Quality of life measures and physical activity in childhood systemic lupus erythematosus

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Abstract
Childhood systemic lupus erythematosus (cSLE) is a life-long disease with significant morbidity and mortality, and with associated significant impact on health-related quality of life (HRQOL). Previous literature supports that physical activity has positive impact on HRQOL in patients with chronic diseases, including cSLE. We sought to describe the physical activity of our patients with cSLE and determine the relationship between physical activity, SLE activity, treatment modalities and HRQOL in cSLE. Children ≤18 years of age with cSLE and their parents were enrolled and completed corresponding child and parent Simple Measure of Impact of Lupus Erythematosus in Youngsters© reports (cSMILEY© and pSMILEY©, respectively), and the Physical Activity Questionnaire for Children (PAQ-C) or Adolescents (PAQ-A). Through retrospective chart review, we assessed the SLE Disease Activity Index (SLEDAI) using the SLEDAI-2K assessment tool. Descriptive statistics as well as Pearson’s correlation coefficients were performed with the data obtained. Forty-four children and their parents were enrolled; clinical data, SMILEY© and PAQ-C or PAQ-A scores of cSLE subjects were evaluated. The most frequently reported physical activity modality was walking (61.3%), with mean frequency of 3.7 ± 1.8 days a week, and a median of 3.5 days a week. Although there was no correlation noted between treatment modalities and PAQ-C/PAQ-A, there was weak correlation between SLEDAI and PAQ-C/PAQ-A (Pearson correlation = 0.2, p = 0.1, p = 0.9, n = 44). There was a weak correlation between SMILEY total score and PAQ [cSMILEY© and PAQ-C/PAQ-A combined cohorts (Pearson correlation = 0.2, p = 0.3, p = 0.07, n = 44), and modest correlation between pSMILEY© scores and PAQ-C/PAQ-A combined cohorts (Pearson correlation = 0.3, p = 0.3, p = 0.05, n = 44)]. Our study emphasizes the need for larger samples to understand the prognostic value of activity levels and the extent to which increasing physical activity might be linked to improvements in HRQOL in this vulnerable population.

Keywords
systemic lupus erythematosus, childhood systemic lupus erythematosus, physical activity, health related quality of life, SMILEY

Introduction
Childhood onset systemic lupus erythematosus (cSLE) is a life-long disease with significant morbidity and mortality, and with associated significant impact on health-related quality of life (HRQOL).¹ Prior research in the adult population has shown that SLE patients’ physical activity level is lower than that of healthy individuals.² Physical activity is defined as any voluntary movement that accompanies all activities at varying energy levels in contrast with exercise, which is activity requiring physical effort.²,³ Physical activity is typically lower in adolescent girls in healthy populations, and is associated with improved wellbeing in SLE, as well as reduced depression, improved cardiorespiratory functioning, and reduced fatigue.²,³,⁴

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Furthermore, adult literature has shown that physical inactivity in the SLE population is associated with increased risk of arteriosclerosis.\textsuperscript{17} There is a paucity of literature examining the relationship between physical activity and HRQOL in cSLE. We sought to describe the levels of physical activity and determine the relationship between physical activity, cSLE clinical characteristics, treatment modalities and HRQOL in cSLE. We hypothesized that there would be a direct relationship between physical activity and quality of life. In order to measure HRQOL, we used the Simple Measure of the Impact of Lupus Erythematosus in Youngsters© (SMILEY©), which is validated with parallel child and parent measures.\textsuperscript{5} We used the Physical Activity Questionnaire (PAQ) (full form) to measure physical activity. To our knowledge, this is the first study investigating the relationship between the PAQ and SMILEY© child and parent total scores.

**Methods**

**Participants**

All pediatric patients (age < 21 years) meeting the American College of Rheumatology classification criteria and/or the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE,\textsuperscript{6} followed at Children’s Healthcare of Atlanta (CHOA) in Georgia, USA for at least one year and enrolled in the South Eastern Registry for Childhood Arthritis Study (SEARCH)\textsuperscript{7} were included. Patients diagnosed with central nervous system (CNS) disease met criteria for one or greater neuropsychiatric syndromes in SLE.\textsuperscript{8} This study was approved by the Institutional Review Board at Emory University, who partners with CHOA, under protocol IRB00018494. All study participants gave written informed consent.

**Measures used**

SMILEY© is a validated pediatric cSLE quality of life evaluation tool for children with cSLE less than 19 years of age.\textsuperscript{5} The 24 question SMILEY© consists of parallel child self-reports and parent proxy-reports with responses in the form of a five-step scale with different facial expressions.\textsuperscript{5} The four domains are Effect on Self, Limitation, Social, and Burden of SLE. The total score range is 1–100, with higher scores indicating a better HRQOL. The first two items on the SMILEY© questionnaire are summary questions (global HRQOL and cSLE status) and are not included in the SMILEY© domains or the total score.\textsuperscript{5}

The PAQ is a child-focused questionnaire that assesses participation in various physical activities over the previous week.\textsuperscript{9,10,11} The PAQ-C is recommended for individuals in grades 4–8, approximately between 8 and 14 years of age, while the PAQ-A is recommended for individuals in grades 9–12, approximately between 14 and 20 years of age.\textsuperscript{9,10,11} Accordingly, individuals 14 years or younger filled out the PAQ-C scores, while older individuals filled out the PAQ-A form. Each of the 8 (PAQ-A) or 9 (PAQ-C) questionnaire items is scored between 1 and 5, with a higher number indicating higher frequency of physical activity. The mean score of all items constitutes the overall PAQ score. Patients completed the PAQ-C or PAQ-A at the time of study enrollment.

**Chart review**

Demographic (age, race and gender), clinical and laboratory values from the time of diagnosis to July 2021 were extracted from the Electronic Medical Record (EMR), including those necessary to calculate the SLE Disease Activity Index, or SLEDAI-2K, biomarkers at diagnosis pertaining SLE classification criteria as well as medications utilized to achieve remission, with specific parameters determined (Table 1) from prior literature evaluation of HRQOL and clinical determinants.\textsuperscript{12,13} Current (at the time of enrollment) use of Prednisone, Mycophenolate Mofetil, Azathioprine and Hydroxychloroquine as well as past and current use of Rituximab and Cyclophosphamide were recorded. SLEDAI data were obtained within three months of patient’s enrollment in the study and within three months of PAQ questionnaire assessment. We evaluated the clinical characteristics and SMILEY© questionnaire data of 44 paired samples, to include both parent and patient data, at the time of enrollment and completion of PAQ questionnaire.

Descriptive statistics as well as Pearson’s and Spearman’s rank correlation coefficients were performed with the data obtained. Data distribution was examined for all variables and data was examined for floor and ceiling effects. The p-value for Pearson’s and Spearman’s rank correlation coefficient was calculated using SPSS Statistics Data Editor (v28.0.1.1(14)). The patients were stratified into two cohorts, with Group One consisting of comparatively lower than average levels of physical activity, and Group Two consisting of comparatively higher than average levels of physical activity (PAQ score <2 and ≥2, respectively), based off the average PAQ score of 2 within our cohort. This group stratification was performed to identify both higher risk and lower risk individuals. We utilized a conservative estimate of PAQ scoring, using previous studies which identified normative PAQ scores of 2.7–2.9 in a healthy pediatric population.\textsuperscript{9,14,15} With this stratified data set, categorical data was analyzed using Fisher’s exact test, and numerical data analyzed using Wilcoxon Rank Sum. Remaining data analysis was performed on R Statistical Software (v1.4.1106).
Results

Demographics

Forty-four patients were included, with a mean age of $15.2 \pm 2.2$ years; of this, approximately 82% was female (Table 1). There was a preponderance of African American females, with a mean age of $13.1 \pm 2.7$ years. In our cohort, only 18% were males, with an average age of $15.2 \pm 2.2$ years. Table 1 summarizes demographic and clinical information.

Table 1. Characteristics of cSLE participants stratified by PAQ scores.

| Demographics | Total cohort ($n = 44$) | Group One (PAQ Scores < 2) ($n = 23$) | Group Two (PAQ Scores ≥ 2) ($n = 21$) |
|--------------|-------------------------|--------------------------------------|--------------------------------------|
| Female       | 36 (82%)                | 19 (83%)                             | 17 (81%)                             |
| Male         | 8 (18%)                 | 4 (17%)                              | 4 (19%)                              |
| Age, mean ± SD (median, range) | 15.2 ± 2.2 (16.0, 7–18) | 15.7 ± 1.86 (16.0, 8–18) | 14.6 ± 2.4 (15.0, 7–17) |
| Race         |                         |                                      |                                      |
| Caucasian    | 18 (41%)                | 9 (39%)                              | 9 (43%)                              |
| African American | 22 (50%)            | 13 (57%)                             | 9 (43%)                              |
| Asian        | 3 (6%)                  | 1 (4%)                               | 2 (10%)                              |
| Other        | 1 (2%)                  | 0                                    | 1 (5%)                               |
| Disease characteristics |                      |                                      |                                      |
| cSLE Disease duration in years, mean ± SD (median, range) | 1.6 ± 2.6 (1.0, 0–8) | 2.3 ± 2.5 (1.0, 0–8) | 1.6 ± 2.1 (0.5, 0–8) |
| SLEDAI, mean ± SD (median, range) | 3.1 ± 3.3 (2.0, 0–13) | 3.17 ± 3.2 (2.0, 0–10) | 3.0 ± 3.6 (2.0, 0–13) |
| SLEDAI ≥12   | 2 (5%)                  | 0                                    | 2 (10%)                              |
| Class IV/V Lupus Nephritis | 15 (34%)            | 9 (39%)                              | 6 (29%)                              |
| Neuro-psychiatric | 5 (11%)              | 3 (13%)                              | 2 (10%)                              |
| Mean C- SMILEY Score ± SD | 64.0 ± 16.9            | 61.0 ± 17.2                          | 68.0 ± 17.2                          |
| Mean P- SMILEY Score ± SD*** | 61.0 ± 16.2            | 58.0 ± 15.9                          | 65.0 ± 16.1                          |
| Medication   |                         |                                      |                                      |
| Prednisone (current use) | 31 (71%)             | 18 (78%)                             | 12 (57%)                             |
| High dose Prednisone (≥15 mg daily, current use) | 15 (34%)             | 8 (35%)                              | 7 (33%)                              |
| Mycophenolate Mofetil (current use) | 25 (57%)             | 14 (61%)                             | 12 (57%)                             |
| Azathioprine (current use) | 3 (7%)               | 3 (13%)                              | 0                                    |
| Hydroxychloroquine (current use) | 42 (96%)             | 22 (96%)                             | 20 (95%)                             |
| Cyclophosphamide (current and/or past use) | 12 (27%)             | 8 (35%)                              | 4 (19%)                              |
| Rituximab (current and/or past use) | 5 (11%)              | 3 (13%)                              | 2 (10%)                              |
| Biomarkers at diagnosis |                      |                                      |                                      |
| Positive anti-dsDNA | 25 (57%)             | 13 (57%)                             | 12 (57%)                             |
| Positive anti-Smith | 11 (25%)             | 5 (22%)                              | 7 (33%)                              |
| Low C3 and/or low C4 | 15 (34%)             | 9 (39%)                              | 6 (29%)                              |
| Arthritis    | 22 (50%)                | 9 (39%)                              | 11 (52%)                             |
| Serositis    | 13 (30%)                | 7 (30%)                              | 5 (24%)                              |
| Cytopenia    | 28 (64%)                | 14 (61%)                             | 13 (62%)                             |
| Rash         | 28 (64%)                | 12 (52%)                             | 13 (62%)                             |

This table depicts the patient demographics, clinical features and management of enrolled pediatric systemic lupus erythematosus patients in Group One and Two (PAQ scores < 2 and ≥2, respectively). Categorical variables expressed as n(percentage).

Abbreviations: PAQ: cSLE. Childhood-onset Systemic Lupus Erythematosus. C-SMILEY: Child- Simple Measure of Impact of Lupus Erythematosus in Youngsters®. PAQ: Physical Activity Questionnaire. P-SMILEY: Parent- Simple Measure of Impact of Lupus Erythematosus in Youngsters®. SLEDAI: SLE Disease Activity Index (SLEDAI-2K). SD: Standard Deviation.

*** Indicates statistical significant (p < 0.05).

Definitions: Low C3 and/or low C4: C3 or C4 decreased lower limit of lab. Arthritis: ≥2 joints with pain and signs of inflammation. Serositis: Pleuritic chest pain, pleural effusion, or pericarditis. Cytopenia: White Blood cell, Hemoglobin, or platelets below lower limit of lab.
score was 2.0, with a range of 0–13. In all, 34% of patients had Class IV/V lupus nephritis, and 11% had neuropsychiatric lupus symptoms. Ninety five percent of patients at diagnosis presented with positive antinuclear antibodies (titer 1:80 or above); and 63% presented with cytopenia and rash. A large number (70%) of patients were on prednisone at the time of data collection, with 34% on high dose prednisone (≥15 mg daily).16 Approximately 56% of patients were on Mycophenolate Mofetil or Mycophenolic Acid along while 27% had received Cyclophosphamide and 11% had received Rituximab. Table 1 summarizes SLE related clinical characteristics.

PAQ scores
Total mean PAQ score was 2.0 ± 0.9, and the median PAQ score was 1.8 (Interquartile Range 1.0–4.7). The most frequently reported physical activity modality was walking (61.3%), with mean frequency of 3.7 ± 1.8 days/week, and a median of 3.5 days/week (Table 2). Running was the second most frequent physical activity reported (56.8%), with mean frequency of 3.1 ± 2.0 days/week, and a median of 1.5 days/week. Skipping and dancing were third and fourth most commonly reported physical activities (34%, respectively), followed by tag (18%) and skating (13.6%). Table 2 details physical activity modalities.

SMILEY© scores and PAQ scores
The total mean cSMILEY© score was 64.0 ± 16.9 and the mean pSMILEY© score was 61.0 ± 16.2. In our cohort, there was a modest correlation between pSMILEY© scores and PAQ-C/PAQ-A (Pearson correlation = 0.3; ρ = 0.3, p = 0.05, n = 44), but only a weak correlation appreciated between cSMILEY© and PAQ-C/PAQ-A (Pearson correlation = 0.2, ρ = 0.3, p = 0.07, n = 44).

cSLE related characteristics and PAQ scores
There was a weak correlation noted between SLEDAI and PAQ-C/PAQ-A (Pearson correlation = 0.2, ρ = 0.1, p = 0.9, n = 44). There was no correlation between the remaining clinical characteristics and PAQ scores.

Stratified Analysis
Among 44 patients within our cohort, 23 were stratified into Group One (comparatively lower physical activity level group (PAQ <2)) and 21 patients into Group Two (comparatively higher physical activity level group (PAQ ≥2)). Compared to Group Two (PAQ ≥2), those in Group One (PAQ <2) had a higher proportion of hypocomplementemia at diagnosis (39% vs 29%; p = 1.0), current Prednisone use (78% vs 57%; p = 0.3), Class IV/V lupus nephritis (39% vs 29%, p = 0.5), and Cyclophosphamide use (35% vs 19%);

Table 2. Activities Reported by SMILEY Participants stratified by PAQ scores.

| Activities  | Total cohort (n = 44) | Group One (PAQ Scores < 2) (n = 23) | Group Two (PAQ Scores ≥ 2) (n = 21) |
|-------------|----------------------|-------------------------------------|-------------------------------------|
| Aerobics    | 4 (9.1%)             | 1 (0.04%)                           | 3 (14.2%)                           |
| Baseball    | 6 (12.6%)            | 3 (13.0%)                           | 3 (14.2%)                           |
| Biking      | 6 (12.6%)            | 1 (0.04%)                           | 5 (23.8%)                           |
| Dance       | 15 (34%)             | 5 (21.7%)                           | 10 (47.6%)                          |
| Football    | 3 (6.8%)             | 1 (0.04%)                           | 2 (9.5%)                            |
| Hockey      | 3 (6.8%)             | 1 (0.04%)                           | 2 (9.5%)                            |
| Horseback   | 1 (0.02%)            | 0                                   | 1 (0.05%)                           |
| Martial arts| 1 (0.02%)            | 1 (0.04%)                           | 0                                   |
| Running     | 25 (56.8%)           | 11 (47.8%)                          | 14 (66.75)                          |
| Soccer      | 1 (0.02%)            | 0                                   | 1 (0.05%)                           |
| Skating     | 6 (13.6%)            | 1 (0.04%)                           | 5 (23.8%)                           |
| Skipping*** | 15 (34%)             | 4 (17%)                             | 11 (52%)                            |
| Swimming    | 3 (6.8%)             | 0                                   | 3 (14.2%)                           |
| Tag         | 8 (18%)              | 1 (0.04%)                           | 7 (33%)                             |
| Volleyball  | 2 (4.5%)             | 1 (0.04%)                           | 1 (0.05%)                           |
| Walking     | 27 (61.3%)           | 11 (47.8%)                          | 16 (76%)                            |

This table depicts the activities of enrolled pediatric systemic lupus erythematosus patients for patients with PAQ scores <2 and ≥2. Categorical variables expressed as n(percentage).

***Indicates statistical significant (p < 0.05).
p = 0.3) in comparison to those in the High Physical Activity level group. cSLE patients in Group Two (PAQ ≥2) had higher cSMILEY© (mean 68.0 ± 17.2; p = 0.2) and pSMILEY© scores (mean 65.0 ± 16.1; p = 0.1) compared to those in Group One (PAQ <2). Among the physical activity modalities utilized, among Group 1 patients (PAQ <2) skipping was reported less commonly in comparison to Group 2 (PAQ ≥2); this determination was found to be statistically significant (Table 2; p = 0.02)

Discussion
To our knowledge, this is the first study investigating the relationship between the PAQ and HRQOL, specifically through evaluation of SMILEY© child and parent total scores. Our study revealed that cSLE patients with comparatively higher physical activity appeared to have better HRQOL, as evidenced by a modest correlation between pSMILEY© scores and PAQ-C/PAQ-A (Pearson correlation = 0.3, p = 0.3, p = 0.05, n = 44) and a weak correlation between cSMILEY© total score and PAQ-C/PAQ-A (Pearson correlation = 0.2, p = 0.3, p = 0.07, n = 44). Our findings suggest that cSLE patients with comparatively higher physical activity appeared to have lower Prednisone use, as well as less Cyclophosphamide use, while patients with hypocomplementemia at diagnosis and Class IV/V lupus nephritis had a higher proclivity towards less activity (PAQ score <2), although these findings were not found to be statistically significant.

Overall, our study has illustrated that patients with cSLE prefer walking followed by running as a form of physical activity. Furthermore, among Group 2 (PAQ ≥2), skipping was reported significantly more (Table 2; p = 0.02). To our knowledge, this preference has not been reported in the pediatric literature. Within our patient cohort, the most frequently reported physical activity modality was walking (61.3%) followed by running (56.8%). Dancing and skipping were also reported at higher rates compared to other activities assessed (34%). Although there is a paucity of pediatric literature, adult studies have shown that cSLE patients tend to have a more sedentary lifestyle compared to controls. Of those SLE patients who were physically active, similarly walking was the most reported activity, followed by strength training and cycling. This is in contrast with the general pediatric population, of which basketball is the most commonly reported physical modality among boys, and running the most commonly reported physical modality among girls. Given the average PAQ score of 2.0 within our cSLE cohort, in contrast with previous studies identifying normative PAQ scores in a healthy pediatric population ranges between a minimum of 2.7–2.9 based on age and gender, these findings overall suggest that cSLE patients, like the adult SLE population, may lead a more sedentary lifestyle. Furthermore, previous studies have shown that in healthy children physical activity levels are lower in females, particularly in adolescence. Given that our patient population was predominantly adolescent female, this may in part explain the physical inactivity of our cohort compared to normative data. It should be noted, however, that physical activity is closely linked with other factors, such as co-morbid fatigue, disease activity, psychiatric health, and socio-economic status.

A modest correlation between parent SMILEY© and PAQ-C/PAQ-A combined cohorts was found in our study, suggesting the relationship between physical activity and HRQOL. With respect to HRQOL measures, studies have shown that physical activity and exercise training can be efficacious in equipping the SLE-related impairment in physical function. Furthermore, Gavilán-Carrera et al showed that, in the adult lupus population, muscle strength and cardio-respiratory fitness are positively associated with HRQOL. Within our patient cohort, however, there was only a weak correlation between physical activity and SMILEY© child score. However, as per the Centers for Disease Control and Prevention, only 23.7% of pediatric patients in Georgia, the setting of our study, are physically active for a total of at least 60 minutes per day. That may explain the lack of a very strong correlation between physical activity and SMILEY© child score.

In our study, cSLE patients with comparatively higher physical activity appeared to have lower steroid and cyclophosphamide use, although this relationship was not statistically significant. Previous studies have shown that patients with cSLE who reported cyclophosphamide use had higher propensity towards lower HRQOL in comparison with those who had not utilized those medications. Previous studies have also elucidated a moderate correlation between child and parent reports of physical function and QOL. In both our study as well as prior literature, neither physical function nor HRQOL correlated strongly with disease activity, suggesting that although these variables are inter-related, a more far-reaching assessment of disease burden should be undertaken to obtain a thorough assessment of disease impact on our specific patient population.

Compared with prior studies, our patients had an overall lower frequency of use of Cyclophosphamide (27%) and higher frequency of use of Mycophenolate and Rituximab (57% and 11%, respectively) in contrast with previous literature, which reported Cyclophosphamide use at 39%, Mycophenolate use at 33%, and Rituximab use at 6%, likely reflecting current treatment preferences. Prior studies have reported an association between increased cyclophosphamide use and lower HRQOL, highlighting the importance of medications utilized to achieve remission. Additionally, our patient population had a higher predominance of African American Females. Similar to prior studies, age at study enrollment was comparable (previous studies reporting 14 years of age ± 3).
Limitations of this study include paucity of data pertaining to control PAQ scoring data within the cSLE patient population, as well as limited sample size. Due to the cross-sectional design, we are unable to infer causality from the associations identified in our study. Furthermore, we did not measure disease damage in this study. Additional limitations of this study include dependence upon the EMR for chart review, which directly impacted SLEDAI assessment as well as reported clinical features, and therefore may present an element of reporting bias. Moreover, given the self-reporting nature of the PAQ-C and PAQ-A, there may be an element of recall bias within our study. Additionally, we did not evaluate related variables of co-morbid fatigue, psychiatric health, and socio-economic status, which have been known to be closely associated with physical activity. As aforementioned, there are distinct differences in our particular patient population as opposed to previously published SMILEY publications, including decreased overall frequency of physical activity within our patient cohort with respect to the general pediatric population. This highlights the importance of measuring physical activity and HRQOL within our population, as well as the importance of increasing physical activity within our population, which can be reinforced within our own patient practices. Our study has also emphasized the need for larger samples to understand the prognostic value of activity levels and the extent to which increasing physical activity through exercise as well as recreational play and sport might be linked to improvements in HRQOL in this vulnerable population.

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