

# Anti-osteoporotic medication and scleroderma

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## ABSTRACT

*Scleroderma (systemic sclerosis) represents a challenging condition, usually requiring a multi-disciplinary team due to multi-organ involvement; it is mostly considered an autoimmune disease; the signature of the malady is the extensive fibrosis at the level of skin and multiple organs, associating endothelial/vessel damage and anomalies of immune response. We point out a few aspects concerning scleroderma-related osteoporosis. This is a literature review. Patients might associate low bone mineral density (the underlying mechanisms are not entirely understood), thus an increased risk of fractures; so early recognition and treatment is mandatory for a better outcome. Some data showed that particularly vertebral fractures are prone to the condition. Almost half of individuals with the malady have osteoporosis (female prevalence, especially post-menopausal) and one third of them have an osteoporotic fracture. Older age and associated vitamin D deficiency increases the risk of fracture. Vitamin D has pleomorphic distribution, also targeting the immune modulation, cytokines puzzle, and the muscle-bone crosstalk in scleroderma. Hypovitaminosis D might be expected in these patients, while general D-supplementation has controversial benefits effects. Chronic inflammatory rheumatic conditions might benefit from the TBS use as fracture risk indicator through micro-architecture evaluation. It seems that patients with systemic sclerosis and malnutrition have lower TBS; high Dkk-1 serum levels (Dickkopf-1) is correlated with reduced TBS and advanced disease; TBS is correlated to the extent of microvascular complications; exposure to glucocorticoids (certain high-dose regimes) supplementary lowers TBS. Gastro-intestinal complications are presented in 90% of patients with systemic sclerosis, involving fibrosis at any level which is a poor prognostic factor; malabsorption of nutrients and weight loss correlates with reduced bone formation while esophageal and gastric anomalies contraindicate the use of oral bisphosphonates for osteoporosis. Other abnormal elements of skeleton frame include: premature ovarian failure, serotonin system anomalies, chronic inflammation, potential side effects of immunosuppressant drugs. In patients with systemic sclerosis, the choices of medication targeting osteoporosis are limited; the use of intravenous bisphosphonates remains first line option (if renal function is adequate); the consideration of skin and esophageal anomalies is mandatory in the management of osteoporosis. Overall, the landscape of bone domain in systemic sclerosis is multi-leveled and some areas are still waiting for clear answers.*

**Keywords:** osteoporosis, scleroderma, systemic sclerosis, DXA, bone, skeleton, fracture, TBS, vitamin D, menopause, nutrition, autoimmune

## INTRODUCTION

Osteoporosis, especially menopause-related as well as age-related osteoporosis (namely primary osteoporosis which might also affect men) represents a significant economic burden for health care systems in terms of associated costs for osteoporotic fractures in addition to management of the condition in terms of diagnostic and starting/following the medication against the disease in order to prevent fragility fractures (primary and secondary prevention) (1-12).

Scleroderma (systemic sclerosis) represents a challenging condition, usually requiring a multi-disciplinary team due to multi-organ involvement; it is mostly considered an autoimmune disease; the signature of the malady is the extensive fibrosis at the level of skin and multiple organs, associating endothelial/vessel damage and anomalies of immune response; due to complicated medical picture, a dramatic impact on life quality and economic burden is expected (13-22).

## METHOD

We point out a few aspects concerning scleroderma-related osteoporosis. This is a literature review. 73 references are cited based on clinical relevance following the micro-sections of the paper. We only refer to *in extenso* English papers. For example purpose, two figures are introduced (previously unpublished figures are related to a case patient who is followed by a multi-disciplinary team; she agreed for the use of the images below).

## OSTEOPOROSIS IN SYSTEMIC SCLEROSIS

Patients with multi-organ damage due to systemic sclerosis associate low bone mineral density (the underlying mechanisms are not entirely understood), thus an increased risk of vertebral and potentially non-vertebral fractures; so early recognition and treatment is mandatory for a better outcome (23-28).

A meta-analysis from 2021 included 18 studies that confirmed a statistically significant lower bone mineral density at central DXA (dual-energy X-ray absorptiometry) than control at all sites (lumbar, femoral neck, total hip) and whole body assessment and a statistically significant higher risk of vertebral fractures (23).

Another meta-analysis selected from 1032 original papers, 19 studies (including 15 controlled studies) focusing on scleroderma-related osteoporosis; the results showed a 74-100% prevalence of female sex; menopausal status ranges from 45% to 100%; the diagnostic of osteoporosis was established in almost half of patients among all the patients with systemic sclerosis;

most of studies (not all) confirmed low bone mineral density at DXA; the highest fracture ratio is 33% (24).

A cross-sectional study from 2021 showed on 71 patients with systemic sclerosis versus 139 subjects with rheumatoid arthritis and 277 healthy control that the prevalence of osteoporosis is higher in both rheumatologic conditions versus control (one third of each sub-group) while the fracture rate was of 35% in scleroderma (age and 25-hydroxyvitamin D are collateral high risk factors) (25).

## VITAMIN D DEFICIENCY

Hypovitaminosis D represents a worldwide medical problem, affecting multiple rheumatologic, endocrine, and gynecologic conditions (29-31). An analysis published in 2021 on 40 studies concerning vitamin D and systemic sclerosis showed an increased prevalence of its deficiency with controversial improvement on regular supplementation (32). Vitamin D has pleomorphic distribution, also targeting the immune modulation, cytokines puzzle, and muscle-bone crosstalk in scleroderma (33-40).

## TRABECULAR BONE SCORE (TBS)

TBS expresses the micro-architecture damage as a bone quality feature and it became an additional tool for fracture risk evaluation in primary osteoporosis as well as type 2 diabetic and menopausal women or high glucocorticoid exposure etc. (41-48). Chronic inflammatory rheumatic conditions might benefit from the TBS use (49). It seems that patients with systemic sclerosis and malnutrition have lower TBS (50). Also, high Dkk-1 blood levels (Dickkopf-1) is correlated with reduced TBS and advanced disease (51). Moreover, TBS is correlated to the extent of microvascular complications (52). Exposure to glucocorticoids (certain high-dose regimens) supplementary lowers TBS (53).

## DIGESTIVE COMPLICATIONS AND BONE

Gastro-intestinal complications are presented in 90% of patients with systemic sclerosis, involving fibrosis at any level which is a poor prognostic factor; malabsorption of nutrients and weight loss correlates with reduced bone formation while esophageal and gastric anomalies contraindicate the use of oral bisphosphonates for osteoporosis (54-57).

## CUTANEOUS INVOLVEMENT FACING BONE STATUS

Multiple dermatological aspects in scleroderma affects vitamin D absorption (which is 80% related to

sun-associated skin absorption) while subcutaneous medication against osteoporosis (like teriparatide or denosumab) might not work due to cutaneous fibrosis (58-60). Isolated cases reports with teriparatide worsening calcinosis cutis or soft tissue dystrophic calcification are reported (61,62).

## MENOPAUSAL STATUS

In females with systemic sclerosis there is a report of higher risk to associate estrogen-related conditions like low rate of fertility, premature ovarian failure, low ovarian reserve, early menopause; all of these with negative effects on vitamin D, but, also, on bone metabolism; the pathogenic elements varies from autoimmune-related anomalies, chronic inflammation, low body mass index, microvascular impairment etc. (63-68).

## PHARMACOLOGICAL APPROACH

In patients with systemic sclerosis, the choices of medication targeting osteoporosis are limited; the use of intravenous bisphosphonates remains a first line option (if renal function is adequate); the consideration of

skin and esophageal anomalies is mandatory in the management of osteoporosis as mentioned above (69,70).

## DISCUSSIONS

Other mechanisms that are contributors to low bone mineral density and increased fracture risk include chronic inflammation status plus anomalies of nutritional balance (due to malnutrition, malabsorption etc.) (71,72). Interferences with serotonin system is also a contributor to bone damage; peripheral 5-hydroxytryptamine targets the skeleton on a negative way (73). Vascular damage at micro level affects bone vessels, as well and bone regenerative capacity (74). Many of the drugs against systemic sclerosis like immunosuppressant regimes are additional contributors to bone anomalies (75).

## CONCLUSION

The landscape of bone domain in systemic sclerosis is multi-leveled while some areas are still waiting for clear answers.

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