

Vitamin D and Health

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Scientific Advisory Committee on Nutrition

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Summary

Background

- s.1 Vitamin D is required for regulation of calcium and phosphorus metabolism and is therefore important for musculoskeletal health. It is synthesised in the skin upon exposure to sunlight containing sufficient ultraviolet B (UVB) radiation and this is the main source for most people. It can also be obtained from foods or dietary supplements. Dietary sources are essential when sunlight containing UVB radiation is limited (e.g., during the winter months) or exposure to it is restricted (e.g., due to lack of time spent outdoors or little skin exposure).
- s.2 Dietary Reference Values (DRVs) for vitamin D were set by the Committee on Medical Aspects of Food Policy (COMA) in 1991 and were based on prevention of rickets in children and osteomalacia in adults. A Reference Nutrient Intake (RNI)¹ for vitamin D was not set for individuals (aged 4-64 y) with regular exposure to sunlight because it was considered that enough vitamin D would be synthesised in the summer to cover their needs in the winter. RNIs for vitamin D (7-10 µg/280-400 IU per day) were set only for UK population groups considered to be at risk of vitamin D deficiency: infants (0-3 y); pregnant and breast-feeding women; adults age 65y and above; those with limited sunlight exposure; and women and children of Asian ethnic origin. The DRVs were reviewed and endorsed by COMA in 1998.
- s.3 Although the DRVs were based on bone health, emerging evidence has also suggested a range of other health benefits of vitamin D. In 2007, the Scientific Advisory Committee on Nutrition (SACN) concluded that there was insufficient evidence at that time to warrant reviewing the DRVs for vitamin D set by COMA and that evidence on vitamin D and non-musculoskeletal health was inconclusive. In 2010, SACN agreed to review the DRVs for vitamin D because a substantial amount of published data had accumulated since its previous considerations.

Terms of reference

- s.4 The terms of reference were: *to review the Dietary Reference Values for vitamin D and make recommendations*. This required a risk assessment of the vitamin D status of the UK population and consideration of the following:
- a) biochemical indicators of vitamin D status and the validity of the values used to assess risk of deficiency and excess;
 - b) association between vitamin D status and health outcomes at different life stages and different population groups and the effects of biological modifiers;
 - c) contribution of cutaneous vitamin D synthesis to vitamin D status in the UK taking account of the effects of modifiers of skin exposure to sunlight; risks of skin damage and other adverse health outcomes associated with sunlight exposure;
 - d) potential adverse effects of high vitamin D intakes;
 - e) relative contributions made by dietary vitamin D intake (from natural food sources, fortified foods and supplements) and cutaneous vitamin D synthesis, to the vitamin D status of the UK population.

¹ The RNI represents the amount of a nutrient that is likely to meet the needs of 97.5% of the population.

Metabolism

- s.5 Vitamin D is converted to its active metabolite, 1,25-dihydroxyvitamin D (1,25(OH)₂D), in two hydroxylation steps. The first hydroxylation is in the liver, where vitamin D is converted to 25-hydroxyvitamin D (25(OH)D), which is the major circulating metabolite of vitamin D and is widely used as a biomarker of vitamin D status; the second hydroxylation is in the kidney where 25(OH)D is converted to 1,25(OH)₂D.

Photobiology

- s.6 Vitamin D is synthesised endogenously by the action of sunlight containing UVB radiation, which converts 7-dehydrocholesterol (7-DHC) in the epidermis to previtamin D followed by thermal isomerisation to vitamin D. Exposure of skin to UVB radiation is influenced by many factors; these include time of day, season, latitude, altitude, cloud cover, air pollution, clothing and sunscreen use.
- s.7 At latitudes below 37°N, UVB radiation is sufficient for year round vitamin D synthesis. At higher latitude, vitamin D is not synthesised during the winter months. In the UK, sunlight-induced vitamin D synthesis is only effective between late March/early April and September and not from October onwards throughout the winter months.
- s.8 Lower plasma/serum 25(OH)D concentrations have been observed in people with dark skin pigmentation compared to those with lighter skin colour. It is not clear, however, if this is due to skin pigmentation or to physiological or lifestyle differences since dark skin is only one of many cultural and biological factors that could influence the plasma/serum 25(OH)D concentration of individuals from ethnic groups with darker skin pigmentation.
- s.9 Efficiency of cutaneous vitamin D synthesis may be lower in people with dark skin and in older people but the evidence is limited.

Biomarkers of vitamin D exposure

- s.10 Plasma/serum 25(OH)D concentration is widely used as a biomarker of vitamin D status because it reflects vitamin D supply from cutaneous synthesis and diet but also because it has a long half-life in the circulation (about 2-3 weeks) and is not under tight homeostatic control. A limitation of its use is that it has been observed to decrease in response to acute inflammation, so low concentrations (e.g., observed in conditions such as cancer) may reflect an underlying inflammatory state. The relationship between vitamin D exposure and serum 25(OH)D concentration may also be influenced by Body Mass Index and genetic variation.
- s.11 There are also limitations associated with the methods used for measurement of serum 25(OH)D concentration, since measurements can vary considerably (15-20%) depending on the type of assay used. In addition, there is considerable variation between different laboratories using the same methods. These limitations have implications for interpretation of studies that have examined the relationship between serum 25(OH)D concentration and health outcomes.

Vitamin D and health outcomes

- s.12 The purpose of reviewing data on vitamin D and a range of health outcomes was to assess whether they might inform the setting of DRVs for vitamin D. In assessing the evidence, data from randomised controlled trials (RCTs), then prospective studies, were preferred in terms of informing the setting of DRVs; however, evidence from other study types was also considered.

- s.13 For each of the potential health outcomes considered, a judgement was made on whether the evidence suggested a relationship with vitamin D supplementation or serum 25(OH)D concentration. If the evidence was suggestive of a relationship then the data were examined further to assess whether a range of serum 25(OH)D concentrations or a threshold serum 25(OH)D concentration associated with beneficial effects could be identified. An important limitation to this task was that there is no clear consensus on the threshold serum 25(OH)D concentration used to define vitamin D deficiency or low status and cut-offs varied across studies and were predefined according to different criteria for deficiency. As a consequence, the selected cut-offs were insecure and made it difficult to assess if there was a dose-response relationship.

Musculoskeletal health outcomes

Rickets

- s.14 Evidence was mainly from cross-sectional observational studies and case reports and may therefore have been influenced by confounding. Since most studies did not measure calcium intake it was not clear whether the cause of rickets was vitamin D deficiency and/or calcium deficiency. A distinct threshold serum 25(OH)D concentration above which there is no risk of rickets could not be identified but the data suggested overall that the risk increased at serum 25(OH)D concentration < 25 nmol/L; this concentration is, however, not a clinical threshold diagnostic of the disease.

Osteomalacia

- s.15 Evidence was limited mainly to case reports. There was no clear serum 25(OH)D threshold concentration below which risk of osteomalacia increased but individual concentrations were < 20 nmol/L in case reports and mean concentrations were ≤ 15 nmol/L in cross-sectional analyses.

Bone health indices (bone mineral content, bone mineral density, biochemical markers of bone turnover)

- s.16 Findings varied by life stage. Evidence suggested a positive association between maternal serum 25(OH)D concentration during pregnancy and bone health indices in the fetus/newborn and beneficial effects of vitamin D supplementation on bone health indices in adults aged ≥ 50y. Effects of vitamin D supplementation on bone health indices in infants, children, adolescents and adults < 50y were inconsistent. The evidence base for children (1-3y) and adults < 50y was insufficient to draw conclusions.

Fracture prevention

- s.17 Data in adults ≥ 50y are mixed but, on balance, suggest that vitamin D supplementation does not reduce fracture risk. The evidence base on the effect of vitamin D supplementation on stress fracture risk on adults < 50y was insufficient to draw conclusions.

Muscle strength and function

- s.18 Limited evidence suggested a beneficial effect of vitamin D supplementation on muscle strength and function in adolescents and adults < 50y with a pre-intervention mean serum 25(OH)D concentration < 20 nmol/L and < 30 nmol/L respectively. For adults ≥ 50 y, with mean baseline serum 25(OH)D concentrations across a range of values, the evidence was mixed but overall suggested that vitamin D supplementation improves muscle strength and function.

Falls

- s.19 Evidence was mixed but, overall, suggested vitamin D supplementation reduces fall risk in community dwelling adults ≥ 50y with mean baseline serum 25(OH)D concentrations across a range of values.

Two studies reported an increase in fall risk with vitamin D supplementation; however, doses were very high and administered annually² or monthly³ which may produce different effects from daily supplementation at lower doses.

Non-musculoskeletal health outcomes

- s.20 Non-musculoskeletal health outcomes considered were: reproductive health (on maternal & newborn outcomes), cancer, cardiovascular disease, hypertension, all-cause mortality, immune modulation, infectious diseases, neuropsychological functioning, oral health and age-related macular degeneration.
- s.21 Evidence on vitamin D and non-musculoskeletal health outcomes is drawn mainly from observational studies so findings of beneficial effects could be due to reverse causality or confounding by other factors associated with a specific health outcome. Results from RCTs of vitamin D supplementation are inconsistent.

Selection of health outcomes to be used as basis for setting DRVs for vitamin D

- s.22 Data on vitamin D and non-musculoskeletal health outcomes were considered insufficient to inform the setting of DRVs for vitamin D. Musculoskeletal health (based on rickets, osteomalacia, falls and muscle strength and function) was selected as the basis for setting the DRVs for vitamin D.
- s.23 Studies on musculoskeletal health outcomes suggesting beneficial effects of vitamin D (rickets, osteomalacia, falls, muscle strength & function) were considered further to assess whether a range or threshold serum 25(OH)D concentration associated with beneficial effects could be identified. With the exception of case reports, most studies considered provided only mean/median serum 25(OH)D concentrations of participants so it was not possible to establish a range of serum 25(OH)D concentrations associated with the selected musculoskeletal health outcomes.
- s.24 There were many uncertainties in the data and wide variability in the mean and individual serum 25(OH)D concentrations associated with increased risk of rickets, osteomalacia and falls or improvement in muscle strength and function. However, the evidence overall suggested that risk of poor musculoskeletal health was increased at serum 25(OH)D concentrations below about 20-30 nmol/L. It was not possible to identify a *specific* serum 25(OH)D threshold concentration between 20-30 nmol/L associated with increased risk of poor musculoskeletal health since various assay methods were used in the studies considered and measurement is influenced by the analytical methodology. The current threshold of 25 nmol/L, used to define the concentration below which risk of vitamin D deficiency increases, was therefore retained. This is not a clinical threshold diagnostic of disease but indicative of increased risk of poor musculoskeletal health.

Vitamin D intakes and plasma/serum 25(OH)D concentrations in the UK population

Vitamin D intakes

- s.25 Mean dietary intakes of vitamin D from all sources (including supplements) were: 8-10 µg/d (320-400 IU/d) and 3.5 µg/d (140 IU/d) for non-breastfed infants aged 4-11m and 12-18m respectively; 2-3 µg/d (80-120 IU/d) for breast fed infants aged 4-18m; 2-4 µg/d (80-160 IU/d) for ages 1.5-64y; 5 µg/d (200 IU/d) for adults aged ≥ 65y and 3-4 µg/d (120-160 IU/d) for institutionalised adults aged ≥ 65y.

² 12,500 µg/500,000 IU.

³ 1500 µg/60,000 IU or 600 µg/24,000 IU vitamin D₃ + 300 µg 25(OH)D₃.

Plasma/serum 25(OH)D concentration

- s.26 Annualised⁴ mean plasma 25(OH)D concentrations across the different age groups in the UK ranged between 40 and 70 nmol/L but were lower for institutionalised adults (around 30 nmol/L).
- s.27 The proportion of the population (by age) with a plasma 25(OH)D concentration < 25 nmol/L was: 2-8%, 5m-3y; 12-16%, 4-10y; 20-24%, 11-18y; 22-24%, 19-64y; 17-24%, ≥ 65y and above. Nearly 40% of institutionalised adults had a plasma 25(OH)D concentration < 25 nmol/L.
- s.28 For all age groups in the UK, mean plasma 25(OH)D concentration was lowest in winter and highest in summer. Around 30-40% of the population had a plasma 25(OH)D concentration < 25 nmol/L in winter compared to 2-13% in the summer. A large proportion of some population groups did not achieve a plasma/serum 25(OH)D concentration ≥ 25 nmol/L in summer (17% of adults in Scotland; 16% of adults in London; 53% of women of South Asian ethnic origin in Southern England; and 29% of pregnant women in NW London).
- s.29 Analysis by ethnicity showed that the annualised mean serum 25(OH)D concentration was higher in white adults aged ≥ 16y (45.8 nmol/L) compared to Asian (20.5 nmol/L) and black (27.7 nmol/L) adults.

Review of DRVs

- s.30 Evidence suggests that the risk of poor musculoskeletal health is increased at serum 25(OH)D concentrations below 25 nmol/L. This concentration therefore represents a '*population protective level*'; i.e., the concentration that individuals in the UK should be above, throughout the year, in terms of protecting musculoskeletal health.
- s.31 It was not possible to quantify the sunlight exposure that would be required in the summer to achieve a winter serum 25(OH)D concentration ≥ 25 nmol/L because of the number of factors that affect cutaneous vitamin D synthesis.
- s.32 The RNI for vitamin D was therefore derived by estimating the average vitamin D intake that would be required for individuals in the UK to achieve a serum 25(OH)D concentration ≥ 25 nmol/L. The average vitamin D intake refers to average intake over the long term and takes account of day to day variations in vitamin D intake.
- s.33 The RNI was estimated by modelling data from individual RCTs conducted in winter (so that cutaneous vitamin D synthesis arising from current UVB exposure was minimal) with adults (20-40y & ≥ 64y) and adolescent girls (11 y). The average daily vitamin D intake required to maintain serum 25(OH)D concentration ≥ 25 nmol/L in winter by the majority (97.5%) of the population was estimated to be around 10 µg (400 IU). Data from these RCTs were extrapolated to younger age groups.
- s.34 Data were not available to relate serum 25(OH)D concentration in the infant clearly to current or long term health. *Safe Intakes*⁵ rather than RNIs were therefore recommended for infants and children aged under 4y in the range of 8.5-10 µg/d (340-400 IU/d).

⁴ Average of reports from different months of the year.

⁵ COMA (DH, 1991) set a '*Safe Intake*' for some nutrients if there were insufficient reliable data to set DRVs. They are '*judged to be a level or range of intake at which there is no risk of deficiency, and below a level of where there is a risk of undesirable effects*' (DH, 1991).

Recommendations

- s.35 Serum 25(OH)D concentration is an indicator of exposure to vitamin D (from skin synthesis and dietary intake). In order to protect musculoskeletal health, it is recommended that the serum 25(OH)D concentration of all individuals in the UK should not fall below 25 nmol/L at any time of the year.
- s.36 In the UK, individuals in population groups at increased risk of having a serum 25(OH)D concentration < 25 nmol/L are those with minimal sunshine exposure as a result of not spending time outdoors (e.g., frail and institutionalised people) or habitually wearing clothing that covers most of the skin while outdoors and those from minority ethnic groups with dark skin.
- s.37 It is not possible to make any recommendations regarding the amount of sunlight exposure that would be required during the summer to maintain serum 25(OH)D concentration \geq 25 nmol/L in 97.5% of the UK population during the following winter because of the number and complexity of factors that affect endogenous vitamin D production.
- s.38 An RNI for vitamin D, of 10 $\mu\text{g}/\text{d}$ (400 IU/d), is recommended for the UK population aged 4y and above. This is the average amount needed by 97.5% of the population to maintain a serum 25(OH)D concentration \geq 25 nmol/L when UVB sunshine exposure is minimal. It refers to average intake over a period of time (e.g., a week) and takes account of day to day variations in vitamin D intake.
- s.39 The RNI of 10 $\mu\text{g}/\text{d}$ (400 IU/d) proposed for the general UK population (aged 4y and above) includes pregnant and lactating women and population groups at increased risk of having a serum 25(OH)D concentration < 25 nmol/L. A separate RNI is not required for these groups. This is a change from previous advice.
- s.40 Data are insufficient to set RNIs for infants and children aged under 4y. As a precaution, a 'Safe Intake' of vitamin D is recommended for these ages: in the range 8.5-10 $\mu\text{g}/\text{d}$ (340-400 IU/d) for ages 0 up to 1y (including exclusively breast fed and partially breast fed infants, from birth); and 10 $\mu\text{g}/\text{d}$ (400 IU/d) for ages 1 up to 4y. The recommendation for exclusively breast fed infants is a change from previous advice.
- s.41 It is recommended that the RNI/Safe Intakes are applicable throughout the year, as a precautionary measure, to cover population groups in the UK identified to be at risk of having a serum 25(OH)D concentration < 25 nmol/L (see paragraph S.36 above) as well as unidentified individuals in the population at risk of having a serum 25(OH)D concentration < 25 nmol/L in summer.
- s.42 The RNI/Safe Intake for vitamin D refers to intakes from *all* dietary sources: natural food sources; fortified foods (including infant formula milk); and supplements. Since it is difficult to achieve the RNI/Safe Intake from natural food sources alone, it is recommended that the Government gives consideration to strategies for the UK population to achieve the RNI of 10 $\mu\text{g}/\text{d}$ (400 IU/d) for those aged 4y and above and for infants and younger children to achieve a Safe Intake in the range 8.5-10 $\mu\text{g}/\text{d}$ (340-400 IU/d) at ages 0 to < 1y and 10 $\mu\text{g}/\text{d}$ (400 IU/d) at ages 1 to < 4y.