Original article

Does vitamin D affect disease severity in patients with ankylosing spondylitis?

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Keywords: *ankylosing spondylitis; 25(OH)D3; disease activity; functional status; quality of life*

Background Vitamin D has been found to have a role in the function of the immune system. There have been a lot of studies investigating a relation between vitamin D and disease activity in ankylosing spondylitis (AS). However, there have not been any studies arranging AS in groups according to vitamin D levels and determining any differences among these patients in terms of disease activity, functional status, quality of life, and other clinical parameters. The aim of this study is to compare 25-hydroxy-vitamin D3 (25(OH)D3) levels in AS patients with those in normal healthy subjects and to determine the relationship between 25(OH)D3 levels and AS disease activity, functional status, and quality of life.

Methods Ninety-nine consecutive patients and 42 healthy volunteers were included in this study. After a comparison between the patient group and the control group, the patient group was divided into normal, insufficient and deficient subgroups according to the plasma 25(OH)D3 levels for another comparison.

Results The differences in the 25(OH)D3 level between the patient and the control groups were statistically insignificant. The number of AS patients whose 25(OH)D3 levels were classified as normal, insufficient, and deficient were 34, 29, and 36, respectively. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and Bath AS Disease Activity Index (BASDAI) scores were higher in the low (including insufficient and deficient) 25(OH)D3 level subgroups (P <0.05). The Bath AS Functional Index (BASFI) and AS Quality of Life (ASQoL) scores were significantly different between the normal and the deficient subgroups (P <0.05). Pain, BASDAI, ESR, and CRP were inversely correlated to the 25(OH)D3 levels (P <0.05).

Conclusions The plasma 25(OH)D3 levels may decrease in AS patients and this may negatively affect disease activity, functional status and quality of life.

Chin Med J 2012;125(14):2511-2515

Until recently, the function of vitamin D has been considered to be confined to the areas of calcium, phosphorus, and bone metabolism,[1] but vitamin D has also been found to have a role in the function of the immune system.[2,3] For example, *in vitro* studies showed that vitamin D inhibits T-cell proliferation and decreases the production of Th1 cytokines interleukin-2 (IL-2), interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α).[4] Furthermore, *in vivo* studies suggested that vitamin D supplementation prevents the initiation and progression of inflammatory arthritis (collagen-induced arthritis) in rodents.[5] Rheumatoid arthritis was another example of an inflammatory arthritis that can be largely prevented by the administration of the vitamin D compounds.[6] As these findings suggest that vitamin D status may be important in the inception of disease, it is also reasonable to suggest that vitamin D may play an important role in disease activity as well. Supporting this suggestion, it was reported that there exists a relation between vitamin D and disease activity in patients with early inflammatory arthritis.[4]

Another disease which causes inflammatory arthritis is ankylosing spondylitis (AS), a chronic and systemic disease belonging to the spondylarthropathies group. Characteristically, AS involves the axial skeleton and the enthesis regions, although in some patients peripheral joints are also affected.[7] There have been a lot of studies investigating a relation between vitamin D and disease activity in AS. However, to our knowledge, there have not been any studies arranging AS patients in groups according to vitamin D levels and determining any differences among these groups in terms of disease activity, functional status, quality of life, and other clinical parameters.

The aim of this study is to find out whether the plasma 25-hydroxy-vitamin D3 (25(OH)D3) levels in AS patients are different from those in healthy individuals, and to compare disease activity, functional status, and quality of life among normal, insufficient and deficient subgroups of AS patients according to the plasma 25(OH)D3 levels.

DOI: 10.3760/cma.j.issn.0366-6999.2012.14.021
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METHODS

Subjects

Ninety-nine consecutive patients diagnosed with AS according to the 1984 Modified New York Criteria,[8] and 42 healthy individuals serving as controls without any diseases were included in the study. The study was approved by the local ethical committee and was carried out in accordance with the principles in the Declaration of Helsinki. Each participant provided a written informed consent to participate in this study.

Methods

This study was designed as a cross-sectional, controlled, clinical trial. Following a comparison between the patient and the control groups, we divided the patient group into three subgroups (normal, insufficient and deficient) according to the plasma 25(OH)D3 levels, and made comparison with clinical parameters. The plasma 25(OH)D3 level for normal was ≥30 ng/ml, deficiency was ≤20 ng/ml, and insufficiency was between 20.1–29.9 ng/ml.[9,10]

The plasma levels of 25(OH)D3 of patients and controls were assessed at the Department of Clinical Biochemistry. Samples were analyzed for their 25(OH)D3 contents according to a high-performance liquid chromatography (HPLC) method using the Shimadzu system (Deutschland GmbH, Duisburg, Germany).

1,25-dihydroxy-vitamin D (1,25(OH)D) is the biologically active form of vitamin D whose half-life is as short as 4 to 6 hours and whose circulatory level is 1000 times lower than that of 25(OH)D3, which is the storage form of vitamin D. As a consequence, 25(OH)D3 remains in the blood for a longer time, and it is more convenient to analyze the 25(OH)D3 content to calculate the plasma level of vitamin D.[11] Since vitamin D levels are sensitive to seasonal and altitude changes, biochemical analysis of the patients were performed for a short term (June–August), during which there is not too much seasonal change. For the same reason, individuals from outside the local area were not included in the study. The altitude where the individuals included in the study lived is about 900–1000 meters.

The following serum parameters were also measured: parathyroid hormone (PTH), alkaline phosphatase (ALP), serum calcium (Ca), phosphorus (P), and osteocalcin (OC). Additionally, erythrocyte sedimentation rate (ESR) was determined using the Westergreen method and C-reactive protein (CRP) was measured using the nephelometric method.

The patients were evaluated for both systemic and rheumatologic symptoms. They were screened for age, sex, weight, height and the durations of disease and morning stiffness. Subjective assessment of the pain and the health status, the patient's global assessment of disease activity (PGA) and medical doctor's global assessment of disease activity (MDGA), during the last month were recorded for each patient using a visual analogue scale (VAS). A 100 mm rating scale was used, with one end being 'no problem whatsoever' and the other end 'unbearable'. Patients were instructed to place a vertical mark on the scale reflecting their own health status. The distance from the 'no problem whatsoever' end was measured for each patient.[12]

Any patient with concomitant disorders, like serious infections or systemic diseases (such as cardiac, respiratory, gastrointestinal, neurological, endocrine, etc.) that could influence disease activity and biochemical analysis, was excluded from the study. All study subjects had been physically active for the previous 12 months. Patients and controls had no signs of renal insufficiency and did not take any vitamin D supplements during the study.

We used the Turkish version of Bath AS Disease Activity Index (BASDAI)[13] and Bath AS Functional Index (BASFI)[14] to determine the patients' disease activity and functional level, respectively. Finally, we assessed patients' mobility, quality of life, and fatigue with BASMI,[15] AS Quality of Life (ASQoL),[16] and Multidimensional Assessment of Fatigue (MAF)[17] scales, respectively.

Statistics

Statistical analysis was performed using version 16.0 of the Statistical Package for Social Science (SPSS, Chicago, IL, USA) for Windows. Whenever variables were normally distributed, as assessed using Saphiro-Wilk test, we performed parametric test statistics; such as Pearson correlation, or one-way analysis of variance (ANOVA). The post HOC Tukey's test was applied to results that were found to be significantly different. The Chi-square test was used for categorical variables. The data were expressed as the mean ± standard deviation for continuous variables and as frequency (in counts) for categorical variables. All *P* values of less than 0.05 were considered to indicate statistical significance.

RESULTS

Patients and controls

Demographic characteristics and laboratory results of the patient and control groups are presented in Table 1. The mean age of the patients was (36.8±10.5) years (84 males and 15 females with an age range of 20–65 years), and that of the controls was (36.0±7.3) years (33 males and 9 females with an age range of 22–57 years). As well as age, there were no significant differences between patient and control groups in height, weight, and sexual composition. From the results of our experiments we observed that the average plasma 25(OH)D3 level in the

Table 1. Demographic characteristics and laboratory results of patients with ankylosing spondylitis and healthy controls

Indices	Ankylosing spondylitis (n= 99)	Control (n= 42)	P values
Age (years)	36.8±10.8 (20–65)	36.1±7.2	0.415
Sex (M/F)	84/15	33/9	0.204*
Weight (kg)	71.9±13.2 (52–110)	70.7±11.3	0.612
Height (cm)	167.8±13.7 (67–190)	170.3±6.6	0.270
25(OH)D3 (ng/ml)	26.8±11.7	31.1±15.5	0.073
PTH (pg/ml)	34.5±18.0	30.1±13.5	0.172
ALP (U/L)	88.2±44.6	78.1±27.1	0.180
Serum Ca (mg/dl)	9.75±0.5	9.5±0.7	0.297
P (mg/dl)	3.3±0.7	3.51±0.5	0.149
OC (ng/ml)	6.9±3.8	7.0±2.9	0.965
Urine Ca (mg/dl)	14.3±6.8	14.9±8.2	0.702
ESR (mm/h)	39.1±28.5	7.5±6.3	< 0.001
CRP (mg/dl)	21.3±25.5	4.1±2.0	< 0.001

*Chi-square test.

patient group was insignificantly lower than the control group. Moreover, there were no significant differences in the plasma PTH, ALP, Ca, P, OC, and urine Ca excretion between patient and control groups.

Patient subgroups according to the plasma 25(OH)D3 levels

The demographic, laboratory and clinical parameters of the patients who were assigned to the three subgroups depending on their plasma 25(OH)D3 levels are summarized in Table 2. The plasma 25(OH)D3 levels were detected as normal, insufficient and deficient in 34, 36 and 29 patients, respectively. There was no significant difference among patient subgroups in age, body weight and height, sex, disease duration, pain, PGA, MDGA scores and bone turnover markers.

While there were no statistically significant differences in ALP, Ca, P, OC and PTH levels and PDA, MDGA, pain, BASMI results; ESR, CRP, and BASDAI scores were found to be higher in the low 25(OH)D3-level subgroups (P <0.05). Another significant difference was detected between normal and deficient subgroups (P <0.05) in the BASFI, MAF and, ASQoL scores. Moreover, in correlation analysis, serum levels of 25(OH)D3 were inversely associated with markers of disease activity and severity, such as ESR, CRP, pain, PGA, BASDAI, BASFI and MAF (P <0.05) (Table 3).

DISCUSSION

In recent years, there has been an effort to understand possible non-calcemic roles of vitamin D, such as its role in the immune system, cardiovascular diseases, cancers

Table 2. Demographic, clinic and laboratory characteristics of patients with ankylosing spondylitis according to the plasma 25(OH)D3 level

Indices	Normal (n=34)	Insufficiency (n=36)	Deficiency (n=29)	P values*
Age (years)	38.7±12.6	37.5±9.2	33.6±10.1	0.165
Weight (kg)	71.1±12	74.7±13.4	69.2±14.1	0.232
Height (cm)	167.0±19.7	170.3±8.8	165.5±9.1	0.336
Disease duration (months)	147.3±121.9	130.0±111.3	95.2±73.9	0.150
PTH (pg/ml)	33.2±16.5	33.6±21.2	36.7±16.2	0.737
ALP (U/L)	79.7±44.0	96.6±45.1	86.2±44.3 (27–167)	0.301
Serum Ca (mg/dl)	10.0±0.4	9.7±0.5	9.4±0.7 (8–10.5)	0.177
P (mg/dl)	3.6±0.5	3.2±0.7	3.3±0.7 (2.3–4.6)	0.077
OC (ng/ml)	6.7±3.2	7.1±3.8	7.1±4.5 (0.9–19.3)	0.928
Urine Ca (mg/dl)	15.7±6.7	13.4±6.3	13.7±7.5 (2.4–31.2)	0.423
ESR (mm/h)	28.6±20.7	37.0±27.0	53.3±32.6 (4–120)	0.002
CRP (mg/dl)	10.9±8.6	19.6±22.4	35.2±34.8 (3.2–133)	0.001
PGA VAS	39.7±20.9	44.6±27.1	51.7±22.2 (0–90)	0.308
MDGA VAS	39.4±22.2	44.4±25.5	47.2±19.4 (0–80)	0.142
Pain VAS	42.5±23.4	47.2±28.9	51.7±24.5 (0–100)	0.383
BASDAI	3.5±1.7	3.6±2.2	4.97±2.5 (0–8.4)	0.014
BASFI	3.2±2.4	3.4±2.6	4.8±3.1 (0–9.1)	0.039
BASMI	3.5±2.6	3.2±2.8	3.8±3 (0–9)	0.743
ASQL	7.9±5.7	9.2±5.8	11.6±6.2 (0–18)	0.045
MAF	24.3±13.6	29.7±13.4	32.1±10.7 (0–50)	0.025

*ANOVA test. P <0.05 different from the other two groups by ANOVA.

Table 3. The association of 25(OH)D3 and bone turnover markers with clinical parameters (n=99)

Indices	25 (OH)D3		PTH		ALP		Serum Ca		P		OC		Urine Ca	
	r	P	r	P	r	P	r	P	r	P	r	P	r	P
ESR (mm/h)	–0.366†	<0.001	–0.195	0.083	0.155	0.138	–0.158	0.149	0.110	0.336	–0.158	0.166	0.049	0.671
CRP (mg/dl)	–0.344†	<0.001	–0.070	0.445	0.051	0.555	–0.004	0.965	0.054	0.560	–0.076	0.436	0.042	0.665
Disease duration (years)	0.157	0.121	0.113	0.315	–0.029	0.785	–0.142	0.195	–0.139	0.221	–0.041	0.717	–0.202	0.074
Pain VAS	–0.215*	0.033	0.149	0.183	–0.134	0.199	–0.197	0.071	0.172	0.129	–0.204	0.071	–0.130	0.254
PGA VAS	–0.278†	0.005	0.133	0.238	–0.187	0.072	–0.201	0.065	0.187	0.099	–0.179	0.114	–0.131	0.251
MDGA VAS	–0.196	0.052	0.115	0.307	–0.129	0.216	–0.215*	0.048	0.122	0.284	–0.178	0.116	–0.102	0.373
BASDAI	–0.304†	0.002	0.083	0.460	–0.009	0.935	–0.118	0.282	0.205	0.070	–0.126	0.267	0.002	0.988
BASFI	–0.266†	0.008	0.227*	0.041	–0.053	0.613	–0.158	0.149	0.023	0.840	–0.066	0.563	–0.022	0.846
BASMI	–0.041	0.695	0.131	0.263	0.005	0.960	–0.235*	0.036	–0.315†	0.006	–0.015	0.895	–0.111	0.345
ASQL	–0.179	0.077	0.139	0.217	–0.080	0.447	–0.173	0.113	0.061	0.591	–0.153	0.178	–0.070	0.118
MAF	–0.344†	<0.001	–0.041	0.720	0.002	0.988	–0.195	0.074	0.232*	0.040	–0.191	0.092	–0.301	0.488

*P <0.05, †P <0.01. r: Pearson correlation coefficient.

and musculoskeletal pain. In such studies, the effects of vitamin D insufficiency on etiopathogenesis, activity and severity of diseases have been investigated.[18-20] In our study, we aimed to find out whether the plasma 25(OH)D3 levels in AS patients was in general different than that in healthy controls. Moreover, we compared disease activity, functional status, quality of life, and fatigue results among normal, insufficient and deficient subgroups of the patient group. Even though the 25(OH)D3 levels were found to be lower in the patients with AS, this difference was insignificant. The 25(OH)D3 levels were below the normal level (26.78 ng/ml on average) in patients with AS, whereas it was normal but close to the lower boundary of the normal level (31.10 ng/ml) in the healthy controls. We concluded that the small difference in vitamin D levels between the patient group and the healthy group might indicate the existence of vitamin D insufficiency in the common population. As a supporting fact, the east part of Turkey is known have endemic vitamin D insufficiency.[21] It is estimated that approximately one billion people worldwide have blood concentrations of vitamin D that are considered suboptimal.[10]

The results of published studies relating vitamin D to AS vary and that may lead to controversy. In a recent study, the 25(OH)D3 level was found to be significantly lower in patients with AS than in healthy patients.[7] In another study no such difference was observed.[22] Whereas, in a third study it was reported that both the plasma 25(OH)D3 and 1,25(OH)D3 levels were significantly higher in both male and female patients with AS.[23]

In our study we conducted a comparison among the patients by classifying them in subgroups as normal, insufficient, and deficient, according to the plasma 25(OH)D3 levels. In this comparison, we aimed to find out whether there were differences in disease activity and severity, and other clinical parameters among those subgroups. ESR, CRP levels and BASDAI scores were higher in the subgroups with low 25(OH)D3 levels. It was concluded, then, that the severity of the inflammatory process may increase with the lack of vitamin D. In one study, ESR and CRP were found to be significantly higher when vitamin D levels were lower.[24] It was observed in another study that Ca, P, OC, and ALP levels in patients with AS were similar to those in healthy individuals, and that there was no relation between disease activity and bone turnover markers.[25] Similarly, in our study, PTH, ALP, Ca, P, OC and urine Ca excretion were similar in all patient subgroups. Moreover, we did not observe any correlation between bone turnover markers and clinical parameters. However, we observed that ESR, CRP, BASDAI, MAF, pain, PGA were correlated with the plasma 25(OH)D3 level. Similar to our results, Lange et al found a correlation between 1,25(OH)D3 and BASDAI, CRP, and ESR in two different studies.[22,24] These facts support the possibility that vitamin D may be an important factor in AS pathogenesis.

TNF-α has an important role in chronic inflammatory events and high levels of plasma TNF-α have been demonstrated in patients with active AS[26] and TNF-α has been suggested to down-regulate the 24-hydroxylase activity in the vitamin D system in the kidney.[27] The absorption disturbance, which is caused by the intestinal vitamin D receptor defect observed in AS, may cause a decrease in vitamin D level.[28] Immobilization and functional disability, which prevent the patients from sunlight exposure, may be other possible causes for the decrease in vitamin D level in AS patients.

The relation of vitamin D with functional disability and quality of life in AS patients has not been previously investigated. In our study, the BASFI, ASQoL, and MAF scales, which are used to evaluate the functional status, quality of life, and fatigue in AS, showed a significant difference between the normal and deficient subgroups. These findings showed that decreased vitamin D levels may lead to deterioration in functional capacity, quality of life, and fatigue in AS patients.

The main limitations of our study are the fact that it is a cross-sectional study, not investigating whether the increase in plasma 25(OH)D3 levels by vitamin D supplementation causes changes in disease activity and other clinical parameters. We also did not take into consideration other bone turnover markers such as pyridinoline, N-telopeptide and bone specific ALP. Bone mineral density was not taken into account in this study since it reflects bone loss that has existed for a long time.

The plasma vitamin D levels can decrease in AS patients due to both nutritional deficiency and inadequate exposure to sunlight, or for etiopathogenetic reasons. They also led us to the conslusion that insufficiency of vitamin D may cause increased disease activity and fatigue, and decreased functional capacity and quality of life. However, because of some contradictory findings with previous studies, there is need for more investigation dealing with this issue.

In conclusion, our findings suggested that the plasma 25(OH)D3 level may be lower in AS patients and this may have negative effects on disease activity, functional status, quality of life, and fatigue in AS patients.

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(Received July 28, 2011)
Edited by HAO Xiu-yuan