

**Vitamin D in rheumatoid arthritis: a magic bullet or a mirage? The need to improve
the evidence base prior to calls for supplementation**

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Conflict of interest

We declare no conflict of interest

Funding

Paul Welsh is supported by British Heart Foundation Fellowship FS/10/005/28147

Background

25-hydroxyvitamin D (25OHD) is the major circulating “storage” metabolite of the secosteroid vitamin D, and is frequently used as objective biomarker of vitamin D status. Vitamin D deficiency plays a crucial role in the pathogenesis of osteoporosis and osteomalacia, and vitamin D (together with calcium) supplementation is routinely recommended in the elderly to reduce risk of fractures [1]. Beyond this established role, interest is mounting in the potential role of vitamin D deficiency in of the pathogenesis of several chronic diseases such as, cancer, cardiovascular disease, depression, pain perception, autism, obesity, type 2 diabetes, as well as autoimmune diseases including rheumatoid arthritis and psoriasis [2, 3].

Concomitant with a frenzy of research activity, the lay media has frequently reported ‘hot’ vitamin D research findings [4, 5], and a self-styled “Vitamin D Council” has been established [6]. Requests for 25OHD measurement are also rapidly expanding, particularly in primary care [7]. Many researchers advocate “correction” of vitamin D deficiency in RA, as well as in other conditions [8-14]. In this commentary, we sought to determine the evidence base for such recommendations and, in doing so, highlight potential limitations in the ‘vitamin D hypothesis’.

Vitamin D deficiency: What is it and who has it?

The answer to this question is unclear. “Normal” serum 25OHD is ill-defined because 1) there is considerable inter-individual variability in 25OHD levels related to differences in sunshine exposure (latitude and seasonal variation), clothing style, skin pigmentation, skin thickness (age), and adiposity and 2) a standardized analytical method has not been adopted [2]. Thus, no formal consensus exists on a circulating 25OHD concentration defining “deficiency.” Frequently, < 20ng/ml (<50nmol/L) is quoted as being “deficient”, and <30ng/ml (<75nmol/L) as “insufficient” [15], but there are other definitions. The Vitamin D Council goes further and recommends serum levels of 50ng/ml (125mmol/L) as a minimum to confer optimal health [6].

Table 1 illustrates the prevalence of vitamin D deficiency in different groups, by health status, including populations with RA. By current definitions, a significant proportion of mankind around the world is vitamin D deficient. Indeed, it has been stated that over one billion people worldwide need to increase their vitamin D intake to counter 'vitamin D deficiency' [3, 27]. This number equates to roughly one sixth of the world's population which, if true and this deficiency is causing widespread deterioration in health, would be an astonishing public health revelation. What is the evidence then that vitamin D deficiency causes disease and that vitamin D supplementation is beneficial? Before we consider these issues, it is worth considering the immunological and epidemiological associations of vitamin D.

Vitamin D and inflammation

The discovery that the active vitamin D metabolite 1,25-dihydroxyvitamin D (1,25OH₂D; which is enzymatically derived from 25OHD in the kidney) has immunomodulatory properties in animal and tissue models has stimulated much excitement. The potential immunomodulatory properties of vitamin D, through interaction of the 1,25OH₂D: vitamin D receptor transcription factor complex with nuclear vitamin D response element (VDRE) genetic sequences, have been excellently reviewed [28]. The general theme in these studies is that vitamin D, via VDREs, regulates the immune response via a variety of mechanisms such as decreasing antigen presentation [29], inhibiting pro-inflammatory Th1 profile, [30] and inducing regulatory T-cells [31]. Such effects provide a clear theoretical background for a role of vitamin D deficiency in the development and progression of autoimmune inflammatory conditions. Indeed, there are data from animal models from over a decade ago indicating that the 1,25OH₂D metabolite and its analogues may suppress collagen induced arthritis [32-34]. Furthermore, other data suggest vitamin D receptor agonists may also prevent and suppress established collagen induced arthritis [35].

Vitamin D status in inflammatory arthritis patients

In line with animal and tissue models, evidence suggests that vitamin D deficiency may be more prevalent in a variety of inflammatory arthritis patients compared to healthy matched controls [36]. In addition, circulating 25OHD and 1,25OH₂D levels may be inversely

associated with disease activity within populations with inflammatory arthritis [37], RA [14, 38-40], ankylosing spondylitis [41], and SLE [42]. Indeed there are some data that suggests that RA is more common in populations at latitudes further away from the equator (perhaps in line with a causal role for vitamin D in RA) [43], although not all data concur with this observation [44].

Data are also conflicting in prospective studies investigating dietary vitamin D and risk of inflammatory arthritis. Merlino et al report that among a cohort study of 29,368 women of ages 55–69 years without a history of RA, greater ingestion of vitamin D (comparing top with bottom thirds) was associated with lower incident RA (RR 0.67 95% CI 0.44–1.00) [45]. However, among 186 389 women from the Nurses' Health Study followed 22 years, baseline dietary vitamin D (based on recall dietary questionnaires) did not relate to risk of subsequent incidence of RA and SLE [46]. Since 90% of 25OHD is derived from sunlight, many argue that vitamin D ingestion is a poor measure of vitamin D status. Thus the value of dietary studies without serum 25OHD measures is questionable. Of note, a small prospective study found, where serum 25OHD levels were measured on samples taken 1-5 years before onset of clinical RA symptoms, no evidence that prevalence of vitamin D deficiency was greater in those who developed RA than those who did not [47].

Despite limitations, the available epidemiological evidence linking vitamin D to RA allied to credible biological pathways involving immune regulation, have led a number of commentators to advocate “correction” of vitamin D deficiency in inflammatory arthritis [12-14]. Such calls however may be premature.

Reverse causality and residual confounding as potential limitations in Vitamin D epidemiology?

Many studies often fail to consider potential reverse causality or residual confounding when interpreting epidemiological findings. Confounding is not a new phenomenon in the world of vitamin epidemiology. We and others have shown social class and other lifestyle factors influence circulating levels of Vitamins C and E, and carotenoids, and as such confound associations of circulating vitamin levels with risk of chronic disease [48, 49].

Many similar confounding factors are potentially also relevant in vitamin D epidemiology, including studies in the field of inflammatory arthritis (**Figure 1**).

Serum 25OHD is not only inversely associated with disease activity in arthritis patients, but is also inversely associated with chronic kidney disease severity [50], prognosis in cancer [51], left ventricular function in heart failure patients [52] and severity of other disease states. Such promiscuous associations with chronic disease severity perhaps argue against a causal role in the pathogenesis of disease [53], and, rather, hint towards a potential for reverse causality (**Figure 1** pathway B). This makes perfect sense when considering the biology of vitamin D; the primary determinant of vitamin D status is sunlight exposure. Patients who are elderly, who are sedentary due to illness, who spend more time in hospital, or who have a greater burden of chronic pain (e.g. greater DAS-28) tend to have lower activity levels, spend less time outdoors, and, as a result, may have lower sunlight exposure and lower 25OHD levels. In other words, there is a chance that disease leads to vitamin D deficiency, rather than the reverse.

Several other factors linked to RA development and severity could also confound associations. In the healthy British 1958 birth cohort, serum 25OHD was inversely associated with adiposity, smoking, alcohol consumption and positively associated with physical activity and affluent social class [54]. Compare these potential confounders to a typical cohort of RA patients; those with greater disease activity are less physically active, smoke more and consume more alcohol [54, 55]. In addition, RA disease activity is generally worse among the deprived [56]. Even if studies perform relevant adjustments for all such factors (many do not), residual confounding may still be present due to inability to fully capture differential exposures (**Figure 1** pathway C).

Circulating 25OHD levels subject to acute phase response behaviour?

We now know that many antioxidants and micronutrients follow acute phase response behaviour, an observation which further enhances potential for reverse causality in some studies [57]. Of interest, in a recent study of 34 elective knee replacement patients 25OHD concentrations fell 30% within 6 hours of the operation ($p < 0.001$) and stayed at this level

for 5 days (concomitant with CRP persistently >100mg/L) [58]. Similar findings (a 15-20% decline in serum 25OHD) have been reported in another study following uncomplicated orthopaedic surgery [59]. The inverse acute phase response is a well known effect for other circulating vitamins [57,59], and it also therefore a plausible mechanism for serum 25OHD (despite being a steroid metabolite). Therefore, it may be that high-grade systemic inflammation leads to lower circulating 25OHD levels. To further test this we determined whether the TNF α blocker adalimumab, through dampening of inflammation, increases serum 25OHD in 170 RA patients with moderate to high disease activity. We observed no change in mean serum 25OHD concentration or in the prevalence of vitamin D deficiency after 16 weeks of therapy, although the study lacked a control group [40]. Therefore, it may be that circulating 25OHD levels decline only above a threshold level of inflammation, as may be the case for some other vitamins [58,59]. Alternatively, it may be the case that the highly specific adalimumab intervention is not conducive to a direct biological effect on serum 25OHD. The possibility that 25OHD concentrations exhibit acute phase behaviour, in at least some settings, requires further investigation given the important clinical implications that would arise since many chronic conditions exhibit an inflammatory component.

Clinical trials and causality

In those who are at risk of falls and fractures due to poor bone mineral density, vitamin D (plus calcium) supplementation at appropriate doses shows clear evidence of benefit [1]. In contrast, there is as yet no evidence from RCTs that vitamin D supplementation reduces risk of autoimmunity or that it eases disease activity, and there is also some evidence that supplements may not impact upon chronic pain [60]. Recent meta-analysis of trials that have investigated vitamin D supplementation and cardiovascular risk have also shown no significant benefit of supplementation [61]. An earlier meta-analysis suggested that vitamin D supplementation may reduce relative mortality risk by 7% (95%CI: 1%,13%), although in a sensitivity analysis including data from a cluster-randomised trial, the beneficial effect was no longer significant (3%, 95% CI: -6%, 11%) [62]. In addition, slightly increased longevity in elderly cohorts at risk of osteoporosis following vitamin D supplementation might be expected, on the basis of reduced risk of immobility and long-term hospitalization

following major fractures. The same small effect may not be generalisable to younger cohorts. There are further complications in interpreting available trial data. The recent finding that the concomitant calcium supplementation (given in many trials with vitamin D) may increase risk of MI but not mortality [63], render data from many trials unhelpful in teasing out the specific effect of vitamin D supplementation. Nevertheless, any benefit of vitamin D supplementation, if it exists, is likely to be small.

A recent report by the Institute of Medicine supports our own interpretation of the data "The committee found that the evidence supported a role for these nutrients [calcium and vitamin D] in bone health but not in other health conditions.....the majority of Americans and Canadians are receiving adequate amounts of both calcium and vitamin D. Further, there is emerging evidence that too much of these nutrients may be harmful" [64]. The latter point emphasising potential risk derived from over-supplementation and over-fortification with vitamin D has been apparent in the UK for many decades; the milk in schools scheme of 1934 saw a dramatic reduction in rickets, but subsequent over-fortification of processed foods with vitamin D in the 1950s led to increased incidence of infantile hypercalcaemia [65].

The only thing that is currently clear is the need for further well designed randomized placebo controlled trials of vitamin D supplementation to include targeting inflammatory arthritis. The design of such studies is difficult given our current lack of understanding of what true vitamin D deficiency is, what an optimal circulating 25OHD level is, and thus what the ideal dosage of supplement might be to facilitate correction of deficiency.

However, given the highlighted limitations in epidemiological studies of vitamin D, RCTs are needed to able to prove or disprove a causal role for vitamin D in RA (or other chronic diseases). That noted, Mendelian randomization studies may also offer insights into causal pathways, and appropriate genetic determinants of vitamin D deficiency have recently been identified to facilitate such studies [66]. In an era of evidence-based medicine, proof of causality is vital before widespread supplementation public health programs are implemented.

Bone mineral disease management in RA patients and others

Despite our cautionary notes, we recognize that the prescription of calcium and vitamin D supplements to those at high risk of osteoporosis is warranted according to current recommendations [64]. RA, like age, lifestyle, hormonal, and nutritional factors, should be considered as a risk factor for osteoporosis. The presence of one or more of these risk factors (as well as corticosteroid prescription) [67] may lead to measurement of bone mineral density by DEXA scan, and should result in giving the patient advice on adequate calcium and vitamin D intake (400-800 IU per day [64]), exercise, and lifestyle modification. Intervention for the prevention of bone loss should be considered when the DEXA scan T score is less than around -1.0 to -1.5 (depending on local practice) in the presence of osteoporosis risk factors. This intervention may include vitamin D and calcium supplements as well as lifestyle advice. Note that presently the decision to treat a patient (with or without RA) with vitamin D and calcium supplements is commonly based on simple osteoporosis risk factors and DEXA scans rather than serum 25OHD levels. This practice may be analogous to giving statins to individuals at high cardiovascular risk irrespective of their cholesterol level. Whether measurement of serum 25OHD helps to further improve risk stratification for risk of osteoporosis remains to be seen, although there is some evidence that a sizeable proportion of postmenopausal women with osteoporosis (prior to commencing treatment) are not necessarily vitamin D deficient [68].

Conclusions

The definition, causes, and the non-bone mineral consequences of vitamin D deficiency are ambiguous. Observational studies linking low circulating 25OHD levels to prevalent or incident arthritis and other medical conditions are likely to be subject to reverse causality and residual confounding. There is also the possibility that under certain conditions circulating 25OHD exhibits negative acute phase response behaviour, a potentially clinically important issue which needs further detailed study. There is also, as yet, no clear evidence that supplementation prevents or lessens RA disease activity. Therefore the current evidence base to support widespread vitamin D deficiency in RA patients (as in the wider population) as a major public health concern for non bone-mineral diseases is

relatively weak. Furthermore, the impact of vitamin D supplementation in these patients, beyond management of osteoporosis risk, is unknown. Given the aforementioned limitations of epidemiological data in this area, we suggest that only well conducted large RCTs with appropriate clinical end-points can demonstrate whether vitamin D supplementation is indeed a magic bullet, or represents another false dawn.

Accepted, not yet copyedited

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Table 1 Examples of high vitamin D deficiency prevalence from healthy groups, arthritis patients, and other chronic disease groups around the world *

Study	Location	Latitude	Population	Mean age	n	Vitamin D insufficient Definition	Vitamin D insufficient Prevalence	Vitamin D deficient Definition	Vitamin D deficient Prevalence	
Generally healthy populations										
Hyponnen et al [16]	Great Britain	50-60°N	45 year old Caucasians:	45	2850	<30ng/ml	87.1%	<10ng/ml	15.5%	
			Dec-May	45	4587		60.9%		3.2%	
Tseng et al [17]	Philadelphia, PN	39°N	African-American men	50	194	<15ng/ml	39%	<10ng/ml	34%	
Patients with arthritis										
Craig et al [18]	Omaha, Nebraska	41°N	African-Americans with recent onset RA	51	266	<15ng/ml	50%	-	-	
Zold et al [19]	Debrecen, Hungary	48°N	Undifferentiated connective tissue disease patients:	Summer	45	161	<30ng/ml	41.6%	<10ng/ml	3.1%
				Winter	45	161		54.3%		3.1%
Glowacki [20]	Boston, MA	42°N	Postmenopausal women with osteoarthritis undergoing hip arthroplasty	66	68	-	-	<15ng/ml	22%	
Braun-Moscovici et al [21]	Haifa, Israel	32°N	Inflammatory arthritis patients	52	121	-	-	<12ng/ml	42.1%	
Patients with other disease										
Tahrani et al [22]	Birmingham UK	52°N	Asian patients with type 2 diabetes	63	170	-	-	<20ng/ml	83%	
Ford et al [23]	Birmingham, UK	52°N	Random selection of outpatients (multiethnic)	53	830	-	-	<10 ng/ml	24%	
Clayton et al [24]	Canberra, Australia	35°S	Dialysis patients:	Haemodialysis	64	120	<30ng/ml	82%	<20ng/ml	49%
				Peritoneal dialysis	39	31		96%		77%
Evatt et al [25]	Atlanta, Georgia	33°N	Parkinson's patients	65	100	<30ng/ml	55.0%	<20ng/ml	23%	
			Alzheimer's patients	66	97		41.2%		16%	
Lee et al [26]	Sydney, Australia	33°S	Intensive care patients referred for endocrine	?	42	<24ng/ml	93%	<12ng/ml	38%	

*These data are not intended for direct comparisons between studies, but to illustrate high 25OHD deficiency prevalence in all groups regardless of disease status

Accepted, not yet converted

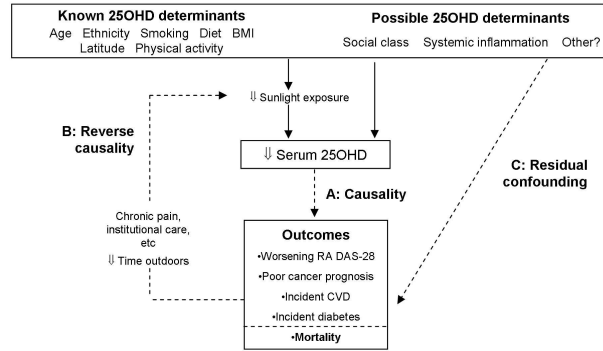


Figure 1: Associations of 25OHD with other risk factors, lifestyle factors and with risk of disease outcomes. Associations of circulating 25OHD with outcomes may represent true causal pathways (pathway A), or be subject to reverse causality where prevalent and subclinical disease causes low vitamin D (B) or to residual confounding (C), or some combination of the possibilities.

254x190mm (300 x 300 DPI)