Quality of Life Issues in Pediatric Immune-Mediated Inflammatory Disease

CIARÁN M. DUFFY, GEORGE A. WELLS, ANTHONY S. RUSSELL, and BOULOS HARAOUI

ABSTRACT. It has been well established that children with a chronic disease, including those with inflammatory bowel disease (IBD) and juvenile idiopathic arthritis (JIA), report lower health-related quality of life (HRQOL) as compared to their healthy peers. Over the past 20 years there has been a significant emphasis on the development of measures of function and HRQOL for application in JIA and pediatric IBD. Several of the instruments currently used to assess HRQOL in children with immune-mediated inflammatory diseases (IMID), including the Juvenile Arthritis Quality of Life Questionnaire (JAQQ) and IMPACT questionnaire for pediatric IBD, were developed and validated by Canadian-based research teams. This review describes several disease-specific and generic instruments used to assess QOL in children with IBD or JIA. It also provides an overview of findings from several outcomes studies that applied the described tools in assessing HRQOL in children and adolescents with these conditions. (J Rheumatol 2011;38:Suppl 88; 20–5; doi:10.3899/jrheum.110905)

Key Indexing Terms:
QUALITY OF LIFE
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A historical focus in assessment of children with immune-mediated inflammatory diseases (IMID), including inflammatory bowel disease (IBD) and juvenile idiopathic arthritis (JIA), has been based on "hard" outcomes such as persistent disease activity, remission, and organ damage. However, like many other chronic diseases of childhood, IMID affect virtually all aspects of a child's life, including physical, social, and emotional well-being. Hence, there is need for a more in-depth assessment of the health status in children with IMID, including HRQOL.

As per Ronen, *et al*[1], HRQOL in childhood can be defined as a "multidimensional functional effect of a disease or a medical condition and its consequent therapy upon the child or adolescent as perceived by the child, adolescent and family." While adult HRQOL can be influenced by sociological, economic, philosophical, and ethical factors, these may not be applicable to childhood HRQOL. Therefore, not all items on adult HRQOL instruments are pertinent to pediatric populations. It is important to consider that both disease symptoms and time-consuming therapies can alter the quality of a child's life by affecting numerous aspects of daily living, including physical activities and psychological and social functioning. A complete assessment of children with IMID, therefore, necessitates an understanding of the influence of the disease on the child's overall well-being. Further, multidisciplinary approaches are required to address the needs of children with these conditions as well as their families.

This article describes a number of measures used to assess HRQOL in children with JIA or IBD and the use of these measures in defining overall and specific outcomes, as well as predictors of these outcomes upon which future therapeutic approaches can be built.

OUTCOME MEASURES IN PEDIATRIC IBD

Several instruments are now available to measure IBD-relat-

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ed QOL. To date, the IMPACT questionnaire is the most commonly used disease-specific instrument for pediatric IBD. It was originally developed and intended for use by older children (> 9 yrs) and adolescents with established disease (> 6 mo duration)[2,3]. The item-generation phase was developed and validated by a Canadian multidisciplinary research team and included 82 children with IBD in Toronto[2,3]. The children were asked to describe the ways in which IBD affected their lives[2]. The followup phases of instrument development and validation involved children from the United States and England[3,4]. The comparison of the original IMPACT questionnaire and subsequent versions is provided in Table 1[5]. The most recent form of the instrument (IMPACT-III) consists of 35 questions encompassing 6 domains: disease-related symptoms, body image, functional/social impairment, emotional impairment, treatment/interventions, and systemic impairment[5]. Each question reflects on the previous 2 weeks and is rated on a 5-point Likert scale, with higher scores signifying better QOL. The questionnaire can typically be completed in 10–15 minutes. Although the IMPACT questionnaire is the most widely used and validated tool for pediatric IBD available, it is still in evolution in studies utilizing large numbers of individuals. Data from these studies will allow the assessment of IMPACT-III performance characteristics, including responsiveness and the determination of a minimal clinically significant change in score.

Of the generic instruments, it is important to mention the Pediatric Quality of Life Inventory (PedsQL) Multidimensional Fatigue Scale[6,7,8], PedsQL 4.0 Generic Core Scales[9,10,11], and the Children's Depression Inventory (CDI)[8,12]. The PedsQL Multidimensional Fatigue Scale was developed to measure child and parent perceptions of fatigue and has been validated in a variety of pediatric chronic diseases, including JIA and IBD (Table 2)[6,7,8]. In a recent cross-sectional validation study of the PedsQL Multidimensional Fatigue Scale, investigators found that children with various cancers have significantly higher levels of fatigue (70.98 ± 18.20) than healthy controls (80.49 ± 13.33; $p < 0.001$)[6]. Similarly, Varni, *et al*[7] found children with various rheumatologic conditions to have significantly more fatigue (73.82 ± 21.93) than healthy controls (80.49 ± 13.33; $p < 0.05$).

The PedsQL 4.0 Generic Core Scales are a set of HRQOL scales consisting of 23 items[9,10,11]. The instrument has been validated in children and adolescents (ages 2–18 yrs) and comprises parallel child self-report and parent proxy-report formats. It includes 4 domains, including physical functioning (8 items), emotional functioning (5 items), social functioning (5 items), and school functioning (5 items).

QOL IN CHILDREN AND ADOLESCENTS WITH IBD

Pediatric IBD carries significant implication on HRQOL. It is generally believed that QOL in children with IBD is related to the severity of their symptoms. Bowel symptoms may affect the psychological health of a child in many ways. Children with IBD often suffer from depression, anxiety, social isolation, altered self-image, family conflict, medication adherence problems, and school absences. A child with IBD might also have difficulties maintaining social activities[13,14,15,16,17,18]. Moody, *et al*[13] reported that 60% of children with Crohn's disease (CD) experienced prolonged absences from school, 67% were unable to participate in sports on a regular basis, 60% felt unable to leave the house, and 50% were unable to play with their friends.

It has also been suggested that the first year post-diagnosis is an important time for a child to psychologically adjust to the possibility of a lifelong condition. Recently, Hill, *et al*[19] examined the QOL of children with CD in relation to disease duration, disease activity, and medications. As expected, total QOL was highest in children not requiring any medication and the lowest in children on enteral nutrition. The study also showed that, during the first 6 months post-diagnosis, children had significantly lower HRQOL and significantly higher disease activity compared to those with diagnosis beyond 6 months. Similarly, in a cohort of 218 children, Otley, *et al*[20] demonstrated that HRQOL markedly improved 6 months post-IBD diagnosis and additionally improved by 1 year (Table 3). The authors speculated that the improvement in HRQOL with longer duration of the disease may be the result of better-controlled disease and reduced disease activity.

Marcus, *et al*[8] found that children with IBD experience significantly more fatigue than healthy controls (Table 4). These findings are similar to recent studies investigating fatigue in children with other chronic conditions (Table 2). The study also indicated that children with IBD had lower

Table 1. Comparison of original IMPACT Questionnaire and subsequent versions. Reproduced with permission from Griffiths AM, *et al*. Inflamm Bowel Dis 2005;11:185-96. Copyright© 2005, John Wiley and Sons.

Variable	IMPACT	IMPACT-II	IMPACT-III
Description	Original questionnaire 33 questions, VAS	Modified version; 35 questions (see text for changes in terms), VAS but simplied wording	Same 35 questions as IMPACT II, 5-point Likert scale for response options
Range of possible scores	0–231	0–245	35–185

VAS: visual analog scale.

Table 2. PedsQL Multidimensional Fatigue Scale comparisons across different pediatric indications. Effect sizes (ES) are designated as small (0.20), medium (0.50), and large (0.80). Values are mean (SD). Reprinted from Marcus SB, *et al*. Clin Gastroenterol Hepatol 2009;7:554-61. Copyright© 2009, with permission from Elsevier.

Indication	Total Fatigue	General Fatigue	Sleep/Rest Fatigue	Cognitive Fatigue
Health control	82.19 (± 12.27)	86.36 (± 13.11)	77.44 (± 15.41)	82.78 (± 16.26)
IBD	73.89 (± 16.82)	75.30 (± 17.53)	68.75 (± 19.27)	77.62 (± 22.55)
Juvenile RA	73.82 (± 21.93), ES < 0.01	72.76 (± 25.48), ES = 0.01	68.70 (± 24.77), ES < 0.01	79.84 (± 22.65), ES = 0.10
Cancer	70.98 (± 18.20), ES = 0.20	74.99 (± 19.59), ES = 0.02	67.03 (± 23.08), ES = 0.08	70.92 (± 22.35), ES = 0.30

PedsQL: Pediatric Quality of Life Inventory; IBD: inflammatory bowel disease; RA rheumatoid arthritis.

Table 3. IMPACT-II total and domain scores at baseline, 6 months, and 1 year after diagnosis. Mean total and domain scores for each of the 3 time periods are reported. Reproduced with permission from Otley AR, *et al*. Inflamm Bowel Dis 2006;12:684-91. Copyright© 2006, John Wiley and Sons.

IMPACT Score	Maximum Possible Score	Baseline, n = 218 (SD)	6 Months, n = 189 (SD)	12 Months, n = 170 (SD)
Total	238*	154.3 (± 37.0)	180.7 (± 37.1)**	191.0 (± 44.6)†
Bowel	49	31.6 (± 10.3)	38.6 (± 8.9)**	40.3 (± 9.7)
Systemic	21	11.0 (± 5.6)	15.0 (± 5.0)**	15.9 (± 5.8)
Emotional	49	30.2 (± 10.4)	36.0 (± 10.3)**	37.5 (± 11.8)
Social/functional	70*	54.7 (± 12.2)	61.6 (± 12.1)**	65.4 (± 13.8)†
Body image	21	14.5 (± 4.6)	15.3 (± 4.8)	16.2 (± 5.1)
Test/treatment	21	12.4 (± 4.5)	14.2 (± 5.1)**	15.2 (± 5.1)

* Question 35 was removed from both calculations of all the total IMPACT scores and social/functional domain scores because question 35 of IMPACT-II could be skipped if participant was on a school break (e.g., summer holidays, vacation), creating difficulty for analysis and reporting. ** Significant difference in scores between baseline and 6 months ($p < 0.01$). † Significant difference in scores between 6 and 12 months ($p < 0.01$).

sleep subscale scores than healthy controls on the PedsQL Multidimensional Fatigue Scale. It has also been reported that children with IBD were prone to depressive symptoms[21,22]. For example, Szigethy, *et al*[21] found that 25% of children and adolescents with IBD had CDI scores ≥ 12, which is the level that is consistent with clinically relevant depressive disorders. Further, subjects taking corticosteroids were more likely to have CDI scores ≥ 12, and those with higher scores were receiving higher doses of steroids compared to children without clinically significant depressive symptoms. Depression in children with IBD might also be age-related. In a large-scale study assessing pediatric HRQOL, age was shown to affect HRQOL, but there was no effect from sex[20]. Children aged 8–12 years showed less impairment in HRQOL compared to adolescents[20,23]. Adolescents are also more likely to dislike their self-image compared to younger children[18]. This is not surprising; adolescence, even without the presence of chronic illness, can be a challenging life phase with significant physical and psychological changes. Thus, as outlined in a review by Karwowski, *et al*[24], identifying the scope of QOL impairments in adolescents with IBD is of paramount importance, as is implementing strategies that may improve different aspects of their daily living and make their transition to adulthood easier.

OUTCOME MEASURES IN USE IN JIA

Over the past 20 years, several JIA-specific measures of functional status and HRQOL have been developed (Table 5)[25]. These include the Childhood Health Assessment Questionnaire (CHAQ)[26], which, although a functional index, has been used in the absence of a specific QOL index, the PedsQL 3.0 Rheumatology Module[27], and the JAQQ[28].

Childhood Health Assessment Questionnaire. The CHAQ is a disease-specific measure with excellent reliability and validity, and reasonable responsiveness[26]. It comprises 2 indices, disability and discomfort, that focus on physical function. The disability index includes 30 items that assess function in 8 areas such as dressing, grooming, eating, and general physical activities. Each question is rated on difficulty in performance and is scored on a 4-point scale (0 to 3). The disability index is calculated as the mean of the 8 functional areas. Discomfort is evaluated by the presence of pain measured by a 100-mm visual analog scale.

The median CHAQ scores of 0.13, 0.63, and 1.75 represent mild, mild-moderate, and moderate disability, respec-

Table 4. PedsQL 4.0 for child self-report and parent proxy-report for IBD and healthy control samples and reliability for IBD sample. Effect sizes are designated as small (0.20), medium (0.50), and large (0.80). Reprinted from Marcus SB, *et al*. Clin Gastroenterol Hepatol 2009;7:554-61. Copyright© 2009, with permission from Elsevier.

PedsQL 4.0	IBD, n = 70 α	IBD, n = 70 Mean (SD)	Health Control, n = 157 Mean (SD)	Health Control, n = 157 ES
Child self-report				
Total score	0.89	76.69* (14.22)	85.93 (10.40)	0.89
Physical health	0.93	77.90* (17.32)	90.86 (8.44)	1.50
Psychosocial health	0.90	76.29* (14.44)	84.29 (11.82)	0.68
Emotional functioning	0.93	74.00 (20.50)	79.27 (16.40)	0.32
Social functioning	0.93	86.43** (14.67)	90.22 (12.15)	0.30
School functioning	0.94	68.43* (18.21)	83.38 (13.18)	1.13
Parent proxy-report				
Total score	0.90	70.37* (16.61)	88.51 (9.39)	1.93
Physical health	0.93	71.70* (20.37)	93.53 (8.05)	2.71
Psychosocial health	0.90	69.93* (16.56)	86.84 (10.80)	1.57
Emotional functioning	0.93	66.00* (20.55)	82.99 (15.18)	1.12
Social functioning	0.94	78.14* (19.27)	91.43 (11.85)	1.12
School functioning	0.94	65.64* (21.95)	86.08 (13.03)	1.57

Effect size = (IBD mean – healthy control mean) / healthy control SD. α: Cronbach internal consistency reliability coefficient alpha. * $p < 0.001$. ** $p < 0.05$.

Table 5. Comparison of measures used to assess health-related quality of life in juvenile idiopathic arthritis. Reprinted from Duffy C, *et al*. Rheum Dis Clin North Am 2007;33:389-402, with permission from Elsevier.

Measure	CHAQ	JAQQ	PedsQL
Reliability	Very good	Good	Moderately good
Validity	Very good	Very good	Good
Responsiveness	Moderately good	Excellent because patients can select items	Moderately good
Discriminative ability	Excellent, but has ceiling and floor effects	Moderately good; does not have ceiling and floor effects	NA
Applicable to a heterogeneous population	Excellent	Excellent because patients can select items	Very good
Measures physical function comprehensively	Good	Very good	Very good
Measures quality of life comprehensively	No	Very good	Very good
Measures pain	Good	Good	Good
Tested widely	Excellent; used most widely and available in many languages	Moderately good; available in several languages	No
Easy to use	Excellent	Very good	Very good
Time to complete	5 min	15 min initially, 5 min subsequently	15 min
Clinical application	Excellent	Very good	Very good
Parent completion	Yes	Yes	Yes
Patient completion	Yes, > 9 yrs	Yes, > 7 yrs	Yes, various forms for different ages

NA: not applicable.

tively[29]. Further, a reduction in score of 0.13 seems to represent the minimal clinically important improvement. The instrument also has good discriminative properties and can be administered to children of different ages and in several languages[25].

The CHAQ has been shown to be a useful instrument for

longitudinal studies, clinical trials, and in the evaluation of rehabilitative interventions[30,31,32].

PedsQL 3.0 Rheumatology Module. The PedsQL is a modular instrument with a 15-item generic core of global HRQOL integrated with 8 symptom- and treatment domain-specific modules[27]. As outlined earlier, the generic core contains 23 items divided into 4 scales (physical, emotional, social, and school functioning). The PedsQL 3.0 Rheumatology Module contains 22 items distributed in 5 scales: pain, daily activities, treatment, worry, and communication. Each item is scored on a 5-point scale (0–4), with the higher score indicating worse function. Total scale scores are calculated as the mean across all items scored in that scale. The instrument was validated in a study of 271 subjects (accrued from 231 children and 244 parents) where its reliability varied with the age of the child[33]. The instrument was found to be less reliable for younger children.

Juvenile Arthritis Quality of Life Questionnaire. The JAQQ is another disease-specific measure of HRQOL in children with JIA[28]. It comprises 4 dimensions (gross-motor function, fine-motor function, psychosocial function, and general symptoms), each with about 20 items measured on a 7-point scale (scored 1–7, with higher scores indicating worse function). The final JAQQ score is computed as the mean of the 4 dimension scores.

Excellent validity and responsiveness accompanied with short completion time (~15 min) and the fact that it can be administered to children of all ages and disease-onset types make JAQQ practical for use in the clinical setting[25].

HEALTH, FUNCTIONAL STATUS, AND QOL IN CHILDREN WITH JIA

With an estimated annual incidence of 3.2–6.1 per 100,000, depending on the population studied, JIA is the most common rheumatic disease in childhood and a leading cause of childhood disability[34]. The disease affects fine- and gross-motor skills, contributing to reduced activities and physical functioning. Pain experienced by children with JIA also plays an important role in difficulties in daily living. Thus, a complete assessment of children with JIA requires an understanding of the effect of the disease on their QOL.

Several studies have evaluated the relationships between the clinical status and the HRQOL of children with JIA both for outcomes research and for clinical trials[35,36,37,38]. A study conducted by Shaw, *et al*[35] indicated that the HRQOL of adolescents with JIA was less than optimal, particularly in the domains of gross-motor and systemic functioning. Further, HRQOL was significantly and independently associated with pain, disease activity, and functional disability. Similarly, using CHAQ, Gutierrez-Suarez, *et al*[36] determined that disability and pain were the important determinants of physical and psychological well-being, irrespective of geographic area.

April, *et al*[37] assessed level of agreement between the perceived QOL of children with JIA and that perceived by their parents. Children's and parents' scores were compared using paired t tests, and agreements were evaluated by intraclass correlation coefficients. There were higher levels of agreement on pain for children with more severe disease, as well as a higher parent-child agreement on overall QOL for children with long-standing disease. This is likely because, over time, parents become more aware of their child's difficulties. A higher level of agreement on psychosocial function between parents and younger children observed in the study is likely because older children might be less communicative, particularly regarding psychosocial issues.

In another study, however, April, *et al*[38] found that parents and children perceive adherence to treatment to be associated with different outcomes. While, according to children, perceived adherence to medications is associated with an improvement in HRQOL, their parents believed that adherence to exercise led to better QOL.

REACCH-OUT STUDY: CANADIAN-BASED JIA INITIATIVE

The ReACCh-Out (Research on Arthritis in Canadian Children; emphasizing Outcomes) research program[39] can be considered a landmark for pediatric rheumatology research in Canada. This ongoing, prospective, inception cohort study of newly diagnosed children and adolescents with JIA involves 16 pediatric rheumatology centers in Canada and anticipates following more than 1500 children with JIA. Participating children are monitored for at least 5 years and all information collected is put together in a national database. Demographic data and rheumatologic, family, and medication histories are prospectively collected on standardized prepared forms at enrolment. Interim and medication histories are collected at subsequent study visits every 6 months during the first 2 years and then yearly. At each study visit, subjects complete several questionnaires, including the 6-item Juvenile Rheumatoid Arthritis core criteria questionnaire, the JAQQ, CHAQ, PedsQL, and the Quality of My Life Questionnaire. The objective is to determine predictors of longterm disease and QOL outcomes upon which future therapeutic approaches can be determined.

CONCLUSION

Outcome assessments in IMID are attracting more attention, not only in adults but also in the pediatric population. HRQOL is an important outcome measure in understanding the impact of chronic illness, including childhood-onset rheumatic disease and IBD. Several outcome studies demonstrated that evaluating the perception of children about their QOL and pain can be easily done in a clinical setting. Use of validated pediatric tools can help healthcare professionals gather children's opinions regarding their condition, which may help guide further therapeutic approaches.

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