The natural course of pain in Fibrous dysplasia/McCune Albright syndrome: a prospective follow up study

Bulaicon, O.O.; Hagelstein-Rotman, M.; Meier, M.E.; Geest, I. van der; Haalen, F.M. van; Hogewoning-Rewijk, J.; ... ; Appelman-Dijkstra, N.M.

Calcified Tissue International (2025) 116:140
https://doi.org/10.1007/s00223-025-01452-z

ORIGINAL RESEARCH

The Natural Course of Pain in Fibrous Dysplasia/McCune Albright Syndrome: A Prospective Follow Up Study

O. O. Bulaicon[1,2] · M. Hagelstein-Rotman[1] · M. E. Meier[6] · I. van der Geest[3] · F. M. van Haalen[1,2] · J. Hogewoning-Rewijk[1] · S. W. van der Meeren[4] · S. E. C. Pichardo[1,5,6] · A. C. van de Ven[7] · P. B. de Witte[8] · Natasha M. Appelman-Dijkstra[1,2]

Received: 21 August 2025 / Accepted: 30 October 2025 / Published online: 1 December 2025

Abstract

Fibrous dysplasia/McCune–Albright (FD/MAS) syndrome is a rare bone disorder with a broad clinical manifestation. Pain is the most frequently reported complaint and can significantly impair quality of life. While most existing data are cross-sectional, little is known about symptom progression over time. This study aimed to assess changes in pain and QoL over 2 years follow-up. Patients in the PROFID study completed yearly questionnaires aligned with check-ups or independently if check-ups were less frequent. At baseline, 143 (85.6%) reported pain, of which 38 (26.6%) mild, 105 (73.4%) moderate/severe pain, and 24 (14.4%) had no pain. Emotional wellbeing and energy/fatigue were the most affected in the SF-36 domains. Patients viewed their disease as chronic, with moderate daily fluctuation and impact showed that active and palliative coping were the most frequently used coping mechanism. After 2 years, 27.4% of those with no or mild pain at baseline reported a significant increase in pain (1.3–5.0, $p<0.001$), while scores in the moderate/severe group remained stable (6.6–6.3, $p=0.5$). Emotional wellbeing improved significantly (37.6–55.5, $p<0.001$). Patients with moderate/severe pain reported increased disease control, whereas those with no/mild pain felt less control ($p=0.01$). Higher pain scores correlated with poorer physical ($r=-0.627$), social ($r=-0.541$), and general health ($r=-0.452$), worse illness perceptions (e.g., illness identity $r=0.3$), and greater palliative coping ($r=0.4$), all $p<0.05$. These findings emphasize the need to address both physical and psychological aspects of FD/MAS.

Keywords Fibrous dysplasia · McCune Albright syndrome · Pain · Rare bone disease · Quality of life

✉ Natasha M. Appelman-Dijkstra
N.M.Appelman-Dijkstra@lumc.nl

1 Center for Bone Quality, Leiden University Medical Center, Leiden, The Netherlands

2 Division Endocrinology, Department of Internal Medicine, Leiden University Medical Center, Leiden, The Netherlands

3 Department of Orthopaedic Surgery, Radboud University Medical Center, Nijmegen, The Netherlands

4 Department of Ophthalmology, Leiden University Medical Center, Leiden, The Netherlands

5 Department of Oral and Maxillofacial Surgery, University Medical Center Groningen, Groningen, The Netherlands

6 Department of Oral and Maxillofacial Surgery, Leiden University Medical Center, Leiden, The Netherlands

7 Department of Endocrinology, Radboud University Medical Center, Nijmegen, The Netherlands

8 Department of Orthopaedic Surgery, Leiden University Medical Center, Leiden, The Netherlands

Introduction

Fibrous dysplasia/McCune Albright syndrome (FD/MAS) is a rare disease caused by a postzygotic GNAS gene mutation, leading to fibro-osseous lesions (FD) in bones, which can be singular—monostotic fibrous dysplasia (MFD), or multiple—polyostotic fibrous dysplasia (PFD). FD may occur in the entire skeleton or can be confined to specific areas, such as the skull, as seen in Craniofacial Fibrous Dysplasia (CFD). Furthermore, extra-skeletal features may be present, like hyperfunctioning endocrinopathies or myxomas [1].

Pain is present in approximately 50% of patients [2, 3], with adults generally more affected than children, although children may express or report pain differently from adults [4, 5]. Pain is one of the factors leading to an impaired quality of life (QoL) [6], and is experienced regardless of the number of lesions or disease subtype [4, 6, 7]. Moreover,

pain is not the only symptom, as patients also experience lower energy levels for example [6]. Furthermore, patients may experience symptoms related to FD deformity or due to associated hyperfunctioning endocrinopathies.

QoL and disease severity are associated with illness perception, influencing how patients experience daily life and attribute symptoms to their condition [8]. Additionally, patients adopt various coping strategies, with passive coping being in general the most commonly used [9].

The majority of studies on pain and QoL in FD/MAS have been conducted in a cross sectional design without long-term follow up. Previously, we demonstrated that patients treated in a multidisciplinary care pathway reported improved QoL after 1 year [10]. Additionally, research in a French tertiary care center has shown that care in a reference center impacts the management of patients with FD/MAS [11]. Therefore, patient care in expertise centers may play a role in management, symptoms and consequently on how patients experience QoL. The relationship between improvements in QoL and improvements in pain is currently unknown. Also, if this improvement is sustained when transitioned to chronic care remains to be seen, since no studies have been published on the natural course of pain in FD/MAS and its effect on QoL in time. Therefore, we aimed to evaluate the course of pain scores in patients with FD/MAS over time including QoL, patients illness perception, and adaptive coping mechanisms.

Methods

Study Population

The study was carried out amongst participants of the PROspective Fibrous Dysplasia (PROFID) study between July 31, 2018 and August 2023. The PROFID study is a prospective observational cohort study of patients diagnosed with FD/MAS in the Netherlands [10]. Patients included in the PROFID study, regardless of their previous treatment status (previous surgery, previous bone related treatment, no previous treatment), were asked to fill in a set of questionnaires at baseline and yearly thereafter, simultaneously with their annual check-up, while those who required longer periods between check-ups were also asked to complete the questionnaires yearly. Baseline was defined as the moment of completion of the first questionnaire, which was within 1 year after intake at the outpatient clinic after first referral, or during a regular check-up for chronic patients (already under care before the start of PROFID study). First year results on pain and QoL in a multidisciplinary tertiary center were published previously [10]. Current study further explores the course of pain after 2 years and also investigates the influence of pain on patients QoL, illness perception, and adaptive coping mechanisms.

For the current study, all patients of the PROFID study who completed the Brief Pain Inventory (BPI, see below) questionnaire at baseline and during follow-up were included.

Data on age, sex, diagnosis (number of FD lesions, FD location and association with endocrinopathies), age at diagnosis, disease duration, new or chronic status and medical treatment history (usually indicated when pain scores > 4) were collected. Based on the medical records, patients were classified as having monostotic fibrous dysplasia (MFD), polyostotic fibrous dysplasia (PFD), McCune–Albright syndrome (MAS) or Isolated Craniofacial Fibrous dysplasia (ICFD).

Questionnaires

Patients completed the Brief Pain Inventory (BPI) to evaluate pain status [12], while Short Form 36 (SF-36) [13] and EuroQoL-5D-3L (EQ-5D) [14] were used to assess QoL. The revised Illness Perception Questionnaire (IPQ-R) was used to evaluate cognitive and emotional representations of the illness [15, 16], while the Utrecht Coping List (UCL) was used to evaluate patients coping mechanisms [17]. All of these questionnaires have been previously used in studies of our group [3, 6, 8–10, 18]. Since some domains overlap across questionnaires, not all domains from each questionnaire were analyzed, as specified below.

Brief Pain Inventory (BPI) is a validated questionnaire used for pain assessment in the last 24 h [12]. It assesses the pain status on a scale from 0 to 10, higher scores indicating more severe pain. It measures maximal, minimal, and average pain scores, as well as the influence of pain on different domains of daily life, such as General activity, Walking ability, Mood, Normal work, Relations with other people, Sleep, and Life enjoyment.

SF-36 assesses QoL over the last 4 weeks in different domains such as Physical functioning, Role Limitations due to physical health, Role Limitations due to emotional problems, Energy/fatigue, and Emotional wellbeing. Every domain is scored from 0 to 100, higher scores reflecting better quality of life and a mean score of 50 has been chosen as a normative value [13].

EQ5-5D-3L represents a standard measure of health status, comprising the following domains: Mobility, Self-care, Usual activities, Pain/discomfort, and Anxiety/depression. Each dimension has 3 levels: No problems, Some problems, and Extreme problems. Summary score (EQ5 Index value) and health state score (EQ5 health state) were calculated, with final scores ranging from 0 to 1, higher scores representing better health status [14].

Revised Illness Perception Questionnaire (IPQ-R) comprises three distinct sections, focusing on Illness identity,

Illness perception, and Causal attributions [6, 18]. Currently, no cut-off values exist. To present the results, we categorized the scores as follows: high scores are above 75%, moderate scores 25–75%, and low scores<25%. Hence, with maximal score 35, high scores are >26.3, moderate scores 8.8–26.3, and low scores<8.8. For a maximal score of 30, high scores are >22.5, moderate scores 7.5–22.5, and low scores<7.5. For a maximal score of 25, high scores are >18.75, moderate scores 6.25–18.75, and low scores<6.25. Lastly, for a maximal score of 20, high scores are >15, moderate scores 5–15, and low scores<5.

The first section, Illness Identity, contains 14 commonly encountered symptoms and 13 symptoms specifically associated with the studied disease, in this case Fibrous dysplasia. Respondents are prompted to indicate whether they experience any of these 27 symptoms and to express their belief in the connection between these symptoms and their disease. The score on the identity subscale reflects the extent to which patients associate the common symptoms they experience with their specific disease. The illness identity subscale is derived by summing the items that respondents have rated affirmatively as part of their disease (score between 0 and 17).

The second section, Illness Perception, consists of 38 statements addressing views on the studied illness. Participants rate these statements on a scale of five points, ranging from "strongly disagree" to "strongly agree." The statements are organized into seven subscales: (1) Timeline Acute/Chronic assessing how patients perceive the duration of their illness (max score between 0 and 30); (2) Timeline Cyclical, to distinguish between fluctuations in daily symptoms and symptoms that persist consistently over time (score between 0 and 20); (3) Consequences, exploring the impact and consequences of the illness on the daily lives of patients (score between 0 and 30); (4) Emotional Representations, quantifying emotional response (such as anxiety, anger, depression) of patients to their condition (score between 0 and 30); (5) Personal control, reflecting perceived control over the illness (score between 0 and 30); (6) Treatment control, assessing whether patients believe their illness is manageable with the current treatment (score between 0 and 25); (7) Illness coherence, assessing patients' personal understanding of their disease (score between 0 and 25).

The third section, causal mechanism, consists of 18 statements addressing mechanisms that patients might attribute to the cause of their illness. Participants rate these statements on a scale of five points, ranging from "strongly disagree" to "strongly agree" [15, 16]. Based on previous analyses, "psychosocial attributions" (6 questions-scores 0–30) and "environmental factors" (7 questions, scores between 0 and 35) were selected for further analysis, as they seem most relevant for patients with FD/MAS [8, 18].

Utrecht Coping List (UCL) assesses which coping strategies are used by patients in dealing with their disease. It consists of 47 statements covering seven domains (Active coping, Palliative coping, Avoidant coping, Seeking social support, Passive coping, Expressing emotions, Fostering reassuring thoughts), with statements in each domain scored on a four-point scale ranging from 1 (seldom or never) to 4 (very often) [9, 17].

Active coping (seven items, scores ranging from 7 to 28) evaluates an individual's capacity to recognize diverse perspectives when addressing a problem and approach it with confidence for resolution. Palliative coping (eight items, score range of 8–32) involves escaping dealing directly with a problem by engaging in alternative activities. Avoidant coping (eight items, ranging from 8 to 32) implies evading the problem and minimizing attention to the issue. Seeking social support (six items, range of 6–24) gauges a person's inclination to seek help, comfort, and understanding from family and/or friends. Passive coping (seven items, ranging from 7 to 28) explores an individual's negative attitude toward a problem. Expressing Emotions (three items, range of 3–12) assesses the tendency to openly display emotions, while Fostering Reassuring Thoughts (five items, ranging from 5 to 20) evaluates the inclination to maintain a positive attitude toward the problem [9, 17].

Statistical Analysis

Statistical analysis was performed using SPSS for Windows, Version 29.0 (SPSS, Inc., Chicago, IL, USA). The results are shown as percentages for categorical data, and as a means (±SD) or medians (intermediate range) for continuous data. To assess whether the data were normally distributed, visual inspections using histograms and Q–Q plots were conducted. In addition, the Shapiro–Wilk test was performed to statistically evaluate normality.

BPI, SF-36, EQ-5D, IPQ-R and UCL scores were assessed at baseline. Disease severity was measured according to BPI maximal pain value at baseline. As such, patients were stratified in two groups: patients with no pain/mild pain (BPI maximal pain score≤3) and patients with moderate/severe pain (BPI maximal pain score≥4 and≤10). Comparison between different groups at baseline (patients with pain score≤3 vs. patients with pain score≥4) were assessed using independent t-tests in case of normally distributed data and Man–Whitney tests in case of non-normally distributed data, while the comparison between FD subtypes was assessed using one-way ANOVA in case of normally distributed data or Kruskal Wallis test for non-normally distributed data. Correlation between different factors, such as pain with illness perception and coping mechanisms, was assessed using the Pearson's correlation coefficient or the Spearman's rank correlation coefficient, with a significance level set at $p<0.01$ to correct for multiple testing.

To assess the evolution in time (after 1 year and after 2 years), only patients who had completed the mandatory brief pain inventory (BPI) at baseline were included. The relationship of pain with factors like sex, treatment during follow-up and type of FD/MAS were included in a linear mixed model analysis, taking into account repeated measures within subjects, and including Bonferroni correction.

Results

The PROFID cohort consisted of 281 patients, of whom 167 completed the BPI questionnaire at baseline. Further analyses involve only the above mentioned 167 patients. 108 (64.7%) were females. Median age at baseline was 43 (28–55) years. Most patients had PFD 58 (34.7%), followed by MFD 42 (25.1%), Isolated CFD 41 (24.6%) and MAS 26 (15.6%).

Table 1 Patients characteristics at baseline (all patients)

Characteristics	All patients (n = 167)
Sex, female, n (%)	108 (64.7%)
Age at baseline-years, median (Q1–Q3)	43 (28–55)
Type of FD, n (%)	
MFD (non CFD)	42 (25.1%)
PFD	58 (34.7%)
MAS	26 (15.6%)
Isolated CFD	41 (24.6%)
Previous medical treatment n (%)	
No previous bone related treatment (naïve)	73 (43.7%)
Previously treated (BP iv/Denosumab)	94 (56.3%)
Previous surgery n (%)	7 (11.6%)
Antiresorptive treatment at baseline n (%)	
No treatment	100 (59.9%)
Antiresorptive treatment	67 (40.1%)
Treatment during follow-up n (%)	
No treatment	101 (60.8%)
Antiresorptive treatment	65 (39.2%)
Pain medication (analgesics) at baseline	
No pain medication, n (%)	103 (70.1%)
Pain medication, n (%)	44 (29.9%)
Number pain medication, median (Q1–Q3)	0 (0–1)
Opioids	5 (3%)
Pain medication (analgesics) at 1 year	
No pain medication, n (%)	63 (67.7%)
Pain medication, n (%)	30 (32.3%)
Number pain medication, median (Q1-Q3)	0 (0–1)
Pain medication (analgesics) at 2 years	
No pain medication, n (%)	19 (70.4%)
Pain medication, n (%)	8 (29.6%)
Number of pain medication (analgesics), median (Q1–Q3)	0 (0–1)

Of the 167 patients at baseline, 117 (70.1%) completed the questionnaires at 1 year, and 59 (35.3%) completed them at 2 years.

94 (56.3%) were previously treated with bone related medication (bisphosphonates, denosumab or both). During the follow-up period, while 65 (39.2%) patients received bone related medication. As treatment initiation varied across the follow-up period, patients were categorized as either treated or non-treated (Tables 1 and 2).

Baseline Assessment

BPI

143 patients (85.6%) reported pain at baseline (BPI maximal pain score ≥ 1), of which 38 patients (26.6%) reported mild pain (BPI maximal pain score ≥ 1 and ≤ 3) and 105 patients (73.4%) reported moderate/severe pain (BPI maximal pain score ≥ 4 and ≤ 10). 24 (14.4%) patients had no pain at baseline. When analyzed within each FD type, the proportions of patients reporting moderate to severe pain were similar: MFD 64.3%, PFD 63.8%, MAS 69.2%, and isolated CFD 56.1%.

Patients reported a BPI maximal pain median of 5 (IQR 2–7). In the whole group, the influence of pain on different domains of daily life was similarly low, with a median value of 2 (IQR 0–6).

SF36

Most impacted domains, with scores under 50, were Emotional wellbeing with a median of 36 (IQR 16–60) and Energy/fatigue 45 (IQR 30–60). Patients with Isolated CFD reported higher scores on SF-36 Physical function compared to MAS patients, 90 (IQR 72.5–100) versus 67.5 (IQR 38.8–80.01), $p < 0.001$. Males reported higher scores on the Social functioning domain compared to females, 87 (IQR 62.5–100) versus 62.5 (IQR 50.04–100), $p = 0.01$. Previously treated patients reported better scores in role limitations due to physical health, Energy/fatigue and Emotional wellbeing, but lower scores in physical functioning ($p < 0.001$) domains. Patients with moderate/severe pain had lower scores in Physical Functioning, Social Functioning, and General Health, but higher scores in Role Limitations (physical and emotional) (Fig. 1).

EQ5

Patients reported a EQ5 Index value with a median of 0.7 (IQR 0.6–0.8) and a EQ5 health state score of 0.8 (0.6–0.9).

Table 2 Patients characteristics at baseline (details subgroups)

	Pain score at baseline ≤ 3 (no pain/mild pain) N = 62 (37.12%)	Pain score at baseline ≥ 4 (moderate/severe pain) N = 105 (62.87%)
Sex, female, n (%)	35 (56.5%)	73 (69.5%)
Age years, median(Q1-Q3)	44.5 (27–56)	42 (28–55)
Type of FD, n (%)		
MFD (non CFD)	15 (24.2%)	27 (25.7%),
PFD	21 (33.9%)	37 (35.2%)
MAS	8 (12.9%)	18 (17.1%)
Isolated CFD	18 (29%)	23 (21.9%)
Previous medical treatment n (%)		
No previous treatment (naïve)	31 (50%)	42 (40%)
Previously treated (BP iv/Denosumab)	31 (50%)	63 (60%)
Previous Surgery n (%)	2 (3.2%)	5 (4.7%)
Antiresorptive treatment baseline n (%)		
No treatment	44 (71%)	56 (53.3%)
Antiresorptive treatment	18 (29%)	49 (47.7%)
Treatment during follow-up n (%)		
No treatment	42 (68.9%)	59 (56.2%)
Antiresorptive treatment	19 (31.1%)	46 (43.8%)
Pain medication (analgesics) at baseline		
No pain medication n (%)	22 (100%)	81 (64.8%)
Pain medication, n (%)	0	44 (35.2%)
Nr of pain medication, median (Q1–Q3)	0 (0–0) n = 22	0 (0–1) n = 125
Pain medication (analgesics) at 1 year		
No pain medication n (%)	11 (100%)	52 (63.4%)
Pain medication, n (%)	0	30 (36.6%)
Nr of pain medication, median (Q1–Q3)	0 (0–0) n = 11	0 (0–1)n = 82
Pain medication (analgesics) at 2 years		
No pain medication n (%)	5 (100%)	14 (63.6%)
Pain medication, n (%)	0	8 (36.4%)
Number of pain medication, median (Q1-Q3)	0 (0–0) n = 5	0 (0–1) n = 22

Previously treated patients had lower scores in EQ5 Index value, 0.66 (IQR 0.54–0.81) versus 0.80 (IQR 0.66–0.92) ($p = 0.008$). Both EQ5 general health score and EQ5 index were lower in patients with moderate/severe pain at baseline compared to patients with no pain/mild pain, 70 (IRQ 56.3–80) versus 90 (IQR 80–98.8) and 0.66 (IQR 0.54–0.74) versus 0.94 (IQR 0.74–0.94), respectively ($p < 0.001$).

IPQR

Regarding Illness perception, patients viewed their disease as a chronic disease 27 (IQR 21.7–29). They reported moderate fluctuation perception during the day 12 (IQR 9–15), a moderate impact on daily life 17 (IQR 12–19), and a moderate emotional response 14 (IQR 10–17). Patients felt moderate control over their disease 17 (IQR 13–19) and believed it was moderately manageable with current treatment 16 (IQR 14–18). They had a moderate understanding of their disease 18 (IQR 16–19). Illness perception differed across FD subtypes, where patients with MAS attributed more common symptoms to their disease compared to patients with isolated CFD (12.8 vs. 4.9; $p = 0.004$) and experienced a higher impact on their daily life compared to patients with MFD (28.1 vs. 24.1; $p = 0.002$). Previously treated patients had higher scores on the illness identity (11.1 vs. 5.7; $p = 0.002$) and impact on daily life (15 vs. 12; $p = 0.007$) domains.

UCL

In the whole group, the most commonly described coping mechanism at baseline was active coping 19 (IQR 16–21), followed by palliative coping 17 (IQR 15–20), avoidant coping 16 (IQR 14–18), fostering reassuring thoughts 13 (IQR 11–14), seeking social support 12 (IQR 10.5–15), passive coping 11 (IQR 9–13.5), while tendency to openly display emotions was rarely reported 5 (IQR 4–6). Patients with isolated CFD expressed a greater tendency towards passive coping at baseline compared to patients with PFD ($p = 0.003$) and MAS ($p = 0.002$). Women exhibited more coping mechanisms compared to men, such as palliative coping ($p = 0.001$), increased engagement in avoidant

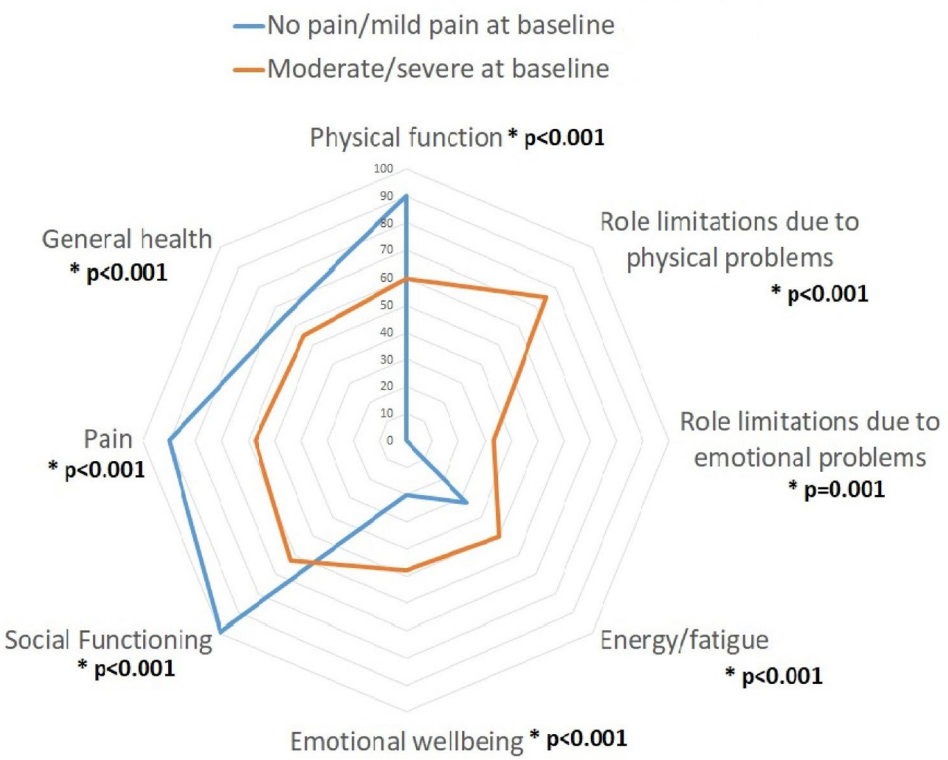

Fig. 1 SF-36 domains in patients with no pain/mild pain and patients with moderate/severe pain at baseline. This figure depicts the comparison of SF-36 domains at baseline in patients with no pain/mild pain versus patients with moderate/severe pain. Comparison were assessed using independent t-tests in case of normally distributed data and Man–Whitney tests in case of non-normally distributed data. Blue line—patients with no pain/mild pain (n = 62); Red line: patients with moderate/severe pain (n = 105). Patients with no pain/mild pain experienced better scores in physical function, general health, pain and social functioning domains compared to patients with moderate severe pain and lower scores in Role limitations to physical problems, Role limitations to emotional problems, Energy/fatigue and Emotional wellbeing

Table 3 BPI domains during follow-up in patients with no pain/mild pain

BPI domains, score/time	Baseline (n = 62)	1 year follow up (n = 37)	2 years follow up (n = 23)	Linear mixed model
Maximal pain	1.3	2.8	5	$p < 0.001$
BPI average pain	1.89	2.54	3.58	$p = 0.01$
Mood	1.29	1.76	3.56	$p < 0.001$
Relations with other people	0.47	0.89	2.59	$p < 0.001$
Sleep	0.88	1.94	3.77	$p < 0.001$
Life enjoyment	1.22	1.49	3.16	$p = 0.02$

coping ($p < 0.001$), sought more social support ($p < 0.001$), and demonstrated heightened fostering thoughts ($p < 0.001$). Patients with moderate/severe pain experienced less treatment control of their disease compared to patients with no pain/mild pain ($p = 0.03$) and used more palliative coping ($p = 0.005$).

There were no additional differences between FD subtypes, gender or previous treatment across BPI, SF 36, EQ5, IPQ-R and UCL domains at baseline.

Follow-Up After 2 Years Assessment

BPI

59 patients completed the BPI questionnaire after 2 years. 55 (93.2%) patients had pain, of which 7 (12.7%) mild pain and 48 (87.3%) moderate/severe pain. 4 (6.8%) patients had no pain. Among the 59 patients, 35 (59.3%) were females, 17 (28.8%) had MFD, 22 (37.3%) had PFD, 9 (15.3%) had MAS, and 11 (18.6%) had isolated CFD.

BPI maximal pain scores changed significantly over the 2-year period. However, this change was not uniform across participants, as pain scores evolved differently depending on the baseline values.

17 (27.4%) of patients with no pain/mild pain at baseline on average experienced worsening of pain scores during the follow-up period of 2 years reflected by increase of BPI maximal pain score from 1.3 (0.7–1.9; 95% CI) at baseline to 5 (4–6; 95% CI) after 2 years, $p < 0.001$.

The same was seen for average pain, but also for impairment of mood, sleep, relations with other people, and life enjoyment (Table 3, Fig. 2).

In the group of patients with moderate/severe pain at baseline the BPI maximal pain score remained stable from 6.6 (6–7.1; 95% CI) at baseline to 6.3 (5.4–7.1; 95% CI) after 2 years ($p = 0.5$), regardless of medical treatment

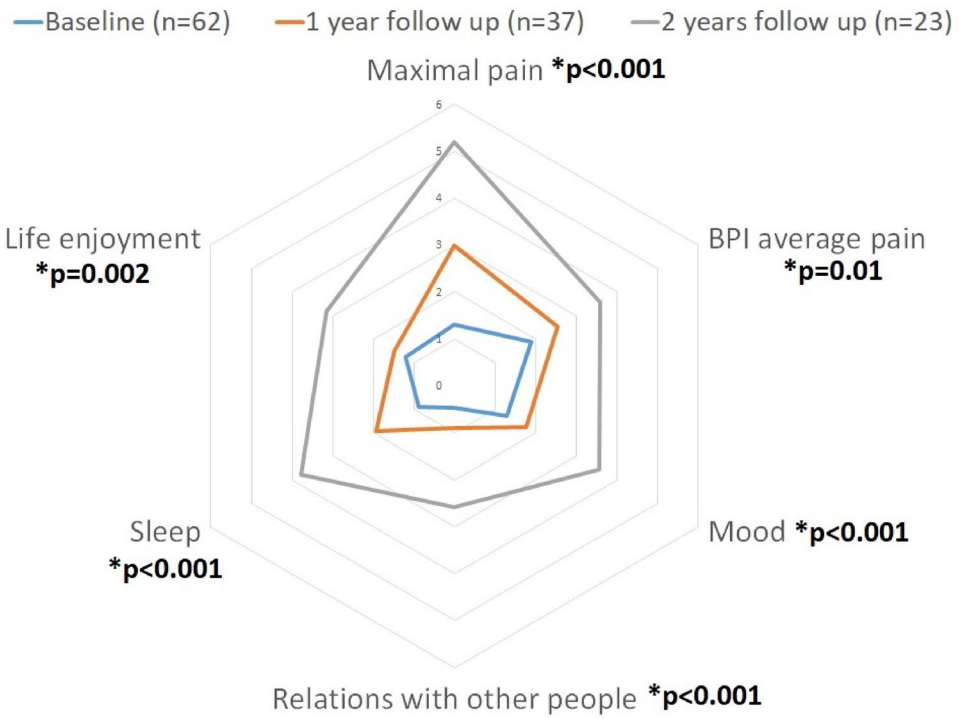

Fig. 2 BPI domains during follow-up in patients with no pain/mild pain. This figure depicts the evolution of BPI domains from baseline (blue line) after 1 year (orange line) and after 2 years (grey line) using a linear mixed model analysis. This figure shows that patients with no pain/mild pain at baseline experienced deterioration in their BPI scores during follow-up

Table 4 BPI domains during follow-up in patients with moderate/severe pain at baseline

BPI domains, score/time	Baseline (n = 105)	1 year follow up (n = 69)	2 years follow up (n = 36)	Linear mixed model
Maximal pain	6.6	5.8	6.3	$p = 0.02$
BPI average pain	4.8	4.1	4.2	$p = 0.7$
Mood	3.9	2.8	2.2	$p = 0.004$
Relations with other people	2.8	2.2	1.8	$p = 0.1$
Sleep	4.5	4	4.1	$p = 0.5$
Life enjoyment	3.5	2.6	2.1	$p = 0.03$

during the follow-up period. None of the included patients required surgery during the follow-up period. The same was found for the other BPI domains (Table 4, Fig. 3).

There were no significant associations found between age, disease duration, between new and chronic patients or gender and the outcome measures at baseline or at the 2-year follow-up.

SF-36

75 patients completed the SF-36 questionnaire after 2 years. Median scores improved for Emotional wellbeing, from 37.6 (32.3–42.9; 95% CI) at baseline to 55.5 (48–63; 95% CI) after 2 years, $p < 0.001$, regardless of the initial status at baseline, FD subtype, gender, age, disease duration or treatment during follow-up.

While no significant changes were observed over time, a significant interaction was found between treatment status and FD subtype, suggesting positive effects of medical treatment across subtypes regardless of time. As such, patients with MAS who received treatment had lower scores in the physical functioning domain compared to those who did not received treatment, 35.3 versus 73.3 ($p < 0.001$).

SF-36 domains score evolution in time showed a similar trend with the BPI questionnaire, with significant change in time, but with a different trajectory for the two groups based on the baseline values of BPI maximal pain in the Role limitations due to physical health and Role limitations due to emotional problems.

Patients with no pain/mild pain at baseline exhibited improved scores in the Role limitations due to physical health domain, Role limitations due to emotional problems domain, higher Energy levels and improved Emotional well-being scores (Table 5).

In the group of patients with moderate/severe pain at baseline SF-36 domains scores remained stable, regardless of FD subtype, age, disease duration, gender, between new or chronic patients or treatment during follow-up (Table 6).

A different trajectory path was also seen for new and chronic patients. In the limitation of emotional problems

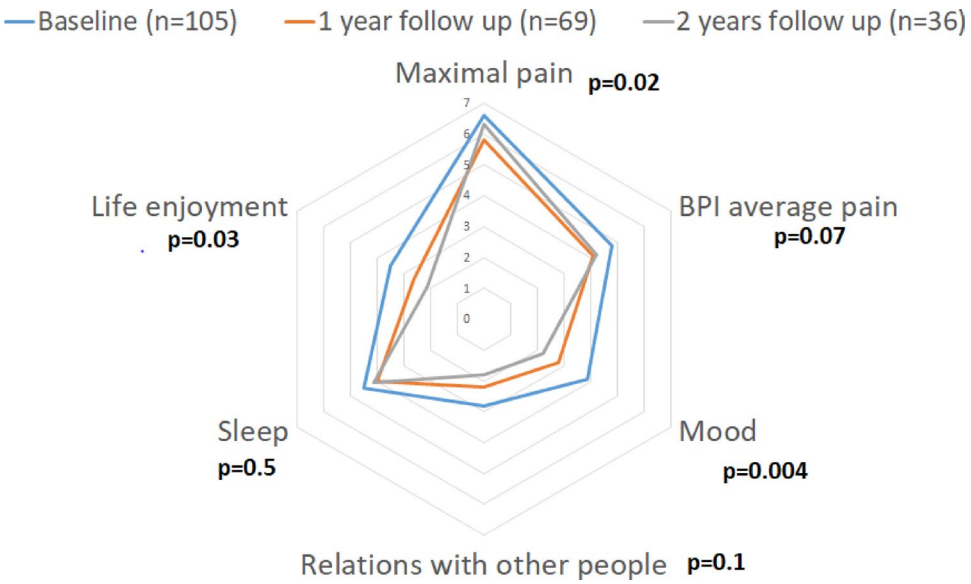

Fig. 3 BPI domains during follow-up in patients with moderate/severe pain at baseline. This figure depicts the evolution of BPI domains from baseline (blue line) after 1 year (orange line) and after 2 years (grey line) using a linear mixed model analysis. This figure shows that patients with moderate/severe pain at baseline experienced stable scores during follow-up

Table 5 SF-36 domains during follow-up in patients with no pain/mild pain at baseline

SF-36 domain, score (95% CI)/ time	Baseline (n = 105)	1 year follow up (n = 72)	2 years follow up (n = 41)	Linear mixed model
Physical function	85.9 (80.9–90.8)	85.4 (79.8–91)	81.5 (75.1–87.9)	$p = 0.5$
Role limitations due to physical health	24.9 (14.3–35.6)	30.1 (17.9–42.3)	59.7 (45.6–73.7)	$\mathbf{p < 0.001}$
Role limitations due to emotional problems	23.7 (13.4–39)	25.6 (13.8–37.5)	71.8 (58.1–85.5)	$\mathbf{p < 0.001}$
Energy/fatigue	37.2 (30.1–43.4)	38.7 (31.5–45.9)	55.6 (47.3–63.8)	$\mathbf{p = 0.001}$
Emotional wellbeing	32.9 (25.1–40.7)	31.6 (22.6–40.6)	60.3 (50–70.7)	$\mathbf{p < 0.001}$
Social functioning	84.5 (78.7–90.2)	85.2 (78.6–91.7)	80 (72.4–87.6)	$p = 0.55$
Pain	81.4 (76.2–86.6)	78.9 (72.9–84.9)	74.9 (67.9–81.8)	$p = 0.3$
General health	64.6 (59.1–70)	60.3 (54–66.5)	59.9 (52.7–67.1)	$p = 0.4$

Table 6 SF-36 domains during follow-up in patients with moderate/severe pain at baseline

SF-36 domain, score (95% CI)/time	Baseline (n = 105)	1 year follow up (n = 73)	2 years follow up (n = 42)	Linear mixed model
Physical function	60.6 (55.3–65.9)	66.7 (60.4–73.1)	63.8 (55.4–72.3)	$p = 0.3$
Role limitations due to physical health	65.6 (56.4–73.7)	45.1 (34.6–55.5)	52.5 (38.5–66.6)	$p = 0.3$
Role limitations due to emotional problems	37.4 (28.7–46.2)	31.6 (21.1–42.1)	38 (23.9–52.2)	$p = 0.6$
Energy/fatigue	50.8 (46.4–55.2)	47 (41.8–52.3)	47.8 (40.7–54.9)	$p = 0.5$
Emotional wellbeing	47.4 (41.8–53.1)	37.1 (30.4–43.8)	45.4 (36.3–54.5)	$p = 0.06$
Social functioning	64.4 (59.4–69.4)	71 (65–77)	70.7 (62.7–78.8)	$p = 0.1$
Pain	50.5 (45.8–55.1)	58.2 (52.7–63.7)	57.9 (50.4–65.3)	$p = 0.06$
General health	51.1 (47–55.2)	51.6 (46.7–56.5)	54.9 (48.4)	$p = 0.6$

domain the scores improved from 29.87 to 70.59 in the new enrolled patients group and from 32.96 to 39.64 in the chronic patients group, $p = 0.01$. Newly enrolled patients experienced improvement in the fatigue domain, from 41.75 to 63.09, $p < 0.01$ and the emotional well-being domain, from scores from 37.30 to 65.77, $p < 0.01$ while it remained stable in chronic patients group.

EQ5

EQ5 questionnaire was completed by 29 patients after 2 years. Both EQ5 Index value and EQ5 health state score remained stable after 2 years, regardless of treatment, age, disease duration, gender, new vs chronic patients or pain status at baseline.

IPQ-R

26 patients completed the questionnaire after 2 years. Patients with moderate/severe pain at baseline felt increased control over their disease, while patients with no pain/mild pain felt less control over their disease during the follow-up period, $p=0.01$. There were no other changes during follow-up in the other domains of IPQ-R.

UCL

Changes in UCL domains over time could not be analyzed due to insufficient available data.

Influencing Factors

Higher BPI maximal pain scores at baseline were associated with lower SF-36 general health scores ($r=-0.452$, $p<0.001$), lower SF-36 scores on physical impairment ($r=-0.627$, $p<0.001$), lower social functioning ($r=-0.541$, $p<0.001$), and lower quality of life due to pain ($r=-0.804$, $p<0.001$). Furthermore, higher BPI maximal pain scores were associated with lower scores in both the EQ5 general health domain ($r=-0.4$, $p<0.001$) and EQ5 health index ($r=-0.5$, $p<0.001$), indicating a lower QoL. In case of higher BPI maximal pain scores, patients experienced increased Illness identity perception ($r=0.3$, $p=0.01$), higher daily symptoms fluctuations ($r=0.2$, $p=0.03$), increased illness impact on daily life ($r=0.2$, $p=0.01$), increased emotional response ($r=0.19$, $p=0.01$), and lower treatment control perception ($r=-0.22$, $p=0.01$). Patients with higher BPI maximal pain scores also had a tendency to use increased palliative coping mechanisms ($r=0.4$, $p=0.03$).

Discussion

Current study is the first to present data on pain, quality of life and coping mechanism during a 2 year follow-up of FD/MAS patients in a care pathway. This study provides new insights into the evolution of pain over time, as it showed that patients with no pain or mild pain scores experienced worsening of pain scores during follow-up, which could eventually lead to the need for treatment. Patients with moderate/severe pain experienced no changes in time regarding pain scores or QoL, with persistent high pain scores and low QoL after 2 years.

In line with previous studies [4, 19], this large cohort study confirms that patients with FD/MAS experience pain regardless of disease subtype. Pain impacts quality of life (QoL), illness perception, and coping strategies [8]. Differences were noted between pain intensity groups: patients with moderate/severe pain reported worse physical function, social functioning, and general health compared to those with no/mild pain. Interestingly, at baseline, the higher pain group showed better mental health and energy levels, possibly due to increased disease awareness, multidisciplinary care, or longer disease exposure. When comparing newly enrolled patients to chronic patients, our findings align with previous research: chronic patients maintain stable scores over time, whereas newly enrolled patients show improvement in certain areas—such as emotional well-being—after 2 years, while remaining stable in other domains [10].

Pain trajectories varied: some patients with mild/no pain at baseline reported worsening symptoms over time, reaching levels warranting medical treatment, which was offered irrespective of pain duration. Pain was associated with reduced QoL, including mood disturbances, social impairment, sleep issues, and lower life satisfaction, suggesting that deterioration can occur in a relatively short timeframe. Clinicians should be alert to delayed onset of pain, and future studies should explore other pain mechanism components such as explore possible causes such as microfractures, increased disease activity or neuropathic pain development. Future studies should also cover the aspect of duration and intensity of pain, although currently the term flare-up is not used to describe the pain in FD/MAS.

Although this study found no differences between FD subtypes, further research should identify risk factors for pain development, investigate site-specific impacts (e.g., femur, rib), and explore triggers of pain. Patients with moderate/severe pain showed stable pain scores over time, consistent with previous findings [10]. However, no treatment-related differences were observed between patients who did and did not receive antiresorptives (e.g., bisphosphonates, denosumab), likely due to treatment heterogeneity and timing. Prior work has shown limited bisphosphonate efficacy [6]. Additionally, missing follow-up data may introduce nonresponse bias. Selection bias may also be present, as patients with pain might be more likely to engage in research. Standardized prospective or randomized studies are needed to better assess treatment impact of various treatments on pain and QoL.

Regarding illness perception, previous work by Majoor et al. reported variation by FD subtype [8]. Our larger cohort confirmed this and additionally showed that illness perception evolves over time. Patients with persistent moderate/severe pain felt more in control of their condition, whereas those with worsening pain reported decreased disease control. These findings underscore the importance of sustained pain management to support QoL and patient empowerment.

A previous study found no link between disease severity and coping [9]. In contrast, we observed that patients with baseline pain ≥4 were more likely to adopt palliative

strategies, seek social support, and express emotions. However, previous study by Rotman et al. found that patients with FD have more active coping strategies then patients with chronic pain, they seek more distractions and social support [9]. This may explain the lower use of painkillers. Those with isolated craniofacial FD (CFD) showed more passive coping and emotional expression. Differences may reflect sample size and varying definitions of disease severity. Additionally, CFD phenotypes may influence coping [20]. Our findings highlight that pain extends beyond physical effects, emphasizing the need for psychological support and tailored coping strategies, especially for patients with higher pain levels. However, follow-up data on coping mechanisms were insufficient, limiting analysis of their evolution.

This study provides further insights into the natural history of FD/MAS, despite some limitations. Notably, several patients in the PROFID study submitted incomplete questionnaire responses, with some providing data only at baseline, others in the ongoing process of follow-up, which could induce response bias. Additionally, selection bias may also be present as patients with a more severe form of the disease are more likely to engage in research and undergo regular check-up. The relatively short follow-up period may have limited a full assessment of pain progression and fluctuations. Longer follow-up intervals (e.g. 3, 5, or 10 years) would offer a more comprehensive understanding of pain evolution. Pain assessment over only 24 h may not fully capture the chronic and fluctuating nature of FD-related pain and future studies should include pain assessment at multiple times, to capture the fluctuating nature of pain evolution. Moreover, relation between pain, QoL and anatomic FD location, disease activity measured through bone turnover markers, nuclear imaging and radiologic FD appearance was not assessed.

Strengths include the large and diverse cohort spanning all FD subtypes and pain severities, including asymptomatic and incidentally diagnosed cases. Our findings support earlier work that pain may first appear in adulthood, in asymptomatic or incidentally diagnosed cases, reaffirming that FD/MAS is not solely a pediatric condition [4].

Lastly, since our questionnaires primarily measured pain in general, future research should investigate different types of pain, such as nociceptive or neuropathic pain and how pain frequency relates to QoL.

Conclusion

All patients with FD/MAS may experience pain and decreased quality of life, irrespective of disease subtype At baseline, patients with moderate/severe pain demonstrated more impairment in physical function, social function, and QoL, and reported lower general health than patients with no pain/mild pain, but had a better mood. Pain evolution over time varied among patients. 27.4% of patients with no pain or mild pain at baseline experienced worsening of maximal pain scores during follow-up, up to scores justifying (medical) intervention. Patients with moderate/severe pain had stable values during follow-up. Therefore, even though some patients may not need active follow-up, they should be instructed to contact their physician in case of worsening of symptoms.

While pain and impaired quality of life may be experienced by all patients, current study suggests there are differences among patients regarding Illness perceptions and Coping mechanisms, emphasizing the diversity in experienced pain and adaptations to pain associated with FD/MAS. Higher levels of pain lead to decreased QoL, reinforcing the need not only for targeted treatment of fibrous dysplasia lesions, but also for mental health management.

Authors Contribution O.O. Bulaicon: conceptualization, methodology, formal analysis and investigation, writing- original draft, review and editing. M. Hagelstein-Rotman: conceptualization,methodology, writing—review and editing. M.E. Meier: conceptualization,methodology, writing—review and editing. I. van der Geest: writing—review and editing. F.M. van Haalen: writing—review and editing. J. Hogewoning-Rewijk: writing—review and editing. S.W. van der Meeren: writing—review and editing. S.E. C.Pichardo: writing—review and editing. A.C. van de Ven: writing—review and editing. P.B. de Witte: writing—review and editing. N.M. Appelman-Dijkstra: conceptualization, methodology, writing- original draft, review and editing, supervision.

Declarations

Human and Animal Rights The study was approved by the medical committee of the Leiden University Medical Center (project ID: P17.136).

Informed Consent Informed consent was obtained from the patients.

References

1. Boyce AM, Collins MT (2020) Fibrous dysplasia/McCune-Albright syndrome: a rare, mosaic disease of Gαs activation. Endocr Rev 41(2):345–370. https://doi.org/10.1210/endrev/bnz011
2. Benhamou J et al (2016) Prognostic factors from an epidemiologic evaluation of fibrous dysplasia of bone in a modern cohort: the FRANCEDYS study. J Bone Miner Res 31(12):2167–2172
3. Majoor BCJ et al (2019) Pain in fibrous dysplasia: relationship with anatomical and clinical features. Acta Orthop 90(4):401–405
4. Kelly MH, Brillante B, Collins MT (2008) Pain in fibrous dysplasia of bone: age-related changes and the anatomical distribution of skeletal lesions. Osteoporos Int 19(1):57–63
5. Florenzano P et al (2019) Age-related changes and effects of bisphosphonates on bone turnover and disease progression in fibrous dysplasia of bone. J Bone Miner Res 34(4):653–660
6. Majoor BCJ et al (2017) Determinants of impaired quality of life in patients with fibrous dysplasia. Orphanet J Rare Dis 12(1):80
7. Konradi A (2022) Fibrous dysplasia patients with and without craniofacial involvement report reduced quality of life inclusive of stigma, depression, and anxiety. Chronic Illn 18(4):927–936
8. Majoor BCJ et al (2018) Illness perceptions are associated with quality of life in patients with fibrous dysplasia. Calcif Tissue Int 102(1):23–31
9. Rotman M et al (2018) Passive coping strategies are associated with more impairment in quality of life in patients with fibrous dysplasia. Calcif Tissue Int 103(5):469–475
10. Meier ME et al (2022) A multidisciplinary care pathway improves quality of life and reduces pain in patients with fibrous dysplasia/McCune-Albright syndrome: a multicenter prospective observational study. Orphanet J Rare Dis 17(1):439
11. Legrand MA, Bagouet F, Merle B, Gensburger D, Chapurlat R (2023) Value of rare diseases reference centers: impact on diagnosis and access to specialized care in fibrous dysplasia of bone. Eur J Med Genet 66(11):104849. https://doi.org/10.1016/j.ejmg.2023.104849
12. Cleeland CS, Ryan KM (1994) Pain assessment: global use of the brief pain inventory. Ann Acad Med Singap 23(2):129–138
13. Ware JE Jr., Sherbourne CD (1992) The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 30(6):473–483
14. Devlin N et al (2022) EQ-5D-Y-3L value sets, valuation methods and conceptual questions. Pharmacoeconomics 40(Suppl 2):123–127
15. Weinman J et al (1996) The illness perception questionnaire: a new method for assessing the cognitive representation of illness. Psychol Health 11(3):431–445
16. Moss-Morris R et al (2002) The revised illness perception questionnaire (IPQ-R). Psychol Health 17(1):1–16
17. Schreurs P et al (1993) Handleiding utrechtse coping lijst UCL (herziene versie). Zwets & Zeitlinger, Lisse
18. Hagelstein-Rotman M et al (2020) Patients with isolated craniofacial dysplasia report better quality of life compared with those with craniofacial dysplasia and extracranial involvement. Ophthalmic Plast Reconstr Surg 36(3):292–297
19. Majoor BC, Appelman-Dijkstra NM, Fiocco M, van de Sande MAJ, Dijkstra PDS, Hamdy NAT (2017) Outcome of long-term bisphosphonate therapy in McCune-Albright syndrome and polyostotic fibrous dysplasia. J Bone Miner Res 32(2):264–276. https://doi.org/10.1002/jbmr.2999
20. Berry C et al (2025) Identifying pain subtypes in patients with craniofacial lesions of fibrous dysplasia/McCune-Albright syndrome. J Oral Maxillofac Surg 83(3):366–373