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Pilot Study Open Access

Vitamin D Supplementation in the Treatment of Non-Cyclical Breast Pain

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Abstract

Objective: Non-cyclical mastalgia is a common presenting complaint, poorly understood and difficult to manage. Vitamin D deficiency has been linked with breast and musculoskeletal pain in both non-Caucasians populations as well as breast cancer patients receiving aromatase inhibitor treatment. Our catchment has a high proportion of non-Caucasian inhabitants and in the temperate climate of the UK, they are at high risk of Vitamin D deficiency. This study aims to investigate if supplementation can improve non-cyclical mastalgia.

Methods: Prospective pilot survey of all patients with non-cyclical mastalgia and Vitamin D deficiency seen at one centre within a two year period. All patients with low Vitamin D levels were referred to their general practitioners (GPs) for appropriate management. A follow up questionnaire was then sent to analyse treatment response.

Results: A total of 68 out of 110 patients completed questionnaires. 63% of patients were prescribed Vitamin D by their GP and complied with the therapy. 51% of these noted complete or near complete remission of symptoms following therapy. 26% noted a pain score of <5 following therapy. 23% noted a residual pain score of >5 despite therapy. 3 out of the 18 patients who did not receive Vitamin D noted spontaneous improvement in pain.

Conclusion: This pilot study shows a correlation between Vitamin-D deficiency and non-cyclical mastalgia. Improvement of symptoms was seen in 77% of patients following supplementation and only 17% of spontaneous improvement without treatment ($p<0.01$). Further study by way of a blinded randomized control trial is required to quantify this correlation.

Keywords: Vitamin D; Mastalgia; Non-cyclical breast pain

Introduction

Non-cyclical breast pain is a common, potentially debilitating condition affecting 70% of women at some point during their lives and represents a third of all breast pain complaints. It is often difficult to treat, can last for several months, relapses in up to 60% of cases (1) and can represent a significant work load for breast care services. Several treatment modalities have been trialled such as NSAIDs, steroids, antibiotics, hormone modulators, vitamin E and topical treatment, which have had with mixed outcomes and none have been definitively recommended [1,2].

Another group of patients well known to breast care services are cancer patients, and there is a growing body of evidence that vitamin D deficiency is a major contributing factor in the well-recognised side effect of chest and musculoskeletal pain in patients receiving aromatase inhibitors (AI). Vitamin D deficiency has been found to be significantly lower in patients undergoing AI treatment experiencing musculoskeletal pain [3], as well as increased intensity of observed pain [4]. Regimented supplementation has been demonstrated to raise serum vitamin D levels and significantly improve symptoms from Musculoskeletal disability [5-7]. Furthermore, pre-treatment with vitamin D has also been shown to reduce musculoskeletal side effects after starting AI therapy [8] with prolonged improvement in symptoms during and after treatment.

Vitamin D deficiency has also been strongly associated with arthritic pain, fibromyalgia, chronic non-specific pain and other musculoskeletal pain [9-13]. Moreover, severe hypovitaminosis D has been linked with persistent non-specific pain [14], in patients from ethnic minorities such as Afro-Caribbean, Hispanic, American-Indian, aboriginal, non-western immigrants [15,16] and Arab and Indian-Pakistani patients when compared to Caucasian patients [17]. It also been linked to fatigue, secondary hypoparathyroidism [18], headaches low mood and depression [19]. However, little is known about the effects of vitamin D deficiency on non-cyclical breast pain and how supplementation could potentially improve symptoms.

Our local population exhibits a high ethnic diversity with a larger than average percentage of patients from south Asia, Africa and the Middle East. We have observed a similar trend of increased musculoskeletal pain in patients undergoing AI treatment. However, we have also noted a high number of non-Caucasian patients presenting with non-cyclical breast pain. These patients are also those who are at higher risk of vitamin D deficiency due to their ethnic background and prolonged stay in temperate climate of the UK.

Objective

The aim of this exploratory study was to investigate if vitamin D deficiency has any link to non-cyclical breast pain and whether supplementation can deliver symptomatic improvement in a cohort of patients from a range of ethnic backgrounds.

Methods

This is a prospective observational study conducted in City Hospital, Birmingham, over a two-year period. All participants were recruited from the out patients department. Patients who had presented with breast pain had a full history, drug history and clinical examination. Imaging and other clinical investigations were performed to exclude other potential causes of breast pain. Patients who presented with chest wall pain, referred shoulder pain or dermatological conditions were excluded. Patients over 18 years old, with an established diagnosis of non-cyclical breast pain were approached, provided information and consented in clinic and a blood test to investigate vitamin D levels was performed. The cut off selected for defining deficiency was a serum level of vitamin D 25(OH) <50 nmol/L. Though serum 25-OH vitamin D levels of <25 nmol/L is known to be associated with significant bony disease such as osteomalacia and rickets, vitamin D insufficiency with serum levels of <50 nmol/L is also associated with significant morbidity including diabetes, cardiovascular disease, various cancers [20,21] and increased risk of all-cause mortality [22,23]. This is also in accordance with NICE guidelines definitions and recommendations and our local laboratory standards [24]. Blood samples were tested *via* a biochemical assay. All patients with low vitamin D were sent an information sheet detailing our findings and recommendations for vitamin D supplementation. The blood sample findings were also relayed in a letter to the patient's respective general practitioner doctors, explaining our study and a recommendation to commence supplementation in accordance to their normal practice and national guidelines. A follow up questionnaire was then sent to those who had low vitamin D blood levels 12 months following the initial appointment in order to follow uptake of recommended treatment and clinical response. The questionnaire asked the patient to rate the improvement, if any, in pain (Pain Score 1-10) and also, treatment they had received from their general practitioners (GPs), their ethnic origin and also the dose, duration and specific preparation of vitamin D supplementation they were prescribed. The responses were categorised as Poor (pain score >5), Average (pain score 4-5), Good (pain score 2–3) and Excellent (pain score =1). We classified the groups into those who experienced symptomatic improvement (pain score ≤ 5), and those who did not have symptomatic improvement (pain score >5).

This study was registered with the trust Research and Development and audit department. A specific regimented treatment or dosage was not mandated at any point during this study. As this follows national guidelines in diagnosis and treatment of low vitamin D and treatment overseen by GPs, ethical approval was not required. All analysis was performed using SPSS version 16.0.

Results

A total of 110 surveys were sent out, and 68 patients returned completed questionnaires (62% response rate). All participants were female, mean age at recruitment was 48.2 years (±13.7) and baseline serum vitamin D level at recruitment was 24.1 nmol/L (±10.9) (Table 1).

There was no statistical significant difference in the age of the women who in each pain score subcategory (Table 2). The patients were of mixed ethnic origin with the majority originating from the southern Asian territory (61%), followed by Caucasian (25%), with the fewest number of patients of Afro-Caribbean origin (14%).

Total (n=68), 4 patients excluded*		
Age(Years)	48.2 (± 13.7)	
Gender	Female	64
	Male	0
Race	Caucasian	16
	Asian	39
	Afro-Caribbean	9
Menstruation	Pre-menopausal	48
	Peri-menopausal	2*
	Post-menopausal	18
Serum vitamin D (nmol/L)	24.1 (± 10.9)	
Laterality of pain	Bilateral	14
	Unilateral	52
*Patients excluded due to confounding factors: Peri-menopausal, Pregnancy, Change of oral contraceptive pill		

Table 1: Baseline patient demographics.

Of the 68 patients who responded to the questionnaire, 46 patients were prescribed vitamin D supplementation by their GP and 18 patients either had not been prescribed or had chosen not to take vitamin D supplementation. Four patients were excluded from analysis as they had also reported other potential confounding factors: pregnancy (n=1), peri-menopause (n=2), and change in oral contraceptive use (n=1).

From the 46 patients who received vitamin D, 23 patients (51%) experienced complete or near complete remission of all symptoms following therapy, 12 patients (26%) noted a pain score of <5 following therapy, 11 patients (23%) noted residual pain score >5 despite therapy. Of the 18 patients who had not received vitamin D supplementation, 3 patients experienced spontaneous resolution or improvement of symptoms and 15 reported no change in symptomatic relief. Overall, 77% of patients experienced symptomatic improvement of their non-cyclical breast pain after treatment with vitamin D when compared to 17% of those who had not (p=0.0001) (Table 2).

Total (n=64)	**Vitamin D supplementation (n=46)**		**No vitamin D supplementation (n=18)**		**p (Vit D supplementation)**
	improvement	no improvement	improvement	no improvement	versus no supplmentation
Overall (n)	35	11	3	15	<0.001
Age (years)	48.1 (27-84)	47 (26-71)	51 (41-63)	44.2 (29-61)	0.505
Race					
Caucasian	5	3	2	6	0.314
Asian	26	6	1	6	0.002
Afro-Caribbean	4	2	0	3	0.167
Serum Vitamin D 25(OH)					
mean	24.71	17.45	23.90	30.39	0.038
<20 nmol/L	17	8	1	4	0.128
<35 nmol/L	10	3	1	5	0.041
<50 nmol/L	8	0	1	6	0.001

Table 2: Results summary of vitamin D supplementation and improvements in pain alongside ethnic background and baseline serum vitamin D levels.

Patients of an Asian ethnic origin demonstrated the most significant improvement of symptoms with vitamin D supplementation (p=0.002). Afro-Caribbean patients also tended to experience symptomatic improvement, though the observed improvement was not significant. Perhaps this is due to the small number in this cohort (n=9, p=0.167), whereas within the Caucasian patients there was no significant improvement above background spontaneous recovery (n=16, p=0.314).

The overall average baseline serum vitamin D level was 25.2 nmol/L (± 11.2 SD). The patients who had baseline serum vitamin D levels between 35-50 nmol/L demonstrated the most improvement of symptoms with treatment (p=0.0001) and those with baseline levels between 20 to <35 nmol/L also had a significant improvement in symptoms (p=0.041). Whereas in patients with a baseline serum vitamin D of <20 nmol/L, a weak trend towards association of supplementation and pain relief was observed, however this was not significant (p=0.128). This suggests that perhaps those patients who are mild to moderately deficient have a shorter gap to close to achieve therapeutic benefit, whereas those with severe deficiency reap some benefit but still experience persistent pain.

Patients who had been treated with vitamin D had a significantly lower baseline serum level compared to those who were not treated (p=0.038). This may be a reflection of the normal practice for GPs managing those who are only mildly vitamin D deficient versus those who are profoundly deficient. NICE guidelines recommends treating all patients with a serum level <30 nmol/L, but only recommends treatment for those with a serum level 30-50 nmol/L if the patient has other risk factors such as concurrent metabolic or malabsorption disorders, or are at risk of fractures or display symptoms suggestive of vitamin D deficiency.

The final decision to offer treatment was left to the discretion of the GP. Furthermore, the patients with poor response tended to have received a shorter treatment course 1 month (median, IQR range 0.6-5.25 months), compared with patients with symptomatic response 2.5 months (median, IQR range 0.8-8.5 months), p=0.267.

The exact type and strength of vitamin D supplementation was managed by the GP in line with their normal practice, which varied between differing preparations and strengths from 400 iu to 10,000 iu per day (Table 3), a relatively low treatment dose compared to other studies (5,7,8). There was no difference in the dosages of vitamin D supplementation between those who did and did not experience symptomatic improvement (p=0.957) (Table 3).

However, if the cumulative dose of vitamin D is calculated, the patients who had symptomatic improvement received almost twice as much (11361 iu) vitamin D supplementation as the patients had no improvement (6480 iu), which suggests that beneficial effects are not only dependent on the daily regimented dose, but the duration of treatment and aggregate of total supplemented vitamin D that has been delivered.

	Vitamin D supplementation (n=46)		p
	Improvement	No improvement	
Vitamin D dose (per day)	n=35	n=11	
400 iu	11	6	
800 iu	14	2	
>800 iu	6	2	
Unknown	4	1	
mean (iu / day)	2438	2400	p=0.957
Cummulative dose (iu)	11361	6480	
Duration of treatment (months)	4.66 (0.1-12)	2.70 (0.1-9)	p=0.267

Table 3: Summary of daily and cumulative dosages of vitamin D taken and duration of treatment.

Discussion

Vitamin D has a significant role in bone, joint and muscle metabolism [25], is critical to calcium and phosphorus homeostasis and has been implicated in cancer, metabolic syndromes, heart failure, infection and immune disorders [26-29]. There are two main sources of non-prescriptive vitamin D: Diet and sun exposure. For dermal synthesis of vitamin D to occur exposure to ultraviolet B radiation is necessary. Due our northern location, 90% UK and other countries lying on or situated further north of these latitudes experience ultraviolet B radiation for only 6 months of the year [21,30]. Though Caucasian patients can achieve adequate vitamin D synthesis from 10 minutes of sun exposure three times a week during the summer, this is wholly insufficient for an individual with darker skin who requires 2-10 times more sun exposure [31]. Other factors such as diet, occlusive clothing, age and pregnancy can also compound this risk. In the current climate of ethnic fluidity and migration, many communities living in the UK's temperate climate are risk of vitamin D deficiency.

In our study, we have shown that not only a large majority of patients presenting with non-cyclical breast pain are of a non-Caucasian ethnic origin, but also that they experience symptomatic improvement with low dose vitamin D supplementation. There is a substantial body of research linking vitamin D deficiency and non-specific chronic pain, however there are no studies specifically investigating the link between breast pain and vitamin D deficiency outside the realm of aromatase inhibitor treatment in breast cancer.

Several mechanisms have been proposed for developing musculoskeletal pain in vitamin D deficient states. One proposed explanation is an interruption of calcium deposition in collagen matrices of bone, which results in malformation of pathologically soft bone that continues to expand and exerts pressure on periosteal surfaces and subsequently on sensory pain receptors [32]. Other mechanisms that have been suggested include a reduction in nerve conduction velocity resulting in muscular atrophy and myopathy [33,34] and hyperparathyroidism by way of proteolysis of muscle leading to fatigue and muscle, bony and joint pain, however the mechanism for vitamin D deficiency in non-cyclical breast pain is unclear. Recent studies have shown that vitamin D receptors are available in almost all cells [35] and current theories around the pathogenesis of this heightened pain response implicates an exaggerated immune possibly as a reaction to infection and sensitisation of pain signalling pathways [19,36-38]. This would reflect how vitamin D deficiency is linked to a number of multi-organ disease states and could be the underlying mechanism by which vitamin D deficiency results in breast tissue tenderness. We attempted to exclude patients who were experiencing chest wall pain or costochondritis to isolate a cohort with breast tissue tenderness, though it is possible some of these patients were suffering from referred pain and that the perceived breast tenderness have a musculoskeletal origin. Nevertheless, this highlights a group of patients whose vitamin D deficiency may have been overlooked when the focus is on investigating the breast.

The lowest serum level of vitamin D 25(OH) necessary for promotion of optimal bone health is considered to be approximately 12-30 nmol/L, as this is the level required to prevent increases in parathyroid hormone (4). However, this standard may be insufficient to achieve improvement in pain and may not represent the therapeutic threshold we should be targeting treatment. Our results show that that those with a mild vitamin D deficiency (35-50 nmol/L) have the most demonstrable improvement in pain from low dose supplementation when compared with those with severe deficiency (<20 nmol/L), suggesting that low dose supplementation is not enough to elevate vitamin D levels sufficiently to yield therapeutic results in those with severe deficiency. This reflects the findings of a systematic review study looking into the optimum target vitamin D levels for multiple end points, including reduced myopathy. Bischoff found that a post-treatment serum level of at least 30 nmol/L produces the most detectable adventitious outcomes and demonstrates continuing improvement with higher concentrations, though not as pronounced [39]. This is also in line with several other studies that have noted a threshold of demarcation whereby improvement in musculoskeletal pain was achieved with serum vitamin D level of 30-66 ng/ml (75-165 nmol/L) [5-8], and conversely, post-treatment serum vitamin D levels of <30 ng/ml (75 nmol/L) did not achieve a significant improvement in musculoskeletal pain. However the serum vitamin D targets suggested

by these studies are considerably higher than what was found in our study. One possible explanation is that all of these studies were conducted on patients undergoing AI treatment for breast cancer. These patients are at higher risk of vitamin D deficiency due to reduced oestrogen levels and subsequent diminished joint vitamin D receptors, which leads to development of myopathy and joint pain, and increased metabolic requirements as vitamin D plays a crucial role in the detoxification of aromatase inhibitors by the liver [40]. Therefore, a therapeutic threshold can still be observed, but is likely to be observed at much higher level. In light of this, perhaps we should not only be supplementing simply to improve serum vitamin D, but calibrating our treatment towards achieving a therapeutic threshold and clinical reduction in pain.

The aim of this exploratory study was to probe the link between vitamin D deficiency and non-cyclical breast pain and establish a connection in view of opening up further inquiry. The limitations of this study include the lack of a blinding between the treatment and control group, and no follow up vitamin D 25-OH blood test to investigate post treatment serum vitamin D levels. Indeed a larger scale blinded investigation with greater power to detect smaller variations between the subgroups is warranted. Consideration must be given to dosing, and cumulative vitamin D that is given, as previous studies have regimented supplementation 400 iu daily to 150,000 iu single dose in previous studies and cumulatively up to 800,000 has been given before. The method for delivery and duration of treatment requires thought: Daily oral supplementation is less invasive and more acceptable for patients, however regular injectable high dose supplementation can have a greater impact and ensure compliance. Information on biochemical serum concentrations of vitamin D, pre, during and post treatment as well as calcium, phosphate, parathyroid hormone would also be informative. Clinical symptoms should be collated alongside menstrual status and hormonal contraceptive use as oestrogen levels has linked to musculoskeletal pain, and smoking and BMI as these have been found to be independent factors affecting breast pain.

In conclusion, in patients experiencing non-cyclical breast pain who have vitamin D deficiency, low dose supplementation reduces breast pain, in particular in patients of a non-Caucasian ethnic origin. Further work is required, but this could establish a treatment option for those patients who present with non-cyclical breast pain that is unresponsive to conventional treatment.

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