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Femoral Cartilage Thickness and Vitamin D Level in Systemic Sclerosis Patients and Relation to Disease Severity

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ABSTRACT

Background: Systemic sclerosis (SSc) is a heterogeneous autoimmune disorder associated with vascular dysfunction and fibrotic changes. Low vitamin D levels and decreased femoral cartilage thickness (FCT) have been observed in SSc.

Objectives: This study aimed to evaluate the relation between serum level of vitamin D and FCT among SSc patients and to correlate both with clinical features and disease severity score.

Patients and Methods: This study included 40 SSc patients, divided into 2 groups; group 1: sufficient vitamin D (level $\geq$ 30 ng/ml), group 2: insufficient vitamin D (level < 30 ng/ml). All patients were subjected to history taking, clinical examination, and assessment of disease severity by Medsger Disease Severity Index (MDSI), laboratory investigations, 25 (OH) vitamin D level and musculoskeletal ultrasound of both knees to assess FCT. Three midpoint measurements of FCT were taken from each knee: lateral femoral condyle (LFC), femoral intercondylar area (ICA) and medial femoral condyle (MFC).

Results: Thin FCT was found in 60% of patients. There was insufficient vitamin D level in 65% of patients. Age was negatively correlated with FCT at right MFC area and female parity was also negatively correlated with right ICA and MFC areas. FCT was significantly lower in group 1 at areas of left MFC and LFC areas, but no relation between femoral cartilage thickness and vitamin D level with disease severity.

Conclusion: There is significant relation between femoral cartilage thickness and vitamin D level in scleroderma patients, both decline in SSc patients but not related to disease severity score.

Keywords: Scleroderma, Vitamin D, Femoral cartilage thickness, Disease severity score, Musculoskeletal ultrasound.

INTRODUCTION

Systemic sclerosis (SSc) is a connective tissue disease characterized by different degrees of skin fibrosis and visceral organ involvement. The etiology of SSc remains obscure; the disease appears to be the result of a multistep and multifactorial process, including immune system alterations, under the influence of genetic and exogenous (toxic or infectious) factors [(1)].

Vitamin D had been the focus of a growing number of studies in the past years, demonstrating its function not only in calcium metabolism and bone formation, but also the interaction with the immune system since vitamin D receptors are expressed in different tissues. Numerous studies have been conducted to study whether vitamin D is associated with SSc. However, they produced varying results [(2)]. Vitamin D deficiency was identified to be frequent in SSc patients and associated with disease activity or phenotype characteristics such as pulmonary hypertension, lung involvement, and extensive cutaneous forms [(3)]. Vitamin D deficiency may change the balance of cartilage metabolism via reducing the synthesis of proteoglycan and/or increasing the metalloproteinase activity, leading to cartilage loss [(4)].

Patients with SSc had thinner femoral cartilage. The underlying possible mechanisms of thin femoral cartilage may be multifactorial, and there may be many influencing factors like immune activation, vasculopathy, oxidative stress and synovial fibrosis or markers of cartilage degradation. The possible factors influencing the change in cartilage thickness or metabolism in patients with SSc require further research [(5)].

This study was performed to evaluate the relationship between serum levels of vitamin D and femoral cartilage thickness (FCT) among the studied SSc patients and to correlate with both disease severity score and clinical features.

PATIENTS AND METHODS

The present cross-sectional study enrolled forty SSc patients aged >18 years based on 2013 European League against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria

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of systemic sclerosis [6]. Patients were selected from Rheumatology Outpatient Clinic and Inpatient Department, Ain Shams University Hospital. The patients were divided into two groups according to vitamin D sufficiency.

Group 1: sufficient vitamin D (level ≥ 30 ng/ml) and group 2: insufficient vitamin D (level < 30 ng/ml). The exclusion criteria for this study included other connective tissue diseases, juvenile scleroderma, metabolic diseases, traumatic knee injury, osteoarthritis, septic arthritis, endocrine diseases and obese individuals (body mass index ≥ 30). Patients were recruited from June 2018 to December 2018.

Ethical considerations:

The study protocol was approved by the Local Ethical Committee of Ain Shams University. Informed consent was obtained from each participant after receiving an explanation about the study's aim and procedures.

All patients were subjected to detailed history taking with special emphasis on age, sex, body mass index, marital status, parity in females and full clinical examination with special emphasis on symptoms and signs of systemic sclerosis. Different laboratory investigations included complete blood count (CBC), erythrocyte sedimentation rate (ESR), C reactive protein (CRP) level with titer, kidney function tests (serum creatinine, blood urea nitrogen), liver enzymes (ALT, AST), antinuclear antibody (ANA) and serum 25 (OH) vitamin D was measured by using (ELISA). Imaging investigations included musculoskeletal ultrasound of both knees to assess femoral cartilage thickness. All measurements were done bilaterally using (esaote) MyLab^{TM}Six ultrasound machine, equipped with a 6-18 MHz linear probe.

Distal femoral cartilage thickness was assessed while patients lied in supine position with their knees in maximum flexion. Three midpoint measurements were taken from each knee: lateral femoral condyle (LFC), femoral intercondylar area (ICA) and medial femoral condyle (MFC) that was done in Rheumatology Department of Ain Shams University. Normal range of mean femoral cartilage thickness used in the present study ranged from 1.65 to 2.65 mm [7].

Assessment Degree of skin tightness:

Degree of skin tightness was assessed by modified Rodnan Skin Score (mRSS) [8] (estimating skin thickness using a 0–3 scale in 17 body areas. Nine of the original areas (neck [1], shoulders [2], breasts [2], upper back [1], lower back [1], toes [2]).

Assessment of Disease severity:

Assessment of disease severity was evaluated in SSc patients according to Medsger Disease Severity Index (MDSI) [9] who defined severity as the total effect of the disease on organ function if two items are included for a severity grade. Patient scored as having that severity level with grading as follows (Grade 0: normal, Grade 1: mild, Grade 2: moderate, Grade 3: severe, Grade 4: end stage).

Statistical Analysis

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 22. Data was summarized using mean, standard deviation, median, minimum, and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Non-parametric Kruskal-Wallis and Mann-Whitney tests for comparisons between quantitative variables. Chi-square ($\chi 2$) test was performed for comparing categorical data, exact test was used instead when the expected frequency is less than 5. Spearman correlation coefficient was done for correlations between quantitative variables. Probability (P-value) P-value ≤ 0.05 was considered significant, P-value < 0.001 was considered as highly significant and P-value > 0.05 was considered insignificant.

RESULTS

Demographic data among studied SSc patients are presented in table (1). Distribution of different clinical data among studied SSc patients is presented in figure (1). With respect to modified Rodnan Skin Score, it was ranged from 0 to 30 with a mean of 8.25 ± 8.13. The most common affected area was fingers (72.5%) followed by hands (55%), forearm (25%), upper arms (20%), face (20%), feet (17.5%), legs (12.5%), abdomen (12.5%), chest (10%) and thigh (7.5%), while (12.5%) of studied patients didn't suffer from skin tightness. Antinuclear antibodies (ANA) were positive in 65% of patients. For disease severity between studied SSc patients according to MDSI, 42.5% of cases were mild and moderate form followed by severe form (12.5%) and only one case was end stage (2.5%) as shown in figure (2).

Distribution of femoral cartilage thickness and vitamin D level among studied SSc patients is presented in table (2). As regards distribution of FCT at different areas among studied SSc patients; 18 (45%) had thinning in femoral cartilage at right medial condyle, followed by 12 (30%) patients at right lateral condyle. Besides, 9 (22.5%) patients at both left medial and lateral condylar areas, 5 (12.5%) patients

at left intercondylar area and only 3 (7.5%) patients had thin cartilage at right intercondylar area (Fig. 3). Female patients had significantly more vitamin D insufficiency in comparison with males (P=0.037). No differences were found between the two groups for clinical characteristics features, disease severity score and Rodnan score. Patients in group 1 had significantly lower FCT at areas of left medial condyle (P=0.039) and left lateral condyle (P=0.036) in comparison with group 2 (Table 3).

There was a significant inverse correlation between age and FCT at right medial condylar area (P=0.006), and also a significant inverse correlation between parity in females, right intercondylar area (P=0.046) and medial condylar area (P=0.003) (Table 4). Likewise, there was a significant inverse correlation between skin tightness and FCT at two points, right medial condyle (P=0.02) and right lateral condyle (P=0.03) (Fig. 4). Meanwhile, there was no significant correlation between both FCT and vitamin D level with disease severity score.

Table (1): Distribution of socio-demographic data among studied SSc patients:

	Mean	SD	Minimum	Maximum
Age (years)	41.65	10.19	20	58
Duration of illness (years)	5.71	4.83	1	20
Parity in females	3.03	1.31	1	6
			N	**%**
Sex	**Male**		3	7.5%
	Female		37	92.5%

SSc: Systemic sclerosis, SD: Standard deviation, N: number, %: percentage

Table (2): Distribution of femoral cartilage thickness assessed by musculoskeletal ultrasound and vitamin D level among studied SSc patients

		N		%	
Vitamin D level (ng/ml)	**Group I (vitamin D sufficiency)**	14		35%	
	Group II (vitamin D insufficiency)	26		65%	
		N	**%**	**Mean**	**SD**
Femoral cartilage thickness (mm)	**Normal thickness**	16	40.0%	2.26	0.28
	Thinning	24	60.0%	1.78	0.16

SSc: Systemic sclerosis, N: number, %: percentage, SD: Standard deviation

Table (3): Comparison between vitamin D sufficiencies in SSc groups as regards femoral cartilage thickness

Different areas of femoral cartilage	Vitamin D level				P value
	Group I (vitamin D sufficiency)		Group II (vitamin D insufficiency)		
	Mean	SD	Mean	SD	
Right intercondylar area	2.14	0.39	2.16	0.38	0.944
Right medial condyle	1.79	0.11	1.73	0.10	0.769
Right lateral condyle	2.07	0.51	1.95	0.12	0.474
Left intercondylar area	2.10	0.33	2.12	0.51	0.856
Left medial condyle	2.06	0.33	1.83	0.38	0.039*
Left lateral condyle	2.12	0.49	1.81	0.27	0.036*

SSc: Systemic sclerosis, SD: Standard deviation P-value > 0.05: Non-significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS).

Table (4): Correlation between different areas of femoral cartilage thickness and demographic data among studied SSc patients

		Rt ICA	Rt MCA	Rt LCA	Lt ICA	Lt MCA	Lt LCA
Age (years)	**Correlation Coefficient**	-0.151-	-0.431-	-0.237-	0.019	-0.114-	-0.223-
	P value	0.354	0.006*	0.140	0.907	0.485	0.167
	N	40	40	40	40	40	40
Parity in females	**Correlation Coefficient**	-0.350-	-0.496-	-0.313-	-0.092-	-0.306-	-0.175-
	P value	0.046*	0.003*	0.076	0.609	0.083	0.331
	N	33	33	33	33	33	33
Duration of illness (years)	**Correlation Coefficient**	0.039	-0.008-	-0.130-	0.110	0.047	0.044
	P value	0.811	0.962	0.422	0.499	0.774	0.786
	N	40	40	40	40	40	40

SSc: Systemic sclerosis, N: number, Rt ICA: right intercondylar area, Rt MCA: right medial condyle area, Rt LCA: right lateral condyle area, Lt ICA: left intercondylar area, Lt MCA: left medial condyle area, Lt LCA: left lateral condyle area. P-value >0.05: Non-significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS).

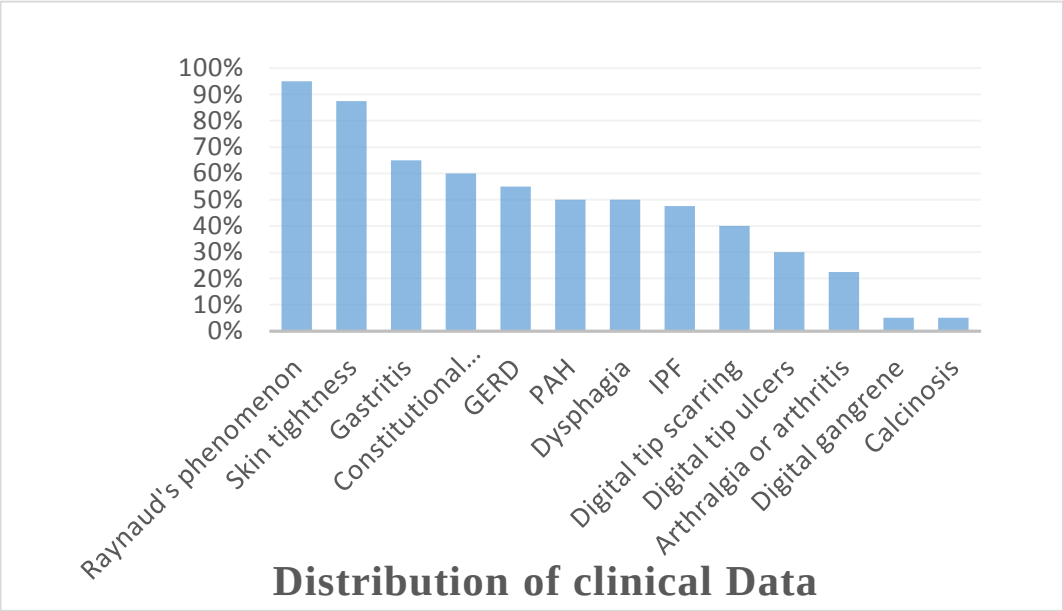

Figure (1): Distribution of different clinical data among studied SSc patients.

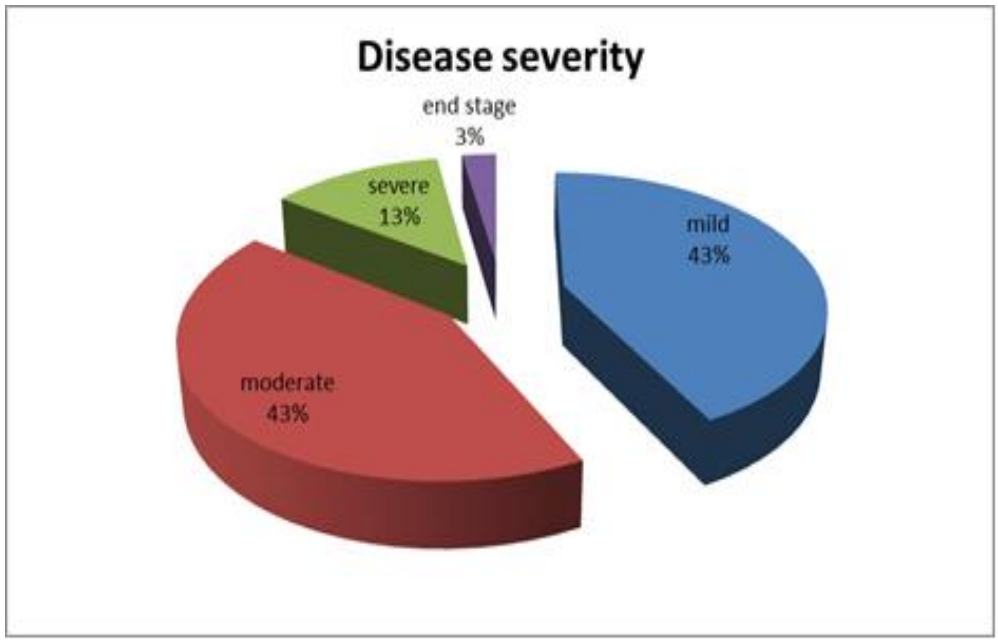

Figure (2): Distribution of disease severity score among studied scleroderma patients.

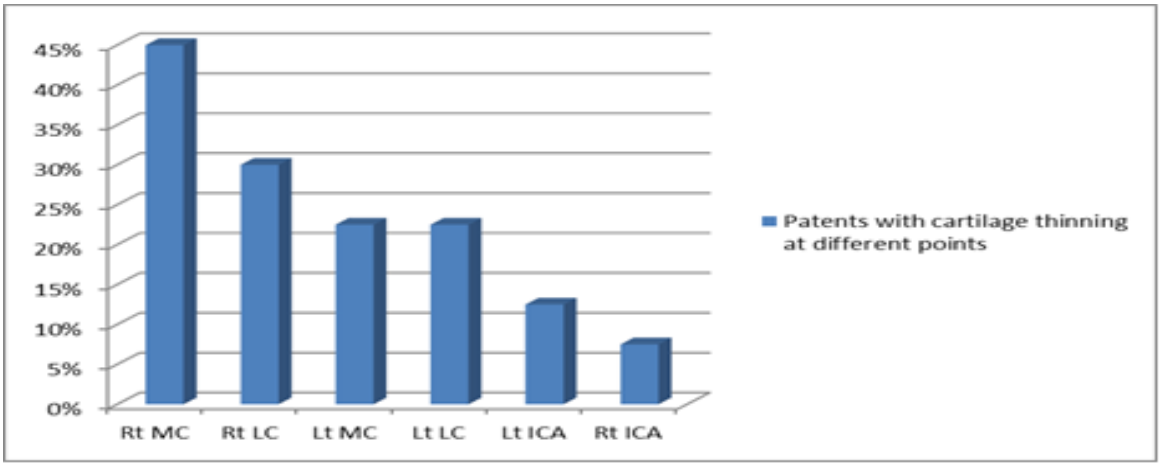

Figure (3): Distribution of femoral cartilage thickness at different points among studied SSc patients.

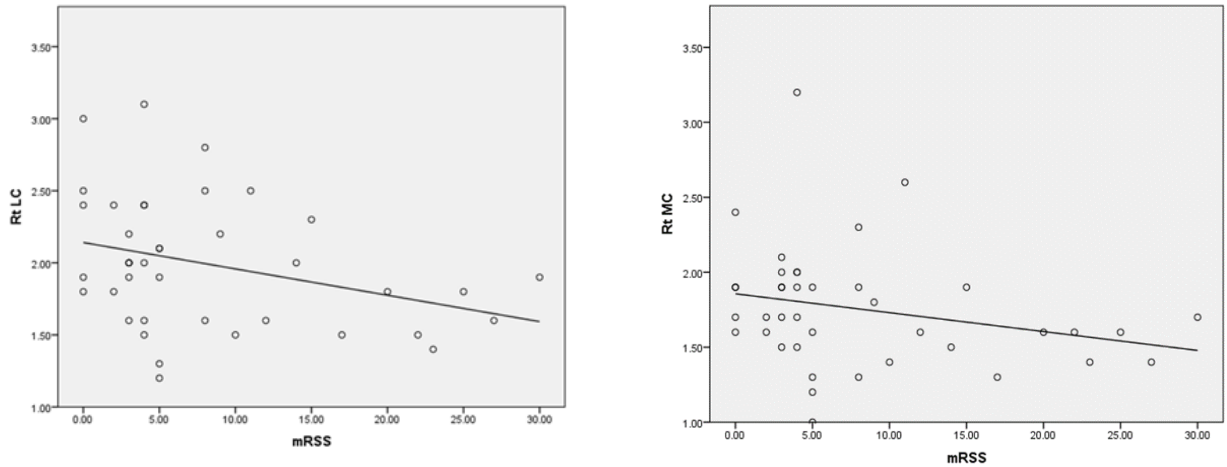

Figure (4): Correlation between femoral cartilage thickness at two points (Right medial and lateral condyles) and skin tightness assessed by modified Rodnan Skin Score (mRSS).

DISCUSSION

Systemic sclerosis (SSc) is a heterogeneous autoimmune disorder associated with vascular dysfunction and fibrotic changes in the skin, vasculature, and internal organs [10]. Low vitamin D levels have been observed in several autoimmune diseases, including SSc. Some studies have shown the importance of vitamin D in SSc, but its significance has not yet been determined [11].

In our study, the age of the studied SSc patients ranged from 20 to 58 years old with a mean of 41.65 ± 10.19 years. The duration of their illness ranged from 1 to 20 years with a mean of 5.71 ± 4.83. This is close to the result of **Mahmoud *et al.*** [12], but different from results of another study done by **Ghosh *et al.*** [13]. In the present study, 37 patients (92.5%) were females, and 3 cases (7.5%) were males, with female to male ratio of 12.3:1. This finding is near to the result of **Lo Monaco *et al***. [14]. Lower result was obtained by **Mahmoud *et al.*** [12] in which female to male ratio was 5.2:1.

Regarding the clinical manifestations, the commonest cutaneous manifestations were Raynaud's phenomenon (95%), skin tightness (87.5%), digital tip scarring (40%), digital tip ulcers (30%) and the least was digital tip gangrene and calcinosis (5% each). These are in agreement with **Ghosh *et al.*** [13] who found that the commonest cutaneous manifestations were Raynaud's phenomenon (84.8%) and sclerodactyly (82.6%), followed by fingertip ulceration and scarring in 63%, and the least was calcinosis (2.2%). Also, **Mahmoud *et al***. [12] found that the commonest cutaneous manifestations were sclerodactyly (100%) and Raynaud's phenomenon in close ratio (94%), followed by pitting scars in 72%, digital tip ulcers in 68%, and the least was calcinosis in 32% of patients. Regarding gastrointestinal tract (GIT) manifestations, our study demonstrated that most of the studied patients suffered from gastritis (65%) followed by gastro-esophageal reflux disease (GERD) that was reported in 55% of our studied patients. This result agrees with **Thonhofer *et al.*** [15], while disagrees with **Park *et al.*** [16] who found a lower percentage (37.2%), (40%) for both gastritis and GERD respectively. Our study reported that 50% of the studied patients had pulmonary hypertension. This result closely agrees with **Gadre *et al.*** [17], who found that 45.1% had pulmonary hypertension, while disagrees with **Bauer *et al.*** [18] and **El Basel and Khalil** [19] who found lower incidences (21.87% and 14.7% respectively). Interstitial pulmonary fibrosis (IPF) was found in 47.5% of our studied patients. This is close to result of **Mahmoud *et al***. [12], which was 50%. Other studies found lower incidence of IPF as **Hunzelmann *et al.*** [20], and **Phung *et al.*** [21], which were 34.5% and 17.4% respectively.

The modified Rodnan skin score (mRSS) in this study ranged from 0 to 30 with mean of 8.25 ± 8.13. The most common affected areas of skin tightness were fingers (72.5%). **Mahmoud *et al***.[12] agrees with this finding, as fingers was the most affected area in their study, but with higher mRSS that ranged from 4 to 45 with a mean of 17.48 ± 10.44.

Our study showed that most of the studied patients were in mild and moderate grades of disease severity by 42.5% for each, while severe form represented 12.5% and only 1 end stage case (2.5%). In agreement with our result, **La Torre *et al.*** [22] found that most relevant grade was mild grade (48.6%), followed by moderate (28.6%), then severe (22.8%). Another Egyptian study of **Omar *et al.*** [23] found that most of their studied patients were in moderate form (52%) followed by severe form (28%) and mild form (20%).

Vitamin D is involved in modulation of immune responses and has an important role in some autoimmune diseases like multiple sclerosis, diabetes mellitus, psoriasis, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), etc. [24]. The results of our study emphasized that there was a high prevalence of hypo-vitaminosis D in SSc patients. Low levels of 25 (OH) Vitamin D were recorded, with clear-cut insufficiency (< 30 ng/ml) in 65% of cases. Vitamin D insufficiency in SSc patients may be explained by reduced drawing of pro-vitamin D3 synthesized from dehydrocholesterol by UVB radiation in the epidermis due to dermal fibrosis or malabsorption of dietary vitamin D from gastrointestinal involvement [25]. In agreement with our result, **Omar *et al.*** [23] found that SSc patients had significant low levels of vitamin D, as 64%. In addition, **Gupta *et al.*** [26] agree with our result but with lower incidence, they recorded 13 (34.2%) patients with vitamin D deficiency, meanwhile 10 (26.3%) patients had insufficient levels.

Based on our results, no differences were found between the two groups for the clinical characteristics, disease severity score and Rodnan score. Therefore, vitamin D decrease might not be an accelerating factor of SSc severity. In agreement with our result, **Gupta *et al.*** [26] when they sorted vitamin D level by clinical and serological parameters, they showed no significant correlation statistically except for inverse correlation with modified Rodnan skin score. In addition, **An *et al***. [27] agree with our study. On the other hand, **Atteritano *et al.*** [25] found that skin

involvement (assessed by Rodnan skin score) and pulmonary hypertension were associated with vitamin D insufficiency.

Cartilage and bone destruction occur in many rheumatic diseases, as ankylosing spondylitis (AS) systemic lupus erythematosus (SLE) and systemic sclerosis (SSc) [28]. We found in our study by ultrasound imaging of femoral cartilage thickness, that 60% of our studied SSc patients had thin femoral cartilage. **Omar *et al.*** [23] and **Kilic *et al.*** [5] agree with our results, which can be explained by different factors like immune activation, vasculopathy, oxidative stress and synovial fibrosis or markers of cartilage degradation [5].

We compared the two studied groups as regard the FCT, we concluded that patients with vitamin D insufficiency had significantly lower FCT at areas of left medial condyle (p-value < 0.05) and left lateral condyle (p-value < 0.05). In agreement with our result, **Omar *et al.*** [23] who found significant relation of vitamin D level with five areas of FCT.

Our study showed that multiparity in females was inversely correlated with FCT at right intercondylar and medial condyle areas (p-value < 0.05). **Wei *et al*.** [29] agree with our result, as they studied the impact of multiparity on knee joint by MRI and found that parity was associated with knee cartilage defects. This result may be explained by increased joint load because of weight gain; increased levels of sex hormones such as estrogen and progesterone and changes in lifestyle behavior [30].

In our study, we found no relation between disease severity and femoral cartilage thickness, this can be explained by that we used Medsger severity score to assess disease severity, which is a measure capturing both disease activity and damage, and quantifies the overall effect of SSc on nine affected organ systems, joint accounted for only one affected system [31]. Also, we found a significant inverse correlation between skin tightness degree (by mRSS) and femoral cartilage thickness at right medial condyle and right lateral condylar areas (p-value < 0.05). This result can be explained by the hypothesis that skin thickening associated with reduced synthesis of vitamin D by UVB radiation in the epidermis [32], which might be reflect on cartilage thickness as vitamin D level is significantly associated with knee joint morphology and composition [33].

CONCLUSION

There is significant relation between femoral cartilage thickness and vitamin D level in scleroderma patients. However, both are not related to disease severity score, so we need to follow up the femoral cartilage thickness in scleroderma patients especially those with vitamin D insufficiency, multiparous females and those patients with high degrees of skin tightness. We recommend further studies to evaluate the effect of vitamin D supplementation on musculoskeletal manifestations and thickness of femoral cartilage in systemic sclerosis patients. Overall, we advise SSc patients for sun light exposure and quality of diet rich or fortified by vitamin D.

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