

Alterations of Nutritional Status of Scleroderma Patients and Associations with Disease-specific Features

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Background: Systemic sclerosis (SSc) is characterized by skin and organ involvement and chronic course. Especially involvement of the gastrointestinal tract and systemic inflammation can have a negative impact on nutritional status. The aim of this study was to assess the differences in the nutritional status of SSc patients and healthy controls (HC) and the association with disease-specific features.

Conclusion: We have observed significant alterations in nutritional parameters in our SSc patients compared to healthy age-/sex-matched individuals. These changes were associated predominantly with disease activity and skin involvement. Patients with dcSSc tended to have worse disease activity and more pronounced alteration of nutritional status compared to lcSSc patients.

Methods:

100 patients with SSc (85 females; mean age 55.5; disease duration 4.0 years; lcSSc 59 / dcSSc 41) and 100 age-/sex-matched HC (85 females, mean age 55.3) without rheumatic diseases were included. Patients with SSc fulfilled the ACR/EULAR criteria. Levels of selected parameters of nutrition were measured in sera drawn after 8 hours of fasting by routine analytic methods. In SSc patients, disease activity was evaluated by ESSG composite index, skin involvement by modified Rodnan skin score (mRSS), and organ involvement and current treatment was recorded. Data are presented as median (IQR).

Baseline characteristics

Parameter	SSc (n = 100)	lcSSc (n = 59)	dcSSc (n = 41)	HC (n = 100)
Gender, n (%): female / male	85 (85) / 15 (15)	51 (86) / 8 (14)	34 (83) / 7 (17)	85 (85) / 15 (15)
Age (years); median (IQR)	55.5 (45.7 – 61.8)	57.4 (46.4 – 64.7)	51.3 (45.6 – 59.8)	SSc-HC: 55.3 (45.8 – 61.9); lcSSc-HC: 56.7 (47.4 – 64.3); dcSSc-HC: 52.6 (44.6 – 62.2)
BMI (kg/m ²); median (IQR)	22.6 (20.6 – 25.8)	23.1 (20.7 – 26.8)	22.2 (20.0 – 25.5)	
Disease duration (years); median (IQR)	4.0 (1.5 – 8.2)	4.0 (1.1 – 10.0)	4.0 (1.6 – 7.0)	
Disease activity (ESSG); median (IQR)	3.0 (1.5 – 4)	2.5 (1.1 – 4.0)	3.5 (2.0 – 4.0)	
mRSS; median (IQR)	10 (5 – 18)	6 (3 – 10)	17 (13 – 24)	
FVC (%); median (IQR)	87 (69 – 106)	88 (70 – 105)	87 (67 – 106)	
FEV1 (%); median (IQR)	83 (67 – 98)	83 (67 – 97)	83 (59 – 101)	
DLCO (%); median (IQR)	71 (56 – 86)	71 (55 – 87)	71 (56 – 81)	
SSc-associated clinical manifestations, n (%):				
ILD / PAH / OD / CI / RP / RI	6 (6) / 96 (96) / 6 (6)	1 (2) / 57 (97) / 2 (3)	5 (12) / 39 (95) / 4 (10)	
CRP (mg/L); median (IQR)	3.8 (1.8 – 7.5)	3.4 (1.7 – 6.9)	4.2 (1.8 – 8.5)	
ESR (mm/h); median (IQR)	14 (10 – 27)	13 (8 – 22)	18 (11 – 29)	
Glycemia (mmol/L); median (IQR)	5.1 (4.8 – 5.5)	5.5 (4.8 – 5.5)	5.1 (4.6 – 5.6)	
Autoantibodies (positive), n (%): ANA / Scl-70 / ACA	96 (96) / 54 (54) / 20 (20)	57 (97) / 24 (41) / 18 (31)	39 (95) / 30 (73) / 2 (5)	
Prednisolone equivalent dose (mg/day); median (IQR)	0 (0 – 5)	0 (0 – 5)	0 (0 – 6)	
Treatment, n (%): GC / CPA / MTX / AZA / MMF / HQ / RTX	61 (61) / 28 (28) / 19 (19) / 6 (6) / 0 (0) / 2 (2) / 2 (2)	36 (61) / 18 (31) / 9 (15) / 4 (2) / 0 (0) / 1 (2) / 0 (0)	25 (61) / 10 (24) / 10 (24) / 2 (5) / 0 (0) / 1 (2) / 2 (5)	
Arterial hypertension measured (treated), n (%)	17 (17)	10 (17)	7 (17)	
Diabetes mellitus, n (%):				
Untreated / PAD / Insuline treatment	18 (18) / 2 (2) / 0 (0)	10 (17) / 0 (0) / 0 (0)	8 (20) / 2 (5) / 0 (0)	
Treated dyslipidaemia (statin or hypolipidemic drugs), n (%)	13 (13)	7 (12)	6 (15)	
Smoking (current), n (%)	7 (7)	3 (5)	4 (10)	

Abbreviations: SSc, systemic sclerosis; lcSSc, limited cutaneous systemic sclerosis; dcSSc, diffuse cutaneous systemic sclerosis; HC, healthy controls; BMI, body mass index; ESSG, European Scleroderma Study Group – disease activity index; mRSS, modified Rodnan skin score; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ILD, interstitial lung disease; PAH, pulmonary arterial hypertension; OD, oesophageal motility disorder; CI, cardiac involvement; RP, Raynaud's phenomenon; RI, renal involvement; DLCO, diffusing lung capacity for carbon monoxide; FVC, forced vital capacity; FEV1, forced expiratory volume during the first second; ANA, antinuclear antibodies; Scl-70, anti-topoisomerase I antibodies; ACA, anti-centromere antibodies; GC, glucocorticoids; CPA, cyclophosphamide; MTX, methotrexate; AZA, azathioprine; MMF, mycophenolate mofetil; HQ, hydroxychloroquine; RTX, rituximab

Results:

Nutrition markers in SSc patients, SSc subsets and healthy controls

Nutrition parameters	SSc vs. HC	SSc (n=100): Median (IQR)	HC (n=100): Median (IQR)	p-value
Total protein (g/dL)	↔	73.3 (70.6 – 78.1)	75.9 (72.3 – 78.4)	0.060
Albumin (g/dL)	↓	42.4 (39.4 – 44.1)	45.2 (43.3 – 47.3)	<0.001
Prealbumin (g/dL)	↓	0.21 (0.17 – 0.26)	0.27 (0.25 – 0.31)	<0.001
Transferrin (g/L)	↓	2.40 (2.20 – 2.80)	2.70 (2.50 – 3.13)	0.006
Orosomucoid (g/L)	↑	0.98 (0.79 – 1.2)	0.81 (0.66 – 0.91)	<0.001
Complement C4 (g/L)	↓	0.28 (0.20 – 0.32)	0.32 (0.26 – 0.38)	<0.001
Complement C3 (g/L)	↔	1.38 (1.23 – 1.53)	1.41 (1.25 – 1.67)	0.251
Cholinesterase (ukat/L)	↓	124 (106 – 144)	144 (127 – 162)	<0.001
Amylase (ukat/L)	↔	1.19 (0.88 – 1.59)	0.96 (0.75 – 1.32)	0.114
Lipase (ukat/L)	↔	0.49 (0.37 – 0.68)	0.53 (0.36 – 0.71)	0.852
Vitamin D (calcidiol) (nmol/L)	↔	55.2 (34.6 – 72.0)	57.3 (42.7 – 70.3)	0.584
Calcitriol (1,25(OH)2D) (pmol/L)	↓	115 (85.8 – 141)	145 (106 – 179)	<0.001
Fe (umol/L)	↓	13.1 (8.08 – 17.0)	17.5 (12.4 – 21.4)	<0.001
Mg (mmol/L)	↓	0.85 (0.8 – 0.9)	0.88 (0.84 – 0.93)	0.001
Zn (umol/L)	↓	800 (708 – 960)	1000 (795 – 1208)	<0.001
ft4 (pmol/L)	↔	15.4 (14.2 – 17.4)	15.2 (14.3 – 16.4)	0.354
TSH (mIU/L)	↔	2.56 (1.68 – 3.80)	2.25 (1.66 – 3.19)	0.161
LDH (ukat/L)	↔	2.87 (2.42 – 3.30)	2.91 (2.32 – 3.42)	0.727
Vitamin B12 (pmol/L)	↔	72.4 (51.1 – 103)	74.6 (58.6 – 98.2)	0.549
Folic acid (mg/L)	↔	4.81 (2.98 – 6.78)	5.86 (3.31 – 9.16)	0.086
C-peptide (ng/mL)	↑	0.69 (0.48 – 0.97)	0.61 (0.16 – 0.87)	0.038
Insulin (uU/mL)	↔	7.92 (5.39 – 13.6)	8.57 (6.63 – 14.3)	0.206

Serum levels of proteins (albumin, prealbumin, complement C4), minerals (Fe, Mg, Zn) and cholinesterase were significantly decreased in SSc patients compared to HC. This finding indicates a worse nutritional status. Levels of vitamin D (calcidiol) were comparable in SSc and HC, whereas the active form (calcitriol) was decreased in SSc. Orosomucoid, a potential acute phase reactant, was increased, and C-peptide levels were increased in SSc patients compared to HC, while insulin levels were comparable in both groups.

Nutrition parameters	lcSSc vs. HC	lcSSc (n=59): Median (IQR)	HC (n=59): Median (IQR)	p-value	Nutrition parameters	dcSSc vs. HC	dcSSc (n=41): Median (IQR)	HC (n=41): Median (IQR)	p-value
Total protein (g/dL)	↔	73.5 (70.4 – 79.6)	76.6 (72.6 – 79.1)	0.188	Total protein (g/dL)	↔	72.9 (70.2 – 77.7)	74.3 (71.6 – 77.9)	0.188
Albumin (g/dL)	↓	42.7 (39.8 – 44.8)	44.9 (43.2 – 47.4)	<0.001	Albumin (g/dL)	↓	42.1 (39.1 – 43.5)	45.3 (43.6 – 47.3)	<0.001
Prealbumin (g/dL)	↓	0.22 (0.18 – 0.27)	0.27 (0.25 – 0.31)	<0.001	Prealbumin (g/dL)	↓	0.19 (0.15 – 0.23)	0.27 (0.25 – 0.30)	<0.001
Transferrin (g/L)	↓	2.50 (2.30 – 2.90)	2.80 (2.6 – 3.3)	<0.001	Transferrin (g/L)	↓	2.40 (2.10 – 2.80)	2.6 (2.4 – 2.9)	<0.001
Orosomucoid (g/L)	↑	0.93 (0.79 – 1.13)	0.83 (0.69 – 0.93)	<0.001	Orosomucoid (g/L)	↑	1.04 (0.80 – 1.28)	0.75 (0.64 – 0.90)	<0.001
Complement C4 (g/L)	↓	0.28 (0.20 – 0.32)	0.32 (0.27 – 0.36)	0.005	Complement C4 (g/L)	↓	0.25 (0.19 – 0.32)	0.32 (0.26 – 0.40)	0.002
Complement C3 (g/L)	↔	1.40 (1.22 – 1.51)	1.43 (1.26 – 1.70)	0.120	Complement C3 (g/L)	↔	1.35 (1.24 – 1.56)	1.32 (1.23 – 1.59)	0.980
Cholinesterase (ukat/L)	↓	125 (111 – 153)	145 (130 – 162)	0.001	Cholinesterase (ukat/L)	↓	123 (99.5 – 140)	140 (123 – 163)	0.001
Amylase (ukat/L)	↔	1.17 (0.88 – 1.56)	0.94 (0.77 – 1.37)	0.123	Amylase (ukat/L)	↑	1.26 (0.90 – 1.64)	1.05 (0.71 – 1.29)	0.013
Lipase (ukat/L)	↔	0.49 (0.40 – 0.73)	0.53 (0.35 – 0.71)	0.782	Lipase (ukat/L)	↔	0.47 (0.37 – 0.66)	0.54 (0.38 – 0.71)	0.426
Vitamin D (calcidiol) (nmol/L)	↔	55.8 (33.6 – 74.1)	55.4 (37.6 – 65.65)	0.584	Vitamin D (calcidiol) (nmol/L)	↔	52.2 (36.8 – 70.6)	62.4 (49.9 – 73.1)	0.125
Calcitriol (1,25(OH)2D) (pmol/L)	↓	115 (88.8 – 143)	145 (107.5 – 177)	0.004	Calcitriol (1,25(OH)2D) (pmol/L)	↓	113 (79.5 – 136)	146 (106 – 182)	0.001
Fe (umol/L)	↓	13.3 (9.15 – 17.1)	15.9 (11.6 – 21)	0.064	Fe (umol/L)	↓	12.4 (7.10 – 16.6)	19.5 (14.9 – 23.9)	<0.001
Mg (mmol/L)	↓	0.87 (0.82 – 0.91)	0.89 (0.84 – 0.93)	0.067	Mg (mmol/L)	↓	0.83 (0.77 – 0.88)	0.87 (0.83 – 0.94)	0.005
Zn (umol/L)	↓	860 (725 – 1000)	960 (780 – 1190)	0.017	Zn (umol/L)	↓	780 (685 – 890)	1050 (830 – 1230)	<0.001
ft4 (pmol/L)	↔	15.4 (14.2 – 17.4)	15.2 (14.3 – 16.2)	0.461	ft4 (pmol/L)	↔	15.5 (14.1 – 17.2)	15.3 (14.3 – 16.7)	0.626
TSH (mIU/L)	↔	2.57 (1.66 – 4.12)	2.25 (1.71 – 3.07)	0.298	TSH (mIU/L)	↔	2.54 (1.69 – 3.78)	2.23 (1.62 – 3.32)	0.426
LDH (ukat/L)	↔	2.70 (2.41 – 3.28)	2.96 (2.31 – 3.53)	0.816	LDH (ukat/L)	↔	2.95 (2.47 – 3.39)	2.84 (2.37 – 3.23)	0.359
Vitamin B12 (pmol/L)	↔	82.7 (51.4 – 103)	71.1 (55.1 – 93.6)	0.618	Vitamin B12 (pmol/L)	↔	64.4 (49.3 – 105)	76.9 (64.3 – 98.6)	0.174
Folic acid (mg/L)	↔	4.64 (3.01 – 6.71)	5.99 (3.24 – 9.39)	0.199	Folic acid (mg/L)	↔	4.93 (2.65 – 7.18)	5.71 (3.32 – 7.57)	0.324
C-peptide (ng/mL)	↑	0.73 (0.49 – 0.97)	0.63 (0.13 – 0.85)	0.065	C-peptide (ng/mL)	↔	0.66 (0.48 – 0.94)	0.57 (0.29 – 0.90)	0.331
Insulin (uU/mL)	↔	8.79 (5.35 – 15.0)	9.25 (7.05 – 14.52)	0.556	Insulin (uU/mL)	↔	7.55 (5.41 – 10.8)	8.31 (5.73 – 13.84)	0.255

Nutrition parameters	lcSSc vs. dcSSc	lcSSc (n=59): Median (IQR)	dcSSc (n=41): Median (IQR)	p-value
Total protein (g/dL)	↔	73.5 (70.4 – 79.6)	72.9 (70.2 – 77.7)	0.435
Albumin (g/dL)	↑	42.7 (39.8 – 44.8)	42.1 (39.1 – 43.5)	0.095
Prealbumin (g/dL)	↑	0.22 (0.18 – 0.27)	0.19 (0.15 – 0.23)	0.033
Transferrin (g/L)	↔	2.50 (2.30 – 2.90)	2.40 (2.10 – 2.80)	0.270
Orosomucoid (g/L)	↔	0.93 (0.79 – 1.13)	1.04 (0.80 – 1.28)	0.210
Complement C4 (g/L)	↔	0.28 (0.20 – 0.32)	0.25 (0.19 – 0.32)	0.362
Complement C3 (g/L)	↔	1.40 (1.22 – 1.51)	1.35 (1.24 – 1.56)	0.982
Cholinesterase (ukat/L)	↔	125 (111 – 153)	123 (99.5 – 140)	0.180
Amylase (ukat/L)	↔	1.17 (0.88 – 1.56)	1.26 (0.90 – 1.64)	0.362
Lipase (ukat/L)	↔	0.49 (0.40 – 0.73)	0.47 (0.37 – 0.66)	0.336
Vitamin D (calcidiol) (nmol/L)	↔	55.8 (33.6 – 74.1)	52.2 (36.8 – 70.6)	0.892
Calcitriol (1,25(OH)2D) (pmol/L)	↔	115 (88.8 – 143)	113 (79.5 – 136)	0.542
Fe (umol/L)	↔	13.3 (9.15 – 17.1)	12.4 (7.10 – 16.6)	0.251
Mg (mmol/L)	↑	0.87 (0.82 – 0.91)	0.83 (0.77 – 0.88)	0.051
Zn (umol/L)	↑	860 (725 – 1000)	780 (685 – 890)	0.092
ft4 (pmol/L)	↔	15.4 (14.2 – 17.4)	15.5 (14.1 – 17.2)	0.965
TSH (mIU/L)	↔	2.57 (1.66 – 4.12)	2.54 (1.69 – 3.78)	0.798
LDH (ukat/L)	↔	2.70 (2.41 – 3.28)	2.95 (2.47 – 3.39)	0.459
Vitamin B12 (pmol/L)	↔	82.7 (51.4 – 103)	64.4 (49.3 – 105)	0.259
Folic acid (mg/L)	↔	4.64 (3.01 – 6.71)	4.93 (2.65 – 7.18)	0.976
C-peptide (ng/mL)	↔	0.73 (0.49 – 0.97)	0.66 (0.48 – 0.94)	0.595
Insulin (uU/mL)	↔	8.79 (5.35 – 15.0)	7.55 (5.41 – 10.8)	0.299

Markers of nutrition such as proteins (albumin, prealbumin, complement C4), minerals (Fe, Mg, Zn) and cholinesterase were decreased in both dcSSc and lcSSc compared to HC, while the changes were slightly more pronounced in dcSSc. When comparing the two SSc subsets, dcSSc had significantly decreased levels of prealbumin and a trend to decreased albumin, magnesium and zinc compared to lcSSc. Beside these differences, the nutritional status was similar in both groups.

Correlation of nutritional parameters and disease-related features in all SSc patients (n=100):

Lipid profile parameters	Disease-related features	p-value	Spearman's r
Total protein	Age	0.018	-0.238
	Prednisone equivalent dose	0.019	-0.237
	DLCO	0.064	0.197
Albumin	FEV1	0.100	0.176
	Disease duration	0.003	0.300
	Disease activity (ESSG)	0.003	-0.309
Prealbumin	CRP	0.017	-0.253
	ESR	0.021	-0.232
	BMI	0.040	0.215
Complement C3	Disease activity (ESSG)	0.031	-0.228
	mRSS	<0.001	-0.354
	CRP	<0.001	-0.343
Complement C4	ESR	0.003	-0.300
	Prednisone equivalent dose	0.003	0.300
	FVC	0.090	-0.181
Orosomucoid	Disease activity (ESSG)	0.003	0.308
	mRSS	0.013	0.253
	CRP	<0.001	0.482
Transferrin	Prednisone equivalent dose	0.014	0.250
	FVC	0.090	-0.181
	Disease activity (ESSG)	0.006	0.286
Fe	CRP	0.033	0.226
	ESR	0.005	0.277
	BMI	0.008	0.276
Mg	Disease duration	0.004	0.286
	BMI	0.071	0.190
	Disease duration	0.001	0.322
Zn	CRP	0.048	-0.211
	Prednisone equivalent dose	0.049	-0.200
	Disease activity (ESSG)	0.014	-0.261
Amylase	CRP	0.003	-0.314
	ESR	0.003	-0.293
	BMI	0.040	0.216
Lipase	Disease activity (ESSG)	0.048	-0.209
	mRSS	0.073	-0.184
	mRSS	0.078	-0.182
Cholinesterase	CRP	0.040	-0.218
	DLCO	0.050	0.208
	Disease duration	0.070	-0.183
ft4	BMI	0.003	0.307
	Disease duration	0.037	0.210
	mRSS	0.047	-0.203
TSH	mRSS	0.060	-0.193
	BMI	0.041	-0.214
	Disease duration	0.091	-0.171
Calcitriol (1,25(OH)2D)	Age	0.001	0.319
	Disease activity (ESSG)	0.030	-0.228
	BMI	0.089	0.179
Vitamin B12	mRSS	0.071	-0.185
	mRSS	0.006	-0.278

Acronyms: DLCO, diffusing lung capacity for carbon monoxide; ESSG, European Scleroderma Study Group – disease activity index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; mRSS, modified Rodnan skin score; BMI, body mass index; Fe, Ferrum; Mg, Magnesium; Zn, Zinc; ft4 – free thyroxine; TSH – thyrotropin

High disease activity, increased levels of CRP or ESR, more extensive skin involvement (mRSS), and low BMI were associated with negative changes of nutritional markers, especially decreased levels of albumin, prealbumin, transferrin, minerals, and vitamins. Other factors significantly associated with parameters of nutrition were the current dose of glucocorticoids, disease duration, lung involvement, and age.

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