Predictors of the Progression of Functional Disability in Patients with Ankylosing Spondylitis

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ABSTRACT. ***Objective.*** To identify patient characteristics that predict the short term (5 yr) rate of progression of functional disability in ankylosing spondylitis (AS).

Methods. In a prospective longitudinal study, 212 patients with AS reported information on health status on biannual mailed questionnaires. The median duration of followup was 5 yrs (range 1–7.5 yrs). Functional disability was measured using the Health Assessment Questionnaire for the Spondyloarthropathies (HAQ-S; possible range 0–3). Predictors of the rate of change in the HAQ-S over time included demographic characteristics, number of comorbid conditions, age at onset of AS, peripheral arthritis, smoking, body mass index, social support (measured by the Interpersonal Support Evaluation List, ISEL), current and past physical activity at work, current and past recreational activity, severity of pain and stiffness, nonsteroidal antiinflammatory drug use, and frequency of back exercise. Associations between the predictors and the rate of progression of functional disability (HAQ-S units/yr) were tested using pooled time series regression analysis.

Results. Patients were mostly middle-aged (mean 48 yrs), male (70%), white (86%), and well educated (mean 15.5 yrs), with an average duration of AS of 20 yrs and little functional disability at study entry (mean HAQ-S 0.66). Over a median of 5 yrs, the HAQ-S increased at an average rate of 0.0168 units/yr. In multivariate analyses, older age (change in slope +0.0007 units/yr of age; $p = 0.0008$) and smoking (change in slope +0.0313 units/yr; $p < 0.0001$) were associated with more rapid progression, while more frequent back exercise (change in slope –0.0019 units/yr per each additional day/week; $p < 0.0001$) and better social support (change in slope –0.003 units/yr per 10 point increase in ISEL score; $p = 0.05$) were associated with improvement in functional disability over time. Smoking and lack of social support were also associated with the progression of functional disability in the subgroup of 58 patients who had AS < 10 yrs at entry.

Conclusion. Functional disability in AS progresses more rapidly in older patients and smokers, and less rapidly in those who regularly do back exercises and have better social support. (J Rheumatol 2002;29:1420–5)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS DISABILITY HEALTH STATUS
EXERCISE SOCIAL SUPPORT

Functional ability is a major component of health related quality of life, and an important health outcome for patients with ankylosing spondylitis (AS)[1]. Functional disability also predicts future work loss and is the main determinant of medical costs in AS[2-5]. The development of interventions to improve functional ability depends on understanding the mechanisms by which disability develops. This understanding may be aided by identification of patients at greater risk for functional disability.

Functional disability cumulates slowly over time in AS, but the variation among patients is substantial[6-10]. In addition to the duration of AS, reported risk factors for functional disability include older age[9], younger age at onset[7], lower education level[8], female sex[8-10], presence of peripheral arthritis[2,7,11] or comorbid illnesses[2], and higher levels of pain, depression, anxiety and neuroticism[12-14]. Most studies of risk factors for functional disability in patients with AS were cross sectional, and therefore were unable to determine the causal direction of these associations. Most studies also examined only a limited number of potential risk factors, and few studies used multivariate statistical techniques to identify factors that were independently associated with functional disability. In this study, a prospective longitudinal design was used to examine a wide variety of potential predictors of the progression of functional disability in patients with AS over a median of 5 yrs.

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MATERIALS AND METHODS

Patient recruitment and study protocol. Patients in this study were participants in the Longitudinal Study of Outcomes in Ankylosing Spondylitis, a prospective study of health status, treatments, and outcomes of patients with AS[15]. Participants represented a volunteer sample recruited from 1992 to 1997 from the rheumatology clinics at Stanford University Medical Center and the VA Palo Alto Health Care System, by referral from local

rheumatologists, and from the community by advertisement. To be eligible, participants had to have a diagnosis of AS by the modified New York criteria[16], be age 18 or older, and be able to read English. Patients with a history of inflammatory bowel disease were excluded. Radiographs of the sacroiliac joints were not obtained for this study, but prior radiographs or radiograph reports documenting sacroiliitis were required.

Two hundred forty-one patients were enrolled [79 (33%) from the Stanford University and VA Palo Alto rheumatology clinics; 41 (17%) from local rheumatologists; and 121 (50%) from the community]. Study participation included a physical examination and completion of questionnaires at entry, and completion of mailed questionnaires every 6 months thereafter. Patients were followed from study entry to death, withdrawal from the study, or the end of data collection for this analysis (March 31, 2001). Because we were interested in the progression of functional disability over time in this study, we included in this report only patients who completed at least 3 consecutive questionnaires. Compared to the 212 patients included in this analysis, the 29 patients excluded from this analysis were younger (41.6 vs 47.8 yrs; $p = 0.03$), thinner [body mass index (BMI) 23.6 vs 26.1 kg/m^2; $p = 0.007$], and exercised less (79 vs 139 min/wk; $p = 0.003$), but these groups were otherwise similar in demographic and clinical characteristics.

Study variables. The initial questionnaire asked information on demographic characteristics, duration of AS, comorbid medical conditions, past and current employment and work activity, past and current recreational activity, social support, and health status. The demographic characteristics included age at study entry, sex, ethnicity, years of formal education, marital status, employment status, and occupation. For patients' current and previous jobs, we classified the physical activity of each job using the ratings assigned by the US Department of Labor in the *Dictionary of Occupational Titles* (1: sedentary, 2: light, 3: medium, 4: heavy, 5: very heavy)[17]. We also asked patients to report the proportion of a typical workday spent sitting, standing, walking, carrying, lifting, bending, kneeling, and crawling in their current job, and classified those who spent 20% or more of their workday lifting, bending, kneeling, or crawling as having a physically demanding job. Patients also reported their level of recreational physical activity in each decade of life (1: less active than peers, 2: as active as peers, 3: more active than peers), from which we computed an average index of past recreational activity. The clinical characteristics studied included age at onset of AS, BMI, current smoking, and number of comorbid medical conditions. Social support was measured using the Interpersonal Support Evaluation List (ISEL), a 40 item instrument that rates a person's perception of the quality of emotional, appraisal, self-esteem, and tangible support received from others[18]. Possible scores on the ISEL range from 0 (low perceived quality) to 120 (high perceived quality). The presence of peripheral arthritis was determined on physical examination.

On the initial questionnaire and each followup questionnaire, patients were asked about health status, treatment, and exercise. Functional disability, the outcome of this study, was measured using the Health Assessment Questionnaire Disability Index modified for the Spondyloarthropathies (HAQ-S)[19]. This modification of HAQ is a 25 question self-report instrument that asks respondents to rate the degree of difficulty they have performing tasks in 10 functional areas (dressing, arising, eating, walking, hygiene, reaching, gripping, errands and chores, bending, and driving). Responses to each question can range from 0 (no difficulty) to 3 (unable to do), and the scores of each functional area are averaged to compute the HAQ-S (possible range 0–3). Pain was measured using the pain score of the HAQ, a 15 cm horizontal visual analog scale (VAS) labeled 0 = no pain and 3 = severe pain. Stiffness was also measured using a 15 cm horizontal VAS, labeled 0 = no stiffness and 100 = severe stiffness. Patients reported the duration of use of medications taken to treat their AS symptoms, from which we computed the proportion of time during followup that each patient took nonsteroidal antiinflammatory drugs (NSAID). Patients also reported the number of days per week that they exercised and the duration of each exercise session, from which we computed the number of exercise minutes per week. They also reported the number of days per week they performed back stretching or strengthening exercises.

Statistical analysis. To determine the association between demographic and clinical characteristics and the rate of progression of functional disability over time, we used pooled time series regression analysis[20,21]. This technique is a modification of classical linear regression that accommodates multiple time ordered observations on multiple subjects in a single regression model. Random effects models were specified. The dependent variable in these models was the HAQ-S recorded on each questionnaire. In the initial models, individual predictors were tested by including as independent variables the duration of AS, the potential predictor variable (e.g., sex, education level, or exercise min/wk), and an interaction term between duration and the predictor variable. The coefficient of the interaction term indicated the average change in the rate of progression of functional disability (in HAQ-S units/yr) with each unit change in the predictor variable (e.g., male vs female; each additional yr of education; each additional 10 min/wk of exercise). Values at study entry were used as predictors for age, marital status, employment status, professional occupation, current work activity (by the *Dictionary of Occupational Titles*), physically demanding job (by patient report of work activities), past work activity, past recreational activity, age at onset of AS, number of comorbid conditions, smoking status, BMI, presence of peripheral arthritis, and social support (by the ISEL). Values obtained at study entry and during followup were used as predictors for pain severity, stiffness severity, exercise min per wk, and days per wk of back exercises. A single summary value of the proportion of time of treatment with NSAID, based on longitudinally collected information, was used as the predictor value for this variable. To assess the combined association of several predictors on the rate of progression of functional disability, a multivariate model that included interaction terms that were significant in the initial models was developed.

Limdep programs (Econometric Software Inc., Bellport, NY, USA) were used to perform the pooled time series regression analyses. All other analyses were performed using SAS programs (SAS Institute, Cary, NC, USA). All hypotheses were 2 tailed, and p values < 0.05 were considered statistically significant.

RESULTS

Study participants were predominantly middle-aged, male, white, and well educated (Table 1). Many had professional occupations, and most had jobs that were sedentary or involved light physical activity. The mean duration of AS at study entry was 20.1 years (median 18.2 yrs, range 6 mo to 61 yrs). At study entry, the mean HAQ-S was 0.66 (median 0.5), indicating mild functional disability. The HAQ-S at study entry was 1.0 or higher in 25% of patients. Initial scores of pain severity and stiffness severity were both moderately high.

Participants were followed for a median of 5 years (range 1.0 to 7.5), and contributed 2297 HAQ-S scores over 1049.5 person-years of followup. Over all observations, the mean (± standard deviation) HAQ-S was 0.75 ± 0.59. The mean within-patient SD of the HAQ-S was 0.19, indicating little variation in scores within individual patients over time. HAQ-S scores were unchanged from the score reported 6 months previously in 26% of sequential observations, and were within 0.2 HAQ-S units in 74% of sequential observations. The HAQ-S improved by more than 0.2 units in 14% of sequential observations, and worsened by more than 0.2 units in 12% of sequential observations. Over the duration of followup, the initial and final HAQ-S differed by 0.2

Table 1. Characteristics of patients at study entry (n = 212).*

Age, yrs	47.8 ± 13.6
Male, n (%)	149 (70.3)
White, n (%)	183 (86.3)
Education level, yrs	15.5 ± 2.7
Employed, n (%)	128 (60.4)
Professional occupation, n (%)	91 (42.9)
Married, n (%)	146 (68.9)
ISEL (0–120)	96 ± 19
BMI, kg/m^2	26.1 ± 4.7
Current smoker, n (%)	31 (14.6)
Number of comorbid conditions, n (%)	
0	55 (26.0)
1	63 (29.7)
2	48 (22.6)
3 or more	46 (21.7)
Average past work activity (1–5)**	1.8 ± 0.7
Current work activity (1–5)**	1.7 ± 0.8
Current physically demanding job, n (%)	23 (10.9)
Past recreational activity (1–3)***	2.0 ± 0.6
Current recreational exercise, min/wk	139 ± 161
Back exercise, days/wk	3.0 ± 2.6
Duration of AS, yrs	20.1 ± 13.9
Age at onset of AS, yrs	27.7 ± 11.2
HAQ-S (0–3)	0.66 ± 0.6
Pain severity (0–3)	1.2 ± 0.8
Stiffness severity (0–100)	47 ± 24
Peripheral arthritis, n (%)	45 (21.2)
Proportion of time using NSAID	68 ± 36

* Plus-minus values are mean ± SD. Value in parentheses after the variable name is the possible range for that variable. ISEL: Interpersonal Support Evaluation List. HAQ-S: Health Assessment Questionnaire Disability Index modified for the Spondyloarthropathies. ** By the *Dictionary of Occupational Titles* physical activity rating (1–5). *** Patient self-report compared to peers (1–3).

units or less in 53% of patients, while HAQ-S scores improved by more than 0.2 units in 14% and worsened by more than 0.2 units in 33%. By pooled time series regression analysis, which includes all HAQ-S values of all patients, the HAQ-S increased at an average rate of 0.0168 units/yr.

In univariate analyses, HAQ-S scores increased more rapidly in older patients, whites, those with more comorbid medical conditions, smokers, and those who had more physically demanding jobs during their lifetime (Table 2). HAQ-S scores improved over time among patients with higher education levels and ISEL scores (indicating better social support) and with more frequent back exercise. A higher BMI was marginally associated with more rapid increases in HAQ-S scores. There was no association between the slope of HAQ-S scores and age at onset of AS, sex, marital status, current employment, professional occupation, physical activity at work at study entry (by the *Dictionary of Occupational Titles* rating), physically demanding job at study entry (by patient report of work activities), past recreational activity, frequency of current recreational exercise, presence of peripheral arthritis, pain severity, stiffness severity, or frequency of NSAID use.

In a multivariate analysis that included all predictors that were significant in univariate models, only age, smoking, ISEL scores, past physical activity at work, and the frequency of back exercise were associated with the rate of progression of HAQ-S scores, while ethnicity, education level, and number of comorbid conditions were not (Table 2). The rate of progression of the HAQ-S increased by 0.0006 units/yr with each additional year of age, and increased by an additional 0.025 units/yr among smokers, compared to nonsmokers. In contrast, the rate of progression of the HAQ-S decreased by 0.005 units/yr with every 10 point increase in ISEL score (indicating better social support), and decreased by 0.0023 units/yr with each additional day per week of back exercise. In the multivariate model, having a history of more physically demanding jobs was associated with a slight decrease in the rate of progression of HAQ-S scores, while in the univariate analysis this predictor was associated with more rapid progression. This change in the direction of association was due to confounding by smoking status, as the average physical activity of previous jobs among smokers was higher than that among nonsmokers (average *Dictionary of Occupational Titles* rating 2.18 vs 1.75; p = 0.02). BMI was not significantly associated with the progression of HAQ-S scores when added to this model (p = 0.78).

In a model that included only the significant predictors, the associations between age, smoking, ISEL scores, and frequency of back exercise and the rate of progression of HAQ-S scores were essentially unchanged, but the association of past physical activity at work with the rate of change of HAQ-S scores was only marginally statistically significant (Table 3).

To determine if there were additional or unique predictors of the progression of functional disability in early AS, analyses were repeated in the 58 patients who had AS for less than 10 years at study entry. Their median age was 36.5 years, and 23 (40%) were women. In univariate analyses of this subgroup, HAQ-S scores increased more rapidly in older patients (change in slope 0.0032 units/yr with each additional yr of age; p = 0.05), women (0.0774 units/yr; p < 0.0001), whites (0.0631 units/yr; p = 0.0006), smokers (0.0173 units/yr; p = 0.05), and those with more comorbid conditions (0.006 units/yr with each additional condition; p < 0.0001). HAQ-S scores improved over time in married subjects (–0.1332 units/yr; p = 0.008), those with higher ISEL scores (–0.028 units/yr with each 10 point increase), and those who performed back exercise more frequently (–0.0135 units/yr with each additional day per wk). In multivariate analyses, smoking (0.0545 units/yr; p = 0.004) and ISEL scores (–0.018 units/yr with each 10 point increase; p = 0.02) were significantly associated with the progression of functional disability, and women tended to have higher rates than men (0.0229 units/yr; p = 0.06).

Table 2. Association of predictors with the rate of progression of HAQ-S scores over time. Values of change in slope represent the change in HAQ-S units/yr with each 1 unit change in the predictor*.

Predictor	Unit	Univariate Change in Slope	Univariate 95% CI	Univariate p	Multivariate Change in Slope	Multivariate 95% CI	Multivariate p
Age	1 yr	0.0018	0.0009, 0.0027	0.0001	0.0006	0.0002, 0.0011	0.007
Male	No/yes	–0.0009	–0.094, 0.0923	0.99	—	—	—
White	No/yes	0.0618	0.024, 0.0995	0.002	–0.0057	–0.0205, 0.009	0.45
Education level	1 yr	–0.0059	–0.0117, 0	0.05	0.0027	–0.0142, 0.0195	0.76
Employed	No/yes	–0.0029	–0.0712, 0.0654	0.94	—	—	—
Professional occupation	No/yes	–0.0534	–0.1438, 0.0369	0.25	—	—	—
Married	No/yes	0.0031	–0.0658, 0.072	0.93	—	—	—
ISEL	10 points	–0.021	–0.037, –0.005	0.009	–0.005	–0.008, –0.001	0.03
BMI	1 kg/m^2	0.0059	–0.0003, 0.0122	0.07	—	—	—
Current smoker	No/yes	0.0557	0.0243, 0.0871	0.0005	0.025	0.0071, 0.0429	0.007
Comorbid conditions	1 condition	0.0182	0.0035, 0.0328	0.02	–0.0027	–0.0081, 0.0028	0.34
Average past work activity	1 category**	0.0224	0, 0.0448	0.05	–0.0091	–0.0173, –0.0009	0.04
Current work activity	1 category**	0.0065	–0.0174, 0.0305	0.60	—	—	—
Physically demanding job	No/yes	0.0067	–0.0503, 0.0636	0.82	—	—	—
Past recreational activity	1 category***	–0.0011	–0.0719, 0.0697	0.98	—	—	—
Current recreational exercise	10 min/wk	0.0000	–0.003, 0.004	0.85	—	—	—
Back exercise	1 day/wk	–0.0022	–0.001, –0.0034	0.0004	–0.0023	–0.0032, –0.0014	< 0.0001
Age at onset of AS	1 yr	0.0016	–0.0022, 0.0055	0.41	—	—	—
Pain severity	1 point	–0.0022	–0.0132, 0.0088	0.70	—	—	—
Stiffness severity	10 points	–0.003	–0.008, 0.002	0.23	—	—	—
Peripheral arthritis	No/yes	–0.0018	–0.0396, 0.0361	0.93	—	—	—
Time using NSAID	1%	0.0067	–0.0646, 0.0779	0.86	—	—	—

* ISEL: Interpersonal Support Evaluation List. HAQ-S: Health Assessment Questionnaire Disability Index modified for the Spondyloarthropathies. ** By the *Dictionary of Occupational Titles* physical activity rating (1–5). *** Patient self-report compared to peers (1–3).

Table 3. Association of predictors with the rate of progression of HAQ-S scores over time, including only significant predictors. Values of change in slope represent the change in HAQ-S units/yr with each 1 unit change in the predictor.*

Predictor	Unit	Change in Slope	95% CI	p
Age	1 yr	0.0007	0.0003, 0.001	0.0008
ISEL	10 points	–0.003	–0.006, –0.0001	0.05
Current smoker	No/yes	0.0313	0.019, 0.0435	< 0.0001
Average past work activity	1 category**	–0.0073	–0.0154, 0.0008	0.08
Back exercise	1 day/wk	–0.0019	–0.0027, –0.001	< 0.0001

* ISEL: Interpersonal Support Evaluation List. HAQ-S: Health Assessment Questionnaire Disability Index modified for the Spondyloarthropathies. ** By the *Dictionary of Occupational Titles* physical activity rating (1–5).

DISCUSSION

Among the patients in this study, 4 factors predicted the rate of progression of functional disability: older age, smoking, social support, and back exercise. Older age and current smoking were associated with more rapid rates of progression, while better perceived social support and more frequent back exercise were associated with improvement in functional disability over time. Using the change in rate of progression with age as a metric, current smokers had, on average, a rate of progression of functional disability similar to someone 44 years older. A difference in the ISEL score of 10 points was similar to a 4.3 year difference in age in its association with changes in functional disability, and a difference of 1 day per week in the frequency of back exercise was similar to a 2.7 year difference in age.

The effect of age on functional disability in patients with AS has been difficult to distinguish from the effect of the duration of AS, because age and the duration of AS tend to be highly collinear. Our findings indicate that age has an important influence on functional disability, apart from its association with disease duration. The results also indicate that functional disability accelerates with age, suggesting that models of the longterm course of functional disability in AS would be expected to have a curvilinear up slope at older ages. Age may influence functional disability through asso-

ciated limitations in flexibility, strength, endurance, or coordination. However, the association of age and functional disability was independent of the frequency of back exercise, and the intensity of recreational exercise in general was not associated with the progression of functional disability, suggesting that the effects of age were not solely related to physical conditioning. Comorbid medical conditions may contribute to the association of age and functional disability, but in this analysis, age was a more important predictor of functional disability than was the number of comorbid conditions. Whether an alternative measure of comorbidity would have altered the association between age and the progression of functional disability is unclear.

Smoking was strongly associated with the rate of progression of functional disability, independent of age, education level, comorbidity, and exercise frequency. Smoking may directly influence functional ability in patients with AS by worsening lung function, which may already be compromised by a rigid thorax and restrictive ventilatory deficits, leading to decreased exercise capacity and greater deconditioning. Smoking may also cause cardiovascular disease or contribute to osteoporotic fractures, which may contribute to functional disability in ways not captured by our measure of comorbidity. While these represent plausible mechanisms by which smoking may directly affect functional ability in patients with AS, the possibility that smoking is a surrogate of some other health behavior, lifestyle factor, or predisposition that is more directly associated with functional disability cannot be excluded. However, the strength of the association, and its independence of several potential confounding factors, suggests that some of the association between smoking and the rate of progression of functional disability is likely a direct effect.

Better social support has been associated with lower prevalences of functional disability and slower rates of progression of functional disability in many, but not all, studies of community dwelling elderly and patients with osteoarthritis, rheumatoid arthritis, and systemic lupus erythematosus[22-36]. Social support has not previously been linked to the progression of functional disability in patients with AS, but the association reported here is consistent with those found in patients with other rheumatic diseases. The mechanisms by which social support may influence the development of functional disability are unclear, but may include reinforcement of healthy behaviors or adherence to medical treatment, enhanced self-efficacy, better coping resources, improved economic status, or direct physiologic effects[37]. The development of effective interventions to improve social support has proceeded despite uncertainty about its mechanisms of action. Telephone counseling has been observed in controlled clinical trials to improve physical functioning in patients with osteoarthritis and systemic lupus[28,29,32]. Our findings suggest that similar interventions may be able to affect the progression of functional disability in AS.

Back exercise has long been prescribed for AS, primarily to reduce symptoms and maintain good posture. Short term studies of inpatient or outpatient physical therapy have also reported improvements in functional ability[38-41]. Our findings suggest that more frequent back exercise, performed unsupervised by patients, is also associated with slower rates of progression of functional disability over a period of several years.

Smoking and social support were also associated with the progression of functional disability in patients with AS for less than 10 years, while age and the frequency of back exercise were not. That back exercise appears to have greater beneficial effect in later, rather than in early AS, may be related to the relative contribution of inflammatory and mechanical factors to functional disability during the course of AS and a differential effect of back exercise on functional disability arising from these 2 different sources. No additional predictors of progression were evident among those with early AS, although women in this subgroup appeared to have more rapid progression than men.

The strengths of this study are the large sample and the wide variety of predictors examined. The prospective design and moderately long followup allowed us to examine predictors of the rate of change in functional disability over time. However, the generally slow rate of progression may have decreased the statistical power to detect associations with some predictors. Also, we assumed a linear rate of progression over the median of 5 years that was studied. It is important to note that models of functional disability over the entire life course of AS were not developed in this study. These models would likely not be linear. The possible association of work physical activity and the progression of functional disability is uncertain. Having a history of more physically demanding jobs was associated with more rapid progression in the univariate analysis, and is associated with higher risks of work disability[4], but was marginally associated with lower rates of progression in the multivariate analysis. The absence of an association between patients' physical activity in their current job and the rate of progression of functional disability suggests either that work physical activity has a delayed effect on functional ability, that patients with histories of physically demanding jobs were self-selected for low rates of progression or that they preferentially moved to less demanding jobs before the start of the study, or that the association between heavier prior work activity and slower rates of progression was spurious. Because the sample was a volunteer sample, the findings may not be applicable to all patients with AS.

These findings support longstanding recommendations that patients with AS avoid smoking and perform back exercises regularly with evidence that these practices are associated with slower rates of progression of functional disability. Interventions that enhance social support may be another mechanism to accomplish this goal.

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