

Perceived Functioning Has Ethnic-specific Associations in Systemic Sclerosis: Another Dimension of Personalized Medicine

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ABSTRACT. Objective. To measure self-reported physical and mental functioning and associated clinical features at study entry in 3 ethnic groups with systemic sclerosis (SSc).

Methods. Sixty Hispanic, 39 African American, and 104 Caucasian patients with recent-onset SSc (< 5 yrs) were assessed for perceived physical and mental functioning, using the Medical Outcomes Study Short Form-36 (SF-36) and Scleroderma-Health Assessment Questionnaire (Scleroderma-HAQ). Socioeconomic, demographic, clinical, immunologic, immunogenetic, behavioral, and psychological variables (Interpersonal Support Evaluation List, ISEL; Illness Behavior Questionnaire, IBQ; and Arthritis Helplessness Index, AHI) were analyzed by linear regression models for associations with SF-36 and mHAQ scores as dependent variables.

Results. Perceived physical functioning scores had ethnic-specific associations with AHI > fatigue scores > IBQ > clinical variables (hypertension, skin score, and percentage predicted DLCO). Scleroderma-HAQ scores had ethnic-specific associations with IBQ > AHI scores > most clinical and laboratory variables. Decreased mental component summary (MCS) scores associated with AHI > ISEL. Ethnic-specific immunogenetic variables HLA-DQB1*0202 (Caucasian) and HLA-DRB1*11 (African American), and HLA-DQA1*0501 (Hispanic) also associated with MCS. Antinuclear autoantibodies, anti-topoisomerase I, and RNA polymerases I and III also demonstrated associations with functioning in African American and Hispanic groups.

Conclusion. Clinical, psychosocial, and immunogenetic variables had ethnic-specific associations with perceived physical and mental functioning. Consideration of ethnic-specific psychological and behavioral support in designing more personalized, relevant therapeutic interventions for the patient may improve therapeutic efficacy in SSc. (J Rheumatol First Release Nov 15 2009; doi: 10.3899/jrheum.090295)

Key Indexing Terms:

MEDICAL OUTCOMES STUDY SHORT FORM-36 ILLNESS BEHAVIOR QUESTIONNAIRE
SCLERODERMA HEALTH ASSESSMENT QUESTIONNAIRE HISPANIC
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Systemic sclerosis (scleroderma, SSc) is an autoimmune disease in which fibrosis of the skin and internal organs occurs in association with small-vessel vasculopathy and autoantibody production^{1,2}. A wide spectrum of organ- and non-organ-specific impairments ensue that may lead to severe limitations in physical, work, and social activities.

The influence of health-related quality of life (HRQOL) has been increasingly appreciated in SSc³⁻⁶, and is reportedly an important contributor to disease outcomes^{7,8}. Nonclinical variables such as social support, illness behaviors, (learned) helplessness, and perceptions of illness may be more sensitive indicators of QOL or perceived function-

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ing than objective clinical measurements. We hypothesized that some associations to perceived functioning with clinical, psychological, and behavioral factors in SSc would be culturally defined, or ethnic-specific. Self-reported physical and mental functioning were measured in patients with SSc in the GENISOS (Genetics vs ENvironment in Scleroderma Outcomes Study) cohort at study entry, using the Medical Outcomes Study Short-Form 36 Health Survey (SF-36⁹) and the Scleroderma-Health Assessment Questionnaire (Scleroderma-HAQ¹⁰). The primary objective of our study was to measure self-reported physical and mental function and associated clinical, laboratory, demographic, psychological, and behavioral features at study entry in 3 ethnic groups with SSc. As a secondary objective, we analyzed scores of perceived functioning for ethnic-specific associations to clinical, cultural, behavioral, and laboratory variables from the GENISOS database. From these studies, a hypothetical model of clinical, behavioral, and cultural influences was developed to explain their contributions to HRQOL in SSc. Identification of these ethnic-specific associations is predicted to enhance development of medical therapy that is more tailored to and effective for the patient with SSc.

MATERIALS AND METHODS

The GENISOS cohort has been part of a study of the Specialized Center of Research (SCOR) and is currently part of a Center for Research in Translation (CORT), both sponsored by the US National Institutes of Health. The study was designed to identify predictive factors of outcome in early SSc from the 3 largest ethnic groups in Texas¹¹. This multicenter study is a collaborative effort between the University of Texas-Houston Health Science Center, the University of Texas Medical Branch at Galveston, and the University of Texas-San Antonio Health Science Center. Each study site obtained approval from their institutional review board and general clinical research centers (GCRC) before beginning enrollment, and written informed consent was obtained from all subjects. Baseline study visits took place in the GCRC of the participating institutions as scheduled outpatient visits and, occasionally, on the inpatient services of the respective hospitals staffed by the investigators. Patients were recruited from the 3 participating centers, surrounding private outpatient practices, and the outpatient clinics of county hospital rheumatology clinics. Our cohort represents SSc patients in the Southeastern Texas catchment area.

Patients. Patients were eligible for the study if they (1) met defined preliminary criteria for the classification of SSc¹², with disease duration < 5 years (from date of first non-Raynaud's phenomenon manifestation of scleroderma); (2) had defined ethnicity as explained below; and (3) received medical care in the geographic catchment area of the participating centers.

For our study, the term ethnic group is used to refer to both racial and ethnic identification of patients (total N = 203). Caucasian (Cauc, N = 104) and African American (AA, N = 39) patients were those that identified themselves as Caucasian or African American. Hispanic patients (Hispanic, N = 60) were those of predominantly Mexican or Central American ancestry. Only those patients with all 4 grandparents of the same ethnic group were included to more clearly delineate how ethnicity contributes to the factors being examined. Thirteen patients in the catchment area who satisfied inclusion criteria for enrollment refused to participate, as described¹¹.

Variables

The comprehensive GENISOS baseline database includes variables from the following data sets, as described^{11,13} and as detailed below.

Demographic and clinical variables. Socioeconomic and demographic data obtained for each patient included ethnicity, sex, age, level of education, income, health-related habits, and disease duration. Disease duration was defined as the time between the date of the first non-Raynaud's phenomenon manifestation of scleroderma and the date to the study entry visit.

Clinical manifestations. Clinical manifestations in all organ systems were ascertained by history, physical examination, and review of medical records. Disease manifestations, medication history, and laboratory, clinical and radiologic variables were recorded on a comprehensive clinical manifestation form. The extent of skin involvement, the total skin score (TSS), was measured by the modified Rodnan skin score as the sum of the scores of 17 body areas ranging from 0 to 3 per area, and a total range 0–51^{14,15}. SSc patients were evaluated for Raynaud's phenomena, sclerodactyly, digital ulcers, digital pulp loss, digital pitting, digital gangrene, calcinosis, heart and lung examination, pleuropericarditis, upper and lower gastrointestinal symptoms and involvement, vasculitis, muscle weakness/myositis, active synovitis, depression, peripheral neuropathy, history of renal disease, and cerebrovascular accident. Also noted were comorbidities (systemic hypertension, thyroid disease, diabetes mellitus, malignancy) and additional autoimmune diagnoses. Results from chest radiographs (posteroanterior and lateral views), 12-lead electrocardiogram, and pulmonary function tests including spirometry, lung volumes and diffusing capacity in liters of carbon monoxide (DLCO) were also collected.

Laboratory tests. Laboratory tests included complete blood count, serum creatinine, creatine kinase, and urinalysis.

Immunological variables. Autoantibodies, including SSc associated autoantibodies, antinuclear antibodies (ANA), anti-Scl-70 (topoisomerase I, topo-I), anticentromere antibodies (ACA), anti-RNA polymerase I, II and III, anti-Sm (Smith), anti-U1-RNP, anti-Ro/SSA, anti-La/SSB, and anti-U3-RNP (fibrillarin) antibodies, were determined at baseline visit as described^{11,16–18}.

Immunogenetic variables. Class II HLA genotyping on SSc patients and ethnically matched healthy controls was performed on extracted and purified genomic-amplified DNA using standard laboratory procedures as described^{11,16–18}.

Fatigue ratings. Fatigue ratings were measured using the revised Fatigue Severity Scale (FSS), a 29-item validated instrument^{18–21} that includes statements concerning the respondent's fatigue (how fatigue affects motivation, exercise, physical functioning, daily activities, and interference with work, family, or social life). The FSS scores each item on a scale from 0 to 7, measuring no fatigue to most fatigue possible, the final score being the mean of all scores and with higher scores indicating greater fatigue. The FSS was not previously validated in SSc patients.

Behavioral and psychological variables. Three constructs for social support, coping with illness, and learned helplessness were established. Social support was ascertained using the Interpersonal Support Evaluation List (ISEL), a 40-item validated instrument comprising 4 scales with a range of 0–3 (tangible, appraisal, belonging, and self-esteem) and a summary measure^{22,23}. To obtain a score, the mean of the subscale items is multiplied by 10. The overall score is the sum of the subscales divided by 4. Higher scores indicate better social support. The ISEL has not been previously validated in SSc.

Coping with illness was determined using the Illness Behavior Questionnaire (IBQ), a 62-item validated instrument comprising 7 scales measuring generalized hypochondriasis, disease conviction, denial, affective disturbance, affective inhibition, psychological versus somatic, and irritability, plus a summary measure with a range 0–35²⁴. The questionnaire also includes 2 second-order factors, which are composites of scores from the IBQ scales: (1) disease affirmation and affective state and (2) the Whitley Index of Hypochondriasis. Higher IBQ scores indicate more illness behaviors. The IBQ has not been previously validated in SSc.

Helplessness or learned helplessness was ascertained with the Arthritis Helplessness Index (AHI), a 15-item validated instrument in which higher

scores indicate a higher degree of learned helplessness^{25,26}. In the case of diseases other than rheumatoid arthritis, the word “condition” is substituted for “arthritis.” Scoring ranges from 1 to 4 on a Likert-type scale and total scores ranging from 15 to 60. A higher score indicates more perceived helplessness, or that patients have less belief that they can influence their disease course. The AHI has not been previously validated in SSc.

Perceived functioning. The SF-36 (with 4-week recall) Version 1.0 was used to evaluate patient HRQOL^{9,11,27}. The SF-36 is a standard 36-item survey instrument designed to evaluate QOL issues by self-perceived psychological and physical limitations due to an underlying illness⁹. It yields a score for each of 8 domains, as well as summary scores for both physical component summary (PCS) and mental component summary (MCS). All scores are rated so that higher values indicate higher levels of perceived functioning (range 0–100). Raw SF-36 version 1.0 domains were normalized to the more current version (2.0) using a 2.0 conversion kit (SF Health Outcomes Scoring Software, QualityMetric Incorporated, Lincoln, RI, USA). The converted data can be compared with normative data for the US population as well as 2.0 version scores from other studies of rheumatic diseases. The SF-36 has been validated in patients with SSc^{4,6}.

The Scleroderma-HAQ, measuring self-reported physical disability, was also administered^{28,29}. The Scleroderma-HAQ includes the HAQ-Disability Index (DI) score and the addition of 5 visual analog scales (VAS) to evaluate SSc organ system symptoms (Raynaud’s phenomenon, gastrointestinal tract and lung involvement, pain, and overall disease severity²⁹). The Scleroderma-HAQ was not corrected for assistive devices. The length of the VAS was from 0 (“does not interfere”) to 15 cm (“very severe limitation”). Scoring of the HAQ-DI was performed by linear regression

analysis as described²⁷. The Scleroderma-HAQ VAS was scored by addition of the scales. The Scleroderma-HAQ has been validated and is useful in assessing function and response to treatment in patients with SSc^{30,31}.

Statistical analysis. Data are presented as mean \pm standard deviation unless otherwise noted. Chi-square or Fisher’s exact tests were used for comparison among ethnic groups for categorical variables. Group comparisons were measured using the analysis of variance (ANOVA) or nonparametric Kruskal-Wallis tests for continuous variables. For the variables that are significantly different among 3 ethnic groups, pairwise comparison tests using Bonferroni corrections were conducted to determine which pairs are significantly different. Since the number of pairwise comparisons was 3 (Cauc vs AA, Cau vs Hisp, and AA vs Hisp), a p-value < 0.017 was considered statistically significant due to multiple comparisons.

Socioeconomic, demographic, clinical, immunological, immunogenetic, and behavioral-psychological variables were entered as independent variables into stepwise linear regression models by the stepwise selection procedure. The PCS, MCS, and Scleroderma-HAQ scores served as dependent variables. Ethnicity was entered into multivariable analyses, along with variables with $p < 0.1$ in the univariate analyses.

The mean highest grade levels completed for all patient groups were above 10th grade (Table 1). The SF-36, ISEL, and IBQ instruments were written at the 8th grade level, and all patients were able to complete these forms³². Eleven patients reported English as their second language. All forms were available in Spanish and 8 patients requested forms written in Spanish. Out of the 203 enrolled patients, 6 patients did not complete the SF-36 instrument; therefore the SF-36 completion rate was 97%. The proportion of data missing from all data was $< 8\%$. For outcome variables pre-

Table 1. Sociodemographic, functioning, and behavioral scores in SSc patients by ethnicity. Variables are stated as percentages or average \pm SD. Comparing all 3 groups by ANOVA for means and by chi-square or Fisher’s exact test for proportions with Bonferroni corrections.

Variables	All Patients, n = 203	Caucasian, n = 104	African American, n = 39	Hispanic, n = 60	p*
Female, %	84	80	87	90	0.193
Age, yrs	50 \pm 13	51 \pm 12	49 \pm 13	48 \pm 14	0.172
Highest grade completed	12.6 \pm 3.2	13.6 \pm 3.0	12.7 \pm 2.5	10.8 \pm 3.3	< 0.001
Disease duration, mo	34.1 \pm 29.2	29.8 \pm 20.2	33.6 \pm 19.9	35.2 \pm 19.1	0.218
Diffuse cutaneous SSc, %	58	55	62	62	0.617
Employed, %	40	50	34	27	0.010
Insured, %	75	82	64	69	0.060
Own homes, %	71	78	68	62	0.079
Married, %	56	61	47	55	0.359
Income, monthly \$US	3147 \pm 2972	4016 \pm 3411	1869 \pm 1310	2474 \pm 2437	0.0001
Unhealthy behaviors [†] , %	82	84	85	78	0.631
Smoke tobacco	20	26	27	5	0.002
Drink ethanol	39	51	26	25	0.0007
No exercise	62	59	65	65	0.674
Social support (ISEL)	8.0 \pm 11.6	8.5 \pm 1.3	7.2 \pm 1.8	7.8 \pm 1.6	< 0.0001
Illness behavior (IBQ)	11.0 \pm 5.8	9.8 \pm 5.1	11.7 \pm 6.2	12.7 \pm 6.2	0.006
Helplessness (AHI)	40.0 \pm 7.0	39.5 \pm 7.3	40.3 \pm 8.3	40.6 \pm 5.4	0.573
PCS (SF-36)	38.6 \pm 7.0	40.4 \pm 6.6	36.8 \pm 7.4	36.8 \pm 7.4	0.002
MCS (SF-36)	43.4 \pm 7.0	42.4 \pm 6.1	44.3 \pm 8.7	44.7 \pm 7.4	0.104
SSc-HAQ	0.87 \pm 0.68	0.71 \pm 0.66	1.19 \pm 0.74	0.92 \pm 0.69	0.001

* Computed comparing all 3 groups by ANOVA for means, and by Fisher’s exact test for proportions. Caucasians vs African-Americans: alcohol drinking ($p = 0.006$); monthly income ($p < 0.0001$); ISEL ($p = 0.0003$); PCS ($p = 0.006$); SSc-HAQ ($p = 0.0003$). Caucasians vs Hispanics: percentage employed ($p = 0.004$), smoke tobacco ($p = 0.0006$), alcohol drinking ($p = 0.001$), highest grade completed ($p < 0.0001$), monthly income ($p = 0.001$), ISEL ($p = 0.005$), IBQ ($p = 0.002$), PCS ($p = 0.002$), physical functioning ($p = 0.008$). African Americans vs Hispanics: smoke tobacco ($p = 0.003$), highest grade completed ($p = 0.006$). [†] Unhealthy behavior: presence of smoking tobacco, drinking > 2 alcohol drinks/day, and/or no formal exercise, with sedentary lifestyle. Disease duration: no. of months diagnosed with SSc at study entry; Diffuse cutaneous SSc disease: percentage diagnosed with diffuse cutaneous disease subset; Employed: percentage employed full-time; Insured: percentage with private insurance, Medicare, or Medicaid; ISEL: Interpersonal Support Evaluation List; IBQ: Illness Behavior Questionnaire; AHI: Arthritis Helplessness Index; PCS: physical component summary score; MCS: mental component summary score of the SF-36; Scleroderma-HAQ: Scleroderma Health Assessment Questionnaire, HAQ-DI, and 5 visual analog scale-type questions related to scleroderma, also referred to as SHAQ.

sented, missing data were not imputed. Significance of these data did not change by imputing missing values of independent variables.

Instrument validation. Cronbach's coefficient alpha values were computed to measure consistency of ISEL, IBQ, AHI, and FSS questionnaires as a test of reliability of these scales and their validation in SSc patients. Reliability coefficient scores above 0.70 were deemed acceptable for the validity and reliability of these tests as given by Nunnally and Bernstein³³.

RESULTS

A comprehensive description of the GENISOS study population at baseline has been published¹¹. Selected features of demographic, clinical, and behavioral-psychological variables are included in Table 1. As expected, the majority of the patients were women, although the Caucasian group had a larger proportion of men. The mean ages for all groups ranged from 48 ± 12 to 51 ± 13 years. There were no significant differences among the 3 ethnic groups at study entry for age, gender, disease duration, or percentage with diffuse cutaneous involvement. Caucasians had completed significantly more grades of formal education than African Americans or Hispanics (Caucasians 13.6 ± 3 , compared to African Americans 12.7 ± 2.5 and Hispanics 10.8 ± 3.3 ; $p < 0.001$). There were significant differences in monthly incomes between Caucasian, African American, and Hispanic groups ($p = 0.0001$). There were no significant differences among ethnic groups for percentages of those who were employed, had medical insurance, owned homes, or were married. No differences in access to either SSc-related or non-SSc-related healthcare were seen among the 3 ethnic groups, as reported¹¹ (data not shown).

Unhealthy behaviors. The frequency of unhealthy behaviors, described as smoking tobacco, ingestion of > 2 drinks with alcohol/day, or no exercise (sedentary) lifestyle, are shown in Table 1. Hispanics self-reported less frequency of smoking tobacco or drinking > 2 alcohol drinks/day compared to Caucasians (5% vs 26%, $p = 0.002$, and 25% vs 51%, $p = 0.0007$, respectively). African Americans also reported less frequency of ingesting > 2 alcohol drinks/day compared to Caucasians (26% vs 51%, respectively; $p = 0.006$). There were no differences among the groups regarding reported exercise activity.

Social support scores. There were higher scores of social support measured by all 4 components of the ISEL (Tangible, Appraisal, Belonging, and Esteem) and for average total ISEL scores among Caucasians, shown in Table 1 (Caucasians 8.51 ± 1.3 vs African Americans 7.2 ± 1.8 and Hispanics 7.8 ± 1.6 ; $p < 0.001$). Cronbach's alpha reliability coefficient for the ISEL was 0.825³³.

Illness behavior scores. Higher overall IBQ scores were noted in African Americans and Hispanics compared to Caucasians (Caucasians 9.8 ± 5.1 compared to African Americans 11.7 ± 6.2 and Hispanics 12.7 ± 6.2 ; $p = 0.007$). Specifically, African Americans and Hispanics had higher subscale scores of general hypochondriasis, psychological

versus somatic, denial scores, and a higher index of hypochondriasis, indicative of more illness-related behaviors. Cronbach's alpha reliability coefficient for the IBQ instrument was 0.778.

Helplessness scores. Helplessness, measured by the AHI, reflecting perceived (learned) helplessness was comparable in SSc patients among the 3 ethnic groups (Caucasians 39.5 ± 7.3 , African Americans 40.3 ± 8.3 , and Hispanics 40.6 ± 5.4 ; $p = 0.240$). Cronbach's alpha reliability coefficient for the AHI was 0.979.

Perceived functioning. Perceived functioning, using the PCS and MCS of the SF-36 and the Scleroderma-HAQ, are also shown in Table 1. Both instruments showed lower reported physical functioning in all 3 ethnic groups, compared to the normative population. The PCS scores demonstrated significant differences between Caucasian (40.4 ± 6.6) and African American and Hispanic groups (36.8 ± 7.4 ; $p = 0.002$). SSc patients did not show any significant differences in the SF-36 MCS among the 3 ethnic groups (Caucasians 42.6 ± 6.1 , African Americans 44.3 ± 8.7 , and Hispanics 44.7 ± 7.4 ; $p = 0.104$) and were within 1 standard deviation for control populations. Lower SF-36 PCS scores in SSc patients have been reported^{4-6,11}.

Scleroderma-HAQ scores. Scleroderma-HAQ scores were significantly lower in the Caucasian group, reflecting significantly higher levels of physical abilities compared to the African American and Hispanic groups (Caucasians 0.71 ± 0.66 , African Americans 1.2 ± 0.74 , and Hispanics 0.92 ± 0.69 ; $p = 0.001$).

Ethnic-specific associations with SF-36 and scleroderma-HAQ scores (Tables 2-4)

Regression analyses were performed to determine associations between laboratory values, clinically measurable variables, and scores from psychological and behavioral instruments to perceived functioning by PCS, MCS, and Scleroderma-HAQ scores in Caucasian, African American, and Hispanic groups. In Caucasians (Table 2), the presence of HLA-DRB1*0301 genotype was associated with higher PCS scores ($p = 0.022$). Lower PCS scores were associated with the presence of HLA-DQB1*0604 genotype, systemic hypertension, and percentage of predicted DLCO ($p = 0.032$, 0.031, and 0.044, respectively). Higher fatigue severity and helplessness scores were associated with lower PCS scores ($p = 0.0002$ and < 0.0001 , respectively). The presence of HLA-DQB1*0202 genotype was associated with lower MCS scores ($p = 0.016$). The presence of HLA-DQA1*0201 genotype, systemic hypertension, total skin score, and muscle weakness was associated with higher Scleroderma-HAQ scores ($p = 0.031$, 0.042, 0.006, and 0.004, respectively). Higher fatigue severity and helplessness scores were also associated with higher Scleroderma-HAQ scores ($p < 0.001$ and 0.012, respectively). The asso-

Table 2. Ethnic-specific associations with SF-36 and Scleroderma-HAQ scores in Caucasian subjects.

	Variable	Direction of Association	p
(1) PCS	HLA-DRB1*0301	2.76	0.022
	HLA-DQB1*0604	-4.48	0.032
	Systemic hypertension	-2.76	0.031
	% Predicted DLCO	-2.21	0.044
	Fatigue severity	-3.22	0.0002
(2) MCS	Helplessness	-0.37	< 0.0001
	HLA-DQB1*0202	-2.84	0.016
	Social support	1.27	0.004
(3) SHAQ	HLA-DQA1*0201	0.30	0.031
	Systemic hypertension	0.27	0.042
	Total skin score	0.01	0.006
	Muscle weakness	0.38	0.004
	Fatigue severity	0.30	< 0.001
	Helplessness	0.02	0.012

MCS: mental component summary score; PCS: physical component summary score of the SF-36; SHAQ:SSc-HAQ, HAQ-DI with 5 questions focused on scleroderma patients; social support: scores from the ISEL; fatigue severity: scores from the Fatigue Severity Scale (FSS); helplessness: scores from the Arthritis Helplessness Index (AHI).

Table 3. Ethnic-specific associations with SF-36 and Scleroderma-HAQ scores in African American subjects.

	Variable	Direction of Association	p
(1) PCS	Illness behavior	-0.71	0.001
(2) MCS	HLA-DRB1*11	6.75	0.030
	Helplessness	-0.66	< 0.001
(3) SHAQ	RNA Polymerase III	0.97	0.003
	Topo-I	0.57	0.020
	Illness behavior	0.08	< 0.001

Illness behavior: scores from the illness behavior questionnaire (IBQ); RNA polymerase III: seropositive for anti-RNA polymerase III; Topo-I: seropositive for anti-topoisomerase antibody.

Table 4. Ethnic-specific associations with SF-36 and Scleroderma-HAQ scores in Hispanic subjects.

	Variable	Direction of Association	p
(1) PCS	ANA pattern-speckled	4.43	0.003
	Systemic hypertension	-4.24	0.011
	Fatigue severity	-3.26	0.009
	Illness behavior	-0.36	< 0.001
(2) MCS	Age	0.17	0.007
	HLA-DQA1*0501	-3.72	0.031
	ANA pattern-speckled	-4.80	0.007
	Helplessness	-0.51	0.001
(3) SHAQ	HLA-DQB1*03	0.41	0.005
	RNA polymerase I	0.37	0.022
	Muscle weakness	0.69	< 0.001
	Tendon friction rub	0.49	< 0.001

ANA pattern-speckled: seropositive for ANA in speckled pattern; Muscle weakness: presence of proximal muscle weakness on physical examination, presence of myositis on muscle biopsy, or elevated serum creatine kinase on laboratory testing.

ciations between clinical, psychosocial, and fatigue variables with PCS and Scleroderma-HAQ scores were robust in Caucasians.

Table 3 demonstrates significant clinical and psychosocial associations with perceived functioning in the African American patients with SSc. In African Americans, lower

PCS scores were significantly associated with higher illness behavior scores ($p = 0.001$). Lower MCS scores were associated with the presence of HLA-DQB1*11 genotype ($p = 0.030$) and higher helplessness scores ($p < 0.001$). Higher Scleroderma-HAQ scores were associated with the presence of anti-RNA polymerase III and anti-topoisomerase I autoantibodies ($p = 0.003$ and 0.020 , respectively). Higher Scleroderma-HAQ scores were also associated with higher illness behavior scores ($p < 0.001$). The associations of laboratory, clinical, and behavioral variables with Scleroderma-HAQ scores were robust in African Americans.

Table 4 demonstrates significant laboratory, clinical, psychological, and behavioral associations with perceived functioning in Hispanic patients with SSc. Higher PCS scores were associated with the presence of ANA, speckled pattern ($p = 0.003$). Lower PCS scores were associated with the presence of systemic hypertension ($p = 0.011$). Lower PCS scores were also associated with higher fatigue severity and illness behavior scores ($p = 0.009$ and < 0.001 , respectively). The associations of laboratory, clinical, and behavioral variables with PCS scores were robust in Hispanics.

Higher MCS scores were associated with increasing age and the presence of HLA-DQA1*0501 ($p = 0.007$ and 0.031 , respectively). Lower MCS scores were associated with the presence of ANA speckled pattern and higher helplessness scores ($p = 0.007$ and 0.001 , respectively).

Higher Scleroderma-HAQ scores were robustly associated with the presence of HLA-DQB1*03, RNA polymerase I antibody, muscle weakness, and tendon friction rub ($p = 0.005$, 0.02 , < 0.001 , and < 0.001 , respectively).

Across all ethnic groups, psychological or behavioral factors were often more significantly associated with PCS, MCS, and Scleroderma-HAQ scores compared to clinical, immunogenetic, or serologic variables.

Figure 1 shows a hypothetical model to explain how upstream contributors to quality of life in patients with SSc are influenced by race/ethnicity. This template was modified from a model of previous studies using populations infected with human immunodeficiency virus^{7,34}. Centrally, disease expression influences symptom manifestations, which in turn influence perceived functioning, all of which contribute to overall patient quality of life. Peripherally, our expanded model incorporates the relative influences of social support and behaviors and socioeconomic status. Ethnic cultural influences directly promote social support, socioeconomic status, and illness beliefs. Consequently, the individual's cultural environment also fosters or permits behaviors and aspects of coping, such as helplessness. Thus, genetic background has direct and indirect contributions to the individual's quality of life via disease expression, symptom manifestation, and the cultural environment.

DISCUSSION

Potentially important ethnic-specific associations were

noted between perceived functioning and clinical, laboratory, psychological, behavioral, and immunogenetic variables in patients with SSc. Clinically, ethnic-specific associations with perceived functioning were seen with organ-specific dysfunction and autoantibodies. Higher HAQ-DI and Scleroderma-HAQ scores were previously reported to be associated with greater disease involvement, including organ-specific dysfunction^{28-31,35-37}. Cultural messages and subjective experiences contribute to unique and potentially modifiable psychological and behavioral influences on patient perceptions. Perceived functioning was often robustly associated with behavioral and psychological variables by ethnicity. In Caucasians, fatigue severity, helplessness, and social support scores showed significant associations with PCS, MCS, and Scleroderma-HAQ scores. In African American and Hispanic groups, illness behavior scores were associated with PCS and Scleroderma-HAQ scores, while helplessness scores were associated with MCS. Previous studies also report that disability, pain, and psychosocial adjustment are important contributors to QOL outcomes in SSc^{37,38}. The robust associations of fatigue severity with PCS and Scleroderma-HAQ in Caucasians and PCS in Hispanics might be expected, as many fatigue severity scale items directly assess physical functioning^{20,21}. The association of fatigue with physical functioning has been reported in SSc^{39,40}.

Ours is the first study to report associations between perceived functioning and ethnic-specific HLA genotypes and autoantibodies in SSc. This may indirectly reflect disease severity in the ethnic population expressing a greater frequency of a specific genotype. For example the HLA-DRB1*11 genotype was associated with lower MCS scores in African Americans. The HLA-DRB1*11 genotype is also associated with topo-1 autoantibodies. The presence of topo-1 autoantibodies was reported more frequently in African Americans¹¹ (18% vs 10% in Caucasians or Hispanics) and was associated with more severe cutaneous and pulmonary involvement and decreased survival in SSc⁴¹. The association of HLA-DRB1*11 genotype with lower MCS may merely reflect the higher frequency of HLA-DRB1*11 in African Americans, although the sample size of the Caucasian group was sufficient to have detected this association if present. Lower MCS scores may reflect more severe disease involvement, also reflected by the association of topo-I with higher Scleroderma-HAQ scores. Or possibly, the association reflects the interactions of gene products with moderating environmental or cultural factors that are more predominant in one ethnicity. Higher Scleroderma-HAQ scores were also significantly associated with the presence of autoantibodies to RNA polymerase III in African Americans.

The presence of HLA-DQA1*0501 was associated with lower MCS scores in Hispanics. HLA-DQA1*0501 was recently identified as a significant predictor of mortality in

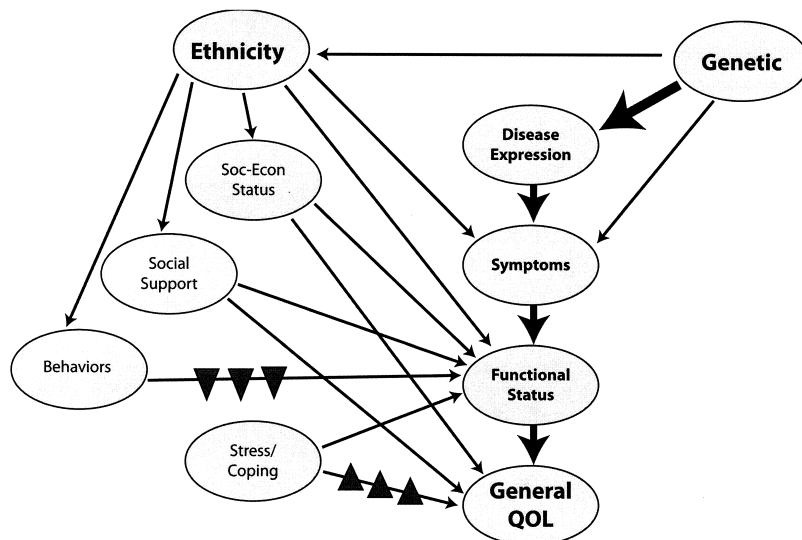


Figure 1. Hypothetical model of variables contributing to quality of life for patients with systemic sclerosis. Strong (block arrows) and weaker (line arrows) proposed contributions of the constructs to general quality of life are illustrated. Disease expression influences symptoms, which influence role-specific functional status. Ultimately, all constructs directly or indirectly contribute to general quality of life. Genetic contributions to central constructs are both direct and/or indirect (ethnic-specific). ▲: May have greater influence in non-Caucasian groups. ▼: May have greater influence in Caucasian groups. Modified from Vidrine DJ, *et al*⁷, *Qual Life Res* 2005;14:923-33, with permission of Springer Science and Business Media.

SSc⁴². The presence of HLA-DQB1*03 genotype was reported in higher frequency in Hispanic patients with SSc¹¹ and was associated with higher Scleroderma-HAQ scores in the Hispanic group.

Figure 1 incorporates proposed ethnic and genetic contributions to overall patient quality of life and demonstrates 2 major points of this study: (1) Genetic background may significantly affect disease expression (central modifiers), but to a great extent also defines the ethnic experience (peripheral modifiers). (2) Cultural experiences critically affect social support, disease belief systems, and behavior, often independent of demographic, accessibility, or economic factors, and thus influence daily living and ultimately burden of disease.

Our cross-sectional study had limitations that need further elucidation. The ethnic, clinical, and psychological contributors to perceived functioning in SSc identified at study entry may change with disease progression. Longitudinal analyses of our cohort will determine if ethnic-specific associations to functioning persist throughout disease progression and with therapeutic interventions. Improved functioning scores along with clinical improvement following therapeutic intervention have been described in SSc^{4,30,31}.

We demonstrated validation of the ISEL, fatigue severity, IBQ, and helplessness questionnaires, which reflect the individual's social support and illness beliefs and illness behaviors. A reported strength of these questionnaires is identification of potentially modifiable beliefs and behaviors that affect perceived functioning that may also be

dependent on ethnicity. Our study and others have reported differences in the frequency of modifiable behaviors such as smoking tobacco or drinking alcohol by ethnic groups⁴³⁻⁴⁶. A possible assumption is to place the primary onus of improving quality of life by behavior modification on the individual and culture, based on coping behavior scores and behaviors, but 2 issues need clarification. First, there is little direct evidence that validates the relative item weights of these questionnaires based on genetically distinct cultures in SSc or other illnesses. Therefore, direct comparisons of scores across ethnic groups may not be valid. Lower scores may not necessarily denote lower functioning, social support, or coping with illness within a defined ethnicity. Moreover these associations may be inconsistent. For example, in Hispanics, ACA was associated with higher PCS but lower MCS scores. Further, genotypes that are reported to be protective in SSc populations may not be associated with higher scores of perceived functioning⁴⁷. However, we demonstrated that ethnic-specific associations of clinical and laboratory data, social support, illness behaviors, and helplessness and fatigue score variables with perceived functioning were often robust.

Second, our study and others showed no significant differences in access to healthcare across ethnic groups in SSc (or systemic lupus erythematosus^{11,36,43}). However, external to the individual or culture, recent studies also show ethnically defined disparities in potentially modifiable treatment practices of the healthcare system, including primary care

providers, independent of income or accessibility issues^{48,49}.

Personalized medicine traditionally emphasizes genetic background in the context of disease manifestations in designing optimal therapeutic interventions for the individual. However, therapeutic interventions in SSC may be sub-optimal unless important psychological or behavioral factors are adequately addressed⁵⁰⁻⁵³. The patient's cultural environment may offer beneficially malleable influences on quality of life. For example, will culturally tailored interventions to culturally affected behaviors such as smoking cessation improve success rates and ultimately, clinical outcomes⁵⁴? Scoring and use of functioning, social support, and coping questionnaires may offer relatively cheap insight to improving individualized therapeutic interventions. Routine and meaningful clinical use of these instruments will require further validation based on cultural background.

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