

Vitamin D status among patients with Rheumatoid Arthritis: A longitudinal multicenter study (Original article)

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Abstract:

Introduction: Rheumatoid arthritis and vitamin D deficiency are common disorders, when present together they exacerbate each other deleterious effects.

Objectives: This study aimed to assess vitamin D status among patients with rheumatoid arthritis.

Subjects & Methods: This cross-sectional longitudinal Hospital-based study was conducted among 85 adult patients with rheumatoid arthritis, recruited from the rheumatic departments of Omdurman Teaching Hospital, and the Military Hospital during the period from April 2012 to May 2014. A structured questionnaire was used to collect socio-demographic data and the duration of rheumatoid arthritis. A blood sample was taken to assess the 25-HO vitamin D level. The Statistical Package for Social Sciences (IBM, SPSS, version, 16) was used for data analysis. The ethical committee of the Sudan Council for Health Specialties approved the research.

Results: There were 85 patients with rheumatoid arthritis, vitamin D deficiency and insufficiency were reported in 34.1% and 37.6% respectively, while 9.4% were reported to have vitamin D overdose and intoxication, females were more likely to be affected than men.

Conclusion: Vitamin D deficiency and insufficiency were prevalent among patients with rheumatoid arthritis in Khartoum, Sudan. While vitamin D overdose and intoxication were observed in ten percent of patients. Further larger case-control studies controlling for various factors associated with vitamin D deficiency are needed.

Keywords: Vitamin D level, Rheumatoid Arthritis, Sudan.

1. Introduction

Rheumatoid arthritis is a chronic inflammatory disease of joints and surrounding tissues, it is a long term autoimmune disease characterized by symmetric, erosive synovitis and sometimes multisystem involvement^[1]. The prevalence of rheumatoid arthritis is on the rise globally with increasing cost, morbidity, and mortality^[2].

The discovery of vitamin D receptors in the cells of the immune system and the fact that active dendritic cells can produce this hormone raises a concern about its role as an immune-regulator and hence the association with rheumatoid arthritis. Vitamin D exerts immune-modulatory and anti-inflammatory effects through T-helper17 regulation^[3,4]

Vitamin D deficiency or insufficiency is estimated to affect about one billion people worldwide^[5]. Studies suggest that vitamin deficiency may be common in rheumatoid arthritis^[6]. Steroids (prednisolone of less than 10mg/day) and vitamin D supplements are commonly prescribed together with calcium to those with rheumatoid arthritis to relieving rheumatoid symptoms and slow joint damage^[1,7] However, vitamin D levels are not usually checked in Sudan neither followed, thus, vitamin D overdose may result with detrimental cardiovascular consequences, due to narrow therapeutic window^[8].

To our knowledge, this is the first research to estimate vitamin D levels among patients with rheumatoid arthritis in Sudan. This study aimed to provide information about vitamin D status in rheumatoid arthritis patients taking supplements of this important vitamin

2. Material and methods:

A total of 85 patients above 18 years with rheumatoid arthritis, recruited from the rheumatic departments of Omdurman Teaching Hospital, and the Military Hospital during the period from April 2012 to May 2014. Patients with chronic kidney or liver disease as well as those with other connective tissue disorders were not included. Participants gave consent then interviewed and examined by the principal researcher. Information collected includes socio-demographic, time since diagnosis, number of affected joints, morning stiffness, joint tenderness or swelling, extra-articular manifestations, and other co-morbidities. A blood sample for full blood count, renal function, inflammatory markers, and 25- hydroxyl- vitamin D level was obtained. For this research 25-HO vitamin D level of 20-30ng/ml was considered suboptimal, 10-20 as deficiency^[9], 5-10ng/ml as a severe deficiency, and <5 as a very severe deficiency. Vitamin D level of >150ng/ml was considered as intoxication^[10], 70-150 as overdose, 50-70 as the upper norm, while 30-50ng/ml was considered optimal.

This research was approved by the Sudan Medical Specialization Board and the ethical committees of Omdurman Teaching and Military Hospitals. The Statistical Package for Social Sciences (SPSS) version 19 was used for data analysis.

3. Observations and Results:

There were 85 patients with rheumatoid arthritis participated in this study, their ages ranged from 19-80 years. Sixty-six (77.7%) were housewives. Regarding disease duration 64 (75.3%) had the disease for more than 1 year, 7 (8.2%) from 6 months-1 year, 3(3.5%) from 3-6 months, and 11 (12.9%) <3 months duration. Table (1)

Table (2) illustrated the vitamin D level among the study group. Vitamin D deficiency was reported in 34.1 % of patients and insufficiency in 37.6%, while vitamin D overdoses and toxicity were detected in 8.1% and 1.2% respectively.

The current data showed that vitamin D deficiency was more common in females (81.3%) compared to males (31.6%), whereas vitamin D overdose was common in males (15.8%) versus (6.1%). Table (3)

In the present study, severe vitamin D deficiency was more common in patients who had the disease for >year (20.3%), the deficiency was more evident in those of 6-months duration. Table (4) showed the relationship between vitamin D level and the disease duration.

Table 1. Characteristic of 85 rheumatoid arthritis patients on vitamin D supplement

Character	No%
Age range	
19-38	16 (18.8%)
39-58	50 (58.8%)
59-78	17 (20%)
79+	2 (2.4%)
Gender	
Males	19 (22.4%)
Females	66 (77.6%)
Occupation	
Housewife	66 (77.7%)
Laborer	18 (21.1%)
Retired	1 (1.2%)
Disease duration	
> 1 year	64 (75.3%)
6 months-year	7 (8.2%)
3-6 months	3 (3.5%)
<3 months	11 (12.9%)

Table 2. 25-hydroxy vitamin D concentration of the study group.

Vitamin D status	No%
Deficiency	29 (34.1%)
Suboptimal (insufficiency)	32 (37.6%)
Optimal	2 (2.4%)
Upper norm	14 (16.5%)
Overdose	7 (8.2%)
Intoxication	1 (1.2)

Table 3. Vitamin D status according to gender among the study group

	Females	Males
Vitamin D deficiency	81.3%	31.6%
Vitamin D insufficiency	19.7%	21.1%
Vitamin D overdose	6.1%	15.8%
Vitamin D intoxication	1.5%	0

Table 4. Relation of disease duration and vitamin D level among the study group

25-OH vitamin D status%	Disease duration			
	<3 months	3-6 months	6 months-year	> year
Very severe deficiency	0	0	0	1.6%
Severe deficiency	18.2%	0	0	20.3%
Deficiency	9.1%	0	42.9%	14.1%
Suboptimal	54.5%	66.7%	42.9%	32.8%
Optimal	0	0	0	3.1%
Upper norm	18.2%	33.3%	14.3%	15.6%
Over dose	0	0	0	10.9%
Intoxication	0	0	0	1.2%

4. Discussion:

Vitamin D deficiency is common worldwide and epidemiologic studies suggest that it may be common in rheumatoid arthritis^[5, 6]. In the present study, female dominance and the high rates of rheumatoid arthritis among the age group 19-59 years are obvious.

In the current study, vitamin D deficiency was present in 34.1% of patients with rheumatoid arthritis on supplements, in similarity to Anaparti et al. who published a recent study in Canada and concluded that 37.6% of patients are vitamin D deficient^[11]. Anaparti and colleagues showed that the level of vitamin D was lower during the winter and those who showed seropositivity. This study result is also similar to a study published by Craig et al^[12] in which vitamin D deficiency in rheumatoid arthritis patients, ranging from 30-63%.

A study conducted among patients with rheumatoid arthritis in India showed that 90% of patients were either vitamin D deficient or in-sufficient and higher than the present result^[13].

It is interesting to know that only 2.4% of the studied patients showed optimal vitamin D level, in spite of vitamin D and calcium supplements, this reflects the magnitude of the problem in patients with rheumatoid arthritis in this country. The low level of the vitamin despite supplementation could be due to inadequate doses or alteration of downstream regulation of genes^[14].

Vitamin D intoxication can rarely occur from replacement therapy, but due to the raising awareness of its role in many diseases and increasing supplements intake^[15, 16], overdose and intoxication are on the rise. At physiological levels, vitamin D maintains vascular homeostasis. However, a narrow therapeutic window is there, but at the end of the spectrum, both vitamin D deficiency and overdose lead to

vascular damage and kidney damage^[17]. In the current study, vitamin D overdose was observed in 8.2% of patients, intoxication in 1.2%, and in 15.6% the level was in the upper norm. There is significant variation among individuals regarding the intoxication dose due to vitamin D receptors polymorphism^[18, 19]. It is imperative to raise the awareness of people about the bad consequences of inappropriate use of vitamin D supplements. Physicians may also need to estimate vitamin D levels at baseline in patients with rheumatoid arthritis before supplements prescription.

Limitations of the study are the small size of the sample, and the fact that the study was conducted at two rheumatic centers, so generalization cannot be insured.

5. Conclusion: Vitamin D deficiency and insufficiency were prevalent among patients with rheumatoid arthritis in Khartoum, Sudan. While vitamin D overdose and intoxication were observed in ten percent of patients, further larger studies are highly needed to determine the relationship of vitamin D deficiency and rheumatoid arthritis activity and complications and controlling for various confounders.

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Conflict of Interest: The authors declare that there are no conflicts of interest.

References:

1. McInnes IB, Schett G. Pathogenetic insights from the treatment of rheumatoid arthritis. *Lancet*. 2017 Jun 10;389(10086):2328-2337. doi: 10.1016/S0140-6736(17)31472-1.
2. Fazal SA, Khan M, Nishi SE, Alam F, Zarin N, Bari MT, et al. A Clinical Update and Global Economic Burden of Rheumatoid Arthritis. *Endocr Metab Immune Disord Drug Targets*. 2018 Feb 13;18(2):98-109. doi: 10.2174/1871530317666171114122417
3. Elena M, Cynthia S, Terry MT, Sherine EG. Is the incidence of rheumatoid arthritis rising? Result from Olmsted country, Minnesota 1955-2007. *Arthritis and Rheumatism* 2010.
4. Hewison M. Vitamin D and the immune system: new perspectives on an old theme. *Endocrinol Metab Clin North Am* 2010; 39(2):365-379.
5. Hollick MF. Vitamin D deficiency. *N Engl J Med* 2007; 357:266-281-7.
6. Chandrashekhara S, Patted A. Role of vitamin D supplementation in improving disease activity in rheumatoid arthritis: An exploratory study. *Int J Rheum Dis*. 2017 Jul;20(7):825-831. doi: 10.1111/1756-185X.12770. Epub 2015 Oct 20.
7. Yan F, Li H, Zhong Z, Zhou M, Lin Y, Tang C et al. Co-Delivery of Prednisolone and Curcumin in Human Serum Albumin Nanoparticles for Effective Treatment of Rheumatoid Arthritis. *Int J Nanomedicine*. 2019 Nov 22;14:9113-9125. doi: 10.2147/IJN.S219413. eCollection 2019.
8. Uwe Q, Robert H. Vitamin D deficiency and toxicity in patients with chronic kidney disease: in search of the therapeutic window. *Pediatr Nephrol* 2010; DOI 10.1007/s00467-010-1574-2
9. Holick MF. Vitamin D deficiency 2007. *N Engl JMed* 357:266–281
10. Lee JH, O'Keefe JH, Bell D, Hensrud DD, Holick MF. Vitamin D deficiency an important, common, and easily treatable cardiovascular risk factor? *J Am Coll Cardiol* 2008; 52:1949–1956
11. Anaparti V, Meng X, Hemshekhar M, Smolik I, Mookherjee N, El-Gabalawy H. Circulating levels of free 25(OH)D increase at the onset of rheumatoid arthritis. *PLoS One*. 2019 Sep 26;14(9):e0219109. doi: 10.1371/journal.pone.0219109. eCollection 2019.

12. Craig SM, Yu F, Curtis JR, Conn DL, Jonas B, Callahan LF et al. Vitamin D status and its association with disease activity and severity in African Americans with recent-onset rheumatoid arthritis. *J Rheumatol* 2010; 37:275-281
13. Rajeev S, Renu S, Laxmikant G, Pradeep M, RN Yadav, PD Meena, Abhishik A. Estimation of vitamin D Level in Rheumatoid Arthritis Patients and its Correlation with the Disease Activity. *JAPI* 2014; 62:678-81
14. Sepulveda-Villegas M, Elizondo-Montemayor L, Trevino V. Identification and analysis of 35 genes associated with vitamin D deficiency: A systematic review to identify genetic variants. *J Steroid Biochem Mol Biol*. 2019 Oct 31;196:105516. doi: 10.1016/j.jsbmb.2019.105516. [Epub ahead of print]
15. Araki T, Holick MF, Alfonso BD, et al. Vitamin D intoxication with severe hypercalcemia due to manufacturing and labeling errors of two dietary supplements made in the United States. *J Clin Endocrinol Metab* 2011; 96: 3603-3608.
16. Wani M, Wani I, Banday K, Ashraf M. The other side of vitamin D therapy: ^{[[[SEPA]]]} a case series of acute kidney injury due to malpractice-related vitamin D intoxication. *Clin Nephrol*. 2016 Nov;86 (2016)(11):236-241.
17. Doneray H, Ozkan B, Ozkan A, Koşan C, Orbak Z, Karakelleoğlu C. The clinical and laboratory characteristics of vitamin D intoxication in children. *Turk J Med Sci* 2009; 39: 1-4.
18. Behzat O, Sukru H, Abdullah B. Vitamin D intoxication. *The Turkish Journal of Pediatrics* 2012; 54:93-98
19. McGrath JJ, Saha S, Burne TH, Eyles DW. A systematic review of the association between common single nucleotide polymorphisms and 25-hydroxyvitamin D concentrations. *J Steroid Biochem Mol Biol* 2010; 121: 71-77.