Vitamin D and rheumatoid arthritis

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Abstract

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.

Methods: In a cohort of 44 patients with RA, 25-hydroxyvitamin D_3 [25(OH)D_3] levels, parathyroid hormone levels, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured. Disease activity was evaluated by calculating the 28-joint Disease Activity Score (DAS28). A control group (n = 44), matched for age and sex, was evaluated as well.

Results: In the cohort of 44 patients with RA 25(OH)D_3 levels were found to be low compared with the control group, 25(OH)D_3 being 15.26 ± 1.07 ng/ml [mean ± standard error of the mean (SEM)] and 25.8 ± 1.6 ng/ml in the patient and control group respectively (Student's t test, $p < 0.001$). Parathyroid hormone levels were 71.08 ± 7.02 pg/ml (mean ± SEM) (normal values 10.0–65.0 pg/ml), CRP 7.6 ± 1.57 mg/litre (mean ± SEM) (normal values < 3 mg/litre) and ESR was 38.0 ± 4.6 mm/h (mean ± SEM) in the group of patients with RA. Levels of 25(OH)D_3 were found to be negatively correlated to the DAS28, the correlation coefficient being –0.084. Levels of 25(OH)D_3 were also found to be negatively correlated to CRP and ESR, the correlation coefficient being –0.115 and –0.18, respectively.

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 both for the prevention of osteoporosis as well as for pain relief in patients with RA.

Keywords: disease activity, rheumatoid arthritis, vitamin D

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

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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].

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.

Methods

The study cohort consisted of 44 patients with RA. The patients entered the study as they came for evaluation at the Rheumatology Department's outpatient clinic. All patients fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism RA classification criteria [Aletaha *et al*. 2010]. A control group ($n = 44$), matched for age and sex, was evaluated as well. In the cohort of 44 patients with RA, 25-hydroxyvitamin D_3 [$25(OH)D_3$] levels, parathyroid hormone levels, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured. Disease activity was evaluated by calculating the 28-joint Disease Activity Score (DAS28). Additionally, the Health Assessment Questionnaire (HAQ) index and the visual analogue scale (VAS) pain score were calculated.

$25(OH)D_3$ levels were measured by radioimmunoassay using a two-step procedure. The first step involved a rapid extraction of 25(OH)D and other hydroxylated metabolites from serum or plasma with acetonitrile. Following extraction, the treated samples were then assayed by competitive, radioimmunoassay (RIA) using an antibody with specificity to 25OHD. The sample, antibody and tracer were incubated for 90 min at 20–25°C. Phase separation was accomplished after 20 min incubation at 20–25°C with a second antibody precipitating complex. To reduce nonspecific binding, buffer was added after this incubation prior to centrifugation. The final measurement was performed by a gamma counter manufactured by Packard. The sensitivity of the assay was less than 1.6 ng/ml. The recovery was approximately 100% for $25(OH)D_3$. Within and between batch precision was less than 12% and less than 11%, respectively.

Parathyroid hormone was measured by a solid phase two-site immunoradiometric assay, with a sensitivity of 0.7 pg/ml and within assay and between assay coefficient of variation of 7.5% and 6.8% respectively at 5.7 pg/ml.

All patients had a full clinical and laboratory evaluation. The DAS28 score was calculated for all patients. In addition, the HAQ disability index and the VAS pain score were calculated.

Statistical analysis was performed using the statistical package SPSS19. Student's *t*-test was used to compare the patient group with the control group. Regression analysis was performed to analyze the relationship between indices of disease activity and $25(OH)D_3$ levels.

Results

In the cohort of 44 patients with RA $25(OH)D_3$ levels were found to be low compared with the control group, $25(OH)D_3$ being 15.26 ± 1.07 ng/ml [mean ± standard error of the mean (SEM)], range 7.00–44.8 ng/ml and 25.8±1.6 ng/ml, range 6.8–80.0 ng/ml in the patient and control group respectively (Student's *t*-test, $p < 0.001$) (Figure 1).

Parathyroid hormone levels were 71.08 ± 7.02 pg/ml (mean ± SEM) (normal values 10.0–65.0 pg/ml), CRP 7.6 ± 1.57 mg/litre (normal values < 3 mg/litre) and ESR 38.0 ± 4.6 mm/h in the group of patients with RA. The DAS28 index was 4.26 ± 0.26 in this group.

Levels of $25(OH)D_3$ were found to be negatively correlated to the DAS28 score, the correlation coefficient being –0.084, r being 0.084 (Figure 2). Levels of $25(OH)D_3$ were also found to be negatively correlated to CRP (Figure 3) and ESR (Figure 4), the correlation coefficient being –0.115 and −0.18 and r being 0.115 and 0.18, respectively.

Discussion

In the present study vitamin D levels were found to be low in a group of patients with RA. Vitamin D levels were found to be negatively correlated with disease activity in RA.

Vitamin D levels have been studied in RA. Vitamin D deficiency may be associated with an increased risk for the development of RA. The Iowa

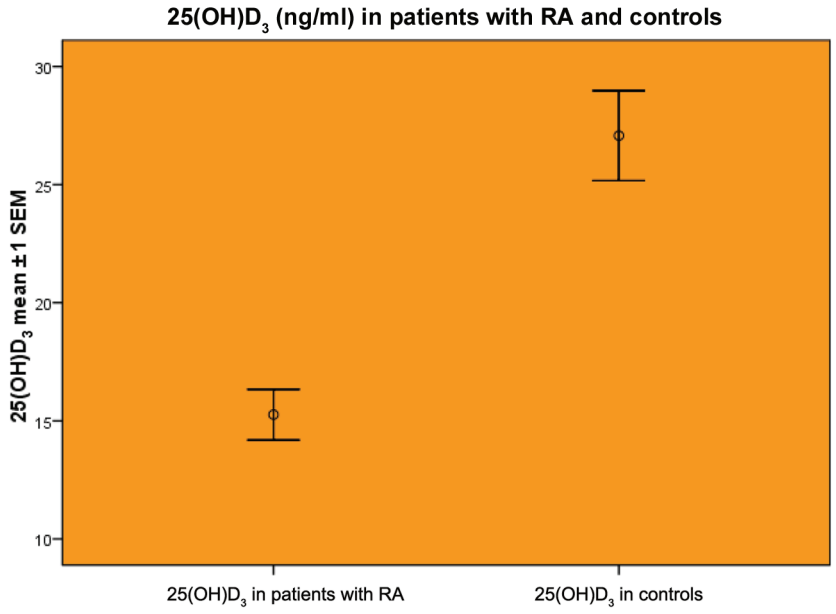

Figure 1. 25-Hydroxyvitamin D_3 [25(OH)D_3] levels [ng/ml, mean ± standard error of the mean (SEM)] in the group of patients with rheumatoid arthritis (RA) and in controls.

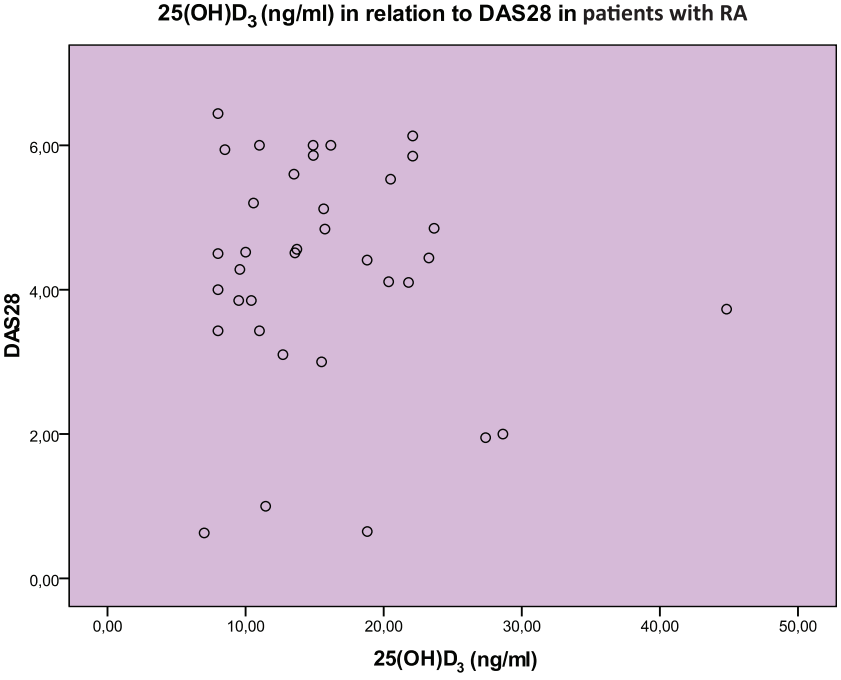

Figure 2. Scatterplot of 25-hydroxyvitamin D_3 [25(OH)D_3] in relation to the 28-joint Disease Activity Score (DAS28) index in the group of patients with rheumatoid arthritis (RA).

Women's Health Study by Merlino and colleagues analyzed data from a prospective cohort study of 29,368 women aged 55–69 years [Merlino *et al.* 2004]. Merlino and colleagues found that greater intake of vitamin D might be associated with a lower risk of RA. Through 11 years of follow up, 152 cases of RA were reported. Greater intake of vitamin D was found to be inversely associated with risk of RA. Inverse associations were apparent for both dietary and supplemental vitamin D. In contrast, in two cohort studies conducted by Costenbader and colleagues vitamin D intake was not found to be associated with the risk of RA [Costenbader *et al.*

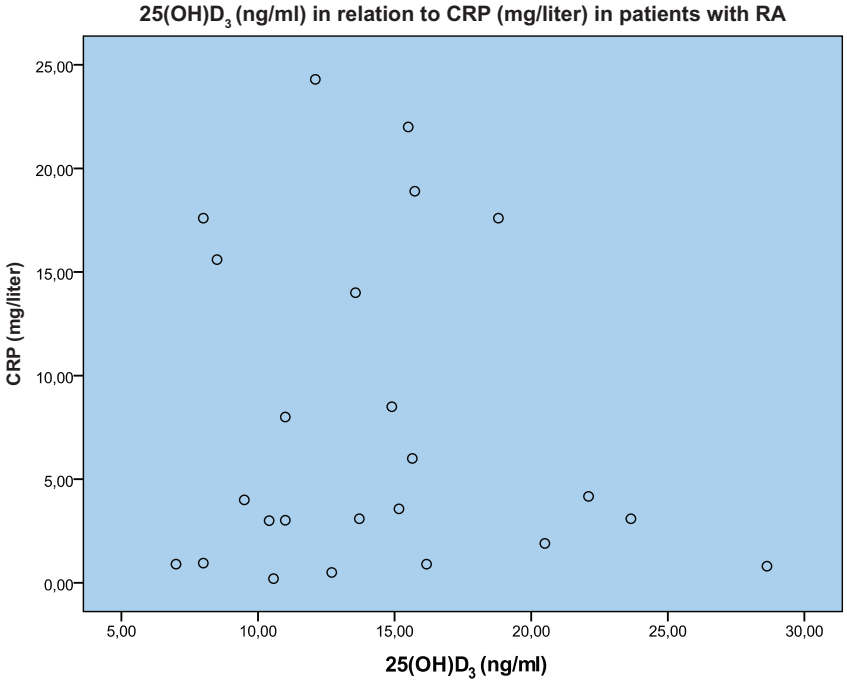

Figure 3. Scatterplot of 25-hydroxyvitamin D_3 [25(OH)D_3] (ng/ml) in relation to C-reactive protein (CRP) (mg/litre) in the group of patients with rheumatoid arthritis (RA).

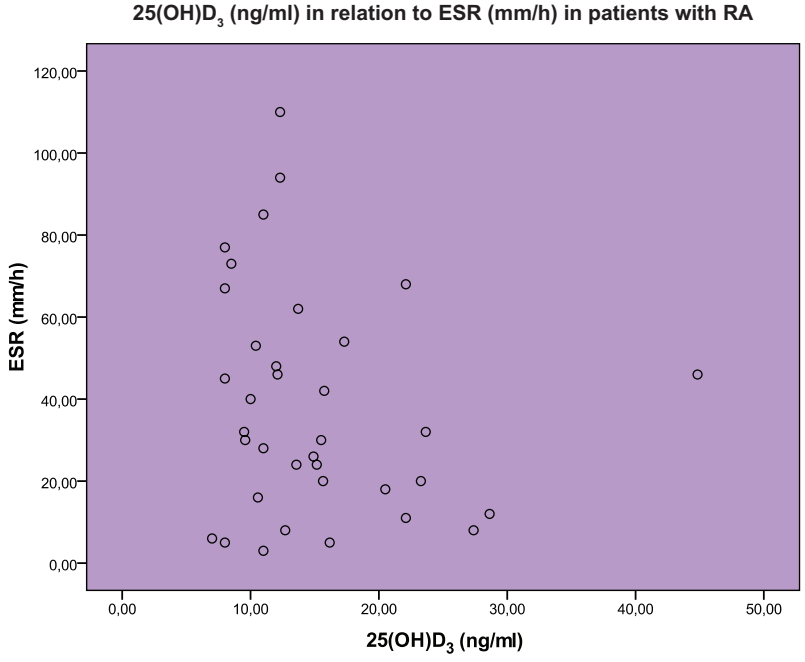

Figure 4. Scatterplot of 25-hydroxyvitamin D_3 [25(OH)D_3] in relation to erythrocyte sedimentation rate (ESR) (mm/h) in the group of patients with rheumatoid arthritis (RA).

2008]. The first cohort included 91,739 women followed from 1980 to 2002 in the Nurses' Health Study, and the second included 94,650 women followed from 1991 to 2001 in the Nurses' Health Study II. They observed no associations between cumulative average vitamin D intake and the risk of RA. In a meta-analysis of studies assessing the association between vitamin D intake and the risk

of RA Song and colleagues showed an association between vitamin D intake and RA incidence without between study heterogeneity [Song *et al.* 2012]. The cohort studies considered included 215,757 participants and 874 cases of RA. Individuals in the highest group for total vitamin D intake were found to have a 24.2% lower risk of developing RA than those in the lowest group. Subgroup meta-analysis also showed a significant association between vitamin D supplement intake and RA incidence. By contrast, a recent study did not find an association between vitamin D intake and the risk of RA [Baker *et al.* 2012]. In the present study, lower levels of vitamin D compared with a control group were observed in a cohort of patients with RA.

In the present study an inverse association was observed between vitamin D levels and RA disease activity. Several studies have evaluated the association between vitamin D levels and RA activity. In a study involving 1191 patients with RA and 1019 controls, Rossini and colleagues found an inverse association between vitamin D levels and disease activity in RA [Rossini *et al.* 2010]. Welsh and colleagues and Kerr and colleagues found that vitamin D deficiency is linked with disease activity in RA [Welsh *et al.* 2011; Kerr *et al.* 2011]. Also Cutolo and colleagues and Haque and Bartlett found an inverse relationship between vitamin D levels and disease activity in RA [Cutolo *et al.* 2006; Haque and Bartlett, 2010]. By contrast, others did not find a relationship between vitamin D deficiency and disease activity in RA [Craig *et al.* 2010; Braun-Moscovici *et al.* 2011; Baker *et al.* 2012]. In the study by Braun-Moscovici and colleagues they found no correlation between vitamin D levels and disease activity among 85 patients with RA [Braun-Moscovici *et al.* 2011]. However, overall, their subjects had high disease activity and low 25(OH)D_3 levels, accounting for a high vitamin D deficiency rate, which might have influenced the study outcome and the lack of correlation with disease activity. Given the increased risk for the development of cardiovascular disease in RA, Haque and colleagues further investigated the matter and found an association of vitamin D deficiency with cardiometabolic risk factors in RA [Haque *et al.* 2012].

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$(OH)_2D_3$ suppresses 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$(OH)_2D_3$ 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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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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