

Physical function is impaired but quality of life preserved in patients with fibrous dysplasia of bone

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Abstract

Fibrous dysplasia of bone (FD) is a congenital, non-heritable skeletal disorder that is associated with multiple skeletal complications, including repeated fractures, limb length discrepancy, and bone pain. The disease-specific impact of FD on quality of life outcomes is unknown. We sought to understand the impact of the scope and extent of the skeletal disease on quality of life in adults and children with FD.

The health-related quality of life was quantified in a population of adults ($n = 56$) and children ($n = 22$) with FD using validated health assessment questionnaires, the Medical Outcomes Study 36 Item Short-Form Health Survey, volume 2 (SF36) (adults) and the Child Health Questionnaire Parent Form 50 (CHQ-PF50) (children). Clinical demographic data and skeletal disease burden scores (SDBS, amount of skeleton involved with FD) were measured, and correlations with health-related quality of life were sought.

The SF36 and CHQ-PF50 revealed lower Physical Function Summary scores in FD patients compared to the U.S. population norms (adult 41 vs. 50, Z score < -5.0 , pediatric 39 vs. 50, Z score < -5.0). However, the SF36 and CHQ-PF50 Mental/Psychological summary scores were not different from those of U.S. population norms (adult 50 vs. 50, Z score = 0, pediatric 48 vs. 50 Z score = -0.9). The score on the Physical Function Domain of both tools was strongly negatively associated with the SDBS (adult Spearman $\rho = -0.43$, $P = 0.009$, pediatric Spearman $\rho = -0.72$, $P = 0.005$). The groups of adult and pediatric patients with SDBS > 30 had decreased Physical Function Domain scores when compared to those with scores < 30 (adult 35 vs. 45, $P = 0.002$, pediatric 57 vs. 78, $P = 0.04$, respectively). One of the largest effects was seen in the parents of children with FD, who had significantly lower Parental Emotional scores than those of the parents of healthy norms (54 vs. 88, Z score < -5.0), suggesting a high degree of emotional morbidity in the parents of children with FD.

Despite measurable functional limitations in adults and children, and significant parental emotional impairment, patients with FD achieve a high level of social and emotional function. These data are important for prognosis and parental reassurance.

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Introduction

Fibrous dysplasia (FD) is a congenital, non-heritable skeletal disorder which affects both sexes equally and is usually diagnosed in childhood [1]. In FD, normal bone and bone marrow are replaced by a fibrous tissue consisting of an expanded population of pre-osteoblastic cells

[2,3]. The etiology is somatic activating mutations in osteoprogenitor cells of the cAMP regulating protein $G_s\alpha$, which is coded for by the *GNAS* gene [4–6].

The extent of the disease can vary greatly. It can affect a single skeletal site (monostotic FD, MFD), multiple sites (polyostotic FD, PFD), or involve essentially the entire skeleton (panostotic FD) [7,8]. FD can be associated with multiple skeletal complications, including fractures, limb length discrepancy, bowing, and bone pain [9]. The degree

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of deformity can be disabling [10]. Pain is a frequent complaint among adults but is not commonly reported by children. The pathogenesis of pain in FD is not known and may require narcotic analgesics [1].

PFD is frequently seen with some combination of café-au-lait skin pigmentation, renal phosphate wasting [11], and/or hyperfunctioning endocrinopathies such as gonadotropin-independent precocious puberty [12], peripheral hyperthyroidism [13], and/or growth hormone excess [1]. When FD presents with these skin or endocrine findings, it is known as McCune–Albright syndrome (MAS) [14–16].

Health-related quality of life (HRQOL) has been defined as the attributes valued by patients. These include their comfort or sense of well-being, their physical, emotional, and intellectual function, and the degree to which they are able to participate in valued activities with the family, in the workplace, and in the community [17]. HRQOL measures have become an expected measure of success in health-related research and clinical trials [18], and are used to estimate disease burden, compare health profiles, calculate treatment effects, and monitor outcomes.

While much is known about the molecular, cellular, and metabolic defects in FD, little has been reported on the important aspect of HRQOL in these patients. A review of the literature on FD and MAS yields no published studies of function and/or quality of life in the FD population, and only a few studies that address it at all [19,20].

This study was initiated in an attempt to quantify the physical and mental health of a relatively large cohort of adults and children with FD. Standardized HRQOL assessment tools, the Medical Outcomes Study 36 Item Short-Form Health Survey, volume 2 (SF36) and the Child Health Questionnaire Parent Form 50 (CHQ-PF50) were used. These results were correlated with the skeletal disease burden score (SDBS) (an objective measure of the extent or “amount” of diseased bone that a patient has) [21], and with endocrine function and renal phosphate wasting.

Patients and methods

Patients

Ninety-two consecutive patients, enrolled in a National Institutes of Health (NIH) Institutional Review Board approved study of FD and MAS, were invited to complete an HRQOL and demographic data questionnaire during their annual hospital admission or via mail between January and June 2003. Written informed consent was obtained from each patient or from a parent of minor participants. The diagnosis of FD was established in all patients based on clinical history, histopathological findings, radiographic findings, and when necessary, an analysis of the *GNAS*

gene for R201C or R201H mutations. Fourteen subjects (17%) did not return their survey.

Seventy-eight subjects participated in the study, 56 adults age 14 or older (72%), and 22 children (28%). The average age was 34.7 years (range 14–86 years) for the adult cohort of 19 males (34%) and 37 females (66%). The average age was 10.1 years (range 6.7–14 years) for the 11 male and 11 female children (Table 1). Non-responders were not significantly different from responders in regard to age, education, or skeletal disease burden score (Tables 1 and 2).

All patients underwent an endocrine and metabolic evaluation to assess gonadal function, phosphorus metabolism, thyroid function, and the GH/IGF-1 axis. In addition to FD, 54% of the adults, and 73% of the children had one or more endocrinopathies (Table 2). All endocrinopathies were being treated at the time of the HRQOL data collection. Prior to data collection, all patients had been evaluated at the NIH Pain Clinic, and, when indicated, analgesic treatment was initiated to maximize pain control.

HRQOL measures

Two different validated, standardized HRQOL questionnaires were utilized: the SF36 (adults) and the CHQ-PF50 (children). Both forms were used through a licensing arrangement with Quality Metric Incorporated (Lincoln, RI). Demographic information was collected from the patients' medical records.

SF36

The SF36 is a generic measure that has proven to be a reliable and valid instrument for measuring HRQOL in individuals who are older than age 14 [22]. It is a short, multi-purpose self-reported health assessment tool composed of 36 questions in eight different domains that examine aspects of physical and mental health (Table 3). Each domain is scored from 0 to 100, with a higher score correlating with better physical function or mental health.

CHQ-PF50

The CHQ-PF50 is a fifty-item proxy report form designed to be completed by parents of children age 5 to 18. The CHQ-PF50 has proven to be a reliable and valid instrument for measuring HRQOL in children [23]. It contains 50 questions measuring 14 domains of physical and emotional health (Table 4). Each domain is scored from 0 to 100, with a higher score indicating better physical function or mental health.

Tool scoring

For the SF36, norm-based methods were used to standardize scores using means, standard deviations, and factor score coefficients for SF36 scales in the general U.S. population [24]. A linear *t* score transformation method was used in this “normalization” process, so that all domain

Table 1
Demographic and social data

	Adult respondents ^a	Adult non-respondents ^a	Child respondents	Child non-respondents
Number of subjects	56	12	22	2
Mean age (range)	33.7 (14–86)	29 (14–72)	10.1 (6–13)	13 (13)
<i>Gender</i>				
Male (%)	34	17	50	100
Female (%)	66	83	50	0
<i>Race</i>				
Caucasian (%)	78	92	86	100
Black (%)	4	8	0	0
Hispanic (%)	11	0	9	0
Asian (%)	5	0	5	0
American Indian (%)	2	0	0	0
<i>Highest education</i>				
Still in school (%)	16	50	100	100
Graduated HS (%)	14	NK	NA	NA
Some college (%)	30	8	NA	NA
Graduated college (%)	22	25	NA	NA
>College (%)	18	17	NA	NA
<i>Employment</i>				
Employed (%)	54	33	NA	NA
Student <18 (%)	14	43	NA	NA
Student >18 (%)	16	8	NA	NA
Disabled (%)	11	8	NA	NA
Not in workforce (%)	5	8		
<i>Marital status</i>				
Married/living with significant other (%)	49	33	NA	NA
Divorced/widowed/single (%)	36	25	NA	NA
Adolescent (14–18) (%)	16	42	NA	NA

^a Respondent and non-respondent refers to whether or not the patient returned the questionnaire, NK = not known, NA = not applicable.

scores have a mean of 50 and a standard deviation of 10 in the 1998 general U.S. population.

Table 2
Clinical data

Parameter	Adults	Children
<i>Endocrinopathies</i>		
Precocious puberty (%)	46	54
Hyperthyroid (%)	20	31
Growth hormone excess (%)	18	14
3 Endocrinopathies (%)	7	<1
2 Endocrinopathies (%)	18	18
1 Endocrinopathies (%)	29	50
Renal phosphate wasting (%)	50	14
FD only — no Endocrinopathies (%)	46	27
<i>Ambulatory status</i>		
Walks independently (%)	70	82
Uses cane or crutches (%)	16	9
Uses wheelchair (%)	14	9
Skeletal disease burden score ^a (mean and range)	31 (<1–75)	24 (4–45)

^a Possible scores: 0 (no FD)–75 (100% of the skeleton involved).

Summary scores

For each tool, two summary scores were derived from the domain scores. In the SF36 population, the Physical Component Summary, and the Mental Component Summary are the summary scores determined from the eight domain scores. In the CHQ-PF50, the Physical and Psychological Summary scores are the summary scores based on the fourteen domains of the tool. All summary scores are constructed on the basis of factor analyses of correlations among the various domains in the study population and in the general U.S. population [23,24]. All summary scores have a mean of 50 and a standard deviation of 10 [23,24]. Scores were tabulated using the scoring algorithms provided with the scoring manual and interpretation guide [23,24]. Scores were compared with U.S. population norms from the same sources [23,24,25].

Skeletal disease burden score (SDBS)

The extent of skeletal disease was quantified using a validated tool developed by the authors [21]. It is based on calculations and assessments derived from a 99Tc-MDP bone scan [21]. The SDBS has been shown to correlate with both laboratory markers of bone turnover

Table 3
Medical outcomes study 36 -item short-form health survey, volume 2 (SF36) domains (adult)

Domains	Meaning of scores	
	Low score	High score
Physical function	Significantly limited in performing all physical activities including bathing or dressing due to health	No physical limitations due to health
Role-physical	Problems with work or other daily activities as a result of physical health	No problems due to physical health
Bodily pain	Severe and limiting pain	No pain or limitations
General health	Evaluates personal health as poor and believes it is likely to get worse	Evaluates personal health as excellent
Vitality	Feels tired and worn out all of the time	Feels full of pep and energy all of the time
Social functioning	Extreme and frequent interference with normal social activities due to physical or emotional problems	Performs normal social activities without interference due to physical or emotional problems
Role-emotional	Problems with work or other daily activities as a result of emotional problems	No problems due to emotional problems
Mental health	Feelings of nervousness and depression all of the time	Feels peaceful, happy and calm all of the time

Source: adapted from Ref. [24].

and with ambulatory status [21]. The range of possible scores on the skeletal disease burden assessment is from 0 (no disease) to 75 (the entire skeleton involved). The mean SDBS was 31 for adults [range: <1 (MFD)–75 (panostotic FD)]. The mean SDBS in children was 24 (range: 4–45; Table 2).

Ambulatory status

Ambulatory status was self-reported by the subjects and confirmed by a review of their medical record. Subjects were categorized as those who walked independently, those who walked with the assistance of a cane or crutch, or those who use a wheelchair (Table 2).

Statistical analysis

Data are presented as means unless otherwise specified. Non-parametric analyses were used throughout. Differences between the sample means and U.S. population means are expressed as Z scores. A Mann–Whitney test was used to compare the means of the SF36 Physical Function domain

scores for groups of subjects with skeletal burden scores of less than and greater than 30. Spearman correlation coefficients were calculated to measure association. Spearman rho and P values of <0.05 were considered to indicate statistical significance. All the analyses were performed

Table 4
Child health questionnaire-parent form 50 (CHQ-PF50) domains

Concepts	Meaning of scores	
	Low score	High score
Physical function	Significantly limited in performing all physical activities including self care due to health	No physical limitations due to health
Role-physical	Problems with school work or other daily activities as a result of physical health	No problems due to physical health
General health	Evaluates personal health as poor and believes it is likely to get worse	Evaluates personal health as excellent
Bodily pain	Severe and limiting pain	No pain or limitations
Role-emotional–behavioral	Problems with school work or other daily activities as a result of emotional or behavioral problems	No problems due to emotional or behavioral problems
Parental time	Parent experiences a lot of limitations in time due to child's physical or psychological health	No limitations on parental time due to child's physical or psychological health
Parental emotional	Parent experiences a great deal of emotional worry or concern as a result of child's physical or psychological health	No feelings of parental emotional worry or concern as a result of child's physical or psychological health
Self-esteem	Child is very dissatisfied with abilities, looks, family/peer relationships and life overall	Child is very satisfied with abilities, looks, family/peer relationships and life overall
Mental health	Feelings of nervousness and depression all of the time	Feels peaceful, happy and calm all of the time
Behavior	Exhibits aggressive, immature, delinquent behavior	Never exhibits aggressive, immature, delinquent behavior

Source: adapted from Ref. [23].

with SAS statistical software (version 6.12, SAS Institute, Cary, NC).

Results

SF36 and CHQ-PF50 domain scores

The adult FD population was different from the U.S. population in: Physical Function (40 vs. 50, Z score < -5.0), Role-Physical (43 vs. 50, Z score $= -4.7$), Bodily Pain (43 vs. 50, Z score < -5.0), and General Health (44 vs. 50, Z score $= -3.4$). However, this population was not different from the U.S. population in the domains of Vitality, Social Function, Role-Emotional, and Mental Health (Fig. 1A).

The pediatric population scored lower than the general U.S. population in the domains of Physical Function (72 vs. 96, Z score $= -3.8$), General Health (55 vs. 73, Z score $= -4.4$), Bodily Pain (64 vs. 82, Z score $= -3.8$), and Parental Emotional (54 vs. 88, Z score < -5.0). The FD population average scores were not different in the domains of Role-Physical, Role-Emotional, Parental Time, Self-Esteem, and Behavior, and Mental Health (Fig. 1B).

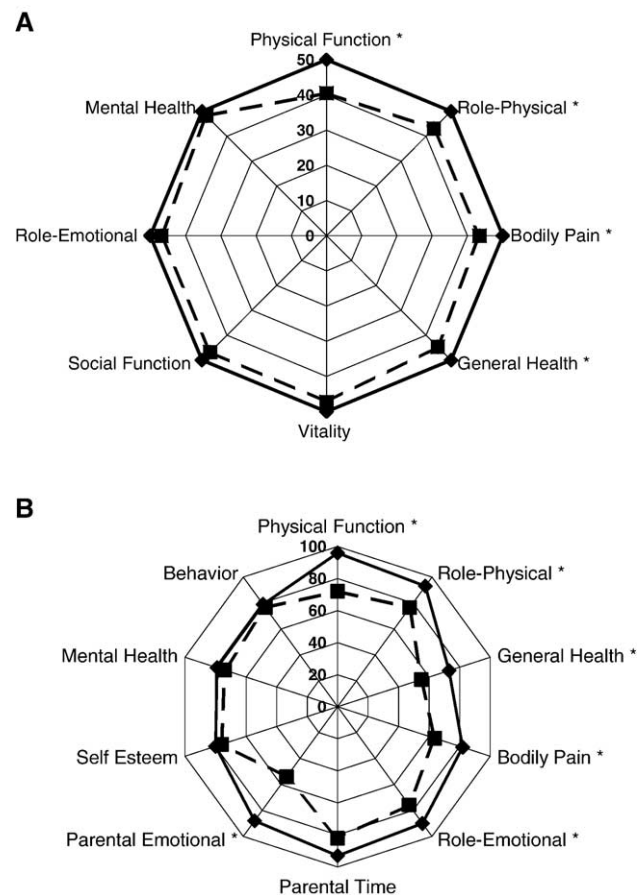


Fig. 1. Individual domain scores of the SF36 (adults) (A) and CHQ-PF50 (children) (B). The FD population is represented by squares, and the national norms by diamonds. Significant differences (Z score < -2.5) are designated by *.

Function scores and skeletal disease burden

The Physical Function domain score of both the adult and pediatric FD population inversely correlated with the SDBS (adult, Spearman rho $= -0.43$, $P = 0.009$; pediatric, Spearman rho $= -0.72$, $P = 0.0005$). Since an SDBS of >30 has been shown to predict functional impairment in patients with FD [21], the mean Physical Function Domain score was analyzed in the groups of adults and children who had an SDBS of <30 and >30 . The Physical Function Domain scores for the 2 groups of adults and children with SDBS less than and greater than 30 were significantly different (adult, 45 vs. 35, $P = 0.002$; children, 78 vs. 57, $P = 0.04$), demonstrating that subjects with more bone disease have decreased physical function.

Summary scores

When the summary scores were calculated, both the adult and pediatric FD population scored lower than the U.S. general population in the Physical Component (SF36) Score/Physical Summary (CHQ-PF50) (adult 41 vs. 50, $Z < -5.0$; pediatric 39 vs. 50, $Z < -5.0$). In contrast, there was no significant difference in the Mental Component Score (SF36)/Psychological Summary (CHQ-PF50) (adult, 50 vs. 50, Z score $= 0$; pediatric, 48 vs. 50, Z score $= -0.9$) (Table 5).

As a point of reference, the SF36 and CHQ-PF50 average Physical Component Score/Physical and Mental Component Score/Psychological Summary scores of the FD population were compared to those of populations of patients with relatively comparable diseases. The SF36 scores were compared to individuals with osteoarthritis (OA, $n = 1006$), rheumatoid arthritis (RA, $n = 510$), and cancer ($n = 253$), and the CHQ-PF50 scores were compared to children with asthma ($n = 178$) and juvenile rheumatoid arthritis (JRA, $n = 74$) [23,25]. The degree of physical impairment was similar, and all of the medical condition groups, as well as the FD population, scored lower than the general U.S. population in the Physical Component Score/Physical Summary scores (Table 5). The average Mental Component Score/Psychological Summary scores of the FD population were not different from the Mental Component Score/Psychological Summary scores of the populations of RA (adults) or childhood asthma. However, they were different from Mental Component Score/Psychological Summary scores of the OA (41 vs. 47.9, Z score $= -5.0$) and cancer (41 vs. 47.7, Z score $= -4.4$) populations (adults) and that of the JRA (48 vs. 53.4, Z score $= 3.1$) population (pediatric).

Correlations

Average Physical Component Score/Physical and Mental Component Score/Psychological Summary scores were analyzed separately for groups of adults and children with precocious puberty, hyperthyroidism, growth hormone

Table 5
HRQOL summary scores for U.S. norms, NIH FD, and disease populations

Summary scores	NIH FD	U.S. norms	OA	RA	Cancer	Childhood asthma	JRA
SF36 physical component	41 (<−5.0)*	50	39 (<−5.0)*	40 (<−5.0)*	41 (<−5.0)*		
SF36 mental component	50 (0)	50	48 (<−5.0)*	48 (−4.4)	48 (−4.0)*		
CHQ-PF50 physical	39 (<−5.0)*	50				48 (<−5.0)*	42 (−4.0)*
CHQ-PF50 psychological summary	48 (−0.9)	50				51 (1.9)	53 (3.0)*

OA = osteoarthritis, RA = rheumatoid arthritis, JRA = juvenile rheumatoid arthritis.

() = Z score.

* Different from U.S. norms (Z score greater/less than 2.5, −2.5).

excess, and renal phosphate wasting. In the adult population, the diagnosis of precocious puberty ($n = 27$) correlated with a lower Physical Component Score ($P = 0.031$), as well as with a higher SDBS ($P = 0.035$). Age also inversely correlated with the Physical Component Score (Spearman $\rho = -0.36$, $P = 0.0062$). The Physical Function Domain score inversely correlated with the SDBS in adults (Spearman $\rho = -0.43186$, $P = 0.0009$), indicating that patients with more bone disease had lower Physical Function scores. In the pediatric population, hyperthyroid children had significantly lower physical summary scores ($P = 0.0018$), as well as a higher mean SDBS ($P = 0.0381$). There was no correlation between the FD population mean Physical Component Score/Physical and Mental Component Score/Psychological Summary scores and any other endocrinopathy, ambulatory status, or gender.

Discussion

This study demonstrates that adults and children with FD have lower HRQOL Physical Component Score/Physical Summary scores than members of the U.S. general population, confirming that FD is a physically disabling condition. The fact that the physical function domain scores inversely correlate with the skeletal disease burden scores in both children and adults demonstrates that individuals with more bone disease have more physical limitations. The data also suggest that a skeletal disease burden score of >30 (approximately 40% of the skeleton involved) predicts functional impairment. Depending on the extent of FD involvement, a patient can expect to have some degree of functional limitation. Yet, these data suggest that the level of functional limitation in the FD population will be comparable to that of patients with similar chronic diseases.

This study also demonstrates that adults and children with FD have HRQOL Mental Component Score/Psychological Summary scores equal to those of the general U.S. population. The data suggest that the FD study population are well adjusted to their condition, and are coping with their physical limitations. The data show that in FD patients, the mental/psychological findings are comparable to that of patients with similar chronic diseases such as RA in adults and asthma in children. This supports the concept that it is possible to mentally adjust to a chronic physical condition like FD and to maintain good emotional, social, and

behavioral mental health. The high level of education and employment in our adult population shows that functional limitation need not prevent a FD patient from living independently and working in his/her community.

The CHQ-PF50 Parental Emotional domain score is of particular interest. The lower score, compared to that of the general U.S. population, reflects the fact that parents of FD children (like the parents of children with asthma and JRA) experience a great deal of emotional worry and concern as a result of their child's disease. The parental concern may be due to the fact that FD can be associated with the need for multiple surgeries, physical dysmorphism, and in some cases, precocious puberty. Any of these factors is likely to increase the emotional burden of parents. Knowledge that patients with FD (both children and adults) have normal emotional and social function may supply some measure of reassurance and comfort to the parents, and may help to alleviate parental worry. FD is a chronic disease that will affect the individual across the life span, but the implications are that psychological adjustment is possible, so that individuals can lead satisfying, fulfilling lives.

Several possible explanations exist for the correlations between precocious puberty and HRQOL Physical Component Score and SDBS in our adult population, and hyperthyroidism and the HRQOL Physical Summary Scores and SDBS in children. It is possible that the higher SDBS is actually the predictor of decreased physical HRQOL scores, and that a history of precocious puberty in adults and hyperthyroidism in children is a surrogate marker for an increased bone disease burden.

These results must be interpreted in the light of possible referral bias. As a tertiary referral center, we are likely to have seen patients with more severe disease, thus resulting in a greater degree of disability in this population than would be found in a general population of patients with FD. If this is the case, then use of the SDBS tool [21] to assess an individual patient's degree of skeletal involvement would allow practitioners to compare their patients to those in this study population. Also, greater than 80% of the patients in this study were self-referred via the Internet. This may reflect a higher level of education in this study population.

HRQOL is a critical outcome measure. Patients' perception of their condition needs to be taken into account when planning care and interventions for individuals with FD. Clinicians and families can use these data to set expectations for children with FD and to measure patient outcomes.

Despite significant measurable functional limitations, both adults and children with FD demonstrated high social achievement and mental adjustment. The presence of FD in a child had a marked emotional impact on the parents. This information is important to patients and parents for prognosis, and may provide a measure of relief to the high degree of emotional discomfort parents suffer.

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