Assessment of Health-Related Quality of Life and Patient Satisfaction in Children and Adolescents with Growth Hormone Deficiency or Idiopathic Short Stature – Part 1: A Critical Evaluation of Available Tools

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Key Words

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Abstract

The concept of health-related quality of life (HrQoL) reflects the subjective perception of health and includes aspects of well-being and functioning in physical, emotional, mental and social life domains. Nowadays, HrQoL has become a relevant treatment outcome from epidemiological and clinical perspectives and is also broadly employed in health economic analyses. To assess HrQoL generic as well as condition-specific instruments are used. The former are applicable to a wide range of health conditions and aim at measuring HrQoL across different conditions. The latter focus on capturing the impact of a specific disease. Although HrQoL research in adults is now well-advanced, there are still open questions regarding how to assess HrQoL in pediatric conditions, such as short stature. Eight generic (one chronic-generic) and seven condition-specific (one treatment-spe-

cific) instruments used in HrQoL research in short stature of youth are described. Additionally, this mini review identifies a need for further research and indicates potential directions.

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Quality of Life

As stated by the World Health Organization, health is 'the state of complete physical, mental and social well-being and not merely the absence of disease or infirmity' [1]. Health-related quality of life (HrQoL) reflects physical, psychological, social, cognitive, functional and behavioral dimensions of well-being and functioning as perceived by the person concerned, in a wide range of conditions between excellent and poor health [2]. The concept of HrQoL is therefore increasingly considered as a relevant 'patient-reported outcome' [3]. As a multidimensional construct, HrQoL offers the possibility to focus on different aspects of well-being and functioning and addresses

Fig. 1. Levels of HrQoL assessment.

the subjective perceptions of individuals. HrQoL evaluation of short stature (SS) broadens our understanding of the psychosocial impact of this condition, by providing insights into potential impairments of functioning and well-being in comparison to other clinical and non-clinical populations. In addition, the effects of treatment in patient cohorts can serve as an empirical basis for clinical decision making as well as individual tailoring of treatment.

HrQoL reflects the subjective perception of health.

Over the last decades, HrQoL research has expanded from adults to include children and adolescents. Comprehensive reviews of HrQoL measures for pediatric populations are available [2, 4, 5]. Instruments measuring HrQoL can be categorized according to the following levels (fig. 1):

- generic level: assessing HrQoL regardless of the presence or absence of health problems;
- chronic generic level: focusing on a chronic condition independent of its specific characteristics;
- condition-specific level: tailored to problems associated with a specific condition;
- treatment-specific level: addressing the patient's perceptions of care received.

Taking growth hormone deficiency (GHD) as an example, the classification scheme presented above can be illustrated as follows. Generic measures developed for children in the general population fall within the first level. The second level measures the distress associated with a chronic condition. The third level focuses on problems specifically related to SS, regardless of the underlying etiology. And the fourth level evaluates the impact of growth hormone (GH) treatment, in addition to the purported burden stemming from the chronic state of being short.

Evaluations of therapeutic interventions (e.g. clinical trials) benefit from the conjoint use of generic and condition-specific assessment measures. Such an approach facilitates cross-condition comparisons (generic) as well as sensitive assessments of problems associated with a particular condition or state (specific) [4].

Self- and proxy-reported HrQoL instruments are available for children and adolescents. Self-report instruments can be used with children able to read and write (i.e., from age 8 onward), whereas younger children, beginning at age 4, can be interviewed [4, 6]. Research on the relationship between child self-reports and parent proxy reports shows that concordance is higher in physical than in social or emotional domains of HrQoL. Additionally, the correlations depend on the instrument used [7]. Proxy-reported measures are frequently used in very young children, where responses are obtained from caretakers/family members (parent), medical staff or teachers. Although not equivalent, both self- and proxy ratings give information on the HrQoL of children. Since they represent the perspectives of different sources of information, they should be interpreted independently without one being considered the 'gold standard'. Depending on the measure chosen, HrQoL assessment can be reported as a profile covering different dimensions of HrQoL or as a total score, i.e., as an indicator of global HrQoL [2, 5]. Age-adjusted versions of questionnaires are recommended as they take into account the age-dependent experiences and cognitive development of children and adolescents [6].

HrQoL measures are characterized as generic, condition or treatment-specific, and are available as self- or proxy reports reportable as dimension-specific or global scores.

HrQoL in Pharmacoeconomic Evaluation

Cost-utility analysis is a special form of cost-effectiveness analysis and requires a primary outcome measured as a gain in quality-adjusted life year (QALY) [8]. This unit of measurement combines information on the length of life (quantity) and the quality of life, where the latter is measured by utilities on a scale ranging from 0 (death) to 1 (full health). The QALY unit is therefore defined as 1 year of life with full health [9]. According to the theoretical underpinnings for QALY advanced by Torrance [10], full health is defined as 'perfect functioning'.

Utilities are the individual's preferences for a certain health state assigned under conditions of uncertainty [11].

Methods used for assessment of utilities are ‘time-trade-off’ (the respondent must answer questions concerning trading of life-years for being totally healthy), ‘standard gamble’ questions (concerning the choice of treatment and treatment costs) and visual analogue scales [12]. These measures lead to the identification of utilities which can then be used for health economic analyses. Derivation of utilities in pediatrics usually requires a parent to act on behalf of the patient [13].

Disease-specific measures are not preference-based and therefore lack information for direct use in cost-utility analysis.

Treatment Satisfaction

Results from studies with adult participants suggest that patient satisfaction with medical care is a multidimensional construct and is associated with different psychosocial aspects. Different domains of patient satisfaction have been described, depending on the type of service or intervention studied. Patient satisfaction can address an intervention, desired and undesired effects, the surroundings in which treatment is provided, and the staff involved. Current models of healthcare utilization also take into account characteristics of patients (including demographics, attitudes and beliefs) which influence treatment decisions and patient satisfaction. While it is unclear whether children would respond similarly to adults to questions about satisfaction, parents of pediatric patients are likely to report satisfaction or dissatisfaction with medical care based on their perceptions of their child’s HrQoL outcomes as a result of treatment [14]. The importance of patient satisfaction as a factor in medical decision-making in children is rising.

Instruments for Adults

Instrument development and research findings in adult patients often help shape practice and research in pediatrics.

HrQoL

A range of generic and disease-specific instruments have been developed and tested in adults with GHD, for example the Quality of Life – Assessment of Growth Hormone Deficiency in Adults (QoL-AGHDA) [15]. This instrument consists of 25 items that can be answered with ‘yes’ or ‘no’, resulting in a maximum score of 25; higher

scores represent lower HrQoL. The QoL-AGHDA statements address problems associated with energy level, concentration and memory, irritability and temper, strength and stamina, social isolation, coping with stress as well as physical and mental drive. The Growth Hormone Deficiency Questionnaire [16] examines energy, mood and sleep. The Questions on Life Satisfaction – Hypopituitarism [17] is a disease-specific instrument which takes into account the importance of single aspects of functioning by a weighting scale for each of the 9 items (i.e., body shape, coping, self confidence). The values (calculated by importance and satisfaction) range from –12 to 20, with negative values indicating dissatisfaction and positive values indicating degrees of satisfaction [17]. Both, generic and disease-specific quality of life instruments have been used in studies of adults with GHD [18, 19]. Among the generic variety, the Nottingham Health Profile [20, 21], the Psychological General Well-Being [22] and the Short Form 36 Health Survey (SF-36) [23–25] have frequently been employed.

Pharmacoeconomic Evaluations

Both time-trade-off and standard gamble have been used in adults to assess patient preferences, e.g. Rekers-Mombarg et al. [24]. Busschbach et al. [25] assessed the impact of SS on HrQoL using time-trade-off.

Patient Satisfaction

Several studies have been conducted on the impact of long-term GH replacement therapy on patient satisfaction, HrQoL, and healthcare utilization [26–28]. Saller et al. [26] examined a large cohort (n = 503) of adult patients with GHD originating from 3 European countries. Patient satisfaction with GH treatment was rated by patients using the Likert rating scale, and physical activity was assessed on the visual analogue scale. Significant improvements observed during the first year of treatment were maintained during the second year [26]. The main interest of studies in adults with GHD is the putative benefits of low-dose GH replacement on metabolism (e.g. lean to fat body mass), energy level, and general well-being.

Quality of life outcomes in treated adults are believed to be a consequence of the metabolic effects of GH rather than being mediated by GH effects on growth/height attained earlier in the treatment cycle. In contrast, research in children and adolescents focuses, in particular, on the potential effects of GH-promoted growth on subjective well-being and functioning.

Table 1. Generic, chronic generic, condition-specific and treatment-specific QoL questionnaires for children

Questionnaire	Author	Items, n	Scales, n	Dimensions	Respondent	Age groups
Generic questionnaires						
Pediatric Quality of Life Inventory (PedsQL)	Varni et al. (1999) [29]	23	4 plus 2 summary scores	Physical health summary score, physical psychosocial health summary score: emotional, social, school	Child Parent	5–18 years 2–18 years
Child Health Questionnaire (CHQ)	Landgraf et al. (1996) [30]	87 and 98/50/28 items (age specific)	14 plus 2 summary scores	Physical functioning, role/social limitations (physical), general health perceptions, bodily pain, role/social limitations (emotional/behavioral), self-esteem, mental health, general behavior, change in health	Child Parent	10–18 years
TNO-AZL children's quality of life (TACQOL) questionnaire	Verrips et al. (1999) [31]	56	7	Physical complaints, motor functioning, autonomy, cognitive functioning, social functioning, positive emotions, negative emotions	Child Parent	6–12 years
Dutch children's AZL/TNO quality of life (DucatQoL) questionnaire	Koopman (1998) [33]	25	4 domains plus total score	Home, physical, emotional, social		5–16 years
Self-Perception Profile (SPP)	Harter (1985) [35]	36	6	Scholastic competence, social acceptance, athletic competence, physical competence, behavioral conduct, general self-worth	Child	
QOL-Questionnaire	Pilpel et al. 1995 [32]	45	5	Academic achievement level, leisure activities, physical self-esteem, emotional self-esteem, relationships with peers and family members	Child	≥8 years
Child Behavior Checklist (CBCL)	Achenbach (1991) [36]		5 plus 2 summary scores	Competencies: activities, social, school; behavior problems: internalizing, externalizing	Parent	4–18 years
Chronic generic questionnaire						
Vécu et Santé Percue de L'Adolescent Malade (VSP-AM)	Simeoni et al. (1999) [34]	39	8	Psychological well-being, physical well-being, self-esteem, vitality, relationships with friends and personal life, relationships with family, relationships with teachers, relationships with medical staff	Child	11–17 years
Condition-specific questionnaires						
Questionnaire on coping and satisfaction with GH treatment	Leiberman et al. (1993) [37]	53	9	Emotional self-esteem, physical self-esteem, perception of treatment and medical outcome, relationships with peers, relationships with family members, compliance, satisfaction with accessibility of treatment, satisfaction with doctor-patient relationship, satisfaction with outcome of treatment	Child	6–16 years
Self-assessment questionnaire to measure well-being in children, particularly those with SS	Wiklund et al. (1994) [38]	39	6 plus total score	Alertness, self-esteem, mood, emotion, elation, stability, vitality	Child	9–18 years
Idiopathic Short Stature quality of life (ISSQOL) questionnaire	Theunissen et al. (2002) [40]	8		Vitality		
TACQOL-S (module of TACQOL)	Bannink et al. (2005) [41]	37	5	Physical abilities, vitality, contact with peers, contact with adults, body image	Child Parent	5–15 years
Short Stature in Children – a Questionnaire for Parents	Haverkamp and Noeker (1998) [45]	34	4	Suffering, future anxieties, behavioral problems, coping efforts	Parent	
Issues Related to Growth Problems and Height Questionnaire (IRGPH)	Sandberg and Mazur (1990) [42]	32 (parent) 22 (child)		Selected topics: reason for referral to pediatric endocrinologist, satisfaction with child's height and other aspects of appearance, experiences of stigmatization and juvenilization related to height, participation in individual or team sports, reputation in the school setting (e.g. class clown, mascot, teacher's pet), presence of a younger, taller sibling	Child Parents	≥8 years Child ≥6 years
Treatment-specific questionnaire						
Growth Hormone Injection Questionnaire (GHtQ)	Cramer et al. (2004) [44]	9	2	Feelings, injection issues		Adolescents 11–19 years

Instruments for Children

A number of generic HrQoL instruments for use in children are available. The following generic and condition-specific measures were included in studies of youths with growth disorders (table 1).

The Pediatric Quality of Life Inventory [29] is a generic measure developed in the USA. The 23-item questionnaire, available in self- and parent-reported versions, measures HrQoL of healthy and ill children, aged 2–18 years. The self-report version is designed for children above 5 years. In addition to a total score, scale scores are available for physical, emotional, social and school-related domains. The instrument is psychometrically robust and translations exist in multiple languages.

Another widely used instrument developed in the US and applied to children with SS is the Child Health Questionnaire [30]. Self- and proxy-reported forms for children 5–18 years old are available. Its 87 items cover 14 domains which can be aggregated into physical and psychological sum scores. Construct and convergent validity as well as sensitivity to change have been demonstrated.

The Netherlands Organization for Applied Scientific Research Academic Medical Centre created the child quality-of-life questionnaire (TACQOL). Available in self- and proxy-reported versions for youths 5–15 years old, the TACQOL's 56 items cover 7 dimensions. Questionnaire reliability as well as construct and convergent validity have been established [31]. A SS-specific version of this questionnaire also exists and is described below.

Pilpel et al. [32] developed a questionnaire for use in a study on GH treatment. It did not include items specifically related to SS. Instead, the 45-item measure assessed the dimensions 'academic achievement level', 'leisure activities', 'physical self-esteem', 'emotional self-esteem', and 'relationships with peers and family members'; all domains hypothesized to be negatively affected by SS. The rating scale ranges from 1 to 4, each value defined by verbal anchors. For analysis, scores are transformed, such that '4' and '1' represent the most positive and negative views of HrQoL, respectively. The dimension score is calculated as the mean of items. Data on psychometric characteristics of the questionnaire are not available.

The DucatQoL consists of 25 items, scored on a 5-point scale. The questionnaire assesses home, physical, emotional and social functioning, and provides a total score [33].

The French instrument *Vécu et Santé Perçue de l'Adolescent Malade* [34] has been developed for measuring self-reported HrQoL in chronically ill adolescents

aged 11–15. The 37 items assess 10 dimensions and can be further summarized into a global index. Reliability as well as construct and convergent validity have been assessed.

Two instruments not explicitly measuring HrQoL, but often administered to children with SS, are the Self-Perception Profile [35] and the Child Behavior Checklist [36].

There are 5 condition-specific HrQoL questionnaires specifically designed for SS. In addition, 2 proxy-report questionnaires are available.

Self-Report Questionnaires

- (1) Leiberman et al. [37] developed a 53-item questionnaire to assess coping and satisfaction with GH treatment. The questionnaire covers the following domains: emotional self-esteem, physical self-esteem, perceptions of treatment and medical outcome, relationships with peers, relationships with family members, compliance with treatment regimen, satisfaction with accessibility of treatment, with doctor-patient relationship, and satisfaction with outcome of treatment. In addition, a total score can be calculated. The domains were created a priori according to content. The reliability of the scale domains (assessed by Cronbach's α) ranged from 0.7 to 0.9 for the sample ($n = 96$) studied. No further information regarding psychometric properties were provided.
- (2) Wiklund et al. [38] developed a measure consisting of 39 bipolar adjectives (i.e., happy-sad, strong-weak, lazy-energetic) which were selected and tested for understanding in a group of teachers and pupils. Respondents rate themselves using a visual analogue scale (100 mm in length) with the endpoints defined by words denoting the extreme opposites of the attribute to be measured. Psychometric testing was performed using a sample of 342 healthy children of 3 different age groups (9, 11 and 13 years) as well as a sample of 65 short children (mean $\pm$ SD = 12 $\pm$ 1.5 years) referred to a growth research center (Gothenburg, Sweden). The 6, factor-analytically derived domains include 'alertness', 'self-esteem', 'mood', 'elation', 'stability' and 'vitality'. Internal consistencies (Cronbach's α) for the different dimensions ranged from 0.63 to 0.81. Inter-correlations among the 6 factors were modest ($r = 0.17$ – 0.53) indicating that relatively unique information was being captured. Construct validity was estimated with a Swedish self-perception questionnaire [39]. The strongest relationships were found in domains related to emotion.

- (3) Another condition-specific, self-report questionnaire for SS children is the Idiopathic Short Stature QoL questionnaire. It focuses on the domain of vitality, because GH treatment can improve energy levels in children with GHD [40]. Psychometric properties are reported with Cronbach's $\alpha = 0.71$ (parent report) and $\alpha = 0.66$ (child report). No further information on the questionnaire or its psychometrics is available.
- (4) The TACQOL-S [41] is a condition-specific questionnaire designed in the Netherlands to measure the impact of SS on HrQoL for children aged 5–15 years. The TACQOL-S is one module of the generic TACQOL. The identification of items was based on clinical experience and interviews with children with SS. The 37-item TACQOL-S is a self-report questionnaire comprising 5 scales, including physical abilities (e.g. 'Did you experience the tables at school as being too high?'), vitality (e.g. 'Have you been getting tired quickly?'), contact with peers (e.g. 'Have other children been bullying you?'), contact with adults (e.g. 'Were adults surprised when they heard your age?'), and body image (e.g. 'Would you like to look different?'). The time-frame for all items is the last few weeks. Internal consistency of the TACQOL-S scales was studied in a SS group ($n = 63$) and Cronbach's α were above 0.70, except for vitality ($\alpha = 0.57$). This questionnaire has yet to be used in studies assessing the HrQoL of children with GHD or idiopathic SS.
- (5) The Issues Related to Growth Problem and Height Questionnaire (IRGPH) [42] collects information concerning factors which the research literature on SS and the clinical experiences of the investigators suggested are important in modulating the psychosocial impact of SS. The IRGPH was designed for clinic-referred samples, comprises both open-ended and closed questions, and is suitable for administration to patients 8 years or older. A selection of domains assessed include: current concerns/worries about height, satisfaction with height and other aspects of appearance, advantages/disadvantages of current height, self-disclosure regarding visit to pediatric endocrinologist, experiences of stigmatization and juvenilization related to SS, self-perceptions of competence in physical activities/gym, and reputation in the school setting (e.g. class clown, teacher's pet) [43]. The psychometric properties of the IRGPH have not been reported.

Treatment-Specific Questionnaire

A growth hormone injection questionnaire (GHIQ) for adolescents has also been developed [44]. It covers the

dimensions 'feelings' and 'injection issues', and includes a total score. Psychometric properties have been tested in the UK and USA on 172 adolescents receiving GH treatment. Internal consistencies for the 'feelings', 'injection issues' and total scores are $\alpha = 0.68$, $\alpha = 0.78$ and $\alpha = 0.77$, respectively. A retest of 149 subjects showed a reliability of $\alpha = 0.72$. Psychometric testing also revealed weak correlations with external validation measures; accordingly, the GHIQ is assessing a relatively independent construct.

Proxy Questionnaires

- (1) The Short Stature in Children – A Questionnaire for Parents is a 34-item instrument covering the domains 'suffering', 'future anxieties', 'behavioral problems' and 'coping efforts'. Items are formulated as whole sentences (e.g. 'On the whole, our child suffers from their short stature', 'At adult age, it would be more difficult for our child to build up a partnership', 'Due to short stature, our child experiences additional problems, but by doing so also matures, in a positive sense, to an extraordinary personality'). Respondents rate the degree of applicability of the statement to their child's situation on a 4-point scale: 'not at all', 'slightly', 'more' or 'very much'. Psychometric properties were tested within a sample of 442 parents of short children recruited through outpatient clinics and patient support groups in Germany. Internal consistency for the 4 scales ranged between $\alpha = 0.60$ (coping efforts) and $\alpha = 0.91$ (future anxieties). Construct validity was determined by expert ratings (physicians, affected families) and divergent validity was tested (parents of children with GHD vs. achondroplasia), although differences were not as pronounced as proposed [45].
- (2) The IRGPH (see above) is also available in a parent-report version for those with children of 6 years or older [41]. In addition to the domains common to both the parent and self-report versions, the proxy measure assesses the reason(s) for referral to a pediatric endocrinologist (concerns over physical health or psychological development), parent satisfaction with child's height and perception of child's satisfaction, child's participation in individual or team sports, years spent in current school and anticipated move to next school, perception of age-appropriateness of child's social maturity, presence of a younger, taller sibling, and number of geographic relocations made by the family since the child's birth [42].

Utility-Based Measures

The 17D measure [46] was specifically developed for assessing a utility index for children aged 7–11 years, both for healthy and chronically ill children. It covers 17 domains of HrQoL. The adult instrument EQ-5D has been used in several studies in children for the measurement of health status. Furthermore, a child-friendly version is in preparation [47]. In contrast, the Health Utility Index Mark 2 System is an instrument especially developed for children and adolescents. This 7-item instrument has demonstrated test-retest reliability and construct validity [48]. However, none of these instruments have been applied to youths with isolated GHD or idiopathic SS.

Patient satisfaction questionnaires designed specifically for youths with idiopathic SS or GHD have yet to be developed.

In addition to generic HrQoL instruments, condition-specific and treatment-specific instruments for children with SS have been developed. Utility-based measures have not yet been used in pediatric populations with growth disorders.

Discussion

This mini review identified 5 pediatric, condition-specific HrQoL measures relevant to youths with SS. Each method has strengths and weaknesses; however, none provide adequate coverage of all the domains potentially influenced by SS, whether as an isolated physical characteristic (e.g. idiopathic SS), or as a consequence of an underlying medical condition (e.g. GHD). Following the strategy employed in psychosocial assessment that relies on incorporating information collected from multiple sources, the optimal condition-specific HrQoL measure should be available in both self- and parent-report versions [49]. Further, desirable characteristics of a HrQoL instrument for children include cross-cultural comparability, a modular approach with generic and condition-specific modules, and an emphasis on positive health-promoting facets of HrQoL [50]. This new instrument would assist clinicians in the formulation of medical and psychosocial treatments and, in parallel to the measurement of height and growth, would provide the means of assessing the HrQoL response to medical and/or psychosocial interventions. A relatively neglected area of subjective experience relevant to GH treatment is patient and family perceptions of the child's height (versus measured height) [51] and their satisfaction with their height [40]. Perceptions of and satisfaction with height

may be strongly associated with HrQoL outcomes in young persons with SS [52].

The age at which children can begin to reliably inform others of their subjective HrQoL is a topic of considerable inquiry. While children as young as 4 years can provide valuable information about their emotional reactions and behaviors, the challenges of creating reliable and valid instruments for this very young age group are substantial [53, 54]. Among the challenges are children's vocabulary and cognitive limitations which may reduce their comprehension of complex ideas. For this reason, the value of self-report condition-specific measures in young children is debatable. However, condition-generic measures such as those developed in the DISABKIDS study or generic measures such as the KINDL-R [55] or the Kid-screen may be used.

Utilizing peers as a source of information about the child's psychosocial adaptation is another source of information deserving serious consideration. The problems purported to stem from SS are believed to be linked to negative social interactions in the peer group, and yet there exists only limited research that has directly examined peer relations among youths with SS [56, 57].

To promote its utility in both clinical care and research, the development of a new instrument would need to meet stringent criteria for HrQoL questionnaire construction, guidelines for which are available in the literature [58]. For cross-cultural purposes, questionnaire development in participating countries should include: (1) focus groups with children and parents; (2) a structured item writing process; (3) cognitive debriefing and pilot testing; (4) field testing with analysis of psychometric properties, including cross-cultural differences, and (5) norming. Examples of such cross-cultural measures are the DISABKIDS [59] and the KIDSCREEN [60] questionnaires for children. Validation of a newly developed measure for SS would include examination of the conjoint influences of clinical, sociodemographic and psychosocial determinants on variance in HrQoL ratings. Finally, to maximize its utility, it would need to be demonstrated that use of this new measure is feasible in treatment settings and acceptable to both clinicians and families.

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