Mini Review

The role of vitamin D in osteoporosis

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ABSTRACT

It is known that circulating vitamin D predominantly originates from cutaneous synthesis and therefore should be considered as a hormone rather than a vitamin. Vitamin D deficiency (<50 nmol/L) is a worldwide epidemic with multiple implications on human health, due to its role in various physiological systems. Various studies have shown that with higher serum 25 hydroxyvitamin D levels, there is a decrease in the incidence of non-vertebral and hip fractures. There is limited research data on the management of vitamin D deficiency using therapeutic doses. The majority of studies focus on lower physiological doses rather than high pharmacological doses. In order to reach serum levels of 75 nmol/L from a deficiency state, higher doses than 800–1000 IU/day are required. Future focus should be on the implications of a rise in systemic 25(OH)D3 levels from a deficiency state to 75 nmol/L on bone density and fracture risk, and the use of high doses in cases of vitamin D deficiency. Vitamin D treatment and supplementation need to be re-evaluated in the light of new evidence suggesting that high pharmacological doses need to be used in order to obtain the desired effect in the prevention of osteoporosis and recurrence of osteoporotic fractures.

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1. Introduction

Q4 For far too long, the vitamin D story has been enmeshed with the calcium story. This is quite clearly wrong, as the two need to be dissociated. Calcium has been shown to be not entirely free of problems, with the potential to cause cardiovascular problems [1]. The vitamin D used in combination with calcium has been shown to be quite clearly far too low to exert any significant pharmacological effect [2]. Vitamin D therefore needs to be considered entirely on its own.

The role of vitamin D in endocrinology and especially in the postmenopausal years, has raised a lot of research interest, especially due to the discovery that the vitamin D receptor (VDR) for 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] is present in over 40
target tissues [3]. Cystolic/nuclear VDR receptors belong to the family of trans-acting transcriptional regulatory factors and shows sequence similarity to the steroid and thyroid hormone receptors. The biological actions of 1,25(OH)2D3, are mediated by VDR, and include regulation of calcium homeostasis, cellular differentiation, and immune function. This function was deduced originally from the observations that patients with severe vitamin D deficiency become hypocalcemic, with other consequences, such as rickets/osteomalacia following from that.

Nearly every tissue and cell type in the body has receptors for vitamin D. This has enabled us to re-evaluate its role not simply in osteoporosis, but also in the conditions ranging from cardiovascular disease, oligospermia, and breast cancer prevention [4-6]. It has also led to re-evaluating the current dose needed to address the vitamin D deficiency problem, as to the therapeutic dose needed to treat various vitamin D responsive conditions. This review is concerned with bone health and osteoporosis. Substantial evidence has arisen over the past decade that conversion of 25(OH)D3 to 1,25(OH)2D3 via the 1α hydroxylase enzyme in osteoblasts, osteocytes, chondrocytes and osteoclasts regulates other processes such as maturation and cell proliferation, bone resorption and mineralisation. These processes are VDR dependent [7].

2. Vitamin D synthesis

Circulating vitamin D3 (cholecalciferol) predominately arises from synthesis in the skin from a cholesterol derivative, 7-dehydrocholesterol, under the effect of sunlight and its UV radiation [8]. However, a small percentage of the total circulating vitamin D also originates from dietary intake and is primarily found in foods such as fatty fish, eggs and milk. Typical dietary intake of vitamin D is estimated to be as low as 3.7-5.9 mcg [9]. The amount of circulating vitamin D predominantly originates from cutaneous synthesis, while dietary vitamin D intake and only minimally contributes to the total concentration. Vitamin D is entirely synthesised in the body, with its own vitamin D receptors. Therefore there are grounds to classify it as a hormone rather than a vitamin. Vitamin D3 is then metabolised finally in the liver by the enzyme 25-hydroxylase and then in the kidneys by 1-hydroxylase.

The same happens with the plant-derived vitamin D3 (ergocalciferol) when obtained through dietary sources.

Vitamin D acts on four physiological systems, acting via VDRs activated by the metabolically active 1,25(OH)2 vitamin D: (i) immune system (innate & adaptive); (ii) cardiovascular system; (iii) muscle & (iv) pancreas & metabolic homeostasis [10].

3. Dosage

It is now clear that previous recommendations of 400 IU a day of vitamin D3 are far too low certainly for adults. The Canadian Cancer Society recommends that all Canadians take 1000 IU vitamin D3 per day. This however has been shown to be far from ideal [11]. At 2000 IU per day at the end of one year, given to Afro-Americans, one study showed that 40% failed to reach their target level of 32 ng/ml [12]. In another study, 4000 IU of vitamin D3 per day for at least six months did manage to achieve serum levels of 44 ng/ml [13]. This same study concludes by recommending that adults, particularly those who avoid sunlight, should take as much as 5000 IU of vitamin D per day.

One also has to keep in mind that different formulations have different biological actions. Hence ergocalciferol (vitamin D2) is less effective than vitamin D3, and one alpha cholecalciferol, which is synthetically derived, is much more effective than vitamin D3.

There are no significant trials that have been carried out looking at the effect of higher pharmacological doses of vitamin D3 or its analogues on osteoporotic fracture prevention. The significant studies carried so far were carried out with dosages that fall far below what is now the recommended daily dose in adults not regularly exposed to sunlight, let alone pharmacological doses. It is clear, as indicated in the introduction, that vitamin D, through vitamin D receptors, has effects that are more profound on osteoclasts, osteoblasts and chondrocytes than have previously been appreciated.

4. Vitamin D deficiency

There has been much debate regarding the cut-off point for diagnosing vitamin D deficiency. An Institute of Medicine report concluded that vitamin D deficiency was defined as 25(OH)D < 50 nmol L-1 [14]. Vitamin D deficiency is recognised as a worldwide epidemic. More than 60% of postmenopausal women have deficient 25(OH)D serum levels [15], including populations in sunny countries such as countries in the Middle East, Australia [16], and Spain [17], and is a public health concern.

Human physiology requires maintenance of a normal circulating calcium concentration, if necessary at the expense of increased bone remodelling. As such, vitamin D deficiency could, over time, contribute to age-related bone loss. However, there are conflicting results among the several studies which have been carried out to evaluate the relationship between serum 25(OH)D and bone density [18].

5. Vitamin D anti-fracture efficacy and risk of falls

Osteoporotic fractures are common and a serious health issue among postmenopausal women. Vitamin D affects fracture risk through its effects on bone metabolism and on risk of falling. Randomised controlled trials indicate that supplementation with vitamin D reduces rates of bone loss in older women. The impact of supplemental vitamin D on fracture risk has been examined mainly in men & women aged 65 and older. A recent meta-analysis revealed that vitamin D in doses in the range of more than 10 through 20 μg/day had no evident effect [19] Other analysis shows that vitamin D alone appears unlikely to be effective in preventing hip fracture (nine trials, 24,749 participants, RR 1.15, 95% CI 0.99–1.33), vertebral fracture (five trials, 9138 participants, RR 0.90, 95% CI 0.42–1.92) or any new fracture (10 trials, 25,016 participants, RR 1.01, 95% CI 0.93–1.09) [18]. However in a nested, case-control study of 7.1 years duration, baseline serum 25(OH)D levels in 400 hip fracture patients and 400 controls were compared and lower serum 25(OH)D concentrations were associated with increased hip fractures. Importantly, this increase in fracture risk was independent of the number of falls, physical function, frailty, renal function and sec-steroid hormone levels, but was, in part, mediated by increased bone resorption. Thus serum 25(OH)D concentration <20 ng/ml are associated with higher hip fracture [20]. Bergman et al.’s meta-analysis supports the use of vitamin D3 of 800 IU daily to reduce the incidence of osteoporotic non-vertebral non-hip fractures in elderly women. Vitamin D3 with calcium appears to achieve benefits above those attained with calcium supplementation alone for non-vertebral and non-vertebral non-hip fractures [21]. Poole et al.’s meta-analysis used only 1-year horizon, and considered only reduction in hip fracture, concluded that prescribing colecalciferol 800 IU daily to all adults aged 65 and over, could reduce the number of incident hip fractures in the UK from 65,400 to 45,700, saving almost 1700 associated deaths, whilst saving the UK taxpayer £22 million [22].

Another meta-analysis included eight RCTs, studying individuals with a mean age of 65 or older. It showed that individuals who received a high dose of vitamin D (700–100 IU/day) had a reduced
risk of falling of 19% and if serum levels reached 60 nmol/L there was a 23% fall reduction rate. However, daily vitamin D doses of less than 700 IU or serum 25(OH)D levels <60 nmol/L did not reduce the risk of falls [23].

In prospective studies, lower serum 25OHD levels have been associated with decreased grip strength and muscle mass in older men and women. In several trials of individuals at risk of vitamin D deficiency, vitamin D supplementation improved factors such as strength, function and balance in a dose related pattern, which ultimately led to a reduction in falls [24].

Several studies have been carried out on native vitamin D: alpha calcidol and calcitriol. Vitamin D analogues alpha calcidol and calcitriol, as compared to native vitamin D, may exhibit better efficacy in preventing spinal bone loss and spinal and/or non-spinal fractures primary osteoporosis. Subgroup analysis showed a possible better fracture reduction with vitamin D analogue cholecalciferol (significant pooled effect of 23% fracture reduction) that with ergocalciferol (not significant pooled effect of 10% fracture reduction), whereas additional calcium did not further optimise antifracture efficacy [25].

Recently, two Swedish studies show that there is a seasonal effect on the risk of fractures, which is highest in winter, when there are lower serum and plasma levels of 25-hydroxyvitamin D [26,27]. This supports the results of a meta-analysis which confirms the strong association between 25-hydroxyvitamin D concentrations and cause specific and all cause mortality [28].

6. Dose recommendations

In light of the evidence discussed above it is recommended that a deficiency in vitamin D should be treated with pharmacological doses of vitamin D (for example 800–1000 IU of vitamin D3 daily) to rapidly restore vitamin D levels and have minimal risk of toxicity. In 2011 The National Osteoporosis Guideline Group (NOGG) recommended a daily intake of at least 1000 mg of calcium, 800 IU of vitamin D, and 1 g/kg body weight of protein as a general measure for osteoporosis prevention [29]. Currently NOGG states that Calcium and vitamin D supplementation is widely recommended in older people who are housebound or living in residential or nursing homes, whereas vitamin D deficiency and low dietary calcium intake are common [30].

Literature suggests that 50–75 nmol/L (20–30 ng/mL) may be the appropriate target level of 25OHD for older individuals. However to reach a level of 75 nmol/L would require higher doses than 800–1000 IU/day. Efficacy of doses higher than 800 IU/day for fractures and >1000 IU for falls has not been evaluated in RCTs and therefore it would be premature to recommend higher intakes for all older adults at this time [8,11].

Clinical studies have demonstrated that only when 25(OH)D3 levels fall below 20 nmol/L does marked secondary hyperparathyroidism develop as a consequence of impaired 1,25(OH)2D3 synthesis and intestinal calcium malabsorption [14]. However it is still not clear how the rise in systemic 25(OH)D3 levels to 75 nmol/L can increase bone density and reduce fracture risk. It may be possible that the need to maintain higher levels of serum 25(OH)D3 than that required to normalise intestinal calcium absorption is the fact that several bone cells types such as osteoblasts and osteoclasts, are sites for substrate-dependant synthesis of 1,25(OH)2D3.

7. Conclusion

In spite of ongoing debates on the precise role vitamin D in the human body, there is general consensus that managing vitamin D deficiency may in future reduce such health issues as fractures, falls, muscle power loss and possibly more. The worldwide endemic of vitamin D deficiency is increasingly being linked to having roles in various different conditions.

It has been shown that higher serum levels of 25-hydroxyvitamin D reduces non-vertebral and hip fracture rate, however there still is not a wide spread consensus, with some analysis contradicting the effects of vitamin D on fracture risk. It is still not clear as to whether 25 hydroxyvitamin D alone or in conjunction is calcium supplementation may be responsible for such reductions. In order to achieve 25 hydroxyvitamin D levels of 75 nmol/L one would require high pharmacological doses. The implications of such high doses requires further future research, in order to ascertain whether there is a direct effect on health issues such as fractures, and also to determine side effects of such doses.

However, empirical evidence is encouraging and it is clear that our appreciation of the role of vitamin D treatment as opposed to supplementation needs to be completely re-evaluated. This is based on the findings that vitamin D deficiency is much more ubiquitous than previously assumed, and is reaching epidemic proportions. There also needs to be re-evaluation of the recommended doses of vitamin D supplementation, which in the past have been inadequately too low. Higher pharmacological doses need to be used to obtain positive effects in preventing osteoporosis and recurrent osteoporotic fractures. The final message is that vitamin D receptors, which are present in such a variety of tissues in the body, are there for a reason. The realisation that vitamin D is a hormone, since it is mostly synthesised in the body and, like many related hormones, has a mode of action that is vitamin D receptor dependent, goes a long way to changing our perception on the possibilities of re-evaluating the role of this hormone, vitamin D3. Is it a case where the best way of disguise is to place it somewhere obvious?

8. Practice points

- Circulating vitamin D predominately arises from synthesis in the skin after exposure to sunlight (ultraviolet B photons with wavelengths between 290 and 315 nm) and should therefore be considered as a hormone.
- Vitamin D deficiency is world-wide epidemic and presents when serum 25 hydroxyvitamin D levels fall below 50 nmol/L.
- Vitamin D deficiency is a factor in the multifactoral causes of non-vertebral & hip fractures, falls and loss of muscles power.
- It is recommended that a deficiency in vitamin D should be aggressively treated with higher pharmacological doses with the aim of achieving serum levels above or equal to 75 nmol/L.

9. Research agenda

- Further RCTs are needed to evaluate a possible isolated or combined role for vitamin D in reduced bone mass density, non-vertebral fractures, falls and muscle strength.
- Future research should focus on the effects and implications of treating vitamin D deficiency with high pharmacological doses (>1000 IU).
- The aim is to achieve a general consensus on recommended doses of vitamin D supplementation.

Contributors

All authors contributed equally to this manuscript. MB and JG started to contribute to this work while still finishing their medical studies.

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