ORIGINAL ARTICLE

Musculoskeletal pain: Should physicians test for vitamin D level?

Khaled AL-JARALLAH,1 Diaa SHEHAB,1 Mini ABRAHAM,1 Olusegun A. MOJIMININYI2 and Nabila A. ABDELLA1

Departments of 1Medicine, and 2Pathology, Faculty of Medicine, Kuwait University, Jabriya, Kuwait

Abstract

Aim: The aim of this study was to evaluate vitamin D levels using a reliable method in patients with regional and generalized musculoskeletal (MSK) pain in comparison to healthy controls.

Methods: A consecutive prospective case control cohort was recruited. Patients with generalized MSK pain, for example, fibromyalgia (FM), and regional MSK pain, for example, nonspecific low back pain (LBP) and knee osteoarthritis (OA) were screened for 25 hydroxy-vitamin D [25(OH)D3] levels over a period of 9 months in a hospital-based setting.

Results: One hundred and twenty-four patients and 82 age–sex matched controls were evaluated. The mean age for patients was 41.71 ± 13.86 years. Of the 124 patients, 118 (95%) were female, 77 (62.6%) had FM, 18 (14.6%) had LBP and 28 (22.8%) had knee OA. All patients had normal muscle power; 83.7% of females wore long garments, 11.4% wore veils, 95.5% had sun exposure < 10 min/day and 58.5% were multiparaous; 7.3% were strict vegetarians, 45.5% took inadequate dairy products. The mean calcium, parathyroid hormone, alkaline phosphatase and albumin levels were within normal limits for all study subjects. The vitamin D level was deficient in all patients. There was no statistical difference between the mean vitamin D values of the patients and controls, 27.61 ± 13.06 and 25.82 ± 15.06 nmol/L respectively, (P = 0.368).

Conclusion: Our findings suggest that it is unlikely that measuring vitamin D will be of diagnostic value in the routine assessment of regional and generalized MSK pain.

Key words: fibromyalgia, low back pain, osteoarthritis, vitamin D.

INTRODUCTION

The interest in vitamin D [25 hydroxy-vitamin D or 25 (OH)D3] has mounted to a great extent internationally due to the increased detection of vitamin D insufficiency or deficiency under different conditions. Many studies have been published relating the association of vitamin D deficiency and different musculoskeletal (MSK) pain with controversial conclusions.1–10 Two systematic review articles regarding the association between vitamin D deficiency and MSK pain reported mixed results.7,11 Jan et al.10 have reported an association between vitamin D deficiency and fibromyalgia (FM), and vitamin D replacement may have a therapeutic role in management of FM symptoms. In cross-sectional and longitudinal studies in knee and hip osteoarthritis (OA)12–19 some studies have shown association with progression of OA,12,14,17 while others did not find a relation between vitamin D levels and OA.13,18 In studies relating to low back pain (LBP), Al Faraj20 reported that 83% of patients with LBP had low vitamin D levels and clinical improvement in symptoms was seen in all patients with low vitamin D after vitamin D supplementation.
The main drawbacks of these studies include poor definition of the study cohorts and lack of healthy controls. Moreover, definition of normal vitamin D cut-off values differs in different studies. The accuracy of 25(OH)D3 using different automated assays in the clinical laboratory has been reviewed and it was reported that vitamin D results were method-dependent and hence careful consideration of the measurement method is necessary before conclusions and decisions could be made for patients.

Hence, the objective of this study was to evaluate vitamin D levels in patients with MSK pain which are commonly encountered, namely FM, LBP and knee OA, in comparison to healthy controls using a reliable method.

PATIENTS AND METHODS

Study design and patient cohort and controls

This study is a consecutive prospective case control study over a 9-month period from May 2008 to January 2009. Patients who were referred to the rheumatology/rehabilitation clinics in a university hospital (Mubarak Al-Kabeer) were evaluated for MSK pain. The study was approved by the local ethics committee with the provisions for human research based on the Helsinki Declaration. Consent was obtained from all subjects who participated in the study. Inclusion criteria for the present study integrated patients with a diagnosis of fibromyalgia according to American classification criteria for fibromyalgia, knee OA based on clinical and radiological evidence and mechanical LBP with no evidence of neurological, inflammatory or infectious processes. Patients with evidence of inflammatory arthritis, malignancy, endocrine diseases and chronic renal or liver failure, and patients on drugs which may cause muscle pain were excluded from the study. Data were acquired by taking histories regarding symptoms related to MSK, sun exposure (<10 min/day was considered inadequate), dietary habits (<500 mg of calcium/week in any form of calcium-containing product was considered inadequate) and multiparity, along with history of renal and gastrointestinal diseases and drug intake. Further, physical examination of MSK systems and biochemical assays, including estimation of 25(OH)D3 levels, parathyroid hormone (PTH), serum calcium, alkaline phosphatase (ALP), serum albumin levels, as well as radiological evaluations in cases of knee pain and LBP, were also performed.

A total of 124 patients who met the inclusion criteria entered the study. All our patients with FM fulfilled the American College of Rheumatology (ACR) criteria and the diagnosis of knee OA was established by classic ACR criteria and patients with LBP were evaluated to exclude neurological, inflammatory and infectious causes.

The control group included 82 healthy volunteers (79 female, 3 male) who were medical professionals recruited from the Health Science centre, Kuwait University. They had no MSK pain and had normal clinical and laboratory parameters (with normal complete blood count, erythrocyte sedimentation rate, renal function tests, liver function tests, lipid profile, serum electrolytes, serum calcium and serum albumin). The exclusion criteria were also appropriated to subjects in the control group.

Vitamin D analysis

Blood samples for determining the plasma levels of 25(OH)D3 were collected from the study subjects. Plasma samples were stored at −70°C until used for analysis. Plasma 25(OH)D3 concentration was determined by radioimmunoassay kits (DiaSorin, Stillwater, MN, USA). The analysis consisted of two procedures: the first procedure involved rapid extraction of 25(OH)D3 and other hydroxylated metabolites from plasma which were treated with acetonitrile and were then assayed using an equilibrium radioimmunoassay procedure. The intra- and inter-assay coefficients of variation (CVs) were obtained and were 5.4% and 7.8%, respectively, at a vitamin D concentration of 26.5 nmol/L. Vitamin D levels were defined as deficient when the 25(OH)D3 was <50 nmol/L.

Statistical analysis

Results were analyzed using Statistical Package for Social Sciences (SPSS) version 17.0 (SPSS Inc., Chicago, IL, USA). Pearson Chi-square tests or independent samples t-test were used to find the associations between different variables, as appropriate. Skewed values were log-transformed before analysis. Values of \( P < 0.05 \) were considered to be statistically significant.

RESULTS

One hundred and twenty-four patients and 82 age–sex matched controls were evaluated. All patients had normal muscle examination and normal gait. The mean ages of the patients did not differ from controls: 41.71 ± 13.86 and 43.73 ± 7.40 years, respectively. Ninety-five percent were female. Of the 124 patients, 77 (62.6%) had FM, 18 (14.6%) had LBP and 28 (22.8%)
had knee pain secondary to OA. Long garments were worn by 83.7% of the women, with 11.4% wearing veils; 95.5% had sun exposure < 10 min/day, 58.5% were multiparous, 7.3% were strict vegetarians and 45.5% took inadequate dairy products.

The mean ± SD of the biochemical parameters of patients were within normal limits: PTH = 7.0 ± 2.3 pmol/L (normal = 1.3–9.3 pmol/L; high PTH values were observed in 11 [8.8%] patients); serum calcium = 2.28 ± 0.13 mmol/L (normal = 2.2–2.6 mmol/L); alkaline phosphatase = 87.8 ± 1.82 mmol/L (normal = 26.0–88.0, with high alkaline phosphatase values in 29 [8.8%] patients); serum albumin 38.0 ± 5.0 g/L (normal = 35.0–47.0 g/L), and did not show a significant difference from that of the control group. Vitamin D levels were deficient in all the patients (< 50 nmol/L). No significant difference (P = 0.368) was observed between the mean vitamin D values of patients and controls, 27.61 ± 13.06 nmol/L versus 25.82± 15.06 nmol/L, respectively.

DISCUSSION

Musculoskeletal pain is a common problem encountered in the daily practice of the general practitioner, internists, rheumatologists and physiatrists with approximately 33%25 and 10%27 of the general population reporting LBP and chronic widespread pain, respectively. The incidence of MSK pain among Kuwaiti adults was reported to be 6.6% in a community-based study in Kuwait,28 with knee OA, LBP and FM being the most common presentations. The incidence of vitamin D deficiency in the general population is 25% in the USA and more than 40% in the elderly population.11 Vitamin D deficiency is not uncommon in a sunny country like Kuwait or the Gulf states.2,18,20,29–31 Vitamin D deficient patients are usually seen by the general practitioner or internist, therefore should they test vitamin D in all the patients presenting with MSK pain?

The studies addressing the correlation between low blood levels of 25(OH)D3 in relation to MSK pain were conflicting with no convincing answers regarding its diagnostic validity. Reviewing the literature concentrating mainly on FM, knee OA and mechanical LBP showed that several studies conducted in the last decade examining the association between vitamin D and MSK pain demonstrated contradictory results. Table 1 summarizes the studies in the last decade which examined the relation between vitamin D and MSK pain in different populations.

Several drawbacks were observed upon reviewing these studies, which included poor definition of the study cohorts, lack of a healthy control group and pitfalls of measuring vitamin D. Regarding the study design, in a letter to editors by Block et al.3 the author criticized one of the articles reporting a positive correlation32 for the absence of a control group and lack of definition of patients with FM, which did not fulfill the ACR classification criteria. Therefore, part of the controversy is related to the population studied and the selection criteria. Regarding the different methods of vitamin D analysis, in an article by Heijboer et al.21 the authors stressed that careful interpretation of vitamin D

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study design</th>
<th>Population</th>
<th>Year</th>
<th>No. patients (MSK condition)</th>
<th>Relation to vitamin D</th>
</tr>
</thead>
<tbody>
<tr>
<td>McAlindon et al.</td>
<td>Prospective</td>
<td>USA</td>
<td>1996</td>
<td>556 (OA knee)</td>
<td>Positive</td>
</tr>
<tr>
<td>Al Faraj and Al Mutairi</td>
<td>Prospective</td>
<td>Saudi</td>
<td>2003</td>
<td>360 (LBP)</td>
<td>Positive</td>
</tr>
<tr>
<td>Block</td>
<td>Prospective</td>
<td>USA</td>
<td>2004</td>
<td>101 (MSK pain)</td>
<td>Negative</td>
</tr>
<tr>
<td>Macfarlane et al.</td>
<td>Cross-sectional</td>
<td>Caucasian</td>
<td>2005</td>
<td>114 (fibromyalgia)</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asians</td>
<td></td>
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</tr>
<tr>
<td>Felson et al.</td>
<td>Prospective</td>
<td>USA</td>
<td>2007</td>
<td>715 (OA knee)</td>
<td>Negative</td>
</tr>
<tr>
<td>Heidari et al.</td>
<td>Prospective</td>
<td>Iran</td>
<td>2008</td>
<td>276 (MSK pain)</td>
<td>Positive</td>
</tr>
<tr>
<td>Warner and Arnspiger</td>
<td>Prospective case-control</td>
<td>USA</td>
<td>2008</td>
<td>184 (MSK pain)</td>
<td>Negative</td>
</tr>
<tr>
<td>Badsha et al.</td>
<td>Prospective</td>
<td>UAE</td>
<td>2009</td>
<td>139 (fibromyalgia)</td>
<td>Positive</td>
</tr>
<tr>
<td>Tandeter et al.</td>
<td>Prospective case-control</td>
<td>Israel</td>
<td>2009</td>
<td>68 (fibromyalgia)</td>
<td>Negative</td>
</tr>
<tr>
<td>Ding et al.</td>
<td>Longitudinal</td>
<td>Australia</td>
<td>2009</td>
<td>880 (OA knee)</td>
<td>Positive</td>
</tr>
<tr>
<td>McBeth et al.</td>
<td>Cross-sectional</td>
<td>European</td>
<td>2010</td>
<td>3075 (fibromyalgia)</td>
<td>Positive</td>
</tr>
<tr>
<td>Heidari et al.</td>
<td>Prospective</td>
<td>Iran</td>
<td>2010</td>
<td>148 (OA)</td>
<td>Positive</td>
</tr>
<tr>
<td>Al-Jarallah et al.</td>
<td>Cross-sectional</td>
<td>Kuwait</td>
<td>2012</td>
<td>99 (OA knee)</td>
<td>Negative</td>
</tr>
</tbody>
</table>

OA, osteoarthritis; LBP, low back pain; MSK, musculoskeletal.
results should be made based on the measurement method used for analysis of vitamin D.

Another dimension to the issue of vitamin D measurement is the economics. The cost of the test has not been addressed in these studies. The average lowest cost of measuring 25(OH)D₃ in most countries can be US $25. Since vitamin D tests have been frequently overused to evaluate patients with MSK pain, this issue also needs to be examined. The question which our study tried to address is whether there is any relation between MSK pain and vitamin D levels which justify its measurement, hence its cost.

The patients and controls in our study were drawn from the general population living in Kuwait, a geographic region with a tropical climate, which is a sunny place almost all the year round, hence seasonal variation did not confound the results. We have explored the data relating to the dress code, sun exposure and dietary habits of the study subjects, the factors which can affect vitamin D levels. The preponderance of female patients compared to male patients suffering from vitamin D deficiencies possibly reflects social factors like women using veils outside, staying indoors and diets that contained few vitamin D-rich foods. Vitamin D deficiency was studied in veiled women in Kuwait³⁰ and in relation to osteomalacia³¹ where the evidence of low Vitamin D was clearly attributed to lack of sun exposure, traditional clothing and dietary intake. Most of the literature relating to vitamin D had female preponderance of hypovitaminosis D.

The current study has several strengths. Our cohort study included patients that fulfilled ACR criteria for FM and knee OA. Matching controls in our study were also drawn from the general population with similar diet and sunlight exposure. The DiaSorin radioimmunoassay, the method used in this study, is regarded as the reference method because it is the assay used in all the studies linking circulating 25(OH)D₃ to health outcomes and reference values. In this and other studies²¹ the method has been shown to have acceptable analytical performance characteristics.

There are several factors that could affect observed associations between vitamin D and MSK. Methodological problems as well as the definition of vitamin D deficiency are significant factors. More importantly, the study by Heijboer et al.²¹ suggests that vitamin D-binding protein could play a significant role in the ability of assays to detect the various molecular forms of vitamin D. Therefore, the controversial association of vitamin D with MSK needs to be re-examined in the light of these factors. Furthermore, current definitions of vitamin D status relate to bone health and not muscle health. Perhaps further studies are needed that define vitamin D levels in relation to muscle health, so that appropriate treatment could be given to address the multiple factors that are involved in the pathogenesis of MSK.

In conclusion, based on our findings and a literature review, the current data does not support measuring vitamin D routinely in all patients with generalized MSK pain, specifically fibromyalgia, and with regional MSK pain, for example, nonspecific LBP and knee OA pain, given the tremendous cost of the test on the healthcare system. Yet, the possibility that vitamin D deficiency can aggravate or precipitate MSK pain in genetically predisposed individuals cannot be ruled out.

CONFLICT OF INTEREST
None declared.

SUPPORTING FUNDS
None.

AUTHOR CONTRIBUTIONS
K. Al Jarallah: study planning, study design, protocol development, data analysis, interpretation and manuscript writing. D. Shehab: study planning, data analysis, data collection, data management, manuscript writing, review and editing; M. Abraham: data collection, data management, manuscript review and editing; O.A. Mojiminiyi: data collection, data management; N.A. Abdella: data collection, data management.

ETHICAL APPROVAL
The study was approved by the local ethical committee.

REFERENCES
