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Fibromyalgia

Should we be testing and treating for vitamin D deficiency?

Aim

This review aims to synthesise the evidence regarding any association between vitamin D deficiency and fibromyalgia, addressing whether general practitioners should be testing and treating these patients for vitamin D deficiency.

Methods

A systematic literature review was performed, using MEDLINE as the primary database, to find and critically appraise all relevant research fulfilling inclusion criteria from January 1990 until September 2010.

Results

There were conflicting results in the cross sectional studies obtained, with no association in studies using control groups and mixed results in larger population based studies. One adequately powered randomised controlled trial suggests fibromyalgia pain is not improved by vitamin D supplementation.

Discussion

The evidence for an association between fibromyalgia and vitamin D deficiency is inconclusive, with no improvement in pain on supplementation. However, patients with concurrent risk factors for deficiency should be tested and treated for vitamin D deficiency to minimise osteoporosis risk and maximise muscular strength.

Keywords: fibromyalgia; vitamin D; pain; review

Internationally, interest in vitamin D is high, due to increased detection of vitamin D insufficiency, combined with better knowledge of the role of vitamin D in health outcomes.¹ With the explosion of ordering of vitamin D assays in recent years (Table 1), and questions about the appropriateness of screening, general practitioners should target vitamin D testing and supplementation to specific populations with evidence of health benefit.

While vitamin D can be ingested through some foods or tablet supplements, in humans the majority of natural vitamin D is produced in the skin after exposure to ultraviolet B (UVB) light, producing 25-hydroxyvitamin D (25-OHD), which undergoes hydroxylation in the liver and kidneys, to its active form of 1,25-dihydroxyvitamin D (1,25-OHD). Age, latitude, time of day, season, skin pigmentation, adiposity, smoking status and amount of exposure to UVB sunlight can all dramatically affect the production of vitamin D in the skin.²⁻⁵ Therefore, populations at risk of vitamin D deficiency include naturally dark skinned or veiled people, obese people, older people or those with a chronic disease or disability who spend more time indoors.⁶

Policy makers acknowledge the need to balance sufficient sun exposure for adequate vitamin D synthesis with the risk of skin cancer. Together, the Cancer Council, the Australasian College of Dermatology, Osteoporosis Australia, and the Bone and Mineral Society have produced guidelines for Australians regarding safer sun exposure.⁷

The activated form of vitamin D, 1,25-OHD, acts at cell nuclei (genomic effects causing gene upregulation) and cell membranes (nongenomic effects causing a rapid response) in over 30

tissues and organs,⁸ primarily via specific vitamin D receptors on target tissues.

Muscles are a known target organ for vitamin D metabolites, with vitamin D receptors identified in animal and human muscle tissues,⁹ leading to genomic and nongenomic effects which alter calcium, phosphate and phospholipid metabolism. These changes are important for normal skeletal muscle development and function, with evidence of improvement of muscle strength and functional ability, and decreased falls in elderly populations after vitamin D supplementation.¹⁰ Bone and muscle pain are known symptoms of osteomalacia, the syndrome of severe adult vitamin D deficiency. Case reports suggest an association between chronic muscular pain and vitamin D deficiency, even without biochemical changes of osteomalacia¹¹⁻¹³ that may improve with vitamin D supplementation. These observations have stimulated a decade of research exploring whether a relationship exists between muscle pain and low vitamin D.

Fibromyalgia affects 2–4% of the adult population in the United States of America,¹⁴ and is characterised by widespread musculoskeletal pain for which no alternative cause can be identified.¹⁵ While the legitimacy of fibromyalgia is controversial,¹⁶ chronic muscular pain as an entity causes significant disability and poor quality of life, with few effective treatments. Therefore, research exploring novel causation or treatment options is valuable.

Is a relationship between muscle pain and vitamin D biologically plausible?

The pathophysiology of chronic, widespread 'fibromyalgia-type' pain syndrome, is controversial. Emerging theories involve a combination of genetic and environmental factors leading to an aberration of central

sensitisation of pain processing, with heightened responses to nonpainful and painful stimuli.¹⁷

One theory suggests infection activates inflammatory cytokines that might modulate central and peripheral pain perception in fibromyalgia.¹⁸ The involvement of 1,25-OHD in immune system regulation could therefore link muscle pain with vitamin D deficiency.¹⁹

Alternatively, patients with fibromyalgia could be vitamin D deficient due to pain, poor mobility or associated depression potentially leading to less time spent outdoors, or high rates of adiposity leading to decreased synthesis of vitamin D.

In this review, we aim to synthesise the evidence regarding an association between vitamin D deficiency and fibromyalgia, and address the clinical question of whether GPs should be testing and treating these patients for vitamin D deficiency.

Unless otherwise stated, we use the term ‘fibromyalgia’ to describe the syndrome of chronic, widespread muscular pain, as defined in the 1990 American College of Rheumatology (ACR) diagnostic framework.¹⁶

Methods

We searched the medical literature using MEDLINE to identify relevant research from January 1990 until September 2010. The search terms used were: ‘vitamin D’ or ‘vitamin D deficiency’ [MESH] and ‘fibromyalgia’ or ‘muscular diseases’ or ‘muscles’ [MESH], and ‘hypovitaminosis D myopathy’ [MESH]. Additional inclusion and exclusion criteria are contained in *Table 2*.

The abstracts of retrieved articles were read, with full text of all relevant studies obtained. Pertinent articles from reference lists were also retrieved.

Randomised controlled trials (RCTs) were assessed using Jadad criteria,²⁰ and included if scored greater than three out of five.

The quality of observational and cross sectional studies was assessed using the STROBE checklist.²¹ Only studies judged to be of adequate quality in all checklist components were included. Checklist components included adequate explanation of scientific rationale and methodology, discussion of appropriate statistical methods, adequate statistical analysis, full reporting of participant characteristics and

outcome data, appropriate summarising and interpreting of results, discussion of strengths, limitations and biases, and a lack of conflicts of interests in regards to funding.

Methodologically flawed studies were excluded for reasons of inadequate sample size, lack of validated tools for measuring muscle pain, and lack of sufficient description or discussion in the STROBE checklist/Jadad scoring components.

Results

A total of nine cross sectional studies satisfied the inclusion criteria, one of which also

undertook the only rigorous therapeutic RCT found that examined the effect on pain of treating vitamin D deficiency.²² Many factors limited the usefulness of the cross sectional studies and made comparisons across them difficult (*Table 3*).

Association between vitamin D deficiency and fibromyalgia in subpopulations

Six of the nine eligible studies (*Table 4*) were cohorts of patients with fibromyalgia or similar chronic muscular pain, with or without a control group, measuring 25-OHD levels as an outcome.

Table 1. MBS Item 66608 (vitamin D or D fractions) tests

	July 1999 – June 2000	July 2009 – June 2010
Number of tests	22 670	2 219 553
Cost per test (as at January 2011) on MBS schedule	N/A	\$42.55
Total MBS cost during testing period	N/A	\$94 441 980.20

Source: Medicare Australia³⁴

Table 2. Inclusion and exclusion criteria for literature search

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> • Study participants >18 years of age • Randomised controlled trials or cross sectional studies • English language • Human studies • Meet methodological quality criteria (see text) 	<ul style="list-style-type: none"> • Studies including paediatric participants • Case studies/case series • Not clinically focused (eg. molecular studies) • Not specific/little reference to chronic muscle pain (eg. bone pain or muscle strength)

Table 3. Factors complicating comparison of studies

<ul style="list-style-type: none"> • Variability in population studied (eg. ethnicity, latitude of study location) and small samples, limiting external validity
<ul style="list-style-type: none"> • Lack of a comparison group, limiting the ability to control for confounders known to influence vitamin D levels, such as body mass index or sun exposure
<ul style="list-style-type: none"> • Variability in confounding factors documented
<ul style="list-style-type: none"> • Cross sectional studies do not examine the temporal nature of relationships. For example, do suboptimal vitamin D levels result in increased risk of fibromyalgia, or do alterations in behaviour of those with fibromyalgia lead to reduced 25-OHD levels?
<ul style="list-style-type: none"> • Differing definitions of vitamin D deficiency, and methods of testing. Most commonly <20 ng/mL (equivalent 50 mmol/mL) 25-OHD is used as a marker of severe deficiency, corresponding to physiological insufficiency. In addition, 25-OHD is the best measure of the past 3–4 weeks vitamin D levels, but may not represent participants’ status during the time of pain¹⁹

The other three studies were population based. The results were mixed. Uncontrolled studies of people with fibromyalgia-type pain^{23–24} tended to find lower vitamin D levels in veiled populations compared to studies in patients with fibromyalgia in Caucasian populations.²⁴ However, there was no adjustment for potential confounding characteristics, such as amount of sun exposure. No variation in vitamin D levels was found when comparing Israeli women with and without fibromyalgia.²⁵ Three studies used as control populations people with other rheumatological diagnoses that cause pain, such as systemic lupus erythematosus or osteoarthritis.^{22,26,27} These patients may be more comparable to patients with fibromyalgia than healthy people, in terms of comorbidities and time spent outdoors. These studies found that mean levels of 25-OHD in patients with fibromyalgia were low, but did not significantly differ with levels in matched controls suffering from rheumatological pain.

Three large, population based cross sectional studies aimed to investigate this postulated association while adjusting for potential lifestyle confounders, providing arguably the best level of evidence so far on the prevalence of vitamin D deficiency in fibromyalgia.^{19,28,29} Unfortunately, their results are also conflicting (Table 4).

Overall, study results are inconclusive. While earlier, poorer quality studies suggested a positive association between fibromyalgia and low vitamin D levels, studies using control groups suggested no association, and larger population based studies had mixed results.

Treatment effect of vitamin D on fibromyalgia

General practitioners need to know whether treating vitamin D deficiency improves fibromyalgia. Only one eligible RCT testing this hypothesis was found.²²

In this RCT, 50 predominantly fair skinned patients with chronic muscular pain diagnosed by a rheumatologist as primary fibromyalgia, with 25-OHD levels less than 20 ng/mmol, were recruited and randomised to receive 50 000 IU oral vitamin D once weekly for 3 months (n=25) or an identical placebo (n=25), in a double blind process. There was no significant improvement

in pain scores despite the active treatment group achieving significantly higher vitamin D levels than the placebo group.

Limitations in this study include the small sample size, the unexpected normalisation of vitamin D levels in 50% of the placebo group, a significant improvement in placebo group pain scores, and a restriction of follow up of the participants to 3 months. This timeframe was based on resolution of bone pain within 1–3 months in osteomalacia treatment, not on resolution of muscle pain; longer follow up would potentially allow improvement in muscle fibre regeneration.

Despite these limitations, this study is currently the best evidence and does not support any therapeutic effect of vitamin D supplementation on muscle pain in fibromyalgia.

Discussion

We have not found strong evidence that vitamin D deficiency contributes to fibromyalgia, with any observed association potentially explained by other mechanisms, such as less sun exposure in chronic disease.

Testing and treating for vitamin D deficiency could be warranted in these patients for bone health rather than pain relief. Vitamin D deficiency has significant long term implications by lowering bone density, decreased muscle strength and increased risk of falls.^{10,27,30} The Royal Australian College of General Practitioners *Guidelines for preventive activities in general practice*³¹ (the ‘red book’) recommends that a vitamin D supplement should be recommended if patients have inadequate sun exposure, particularly after 65 years of age, to reduce the risk of fracture. Al-Allaf et al³² conclude that patients with fibromyalgia-type pain are more likely to have poorer bone health in the future given their susceptibility to low vitamin D levels and poor lifestyle factors, and therefore should be screened and supplemented for deficiency.

General practitioners should consider testing and treating vitamin D deficiency in patients with fibromyalgia when they are clinically identified as having risk factors for vitamin D deficiency to optimise long term bone health and muscle strength, rather than to treat

Table 4. Comparison of cross sectional studies

Authors	Population size and characteristics	Control population
Block, 2004 ²⁴	N=101 Muscle pain Mostly Caucasian	Nil
Badsha et al, 2009 ²³	N=130 Muscle pain Mostly Arab/Indian women	Nil
Tandeter et al, 2009 ²⁵	N=68 Muscle pain Premenopausal Israeli women	Healthy controls (82 age matched premenopausal women)
Warner et al, 2008 ²²	N=184 Muscle pain Mostly Caucasian	104 osteoarthritis patients
Huisman et al, 2001 ²⁶	N=25 fibromyalgia Caucasian population	Controlled against 25 patients with SLE
Mouyis et al, 2008 ²⁷	N=263 with rheumatological diagnosis 15 patients fibromyalgia	Controlled against other rheumatological outpatients
Erkal et al, 2006 ²⁸	N=994 (101 Germans, 327 Turkish residents of Turkey, 566 Turkish immigrants living in Germany)	Population based
McBeth et al, 2010 ²⁹	N=3075 Middle aged European men	Population based
Atherton et al, 2009 ¹⁹	N=6824 Caucasian population, mixed gender	Population based

Note: ACR = American College of Rheumatology; SLE

Muscle pain definition	Confounders adjusted for	Association	Limitations
ACR (1990) defined fibromyalgia	Age, gender	Low vitamin D levels consistent with studies of similar (pain free) Caucasian populations	No controls Lack of adjustment for confounders
Fibromyalgia/nonspecific musculoskeletal pain	Age, gender, style of dress, comorbid diagnoses	74% low vitamin D level (<20 ng/dL), mostly Arab and Indo-Pakistani people	No controls Limited confounders controlled for Lack of <i>p</i> values/confidence intervals
ACR (1990) defined fibromyalgia	Age, country of birth, education	No statistically significant differences in 25-OHD levels	Lack of adjustment for confounders (variables examined not established predictors of low vitamin D) Religious status, dress code, sun exposure, use of medicines/supplements unknown
ACR (1990) defined fibromyalgia, apart from tender points (deemed lacking in specificity and reproducibility by authors)	Age, gender, race, duration and distribution of pain, pain scores, functional ability, analgesic use, supplements use, calcium intake, time outdoors, psychiatric history	No statistically significant differences in 25-OHD levels	Higher mean age of control patients Adiposity (prevalent in both muscular and osteoarthritic pain) not accounted for, therefore possible underestimation of association between CWP and low vitamin D
ACR (1990) defined fibromyalgia	Age, vitamin D supplementation, milk consumption, sunblock use, diet, medicines used, life habits, weight loss, previous operations	No statistically significant differences in 25-OHD levels, including after adjusting for age, vitamin D, milk consumption, sunblock use	Small sample sizes Study outcomes focused on SLE patients rather than fibromyalgia patients
Chronic pain/fibromyalgia, poorly defined (due to retrospective nature of audit)	Retrospective audit, therefore little data on potential confounding factors	25-OHD levels substantially lower in inflammatory arthritis and CWP/fibromyalgia, compared to other diagnostic groups	Retrospective audit of electronic records Some patients possibly already on vitamin D tablets Small numbers in individual disease categories
Nonspecific measurements of pain, termed 'bone and/or muscle aches and pains', poorly defined	Age, gender, location, body mass index, wearing a scarf, duration of pain, smoking status, nutritional habits, sun exposure, physical activity, number of children	Significant correlation between low 25-OHD levels and higher rates and longer duration of pain in the Turkish groups	Self reporting only Nonspecific, poorly defined definition of pain
ACR (1990) defined fibromyalgia (263 patients, plus 1550 patients with 'other pain')	Age, body mass index, physical activity, smoking, depression, alcohol consumption	Those with pain had lower 25-OHD levels and were at higher risk of low 25-OHD even after adjusting for confounders	Few limitations, with standardised, well validated instruments to assess pain and confounders Extra confounders could have been considered
ACR (1990) defined fibromyalgia (11.4% of men, 12.5% of women)	Social class, smoking, alcohol, time spent outdoors, time using TV/PC, supplements used, consumption of fish, physical activity, body mass index, geographical location	Prevalence of pain varied by 25-OHD level in women, but not in men; not fully explained by difference in lifestyle or social factors	Few limitations Period of pain might not correlate with low vitamin D level Attrition during follow up Under-representation of minority groups

= systemic lupus erythematosus; CWP = chronic widespread pain

their pain. For example, obesity and prolonged periods indoors (due to poor mobility, pain or associated depression) have been recently identified by the National Prescribing Service to be risk factors for vitamin D deficiency.⁶

There is a need for a prospective long term study to provide stronger evidence regarding the true prevalence and association of vitamin D deficiency in patients with fibromyalgia. However, the Australian New Zealand Clinical Trials Registry³³ reveals no forthcoming trials in this area. Larger, more rigorous RCTs are also required to answer the question of whether vitamin D might be an effective treatment for fibromyalgia.

Summary of important points

- There are conflicting results regarding prevalence of vitamin D deficiency in patients with fibromyalgia.
- The best evidence shows no effect on fibromyalgia with vitamin D supplementation.
- Treating vitamin D deficiency can benefit long term bone health and muscle strength, both of which are important for patients with fibromyalgia and concurrent risk factors for vitamin D deficiency.

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