

Scleroderma and osteoporosis

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Why pay attention to osteoporosis in patients with systemic sclerosis (SSc)?

- 75% females
- Early menopause
- Malnutrition → low BMI / lean body mass
- Vitamin D deficiency
- Renal failure
- Reduced physical activity
- Medication: glucocorticoids, cyclophosphamide
- Increased incidence of fractures

Avouac, Arthritis Care Res 2012

Atteritano, PLoS one 2013

Lai, Ann Rheum Dis 2015



Overview: Osteoporosis in SSc

- Background
- Epidemiology of osteoporosis in SSc
- Etiology of osteoporosis in SSc
- Fractures in SSc
- Conclusions
- Diagnostic and therapeutic implications



Background Systemic Sclerosis

- Connective tissue disease characterized by
 - Fibrosis of the skin and internal organs
 - Alterations in vasculature
 - Activation of the immune system
- Prevalence: 8-350 / million (Europe)
- Incidence: 4-90 / million / year (Europe)
- Disease onset: usually between 30 – 55 years
- Female : male = 3 : 1

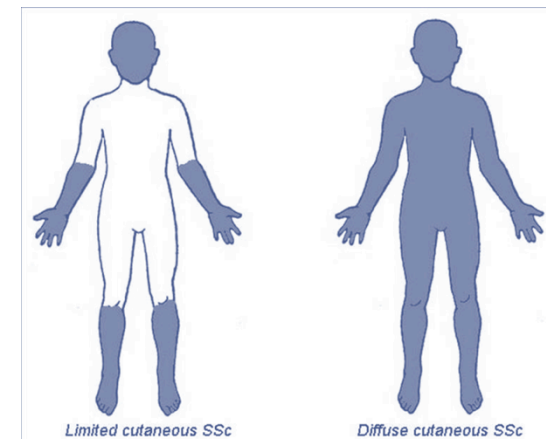




Background Systemic Sclerosis

Classification

- Limited cutaneous SSc (lcSSc)
- Diffuse cutaneous SSc (dcSSc)
- SSc sine scleroderma
- SSc overlap syndromes
- Pre-SSc





Background Systemic Sclerosis

Prognosis: improved over the last decades (European data^{1,2,3})

- All SSc 10-year survival \pm 70–75%
- dcSSc 10-year survival \pm 49%
- lcSSc 10-year survival \pm 82%



Improved survival in SSc \rightarrow more attention for complications

Complications of systemic sclerosis



... but also osteoporosis
and fractures

1 Ferri, Medicine 2002

2 Czirjak, Ann Rheum Dis 2008

3 Joven, Semin Arthritis Rheum 2010



Epidemiology of osteoporosis in SSc

1982: First study on bone mineral content (BMC) in SSc

- 37 SSc patients (30 female, 7 male) + matched controls
- BMC of nondominant radius measured by photon absorptiometry
- X-ray: soft tissue calcification of the hands

Results

- BMC significantly ↓ in SSc compared to controls
- Calcium metabolism: no difference
- Soft tissue calcification (20/37 patients) was significantly more frequent in patients with low BMC

Serup, Acta Dermatovener 1982



Epidemiology of osteoporosis in SSc

1991: First study on BMD in SSc

- 90 females with SSc, 90 age-matched healthy controls
- BMD and BMC of nondominant radius measured with dual-photon-absorptiometry

Results

- BMD and BMC significantly ↓ in SSc compared to controls
- Calcium metabolism: no differences
- No influence of the extent of skin involvement or internal organ involvement
- SSc: significantly earlier menopause compared to controls

La Montagna et al, Clin Rheumatol 1991



Epidemiology of osteoporosis in SSc

Until May 2016: 20 studies on BMD in SSc (19/20 controlled)

- Cross-sectional studies only
- All studies: BMD significantly ↓ in SSc patients compared with healthy controls
- Number of SSc patients included: 15 – 159
- Predominantly females studied (74-100%)

Results	
Osteoporosis (T-score \leq -2.5)	3 – 51%
Osteopenia (T-score between -1.0 and -2.5)	27 – 53%
Osteopenia / osteoporosis	up to 70%

Caimmi, Calcif Tissue Int 2016



Etiology of osteoporosis in SSc

1. Traditional risk factors
2. Inflammation / SSc specific risk factors
3. Serological factors
4. Metabolic factors
5. Genetic factors
6. Role of medication



Influence of traditional risk factors

Risk factor	Studies supporting factor	Studies against factor
Age	+++++	++
Female sex	?	+++
Postmenopausal status	++++	none
Low BMI/lean body mass	+++++++	+
Caucasian ethnicity	-	<ul style="list-style-type: none">• Omail, Clin Exp Rheumatol 2014: non-Caucasian risk factor• Carbone, Rheumatology 1999: no difference between Caucasians and African Americans
Alcohol use	?	?
Smoking	?	-



Inflammation / SSc specific risk factors

Markers of inflammation (ESR, CRP)

	Studies supporting factor	Studies against factor
Increased ESR and/or CRP	none	<ul style="list-style-type: none">• Frediani, Clin Exp Rheum 2004• Atteritano, PLoS one 2013• Spanjer, ASBMR 2015 (SU0367)

Disease duration

	Studies supporting factor	Studies against factor
Disease duration	<ul style="list-style-type: none">• Di Munno, Clin Rheumatol 1995• Ibn Yacoub, Rheumatol Int 2012	<ul style="list-style-type: none">• Yuen, J Rheumatol 2008• Mok, Rheumatology 2013• Atteritano, PLoS one 2013• Caimmi, Calcif Tissue Int 2016

Inflammation / SSc specific risk factors



SSc subtype

	Studies supporting factor	Studies against factor
DcSSc subtype	<ul style="list-style-type: none">• Carbone, Rheumatology 1999• Frediani, Ann Rheum Dis 2004	<ul style="list-style-type: none">• La Montagna, Clin Rheumatol 1991• Yuen, J Rheumatol 2008• Mok, Rheumatology 2013• Spanjer, ASBMR 2015 (SU0367)• Caimmi, Calcif Tissue Int 2016

Internal organ involvement

	Studies supporting factor	Studies against factor
Internal organ involvement	<ul style="list-style-type: none">• Frediani, Ann Rheum Dis 2004	<ul style="list-style-type: none">• La Montagna, Clin Rheumatol 1991• Di Munno, Clin Rheumatol 1995• Mok, Rheumatology 2013



Inflammation / SSc specific risk factors

Lung involvement

	Studies supporting factor	Studies against factor
Lung involvement - Interstitial lung disease and / or - Pulmonary arterial hypertension	Caimmi, Calcif Tissue Int 2016	None



Inflammation / SSc specific risk factors

Calcinosis

	Studies supporting factor	Studies against factor
Calcinosis	<ul style="list-style-type: none">Serup, Acta Derm Venereol 1983	<ul style="list-style-type: none">Di Munno, Clin Rheumatol 1995Rios Fernandez, J Rheumatol 2010Caimmi, Calcif Tissue Int 2016

Malabsorption

	Studies supporting factor	Studies against factor
Malabsorption	<ul style="list-style-type: none">Ibn Yacoub, Rheumatol Int 2012	none



Inflammation / SSc specific risk factors

Medsger disease severity scale

	Studies supporting factor	Studies against factor
Medsger disease severity scale	<ul style="list-style-type: none">Kilic, Int J Rheumatic Diseases 2013	<ul style="list-style-type: none">Mok, Rheumatology 2013Spanjer, ASBMR 2015 (SU0367)

Modified Rodnan skin score

	Studies supporting factor	Studies against factor
Modified Rodnan skin score	<ul style="list-style-type: none">Kilic, Int J Rheumatic Diseases 2013	<ul style="list-style-type: none">Mok, Rheumatology 2013Spanjer, ASBMR 2015 (SU0367)



Inflammation / SSc specific risk factors

Physical activity

- Significantly reduced in SSc patients (n=15)

Carbone, Rheumatology 1999

- Suggested factors: skin involvement, muscle weakness, arthralgia, myalgia, fatigue, lung involvement, cardiac involvement, PAH
- However, no relationship between physical activity and BMD in SSc patients (1 small study)

Carbone, Rheumatology 1999



Serological factors

Risk factor	Studies supporting factor	Studies against factor
Anti-Scl 70 antibodies (anti-topoisomerase I)	<ul style="list-style-type: none">Ibn Yacoub, Rheumatol Int 2012	<ul style="list-style-type: none">Frediani, Ann Rheum Dis 2004Mok, Rheumatology 2013
Anti-centromere antibodies	<ul style="list-style-type: none">Marot, Oncotarget 2015	none



Metabolic factors

Vitamin D deficiency/insufficiency

- Highly frequent in SSc patients

Italy

Dovio, J Rheumatol 2008, Atteritano PLoS one 2013

Spain

Rios Fernandez, J Rheumatol 2010

Rios Fernandez, Clin Exp Rheumatol 2012

Morocco

Ibn Yacoub, Rheumatol Int 2012

Turkey

Kilic, Int Journal Rheumatic Diseases 2013

Canada

Omair, Clin Exp Rheumatol 2014

- Study in Spain (n = 48 SSc patients) Rios Fernandez, J Rheumatol 2010
 - 81% 25(OH)D level < 30 ng/ml
 - 9.5% 25(OH)D level < 10 ng/ml
 - despite 60.4% using vit D supplements (800 IU/day)

Influence of 25(OH)D levels on BMD in SSc



Significant association between 25(OH)D levels and BMD in SSc patients was demonstrated in 2 cross-sectional studies:

1) Study in Italy

Atteritano, PLoS one 2013

N=54 postmenopausal women with SSc + 54 matched controls

2) Study in Morocco

Ibn Yacoub, Rheumatol Int 2012

N=60 women with SSc + 60 matched controls

Other cross-sectional studies: no association

Rios Fernandez, J Rheumatol 2010 (N=48 patients)

Avouac, Arthritis Care Res 2012 (N=71)

Marot, Oncotarget 2015 (N=33)

Caimmi, Calcif Tissue Int 2016 (n=106)



Vitamin D deficiency/insufficiency in SSc

Supposed contributing factors

1. Intestinal malabsorption
2. Decreased vitamin D production in the skin due to
 - Fibrous thickening of the skin and/or
 - Reduced sun exposure
3. Renal failure



Metabolic factors

→ Increased bone turnover in SSc patients

Cross-sectional study by Atteritano et al

- 54 postmenopausal women with SSc + 54 age-matched controls
- Bone markers:
 - Serum osteocalcine (osteoblast activity) ↑ in SSc
 - Urine deoxypyridinoline (osteoclast activity) ↑ in SSc
- No association between bone markers and BMD, but cross-sectional study

Atteritano et al, PLoS one 2013



Metabolic factors

Cross-sectional study by Caimmi et al

- 106 SSc patients (85% female, 63% postmenopausal)
- Bone turn-over markers in serum:
 - CTX (C-terminal telopeptide of type I collagen)
 - b-ALP (bone-specific alkaline phosphatase)

Results:

- Mean serum CTX and b-ALP in normal range
- Serum CTX level negatively correlated with lumbar spine BMD

Caimmi, Calcif Tissue Int 2016



Genetic factors

Only one study on the relationship between genetic factors and BMD in SSc

- N = 25 patients
- Results: HLA class I and class II alleles (HLA-A2, HLA-B18, HLA-Cw4, HLA-Cw7, HLA-DR11, HLA-DQ7)
→ no relationship with BMD in SSc patients

D'Amore, Minerva Med 2005



Role of medication

	Studies supporting factor	Studies against factor
Glucocorticoids	<ul style="list-style-type: none">Koumakis, J Rheumatol 2015: daily GC dose is significant risk factor for low <u>trabecular bone score</u> (TBS)	<ul style="list-style-type: none">Sampaio-Barros, Clin Exp Rheumatol 2005Rios-Fernandez, J Rheumatol 2010Mok, Rheumatology 2013Atteritano, PLoS one 2013Spanjer, ASBMR 2015Caimmi, Calcif Tissue Int 2016
Cyclophosphamide	none	<ul style="list-style-type: none">Sampaio-Barros, Clin Exp Rheumatol 2005

→ No longitudinal studies on factors associated with BMD change in SSc published yet



Role of GCs

Study of Koumakis

- 65 women with SSc, 138 women with RA, 227 age-matched controls
- Assessments: Trabecular bone score (TBS) and aBMD (DXA)

Koumakis, J Rheumatol 2015

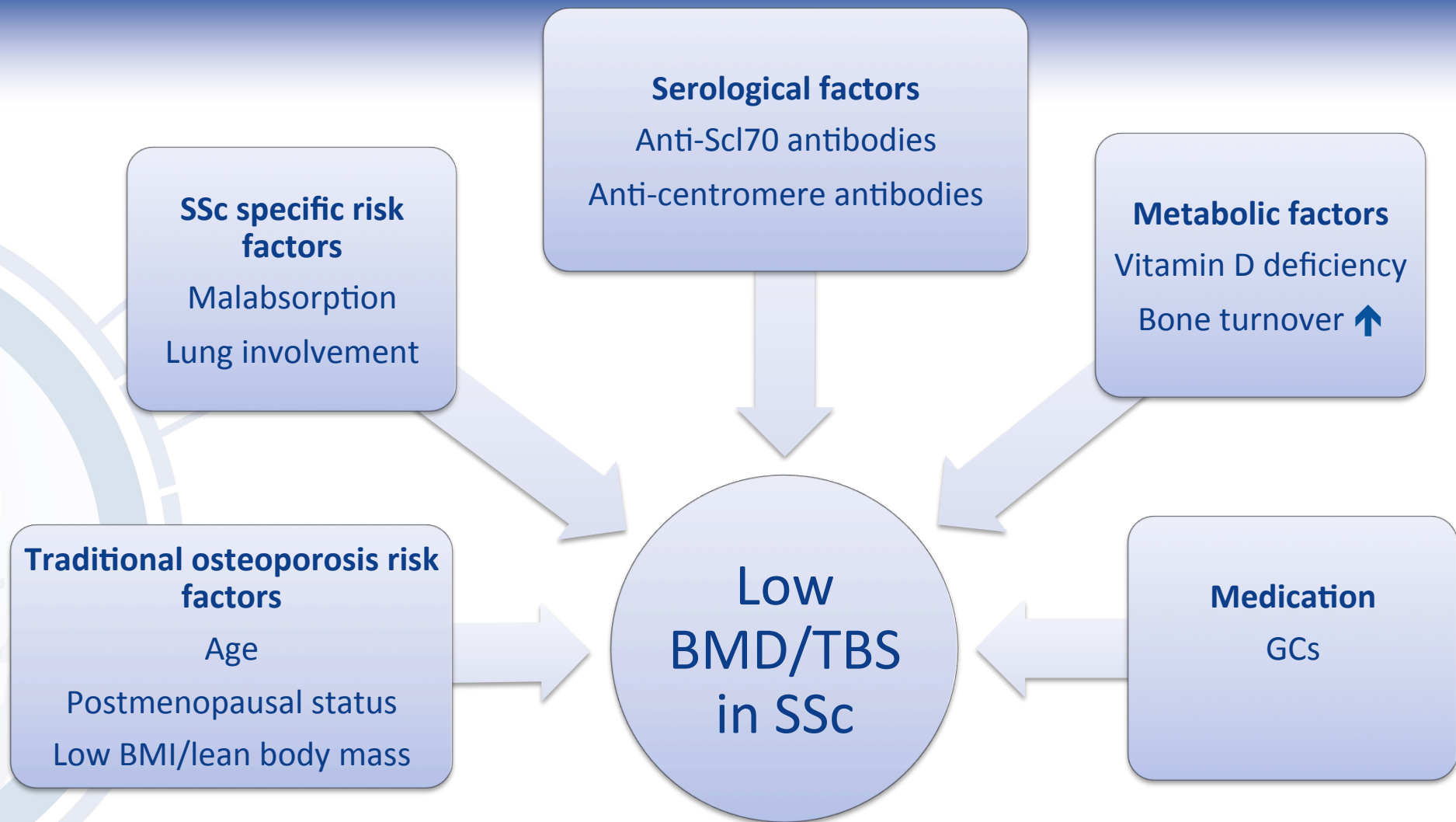
Results:

- TBS significantly ↓ in SSc compared to controls and similar to RA despite lower cumulative and daily GC dose
- Low TBS is independently associated with daily GC dose in SSc, not in RA

→ The negative effect of GCs on bone in SSc might be related to impaired bone quality (microarchitecture), not bone density



Risk factors for osteoporosis in SSc





Fractures in SSc



Studies on symptomatic fractures in patients with SSc



Study	N	Follow-up (years)	Fractures	Point prevalence or IRR	Risk factors
Avouac (France)	71 SSc + 227 HC	10	all	30% vs 11%	<ul style="list-style-type: none"> Age Low 25(OH)D
Atteritano (Italy)	54 SSc + 54 HC	5.0	vertebrae	24% vs 1.8%	NA
Lai (Taiwan); nation-wide study	1712 SSc + 6400 HC	5.2	hip vertebrae radius	All: IRR 1.69 (1.30-2.18) Hip: IRR 1.89 (1.05-3.22) Vertebrae: IRR 1.78 (1.30-2.39) Radius: IRR 0.12 (0.47-2.72)	<ul style="list-style-type: none"> Age Female sex GC >7.5 mg/day Metoclopramide IV



Mortality after osteoporotic fractures

Nation-wide study Taiwan

- 1712 SSc patients + 6400 matched healthy controls
- Fractures: hip, vertebrae, radius, overall
- Median FU: 5.2 years (2.5 – 7.0)

1-year mortality rate after fracture

Fracture event	SSc (n = 1712)	Controls (n = 10272)	P value
Overall	9 (12.3%)	17 (4.5%)	0.023
Vertebral	7 (13.0%)	8 (3.0%)	0.006
Hip	2 (11.8%)	9 (11.4%)	1
Radius	1 (14.3%)	2 (4.0%)	0.330

Prevalent vertebral fractures in SSc?



?

Prevalent vertebral fractures in females with SSc



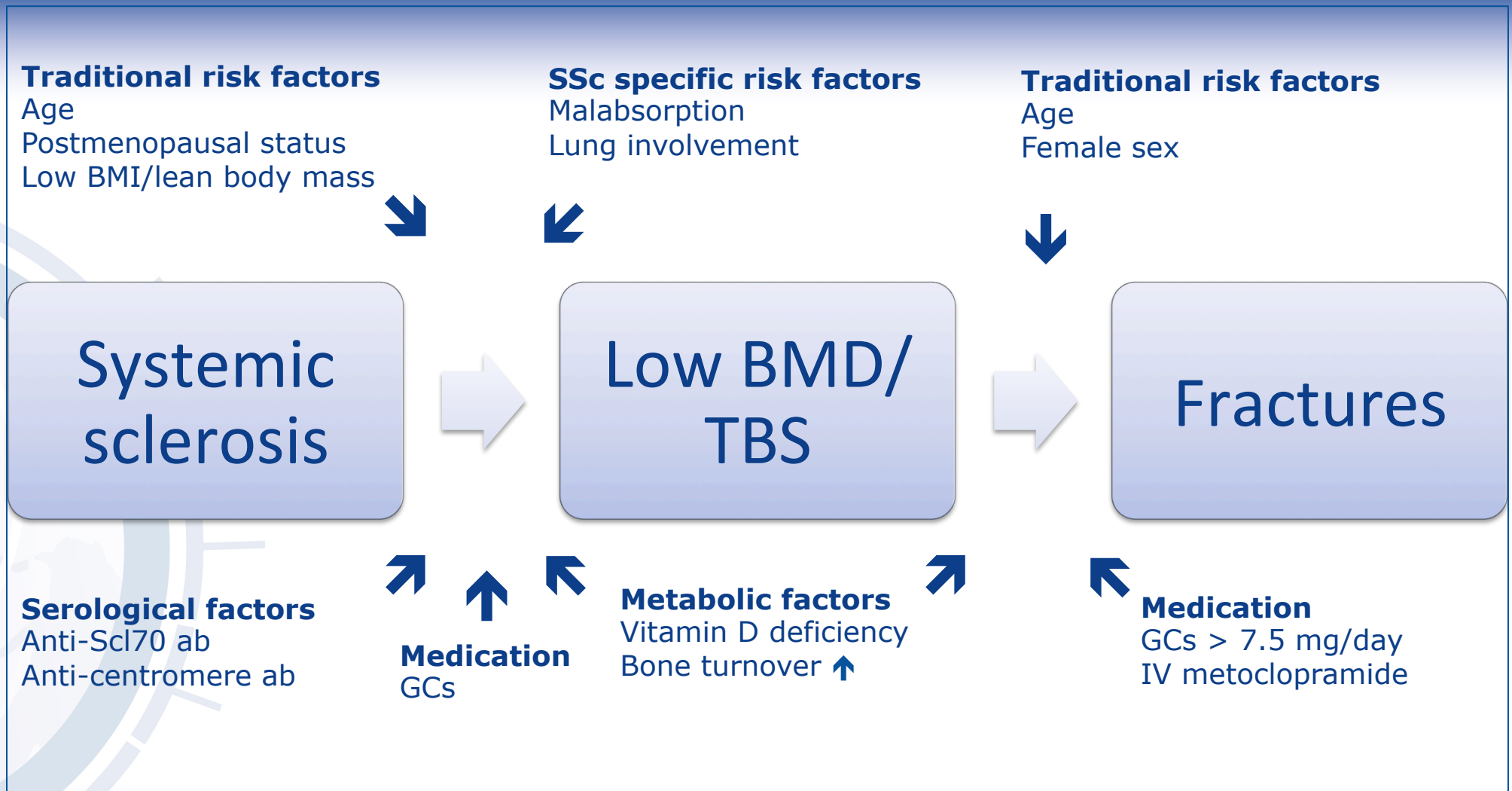
- Two controlled studies
- Semi-quantitative measurement of vertebral fractures using spine X-rays

Study	N	Mean age (years)	% with vertebral fracture(s)	Risk factors
Avouac (France)	71 SSc + 227 HC	62 ± 12	24% (SSc) versus 1.8% (HC)	N.A.
Atteritano (Italy)	54 SSc + 54 HC	54 ± 1.7	25% (SSc) versus 1%	N.A.

Avouac, Arthritis Care Res 2012
Atteritano, PLoS one 2013



Risk factors for low BMD and fractures in SSc





Underdiagnosis and undertreatment

Underdiagnosis of:

- Low BMD: Assessment of BMD and vertebral fractures (DXA + VFA) often not performed in SSc patients
 - Focus on other disease complications (lungs, heart, renal, gastrointestinal)
 - Patients with poor prognosis
- Vitamin D deficiency: highly prevalent in SSc patients
- Premature menopause: increased occurrence in SSc

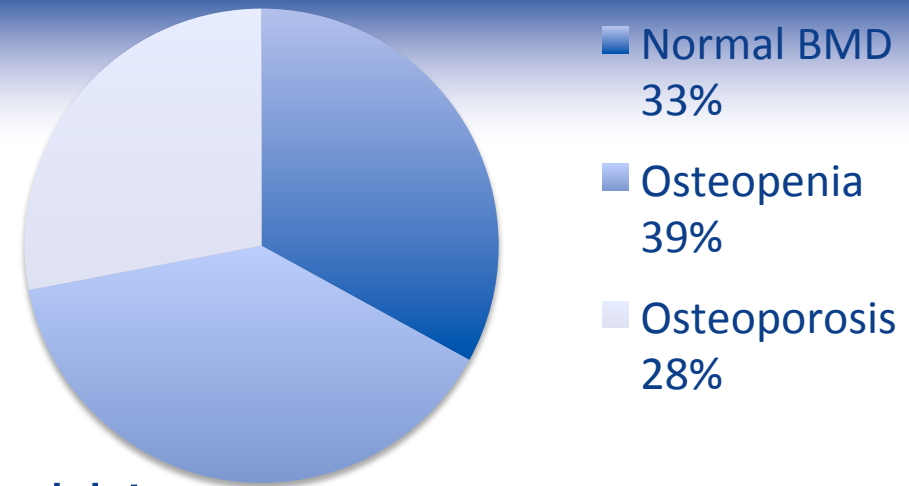


Underdiagnosis and undertreatment

Undertreatment

Dutch study

- N=61 SSc patients
- DXA measurement lumbar spine and hip
- 67% osteopenia or osteoporosis in ≥ 1 site
- 28% with osteoporosis \rightarrow 91% did not use bisphosphonates or other anti-osteoporosis agents

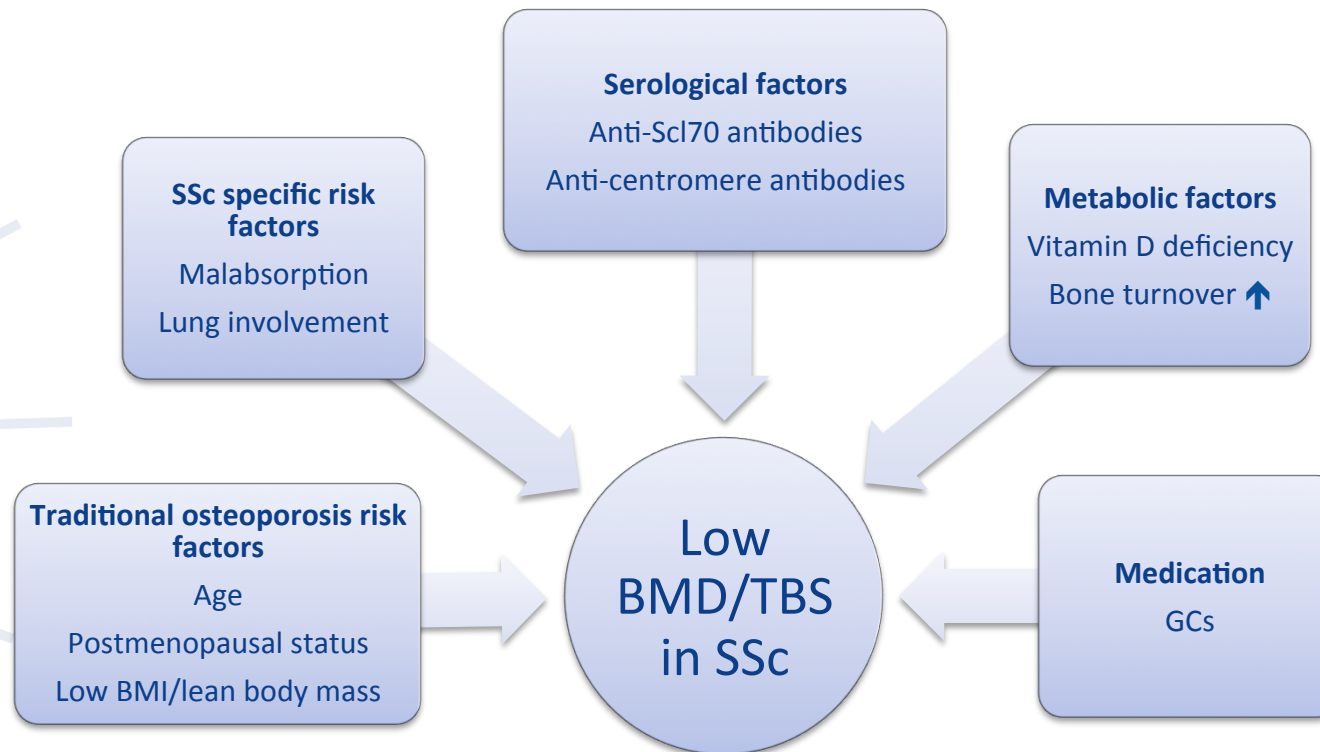


Spanjer et al, ASBMR 2015 (SU0367)



Conclusions

1. High prevalence of low BMD in patients with SSc
2. Multifactorial etiology of osteoporosis in SSc





Conclusions

3. Symptomatic fractures: incidence 1.7 times increased

→ Risk factors:

- Age
- Female sex
- Low 25(OH) D serum levels
- Use of GCs > 7.5 mg/day
- Use of metoclopramide IV (bowel dysmotility)

→ Increased 1-year mortality rate after fracture

4. Prevalent vertebral fractures: 24-25% (versus 1-2% in HC)



Conclusions

5. Underdiagnosis and undertreatment of osteoporosis in SSc



Screening for reduced BMD and vertebral fractures and treatment of osteopenia / osteoporosis in SSc patients is important to reduce morbidity and mortality and improve quality of life

Limitations of anti-osteoporosis therapy in SSc



- Ability to exercise is often limited
- Malabsorption leading to low lean body mass → often hard to treat due to gastrointestinal disease complications
- Use of calcium/vit D supplements and oral bisphosphonates → often hampered by esophageal dysmotility
 - Alternatives:
 - enteral or IV supplements
 - IV bisphosphonates
 - PTH analogues
 - denosumab
- Polypharmacy



Thank you
for your attention

Paul Klee 'Senecio' (1922)