Clin Rheumatol (2009) 28:719–722
DOI 10.1007/s10067-009-1113-3

BRIEF REPORT

Application of a nomogram for exercise capacity in women with systemic lupus erythematosus

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Received: 16 January 2009 / Accepted: 27 January 2009 / Published online: 17 February 2009

Abstract The aim of this study is to examine the exercise capacity in women with systemic lupus erythematosus (SLE). Women with SLE underwent exercise testing; their performance was compared to nomogram predictions. We assessed the potential effects of disease activity and cumulative damage on exercise capacity. We evaluated 52 female SLE patients aged >35 years. The mean workload achieved was somewhat higher than the nomogram predictions. However, over one fifth of the women performed at a very poor level, which in the general population is associated with a twofold increased risk of cardiovascular disease. Compared to other subjects, participants who did poorly tended toward higher disease activity, higher body mass index, and greater smoking prevalence, although the results were not definitive. Exercise testing may be used to identify a subpopulation of lupus patients with a low level of fitness. Extrapolating from general population data, these individuals are likely at particular risk for cardiovascular disease and may, therefore, benefit the most from aggressive cardiovascular risk factor reduction.

Keywords Cardiac risk · Exercise capacity · Nomogram · SLE · Systemic lupus erythematosus

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Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease predominantly affecting women. SLE patients have up to a 50-fold increased risk of coronary artery disease (CAD) [1]. The contribution of CAD to mortality in SLE is especially significant in patients with longer disease duration and seems to be independent of lupus disease activity [2, 3]. The mortality attributable to CAD is as high as 36.4% in SLE patients [4, 5]. However, the uniform application of aggressive risk reduction strategies may expose some patients to untoward side effects [6]. Consequently, there has been much debate about how to prioritize those patients who would most benefit for treatment [7].

In the general population, the Framingham study identified age, abnormal cholesterol levels, elevated blood pressure, diabetes, and smoking as risk factors for the development of CAD [3]. The excess of cardiac events in SLE is not explained by the Framingham risk factors alone [8]. However, lupus-related factors including markers of disease activity and damage have not been shown to be accurate predictors of CAD in these patients [5].

Exercise capacity has been demonstrated to be an independent predictor of cardiac events and mortality in the general population [9]. Until recently, the majority of work on exercise capacity and CAD has been conducted in men. This has complicated the extrapolation of the data to SLE, a disease affecting predominantly women. Two small studies of exercise capacity in SLE patients concluded that

SLE patients have a diminished capacity compared to sedentary control groups [10, 11]. However, it is unclear how this difference in exercise capacity compares to the general population and whether this could have implications for CAD risk.

A nomogram in women from the general population has recently been established [12] where predicted exercise capacity for age, as determined by performance on a treadmill according to the Bruce protocol, is calculated with the following formula: predicted metabolic equivalents (MET)=14.7−(0.13×age). In this longitudinal cohort study, a model was developed wherein exercise capacity was a predictor of 10-year mortality from CAD. Participants who performed at a level of less than 85% predicted performance had a twofold greater risk of cardiac death than those with normal performance. Another recent study confirmed that exercise capacity is an independent predictor of death in asymptomatic women, to an even greater degree than men [13]. Since decreased exercise capacity represents a potential contributing factor for excess CAD in SLE patients, we assessed the potential application of this new sex-specific nomogram in women with SLE. Identifying those SLE patients with the worst CAD risk profile may be important in targeting those who would most likely benefit from aggressive modification of traditional risk factors.

Materials and methods

Participants

The McGill University Health Centre (MUHC) lupus cohort enrolls consecutive patients with American College of Rheumatology (ACR) criteria for SLE at the time when they present for their first clinic visit. Clinical and laboratory data are collected prospectively on an annual basis. Women enrolled in this cohort were invited to participate in a study of fatigue between January 2002 and March 2004. The subgroup of patients who performed exercise testing for this fatigue study formed the subject pool for the present study, as approved by our ethical review board. Women were excluded if they had pre-existing CAD, were unable to walk on a treadmill at a moderate pace, or were younger than 35 years of age (as the nomogram was developed using this population).

After obtaining informed consent, participants provided data on demographics, lifestyle, behavioral variables, and medical history by self-administered questionnaires. A comprehensive physical examination was performed, which included height, weight, blood pressure, and a general medical exam. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Resting blood pressure was measured by standard clinical procedures. Random urine and fasting blood samples were collected for laboratory analysis. Lupus disease activity was assessed using the SLE Activity Measure-2 (SLAM), and cumulative damage was evaluated with the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SLICC/ACR DI), a standardized measure of nonreversible damage related to SLE activity, its treatment, or comorbidities.

Exercise testing

Participants underwent a symptom-limited treadmill test according to the Bruce protocol with continuous cardiac rhythm monitoring. Heart rate and blood pressure were measured, and a 12-lead ECG was recorded before exercise, at the end of each exercise stage, at peak exercise, and at 1-min intervals during recovery. The test was discontinued for limiting symptoms (angina, dyspnea, and fatigue), abnormalities of rhythm or blood pressure, or marked and progressive ST segment deviation. Target heart rates were not used as a predetermined end point.

Exercise capacity is expressed in units of METs and is an estimate of the maximal oxygen uptake for a given workload. A MET is a measure of ventilatory oxygen consumption expressed as multiples of basal resting requirements where 1 MET is 1 U of basal oxygen consumption, which equals 3.5 mL of oxygen consumption per kilogram of body weight per minute for an average adult. The exercise capacity (in METs) is estimated by the speed and grade of the treadmill.

Statistical analyses

Descriptive analyses of all variables were examined. For each participant, the percentage of the predicted exercise capacity achieved for age was then calculated using the following equation: percentage of predicted exercise capacity for age=(observed MET/age−predicted MET)×100. Demographic and clinical characteristics were compared between those who performed poorly (<100% predicted) and those who performed well (≥100% predicted). We also examined the clinical characteristics of the subgroup of those who performed below the threshold of 85% predicted. The baseline characteristics of the 52 participants in the study were also compared with 50 SLE patients who declined to participate.

Results

Of the 130 patients initially approached to undergo exercise stress testing, 50 declined and a further 28 were excluded because they were below 35 years of age. Table 1 compares the characteristics of the 52 women who completed the study versus the 50 who declined. The latter group had a significantly higher SLICC/ACR DI scores, and there was a

Table 1 SLE study participants and nonparticipants

	Study participants (*N*=52)	Nonparticipants (*N*=50)
Age (years), average (standard deviation)	50.3 (10.2)	51.0 (11.4)
Disease duration (years), average (standard deviation)	13.6 (8.6)	18.6 (10.4)
Education (years), average (standard deviation)	13.8 (3.2)	12.5 (3.0)
Damage index, average (standard deviation)	1.3 (0.9)	2.5 (2.3)
SLE activity measure, average (standard deviation)	8.0 (5.3)	7.5 (5.6)
BMI (kg/m^2), average (standard deviation)	24.7 (4.7)	26.4 (6.4)
Ever smoked, *N* (%)	32 (61.5)	27 (54.0)
Current smoker, *N* (%)	9 (17.6)	6 (12.2)
Caucasian, *N* (%)	46 (88.2)	40 (80.0)

trend toward longer disease duration, lower education, and higher BMI.

The mean performance of the group was 9.33 MET. This average result was 0.62 METs higher than the mean predicted by the nomogram (110% of the predicted). Over half (59.6%) of the subjects exceeded their predicted exercise capacity for age.

However, over one fifth (21.2%) of the patients performed at a level less than 85% predicted. Compared to the participants who met or exceeded their expected performance, the participants who did poorly tended toward higher SLAM scores, higher BMIs, and greater smoking prevalence, although the confidence intervals for the estimates were wide and overlapping (Table 2).

Discussion

SLE is a serious, complex, chronic disease, and there is increasing awareness of the high morbidity accruing over time. There is increasing focus on preventing long-term sequelae, in particular, the prevention of CAD. Unfortunately, to date, predicting which patients might benefit most from aggressive risk reduction has been problematic.

Our novel study took advantage of a newly described, sex-specific nomogram for exercise capacity and applied it to a group of women with SLE. Whereas previous studies have compared SLE patients with a small group of sedentary controls, we were able to compare a group of SLE patients with age- and sex-appropriate population norms. As with any exercise study recruiting volunteers, the interpretation of our overall results must be tempered by the probable selection bias. Nonetheless, we were able to identify a subgroup of SLE patients who, according to recent data, may have a higher risk of death from cardiac disease. The approximately one in five women who performed poorly on the exercise stress test (EST) should probably be aggressively targeted in their modifiable cardiac risks.

More than half of our SLE sample performed better on the EST than the level predicted by the nomogram. This is despite the fact that these SLE patients had a significant disease burden, as evidenced by their baseline SLICC and SLAM scores. One possible explanation for this is the fact that the nomogram was not adjusted for BMI; our sample had a lower BMI than the American average, possibly reflecting a difference in US and Canadian populations. In addition, patients with more disease-related damage were

Table 2 Comparison of characteristics of participants, according to level of exercise capacity reached

	Participants reaching level of exercise capacity	
	Greater or equal to 0.85×norm (*N*=41)	Less than 0.85×norm (*N*=11)
Age (years), average (SD)	46.3 (9.2)	46.3 (9.2)
Disease duration (years), average (SD)	13.6 (8.7)	13.8 (8.9)
Education (years), average (SD)	13.8 (3.0)	14.0 (4.1)
Damage index, average (SD)	1.3 (0.2)	1.1 (0.5)
SLE activity measure, average (SD)	6.2 (1.1)	14.4 (14)
BMI (kg/m^2), average (SD)	24.1 (3.9)	27.5 (7.0)
Ever smoked, *N* (%)	26 (63.4)	6 (54.5)
Current smoker, *N* (%)	6 (15.0)	3 (27.3)
Caucasian, *N* (%)	36 (87.5)	10 (90.9)

less likely to participate (Table 1). Thus, a limitation of our findings is that EST is not always possible in some individuals; however, this does not negate the fact that it may be useful in a significant proportion.

Compared to the participants who met or exceeded their expected performance, the participants who did poorly tended toward higher SLAM scores, higher BMIs, and greater smoking prevalence, although the confidence intervals for the estimates were wide and overlapping. A possible association between poorer exercise capacity and higher SLAM scores has biologic plausibility, in that clinical lupus involvement (e.g., anemia, arthritis, cardiorespiratory disease) may directly impact performance. On the other hand, some items of the SLAM are nonspecific (fatigue, myalgias) and may be markers for the presence of chronic fatigue syndrome and general deconditioning, which is common in SLE and which might potentially limit performance. Still, it is worth noting that a current popular hypothesis links inflammation related to lupus disease activity as an independent risk factor for CAD [14].

Both smoking and obesity are traditional risk factors not only for poor exercise tolerance, but also for CAD. Previous work in SLE cohort studies has suggested that these exposures are not as aggressively treated as they should be [15]. Obviously, these factors are important to address for a number of reasons, given that they are key risk factors for a number of adverse outcomes, particularly atherosclerosis.

In summary, the additional information provided by exercise testing may help to identify a subpopulation of lupus patients who are likely at high risk of death due to CAD and who thus might benefit most from aggressive cardiac risk reduction strategies.

Disclosures None.

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