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Research Article

The Role of Vitamin D-Binding Protein, and Procalcitonin in Patients with Arthritis on Vitamin D

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ABSTRACT

Background: Arthritis is a term often used to mean any disorder that affects joints. Symptoms generally include joint pain and stiffness. Other symptoms may include redness, warmth, swelling, and decreased range of motion of the affected joints. In some types of arthritis, other organs are also affected. **Aim:** This study aimed to identify the impact of vitamin D therapy on serum level of vitamin D-binding protein and procalcitonin in Patients with arthritis. **Methods:** This cross-sectional study, was conducted in Kirkuk city between January 1st and March 1st, 2024. A total of 180 subjects were included, categorized into three groups: arthritis patients not receiving vitamin D (Group 1), arthritis patients receiving vitamin D for at least 2 months (Group 2), and a control group comprising 40 healthy subjects. Blood samples were collected from participants, processed, and stored for subsequent analysis. Various biomarkers, including vitamin D-binding protein and procalcitonin, were determined using ELISA kits. **Results:** The study revealed a higher prevalence of females among arthritis patients (54.29%), with most affected individuals aged above 60 years. Urban residency was predominant among arthritis patients (75.71%). The majority of RA patients had been affected for 6-10 years (40%). Comparative analysis demonstrated significantly higher procalcitonin levels in RA patients without vitamin D supplementation (112.4±24.3 ng/ml) compared to those with supplementation (48.33±10.73 ng/ml) and healthy controls (9.68±5.49 ng/ml). Furthermore, vitamin D binding protein levels were significantly lower in arthritis patients without supplementation (1.26±0.12 ng/ml) compared to those with supplementation (0.75±0.15 ng/ml) and healthy controls (0.23±0.14 ng/ml). **Conclusion:** These findings underscore the potential role of vitamin D supplementation in modulating inflammatory markers and enhancing vitamin D binding protein levels in arthritis patients, suggesting its therapeutic implications in disease management.

Keywords: Vitamin D-binding Protein, Procalcitonin, Arthritis, Vitamin D.

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INTRODUCTION

Arthritis is a term often used to mean any disorder that affects joints. Symptoms generally include joint pain and stiffness.[1] Other symptoms may include redness, warmth, swelling, and decreased range of motion of the affected joints. In some types of arthritis, other organs are also affected.[2] Onset can be gradual or sudden. There are over 100 types of arthritis. The most common forms are osteoarthritis (degenerative joint disease) and rheumatoid arthritis.[3] The vitamin D binding protein (DBP) is a multifunctional protein that is well-conserved in the evolution of vertebrates. Vitamin D-binding protein belongs to the albumin gene family, together with human serum albumin and alpha-fetoprotein.[4] It is a multifunctional protein found in plasma, ascetic fluid, cerebrospinal fluid and on the surface of many cell types. It can bind the various forms of vitamin D including ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3), the 25-hydroxylated forms (calcifediol), and the active hormonal product, 1,25-dihydroxyvitamin D (calcitriol).[5] Vitamin D-binding protein belongs to the albumin gene family, together with human serum albumin and alpha-fetoprotein. It is a multifunctional protein found in plasma, ascitic fluid, cerebrospinal fluid and on the surface of many cell types.[6] It can bind the various forms of vitamin D including ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3), the 25-hydroxylated forms (calcifediol), and the active hormonal product, 1,25-dihydroxyvitamin D (calcitriol). The major proportion of vitamin D in blood is bound to this protein. It transports vitamin D metabolites between the skin, liver and kidney, and then on to the various target tissues.[7] Vitamin D, a hormone that has, due to its immunomodulatory properties, been implicated as an aetiological factor of autoimmune diseases, including rheumatoid arthritis (RA).[8] Furthermore, vitamin D has been shown to influence several immune cells, including T-, B- and dendritic cells. Vitamin D3 is produced in the skin as well as taken up from dietary sources, whilst vitamin D2 is found mainly in supplements. In circulation vitamin D binding protein (DBP), also known as group-specific component (GC)-globulin, is the major protein transporter of vitamin D, accounting for the transportation of 85–90% of all vitamin D in plasma, with the remaining fraction 10–15% bound to albumin and less than 1% in an unbound form.[9]

Procalcitonin (PCT) is a peptide precursor of the hormone calcitonin, the latter being involved with calcium homeostasis. It is composed of 116 amino acids and is produced by parafollicular cells (C cells) of the thyroid and by the neuroendocrine cells of the lung and the intestine.[10,11] Early differentiation between septic and non-septic arthritis and the possible decision for therapy remains a difficult task for the physician because clinical signs and traditional markers of infection are of limited value.[12,13] Arthrocentesis with synovial

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gram stain and culture is considered as gold standard, however, the sensitivity of the gram stain is only 50-75% and culture is not available immediately.[14,15] Serum procalcitonin (PCT) has emerged as a biomarker for the diagnosis of various bacterial infections and was found to have higher diagnostic accuracy as compared to clinical characteristics or commonly used laboratory parameters, such as white blood cell count (WBC) and C-reactive protein (CRP). In previous studies, the diagnostic accuracy of serum PCT has been analyzed in septic, crystal and rheumatoid arthritis with contradicting results.[16] This study aims to identify the impact of vitamin D therapy on serum level of vitamin D-binding protein and procalcitonin in Patients with arthritis

MATERIAL AND METHODS

The cross-sectional study was conducted in Kirkuk City (Iraq) during the period between the 1st of January to the 1st of March 2024. The study included 180 subjects divided as follows:

Arthritis not receiving vitamin D.

Arthritis receiving vitamin D for at least 2 months.

The control group consisted of 40 healthy subjects.

Exclusion Criteria

Kidney disease

Diabetes Mellitus

Liver and pancreatic disease.

Documented diagnosed reasons for malabsorption (Gastrointestinal disturbances).

Pregnancy.

Alcohol consumption

Ethical approval

Approval of the council of the College of Medicine/ Tikrit University was obtained for the proposal of the study.

Approval permission was presented to the director of the Kirkuk Health Directorate

The questionnaire was developed by the researcher for the study to assess the domains related to RA patients (Age, Sex, BMI).

In this study, blood samples were collected from participants using 5 ml syringes via vein puncture and subsequently divided into two sterile test tubes. Following centrifugation at 3000 rpm for 15 minutes, the clear serum fraction was carefully pipetted into Eppendorf tubes. These serum samples were then stored at -20°C until further analysis. The analysis included the determination of various biomarkers, such as vitamin D-binding protein and procalcitonin by using an ELISA kit (Sunlong, China)

Statistical analysis: Computerized statistical analysis was performed using SPSS statistic program version 26.1. Comparison was carried out using; and T-Test and ANOVA probability (P value). The P value> 0.05 was considered statistically significant, and the result which a P value was less than 0.01 was considered highly significant, while those whose P value was greater than 0.05 were considered non-significant statistically.

RESULTS

Our data revealed that most of the arthritis patient involved in the study were females 38(54.29%), while 32(45.71%) were males as depicted in Table 1.

Regarding age group, most arthritis patients were recorded in age group >60years 27(38.57%) followed by 51-60years 22(31.43%) then age group 41-50 12(17.14%), while the least affected age group was <20 years 2(2.86%) as demonstrated in Table 2

The RA patient residency distribution illustrated that most of them 75.71% were residing in urban areas, while, 24.29% were from rural areas as shown in Table 3

On the other hand, the disease duration inpatient group was diagnosed at various time points, most of the RA patients 40% were found to be affected for 6-10 years, followed by 22.86% of them suffering of arthritis over 2-5 years and only 17.14 were diagnosed with arthritis during less than one year as revealed in Table 4

Table 5 presents a comparative analysis of Procalcitonin levels in rheumatoid arthritis (RA) patients with and without vitamin D supplementation, as well as healthy control subjects. The mean Procalcitonin level in RA patients without vitamin D supplementation was significantly higher at (112.4±24.3 ng/ml) compared to RA patients receiving vitamin D supplementation with a mean level of (48.33±10.73 ng/ml) and healthy controls with a mean level of (9.68±5.49 ng/ml), p<0.00).

In the current study, vitamin D binding protein levels were significantly lower in arthritis patients without supplementation (1.26±0.12 ng/ml) compared to those with supplementation (0.75±0.15 ng/ml) and healthy controls (0.23±0.14 ng/ml), (p<0.00), as shown in Table 6 and Figure 2.

Table 1: Gender distribution of arthritis patients and control group.

Gender	Patients		Control	
	No.	%	No.	%
Male	32	45.71	6	30
Females	38	54.29	14	70
Total	70	100	20	100

Table 2: Age distribution of arthritis patients and control group.

Age group	Patients		Control	
	No.	%	No.	%
21-30	2	2.86	2	10
31-40	7	10	3	15.00
41-50	12	17.14	4	20
51-60	22	31.43	6	30
>60	27	38.57	5	25.00
Total	70	100	20	100

Table 3: Distribution of arthritis patients and control group according to residency.

Residency	Patients		Control	
	No.	%	No.	%
Urban	53	75.71	16	80
Rural	17	24.29	4	20
Total	70	100	20	100

Table 4: Duration of arthritis in affected patients.

Arthritis duration (years)	Patients	
	No.	%
<1	12	17.14
2-5	16	22.86
6-10	28	40
>10	14	20
Total	70	100

Table 5: Comparison of procalcitonin in RA patients and control group.

Procalcitonin (ng/ml)	Arthritis patients Without Vit. D	Arthritis patients With Vit. D	Control Healthy
Mean±SD	112.4±24.3	48.33±10.73	9.68±5.49

p<0.001

Table 6: Comparison of Vitamin D binding protein in RA patients and control group.

Vitamin D binding protein (ng/ml)	Arthritis patients Without Vit. D	Arthritis patients With Vit. D	Control Healthy
Mean±SD	1.26±0.12	0.75±0.15	0.23±0.14

p<0.001

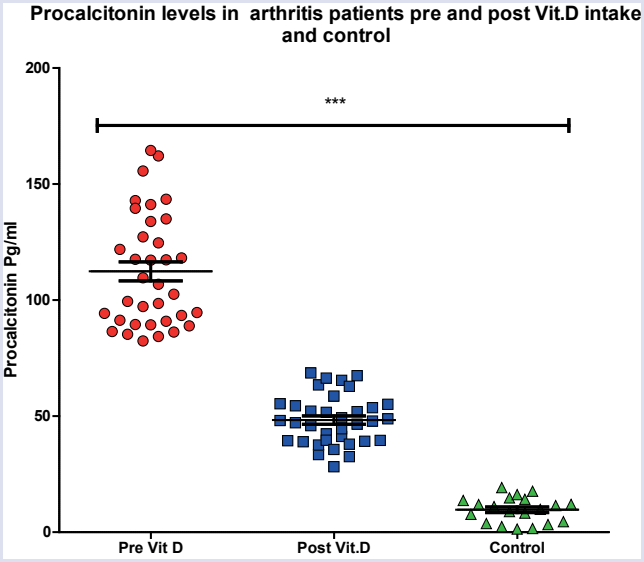

Figure 1: Comparison of procalcitonin in patients and control group

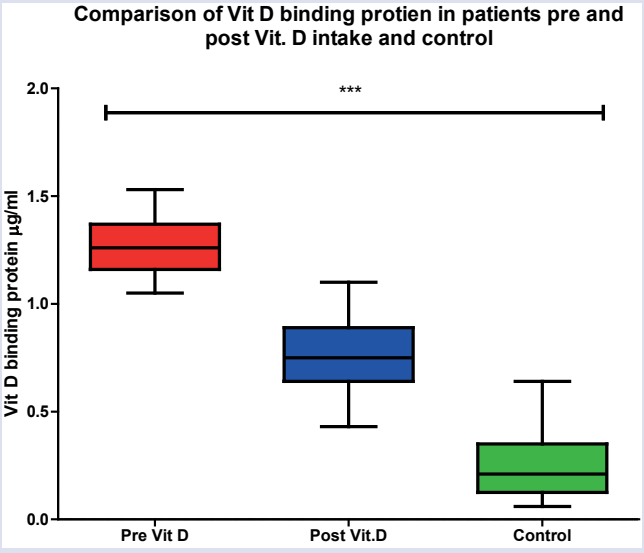

Figure 2: Comparison of vitamin D binding protein in patients and control group

DISCUSSION

Our data revealed that most of the arthritis patients involved in the study were females 38(54.29%), while 32(45.71%) were males. Regarding age group, most arthritis patients were recorded in the age group >60years 27(38.57%) followed by 51-60years 22(31.43%) then age group 41-50 12(17.14%), while the least affected age group was <20 years 2(2.86%).

Several studies have consistently shown that arthritis, particularly rheumatoid arthritis (RA), disproportionately affects women compared to men.[16,17] Other studies also found that women are more affected by rheumatoid arthritis (RA) than men.[18,19] One potential explanation for this gender disparity is hormonal differences between males and females. Estrogen, for example, has been suggested to play a role in the development and progression of certain types of arthritis. Additionally, genetic predispositions and immune system differences between genders may contribute to variations in arthritis prevalence.[20] Furthermore, social and cultural factors might also influence the higher prevalence of arthritis among females. Women tend to seek medical attention more frequently than men, which could lead to higher rates of diagnosis. Moreover, societal roles and expectations may impact women's susceptibility to stress, which can exacerbate inflammatory conditions like arthritis.[21] The age distribution of arthritis patients, as revealed by our data, mirrors established patterns observed in numerous studies.[10] Consistently, the prevalence of arthritis increases with age, with the majority of patients being older adults. Other studies collectively demonstrate a higher prevalence of arthritis among older age groups, highlighting the cumulative impact of ageing on joint health.[3]

On the other hand, the disease duration in the patient group was diagnosed at various time points, most of the RA patients 40% were found to be affected for 6-10 years, followed by 22.86% of them suffering from arthritis over 2-5 years and only 17.14% were diagnosed with arthritis during less than one year. The study was in agreement with similar studies, Agreed studies such as Scott *et al*[21] and Albrecht *et al*[22] have reported findings consistent with our data, highlighting the chronic nature of rheumatoid arthritis (RA) and the distribution of disease durations among patients. Scott *et al.* conducted a longitudinal study examining the long-term outcomes of RA patients, while Albrecht *et al.* explored the duration of RA symptoms in a population-based cohort. These studies provide valuable insights into the prolonged burden of RA on patients' lives. While the study disagreed with those done by Singh *et al*[23] and Smolen *et al*[24] may present alternative perspectives on the distribution of disease durations among RA patients. In the current study, the observed significant elevation in Procalcitonin levels among RA patients without vitamin D supplementation compared to those with supplementation and healthy controls.

Buhaescu *et al*[25] observed a significant elevation in Procalcitonin levels among RA patients and indicated that PCT provided a good diagnostic tool for the detection of systemic infection in patients with systemic autoimmune diseases. Liu *et al*[26] in a recent study showed that the median serum PCT concentrations were significantly higher in patients with early RA when compared with healthy controls. Most of the studies have stated that the levels of serum PCT,[27-29] considerably improve the diagnostic accuracy of serum inflammatory markers in infectious arthritis. Studies have suggested that PCT can be applied in the differential diagnosis of noninfectious arthritis, such as RA and other noninfectious arthritis.[30-32] Although high levels of PCT usually occur at the time of infection, PCT levels may also increase under noninfectious conditions, including the stress associated with surgery or trauma[33] and high inflammatory states associated with certain autoimmune diseases.[34-36] The current result indicated that the mean Procalcitonin level in rheumatoid arthritis (RA) patients without vitamin D supplementation was significantly higher compared to RA patients receiving vitamin D supplementation suggesting a potential association between vitamin D supplementation and Procalcitonin levels in RA patients. In agreement with this finding, Maharajan *et al*[15] investigated the effects of vitamin D supplementation on inflammatory

markers in RA patients and found that RA patients receiving vitamin D supplementation showed lower levels of various inflammatory markers, including Procalcitonin, compared to those without supplementation. In addition, Paosong *et al*[37] conducted a meta-analysis of randomized controlled trials examining the effects of vitamin D supplementation on inflammatory markers in various autoimmune diseases, including RA, they found a consistent trend of reduced inflammatory markers, including Procalcitonin, in patients receiving vitamin D supplementation compared to controls. In RA, an autoimmune disease characterized by chronic inflammation, vitamin D supplementation may help reduce inflammation by suppressing the production of pro-inflammatory cytokines that stimulate Procalcitonin release. Vitamin D plays a crucial role in modulating immune cell function, including macrophages and dendritic cells. These cells are involved in the immune response and can produce Procalcitonin in response to inflammatory stimuli. Vitamin D may regulate the activity of these cells, thereby reducing Procalcitonin production in RA patients.[38] In the current study, vitamin D binding protein levels were significantly lower in arthritis patients without supplementation (1.26±0.12 ng/ml) compared to those with supplementation (0.75±0.15 ng/ml) and healthy controls (0.23±0.14 ng/ml), ($p<0.00$). In the current study, vitamin D binding protein levels were significantly lower in arthritis patients without supplementation (1.26±0.12 ng/ml) compared to those with supplementation (0.75±0.15 ng/ml) and healthy controls (0.23±0.14 ng/ml), ($p<0.00$). In agreement with our findings, Zhang *et al*[39] demonstrated that the levels of total vitamin D binding protein were notably lower in rheumatoid arthritis patients compared to control persons and when they with a combination of 1,25(OH)2D3, they observed a slight increase of in vitamin D binding protein. In addition, it is reported that the expression of VDBP in RA patients was lower than that of OA patients.[40] Previous studies investigating the relationship between future RA and assessed vitamin D status, based on food frequency questionnaires, have reached different results, such as a suggestive lower risk of developing RA following a higher vitamin D intake or no association with vitamin D intake and risk for RA, respectively.[8-10] By measuring circulating vitamin D levels in serum before the clinical onset of RA symptoms, one study found no difference in vitamin D levels in pre-symptomatic individuals compared with controls, whilst another study demonstrated that pre-symptomatic individuals had a 20% decreased risk per unit of 25(OH)D, in those sampled 3 months to <4 years before the onset of symptoms. The fact that the association between RA and vitamin D varies between studies could, at least partly, be the result of different methods of determining the vitamin D status, where the LC-MS/MS is considered the gold standard.[11] The observed significant difference in vitamin D binding protein (VDBP) levels between arthritis patients without and with supplementation in the current study raises several intriguing questions regarding the potential role of VDBP in arthritis pathophysiology and the influence of vitamin D supplementation on this protein. Firstly, the lower VDBP levels in arthritis patients without supplementation suggest a potential dysregulation in vitamin D metabolism or utilization in this patient population.[41] VDBP serves as a carrier protein for vitamin D metabolites, facilitating their transport in the bloodstream. Decreased VDBP levels could affect the availability and distribution of vitamin D metabolites, potentially impacting various physiological processes beyond bone health.[42]

The association between VDBP levels and arthritis may reflect underlying mechanisms related to inflammation, immune dysregulation, or altered bone metabolism characteristic of arthritis. It's plausible that chronic inflammation in arthritis could influence VDBP synthesis or turnover, leading to decreased circulating levels.[43] Additionally, VDBP has been implicated in modulating immune responses and inflammatory pathways, suggesting a potential link between VDBP dysregulation and arthritis pathogenesis.[44] Furthermore, the impact of vitamin D supplementation on VDBP levels raises intriguing questions about the interplay between vitamin D status and VDBP regulation in arthritis. It's unclear whether vitamin D supplementation directly influences VDBP synthesis or secretion or if changes in VDBP levels are secondary to alterations in vitamin D metabolism or immune function[8,45] electrolyte disturbance[46] or kidney disease.[47]

CONCLUSION

The study found that arthritis predominantly affects females, with the highest incidence in patients over 60 years old. Urban areas had a higher proportion of arthritis patients. Arthritis patients without vitamin D supplementation had significantly higher procalcitonin levels compared to supplemented patients and healthy controls. Levels of vitamin D binding protein were significantly lower in arthritis patients without supplementation compared to supplemented patients and healthy controls.

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