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Topical review

Vitamin D and chronic pain

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1. Introduction

A number of studies have suggested a link between low levels of vitamin D and higher incidence of chronic pain [4,7,22]. There is a well-established link between low vitamin D and pain due to osteomalacia. There is no clear biological mechanism of how low vitamin D might be causally related to other types of chronic pain, though vitamin D is thought to be involved in regulating inflammatory cytokine synthesis [17], and might be implicated in some chronic pain conditions.

Associations of pain with latitude and season of the year offer circumstantial evidence that vitamin D may be involved. These associations have been suggested for such diverse types of pain as headache, abdominal pain, knee pain and back pain; but the evidence is far from convincing [24,29,34]. This paper undertakes an assessment of the relationship between vitamin D and chronic pain. Before vitamin D supplementation can be advocated for chronic pain, evidence for health benefits and adverse effects needs to be assessed rigorously.

Vitamin D and its roles in health and disease have been of interest in the scientific community [17] and the general media [20]. Many tissues express vitamin D receptors, and it is not surprising that a physiological role beyond the skeleton has been proposed. Vitamin D deficiency has been implicated in conditions like autoimmune and cardiovascular diseases, cancers, and chronic pain [17]. A recent meta-analysis even suggested reduced all-cause-mortality with vitamin D supplementation [5]. This contrasts with antioxidant vitamins A and E, where a review suggested a possible increase in mortality rates [8].

Some experts advocate limited and sensible sun exposure and vitamin D supplementation [17] in order to ensure adequate blood levels. Excessive dietary supplementation can lead to vitamin D intoxication [1], and excessive sun exposure increases the risk of skin cancers, already a substantial health problem. Although cases of vitamin D intoxication have been reported infrequently, they could become more common with widespread use of vitamin D supplements.

If there is a link between vitamin D deficiency and chronic pain, a systematic review of the evidence would be expected to uncover two things: firstly, an inverse association between pain and 25-OH vitamin D levels and, secondly, a demonstrable benefit of vitamin D treatment.

2. Methods

We searched Medline (PubMed) using various search terms for vitamin D (vitamin D; vitamin D_2; vitamin D_3; 1-alpha-hydroxyvitamin D_3; 1-alpha hydroxycalciferol; 1,25-dihydroxyvitamin D_3; 1,25-dihydroxycholecalciferol; 25 hydroxycholecalciferol; 25-hydroxyvitamin D; alfacalcidol; calcidiol; calcitriol; calcifediol; calciferol; ergocalciferol; cholecalciferol; and spelling variations thereof) and "pain*". The last search was conducted on 8 September 2008. The limits in PubMed were set to "humans". Bibliographies of review articles were also searched for additional relevant publications. Full publications in any language were included; case reports or studies in children were excluded. Studies involving patients with osteomalacia were included only if they reported on pain. Clinical studies were accepted provided they reported on populations with chronic pain conditions and gave mean or median values for 25-OH vitamin D levels in these populations and investigated pain outcomes after vitamin D treatment, or both.

We extracted data regarding study design, study location, condition and population, patient characteristics, mean or median 25-OH vitamin D levels, types and doses of vitamin D preparations used, concurrent other therapy, study duration, pain outcomes, and adverse events. We defined chronic pain in the broadest possible sense in order to be inclusive and uncover any possible association. We defined an improvement of chronic pain with vitamin D treatment as a statistically significant improvement compared with placebo, or an improvement over time (significant, or in more than half the cases). Guidelines for quality of reporting of meta-analyses were followed where appropriate [25]. Lat–Long Finder (www.satsig.net/maps/lat-long-finder.htm) was used to determine the latitude of the study locations.

3. Results

We identified 22 relevant studies that reported mean 25-OH vitamin D levels and/or investigated the results of vitamin D treatment in patients with chronic pain conditions. Five were randomised double blind trials of vitamin D treatment [12,13,15,23,33]. Eight studies with weaker designs more prone to bias also evaluated vitamin D treatment; two were randomised but not double blind [19,32] and six were case series [2,9,11,14,21,28]. Nine

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purely observational studies were without treatment [3,4,7,16,18,22,26,27,30]. One study [4] reported results separately for men and women and was treated as two data sets. These 23 data sets ranged in size from 5 to 3459 patients. The total number of patients in "pain" and "control" groups was 8644; 58% were women. Few studies actually measured vitamin D status, and there was no common definition of what constituted deficiency.

The expected dependence of 25-OH vitamin D level on latitude was confirmed, with lower average levels at higher latitude, though with considerable variability between populations (Fig. 1).

Three observational studies explored differences in 25-OH vitamin D levels between patients with and without chronic musculoskeletal or widespread pain. Two very small studies (104 patients in total) [7,22] claimed significantly reduced 25-OH vitamin D levels in pain subjects compared with controls. In a large study [4], a significant association between 25-OH vitamin D levels and increased pain was found in only one of the several analyses for 3495 women, but not for 3365 men. Another study [33] investigated 25-OH vitamin D levels in patients with diffuse musculoskeletal pain and used patients with osteoarthritis as a "control" group. It found no difference in 25-OH vitamin D levels between these two populations; because the control group also consisted of patients with a chronically painful condition, both groups of patients from this study are treated as "pain" populations for the purpose of this review.

Characteristics of treatment studies are in Table 1. Vitamin D treatments involved monthly equivalent doses between 1200 and 400,000 IU. Fourteen studies were in musculoskeletal pain [2,7,11–14,16,19,22,23,27,28,32,33], five in chronic widespread pain or fibromyalgia [3,4,9,18,26], one in diabetic subjects with neuropathic pain [21], one addressing an unusual hyperaesthetic pain syndrome [14], and one with various conditions [30]. Patients in these studies may have had ill-defined subclinical or overt osteomalacia, as is not infrequently the case with vitamin D deficiency. Duration of treatment was from a few days to 12 months, though most studies lasted two months or more. It was rare for studies to report on adverse events.

Treatment studies involved 733 patients. Randomised double blind trials involved 229 patients, of whom only 22 (10%) were in a trial with a significant improvement in pain with vitamin D, and then only on a pain mobility measure; 207 patients were in trials with no significant improvement in pain with vitamin D. Only one of these randomised trials [33] measured 25-OH vitamin D, demonstrating both deficiency at baseline and significant change with treatment. By contrast, six of eight treatment studies that were not double blind showed significant improvement in pain with vitamin D (457 of 504 patients, 93%). Only three of these trials [9,11,28] measured vitamin status. There was no apparent correlation between significant improvement in pain with vitamin D and a particular preparation, dose, or condition (Table 1).

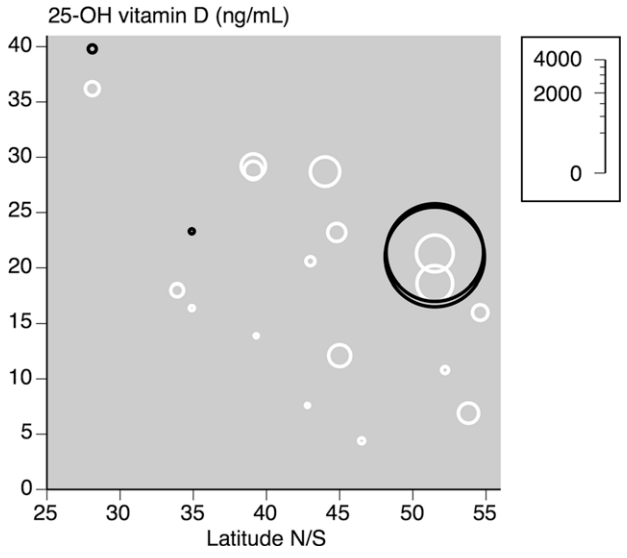

Fig. 1. 25-OH vitamin D levels in pain subjects (white circles) and non-pain controls (black circles) according to latitude (northern or southern hemisphere). The size of the symbol is proportional to the size of the study populations (inset scale).

4. Conclusion and design of future studies

There is no convincing evidence of a link between chronic pain prevalence or incidence and latitude. In Greece, there was only a weak correlation of daily headache with latitude, though a similar size of correlation was also found with temperature [24]. Lower prevalence of knee and back pain in southern China compared with northern China was complicated by rural versus urban lifestyle [34]. A suggested seasonal variation in the presentation of abdominal pain (higher in winter months) was less apparent at southern latitudes [29]. If vitamin D were important, we would expect to see substantial evidence of higher chronic pain incidence at higher latitudes, as with the incidence of multiple sclerosis [31].

There was no persuasive evidence of lower levels of 25-OH vitamin D in chronic pain than in control populations (Fig. 1).

There was a striking contrast in treatment effects between randomised, double blind trials that minimised bias and those with designs known to be subject to bias. In the former, only 10% of patients were in trials showing a benefit of vitamin D treatment; in the latter, 93% were in trials showing a benefit of vitamin D treatment.

Is this enough to conclude that vitamin D is not linked to chronic pain? There may not be quite enough evidence for a conclusively negative answer, but we have been here before. Examples include TENS for postoperative pain, where randomised trials were overwhelmingly negative and non-randomised, overwhelmingly positive [10], or hyperbaric oxygen for multiple sclerosis, where the early observational and non-randomised studies suggested substantial benefits, but where a dozen subsequent RCTs found none [6].

The presently available evidence does not allow us to conclude that vitamin D is relevant to chronic pain. To overturn this verdict will demand substantially better evidence, specifically large, double blind RCTs, stratified by baseline vitamin D level, with defined treatments, possibly with outcome analysed by post-treatment 25-OH vitamin D level, and ideally conducted in different painful conditions, and over a sensible period of time. Vitamin D treatments can be of low intensity (typically 1000 IU per day, or 30,000 IU per month), or of high intensity (150,000–400,000 IU per month). There may be a threshold and not a simple dose response; non-linearity may be expected because vitamin D acts on gene transcription. Given the limited level of knowledge, a placebo group is essential to underline causation and effect. Trials should use standardized, validated pain outcomes (such as the number of patients achieving at least 50% pain relief), and also report on adverse events.

There is a beguiling attraction in a link between low levels of vitamin D and chronic pain, because it offers a simple treatment with known and probably limited adverse effects, and with a favourable public perception of vitamin treatment. The RCTs we have are too small, and supporting studies are insufficient to support the hypothesis that vitamin D supplementation is a useful treatment for chronic pain. We need to better understand how Vitamin D could generate or maintain pain, especially musculoskeletal pain (other than osteomalacia, which is known to be due

Table 1
Characteristics of treatment studies. *M* = male, *F* = female, *IU* = international units, *Ca* = calcium, signif. = significant, *mcg* = micrograms; 25-OHD = 25-hydroxyvitamin D; 1-alpha-OHD = 1-alpha-hydroxyvitamin D; 1,25-$(OH)_2$D = 1,25-dihydroxyvitamin D.

Reference	Condition or population	Patient characteristics (total number, M/F, age)	Groups and vit. D preparation used (group size)	Other therapy	Study duration	Pain outcomes	Improvement with vitamin D	Adverse events
Double blind RCTs								
Di Munno et al. [12]	Polymyalgia rheumatica	24 total, 9M/15F, age range 51–82	35 mcg/day 25-OHD for 25 day/month(12); placebo (12) Monthly equivalent = 35,000 IU	500 mg Ca (all), 6-methylprednisolone (all)	9 Months	Subjective pain on movement (scale 0–4): decreased in both groups over time, no great difference between groups	NO	None observed
Dottori et al. [13]	Rheumatoid arthritis with osteoporosis and pain	45 total, 9M/36F, age range 20–64	50 mcg/day calcifediol (15); calcitonine (15); basic therapy only (15) Monthly equivalent = 60,000 IU	Basic therapy (Ca, dichlophenac, nor-androstenolone) (all)	1 Month	Pain scale (0–3): no signif. difference between calcifediol and basic therapy only groups	NO	None observed
Grove et al. [14]	Backache in postmenopausal women	22 total, all F, age range 59–86	50,000 IU calciferol twice weekly (12), placebo (10) Monthly equivalent = 400,000 IU	Sodium fluoride, Ca (just vit. D group)	3 Months	Active group showed significantly better improvement in 'pain-mobility score' compared to placebo	YES	Nausea, dyspepsia, elevated serum calcium, one death from MI
Lyritis et al. [23]	Vertebral osteoporotic collapse in postmenopausal women	88 total, all F, mean age in vit. D group (SD): 66.3 (8.5)	50 mg nandrolone deconoate every 3 weeks (44); 1 mcg/day 1-alpha OHD (44) Monthly equivalent = 1200 IU	–	12 Months	Pain (0–5 scale) decreased nonsignificantly	NO	Not commented on
Warner and Arnspiger [33]	Patients with diffuse musculoskeletal pain and 25-OHD between 9 and 20 ng/mL	50 total, all F, mean age (SD): 56.2 (9.3)	50,000 IU ergocalciferol weekly (25), placebo (25) Monthly equivalent = 200,000 IU	–	3 Months	Visual analogue scale, face pain scale: no signif. difference compared to placebo	NO	No adverse events withdrawals, otherwise not discussed
Other studies								
Al Faraj and Al Mutairi [2] (case series)	Chronic low back pain without obvious cause	360 total, 36M/324F, age not specified	25-OH cholecalciferol 5000–10,000 U/day (depending on weight) Monthly equivalent = 150,000 IU	–	3 Months	"Clinical assessment of pain": in 341/360 dissappearance of low back pain after vitamin D therapy	YES	Not commented on
Block [9] (case series)	White patients with chronic widespread pain, with 25-OHD < 10 ng/mL	7 patients for intervention, no further details given	50,000 IU vitamin D weekly, Monthly equivalent = 200,000 IU	–	2 Months	Patient impression (not detailed further): better 1/7, no benefit 5/7	NO	Not commented on
De Torrente de la Jara et al. [11] (case series)	Hypovitaminosis D3 and musculoskeletal pain in female asylum seekers	11 total, all F, age range 20–63	300,000 IU IM cholecalciferol (twice) and 800 units oral cholecalciferol (ongoing course) "for most patients" Monthly equivalent = 325,000 IU	Ca given with oral cholecalciferol, one patient (lower limb pain) concurrently treated for venous insufficiency	2 Months	Pain disappeared in 11/11 within 7 months, in 10/11 within three months	YES	Not commented on
Gloth et al. [14] (case series)	Unusual pain resistant to analgesics in people confined indoors for > 6 months	5 total, 1M/4F, age range 24–94	Ergocalciferol (various doses) Monthly equivalent = 20,000 IU to 350,000 IU	–	Days to weeks	Pain resolved 5–7 days after ergocalciferol supplementation	YES	Not commented on
Iwamoto 2003 [19] (open label study)	Osteoporosis in postmenopausal women	40 total, all F, age range 60–86	1 mcg/day alphacalcidiol (20); etidronate only (20) Monthly equivalent = 1,200 IU	200 mg etidronate for 2 weeks every 3 months (all)	12 Months	Face scale score: similar decrease with time in both groups	NO	None observed
Lee and Chen [21] (case series)	Patients with type 2 diabetes and neuropathic pain	51 total, 14M/37F, mean age (SD): 62 (13)	Vitamin D3 tablets, mean dose 2059 IU Monthly equivalent = 63,000 IU	–	3 Months	Visual analogue scale and McGill pain questionaire: scores signif. reduced after 3 months	YES	Not commented on

Table 1 (*continued*)

Reference	Condition or population	Patient characteristics (total number, M/F, age)	Groups and vit. D preparation used (group size)	Other therapy	Study duration	Pain outcomes	Improvement with vitamin D	Adverse events
Prabhala et al. [28] (case series)	Wheelchair bound patients with pain and vitamin D deficiency	5 total, 1M/4F, age range 37–77	Oral and IV vitamin D Monthly equivalent: 260,000 IU	–	1–2 Months	Pain assessed (not detailed how): all improved	YES	Not commented on
Wandless et al. [32] (single blind RCT)	Osteoporotic back pain	25 total, 5M/20F, average ages (SD) for treatment and placebo groups: 69.9 (9.8) and 73.0 (8.6)	0.5–1 mg 1-alpha OHD or 1, 25-$(OH)_2$D/ day (15); placebo (10) Monthly equivalent = 1200 IU	–	6 Months	Patient impression (no further details given): severity of back pain decreased in 11/15 (vit. D) and in 1/10 (placebo)	YES	Not commented on

to vitamin D deficiency). This should lead to better and more focussed research.

5. Authors' contributions

R.A.M. and S.S. were involved with the original concept, planning the study, searching, writing it, analysing, and preparing a manuscript; S.S. and R.A.M. performed calculations and analysis; S.D. and H.J.M. were involved with planning, and writing. All authors read and approved the final manuscript.

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