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OSTEOPOROSIS IN SYSTEMIC SCLEROSIS

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Background. Osteoporosis (OP) and fragility fractures are common and well-known comorbidities in patients with rheumatic diseases. However, the prevalence and risk factors for OP in systemic sclerosis (SSc) are not well understood. According to the literature, the incidence of OP in SSc ranges from 8.8% to 51.6%. Predictors of bone loss in systemic sclerosis have not been definitively established.

Aim. This study presents the clinical case of osteoporosis in patients with systemic sclerosis and provides comprehensive data on the prevalence and associated risk factors for bone loss in this disease.

Materials and methods. This article describes the clinical case of OP in patients with SSc and reviews the literature using PubMed, Medline, and the Cochrane Library with keywords such as bone mineral density, osteoporosis, prevalence, risk factors, and systemic sclerosis.

Results. We demonstrate the clinical case of OP in a patient with SSc and the prompt positive effect of bisphosphonate treatment. The patient's additional risk factors for bone loss associated with SSc were diffuse cutaneous SSc subtype, sclerodactily with active digital ulcers, late scleroderma pattern on capillaroscopy, ILD, gastrointestinal involvement, and treatment with PPI.

Conclusion. OP is rather prevalent in patients with SSc. According to published data, specific disease-related factors associated with OP are: disease duration, digital ulcers, calcinosis, pulmonary and gastrointestinal involvement as treatments with PPI and GCs. These findings support the identifying SSc patients at a higher risk for OP in clinical practice and its complications.

Keywords: bone mineral density, osteoporosis, prevalence, risk factors, systemic sclerosis.

Background. Rheumatic diseases, including systemic sclerosis (SSc), are associated with a higher risk of developing osteoporosis (OP) [1]. According to various literature sources, the prevalence of OP in SSc patients ranges from 8.8% to 51.6%. SSc is a chronic autoimmune disease characterized by skin and internal organ fibrosis, vasculopathy, and immune system abnormalities [2]. Several studies have indicated reduced bone mineral density (BMD) in patients with SSc. However, the data is inconsistent, as the determinants of osteopenia and OP in this disease are not well understood, and the exact pathophysiological mechanism behind BMD loss remains unclear. Understanding this association is important to manage potentially low bone mass and reduce the risk of fragility fractures, thereby improving clinical outcomes in patients with SSc.

Aim: This study presents the clinical case of osteoporosis in patients with systemic sclerosis and provides comprehensive data on the prevalence and associated risk factors for bone loss in this disease.

MATERIALS AND METHODS

This article describes the clinical case of OP in patients with SSc and reviews the literature using PubMed, Medline, and the Cochrane Library with keywords such as bone mineral density, osteoporosis, prevalence, risk factors, and systemic sclerosis.

Clinical Case. Patient V., a 59-year-old female, has been diagnosed with SSc since 2019. She has been regularly followed up in the rheumatology department of St. Michael's Clinical Hospital in Kyiv.

During the examination, the patient presented with typical diffuse SSc skin lesions, with a modified Rodnan skin score (mRSS) of 22 points. She had digital ulcers, sclerodactyly (Fig. 1), and telangiectasias on her face and body. High-resolution computed tomography (HRCT) of the chest revealed interstitial lung disease (ILD). Fibrogastroscopy identified gastroesophageal reflux disease, grade II according to the Los Angeles classification, for which she takes proton pump inhibitors (PPIs) regularly. Nailfold capillaroscopy demonstrated a late scleroderma pattern characterized by a low capillary density of 3–4 per mm², absence of giant capillaries, absence of microhemorrhages, and abnormal morphology, including multiple bushy capillary formations (Fig. 2).

Since September 2020, the patient has been receiving therapy with mycophenolate mofetil, calcium channel blockers, PPIs, and intravenous infusions of iloprost. She does not smoke or drink alcohol, has no family history of osteoporosis or fragility fractures, and has not received glucocorticoid therapy during her illness.

Bone mineral density (BMD) was assessed using dual-energy X-ray absorptiometry (DXA):

- Right femoral neck (FN): BMD was 0.623 g/cm², T-score – 2.6 SD.
- Left FN: BMD was 0.673 g/cm², T-score – 2.2 SD.
- Lumbar spine (LS): BMD was 0.696 g/cm², T-score – 3.2 SD.

Vitamin D deficiency was identified, with a 25(OH)D level of 22.6 nmol/L. The patient's FRAX score indicated a high 10-year probability of fractures: 15% for major osteoporotic fractures and 7.8% for hip fractures. These findings highlighted a significant fracture risk, necessitating prompt therapeutic intervention. Consequently, intravenous bisphosphonate therapy with zoledronic acid was initiated after normalizing vitamin D levels.

After initiating treatment, follow-up assessments demonstrated improvements in BMD across all sites:

- Right FN: BMD increased to 0.654 g/cm², T-score – 2.4 SD.
- Left FN: BMD increased to 0.708 g/cm², T-score – 1.9 SD.
- LS: BMD increased to 0.731 g/cm², T-score – 2.9 SD.

Fig.1. Biletaral sclerodactyly with flexion contracture of fingers and active digital ulcers

The increase in BMD at the LS was 5%, and at the FN, 4.9% (Fig. 3). During this follow-up period, no osteoporotic fractures occurred.

The patient's vitamin D level also improved, reaching 78.2 nmol/L, which is within the optimal range for bone health. Notably, the FRAX score showed a reduction in the 10-year hip fracture risk, decreasing from 7.8% to 5.9%, indicating improved hip structural integrity. However, the risk for major osteoporotic fractures remained unchanged at 15%.

The treatment regimen, including zoledronic acid and vitamin D optimization, effectively improved BMD at all sites measured. Despite these improvements, osteoporosis persists, particularly at the LS and right FN, maintaining a significant fracture risk.

We recommended annual monitoring of bone health via DXA and ensuring adequate calcium and vitamin D intake. Long-term monitoring and fracture risk assessment remain critical for this patient, considering the interplay between SSc and the predisposition to OP.

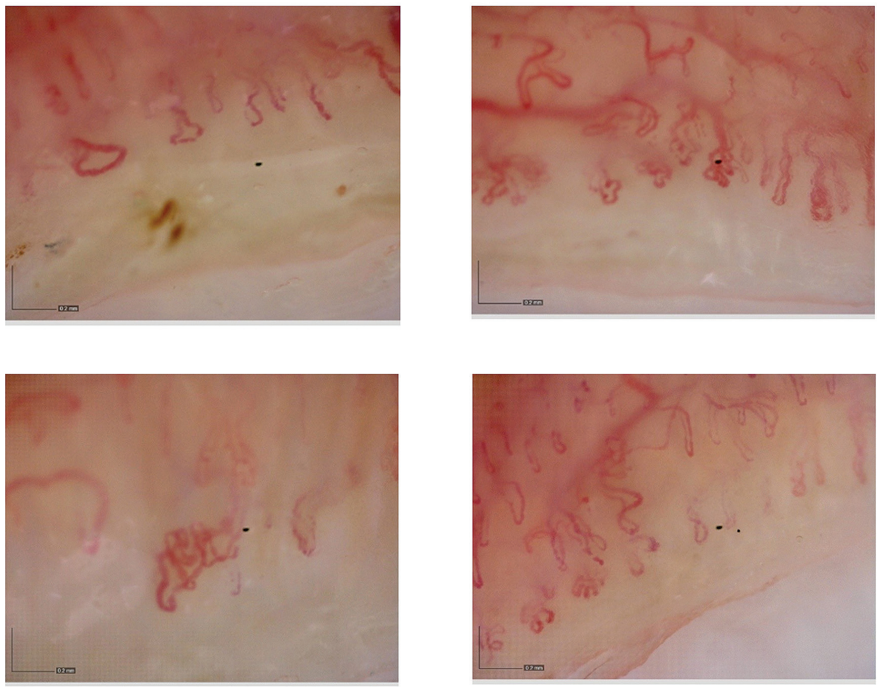

Fig.2. Nailfold capillaroscopy demonstrated a late scleroderma pattern

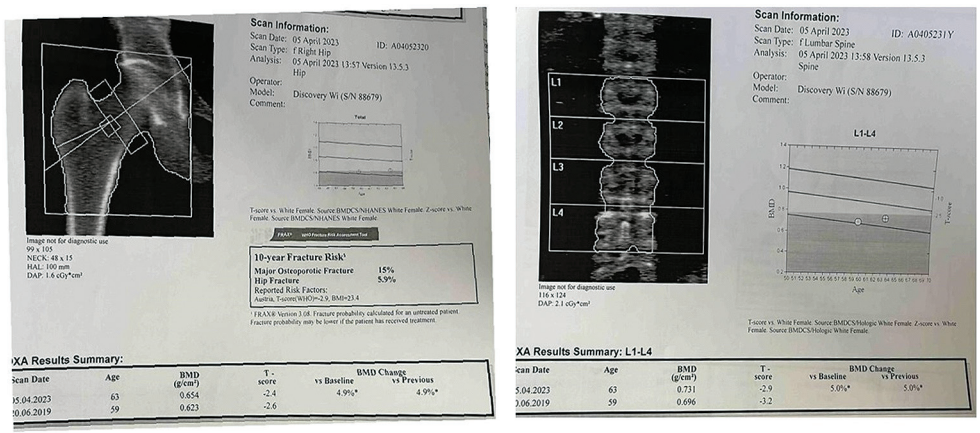

Fig.3. Dual X-ray absorptiometry follow-up of the total hip and the lumbar spine

DISCUSSION

Prevalence of Osteoporosis in Systemic Sclerosis. A study involving 25.5 million women and 6.5 million men found the overall prevalence of OP in Europe in 2019 was 5.6% across all age groups, 6.6% in men over 50 years old, and 22.1% in women over 50 years old [3]. OP is detected more frequently in patients with rheumatic diseases. Horváth et al. found a prevalence of OP in SSc at 22.7% for both LS and FN in a cohort of 44 patients with a mean age of 64.1 years and a mean disease duration of 18 years [4].

In a cross-sectional case-control study investigating BMD and OP prevalence in SSc patients, OP was observed in 14.7%, while osteopenia was found in 51.2% of patients. This was significantly higher than in controls (OP: 9.7%; osteopenia: 41.2%; p = 0.001) [5]. Runowska et al. recorded an OP prevalence of 16.7% in 44 patients with a mean age of 56.5±12.15 years [6].

In Thailand, Chuealee et al. found an overall prevalence of OP in SSc at 29.3% in patients with a mean age of 53.6±10.6 years, where 62.9% had a disease duration of five years or more. The prevalence of OP at the LS was 28.3%, with higher rates in women than men (32.2% vs. 19.4%). At the FN, the prevalence was lower at 8.8%, with a trend toward higher rates in women (11.2% vs. 3.2%; p = 0.06) [7].

Midol et al. found varying prevalence rates of OP in comparative studies: 32% in a Berlin cohort of 477 patients and 23% in a Lille cohort of 485 patients. Fragility fractures were reported in 22% and 18% of patients, respectively [8].

Bimal et al. indicated a prevalence of OP at 33% in a cohort from Australia in which 91 patients were included [9], while Schulz et al. recorded a prevalence of OP at 31.6% in 79 Caucasian SSc patients with a mean age of 66.3±11.2 years and a mean disease duration of 14±7.9 years [10].

OP was the second most common comorbidity (12.9%) after arterial hypertension (23.7%) in an Italian study on comorbidities in SSc that observed 1910 patients [11].

Risk factors for osteoporosis in systemic sclerosis. In addition to the well-known general reasons for OP in rheumatic disorders, there are additional factors associated with the disease. Systemic GC administration, which is much less common in SSc than in other rheumatic diseases, remains a significant contributor to bone loss [1].

Multivariate analysis from a retrospective study in the Berlin university hospital cohort indicated that higher age (OR 1.05; 95% CI 1.03-1.07, p<0.001), female sex (OR 2.70; 95% CI 1.29-5.65, p=0.009), diffuse skin extent (OR 5.03; 95% CI 2.50-10.10, p<0.001), low BMI (OR 0.94; 95% CI 0.88-0.99, p=0.009), WHO-FC III-IV dyspnoea (OR 2.06; 95% CI 1.16-3.67, p=0.014), receiving GCs (OR 1.78; 95% CI 1.10-3.17, p=0.026) or proton pumps inhibitors (PPI) (OR 1.87; 95% CI 1.10-3.17, p=0.020) were associated with OP. As for the other patient populations from this study - the Lille University Hospital cohort - multivariable analysis confirmed the association of OP with older age (OR 1.06; 95% CI 1.04-1.08, p<0.001), GC use (OR 4.48; 95% CI 2.42-8.26, p<0.001), and anti-topoisomerase I antibody positivity (OR 2.22; 95% CI 1.18-4.16, p=0.013) [8].

Duration of the disease may be another potential risk factor for OP in SSc. Patients with longer disease duration have a higher prevalence of low BMD among Italian patients with SSc [12]. In a cross-sectional study by Wang et al., patients diagnosed with OP had a longer duration of disease and were more likely to exhibit sclerodactyly, telangiectasias, interstitial lung disease, and gastroesophageal reflux. They were also more frequently treated with GC and non-corticosteroids immunosuppressants. In logistic regression models adjusted for common risk factors duration of the disease since the first non-PR symptom (OR = 1.05; 95% CI 1.01-1.08) and use of immunosuppressant (OR 2.15; 95% CI 1.18-3.93) were associated with an increased risk of OP [13].

Horváth et al. found that the BMD of LS and FN positively correlated only with BMI (p = 0.002 and p = 0.015 respectively). According to peripheral quantitative computed tomography (pQCT), an inverse correlation between pulmonary manifestation and total (p = 0.024), trabecular (p = 0.035), and cortical density (p = 0.015) was estimated. Anti-Scl70 positivity inversely correlated with pQCT total density (p = 0.015) and the presence of digital ulcers (DU) with cortical density (p = 0.001) [4].

In the Thai study, only low BMI (≤18.5 kg/m2) and menopause were associated with OP at both LS and FN. Other factors including SSc subset, severity of skin tightness, GC used, VD insufficiency or deficiency, smoking history, previous fracture, and family history of fracture were not associated with OP at any sites. In multivariate analysis, low BMI and menopause increased the risk of OP at the LS (OR 7.78; 95% CI 3.21–18.88 and OR 5.32; 95% CI 1.84–15.35, respectively), while only low BMI was significantly associated with OP at FN (OR 4.54; 95% CI 1.41–13.64) [7].

The type of SSc also may play a role in OP development. According to Corrado et al., BMD at the LS and total hip (TH) was significantly lower in dcSSc patients in comparison with the control group (in control 0.853 g/cm2 vs. 0.963 g/cm2, p<0.001; 0.755 g/cm2 vs. 0.932 g/cm2, p<0.00 respectively), whereas there was no significant difference between healthy subjects and lcSSc patients. BMD at LS, TH, and FN were significantly lower in dcSSc patients compared to lcSSc patients. No difference in total mineral content was observed between the control group and lcSSc, whereas total mineral content was significantly lower in dcSSc compared to both the control healthy group (p<0,001) and lcSSc group (p<0,01) [7].

In multivariate analysis, a low lean body mass, the presence of anticentromere antibodies, and older age were identified as independent factors for decreased BMD at the LS (r^2=0.43), FN (r^2=0.61), and TH (r^2=0.73). History or current digital ulcers (DUs) were also identified as an independent factor for microarchitecture alteration of bone [15].

A single-center, cross-sectional controlled study also failed to identify any associations between BMD and specific characteristics of SSc-associated diseases. In univariate analysis, no significant correlation was observed between BMD and the cutaneous subset, heart/lung involvement, calcinosis or acroosteolysis, BMI, vitamin D deficiency, dose of GC, or systemic inflammation. Only age was estimated as an independent risk factor of OP in SSc patients [16].

In contrast, in univariate analysis, age, low BMI, post-menopausal status, dcSSc, gastrointestinal involvement, DUs, and pulmonary arterial hypertension were found to be significantly associated with OP. Multivariate analysis revealed that the presence of OP was significantly associated with lower BMI, post-menopausal status, and the presence of DUs in SSc patients [17].

Calcinosis cutis, or the deposition of calcium in the skin and subcutaneous tissues, is a prevalent and potentially debilitating condition that can affect up to 20-40% of SSc patients The calcinotic material in SSc closely resembles bone, and there is evidence that bone metabolism dysregulation may be a contributing factor in the development of calcinosis. A retrospective study of 5218 SSc patients from an international multicentre cohort found an association between calcinosis and OP (OR 4.2; 95% CI 2.3–7.9, p < 0.0001) [18].

Calcification or calcinosis has been identified as a significant risk factor for low BMD in SSc patients. Calcinosis is a notable risk factor for low BMD (50.5% vs. 36.4%, p = 0.028) [12] and therefore associated with a higher prevalence of OP (43.5% vs. 24.9%, p=0.009) [19]. A statistically relevant correlation between calcinosis was also found by Cadar M. et al. (OR 12.52; 95% CI 2.2-237.3, p=0.02), which suggested common pathogenetic pathway linking calcinosis and OP [20]. Studies investigating the increased prevalence of OP in patients with SSc explore several mechanisms, including the role of bone turnover markers, the Wnt signalling pathway, the RANK-RANKL system, and systemic inflammation, all contributing to bone loss in SSc [21].

In an Australian cohort of 90 SSc patients, a significant correlation was found among those with a history of nasogastric feeding, percutaneous endoscopic gastrostomy feeding, or intravenous total parenteral nutrition and OP (6.9% vs. 0.0%, P = 0.038) [9].

A case-control study in Brazil found a significant association with densitometric OP (p < 0.001), lower weight (p = 0.032), bone mineral index (p = 0.044), anti-RNA polymerase III (p = 0.040), use of GC (p = 0.019), and bisphosphonates (p < 0.001), as well as with densitometric T-scores of LS (p < 0.001), FN (p = 0.025), and TH (p = 0.013). Multivariate analysis showed that the variables significantly associated with fractures were high doses of GC (OR 4.10; 95% CI 1.290–13.090; p = 0.017), bisphosphonates (OR 3.91; 95% CI

Author	Country, year	Parameters
Risk factors for the development of osteoporosis		
Cadar et al.	Italy, 2023	calcinosis (OR 12.52; 95% CI 2.2-237.3, p=0.02) pitting scars (OR 2.02; 95% CI 1.08-11.97, p=0.04) telangiectasia (OR 2.24; 95% CI 1.21-12.09, p=0.02)
Midol et al.	Germany/ France, 2023	Berlin cohort: age (OR 1.05; 95% CI 1.03 - 1.07, p<0.001) female sex (OR 2.70; 95% CI 1.29 - 5.65, p=0.009) diffuse skin extent (OR 5.03; 95% CI 2.50 - 10.10, p<0.001) BMI (OR 0.94; 95% CI 0.88 - 0.99, p=0.009), WHO-FC III-IV dyspnoea (OR 2.06; 95% CI 1.16-3.67, p=0.014), GCs (OR 1.78; 95% CI 1.10 - 3.17, p=0.026) PPIs (OR 1.87; 95% CI 1.10 - 3.17, p=0.020) Lille cohort: age (OR 1.06; 95% CI 1.04 - 1.08, p<0.001) GCs (OR 4.48; 95% CI 2.42 - 8.26, p<0.001) anti-topoisomerase I antibody positivity (OR 2.22; 95% CI 1.18 - 4.16, p=0.013)
Bimal et al.	Australia, 2021	nasogastric feeding, percutaneous endoscopic gastrostomy feeding or intravenous total parenteral nutrition (6.9% vs 0.0%, P = 0.038) prednisolone (58.6% vs 85.2%, P = 0.005)
Chuealee et al.	Thailand, 2021	at the LS: BMI (OR 7.78; 95% CI 3.21 - 18.88) and menopause (OR 5.32; 95% CI 1.84 - 15.35) at the FN: BMI (OR 4.54; 95% CI 1.41 - 13.64)
Wang et al.	USA, 2020	disease duration from first non-RP symptom (Adjusted OR = 1.05, 95% CI 1.01-1.08) immunosuppressants (Adjusted OR = 2.15; 95% CI 1.18 - 3.93)
Avouac et al.	France, 2012	age (mean +/- SD age 67 +/- 12 years versus 60 +/- 10 years; p = 0.03) disease duration (mean +/- SD 15 +/- 10 years versus 8 +/- 8 years; P < 0.001)
Risk factors for reduced BMD according to DXA		
Parlati et al.	Italy, 2024	disease duration (19.9 years vs. 15.2 years, P = 0.002) calcinosis (50.5% vs. 36.4%, P = 0.028) myositis (12.6% vs. 0.7%, P <0.001) synovitis (42.7% vs. 28.6%, P = 0.022) gastrointestinal involvement (76.7% vs. 47.1%, P <0.001) interstitial lung disease (53.0% vs. 40.0%, P <0.001)
Horváth et al.	Hungary, 2019	BMI for LS (B = 0.014, β = 0.471, p = 0.002) and for FN (B = 0.009, β = 0.346, p = 0.027)
Corrado et al.	Italy, 2015	dcSSc subtype for LS and TH (p<0,001)
Marot et al.	France, 2015	age, lean mass, and anti-centromere antibodies for TH (r2= 0.73; p < 0.00001)

Risk factors for bone loss according to pQCT		
Horváth et al.	Hungary, 2019	anti-topoisomerase I antibody positivity for total density (B = -50.693, β = -0.313, p = 0.015) and for cortical density (B = -94.645, β = -0.401, p = 0.007) pulmonary manifestations for total density (B = -51.367, β = -0.423, p = 0.024), for trabecular density (B = -48.234, β = -0.318, p = 0.035) and for cortical density (B = -82.502, β = -0.326, p = 0.015), digital ulcers for total density (B = -56.903, β = -0.402, p = 0.007) and cortical density (B = -92.848, β = -0.450, p = 0.001)
Marot et al.	France, 2015	Anti-centromere antibodies, digital ulcers, lean mass, number of previous fractures for Dtrab at the tibia (r2 = 0.33; p = 0.007), current digital ulcers, number of previous fractures, lean mass, and menopause duration for Tb.Sp at tibia (r2 = 0.66, p < 0.0001)

1.699–8.984, p=0.001), negative anti-Scl70 (OR 0.34; 95% CI 0.124–0.943, p=0.038), and lumbar T-score (OR 0.39; 95% CI 0.034–0.460, p=0.010) [22].

In multivariate analysis, only age (mean age 67±12 years vs. 60±10 years; P = 0.03) and longer disease duration (15±10 years vs. 8±8 years; P < 0.001) were identified as independent risk factors for fracture in patients with SSc [16].

In the Table, we summarise the data relating to the factors associated with reduced bone mass.

Risk factors for bone status deterioration in patients with systemic sclerosis

Note B: (+95% CI) regression coefficient; DXA: dual-energy X-ray absorptiometry; BMI: body mass index; BMD: bone mineral density; CI: confidence interval; dcSSc: diffuse cutaneous systemic sclerosis; Dtrab: volumetric trabecular bone mineral density; FN: femoral neck; GC: glucocorticoids; LS: lumbar spine; OR: odds ratio; PPI: proton pump inhibitor; pQCT: peripheral quantitative computed tomography; RP: Raynaud's phenomenon; Tb.Sp: trabecular separation; TH: total hip; WHO-FC: World Health Organization-Functional Class; β: standardized linear coefficients.

Our review has several limitations. We included a relatively small number of papers of the different types and designs which may have resulted in bias in conclusions on the true prevalence and role of disease-associated risk factors of OP in SSc. Our review has highlighted the problem of OP in SSc and shown that more large longitudinal cohort studies are needed to provide clear conclusions and

Our review has provided a platform for future advanced studies. These findings support the identifying SSc patients at a higher risk for OP in clinical practice. Further longitudinal researches are needed into the identification of patients with SSc who are at risk of OP and its complications for successful management.

CONCLUSION

OP is rather prevalent in patients with SSc. BMD at different sites in the skeleton appears to be lower in SSc than in control subjects. The causes of OP in SSc are multifactorial. It includes common risk factors such as older age, female sex, menopause, and BMI. According to published data, specific disease-related factors associated with OP are disease duration, diffuse skin subset, digital ulcers, calcinosis, anti-topoisomerase I antibody positivity, pulmonary and gastrointestinal involvement as treatments with PPI and GCs. The misalignment of results analyzed resources may be due to differences in study design, sample size and assessment tools.

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Consent to publish. The patient's consent for publication was obtained. All personal data of the patient are hidden in this article.

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ОСТЕОПОРОЗ ПРИ СИСТЕМНІЙ СКЛЕРОДЕРМІЇ

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Актуальність. Остеопороз (ОП) та атравматичні переломи є поширеною та добре відомою коморбідною патологією у пацієнтів з ревматичними захворюваннями. Проте, поширеність та фактори ризику ОП при системній склеродермії (ССД) вивчені недостатньо. Частота ОП при ССД за даними літератури коливаються в межах від 8,8% до 51,6%. Остаточно не встановлені предиктори втрати кісткової тканини при ССД.

Мета. У статті ми наводимо клінічний випадок остеопорозу у пацієнтки із системною склеродермією та демонструємо дані літератури щодо поширеності та асоційованих факторів ризику втрати кісткової маси при цьому захворюванні.

Матеріали і методи. У статті описано клінічний випадок ОП у пацієнтки із ССД та проведено огляд літератури з використанням PubMed, Medline та Кокранівської бібліотеки за такими ключовими словами, як мінеральна щільність кісткової тканини, остеопороз, поширеність, фактори ризику та системна склеродермія.

Результати. Продемонстровано клінічний випадок ОП у пацієнтки з ССД та позитивний ефект лікування бісфосфонатами. Додатковими факторами ризику втрати кісткової маси, які пов'язані із основним захворюванням вірогідно є: дифузний шкірний підтип ССД, склеродактилія з активними виразками на пальцях рук, пізній склеродермічний патерн при капіляроскопії, інтерстиційне захворювання легень, ураження шлунково-кишкового тракту та лікування інгібіторами протонної помпи.

Висновки. ОП є досить поширеним у пацієнтів з ССД. Згідно з опублікованими даними, специфічними факторами, пов'язаними із захворюванням, асоційованими з ОП, є: тривалість захворювання, дигітальні виразки, кальциноз, ураження легень та шлунково-кишкового тракту, а також лікування інгібіторами протонної помпи та глюкокортикоїдами. Ці результати підтверджують, що в клінічній практиці пацієнти з ССД мають вищий ризик розвитку ОП та його ускладнень.

Ключові слова: мінеральна щільність кісткової тканини, остеопороз, поширеність, фактори ризику, системна склеродермія.