Ir J Med Sci
DOI 10.1007/s11845-010-0512-4

REVIEW ARTICLE

Vitamin D insufficiency: a common and treatable problem in the Irish population

G. O'Malley · E. Mulkerrin

Received: 4 September 2009 / Accepted: 20 May 2010
© Royal Academy of Medicine in Ireland 2010

Abstract
Introduction Vitamin D insufficiency is an extremely common condition particularly in the older Irish population. This is a consequence of Ireland's geographical position and climate. A recent study showed more than 75% of a cohort of older Irish females had vitamin D insufficiency.
Objectives We outline the definition of vitamin D insufficiency and deficiency, its sources and metabolism as well as the clinical consequences of deficiency. We explore the current guidelines and discuss the pitfalls in the management of vitamin D replacement and in particular address recent Irish data on the feasibility and efficacy of intramuscular treatment.
Conclusion Vitamin D is important for calcium homeostasis and bone metabolism and reduced levels lead to osteomalacia, exacerbate osteoporosis and increase the risk of falls. Evidence is emerging that vitamin D has a role beyond musculoskeletal health and may impact on the cardiovascular and autoimmune systems, as well as the risk of malignancy.

Keywords Vitamin D · Insufficiency · Osteoporosis · Falls · Ireland

Introduction

Vitamin D deficiency is characterised by hypocalcaemia or hypophosphataemia leading to rickets or osteomalacia and is now uncommon in most developed countries. However, vitamin D insufficiency is extremely common. Vitamin D is necessary for adequate calcium and phosphorous absorption from the intestine and is important for proper mineralization of the bone. Low vitamin D has been associated with osteoporosis, risk of falls and fractures. Treatment of vitamin D deficiency is important for musculoskeletal health and for extra-skeletal health including the normal functioning autoimmune and cardiovascular systems [1].

Prevalence

Vitamin D deficiency is commonly associated with the older population. A study in this department on older Irish female patients by DeLappe et al. [2] confirmed that more than 75% have vitamin D insufficiency. Vitamin D deficiency has also been well recognised in the adolescent age group [3].

In recent years it has become clear that vitamin D insufficiency affects all age groups and is common throughout the entire Irish population as demonstrated by Hill et al. [4]. This study showed vitamin D inadequacy of 11% during the summer and 45% in winter in all age groups. Climate, season and geographical location have an important impact on adequate exposure to vitamin D. Vitamin D stores decline particularly in older subjects and especially in the winter. In areas such as Edmonton and Boston, vitamin D production has been found to cease in winter [5].

Definition of vitamin D deficiency

There is no clear consensus regarding the definition of vitamin D deficiency and adequate vitamin D status. Various thresholds have been used in the different studies.

G. O'Malley (✉) · E. Mulkerrin
Department of Medicine for the Elderly,
University Hospital, Galway, Ireland
e-mail: gmnimhaille@yahoo.co.uk

Published online: 09 August 2010

Studies have demonstrated that 25-hydroxyvitamin D reduces parathyroid hormone concentration and biochemical markers of bone turnover. Some researchers have used the 25-hydroxyvitamin D levels required to suppress the release of parathyroid hormone as a cutoff for deficiency. Holick et al. [6] recommend a minimum 25-hydroxyvitamin D concentration of 50 nmol/l for deficiency but for maximum bone health, a concentration between 78 and 100 nmol/l is recommended. It is important to distinguish insufficiency from deficiency; the former has a biological effect on calcium homeostasis and skeletal metabolism and the latter leads to osteomalacia. It has been demonstrated that calcium, inorganic phosphate and alkaline phosphatase do not identify 25-hydroxyvitamin D insufficiency except when 25-hydroxyvitamin D is deplete (<25 nmol/l) [7].

Sources and metabolism

Vitamin D without subscripts refers to either vitamin D2 or vitamin D3. Vitamin D3, also known as cholecalciferol, is either synthesised in the skin or obtained from the diet. Vitamin D2, also known as ergocalciferol, is obtained from irradiated fungi, such as yeast. Dietary sources of vitamin D are limited and are found in oily fish and to a lesser extent eggs. Food is not routinely fortified with vitamin D in Ireland. Sunlight exposure provides in excess of 80% of vitamin D. Vitamin D is stored throughout the summer and lasts for approximately 12 weeks. When levels start to decline in the winter months, parathyroid hormone levels start to rise with a lag of 1 month. Lack of 1,25-dihydoxyvitamin D leads to a decline in calcium absorption with a consequent increase in parathyroid hormone levels leading to an increase in bone resorption, accelerated bone loss and reduction in bone mineral density. In the summer months, this process is reversed [6]. Of note, prolonged exposure to the sun does not cause vitamin D toxicity. This is because after prolonged UV-B radiation exposure, the vitamin D made in the skin is further degraded to the inactive vitamin D metabolites tachysterol and lumisterol.

Once vitamin D is formed on the surface of the skin, it undergoes two sequential hydroxylations in the liver (25 hydroxyvitamin D) and the kidney (1,25-dihydoxyvitamin D) to form the active metabolite. The metabolism of vitamin D to 1,25-dihydoxyvitamin D is closely coupled to calcium homeostasis, and is modulated by parathyroid hormone, serum calcium, and phosphorous levels. When calcium levels drop, serum parathyroid hormone increases, enhancing tubular reabsorption of calcium, as well as increasing activity of alpha-1-hydroxylase in the kidney. This results in increased 1,25-dihydoxyvitamin D production, in turn leading to increased intestinal calcium absorption. Parathyroid hormone also stimulates bone osteoclast activity to mobilize bone calcium stores, thus increasing serum calcium. By this mechanism, serum 1,25-dihydoxyvitamin D are kept at nearly normal levels at the expense of raising parathyroid hormone levels, causing secondary hyperparathyroidism. Secondary hyperparathyroidism leads to accelerated bone loss with a consequent reduction in bone mineral density and an increased fracture risk, and without further treatment causes osteomalacia in adults and rickets in children.

It is well established that vitamin D nutritional status is best assessed using serum 25-hydroxyvitamin D levels. This is due to its long serum half-life (approximately 3 weeks) and because the 25-hydroxylation step is unregulated, thus reflecting substrate availability [8].

Causes of vitamin D deficiency and resistance

The most common causes of vitamin D deficiency are due to impaired availability of vitamin D secondary to lack of photoisomerisation, inadequate dietary intake and fat malabsorption. Adults in nursing homes or health care institutions are at a particularly high risk of vitamin D deficiency [9]. Ageing and treatment with glucocorticoids lead to a marked reduction in skin thickness and reduces the efficiency of the skin in producing vitamin D [10]. Glucocorticoids when used in chronically high doses inhibit vitamin D-dependant intestinal absorption of calcium and cause osteomalacia [11]. Resection of the small intestine may lead to malabsorption of vitamin D and vitamin D deficiency is also associated with coeliac disease and cystic fibrosis [12, 13].

There are minimal amounts of vitamin D in human breast milk. The American Academy of Paediatrics recommends vitamin D supplementation starting at age 2 months for infants fed exclusively with breast milk [14]. Medications such as phenytoin, phenobarbital, and rifampicin can induce hepatic p450 enzymes to accelerate the catabolism of vitamin D. Decreased synthesis of 25-hydroxyvitamin D occurs when more than 90% of liver is not functioning [15]. In stage 2 kidney disease, hypophosphataemia leads to increased fibroblast growth factor 23 which decreases 25 hydroxyvitamin D-1-alpha-hydroxylase activity. This causes decreased fractional excretion of phosphorous and decreased serum levels of 1,25-dihydroxyvitamin D. In stage 4 and 5 kidney disease there is an inability to produce adequate amounts of 1,25-dihydroxyvitamin D leading to hypocalcaemia, secondary hyperparathyroidism and renal bone disease [16]. There are a number of heritable disorders that can cause osteomalacia and include pseudovitamin D deficiency, vitamin D resistant rickets, vitamin D-dependant rickets type 3, autosomal dominant hypophosphataemic rickets and X-linked

hypophosphataemic rickets. Acquired disorders leading to vitamin D deficiency are tumour-induced osteomalacia, primary hyperparathyroidism, granulomatous disorders and hyperthyroidism.

Vitamin D supplementation and osteoporosis

Osteoporosis is characterised by reduced bone mineral density, disruption of the bony microarchitecture, and of the amount and variety of non-collagenous proteins in bone. Osteoporosis increases risk of fractures and mortality. Studies have shown that calcium and vitamin D repletion improve bone mineral density. An analysis of the Third National Health and Nutrition Examination Survey (NHANES III) demonstrated a positive correlation between circulating 25-hydroxyvitamin D levels and bone mineral density [17].

However, the data regarding fracture reduction is not as clear-cut. Study outcomes are also likely to be influenced by the participant's compliance. Chapuy et al. were the first group to show that vitamin D and calcium had a significant effect on fracture reduction. This study looked at 3,270 elderly French women who were randomised to take placebo or 1,200 mg of calcium and 800 IU of vitamin D3 daily. Patients in the study group had substantial reduction (17–23%) in hip fractures over a period of 3 years [18]. Compliance was not an issue for this group as the participants were resident in a nursing home. A further paper published by Trivedi et al. [19] showed a fracture reduction of 22% after 5 years.

Porthouse et al. did not show a significant reduction in fracture risk in a randomised controlled trial involving 3,000 women over the age of 70 in a community setting. Participants were randomised by an independent party who was blinded to the patient's characteristics to receive calcium and vitamin D3 (800 IU) [20]. The RECORD study examined the role of vitamin D in secondary prevention. This study looked at over 5,000 men and women who had previously had a fracture. There was no significant reduction in fractures in the group randomised to receive calcium and vitamin D; however, compliance may have been as low as 45% in this study [21]. A large randomised controlled trial by Lips et al. [22] found no reduction in fracture risk for vitamin D, but the population studied did not have a high prevalence of vitamin D deficiency.

Recent results from the Women's Health Initiative showed that supplementation with calcium and vitamin D (400 IU of vitamin D3) in the postmenopausal population resulted in a nonsignificant 12% reduction in hip fractures [23]. However, when those who were noncompliant were excluded there was a significant 29% reduction in hip fractures. The results of this trial may also have been influenced by the low fracture rate, high personal intake of vitamin D and calcium as well as the young age of the population studied. Compliance may also have an important role in the trials that showed negative fracture outcomes for patients randomised to vitamin D and calcium. In the study by Porthouse et al. compliance with vitamin D supplements was 54.5% at 2 years. With calcium supplementation the figure was only 9.4% [20]. Even within the subgroup most likely to benefit from supplementation, compliance is very poor. A study by Solomon et al. [24] found that most patients with hip fractures did not take supplements despite receiving detailed information about their importance.

The dose of vitamin D used in the various trials has been found to have an impact on results. Bischoff-Ferrari et al. [25] performed a meta-analysis of randomised controlled trials published prior to 2005. The meta-analysis found that vitamin D supplementation of 400 IU has no impact, and vitamin D in a dose of 800 IU daily reduced the risk of a first hip fracture and new vertebral fracture by 26 and 23%, respectively. Outcomes for fracture data may also be influenced by the type of vitamin D used, which may related to the efficacy and length of action of the different preparations of vitamin D. Ergocalciferol (vitamin D2) was used in the study by Law et al. [26]. It found that supplementation with vitamin D2 of 1,100 IU daily did not reduce the risk of fractures or falls among older women in care home accommodation. Trivedi et al. [19] used cholecalciferol (vitamin D3) in older women in a community setting and were given 800 IU daily. This study found a statistically significant reduction in fractures. In both studies the mean rise in serum vitamin D levels was 27 nmol/L (47–74) and 21 nmol/L (53–74), respectively. However, in the Porthouse and RECORD studies where cholecalciferol was used, there was no significant fracture reduction [20, 21]. Past studies suggested that vitamin D3 may be more effective than vitamin D2 in establishing normal vitamin D stores [27]. However, a study by Holick and colleagues [28] demonstrated that vitamin D2 and vitamin D3 appear to be equipotent in raising 25-hydroxyvitamin D concentrations when given in daily doses of 1,000 IU.

It has been increasingly recognised that vitamin D has an important role in musculoskeletal health beyond management of osteoporosis and fracture prevention. Vitamin D deficiency is important in the prevention of falls in the elderly. A meta-analysis by Bischoff-Ferrari et al. [29] has shown that supplementation of vitamin D reduces the risk of falls in an elderly population by 22%. This meta-analysis showed that 400 IU of vitamin D_3 per day was not effective in preventing falls, whereas 800 IU of vitamin D_3 per day plus calcium reduced the risk of falls (corrected

pooled odds ratio, 0.65; 95% CI 0.4–1.0). The effect of vitamin D was independent of calcium use with benefits occurring within 2–3 months of supplementation. This emphasises the potentially important role of vitamin D in body sway and muscle power. A further study in a placebo-controlled randomised controlled trial found that combined supplementation with calcium and vitamin D reduced the odds of falling in an ambulatory older female population by 46% over 3 years [30].

Severe vitamin D deficiency leads to osteomalacia and rickets in adults and children, respectively. Osteomalacia refers to defective mineralisation of bone matrix due to deficiency or resistance to vitamin D. It can be associated with isolated or generalised bony pain and muscle weakness. Pain is caused by hydration of the demineralised matrix as it presses out against the periosteum [31].

Diagnosis is based on clinical, biochemical and radiological findings. Biochemical changes include reduced serum calcium, phosphate and urinary calcium as well as a raised alkaline phosphatase. Radiological changes are characterised by Loosers zones, but more commonly there is a general picture of skeletal deformity with vertebral fractures, fractures of other bones and bowing of long bones.

A study by Plotnikoff et al. investigated 150 people aged between 10 and 65 and showed that 93% of patients who attended a primary care facility with chronic musculoskeletal pain, with a variety of diagnoses including fibromyalgia and depression were actually deficient in vitamin D. Osteomalacia can run an insidious course and may be difficult to diagnose, as biochemical changes may be subclinical [32].

Nonskeletal actions of vitamin D

Epidemiological studies suggest that those living at higher latitudes are at increased risk of malignancy and also have higher mortality rates from cancer. Solar UV-B radiation is used as a marker in studies for vitamin D deficiency. A study by the American Cancer Society looking at geographical variation in cancer mortality found that higher amounts of UV-B radiation were associated with reduced risk of cancer of the breast, colon, ovary, and prostate as well as non-Hodgkins lymphoma. Eight additional malignancies were found to exhibit an inverse correlation between mortality rates and UV-B radiation, namely cancer of the bladder, oesophagus, kidney, lung, pancreas, rectum, stomach, and corpus uteri [33].

An analysis from the Nurses' Health Study cohort (32,826 subjects) showed that the odds ratios for colorectal cancer were inversely associated with median serum levels of 25-hydroxyvitamin D [the odds ratio at 16.2 ng/ml (40.4 nmol/l) was 1.0, and the odds ratio at 39.9 ng/ml (99.6 nmol/l) was 0.53; $P \leq 0.01$] [34].

However, to date there have been no large, randomised clinical trials that have established the role of vitamin D in preventing cancer. A large randomised placebo-controlled double blinded study also involving participants from the Nurses Health study examined the role of vitamin D in preventing colon cancer. There was no significant reduction in colorectal cancer in women randomised to vitamin D/calcium, though the long latency period may have contributed to the negative finding [35].

Living at higher latitudes increases the risk of autoimmune conditions such as multiple sclerosis, and Crohn's disease [36]. Vitamin D insufficiency may also increase the risk for type I and type II diabetes mellitus [37]. In NHANES III, lower vitamin D status was associated with higher fasting glucose and 2-h glucose after an oral glucose tolerance test [38].

Experimental data suggest that 1,25-dihyroxyvitamin D affects cardiac muscle directly, regulates the renin–angiotensin–aldosterone system, and modulates the immune system [39]. Because of these biologic effects, vitamin D deficiency has been associated with hypertension, several types of vascular diseases, and heart failure. Treatment with vitamin D lowered blood pressure in patients with hypertension and modified the cytokine profile in patients with heart failure [39]. However, vitamin D supplementation is not recommended as routine treatment for heart disease until prospective trials have fully assessed its effects.

A meta-analysis evaluated the effect of vitamin D supplementation (using a mean supplementation dosage of about 500 IU daily) on all-cause mortality in 18 randomised controlled trials and found a 7% relative risk reduction for death [40].

Management

Recommended levels of adequate vitamin D intake are between 400 and 600 IU daily The American Institute of Medicine recommends 600 IU >70 years and 400 IU <70 years [41], while the Scientific Committee for Food in the EU recommends 400 IU daily [42]. However, many experts would agree that these recommended intakes of vitamin D are too low [31].

Sunlight is a very important source of vitamin D and exposure of arms and legs for 5–30 min between the hours of 10 a.m. and 3 p.m. twice a week is often adequate to prevent vitamin D deficiency [31]. However, this depends on a number of factors including time of day, season and latitude. Vitamin D supplementation may be required in those at risk of deficiency due to reduced sun exposure or

dietary intake. Infants who are breastfed require 400 IU vitamin D3 per day and children (ages 1–18 years) require 400–1,000 IU vitamin D3 per day [43]. To prevent deficiency in adults 800–1,000 IU is required and doses of 1,000–2,000 IU are safe [43]. Other regimens include 50,000 IU vitamin D2 every month [44]. In pregnant and lactating women, 1,000–2,000 IU of vitamin D2 per day or 50,000 IU every 2 weeks is recommended [45].

Vitamin D deficiency can be corrected using various methods, although no standard treatment regimen exists and management is often guided by expert opinion [31]. In children and adults with vitamin D deficiency, 50,000 IU of vitamin D2 or D3 can be given every week for 8 weeks until vitamin D levels are satisfactory [44]. In malabsorption syndromes, 50,000 IU may be required on a daily, weekly or monthly basis based on levels [31]. UV-B irradiation (tanning bed or portable UV-B device) can also be used, but the risk of skin damage and malignancy must be considered [46].

To prevent deficiency in chronic renal failure, in stage 2 and 3 disease, 1,000 IU of vitamin D2 or D3 per day or 50,000 IU is recommended every 2–4 weeks to maintain levels. In vitamin D deficiency, 50,000 IU of vitamin D2 may be given weekly for 8 weeks and may need to be repeated according to levels [47]. Patients with an eGFR <30ml/min kidneys are unable to make active vitamin D and activated vitamin D should be prescribed to maintain calcium metabolism and reduce the risk of bone disease, i.e. 0.25–1 μg of alfacalcidol orally twice daily [47]. Alfacalcidol is associated with a risk of hypercalcaemia and thus serum calcium levels must be monitored closely.

Intramuscular vitamin D would appear to be an attractive alternative to oral supplementation as it avoids potential problems with compliance. A previous study performed by DeLappe et al. in Galway in a group of older females demonstrated that oral calcium and vitamin D supplementation in our unit failed to normalise plasma levels in most patients [9]. However, there are a limited number of studies looking at intramuscular vitamin D as a management option. A study by Burns et al. [48] included just seven patients who received 1,200,000 IU of vitamin D and there were no cases of hypercalcemia. A study performed in Galway, published in a recent issue of this journal randomised 90 women over the age of 65 to receive 300,000 IU of vitamin D3 or placebo. Patients who received intramuscular treatment showed a significant improvement in 25OH vitamin D levels, from 25.5–81 nmol/l with 11% remaining deficient [49]. A recent study by Smith et al. [50] concluded that an annual injection of vitamin D2 (300,000 IU) was not effective in preventing nonvertebral fractures among older men and women resident in the community. The precise frequency of injections required to maintain adequate serum levels of vitamin D is the subject of ongoing research in our department.

Vitamin D excess

Hypercalcaemia was reported in children in the 1940s and 1950s which was felt to be due to high levels of vitamin D in fortified milk. It has also been documented in adults taking more than 60,000 units a day. Manifestations include symptoms of hypercalcaemia and hypercalciuria, including confusion, polyuria, polydipsia, anorexia, vomiting, and bony demineralisation with pain. This may occur in those who take excess supplementation, or in patients prescribed vitamin D for malabsorption, renal osteodystrophy, osteoporosis and psoriasis. There is no clear data on when intake of vitamin D becomes toxic. However, doses of 10,000 IU of vitamin D_3 per day for up to 5 months, however, do not cause toxicity [51].

Conclusion

Vitamin D insufficiency is a very common, under diagnosed problem in Ireland affecting all age groups, but especially the older population. It is associated with skeletal and nonskeletal conditions which cause significant morbidity and mortality. It is both treatable and preventable and innovative approaches to its management such as intramuscular replacement and supplementation are both practically feasible and promising as demonstrated by Nugent et al. [49] in the current issue of this journal.

References

1. Holick MF (2005) Vitamin D: important for prevention of osteoporosis, cardiovascular heart disease, type 1 diabetes, autoimmune diseases, and some cancers. South Med J 98:1024–1027
2. DeLappe E, McGreevy C, Ni Chadhain N et al (2006) Vitamin D insufficiency in older female community-dwelling acute hospital admissions and the response to supplementation. Eur J Clin Nutr 60:1009–1015
3. Gordon CM, DePeter KC, Feldman HA et al (2004) Prevalence of vitamin D deficiency among healthy adolescents. Arch Pediatr Adolesc Med 158:531
4. Hill TR, Flynn A, Kiely M, Cashman KD (2006) Prevalence of suboptimal vitamin D status in young, adult and elderly Irish subjects. Ir Med J 99(2):48–49
5. Webb AR, Kline L, Holick MF (1988) Influence of season, latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston, Edmonton will not promote vitamin D3 synthesis in human skin. J Clin Endocrinol Metab 67:373
6. Holick MF (2004) Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr 80:1678S–1688S

7. Hashemipour S, Larijani B, Adibi H et al (2006) The status of biochemical parameters in varying degrees of vitamin D deficiency. J Bone Miner Metab 24:213–218
8. Iqbal SJ (1994) Vitamin D metabolism and the clinical aspects of measuring metabolites. Ann Clin Biochem 31:109–124
9. Theiler R, Stahelin HB, Tyndall A et al (1999) Calcidiol, calcitriol and parathyroid hormone serum concentrations in institutionalised and ambulatory elderly in Switzerland. Int J Vitam Nutr Res 69:96–105
10. Need AG, Morris HA, Horowitz M et al (1993) Effects of skin thickness, age, body fat, and sunlight on serum 25-hydroxyvitamin D. Am J Clin Nutr 58:882–885
11. Holick MF, Krane SM, Potts JT (1995) Calcium, phosphorous, and bone metabolism: calcium-regulation hormones. In: Fauci AS, Braunwald E, Isselbacher KJ et al (eds) Harrisson's Principles of internal medicine, 14th edn. McGraw–Hill, New York, pp 2214
12. Sermet-Gaudelus I, Castanet M, Retsch-Bogart G et al (2009) Update on cystic fibrosis-related bone disease: a special focus on children. Paediatr Respir Rev 10(3):134–142 (Epub 2009 Jul 17)
13. Zanchi C, Di Leo G, Ronfani L et al (2008) Bone metabolism in celiac disease. J Pediatr 153(2):262–265 (Epub 2008 Apr 14)
14. Gartner LM, Greer FR (2003) Prevention of rickets and vitamin D deficiency: new guidelines for vitamin D intake. Pediatrics 111(4 Pt 1):908–910
15. Bouillon R (2001) Vitamin D: from photosynthesis, metabolism, and action to clinical applications. In: DeGroot LJ, Jameson JL (eds) Endocrinology. Saunders, Philadelphia, pp 1009–1028
16. Dusso AS, Brown AJ, Slatopolsky E (2005) Vitamin D. Am J Physiol Renal Physiol 289:F8–F28
17. Bischoff-Ferrari HA, Dietrich T, Orav EJ et al (2004) Positive association between 25-hydroxy vitamin D levels and bone mineral density: a population-based study of younger and older adults. Am J Med 116(9):634–639
18. Chapuy MC, Arlot ME, DuBoeuf F et al (1992) Vitamin D3 and calcium to prevent hip fractures in elderly women. N Engl J Med 237:1637–1642
19. Trivedi DP, Doll R, Khaw KT (2003) Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: a randomised double blind controlled trial. BMJ 326:469
20. Porthouse J, Cockayne S, King C et al (2005) Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D3) for prevention of fractures in primary care. BMJ 330:1003–1008
21. The RECORD Trial group (2005) Oral Vitamin D3 and Calcium for secondary prevention of low trauma fractures in elderly people (randomized evaluation of calcium or vitamin D): a randomised placebo-controlled trial. Lancet 365:1621–1628
22. Lips P, Graafmans WC, Ooms MEB et al (1996) Vitamin D supplementation and fracture incidence in elderly persons: a randomized, placebo-controlled clinical trial. Ann Intern Med 124:400–406
23. Jackson RD, LaCroix AZ, Gass M, Women's Health Initiative Investigators et al (2006) Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med 354:669–683
24. Solomon DH, Avorn J, Katz JN et al (2005) Compliance with osteoporosis medications. Arch Intern Med 165:2414–2419
25. Bischoff-Ferrari HA, Willett WC, Wong JB et al (2005) Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. J Am Med Assoc 293:2257–2264
26. Law M, Withers H, Morris J, Anderson F (2006) Vitamin D supplementation and the prevention of fractures and falls: results of a randomised trial in elderly people in residential accommodation. Age Ageing 35:482–486
27. Trang HM, Cole DE, Rubin LA et al (1998) Evidence that vitamin D3 increases serum 25hydroxyvitamin more efficiently than does vitamin D2. Am J Clin Nutr 68(4):854–858
28. Holick MF, Biancuzzo RM, Chen TC et al (2008) Vitamin D2 is as effective as vitamin D3 in maintaining circulating concentrations of 25-hydroxyvitamin D. J Clin Endocrinol Metab 93(3):677–681
29. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC et al (2004) Effect of vitamin D on falls: a meta-analysis. J Am Med Assoc 291:1999–2006
30. Bischoff-Ferrari HA, Orav EJ, Dawson-Hughes B (2006) Effect of cholecalciferol plus calcium on falling in ambulatory older men and women: a 3-year randomized controlled trial. Arch Intern Med 166:424–430
31. Holick MF (2007) Vitamin D deficiency. New Engl J Med 357:266–281
32. Plotnikoff GA, Quigley JM (2003) Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. Mayo Clin Proc 78:1463–1470
33. Grant WB (2002) An estimate of premature cancer mortality in the US due to inadequate doses of solar ultraviolet-B radiation. Cancer 94:1867–1875
34. Feskanich D, Ma J, Fuchs CS et al (2004) Plasma vitamin D metabolites and risk of colorectal cancer in women. Cancer Epidemiol Biomark Prev 13:1502–1508
35. Wactawski-Wende J, Kotchen JM, Anderson GL et al (2006) Calcium and vitamin D supplementation and the risk of colon cancer. N Engl J Med 354(7):684–696 (erratum in N Engl J Med 354(10):1102)
36. Ponsonby A-L, McMichael A, van der Mei I (2002) Ultraviolet radiation and autoimmune disease: insights from epidemiological research. Toxicology 181:71–78
37. Mathieu C, Gysemans C, Giulietti A et al (2005) Vitamin D and diabetes. Diabetologia 48(7):1247–1257
38. Scragg R, Sowers M, Bell C (2007) Serum 25-hydroxyvitamin D, ethnicity, and blood pressure in the Third National Health and Nutrition Examination Survey. Am J Hypertens 20(7):713–719
39. Nemerovski CW, Dorsch MP, Simpson RU, Bone HG, Aaronson KD, Bleske BE (2009) Vitamin D and cardiovascular disease. Pharmacotherapy 29(6):691–708 (review)
40. Autier P, Gandini S (2007) Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. Arch Intern Med 167(16):1730–1737
41. Institute of Medicine (1997) Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and flouride. National Academy Press, Washington, DC, pp 250–287
42. Scientific Committee on Food (1992) Nutrient and energy intakes for the European Community (opinion expressed on 11 December 1992) (online). Available from http://ec.europa.eu/food/fs/sc/scf/out89.pdf
43. Holick MF (2006) Resurrection of vitamin D deficiency and rickets. J Clin Invest 116:2062–2072
44. Malabanan A, Veronikis IE, Holick MF (1998) Redefining vitamin D insufficiency. Lancet 351:805–806
45. Hollis BW, Wagner CL (2004) Assessment of dietary vitamin D requirements during pregnancy and lactation. Am J Clin Nutr 79:717–726
46. Koutkia P, Lu Z, Chen TC, Holick MF (2001) Treatment of vitamin D deficiency due to Crohn's disease with tanning bed ultraviolet B radiation. Gastroenterology 121:1485–1488
47. Holick MF (2005) Vitamin D for health and in chronic kidney disease. Semin Dial 18:266–275
48. Burns J, Patterson CR (1985) Single dose vitamin D treatment for osteomalacia in the elderly. BMJ (Clin Res Ed) 290:281–282
49. Nugent C, Roche K, Wilson S et al (2010) The effect of intramuscular vitamin D (cholecalciferol) on serum 25OH vitamin D

levels in older female acute hospital admissions. Ir J Med Sci 179:57–61
50. Smith H, Anderson F, Raphael H et al (2007) Effect of annual intramuscular vitamin D on fracture risk in elderly men and women—a population-based, randomized, double-blind, placebo-controlled trial. Rheumatology (Oxford) 46:1852–1857
51. Vieth R (2004) Why the optimal requirement for vitamin D_3 is probably much higher than what is officially recommended for adults. J Steroid Biochem Mol Biol 89:575–579