

Relationship between Unexplained Arthralgia and Vitamin D Deficiency: a Case Control Study

Behzad Heidari^{1,2*}, Parham Heidari³, and Karim HajianTilaki⁴

¹ Department of Internal Medicine, Rouhani Hospital, Babol, Iran

² Mobility Impairment Research Center, Babol University of Medical Sciences, Babol, Iran

³ Avina Clinic, Tehran, Iran

⁴ Department of Social Medicine, Faculty of Medicine, Babol University of Medical Sciences, Babol, Iran

Received: 14 Feb 2013; Accepted: 7 Jun. 2013

Abstract- Arthralgia is a common presenting symptom of many rheumatic diseases. Vitamin D deficiency may lead to progression of skeletal symptoms to definite disease in susceptible subjects. This study was conducted to determine the relationship between vitamin D deficiency and unexplained arthralgia. Patients with arthralgia not related to a definite clinical condition were selected prospectively among subjects presented to a rheumatology clinic. Serum 25-hydroxyvitamin D (25-OHD) was measured by ELISA method and levels less than 20 ng/ml were considered as deficient levels. Serum 25-OHD levels and proportion of 25-OHD deficiency was compared in patients versus control. The association of serum 25-OHD and arthralgia was assessed by calculation of odds ratio (OR) using regression analysis. 167 patients with mean age of 38 ± 13.3 and 283 controls with mean age of 42.6 ± 14.37 years ($P=0.001$) were studied. In patients mean serum 25-OHD was lower and proportion of deficiency was higher ($P=0.001$ for both). Serum 25-OHD deficiency was associated with 3.01 times increased risk of arthralgia ($OR=3.01$, 95% CI, 2.0- 4.25, $P=0.001$). After adjustment for age and sex, the risk of arthralgia remained significant at $OR= 2.71$ (95%CI, 1.79-4.11, $P=0.001$). The odds of arthralgia decreased with increasing serum 25-OHD from $OR=3.48$ (95% CI, 1.97-6, $P=0.001$) at serum <10 ng/ml to 3.39 (95%CI, 1.93-5.98, $P=0.001$) at 10-19.9; and 1.31 (95%CI, 0.69-2.5, $P=0.42$) at 20-29.9 ng/ml. These findings indicate significant association of vitamin D deficiency and arthralgia. Regarding vitamin D deficiency as an environmental factor for development or progression of rheumatic diseases, this study justifies identification and correction of vitamin D deficiency in patients with arthralgia.

© 2014 Tehran University of Medical Sciences. All rights reserved.

Acta Medica Iranica, 2014;52(5):400-405.

Keywords: Arthralgia; Vitamin D; Association; Deficiency; Rheumatic disease

Introduction

Arthralgia is a frequent manifestation of inflammatory arthritis including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). It is associated with limitation of daily physical activity and a reason for medical help-seeking (1-4). Arthralgia alone or in combination with other nonspecific skeletal symptoms is the presenting symptom of much inflammatory arthritis, which may predate clinical arthritis, seropositivity or fulfilling diagnostic criteria by several months (5-8). Arthralgia has been reported in vitamin D deficiency due to insufficient intake of vitamin D (9) or taking aromatase inhibitors drugs for

breast cancer (10-12).

Vitamin D deficiency is linked to the development, activity, and progression of several rheumatic diseases (13-17). In patients with RA, vitamin D deficiency is prevalent and is inversely related with the disease activity (18,19). The number of tender joint and the level of serum C-reactive protein (CRP) in vitamin D deficient or insufficient RA was significantly higher compared with vitamin D sufficient RA (19). Low intake of vitamin D increases the risk of RA development and disease activity (20) whereas, higher intake of vitamin D decreases the occurrence of RA (21). In a study from Iran most of the new cases of SLE patients had vitamin D deficiency at the time of

Corresponding Author: B. Heidari

Mobility Impairment Research Center, Babol University of Medical Sciences, Babol, Iran
Tel: +98 111 3298808, Fax: +98 111 2238284, E-mail address: heidaribeh@yahoo.com

diagnosis (22). In another study, ANA-positive healthy controls had higher prevalence of vitamin D deficiency compared to ANA-negative individuals (23). Our earlier studies have shown a significant association between vitamin D deficiency and several nonspecific skeletal symptoms including arthralgia, knee osteoarthritis, and undifferentiated arthritis (24-26). Other investigators have also shown an association between vitamin D deficiency and musculoskeletal pain or development or progression of inflammatory arthritis in vitamin D deficient subjects (10,14,17,19-21,23). Recent data indicate that 1, 25-Dihydroxyvitamin D₃ acts as a potent anti-inflammatory agent on T-cells and inhibits production of inflammatory cytokines from T cells (28). These observations indicate a contributive role for vitamin D deficiency in the development of rheumatic diseases (16,18,28) and justify earlier recognition and correction of vitamin D deficient subjects with skeletal symptoms. Until now the status of serum vitamin D has been investigated in several musculoskeletal conditions (10,12,14,16,17,19-21,23,27) but its relationship with isolated arthralgia has not been investigated yet.

We postulated a hypothesis that patients with arthralgia are at greater risk of vitamin D deficiency compared with healthy controls, and therefore we conducted the present study to determine the relationship between arthralgia and vitamin D deficiency.

Materials and Methods

The study population consisted of patients with unexplained arthralgia defined as joint pain without tenderness, limitation of motion and swelling, persisted for six weeks or longer period which could not be attributed to any definite condition based on clinical, radiographic and laboratory examinations. These patients presented to a rheumatology clinic in Babol, Iran, between June 2008 to July 2011 and analyzed in November 2011.

All patients with the following characteristics were included to study:

1- Aged 15 years and more

2- Joint pain in small and medium joints of the upper and lower limbs particularly joints of fingers, carps, ankles, toes with or without arthralgia in large joints.

3- Negative test results in regard to antinuclear antibody (ANA), rheumatoid factor (RF), anti-citrullinated peptide antibody (Anti-CCP), CRP, erythrocyte sedimentation rate (ESR), calcium, phosphate, alkaline phosphatase.

Exclusion criteria included:

1- Presence of current or history of inflammatory arthritis or metabolic bone diseases, fibromyalgia, systemic illness involving gastrointestinal, respiratory, renal, and hematological systems.

2- Patients with clinical or radiographic features suggestive of osteoarthritis or periarticular diseases (tendinitis, bursitis).

3- Patients with limited physical activities, taking multivitamins or vitamin D, or drugs interfering with vitamin D metabolism. Subjects in the control group were selected among patients presented to a medical clinic because of non-skeletal complaints. A similar exclusion criterion was also applied for the control group. All patients accepted to take part in this study and the proposal of this study was approved by the Ethic Committee of Babol University of Medical Sciences. Data were collected by clinical examination and interview and review of medical records. Serum vitamin D was assessed by determination of 25-hydroxyvitamin D (25-OHD) with enzyme-linked immunosorbent assay (ELISA) method according to the manufacturer's instruction using lyophilized competitive protein binding assay kit (DRG, instruments GmbH, Germany). Serum 25-OHD levels less than 20 ng/ml were considered as vitamin D deficiency, levels at 20-29 ng/ml as insufficiency and levels \geq 30 as sufficient. (29).

Sample size was calculated based on detection of 20% difference in proportion of vitamin D deficiency between the patients with arthralgia and the control group (25). Regarding to 36% vitamin D deficiency in the general population of the geographic region of the study population (25) a sample size of 125 participants for each arm were needed to detect a significant difference at 20%, with 95% confidence level ($\alpha = 0.05$) and 80% statistical power ($\beta = 0.20$).

In statistical analysis mean serum 25-OHD and proportion of deficiency was compared between patients and controls according to age. Correlation between 25-OHD and arthralgia was assessed using Spearman test with calculation of correlation coefficient. The association of serum 25-OHD deficiency and arthralgia was determined by calculation of odds ratio (OR) and corresponding 95% confidence interval (95%CI) using regression analysis adjusted for sex and age. In an additional analysis the associations were determined according to various levels of serum 25-OHD concentrations compared with the sufficient level (>30 ng/ml) after adjustment for sex. Quantitative data with normal distributions were compared using t test, otherwise Mann-Whitney U test and Kruskal-Wallis

Relationship between Unexplained Arthralgia ...

test was used for comparisons. SPSS software version 18 was used for analysis.

Result

One-hundred and sixty-seven patients (81% females) and 286 controls (77.3% females), with respective mean (\pm SD) age of 38 ± 13.3 years and 42.6 ± 14.37 years of age ($P=0.001$) were studied.

Mean serum 25-OHD level in the patient group was significantly lower than in the control group (20.9 ± 28.9 vs 30 ± 30.3 , $P=0.001$). Proportion of serum 25-OHD deficiency in patients was significantly higher than in control (70.7% vs 44.4% OR=3.01 (95%CI, 2.0-4.52, $P=0.001$). The differences were evident across various age groups particularly in younger age decades (Table 1).

Proportion of arthralgia in subjects with serum 25-OHD levels less than 10 ng/ml was 34.7% compared with 15% ($P=0.001$) in subjects with the serum 25-OHD at 30 ng/ml or higher (Table 2). In regression analysis the risk of arthralgia increased by OR=3.01(95% CI, 2.0- 4.25, $P=0.001$). After adjustment for age and sex the risk remained significant at OR= 2.71(95%CI, 1.79- 4.11, $P=0.001$). Proportion of arthralgia was inversely correlated with serum 25-OHD level ($r=0.24$, $P=0.001$). After controlling for sex, the risk of arthralgia decreased with increasing serum 25-OHD levels from OR=3.48(95% CI, 1.97-6, $P=0.001$) at serum levels of less than 10 ng/ml to OR= 3.39 (95%CI, 1.93-5.98, $P=0.001$) at 10-19.9 ng/ml, and 1.31(0.69-2.5, $P=0.39$) at serum 25-OHD of 20-29.9 ng/ml compared with serum 25-OHD ≥ 30 ng/ml.

Table 1. Mean serum 25-hydroxyvitamin D (25-OHD) and proportion of 25-OHD deficiency in patients with arthralgia and controls according to decades of age

Age decades	Patients(n =167)		Controls(n =286)		Total (n= 453)		P values
	Mean(\pm SD) ng.ml \neq	Deficiency n(%) \neq	Mean(\pm SD) ng/ml \neq	Deficiency N(%) \neq	Mean(\pm SD) ng/ml	Deficiency n(%)	
<30 (n=113)	16.6 \pm 17.1	39(73.63)	25.8 \pm 33.1	36(60)	21.5 \pm 27.1	75(66.6)	0.026
30-39(n=87)	16.9 \pm 13.3	30(75)	24.9 \pm 25.3	25(53.2)	21.2 \pm 20.9	55(63.2)	0.084
40-49(n=93)	20.4 \pm 38.9	24(77.4)	26.1 \pm 20.7	26(41.9)	24.2 \pm 28	50(53.8)	0.005
50+ (n=160)	30.4 \pm 39.4	25(58.1)	36.2 \pm 34	40(34.2)	34.6 \pm 35.5	65(40.6)	0.042
Total(n=453)	20.9 \pm 28.8	118(70.7)	30 \pm 30.3	127(44.4)	26.6 \pm 30.1	245(54.1)	0.001
P values	0.048	0.21	P=0.007	0.006	P=0.001	P=0.001	--

\neq : Compared with Mann-Whitney U test , \neq : Compared with chi square test

Table 2. Association of serum 25-hydroxyvitamin D (25-OHD) and arthralgia according to levels of serum 25-OHD with calculation of odds ratio (OR) and corresponding 95% confidence interval(95%CI) \neq

Comparison groups Serum 25-OHD ng/ml	Arthralgia n (%)	Unadjusted values		Adjusted values \neq		
		OR(95CI)	P values	OR	95%CI	P values
<10 (n=120)	58(34.7)	3.48 (1.97-6)	0.001	2.95	1.64-5.3	0.001
10-19.9 (n=125)	60(35.9)	3.39 (1.93-5.97)	0.001	3.18	1.79-5.67	0.001
20-29.9 (n=91)	24(14.4)	1.31(0.69-2.5)	0.39	1.3	0.68-2.50	0.42
30 + (n=117)	25(15)	1	-	1	-	-

\neq : Serum 25-OHD 30 ng/ml and higher were considered as reference value, \neq : Adjusted for age and sex

Discussion

The results of this study demonstrated a significant relationship between serum 25-OHD deficiency and unexplained arthralgia irrespective to age and sex.

Proportion of arthralgia was conversely correlated with serum 25-OHD levels particularly in the younger age groups irrespective to sex.

The results of this study in consistent with previous publications present further informations in relation to

vitamin D deficiency and joint pain. Previous studies have shown low serum 25-OHD in patients with joint pain (9-11,24,27,30) or improvement of joint pain with vitamin D supplements (9,10)

In a study of postmenopausal women with breast cancer treated with aromatase inhibitor drugs, joint pain score was inversely related to serum 25-OHD levels (11), vitamin D supplement relived the joint pain and the response to treatment was positively related to serum 25-OHD levels (10).

In another study, a subgroup of children with unexplained arthralgia, 82 % had abnormally low serum vitamin D concentrations, while 40% of them had serum concentrations at deficient levels (7).

The status of serum vitamin D in patients with arthralgia has not been compared with the healthy controls yet. This issue is important, because vitamin D deficiency in adults can cause bone pain, joint and muscle pain. These patients may be misdiagnosed with fibromyalgia, polymyositis, rheumatism, or degenerative joint disease (31).

Many symptoms and signs of vitamin D deficiency are subtle and are difficult to be attributed to vitamin D deficiency and so remain undiagnosed. However, a proportion of these patients who respond to vitamin D supplement may be classified as subclinical osteomalacia (32).

Vitamin D deficiency is considered as an environmental agent for development of Th-1 mediated autoimmune diseases (16). These patients are at higher risk of developing autoimmune rheumatic diseases (13,14,20,31,33). Low intake of vitamin D has been shown to increase the risk of RA whereas, higher intake of vitamin D was associated with reduced risk of RA development (18,20). In addition, vitamin D deficiency increases the disease activity of SLE and RA (19,21,22) and results in progression of undifferentiated inflammatory arthritis to a definite disease (17, 28). A number of patients presenting with arthralgia may progress to definite rheumatic diseases several months later (1-3,5-8,17). In one study the mean delay time from the onset of arthralgia to definite diagnosis of SLE ranged from 6 months to 30 months (1-2,8).

These observations indicate that vitamin D deficiency in patients with arthralgia require further clinical consideration. In particular, a proportion of these patients without clinical arthritis may have features of synovitis by ultrasonographic examination or show early stage of inflammatory arthritis by performing radioisotope scanning, or MRI examination (8,36,37).

Vitamin D deficiency can stimulate production of autoantibodies (23) and may initiate systemic inflammatory responses (21,34).

Therefore, arthralgic patients with vitamin D deficiency are expected to be at greater risk of progression to inflammatory state. It was shown that 1,25 (OH)₂ D and IL-2 through direct synergistic effects on activated T cell, regulate T cell function (38). These justify correction of vitamin D deficiency in patients with arthralgia. Raising serum vitamin 25-OHD to optimal

levels is expected to inhibit various inflammatory cytokines such as TNF- α , interleukins and reduce the immune cell activity and progression to inflammatory state (16,34).

This study has limitations for collection of data in regard to severity of joint pain and its contribution to development of inactivity and resultant vitamin D deficiency. However, the observed association in this case-control study does not indicate causality in particular subjects with limitation of physical activity was not included to study.

Joint pain in patients of this study cannot be attributed to osteoarthritis. because, the observed association was significant in age groups of less than 40 years old, whereas, osteoarthritis is more common in older population, nevertheless, in our earlier study, we have shown a significant association between vitamin D deficiency and knee osteoarthritis as well (25).

We have not followed patients to compare the future status of arthralgia in subjects with or without vitamin D deficiency. This issue was not the aim of our study.

Nevertheless, these findings emphasize a prospective clinical trial to compare the effect of vitamin D replacement treatment with placebo on joint pain.

The strength of our study is dependent to study population who has been derived from a homogenous population presented to a single clinic. The participants had similar characteristics regarding lifestyle, diet, daily physical activities. Almost, all patients had similar joint symptoms for at least six weeks and the reliability of presenting joint symptoms at the first visit was confirmed in second visit performed at least one to two weeks later.

In conclusion this study indicated that unexplained arthralgia is significantly associated with vitamin D deficiency. Regarding vitamin D deficiency as an environmental factor of autoimmune disorders and arthralgia as the most common presenting feature of many rheumatic disorders, coexistent of these two conditions require further clinical consideration in regard to susceptibility for possible progression to future inflammatory state. However, this issue requires further prospective follow up studies of arthralgic patients with and without vitamin D deficiency in respect to future development of inflammatory joint diseases.

References

1. Buckwalter JA, Lappin DR. The disproportionate impact

Relationship between Unexplained Arthralgia ...

- of chronic arthralgia and arthritis among women. *Clin Orthop Relat Res* 2000;(372):159-68.
- Vaz CC, Couto M, Medeiros D, et al. Undifferentiated connective tissue disease: a seven—center cross-sectional a study of 184 patients. *Clin Rheumatol* 2009;28(8):915-21.
 - Ozbek S, Sert M, Paydas S, et al. Delay in the diagnosis of SLE: the importance of arthritis/arthralgia as the initial symptom. *Acta Medica Okayama* 2003;57(4):187-90.
 - van Nies JA, Brouwer E, de Rooy DP, et al. Reasons for medical help-seeking behaviour of patients with recent-onset arthralgia. *Ann Rheum Dis* 2013;72(8):1302-7.
 - Bos WH, Wolbink GJ, Boers M, et al. Arthritis development in patients with arthralgia is strongly associated with anti-citrullinated protein antibody status: a prospective cohort study. *Ann Rheum Dis* 2010;69(3):490-4.
 - van de Stadt LA, van der Horst AR, de KoningMH, et al. The extent of the anti-citrullinated protein antibody repertoire is associated with arthritis development in patients with seropositive arthralgia. *Ann Rheum Dis* 2011;70(1):128-33.
 - Mcnally JD, Matheson LA, Rosenberg AM. Epidemiologic considerations in unexplained pediatric arthralgia: the role of season, school, and stress. *J Rheumatol* 2009;36(2):427-33.
 - Sugimoto H, Takeda A, HyodohK, et al. Early-stage rheumatoid arthritis: prospective study of the Effectiveness of MR Imaging for diagnosis. *Radiology* 2000;216(2):569-75.
 - Chlebowski RT, Johnson KC, Lane D, et al. 25-hydroxyvitamin D concentration, vitamin D intake and joint symptoms in postmenopausal women. *Maturitas* 2011;68(1):73-8.
 - Prieto-Alhambra D, Javaid MK, Servitja S, et al. Vitamin D threshold to prevent aromatase inhibitor-induced arthralgia: a prospective cohort study. *Breast Cancer Res Treat* 2011;125(3):869-78.
 - Khan QJ, Reddy PS, KimlerBF, et al. Effect of vitamin D supplementation on serum 25-hydroxy vitamin D levels, joint pain, and fatigue in women starting adjuvant letrozole treatment for breast cancer. *Breast Cancer Res Treat* 2010;119(1):111-8.
 - Friedman CF, DeMichele A, Su HI, et al. Vitamin D deficiency in postmenopausal women breast cancer survivors. *J Womens Health* 2012;21(4):456-62.
 - Szodoray P, Nakken B, Gaal J, et al. The complex role of vitamin D in autoimmune diseases. *Scand J Immunol* 2008;68(3):261-9.
 - Kamen DL, AranowC. The link between vitamin D deficiency and systemic lupus erythematosus. *Curr Rheumatol Rep* 2008;10(4):273-80.
 - Braun-Moscovici Y, Toledano K, Markovits D, et al. Vitamin D level: is it related to disease activity in inflammatory joint disease? *Rheumatol Int* 2011;31(4):493-9.
 - Arnson Y, Amital H, Shoenfeld Y. Vitamin D and autoimmunity: new etiological and therapeutic considerations. *Ann Rheum Dis* 2007;66(9):1137-42.
 - Zold E, Szodoray P, KappelmayerJ, et al. Vitamin D deficiency in undifferentiated connective tissue disease. *Arthritis Res Ther* 2008;10(5):R123.
 - Merlino LA, Curtis J, Mikuls TR, et al. Vitamin D intake is inversely associated with rheumatoid arthritis: results from the Iowa Women's Health Study. *Arthritis Rheum* 2004;50(1):72-7.
 - Rossini M, Maddali Bongi S, La Montagna G, et al. Vitamin D deficiency in rheumatoid arthritis: prevalence, determinants and associations with disease activity and disability. *Arthritis Res Ther* 2010;12(6):R216.
 - Kerr GS, SabahiI, Richards JS, et al. Prevalence of Vitamin D Insufficiency/Deficiency in Rheumatoid Arthritis and Associations with Disease Severity and Activity. *J Rheumatol* 2011;38(1):53-9.
 - Song GG, Bae SC, Lee YH. Association between vitamin D intake and the risk of rheumatoid arthritis: a meta-analysis. *Clin Rheumatol* 2012;31(12):1733-9.
 - Bonakdar ZS, Jahanshahifar L, Jahanshahifar F, et al. Vitamin D deficiency and its association with disease activity in new cases of systemic lupus erythematosus. *Lupus* 2011;20(11):1155-60.
 - Ritterhouse L, CroweSR, NiewolTB, et al. Vitamin D deficiency is associated with an increased autoimmune response in healthy individuals and in patients with systemic lupus erythematosus. *Ann Rheum Dis* 2011;70(9):1569-74.
 - Heidari B, Shirvani JS, Firouzjahi A, et al. Association between nonspecific skeletal pain and vitamin D deficiency. *Int J Rheumatic Dis* 2010;13(4):340-6.
 - Heidari B, Heidari P, Hajian-Tilaki K. Association between serum vitamin D deficiency and knee osteoarthritis. *Int Orthop* 2011; 35(11):1627-31.
 - Heidari B, Hajian-Tilaki K, Heidari P. The status of serum vitamin D in patients with rheumatoid arthritis and undifferentiated inflammatory arthritis compared with controls. *Rheumatol Int* 2012;32(4):991-5.
 - Plotnikoff GA, Quigley JM. Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. *Mayo Clin Proc* 2003;78(12):1463-70.
 - Jeffery LE, Burke F, Mura M, et al. 1,25-Dihydroxyvitamin D3 and IL-2 combine to inhibit T cell production of inflammatory cytokines and promote development of regulatory T cells expressing CTLA-4 and Fox3. *J Immunol* 2009;183(9):5458-67.

29. KulieT, Groff A, RedmerJ, et al. Vitami D: An evidence-based review. *J Am Board Fam Med* 2009;22(6):698-706.
30. Badsha H, Daher M, Ooi Kong K. Myalgia or nonspecific muscle pain in Arab or Indio-Pakistani patients may indicatre vitamin D defecirncy. *Clin Rheumatol* 2009;28(8):971-3.
31. Holick MF, Chen TC. Vitamin D deficiency:a world wide problem health consequences. *Am J ClinNutr* 2008;87(4):1080S-6S.
32. Haroon M, FitzGerald O. Vitamin D Deficiency: Subclinical and Clinical Consequences on Musculoskeletal Health. *Curr Rheumatol Rep* 2012;14(3):286-93.
33. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;357(3):266-81.
34. Reid D, Knox S, Talwan D, et al. Acute changes in the systemic inflammatory response are associated with transient decreases in 25-hydroxyvitamin D concentrations following elective knee arthroplasty. University of Glasgow. (Accessed in Feb 20, 2014, at <http://eprints.gla.ac.uk/29889/1/29889.pdf>).
35. Kudo-Tanaka E, Ohshima S, Ishii M. Autoantibodies to cyclic citrullinated peptide 2 (CCP2) are superior to other potential diagnostic biomarkers for predicting rheumatoid arthritis in early undifferentiated arthritis. *Clin Rheumatol* 2007;26(10):62733.
36. van de Stadt LA, Bos WH, Meursing Reynders M, et al. The value of ultrasonography in .predicting arthritis in auto-antibody positive arthralgia patients: a prospective cohort study. *Arthritis Res Ther* 2010;12(3):R98.
37. de Bois MH, Arndt JW, Speyer I, et al. Technetium-99m labelled human immunoglobulin scintigraphy predicts rheumatoid arthritis in patients with arthralgia. *Scand J Rheumatol* 1996;25(3):155-8.
38. Haroon M, FitzGerald O. Vitamin D and its emerging role in immunopathology. *Clin Rheumatol* 2012;31(2):199-202.