Clinical aspects of vitamin D in the management of rheumatoid arthritis

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There is an increasing interest in the role of vitamin D as a potential treatment for a number of disparate diseases. In addition to its role in calcium homeostasis, vitamin D has a plethora of effects including immunomodulation, pleiotropic effects, modulating propensity to infection and blood pressure regulation. Detection and treatment of vitamin D deficiency in selected patients with RA is relevant as deficiency is common. Vitamin D therapy may modify the increased risk of falls and fracture in this group, and possibly exert additional immunomodulatory effects on disease onset and activity although data are largely epidemiological. Currently, there is no consensus view on vitamin D replacement regimens, nor an agreed optimal level of serum 25-hydroxyvitamin D [25(OH)D] for health. Indeed levels may vary for different organ systems and the concept of ‘tissue specific vitamin D deficiency’ needs to be considered. Therefore, there is clinical uncertainty regarding both when and how to correct vitamin D deficiency. Older patients, particularly post-menopausal women, and others at high risk of vitamin D deficiency should be preferentially targeted since they are likely to benefit most from supplementation. Clinicians should be aware of the technical difficulties associated with measuring and interpreting 25(OH)D levels. The administration of high-dose vitamin D as an oral weekly bolus is safe and can rapidly correct vitamin D deficiency followed by regular lower doses to maintain adequate levels.

KEY WORDS: Vitamin D, Rheumatoid arthritis, Parathyroid Hormone, 25-hydroxyvitamin D, Ergocalciferol, Colecalciferol, Falls, Fractures, Hypovitaminosis D.

Introduction

There is an increasing interest in the role of vitamin D as a potential treatment for a number of disparate diseases. In addition to its role in calcium homeostasis, vitamin D has a plethora of effects including immunomodulation and pleiotropic effects, affecting propensity to infection and blood pressure regulation. Vitamin D analogues are used for the treatment of psoriasis. A number of commercial assays for 25-hydroxyvitamin D [25(OH)D] are now widely available and low levels are commonly found [1, 2]. Currently there is no consensus view on vitamin D replacement regimens, nor an agreed optimal level of serum 25(OH)D. Indeed the latter may vary with different diseases, leading to clinical uncertainty as to when and how to correct vitamin D insufficiency.

In patients with RA measuring vitamin D levels seems particularly pertinent as deficiency is highly prevalent in this group [3–5]. Vitamin D may also have a role in modulating RA disease activity and is already known to be important in osteoporosis and falls, which are common in RA. In this article, we review the rationale for measuring and correcting vitamin D in RA patients, with the focus on clinical issues that are relevant for patient care, as opposed to the basic immunological effects of vitamin D.

Relevant vitamin D physiology

Vitamin D can be obtained from dietary sources and the action of sunlight on skin. There are relatively few foods containing substantial amounts of vitamin D and food fortification is not widespread [6]. Cutaneous exposure to ultraviolet B photons (290–315 nm) results in the photolytic conversion of 7-dehydrocholesterol to previtamin-D3 followed by thermal isomerization to vitamin D3. Subsequently, a two-step activation process occurs with hepatic hydroxylation to form 25(OH)D and further, chiefly renal hydroxylation, to form 1,25 dihydroxyvitamin D [1,25(OH)2D]. 25-Hydroxylation is poorly regulated, with levels of 25(OH)D increasing proportionately with increases in dietary vitamin D intake and cutaneous production [7]. Serum 25(OH)D levels are therefore used as a marker of vitamin D status. Circulating serum levels of 1,25(OH)2D act in an endocrine manner to effect calcium homeostasis along with other actions such as blood pressure regulation and control of insulin secretion. The recognition that extra-renal 1-alpha hydroxylation of 25(OH)D occurs in many different tissues represents a major advance in our understanding of the actions of vitamin D [7]. Importantly, this extrarenally produced 1,25(OH)2D primarily acts in an autocrine/paracrine manner, with cell-specific functions such as inhibition of cell proliferation, promotion of cell differentiation and immune regulation (Fig. 1). Regulation of renal and extra-renal 25(OH)D-1-alpha hydroxylase activity differs [7, 8]. Renal hydroxylation is highly regulated by dietary calcium and phosphate, circulating levels of the 1,25(OH)2D metabolite and PTH. Levels of 1,25(OH)2D are therefore relatively constant and independent of 25(OH)D concentrations except at very low levels [9]. In contrast, extra-renal 25(OH)D-1-alpha hydroxylase activity is determined by local factors such as cytokines and growth factors that optimize the levels of 1,25(OH)2D for these cell-specific actions. Moreover, extra-renal 25(OH)D-1-alpha hydroxylase activity is dependent on 25(OH)D levels [8]. Thus, deficiency of vitamin D results in ‘substrate deficiency’ of 25(OH)D, particularly for the extra-renal 25(OH)D-1-alpha hydroxylase enzyme activity, with consequent reduction of 1,25(OH)2D actions. The prevailing hypothesis is that chronic vitamin D deficiency results in chronically low circulating and tissue levels of 1,25(OH)2D with increased risk of skeletal and non-skeletal diseases [6, 10]. The majority of the biological actions of 1,25(OH)2D are mediated through the vitamin D receptor (VDR), which is both nuclear and cell membrane associated, and results in genomic and non-genomic effects [7, 11]. Polymorphisms of the VDR have
been described and their expression is associated with a variety of disease states [12]. More detail on vitamin D physiology can be found in recent review articles [7].

**Vitamin D and RA—experimental evidence**

The 25(OH)D-1-α-hydroxylase enzyme is expressed in many cells of the immune system including activated macrophages and dendritic cells. The 1,25(OH)2D that is produced acts in an autocrine/paracrine manner, resulting in down-regulation of antigen-presenting cells, inhibition of T-cell proliferation and decreased production of Th1 cytokines IL-2, IFN-γ and TNF-α. The VDR has been demonstrated in macrophages, chondrocytes and synoviocytes in rheumatoid synovium and sites of cartilage erosion in RA patients, but not in tissues from control subjects [13]. In the CIA model in rodents, 1,25(OH)2D supplementation prevents initiation and progression of inflammatory arthritis [14]. Further detail can be found in a recent review article by Aronson et al. [15].

**Vitamin D and RA—clinical studies**

**RA onset**

Vitamin D levels reach a peak in autumn and a nadir in spring. There is no evidence for a relationship between season and incidence of RA, but season may influence disease activity. A recent large observational study reported higher RA disease activity in spring and lower activity in autumn [16]. Although this was statistically significant the differences were very small [spring 25-joint disease activity score (DAS28) = 3.80 and autumn DAS28 = 3.68]. Furthermore, vitamin D metabolites were not measured; therefore, the mechanism behind this finding is unclear.

Estimated baseline dietary vitamin D intake has been inversely associated with RA onset in an inception cohort study [17]. In contrast, a small study of blood donors who subsequently developed RA did not show any difference in baseline pre-RA vitamin D levels compared with controls [18].

The genetic contribution to the aetiology of RA has been estimated to be 50% [19]. There may also be a relationship between VDR gene polymorphisms and rheumatoid disease onset and activity [20, 21]. A weak, but significant association was found between early RA and homozygosity for the absence of BsmI and presence of TaqI restriction site (BbI) [20]. However, this was not supported by a German study that showed no association between RA susceptibility and VDR polymorphisms [22]. In a recent study, RA patients with the BB or Bb genotypes had higher HAQ scores, ESR, cumulative corticosteroid use and number of DMARDs prescribed than patients with the bb genotype [21]. In contrast, a previous study in Korean patients showed no correlation between VDR polymorphisms and erosive disease, but this may be explained by the rare expression of the BB genotype within this population [23].

**RA disease activity**

Two previous studies have examined vitamin D levels in patients with established RA. Both showed no relationship between 25(OH)D and CRP or ESR [4, 5]. The interpretation of these data is difficult, partly because of long disease duration of RA, and because participants were also using DMARDs and other treatments that could confound any relationship to disease activity. No correction was made for renal function and data were unavailable regarding the potentially important effect of physical incapacity on sunlight exposure and therefore vitamin D levels. We recently reported an inverse association between disease activity and vitamin D metabolite concentrations in patients with early polyarthritis [24]. The design of this inception cohort study, which is recruiting patients with recent onset of symptoms (median duration 4 months), helped limit the bias of disability on vitamin D levels. Only one small open-label intervention study of 1,25(OH)2D in patients with established RA has been published. This demonstrated reduction in RA disease activity with 1,25(OH)2D supplementation [25].

**RA and falls**

Falls are common in the general population, increase with age and cause significant injuries, such as fractures, with resultant increases in morbidity and mortality. It is generally accepted that low levels of vitamin D are associated with an increased incidence of falling in older people [26, 27], and the consensus view is that this is a causal link. This may be due to the actions of vitamin D on muscle function, by virtue of calcium homeostasis, and a direct effect on skeletal muscle growth and differentiation [7]. Studies examining the effect of vitamin D supplementation on falls risk yield conflicting results, but recent meta-analyses suggest that there may be some benefit [28–30]. Falls are common in patients with RA [31–33] and RA patients have more risk factors for falls than controls [31]. In RA, the mechanism for increased falls is complex, and is likely to involve reduced muscle mass and impaired lower limb function [32], poor visual acuity [33] and disability [32, 33]. Vitamin D may reduce falls in these patients due to improvements in muscle strength as well as reduced lower limb joint RA disease activity, although no intervention studies have been performed.

**RA and osteoporotic fractures**

Patients with RA are at an increased risk of osteoporosis and associated fractures [34]. Generally applicable non-disease-specific risk factors include increasing age, low bone density, previous fracture, low body weight, female sex and post-menopausal status. Additional disease-specific risk factors, pertinent to inflammatory polyarthritis, include inflammation, immobility and steroid usage. VDR polymorphisms have also been associated with increased bone loss in patients with RA [35, 36]. Patients with established RA tend to have low levels of vitamin D [3–5] that may be associated with raised PTH levels and bone loss. The disease-specific risk factors mentioned above may accelerate bone loss associated with low vitamin D and raised PTH. In addition to increased bone loss, raised PTH has been associated with poor muscle function, mortality and falls [37–39]. Vitamin D supplementation (with or without calcium) may not reduce RA-associated bone loss [40] or fractures in patients without RA.
Measurement of vitamin D in patients with RA

The patient group whom we suggest may benefit most from correction of vitamin D deficiency are older, post-menopausal women with RA. Vitamin D deficiency is very common in this group and they are at higher risk of falls and fractures by virtue of age and gender. In addition to post-menopausal women, other groups prone to vitamin D deficiency (such as those with little or no sunlight exposure, non-white skin, individuals with malabsorption) should also be considered. If measurement of vitamin D status is clinically indicated, the usual metabolite to measure is 25(OH)D. Whilst HPLC is the gold standard, this is expensive, time-consuming and not widely available. A number of other assays are therefore used by laboratories with substantially different methodologies, not all of which have been standardized relative to HPLC. The Nichols Advantage chemiluminescence protein-binding assay has been shown to consistently underestimate serum 25(OH)D3 at concentrations <30 nmol/l and overestimate values at concentrations >50 nmol/l compared with HPLC [42, 43]. Furthermore, not all RIA assays cross-react equally with both 25(OH)D2 and 25(OH)D3. Some underestimate the contribution of 25(OH)D2 to total 25(OH)D concentration, which is pertinent in the follow-up of patients treated with ergocalciferol [44]. Ideally the analytical method should be operator independent and reliably recover both vitamin D2 and D3 to accurately estimate total circulating 25(OH)D independent of source. Indeed, the determination and efficacy of a threshold for optimal vitamin D status is dependent upon accurate and consistent assays. This is clinically important for patient follow-up as some assays have high inter-assay coefficients of variability (up to 25%), so that large changes are needed to be sure that a true change has occurred [45]. This difficulty in assessing the effect of treatment will be worsened if an assay is used that underestimates vitamin D2 (ergocalciferol), which is commonly used for treatment of vitamin D deficiency. Therefore, it is essential that clinicians have knowledge of the performance of their local vitamin D assays with respect to these issues.

Interpretation of vitamin D levels

No consensus exists for what level of 25(OH)D is adequate for health, which is not surprising given the different roles that 25(OH)D plays in human health. Most discussion and expert opinion has focused on the need to maintain 25(OH)D levels above a point where PTH is in the normal range (based on cross-sectional data). On examination of this relationship a level of >80 nmol/l would be required for most patients [46]. The relationship between 25(OH)D and PTH is not straightforward, partly because PTH varies according to age, dietary calcium intake [47], magnesium levels and renal function [48]. Indeed the increase in PTH for low levels of 25(OH)D is greater when glomerular filtration rate is lower [48].

Increasing 25(OH)D to >80 nmol/l may reduce secondary hyperparathyroid bone loss, but it is unclear what level is needed for other benefits such as improvements in muscle strength, falls risk and a putative reduction in RA disease activity. Studies of the non-skeletal effects of vitamin D are often observational with unknown disease onset across the full spectrum of vitamin D status. One study showed that insulin sensitivity in non-diabetic patients is positively correlated with vitamin D status [49]. Regression analysis implied optimal glycaemic control at serum 25(OH)D level of 114 nmol/l [50]. With respect to RA it is conceivable that higher levels than 80 nmol/l may be needed for an immunomodulatory effect. There are currently little data to guide clinical practice. With respect to RA disease activity, in an early polycrystalline cohort the cross-sectional relationship between 25(OH)D and DAS28 scores implied that an increase in 25(OH)D of ~30 ng/ml (75 nmol/l) would be needed to reduce DAS28 score by 1 point [24]. We would suggest that the concept of tissue-specific vitamin D deficiency is important to consider rather than one serum level being relevant for all organ systems.

Correction of vitamin D deficiency

Two forms of vitamin D are available to correct deficiency—cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2). The content of each is given as either international units or in metric units (Table 1). Cholecalciferol is derived from dietary sources, such as oily fish and fortified products and cutaneously manufactured as described above. Ergocalciferol is derived by UV exposure of yeast lipid extract patented in the 1920s, when both preparations were supposed equipotent; however, subsequent studies have shown that this may not be the case [51].

Until recently there was a lack of dose-response studies comparing both forms of vitamin D and their effects on serum 25(OH)D and PTH. Additionally, very limited work has been done on response to different dosing regimes and routes of administration [intramuscular (i.m.) vs oral and continuous vs intermittent dosing] in different populations. When given as a single bolus or for a short period, ergocalciferol has been demonstrated to be less effective compared with cholecalciferol in raising levels of 25(OH)D [52–54]. Trang et al. [52] showed that following 2 weeks of treatment with 100 μg/4000 IU per day of each form of vitamin D the mean increase in serum 25(OH)D, was 70% higher in healthy subjects receiving cholecalciferol compared with ergocalciferol. In a further study of a single dose of 1.25 mg/50,000 IU of each form of vitamin D, the mean 25(OH)D level in healthy subjects receiving ergocalciferol fell back to baseline by 14 days, whilst the increment was maintained in the cholecalciferol group [53]. At 28 days from 25(OH)D levels were higher in the cholecalciferol group than the peak achieved with ergocalciferol [53]. Single bolus large (7.5 mg/300,000 IU) oral and i.m. doses of cholecalciferol and ergocalciferol have been examined in older women in nursing homes [54]. Those administered oral cholecalciferol clearly reached higher levels of 25(OH)D, and maintained these levels for longer with greater reductions in serum PTH compared with oral ergocalciferol. In the i.m. group, the increase in 25(OH)D was much less than the oral group for each form of vitamin D, and colecalciferol was shown to be almost twice as effective as ergocalciferol. Based on these and other observations, it seems that cholecalciferol is two to three times more effective than ergocalciferol in raising 25(OH)D levels [51]. However, longer periods of supplementation may be different. A recent randomized study in healthy subjects comparing 25 μg/1000 IU per day of both forms of vitamin D given over 11 weeks, demonstrated equal increases in 25(OH)D concentrations [55]. Potential reasons as to why the findings from this study are different to previous studies include the daily dosing and longer duration of dosing. The authors also suggest that the carrier for the vitamin D in the tablets used in different studies may affect bioavailability. These findings further emphasize the need for dose-response studies that are clinically relevant.
(dose, duration of dosing and routes of administration) and ideally, individualized for each available preparation.

To compound the situation, there are also significant differences in availability in most countries, with the main preparations of vitamin D being ergocalciferol rather than cholecalciferol. Moreover, when available, cholecalciferol is usually combined with relatively large doses of calcium in fixed-dose combination regimens (e.g. 10 μg/400U cholecalciferol and 500 mg calcium, Adcal-D3® Prostrakan, and Calcichew-D3® Forte, Shire Pharmaceuticals) licensed as an adjunctive treatment for osteoporosis. In the UK, ergocalciferol is available in a generic form with smaller amounts of calcium (10 μg ergocalciferol and 97 mg calcium). Larger doses of ergocalciferol (e.g. 2.5 mg/100 000 IU) are available, although most community pharmacists will not stock these doses, which makes maintenance prescribing by general practitioners difficult. An alternative would be i.m. preparations of large doses of ergocalciferol or cholecalciferol, but there is uncertainty about the effect of adsorption onto plastic syringes limiting delivered dose and bioavailability of the oily depot injection from muscle [41]. Serum levels of 25(OH)D rise slowly after injection and may take up to a year to peak [54].

Whilst cholecalciferol can be imported to the UK, its use would be unlicensed. Although feasible in hospitals, it is more difficult to ensure that all potential patients will have availability in the community setting and that general practitioners would prescribe an unlicensed preparation. Clearly there is a need for cholecalciferol in a variety of doses to be made available for clinical use particularly in the UK. This is most pertinent as at the time of writing ergocalciferol has limited availability. Although smaller amounts of both are available over the counter from pharmacies, large doses cannot be easily obtained. Also, without a certificate of analysis, the actual dose of vitamin D per tablet and inter-brand variability limits confidence in over-the-counter preparations. Possibly, national or EU-wide initiatives to make this information available may be helpful.

Clinical practice is therefore very variable as to how vitamin D deficiency can be corrected and dependent on the local availability of the two forms of vitamin D. We recognize that monotherapy with cholecalciferol would be the ideal preparation, and when available it should be used in preference to ergocalciferol. However, due to the lack of cholecalciferol at our institution we use the following regimen and have found this to be effective although there are no trial data:

- For all patients with vitamin D deficiency we start by initially giving large doses of oral ergocalciferol (2.5 mg/100 000 IU) either as a one-off dose or weekly for up to four doses depending on baseline levels of 25(OH)D. Those patients with very low levels (e.g. <20 nmol/l with raised PTH levels) are given four doses.
- For patients with osteoporosis we add at the same time two tablets per day of a calcium and cholecalciferol preparation (e.g. Adcal D3® or Calcichew D3® forte, which have cholecalciferol 10 μg/400 IU and calcium 500 mg per tablet), used for adjunctive treatment for osteoporosis, which general practitioners are able to prescribe, and patients can obtain from community pharmacists.
- For patients without osteoporosis we add at the same time two to six tablets per day of generic calcium and ergocalciferol (ergocalciferol 10 μg/400 IU and calcium 92 mg per tablet). This preparation can also be prescribed by general practitioners and allows for larger doses of ergocalciferol without too much calcium.
- We aim to increase 25(OH)D levels to at least >50 nmol/l and preferably >80 nmol/l, as well as to ensure PTH suppression within normal range in patients with secondary hyperparathyroidism.

Vitamin D intoxication is extremely rare and does not seem to occur when levels of 25(OH)D are <150 ng/ml (374 nmol/l) [6]. Vieth et al. [56] demonstrated a lack of toxicity following supplementation with cholecalciferol 700 μg (28 000 IU) per week for >6 months. Similarly, Heaney et al. [57] showed that 20 weeks supplementation at 125 μg and 250 μg (5000 and 10 000 IU, respectively) of cholecalciferol per day did not cause hypercalcaemia in any subject.

Calcitriol [1,25(OH)2D] may have a role in patients with chronic kidney disease where renal hydroxylation is poor. It is possible that increasing circulating levels of 1,25(OH)2D may act in an endocrine manner to immunomodulate. This is suggested by the inverse relationship of both 25(OH)D and 1,25(OH)2D with RA disease activity [24] and the only intervention study of vitamin D used calcitriol [25]. However, calcitriol is unregulated by the body and can cause hypercalcaemia, hypercalciuria and subsequent risk of renal stones that limits use. There is the future potential for vitamin D analogues that are tissue selective with more non-classical actions and less propensity to mobilize calcium stores, which may limit this hypercalcaemic effect.

Summary

There is a growing body of evidence indicating that vitamin D is important in the initiation and propagation of a range of autoimmune diseases. In selected patients with RA who are at high risk of vitamin D deficiency, correction of deficiency may be important in both the management of osteoporosis and modifying falls and fracture risk. Vitamin D supplementation in this patient group may also reduce RA disease activity, though there is currently a paucity of intervention data supporting this premise. There is a clear research need to provide a firm determination of the lower end of the physiological range of vitamin D status compatible with immunological homeostasis. Indeed, the term vitamin D deficiency is simplistic and tissue-specific vitamin D deficiency needs to be considered as levels for optimal health may vary between organ systems. Carefully constructed clinical intervention studies are required to address key questions pertaining to both the importance of vitamin D in RA disease onset and propagation as well as the optimal means of supplementation. If disease activity can be modulated with vitamin D replacement, should this be a fixed-dose supplement regardless of baseline vitamin D levels or titrated to achieve minimum target levels of serum vitamin D metabolites?

Clinicians should be aware of the issues surrounding interpretation of vitamin D levels and know the coefficients of variability of their local assay to allow interpretation of sequential measurements. The administration of high-dose vitamin D as an oral weekly bolus is safe and can rapidly correct vitamin D deficiency. Recommendations would therefore include bolus oral dosing (e.g. 2.5 mg/100 000 IU vitamin D as described above), along with daily oral vitamin D tablets (with or without significant calcium), with monitoring and repeat dosing at regular intervals.

Rheumatology key messages

- Vitamin D insufficiency is highly prevalent in patients with RA.
- Vitamin D supplementation as described reduces falls and fracture risk, and may also modulate rheumatoid disease onset and activity.

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References