Quality of Life in Osteogenesis Imperfecta: A Mixed-Methods Systematic Review

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Clinical interventions and research have mostly focused on the orthopedic, genetic, and pharmacological outcomes of individuals with osteogenesis imperfecta (OI), and although quality of life (QoL) has gained recognition as an important patient-outcome, it has received little attention in individuals with OI. This mixed-methods systematic review of the literature included five search engines and identified a total of 212 articles. Once study eligibility was reviewed, 10 studies met the inclusion criteria and were included in this mixed-methods review (9 quantitative and 1 qualitative). Among the 10 included QoL studies, six reported on children with OI, three on adults with OI, and one on the parents of children with OI. Physical QoL in children and adults with OI appears to be less than that of the general population, with individuals with more severe OI types reporting worse QoL. On the other hand, mental and psychosocial QoL is the same or better in individuals with OI than that of the general population. Pain, scoliosis activity limitations and participation restrictions due to decreased function are associated with lower levels of physical QoL. Researchers must agree on a definition of QoL as it relates to OI and use validated measures appropriate for evaluating QoL in OI. Pediatric studies should consider both the child and the parent's QOL perceptions as these may differ. QoL in the adult population should not be dismissed in order to offer proper client-centered interventions throughout the lifespan. © 2015 Wiley Periodicals, Inc.

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blue sclera, dentinogenesis imperfecta (discoloration and brittleness of teeth), skin and ligamentous hyperlaxity, hearing impairments, presence of Wormian bones on skull radiographs, short stature and skeletal deformities. In the majority of cases, OI is caused by mutations affecting collagen type I, the most prevalent protein in bone, skin, and other connective tissues [Rauch and Glorieux, 2004]. The broad clinical spectrum of OI has led to clinical classification systems that distinguish five [Warman et al., 2011; Van Dijk and Sillence, 2014] to seven types of OI [Rauch and Glorieux, 2004], with varying severity and inheritance patterns. Additional types based on genetic findings have been proposed [Marini and Blissett, 2013]. OI type I is the most frequent type, with an incidence of almost 50% [Rauch and Glorieux, 2004] and is the mildest form of the disease. OI type II is the most severe form and results in perinatal death whereas the most severe form compatible with survival is OI type III. Type IV is a clinically diverse group in which the phenotype can vary from mild to severe. Prior to the analysis of bone structure, OI types V to VII were included in this category [Roughley et al., 2003].

INTRODUCTION

Osteogenesis imperfecta (OI) is a heritable connective tissue disorder with an incidence of approximately one in 10,000 births [Glorieux, 2008]. It affects males and females equally and occurs in all racial and ethnic groups. The principal clinical feature of OI is bone fragility, leading to frequent fracture after minimal trauma [Rauch and Glorieux, 2004]. Other clinical features may include

The traditional focus of health care services for children with OI has been primarily directed on pharmacologic and orthopedic interventions that address the underlying impairments of bone fragility, deformity, and fractures. Rehabilitation interventions were traditionally aimed primarily at improving mobility and self-care [Cheung and Glorieux, 2008] but have shifted recently to include enabling community participation and quality of life (QoL) [WHOQOL Group, 1995; King et al., 2002]. The World Health Organization (WHO) defines QoL as the "individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns" [WHOQOL Group, 1995]. This broad concept encompasses many different components of overall health and well-being (e.g., physical, psychosocial, emotional) [Voll, 2001]. QoL provides a unique and comprehensive view that is not captured by traditional outcome measures. It is therefore a central issue in evaluating the impact of chronic disease as perceived by the individual. QoL is also a common outcome measured used in clinical trials and research on health care delivery [Eiser, 2004; Waters et al., 2009].

Medical and rehabilitation services typically start early in life for individuals with OI, with the long-term goal of optimizing health and well-being, in spite of bone fragility and deformity. Bisphosphonates are used in an attempt to increase bone mineral density and reduce fractures in individuals with OI and our standard protocol consists of intravenous infusions every 4 or every 6 months. A recent Cochrane review on the effectiveness of bisphosphonates included 14 trials and concluded that although significant improvements in bone mineral density after treatment were shown, bone pain, growth, and QoL indicators were not reported in enough detail [Dwan et al., 2014]. Studies have shown that children and adults with moderate to severe OI types may have activity limitations in self-care and mobility [Engelbert et al., 2004], and participation restrictions in employment, sporting activities, and transportation [Montpetit et al., 2011]. These findings may be associated with diminished QoL yet the assumption that individuals with disabilities have a lower QoL and general satisfaction with life has been challenged [Savage et al., 2014]. Promoting QoL has been advocated as a pediatric goal by the WHO and has become the goal of the next frontier in the healthcare of individuals with rare genetic diseases [Cohen and Biesecker, 2010], yet it is unclear whether: (i) individuals with OI and the general population differ in their QoL assessment; (ii) QoL varies across OI severity types; and (iii) QoL varies across age groups. Furthermore, identifying the factors that are associated with better or worse QoL is important [Wilson and Cleary, 1995] to guide interventions and design research aimed at optimizing well-being. The value of systematic reviews to guide evidence-based practice is recognized [Lavis et al., 2009]. Although systematic reviews have traditionally focused mostly on quantitative research, the inclusion and integration of qualitative research will contribute to the presentation of varied perspectives on QoL [Thomas et al., 2004; Whittemore and Knafl, 2005] and improving best practice for individuals with OI. Therefore, given the importance of understanding the impact of OI on the individual's QoL, the primary objectives of this mixed-methods systematic review were to describe the QoL of individuals with OI across severity levels and throughout the lifespan and investigate how to promote QoL of individuals with OI by integrating the quantitative and qualitative evidence base into practice.

MATERIALS AND METHODS
Search Strategy and Selection Criteria

Studies for inclusion in this mixed-methods systematic review were primarily accessed through the following electronic databases: Medline via Ovid (1997–2014), Embase via Ovid (1996–2014), PsycInfo via Ovid (1987–2014), CINAHL via EBSCOHOST (1990–2014) and PubMed. MeSH-term and/or text word combinations were used for (i) OI; and (ii) QoL: QoL; health-related quality of life (HRQL or HRQOL); life quality; health status; well-being, life style, value of life. The QoL terms were based on a search strategy established by the University of York Centres for Review and Dissemination [Paisley et al., 2005]. To limit publication bias, the search did not have any restriction based on language of publication. No attempt was made to locate unpublished material or contact researchers for unpublished studies. The date of the last search attempt was March 2015. Table I illustrates the full electronic search strategy for Medline.

After removing duplicates, two reviewers independently reviewed all titles and abstracts for relevance and reviewed selected full-text articles according to the inclusion criteria (Table II). Any disagreements were resolved by discussion with a third reviewer until consensus was met. To be included for review, studies (i) included individuals with any OI type and of any age (to permit potential comparison of QoL findings across OI types and lifespan); (ii) used a quantitative, qualitative, or mixed methods methodology; and (iii) measured QoL or well-being using a validated or non-validated tool (such as a visual analog scale). Articles were excluded from review if the study (i) did not focus on individuals with OI or (ii) did not provide quantitative, qualitative or mixed methods QoL findings. Abstracts, editorials, commentaries, letters, and study protocols were excluded from the review;

TABLE I. Search Strategy for Medline Using Ovid (1996–2015)

	Searches	Results
1	exp Osteogenesis Imperfecta	1,633
2	Quality of life	195,263
3	Health related quality of life	25,148
4	QoL	21,668
5	HRQOL	8,728
6	Life quality	3,764
7	Health Status*	25,211
8	Well-being	37,811
9	Life Style	51,587
10	"Value of Life"	2,367
11	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	290,301
12	1 and 11	42

MESH terms were used whenever appropriate. The explode box (exp) was used to retrieve results using all of the more specific terms. The focus box identified by an asterisk (*) was used to exclude irrelevant terms (e.g., geriatric assessment).

TABLE II. Selection Criteria

	Inclusion criteria	Exclusion criteria
Population: age	Any age	None
Population: diagnosis	Any type of OI	Does not provide separate results for OI in studies with more than one condition
Study design	Qualitative, quantitative or mixed methods	Abstracts, editorials, commentaries, review articles, letters, and study protocols
Quality of life measurement	Interviews to gather quality of life	Only tools measuring concepts other than QoL are used (e.g., exercise capacity, school achievement); QoL is not measured
	Use of a tool, questionnaire devised for the study, or/and LAS to assess QoL	

LAS, Linear Analogue Scale; QoL, quality of life; OI, osteogenesis imperfecta.

however, all articles were reviewed for possible relevant references. References from included full-text original papers were also reviewed to identify any further relevant articles.

Methodological Quality Rating

The Mixed Methods Appraisal Tool (MMAT)—Version 2011 [Pluye et al., 2009] was used to assess the methodological quality rating of included studies. The methodological quality criteria of the MMAT are illustrated in Table III. The MMAT is a recently developed tool that has demonstrated an intra-class correlation of 0.8 based on pilot testing in 2009, its use is effective and practical for the quality assessment of quantitative, qualitative, or mixed-methods designs. There are four criteria for appraising quantitative and qualitative studies. For a mixed-methods study, both the appropriate section for the quantitative component and the qualitative component are used. Scores vary from 25%—one criterion met, to 100%—all criteria met. For qualitative and quantitative studies, this score is the number of criteria met divided by four. For mixed methods studies, the overall quality score is the lowest score of the quantitative and qualitative study components. The methodological quality scores using the MMAT were calculated for the studies included in this review. No eligible study was excluded based on methodological quality.

Data Extraction and Synthesis

Two reviewers extracted data on the study design, sample characteristics (e.g., size, age, and OI types), instrumentation, and findings. Studies that used both a quantitative and a qualitative methodology were classified as mixed methods. For quantitative and mixed-methods studies, only data from outcome measures directly measuring QoL were considered. This precluded a formal meta-analysis, as the assessment methods and the presentation of the results were heterogeneous. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist and flowchart [Moher et al., 2009] and the Enhancing Transparency in Reporting the Synthesis of Qualitative Research (ENTREQ) checklists and flowcharts were used to verify that all aspects of the review

were considered. A narrative approach was used to synthesize the data stratified by age group.

RESULTS

Search Strategy and Selection Criteria

The search strategy yielded a total of 212 articles; OVID (Medline, Embase, and PsycInfo) = 171, CINAHL = 4, Pubmed = 37; Figure 1. After removing duplicates, abstracts, letters, commentaries, reviews, editorials, and protocols, a total of 172 abstracts were reviewed for study eligibility. From the reviewed abstracts, 34 full-text articles were eligible of which 10 studies met the inclusion criteria for this review.

Methodological Quality Rating

Ten studies were included in this mixed-methods systematic review, nine quantitative and one qualitative. There were six observational studies, two randomized control trials, one randomized cross-over study, and one qualitative design. Seven of the nine quantitative studies received a 100% score on the MMAT quality rating scale, denoting high methodological rating as all four criteria were met [Widmann et al., 1999; Widmann et al., 2002; Kok et al., 2007; Löwing et al., 2007; van Brussel et al., 2008; Balkefors et al., 2013; Fano et al., 2013]. Studies with lower ratings lost points for not having provided a clear description of the randomization process, or having used non-validated QoL measurement tools. Regarding OI severity, most studies used the Sillence classification [Sillence et al., 1979] to categorize OI and samples usually consisted of the three most common OI types: I, III, and IV. The two studies by Widmann et al. [1999, 2002] used an abbreviated classification whereby OI was classified according to time of fracture presentation, either at birth (congenital) or later during infancy (tarda). Consequently, studies were attributed maximal points for representativeness of the sample since other OI types (V–XI) are rarer and have been discovered in the recent years. See Table III for the quality rating for each of the included studies.

TABLE III. Quality Rating Using the Mixed Methods Appraisal Tool (MMAT)—Version 2011

Study designs	Methodological quality criteria										
		Studies									
		1									
1. Qualitative	1.1. Are the sources of qualitative data (archives, documents, informants, observations) relevant to address the research question (objective)?	*									
	1.2. Is the process for analyzing qualitative data relevant to address the research question (objective)?	*									
	1.3. Is appropriate consideration given to how findings relate to the context, for example, the setting, in which the data were collected?	*									
	1.4. Is appropriate consideration given to how findings relate to researchers' influence, for example, through their interactions with participants?	*									
			2	3	4						
2. Quantitative randomized controlled (trials)	2.1. Is there a clear description of the randomization (or an appropriate sequence generation)?		*		*						
	2.2. Is there a clear description of the allocation concealment (or blinding when applicable)?		*	*	*						
	2.3. Are there complete outcome data (80% or above)?		*	*	*						
	2.4. Is there low withdrawal/drop-out (below 20%)?		*	*	*						
3. Quantitative non-randomized	3.1. Are participants (organizations) recruited in a way that minimizes selection bias?										
	3.2. Are measurements appropriate (clear origin, or validity known, or standard instrument; and absence of contamination between groups when appropriate) regarding the exposure/intervention and outcomes?										
	3.3. In the groups being compared (exposed vs. non-exposed; with intervention vs. without; cases vs. controls), are the participants comparable, or do researchers take into account (control for) the difference between these groups?										
	3.4. Are there complete outcome data (80% or above), and, when applicable, an acceptable response rate (60% or above), or an acceptable follow-up rate for cohort studies (depending on the duration of follow-up)?										
						5	6	7	8	9	10
4. Quantitative descriptive	4.1. Is the sampling strategy relevant to address the quantitative research question (quantitative aspect of the mixed methods question)?					*	*	*	*	*	*
	4.2. Is the sample representative of the population under study?					*	*	*	*	*	*
	4.3. Are measurements appropriate (clear origin, or validity known, or standard instrument)?						*	*	*	*	*
	4.4. Is there an acceptable response rate (60% or above)?						*	*	*	*	*

Narration of Synthesized Data

All of the studies included in the review recruited the study participants from hospital or clinical settings in the Netherlands, the United States, the United Kingdom, Poland, Sweden, and Argentina, five of which indicated having a specialized unit for bone disease, multidisciplinary team, or an OI clinic [Fano et al., 2013; Kok et al., 2007; Szczepaniak-Kubat et al., 2012, Balkefors et al., 2013; Hill et al., 2014]. In addition, two studies also recruited participants from support organizations, including the National Support Group for children with OI in Poland [Szczepaniak-Kubat et al., 2012] and the OI Association in Sweden [Balkefors et al., 2013]. Nine studies measured QoL in children, adolescents, or adults with OI and one study measured the QoL of parents of children with OI. The results are presented by the age group of the individual with OI (childhood and adulthood); such that the study on the parents of children with OI was included in the childhood group (Table IV).

FIG. 1. Flow chart.
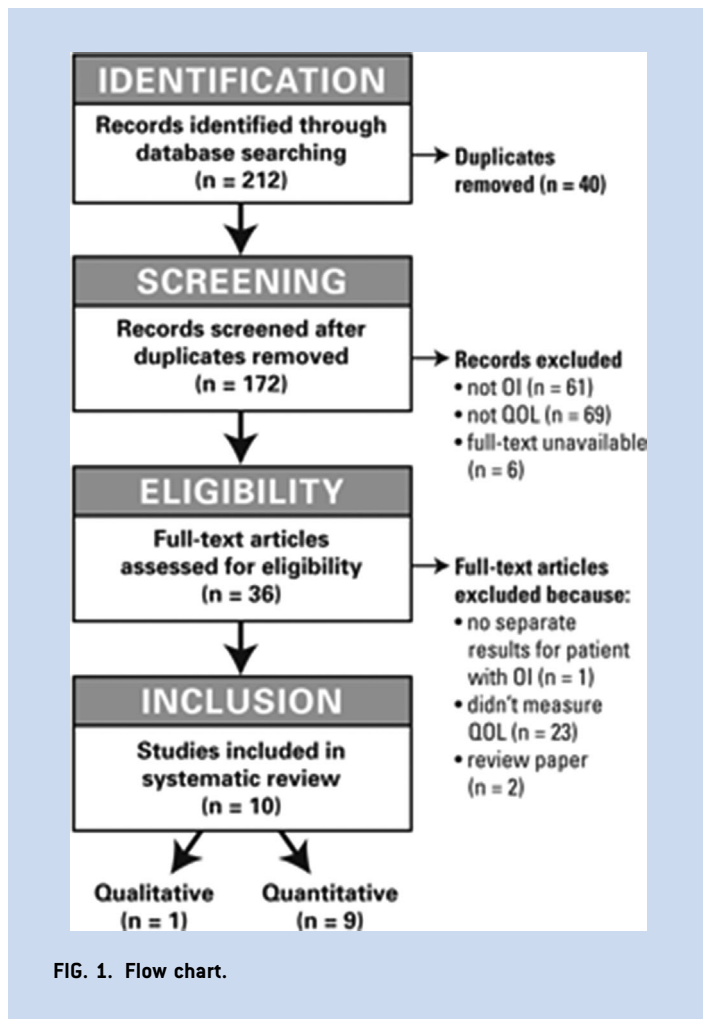
Children and Adolescents With OI (n = 6) and Parents of Children With OI (n = 1)

Recruitment of participants. The number of child participants for these studies ranged from 10 to 65 with an average and median sample size of 34 participants, and involved a total of 202 children. Five studies included children with types I, III, and IV and one study included only children with OI types I and IV [van Brussel et al., 2008]. van Brussel et al. [2008] studied the effect of a physical training program on health outcomes in children with mild to moderate forms of OI (types I and IV). No studies included children with rarer OI types (e.g., types V–VII). Although OI is a genetic condition, only the study by Hill et al. [2014] mentioned that some of the parents had OI themselves in the context of feeling guilt for passing on the genetic cause when discussing fracture-associated pain, and none of the studies mentioned whether participants were from the same family (e.g., siblings). Three studies (two randomized and one prospective observational study) explored the effect of undergoing bisphosphonate treatment (olpadronate, alenodrate, or pamidronate) on the children's QoL at the end of treatment [Seikaly et al., 2005; Kok et al., 2007; Löwing et al., 2007]. Another study randomized children either to a 12-week (30

sessions) training program consisting of a bi-weekly 45 min session supplemented by home-based exercises or usual therapy to evaluate the effect of physical training program on exercise capacity and QoL [van Brussel et al., 2008]. The number of assessment points as well as time of measurement of QoL varied across studies. Although the four intervention studies measured QoL at several time points along the intervention course, only one analyzed QoL scores at more than two timepoints and included assessment of baseline, 3, 6, and 9 months follow-up values [van Brussel et al., 2008]. Two studies investigated QoL at one point in time [Fano et al., 2013; Hill et al., 2014].

Self and parent-report for QoL. The cut-off age for children to report their own QoL was not clear in the studies using a self-report assessment [Kok et al., 2007; Löwing et al., 2007; Fano et al., 2013]. In Löwing and colleagues' study, eight children (out of 43) scored their own well-being, of those three were younger and five older than 7 years, and seven children were too young for well-being assessments. In Fano and colleagues' study [2013], the QoL of children between 2 and 4 years of age was evaluated according to parental report, and assistance was provided for children between 5 and 7 years of age for questionnaire completion. QoL was rated according to both self and parent-report for the older children in accordance with the PedsQL guidelines. QoL was assessed exclusively by parent proxy in two studies [Kok et al., 2007; van Brussel et al., 2008]. Three quantitative studies [Seikaly et al., 2005; Löwing et al., 2007; Fano et al., 2013] considered both self- and parent-proxy reports, and yet none included a comparison of the two groups. Upon communicating with the authors, Fano et al. reported that parents of children with OI reported significantly lower scores on the physical (mean = 53.9 ± 23.7 vs. 59.1 ± 23.4, $P = 0.01$) and emotional (mean = 56.5 ± 18.6 vs. 67.6 ± 17.6, $P = 0.002$) domains of the PedsQL than their children, but no differences on the school and social domains were noted (unpublished data). One qualitative study [Hill et al., 2014] interviewed health care professionals' perception (n = 5) in addition to child (n = 10) and parental (n = 10) on the impact of OI on QoL. Six main themes were identified; being safe and careful, reduced function, pain, fear, isolation, and independence. There was generally good agreement between the three groups of interviewees, although discrepancies did occur between parents and children, with regard to the themes independence and fear. Parents described struggling from an early age with letting go and over protection, but they were aware of their child's drive for independence. The high school children reported striving for independence even when they had sustained a fracture, and expressed their dislike of parents attempts to keep them safe and doing everything for them. The younger children did not talk of independence and were unaware of the overprotective actions of their parents. The impact of fear varied across the group; the very young children did not report fear and the older children had a fear of activities that previously resulted in a fracture. Furthermore, the fear reported by parents was related to the handling and of safety/separation when the child was not at home (e.g., at day care, school, or play dates).

Definition of QoL, measurement, and interview process. Three studies defined QoL [Kok et al., 2007; Fano et al., 2013; Hill et al., 2014] and the choice of their QoL measure/interview process was influenced by their definition. One study defined well-

TABLE IV. Data Extraction

Study #	First Author, Date (Country)	Age (years)	Sample size (experimental group)	Type of OI (n)	Study design	Control group (y or n)	Intervention	QOL outcome measure	Type of report	Findings	Other measures used
Children and adolescents											
1	Hill et al. [2014] [UK]	7–18, mean age = 12.6	10 children, 10 parents, 5 health care professionals	Mild (3), moderate (4), severe (3)	Qualitative	No	N/A	Interview	Self and proxy-report (parent, health care professionals)	Six main themes were identified; being safe and careful, reduced function, pain, fear, isolation, independence. High agreement between the three groups of interviewees, but discrepancies between parents and children with regard to independence and fear.	N/A
2	Kok et al. [2007] [Netherlands]	3–16, mean age Olpadronate group = 10.0 ± 3.1, placebo group = 10.7 ± 3.9	16 children	Type I (4), Type III (4), Type IV (8)	RCT with 2 year follow-up	Yes, n = 18 Type I (9), Type III (5), Type IV (4)	Oral Olpadronate in a dose of 10 mg/m2/day or placebo for a total period of 2 years	HUI	Proxy-report (parent)	Sub-maximal scores for ambulation and pain attributes at baseline. Within the Olpadronate group there was a significant decrease in pain utility	SPPC
3	Seikaly et al. [2005] [Texas, USA]	3–15, mean = 9.8 ± 1.1	15 children	Type III and Type IV	Prospective double-blind crossover study cross over	Yes	Oral alendronate (dose of 5 or 10 mg/d weight-dependent) for 12 months, then cross-over to placebo for 12 months	Well-being score recalling degree of pain on a 10-point scale	Self and/or proxy-report (parent)	Alendronate had a mean change in well-being score of 3.25 ± 04.1; placebo had a mean change of 0.0625 ± 0.25 (P < 0.001) after 12 months	WeeFIM PEDI Pain-free days per month
4	van Brussel et al. [2008] [Netherlands]	8–19, mean age intervention group = 12.3 ± 3.3, control = 13.2 ± 3.6	16 children	Types I and IV	RCT (9 months follow-up)	Yes, n = 17	12-week graded exercise program or care as usual for 3 months	CHQ	Proxy-report (parent)	QoL for the physical summary score was ~50, similar to healthy population and >50 for the psychosocial summary score, which is higher than normal population. No improvement during training or	Peak oxygen consumption, relative VO2 peak, maximal working capacity, Muscle force, Perceived fatigue, SPPC

(Continued)

TABLE IV. (Continued)

Study #	First Author, Date (Country)	Age (years)	Sample size (experimental group)	Type of OI (n)	Study design	Control group (y or n)	Intervention	QOL outcome measure	Type of report	Findings follow-up	Other measures used
5	Löwing et al. [2007] (Sweden)	4 months–16, median = 7	43 children	Type I (15), Type III (13), Type IV (15)	Prospective observational study with 1 year follow-up	No	Monthly intravenous pamidronate infusions	Well-being score on a scale from 1 to 10	Self and/or proxy-report (parent)	The well-being score increased for all children over the treatment period ($P < 0.001$)	PEDI, Pain, Bone density
6	Fano et al. [2013] (Argentina)	2–18, median = 7.8	65 children	Type I (35), Type III (28), Type IV (2)	Cross-sectional study	No	N/A	Peds-QL Argentinean Spanish version	Self and proxy-report (parent)	Significantly lower scores in physical domain for OI types III and IV compared to OI type I ($P = 0.01$ for self-report and $P = 0.0002$ for parent-report). Parents of children with OI types III reported lower social QoL than parents of children with OI type IV ($P = 0.01$)	None
7	Szczepaniak-Kubat et al. [2012] (Poland)	Not provided	25 parents of children with OI	Type I (7), Type IV (4) Type III (14)	Cross-sectional study	No	N/A	WHOQO L-BREF	Parent self-report	Parents of children with OI assigned the highest score to the psychological domain and the lowest to the physical health domain. The environmental domain received a lower score from parents of children with OI type III than those of children with OI types I and IV ($P = 0.025$)	ISCED PFW FAS
					Adults						
8	Balkefors et al. [2013] (Sweden)	21–71, median = 41	29 adults	Types I and IV	Cross-sectional study	No	N/A	SF-36	Self-report	QoL was lower than Swedish norm data in all domains ($P < 0.01$)	IPAQ DRI Li-Sat Pain Range of motion Muscle function
9	Widmann et al.	Mean = 33.4	30 adults	Conge-nita	Cross-sectional	No	N/A	SF-36	Self-report	Significantly lower	FIM

(Continued)

TABLE IV. (*Continued*)

Study #	First Author, Date (Country)	Age (years)	Sample size (experimental group)	Type of OI (n)	Study design	Control group (y or n)	Intervention	QOL outcome measure	Type of report	Findings	Other measures used
	[2002] (USA)			(n = 18) and tarda (n = 12)	study					scores for the OI group as a whole as well as according to OI group compared to norms in Physical Function, Bodily Pain, and Physical Role. Mental summary scores were higher than norms but not statistically different	
10	Widmann et al. [1999] (NYC; USA)	20–45, mean = 33.3	15 adults	Congenita (n = 7), Tarda (n = 8)	Cross-sectional study	No	N/A	SF-36	Self-report	Increased scoliosis associated with decreased QoL physical score (r = 0.52), decreased VC, FVC, FEV (r between 0.57 and 0.65). Parameters were not associated with mental QoL	VC, RV, TLC, FVC, FEV1

IPAQ, International Physical Activity Questionnaire; DRI, Disability Rating Index; Li-Sat 11, Life Satisfaction; FIM, Functional Independence Measure; SF-36, Short-Form 36 health survey; VC, vital capacity; RV, residual volume; TLC, total lung capacity; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 sec; ISCED, International Standard Classification of Education; PFW, Perceived Family Wealth; FAS, Family Affluence Scale.

TABLE V. Validated Tools Used to Measure Quality of Life in the Included Studies

Tool	# items	Scoring	Domains	Used in
Quality of life tools				
Short Form 36 Health Survey (SF-36)	36	0–100 (better score better quality of life)	1. Physical function 2. Role physical 3. Bodily pain 4. General health 5. Vitality 6. Social functioning 7. Role emotional 8. Mental health	Balkefors et al. [2012] (Sweden); Widmann et al. [2002] (USA); Widmann et al. [1999] (USA)
Life-Satisfaction Questionnaire (Li-Sat)	11	1–6 (not satisfied → completely satisfied)	None	Balkefors et al. [2012] (Sweden)
Pediatric Quality of Life Inventory (PedsQL)	23	1–100 (higher better)	1. Physical aspect 2. Emotional aspect 3. Social aspect 4. Academic aspect	Fano et al. [2013] (Argentina)
Child Health Questionnaire (CHQ)	50	0–100 (higher is better)	1. Physical 2. Psychosocial	Van Brussel et al. [2007] (Netherlands)
Health Utilities Index (HUI)	15	1–6 (normal → severely impaired)	1. Vision 2. Hearing 3. Speech 4. Ambulation 5. Dexterity 6. Emotion 7. Cognition 8. Pain	Kok et al. [2006] (Netherlands)
WHO Quality of Life-Bref (WHOQOL-BREF)	24	1–5 (higher the better assessment of each life domain)	1. Physical health 2. Psychological 3. Environment 4. Social relationship	Szczepaniak-Kubat et al. [2012] (Poland)
Other tools used				
Pediatric Functional Independence Measure (WeeFim)	18	1–7 (dependent to independent)	1. Self-care 2. Mobility 3. Cognition	Seikaly et al. [2005] (USA)
Self-Perception Profile for Children (SPPC)	36	1–4 (worst to best)	1. Scholastic competence 2. Social acceptance 3. Athletic performance 4. Physical appearance 5. Behavioural conduct 6. Global self-worth	Kok et al. [2006] (Netherlands)
Functional Independence Measure (FIM)	18	1–7 (complete dependence to independence)	1. Cognition 2. Mobility 3. Self-care	Widmann et al. [2002] (USA)
Disability Rating Index (DRI)	12	0–100 (0 is no problem, 100 is impossible to perform)	None	Balkefors et al. [2012]

Tool	# items	Scoring	Domains	Used in (Sweden)
TABLE V. (Continued)				
Pediatric Evaluation of Disability Inventory (PEDI)	10–15 items/domain	1–5 (easy to can't do)	1. Mobility 2. Social/cognitive 3. Daily activities	Seikaly et al. [2005] (USA); Löwing et al. [2007] (Sweden)

being [Löwing et al., 2007] and measured this construct using a visual analog scale. Three of the quantitative studies measured QoL as a primary outcome [Seikaly et al., 2005; Kok et al., 2007; Fano et al., 2013] from which two used a validated generic QoL measure including the Pediatric Quality of Life Inventory (PedsQL) [Fano et al., 2013] and the Health Utilities Index (HUI) [Kok et al., 2007]. Although the study by Seikaly et al. [2005] aimed to evaluate the impact of daily pamidronate on QoL (and bone parameters) and used three QoL indicators, the validated measures used were developed to assess mobility (Pediatric Evaluation of Disability Inventory-PEDI) and self-care (WeeFIM system). This study also used the number of pain free days as rated by the parents and/or child, as well as the number of days requiring analgesia as a QoL indicator. QoL was measured as a secondary outcome in two studies. Löwing et al. [2007] evaluated the effect of pamidronate on everyday activities (main outcome) as well as on secondary outcomes consisting of well-being (rated on a visual analog scale), skeletal pain and bone density. van Brussel et al. [2008] main outcome were exercise capacity and muscle force, and also included perceived competence, fatigue and QoL, the latter which they measured using the Child Health Questionnaire (CHQ). No study used a disease-specific measure of QoL. Apart from the one qualitative study [Hill et al., 2014], no study supplemented data collection with interviews as a means to gather QoL data. Table V reports on the validated tools used to measure QoL.

Comparison of QoL scores to general population and between OI types. Few studies compared QoL scores to the healthy population as provided by the measures' normative data [Kok et al., 2007; van Brussel et al., 2008]. Aside for reporting lower scores in the physical domain [Fano et al., 2013], children and adolescents with OI reported QoL scores equivalent to the healthy population [Kok et al., 2007; van Brussel et al., 2008]. The QoL of children with OI was also compared across OI severity groups in two studies [Fano et al., 2013; Löwing et al., 2007] and age in one study [Löwing et al., 2007]. Physical QoL scores on the PedsQL were significantly lower for children with OI types III and IV compared to those with type I, according to self-report ($P = 0.014$) and to parent-report ($P = 0.0002$) [Fano et al., 2013]. Parents of children with more severe OI also reported lower QoL scores on the social domain compared to parents of children with milder OI ($P = 0.01$). Yet, the children reported no difficulty in the emotional, school, and social QoL domains. These QoL results [Fano et al., 2013] are similar to that of Argentinian children with chronic diseases (such as chronic pulmonary disease, renal insufficiency, congenital cardiopathies)

from the same institution [Roizen et al., 2007]. No significant differences were found in the amount of improvement following pamidronate therapy related to the type of OI [Löwing et al., 2007]. Regarding age differences, children younger than seven years showed greater improvement ($P < 0.01$) than those above 7 years on the PEDI [Löwing et al., 2007].

QoL and bisphosponate treatment. The three studies that looked at the effect of bisphosphonates treatment found that QoL scores significantly improved after treatment [Seikaly et al., 2005; Kok et al., 2007; Löwing et al., 2007]. Collectively, these researchers found that bisphosphonate treatment significantly increased children's ability for self-care on the PEDI [Seikaly et al., 2005; Löwing et al., 2007], improved well-being scores on a visual analog scale ($P < 0.001$) [Seikaly et al., 2005; Löwing et al., 2007], and decreased pain as assessed on the HUI ($P < 0.05$) [Kok et al., 2007], and number of days with/without pain ($P < 0.001$) [Seikaly et al., 2005; Löwing et al., 2007]. Löwing et al. [2007] reported that it was common for the children to experience pain daily before treatment, but only four children reported pain daily after treatment. No effect of bisphosphonates was noted on mobility/ambulation in two studies using the HUI and the WeeFIM [Seikaly et al., 2005; Kok et al., 2007]; however Löwing et al. [2007] showed an improvement in the mobility domain of the PEDI after 1 year of intravenous pamidronate ($P < 0.001$). The study by van Brussel et al. [2008] looking at the effect of an exercise training program found that although the CHQ physical and psychosocial summary scores improved by 7.7% and 6.2%, respectively at 3 months post-intervention favoring the intervention (not statistically significant), these gains were not maintained 6 months after the program.

QoL of parents of children with OI. One study looked at the QoL of 25 parents of children with mild OI (types I and IV) and severe OI (type III) using a measure developed by the WHO Quality of Life Group called the WHOQOL-BREF [Szczepaniak-Kubat et al., 2012]. Mean scores in two of the four domains, environment and social relationships, were not significantly different from the values obtained among 11,830 inhabitants of 23 countries (general population). The authors report that parental scores on the psychological domain were slightly higher than that of the general population (15.04 ± 2.13 vs. 15.0 ± 2.8) and lower scores in the physical domain (12.24 ± 1.23 vs. 16.2 ± 2.9). The environment domain (e.g., feeling of safety, accommodation, access to information, opportunity for fulfilling one's interests) was the only domain to vary significantly ($P = 0.025$) among parents of children with mild (mean $= 14.5 \pm 1.73$) versus severe OI (12.57 ± 2.06).

Adults With OI

Recruitment of participants. Three studies using a cross-sectional design assessed the QoL in adults. The number of participants in these studies varied between 15 and 30 with an average of 25 adults with OI and involved a total of 74 adults. One study included adults with types I and IV OI [Balkefors et al., 2013] and the two studies by Widmann et al. [1999, 2002] categorized participants in two main clinical groups based on time of the fracture (congenita or tarda). All three studies utilized the Short Form Health Survey (SF-36), a generic QoL measure, and compared the participants' scores to normative data on the measure. One study compared SF-36 scores according to OI type (congenita vs. tarda) [Widmann et al., 2002]. The study by Balkefors et al. [2013] also evaluated physical activity, pain, and life satisfaction. Other outcomes that were considered in the studies by Widmann et al. included having a scoliosis, kyphosis or chest wall deformity, and pulmonary function indicators (e.g., forced expiratory volume, vital capacity) [Widmann et al., 1999], as well as education and employment) [Widmann et al., 2002]. No study used a disease-specific measure of QoL. The number of assessment points as well as time of measurement of QoL varied.

QoL measurement and comparison with general population. Overall, adults with OI reported significantly lower physical QoL scores using the SF-36 than the general population [Widmann et al., 1999, 2002; Balkefors et al., 2013]. The average Physical Component Summary (PCS) score in the study by Widmann et al. [1999] on 15 American adults with OI was 39 (range, 10–63), lower than the US population mean of 50. As well, adults with OI (n = 30) scored significantly lower than the US adult norm ($P < 0.05$) in three of the four domains measuring physical health (physical function, role physical, bodily pain) [Widmann et al., 2002]. Similarly, 28 adults with mild to moderate OI (types I and IV) scored significantly lower than Swedish norms on all four physical domains of the SF-36 ($P < 0.001$). All three aforementioned studies report no significant difference in the mental domain scores, although social function and role emotional were somewhat higher, but not significantly so, for the OI group compared to the US norms [Widmann et al., 2002]. Balkefors et al. [2013] reports a high life satisfaction as shown with median scores of five to six (6 = total satisfaction) on 10 of the 11 items on the life satisfaction measure (LiSat-11), despite participants having pain, scoliosis, contractures, and functional limitations (e.g., trouble running/walking fast, difficulties lifting heavy objects). In terms of participation levels, two studies found that adults with OI have similar academic achievements or employment rates (75% work full-time) which are no different when compared to the general population, but these rates drop in non-ambulatory individuals [Widmann et al., 2002; Balkefors et al., 2013]. Table V reports on the validated tools used to measure QoL.

Comparison of QoL scores between OI types. Looking at potential QoL differences among severity groups, individuals with congenita type OI (i.e., fractures present before or at birth) had a lower (not statistically significant) physical component summary (mean = 37) than those with tarda type OI (mean = 43), but the mental component summary was similar among both OI groups [Widmann et al., 2002]. Looking at associations between spinal/chest deformity, pulmonary function and QoL, significant correlations between scoliosis and PCS ($P < 0.01$) but not with the presence of kyphosis or chest wall deformity, and between vital capacity and PCS ($P < 0.01$) were found. Balkefors et al. [2013] reported that 25 of the 29 (86%) individuals with types I and IV OI experienced pain on a pain-drawing instrument; however, the frequency and intensity of the pain were not reported.

DISCUSSION

The objective of this mixed-methods systematic review was to describe the QoL of individuals with varying severity of OI across the lifespan and investigate how to promote QoL. Ten studies were included, with only one using a qualitative design. Among children with OI, aside for children and their parents reporting lower scores in the physical sphere of QoL, children and adolescents with OI reported psychosocial QoL equivalent to the healthy population. The use of bisphosphonates in children with OI seems to have a positive effect on their QoL, but the small sample sizes, the use of non-validated measures of QoL and differing reporting types (child vs. parent) warrants continued assessment of QoL in future trials. Better physical QoL was reported by children with milder OI as well as their parents compared to those with severe OI. Similarly to the QoL findings in children, the results in adults with OI show that physical QoL was lower than that of the general population, whereas similar or higher levels of QoL on the mental domain of the SF-36 were reported by the adults with OI. Again, worse QoL was reported by adults with a more severe type of OI; however, the relationship between the classification system used (based on onset of fracture) with clinical severity is unclear. Integrating the findings from the quantitative and qualitative studies in both the children and adult studies indicate that experiencing pain, scoliosis, activity limitations, and participation restrictions seem to negatively affect QoL.

Pain and QoL

It is unclear whether the association between pain and QoL is a direct one, or whether it is mediated by physical function and community participation, that is, pain limits daily activities which in turn negatively influences QoL. Although the evidence recognizes that individuals with OI experience pain [Dwan et al., 2014], the design used in current studies neither addresses pain thoroughly, nor does it provide a good understanding of the type, etiology, and mechanism of the pain experienced. Our mixed-methods systematic review confirms that one must consider pain in the evaluation of children and adults with OI, and further clinical and research efforts must be made in guiding the proper management of pain for these individuals. For example, the treatment for chronic bone pain or for acute fracture-related pain will differ.

Physical Function and QoL

The correlation between vital capacity, scoliosis, and physical QoL [Widmann et al., 1999] as well as the finding that individuals with more severe OI report worse physical QoL (although not significantly so) but similar mental QoL than that of individuals with mild OI [Widmann et al., 2002] indicates that physical function influences physical, but not mental QoL. Engelbert and colleagues

indicate an association between diminished physical function (e.g., limited range of motion, decreased muscle strength) and limited ambulation experienced by children and adults with OI with worse physical QoL [Engelbert et al., 2014]. These findings indicate that physical function plays a role in the physical QoL of individuals with OI and must be managed in a timely fashion.

Physical Fitness and QoL

A research group in the Netherlands [van Brussel et al., 2011] was the first to study the physical fitness in children with mild OI and found that aerobic capacity as well as muscle strength was significantly lower than that of peers without OI [Takken et al., 2004]. Muscle atrophy and deconditioning are the probable causes of the decreased aerobic capacity in individuals with OI, but other factors such as impaired bone development and impaired skeletal, cardiac, and pulmonary muscle tissue, hypoactivity, and fear of fracture may play a role [Takken et al., 2004]. Although two studies [van Brussel et al., 2008; Balkefors et al., 2013] reported that children and adults are able to participate in exercise programs safely, participants in those studies had mild OI and there is currently limited evidence as to the exercise capacity of children and adults with more severe OI types who have limited mobility (e.g., III and IV). Interventions aimed at promoting exercise for individuals with OI following safe guidelines [van Brussel et al., 2011] may be promising for preventing weight gain, maintaining an active and healthy lifestyle in children and youth with OI, and thus may contribute to a good QoL. Future studies should explore the effect of participating in preferred and chosen physical activity on physical and mental QoL using self-report.

Activity, Participation, and QoL

The finding of lowered participation levels in non-ambulatory individuals [Widmann et al., 2002; Balkefors et al., 2013] is corroborated by both quantitative and qualitative studies. Engelbert and colleagues found decreased community participation in individuals with OI [Engelbert et al., 2014]. When interviewed, youth with OI reported experiencing challenges in everyday life and in participating in activities like their healthy peers [Dogba et al., 2013; Hill et al., 2014]. To improve QoL, physical aspects should be taken into account by encouraging age-appropriate, safe, and enjoyable physical activity and exercise, as well as avoiding unnecessary restrictions and overprotection by parents by providing education and support to patients and their families. Emerging evidence suggests that the relatively poor physical QoL of youth with disabilities reflects, at least in part, poor access to opportunities for community participation rather than the health condition per se [Edwards et al., 2003; Jemta et al., 2005]. These findings indicate that the disparities in the QoL of youth with disabilities may be preventable and that promoting accessible and adapted opportunities for meaningful activities and community participation across the lifespan (e.g., leisure, socialization, education, employment, transportation, independent living), may be one factor to consider for optimal QoL.

Suggestions for Management of OI

This systematic review identified pain, scoliosis, physical impairments, activity limitations, and participation restrictions as key factors to consider in the management of OI to optimize QoL. Pain in OI should be better understood to ensure proper management. A recent qualitative study conducted by Dogba et al. [2013] reported that although living with a diagnosis of severe OI can be devastating for parents, most of them eventually redefine life, create a "new normal" life characterized by ups and downs, challenges and change, but also positive experiences. Although the findings of this systematic review indicate that the mental QoL of children and adults with OI and that of caregivers of children with OI is not different to that of the general population, clinicians should monitor the mental health of their patients and offer resources and appropriate support to individuals with OI as well as to their caregivers as needed. Fear of fractures is the most frequently heard explanation for not participating in sports and other physical activities [van Brussel et al., 2011; Dogba et al., 2013], often promoted by parents and physicians in the interests of safety. This protective attitude may result in an unnecessarily hypoactive lifestyle and physical deconditioning [van Brussel et al., 2011]. Psychological interventions and education can improve child mental health and parental stress [Bozkurt et al., 2014] and should be available to provide support and reassurance to children with OI and their parents.

The finding of worse physical QoL in individuals with greater disease severity suggests that environmental barriers and decreased opportunities for meaningful activities and community participation are experienced to a greater degree by those with more severe physical impairments. This is clearly denoted in the only study that considered the effect of the environment on QoL [Szczepaniak-Kubat et al., 2012]. Therefore, another aspect to consider when promoting the QoL of individuals with OI is the influence of the environment on daily life. Hill et al. [2014] reported that children with OI sometimes felt isolated and different. Therefore, if modifications were made to activities, children would have more opportunities to participate and feel less isolated and less fearful if safe activities were made available. Indeed, studies have shown that participating in leisure activities contributes to the mental and physical well-being of children with disabilities [Dahan-Oliel et al., 2012; Shikako-Thomas et al., 2014].

The pathogenesis of OI involves bone fragility predisposing to fractures, which poses unique challenges for community participation. Nevertheless, it is important to encourage children and adults with OI to participate in the community by selecting appropriate activities and offering support, supervision and adaptations as required. Thus modifications to the physical and social environment may promote community participation and optimize QoL. A life-span approach to make services more family centered which extends beyond adolescence is needed to effectively handle the chronicity for OI, as needs and challenges may change from childhood to adolescence and into adulthood.

Limitations of Included Studies and Suggestions for Assessing QoL in OI

This mixed-methods systematic review raised important clinical implications, yet the reviewed papers had some methodological limitations.

First, only a few studies used validated QoL measures and those differed across the pediatric studies thus preventing direct com-

parisons and pooling of the findings for a meta-analysis. Although the SF-36 was used in several adult papers, standard deviations were unreported precluded pooling of results. Some researchers define QoL according to functional ability and health status, but QoL is not necessarily based on an individual's ability to function. Some define QoL as functional ability or a sense of well-being, others report health related QoL, and it is hard to make comparisons between research papers if different definitions are used. Difficulties arise when attempting to measure QoL, if it is not well predefined. The choice of a pediatric QoL measure must consider type of reporting. Only a measure which can be completed by the child and complemented by the parent should be used in OI studies. Although no studies in this review compared child and parent QoL reports, the evidence shows that children with disabilities and their parents have differing QoL appraisals [Eiser and Varni, 2013; McDougall et al., 2013]. Although it may be challenging to obtain a child's QoL assessment in some childhood-onset conditions (e.g., cerebral palsy), this is not the case for children with OI as they typically do not exhibit cognitive or communicative difficulties. Therefore, whenever possible, QoL assessment should include both the perspectives of the child and of the family to inform clinical practice and research. Currently, only generic measures of QoL can be used in individuals with OI as no disease-specific measure currently exists. Using a generic measure could provide a useful account of one's personal view of their QoL despite having a chronic condition as compared to that of individuals with no health condition. On the other hand, a generic measure does not provide information on specific aspects related to OI that may affect QoL (such as pain, fear, social isolation, resilience, and being careful) [Dogba et al., 2013; Hill et al., 2014]. This gap is being addressed by a group of researchers in the UK who are currently developing a disease-specific measure of QoL in OI [Hill et al., 2014].

Second, the sample size of the included studies was small, which is to be expected of single-site studies on rare diseases such as OI. Therefore, evaluating QoL according to age or OI severity may not have been possible or adequately powered, and external validity of the findings may be limited. The two recruitment methods used in the reviewed studies each have their advantages and disadvantages regarding recruitment/selection bias. The hospital/clinic-based studies may have oversampled more severely affected individuals, since they are more likely to seek medical care from a specialized clinic than less severely affected individuals. Similarly, members of support organizations may differ from non-members in such a way that individuals who are having difficulty coping with their condition may be more likely to seek support than individuals who are coping well [Cohen and Biesecker, 2010]. One strategy to limit recruitment bias may be by identifying potential participants directly from the general population to reach a spectrum of affected individuals in a given geographic region. However, our experience at an internationally renowned pediatric OI center indicates that the great majority, if not all our children with OI are followed in a hospital setting, therefore the risk for recruitment bias from a hospital/clinic setting may be very small. On the other hand, adults with OI are not followed with the same rigor once they become 21 years of age. Therefore, supplementing recruitment from support organizations is advisable.

Third, none of the studies used a longitudinal design to evaluate whether QoL changes over time in individuals with OI. As well, it is of definite clinical value to understand which personal (e.g., motivation, coping, spirituality), family (e.g., socio-economic status, parenting style) and environmental factors (e.g., physical barriers, social supports, policy) could influence QoL and potential QoL changes over time.

Fourth, studies varied as to how they categorized individuals of different severity, such that type IV OI was sometimes considered to be a more mild-type and hence coupled with type I, and in other cases was considered moderate and was grouped with the most severe OI type (III), indicating the need to use the classification system consistently between centers. Future studies should be multi-centric to represent a large population of individuals with OI across severities and cultural groups using a longitudinal design to provide a comprehensive understanding of the factors that affect QoL in children, adolescents, and adults with OI using validated QoL measures. This understanding would assist clinicians and health-care professionals identify individuals most at risk for low QoL and tailor interventions aimed at improving the QoL of individuals with OI.

In conclusion, physical QoL in children and adults with OI appears to be less than that of the general population, with individuals with more severe OI types reporting worse physical QoL. On the other hand, mental and psychosocial QoL is the same or better in individuals with OI than that of the general population. Pain, scoliosis, activity limitations, and participation restrictions due to decreased limited function are associated with lower levels of physical QoL, and need to be addressed to promote QoL. Researchers must agree on a definition of QoL (such as the WHO's definition) as it relates to OI and use validated measures appropriate for evaluating QoL in OI, and not be confused with functional measures. Pediatric studies should consider both the child's and the parent's QoL perceptions as these may differ. QoL in the adult population should not be dismissed in order to offer proper client-centered interventions throughout the lifespan.

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