Proceedings of the Nutrition Society (2013), **72**, 372–380 doi:10.1017/S0029665113002036
 First published online 11 September 2013

The 13th International Congress of Nutrition, Longevity and Quality of Life, Mega Evento Nutrição was held at the Centro de Convenções e Eventos Frei Caneca, São Paulo, Brazil on 4–6 October 2012

The 5th International Symposium of the Nutrition Society

Vitamin D and bone health outcomes in older age

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The aim of this review is to summarise the evidence linking vitamin D to bone health outcomes in older adults. A plethora of scientific evidence globally suggests that large proportions of people have vitamin D deficiency and are not meeting recommended intakes. Older adults are at particular risk of the consequences of vitamin D deficiency owing to a combination of physiological and behavioural factors. Epidemiological studies show that low vitamin D status is associated with a variety of negative skeletal consequences in older adults including osteomalacia, reduced bone mineral density, impaired Ca absorption and secondary hyperparathyroidism. There seems to be inconsistent evidence for a protective role of vitamin D supplementation alone on bone mass. However, it is generally accepted that vitamin D (17·5 μg/d) in combination with Ca (1200 mg/d) reduces bone loss among older white subjects. Evidence for a benefit of vitamin D supplementation alone on reducing fracture risk is varied. According to a recent Agency for Healthcare Research and Quality review in the USA the evidence base shows mixed results for a beneficial effect of vitamin D on decreasing overall fracture risk. Limitations such as poor compliance with treatment, incomplete assessment of vitamin D status and large drop-out rates however, have been highlighted within some studies. In conclusion, it is generally accepted that vitamin D in combination with Ca reduces the risk of non-vertebral fractures particularly those in institutional care. The lack of data on vitamin D and bone health outcomes in certain population groups such as diverse racial groups warrants attention.

25-hydroxyvitamin D: Vitamin D requirements: Older age: Bone mineral density: Fractures

Osteoporosis is a condition characterised by a low bone mass and microarchitectural deterioration of bone with a consequent increase in bone fragility and susceptibility to fracture. In the UK, it is estimated that 3 million people are affected with osteoporosis. Furthermore, one in two British women and one in five British men aged >50 years will experience an osteoporotic fracture in their lifetime with the estimated costs in the UK being about £1·7 billion annually. In the European Union, it has been estimated that previous and incident fractures accounted for 1 180 000 quality-adjusted life years lost during 2010[(1)]. Furthermore, with an ageing population, the costs associated with treating osteoporosis in the EU are expected to increase by 25 % in 2025[(1)].

Bone is a dynamic tissue that responds to the external and internal environments to which it is exposed during an individual's lifetime. While a considerable proportion (up to 70 %) of the inter-individual variation in bone mass is genetically determined, lifestyle factors such as diet and exercise are well established modifiable factors of bone mass. Bone turnover is important for the self-repair of skeletal tissue[(2)] as well as maintaining mineral homoeostasis (e.g. Ca and P) and the balance between the rate of bone formation and bone resorption (which together constitute

Abbreviations: BMD, bone mineral density; IOM, Institute of Medicine; PTH, parathyroid hormone; RANK, receptor activator of NF-κβ; RANKL, RANK ligand; RCT, randomised controlled trial.

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bone turnover rate) ultimately determines bone mass. In growing children, bone formation exceeds resorption, balances resorption in young adults and lags behind resorption with ageing in both sexes, but particularly after the menopause in women. The rate of bone formation and bone resorption can be assessed by blood and/or urinary-based biochemical markers[3]. An increased rate of bone turnover has been suggested as a potential risk factor for osteoporotic fractures[4,5]. The only readily measured surrogate of bone strength is bone mineral mass, which may be expressed as bone mineral content and bone mineral density (BMD). Bone mineral content as well as BMD is measured by dual-energy X-ray absorptiometry, which is associated with a low-radiation exposure and relatively high precision and accuracy. Bone mineral content measures the amount of bone mineral in g/cm. BMD expresses bone mineral mass as a function of the bone area scanned area in g/cm^2. Volumetric BMD measures bone mineral content as a function of true bone volume in g/cm^3 but cannot be assessed using dual-energy X-ray absorptiometry and is best assessed by quantitative computerised tomography. A decrease in BMD is associated with an increased risk of osteoporotic fractures. However, increases in BMD (by dietary modification or drugs) have not generally been shown to reduce the risk of osteoporotic fractures in human subjects[6]. Quantitative ultrasound densitometry measurements reflect not only BMD but also other aspects of bone tissue, such as elasticity, structure and geometry which are involved in the occurrence of fractures, and they could be considered as surrogated for bone quality and, with a great ability to predict fracture risk[7].

Ca and vitamin D are major nutritional determinants of bone health throughout the life-course and both nutrients have an interdependent role in bone metabolism. The present review will examine the role of vitamin D in maintaining bone health in older (generally 60 + years) adults with particular emphasis on outcomes such as BMD and fracture. Vitamin D status and particularly dietary intake in older adults, as well as the effect of ageing on vitamin D metabolism will be explored. Finally, dietary vitamin D requirements will also be discussed in the context of the recent comprehensive Institute of Medicine (IOM) Dietary Reference Intake report on vitamin D[8].

Vitamin D metabolism and function

The term 'vitamin D' was given during the early 1920s to a group of closely-related secosteroids with antirachitic properties. Two of the most important nutritional forms of vitamin D are cholecalciferol (vitamin D_3, derived from animal origin) and ergocalciferol (vitamin D_2, derived from plant origin). However, natural dietary sources of vitamin D are limited with oily fish, egg yolk and meat contributing up to 90% of vitamin D intake from non-fortified food sources[9]. Vitamins D_3 and D_2 can also be derived by photoirradiation from their precursors 7-dehydrocholesterol and ergosterol, respectively. In vertebrates, the cholesterol-like precursor, 7-dehydrocholesterol, present in the skin epidermis, undergoes photolysis when exposed to UV-B-light of wavelengths 290–315 nm to yield a variety of photoirradiation products including tachysterol, lumisterol and previtamin D_3. Previtamin D_3 then undergoes spontaneous thermal rearrangement to vitamin D_3. Because of the skin's ability to synthesise the vitamin upon exposure to appropriate sunlight, vitamin D is only an essential nutrient when sunlight is limited.

Vitamin D_3 (obtained from dermal synthesis or from dietary sources), which is biologically inactive, is transported via vitamin-D-binding protein to the liver where it is hydroxylated at the C_{25} position by the 25-hydroxylase enzyme (CYP2R1) to yield 25-hydroxyvitamin D_3 (25(OH)D or calcidiol) which is the most commonly used index of vitamin D status[8]. The CYP2R1 enzyme regulates 25-hydroxylation of vitamin D_3 to produce $25(OH)D_3$, which is dependent on the concentrations of vitamin D_3 in serum/plasma. From the liver, $25(OH)D_3$ is returned to the circulation, bound to vitamin-D-binding protein, and transported to the kidney where the enzyme 1-α-hydroxylase (CYP27B1) converts it to 1,25-dihydroxycholecalciferol ($1,25(OH)_2D_3$ or calcitriol), which is the major active metabolite of vitamin D. When $1,25(OH)_2D_3$ is in excess, the enzyme 24-hydroxylase (CYP24) in the kidney converts $25(OH)D_3$ to 24,25-dihydroxycholecalciferol, which is believed to be biologically inactive. Furthermore, $25(OH)D_3$ can be converted to other inactive metabolites such as 23,25-dihydroxycholecalciferol, 25,26-dihydroxycholecalciferol and 1,24,25-trihydroxycholecalciferol and excreted mainly in faeces, but the biological roles of these metabolites are not well understood (for reviews, see[10,11]).

The major biological role of $1,25(OH)_2D_3$ is to promote intestinal Ca absorption. In addition, $1,25(OH)_2D_3$ increases the absorption of other essential minerals across the intestine, such as P, Mg, Zn and Mn[12,13], and enhances the net renal reabsorption of Ca and P[14]. Thus, $1,25(OH)_2D_3$ is a major regulator of Ca homoeostasis. The classical target organs for $1,25(OH)_2D_3$ are the intestine, bone, the kidneys and the parathyroid glands; however, $1,25(OH)_2D_3$ also acts at several sites in the body in an intracrine or paracrine manner[15]. Normal physiological concentrations of Ca are required for proper neuromuscular and cellular functions. Low serum Ca (hypocalcaemia) stimulates the secretion of parathyroid hormone (PTH) from the parathyroid gland, which, in turn, enhances the conversion of $25(OH)D_3$ to $1,25(OH)_2D_3$. $1,25(OH)_2D_3$ acts on the intestine, kidneys and bone to restore normal serum Ca concentrations. In addition to PTH, it is also well recognised that other hormones, such as calcitonin, glucocorticoids, growth hormones and sex steroids regulate the production of $1,25(OH)_2D_3$[16]. In addition to its classical role in the skeleton, a number of key hydroxylase enzymes together with vitamin D receptors have been identified in over thirty different extra-skeletal tissues suggesting an important regulatory role of vitamin D in these target tissues[16]. Furthermore, although not the subject of this review, data from epidemiological and (some) intervention studies have provided fascinating and really exciting hypotheses about relationships between vitamin D status and risk of several chronic conditions (including multiple sclerosis, tuberculosis, rheumatoid arthritis, CVD,

https://doi.org/10.1017/S0029665113002036 Published online by Cambridge University Press

hypertension, cognitive decline, lung conditions and certain cancers; for reviews see[8,17]).

The biological actions of $1,25(OH)_2D_3$ in target tissues are mediated either through: (i) a nuclear vitamin D receptor, which, once complexed with $1,25(OH)_2D_3$ and retinoic acid receptors, can regulate gene expression (genomic effects); (ii) intra-cellular signalling pathways activated through putative plasma membrane receptors (non-genomic effects)[16].

It is well established that $1,25(OH)_2D_3$ is essential for the normal growth and development of bone. In bone cells, $1,25(OH)_2D_3$ acts on osteoblasts to increase osteoclastogenesis and bone resorption, which contribute to mineral homoeostasis[18]. The discovery of the molecular triad of receptor activator of NF-κβ (RANK), RANK ligand (RANKL) and osteoprotegerin (RANK/RANKL/osteoprotegerin) in the 1990s represented a significant breakthrough in the understanding of the pathophysiology of bone remodelling (for review see[19]). RANK, on the surface of osteoclasts binds to its ligand (RANKL) present on the surface of osteoblasts following their stimulation by $1,25(OH)_2D_3$. Binding of RANK to RANKL initiates the maturation of osteoclasts and is enhanced by the antagonistic effect of $1,25(OH)_2D$ on the protein osteoprotegerin. As osteoprotegerin normally binds RANKL, it prevents binding to RANK therefore inhibiting osteoclast maturation. It should be noted that $1,25(OH)_2D_3$ also regulates the transcription of a number of key osteoblastic genes such as those coding for the bone proteins osteocalcin, osteopontin, osteonectin and proteoglycan[20].

Assessment of vitamin D status

Circulating $1,25(OH)_2D_3$ concentrations are under homoeostatic control, which limits its value as a nutritional marker of vitamin D status[8]. However, serum or plasma total 25(OH)D (i.e. that derived from adding $25(OH)D_2$ and $25(OH)D_3$) concentration is widely accepted as a good biomarker of vitamin D status, because the concentration of this metabolite closely reflects the amount of vitamin D synthesised in the skin and ingested in the diet[8]. During winter, in countries of latitudes greater than 40° North or South the skin is incapable of synthesising vitamin D for 4–5 months of the year as sunlight must pass a much longer distance through the atmosphere and most UV-B-light is absorbed by the atmosphere, preventing any effective UV irradiation of the skin[21]. Therefore, it is assumed that during winter the circulating 25(OH)D concentration is directly related to late-summer concentrations, oral intake and body stores of its precursor vitamin D_3. Although circulating 25(OH)D is generally regarded as a good biomarker of exposure (i.e. that derived from sun and diet), its use as a biomarker of function and outcome is less clear owing to the multitude of factors influencing this prohormone[22]. Notwithstanding such difficulties, the concentration of 25(OH)D is widely used to diagnose vitamin D deficiency in both the clinical and non-clinical settings.

Dietary vitamin D requirements and vitamin D intakes

Using the risk-assessment framework commonly used to set upper levels for nutrients, the IOM in their recent Dietary Reference Intake report[8] set a 25(OH)D concentration of 30 nmol/l as indicative of vitamin D deficiency based on integrating a number of key bone health outcomes, including rickets, osteomalacia, impaired Ca absorption and lower BMD. The nature of the relationship between 25(OH)D concentration and bone health outcomes will be discussed in detail later in this review. It is noteworthy that the IOM committee concluded that there was insufficient evidence to define vitamin D deficiency based on non-skeletal outcomes. Based on the relationship between 25(OH)D status and those aforementioned bone health outcomes, and using data from both epidemiological and intervention studies, the IOM established a population 25(OH)D concentration of 40 and 50 nmol/l as the basis for setting an estimated average requirement of 10 μg/d and a recommended daily allowance of 15 μg/d, respectively in people aged 1–70 years. The IOM set a recommended daily allowance of 20 μg/d for individuals aged >70 years, while it could only establish an adequate intake of 5 μg/d for infants aged <1 year[8]. The estimated average requirement is the amount of a nutrient which meets the needs of half (50 %) the population, whereas the recommended daily allowance is the amount of a nutrient which will meet the needs of practically all (97·5 %) healthy persons in a population. The adequate intake is an estimation of the observed dietary intake of an asymptomatic population. The approach and conclusions of the recent IOM report[8] was a significant deviation from those of the previous IOM Dietary Reference Intake report of 1997[21] in that for the first time an estimated average requirement and recommended daily allowance was established for children and adults. In the past[23] only an adequate intake of 5 μg/d could be derived for persons aged up to 70 years. Two of the caveats of the IOM report are that the vitamin D recommendations (1) assume an adequate dietary Ca intake and (2) assume a negligible contribution from sunlight to 25(OH)D concentrations. It is also noteworthy that in terms of adverse effects, the tolerable upper intake level for vitamin D, which is the highest level of daily consumption that current data have shown to cause no side effects is 100 μg/d[8], whereas in the older Dietary Reference Intake report[23] it was set at 50 μg/d. In 1998, the UK Committee on Medical Aspects of Food and Nutrition Policy concluded that a prudent public health approach to safeguard against vitamin D deficiency and its adverse effect on bone health would be to retain the Reference Nutrient Intake set in 1991 (10 μg/d for those aged >65 years). However, vitamin D requirements are currently under review in the UK by the Scientific Advisory Committee for Nutrition and a report is due in 2014.

There can be no doubt (and ample evidence exists) that dietary vitamin D intakes are a concern in large proportions of the European population (for review see[24]). For example, mean vitamin D intakes are between 4 and 5 μg/d among adults from National Diet and Nutrition Surveys in the UK[25], mostly from meat, fish and eggs, fortified foods and supplements. Therefore, current vitamin D intakes are

https://doi.org/10.1017/S0029665113002036 Published online by Cambridge University Press

considerably lower than recommendations and urgent dietary-based strategies are needed to bridge the gap. Indeed, this area of research has gained attention at European level recently with the release of a major EU-wide Framework 7 funded project investigating food-based strategies to eradicate vitamin D deficiency across Europe.

Circulating 25(OH)D concentrations in older age

An extensive array of studies including a mix of both representative and convenience sampling frames have reported 25(OH)D concentrations among older adults all over the globe[8,26–28]. Without doubt, the region with the most available data on 25(OH)D concentrations is Europe, followed by North America and Asia. Limited data exist for South America and Africa with very few studies in children and adolescents in these regions[26]. Cross-sectional data predominate and year-round 25(OH)D concentrations are only available in some studies. In addition, comparisons of the prevalence of hypovitaminosis D between studies is compounded by the heterogeneity with regard to circulating 25(OH)D concentrations used to define vitamin D status. Furthermore, the very low Ca intakes seen in some communities complicate the interpretation and subsequent treatment of vitamin D deficiency in these population groups.

Data from three multi-centred, standardised studies show that between 17 and 58% of older Europeans are vitamin D deficient (defined as serum 25(OH)D) <30 nmol/l[29–31]). National representative data on 25(OH)D concentrations from the National Diet and Nutrition Surveys in UK adults aged over 64 years show that up to 10% of free-living and 40% of institutionalised adults have plasma 25(OH)D concentrations <25 nmol/l throughout the year (reviewed in[32]). Moreover, if the higher IOM cut point of 40 nmol/l is applied (defining an estimated average requirement) the proportion of adults with inadequate 25(OH)D concentrations rises considerably. While older adults are well-established as an 'at risk' group for vitamin D deficiency, it should be noted that ethnic populations residing in less sunnier climates are also particularly at risk of vitamin D deficiency. For example, in a large study of vitamin D status among South Asian (*n* 1105) and Black African and Caribbean adults (*n* 748) >45 years living in the West-Midlands region of the UK[33] plasma 25(OH)D concentrations <30 nmol/l were found in 76% of South Asians and 55% of Black African and Caribbean adults throughout the year. Another study involving thirty-five South Asians living in Surrey[34] found that 81% and 79% of the participants had serum 25(OH)D concentrations <25 nmol/l during winter and autumn, respectively. These studies suggest an extremely high prevalence of vitamin D deficiency in these population groups which require urgent attention.

Changes in vitamin D metabolism with ageing

Calcium absorption

Ca is absorbed from the bowel by an active vitamin-D-dependent transport mechanism and by passive diffusion. The active transport mechanism plays an important role in Ca homoeostasis, as the amount absorbed is inversely related to dietary Ca intake[35]. Fractional Ca absorption therefore increases when dietary Ca intake is reduced[36]. Ca absorption decreases with advancing age[37], which has been attributed to a number of mechanisms, including the reduction in serum 25(OH)D with age[38], impaired hydroxylation of 25(OH)D to $1,25(OH)_2D$ with declining renal function[39], resistance to the action of vitamin D metabolites on the bowel mucosa[40] and low circulating oestrogen concentrations in women after the menopause[41]. Increasing serum 25(OH)D concentrations by oral vitamin D supplementation improves Ca absorption in older women, but this is attenuated by renal impairment[42], suggesting that lower levels of substrate serum 25(OH)D) and impaired hydroxylation of 25(OH)D to $1,25(OH)_2D$ both contribute to the decrease in Ca absorption with age. Despite the inverse relationship between dietary Ca intake and Ca absorption, the increase in Ca absorption when dietary Ca is reduced is less marked in older people than younger adults[35]. This may be due to reduced production of $1,25(OH)_2D$, but it may also reflect resistance to the actions of vitamin D metabolites on the bowel, as some studies have shown an attenuated response in Ca absorption to increases in $1,25(OH)_2D$ in older women[40].

Although the decline in Ca absorption with advancing age is multifactorial in origin, the improvement in absorption with vitamin D supplementation suggests that vitamin D deficiency is the major cause of malabsorption of Ca in older people[42]. The positive relationship between serum 25(OH)D and fractional absorption extends to 25(OH)D concentrations above 100 nmol/l[42,43], leading some experts to advocate that these concentrations are necessary for optimal bone health. Nevertheless, although a recent randomised controlled trial (RCT) comparing the effect of different doses of vitamin D showed higher Ca absorption in subjects with a serum 25(OH)D of 75 nmol/l than those with 50 nmol/l, the magnitude of the difference was small[43].

Renal 1-α-hydroxylase

Renal function declines with advancing age and this is accompanied by a decrease in serum $1,25(OH)_2D$ concentration[44]. As mentioned earlier, the effect of vitamin D supplementation on Ca absorption is attenuated by renal impairment[42]. An early study showed that as glomerular filtration rate falls below 50 ml/min, there is a reduction in serum $1,25(OH)_2D$ and lower fractional absorption of Ca[39], together with increased serum PTH. Other studies show an inverse relationship between serum 25(OH)D and PTH across all adult age groups, but that PTH is higher in older people than young adults for any given serum 25(OH)D concentration[45], possibly due to reduced renal 1-α-hydroxylation.

Dermal vitamin D production

The dermal capacity to produce vitamin D in persons aged 65 years has been estimated to be about 25% of that in

https://doi.org/10.1017/S0029665113002036 Published online by Cambridge University Press

persons aged 20–30 years exposed to the same amount of sunlight[46,47]. This reduction cannot be explained by the decrease in mass of the epidermis with ageing, but rather seems to be related to the reduction in the concentration of skin 7-dehydrocholesterol. Other indirect factors that affect exposure to sunlight in older adults include the wearing of more concealing clothing[48], an increased use of sunscreen[49] and reduced sun exposure, arising from less physical activity and time outdoors compared with the younger age groups[50].

Changes in vitamin D receptors numbers

Vitamin D deficiency is associated with muscle weakness which potentially increases the risk of falls and fractures, possibly mediated through effects on $1,25(OH)_2D$ receptors, which have been discovered in muscle[51,52]. Bischoff-Ferrari *et al.*[53] demonstrated a strong negative correlation between age and vitamin D receptors expression in muscle as measured by the number of vitamin D receptor-positive nuclei per 500 counted nuclei. This association was independent of biopsy location and circulating 25(OH)D concentrations. This finding may have significant clinical ramifications in older age owing to the importance of $1,25(OH)D_3$ in regulating transcription of muscle-related genes. It is worth noting that the role of vitamin D in muscle atrophy in older adults has been the subject of a recent review within this journal[54] and therefore will not be discussed here.

Circulating 25(OH)D concentrations and bone health outcomes in older age

As mentioned previously, vitamin D requirements together with the definition of vitamin D deficiency is currently under review by the Scientific Advisory Committee on Nutrition in the UK, which is scheduled to present its recommendations in 2014. Previous Scientific Advisory Committee on Nutrition recommendations (which currently apply to the UK) define vitamin D deficiency as a serum 25(OH)D <25 nmol/l, which corresponds to the upper end of the range at which vitamin D deficiency osteomalacia and rickets has been observed[22]. However, higher levels of serum 25(OH)D have been associated with secondary hyperparathyroidism, increased bone resorption, bone loss, impaired muscle function and an increased risk of falls and fragility fracture[55–59], and there remains contention about the thresholds applied.

Osteomalacia

Recommended circulating levels of 25(OH)D in adult life are commonly set against the clinical risk of developing osteomalacia, although falls and fracture risk are important considerations. The gold standard diagnostic test for mineralisation disorder associated with vitamin D deficiency (vitamin D deficiency osteomalacia) is the identification of mineralisation defect with increased osteoid thickness and reduced calcification fronts, which are identified by bone histomorphometry after tetracycline labelling. However, population-based studies, using this invasive technique, are impractical. One recent study used bone histomorphometry in post-mortem specimens in Germany, apparently finding that abnormal bone mineralisation was only seen in a proportion of subjects whose circulating 25(OH)D was less than 75 nmol/l[60]. The study has been criticised because it uses post-mortem bone histomorphometry without tetracycline labelling, so both generalisability is compromised and causes other than vitamin D deficiency may explain histomorphometric changes seen, while the use of such post-mortem data to make dietary recommendations seems bizarre[61]. This theme has been addressed comprehensively in the IOM report[8] where, even ignoring the technical limitations in Priemel's study, osteomalacia is sometimes reported at serum 25(OH)D levels <30 nmol/l, but rarely observed at 25(OH)D levels >50 nmol/l.

Secondary hyperparthyroidism

The circulating concentration of 25(OH)D below which PTH increases outside the normal range may be used to establish a threshold value for vitamin D insufficiency and this is of particular importance for bone metabolism, because elevated PTH is associated with increased bone loss[55–59]. The relationship of circulating blood levels of 25(OH)D to PTH is contentious. Some studies suggest that PTH reaches a plateau with increasing serum 25(OH)D concentration[62,63], while others demonstrate an inverse relationship throughout the physiological range of 25(OH)D concentrations[45,64–67]. It is important to consider that the relationship between 25(OH)D and PTH may be influenced by the effects of many other factor including co-morbidities. advancing age, dietary Ca and phosphate intake, renal function, plasma vitamin-D-binding protein, Mg concentration, IGF-1, testosterone, smoking and physical inactivity which may all have important roles in the development of secondary hyperparathyroidism[45,64,66–68]. Moreover, comparisons between studies may be hampered by the use of different assays for 25(OH)D and PTH[69,70].

Bone mineral density

The National Health and Nutrition Examination Survey III examined the relationship between serum 25(OH)D and BMD at the hip in 4958 women and 5003 men aged 20 years and above[71]. This showed a positive association between serum 25(OH)D and BMD in both sexes, with the highest BMD found in subjects with a serum 25(OH)D >75 nmol/l. Although these results were adjusted for potential confounding variables, the authors acknowledged that one cannot infer a causal relationship between serum 25(OH)D and BMD from a cross-sectional study. The evidence-based reviews performed for the IOM report also examined the relationship between vitamin D and BMD[8]. Among the observational studies reviewed, there was fair evidence to support an association between serum 25(OH)D levels and BMD or changes in BMD at the femoral neck.

https://doi.org/10.1017/S0029665113002036 Published online by Cambridge University Press

Fracture risk

The IOM report also examined the relationship between serum 25(OH)D and fracture risk[8]. Only one of the three prospective cohort studies reviewed found an inverse relationship between serum 25(OH)D and fractures, but in contrast nine of the twelve case–control studies observed lower 25(OH)D levels in patients with fractures than in the control subjects. The apparent inconsistency between the results of prospective cohort and case–control studies may reflect a failure to fully adjust for confounding variables in the latter, not least the effect of the fracture, any hospital admission, surgical procedure and associated inflammation on vitamin D production and metabolism[72].

Intervention effects of vitamin D supplementation on bone mineral density and fractures

Vitamin D and bone mineral density

The largest RCT of the effects of vitamin D supplementation on bone health was the Women's Health Initiative study, where 36 282 postmenopausal women aged 50–79 years were randomised to receive Ca (1000 mg) and vitamin D (10 μg) or placebo daily[73]. In a sub-set of 2431 women who underwent bone density measurements, there was greater preservation of BMD at the hip with supplementation than with placebo, which consisted 0·59 %, 0·86 % and 1·06 % after 3, 6 and 9 years, respectively. The IOM report highlighted that the combined results of RCT comparing Ca and vitamin D supplementation with placebo were consistent with a small effect on lumbar spine, femoral neck and total body BMD[8]. In contrast, in trials comparing combined Ca and vitamin D supplementation with Ca alone, no significant difference in change in BMD was seen, suggesting that vitamin D supplementation may be less beneficial in Ca replete subjects.

Vitamin D and fractures

One of the earliest RCT investigating the anti-fracture efficacy of vitamin D supplementation compared the effect of combined Ca (1200 mg daily) and vitamin D (20 μg daily) and placebo in 3270 women with an average age of 84 years living in French nursing homes or apartment blocks for the elderly[74]. In a small sub-set of subjects undergoing venipuncture and BMD measurement, there was correction of vitamin D deficiency and secondary hyperparathyroidism with supplementation, together with a small increase in BMD. Intervention also reduced the risk of hip and other non-vertebral fractures. It was unclear from this study if both Ca and vitamin D was required for the beneficial effect of supplementation or if this would be effective in community-dwelling older people. The RECORD study sought to address this question, by comparing the effect of placebo or Ca (1000 mg daily) and vitamin D (20 μg daily), either alone or in combination, in 5292 community-dwelling older women or men with a low-trauma fracture[75]. Over the 24–62 month follow-up period there was no difference in the incidence of all clinical fractures or hip fractures. Compliance with supplementation in the RECORD study was relatively poor, especially when this included Ca. Nevertheless, pre-planned analysis showed no difference in outcome in subjects with good compliance with supplementation compared with participants who were less compliant.

Although the Women's Health Initiative study showed a small improvement in BMD with Ca (1000 mg) and vitamin D (10 μg) supplementation, there was no overall effect on fracture incidence[73]. Among the subjects who remained compliant with supplementation there was a significant reduction in the risk of hip fractures. The results of other RCT of vitamin D supplementation, with or without additional Ca, on the risk of fracture have yielded inconsistent results. Meta-analyses indicate that combined Ca and vitamin D supplementation reduces the incidence of hip fractures in older people, but vitamin D alone is ineffective[76–79]. Nevertheless, much of the beneficial effect of combined supplementation in these meta-analyses is driven by the results of the study in institutionalised French women, where vitamin D deficiency is common.

A meta-analysis by Bischoff-Ferrari, which adjusted the dose of vitamin D for compliance, suggested that vitamin D decreased the incidence of non-vertebral fractures independent of additional Ca supplementation[80]. The reduction in fracture risk was more marked in studies where the received vitamin D dose exceeded 10 μg daily, whereas there was no decrease in fractures in studies where the subjects received 10 μg daily or less. An individual patient data meta-analysis by Bischoff-Ferrari, which also adjusted the dose of vitamin D for compliance, showed a trend for reduction in the risk of hip fractures but a small reduction in non-vertebral fractures[81].

The inconsistency of the results of the anti-fracture trials of vitamin D is likely to reflect heterogeneity in the populations studied, their baseline vitamin D status, dose of vitamin D, frequency and route of administration, compliance with supplementation and the use of additional Ca supplementation. Nevertheless, it would appear that vitamin D supplementation is most likely to be beneficial in older people with vitamin D deficiency, such as those who are housebound or living in residential or nursing homes. Although the study in institutionalised French women[74] and several meta-analyses[76–79] suggest that additional Ca supplementation is required, it is unclear if a high dietary Ca intake is sufficient to obtain the benefit of vitamin D supplementation. Although the concept of the annual administration of high-dose vitamin D is potentially attractive, either by the intramuscular or oral route, this may be associated with an increase in fracture risk[82,83]. For example, a recent study of high-dose vitamin D supplementation (12 500 μg once yearly) reported an increased rate of falls and fractures, particularly in the first 3 months[82]. Similar findings have been reported in another study which, gave 7500 μg to older people, with a relative risk of hip fracture of 1·49 (95 % CI 1·02–2·18) in older people treated in their own homes for 3 years[83] and a non-significant 1 % increase in non-vertebal fractures over 10 months in care-home residents[84]. These studies offer a concern with regard to what could be perceived as toxicological doses of vitamin D (i.e. 125 times the IOM

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upper intake level) and its potential risks. Unfortunately, 25(OH)D and PTH were only measured in a small minority of participants in all of these interventional studies[85], limiting the ability to explore the relationship between the serum 25(OH)D achieved and fracture prevention.

Concluding remarks and future direction

The last two decades have seen major advances in our understanding of the role of vitamin D in bone health. Although the focus of this review was on the public health significance of the role of vitamin D in bone health in older age, the caveat of the interdependence between vitamin D and Ca intake on bone health although complex, cannot be ignored. The upward shift in the target 25(OH)D threshold set by authoritative bodies to define better bone health has been a significant step in recent years and much of the world's population have a vitamin D status below what is considered optimal for bone health. The debate surrounding the optimal circulating 25(OH)D concentration for both skeletal and non-skeletal health will continue until significant progress has been made in two important areas. The first area centres around assay variability for 25(OH)D measurements, which has been addressed somewhat by the recent introduction of the Standard Reference Material for vitamin D by the National Institute of Standards and Technology in the USA. The second area centres around gaining a better understanding of the production, storage and utilisation of 25(OH)D as a biomarker of effect[23]. A number of potential reasons have been highlighted in this review as to why there is inconsistent evidence for a role of vitamin D supplementation on fracture risk. It should also be pointed out that there is now recognised evidence that genetic variants in key vitamin D regulated genes can influence the response to vitamin D exposure to impact the metabolism and actions of vitamin D. Therefore, future studies investigating the effect of vitamin D supplementation on both musculoskeletal outcomes and health outcomes in general should take advantage of emerging technology which makes genome-wide analysis possible. Appreciably, genotyping studies will need to be large in study design or analysis, because of the very large sample sizes required to adequately account for genotype effects. The dearth of information in many population sub-groups including diverse racial and ethnic groups of older age should be prioritised in future studies on vitamin D status and bone health. In conclusion and in light of the widespread prevalence of dietary and biochemical vitamin D inadequacy in many populations and its negative consequences for bone health, strategies to increase oral vitamin D intake at a population level would benefit bone health and should be a priority.

Acknowledgements

This work did not receive external funding. T. R. H. presented the work and was responsible for the conception of the manuscript. T. R. H., T. J. A. and R. M. F. researched and prepared sections for the manuscript. All authors reviewed the manuscript prior to submission.

Conflicts of interest

Dr Hill has no conflicts of interest. Dr Aspray is Chief Investigator in a clinical trial of vitamin D supplementation and has been a co-investigator in an earlier clinical trial of vitamin D with Ca supplementation. He is a member of the Writing Group for UK National Osteoporosis Society Practical Clinical Guideline for Patient Management on Vitamin D and Bone Health. Professor Francis has been a Co-Principal Investigator in clinical trials of vitamin D supplementation. He was also a member of the DIPART group, which performed a meta-analysis of the anti-fracture efficacy of vitamin D supplementation. He is a member of the UK Department of Health Scientific Advisory Committee on Nutrition Working Group on Vitamin D and is Chair of the Writing Group for UK National Osteoporosis Society Practical Clinical Guideline for Patient Management on Vitamin D and Bone Health. He has also received speaker's honoraria from Shire Pharmaceuticals, who market Ca and vitamin D supplements. The opinions expressed in this paper are those of the authors and do not necessarily reflect the views of the organisations they work with.

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