • The breakdown and utilisation of vitamin D in the body • Mobilisation and use of vitamin D stores (including effects of adiposity on circulating 25(OH)D concentration and its implications for vitamin D requirements) • Metabolic fate of dietary vitamin D compared to that produced endogenously by action of sunlight • Variability in plasma 25(OH)D i.e. correlation with seasonal variation, ethnicity, age, body composition (i.e. fat distribution, muscle mass, bone density) etc • Vitamin D receptors and polymorphisms and regulation of molecular and cellular processes • Genetic determinants of vitamin D status <p>ii) Review evidence relating 25(OH)D to risk and health outcomes, including:</p> <ul style="list-style-type: none"> • Bone health • Cardiovascular disease • Cancer • Diabetes (Type I & II) • Obesity • Multiple Sclerosis • Tuberculosis • Other autoimmune diseases

<ul style="list-style-type: none"> • Immunity and infection • Mental health <p>iii) Consider the appropriate DRV settings (again based on minimal sunshine exposure?):</p> <ul style="list-style-type: none"> • For the general population i.e. those aged 4 - 65 years where there is currently no DRV for vitamin D • For “at risk” groups of the population i.e. pregnant and breastfeeding women, young children, black and minority ethnic groups, people aged 65 years and over • And the efficiency of vitamin D2 (ergocalciferol) and D3 (cholecalciferol) <p>iv) Vitamin D toxicity e.g. safe upper levels and long term toxicity effects of low doses of vitamin D</p>
<p>b) UVB sunlight exposure</p> <p>i) Evidence on the contribution of UVB sunlight exposure to vitamin D status (for consideration when setting the DRVs):</p> <ul style="list-style-type: none"> • The length and intensity of sunlight exposure required to achieve adequate vitamin D status • Effect of size of exposed skin area and of exposure angle (i.e. standing up or lying down) • Season, time of day, latitude • Sufficiency of sunlight exposure to ensure adequate vitamin D status in winter • A risk/benefit analysis for balancing vitamin D status with the risk of developing skin cancer • Exposure to sunbeds and vitamin D • Sunscreen use and vitamin D
<p>c) Risk assessment with regard to the UK population</p> <ul style="list-style-type: none"> • Using newly available data on vitamin D (outlined in earlier section on <i>Vitamin D status in the UK</i>) to determine the current status of the UK population and to identify who is at risk of deficiency
<p>d) Approaches to ensure sufficiency in the UK population</p> <ul style="list-style-type: none"> • Diet • Supplementation • Sunlight exposure

COMMITTEE MEMBERSHIP / APPROACH

22. It is proposed that there is a full independent risk assessment of vitamin D to cover all the issues outlined in the final agreed scope. It is also suggested that

the Committee puts out a call for evidence to inform the review, and uses recent reviews such as the IOM (2010) systematic review as a starting point.

23. It is proposed that a SACN Working Group is set up to undertake the review, comprising Members from SACN and experts from other areas. Suggestions include:

- Representative(s) from the Committee on Medical Aspects of Radiation in the Environment (COMARE)
- Representatives from Committee on Toxicity (COT)
- Dermatologist(s)
- Some expertise in vitamin D metabolism

DISCUSSION

24. The Committee is asked to consider the scope required for a risk assessment of vitamin D, and to specifically consider the following questions:

- 1. In addition to the areas outlined in the above draft scope, is there anything else that should be included?**
- 2. What additional areas of expertise are required for the review?**
- 3. Are there any particular areas of the work that require the evidence to be reviewed systematically?**

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