

Improving quality of life assessment in children with systemic lupus erythematosus

Systemic lupus erythematosus in children is a multisystem disease with extensive organ involvement characterized by its chronic, fluctuating and unpredictable course. The physical, emotional and social effects of systemic lupus erythematosus significantly impact the health-related quality of life (HRQOL) of patients. In the last several years, the need for addressing HRQOL in children with systemic lupus erythematosus has been recognized and there has been significant progress. The current tools offer significantly greater advantages compared with the older scales used to measure HRQOL in these children. The relationship between HRQOL and disease activity and damage has been examined. Research is underway to examine HRQOL globally across different countries and cultures.

KEYWORDS: pediatric • quality of life • systemic lupus erythematosus

Quality of life (QOL), often defined in various ways, is a universal, ever changing, subjective multidimensional paradigm that includes several domains [1,2]. Health-related quality of life (HRQOL), similar to both QOL and health status, yet discrete, takes into account mental, physical, and social aspects, patient's satisfaction with treatment and hopes for the future [2,3] (defined in [4]). Systemic lupus erythematosus (SLE) in children is a multisystem disease with extensive organ involvement characterized by its chronic and fluctuating course. Care of children includes hospital admissions, several visits to different subspecialists, and regular laboratory testing, and can be physically, psychologically and financially stressful for the family. Early aggressive treatments have improved survival at the expense of increased morbidity due to disease and treatment. Clearly SLE significantly impacts the HRQOL of patients. HRQOL is a critical constituent of the core outcome variables for disease activity and damage assessment in childhood SLE [5,6]. It is expected that disease-related factors such as activity, damage and medications, and psychosocial factors would impact HRQOL in children. Thorough HRQOL evaluation in children with chronic diseases such as SLE will lead to an understanding of the specific areas impacted, so that these areas can be targeted with appropriate interventions and caregivers can be given better advice on caring for these patients after the initial diagnosis.

HRQOL in pediatric SLE has been reviewed earlier [4,7,8]. In this review, we will provide updates in improvement of assessment of HRQOL. MEDLINE and PUBMED search

mechanisms were used to find articles related to pediatric SLE and HRQOL measurement.

■ Factors complicating HRQOL assessment in pediatric SLE

These factors have been reviewed in detail in earlier articles [4,7,8]. Several factors such as SLE's protracted and variable course, its heterogeneous presentations, associated psychosocial factors, child's changing developmental stage and patient/parental expectations complicate the measurement of HRQOL in children [4,7–10]. While child reports can be influenced by recall, mood and level of communication, parent reports can be affected by their own expectations, physical and mental health [11,12] (reviewed in [4,7,8]). It is therefore ideal to use child and parent reports together in order to determine HRQOL in children with chronic pediatric diseases (reviewed in [4,7,8]).

Both generic and disease- or system-specific scales have their advantages and disadvantages in the context of a disease with multisystemic involvement such as SLE [9,13,14] (reviewed [4,7,8]) and it is ideal to use them in combination.

The unique needs of the pediatric SLE population and the type of clinical study should be considered while selecting a scale for measuring HRQOL. Based on these requirements, the most suitable generic and disease-specific scales would need to be identified for the assessment of HRQOL in the pediatric SLE population.

■ Available scales for measuring HRQOL, QOL & health status

The majority of pediatric studies use descriptive HRQOL measures to evaluate the

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wellbeing of children with chronic diseases. These scales have been reviewed previously [4,7,8]. The Short Form-36 (SF-36) and Short Form-20 (SF-20) are valid and reliable health status measures that are sometimes used in older children [15]. The Childhood Health Assessment Questionnaire (CHAQ) is a measure of physical function in children with rheumatic diseases and is modified from the Health Assessment Questionnaire (HAQ) [16,17]. The CHAQ is a brief and valid scale, and has parallel child and parent reports, with the main areas of focus being disability and discomfort [16,17]. The Child Health Questionnaire (CHQ) is modeled on the SF-36, a health status tool, with domains adapted for children [18]. It consists of a non-parallel parent (for children over 5 years of age) and child reports (over 10 years of age). The domains of the CHQ are as follows: physical functioning, role/social emotional, role/social behavioral, role/social physical, bodily pain, general behavior, mental health, self-esteem, general health perceptions, change in health, parental impact emotional, parental impact time, family activities and family cohesion. Summary scores are calculated to determine Physical Health (CHQ-PHS) and Psychosocial Health (CHQ-PSS). The CHQ is valid, reliable and has been found to be responsive to clinical changes in children with juvenile idiopathic arthritis [18,19] and has been adapted cross-culturally in a variety of languages [20].

The Pediatric Quality of Life Inventory (PedsQL) Generic 4.0 and Rheumatology 3.0 modules are valid, reliable, brief questionnaires for children between the ages of 2 and 18 years [10,21]. They comprise parallel child and parent reports with different versions for various age ranges. The generic module has the following domains: physical, social, emotional and school. The rheumatology module has the following five domains: pain and hurt, daily activities, treatment, worry and communication. The PedsQL has several translations [101] and is a widely used scale.

The pediatric SLE-specific QOL tool titled Simple Measure of the Impact of Lupus Erythematosus in Youngsters® (SMILEY®) was developed through qualitative research [22] on children with SLE and subsequently validated in US English [23]. The SMILEY has 26 items for children with SLE up to 18 years of age. The similar child and parent reports have answers in the form of a five faces scale. SMILEY has the following domains: effect on self, limitations,

social and burden of SLE. A higher percentage score designates better HRQOL [23].

Moorthy *et al.* have reported the translation and cultural adaptation process undertaken for SMILEY in the following 13 languages: Danish, Dutch, French (France), German (Germany), Hebrew, Italian, Portuguese (Brazil), Slovene, Spanish (USA and Puerto Rico), Spanish (Spain), Spanish (Argentina), Spanish (Mexico) and Turkish [24]. For a detailed description of different HRQOL tools and physical function assessment tools, please refer to earlier reviews [4,7,8,25].

■ HRQOL in children with SLE

In the last several years, pediatric studies have explored the impact of SLE on HRQOL. Using a qualitative approach, Moorthy *et al.* explored the wide-ranging impact of SLE on the HRQOL of children and parents beyond physical aspects of the illness [22]. The children with SLE and their parents were questioned about their feelings about lupus. Their answers were ordered into concepts, and categories using grounded theory and interlinking themes were identified [22]. Children's replies generated the following categories: limitations, impact of/on social and family relationships, effect on self and fear of future and long-term goals. Themes generated from children's responses were related to coping and maintaining control of their life despite SLE. Parents' answers yielded the following categories: psychological, accommodating disease, shifting expectations, social support, worry and medical care [22]. Themes derived from parents' responses were related to their efforts to cope with their child having SLE; and appreciation/sadness in connection with their children's coping process [22].

Children with pediatric rheumatic diseases seem to consistently have a lower HRQOL score compared with healthy children [21]. Their HRQOL was assessed by the PedsQL generic module. The total, physical and psychosocial scores (aggregate of social, emotional and school domains) were lower in children with rheumatic diseases [21]. Children with SLE had the lowest scores in the emotional and school domains compared with healthy children and those with other rheumatic diseases. Surprisingly, children with SLE had the highest social domain scores compared with children with other rheumatic diseases and healthy children [21].

Brunner *et al.* found similar results for child and parent reports using the generic

PedsQL where children with SLE had significantly lower QOL scores (total, physical and school domain scores) compared with healthy children; but social scores were comparable with healthy children [26]. Using the PedsQL Rheumatology module, child and parent reports were lower in worry domain scores in SLE compared with children with arthritis [26]. For the parent report, children with SLE had a higher treatment domain score and a lower communication domain score [26]. There was no significant difference between patients with SLE and arthritis in terms of pain and hurt nor daily activity scores [26]. Using the CHQ, children with SLE had significantly lower CHQ-PHS and CHQ-PSS compared with healthy cohorts [26]. Ruperto *et al.* conducted a large multinational study using the CHQ and found that the mean CHQ-PHS and CHQ-PSS scores were in the lower range of those observed in the juvenile idiopathic arthritis cohort [27]. Children with SLE had decreased scores for all domains of the CHQ compared with the healthy children except for the behavior and change in health domains where the scores were comparable to the scores of healthy children [27].

Reviewing scores from four manuscripts, it appears that using the PedsQL-Generic module, children with SLE had lower scores in the emotional and school domains and the higher scores in the social domain in most cases [21,23,26,28]. Using the PedsQL Rheumatology module, children with SLE had lower scores in the worry domain and higher scores in the daily activities and treatment domains in most cases [21,23,26,28]. Parent-report scores were lower than child-report scores in many of the domains for both questionnaires. Using SMILEY, highest score was found in the social domain and the lowest score was found in burden of SLE domain [23]. Total and domain scores were lower for parent-report [23].

In summary, higher HRQOL scores were found for daily activities, treatment and social domains using the PedsQL generic and rheumatology module and SMILEY, and lower HRQOL scores were found for worry, social, emotional and burden of SLE domains [21,23,26,28]. It suggests that SLE's effect on wellbeing is significant and is beyond physical and medical aspects of disease. It is unclear why children and parents report high social scores and it is possible that there is a desire for acceptance in the teenagers who are largely impacted by SLE. Parent HRQOL scores were lower for several domains,

suggesting that the caregiver may experience a greater awareness of the disruption of a child's life and anxiety about the future. For the available child-parent pairs ($n = 80$), moderate-to-strong correlations were found between the child and parent SMILEY total and domain scores [23].

■ Relationship of HRQOL with disability, self-concept, school, fitness and disease-related factors

The authors found a significant relationship between HRQOL (measured by SMILEY) and disability (measured by the CHAQ), global QOL of the child, days child was sick in bed or too ill to play, number of days child needed someone to care for him/her, interference with parent's daily routine at work, interference with parent's ability to concentrate at work and self-concept (measured by the Piers Harris self-concept scale) [23]. From a previous article, better self-concept and higher socioeconomic scores correlated significantly with both better physical function and HRQOL scores [28].

Children with SLE may have impaired cognitive function that can impact several areas of academic functioning. A recent study showed that executive function, psychomotor speed and fine motor speed were most commonly affected [29]. The authors also found that neurocognitive impairment was prevalent in childhood SLE but differed based on the grouping method [29].

A cross-sectional study from Brazil showed that cognitive impairment was found in about 58% of children with SLE and frequently impacted the verbal ability [30]. The authors found an association of verbal ability impairment with low socioeconomic status and cumulative damage [30].

Authors examined children's and parents' perception of the impact of SLE on school; the relationship between child and parent reports on school-related issues; and the relationship between HRQOL and school-related issues [31]. Forty one patients with SLE and 32 parents participated. Based on patients' response, they had difficulty with schoolwork, problems with memory and concentration; and were sad about the effect of SLE on schoolwork and attendance [31]. A majority (83%) of the patients felt that they would have done better in school if they did not have SLE. SMILEY total score correlated moderately with 'satisfaction with school performance', 'interest in schoolwork', 'remembering what was learned' and

'concentrating in class'. Patients getting intravenous chemotherapy were absent on more school days ($p < 0.05$) compared with patients on oral medications; and those who were absent on more number of school days had higher disease activity [31]. From this study it is evident that SLE and related activities significantly impact children and their families.

Muscal *et al.* reviewed 24 SLE patients' neurocognitive evaluations and from this group 15 patients had prospective data [32]. The patients were primarily African-American and Hispanic adolescent girls of average intelligence. Antiphospholipid positivity and aspirin use was common. Authors found neurocognitive impairment in 70.8% of retrospective, and 46.7% of prospective groups of patients. These deficits were seen during periods of wellbeing, in the absence of prior neuropsychiatric lupus and early in disease. The authors found scores >1.5 standard deviations below normal in tests of executive functioning, visual memory and visual-spatial planning. A third of the patients in the retrospective cohort had characteristics of depression. Cerebral and cerebellar volume loss was seen in majority of the prospective cohort patients [32].

Houghton *et al.* found that SLE patients (12–19 years of age) had moderate impairment in aerobic fitness compared with normative values [33] and that fatigue was a major symptom in them [33]. They found no significant correlation of fatigue or fitness measures with disease activity, disease damage and HRQOL measures [33].

Ruperto *et al.* measured HRQOL in an international cohort of over 250 children with SLE using the CHQ and found the most affected subscales to be global health, general health perceptions and parent impact – emotional. HRQOL was impacted by both disease activity and cumulative damage, especially in the renal, central nervous and musculoskeletal systems [27].

Brunner *et al.* determined the effects of changes of disease activity on HRQOL in children with SLE ($n = 98$) who were followed every 3 months [26]. Patients completed the PedsQL generic and the rheumatology modules as well as the CHQ. SLE activity was assessed using the British Isles Lupus Activity Group Index (BILAG). Higher BILAG scores, notably in the general, musculoskeletal, neurological and vascular domains were related to significantly lower HRQOL. Patients with damage had decreased HRQOL compared with those without damage. According to the authors, all HRQOL

measures, "were at most modestly responsive to clinically important changes with SLE." Increased disease activity and damage were associated with decreased HRQOL as assessed by the PedsQL-rheumatology module and CHQ PHS scales [26].

In an earlier study, authors assessed the association between HRQOL (PedsQL generic/rheumatology modules), physical function (CHAQ) and disease activity through a cross-sectional study [28]. Disease activity was determined using the SLE Disease Activity Index (SLEDAI), and damage was measured using the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI) [28]. Authors found a significant correlation of CHAQ scores with both disease activity and damage; and association of CHAQ scores with disease severity [28]. However, strong correlations were not found with PedsQL scores [28].

In a more recent study (Moorthy *et al.*) of 68 children, authors assessed the relationship of SMILEY scores to patient's/parent's assessment of HRQOL and SLE status, and physician's assessment of disease activity and damage over two visits prospectively [34]. The change in disease activity and damage measures correlated most with the changes in SMILEY domains of limitation and burden of SLE [34].

HRQOL is a broader and distinct construct that assesses impact beyond the disease alone. HRQOL, physical function and disease-related parameters should all be assessed when measuring the effect of SLE on children [28].

■ HRQOL across the world in children with SLE

Ruperto *et al.* assessed HRQOL in an international cohort of 297 patients (described in the previous section) with SLE and found that patients from Mexico had lower HRQOL in both the physical and psychosocial domains of the CHQ [27].

Moorthy *et al.* used SMILEY and compared HRQOL scores in children with SLE from different countries in South America, Europe and Asia [35]. One hundred and twenty five children (106 girls) and parents participated from South America (Brazil = 45 and Argentina = 11), Europe (Italy = 16, Spain = 15 and The Netherlands = 10) and Asia (China = 28). On preliminary analysis, differences in HRQOL were found across continents. Children from Asia (China) had the highest HRQOL scores (SMILEY total and PedsQL generic total). Parents' HRQOL scores were lower compared

with child scores and this difference was most marked for children from South America [35]. Parents reported a lower HRQOL for children with SLE; possibly because of their impression of the child's vulnerability, their own worry or their wellbeing [35]. The current direction of research is more collaborative and there is more focus on multicenter/international research to follow several patients longitudinally and to assess response to medications. Having scales valid in different cultures would be very useful to ensure that these populations can be included and useful information will be obtained.

Future perspective

Survival has improved in patients with SLE with aggressive medical management. Since SLE disease activity is modifiable and we can minimize the number of flares and damage, and therefore improve the HRQOL with newer medications and other interventions.

As per the Outcome Measures in Rheumatology (OMERACT) recommendations, outcomes should be assessed in terms of disease activity and damage in all organ systems involved, as well as by HRQOL scales meaningful to patients, and adverse events [36]. In addition, it is ideal if economic impact is also measured. In clinical trials, it is ideal to use HRQOL measures throughout the trial as it will provide us with valuable data over time and we can determine responsiveness over time.

In the last decade, significant strides have been made in the development of HRQOL

scales in children with SLE. Scales are taking into account disease emphasis, age and the cognitive abilities of children and have parallel child and parent reports. There is also now a SLE-specific HRQOL scale [23]. Since there is variation in disease course and treatment in different populations, efforts are being made to validate scales across countries and ensure that they are culturally appropriate.

The existing HRQOL instruments have sound psychometric properties and are precise enough to measure changes in HRQOL in children. The use of computerized repository of test items can encourage the wider use of these HRQOL measures.

In the next decade, we hope to see an improved understanding of issues that significantly impact HRQOL and interventions in place for these children to improve their HRQOL.

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Executive summary

Background

- Health-related quality of life (HRQOL) is a unique and relevant construct for children with systemic lupus erythematosus (SLE).

Factors complicating HRQOL assessment in pediatric SLE

- The unique needs of the pediatric SLE population and the type of clinical study should be considered while selecting a scale for measuring HRQOL.

Assessment of HRQOL, quality of life and health status

- The Child Health Questionnaire and PedsQL generic module are valid generic measures of HRQOL. The SMILEY® is a disease-specific measure of HRQOL in pediatric SLE. The PedsQL Rheumatology module is a HRQOL scale that can be used in children with rheumatic diseases.

HRQOL in children with SLE

- A qualitative study on children with SLE and parents showed that themes generated from children's responses were related to the coping process. Children with pediatric rheumatic diseases seem to consistently have a lower QOL score compared with healthy children.

Relationship of HRQOL with disability, self-concept, school, fitness & disease-related factors

- HRQOL is related to disability, self-concept and school-related factors. In children with SLE, HRQOL, disease activity and damage should be measured and their relationship may depend upon the measures used. Some studies showed that children with more disease activity and damage had poorer HRQOL.

HRQOL scores across the world in children with SLE

- There is a clear recognition for the need to examine HRQOL in children from different geographic and ethnic backgrounds.

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