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Hypovitaminosis D in patients with systemic sclerosis: Evaluating the role of skin involvement

Sistemik skleroz hastalarında D hipovitaminozu: Deri tutulumunun rolünün değerlendirilmesi

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Abstract

Objective: Systemic sclerosis (SSc) is a rare autoimmune disease characterized by fibrosis of internal organs and the skin. In SSc, skin involvement may be responsible for vitamin D deficiency/insufficiency. We aim to evaluate the frequency of hypovitaminosis D (deficiency/insufficiency) in SSc and to investigate its relationship with skin involvement in this study.

Methods: In this cross-sectional study, 59 SSc (88% female) patients were included. Modified Rodnan Skin Score (mRSS) was used to assess skin involvement. Pulmonary arterial hypertension (PH) and pulmonary involvement were recorded. Spearman correlation analysis and logistic regression analysis were performed.

Results: Fifty-nine SSc patients were enrolled in this study. 50.8% of patients were limited cutaneous SSc and 49.2% were diffuse cutaneous SSc. The frequency of hypovitaminosis D (≤30 ng/mL) was 76.3%. There was no significant correlation between mRSS and hypovitaminosis D in SSc patients. Hypovitaminosis D was highly prevalent in SSc patients with darker skin tone compared to patients with lighter skin tone (p=0.035). SSc patients with PH had low levels of vitamin D than those without PH (p=0.016). Similarly, SSc patients with cardiac involvement had also low levels of vitamin D than those without cardiac involvement (p=0.037). In binary logistic regression analysis, the odds of hypovitaminosis D were almost 4 times higher (odds ratio=3.740 95% confidence interval 1.124-12.443, p=0.031) in patients with darker skin tone.

Conclusion: Skin color, PH, and cardiac involvement are found to be associated with low levels of vitamin D. On the other hand, no significant relationship is observed between mRSS and vitamin D levels in SSc patients.

Keywords: Systemic sclerosis, vitamin D level, modified Rodnan skin score, pulmonary arterial involvement, systemic involvement

Öz

Amaç: Sistemik skleroz (SSc) deri ve iç organların fibrozisi ile karakterize nadir otoimmün bir hastalıktır. SSc'de deri tututlumu D vitamin eksikliği/yetersizliğine neden olabilir. Bu çalışmada SSc'de D hipovitaminoz (eksikliği/yetersizliğine) sıklığının ve bunun deri tutulumu ile ilişkisinin değerlendirilmesi amaçlandı.

Yöntem: Bu kesitsel çalışmaya, 59 SSc'li (%88'i kadın) hasta dahil edildi. Deri tutumu modifiye Rodnan deri skoru (mRSS) ile değerlendirildi. Pulmoner arteriyel hipertansiyon (PH) ve pulmoner tutulumları kaydedildi. Spearman korelasyon analizi ve lojistik regresyon analizi uygulandı.

Bulgular: Çalışmaya 59 SSc hastası dahil edildi. Hastaların %50,8 limited kutanöz SSc ve %49,2'si diffüz kutanöz SSc idi. D hipovitaminoz (≤30 ng/mL) sıklığı %76,3'tü. SSc hastalarında mRSS ile D hipovitaminoz arasında anlamlı ilişki saptanmadı. Koyu tenli SSc hastalarında D hipovitaminozu açık tenlilere göre daha sıktı (p=0,035). PH'li SSc hastalarında D vitamini değerleri PH olmayanlara göre daha düşüktü (p=0,016). Benzer şekilde, kardiyak tutulumu olan SSc hastalarında da D vitamini değerleri kardiyak tutulumu olmayanlara göre daha düşük bulundu (p=0,037). İkili lojistik regresyon analizinde, D hipovitaminoz olasılığı koyu tenli hastalarda yaklaşık 4 kat daha yüksekti (risk oranı=3,740 %95 güven aralığı 1,124-12,443, p=0,031).

Sonuç: Deri rengi, PH ve kardiyak tutulum düşük D vitamin değerleri ile ilişkili bulundu. Diğer yandan SSc'li hastalarda mRSS ve D vitamin değerleri arasında anlamlı ilişki gözlenmedi.

Anahtar Kelimeler: Sistemik skleroz, D vitamini değeri, modifiye Rodnan deri skoru, pulmoner arteriyel tutulum, sistemik tutulum

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Introduction

Systemic sclerosis (SSc) is a rare and chronic progressive connective tissue disease characterized by heterogeneous clinical symptoms with progressive skin fibrosis and multisystemic involvement, playing an important role in morbidity and mortality. In general, SSc patients have been classified as limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) according to the degree of skin involvement.[1] The Modified Rodnan Skin Score (mRSS) is a widely used semi-quantitative method to describe the degree and severity of skin involvement in SSc. Higher scores are associated with the disease severity and mortality, especially in patients with dcSSc.[2]

Vitamin D has a hormone-like function and its major natural source is the synthesis in the skin. The most important effect of vitamin D is on calcium homeostasis and bone health. In the literature, vitamin D deficiency/insufficiency, which is a common health problem, is closely related to many chronic diseases. Accordingly, low vitamin D level has been shown as a risk factor for many autoimmune diseases by modulating the immune system. In addition, vitamin D deficiency can contribute to fibrosis in diseases such as SSc, in which fibrosis is involved in the pathogenesis.[3-5] In line with this, numerous studies have proven that vitamin D deficiency is prevalent in SSc.[6-10] The underlying reasons for vitamin D deficiency have been defined as increased 25 (OH) D antibodies in the blood, decreased vitamin D synthesis in the epidermis due to capillary damaged dermal fibrosis, skin hyperpigmentation, low sunlight exposure, insufficient intake with diet or vitamin D malabsorption due to gastrointestinal involvement. Among these factors, cutaneous fibrosis, characteristic feature of SSc, is of utmost importance to cause hypovitaminosis.[7,11,12] Accordingly, the relationship between skin involvement and hypovitaminosis D in SSc may be described as "a chicken and egg dilemma".

In accordance with the abovementioned studies, we aimed to assess the frequency of hypovitaminosis D in SSc patients and to evaluate its relationship with the skin thickness.

Materials and Methods

Study Population

The present study was designed as a cross-sectional study. Accordingly, 70 SSc patients were screened for eligibility. Exclusion criteria were as follows: i) patients aged <18 years, ii) patients aged >85 years, iii) presence of extremity amputation, iv) history of more than one rheumatological disease or overlap syndrome, v) presence of renal failure, vi) patients with postinflammatory hyperpigmentation in the two skin areas assessed for skin color and vii) history of diseases that affect vitamin D metabolism, such as liver disease and endocrinological disease were excluded. Accordingly, 59 SSc patients who fulfilled 2013 American College of Rheumatology/European League Against Rheumatism classification criteria for SSc[13] were enrolled in the study.

Evaluations

Medical records of SSc patients were used to extract the data on demographic information, clinical and laboratory findings. Vitamin D, calcium and bisphosphonate supplements, smoking, the menopausal status of female patients and dressing style were questioned. Laboratory outcomes such as calcium (Ca), phosphorus, alkaline phosphatase, parathormone and 25 (OH) D levels, which were studied between May and August, were noted. Similar to previous studies, vitamin D level above 30 ng/mL is defined as normal, between 21 and 30 ng/mL as insufficiency and below 20 ng/mL as deficiency of vitamin D. Hypovitaminosis D is regarded as deficiency/insufficiency of vitamin D.[14]

The findings of pulmonary involvement in chest computed tomography were screened. The presence of pulmonary fibrosis on computed tomography scan were noted. The findings of cardiac involvements (myocarditis and arrythmia) diagnosed by electrocardiography, echocardiography (ECHO), and cardiac magnetic resonance imaging were recorded. Patients with pulmonary hipertension (PH) were defined as having a pulmonary artery pressure greater than 45 mmHg as measured by the Doppler flow of the tricuspid regurgitant jet on ECHO. ECHO is accepted as an important non-invasive technique that gives results close to right heart catheterization results. Therefore, right heart catheterization, which is the gold method for evaluating the pulmonary hemodynamics, was not performed.[15]

mRSS was performed to measure skin thickness of 17 different areas (fingers, hands, forearms, upper arms, face, chest, abdomen, upper legs, lower legs and feet) under appropriate conditions. This evaluation was made by two different rheumatologists who had previously been trained with the repetitive teaching method. Each area was scored according to the degree of thickness as; 0= normal, 1= mild thickening, 2= moderate thickening and 3= severe thickening, and total score was noted (the total maximum score is 51).[2]

Evaluator (E.S.) decided on the skin color and categorized SSc patients into two groups as darker skin tone and lighter skin tone. The color was assessed in two skin sites, the back of the hand and the face. Patients with postinflammatory

hyperpigmentation in these two skin sites were not enrolled in the study.

The study was approved by Ethics Committee of Kocaeli University (ethics approval number: KU GOKAEK-2019/12.03). Written informed consent form was obtained from each patient.

Statistical Analysis

IBM SPSS 20.0 (IBM Corp., Armonk, NY, USA) package program was used to assess the data. The Kolmogorov-Smirnov test was performed to evaluate the distribution of variables. The Independent Sample t-test and Mann-Whitney U test were used to compare parametric and non-parametric continuous variables, respectively. Categorical variables were compared using chi-square test and Fisher exact test. Spearman correlation analysis was performed to find the relationships between variables. Logistic regression analysis was used to to examine the association of mRSS, skin involvement, and organ involvement with hypovitaminosis D. For the testing of two-sided hypotheses, $p<0.05$ was considered as sufficient for statistical significance.

Results

Of 59 patients included in our study, 30 (50.8%) were lcSSc and 29 (49.2%) were dcSSc. According to chest computed tomography findings, pulmonary involvement was in 45.8% of patients; PH in ECHO was in 16.9%, and cardiac involvement was in 15.3%. The demographic and laboratory characteristics of the patients are given in Table 1. There was no difference between dcSSc and lcSSc group in terms of demographic, clinical and laboratory findings, except for pulmonary involvement (Table 1). Hypovitaminosis D (≤30 ng/mL) was found in 76.3% of SSc patients. There was no difference between lcSSc and dcSSc subgroups in terms of vitamin D levels (Table 1 and Table 2).

In Spearman correlation analysis, we did not find any correlation between vitamin D level and age, gender, SSc subgroups, disease duration, and skin color. When hypovitaminosis D and demographic findings were compared, a significant difference was observed only between hypovitaminosis D and skin color. Deficiency/insufficiency of vitamin D was found to be significantly higher in patients with darker skin tone ($p=0.035$) (Table 3).

When SSc patients were divided two subgroups according to the systemic involvement, patients with PH (15.1±10.2 vs 23.6±11.2 ng/mL; $p=0.016$) and patients with cardiac involvement (18.6±19.5 vs 22.8±9.5 ng/mL; $p=0.037$) were associated with low level of vitamin D.

In binary logistic regression analysis, no associations were found between vitamin D insufficiency and MRSS and organ involvement. However, the odds of hypovitaminosis D were almost 4 times higher [odds ratio (OR)=3.740 95% confidence interval (CI) 1.124-12.443, $p=0.031$] in patients with darker skin tone. After adjusting for age, mRSS, organ involvement, the odds of hypovitaminosis D were 6.4 times higher (OR=6.431 95% CI 1.502-27.531, $p=0.012$) in patients with darker skin tone (Table 4).

Discussion

In the present study, higher frequency of hypovitaminosis D was observed in patients with SSc. Even though skin thickness was not associated with the level of vitamin D, darker skin color was related to low vitamin D levels. Moreover, some clinical findings such as PH and cardiac involvement were found in SSc patients with vitamin D deficiency/insufficiency.

Vitamin D deficiency is quite common in the general population (30-50%).[16] In SSc patients, vitamin D deficiency has been reported between 29.2% and 86%.[6,8-11] In a study conducted by Hax et al.[17], the prevalence of low vitamin D levels was found higher in patients with SSc than healthy controls, despite taking more vitamin D supplements. Many factors such as antibodies against vitamin D, decline in vitamin D synthesis due to the skin fibrosis, skin hyperpigmentation, insufficient intake, vitamin D malabsorption, and low sunlight exposure play a role in hypovitaminosis D in SSc. The last one is closely associated with latitudinal gradient. While the highest hypovitaminosis rates have been shown in China, northern France and Italy,[10] lower rates have been reported from India, Israel and Italy.[8,11,18] Interestingly, the countries reporting these low rates are those with enough sunlight at right angles. In our study, low vitamin D level was found in 76.3% of SSc patients. This result was similar to the rates reported from regions of similar latitude. Skin fibrosis plays an important role in hypovitaminosis D in patients with SSc. Therefore, unsurprisingly, higher skin thickness may be correlated with lower vitamin D levels. A meta-analysis evaluating the level of vitamin D in SSc showed that patients with diffuse type SSc were more likely to have lower vitamin D status.[19] However, in the current study, we could not be able to demonstrate this difference between two SSc subgroups.

In the present study, we evaluated the laboratory outcomes of our patients between May and August to eliminate the effect of seasonal variations. Recently published review article showed that seasonal vitamin D changes may impact on clinical symptoms of SSc.[20] Accordingly, only one study presented their large data included 2.480 Thai-

Table 1. Demographic, clinical and laboratory findings, and the comparison of lcSSc and dcSSc patients

n (%)	All patients (n=59)	lcSSc (n=30)	dcSSc (n=29)	p[a]
Age (year)[&]	55.02±11.55	54.30±10.92	55.76±12.31	0.632[T]
Disease duration (month)[&]	104.24±59.97	87.80±87.80	121.24±69.78	**0.031***[T]
Gender (Women)	52 (88.1)	27 (90)	25 (86.2)	0.706
Smoking				
Smoker	4 (6.8)	2 (6.7)	2 (6.9)	0.893
Smoked and quit	10 (16.9)	6 (20)	4 (13.8)	
Non smoker	45 (76.3)	22 (73.3)	23 (79.3)	
Skin color				
Dark skin	39 (66.1)	20 (66.7)	19 (65.5)	1.000
Veiled clothing (Only women)	44/52 (84.6)	21/27 (77.8)	23/25 (92)	0.252
Menopause (Only women)	39/52 (75)	19/27 (70.4)	20/25 (80)	0.631
Systemic involvement				
Pulmonary involvement	27 (45.8)	9 (30)	18 (62.1)	**0.027***
Pulmonary hypertension	10 (16.9)	6 (20)	4 (13.8)	0.731
Cardiac involvement	9 (15.3)	4 (13.3)	5 (17.2)	0.731
GIS involvement	18 (30.5)	10 (33.3)	8 (27.6)	0.844
Kidney involvement	1 (1.7)	1 (3.3)	0	1.000[F]
Joint-tendon involvement	18 (30.5)	9 (30)	9 (31)	1.000
Myositis	1 (1.7)	0	1 (3.4)	0.492[F]
Use of replacement				
Only Ca	8 (13.6)	3 (10)	5 (17.2)	0.122
Only vitamin D	9 (15.3)	7 (23.3)	2 (6.9)	
Bisphosphonate	6 (10.2)	2 (6.7)	4 (13.8)	
Ca + vitamin D	3 (5.1)	0	3 (10.3)	
Osteoporosis	15 (25.4)	6 (20)	9 (31)	0.500
Low Ca	2 (3.4)	1 (3.3)	1 (3.4)	1.000[F]
Low P	1 (1.7)	1 (3.3)	0	1.000[F]
ALP elevation	4 (6.8)	4 (13.3)	0	0.112[F]
PTH elevation	13 (22)	6 (20)	7 (24.1)	0.945
25(OH)D (ng/mL)[&]	22.1±11.4	22.1±11.4	23.0±10.2	0.693[T]
Low Serum 25 (OH) D[a]	45 (76.3)	22 (73.3)	23 (79.3)	0.590
Otoantikorlar				
Anti-Scl 70	19 (32.2)	2 (6.7)	17 (58.6)	0.000
Anti-centromer	16 (27.1)	15 (50)	1 (3.4)	
CENP-B	26 (44.1)	22 (73.3)	4 (13.8)	
mRSS [median (25-75 pers.)]		5 (4-8.5)	9 (6-14.5)	**0.005***[M]

**p<0.05 statistically significant; [&]: mean ± SD, [a]: the comparison results of lcSSc and dcSSc; [T]: was used Student t-test; [M]: was used Mann-Whitney U test, [F]: was used Fisher exact test; [a]: serum 25 (OH) D was <30 ng/mL.*

ALP: Alkaline phosphatase, Ca: Calcium, dcSSc: Diffuse cutaneous systemic sclerosis, GIS: Gastrointestinal system, lcSSc: Limited cutaneous systemic sclerosis, mRSS: Modified Rodnan Skin score, P: Phosphorus, PTH: Parathormone

Table 2. Vitamin D levels in two subsets of SSc

n (%)	lcSSc (n=30)	dcSSc (n=29)	p
25(OH)D <20 ng/mL	14 (46.7)	13 (44.8)	0.887
25(OH)D 21-30 ng/mL	8 (26.7)	10 (37.9)	0.514
25(OH)D >30 ng/mL	8 (26.7)	6 (17.2)	0.589

dcSSc: Diffuse cutaneous systemic sclerosis, lcSSc: Limited cutaneous systemic sclerosis, SSc: Systemic sclerosis

Table 3. Demographic features according to vitamin D levels in patients with systemic sclerosis

n (%)	Hypovitaminosis D (n=45)	Normal vitamin D (n=14)	p
Gender			
Woman	40 (76.9)	12 (23.1)	0.748
Skin color			
Light skin (n=20)	12 (60)	8 (40)	**0.035***
Dark skin (n=39)	33 (84.6)	6 (15.4)	
Clothing Style (only women)			
Nonveiling clothing	5 (62.5)	3 (37.5)	0.293
Veiling clothing	35 (79.5)	9 (20.5)	
Smoking			
Smoker	4 (100)	0 (0)	
Smoked and quit	5 (50)	5 (50)	0.067
Non smoker	36 (80)	9 (20)	
mRSS [median (25-75 pers.)]	7 (7.3-11.5)	7 (5.5-11.1)	0.993^{M}

**p<0.05 statistically significant, ^{M}: was used Mann-Whitney U*

Table 4. Logistic regression analysis for factors associated with hypovitaminosis D in patients with systemic sclerosis

	Unadjusted			Adjusted		
	OR	95% CI	p	OR	95% CI	p
Age (years)	0.973	0.923-1.025	0.302	0.947	0.885-1.013	0.113
mRSS	1.028	0.931-1.136	0.582	1.020	0.902-1.054	0.749
Pulmonary involvement	0.560	0.176-1.784	0.327	0.314	0.073-1.352	0.120
Pulmonary hypertension	3.971	0.461-34.205	0.209	4.209	0.198-89.470	0.357
Cardiac involvement	3.429	0.393-29.880	0.265	4.499	0.185-109.118	0.355
Skin color	3.740	1.124-12.443	**0.031**	6.431	1.502-27.531	**0.012**

CI: Confidence interval, mRSS: Modified Rodnan Skin score, OR: Odds ratio

SSc patients and showed that the highest acceptance rate into the healthcare system was observed in rainy season (from mid-May to mid-October). Even though the authors did not clarify the exact reason for this increased admission, the study pointed out the seasonal variations.[21]

Although exposed to the similar rate of sunlight, dark-skinned individuals produce less 25(OH)D than light-skinned individuals. In a single study, the rate of vitamin D deficiency according to skin color has been reported as 68% in dark-skinned and 17% in light-skinned patients.[22] In our study, vitamin D deficiency/insufficiency was found to be higher only in SSc patients with darker skin tone (84.6% vs 60%, p=0.035). In addition, vitamin D deficiency was more common in SSc patients with darker skin color than SSc patients with lighter skin color.

Individuals who use excessive amounts of sunscreens or wear clothes that cover most of their body have minimal exposure to sunlight. Even in the sunny regions of the world such as Beirut and Lebanon, it has been reported that there is a relationship between the veiled clothing style and the frequency of vitamin D deficiency in the healthy population.[23] In the present study, we could not show any significant difference between the groups in terms of veiled clothing style. In addition, veiled clothing was not found to be a significant risk factor for vitamin D deficiency/insufficiency in SSc. However, the reason for the inconsistent results between the aforementioned study and the present study may be due to the different study population and latitudinal gradient.

Vitamin D plays an anti-fibrotic role by decreasing the production of collagen I and collagen III as a result of TGF-β (a profibrotic cytokine) reduction, and it also increases the production of antifibrotic factors such as metalloproteinase-8.[20,24] It is suggested that the most important reason for vitamin D deficiency in SSc is skin fibrosis, which affects active vitamin D synthesis steps.[12] While some studies have reported an inverse relationship between skin fibrosis and low vitamin D levels,[25,26] other studies have not shown this relationship.[7,9,27,28] In the present study, as expected, we found higher skin scores in dsSSc patients. However, no significant relationship was observed between mRSS and vitamin D deficiency/insufficiency in the study population, regardless of subtypes (dcSSc and lcSSc).

According to the recently published systematic literature review article, vitamin D deficiency is likely to be linked with various clinical and serological characteristics of SSc.[29] For instance, in two independent studies, vitamin D deficiency was closely related to the higher pulmonary artery pressure and lower diffusing lung capacity.[8,10] As far as we know, there is no other study on this subject in literature. In our study, no significant relationship was found between vitamin D deficiency/insufficiency and clinical findings, except PH (p=0.016) and cardiac involvement (p=0.037). The study conducted by Clements et al.[30] presented the significant relationship between baseline mRSS (≥20) and baseline cardiac and joint involvement (for cardiac involvement p=0.025; for joint involvement p=0.035) in dSSc patients.

Moreover, this baseline skin score was an important predictor for mortality and scleroderma renal crisis. In our study, no significant relationship was found between mRSS and organ involvement, except pulmonary involvement (p=0.024). The reason why we could not find any association between mRSS and systemic involvement in our study population may be due to the long disease duration (>5 years) leading to atrophic skin characterized by low mRSS. In addition, we may not have found any link between skin involvement and vitamin D level due to low mRSS. Therefore, comprehensive studies are needed to reach a more definite conclusion on this issue.

Study Limitations

There are some limitations in this study. First, we did not exclude the patients having long disease duration (>5 years) leading to atrophic skin. Second, we did not enroll the patients according to the information about vitamin D replacement therapy use. However, studies reported that there was no difference between the patients who received the replacement therapies and those who did not. Third, sample size was not enough to show more accurate results. On the other hand, the study population is generally small due to its rarity in studies evaluating SSc. Fourth, we did not use any validated and/or reliable method to measure the skin color. Last, we did not design this study as a case-control study. Thus, healthy age-matched subjects were not included in this study.

Conclusion

In conclusion, the frequency of hypovitaminosis D in patients with SSc is found to be 76.3%. Darker skin, PH, and cardiac involvement are closely associated with low vitamin D levels. Multicentered studies with a larger sample size are needed to show the exact link between vitamin D level and systemic involvement.

Ethics

Ethics Committee Approval: The study was approved by Ethics Committee of Kocaeli University (ethics approval number: KU GOKAEK-2019/12.03).

Informed Consent: Written informed consent form was obtained from each patient.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: E.S., M.M.S., N.G., D.T.K., Ö.Ö.I., A.C., A.Y., Design: E.S., M.M.S., N.G., D.T.K., Ö.Ö.I., A.C., A.Y., Data Collection or Processing: E.S., M.M.S., N.G., D.T.K., Ö.Ö.I., A.C., A.Y., Analysis or Interpretation: E.S., M.M.S., N.G., D.T.K., Ö.Ö.I., A.C., A.Y., Literature Search: E.S., M.M.S., N.G., D.T.K., Ö.Ö.I., A.C., A.Y., Writing: E.S., M.M.S., N.G., D.T.K., Ö.Ö.I., A.C., A.Y.

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