Seasonal disease activity and serum vitamin D levels in rheumatoid arthritis, ankylosing spondylitis and osteoarthritis

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Abstract

Background: Vitamin D is a steroid hormone that plays essential roles in calcium and phosphorus metabolism, bone formation and mineralization homeostasis, also has a role in the maintenance of immune-homeostasis.

Objective: We aimed to investigate seasonal serum vitamin D levels and seasonal disease activity in patients with Rheumatoid Arthritis, Ankylosing Spondylitis, and Osteoarthritis.

Methods: Seventy-one Rheumatoid Arthritis patients, 72 Ankylosing Spondylitis patients, 74 knee Osteoarthritis patients and 70 healthy controls were recruited for the study. Bi-seasonal measurements of serum 25(OH)D vitamin were checked in either in July or August or September for summertime and either in December or January or February for wintertime. Disease activity were evaluated by Disease Activity Score-28, Bath Ankylosing Spondylitis Disease Activity Index, and Western Ontario and McMaster Universities Osteoarthritis Index in groups of Rheumatoid Arthritis, Ankylosing Spondylitis, and Osteoarthritis respectively.

Results: We did not find any correlation between serum 25(OH)D levels and Disease Activity Score-28, Bath Ankylosing Spondylitis Disease Activity Index, and Western Ontario and McMaster Universities Osteoarthritis Index scores in winter and summer. The difference of Disease Activity Score-28 and Western Ontario and McMaster Universities Osteoarthritis Index scores between winter and summer seasons were not significant in Rheumatoid Arthritis and Osteoarthritis patients ($p>0.05$). The mean Bath Ankylosing Spondylitis Disease Activity Index score was significantly higher in winter than in summer ($p<0.05$). Consequently we did not find any correlation between variations of seasonal serum 25(OH)D and the disease activity in the patients with Rheumatoid Arthritis, Ankylosing Spondylitis, and Osteoarthritis.

Conclusion: These results suggest that vitamin D does not have an important role in the seasonal disease activity of these diseases and that seasonal changes in disease activity may play an important role in evaluating Ankylosing Spondylitis patients rather than Rheumatoid Arthritis and Osteoarthritis patients and should be taken into account when examining these patients. These conclusions need to be validated in multicenter studies with high number of patients.

Key words: ankylosing spondylitis, disease activity, osteoarthritis, rheumatoid arthritis, season, vitamin D

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Introduction

Vitamin D is a steroid hormone that plays essential roles in calcium and phosphorus metabolism, bone formation and mineralization homeostasis, also has a role in the maintenance of immune-homeostasis. The immune-regulatory role of vitamin D affects both the innate and adaptive immune system cells contributing to the immune-tolerance of self-structures[1,2]. Vitamin D can inhibit the synthesis of mRNA of macrophages-derived cytokines such as interleukin (IL)-1, IL-6, IL-12 and tumor necrosis factor alpha (TNF-alpha), decrease the antigen-presenting activity of macrophages to lymphocytes and suppress the IL-2 secretion of Th1 cells[3,4,5,6].

The discovery of the vitamin D receptor (VDR) in antigen presenting cells, T and B cells, and the fact that activated dendritic cells produce the vitamin D hormone further suggest an immunoregulatory role of vitamin D[7]. The overall effect of 1,25-dihydroxyvitamin D [1,25(OH)2D] on immune system is immunosuppressive[8]. It has inhibitory effects on T cells, B cells and dendritic cells (DC). These suppressive immunologic properties have led to considering its role in autoimmune diseases such as rheumatoid arthritis, ankylosing spondylytis etc. Since the 1990s increasing number of findings support the idea that impaired vitamin D homeostasis contributes to autoimmune processes.

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Vitamin D may be acquired from three main sources: food, sun exposure, or dietary supplements. Sun exposure is necessary for humans to maintain adequate vitamin D levels. Factors related to vitamin D levels include ethnicity, body mass index (BMI), geography and seasonal factors, age and some drugs. In studies about geographic and seasonal factors, investigators found that in areas in latitudes below about 35° south or above 37° north there is prominent decrease in UVB incidence during winter days, increasing the risk of vitamin D deficiency (9). And also peak levels of vitamin D usually occurs in late summer, and nadir in the beginning of spring[10].

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune disorder of multifactorial etiology in which both genetic and nongenetic factors (i.e. infectious, hormonal, environmental) contribute to disease susceptibility. Symmetric polyarticular joint inflammation is the prominent finding in RA. Several studies reported contradictory results regarding correlation between disease activity and vitamin D levels in patients with RA[11,12,13]. There is no evidence for relationship between season and incidence of RA, but season may influence disease activity[14]. A recent large observational study reported higher RA disease activity in spring and lower activity in autumn[15].

Ankylosing spondylitis (AS) is a chronic, systemic disease that involves the axial skeleton, enthesis regions, and in some patients the peripheral joints[16]. Also, osteoporosis accompanies these characteristic features from the early stages of the disease. One of the factors that is effective on the development of osteoporosis in AS is vitamin D. Previous studies also demonstrated that the high disease activity was related with the alterations in vitamin D metabolism and increased bone resorption in patients with AS[17,18]. To our knowledge, there is only one study in the literature investigating seasonal disease activity and vitamin D status in patients with AS[19].

Osteoarthritis (OA), the most common cause of musculoskeletal disability, is characterized radiographically by loss of articular cartilage and changes in the bone surrounding the joint. Vitamin D influences bone quality as well as normal bone and cartilage metabolism depends on the presence of vitamin D. Low levels of serum vitamin D have been shown to associate with an increase in radiographic progression of Knee OA and to have adverse effects on articular cartilage turnover, osteoblastic activity, matrix ossification and bone density[20]

OA is traditionally considered to be an inherently noninflammatory disease, but in the disease course, chronic low-grade, persistent, clinically nonapparent inflammation is exist frequently secondary to the presence of calcium-containing crystals. Phagocytosis of these crystals by macrophages leads to the production of interleukin-1 (IL-1), an important mediator of cartilage breakdown in OA[21]. This also suggests us vitamin D status may affect OA disease activity and severity by means of inhibition of IL-1 secretion by macrophages[22,23].

To the best of our knowledge there isn't any study in the literature investigating seasonal vitamin D status and disease activity in patients with OA.

Taking into account the subjects mentioned above, the primary goal of the current trial was to determine seasonal disease activity in patients with RA, AS, and OA**;** the second goal was to investigate seasonal serum 25-hydroxyvitamin D levels in these patients and healthy controls and the correlation of which with the disease activity.

Methods

The study was conducted in Yuzuncu Yil University Medical Faculty Physical Medicine and Rehabilitation and Rheumatology departments, Van, Turkey. Geographical coordinates of the city are 38° 29' 39" North, 43° 22' 48" East. The altitude of the city is 1750 m. The study was funded by Yuzuncu Yil University Science Research Supporting Agency.

Patients

The study was designed as a prospective cohort and approved by the local ethical committee. Consecutive patients with rheumatic diseases followed at our clinic (university hospital, Physical Medicine-Rehabilitation and Rheumatology clinics) and, who agreed to participate in the study, were assessed. The diseases included were RA (diagnosed according to ACR classification criteria[24]. Ankylosing Spondylitis (AS) (diagnosed according to modified New York criteria[25] and Knee osteoarthritis (diagnosed according to ACR classification criteria[26] as well as healthy control subjects aged between 25-65 years old. The patients had to be on stable doses of DMARDs, anti-TNFalfa agents and calcium and vitamin D supplements for 3 months prior to their assessment. The patients were assessed twice both

in summer months (either in july, or august or september) and winter months (either in december or january or february).

Following criteria were used for exclusion; 1) Patients over 65 years old, 2) Patients with active liver disease or cirrhosis 3) Patients with renal failure or active renal disease 4) Patients with malignancy 5) Patients who had undergone hip or knee replacement 6) We also excluded patients with the diseases known to affect bone metabolism such as hyperthyroidism, hyperparathyroidism. In the first assessment in summer months, each group consisted of 100 voluntary participants (A total of 400 participants). All participants were invited to visit the clinic again in winter months for the second assessment. However, only 287 of 400 subjects participated in the second assessment in winter months. Twenty-nine patients from RA group, 28 patients from AS group, 26 patients from OA group and 30 subjects from healthy controls who did not visit our clinic for the second assessment were excluded from the study.

Assessment

Clinical assessment included collection of demographic data, disease duration, history of recurrent diarrhea, recent weight loss, medication history (DMARDs, anti-TNFa agents, calcium and vitamin D supplements), habits of sun exposure (10–30 min daily at noon, 30 min-1 hour, more than 1 hour or less than 5 min daily at noon,), visual analogue scale (VAS) of physician's and patient's assessment of pain, fatigue and disease activity, and physical examination including swollen and tender joint counts. Disease activity was assessed by erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), 28-joint Disease Activity Score (DAS28) and VAS for RA patients, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) for AS patients and WOMAC for OA patients[27,28,29].

Laboratory investigations included ESR (mm/h), CRP (IU/ml), serum levels of calcium (mg/dl), phosphor (mg/dl), 25-hydroxy vitamin D (25(OH)D) (ng/ml) and parathyroid hormone (PTH) (pg/ml). Serum 25 (OH) vitamin D levels were measured using the high-performance liquid chromatography (HPLC)-based Chromsystems diagnostic kit.

Statistycal analysis

While descriptive statistics for continuous variables were expressed as the mean, standard deviation, and categoric variables were expressed as number and percantages. To determine the differences in terms of continous variables among groups, one way analysis of variance (ANOVA) followed by Duncan's post hoc analysis was used for multiple comparisons between different groups. Paired student t test was used for continous variables to identify the differences between summer and winter assessments in each group. To assess the relationship between categoric variables, Chi-square test was used. Correlations between different continous variables were evaluated by Pearson rank correlation (r). Significance was set at a 2-tailed $P < 0.05$. Statistical analysis was performed using SPSS for Windows (version 13.0; SPSS, Chicago, IL, USA).

Results

287 of 400 subjects (71 patients with RA, 72 patients with AS patients, 74 patients with OA 70 healthy control individuals) completed the study. The demographic, clinical features of the groups are presented in table 1.

Table 1: Demographic features of the patients and healthy controls

Feature	RA group n=71	AS group n=72	OA group n=74	HC group n=70
Age (years)	45.30 ± 10.55^{a}	31.24 ± 8.72^{b}	48.70 ± 7.14^{c}	41.39 ± 4.21^{d}
Gender female/male	$49/22^{a}$	$17/55^{b}$	$50/24^{a}$	$26/44^{b}$
Body mass index (BMI) kg/m^2	27.65 ± 5.49^{a}	25.12 ± 4.30^{a}	30.89 ± 5.10^{b}	26.46 ± 3.84^{ab}

(Means which get different lower case express statistically significant difference $p<0.05$)

There were statistically significant differences between groups in terms of age, gender and body mass index (BMI) ($p<0.05$). The highest mean age was in OA group and the lowest was in AS group. Additionally OA group had the highest mean BMI while AS group had the lowest. And habits of daily sun exposure of the groups were presented in table 2.

Table 2: Habits of sun exposure of the patients and healthy controls

Groups	Daily sun exposure				Total n
	More than 1 hour (n)	30 min-1 hour (n)	10-30 min (n)	Less than 5 min (n)	
RA	2	12	56	1	71
AS	3	15	52	2	72
OA	2	17	54	1	74
HC	3	20	44	3	70
Total	10	64	206	7	287

There were no statistically significant differences in terms of habits of daily sun exposure between groups. The mean summer and winter 25(OH)D levels were 28.85, 29.99 ng/ml for RA group, 30.79, 29.57 ng/ml for AS group, 28.62, 28.05 ng/ml for OA group and 30.73, 29.82 ng/ml for HC group respectively. There were no statistically significant differences between groups in terms of seasonal vitamin –D levels (table 3). Additionally winter and summer vitamin-D levels were not markedly different in each group (table 3). Seasonal PTH, calcium, phosphorus levels were not significantly different between groups and in each grooup (table 3). The highest CRP levels were detected in RA group both in summer and winter. We did not detect significant differences between RA and AS groups in terms of CRP levels (table 3). However CRP levels were found significantly higher in RA and AS groups than in OA and HC groups both in summer and winter ($p<0,05$). The seasonal changes in CRP levels in RA, AS and OA groups were found statistically significant ($p<0.05$) (table 3). The mean ESR levels were found significantly higher in RA group both in summer and winter when compared with other groups ($p<0,05$) (table 3). The mean summer and winter ESR levels in AS and OA were statistically similar with each other and higher than that of HC group ($p<0,05$). The seasonal change in ESH level in OA group was found statistically significant ($p<0.05$) (table 3).

Table 3: Comparison of summer and winter levels of some laboratory parameters and 25-OH vitamin D levels of the groups

Parameters	Groups	Mean	St. Dev.	Parameters	Groups	Mean	St. Dev.
Calcium-Summer (mg/dl)	RA	9.38 a	0.46	**25-OH-D-vit-Summer(ng/ml)**	RA	28.85a	21.20
	AS	9.43 a	0.38		AS	30.79a	22.86
	OA	9.40 a	0.39		OA	28.62a	17.93
	HC	9.45 a	0.42		HC	30.73 a	18.53
Calcium-Winter (mg/dl)	RA	9.22 a	0.48	**25-OH-D-vit-Winter(ng/ml)**	RA	29.99a	22.69
	AS	9.35 a	0.38		AS	29.57a	30.47
	OA	9.27 a	0.36		OA	28.05 a	28.06
	HC	9.31 a	0.37		HC	29.82 a	19.19
Phosphorus-Summer(mg/dl)	RA	3.52 a	0.57	**CRP-Summer(IU/ml)**	RA	16.68 a	20.94
	AS	3.45 a	0.64		AS	12.93 a	14.41
	OA	3.71 a	0.51		OA	5.98 b	5.70
	HC	3.66 a	0.71		HC	3.42 b	1.06
Phosphorus-Winter (mg/dl)	RA	3.32 a	0.60	**CRP-Winter (IU/ml)**	RA	15.55 a	19.75
	AS	3.40 a	0.61		AS	15.35 a	19.13
	OA	3.58 a	0.60		OA	6.29 b	11.96
	HC	3.47 a	0.54		HC	3.27 b	0.59
PTH-Summer (pg/ml)	RA	53.07 a	25.51	**ESH-Summer (mm/h)**	RA	25.00 a	16.99
	AS	44.32 a	19.48		AS	15.53 b	14.45
	OA	62.43 a	24.07		OA	15.90 b	10.38
	HC	50.78 a	17.21		HC	7.82 c	6.62
PTH-Winter(pg/ml)	RA	52.21ab	30.59	**ESH-Winter (mm/h)**	RA	23.54 a	16.12
	AS	42.97 b	22.60		AS	16.66 b	13.66
	OA	62.05 a	24.87		OA	16.85 b	11.84
	HC	48.98 b	21.43		HC	7.69 c	7.65

(Means which get different lower case express statistically significant difference $p<0.05$)

The mean DAS28 was 4.01 in summer and 4.24 in winter for patients with RA (table 4). The mean summer and winter BASDAI scores were 2.62, 3.92 for patients with AS respectively and the mean summer and winter WOMAC scores were 8.87, 9.98 for patients with OA respectively (table 4). Winter disease activities scores were higher than that of summer in all disease groups. However, only the changes between summer and winter BASDAI scores in AS group were found significantly different ($p<0.05$) (table 4). Additionally patient evaluation of overall pain and fatigue by VAS was significantly higher in winter season in AS group ($p<0.05$) (table 4).

We did not find any statistically significant correlations between seasonal 25(OH)D and PTH levels (winter and summer) and disease activities in RA, AS and OA groups (table 5). But there were significant correlations between ESH, CRP levels and disease activity in RA both in summer and winter. Also winter ESH levels positively correlated with OA disease activity (table 5).

Table 4: Seasonal vitamin D levels (ng/ml) and disease activity of patients with RA, AS and OA

	RA Group (N=71)			AS group (N=72)			OA group (N=74)		
	Mean	St. Dev.	P	Mean	St. Dev.	P	Mean	St. Dev.	P
Serum. 25.OH. vitaminD. Summer	27.85	21.20	0.669	Serum. 25.OH. vitaminD. Summer	33.79	22.86	0.476	Serum. 25.OH. vitaminD. Summer	22.62	17.93	0.614
Serum. 25.OH. vitamin D Winter	29.99	22.69		Serum. 25.OH. vitamin D Winter	31.57	30.47		Serum. 25.OH. vitamin D	25.05	28.06	
VAS-Over all Pain-patient evaluation. Summer	39.73	32.83	0.412	VAS-Over all Pain-patient evaluation. Summer	33.91	29.43	0.003*	VAS-Over all Pain-patient evaluation. Summer	41.55	37.49	0.121
VAS-Overall Pain- patient evaluation. Winter	43.38	32.12		VAS-Overall Pain- patient evaluation. Winter	47.26	33.40		VAS-Overall Pain- patient evaluation. Winter	49.52	35.67	
VAS-Overall Pain- doctor evaluation. Summer	30.78	31.48	0.171	VAS-Overall Pain- doctor evaluation. Summer	22.46	24.97	0.007*	VAS-Overall Pain- doctor evaluation. Summer	28.10	28.20	0.029*
VAS-Overall Pain- doctor evaluation. Winter	36.95	30.10		VAS-Overall Pain- doctor evaluation. Winter	35.08	30.32		VAS-Overall Pain- doctor evaluation. Winter	37.62	30.55	
VAS- patient evaluation of Fatigue. Summer	49.64	37.80	0.180	VAS- patient evaluation of Fatigue. Summer	34.11	32.07	0.099	VAS- patient evaluation of Fatigue. Summer	41.52	36.89	0.382
VAS- patient evaluation of Fatigue. Winter	43.16	38.52		VAS- patient evaluation of Fatigue. Winter	41.86	32.67		VAS- patient evaluation of Fatigue. Winter	47.17	38.42	
DAS28 Summer	4.01	1.69	0.254	BASDAI Summer	2.62	1.89	0.004*	WOMAC Summer	8.87	6.42	0.235
DAS28 Winter	4.24	1.62		BASDAI Winter	3.92	2.08		WOMAC Winter	9.98	4.92	

* $p<0.05$

Table 5: Correlations between seasonal disease activities and Vit D (ng/ml), PTH (pg/ml), CRP (IU/ml) and ESH (mm/h) levels in patients with RA, AS and OA

	RA		AS		OA	
	DAS-28 Summer	DAS-28 Winter	BASDAI-Summer	BASDAI-Winter	WOMAC-Summer	WOMAC-Winter
Vit-D Summer	-0.099	------	-0.195	------	0.215	------
Vit-D Winter	------	0.067	------	0.047	------	0.145
PTH-Summer	-0.189	------	0.095	------	0.112	-------
PTH-Winter	------	0.039	------	0.163	------	0.054
CRP-Summer	0.453**	------	0.181	------	0.293	------
CRP- Winter	------	0.396**	------	0.157	------	0.035
ESH-Summer	0.534**	------	0.028	------	0.201	------
ESH- Winter	------	0.571**	------	0.224	------	0.379*

*p < 0.05, correlation significant at 0.05 level (two-tailed); **p<0.01, correlation significant at 0.01 level (two-tailed)

Discussion

It is clear that both genetic and environmental factors are related to autoimmune diseases. Therefore, the fact that vitamin D has immunregulatory effects and is related to autoimmunity suggests that vitamin D might be one of the environmental factor that among others normally participates in the control of selftolerance in autoimmune rheumatic diseases[7].

However there are many difficulties in establishing a strong relationship between vitamin D deficiency and disaese activity in rheumatologic disorders in humans. The rarity of the diseases makes it difficult to obtain large samples of subjects. There are also many confounding factors associated with those diseases and vitamin D status such as various drugs intake, inflammatory processess, habits of sun exposure, seasonal vitamin D alterations and the degree of reduced physical activity. Nonetheless, in the literature there is some evidence of the relationship between autoimmune rheumatologic disorders and vitamin D deficiency.

In the current trial, the study region was sunny both in winter and summer. We found no differences between summer and winter 25(OH)D serum levels in patients with RA, AS and OA and also HC. In addition, there were not correlations between summer and winter 25(OH)D serum levels and seasonal disease activity in patients with RA, AS and OA. This suggests that vitamin D does not have an important role in the disease activity of these diseases. Although we found higher disease activity scores in winter season than summer in all patient groups, only the change in seasonal BASDAI scores in AS group were determined significantly different ($p<0.05$). And this suggests that season has an important role in the disease activity of AS.

The role of vitamin D in the pathogenesis of RA is far from clear. Lower levels of vitamin D together with higher prevalence of RA appears common amongst North when compared to South Europe[30]. In some previous studies, lower vitamin D levels have been related to higher disease activity in RA[7,31,32]. Although dietary intake questionnaire report is not the ideal way of evaluating vitamin D status, greater intake of vitamin D was associated with a lower risk of RA in a prospective cohort study of 29, 368 women[33]. In a previous study, Cutolo et al evaluated serum vitamin D levels and correlation of which with the disease activity score (DAS28) in 64 RA patients from north Europe and 54 RA patients from south Europe during winter and summer[12]. Low 25(OH)D values showed a moderately significant negative correlation with RA clinical severity (DAS28) in summer in southern European RA patients, whereas in northern European RA patients the significant negative correlation was found in winter suggesting possible effects of vitamin D among other factors on disease activity[12].

On the other hand, not all studies confirm this relationship. In a small sample of patients with RA (n=29), 25(OH)D levels corresponded to controls[34]. Braun-Moscovici et al also did not find correlations between serum levels of 25(OH)D and seasonal variations, and disease activity in patients with RA, AS and psoriatic arthritis[19]. In our study, we found no differences between summer and winter 25(OH)D serum levels in patients with RA, in addition, there were not correlations between summer and winter 25(OH)D serum levels and seasonal disease activity in patients with RA.

As mentioned above, environmental factors are known to affect prevalence and severity of rheumatologic disorders. Since it is not uncommon for arthritis patients to assume that weather or seasonal changes affect the signs and symptoms of rheumatic disorders, it is important to take into account these fluctuations when examining patients. There are few studies in the literature that have found significant associations with RA and weather or season[35,36]. In another study, Hawley et al[37] evaluated seasonal symptom severity in 1,424 patients with RA, OA, and fibromyalgia (FM). Clinical status was evaluated with standard assessment measures, and reported symptoms were compared with actual seasonal differences measured for periods of up to 24 years. Even when patients who specifically reported worse symptoms in winter and best symptoms in summer were examined, no effect of season could be found in the study of Hawley et al. In our study, similar to the results of Hawley et al trial, patients with RA, AS and OA reported better symptoms in summer than winter but these differences could not reach statistically significant level in RA and OA groups. A recent large observational study by Likuni et al[15] reported higher RA disease activity in spring and lower activity in autumn and they concluded that seasonal changes do affect RA and should be considered when evaluating disease activity. Although we found higher disease activity scores in winter season than summer in patients with RA, this difference did not reach statistically significant level.

Clinical trials have also reported the impact of vitamin D in AS as an endogenous immune regulator, suppressing activated T cells and cell proliferation that may modulate the inflammation process[17]. We found no correlation between 25(OH)D levels and seasonal disease activity among our AS patients. There are also several studies reported contradictory results regarding correlation between disease activity and vitamin D levels in patients with RA and AS. Some trials reported correlation between disease activity (evaluated by ESR and CRP) in AS and 1,25 dihydroxy vitamin D metabolites levels, but not with 25(OH)D[11,17,31]. And the others find relationship between 25(OH)D and disease activity season related[12,13].

In another study, it was found that high disease activity and disorders in vitamin D metabolism are related with increased bone resorption in AS patients[18]. In osteoporotic patients with AS, levels of ESR and CRP were found significantly high while vitamin D level was low[17]. In the current trial, we evaluated the disease activity by DAS28 for RA and BASDAI for AS, which are more specific than CRP or ESR used in the most of the previous studies. In the current study, we didn't find such a correlation. Challier et al examined the links between the quality of life (QOL) and season condition in AS patients[38]. A higher lumbar spine flexibility (Schober index) was associated with a higher climatic temperature and physical QOL improved in the summer. In our study we used BASDAI which is more specific to AS to evaluate disease activity and severity. We determined significantly higher disease activity scores in winter season than summer in AS group ($p<0.05$). And this suggests that season has an important role in the disease activity of AS.

There are prospective epidemiological studies in the literature that have found an association between serum levels of vitamin D and the development of radiographic OA. Mc Alindon et al. showed a 3- to 4-fold increased risk of progression of OA in patients with the lower serum 25-hydroxy vitamin D levels[20]. Bischoff-Ferrari et al found in patients with radiographic knee OA, a positive association between vitamin D status and femoral neck (FN) BMD[39]. In their study, they stated that adjustment of suboptimal vitamin D levels could help reducing
progression of OA. The other study investigating vitamin D levels and OA was performed by Lane et al[40] also showed a 3-fold increased risk of incident joint space narrowing at the hips of women with lower serum 25-hydroxy vitamin D levels at baseline. In a recent study of Berking et al, suggests vitamin D status influences the incidence and progression of knee radiographic OA[41]. In contrast, a recent study by Felson et al suggests that vitamin D status is not related to the progression or cartilage loss in knee OA[42]. To our knowledge, our study is the first trial in the literature evaluating the relationship between seasonal disease activity (assessed by WOMAC) and vitamin D status in patients with OA. In our study, we did not find any correlation between vitamin D status and seasonal disease activity in patients with knee OA.

There were some limitations in our study. The first one was relatively small number of subjects. Secondly, we could not properly assess seasonal differences due to the sunny winter property of the study region. And thirdly, we were unable to estimate the dietary calcium intake of the subjects.

Conclusion

In the current trial there were not correlations between summer and winter 25(OH)D serum levels and seasonal disease activity in patients with RA, AS and OA. This suggests that vitamin D does not have an important role in the disease activity of these diseases. There were higher disease activity scores in winter season than summer in all patient groups (RA, AS, OA), but only the change in seasonal BASDAI scores in AS group were determined significantly different ($p<0.05$). And this suggests that season has an important role in the disease activity of AS rather than RA and OA. Seasonal changes may play an important role in evaluating disease activity of AS patients and should be taken into account when examining these patients. These conclusions need o be validated in multicenter studies with high number of patients.

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