Research article

Profiles of vitamin D among patients with rheumatoid arthritis at the Kenyatta National Hospital

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Abstract

Background: Rheumatoid Arthritis (RA) is an autoimmune, chronic debilitating condition of undetermined cause. It affects numerous extra- articular organ systems. Vitamin D is a steroid hormone synthesized in the skin by the action of ultraviolet B (UVB) irradiation. Active vitamin D is important in the inhibition of T cell proliferation and down-regulation of key inflammatory cytokines responsible for the pathogenesis of RA. There is growing evidence demonstrating the association between vitamin D insufficiency and higher incidence of RA as well as increased severity of disease and increased functional disability in RA patients.

Objective: The purpose of this study was to determine serum vitamin D levels among patients with rheumatoid arthritis at the Kenyatta National Hospital (KNH) and its association with disease activity and functional disability.

Design: This was a descriptive cross-sectional survey.

Methods: The study involved subjects with RA at the Kenyatta National Hospital. Consecutive sampling technique to recruit patients with rheumatoid arthritis, having met the 2010 American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) classification criteria was selected. Ten mls of peripheral blood was collected from the recruited subjects to determine serum vitamin D levels. Every participant had their demographics, clinical history and disease duration documented. Clinical Disease Activity Index (CDAI) was used to assess disease activity and severity. It comprised of number of tender joint out of 28 joints (T-28), number of swollen joints out of 28 (S-28) global health assessment score by both the physician and the patient level of disability was determined by the standard Modified Health Assessment Questionnaire (MHAQ). Data analyzed was correlated to determine their association with serum vitamin D levels. SPSS version 21 was used to analyze the data collected and this entailed descriptive statistics, chi-square, ANOVA and students'-test to compare and correlate vitamin D levels with age, duration of disease, CDAI score and modified HAQ score in RA.

Results: Eighty one patients with a mean age of 48.7 (SD 13.9), median of 48.0 (IQR 40.0-59.0) were evaluated. The female to male ratio was 4:1. The mean serum 25-VD concentration was 34.9ng/ml (SD11.6). Thirty five participants (43.2%) had insufficient vitamin D levels (<30ng/ml), whereas 46 study participants (56.8%) had sufficiency of vitamin D. Majority of the patients 54 (67.5%) had low disease activity. Fourteen subjects 17.5% had high disease activity and while 2.5% were on remission. Functional disability was assessed using the modified health assessment questionnaire. Thirty eight participants (46.5%) demonstrated no disability, 33.8% had mild disability while 9% had severe disability. Correlation between vitamin levels with age, duration of disease, CDAI and HAQ did not attain statistical significance.

Conclusion: Vitamin D insufficiency is high among patients with rheumatoid arthritis with no correlation with age, duration of disease, functional disability and disease activity.

Key words: Rheumatoid arthritis, Vitamin D, Disease activity, Functional disability, Cytokines

Introduction

Rheumatoid Arthritis (RA) is a chronic debilitating autoimmune disorder whose origin is not fully understood[1]. It is believed to be due to the breakdown of self-tolerance, and B and T lymphocytes are key in the occurrence of the disease[2]. Importance of T and B lymphocytes is further proved by the introduction of Biologic Disease Modifying Antirheumatic Drugs (DMARDS) in the mitigation of RA, which target both T and B lymphocytes and their cytokine profile[3]. Vitamin D is a hormone existing in the skin as an inactive molecule, pre-vitamin D, which is metabolized in the skin by action of ultraviolet irradiation[4]. Vitamin D has multiple extra skeletal

roles potentiated through its receptor, the Vitamin D Receptor (VDR). In the immune system, it acts as an immunomodulator, a property key in the regulation of B and T cells[5]. Multiple studies have found serum vitamin D to be considerably lower in rheumatoid arthritis patients compared to controls, and these levels have an inverse relationship with the activity and severity of disease in RA[6].

Significance of the study

The deficiency of 25-VD is associated with the occurrence, increased disease activity and a more aggressive disease in RA. Among the black population, various studies have shown vitamin D insufficiency even in healthy subjects due to increased melanin concentration impairing vitamin D absorption. These studies have however found considerably reduced levels of vitamin D in RA individuals in the black population compared to those without the disease[7]. In studies where vitamin D was included as part of wholesome RA management, it was noted that there was substantial improvement in disease severity in the subjects[8,9]. In Kenya, and sub-Saharan Africa, the burden of vitamin D insufficiency in RA individuals is unknown.

Objective

To determine serum vitamin D levels among patients with rheumatoid arthritis in Kenyatta National Hospital and to associate it with age, disease activity and functional disability.

Materials and methods

This was a descriptive cross-sectional study conducted in the rheumatology outpatient clinic at KNH. We included patients aged 18 years and above with a documented diagnosis of rheumatoid arthritis who gave written informed consent. The sample size was calculated using the finite population correction factor and a minimum sample size of 81 was achieved. Patients were recruited by consecutive sampling technique. Data collection was done using a structured demographic data collection tool, CDAI form and Stanford health assessment questionnaires.

Inclusion criteria

(i) Patients above 18 years.
(ii) Confirmed to have RA (as per the 2010 revised ACR/EULAR criteria for the classification of RA.
(iii) Willing to participate and signed an informed consent.

Exclusion criteria

(i) Patients taking multivitamin supplements or any form of vitamin D supplementation.
(ii) Pregnant and lactating mothers

Study variables

Dependent variable

Serum 25-hydroxycholecalciferol: Determined by serum immunoassay. The vitamin D was analyzed using High Performance Liquid Chromatography (HPLC). It was extracted from serum using acetronitryl with 0.4% acetic acid. This was injected into a chromatographic column, Polaris C18-A 3µ 150 x 2.0mm. HPLC uses isocratic mode with eluent (MeCN: 0.4% Acetic acid) as the mobile phase. The flow rate was 0.3mls/min and oven temperature 30 degrees Celsius, and detector will be UV-V at wavelength of 280nm. The amount of vitamin D3 was determined by matching the retention of pure standard and a calibration code.

Independent variables

(i) *CDAI score:* To determine disease activity and severity.
(ii) *Modified HAQ:* To determine functional disability in rheumatoid arthritis patients. It was determined by the Stanford HAQ 8-Item disability scale.
(iii) *Duration of disease from time of diagnosis*: This was stratified at five-year.

Data management and analysis

Each study questionnaire was assigned with a unique study serial number to prevent duplication of data collection. A computer that is protected with a pass word was used to enter the data collected in Microsoft access. The data entered in Microsoft access was integrated into the Statistical Package for Social Sciences (SPSS) software version 21. The socio-demographic characteristics, medical history and vitamin D levels were used to determine the means, standard deviations, medians, proportions and frequencies for continuous data and proportions, frequencies and percentages for categorical data and correlation analysis. Statistical findings where p value of less than 0.05 were considered significant. The findings of this study were presented using tables and graphs.

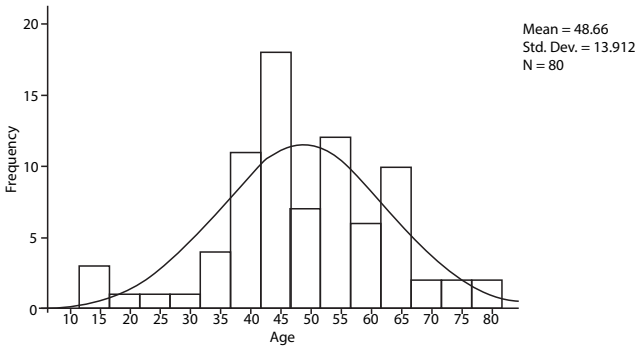
Results

The study participants were relatively young patients with a mean age of 48.7 (median 48). Sixty-five (81.3%) of the participants were female, while 15 (18.8%) were male, giving a female to male ratio of 4:1. Majority of the patients were married, 70% and 55% had received secondary education. Serum 25-VD concentrations ranged from 19.08 to 57.56. The mean (SD) serum 25-VD concentration in this study population was 34.9 ng/ml with a median of 33.6 (11.2) ng/ml and an inter-quartile range of 24.0 - 44.2ng/ml (Table 1). Thirty five (43.2%) participants had insufficient vitamin D levels. No patient was found to have severe vitamin D deficiency of <10ng ml. Ten percent of the subjects had serum vitamin D levels below 20ng/ml.

Table 1: Socio-demographic characteristics of the study participants (n= 81)

Characteristic	Frequency (%)
Age	
Mean (SD)	48.7 (13.9)
Median (IQR)	48.0 (40.0-59.0)
Range	14-78
Age (years)	
<30	5 (6.3)
30-45	33 (40.0)
46-60	27 (33.8)
Above 60	16 (20.0)
Sex	
Male	16 (18.8)
Female	65 (81.3)
Marital status	
Single	18 (22.5)
Married	55 (70.0)
Widowed	7 (7.5)
Level of education	
None	4 (5.0)
Primary	10 (11.3)
Secondary	44 (55.0)
Tertiary	23 (28.7)

Figure 1: Age distribution of the study participants- Histogram



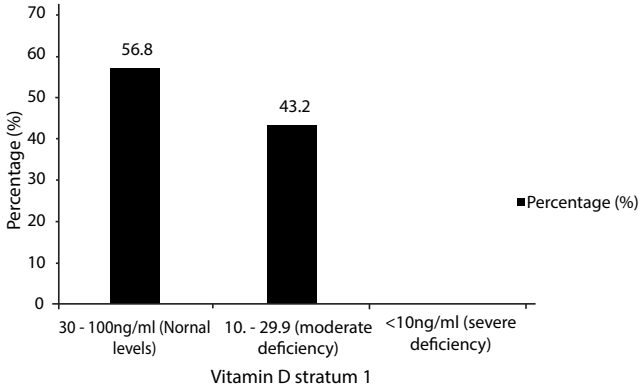


Table 2: Laboratory characteristics of the study population

Characteristic	Frequency (%) (n=80)	95% CI
Serum vitamin D		
Mean (SD)	34.9 (11.6)	
Median (IQR)	33.6 (24.0-44.2)	
Range	16.0-64.4	
Serum vitamin D Stratum 1		
>100 (toxicity)	0	
30 -100ng/ml (Normal levels)	46 (56.8)	(47.2-69.5)
10.-29.9 (Moderate deficiency)	35 (43.2)	(21.6-42.7)
< 10ng/ml (Severe deficiency)	0	
Serum vitamin D Stratum 2		
≥ 20	72 (90.0)	(80.7-95.3)
< 20ng/ml	9 (10.0)	(4.7-19.3)

Table 3: CDAI score in patients with RA

Characteristic	Frequency (%) (n=80)	95% CI
Mean (SD)	14.3 (17.1)	
Median (IQR)	7 (5.0-14.5)	
Range	2-74	
CDAI score		
Remission <0-2.8	3 (2.5)	(0.6-8.6)
Low activity 2.9-10	54 (67.5)	(56.0-77.3)
Moderate activity 10.1-22.0	10 (12.5)	(6.5-22.2)
High activity 22.1-76	14 (17.5)	(10.2-27.9)

We estimated the disease activity of the patients using the CDAI score. Majority of the patients 54 (67.5%) had low disease activity, while 10 (12.5%) had moderate disease activity. Fourteen subjects 17.5% had high disease activity while 2 (2.5%) patients were on remission.

Table 4: HAQ in patients with RA

Characteristic	Frequency (%) (n=80)	95% CI
No disability 0	38 (46.5)	(36.3-58.9)
Mild disability 1	27 (33.8)	(23.8-45.3)
Moderate disability >1 <2	6 (7.5)	(3.1-16.2)
Severe disability >2	9 (11.3)	(5.6-20.8)

Functional disability was assessed using the modified health assessment questionnaire. Thirty-eight (46.5%) participants demonstrated no disability, 27 (33.8%) had mild disability; 6 (7.5%) participants had moderate disability, while 9 (11.3%) had severe disability.

Discussion

The study population was on long term follow up for rheumatoid arthritis (RA). The mean (SD) serum 25-VD concentration in this study population was 34.9 ng/ml with a median of 33.6 (11.2) ng/ml. We found a prevalence of vitamin D deficiency of 10%, and insufficiency of 43.2%. This is lower than what is reported in RA patients in other studies done in Europe, Asia, North America and North Africa. A study done in the US showed a vitamin D insufficiency and deficiency of 84% and 43% respectively[10]. In Amsterdam, 37% of the subjects had vitamin D deficiency while 39% had insufficient levels[11]. An Egyptian study demonstrated 99.1% of patients with RA to have vitamin D insufficiency[12]. In Africa, despite adequate tropical sun exposure, vitamin D levels are thought to be low because of low dietary calcium intake, and increased vitamin D turnover because of high infectious disease burden. Increased melanin is also thought to inhibit proper sun penetration thus leading to reduced vitamin D conversion. There are suggestions that skin colour may influence vitamin D levels. Racial differences in vitamin D deficiency have been reported, with 47%, 54%, 26% and 41% in Asian American, African American, White and Mexican Americans respectively. There is no study reporting the prevalence of vitamin D deficiency in the Kenyan population[13]. Studies have however reported the prevalence of vitamin D deficiency in cancer and HIV patients. Among men with prostate cancer, vitamin D deficiency was found in 88.9%[14]. In a study done among HIV-infected patients in Nairobi, 39% were vitamin D deficient, while 34% were insufficient[15].

Some of the differences observed in vitamin D levels across different populations may be attributable to the cut-off levels adopted by the authors. There are no universally accepted cut-off levels for deficient, insufficient and sufficient vitamin D levels. Recent investigations have suggested that the threshold for vitamin D deficiency should be the 25-VD level below which PTH secretion begins to rise. The authors of these studies have proposed that the cutoff value for vitamin deficiency may be as high as 32ng/ml[16-18] although most studies have adopted <20ng/ml, <30ng/ml and > 30ng/ml for deficiency, insufficiency and sufficiency respectively. For instance, Nesby-O'Dell *et al*[20] used a lower cut-off of 10ng/ml for insufficiency, thereby possibly underestimating the number of subjects with deficiency.

The prevalence of vitamin D deficiency mirrors population vitamin D levels. In normal populations where the prevalence of vitamin D deficiency is high, the same is reflected, at a higher prevalence among RA patients. For instance, in India, a study on vitamin D status in the normal population found a prevalence of 40-100% deficiency in the general population[21]. It is thought that the high prevalence of vitamin D deficiency in the general population in Middle East, India, Turkey and Pakistan is due to inadequate exposure to sunlight because adults, especially women, are covered in veils[21]. In Kenya, a normal population study found a mean vitamin D level of 65.5ng/ml (26.25-114.75) [22].

In our study, all the 81 (100%) patients were on DMARDS which are the cornerstone drugs in the management of RA. These drugs have been shown to mitigate RA manifestations as well as reducing disease activity and improving quality of life. The use of DMARDS in the patients might be the explanation to reduced functional disability and reduced disease activity in the patients. Also, proper follow up and management in a tertiary institution with specialist doctors may be the explanation for better disease control in the patients.

Conclusion

This study found a relatively high prevalence of vitamin D insufficiency in the study population. In long- term rheumatoid arthritis patients, looking for other correlates of disease mitigation like vitamin D levels is prudent. The study however cannot show the causal association between disease activity, age and functional disability with vitamin D levels.

Recommendations

This study recommends further studies needs to be done to explore:

(i) Vitamin D profile – case-control studies in patients with and without rheumatoid arthritis.

(ii) Interventional studies analyzing the impact of vitamin D replacement on rheumatoid arthritis outcomes in patients with vitamin D deficiency.

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