VITAMIN-D AND TREATMENT OF RHEUMATOID ARTHRITIS

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ABSTRACT

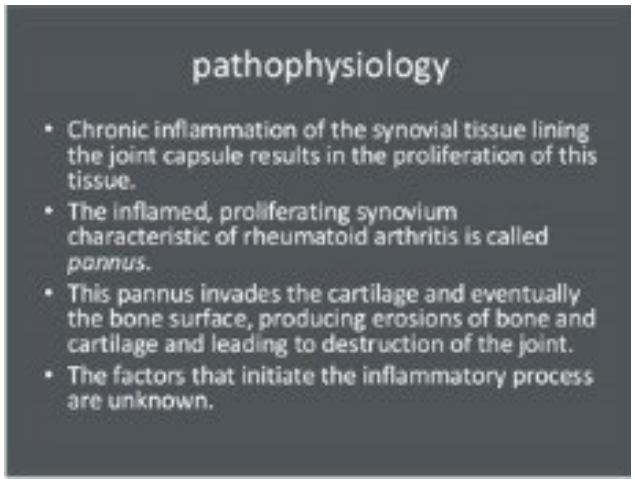
Rheumatoid arthritis (RA) is an autoimmune disease that is characterized by chronic inflammation affecting target tissues including the joints, bones, and synovial membrane. However, the etiology and pathogenesis of RA remain to be determined, and investigations into the treatment of RA are imperative. Vitamin D (Vit D) was previously found to be associated with the activity of RA and exerts therapeutic benefits. The aim of the present study was to investigate the effect of Vit D on the recurrence rate of RA. A total of 100 patients with RA at remission stage were divided into the normal Vit D group and the Vit D-deficient group according to their Vit D levels at baseline. The patients were followed up for 3 months, and the visual analog scale, as well as the number of pain and swelling joints, were recorded. In addition, C-reactive protein and the blood sedimentation rate were measured. Vit D treatment subgroup (n=60), and non-Vit D treatment subgroup (n=40), respectively. However, the difference was not statistically significant between the Vit D treatment subgroup and non-Vit D treatment subgroup. In conclusion, a decreased level of Vit D is a risk factor for the recurrence of RA.

KEY WORDS : Disease activity, Rheumatoid arthritis, vitamin D

OBJECTIVES:

Vitamin D deficiency has been implicated in the pathogenesis of autoimmune diseases, such as diabetes mellitus type 1 and multiple sclerosis. Reduced vitamin D intake has been linked to increased susceptibility to the development of rheumatoid arthritis (RA) and vitamin D deficiency has been found to be associated with disease activity in patients with RA. The objective was to evaluate vitamin D status in patients with RA and to assess the relationship between vitamin D levels and disease activity.

I . INTRODUCTION

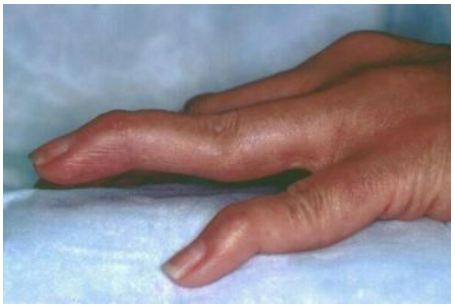


Vitamin D is a secosteroid hormone involved in bone and calcium metabolism. It is involved in the regulation of calcium homeostasis, as it regulates calcium absorption from the gastrointestinal system [Holick, 2011]. The hormone is synthesized in the skin by the action of ultraviolet irradiation [Mason et al. 2011]. Vitamin D has extraskeletal effects as well [Fernandes de Abreu et al. 2009; Hewison, 2012]. The nonclassical actions of vitamin D are currently under discussion. Vitamin D has been found to have immunomodulatory actions [Bartley, 2010; Bikle, 2011]. Vitamin D deficiency has been shown to be correlated with the appearance of autoimmune diseases, such as diabetes mellitus type 1 and multiple sclerosis [Jankosky et al. 2012]. Rheumatoid arthritis (RA) is an autoimmune disease of unknown aetiology [McInnes and Schett, 2011]. Both T and B lymphocytes are involved in the pathogenesis of the disease [Choy, 2012]. The role of T lymphocytes as well as that of B lymphocytes in the pathogenesis of RA has been further proved by the therapeutic efficacy of methods affecting both T and B lymphocytes, namely the biological agents [Keystone et al. 2012; Sharma and Pathak, 2012]. Vitamin D deficiency may increase the risk for the development of RA [Merlino et al. 2004]. Recently, the role of vitamin D deficiency in the pathogenesis of RA, as well as the relationship between vitamin D deficiency and the activity of RA is discussed [Song et al. 2012; Kim et al. 2012]. RA is an inflammatory disease characterized by flares and remissions, flares being characterized by pain. Vitamin D deficiency is also known to be associated with diffuse musculoskeletal pain [Hirani, 2012]. Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation affecting target tissues including the joints, bones, and synovial membrane. RA causes a high rate of disability and ultimately leads to death in patients . However, the etiology and pathogenesis of RA have yet to be determined. Thus, investigations into treatment strategies for RA are crucial. Currently, most studies are based on the premise that RA develops through an antigen-triggered 'challenge-chained immune reaction' process, with infection and autoimmune responses playing central roles in the development and progression of RA, while genetic and environmental factors are important influencing factors that may activate Th1 cells and increase the secretion of cytokines including interleukin-1 (IL-1), IL-6 and TNF-α through the major histocompatibility complex (2, 3). These cytokines are useful in mediating the continuous activation of B cells and eventually induce synovial lesions (2, 3). Vitamin D (Vit D) decreases the production of IL-17, IL-6, IL-1 and tumor necrosis factor-α (TNF-α) by inhibiting the immune response of Th1 cells. In addition, activated Vit D may inhibit the precursors of monocytes by immune modulation effects and inhibit the apoptosis of B-cells (4). It has been previously demonstrated that Vit D is associated with the activity of RA and exerts therapeutic benefits (5, 6). Although in previous studies the association between Vit D and RA was investigated, to the best of our knowledge, no study has investigated whether Vit D affects the recurrence rate of RA or whether Vit D supplementation has various benefits for RA patients through reduction of the recurrence of RA, thereby proving useful for the long-term remission of RA, or reducing the application of slow-acting drugs. In this randomized, open-label clinical study, we investigated the effect of Vit D on the recurrence rate of RA and found that a decreased level of Vit D in the groups examined in the present study is a risk factor for the recurrence rate of RA.

Table-1

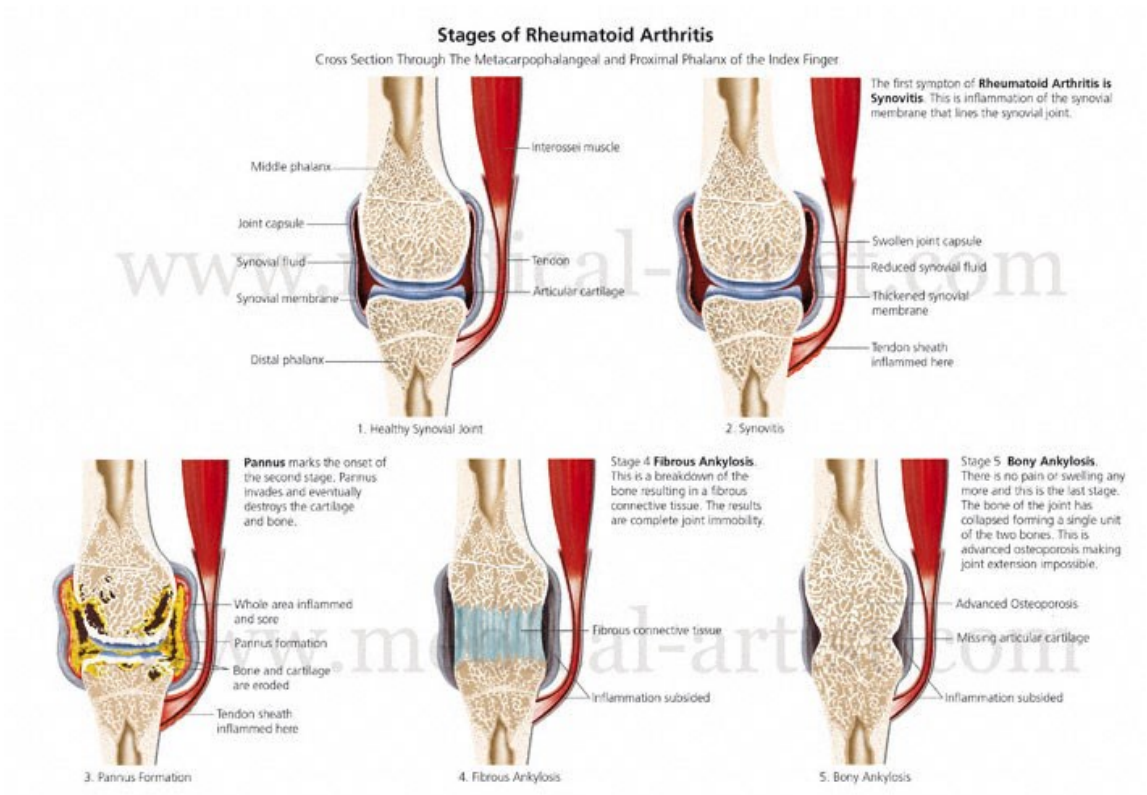
Parameter	Male ($n = 40$)	Female ($n = 2$)	Total ($n = 60$
Age (years)	53.72 ± 13.39	49.28 ± 10.29	50.09 ± 10.98
Height (cm)	169.12[a] ± 8.04	156.96[b] ± 7.65	159.22 ± 9.03
Weight (kg)	83.7[a] ± 14.12	74.49[b] ± 15.45	76.25 ± 15.56
BMI (kg/m^2)	29.35 ± 4.18	30.31 ± 6.69	30.13 ± 6.29
WBC (×1000/µL)	7.7 ± 2.5	7.16 ± 2.5	7.26 ± 2.5
Hb (g/dL)	12.79 ± 1.89	11.66 ± 1.46	11.87 ± 1.6
PLT (×1000/µL)	276.79 ± 74.07	319.07 ± 98.95	311.04 ± 95.85
Vit.D (ng/mL)	17.46 ± 6.79	19.02 ± 8.7	18.73 ± 8.37
Ca (mmol/L)	2.32 ± 0.11	2.35 ± 0.85	2.35 ± 0.77
Phos (mmol/L)	1.31 ± 0.35	1.22 ± 0.32	1.23 ± 0.32
ALP (U/L)	124.12 ± 86.82	108.46 ± 66.84	111.55 ± 70.9
ESR (mm/hr)	48.27 ± 28.69	52.84 ± 23.1	52.02 ± 24.1
DAS28-ESR	3.72 ± 0.64	3.8 ± 0.92	3.79 ± 0.87

BMI: body mass index (18–25 kg/m2); WBC: white blood cells (4.5–11.0 ×1000/µL); Hb: hemoglobin (12.0–16.0 g/dL); PLT: platelets (130–400 ×1000/µL); Vit.D: vitamin D (sufficient >30 ng/mL), Ca: calcium (2.12–2.52 mmol/L); phosphorus (0.81–1.58 mmol/L); ALP: alkaline phosphatase (50–136 U/L); E SR: erythrocyte sedimentation rate (0–20 mm/hr);



METHODS

The objective of the study was to evaluate the relationship between vitamin D and RA, as well as the relationship between vitamin D and RA disease activity. After having the signed consent form from participants, health status, body weight, and height were collected and the body mass index (BMI: Kg/m2) was calculated. Then blood samples (about 6 mL) were taken from each patient. Serums were obtained by centrifuged blood samples and quickly frozen and stored at −70°C until biochemical indicators were measured. The serum level of vitamin D as 25-hydroxy-vitamin D [25(OH) D] was measured using chemiluminescent immunoassay technique. Vitamin D defined normal if serum level was ≥30 ng/mL (≥75 nmol/L) and defined insufficient and deficient if serum level was between 20 and 30 ng/mL (50–75 nmol/L) and less than 20 ng/mL (<50 nmol/L) [xi], respectively. Investigations including calcium (Ca: normal 2.12–2.52 mmol/L), phosphorus (Phos: normal 0.81–1.58 mmol/L), and alkaline phosphatase (ALP: normal 50–136 U/L) were done on ARCHITECT-ci16200 clinical chemistry analyzer instrument from Abbott Laboratories (Abbott Park, Illinois, USA). Erythrocyte sedimentation rate (ESR: normal 0–20 mm/hr) was measured by Westergren method. Hematology tests (complete blood count (CBC)) of white blood cells (WBC: normal 4.5–11.0 ×1000/µL), hemoglobin (Hb: 11–16 g/dL), and platelets (PLT: 130–400 ×1000/µL) were performed on COULTER GEN-S-SYSTEM-2 fully automated hematology analyzer instrument from Beckman coulter. Each parameter was completed according to a specific kit, and all previous instruments and methods were available at the laboratory & department of Medical Biochemistry, GGS Medical College, Faridkot.



STATISTICAL ANALYSIS

Statistical analysis was performed with SPSS software (Statistic Package for Social Sciences) version 20. Analysis of variance (ANOVA) test was used to compare significance between groups and post hoc test (least significance difference [LSD]) was used to compare significance within each variable. Pearson correlation was carried out to study the correlation between the parameters. Multinomial logistic regression was used to calculate odds ratio (OR) and its 95% confidence intervals (95% CI) between vitamin D and disease activity (dependent variable). Receiver operating characteristic (ROC) curves were used to determine the optimal vitamin D cutoff points for identifying disease activity. Youden index was used to determine the optimal cutoff points, as described by Akobeng [ii]. Value less than 0.05 was considered statistically significant.

RESULTS

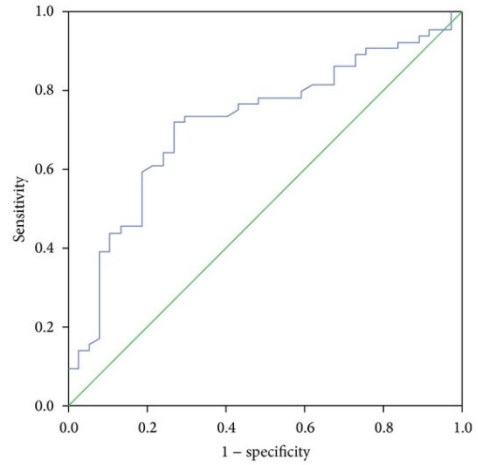
Among the study sample, vitamin D deficiency was detected in 39 patients (57.8%) (25(OH) D <20 ng/mL), while 21 patients (31.4%) had vitamin D insufficiency (25(OH) D 20–30 ng/mL), and only 11 patients (10.8%) had vitamin D sufficiency (25(OH) D value ≥30 ng/mL). Regarding healthy status of the participants, only 24 patients (23.5%) were medically free from any of the chronic diseases. Hypertension (, 27.5%) was the most reported chronic disease in studied sample. Other chronic diseases were shown in low percentages as hyperuricemia (8.8%), fatty liver (4.9%), and hepatitis B (2%) and peptic ulcer, psoriasis, hyperlipidemia, sickle cell anemia, and fibromyalgia were shown in less than 1%. Table 1 shows the baseline characteristics of the participants according to gender. The RA sample was mostly female (80.4%). The mean age of the whole sample was about 50 years and mean BMI for the whole study sample was 30.13 (kg/m2) indicating an obese sample. The mean vitamin D levels for male (17.46 ng/mL) and female (19.02 ng/mL) were within deficient category and no significant differences were found between them [ix]. Calcium, phosphorus, ALP, and CBC parameters all were observed at the normal ranges. The mean value of ESR showed to be greatly higher value than the normal range, and the mean score of DAS28-ESR for the entire sample was 3.79 providing a moderate disease activity group. Table 2 demonstrates the baseline characteristics of the participants according to the disease activity. About 16.7% of the participants were classified as high disease activity, and around 54.9% and 28.4% were classified as moderate and low disease activity, respectively. There were no significant differences among the three groups with regard to age, height, weight, BMI, CBC, calcium, and PLT. The mean value of vitamin D decreased significantly as disease activity increased, and high disease activity subjects were lower in their vitamin D as compared with the other two groups. However, the mean value of vitamin D level was 12.15 ng/mL in the high disease activity group, 20.63 ng/mL in the moderate disease activity group, and 23.41 ng/mL in the low disease activity group. Also, low disease activity group presented the lowest ESR and DAS28-ESR values. Phosphorus results exerted significant difference () among all groups, but no clear tread was observed between groups [vii, viii].

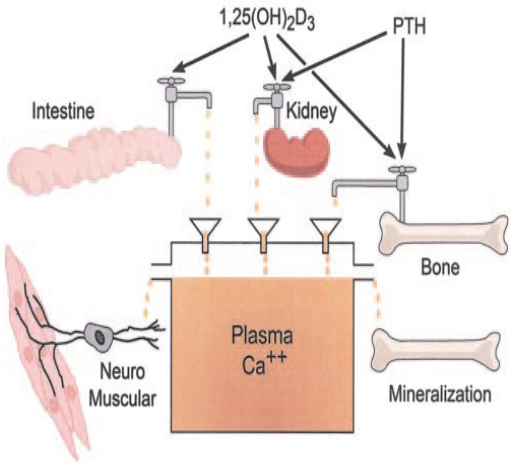
Table 2: Baseline characteristics of the participants according to the DAS28-ESR disease activity.

Parameter	High activity (n = 17)	Moderate activity (n = 56	Low activity (n = 29	P value
Age (years)	49.51 ± 5.13	50.97 ± 11.62	49.66 ± 8.92	0.655
Height (cm)	158.41 ± 6.83	160.66 ± 8.36	158.59 ± 11.29	0.728
Weight (kg)	75.41 ± 8.45	78.19 ± 14.78	72.10 ± 18.3	0.373
BMI (kg/m^2)	30.51 ± 4.51	30.61 ± 5.51	29.32 ± 8.16	0.781
WBC (×1000/µL)	7.41 ± 4	7.23 ± 2.28	7.03 ± 2.37	0.691
Hb (g/dL)	12.01 ± 1.45	11.90 ± 1.80	12.00 ± 1.31	0.964
PLT (×1000/µL)	331.86 ± 194.32	321.44 ± 91.17	289.82 ± 78.99	0.279
Vit.D (ng/mL)	12.15^{b} ± 3.43	20.63^{a} ± 7.35	23.41^{a} ± 8.06	0.023
Ca (mmol/L)	2.33 ± 0.16	2.28 ± 0.22	2.22 ± 0.31	0.526
Phos (mmol/L)	1.16^{b} ± 0.28	1.30^{a} ± 0.3	1.22^{b} ± 0.19	0.014
ALP (U/L)	98.50 ± 27.03	119.86 ± 85.05	113.87 ± 54.97	0.641
ESR (mm/hr)	69.71^{a} ± 16.79	48.52^{ab} ± 25.1	38.65^{b} ± 19.9	0.01
DAS28-ESR	5.34^{a} ± 0.29	4.01^{b} ± 0.52	2.76^{c} ± 0.27	<0.001

BMI: body mass index (18–25 kg/m2); WBC: white blood cells (4.5–11.0 ×1000/µL); Hb: hemoglobin (12.0–16.0 g/dL); PLT: platelets (130–400 ×1000/µL); Vit.D: vitamin D (sufficient >30 ng/mL), Ca: calcium (2.12–2.52 mmol/L); Phos: phosphorus (0.81–1.58 mmol/L); ALP: alkaline phosphatase (50–136 U/L); ESR: erythrocyte sedimentation rate (0–20 mm/hr); DAS28-ESR: disease activity score in 28 joints using ESR.

Figure 3: ROC curve for identifying optimal vitamin D cutoff point in predicting high disease activity(ng/mL).

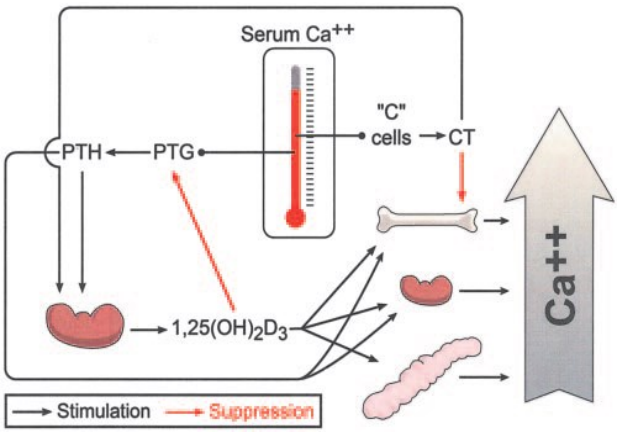




4. DISCUSSION

Vitamin D as 25(OH) D was used in this study to determine the status of vitamin D because serum prohormone 25(OH) D with a half-life of 2 to 3 weeks was the best indicator of reflecting overall vitamin D status, since the half-life of 1, 25-di-hydroxy-vitamin D [1,25(OH)2D] is only 3 to 4 hours, as reported by Khan and Fabian [ii,iii]. Activity of the disease was defined based on the DAS28-ESR, which is extensively validated and superior in interpretation of RA disease activity [ii, i]. Study results showed that females were more susceptible to RA than males with ratio of about 4: 1. Tobón et al. [i] was in consistence with last result which reported that the female-to-male RA ratio is 3: 1, which could be related to differences in sex hormones. In addition, the fifth decade is the peak age for RA onset, which is a time of women hormonal alterations [ii, iv]. The relationship between vitamin D and RA was not totally recognized with inconsistent outcomes between researchers. Some case-control studies did not find differences in vitamin D status between RA patients and controls [v,vi,vii] and Feser et al. [ii,vi] and Craig et al. [ii,vii] investigations exerted that vitamin D had no effect on RA disease activity. Also, another cross-sectional study have found serum 1, 25(OH) 2D, but not 25(OH) D, to be inversely correlated with RA disease activity [ii, viii]. Low serum 25(OH) D was, however, associated with elevated RA disease activity in many researches [vi, vii]. Furthermore, the immunomodulatory effects of vitamin D could confirm this association [iv–vi].

Study results were in agreement with the existence of a relationship between vitamin D and RA disease activity by two effects: (1) vitamin D levels were lower () in patients with high disease activity, with a clear trend toward a continuous increasing in 25(OH) D level along with decreasing disease activity; (2) also there was a significant inverse correlation between serum 25(OH) D levels and disease activity as evaluated by DAS28-ESR. Similar findings were shown in Saudi Arabia in which a significant negative correlation between vitamin D and disease activity of RA patients was obtained 1. In addition, multinomial logistic regression indicated that vitamin D deficient patients have about 26 (OR = 26.28, 95% CI: 8.55–74.13,) and 9 (OR = 9.44, 95% CI: 2.62–30.92,) times higher risk of developing high disease activity (DAS28-ESR) than patients with normal and insufficient vitamin D status, respectively. All these effects determined that vitamin D is a good marker of disease activity. Blaney et al. [i, vii] was in line with the previous result to the effect that vitamin D could be used as clinical biomarker in RA disease. All published studies focused on finding the correlation between vitamin D and RA disease activity without determining the optimal cutoff points of vitamin D related to high or low disease activity. ROC curves (Figures 3 and 4) showed that the sensitivity (true positive) values in predicting high and low disease activity were 82.6% and 78.4%, respectively, which represents good results. Moreover, the AUC for both curves was more than 0.7 indicating good accuracy, since AUC between 0.7 and 0.9 represents moderate accuracy and more than 0.9 represents high accuracy [ii]. Therefore, vitamin D is a good indicator as a predictor of RA disease activity. The best cutoff points of vitamin D that maximizes sensitivity and specificity were 12.3 ng/mL (30.7 nmol/L) and 17.9 ng/mL (44.7 nmol/L) for high and low disease activity, respectively. These results demonstrate that as vitamin D in any Saudi RA patient was less than 12.3 ng/mL, it could be a strong predictor to have high disease activity. On the other hand, low disease activity could be predicted if vitamin D status was more than 17.9 ng/mL. . The study was limited by recruiting low male subjects, which limits us for having optimal vitamin D cutoff point by gender. We suggest further studies with large sample size to evaluate the predictive value of vitamin D with respect to gender as well as other disease activity measures as C-reactive protein.



SUMMARY & CONCLUSIONS

This study concluded that vitamin D is a good predictor of RA disease activity in. The corresponding values of vitamin D for high disease activity (DAS28: >5.1) and low disease activity (DAS28: ≤3.2) are ≤12.3 ng/mL and ≥17.9 ng/mL, respectively. Vitamin D is known to induce immunologic tolerance [Weiss, 2011]. Thus, vitamin D deficiency may perturb immune tolerance and induce the development of autoimmune diseases, such as RA. Vitamin D has immunomodulatory properties, acting on the immune system both in an endocrine and in a paracrine manner [Hewison, 2012; Mora et al. 2008]. It appears to regulate the immune response by a variety of mechanisms, such as decreasing antigen presentation [Bartels et al. 2010], inhibiting the proinflammatory T helper type 1 profile [Jirapongsananuruk et al. 2000] and inducing regulatory T cells [Correale et al. 2009]. 1, 25(OH) 2D3suppresses proliferation and immunoglobulin production and retards differentiation of B-cell precursors into plasma cells [Chen et al. 2007]. These data support a role for vitamin D deficiency in the development and progression of autoimmune inflammatory conditions in general and in particular RA. Earlier data from animal models indicate that the 1, 25(OH) 2D3 metabolite and its analogues may suppress collagen-induced arthritis [Larsson et al. 1998]. Other data suggest that vitamin D receptor agonists may also prevent and suppress established collagen-induced arthritis [Adorini, 2005]. Having said that, however, there are data showing that vitamin D may be negatively affected in acute response, that is, its levels may decrease in the setting of inflammation, such as in active RA [Galloway et al. 2000]. Despite that, treatment with rituximab in RA did not affect vitamin D levels, although it decreased indices of inflammation [Hasan et al. 2012]. Supplementation with vitamin D has been proposed as a means to induce immune tolerance and thus prevent the development of autoimmune diseases [Weiss, 2011]. Recently, the combination of antirheumatic drugs with vitamin D has been suggested for RA [Kim et al. 2012]. Patients with RA are prone to osteoporosis [Deal, 2012] and suffer from pain when the disease is in flare. Vitamin D supplementation has been proposed for patients with RA for the prevention and treatment of osteoporosis as well as for its possible effects on disease activity [Varenna et al. 2012]. In conclusion, it appears that vitamin D deficiency is highly prevalent in patients with RA, and that vitamin D deficiency may be linked to disease severity in RA. As vitamin D deficiency has been linked to diffuse musculoskeletal pain, these results have therapeutic implications. Vitamin D supplementation may be needed for the prevention of osteoporosis and for pain relief in patients with RA.

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