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Effects of Obesity on Health-Related Quality of Life in Juvenile-Onset Systemic Lupus Erythematosus

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Abstract

Objective—Evaluate the effects of obesity on health-related quality of life (HRQOL) measures in juvenile-onset SLE (jSLE).

Methods—Obesity was defined as a body mass index (BMI) $\geq 95^{\text{th}}$ according to the sex-specific Center for Disease Control body mass index-for-age charts and determined in a multicenter cohort of jSLE patients. In this secondary analysis, the domain and summary scores of the Pediatric Quality of Life (PedsQL) Inventory and the Child Health Questionnaire (CHQ) of obese jSLE patients were compared to those of non-obese jSLE patients as well as historical obese

and non-obese healthy controls. Mixed-effects modeling was performed to evaluate the relationship between obesity and HRQOL measures.

Results—Among the 202 jSLE patients, 25% (n=51) were obese. Obesity had a significant negative impact on HRQOL in jSLE, even after adjusting for differences in current corticosteroid use, disease activity, disease damage, gender, and race between groups. Obese jSLE patients had lower physical functioning compared to non-obese jSLE patients, and to non-obese and obese healthy controls. Compared to their non-obese counterparts, obese jSLE patients also had worse school functioning, more pain, worse social functioning, and emotional functioning. Parents of obese jSLE patients worry more. The CHQ scores for obese jSLE patients were also worse compared to non-obese jSLE patients in several other domains

Conclusion—Our study demonstrates the detrimental effects of obesity on patient-reported outcomes in jSLE. This supports the importance of weight management for the therapeutic plan of jSLE.

Key Terms

SLE; Obesity; Children

Introduction

Obesity in children and adolescents is defined as a body mass index (BMI) that exceeds the 95th percentile of reference populations. The 2010 U.S. National Health and Nutrition Examination Survey (NHANES) found childhood obesity had increased since 1990s to an estimated 16.9% (1, 2). Cross-sectional studies report the prevalence of obesity among adults with Systemic Lupus Erythematosus (SLE) at around 28% (3). Not surprisingly, obesity in this population is associated with an added risk of cardiovascular disease, decreased health-related quality of life (HRQOL), and higher disability (3, 4).

Corticosteroids are more commonly prescribed to children with juvenile-onset Systemic Lupus Erythematosus (jSLE) than adults with SLE (5), which may put the former at an even higher risk for obesity. The impact of obesity on the well-being and HRQOL of patients with jSLE has not been well examined and is the focus of this secondary analysis using prospective data from jSLE patients.

Materials & Methods

Patients & visits

We used secondary data (6, 7) from 202 jSLE patients recruited from routine clinic visits at 11 pediatric rheumatology centers in the U.S. and Canada. Patients fulfilled the American College of Rheumatology (ACR) Classification Criteria for SLE prior to the age of 16 years. They constituted a convenience sample with follow-ups every 3 months for up to 18 months (total visits = 815). This study was approved by the institutional review board of the Cincinnati Children's Hospital Medical Center.

Anthropometric measurements

Weight (kg) and height (cm) were measured during the visits, and the BMI was calculated [weight in kg / (height in cm)²]. In children and adolescents (age < 19 years), 'obesity' is commonly defined as a BMI ≥ 95th percentile of the *Sex-Specific Center for Disease Control (CDC) 2000 BMI-For-Age Growth Charts* (www.cdc.gov/growthcharts). Individuals whose BMI is between the 85th and the 95th percentile are considered 'overweight' (8), while those whose BMI is lower than the 5th percentile are regarded as 'underweight'. A normal BMI lies between the 5th and 85th percentile as per the *Sex-Specific CDC 2000 BMI-For-Age Growth Charts*.

Health related quality of life measures

(1) Pediatric Quality of Life Inventory (PedsQL™) is composed of a child self-report and a corresponding parent-report for different age ranges. The *PedsQL-Generic core scale* (PedsQL-GC) consists of 23-items that cover four health domains: physical, emotional, social, and school functioning. The *PedsQL-Rheumatology module* (PedsQL-RM) is a rheumatology-specific HRQOL scale comprised of 22 items encompassing five domains: pain and hurt, daily activities, treatment, worry, and communication. The items are scored on a 5-point Likert scale (never, almost never, sometimes, often, and always), from which summary scores (range: 0 to 100, higher scores indicating higher HRQOL) can be calculated. Previously published norms of the PedsQL-GC in healthy and obese children are available and were used in this study (9).

(2) The Child Health Questionnaire P50 (CHQ™) is a generic parent-completed HRQOL measure and yields scores (0=worst health; 100=best health) in 12 domains: physical functioning; role/social limitations-emotional/behavioral; role/social limitations-physical; bodily pain; behavior; general health perceptions; mental health; self-esteem; parent impact-emotional; parent impact-time; family activities; and family cohesion. Additionally, the CHQ allows for determination of Global Health, Physical Health, and Psychosocial Health summary scores (10).

Disease characteristics and jSLE therapy

Disease activity was assessed using the Safety of Estrogen in Lupus Erythematosus: National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI; range of scores: 0 - 105). For the analysis, '*at least moderate disease jSLE activity*' was defined as SELENA-SLEDAI summary score of > 4. Damage of organs and tissues since the diagnosis with SLE was measured by the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI; range of scores: 0 – 47). For the analysis, '*more than minimal jSLE damage*' was defined as total SDI score > 0.

Medications that were taken at the time of the study were recorded including their use of immunosuppressive agents (i.e. mycophenolate mofetil, azathioprine, methotrexate, cyclophosphamide, and rituximab). Intravenous methylprednisolone pulses (yes/no) and the daily prednisone dose were also noted. For the purpose of our study, '*current low daily prednisone dose*' was defined as daily prednisone-equivalent dose < 5 mg and < 0.2/mg/kg/day.

Statistical analysis

Logistic regression was used to determine which patient and jSLE features are significantly associated with the presence of obesity. Possible covariates of the relationship between obesity and HRQOL were tested (present vs. absent): age < 12 years, race (African American vs. not), Hispanic ethnicity, gender, 'at least moderate disease jSLE activity', 'more than minimal jSLE damage', 'current immunosuppressive use', 'current use of intravenous methylprednisolone pulses', and 'current low daily prednisone dose'.

Mixed effects modeling was performed to determine the association of the presence of obesity (yes/no) with the PedsQL and CHQ (summary and domain scores), while adjusting for other relevant covariates. Covariates associated with the presence of obesity in the univariate analyses of p -values ≤ 0.2 , were considered in the multivariate mixed-effects models.

Using two-sided independent t-test we also compared the PedsQL and CHQ summary and domain scores of obese jSLE patients with: 1) historical healthy non-obese controls, and 2) historical obese controls without jSLE (9).

P -values ≤ 0.05 were considered statistically significant. Statistical analyses were done using SAS (version 9.2; Cary, NC) and Microsoft Excel (version 2008; Redmond, WA).

Results

Patient characteristics and frequency of obesity

Table 1 summarizes the demographic and clinical characteristics of the 202 patients at the baseline visit. The mean \pm SD age was 15.4 ± 3.0 years (range: 5-20).

The historical control groups [non-obese (N=9,565) and obese (N=63)] available for comparison with the jSLE patients were somewhat younger. The mean age \pm SD for non-obese healthy control was 9.8 ± 3.2 years (p -value < 0.0001) and for obese historical controls was 12.1 ± 3.0 years (p -value < 0.0001), in comparison with 15.4 ± 2.3 years for obese jSLE patients. There was a lower proportion of females in the non-obese healthy control (49%, p -value < 0.0001) and obese historical controls (46%, p -value = 0.017), as compared to 78% in the obese jSLE patients.

88% of patients in the obese jSLE group were Non-Hispanics. There were similar proportions of obese jSLE patients between the Hispanic and non-Hispanic groups (21% and 26%, respectively). None of the 19 Asian jSLE patients was obese while the proportion of obesity in African-American jSLE patients was higher than Caucasian jSLE patients (36% vs. 23%; $p = 0.06$). African-American jSLE patients made up 47% of the obese group, although they only made up 33% of the entire cohort.

Minimum follow-up for patients included was 6 months. Mean follow-up since disease presentation was 2 years and seven months. Mean age of onset was 13 years. Mean follow-up was 12.3 months for non-obese jSLE patients while it was 14.3 months for obese jSLE patients. Fifty-one patients (25%) were obese, all of whom remained obese during average

follow-up period of 5 months. Obese and non-obese jSLE patients were similar in terms of disease activity [mean SELENA-SLEDAI \pm SD = 6.5 ± 6.4 vs. 7.9 ± 6.9 ; $p = \text{NS}$ (not significant)], age, ethnic, and gender distribution. Unexpectedly, obese jSLE patients were treated with significantly lower daily prednisone dose than non-obese jSLE patients whether total dose or weight adjusted dose is considered [mean (mg/day) \pm SD = 20.9 ± 24.6 vs. 31.8 ± 35.8 , $p\text{-value} = 0.05$; mean (mg/kg/day) \pm SD = 0.15 ± 0.18 vs. 0.32 ± 0.48 , $p\text{-value} < 0.0001$], respectively]. Data for the cumulative dose of prednisone was not available.

Association of patient characteristics with HRQOL and presence of obesity

In univariate analyses of baseline data, African-American race (OR = 2.3; $p\text{-value} = 0.01$) was significantly associated with the presence of obesity. Among jSLE patients, African-American race was associated with lower HRQOL scores ($p\text{-value} = 0.01$), as was the presence of '*at least moderate disease jSLE activity*' ($p\text{-value} = 0.02$). '*Current low prednisone requirement*' was associated with higher HRQOL scores ($p\text{-value} = 0.03$). Female gender was significantly associated with lower self-reported PedsQL-RM scores ($p\text{-value} = 0.01$, Table 2).

Differences in HRQOL between obese jSLE patients and comparison groups

We found significant differences in HRQOL scores between obese jSLE and non-obese jSLE patients in the analyses that adjusted for group differences (i.e. corticosteroid use, disease activity, disease damage, gender, and race) as are detailed in Table 3. The total and domain scores of the PedsQL-GC and PedsQL-RM were all lower among obese as compared to non-obese jSLE patients, irrespective of whether patient self-report or parent-reports were considered. These differences reached statistical significance for the: (1) self-reported and parent-reported physical, emotional, and pain/hurt domains; (2) parent-reported school functioning and worry domains; and (3) self-reported social domain (all $p\text{-values} < 0.0001$ to 0.047). As expected, parent-reported PedsQL-scores were generally lower than self-reported PedsQL-scores for both the obese and non-obese jSLE groups ($p\text{-values} = 0.04 - < 0.0001$, data not shown).

Obese jSLE patients had lower total and domain scores of the PedsQL-GC compared to healthy non-obese controls and were all statistically significant except for the self-reported emotional and social domain (all $p\text{-values} < 0.0001$ to 0.018).

Obese jSLE patients had lower (1) self-reported and parent-reported physical functioning (PedsQL-GC), and (2) parent-reported school functioning than obese controls without jSLE ($p\text{-values} = 0.002$ to 0.03). Conversely, self-reported social functioning was higher in obese jSLE patients as compared to the obese controls without SLE ($p\text{-value} = 0.009$).

When considering the CHQ to measure HRQOL, we found that the domain and summary scores of the CHQ were generally lower in obese jSLE patients compared to non-obese jSLE patients, reaching statistical significance for global health, physical functioning, role/social limitations-emotional/behavioral, general health perceptions, parent impact-time, family activities, and family cohesion domains ($p\text{-values} = 0.007 - 0.039$, Table 3).

Our exploratory analysis also suggested that being overweight (BMI 85th-95th percentile) did not significantly affect HRQOL scores (data not shown).

Discussion

Obesity is known to be associated with decreased HRQOL and increased disability in adults with SLE (4). In this study, we report a significant negative impact of obesity on the HRQOL of children and adolescents with jSLE, with physical function being most consistently impaired. School function and pain/hurt domains were also negatively affected by the presence of obesity in jSLE. The detrimental effects of obesity were independent of current corticosteroid use (i.e. prednisone dose and use of methylprednisolone pulses), disease activity, disease damage, gender, and race.

Our previous research showed that jSLE patients as a group have lower physical functioning domain scores compared to healthy children (11). This study builds on this earlier report and suggests that this is especially true for obese jSLE patients. The physical functioning is the most negatively affected HRQOL domain, irrespective of the measure (PedsQL and CHQ) used. Underlying this observation may be changed body mechanics, alignment, and mobility in obese individuals (1). Of note, our data did not support that there were differences in disease activity specific to the musculoskeletal system between obese and non-obese jSLE patients (data not shown).

Our previous research also found jSLE patients to have lower school functioning compared to healthy children (11). Our current study suggests that this decrement is even larger in obese jSLE than non-obese jSLE patients. These findings are in line with previous observation among groups of children without jSLE, in which obese children's cognitive functioning was lower, mostly due to poorer visuospatial organization and general mental ability as compared to their non-obese counterparts (12). No data is available at the present time to assess the association of obesity and cognitive dysfunction in jSLE but an association has been shown in aSLE (13).

Likewise, we found that obese jSLE patients reported more impairments of pain on HRQOL (PedsQL-RM) than non-obese children with jSLE. This appears to be of particular relevance since obesity is also associated with the development of pain amplification syndromes in adults with SLE (14).

Interestingly, social and emotional functioning domain scores are lower in jSLE obese compared to non-obese jSLE patients and healthy controls but not in comparison with the obese group without SLE. Although reasons for this observation are not entirely clear, it may be that obese children without jSLE do not receive the same social support as obese children with jSLE. Moreover, being overweight did not impact HRQOL as obesity did, and may reflect a threshold effect of obesity.

There are several limitations to our study. The jSLE patients included in our study constituted a convenience sample and therefore our data are unsuited to estimate the prevalence of obesity in jSLE in the U.S. The demographics of patients included in our study, however, are comparable to other Northern American jSLE cohorts. The available

historical controls also had some differences with the jSLE group in terms of distributions of sex, age, and ethnicity but these were taken into account in the analyses as potential covariates for HRQOL and presence of obesity. It is also unlikely that we measured all possible confounders in our adjusted analyses but we did adjust for all covariates that have been previously shown to affect HRQOL in jSLE (11). We were also unable to assess the impact of duration of corticosteroid use on obesity and impact of duration of obesity on HRQOL. Finally, as done by others, we defined obesity based on BMI which is an imperfect albeit the most commonly used measure of body fat in the clinical setting.

In summary, our study demonstrates the detrimental effects of obesity on many aspects of HRQOL in jSLE, particularly impairing physical functioning. These observations deserve consideration in designing meaningful outcomes of weight management programs in jSLE.

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Table 1
Baseline characteristics of the patients with juvenile-onset SLE (jSLE) †

Characteristics	Obese (N=51)	Non-obese (N=151)	P-value*
<i>Females</i>	40	124	NS
<i>Race</i>			
Asian	0	19	<0.0001**
African-American	24	42	
Caucasian	27	90	
<i>Ethnicity</i>			
Hispanic	6	23	NS***
Non-Hispanic	45	128	
Age (in years)	15.4 ± 2.3	15.8 ± 3.1	NS
<i>Body Mass Index (BMI) ‡</i>			
Obese (BMI 95 th percentile)	51		
Overweight (BMI 85 th but < 95 th percentile)	42		
Normal (BMI 5 th but < 85 th percentile)	106		
Underweight (BMI < 5 th percentile)	3		
<i>Daily prednisone dose (< 0.2 mg/kg)</i>	10	13	0.04
<i>Currently receiving methylprednisolone pulses</i>	6	28	NS
<i>Any immunosuppressive use ††</i>	22	56	NS
<i>Low disease activity (SELENA-SLEDAI/ < 4)</i>	19	45	NS
<i>Minimal disease damage (SDI/ < 1)</i>	34	114	NS

Legend:

† Values are N except for age which is shown as means ± standard deviation (SD); NS = not significant

* P-value from A (obese jSLE) vs. B (non-obese jSLE)

‡ BMI is weight in kilograms divided by height in meters squared (kg/m²). Classification is based on CDC 2000 gender-specific BMI-for-age reference (1)

** P-value based on Fisher's exact test considering race (Asian, African-American and Caucasian) vs. obese/non-obese

*** P-value based on Fisher's exact test considering ethnicity (Hispanic and Non-Hispanic) vs. obese/non-obese

^{FF} Any immunosuppressive use (i.e. mycophenolate mofetil, azathioprine, cyclophosphamide, and/or rituximab) during study period

^J Safety of Estrogens in Lupus Erythematosus: National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index

^{JJ} SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index

Table 2
Relationship of jSLE demographics and disease features to HRQOL and to presence of obesity[‡]

Predictors	Outcomes [¶]	
	HRQOL	Presence of obesity
	Beta-coefficient or slope	Odds ratio
	P-value*	P-value**
<i>Age (< 12 years)</i>	0.1	0.6
<i>Gender: Female</i>	0.2	0.8
<i>Ethnicity: Hispanic</i>	1.5	1.3
<i>Race: African American</i>	-8.8	2.3
<i>At least moderate disease activity (Total SLEDAI score > 4)</i>	-5.5	1.4
<i>More than minimal disease damage (Total SLICC score > 0)</i>	-2.5	0.6
<i>Current low daily prednisone dose (< 0.2 mg/kg/day and < 5 mg/day)</i>	5.4	0.4
<i>Current immunosuppressive use</i>	0.2	1.2
<i>Current use of intravenous methylprednisolone pulses</i>	1.7	0.6

Legend:

[‡] For PedsQL Generic Core Scale. Results similar to summary scores of PedsQL-Rheumatology Module and CHQ. For the PedsQL-Rheumatology Module (self-report), gender is also significant

[¶] Outcomes of univariate analyses are: A) summary scores of HRQOL measures (shown here: PedsQL-Generic Core Scale parent-report) and B) presence of obesity

* P-value from univariate mixed effects analyses to evaluate association of covariate of interest to outcome (i.e. domains scores of HRQOL measures)

** P-value from logistic regression to evaluate association of covariate to presence of obesity

Table 3
Difference in scores of health related quality of life (HRQOL) measures in JSLE according to presence of obesity[‡]

Health Related Quality of Life Measures	JSLE				Historical controls without JSLE			
	A Obese (N=51)	B Non - obese (N=151)	P-value (A vs.B) [*]	C Non-obese (N=9,565) [¶]	P-value (A vs. C) ^{***}	D Obese ^{¶¶} (N=63)	P-value (A vs.D) ^{***}	
<i>Pediatric Quality of Life Questionnaire</i>								
Generic Core Scale: Parent-Report	69.2 ± 2.8	81.7 ± 2.3	<0.0001	82.7 ± 0.2	<0.0001	75.0 ± 1.8	NS ^{‡‡}	
Physical Functioning	66.6 ± 3.9	81.6 ± 3.1	0.0004	84.5 ± 0.2	<0.0001	76.3 ± 2.2	0.025	
Emotional Functioning	70.6 ± 3.2	80.4 ± 2.6	0.032	81.3 ± 0.2	<0.0001	72.6 ± 2.2	NS	
Social Functioning	77.2 ± 3.2	87.7 ± 2.6	NS	83.7 ± 0.2	0.018	73.5 ± 2.2	NS	
School Functioning	64.3 ± 3.3	77.4 ± 2.7	0.0003	78.8 ± 0.2	<0.0001	76.6 ± 2.1	0.002	
<i>Generic Core Scale: Self-report</i>								
Generic Core Scale: Self-report	74.0 ± 2.6	81.4 ± 2.2	0.003	83.8 ± 0.2	0.0004	74.0 ± 1.8	NS	
Physical Functioning	68.6 ± 3.5	80.9 ± 3.0	0.0003	87.5 ± 0.2	<0.0001	77.5 ± 2.3	0.030	
Emotional Functioning	75.8 ± 3.1	82.3 ± 2.7	0.016	79.3 ± 0.2	NS	68.6 ± 2.3	NS	
Social Functioning	81.7 ± 2.5	89.0 ± 2.2	0.047	85.2 ± 0.2	NS	72.6 ± 2.3	0.009	
School Functioning	71.6 ± 3.1	74.6 ± 2.7	NS	81.1 ± 0.2	0.0005	75.0 ± 1.8	NS	
<i>Rheumatology Module: Parent-report</i>								
Rheumatology Module: Parent-report	79.5 ± 2.1	85.6 ± 1.7	0.007					
Pain and Hurt	65.2 ± 4.1	77.5 ± 3.3	0.005					
Daily Activities	92.0 ± 2.4	94.0 ± 1.9	NS					
Treatment	82.0 ± 2.2	85.9 ± 1.8	NS					
Worry	70.3 ± 3.6	80.0 ± 2.9	0.013					
Communication	81.1 ± 3.0	84.0 ± 2.5	NS					
<i>Rheumatology Module: Self-report</i>								
Rheumatology Module: Self-report	74.9 ± 2.1	79.1 ± 1.8	0.043				ND ^{‡‡‡}	
Pain and Hurt	65.6 ± 3.9	80.7 ± 3.3	<0.0001					
Daily Activities	92.2 ± 2.0	95.9 ± 1.7	NS					
Treatment	85.7 ± 2.2	89.4 ± 1.9	NS					
Worry	65.6 ± 3.7	69.9 ± 3.2	NS					
Communication	78.7 ± 3.2	80.6 ± 2.8	NS					

Health Related Quality of Life Measures	jsLE				Historical controls without jsLE		
	A Obese (N=51)	B Non - obese (N=151)	P-value (A vs.B) [*]	C Non-obese (N=9,565) [†]	D Obese ^{††} (N=63)	P-value (A vs. C) ***	P-value (A vs.D) ***
<i>Childhood Health Questionnaire</i>							
Global Health	47.8 ± 3.2	54.4 ± 2.6	0.038				
Global Behavior	74.3 ± 3.0	78.6 ± 2.7	NS				
Physical Function Score	33.1 ± 1.8	37.8 ± 1.6	0.006				
Psychosocial Function Score	44.3 ± 1.4	45.0 ± 0.9	NS				
Physical Functioning	64.5 ± 3.9	75.7 ± 3.3	0.002				
Role/Social Limitations-Emotional/Behavioral	72.5 ± 3.4	79.3 ± 3.1	0.039				
Role/Social Limitations-Physical	70.4 ± 4.3	76.2 ± 3.9	NS				ND
Bodily Pain	56.5 ± 4.2	56.5 ± 3.7	NS				
Behavior	76.8 ± 2.4	79.9 ± 2.1	NS				
Generic Health Perceptions	42.1 ± 2.2	46.4 ± 1.9	0.036				
Mental Health	73.3 ± 2.2	76.6 ± 2.0	NS				
Self Esteem	51.1 ± 4.4	47.6 ± 3.9	NS				
Parent Impact-Emotional	56.6 ± 3.8	53.1 ± 3.5	NS				
Parent Impact-Time	66.1 ± 3.8	75.8 ± 3.3	0.007				
Family Activities	68.4 ± 2.9	73.8 ± 2.6	0.050				
Family Cohesion	67.9 ± 3.4	74.9 ± 3.0	0.029				

Legend:

[†] Values are mean ± standard error of the mean (SEM); for details, please refer to Table 1

* P-value from adjusted mixed effects models with summary and domain scores of HRQOL measures as dependent variable and presence of obesity (yes/no) as independent variable. Models adjusted for 'at least moderate disease activity' (SELENA-SLEDAI scores 4 or not), 'current low daily prednisone dose' (< 0.2 mg/kg/day and < 5 mg/day) and < 5 mg/day or not), race (African American or not), gender, and 'more than minimal disease damage' (total SLICC-DI scores=0 or not)

** P-value from 2-sided t-test comparing HRQOL scores from A (obese jsLE) vs. C (healthy controls)

*** P-value from 2-sided t-test comparing HRQOL scores from A (obese jsLE) vs. D (obese non-jsLE)

^{††} Historical controls. For PedsQL-Generic Module: healthy pediatric patients with no chronic illness (N=9,565) (9)

Historical controls. Obese pediatric patients without rheumatologic disease (N=63) (9)

NS- not significant

ND- comparison data are not available