

Research Report

Health-Related Quality of Life in Children with Duchenne Muscular Dystrophy: A Review

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Abstract.

In pediatric chronic illness, improving health-related quality of life (HRQOL) has become one of the most important goals of disease management. Duchenne muscular dystrophy (DMD) is a debilitating, progressive and chronic neuromuscular disorder affecting boys. The purpose of this review is to provide an overview of published research on HRQOL in the pediatric DMD population, describe the instruments used and summarize the study findings. The databases searched were Medline, Embase and PsycInfo. The literature search yielded 167 articles, of which 19 were included in this review. The studies were published between 2005 and 2013 across nine countries. Thirteen different generic and disease-specific measures were used, the most common being the Pediatric Quality of Life 4.0 Generic Core module.

HRQOL in boys with DMD is worse than that of healthy peers and children with other chronic illnesses, especially in the physical domains. Boys who are at a more severe stage of the disease reported worse physical HRQOL but not necessarily psychosocial HRQOL than boys at a less severe stage. Traditional clinical outcome measures correlated well only with physical HRQOL. Parents' proxy-reports of their sons' HRQOL and the boys' self-reports had poor concordance. More research is needed to assess trends in HRQOL over time and to elucidate factors that affect HRQOL.

Keywords: Health-related quality of life, Duchenne muscular dystrophy, questionnaires, pediatrics

ABBREVIATIONS

CHQ:	child health questionnaire
DMD:	Duchenne muscular dystrophy
FDA:	Food and Drug Administration
HRQOL:	health-related quality of life
ICC:	intraclass correlation coefficient
LSI-A:	Life Satisfaction Index-Adolescent
NM:	Neuromuscular
PODCI :	Pediatric Outcomes Data Collection Instrument
SOLE:	strips of life with emoticons

INTRODUCTION

Duchenne muscular dystrophy (DMD) is the most common and severe form of neuromuscular illness in children, affecting between 1 in 3,500 and 1 in 6,000 newborn boys [1, 2]. It is characterized by progressive muscle loss that begins in proximal, lower extremity muscles. Muscle degeneration eventually leads to loss of ambulation, occurring between 10 to 14 years of age [3]. The respiratory, cardiac and bone health of boys with DMD are compromised. There is also a higher prevalence of cognitive disability in this population [4]. Respiratory or cardiac failure eventually leads to premature death, typically in the second to third decade of life [5, 6].

Medical interventions have extended the quantity of life of DMD patients, however, their quality of life (QOL) remains greatly jeopardized by the condition

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[7]. The World Health Organization Quality of Life group has defined quality of life as ‘individuals’ perception of their position in life, in the context of culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns [8]. Health-related quality of life (HRQOL) narrows the scope of QOL and focuses specifically on the impact of illness and treatments on a person’s life [9–11]. Although the concept of HRQOL has been operationalized rather inconsistently across the various measures developed, there are two elements of the concept that are widely agreed to be core: that it includes both subjective and objective dimensions of the impact a health condition and/or its management has on an individual and that it is multidimensional, encompassing multiple aspects of a person’s life. Thus, most instruments are made up of multiple domains, including emotional, social and physical health [12].

The Food and Drug Administration (FDA) has mandated that all clinical trials include patient reported outcomes such as HRQOL [13]. A number of promising molecular therapies for DMD are currently undergoing various stages of clinical trials [14]. A greater understanding of HRQOL would enable researchers and clinicians to meaningfully interpret forthcoming trial results and better incorporate HRQOL measures into future studies. Furthermore, understanding the state of HRQOL in the DMD population is important in and of itself due to its chronic nature and the prolonged life expectancy that has become possible.

While research on HRQOL in DMD is still scarce, it has gained momentum in the past few years. The aim of this article is to provide a thorough review of existing literature on HRQOL in the pediatric DMD population. Key themes, such as comparison of HRQOL with healthy children and other disease groups will be addressed and the limitations of existing literature will be discussed.

METHODS

A literature search was conducted in between October 2014 and April 2015 in the electronic databases Medline, Embase and PsycINFO using the following key words: 1) Duchenne Muscular Dystrophy; 2) quality of life OR health related quality of life OR health-related quality of life OR health status; 3) pediatri* OR paediatrici OR teenage* OR adolescent OR child OR child* 4) 1 AND 2 AND 3. Medical Subject Heading (MeSH) terms were used whenever

possible. Through the initial search criteria, 167 articles were identified that were published from 1986 to 2015. The abstracts were examined and, if suitable, full-length articles were retrieved (Figure 1). Articles were included in this review if they met the inclusion criteria. The reference lists of relevant studies were used to identify potential studies not discovered upon initial search.

Inclusion criteria:

1) Child or parent-reported QOL or HRQOL was the main outcome of the study; 2) study population was specific to or included children with Duchenne Muscular Dystrophy (≤ 18); and 3) was published in the English language.

RESULTS

Nineteen studies were identified that fit the inclusion criteria. The studies were published between 2005 and 2013 and were conducted in the following countries: United States, the Netherlands, Germany, China, Brazil, France, Australia, Italy, and Canada. There are regional differences in the selection of HRQOL measures: almost all studies carried out in North America used either the PedsQL 4.0 Generic Core or the CHQ-50 while almost none of the European countries used these two measures even though they are available in the languages of these countries. Each of the studies done in Europe used a different HRQOL measure.

Thirteen measures of HRQOL were used. Ten were generic measures and most consisted minimally of physical, psychological and social domains. Four studies used disease specific questionnaires: the English [15] and Chinese [16] versions of the PedsQL 3.0 Neuromuscular module, the PedsQL 3.0 DMD module [17] and the Strips of Life with Emoticons [18]. The development of the PedsQL 3.0 Neuromuscular module was described in detail by Iannacone [19]. It underwent extensive review with input from clinicians and families of children with spinal muscular atrophy and DMD. The Neuromuscular module and DMD module were developed simultaneously. A summary of all measures used can be found in Table 1.

The PedsQL 4.0 Generic Core, PedsQL 3.0 Neuromuscular, PedsQL 3.0 DMD modules as well as the PARS-III have been validated in pediatric DMD populations; none of the other measures has been validated in this population. The PedsQL 4.0 Generic core module and the PedsQL 3.0 Neuromuscular module were tested in a group of 44 boys with DMD and their parents [15]. Both modules were found to be feasible

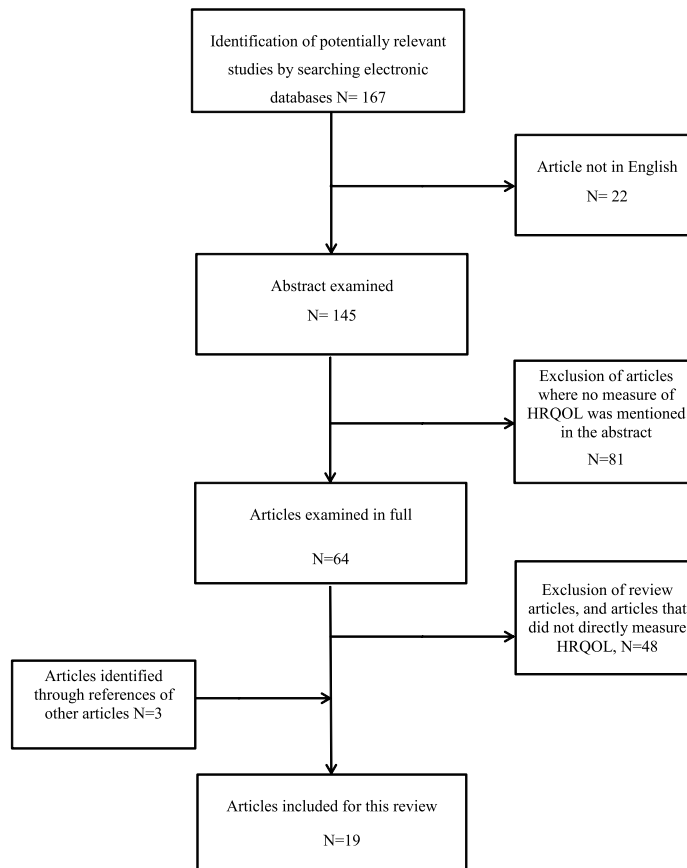


Fig. 1. Process of selecting studies included in this review

and have adequate construct validity for child and parent reports. The internal consistency reliability on the PedsQL Neuromuscular module exceeded the conventional minimum alpha coefficient of 0.7 for all scales in child and parent reports. The internal consistency reliability on the PedsQL Generic Core module exceeded the minimum alpha coefficient for all scales on the parent report. The test-retest reliability of the PedsQL Neuromuscular module is supported for child and parent reports [15]. The PedsQL 3.0 DMD module was tested in a group of 203 families of boys with DMD. All scales on child and parent reported questionnaires exceeded the minimum alpha coefficient needed for group comparisons [17]. Construct validity was also found to be adequate. The PARS-III was tested in a group of 282 males with DMD [20]. Internal consistency reliability was found to be good for the total score and most scale scores. Construct and convergent validities were also found to be adequate.

Six of the studies used parent reports only, seven used child report only, and six used both child reports

and parent reports. Two studies had the same cohort of patients [21, 22], one used parent reports only, one used both child and parent reports. Seventeen of the studies were cross-sectional and two were longitudinal, conducted over the span of nine months and one year [23, 24]. The sample sizes of the studies ranged from 25 to 287. It should be noted, however, that some of studies' patient populations included adults with DMD or children with other types of neuromuscular disorders [18, 25–27].

Although almost all of the studies of HRQOL in children with DMD are descriptive, some comparative analyses were completed. Four recurring themes were identified: 1) comparison of HRQOL between boys with DMD to either healthy peers or those with another chronic illness; 2) comparison among sub-groups within the pediatric DMD sample; 3) investigation of relationship between clinical measures of function and HRQOL; and 4) comparison of children's and parents' perception of children's HRQOL. Each of the four themes will be discussed in detail below.

Table 1
Summary of health-related quality of life instruments used by studies reviewed

Instrument	Dimensions or domains	Scoring	Psychometric properties*
Pediatric Quality of Life 4.0 Generic Core (PedsQL 4.0 Generic)	Physical, emotional, social and school functions	23 items Scores on four domains	English version valid and reliable in DMD population [15]
English and Chinese		Physical and Psychosocial summary scores	$\alpha = 0.45-0.89$
Parent and child reports available		Has total score	
Life Satisfaction Index for Adolescents (LSI-A)	General wellbeing, interpersonal relationship, personal development, personal satisfaction, recreation	45 items Scores on five domains	Validated on adolescents with DMD
English and Dutch		No total score	$\alpha = 0.52-0.88$ [37]
Child report available			
Personal Adjustment and roles Skills Scale (PARS-III)	Peer relations, dependency, hostility, productivity, anxiety/depression, and withdrawal	28 items Scores on six domains	Valid and reliable in US and Dutch DMD populations
Dutch		Has total score	$\alpha = 0.75-0.91$ [20]
Parent report only			
PedsQL Neuromuscular Module	About My Neuromuscular Disease, communication, About our family resources	25 items 3 domain scores	Both English [15] and Chinese [16] versions valid and reliable in children with DMD.
English and Chinese		Has total score	$\alpha = 0.71-0.89$
Parent and child reports available			
PedsQL DMD module	Daily Activities, Treatment, Worry, communication	4 domain scores	Valid and reliable in children with DMD [17].
English version		No total score	$\alpha = 0.66-0.86$
Parent and child reports available			
Child Health Questionnaire Parent Form 50 (CHQ-50)	Physical Functioning, Role/Social Limitations – Physical, General Health Perceptions, Bodily Pain/Discomfort, Family Activities, Role/Social Limitations - Emotional, Role/Social Limitations - Behavioral, Parent Impact Time, Parent Impact Emotion, Self-Esteem, Mental Health, Behavior, Family Cohesion, Change in health	50 items; Scores on 15 domains 2 summary scores: physical and psychosocial	Valid and reliable in UK, US, German and Canadian English and French populations [38]
English		No total score	
Parent report only			
KIDSCREEN-52	Physical, psychological, moods/emotions, self-perception, autonomy, parent relations/home life, financial resources, social support/peers, school environment, social acceptance	52 items Scores on ten domains	Valid and reliable in healthy population [39].
Dutch version		No total score	
Child report only			
DISABKIDS	Independence, emotion, social inclusion, social exclusion, physical limitation, treatment	37 items; Scores on six domains and total score	Valid and reliable in children and adolescents with various chronic illnesses [40].
German version			
Child report only			

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Table 1
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Instrument	Dimensions or domains	Scoring	Psychometric properties*
TACQoL	Motor functioning, physical symptoms, social functioning, cognitive functioning, positive emotions, negative emotions, autonomy	56 items; Scores on seven domains	Valid and reliable in children with various chronic illnesses [41]
Dutch		No total score	
Child report only			
Vecu Sante percu par l'adolescent (VSPA)	Vitality, leisure, relationship with parents, relationship with friends, relationship with teachers, body image, school performance, physical and psychological wellbeing	36 items Scores 9 domains	Valid and reliable in group of healthy and ill adolescents [42].
French		No total score	
Child report only			
Paediatric Outcome Data Collection Instrument (PODCI)	Upper extremity, transfer/basic mobility, sports/physical function, pain, happiness, and global functioning	Scores on five domains Global functioning score is mean of all domains excluding happiness	Valid and reliable in a range of children with functional limitations [43]
English			
Child and parent reports available			
Strips of Life with Emoticons (SOLE)	33 individual items that assess how a child at different times in a typical day	Total score of all 33 items No domain scores	Not validated
Italian			
Child report only			
Short Form 36	Vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health	36 items; Scores on eight domains No total score	Not validated in the pediatric population
English			

*Internal consistency reliability (Cronbach's alpha) of instruments that have been tested in the pediatric DMD population are reported; validity and reliability instruments that have not been tested in other populations are referenced.

A summary of major findings of all nineteen studies reviewed can be found in Table 2.

Comparison to healthy peers or those with another chronic illness

Ten studies compared HRQOL in boys with DMD to a healthy cohort or children with other chronic illnesses, such as diabetes, cerebral palsy and epilepsy. Four of these studies recruited healthy controls along with their DMD sample [18, 24, 28, 29], and six studies used established normative data from the literature as basis of their comparison to healthy children [15, 17, 22, 30–32].

Elsenbruch et al. [31] divided their sample into child and adolescent groups. In the children's group, all domain scores as well as the total HRQOL score were significantly lower than the scores of age-matched

children with other chronic illnesses. In the adolescent group, only the social inclusion domain score was significantly lower in boys with DMD than the normative data. Orcesi et al. [18] developed a new HRQOL instrument targeting young children with neuromuscular illnesses, the Strips of Life with Emoticons (SOLE), which only has an overall score and no domains scores. Compared to healthy boys, boys with DMD had significantly lower scores on the SOLE.

Eight studies found that boys with DMD had significantly worse physical HRQOL than healthy boys or children with other types of chronic illnesses [15, 17, 22, 24, 28–30, 32]. Five studies reported that boys with DMD had significantly lower psychosocial score than healthy controls [15, 22, 28–30]. The difference in physical HRQOL score were consistently larger than difference in psychosocial score, and these deficiencies were observed in both children's and parent's reports.

Table 2
Summary of studies reviewed

Citation	Study design; DMD sample characteristics [N; mean age, (age range)]; Recruitment method	HRQOL measure used	Major findings
[15]	Cross-sectional; [44; 12.9 years; (8–18)] Neuromuscular clinics in the United States	PedsQL 4.0 Generic Core and PedsQL 3.0 Neuromuscular modules Child and parent report	All HRQOL scores significantly poorer than normative sample. Poorer physical HRQOL in both modules among non-ambulatory boys.
[16]	Cross-sectional; [56; 7.5 years; (2–13)] Tertiary hospitals in urban China	Chinese version of PedsQL 4.0 Generic Core and Neuromuscular 3.0 module Child and parent report	The Chinese translation of the Neuromuscular module was feasible, reliable and valid Moderate agreement between parent and child All HRQOL scores significantly lower than healthy children.
[17]	Cross-sectional; [203; 10.4 years; (5–17)] Neuromuscular clinics in the United States (Michigan)	PedsQL 4.0 Generic Core and DMD module Child and parent report	All HRQOL scores significantly lower than healthy children. Self-reported psychosocial scores significantly higher for older than younger boys. Psychosocial score not related to use of mobility aids.
[18]	Cross-sectional; [43; 8.6 years; (range 5–13)] Six tertiary centres in Italy	Strips Of Life with Emoticons (SOLE) questionnaire Child report	Poorer HRQOL than healthy controls. HRQOL not related to degree of functional disability.
[20]	Cross-sectional [287; 10.9 years; (5–18)] Dutch and American Parent Project Muscular Dystrophy organizations	Personal Adjustment and Role Skills Scale (PARS-III) Parent report	Adjustment score did not differ significantly from boys with other chronic conditions. Adjustment score increased with age.
[23]	Longitudinal [95; unknown; (5–17)] Single neuromuscular centre in Brazil	Life Satisfaction Index for Adolescents Child report	HRQOL in most domains improved over time. No significant difference between age groups.
[24]	Longitudinal [24; 7.9 years; (4–12)] Neuromuscular clinics in the United States (California)	PedsQL 4.0 Generic Core PODCI Parent-report	Decline in PODCI score but not PedsQL were significantly correlated with decline in 6 minute walk test.
[25]	Cross-sectional [36; 12.6 years; (8–17)] Dutch Neuromuscular centres	TACQoL children for under 16 year olds TACQoL adult for 16 and older	Only the 'motor functioning' domain was poorer than healthy peers
[26]	Cross-sectional [24 (out of 109 NM patients); 10.5 years; (2–18)] Single Neuromuscular centre in Canada	Child report PedsQL 4.0 General Core Parent-report	Children who required ventilation had significantly lower overall HRQOL than children not on ventilation

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Table 2
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Citation	Study design; DMD sample characteristics [N; mean age, (age range)]; Recruitment method	HRQOL measure used	Major findings
[27]	Cross-sectional [19 (out of 43 NM patients); 13.8 years; (10–17)] Single neuromuscular centre in France	Vecu Sante Percu par L'adolescent (self-perceived perceived health states in adolescents) Self-report	HRQOL scores not significantly different than nondisabled group. HRQOL scores did not correlate with physical impairment
[21]*	Cross-sectional [35; 12.5 years; (9–17)] Neurogenetics clinics and community newsletters in Australia	PedsQL 4.0 Generic Core Child and parent reports	Self-reported scores significantly correlated with physical domain and Vignos scale Parent-child concordance range from poor to modest for different domains.
[22]*	Cross-sectional [34; 9.9 years; (5–18)] Three urban paediatric hospitals in Australia	Child Health Questionnaire 50-Parent Form Parent-report	Parents reported significantly lower HRQOL score than normative sample and Charcot-Marie-Tooth disease sample. Parents experienced greatest stress during disease transition points.
[28]	Cross-sectional [50; 8.0 years; (5–17)] Neuromuscular clinic in the United States (Florida)	PedsQL 4.0 Generic Core Child and parent report	All HRQOL scores poorer than healthy sample except for emotional domain. Participation level is not correlated to HRQOL Older boys had significantly lower participation level, but not lower HRQOL scores than younger boys
[29]	Cross-sectional [52; 8.4 years; (4–17)] Neuromuscular clinics in the United States	PedsQL 4.0 Generic Core Module PODCI	HRQOL in both measures are poorer than controls The physical function domain of PedsQL and of PODCI correlated with age and clinical measures of strength
[30]	Cross-sectional [27, 11.4 years; (unknown)] Neuromuscular clinics in Italy	Parent report Child Health Questionnaire 50- Parent Form Parent report	HRQOL scores significantly poorer than healthy sample Use of wheelchairs and ventilation were significantly associated with lower physical HRQOL.
[31]	Cross-sectional [50; 15.4 years; (8–23)] Single paediatric neurology clinic in Germany	DISABKIDS chronic generic module for children and adolescents; Short Form-36 for young adults Child report	In children, all HRQOL scores poorer than children with other chronic illnesses. In adolescents, only social inclusion domain was poorer. No correlation between total HRQOL score and Vignos function score.
[32]	Cross-sectional [40; 11.5 years; (8–20)]; Dutch Duchenne Parent Database	KIDSCREEN-52 Child report	Apart from physical domain, HRQOL in not significantly different from that of healthy boys. Significant correlations between physical domain and some functional scales Parent scores were significantly lower than child score in three domains.

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Table 2
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Citation	Study design; DMD sample characteristics [N; mean age, (age range)]; Recruitment method	HRQOL measure used	Major findings
[33]	Cross-sectional [N= 35; 17 years; (8–33)] Swiss facility for NM patients	Short Form-36 Child report	Physical and mental HRQOL not found to be correlated with physical impairment or FVC.
[34]	Cross-sectional DMD sample N= 63 parent-child pairs Mean age 10.3 (range 5-16) Florida, United States	PedsQL 4.0 Generic Core Child and parentreport	Parents reported significantly lower physical and psychosocial HRQOL than boys themselves. The agreement between children and parents in physical domain was better than psychosocial domains.

*Participants of two studies by Bray and colleagues were from the same cohort of families.

Comparison among sub-groups within the pediatric DMD sample

In DMD studies, age is often used as a proxy for disease progression given that generally, older children are at a more severe stage of the illness. Patients with DMD may also be classified by ambulation status (ambulant or non-ambulant) or ventilation status (requires ventilation or not).

Three studies used the PedsQL 4.0 Generic Core scale and reported that younger boys had significantly higher physical HRQOL scores than older boys [17, 21, 29]. In contrast, another study reported that boys younger than 10 years of age did not report significantly higher physical score than those who were older [28]. Two studies reported boys using wheelchairs had significantly lower physical domains scores than boys who were still ambulant [15, 30]. Kohler et al. [33], found that boys with DMD who required ventilation did not report significantly lower physical or mental HRQOL scores than those not requiring ventilation. However, this study used the Short Form-36, which was designed to assess HRQOL in adults rather than in children.

There is less consistency across studies assess psychosocial HRQOL. Four studies reported that there were no significant differences between older and younger boys in psychosocial HRQOL scores, [22, 28–30]. Similarly, Davis et al. reported no significant differences in psychosocial HRQOL scores between children using wheelchairs and those who were not [15]. In contrast, Hendriksen et al. found the psychosocial adjustment score to be positively associated with age in a survey of parents of boys with DMD [20].

As well, Uzark et al. found that boys in the oldest age group reported significantly higher psychosocial scores than boys in younger age groups; this difference was not observed in parent report [17]. Mah et al. found that, based on parent reports, children who require ventilation support had significantly lower physical and psychosocial HRQOL scores than children not requiring ventilation [26].

In a longitudinal study, Simon et al. followed a group of boys with DMD over nine months and found that life satisfaction score improved over time for all age groups [23]. One major limitation of the study was that the questionnaire used, the LSI-A, was designed for adolescents, but the majority of the study sample was under 12 years of age. There was no psychometric evaluation to justify this deviation.

On the PedsQL 3.0 Neuromuscular module, boys who were using wheelchairs full-time and their parents reported lower about My Neuromuscular Disease domain score than part-time wheelchair users and those not using wheelchairs [15]. There were no significant differences in the other domains or the total score. On the PedsQL 3.0 DMD module, boys receiving steroids had significantly higher scores on the Daily Activities domain than boys not receiving steroids by parent-reports; and higher Worry score (less worry) by self-reports. Parents of children in the youngest age group reported them to have significantly higher scores in Daily Activities, Treatment Barriers and Worry domains than the two older age groups.

Overall, physical HRQOL in children who are at a more severe stage of the disease is worse than children who are at a less severe stage. Less consistent

is the relationship between disease severity and psychosocial HRQOL. Some studies found older children reported better psychosocial HRQOL despite having more severe disease progressions [17, 20], while others reported no significant differences between older and younger children [22, 28–30]. It is worth noting that no conclusions can be drawn regarding a possible causal relationship between disease severity and HRQOL from cross-sectional studies.

Correlation with clinical measures

Traditional outcomes used in clinical trials of DMD involve quantitative measures of strength and mobility. With the increasing recognition of the importance of patient-reported outcomes such as HRQOL, some studies have examined the relationship between clinical measures and HRQOL.

The self-reported domains of the KIDSCREEN-52 [17, 20] and the DISABKIDS [31] did not correlate well with clinical measures. The only significant correlations were between the physical domain of the KIDSCREEN-52 and the Vignos scale, a measure of upper body strength; and between emotional domain of the DISABKIDS and the Vignos scale. McDonald et al. [29] found that only the physical domains of the parent-reported PedsQL 4.0 Generic Core and the Pediatric Outcomes Data Collection Instrument (PODCI) significantly correlated with functional measures. Similarly, in two separate studies, Bray and colleagues [21, 22] found that only the physical domains of the CHQ-50 parent report and the physical domain of the self-reported PedsQL 4.0 Generic Core module correlated with the Vignos scale. The 6-minute walk test is a recently adopted outcome measure in clinical trials of DMD (NCT01462292). Henricson et al. [24] found that decline in 6-minute walk test over one year correlated significantly with decline in parent-reported PODCI score.

Vuillerot et al. [27] examined self-reported well-being of a group of 43 adolescents with various neuromuscular disorders, 19 of whom were DMD patients. They concluded that HRQOL did not correlate with motor function.

Overall, it appears that while the physical domains of some HRQOL measures correlated significantly with commonly used clinical measures, neither the psychosocial domains nor the overall HRQOL scores correlated with clinical endpoints.

Comparison and agreement between child report and parent report

Parents generally rated their child's HRQOL lower than children themselves did [15–17, 21, 34], although no statistical comparisons were conducted in these studies. This difference tended to be greater in the psychosocial domains than the physical domain.

Six studies included both child self-reports and parent proxy-reports, and of these, five studies examined concordance between child and parent reports. Parent and child concordance is determined by intraclass correlation coefficient (ICC). For the purposes of this review, an ICC of ≤ 0.40 is considered poor, of 0.41 to 0.75 is considered moderate, of >0.75 is considered excellent [17].

In studies that used the PedsQL 4.0 Generic Core module [15, 17, 21], only the school domain had moderate concordance, while other domains had poor concordance. Davis et al. [15] found that all subdomains of the English PedsQL 3.0 Neuromuscular have poor parent-child concordance. Hu et al. [16] tested the Chinese version of the same questionnaire and found that for 50 child-parent pairs, the ICC of the overall score and subdomains were moderate. Lim et al. [34] found that by both classical test analysis, which examines scale-level agreement, and Rasch analysis, which examines item-level agreement, there was better concordance between children and parents on the physical scale than psychosocial scale.

Overall, parents tend to rate their child's HRQOL as worse than children themselves do, and the concordance between parent and child is in the poor to moderate range with the majority of domains and total scores in the poor range. The more observable aspects of a child's life, such as school function tended to yield higher concordance.

DISCUSSION AND LIMITATIONS OF CURRENT STUDIES

There is heterogeneity across studies in the definition and constructs HRQOL. Some measures focus only on individuals' feelings about their well-being (PARS-III, LSI-A), while other instruments are closer to measures of health status in that the questions evaluate the extent of a problem has occurred (CHQ and PedsQL questionnaires). Furthermore, it is difficult to compare results across measures that have different domains, particularly if they do not have summary score(s). Fortunately, the most commonly used

questionnaires are CHQ and PedsQL, both of which have physical and psychosocial summary scores, making it easier to compare the findings.

Many of the studies used convenience sampling and drew participants from a single clinic. Given the severity of the disease, it is reasonable to assume that almost all boys with DMD are managed at a tertiary-care clinic, thus patients recruited through such clinics are likely to be representative of the DMD population. However, most studies did not report a response rate and it is unclear whether the respondents differ from those who chose not to participate.

Most of the studies had relatively small sample sizes, with 10 of the 18 studies having a sample size of 50 participants or less. When subgroup comparisons were made, the sample sizes became even smaller. Thus the lack of any significant differences across groups could be due to insufficient statistical power. Additionally, of all HRQOL measures, only the PedsQL modules and the PARS-III have been validated specifically in a pediatric DMD population [15, 20]. The reliability and validity of other measures in this population are unknown. Some studies have employed measures designed for adults [33] or adolescents [23] to children, without any psychometric evaluation of their appropriateness in pediatric populations.

In four of the studies [18, 25–27], boys with DMD were part of a sample that included children with other types of neuromuscular disorders, making it hard to elucidate specifically the HRQOL of boys with DMD. Some studies excluded boys younger than 8 years old [15, 31], or boys who have lost ambulation [24, 29]. Finally, not all of the studies assessed HRQOL from both parent and child perspectives, and few studies used disease-specific measures [15–18].

CONCLUSIONS

Based on existing literature, the HRQOL of boys with DMD appears to be significantly poorer than that of their healthy peers, particularly in the physical domain. Within the DMD sample, boys who are at a more severe stage of the disease consistently reported poorer physical HRQOL than boys who are at a less severe stage of the disease; such a difference was not as consistent for psychosocial HRQOL. Similarly, while the physical domains of HRQOL instruments correlated well with clinical measures of functioning, psychosocial domains did not. Finally, the parent and child concordance for most measures of HRQOL was poor.

The PedsQL Inventory has both generic and disease-specific measures, available in multiple languages, with the English versions having been validated in the pediatric DMD populations [15, 17]. Their brevity is advantageous in the clinical and research settings. Many past and current clinical trials in DMD have used PedsQL instruments as outcomes [35]. However, the internal consistency reliability of PedsQL instruments is low to moderate in some domains, and none has reached the level of 0.9 ideal for use at the individual patient level [36]. Furthermore, their responsiveness to important clinical changes has not been established, but this is the case for all other HRQOL measures in the DMD population. Although further psychometric testing, as well as establishing values such as minimally clinically important differences should be carried out, the PedsQL inventory at present, appear to be the most comprehensive and validated measures for clinical and research use in this population. Other multidimensional instruments such as DISABKIDS are available in multiple languages, including English, and are also candidates for clinical use. However, psychometric testing in the DMD population should be performed.

Most of the existing studies have significant limitations that restrict generalizability of the data and comparison of results. Further, the methodological variability in this emerging literature makes it difficult to establish conclusive ideas about sensitivity to change and minimally clinically important differences that will be important for interpreting patient reported outcomes in clinical trials. Longitudinal studies, in large and diverse DMD patient populations, with examination of multiple aspects of HRQOL and disease characteristics, are needed to evaluate HRQOL over time, and to potential determinants of HRQOL.

COMPETING INTEREST

The authors declare that they have no competing interests.

AUTHOR'S CONTRIBUTIONS

This review was adapted from the Master's thesis of YW, who contributed to the design of the study, extracted the relevant articles and drafted the manuscript. CC and KS were involved in the design of the study, reviewed relevant articles and contributed to the manuscript at all stages.

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