

# Lipid Profile in Scleroderma Patients Compared to Healthy Controls and the Associations with Disease-specific Features

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**Background:** Systemic sclerosis (SSc) is characterized by skin and organ involvement and chronic course. Systemic inflammation, involvement of the gastrointestinal tract, and glucocorticoid treatment can have a negative impact on intermediate metabolic pathways, especially on lipid metabolism. The aim of this study was to assess the differences in the lipid profile of SSc patients and healthy controls (HC) and the association with disease-specific features.

**Conclusion:** We have observed significant alterations in serum lipid parameters in our SSc patients compared to healthy age-/sex-matched individuals. Differences were also found between lcSSc and dcSSc; more unfavorable alterations were detected in dcSSc. These alterations were associated with disease duration and activity, skin and lung involvement, and the current dose of corticosteroids.

## 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 2013 ACR/EULAR criteria. Levels of selected parameters of lipid metabolism 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).

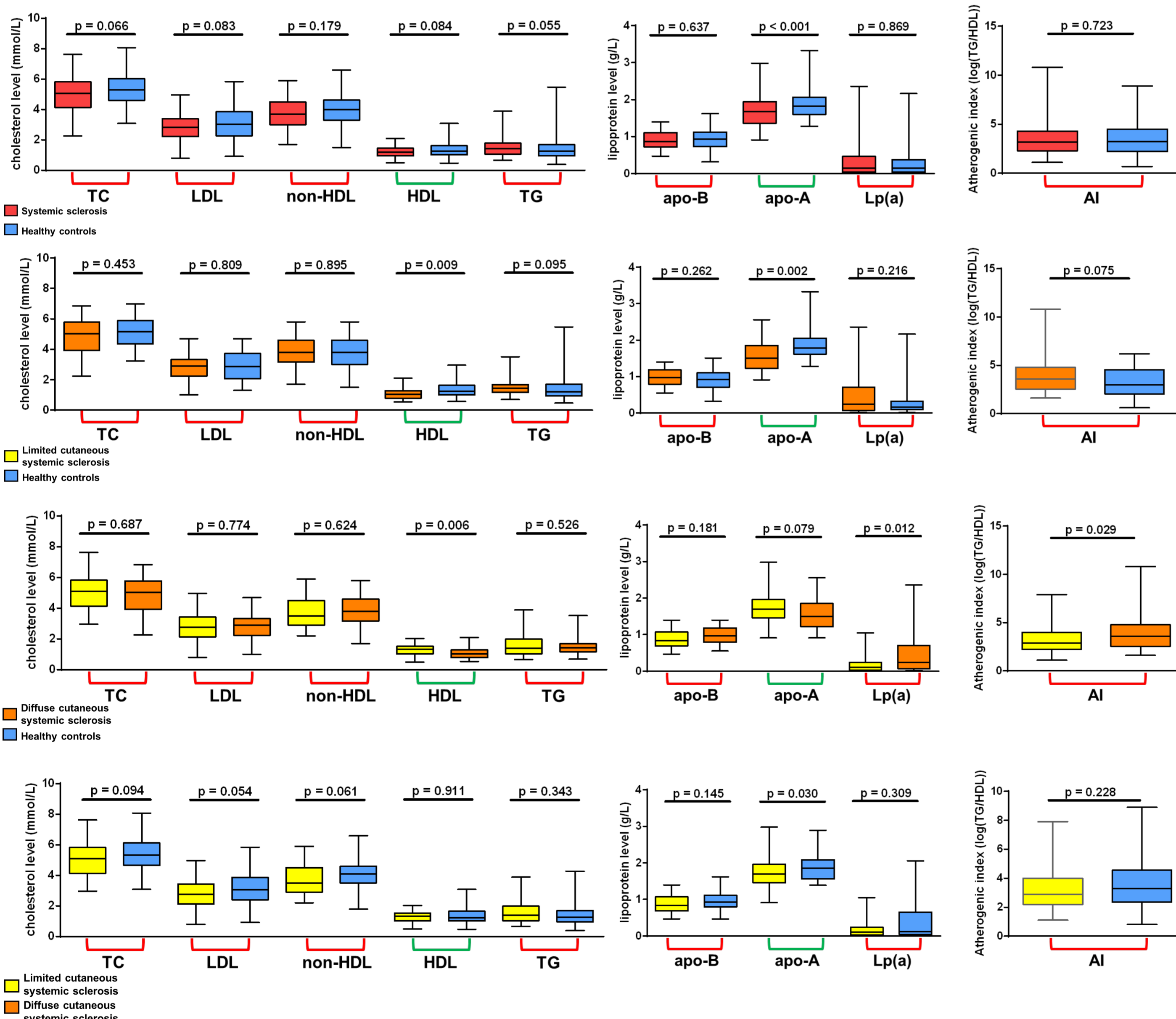
## Baseline characteristics

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)	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 <sup>2</sup> ); 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 (63 – 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	68 (68) / 21 (21) / 61 (61) / 6 (6) / 96 (96) / 6 (6)	41 (69) / 14 (24) / 34 (58) / 1 (2) / 57 (97) / 2 (3)	27 (66) / 7 (17) / 27 (66) / 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 / Insulin 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 autoantibodies; ACA, anti-centromere antibodies; CPA, cyclophosphamide; MTX, methotrexate; AZA, azathioprine; MMF, mycophenolate mofetil; HQ, hydroxychloroquine; RTX, rituximab

## Results:

### Selected parameters of lipid metabolism in SSc patients, SSc subsets and healthy controls



Compared to HC, SSc patients had a trend to lower values of negative predictors, such as total cholesterol (TC), low-density cholesterol (LDL) and triglycerides (TG), but also a trend to lower values of the positive predictor high-density cholesterol (HDL). Apolipoprotein A (apo-A), as the marker of HDL was significantly decreased in SSc patients.

lcSSc patients demonstrated a trend to decreased TC, LDL and non-HDL cholesterol compared to the matched HC. Although HDL levels were comparable, apo-A was significantly lower in lcSSc compared to HC.

dcSSc patients had significantly lower HDL and demonstrated a trend to higher TG compared to the matched HC, but levels of TC and LDL were comparable to HC. In agreement with these findings, the levels of apo-A were significantly lower in dcSSc compared to HC.

In lcSSc and dcSSc we observed a similar lipid profile except for HDL, which was significantly lower in dcSSc. dcSSc patients had higher Lp(a) and atherogenic index (AI) of plasma compared to lcSSc. Both of these parameters are negative cardiovascular risk factors.

### Correlations of lipid profile and disease-related features in all SSc patients (n=100):

Lipid profile parameters	Disease-related features	p-value	Spearman's r
TC	Age	0.096	0.170
	Disease duration	0.026	0.223
	Prednisone equivalent dose	0.012	0.258
LDL	Disease duration	0.013	0.250
	CRP	0.061	-0.200
Non-HDL-C	Disease duration	0.038	0.209
	Prednisone equivalent dose	0.017	0.243
TG	BMI	0.071	-0.190
	Disease activity (ESSG)	0.050	0.207
	Prednisone equivalent dose	<0.001	0.339
Apo-B	Disease duration	0.053	0.195
	Prednisone equivalent dose	0.037	0.212
Lp(a)	mRSS	0.054	0.198
	FVC	0.044	0.214
Atherogenic index (log(TG/HDL-C))	Age	0.014	-0.246
	Disease activity (ESSG)	0.014	0.259
HDL	Age	<0.001	0.378
	Disease activity (ESSG)	0.004	-0.302
Apo-A	Age	0.006	0.273
	Disease activity (ESSG)	0.050	-0.207
	mRSS	0.046	-0.205
	CRP	0.002	-0.322
Prednisone equivalent dose		0.032	0.218
	DLCO	0.044	0.214

We have observed positive correlations of disease duration and the daily dose of glucocorticoids (GC) with negative factors of the lipid profile. Unexpectedly, TG were negatively associated with BMI, and CRP levels were negatively correlated with LDL. We hypothesize that patients with increased systemic inflammation could have paradoxically lower LDL, similarly to the lipid paradox demonstrated for example in rheumatoid arthritis patients. HDL and apo-A levels negatively correlated with disease activity, CRP levels and skin involvement.