Fibrous dysplasia

Majoor, B.C.J.

Fibrous Dysplasia

Bas Majoor

Stellingen

behorende bij het proefschrift

Fibrous Dysplasia

Bas Majoor, 25 april 2018

1. The wide range of possible *GNAS*-induced extraskeletal manifestations, compel us to look at fibrous dysplasia as a systemic disease, the care of which requires a multidisciplinary approach. (This thesis)
2. Women with fibrous dysplasia have an increased risk of developing breast cancer, particularly in the presence of thoracic FD lesions. (This thesis)
3. Adequate patient selection and an individually-tailored approach are advocated in the surgical management of fibrous dysplasia. (This thesis)
4. Stabilizing interventions in fibrous dysplasia have superior outcomes when bridging the whole length of the lesion. (This thesis)
5. Treatment with bisphosphonates and denosumab hold promising results in the management of selected FD patient groups. (This thesis)
6. Quality of life and daily functional activities may be significantly impaired in patients with fibrous dysplasia, also in those with monostotic disease. (This thesis)
7. The McCune-Albright syndrome is a potential in vivo model of the role of G_s signalling pathways in biological systems and human disease. (Weinstein, NEJM, 1991)
8. Currently available medical and surgical therapies for fibrous dysplasia are not satisfactory. (M.T. Collins, Primer on the metabolic bone diseases, 2012)
9. Should cure of FD become feasible in the future, it will be, by default, through innovative approaches. (Riminucci, JBMR, 2006)
10. Fibreuze dysplasie is een slopende ziekte. (Sam)
11. Every time I see an adult on a bicycle, I no longer despair for the future of the human race. (H.G. Wells, 1866–1946)
12. You should never, never doubt something that no one is sure of. (Roald Dahl's Willy Wonka, Charlie and the Chocolate Factory, 1964)
13. Kleine operaties bestaan niet, enkel kleine operateurs. (Anoniem)
14. De statistische toetsingstheorie gaat ook buiten wetenschappelijk onderzoek op. Tenzij ontegenzeggelijk is bewezen dat iets onmogelijk is, is alles mogelijk.

Fibrous Dysplasia

Bas Majoor

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Fibrous Dysplasia

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Voor Pap en Mam

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Chapter 1

General introduction

BACKGROUND

Fibrous dysplasia is a rare, benign, genetic but non-inheritable bone disorder. Although its features were first described at the end of the 19th century by von Recklinghausen (1891), fibrous dysplasia is a very old disease, which has actually been recognised in archaeological remains of a Neanderthal man who lived in Croatia more than 120,000 years ago, making it the oldest 'tumor' ever to be identified in the long history of medicine (Fig. 1.1 and 1.2).[1,2] An honourable record for this rare and to date still often unrecognised bone disorder about which literature is still relatively scarce, offering wide opportunities to explore a number of aspects of its pathophysiology, diagnosis and management.

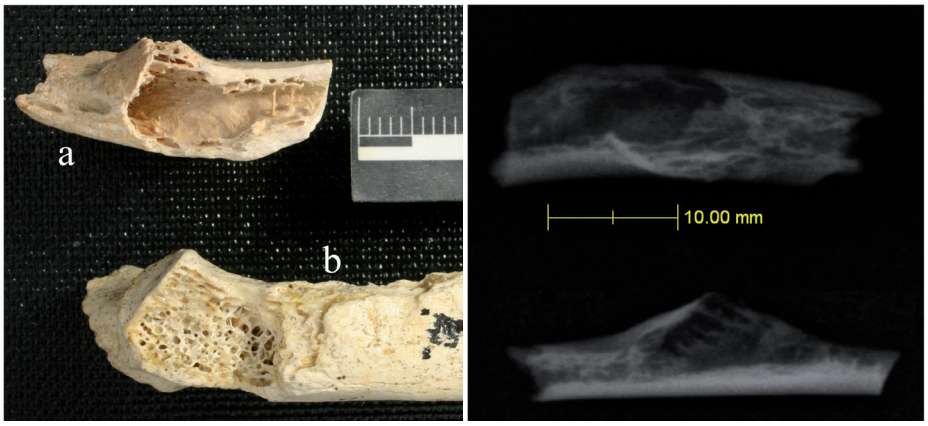

Fig. 1.1 and 1.2 Photograph of the 'first tumor' in medical history, which was discovered in the right rib of a 120,000+ years old Neanderthal who has lived in what is nowadays Croatia. The photograph clearly shows destruction of trabeculae and involvement if the cortex (a) compared to the normal pattern of bony trabeculae in a left rib from the same collection (b). Conventional radiographs of the rib in a position matching photograph 1.1a show a lesion mf approximately 10mm with destruction of bony tissue and a sharp, non-sclerotic margin. Based on these images, the most likely diagnosis if fibrous dysplasia, making it the oldest 'tumor' known to mankind. Consent for the use of these images was given by corresponding author David Frayer.

Historical vignette

In 1891, dr. von Recklinghausen, a pathologist who had studied under Rudolf Virchow, held a lecture to commemorate his tutor's 70th birthday in which he described two patients with typical osseous lesions that caused skeletal deformations.[1] However, it was only in 1936–37 that the paediatrician dr. Donovan McCune, and the endocrinologist dr. Fuller Albright, separately described the combination of areas of skin pigmentation,

endocrine dysfunction in the form of precocious puberty and multiple fibro-osseous lesions, first termed 'osteitis fibrosa disseminata', and later renamed after their combined names as the McCune-Albright Syndrome (MAS).[3,4] A year later in 1938, Lichtenstein and Jaffe described single fibro-osseous lesions without skin lesions or endocrinopathies which they termed "fibrous dysplasia", currently encompassing all types of this disorder (ORPHA-249). It thus took some 50 years after the milestone lecture in honour of Virchow for the name fibrous dysplasia to be coined to this rare bone disorder. Interestingly, in 1926, an association was noted between fibro-osseous lesions of the skeleton and soft tissue myxomas by Henschen,[5] but it was another 40 years before this association was named the Mazabraud's syndrome after dr. Mazabraud who described the association of fibrous dysplasia of bone and myxomas of soft tissues.[6]

Clinical presentation

In fibrous dysplasia, the fibro-osseous lesions replacing normal bone are of poor quality and associated with mineralization defects. The resulting disturbed skeletal microarchitecture is associated with increased risk of pain, deformities and pathological fractures.[7] The lesions may involve a single bone (monostotic fibrous dysplasia) or multiple bones (polyostotic fibrous dysplasia). Local pain symptoms may occur as a result of micro-fractures aggravated by the presence of FGF-23-induced renal phosphate wasting and hypophosphatemia, and may be related to the extent, severity or activity of the fibrous dysplasia lesion, or may be due to sensory nerve involvement and/or the formation of neuromas.[8] Disturbed microarchitecture and mineralization defects, reduce structural strength at the site of the lesion, and increase the risk of deformities, particularly in the weight-bearing lower extremities leading to the typical varus deformity of the proximal femur. These structural changes lead to increased risk for pathological fractures. The extent and severity of symptoms are also influenced by the anatomical localization of the lesions. For instance, craniofacial fibrous dysplasia is seldom associated with fractures, whereas disfigurement, pain, dental problems and cranial nerve compression, particularly of the optical nerve are more common manifestations of this type of fibrous dysplasia.[9] Theoretically, any bone in the human body maybe affected, although fibrous dysplasia lesions are predominantly diagnosed in the proximal femur and craniofacial bones.[10] Fibrous dysplasia predominantly presents at a young age.[10] The more severely affected patients with polyostotic or craniofacial disease are often diagnosed at a younger age compared to the patients with monostotic disease who are more often asymptomatic.[11] Despite the wide spectrum of symptoms associated with fibrous dysplasia, most patients with monostotic fibrous dysplasia are asymptomatic, with the diagnosis often established on the basis of an

incidental finding of a characteristic fibrous dysplasia lesion on radiological imaging, or due the occurrence of a pathological fracture in a previously asymptomatic lesion (Fig. 1.3).[12] The asymptomatic nature of a number of fibrous dysplasia lesions leads to difficulty in determining true prevalence and incidence of this rare disorder. Fibrous dysplasia may also be associated with a wide spectrum of extraskeletal manifestations. The classical triad of polyostotic fibrous dysplasia, café-au-lait-patches and precocious puberty form the basis of the McCune-Albright syndrome and the association of intramuscular myxomas with fibrous dysplasia lesions is termed Mazabraud's Syndrome (Table 1.1). However, over the past 50 years, a number of other endocrine and non- endocrine extraskeletal manifestations have been described to be associated with skeletal fibrous dysplasia lesions, all hypothesized to be due to systemic effects of *GNAS*-mutations. These manifestations, more often observed in patients with polyostotic disease or McCune-Albright syndrome, are summarized in Table 1.2. In very few cases fibrous dysplasia lesions are reported to undergo malignant change, predominantly transforming in osteosarcomas or chondrosarcomas.[13-16]

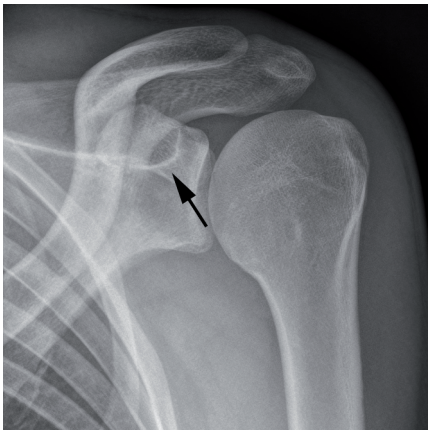

Fig. 1.3 An asymptomatic lesion in the scapula of a 20-year old patient that was discovered accidentally on radiographic imaging.

Aetiology of fibrous dysplasia

Weinstein et al. demonstrated in 1991 that fibrous dysplasia was due to be a post-zygotic, missense mutation of the *GNAS*-gene that encodes the alpha subunit of the stimulatory G-protein ($G_s\alpha$).[29-32] The mutation results in impairment of GTPase activity of $G_s\alpha$, leading to overproduction of adenylyl cyclase and to an increase in intracellular cAMP.[33,34] Because the mutation occurs post-zygotically, it is not inheritable

Table 1.1 Classical classification of fibrous dysplasia

Monostotic fibrous dysplasia	Lesion in a single bone
Polyostotic fibrous dysplasia	Lesions in multiple bones
"Classic" McCune-Albright syndrome	Polyostotic fibrous dysplasia in combination with precocious puberty and café-au-lait patches
Mazabraud's syndrome	Fibrous dysplasia in combination with intramuscular myxomas

Table 1.2 Extra-skeletal manifestations of fibrous dysplasia

Endocrine manifestations
Precocious puberty [3,4]
Growth hormone excess [17]
Prolactin excess [17]
Primary hyperthyroidism [18]
Neonatal Cushing syndrome [19]
Non-endocrine manifestations
Café-au-lait patches [3,4]
FGF-23 induced renal phosphate wasting and hypophosphatemia [20]
Ovarian cysts [21]
Hepatic involvement [22]
Cardiac involvement (tachycardia/aortic root dilatation) [18-20,23,24]
Platelet dysfunction [25]
Neoplasms e.g. intraductal papillary mucinous neoplasms, thyroid carcinoma, breast cancer, testicular cancer [24,26-28]

and is associated with a mosaic pattern of spread believed to be related to the time of pregnancy at which the mutation occurs.[35] It has recently been suggested that the *GNAS*-mutation responsible for fibrous dysplasia affects pluripotent cells in early embryonic development, leading to the formation of dysfunctional osteoblasts and osteocytes in affected parts of the skeleton.[35] In addition to the mutations found in pathological skeletal tissue, similar mutations of the *GNAS*-gene are also found in pathologic tissues of endocrine and non-endocrine lesions such as pituitary adenomas and intramuscular myxomas.[36,37]

Histopathology of fibrous dysplasia

The pathological characteristics of fibrous dysplasia lesions include fibro-osseous tissue that is typically devoid of adipose marrow and hematopoiesis and has abnormal trabeculae in a specific pattern which is often referred to as 'Chinese writing' (Fig. 1.4).[7] The presence of Sharpey fibers and stellate-shaped osteoblasts may help the pathologist to distinguish between fibrous dysplasia and other bone disorders.[38]

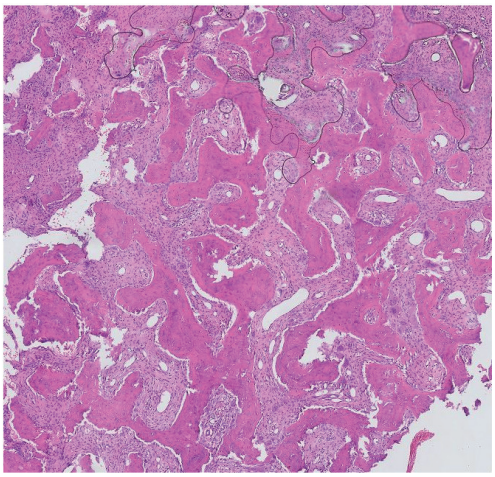

Fig. 1.4 Histological pattern of fibrous dysplasia, commonly referred to as Chinese writing pattern in a patient with craniofacial fibrous dysplasia.

Compared to unaffected bone, fibrous dysplasia lesions demonstrate an excess of unmineralized bone and a reduced mineral content of mineralized bone.[39] These mineralization abnormalities are exacerbated by the presence of FGF-23-induced hypophosphatemia, leading to a disturbance in bone microarchitecture, a decrease in bone quality and an increase risk of deformities and fractures.

Bone remodelling and bone turnover markers in fibrous dysplasia

Normal human bone is constantly remodelled by a continuous process of resorption of old and damaged layers of bone and replacement of resorbed bone by new bone in the process of bone formation as illustrated in Fig. 1.5 (adapted from Seeman et al.).[40] Bone remodelling is different in *GNAS*-mutated bone in fibrous dysplasia. Skeletal progenitor cells carrying the *GNAS*-mutation fail to differentiate into healthy osteoblasts, leading to the formation of immature osteoblasts, which replace normal bone.[35,39,41,42] It is also believed that the *GNAS*-mutated immature osteoblasts and osteocytes are stimulated to produce increased levels of FGF-23 in fibrous dysplasia tissue, further exacerbating the underlying mineralisation defect. Although fibrous dysplasia is primarily a disorder of pathological bone formation, bone resorption is also affected as demonstrated by the presence of unusually high number of osteoclasts at the periphery of fibrous dysplasia lesions.[38,43] Suggested mechanisms for this marked osteoclastogenesis are the increased expression of IL-6 and RANK-ligand by the immature osteoblasts and osteocytes carrying the *GNAS*-mutation.[43-45]

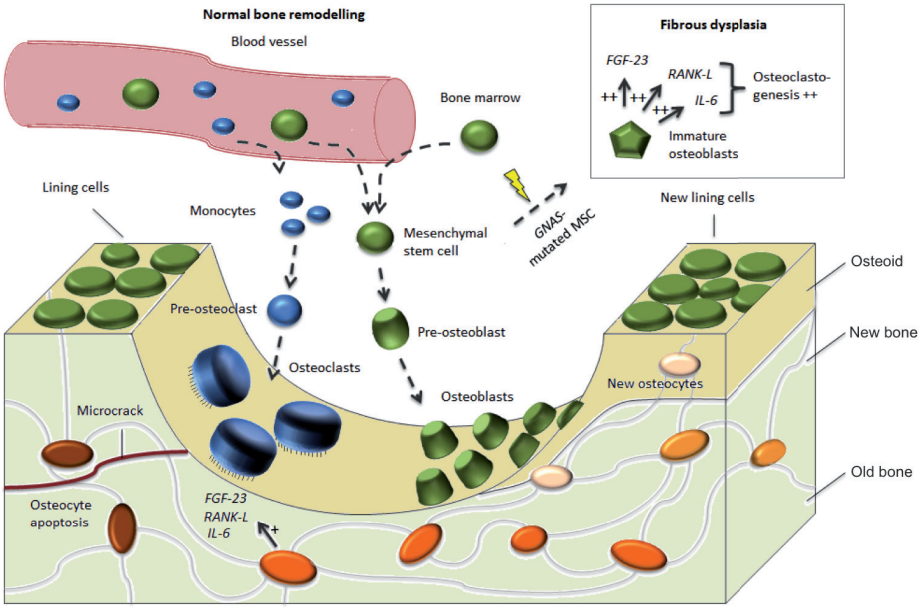

Fig. 1.5 Bone remodelling in normal bone consists of a continuous process of bone resorption by osteoclasts and bone formation by osteoblasts. It starts with damaged bone, for example by microfractures, which induces osteocyte apoptosis, a signal for the bone that remodelling is necessary. Dying osteocytes therefore stimulate the production and recruitment of osteoclasts, which are formed by monocytes that can potentially differentiate into macrophages, lymphocytes or osteoclasts. In bone remodelling, these monocytes bundle together to give rise to multinucleated pre-osteoclasts, which then transform into active osteoclasts that initiate resorption of bone. Simultaneously, mesenchymal stem cells are recruited from the blood stream and from the bone marrow, to form pre-osteoblasts that later differentiate into active osteoblasts. These osteoblasts are responsible for bone formation. Osteoblasts may then differentiate in three ways: they can form a layer of bone lining cells, they can go into apoptosis or they can differentiate into osteocytes that form an intrinsic network within the bone. In normal bone remodelling these osteocytes are responsible for the production of FGF-23, RANK-L and IL-6. Bone remodelling within FD lesions follows a completely different pattern, much of which is still not understood. Mesenchymal stem cells carrying the *GNAS*-mutation fail to differentiate into normal osteoblasts, but instead give rise to erroneous, stellate-shaped, immature osteoblast. These *GNAS*-mutated immature osteoblasts that accumulate in the bone marrow of FD lesions are responsible for its typical pattern on histologic and radiographic evaluation. Both osteogenic and stromal cells in FD produce increased levels of RANK-L and IL-6, stimulating the recruitment en production of osteoclasts and therefore driving bone resorption in FD lesions. Although primarily a disorder of erroneous bone formation, elevated levels of osteoclastogenisis underline the important role of bone resorption in FD, which is the argument for its treatment with antiresorptive agents. Both osteocytes and osteoblasts in FD produce elevated levels of FGF-23 in FD, making FGF-23 a reliable marker of disease severity in FD.

Bone turnover can be assessed by measuring circulating levels of alkaline phosphatase (ALP) and procollagen 1 amino- terminal propeptide (P1NP) as bone formation markers and beta crosslaps (CTX) as bone resorption marker.[45] ALP levels have been found to be produced in high amounts by cells in the endosteal fibrosis of fibrous dysplasia lesions, making it a reliable marker of disease severity in fibrous dysplasia.[45,46] Fibroblast

growth factor 23 (FGF-23) is abundantly produced by osteocytes and osteoblasts carrying the *GNAS*-mutation, but also by the mutated osteoblast-derived fibroblastic cells found in the bone marrow of fibrous dysplasia lesions.[47,48] Serum levels of FGF-23 have been found to be associated with the extent and severity of fibrous dysplasia lesions.[46,47] High levels of FGF-23 are associated with renal phosphate wasting, leading to hypophosphatemia, particularly in patients with extensive disease.[47,49] In patients with fibrous dysplasia, biochemical assessment should thus include the measurement of serum levels of phosphate, calcium, albumin, 25-OH-Vitamin-D, intact PTH and FGF-23. Urine samples should also be tested for phosphate and creatinine levels to calculate the TmP/GFR, which provides the maximum rate of reabsorption of phosphate relative to the GFR, in order to diagnose FGF-23-induced renal phosphate wasting.[48,50] All patients with suspected endocrinopathies should be screened for increased levels of growth hormone, IGF-1, prolactin, TSH or cortisol, and measurements should be repeated at least once especially in patients with polyostotic disease and in children after transition to adult care.

Radiology of fibrous dysplasia

Fibrous dysplasia lesions can be recognised on conventional radiographs on the basis of a typical ground glass effect, endosteal scalloping, well-circumscribed borders, possible cortical thinning and absent periosteal reaction.[10,51-53] The proximal femur may show the characteristic shepherd's crook deformity (Fig. 1.6), which is pathognomic for fibrous dysplasia affecting this skeletal site. Interestingly, in a number of patients, fibrous dysplasia lesions may become sclerotic and less homogenous over time.[11] Next to conventional radiographs, T99m-technetium skeletal scintigraphies are often performed to assess the distribution of fibrous dysplasia lesions.[54] Magnetic Resonance (MR) scans are occasionally performed to discriminate fibrous dysplasia lesions from other skeletal pathologies such as juvenile bone cysts and aneurysmal bone cysts, but also malignancies such as osteosarcomas or malignant transformation of a fibrous dysplasia lesion.[55,56] MR images of fibrous dysplasia can show a variety of features, including areas of calcification, cystic changes, fatty tissue or septations. Fibrous dysplasia lesions are generally more reliably evaluated by MR-scans than by conventional radiographs.[57] Computed tomography scans (CT-scans) are predominantly used in the evaluation of craniofacial fibrous dysplasia, but may also be helpful in preoperative planning of surgical interventions for fibrous dysplasia lesions elsewhere in the skeleton.[58]

Fig. 1.6 Shepherds' crook deformity in the proximal femur of a patient with fibrous dysplasia. This varus deformity that is typically seen in severe fibrous dysplasia of the proximal femur, thanks its name to the form of the crook that shepherds use to catch their sheep.

Current treatment modalities for fibrous dysplasia

There is to date no cure for fibrous dysplasia. Available treatment options are scarce and aim at decreasing symptoms, preventing progression of lesions, decreasing complications such as deformities and fractures and improving function and quality of life. Over the past three decades there have been significant improvements in both surgical and medical treatment options for fibrous dysplasia. However, although associated with more or less positive outcomes, none of the currently available treatment modalities has been shown to achieve cure of the disease.

Historically, fibrous dysplasia was treated only by surgery, initially principally consisting of curettage of lesions.[59] However, it soon became apparent that this surgical modality was associated with 100% recurrence of fibrous dysplasia lesions, although the timeframe at which these recur was difficult to predict.[59,60] Due to these high recurrence rates, this type of surgical intervention was abandoned and other options such as the use of bone grafts to improve structural stability of affected bone and lower the risk of recurrence became more popular.[12,60,61] However, the use of bone grafting remains a matter of controversy, as the type of graft used and the mode of transplantation appear to affect graft survival.[62] Currently used surgical interventions mainly focus on treating the symptoms of fibrous dysplasia, such as deformities and pathological

fractures, which are prevalent in the femur as this is often the site of predilection for an fibrous dysplasia lesion and the weight-bearing forces these lesions are submitted to increase the risk of complications. Although a number of different surgical options, such as different types of plates, intramedullary devices or other forms of bone grafts have been proposed for the treatment of fibrous dysplasia of the proximal femur, there is to date no guideline on the most optimal surgical intervention to use in the management of these patients to achieve best treatment outcomes.

Treatment of fibrous dysplasia with antiresorptive agents was first suggested in the early nineties and the rationale for using these agents was based on the increased bone turnover observed in fibrous dysplasia lesions.[45] However, although increased osteoclasts have been observed in fibrous dysplasia lesions, the primary pathologic mechanism of fibrous dysplasia is abnormal bone formation, so that it seems counterintuitive to choose antiresorptive agents as treatment in a disorder that primarily affects osteoblasts and osteocytes. Notwithstanding, high levels of RANK-L and IL-6 have also been demonstrated in fibrous dysplasia lesions, which also contribute to activation of osteoclastogenesis and bone resorption, thereby providing a further rationale for using antiresorptive treatment in these patients. As expected, decreasing bone resorption leads to decreased levels of bone formation, as demonstrated by the reduction in ALP and P1NP levels following treatment with antiresorptive agents (Fig. 1.6).

To date, medical treatment of fibrous dysplasia consists primarily of treatment with bisphosphonates. In 1994 Liens et al. were the first to demonstrate a positive effect of this type of treatment on bone pain and on arrest of lesional expansion.[63] Since then, several studies reported a beneficial effect of different types of bisphosphonates on pain, markers of bone turnover and radiological features of fibrous dysplasia lesions.[64-71] However, these studies had all a retrospective design, and the only randomized controlled trial using oral alendronate compared to placebo conducted in adults and children with fibrous dysplasia failed to show a beneficial effect of this agent over placebo.[72] A possible explanation for this discrepancy in results could be that although a reduction in bone turnover makers was observed in the actively treated group, ALP levels did not significantly decrease in this group, suggesting that the doses used in this study may have been insufficient to achieve optimal outcome. Treatment with bisphosphonates remains thus a subject of controversy in the management of fibrous dysplasia mainly because of the lack of conclusive evidence from randomized controlled studies conducted in large numbers of patients.

Alternative therapeutic options have recently been proposed.[8] On the basis of increased IL-6 levels, that together with RANK-L drives osteoclastogenesis, it has been suggested that treatment with tocilizumab, an IL-6 inhibitor, may be effective in reducing the activity of fibrous dysplasia lesions.[73,74] However, only one case report of a patient with polyostotic fibrous dysplasia that had become refractory to bisphosphonates has demonstrated good outcome of treatment with tocilizumab, and future studies are warranted to fully evaluate this type of treatment in fibrous dysplasia.

A further antiresorptive agent which has been shown to decrease high bone turnover in patients with metabolic bone diseases such as Paget's disease of bone or malignant disease such as metastatic or haematological bone disease as well as in decreasing fracture risk in osteoporosis and may be of promise in controlling the activity of fibrous dysplasia lesions is the RANK-L antibody denosumab, particularly in view of the demonstrated upregulation of RANK-L in fibrous dysplasia.[41,75,76] To date, outcome of treatment of patients with fibrous dysplasia with denosumab has only been reported in case reports, and the efficacy and safety of this agent in the medical treatment of fibrous dysplasia remain to be established.

In conclusion, fibrous dysplasia is a rare bone disorder with a wide clinical spectrum of manifestations. Although we do understand much more about the aetiology and pathology of this fascinating disorder, and have access to more surgical and medical options for its treatment, there are still many knowledge gaps to fill and issues to be addressed to achieve optimal management of this ubiquitous disorder. The impact of all the variable features of fibrous dysplasia on quality of life have hardly been addressed. The likely much more extensive role of *GNAS*-mutations on tissues other than the skeleton have so far included only patients with the more severe polyostotic forms of the disease. Lastly, the heterogeneity of fibrous dysplasia largely complicates choice of treatment and of appropriate outcome measures. The identification of factors which would enable us to better predict potential problems such as increased risk for deformity and fractures or outcome of specific interventions would certainly be instrumental in guiding our choice of treatment in an individualised, patient-tailored fashion, each according to their specific phenotype and attached risk. This will potentially lead to significant improvement in the outcome of available interventions we are now in a position to offer our patients.

AIM OF THE THESIS

As a result of the rare and heterogeneous character of fibrous dysplasia, and the still relative scarcity of data on this disease, clinicians not familiar with the clinical manifestations of fibrous dysplasia often have difficulties in establishing the diagnosis, and even when they do, in subsequently choosing from available treatment options and following up patients. Even the most experienced treating physician may be confronted with similar difficulties, as a number of aspects of fibrous dysplasia remain unexplained. The aim of this thesis is to address some of the gaps in our knowledge about the clinical course of fibrous dysplasia, explore some of its additional extraskeletal manifestations, evaluate its effect on quality of life of patients affected by the disorder and finally evaluate the outcome of the various available surgical and medical treatment options for its management.

OUTLINE OF THE THESIS

Part I: Pain and quality of life in patients with fibrous dysplasia
Based on the distribution and the extent and severity of the disease, there is a wide variation in the scope of complaints in the daily life of patients with fibrous dysplasia. **Chapter 2** specifically focuses on pain in patients in a combined study with the University Hospital Graz, assessing pain levels and possible associated factors for increased pain levels in 197 patients with fibrous dysplasia and McCune-Albright syndrome. **Chapter 3** addresses the quality of life and levels of pain in 97 patients from the Leiden fibrous dysplasia cohort who completed the Short Form 36 and Brief Pain Inventory questionnaires. Differences in Quality of Life scores and outcome of pain assessment are evaluated and compared between the different types of fibrous dysplasia and with data from the general Dutch population. In **Chapter 4**, results are presented from a study into illness perceptions in patients with fibrous dysplasia, involving the same 97 patients from the previous Quality of Life study, who also completed the Illness Perception Questionnaire – Revised. Negative illness perceptions and where possible associated factors are further evaluated in these patients.

Part II: Extraskeletal manifestations in fibrous dysplasia
Over the past decades, there has been an increasing amount of reports pointing towards a more prominent role of *GNAS*-mutations in the scope of extraskeletal manifestations of FD. **Chapter 5** addresses clinical features and prevalence of the

Mazabraud's syndrome, a rare combination of fibrous dysplasia and intramuscular myxomas carrying the same *GNAS*-mutations as the bony lesions. Because of the rarity of the syndrome, this study was performed in a multicentre, European wide design, presenting the opportunity to study a combined cohort of 32 patients with this rare disorder. **Chapter 6** presents a study evaluating a suggested potential link between fibrous dysplasia and the risk of developing breast cancer, possibly as an extraskeletal manifestation of the *GNAS*-mutation. This study was performed in collaboration with the National Institutes of Health in the United States and results were validated with those of the National Dutch Pathology Database (PALGA).

Part III: Surgical treatment of fibrous dysplasia

Historically, surgery has been the primary and often only treatment option in fibrous dysplasia. Although a large part of the available literature on fibrous dysplasia discusses its various surgical options, there is still much debate about which surgical procedure should be performed in specific patient populations. **Chapter 7** evaluates the use of allogeneic strut grafts in fibrous dysplasia of the proximal femur and identifies specific risk factors for this procedure in order to optimize patient selection and treatment outcomes. In **Chapter 8** the role of angled blade plates and intramedullary nails is further addressed in patients with fibrous dysplasia of the proximal femur in a collaborative study with the University Hospital Graz, in Austria. Clinical outcomes of the use of these distinct implants are discussed and an algorithm for the surgical treatment of fibrous dysplasia of the proximal femur is proposed, based on results of the collaborative study as well as on a review of published literature on the subject. **Chapter 9** addresses different treatment options in fibrous dysplasia of the humerus, which demands a different approach compared to fibrous dysplasia lesions of the weight bearing bones. Outcomes of both conservative and surgical treatment are evaluated and risk factors for fractures of the humerus are identified.

Part IV: Medical treatment of fibrous dysplasia

Over the past decades, medical treatment has taken an increasing role in the management of patients with fibrous dysplasia, hoping that decreasing bone turnover may be associated with decreasing symptoms of pain, prevention of progression of fibrous dysplasia lesions, decreasing the risk of deformity and pathological fractures and overall increasing quality of life of patients with fibrous dysplasia. The first agents used in the nineties were various types of bisphosphonates. **Chapter 10** presents a retrospective study into the clinical and biochemical outcomes of treatment with

bisphosphonates in patients with polyostotic fibrous dysplasia and McCune-Albright syndrome, identifying risk factors for an incomplete response or resistance to treatment which may potentially help in the development of individualised patient-tailored approaches for treatment of fibrous dysplasia with these agents. In **Chapter 11** biochemical and clinical outcomes of treatment with Denosumab, a monoclonal antibody to RANK-Ligand, are reported in a small series of patients with severe fibrous dysplasia who exhibited an incomplete response to long-term treatment with high dose bisphosphonates.

A summary and general discussion of the results of this thesis are presented in **Chapter 12 and 13**. A Dutch description of the clinical picture of fibrous dysplasia on the basis of three cases is presented in **Chapter 14**. A summary of this thesis in Dutch is presented in **Chapter 15**.

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FIBREUZE DYSPLASIE
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PART I

Pain and quality of life in fibrous dysplasia

Chapter 2

Pain in fibrous dysplasia: relationship with anatomical and clinical features

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Submitted

ABSTRACT

Background: Fibrous dysplasia (FD) is a rare bone disorder associated with pain, deformities and pathological fractures. The pathophysiological mechanism of FD-related pain remains ill-understood. The objective of this study was to evaluate the degree of severity of pain and the potential contributory factors in two cohorts from Austria and the Netherlands.

Methods: A total of 197 patients with FD (Graz n = 105, Leiden n = 92) completed a survey about the presence and severity of pain at their FD site. Gender, age, type of FD and localization of FD lesions were examined for a relationship with the presence and severity of pain.

Results: Of 197 patients from the combined cohort (61% female, mean age 49 years ± 16.1 SD, 76% monostotic), who completed the questionnaires, 91 (46%) reported pain at sites of FD lesions, with a mean reported pain score of 1.9/10 (± 2.6) in the whole group and 4.1/10 (± 2.3) in patients who reported having pain. Severity of pain was higher ($p = 0.049$) in patients with lesions of the lower extremities and ribs compared to upper extremity or craniofacial lesions. Severe subtypes of FD (PFD/MAS) were associated with both presence ($p = 0.001$) and severity of pain ($p = 0.002$).

Conclusion: Our data suggests that although < 50% of patients with FD report pain at FD sites, this represents a major clinical manifestation of the disorder, also in monostotic disease. We demonstrate that more severe types of FD are predictive for presence and severity of pain, which are also determined by localization of the lesions in lower extremities and ribs.

INTRODUCTION

Fibrous dysplasia (FD) is a congenital, non-inherited rare bone disorder, first described in the late the thirties.[1-3] FD occurs as a result of a postzygotic activating mutation of the *GNAS*-complex in chromosome 20q13, encoding the α-subunit of the stimulatory G-protein (Gsα), resulting in an intracellular increase in cAMP levels in cells of mesenchymal, endodermal or ectodermal origin.[4,5] Skeletal FD lesions are characterized by poorly differentiated osteoblasts and replacement of healthy bone by fibrous tissue limited to one bone (monostotic FD) or extending to multiple bones (polyostotic FD). Bony lesions may thus be single, asymptomatic and accidentally diagnosed in the course of routine radiological examination, but may also be present in multiple skeletal sites and responsible for a wide range of clinical symptoms, predominantly bone pain, bone deformities and pathological fractures.[6] In severe cases skeletal manifestations may also be associated with extraskeletal manifestations in the form endocrinopathies such as precocious puberty, GH-hormone excess, hyperthyroidism and with non-endocrine manifestations such as café-au-lait skin patches in the McCune-Albright syndrome (MAS) or intramuscular myxomas in the Mazabraud's syndrome.[7]

Although pain is a major clinical manifestation of FD, its pathophysiology remains to date ill-understood. In a previous study we have shown that pain is a major determinant of impaired quality of life in patients with FD.[8] It has also been shown that FD-pain is negatively age-related, suggesting that FD lesions may undergo age-related changes that favor a less active disease-state and may thus exhibit less prevalence and less severity of pain, as a patient gets older.[9,10] This notion is further supported by studies reporting lower fracture rates, denser and more sclerotic changes on plain radiography of FD lesions and fewer characteristic histologic features of FD such as fibrotic changes and ill-woven bone texture in older patients.[11,12] Despite this potential tendency for FD to become more quiescent as a patient ages, pain has also been reported to increase over time in some patients, possibly due to secondary arthritic changes in adjacent joints.[10] Pain is one of the main and most debilitating clinical manifestations of FD at all ages, and its management remains problematic, as its underlying mechanism is as yet to be unravelled.[13]

The aim of the present study was to examine the prevalence and severity of pain in a combined cohort of 197 patients from two specialized bone centers in Austria and the Netherlands, with an established diagnosis of FD and a representative wide clinical spectrum of the disease. A further aim of the study was to examine the relationship

between a number of clinical and demographic factors and the presence and severity of pain.

PATIENTS AND METHODS

Study design

This study addresses the prevalence and severity of pain in FD was conducted using a cross-sectional study design, with in all patients with an established diagnosis of FD seen at the Medical University of Graz [MUG] between 1984 and 2016 and at the Leiden University Medical Center [LUMC] between 2012 and 2015 as identified from the respective centres' Hospital registries. All identified patients were invited to take part in the study either by means of an interview (Graz cohort) or by completing a validated questionnaire (Leiden cohort). Additional demographic, clinical and radiologic data were retrieved from the patients' medical records and the two cohorts were combined into one large single cohort before analysis of data.

Patients and methods

A total of 146 patients who were evaluated and treated at the MUG between 1984 and 2016 were approached by phone for an interview on the presence of pain on the basis of the validated Pain Numeric Rating Scale (PNRS), a standardized 11-step pain score validated for use in the assessment of pain in clinical trials.[14]

A total of 138 patients who were seen at the outpatient clinic of the LUMC over a period of 3 years before the start of the study were invited by mail to complete the Brief Pain Inventory (BPI) questionnaire as previously described.[8] Patients who did not respond to the questionnaires by mail were contacted by phone, with a maximum two attempts in case of no answer.

Out of 146 patients from the MUG cohort who were contacted by phone, 105 agreed to be interviewed by phone (response rate 71.9%) and out of the 138 patients from the LUMC cohort who were invited to take part in the study by mail, 92 returned a completed BPI (response rate 66.7%), resulting in a combined cohort of 197 patients in whom data on pain was available for analysis.

Collected data included data on the presence of absence of pain (yes/no) and when present, the severity of current pain on a scale ranging from 0 to 10 with 0 indicating 'no pain' and 10 indicating 'the worst possible pain imaginable'. Data on gender, age, type

of FD (monostotic/polyostotic/McCune-Albright syndrome/Mazabraud syndrome) were retrieved from the patients' medical records at the respective medical centres. Data were also retrieved on the localizations of FD lesions including the craniofacial region, upper extremity, lower extremity including the pelvis, ribs and spine. Skeletal burden scores (SBS) were independently scored from T^{99m}-skeletal scintigraphy images by two authors (BCJM and NMA-D) only in patients from the LUMC cohort.[15]

Statistical analysis

Statistical analysis was performed using SPSS Statistics 23.0 (SPSS, Inc., Chicago, IL, USA). Results are presented as mean (± SD) or as median (intermediate range) and in case of categorical data as percentages. Difference in pain between FD localizations (e.g., craniofacial, upper extremity, lower extremity, ribs and spine) was assessed using the ANOVA test. Only monostotic patients were included in this sub-analysis in order to evaluate a potential difference in pain symptoms between different FD localizations. Other potential risk factors (e.g., age, gender, type of FD) were analysed using logistic regression analysis for the presence of pain (yes/no), and with linear regression analysis for the extent of current pain on a scale from 0 to 10. Both analyses were primarily performed using univariate analysis followed by a multivariate analysis except for SBS, as only patients from one cohort had available data for SBS.

RESULTS

Patient characteristics

Characteristics of the combined cohort are shown in Table 2.1. There was a distinctive predominance for the female gender (120 women vs. 77 male). Mean age at the time of pain assessment was 49.0 years (± 16.1 SD), and mean overall follow-up was 15.8 years (± 11.3 SD). The majority of patients (n = 149, 76%) had monostotic FD, 38 had polyostotic FD (20%), 9 had McCune-Albright syndrome (5%), and 6 patients (3%) had Mazabraud's syndrome. The lower extremity was the most common localization of FD (n = 103, 52%), followed by the craniofacial region (n = 51, 26%), ribs (n = 38, 19%), upper extremity (n = 32, 16%) and spine (n = 22, 11%). In the LUMC cohort, mean SBS was 8.2 ± 10.8 SD and was significantly higher in patients with MAS compared to those with polyostotic FD (respectively 28.8 ± 16.7 SD and 12.9 ± 7.6 SD, $p < 0.001$), and SBS was in turn significantly higher in PFD compared to monostotic FD (respectively 12.9 ± 7.6 SD and 1.4 ± 1.3 SD ($p < 0.001$). Of the total of 197 patients, 133 patients (68%) had

previous surgical interventions at some time prior to filling the questionnaire and 63 patients (32%) had been previously treated or were currently using bisphosphonates. However, these latter data were not used in the final analysis of factors potentially affecting presence or severity of pain, due to the heterogeneity in agents, doses, schedules and duration of use of these agents in this combined FD cohort.

Differences between the Dutch and Austrian FD cohorts (Table 2.1)

Patients from the LUMC cohort (n = 92) were significantly younger compared to patients from the MUG cohort (n = 105) (46.1 ± 15.3 SD and 51.5 ± 16.4 SD respectively, p = 0.02). The LUMC cohort also included more patients with polyostotic FD and MAS than the MUG cohort (p < 0.001). There were no other differences in demographic or clinical features between the two cohorts. Data on SBS were only available for the LUMC cohort, so that these data were also not included in the analysis of factors potentially affecting presence and severity of pain in FD.

Table 2.1 Cohort characteristics and differences between the two cohorts

	MUC	LUMC	Difference	Total
Number of invited patients	146	138		284
Included patients (response rate)	105 (71.9%)	92 (66.7%)		197 (69.4%)
Male - Female	45–60	32–60	p = 0.249	77–120
Mean age in years	51.5 ± 16.4	46.1 ± 15,3	p = 0.020	49.0 ± 16.1
Mean follow-up in years	15.1 ± 7.80	16.7 ± 14.1	p = 0.296	15.8 ± 11.3
Type of FD				
Monostotic	90 (86%)	58 (63%)	p < 0.001	149 (76%)
Polyostotic	12 (%)	26 (28%)	p < 0.001	39 (20%)
McCune-Albright	1 (1%)	8 (9%)	p < 0.001	9 (5%)
Mazabraud's syndrome	1 (1%)	5 (5%)	p = 0.106	6 (3%)
Localization of FD				
Craniofacial	29 (28%)	22 (24%)	p = 0.556	51 (26%)
Upper extremity	24 (23%)	8 (9%)	p = 0.118	32 (16%)
Lower extremity	63 (60%)	40 (45%)	p = 0.004	103 (52%)
Ribs	27 (26%)	11 (3%)	p = 0.003	38 (19%)
Spine	11 (11%)	11 (13%)	p = 0.902	22 (11%)
Skeletal burden score	-	8.2 ± 10.8	-	-

Prevalence and severity of pain across the clinical spectrum of fibrous dysplasia

Out of a total of 197 survey responders, 91 (46%) reported having pain at the site of their FD lesions (Fig. 2.1). Overall, mean severity of pain was 1.9 ± 2.6 SD in the combined FD cohort as reflected by pain scores on a scale from 0 to 10. In the group of patients reporting having pain at the time of the survey, mean pain score was 4.1 ± 2.3 SD. A higher proportion of patients with monostotic lesions of the lower extremity (49%) or ribs (39%) reported having pain (yes/no) compared to patients with monostotic lesions of the upper extremity (26%) or craniofacial region (26%), although these differences in prevalence of pain were not statistically significant. In contrast, there was a significant difference ($p = 0.049$) in severity of pain between monostotic lesions depending on their localisation. Pain was thus reported to be most severe in patients with monostotic lesions of the lower extremity (2.01 ± 2.7 SD), followed by ribs (1.72 ± 2.5 SD), upper extremity (0.89 ± 2.0 SD) and lastly craniofacial lesions (0.79 ± 1.7 SD).

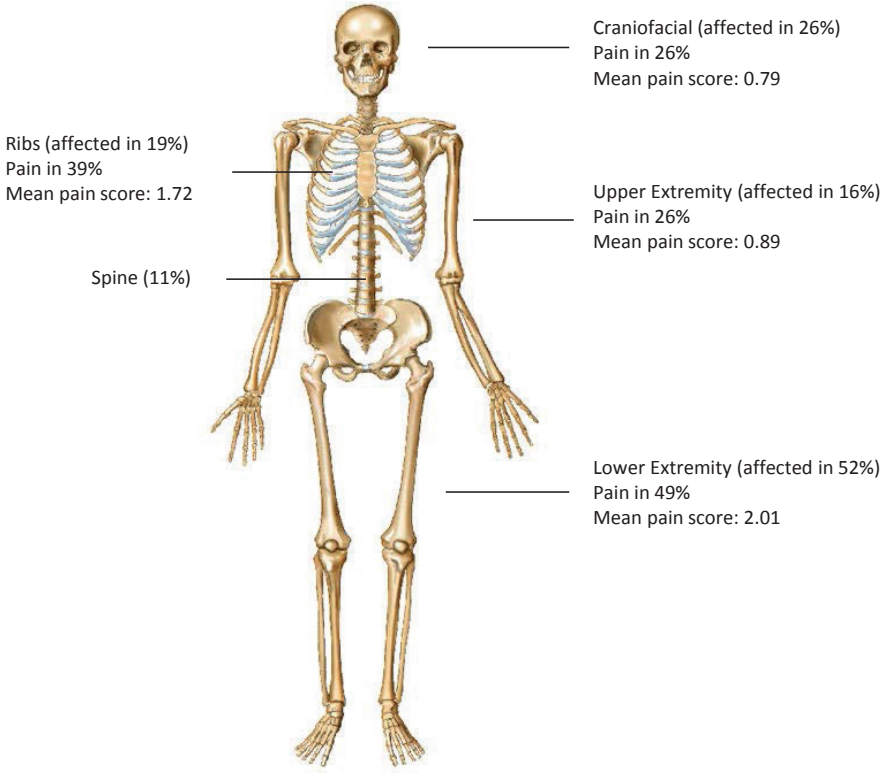

Fig. 2.1 Distribution FD localization in the cohort of monostotic patients. The presence of pain (yes/no) and the mean pain scores in the group of monostotic patients is highest in patients with lesions of the lower extremity and lowest in patients with craniofacial FD. There were no monostotic patients with FD localizations of the spine.

Potential risk factors for pain in fibrous dysplasia (Table 2.2)

Univariate regression analysis showed that only the more severe types of FD were predictive for both the presence (Beta: 1.010, p = 0.001) and severity of pain (Exp. (B): 0.224, p = 0.002). There was no relationship observed between gender or age and the presence or severity of reported pain. After correction for age and gender, severe type of FD remained the only predictor for the presence and severity of pain in multivariate analysis (respectively Beta: 0.359, p = 0.001 and Exp. (B): 0.221, p = 0.002).

Table 2.2 Clinical factors that attribute to pain in FD

	Gender		Age		Type of FD	
	Beta/Exp (B)	**Sig.**	**Beta/Exp (B)**	**Sig.**	**Beta/Exp (B)**	**Sig.**
Univariate analysis						
Pain (yes/no)	0.571	0.055	-0.007	0.457	*1.010*	*0.001*
Severity of pain	0.125	0.079	-0.017	0.811	*0.224*	*0.002*
Multivariate analysis						
Pain (yes/no)	0.556	0.059	0.995	0.575	*0.359*	*0.001*
Severity of pain	0.123	0.083	0.002	0.973	*0.221*	*0.002*

DISCUSSION

This survey on the prevalence and severity of pain in patients with FD from a large combined cohort from Austria and The Netherlands highlights the importance of this clinical manifestation of FD, with nearly one in two patients reporting having pain at the site of their FD lesions. Patients reporting having pain had relatively high pain scores with a mean score of 4.1 ± 2.3 (SD) out of a maximum of 10. In patients with monostotic lesions, pain was more often present and was more severe when the FD lesions were localized in the lower extremities or ribs compared to lesions localized in the craniofacial region or upper extremities. Severity of type of FD was predictive for the presence of pain and for its severity as expressed by higher pain scores.

A high prevalence of pain of 81% has been previously reported among adult patients with FD, although a lesser prevalence of 49% was reported in a similarly conducted more recent study.[10,16] In contrast with the earlier study but in keeping with the latter, we document that in our combined FD cohort less than half of the patients reported pain of any nature or localization at the time of completing the questionnaire/interview. This discrepancy in findings between studies addressing the prevalence of

pain in FD might be explained by the composition of our combined cohort in which a high proportion of patients had monostotic FD (76%). Two studies addressing Quality of Life (QoL) in FD have shown that patients with FD have lower scores in the bodily pain domain of the SF-36 compared to the general population.[8,17] We hypothesized that patients with limited monostotic FD would express less pain than patients with multiple polyostotic lesions, who in turn expressed less pain than patients with McCune-Albright syndrome. Our results are in line with our group's recent report on QoL in FD, which shows similar FD type-related impairments in the SF-36 domain of bodily pain.[8] Our data from this survey suggest that similar to the previously demonstrated prognostic value of type of FD (MFD/PFD/MAS) for physical and social function, type of FD also determines the presence and severity of pain.

Interestingly, monostotic patients with lesions of the lower extremities demonstrated the highest prevalence and severity of pain compared to lesions localized elsewhere in the skeleton. This is in keeping with the previously published observation that FD lesions of the lower extremities are responsible for the majority of pain symptoms in a cohort of mostly polyostotic patients.[10] Our results from the sub-analysis of the prevalence and severity of pain in patients with monostotic FD at different localizations confirm this observation by precluding the potential confounding factor of pain arising from FD lesions at sites other than the lower extremities. FD of the lower extremities, the weight bearing forces acting on these extremities combined with the poor quality of FD bone result in these long bones being more prone to deformities and pathological fractures, and thus to a higher prevalence and severity of pain, particularly in case of the femur.[11,16,18,19] FD lesions in weight-bearing bones of the lower extremities are also less likely to fully benefit from surgical interventions compared to lesions of non-weight bearing bones.[18,20] Although severe pain has been described in patients with CFD, with headaches shown to respond to intermittent treatment with bisphosphonates, our data, in keeping with those of Kelly et al., showed a low prevalence and severity of pain in patients with craniofacial FD.[10,21,22] In the current study we were unable to evaluate the role of different forms of medical or surgical treatment on the presence or severity of pain levels.

High SBS has been reported to be associated with high circulating levels of bone turnover markers and of FGF-23 and with impaired QoL, including pain, in a number of studies.[8,10,15,23] These published data suggest that the extent of the osseous distribution of FD lesions would be a major cause for the presence and severity of pain in patients with demonstrated high skeletal burden scores as seen in polyostotic FD and MAS. Intriguingly, however, we found no association between SBS and pain

in our study, providing further evidence that factors other than extent of FD lesions, such as anatomical location and age-related changes,[10] may also be responsible for the prevalence and severity of pain in patients with FD also those with the milder monostotic types, particularly of the lower extremities. In our study, we indeed show that localization of FD lesions was a main determinant of the presence and severity of pain. Whereas the precise mechanism of pain in FD remains elusive, extra-skeletal factors may also play a role, as observed in patients with MAS, who report significantly more pain than patients with polyostotic FD with no extra-skeletal manifestations of FD. Neurogenic involvement may also play a role as alluded by Chapurlat et al.[24] These results hold significant clinical implications in the management of patients with FD, as they highlight the fact that small, monostotic lesions may be associated with severe pain depending on their anatomical location. For example, a patient with a small monostotic lesion of the proximal femur may experience more pain than a patient with extensive disease of the humerus. The potential contributory role of extra-skeletal factors in the pathogenesis of pain in FD may help explain non-response or poor response to treatment with bone-modifying agents such as bisphosphonates.

In our cohort of patients with FD, age did not appear to influence the prevalence and severity of pain. The discrepancy between our data and those of Kelly who showed a higher prevalence and severity of pain in paediatric than in adult FD patients[11] is likely to be due to the non-inclusion of paediatric patients in our study. The difference in prevalence and severity of pain before and after growth is completed, suggests a contributing role for factors associated with growth in the pathophysiology of pain in FD, a role that fades away as adulthood is attained.

Whereas women are generally believed to experience more pain than men, we observed no gender difference in the severity of pain, although female FD patients did report a higher prevalence of pain.[25,10]

Strengths and limitations of our study

One of the main strengths of our study is the inclusion of patients with different types of FD from two relatively large cohorts from two different countries in whom data on the prevalence of pain and its severity were specifically and individually collected by interview or questionnaire. A further strength of the study is the predominance of patients with monostotic FD, compared to earlier studies including a lesser proportion of these patients, which allowed us to determine the relevance of anatomical localization of isolated FD lesions in the prevalence and severity of pain.

Our study has also a number of limitations, including the use of two different, albeit comparable questionnaires, to calculate pain scores and the single time-point measurement of pain, as opposed to repeated measurements, which might have allowed us to demonstrate a pattern for the pain. Also, we did not include data on previous surgery and treatment with bisphosphonates in our analysis of pain in these patients. Although pain levels are presumably related to these interventions, the heterogeneity of surgical and medical interventions precludes any conclusions on the effect of these interventions on pain in this cross-sectional study. Ideally, analysis of medical and surgical forms of treatment

CONCLUSION

Data from this study addressing the prevalence and severity of pain in patients with FD from one of the largest (combined) cohorts representative of the wide clinical spectrum of the disease confirm that pain is a major clinical manifestation of this disorder in one in two patients, also in case of limited monostotic FD. Our data demonstrate that although the more severe types of FD (PFD/MAS) are predictive for presence and severity of pain, these are also determined by the localization of the lesions in the weight-bearing lower extremities and in the ribs compared to craniofacial lesions and lesions of the upper extremities also when limited to single monostotic lesions. These results hold significant clinical implications in the management of patients with FD, as they highlight the fact that small, monostotic lesions may be the source of severe pain depending on their anatomical location and that these lesions may benefit from treatment with antiresorptive agents that are currently largely restricted to the management of patients with the more severe forms of FD. Further studies are warranted to fully unravel the pathophysiologic mechanism of pain across the wide clinical spectrum of fibrous dysplasia.

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Chapter 3

Determinants of impaired quality of life in patients with fibrous dysplasia

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ABSTRACT

Background: Fibrous dysplasia is a rare bone disorder, commonly associated with pain, deformity and fractures, which may significantly impact on quality of life. In this study we evaluate quality of life in patients with fibrous dysplasia using the Short Form-36 and the Brief Pain Inventory questionnaires. Data were compared with those of the general Dutch population.

Results: Out of 138 patients from a cohort of 255 patients with fibrous dysplasia that were sent questionnaires assessing quality of life and pain, the response rate was 70.3%, with 97 patients, predominantly female (65%), completing the questionnaires. Monostotic fibrous dysplasia was predominant (n = 62, 64%). Fibrous dysplasia patients had significantly lower quality of life outcome scores than the general Dutch population for all tested domains of the Short Form-36 except for the "Mental health" and the "Role emotional" domains. More severe forms of fibrous dysplasia, had the more severe Short-Form-36 quality of life outcomes, but there was no significant difference in Brief Pain Inventory domains between different subtypes of fibrous dysplasia. Quality of life was lower in patients with higher disease burden, as reflected by high skeletal burden scores ($p = 0.003$) and high levels of P1NP ($p = 0.002$).

Conclusion: We demonstrate impairments in all domains of quality of life, except for 'Mental health' and 'Role emotional' domains, across the wide spectrum of fibrous dysplasia including its milder forms. We identified high skeletal burden scores, reflecting disease severity, as the most consistent predictor of impaired quality of life. Our findings hold significant clinical implications as they draw attention to the clinically unmet need to address quality of life issues in the management of patients with all subtypes of fibrous dysplasia, including its milder forms.

BACKGROUND

Fibrous dysplasia (FD) is a rare congenital bone disorder, caused by a missense mutation of the GNAS-gene.[1] The bony lesions may involve one bone (monostotic FD), or multiple bones (polyostotic FD), and be associated with extra skeletal manifestations such as endocrinopathies (precocious puberty and growth hormone excess) and/or café-au-lait patches in McCune-Albright syndrome (MAS), or intramuscular myxomas in Mazabraud syndrome. The disorder often manifests itself in childhood, presenting with bone pain, deformities or a pathological fracture, although the disease may be also asymptomatic, with bony lesions being incidentally identified on radiographic imaging.[2] The clinical spectrum of FD is thus very broad, varying from the mild asymptomatic single bone lesion in the monostotic forms of the disease, to the potentially crippling polyostotic forms, with or without additional extraskeletal manifestations, which may considerably impact on various aspects of quality of life.

Quality of life (QoL) is defined as "the functional effect of an illness and its consequent therapy upon a patient, as perceived by the individual patient" and may thus significantly vary between individual patients with the same disease.[3] QoL can be assessed by the use of generic questionnaires, such as the Short-Form 36 (SF-36) questionnaire, or by disease-specific or domain-specific questionnaires, including questionnaires on symptoms associated with the condition under study such as the Brief Pain Inventory (BPI) to assess pain.[4,5] Data on QoL are scarce in FD. Physical function scores have been reported to be lower in 56 adult patients with polyostotic FD than those reported in the general US population.[3] The same study identified a direct relationship between "Physical function" scores and skeletal burden scores (as calculated from Tc-99m skeletal scintigraphy images), which reflect disease-extent and thus severity. However, Social and Emotional domains were not affected by disease severity, illustrating the relative independence of 'objective' severity of a medical condition and its effects on the quality of life of patients.[6]

The aim of our study was to evaluate QoL in a large cohort of well-characterized FD patients followed up at the Center for Bone Quality of the Leiden University Medical Center for up to 25 years. A further aim of our study was to evaluate whether patients with the different subtypes of FD (monostotic FD, polyostotic FD, or MAS) are differentially affected in their QoL. We hypothesized that patients with MAS, with the more extensive skeletal lesions and endocrinopathies, would exhibit more impaired QoL compared to the less severely affected patients with monostotic and

polyostotic FD. A last aim of our study was to assess potential factors contributing to impaired QoL, including extent of skeletal burden, presence and severity of pain and biochemical parameters of bone turnover as potentially reflecting FD disease activity.

METHODS

Patients recruited for this study belonged to our Center's well-characterized cohort of patients with FD, which consists of 255 patients with a full spectrum of FD subtypes: monostotic, polyostotic, MAS and Mazabraud's syndrome.[7] Patients were invited to participate in this cross-sectional study on the basis of the following criteria: age16 years or older who had a fixed current address (to insure that they could be reached), and who had been seen at least once at our outpatient clinic within the preceding three years. These inclusion criteria were fulfilled by 138 patients who were sent letters to their registered home addresses, inviting them to complete the QoL questionnaires (Fig. 3.1). Patients who failed to respond to our letter of invitation were contacted by telephone.

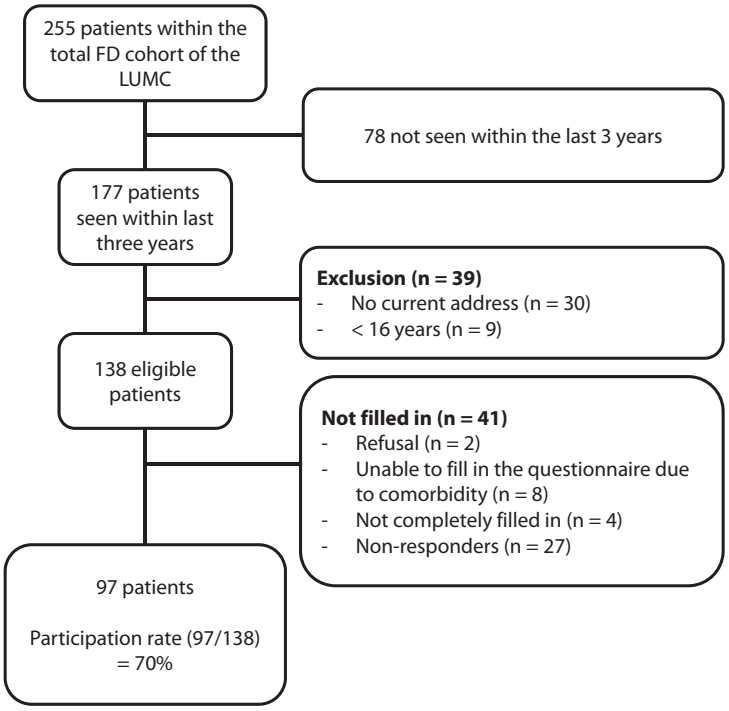


Fig. 3.1 Flowchart of patient inclusion.

Two patients refused to take part in the study, 8 patients were unable to complete the questionnaires because of non-FD related comorbidities, and 27 patients who did not respond to our letter of invitation and could also not be contacted by telephone. There were no significant differences in age, type of FD or skeletal burden scores between patients who responded (n = 97) and those who did not, but more women responded than men (p = 0.039).

The protocol was approved by the Medical Ethics Committee of the LUMC and written informed consent was obtained from all patients who completed the questionnaires.

Clinical and sociodemographic characteristics

The diagnosis of FD was established in all patients on the basis of clinical and radiological features, occasionally requiring additional histologic confirmation. Sociodemographic parameters were retrieved from the patients' electronic medical records. Level of education was determined on the basis of the International Standard Classification of Education (ISCED). A low level of education was defined as a primary to lower secondary education; a medium level of education was defined as an upper secondary to post-secondary non-tertiary education; and a high level of education was defined as the first and second stage of tertiary education. Data on age, gender, age at diagnosis, level of education, type of FD, extra-skeletal manifestations (e.g. precocious puberty, GH-excess, café-au-lait patches), prevalence of fractures and details of therapy, surgical and/or medical, were also documented. Data on biochemical parameters of bone turnover were also retrieved from the patients' records when obtained within two months before or after completing the questionnaires. These included data on total alkaline phosphatase (ALP), as measured by a colorimetric method on the Roche

Modular P800 analyser from Roche Diagnostics, Almere, The Netherlands, and on procollagen 1 amino-terminal propeptide (P1NP) and beta crosslaps (CTX), both measured using an electrochemoluminescent immunoassay with a Modular Analytics E-170 system (Roche Diagnostics, Almere, The Netherlands. Data were also retrieved for C-terminal FGF-23 (Immutopics, San Clemente, CA, USA) as measured using the BioTek ELx50 Washer (BioTek, Bad Friedrichshall, Germany) after short storage at −20°C prior to analysis.[8] Two authors (BCJM and NMA-D), who were blinded to the identity of the patients, evaluated the 99Technetium skeletal scintigraphic images, when performed within the three years preceding entry in the study, for calculation of skeletal burden scores (SBS). Differences in scores were resolved by consensus.[9] In the analysis of potential factors impacting on QoL, we differentiated between constant factors such as SBS, shown not to alter after skeletal growth is completed,

and potentially variable factors such as circulating levels of biochemical markers of bone turnover and FGF-23.

Questionnaires

Short form-36

The SF-36 questionnaire has been shown to be a reliable instrument for the evaluation of various domains of QoL in individuals older than 14 years.[4] In this study, we used all collected domain scores of this validated questionnaire to evaluate various aspects of QoL and data were compared with reference scores of the general Dutch population (n = 1742).[10]

Brief pain inventory

The BPI is an assessment tool that was originally designed to assess pain in patients with cancer.[5] This tool is now also validated in the assessment of nononcological pain and has been widely used in the protocol of a number of clinical trials evaluating pain of different pathophysiologies.[11-13] Domain scores of the BPI include 'Pain severity' and 'Pain interference', which were both used as outcome parameters for our study.

Statistical analysis

Statistical analysis was performed using SPSS for Windows, Version 23.0 (SPSS, Inc., Chicago, IL, USA). Results are presented as mean (±SD) or as median (intermediate range) and in case of categorical data as a percentage. SF-36 domain scores were compared with the SF-36 reference scores of the Dutch population by using pooled T-tests. Outcomes of the SF-36 and BPI domain scores were compared between different types of FD (monostotic/polyostotic/MAS) using an ANOVA test, with post hoc analysis applied when appropriate. Possible predictors for impaired QoL such as skeletal burden score and biochemical markers of bone turnover at time of completing the questionnaire were assessed with both univariate and multivariate linear regression analysis. Level of significance was set at $p \leq 0.01$ to correct for multiple testing.

RESULTS

Patients' characteristics (Table 3.1)

Response rate was 70.3%, with 97 patients, predominantly female patients (n = 63, 65%), completing the questionnaire. Median age at diagnosis was 29 years (range 1–68 years), and median age at completion of the questionnaire was 46 years (range 16–80

Table 3.1 Patient characteristics

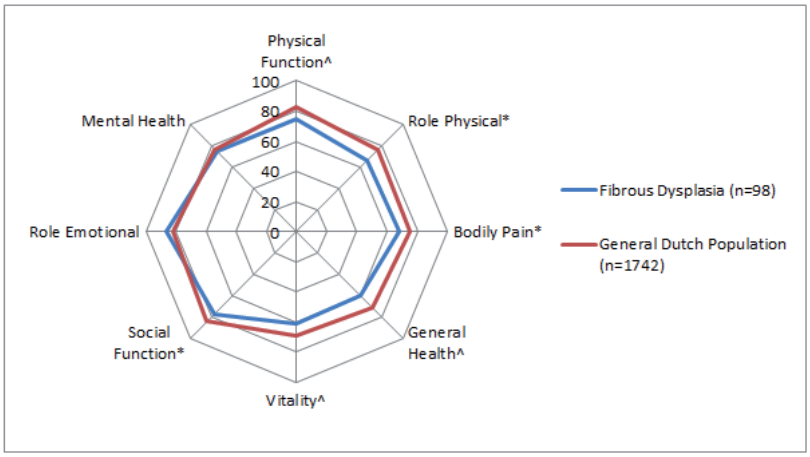
	(n = 97)
Gender (male/female)	34/63
Age	46 (16–80)
Educational level	Low 10 (10%) Medium 24 (25%) High 46 (47%) Unknown 17 (18%)
Type of FD	Monostotic 62 (64%) Polyostotic 26 (27%) McCune-Albright 9 (9%) Mazabraud 5 (5%)
Follow-up (years)	12 (0–62)

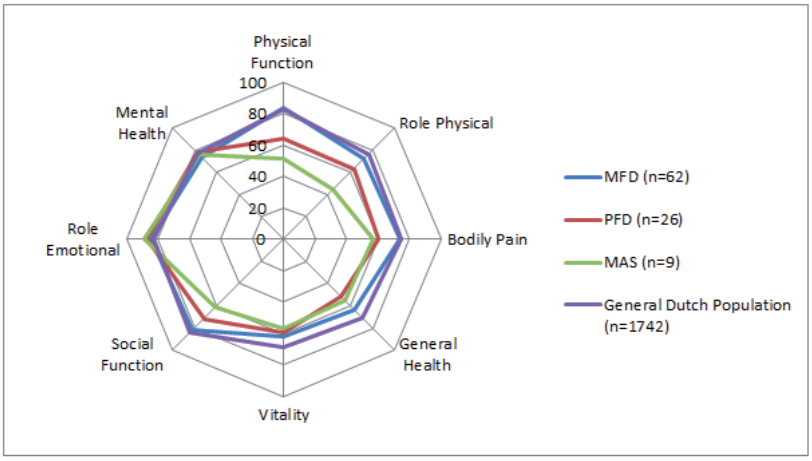
Data are median (range) or number and percentage.

years). Median duration of follow-up after diagnosis of FD was 12 years (range 0–62 years). Level of education was 'low' in 10 patients, 'medium' in 24 patients and 'high' in 46 patients. Data on level of education were missing in 17 patients. Patients included in the study had predominantly monostotic FD (n = 62, 64%), 26 had polyostotic disease (27%), 9 patients had MAS (9%) and five had Mazabraud's syndrome (5%). Mean skeletal burden score was 8.68 ± 12.40 SD. Fifty-six patients (58%) had received bisphosphonate treatment at some stage before completion of the questionnaires. There were significant differences in SBS ($p < 0.001$), average FGF-23 ($p = 0.002$), prevalence of at least one fracture ($p < 0.001$) and a history of surgery ($p < 0.001$) between the various types of FD. There was, thus a consistent trend towards more severe QoL outcomes in the more severe forms of FD, with poorer outcomes observed in MAS compared to polyostotic FD, and in polyostotic compared to monostotic FD.

SF-36 and BPI outcomes

Patients with FD had significantly lower QoL outcome scores than the general Dutch population for all domains of the SF-36 except for the "Mental health domain" and the "Role emotional domain" (Fig. 3.2A).[10] Outcomes were thus significantly worse in FD compared to the general population for the "Physical Functioning domain" (75 vs. 83, $p < 0.001$), "Role Physical domain" (66 vs. 76, $p = 0.007$), "Bodily Pain domain" (68 vs. 75, $p = 0.007$), "General Health domain" (59 vs. 71, $p < 0.001$), "Vitality domain" (61 vs. 69, $p < 0.001$) and "Social Functioning domain" (77 vs. 84, $p = 0.004$). Compared to the general population, MFD patients had significant impairments in "General Health" and "Vitality", PFD patients in "Physical Function", "Bodily Pain", "General Health", "Vitality"





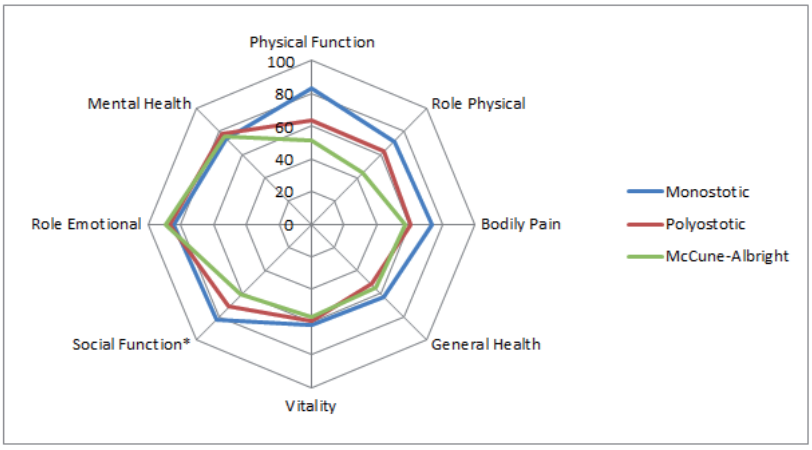


Fig. 3.2 Radar charts comparing the QoL between FD patients and the general Dutch population (a), subtypes of FD and the general Dutch population (b) and differences between de subtypes of FD (c). Significant differences are illustrated by ^ $p < 0.05$ or * $p < 0.001$.

and "Social Function" and lastly, patients with MAS had significant impairments in all domains except for "Vitality", "Role Emotional" and "Mental Health" (Fig. 3.2B and Tables 3.2 and 3.3).

Subgroup analysis yielded a further significant difference between the subtypes of FD for the Physical Functioning ($p < 0.001$), Social Functioning ($p = 0.016$) and Bodily Pain ($p = 0.015$) domains, with increasingly lower QoL scores observed in the more severe types of FD (Fig. 3.2C and Tables 3.2 and 3.3). Patients with MAS demonstrated

Table 3.2 Comparison of SF-36 scores between subgroups of fibrous dysplasia and the general population

SF-36	Monostotic n = 62	Polyostotic n = 26	McCune-Albright n = 9	General population n = 97
Physical Function	83.1 (20)	63.9 (26)$^{\beta}$	51.1 (34)$^{\beta}$	83.0 (22)
Role Physical	71.7 (39)	63 (44)	44.4 (39)$^{\beta}$	76.4 (36)
Bodily Pain	73.9 (25)	60.5 (27)$^{\beta}$	57.1 (25)$^{\alpha}$	74.9 (23)
General Health	63.1 (23)$^{\beta}$	52 (22)$^{\beta}$	55.6 (30)$^{\alpha}$	70.7 (20)
Vitality	62.2 (18)$^{\alpha}$	59.4 (19)$^{\alpha}$	57.2 (16)	68.6 (19)
Social Function	82.3 (21)	71.5 (28)$^{\beta}$	61.1 (33)$^{\beta}$	84.0 (22)
Role Emotional	84.3 (31)	87.5 (29)	88.9 (24)	82.3 (32)
Mental Health	73.6 (18)	77.7 (14)	75.6 (10)	76.8 (17)

Data are mean (SD).
$^{\alpha}$ $p < 0.05$ compared to the general population.
$^{\beta}$ $p < 0.01$ compared to the general population.

Table 3.3 Comparison of SF-36 scores between subgroups of fibrous dysplasia

SF-36	Monostotic n = 62	Polyostotic n = 26	McCune-Albright n = 9
Physical Function	83.1 (20)$^{\beta,\gamma}$	63.9 (26)$^{\alpha}$	51.1 (34)$^{\alpha}$
Role Physical	71.7 (39)	63 (44)	44.4 (39)
Bodily Pain	73.9 (25)$^{\beta}$	60.5 (27)$^{\alpha}$	57.1 (25)
General Health	63.1 (23)	52 (22)	55.6 (30)
Vitality	62.2 (18)	59.4 (19)	57.2 (16)
Social Function	82.3 (21)$^{\gamma}$	71.5 (28)	61.1 (33)$^{\alpha}$
Role Emotional	84.3 (31)	87.5 (29)	88.9 (24)
Mental Health	73.6 (18)	77.7 (14)	75.6 (10)

Data are mean (SD).
$^{\alpha}$ $p < 0.05$ compared to Monostotic.
$^{\beta}$ $p < 0.05$ compared to Polyostotic.
$^{\gamma}$ $p < 0.05$ compared to McCune-Albright.

particularly low scores for the Physical Function (51.1 ± 34) and Role Physical (44.4 ± 39) domains, and both MAS and PFD patients had significantly lower scores for the Bodily Pain (respectively 57.1 ± 25 and 60.5 ± 27), General Health (respectively 55.6 ± 30 and 52.0 ± 22) and Vitality (respectively 57.2 ± 16 and 59.4 ± 19) domains compared to scores in these domains in patients with monostotic FD. Scores did not significantly differ between subtypes of FD in the other 5 SF-36 domains, or in both BPI domains, although polyostotic FD and MAS patients had consistently higher scores than monostotic FD patients in both BPI domains (Table 3.4).

Table 3.4 Comparison of BPI scores between subgroups of FD

BPI	Monostotic n = 62	Polyostotic n = 26	McCune-Albright n = 9	Total n = 97
Pain Severity	3.0 (2.7)	3.9 (2.7)	4.1 (1.9)	3.4 (2.6)
Pain Interference	2.3 (2.6)	3.1 (2.8)	1.0 (0.8)	2.3 (2.6)

Data are mean (SD).
[α] $p < 0.05$ compared Monostotic FD.
[β] $p < 0.05$ compared Polyostotic FD.
[γ] $p < 0.05$ compared with McCune-Albright.

Clinical predictors of impairment in QoL

Univariate regression analysis identified female gender ($\beta = -17.6$; $p = 0.002$), high SBS ($\beta = -1.08$; $p < 0.001$), high serum concentrations of FGF-23 ($\beta = -0.15$; $p = 0.01$) and of P1NP ($\beta = -0.05$; $p = 0.001$) as significant predictors for impaired Physical Function. High SBS was also associated with low Social Function ($\beta = -0.65$; $p = 0.01$) and high levels of P1NP with impaired General Health ($\beta = 0.03$; $p = 0.01$) and impaired Role Emotional ($\beta = 0.06$; $p = 0.001$). Age and serum levels of ALP and CTX were not associated with any of the QoL domains in univariate regression analysis (Table 3.5).

Multiple regression analysis was performed including age, gender, P1NP and SBS. FGF-23 and ALP were excluded, as these parameters are known to be respectively correlated with SBS and P1NP.[7,9] Both high SBS ($\beta = -0.82$; $p = 0.003$) and high levels of P1NP ($\beta = -0.04$; $p = 0.002$), but not female gender, remained significant predictors for impaired physical function as evaluated by SF-36 (Table 3.5). High serum levels of P1NP still predicted impaired Role Emotional ($\beta = -0.06$; $p < 0.001$), but no longer General Health ($\beta = -0.03$; $p = 0.012$) as shown in univariate analysis. Other SF-36 and BPI domains were not affected by any of the factors studied in the multivariate analysis (Table 3.5 and 3.6).

Table 3.5 Attributive factors in SF-36 domains

	SBS		FGF-23		ALP		P1NP		CTX	
SF-36 domains	**R**	**Sig.**	**R**	**Sig.**	**R**	**Sig.**	**R**	**Sig.**	**R**	**Sig.**
PF	*-0.51*	*<0.001*	*-0.49*	*<0.001*	-0.11	0.431	-0.08	0.583	-0.11	0.445
RP	-0.18	0.172	-0.20	0.175	0.01	0.577	-0.06	0.692	-0.01	0.992
BP	-0.11	0.365	-0.22	0.117	0.13	0.328	0.10	0.433	0.07	0.600
GH	-0.01	0.978	-0.22	0.112	0.03	0.835	-0.05	0.700	0.02	0.892
VT	0.03	0.839	-0.13	0.374	0.19	0.147	-0.07	0.628	-0.09	0.516
SF	0.32	0.316	-0.20	0.159	-0.15	0.245	-0.03	0.807	-0.02	0.861
RE	-0.01	0.956	-0.15	0.313	-0.04	0.766	-0.32	0.018	-0.15	0.279
MH	0.21	0.111	-0.07	0.639	0.19	0.180	0.09	0.518	0.03	0.837

Table 3.6 Attributive factors in BPI

	SBS		FGF-23		ALP		P1NP		CTX	
BPI domains	**R**	**Sig.**	**R**	**Sig.**	**R**	**Sig.**	**R**	**Sig.**	**R**	**Sig.**
Worst pain 24 hours	0.22	0.074	0.16	0.288	-0.15	0.281	0.13	0.360	0.07	0.636
Average pain	0.13	0.323	0.20	0.179	-0.27	0.048	0.11	0.410	0.15	0.264
Pain at completion of BPI	0.01	0.961	0.11	0.454	-0.25	0.079	-0.10	0.489	0.07	0.620
Pain Severity	0.13	0.315	0.15	0.314	-0.30	0.035	0.02	0.887	0.04	0.799
Pain Interference	0.07	0.592	0.07	0.659	-0.15	0.288	0.12	0.408	21.00	0.397

DISCUSSION

In this study we demonstrate that patients with FD report significantly impaired quality of life in all tested domains except for Mental Health and Role Emotional. Our data further show that the reported impairment in quality of life is greater in patients with the higher disease burden, as reflected by high SBS and increased concentrations of biochemical markers of bone turnover in the more severe subtypes of FD. As hypothesized, patients with polyostotic FD and MAS had a more pronounced impairment of QoL compared to patients with monostotic FD, likely to be due to their greater risk of developing complications such as deformities and/or fractures.[14] This premise is further supported by the association of higher SBS with higher fracture risk and consistent need for surgical intervention in the more severely affected patients

with MAS. In addition to the skeletal complications related to the high skeletal burden, patients with MAS also have one or more endocrinopathies, also shown to be associated with impaired QoL in their own right, which at least partially explains the significantly low scores in physical and social functions domains observed in these patients.[15] In keeping with findings from Kelly et al. we were unable to detect differences in BPI domains between different subtypes of FD, although patients with MAS or polyostotic FD demonstrate a trend toward higher pain scores in both domains.[16] The mental health and role emotional domains were interestingly not affected in any subtype of FD, suggesting preserved psychological function and adequate emotional adaptation in patients suffering from FD, with the diagnosis likely to have been established in childhood.

Data on impaired Physical Function, Role-Physical, Bodily Pain and General Health scores have previously been reported in a US FD cohort.[6] In contrast with findings in this cohort study, we observe a significant impairment in Vitality scores, as expressed by feelings of tiredness and low-energy, and in Social Function scores, as reflected by the degree of interference with social activities due to physical or emotional problems. Our data suggest that patients with FD experience a decrease in energy level and a general feeling of tiredness compared to the general population, potentially precluding or decreasing their participation in social activities. This discrepancy in outcome between the two cohorts may be partially explained by a difference in cohort characteristics between studies, such as the age or gender distribution of the participants. The median age of our cohort was thus 46 years (range 16–80 years), compared to the younger median age of 34.7 years (range 14–86) in the US cohort and older age has indeed been consistently associated with increasing impairments in QoL.[3] Gender distribution might also play a role, as women have reported lower QoL scores in the Dutch population, but also because MAS, the more severe subtype of FD, is more often diagnosed in women in our cohort.[10] Although in univariate regression analysis female gender appeared to be associated with impaired physical function, multivariate analysis revealed no association between gender and any impairments in QoL in our cohort. Nevertheless, we should take into account that this might be the result the sample size of our cohort, as the cohort study showing these impairments in women accounted over 1,700 persons. Different subtype composition of the two cohorts and management differences, including different medical and surgical approaches, may also have played a role in the discrepancy in outcomes between cohorts.

Our data on QoL outcomes in FD are in keeping with those reported in Paget's disease of bone, a similar benign bone disorder also associated with clinical manifestations of

bone pain, deformity and increased risk for pathological fractures. Patients with Paget's disease of bone have thus also been shown to demonstrate significant reductions in all SF-36 domains, except for the Mental Health domain, suggesting that although benign bone disorders such as Paget's disease of bone and FD do impact on several aspects of QoL, patients appear to be generally able to mentally cope with their QoL impairments.[17]

In addition to confirming the inverse relationship between skeletal burden scores and physical function, our data also show a negative association between FGF-23 concentrations and the SF-36 Physical Function domain.[6,7,9] The relationship between SBS, a reliable parameter of FD disease extent and thus severity, and FGF-23 concentrations has been previously demonstrated.[7,9] SBS has also been shown to be a constant feature of the disease after the growth period, and to alter little or not at all after therapeutic interventions. Taken together, these findings suggest that SBS may be considered to be a reliable predictor for impaired physical function in patients with FD. In contrast, biochemical markers of bone turnover, although also found to be correlated with impaired Physical Function and Role-emotional domains, may prove to be less reliable predictors of impaired physical function as they demonstrate significant variation during the natural course of the disease, which is characterized by periods of activity and remission. These markers are also clearly affected by therapeutic interventions such as the use of bisphosphonates.[7]

Our study has some strengths as well as limitations. Of its main strengths are the relatively large number of patients belonging to a well-characterized cohort included in the study, with good representation of the so far ill-described milder monostotic subtype of FD, and the high response rate of 70.3% of patients invited to take part in the study. A further strength of our study is the opportunity to compare our QoL data in FD with QoL data from the general Dutch population.

The main limitation of our study is shared by all studies in rare and heterogeneous diseases, and a further limitation in FD is the still unclear natural history, particularly that of its milder subtypes. A further limitation of our study is its cross-sectional design, with a single measurement of quality of life parameters undertaken at one point in time in patients with FD of various degrees of severity. Notwithstanding, whereas it is generally accepted that multiple sequential measurements of QoL may be more informative on the impact of the disease on various aspects of quality of life, we believe our single measurement data are still very informative, as they not only show the expected impairment of QoL in patients with the more severe polyostotic

disease, with or without endocrinopathies, but also demonstrate a sizable impact of the milder monostotic type of the disease on quality of life.

Conclusion

In conclusion, data from our cross-sectional study demonstrate impairments in all SF-36 domains of quality of life except for the Mental health and Role emotional domains in a relatively large number of patients with a wide spectrum of FD disease severity including its milder forms. We demonstrate that a high skeletal burden score as reflecting disease severity represents the most consistent predictor of impaired QoL. Our findings from this study hold significant clinical implications as they draw the treating physician's attention to the important clinically unmet need to address quality of life issues in the management of all subtypes of FD, including its milder forms. Whether quality of life can be improved by medical or surgical interventions remains to be established by long-term studies in a large number of patients.

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Chapter 4

Illness perceptions are associated with quality of life in patients with fibrous dysplasia

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ABSTRACT

Purpose: Fibrous dysplasia (FD) is a rare bone disorder in which normal bone is replaced by fibrous tissue resulting in pain, deformities, pathological fractures or asymptomatic disease. Illness perceptions are patients' cognitions and emotions about their illness and its treatment, which may impact on Quality of Life (QoL). Here we explore illness perceptions in patients with FD compared to other disorders, identify factors associated with illness perceptions and evaluate their relationship with QoL.

Methods: Ninety-seven out of 138 eligible patients from the LUMC FD cohort completed the Illness Perception Questionnaire-Revised (IPQ-R) and the Short Form-36 (SF-36). Age, gender, skeletal burden score (SBS), FGF-23 levels, type of FD and SF-36 scores were analysed for an association with illness perceptions.

Results: We observed significant ($p < 0.01$) differences in patients' illness perceptions between FD subtypes in the domains: identity, timeline acute/chronic and consequences. Patients with craniofacial FD reported to perceive more consequences ($p = 0.022$). High SBS was associated with perceiving more negative consequences and attributing the cause of FD to psychological factors ($p < 0.01$), and high FGF-23 levels with attributing more symptoms to the disease and perceiving more consequences ($p < 0.01$). The IPQ-R domains identity, timeline acute/chronic, timeline cyclical, consequences, emotional representations and treatment control were significantly associated with impairments in QoL.

Conclusions: Illness perceptions in patients with FD are related to QoL, differ from those in patients with other disorders, and are associated with disease severity. Identifying and addressing maladaptive illness perceptions may improve quality of life in patients with FD.

INTRODUCTION

Fibrous dysplasia (FD) is a rare bone disorder that is caused by a missense mutation of the GNAS-gene, leading to improper function of the alpha subunit of the heterotrimeric G protein ($G_s\alpha$) that ultimately results in a local disorder of bone formation.[1] This heterogeneous disease can present with a wide spectrum of clinical manifestations from a lesion in a single bone (monostotic FD), in multiple bones (polyostotic FD) with or without endocrinopathies such as precocious puberty, or growth hormone excess in the McCune-Albright syndrome (MAS). FD lesions may be associated with bone pain, skeletal deformities and pathological fractures, although they may also be asymptomatic. Quality of Life (QoL) has been reported to be more severely affected in patients with the more severe types of FD. Determinants of severe disease including a high skeletal burden score (SBS) and increased bone turnover markers (BTM), have been identified as determinants of impaired QoL.[2,3] Other factors than those directly related to the disease which also influence QoL are 'illness perceptions': the thoughts and emotions that a patient has concerning his or her disease and its treatment.[4] These perceptions originate from various sources, such as information from social circles the patient moves in, information from health care providers, experiencing other or previous illnesses, information from other patients with the same disorder, or general or social media.[5,6] The common-sense model (CSM) of self-regulation, which outlines illness perceptions and their relations with sociodemographic and clinical characteristics, and coping and outcome (QOL), aims at examining cognitive and emotional representations to illness.[7,8] The CSM is based on the premise that an individual solves a problem (i.e. a perceived threat to health, an illness) in an active manner by trying to make sense of the threat to his or her health or illness. These perceptions are clustered around 5 components, forming the illness perceptions that determine the patients' coping behaviour. These cognitive components are 1) *identity*; the label that the individual uses to describe the condition and its symptoms, 2) *cause*; ideas that the individual has about the cause(s) of the condition, 3) *timeline*; expectations of the individual about the duration of the condition, 4) *consequences*; effects of the disease on the physical, psychological and social functioning of the individual, and 5) *cure/control*; the extent to which the individual perceives that the condition is amenable to cure and/or control.[9]

The Illness Perception Questionnaire Revised measures these illness perceptions in patients with different diseases.[10,11] Since illness perceptions have been shown to influence QoL, it is important to characterize these perceptions in patients with

FD.[12] In this study we explore illness perceptions in patients with FD, as an extension of a previous study evaluating QoL in the same population.[3] We further explore the relationship between illness perceptions and QoL in patients with FD and also aim at identifying associated factors for maladaptive illness perceptions.

SUBJECTS AND METHODS

Patients (Figure 4.1)

All patients aged 15 years or older and who had been seen at the outpatient clinic of the LUMC in the previous three years were asked to take part in the study. Patients were invited by mail to participate in the study, which implied filling in a number of questionnaires, including the Illness Perception Questionnaire – Revised (IPQ-R) and the Short Form 36 (SF-36), a questionnaire assessing functional status, as previously described.[3] Patients who did not respond were approached by telephone with a maximum of two attempts. The study was approved by the Medical Ethics Committee of the LUMC and written consent was obtained from all patients who responded and were included in the study.

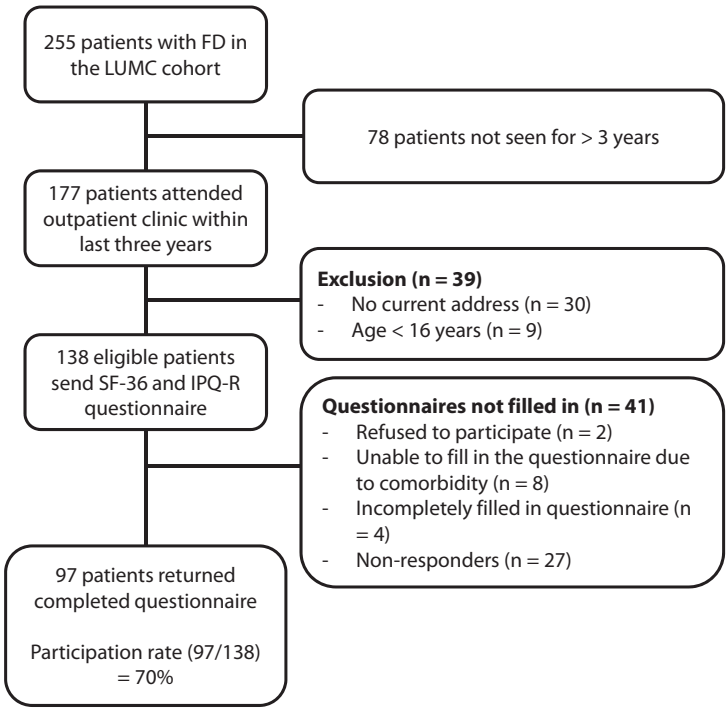

Fig. 4.1 Flowchart of patient inclusion and participation rate.

Clinical and sociodemographic characteristics

Patient data were retrieved from electronic medical records. Level of education was categorized using the International Standard Classification of Education (ISCED).[3] Low level of education was defined as a primary to lower secondary education; medium level of education was defined as an upper secondary to post-secondary non-tertiary education; and high level of education was defined as the first and second stage of tertiary education. Data on age, gender, age at diagnosis, type of FD, fractures and extraskeletal manifestations (e.g. precocious puberty, GH-excess, café-au-lait patches) were collected. Data on medical or surgical treatment were also retrieved from medical records. Fibroblast growth factor 23 (FGF-23) was obtained from serum measurements within two months of completing the questionnaires.[13] Skeletal burden scores (SBS) were blindly assessed by two authors (BCJM and NMA-D) for all patients in whom a 99Technetium skeletal scintigraphy was available.[14]

Illness Perception Questionnaire – Revised (IPQ-R)

The IPQ-R questionnaire was designed to evaluate cognitive and emotional representations of illness in patients with chronic or acute conditions.[10,11] The questionnaire consists of three different parts: illness identity, illness perception and causal attributions.

Identity

This part of the questionnaire is built-up of 14 commonly occurring symptoms and of 13 commonly occurring symptoms related to the disease under study, in this case FD. Patients are asked if they have any of these 27 symptoms and whether they believe that their disease is the cause of these symptoms. The score on the *identity*-subscale represents the degree to which patients relate common symptoms they suffer from to their disease.[10,15]

Illness perceptions

The second part of the questionnaire is built-up of 38 statements concerning views on the illness under study as evaluated on a five-point scale (strongly disagree to strongly agree) that together are divided into seven subscales, including:

1. **Timeline acute/chronic:** Includes six questions that assess the timeline of the disease. Do the patients regard their illness as an acute/temporary condition, or do they believe their condition to be more permanent?
2. **Timeline cyclical:** Includes four questions that differentiate between daily changes in symptoms of the disease and constantly present symptoms.

3. **Consequences:** Includes six questions on the effect and consequences of the condition on patients' daily lives.
4. **Emotional representations:** Includes six questions that aim at quantifying the emotional response (anxiety, anger, depression etc.) of a patient to his or her condition
5. **Personal control:** The combined score of six questions that represent the extent to which patients perceive having control over their illness.
6. **Treatment control:** Five questions about whether a patient perceives the illness to be under control with (current) treatment.
7. **Illness coherence:** Five questions on the patients' personal understanding of their disease.

Causal mechanisms

This part covers any mechanisms that patients may believe to be responsible for their disease and consists of 18 statements regarding perceived causes on a scale ranging from strongly agree to strongly disagree. Using a principal component analysis with varimax rotation, the causal items are clustered into variables with shared variance.[10,16] These variables represent the causes of their disease from the patients' perspective. Higher scores on the subscales indicate stronger beliefs in those attributions causing the disease.

Principal component analysis

The factor analysis generated four factors, accounting for 71% of the total variance. Two factors accounted for the largest part if the variance: psychosocial attributions (accounting for 30% of the variance) and environmental factors (accounting for 23% of the variance), with a Cronbach's α above the lower limit of 0.3 (0.937 and 0.865, respectively). Examples of the factor 'psychosocial attributions' include that FD is caused by daily stress or by a patients' behaviour; for the factor 'environment' that the disease is caused by heredity or a history of poor medical care. The other two factors, 'accident' and 'chance' were excluded from further analysis because of a low Cronbach's α.

Interpretation of the IPQ-R outcomes

In order to put the outcomes of IPQ-R scores of FD patients in perspective, we compared these with reference groups of patients with acute pain,[10] chronic pain,[10] acromegaly[17] and fibromyalgia.[6,17,18] Data on reference groups of patients with acute pain (less than 6 weeks) and chronic pain (longer than 3 months) used in this study, originated

from the study used to develop the revised version of the IPQ-R.[10] We also chose to compare the illness perceptions outcomes of our patients with FD with outcomes from a study on patients with acromegaly (47 male and 34 female), as patients with this disorder have been shown to be self-conscious about their appearance, leading to psychological distress, disruptions in everyday life and eventually impairments in QoL.[19] Although acromegaly is not characterised by facial asymmetry, patients with acromegaly do share a number of similarities with patients with craniofacial FD and MAS, such as excessive GH-production, chronic joint pain, and marked facial deformities, which provided the rationale for choosing patients with this disorder as reference group. Lastly, we compared the scores in our set of patients with those of a cohort of patients with fibromyalgia (FM) (47 female and 4 male), as this is also a chronic disease associated with (multifocal) musculoskeletal pain.

Identification of associated factors for illness perceptions

IPQ-R domain scores were compared between the different types of FD (monostotic/polyostotic/MAS) because of the broad spectrum of clinical manifestations of FD between these sub-types. Scores were also compared between patients with and without craniofacial disease, as we hypothesized that patients with craniofacial disease might score worse on the emotional domains, because these patients may perceive to attract more negative attention as a result of their visible craniofacial deformities.[20] Domain scores of the IPQ-R were evaluated for a possible relationship with two clinical parameters of disease extent and severity, including SBS and serum levels of FGF-23, to evaluate whether patients with more severe disease have different illness perceptions compared to those with milder forms of FD. We also assessed possible relationships between subscales of the SF-36 and different domains of the IPQ-R, for which the outcomes on the SF-36 in a previous study into QoL in persons with FD were used.[3]

Statistical analysis

Statistical analysis was performed using SPSS for Windows, Version 23.0 (SPSS, Inc., Chicago, IL, USA). Results are presented as mean (±SD) or as median (intermediate range) and in case of categorical data as a percentage. Differences between FD subtypes (monostotic/polyostotic/MAS) were compared using ANOVA, with post-hoc analysis undertaken where appropriate. Difference between craniofacial and non-craniofacial FD was assessed using the Student's T-test. The IPQ-R scores of our FD cohort were compared with reference cohorts with the use of the Student's T-test (with level of significance set at $p \leq 0.05$). IPQ-R scores were checked for normal

distribution and correlated accordingly with one another using either the Pearson Correlation Coefficient or the Spearman's Rank Correlation Coefficient (with level of significance set at $p < 0.01$ to correct for multiple testing). Possible associations were assessed between the IPQ-R scores and the SF-36 scores (previously reported SF-36 outcomes in this cohort are included in Supplementary Table S4.1).

RESULTS

Patients' characteristics (Table 4.1)

Out of a total of 138 eligible patients who were invited to participate in the study, two patients refused to take part, 8 patients did not participate due to non-FD related comorbidities (e.g. colon cancer, multiple sclerosis, osteosarcoma (n = 2), chondrosarcoma, severe rheumatoid arthritis, cardiac failure and significant learning disability) and 27 patients did not respond to our invitation. There were no significant differences between responders and non-responders except for gender; significantly more women completed the questionnaires ($p = 0.039$). Response rate was 70.3% with a total of 97 patients, 65% women, completing the questionnaires. Median age at diagnosis of FD was 29 years (range 1–68) and median age at completion of the questionnaires was 46 years (range 16–80). Level of education was low in 10 patients, medium in 24 patients, high in 46 patients and unknown in 17 patients. Sixty-two patients (64%) had monostotic FD, 26 (27%) had polyostotic FD, 9 (9%) had MAS and 5 (5%) had intramuscular myxomas in the context of Mazabraud's syndrome. The craniofacial

Table 4.1 Patient characteristics

	(n = 97)
Gender (male/female)	34/63
Age	46 (16–80)
Educational level	Low 10 (10%) Medium 24 (25%) High 46 (47%) Unknown 17 (18%)
Type of FD	Monostotic 62 (64%) Polyostotic 26 (27%) McCune-Albright 9 (9%) Mazabraud 5 (5%)
Follow-up (years)	12 (0–62)

Data are median (range) or number and percentage.

bones were affected in 23 patients (23%) and mean SBS was 8.68 (± 12.40 SD). SBS ($p < 0.001$), average FGF-23 ($p = 0.002$), a history of at least one fracture ($p = 0.001$) and of surgical interventions ($p < 0.001$) significantly differed between FD subtypes (monostotic/polyostotic/ McCune-Albright syndrome) with increasingly higher SBS, FGF-23 levels and fracture and surgical intervention rates in the more severe subtypes. Median duration of follow up was 12 years (range 0–62 years).

Illness perceptions in FD patients compared to reference groups (Table 4.2)
Compared to patients with acute pain, patients with FD were more aware of the chronicity of their disease ($p < 0.001$), perceived more fluctuations ($p < 0.001$) and had a better personal understanding of their disease ($p < 0.001$). However, patients with FD experienced less personal control ($p < 0.001$) and less treatment control ($p < 0.001$) of their illness.

Compared to patients with chronic pain, patients with FD attributed less of their symptoms to their disease ($p < 0.001$) and perceived more chronicity ($p < 0.01$) and less consequences ($p < 0.001$) of their illness, had a better personal understanding of their disease ($p < 0.001$) and less emotional representations ($p < 0.001$).

Table 4.2 Comparison of IPQ-R scores between fibrous dysplasia patients and different patient groups

IPQ-R	Fibrous dysplasia n = 98	Acute pain[10] n = 35	Chronic pain[11] n = 63	Fibromyalgia[18] n = 51	Acromegaly[17] n = 81
Identity	3.5 (3)	2.8 (2)	6.2 (3)$^{\beta}$	5.5 (2)$^{\beta}$	2.5 (2)
Timeline acute/chronic	25.1 (5)	13.4 (5)$^{\beta}$	23.1 (4)$^{\alpha}$	25.4 (4)	22.9 (6)$^{\alpha}$
Timeline cyclical	12.1 (3)	9.4 (3)$^{\beta}$	12.9 (4)	15.0 (3)$^{\beta}$	10.1 (4)$^{\beta}$
Consequences	16.5 (6)	14.2 (4)	23.5 (4)$^{\beta}$	19.3 (4)$^{\alpha}$	16.9 (5)
Personal control	17.3 (4)	22.9 (4)$^{\beta}$	18.4 (4)	19.5 (4)$^{\alpha}$	17.5 (5)
Treatment control	15.5 (4)	19.4 (3)$^{\beta}$	14.2 (3)	15.7 (3)	18.1 (3)$^{\beta}$
Illness coherence	15.9 (3)	9.3 (3)$^{\beta}$	13.4 (5)$^{\beta}$	15.9 (3)	17.5 (3)$^{\beta}$
Emotional representations	14.7 (5)	16.1 (4)	19.8 (4)$^{\beta}$	16.2 (5)	12.6 (4)$^{\alpha}$
Psychological attributions (score range 8–29)	13.2 (6)	NA	NA	NA	NA
Environmental (risk) factors (score range 7–23)	12.2 (5)	NA	NA	NA	NA

Data are mean (SD). NA, not applicable.
$^{\alpha}$ $p < 0.01$ compared with patients with fibrous dysplasia.
$^{\beta}$ $p < 0.001$ compared with patients with fibrous dysplasia.

Compared to patients with fibromyalgia, patients with FD attributed fewer symptoms to their disease ($p < 0.001$), perceived fewer fluctuations ($p < 0.001$), perceived fewer consequences ($p < 0.01$) and perceived less personal control ($p < 0.01$).

Compared to patients with acromegaly, patients with FD perceived more chronicity ($p < 0.01$) and more fluctuations of their symptoms ($p < 0.001$) and had less control over their treatment ($p < 0.001$). They also had worse personal understanding of their disease ($p < 0.001$) and perceived more emotional representations ($p < 0.01$).

Illness perceptions in different subtypes of fibrous dysplasia (Table 4.3)

There was a significant difference between subtypes of FD for: identity ($p = 0.006$), timeline acute/chronic ($p = 0.002$) and consequences ($p < 0.001$). Patients with MAS consistently demonstrated more negative illness perceptions in these domains compared to patients with polyostotic FD without endocrinopathies. Similarly, patients with polyostotic FD scored higher in these domains compared to patients with monostotic FD, illustrating that patients diagnosed with more severe subtypes of FD more often attribute their symptoms to FD, regularly experiencing their disease as chronic, reporting more consequences of their illness. There were no significant

Table 4.3 Comparison of IPQ-R scores between subgroups of fibrous dysplasia

IPQ-R domain	Monostotic n = 62	Polyostotic n = 26	McCune-Albright n = 9	Craniofacial n = 23	Not craniofacial n = 74
Identity	2.8 (3)$^{\gamma}$	4.4 (4)	6.2 (6)$^{\alpha}$	4.6 (4)	3.2 (3)
Timeline acute/chronic	23.9 (5)$^{\beta}$	27.4 (4)$^{\alpha}$	28.3 (2)	25.5 (5)	25.1 (5)
Timeline cyclical	11.7 (4)	13.3 (5)	13.3 (5)	12.2 (3)	12.2 (4)
Consequences	14.6 (6)$^{\beta,\gamma}$	19.0 (4)$^{\alpha}$	21.4 (6)$^{\alpha}$	18.8 (6)$^{\alpha}$	15.6 (6)$^{\alpha}$
Personal control	17.3 (4)	17.5 (4)	16.3 (4)	16.7 (4)	17.5 (4)
Treatment control	15.6 (4)	15.7 (3)	14.1 (4)	16.5 (4)	15.2 (3)
Illness coherence	15.7 (3)	16.3 (2)	16.3 (3)	15.5 (3)	16.0 (3)
Emotional representations	14.3 (6)	15.8 (4)	13.9 (4)	15.3 (5)	14.5 (5)
Psychological attributions (score range 8–29)	14.1 (6)	12.0 (5)	9.4 (3)	11.4 (5)	13.7 (6)
Environmental (risk) factors (score range 7–23)	12.8 (5)	11.8 (5)	8.6 (3)	11.4 (5)	12.5 (5)

Data are mean (SD).
$^{\alpha}$ $p < 0.05$ compared Monostotic.
$^{\beta}$ $p < 0.05$ compared Polyostotic.
$^{\gamma}$ $p < 0.05$ compared with McCune-Albright.

differences in other subscales of the IPQ-R. Patients with craniofacial FD scored significantly higher in the consequences domain (18.8 ± 5.7SD vs. 15.6 ± 5.6SD; p = 0.022) but this difference disappeared after correction for the presence of MAS. There were no significant differences between patients with and without craniofacial disease in other subscales of the IPQ-R.

Associated factors for illness perceptions (Table 4.4)

High skeletal burden scores as an indicator of severe disease were found to correlate with perceiving more consequences (R = -0.35; p = 0.003) and with more psychological attributions domain (R = 0.312; p = 0.010) of the IPQ-R. High average serum concentrations of FGF-23 correlated with attributing more complaints to FD (identity) (R = -0.389; p = 0.004) and perceiving more consequences of their illness (R = -0.37; p = 0.007).

Table 4.4 Associated factors for illness perceptions in fibrous dysplasia

	SBS		FGF-23	
IPQ-R domain	**SRCC**	**Sig.**	**SRCC**	**Sig.**
Identity	-0.25	0.039	*-0.389*	*0.004*
Timeline (acute/chronic)	-0.27	*0.027*	-0.03	0.822
Timeline (cyclical)	-0.04	0.751	-0.14	0.310
Consequences	*-0.35*	*0.003*	*-0.37*	*0.007*
Personal control	0.07	0.582	-0.06	0.650
Treatment control	0.06	0.625	-0.04	0.804
Illness coherence	-0.19	0.115	-0.18	0.191
Emotional representations	-0.05	0.716	-0.20	0.910
Psychological attributions	*0.312*	*0.010*	0.070	0.620
Environmental (risk) factors	0.268	0.027	0.199	0.158

Attributing factors for illness perceptions in fibrous dysplasia with significance set at p = 0.01.
SRCC = Spearman's Rank Correlation Coefficient.

Relationship between illness perceptions and QoL (Table 4.5)

Attributing more symptoms to the disease was associated with perceiving more limitations in the domains physical functioning (p < 0.001), physical role (p < 0.001), bodily pain (p < 0.001), general health (p < 0.001), social functioning (p < 0.001) and mental health (p < 0.001). A more chronic experience of FD was associated with perceiving more impairments in physical function (p = 0.005) and more bodily pain (p < 0.001).

Table 4.5 Correlations between SF-36 and IPQ-R domains in fibrous dysplasia

	Identity		Timeline (acute/ chronic)		Timeline (cyclical)		Conse-quences		Personal control		Treatment control		Illness coherence		Emotional representa-tions		Psychologi-cal attribu-tions		Environ-mental (risk) factors	
SF-36 domain	**R**	**Sig.**	**R**	**Sig.**	**R**	**Sig.**	**R**	**Sig.**	**R**	**Sig.**	**R**	**Sig.**	**R**	**Sig.**	**R**	**Sig.**	**R**	**Sig.**	**R**	**Sig.**
Physical function	*-0.52*	*<0.001*	*-0.30*	*0.005*	*-0.28*	*0.010*	-0.58	*<0.001*	-0.13	0.246	0.22	0.460	-0.14	0.202	-0.32	*0.003*	-0.11	0.316	-0.06	0.612
Role physical function	*-0.37*	*<0.001*	-0.13	0.255	-0.21	0.053	-0.58	*<0.001*	-0.03	0.789	0.14	0.191	-0.03	0.809	-0.39	*<0.001*	-0.14	0.197	-0.06	0.586
Bodily pain	*-0.58*	*<0.001*	-0.40	*<0.001*	-0.32	*0.002*	-0.38	*<0.001*	0.01	0.935	0.25	0.015	0.11	0.288	-0.33	*<0.001*	-0.01	0.929	-0.02	0.887
General health	*-0.39*	*<0.001*	-0.18	0.093	-0.16	0.125	-0.46	*<0.001*	0.06	0.592	0.36	*<0.001*	0.13	0.223	-0.37	*<0.001*	-0.29	0.006	-0.20	0.053
Vitality	-0.25	0.015	-0.14	0.194	-0.04	0.688	-0.37	*<0.001*	0.22	0.037	0.47	*<0.001*	0.11	0.320	-0.38	*<0.001*	-0.23	0.027	-0.10	0.340
Social function	*-0.50*	*<0.001*	-0.23	0.027	-0.28	*0.010*	-0.56	*<0.001*	-0.04	0.700	0.25	0.017	0.10	0.367	-0.43	*<0.001*	-0.17	0.111	-0.09	0.372
Role emotional	-0.26	0.018	0.05	0.641	-0.20	0.068	-0.36	*0.001*	-0.12	0.289	0.03	0.804	-0.06	0.592	-0.33	*0.002*	-0.16	0.146	-0.05	0.645
Mental health	*-0.37*	*<0.001*	-0.12	0.299	-0.11	0.329	-0.33	*0.002*	0.06	0.624	0.26	0.017	0.17	0.121	-0.43	*<0.001*	-0.22	0.048	-0.12	0.303

Correlations between SF-36 and IPQ-R domains with level of significance set at p = 0.01.
PF = physical function; RP = role physical; BP = bodily pain; GH = general health; VT = vitality; SF = social function; RE = role emotional; MH = mental health.

Experiencing symptoms of FD more chronically throughout the day was associated with more impairments in physical function ($p = 0.005$), social function ($p = 0.01$) and more bodily pain ($p = 0.002$). Both experiencing more consequences of FD and having more emotional representations of FD were associated with more impairments in all domains of the SF-36. Lastly, perceiving less treatment control was associated with more impairments in general health ($p < 0.001$) and vitality ($p < 0.001$). There were no significant correlations found for other IPQ-R dimensions.

DISCUSSION

Our data indicate that illness perceptions significantly differ between patients with FD and patients with a number of other conditions associated with acute or chronic pain. Patients with FD report more negative illness perceptions than patients with acromegaly, but more positive illness perceptions compared to patients with fibromyalgia.

In comparison with the reference groups, personal and treatment control were the most prevalent negative illness perceptions in FD patients, indicating that these patients experience very little control over the course and treatment of their condition. This can partially be attributed to the chronic character of FD, since chronicity of the disease was perceived to be higher in patients with FD compared patients with either acute or chronic pain and those with acromegaly, possibly as a reflection of current limitations in treating the disease. There is no cure for FD and current treatment modalities indeed fail to provide a long-term solution for the symptoms of FD, although surgical interventions or medical therapy are to some extent able to decrease pain and improve function. A significant proportion of these patients need multiple surgical interventions or continuous use of anti-resorptive agents due to persistent symptoms of continuous pain as well as recurrent fractures.[21-23] Further development of effective medical treatments could help to increase the faith that patients would have in their control over their disease. Developing disease-specific self-management skills could possibly boost personal control over the disease, for example with appropriate mobilization aids or more specifically with self-management training, aimed at exploring and changing the illness perceptions and therefore coping strategies of the individual patient.[4,24] In a biopsychsocial approach, this would mean that negative thinking about FD should be identified early to initiate an intervention aiming at better adaption to FD and more adaptive expectations.[9] In FD this could for example mean adaption of unrealistic ideas about mobilizing or actively participating in sports due an increased fracture risk. Once identified, a possible intervention to

address these negative perceptions would be to stimulate patients to develop a personal plan on mobilizing and participating in sports in a fashion that minimizes the risk of fracturing a bone with fibrous dysplasia. Developing a personal plan of action has previously been used to adequately address illness perceptions in persons with other conditions.[9,25] As a result of this personal plan, these patients might increase their physical activity and are likely to similarly increase their appreciating of their QoL.

Data from this study also show that patients with the more severe types of FD attribute a greater part of their symptoms to their illness, experience their FD as more chronic and are perceiving more consequences in their daily life. These findings are in line with the more severely impaired QoL in these severe subtypes and are further underlined by the association of high SBS and serum levels of FGF-23, both indicators of more severe disease, with negative illness perceptions of the consequences of FD.[3,13,14] Interestingly, several studies reporting on pain deriving from bony lesions in patients with fibrous dysplasia fail to find an association between pain severity and SBS, consistently describing a wide variation in pain symptoms between patients with FD who are similarly affected.[3,26] However, our data show that increased perception of bodily pain, as assessed by the SF-36 questionnaire, is associated with attributing more symptoms to the disease, a more chronic experience of FD, experiencing symptoms of FD more chronically throughout the day, experiencing more consequences of FD and having more emotional representations of FD. The precise pathogenic mechanism underlying the development of pain in patients with FD remains to date elusive.[27] Although following a variable pattern across the wide clinical spectrum of FD, the presence of pain appears to predict multiple negative illness perceptions, with pain being probably an important factor contributing to impairments in quality of life in these patients.

As previously shown in patients with other (endocrinological) disorders such as for example Cushing's syndrome and acromegaly, the current study demonstrates that negative illness perceptions are associated with impairments in many QoL domains as assessed by the SF-36 questionnaire.[4,17,28] This especially includes the illness perceptions domains of identity, timeline, consequences and emotional representations. It is therefore plausible that addressing these perceptions might prove to be a useful tool in the management of patients with FD. Current treatment modalities are unable to fully control the symptoms of FD, particularly in the more severe type of the disease. Psychological support aiming at minimizing negative illness perceptions may thus go a long way to improve QoL in the long term in these patients. This is particularly important, as there is no cure for the disease. Cognitive behavioral

therapy, self-management training or information on the possible negative effects of FD applied at an early stage in the course of the disease may therefore improve maladaptive illness perceptions, probably eventually leading to improved function and QoL in patients with FD.[4,7]

Our study has strengths as well as limitations. Despite the fact that we were able to investigate both QoL and illness perceptions in a relatively large cohort of patients with FD, we appreciate that especially the group of MAS patients, and therefore the significant differences found in this group, are underpowered and should be interpreted with care. This limitation is generally shared with all rare and heterogeneous diseases and in future research this could possibly be addressed by extending our levels of collaboration between international centers in these types of disorders. However, it is likely that the differences that we found between the subtypes of FD will be even more evident in stronger powered studies. In addition, we were able to get a good representation of our cohort of FD patients with a response rate of 70.3%. The other main limitation of our study lies in its cross-sectional design, with a single time-point measurement of both illness perceptions and QoL, precluding any statements about cause and effect, therefore. It would be interesting to analyze the course of illness perceptions and QoL over time and especially the effect of self-management on the course of FD. Despite these limitations we believe that our current data holds important leads for physicians involved in medical care for patients with FD, in understanding the impairments of FD in individual patients and the perceptions of these patients regarding their disease.

In conclusion, this first study on illness perceptions in patients with FD demonstrates that illness perceptions are affected throughout the wide spectrum of fibrous dysplasia and that these perceptions are associated with impairments in quality of life. Severity of disease as expressed by high skeletal burden scores and increased serum levels of FGF-23 were associated with these maladaptive illness perceptions. Altering unhelpful illness perceptions in these patients may represent a promising tool in the management of patients with FD, particularly in the more severely affected patient by helping coping behavior and improving quality of life in FD.

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SUPPLEMENTAL DATA

Supplementary Table S4.1 Results of SF-36 in patients with fibrous dysplasia[3]

SF-36	Monostotic n = 62	Polyostotic n = 26	McCune-Albright n = 9	General population n = 97
Physical Function	83.1 (20)	63.9 (26)[β]	51.1 (34)[β]	74.5 (26)
Role Physical	71.7 (39)	63 (44)	44.4 (39)[β]	66.5 (42)
Bodily Pain	73.9 (25)	60.5 (27)[β]	57.1 (25)[α]	68.7 (26)
General Health	63.1 (23)[β]	52 (22)[β]	55.6 (30)[α]	59.4 (24)
Vitality	62.2 (18)[α]	59.4 (19)[α]	57.2 (16)	60.6 (18)
Social Function	82.3 (21)	71.5 (28)[β]	61.1 (33)[β]	77.4 (25)
Role Emotional	84.3 (31)	87.5 (29)	88.9 (24)	85.5 (29)
Mental Health	73.6 (18)	77.7 (14)	75.6 (10)	75 (16)

Data are mean (SD).
[α] $p < 0.05$ compared to the general population.
[β] $p < 0.01$ compared to the general population.


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PART II

Extra-skeletal manifestations in fibrous dysplasia

Chapter 5

Prevalence and clinical features of Mazabraud's syndrome: a multicentre European survey

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ABSTRACT

Background: Mazabraud's syndrome is a rare disorder, characterized by the association of fibrous dysplasia (FD) with intramuscular myxomas. Data are scarce on the prevalence, clinical features, natural history and prognosis of this disorder. In this multicentre study of the European Musculo-Skeletal Oncology Society (EMSOS), we evaluate a series of patients from six European Centers.

Methods: All centers affiliated to the EMSOS were invited to include data on all patients with Mazabraud's syndrome who were seen in their centers between 1980 and 2015. Questions addressed included prevalence of Mazabraud's syndrome, type, severity and localization of FD lesions in relation to the myxomas, histopathology of myxomas and *GNAS*-mutation analysis when available.

Results: Thirty-two patients (22 female) from 6 centres were included in the study. The prevalence of Mazabraud's syndrome was 2.2% in the combined cohort of 1446 patients with FD and the syndrome was diagnosed a mean of 10.1 years after diagnosis of FD. The myxomas were predominantly localized in the upper leg. Excision was performed in 19 patients, recurrence occured in 6 (32%) and revision surgery was necessary in 5 (26%) after a median of 8.5 years (range 1.9–16.0). High cellularity of a myxoma was associated with recurrence ($p < 0.05$). A *GNAS*-mutation was identified in 5 of the 6 (83%) myxomas.

Conclusion: This study is the first to provide data on the prevalence of Mazabraud's syndrome. Although outcomes of surgical resection were good, a quarter of the patients required revision surgery despite free resection-margins. High cellularity of myxomas was identified as a risk factor for recurrence. *GNAS*-mutations were identified in 83%, emphasising the shared origin of FD and myxomas. Our data show that FD patients with disproportionate complaints, irrespective of type, extent or severity, should be investigated for the possible presence of myxomas. Finally, this study represents a fine example of how international collaboration provide unique opportunities for investigating extremely rare entities such as the Mazabraud's syndrome.

INTRODUCTION

Mazabraud's syndrome is an extremely rare syndrome, characterized by the association of skeletal fibrous dysplasia and intramuscular myxomas. The association of fibrous bony lesions with myxomas was first described by Henschen in 1926 and the syndrome was named after Mazabraud who made the link with fibrous dysplasia in 1967.[1,2] Fibrous dysplasia is a rare, genetic non-inheritable bone disorder caused by a postzygotic mutation of the *GNAS*-gene, which may affect a single (monostotic fibrous dysplasia) or multiple bones (polyostotic fibrous dysplasia), resulting in pain, deformities and pathologic fractures.[3] In the McCune-Albright syndrome, polyostotic fibrous dysplasia is associated with extraskeletal endocrine manifestations, such as precocious puberty, growth-hormone excess or hyperthyroidism and café-au-lait skin lesions. The *GNAS*-mutation that is responsible for the phenotype of fibrous dysplasia has also been identified in the soft tissue myxomas in Mazabraud's syndrome, suggesting a similar causality.[4-7] Mazabraud's syndrome is extremely rare in patients with fibrous dysplasia, with less than 100 cases reported to date in the literature.[8-10] Its prevalence has so far been estimated to be less than 1% in fibrous dysplasia. As often the case with very rare disease, little is known about several aspects of this syndrome such as pathophysiology, clinical characteristics, natural history and outcome of management. This formed the rationale for a number of European centres to join forces to participate in a in multicentre study, under the auspices of the European musculo-skeletal oncology society (EMSOS), to evaluate the prevalence and clinical characteristics of a relatively large combined series of patients with Mazabraud's syndrome. Here we studied the outcomes of surgical resection of the myxomas and possible risk factors for their recurrence, assessed the risk of malignant transformation of the fibrous dysplasia lesions as well as the myxomas, and evaluated the presence of *GNAS*-mutations in the myxomas.

PATIENTS AND METHODS

Study design

All affiliated centres of the EMSOS, were asked at the Society's 2016 Conference to collaborate in a study addressing the prevalence and clinical, radiological and pathological characteristics of Mazabraud's syndrome in their series of patients with FD followed up between 1980–2015 (Fig. 5.1). Six tertiary referral centres specialized in musculo-skeletal oncology answered the call, providing data on 32 patients with a confirmed diagnosis of Mazabraud's syndrome on the basis of clinical and radiographic

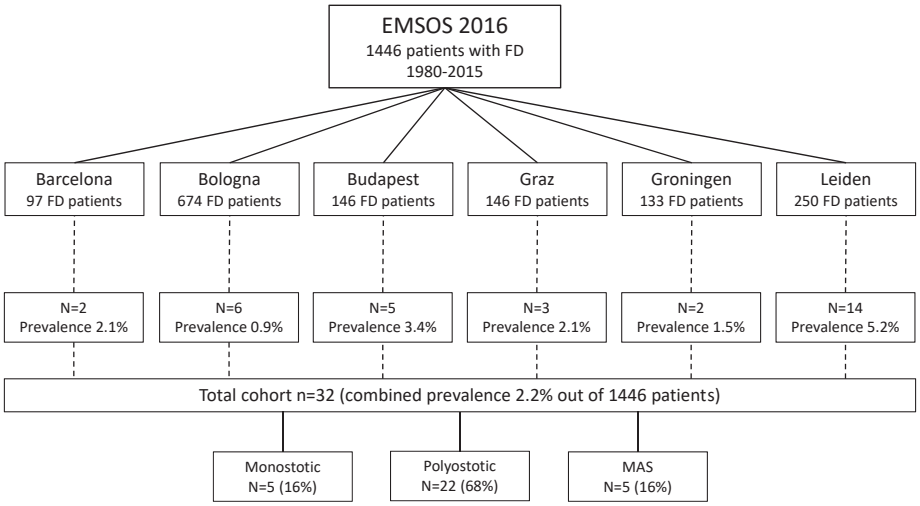


Fig. 5.1 Graph inclusion.

evidence for the association of fibrous dysplasia and myxomas, with additional histologic confirmation when required.

Data collection

The prevalence of Mazabraud's syndrome was evaluated in the combined cohort of 1446 patients with FD from the six centers. In patients identified as having Mazabraud syndrome, data was retrieved from hospital medical records on age, gender, type of fibrous dysplasia, age at diagnosis of fibrous dysplasia, localization of bony fibrous dysplasia lesions and possible malignant transformation of the fibrous dysplasia lesions or myxomas. Data were also retrieved on age at diagnosis of the myxomas, localization of myxomas, number of myxomas, size of the largest myxoma in individual patients.

Histopathology

Data on histopathology of myxomas were available in 17 patients. Myxomas were identified on the basis of the presence of typical bland spindle and stellate shaped cells with small nuclei in abundant extracellular myxoid stroma.[11] The level of cellularity of the myxomas retrieved from local pathology reports to be poorly cellular, intermediately cellular and highly cellular.[11]

Mutation analysis data

Data on *GNAS*-mutation analysis of the myxomas was extracted from the electronical patients records of 3 patients (Sanger sequencing) and was additionally performed in 3 patients using targeted Next Generation Sequencing according to a previously published protocol.[12]

Statistical analysis

Statistical analysis was performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Results are presented as percentage, as mean ± standard deviation or as number and percentage. Differences in age at diagnosis of fibrous dysplasia and at diagnosis of the myxomas were analysed using a paired T-test. A Chi-Square test was used for differences between categorical data.

Source of funding

This study was supported by a research grant from the Bontius Foundation for research into fibrous dysplasia.

RESULTS

Epidemiology

Out of a total of 1446 FD patients from the combined cohort, 32 had an additional diagnosis of Mazabraud's syndrome, resulting in a combined prevalence of 2.2%. Individual prevalences of Mazabraud's syndrome were 5.6% (Leiden), 2.1% (Graz), 3.4% (Budapest), 1.5% (Groningen), 2.1% (Barcelona) and 1.0% (Bologna).

Clinical characteristics (Table 5.1 and 5.2)

The thirty-two patients identified as having the Mazabraud were predominantly female (22 female vs. 10 male). The majority of the patients (84%) had polyostotic FD (22 patients without extraskeletal manifestations and 5 with McCune-Albright syndrome) and only 5 patients had monostotic fibrous dysplasia. Fibrous dysplasia was diagnosed at a significantly younger age than Mazabraud's syndrome at a mean of respectively 37.3 ± 20.6 years vs. 47.4 ± 12 years ($p < 0.001$). The most prevalent localization for myxomas was the upper leg at locations within the quadriceps muscle (65.6%), the hip adductors (31.3%) and the gluteus muscles (21.9%) (Table 5.1). In all but one patient (97%) the myxomas were localized adjacent to the bony fibrous dysplasia lesions. One patient (nr. 32) had fibrous dysplasia of the humerus and

Table 5.1 Cohort characteristics

	(N = 32)
Gender (male/female)	10/22
Age at diagnosis in years	
Fibrous dysplasia	37.3 ± 20.6
Myxoma(s)	47.4 ± 12
Type of fibrous dysplasia	
Monostotic	5 (16%)
Polyostotic	22 (68%)
McCune-Albright syndrome	5 (16%)
Clinical manifestations at diagnosis	
Pain	19 (59%)
Painless swelling	5 (16%)
Neurological complaints	1 (3%)
No complaints	7 (22%)
Localization	
Quadriceps	59%
Hip adductors	31%
Gluteus muscles	22%
Latissimus dorsi	9%
Triceps	9%
Psoas major	9%
Gastrocnemicus	6%
Hamstrings	3%
Number of myxomas	
1	50%
2–5	25%
> 5	25%

Data are mean ± SD or number and percentage.

myxomas not only in the latissimus dorsi but also in the gluteus maximus, although he had no fibrous dysplasia lesions of the lower limb on conventional X-rays and MR-imaging. Fifty per cent of patients had more then one myxoma (range 2–20). Mean size of the largest myxoma per patient was 55.3 ± 26.4 mm. Clinical symptoms at diagnosis of the myxomas were pain (n = 19, 59%), painless swelling (n = 5, 16%) or neurological complaints (n = 1, 3%). Seven patients (22%) had no symptoms related to the myxomas, with these incidentally identified on routine radiological screening of the skeletal fibrous dysplasia lesions. Patients with symptomatic myxomas did not have more ($p = 0.890$) or larger ($p = 0.223$) myxomas than asymptomatic patients, and there were no significant differences in localisation of symptomatic compared

to asymptomatic myxomas. The clinical features and presentation of intramuscular myxomas are highlighted in a description of an illustrative case of Mazabraud's syndrome (Fig. 5.2).

Surgery (Table 5.3)

Nineteen patients (59%) underwent surgical removal of the myxomas(s), the majority (n = 17) because of complaints due to the myxomas(s) and two patients because of the possibility of the lesions being malignant. In all but one patient (case nr. 19), histopathogical evaluation of the myxomas revealed free resection margins. Despite free margins, recurrence of myxoma was reported in 6 cases (32%) after a median period of 8.5 years (range 1.9–16.0) and highly cellular lesions had a significantly higher recurrence rate of the resected myxomas ($p = 0.043$). Five patients (26%) had a second surgery performed, one of whom had a third removal. Only three complications of surgery were described: two patients (patient nr. 25 and 26) had delayed wound healing, which was adequately treated by debridement and one patient (patient nr. 25) developed temporary femoral nerve palsy after removal of the myxomas.

Histopathological reports of resected myxomas from 17 patients revealed variable cellularity between resected spcimens, with 9 myxomas categorized as highly cellular, one as intermediately cellular and 7 as poorly cellular. No malignant transformation was observed in any skeletal FD lesion or myxomas.

***GNAS*-mutation analysis (Table 5.4)**

Of the 6 patients in whom myxoma tissue was available, 5 (83%) had a *GNAS*-mutation. All mutations were found on exon-8; in 4 cases codon 201 was bearing the R201H mutation and one case showed a R202C mutation localized in codon 202. In none of these patients material was available from bony fibrous dysplasia lesions to determine whether mutations of the bony lesions matched those of the soft tissue myxomas.

DISCUSSION

In this European multicentre study we evaluated the prevalence and clinical characteristics of Mazabraud's syndrome in one of the largest cohorts of patients studied to date, including series of patients from 6 European centres. Identifying only 32 patients, representing a prevalence of 2.2%, confirms the very rare nature of this syndrome. Our data also suggest that the syndrome is more common in women (ratio 2.2:1) and in

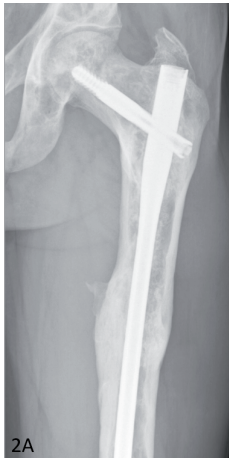
Table 5.2 Patient characteristics

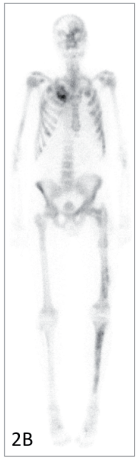
Patient ID	Gender	Type of FD*	Localization FD	Age diagnosis FD	Localization myxomas**	Age at diagnosis myxomas	Number of myxomas	Symptoms myxomas	GNAS-mutation in the myxoma	Follow-up in years
1	Male	PFD	Humerus + femur + pelvis	14	LD	19	1	Swelling	NT	41
2	Female	PFD	Ribs	61	Tr + QL	61	1	None	NT	6
3	Female	PFD	Femur + tibia + pelvis	32	Q + HA	45	8	Pain	R201H	20
4	Male	PFD	Femur + tibia	39	Q + HA + H	39	5	Swelling	No mutation	16
5	Female	PFD	Sternum + femur + pelvis + tibia + fibula	16	Q + HA	46	3	Swelling	R201H	51
6	Male	PFD	Craniofacial + humerus + ribs + pelvis + femur + tibia	38	Q + GM + HA + PM	52	20	Pain	R201H	14
7	Male	PFD	Femur + pelvis + tibia	23	Q + PM	31	1	Pain	R202C	19
8	Female	PFD	Femur + humerus	49	HA + Tr	49	5	Pain	-	2
9	Female	MAS	Ribs + pelvis + femur + tibia	50	Q	50	3	None	R201H	2
10	Female	MAS	Craniofacial + humerus + radius + ribs + spine + pelvis + femur + tibia	0	GM + HA	41	5	None	NT	41
11	Male	MFD	Femur	55	Q	56	1	None	NT	1
12	Female	MFD	Femur + tibia	48	Q	48	1	None	NT	4
13	Female	MFD	Femur	40	Q	40	1	Swelling	NT	1
14	Female	MAS	Craniofacial + humerus + ribs + spine + pelvis + femur + tibia + fibula	0	Qs + HA + GM	43	8	Pain	NT	1
15	Female	MAS	Craniofacial + ribs + pelvis + femur + tibia	19	Q + GM	32	3	Pain	NT	23
16	Female	PFD	Femur + tibia	52	GM	54	3	Pain	NT	13

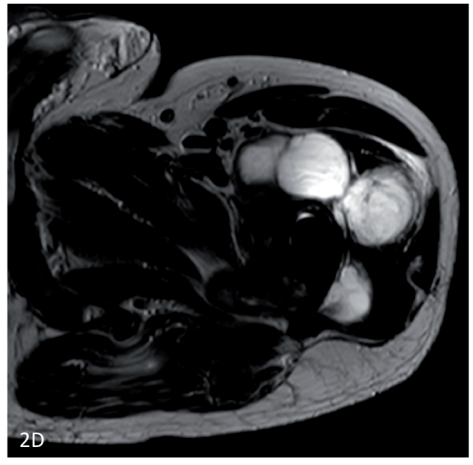
Table 5.2 *Continued*

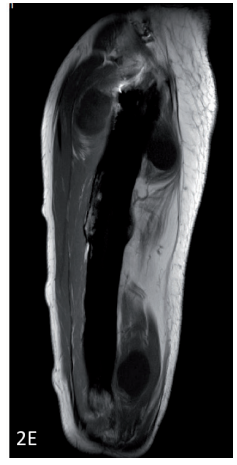
Patient ID	Gender	Type of FD*	Localization FD	Age diagnosis FD	Localization myxomas**	Age at diagnosis myxomas	Number of myxomas	Symptoms myxomas	GNAS-mutation in the myxoma	Follow-up in years
17	Male	PFD	Femur + tibia	51	Q	51	1	Pain	NT	1
18	Female	PFD	Femur + tibia	15	Q	31	1	Swelling/pain	NT	26
19	Male	PFD	Femur + pelvis	63	GM	62	1	Pain	NT	7
20	Male	PFD	Femur + pelvis	49	HA	49	3	Swelling	NT	0
21	Male	PFD	Femur + pelvis + tibia	35	Q	42	1	None	NT	8
22	Female	PFD	Femur + pelvis + tibia	23	Ga	29	1	Pain	NT	9
23	Female	MFD	Femur	65	Q	65	1	Pain	NT	5
24	Female	PFD	Humerus	56	Tr	56	1	Pain	NT	0
25	Female	PFD	Femur	60	Q + PM	56	3	Pain	NT	16
26	Male	PFD	Craniofacial + femur + talus	22	HA	61	1	Pain	NT	47
27	Female	PFD	Femur + fibula	13	Q	54	1	Pain	NT	44
28	Female	PFD	Femur + tibia	40	Q	40	1	Pain	NT	11
29	Female	PFD	Femur + pelvis + tibia	10	Q + HA + Ga	36	8	Pain	NT	11
30	Female	MAS	Craniofacial + ribs + pelvis + femur + tibia	18	Q + HA	40	4	Pain	NT	17
31	Female	PFD	Femur + tibia	70	Q	70	3	Pain	NT	11
32	Female	MFD	Humerus	69	GM + LD	69	2	Pain	NT	2

* MFD = monostotic fibrous dysplasia; PFD = polyostotic fibrous dysplasia; MAS = McCune-Albright Syndrome.
** LD = latissimus dorsi; Tr = triceps; QL = quadratus Lumborum; Q = quadriceps; HA = hip adductors; H = hamstrings; GM = gluteus maximus; PM = psoas major; Ga = gastrocnemicus.
*** Exact localisation of the myxoma is unknown.
NT = not tested.









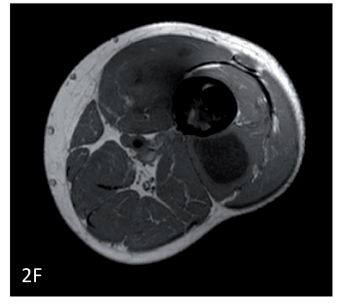


Fig. 5.2 Illustrative case of Mazabraud's syndrome. Images of a male patient (ID 6) with polyostotic FD of the craniofacial region, humerus, ribs, pelvis, femur and tibia, predominantly located on the left side of the body. He first presented with a fracture of the left femur at the age of 11 years, for which he was twice treated with an osteosynthesis. The diagnosis of FD was not made until he was 38 years old and had a recurrence of the femoral fracture for which he was treated with a long intramedullary nail. He was lost to follow-up and presented 15 years later at the age of 52 years to the outpatient clinic with progressive pain in the left upper leg during walking and cycling. Physical examination revealed a swelling in the region of the vastus lateralis. An X-ray of the femur and a T99m-skeletal scintigraphy (Fig. 5.2A and 5.2B) showed no changes in the size or appearance of the bony femoral FD lesions and no complications associated with the angled blade plate. A subsequent MRI investigation (Fig. 5.2C and 5.2D) showed 20 round, well-defined lesions within the muscles of the gluteus, quadriceps, hip adductors and ileopsoas, suggesting a diagnosis of Mazabraud's syndrome and pointing the soft tissue lesions as source of the exercise-related complaints. Three of the soft tissue tumors located proximally in the vastus lateralis who were believed to cause most of the complaints were resected and confirmed on histopathological evaluation to be mutiple intramuscular myxomas of low cellularity. Genetic analysis of the myxomas revealed the presence of a GNAS-mutation (A201H). On return to the out-patient clinic three months postoperatively the patient free of pain during exercise and could fully enjoy cycling and walking again. Unfortunately, two years later he presented again with complaints of pain in the region of the distal femur. MRI (Fig. 5.2E-F) showed growth of previously seen lesions on the posterior side of the distal femur, but no recurrence in the area of the resected myxomas. Because his complaints were mainly located on the anterior side, we chose a wait-and-see policy, as the complaints might also be caused by tissue fibrosis in that region. The patient is currently closely monitored with a view to timely resection of symptomatic lesions when required.

Table 5.3 Outcomes of surgery (total number of patients: 22)

Patient ID	Reason for surgery	Free margins	Cellularity	Recurrence of myxoma	Reoperation ()	Number of resections	Complications
3	Pain	Yes	Poor	No	No	1	None
4	Pain	Yes	High	Yes	Yes	2	None
5	Pain	Yes	-	No	No	1	None
6	Pain	Yes	Poor	No	No	1	None
7	Diagnosis	Yes	High	Yes	No	1	None
12	Diagnosis	Yes	Poor	No	No	1	None
14	Pain	Yes	Poor	No	No	1	None
16	Pain	Yes	High	No	No	1	None
17	Pain	Yes	Intermediate	Yes	No	1	None
18	Diagnosis	Yes	Poor	No	No	1	None
19	Pain	No	High	No	No	1	None
22	Pain	Yes	Poor	No	No	1	None
23	Pain	Yes	High	No	No	1	None
24	Pain	Yes	High	No	No	1	None
25	Pain	Yes	-	Yes	Yes	3	Delayed wound healing + temporary femoral nerve palsy
26	Pain	Yes	-	No	No	1	Delayed wound healing
27	Pain	Yes	High	No	No	1	None
28	Pain	Yes	High	Yes	Yes	2	None
29	Pain + diagnosis	Yes	High	Yes	Yes	2	None
30	Pain + diagnosis	Yes	Poor	No	Yes	2	None

Table 5.4 Results of mutation analysis in myxomas

Type of sequencing	Patient ID	Type of tissue	*GNAS*-mutation	Type	Reads	Frequency
Next generation sequencing	3	Myxoma	Positive	R201H	1364	12%
	5	Myxoma	Positive	R201H	1423	3%
	9	Myxoma	Positive	R201H	2144	3%
Sanger sequencing	4	Myxoma	Negative			
	6	Myxoma	Positive	R201H		
	7	Myxoma	Positive	R202C		

patients with polyostotic FD (ratio 5.4:1), and that myxomas are diagnosed at a later stage in the natural history of the associated skeletal fibrous dysplasia at a mean of 10 years after diagnosis of the latter (47.4 ± 12 years). Surgical resection of the myxoma(s) is associated with a good outcome, with disappearance of pain complaints in the majority of the patients, although recurrence is observed in 32% of cases, possibly related to high cellularity of the initially resected myxoma. Five out of the 6 myxomas genetically analysed were found to have a *GNAS*-hotspot mutation, confirming the shared genetic origin of fibrous dysplasia and intramuscular myxomas. In the sixth case only Sanger sequencing was performed, and since the percentage of cells with a mutation can be very low, as is evident from the tumors that were submitted for targeted NGS (Table 5.4), it can not be excluded that a mutation would have been found in case a more sensitive technique would have been used.

Mazabraud's syndrome has been previously reported to occur in approximately 1% of all cases of fibrous dysplasia.[8] However, Benhamou et al. recently reported a prevalence of 2.4% in a cohort of 372 patients with FD,[13] and we observed a combined prevalence of 2.2% in our study in a largest so far studied combined cohort of 1446 patients with fibrous dysplasia. This discrepancy in prevalence of the syndrome between studies might be at least partially accounted for by the more frequent use of magnetic resonance imaging (MRI) in FD as myxomas are not visible on plain radiographic imaging. It is likely, however, that our prevalence data may still represent an underestimate of the true prevalence of myxomas in patients with FD, as the majority of the intramuscular myxomas are likely to be asymptomatic and only patients with persistent and unexplained symptoms are likely to be referred for an additional MRI. Our data provide further evidence that myxomas may be the source of debilitating unexplained symptoms warrenting further analysis in patients with disproportional pain complaints, ununderstood functional limitations or resistance to treatment that

cannot be explained by findings from plain radiographs or T^{99}-skeletal scintigrams. Additional imaging should focus on the possibility of soft tissue pathology in the form of intramuscular myxomas, especially if the complaints are localized in the upper leg.

Clinical characterisics of Mazabraud's syndrome

Previous reviews suggest that the majority of patients with Mazabraud's syndrome have polyostotic forms of FD, two case reports mentioned linking the syndrome with the McCune-Albright syndrome.[14,15] Data from our combined European cohort suggest a higher prevalence of Mazabraud syndrome in patients with polyostotic fibrous dysplasia, especially those with the McCune-Albright syndrome (respectively 58% and 16%) compared to those with the more common monostotic type of FD (16%). The chance of developing myxomas appears thus to increase in the presence of the more severe types of fibrous dysplasia, possibly related to a higher tissue distribution of the *GNAS*-mutation not only in bone but also in soft tissues. A caveat to this premise is the finding in our study of 16% of patients with Mazabraud syndrome having monostotic fibrous dysplasia suggesting that soft tissue myxomas may also develop in the milder types of fibrous dysplasia and warranting further investigations for unexplained symptoms also in this group of patients.

In keeping with previous reports, myxomas in our cohort were mostly located in the upper leg and in nearly all were located nearby a bony FD lesion.[10,16] Intrestingly, the bony lesions in fibrous dysplasia also have a preference for the upper leg with most lesions found in the proximal femur.[17] *GNAS*-mutations have been identified in fibrous dysplasia lesions as well in intramuscular myxomas, suggesting a likely common causative mechanism.[3,4] *GNAS*-mutations have been indeed shown to play an important role in the development of extra-skeletal manifestations other than myxomas in patients with fibrous dysplasia.[12,18] With 83% of samples analysed in the current study showing this mutation in intramuscular myxomas, this shared origin is further confirmed. As the only myxoma lacking a *GNAS*-mutation reported here was solely analysed with Sanger Sequencing, the mutation rate in our study could even have increased up to 100% if analysis of this myxoma would have been repeated with the more sensitive Next Generation Sequencing technique.

Contrary to previous reports suggesting an increased risk of malignant transformation of bony fibrous dysplasia lesions in Mazabraud's syndrome, none of the patients studied in this combined cohort had evidence for malignant transformation of either a bony FD lesion or a myxoma.[10,19]

Surgical resection of myxomas in Mazabraud's syndrome

Surgical resection of symptomatic myxomas has been reported to be successful in relieving pain symptoms in patients with Mazabraud syndrome.[9,20] However, myxomas have a tendency to recur in the Mazabraud syndrome compared to simple intramuscular myxomas.[21] This was further emphasized in our study by the 26% of patients who were treated with a resection of a myxoma having to undergo further surgery for a recurrence despite having evidence for clear margins of the initially resected lesion. The World Health Organisation describes myxomas as benign soft tissue tumours that consist of bland spindle shaped cells in a matrix of myxoid stroma.[21] So-called 'cellular myxomas' demonstrated increased cellularity, collagen fibres and blood vessels and was described to have an increased risk of local recurrence.[22] Our data suggest that also in Mazabraud syndrome an increased risk of recurrence is seen in tumors in which the pathologists report increased cellularity. However, caution should be exerted in the interpretation of these data with care because of the difficult distinction between the recurrence of a specific resected myxoma and newly developed myxomas in patients with multiple myxomas, as is possible in Mazabraud's syndrome. Another reservation with the interpretation of the role of cellularity of myxomas in the prediction of recurrence in our study is that data on cellularity was extracted from histological reports produced by local pathologists from the 6 different centres taking part in the study, rather than being centrally evaluated, and therefore interobserver variability will exist. This also applies to the evaluation of free resection margins.

Similarities and differences between solitary intramuscular myxomas and myxomas in the context of Mazabraud's syndrome

Our data confirm that similar to published data about solitary myxomas, myxomas in the Mazabraud syndrome are more prevalent in women, have a mean age of diagnosis of about 50 years and are predominantly located in the upper leg.[22,23] The *GNAS*-mutation that causes fibrous dysplasia has been identified in both solitary myxomas and myxomas in the context of Mazabraud's syndrome, suggesting a linked origin.[4] However, there are also differences between solitary intramuscular myxomas and myxomas in the context of Mazabraud's syndrome. Recurrence rates have been reported to be very low after resection of solitary myxomas, compared to several case-reports and data from our study showing recurrence and need for further surgery in myxomas of the Mazabraud syndrome.[22,24] Whether the high recurrence rate observed in the Mazabraud syndrome is due to the presence of multiple myxomas developing at different rates as also shown in our study, or whether histological characteristics

of the myxomas such as high cellularity may be responsible for the higher recurrence rate after resection remains to be established.[22,23]

In conclusion, this is the first study in which the prevalence and clinical characteristics of the very rare Mazabraud's syndrome could be evaluated in a relatively large combined cohort of patients from 6 European centres. It provides an ideal example of how international collaboration and multicentre studies provide a unique opportunity for investigating extremely rare entities, such as the Mazabraud syndrome.. Our data underline the importance of further evaluation of FD patients with disproportional complaints or uexplained resistance to treatment for the presence of soft tissue lesions at their source, also in patients with the milder monostotic forms of FD. Based on these findings, we recommend that all patients with FD regardless of type with inappropriately severe unexplained symtoms may be investigated for the presence of myxomas and offered resection to alleviate their symptoms. Our data further suggest that high cellularity of a myxoma in Mazabraud's syndrome is associated with increased risk of local recurrence and therefore may require closer monitoring.

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Chapter 6

Increased risk of breast cancer at a young age in women with fibrous dysplasia

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ABSTRACT

Background: Fibrous dysplasia is a rare bone disorder caused by mutations of the *GNAS*-gene, which are also identified in malignancies. We explored the potential relationship between breast cancer and fibrous dysplasia in two fibrous dysplasia cohorts from the Netherlands and the USA.

Patients and methods: Data on fibrous dysplasia and breast cancer diagnosis were retrieved from hospital-records of 134 (Netherlands) and 121 (USA) female patients. Results were validated with breast cancer data of 645 female fibrous dysplasia patients from the Dutch Pathology Registry (PALGA). Standardized-morbidity-ratios for breast cancer were estimated with data from Dutch and US general population registries. *GNAS*-mutation was analyzed in 9 available breast cancer specimens.

Results: A combined total of 15 patients (6 polyostotic, 9 McCune-Albright-Syndrome) had breast cancer (87% thoracic localizations). In the Netherlands, a breast cancer incidence rate of 7.5% at median age of 46 years was validated in PALGA (6.5% at 51 years). Breast cancer risk was 3.4-fold increased (95% CI: 1.6–5.9) compared to the Dutch general population; 13.2-fold (95% CI: 6.2–22.8) in thoracic disease. In the USA cohort, breast cancer incidence rate was 4.5% at a median age of 36 years. Breast cancer risk was 3.9-fold increased (95% CI: 1.2–8.2) compared to the general population; 5.7-fold (95% CI: 1.4–13.0) in thoracic disease. *GNAS*-mutation was positive in four breast cancer specimens (44%).

Conclusion: Risk of breast cancer is increased at a younger age, particularly in polyostotic FD, suggesting that screening for breast cancer should be considered in this particular group at a younger age than currently advocated by national guidelines.

INTRODUCTION

Fibrous dysplasia is a genetic but non-inherited rare bone disorder, in which normal bone is replaced by fibrous tissue of poor quality and structure, at one (monostotic) or multiple sites (polyostotic), associated with bone pain, deformities and increased fracture risk. In this disorder, somatic missense mutations of the *GNAS*-gene on chromosome 20q13.3 have been identified not only in cells of the osteogenic lineage, but also in cells from tissues derived from any or all germ layers, including endocrine, skin or intramuscular mesenchymal cells. The post-zygotic and mosaic nature of the mutation and the various germ cells potentially carrying the mutation results in a broad clinical spectrum.[1,2] The skeletal manifestations of fibrous dysplasia may thus be associated with extra-skeletal manifestations such as skin, endocrine or other manifestations in the McCune-Albright syndrome, and with intramuscular myxomas in Mazabraud's syndrome.[3-5] Outside the context of fibrous dysplasia, activating *GNAS*-mutations have also been documented in various malignancies, such as thyroid carcinomas, pancreatic neoplasms and breast cancer.[5-9] To our knowledge, only four case reports have so far documented an association between fibrous dysplasia and breast cancer, all four in patients with McCune-Albright syndrome.[10-13]

In this study we explore the potential association between breast cancer and fibrous dysplasia by examining the prevalence of this malignancy in two relatively large cohorts of patients with fibrous dysplasia from the Netherlands and the United States, comparing breast cancer data with the general population.

PATIENTS AND METHODS

Patients included in this study were part of two well-characterized cohorts of patients with all types of fibrous dysplasia from the Leiden University Medical Center (LUMC) in the Netherlands and from the National Institutes of Health (NIH) in the USA (Figure 6.1). All patients were initially evaluated between 1990 and 2016. A diagnosis of fibrous dysplasia was established in both the Dutch and US cohorts on the basis of clinical and radiological and scintigraphic features, with histological and genetic confirmation of the presence of a *GNAS*-mutation occasionally required, mostly in case of monostotic lesions. Cases from the Dutch cohort with persistent uncertainty about the diagnosis were further discussed at meetings of the National Bone Tumor Committee of the Netherlands. For the LUMC cohort, data on the prevalence of breast cancer were validated using data from PALGA: the National Dutch Pathology Registry.[14]

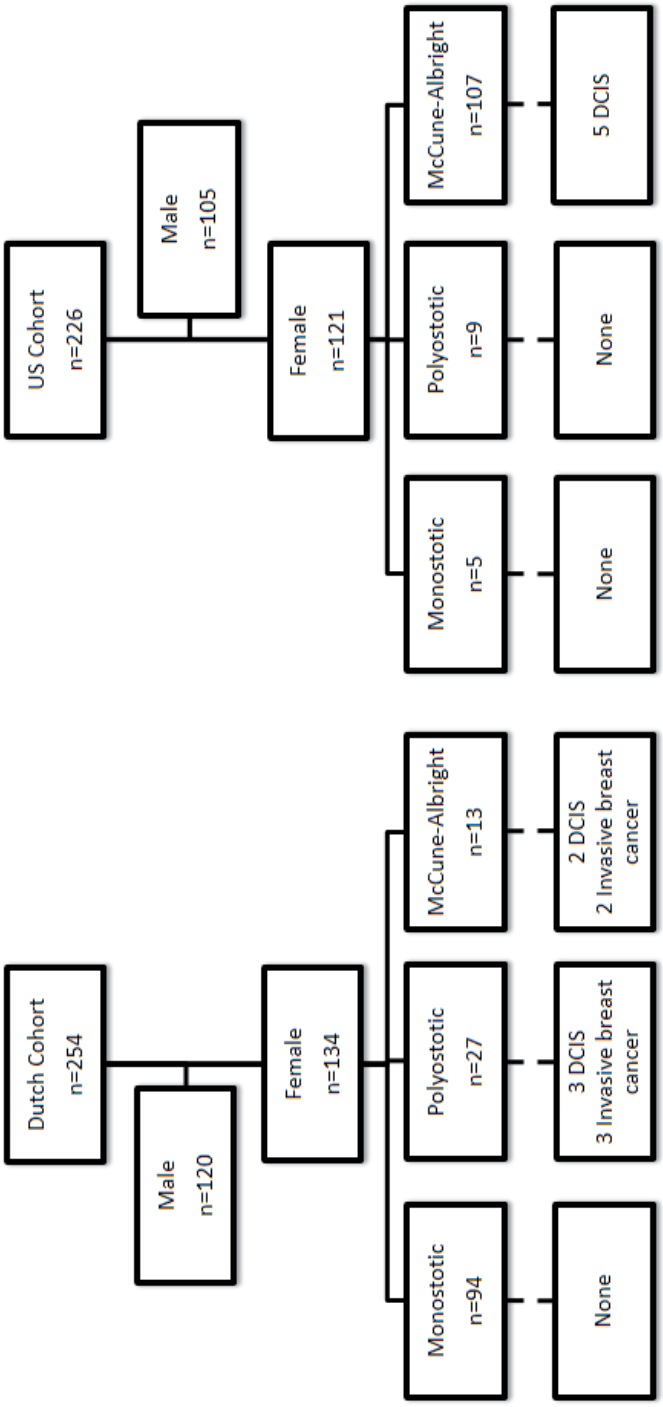

Fig. 6.1 Patient flow chart.

Data on age at diagnosis, type of fibrous dysplasia, localization of lesions (specifically in the thoracic region) and where applicable age at diagnosis of breast cancer, and type and staging of the tumor were retrieved from patient's medical records. Data on risk factors for breast cancer such as family history, radiation therapy, age at menarche, age at menopause, age at first pregnancy, family history, radiation exposure, lifestyle (diet, BMI, alcohol intake and smoking), the use of oral contraceptives and the use of hormone replacement therapy were also retrieved.[15] We also retrieved data on GH/IGF-1 excess. Data on tumor characteristics, TNM-classification, and therapeutic approaches used were documented. The respective medical ethical committees of the LUMC and NIH Centers approved the retrieval and analysis of the data. In the Netherlands, written informed consent was obtained to perform *GNAS*-mutation analysis on breast cancer specimens from patients who underwent surgery for breast cancer. Informed consent was also obtained from patients in the NIH natural history study (www.clinicaltrials.gov/NCT00001727).

Histopathological and genetic characteristics of breast cancer

Immunohistochemistry was performed on paraffin embedded pathological specimens of breast cancer tissue obtained from 10 LUMC patients in order to determine hormone and HER2 receptor status using previously described methods (supplemental data).[16,17] Next-generation sequencing (NGS) was carried out using the Ion PGM™ protocol and supplier's materials, and libraries were generated using Life Technology's Ion AmpliSeq™ Cancer Hotspot Panel v2 (supplemental data).[18] All sequences had a depth of over 100 reads and variances are reported with an allele frequency of 0.1 or more, ensuring a thorough analysis of possible mutations of the *GNAS*-gene.

Epidemiology of breast cancer in the LUMC and NIH cohorts

Standardized morbidity ratios (SMR) were calculated for both cohorts separately, as the ratio of observed versus expected morbidity, using age injunctions of five years (i.e. 0–4 years, 5–9 years etc.) by comparing the incidence rates of breast cancer for each cohort with the respective national incidence rate of breast cancer as retrieved from the Dutch Cancer Registry (IKNL) and the National Cancer Institute registry of the USA.[19,20] Follow-up time was measured from date of birth until time of death, outcome under study (breast cancer) or date of last follow-up.

In view of the potential association of fibrous dysplasia lesions with local development of soft tissue tumors (as observed in Mazabraud's syndrome), we additionally estimated the SMR in patients with documented lesions of the thoracic region,

including lesions in ribs, sternum and thoracic vertebrae. SMRs could not be calculated from the PALGA database as this database lacked information about age of first symptoms, localization or type of fibrous dysplasia.

Statistical analysis

Statistical analysis was performed with the use of SPSS for Windows, Version 23.0 (SPSS, Inc., Chicago, IL, USA). Unless stated otherwise, results are presented as median (range) and as percentage in case of categorical data.

RESULTS

Cohort characteristics (Table 6.1)

The Dutch cohort consisted of 254 patients including 134 women, 27 (20%) of whom had polyostotic disease and 11 (8%) had McCune-Albright syndrome. Median age was 25.5 years (range 0–70 years) at clinical presentation and 37 years (range 8–85 years) at last follow-up. Data on 645 women with a registered histological diagnosis of fibrous dysplasia between 1992-2015 were retrieved from the PALGA database and examined for an associated diagnosis of breast cancer. The US cohort consisted of 226 patients: 121 women, 9 (7.4%) with polyostotic disease and 107 (88.4%) with McCune-Albright syndrome. Median age was 13.0 years (range 1–80 years) at clinical presentation and 19.0 years (range 5–100 years) at last follow-up.

Prevalence of breast cancer in fibrous dysplasia patients in the Dutch and US cohorts (Table 6.1)

In the Dutch cohort, breast cancer was diagnosed in 10 of 134 female patients (7.4%) at a median age of 46 years (range 32–54 years). The PALGA database revealed an additional histological diagnosis of breast cancer documented at a median age of 51 years (range 27–75 years) in 42 of 645 women with a histological diagnosis of fibrous dysplasia (6.5%). In the US cohort, breast cancer was diagnosed in 5 of 121 female patients (4.1%) at a median age of 36 years (27–46 years). Median age at diagnosis of breast cancer was therefore considerably lower compared to the national median age of 61 years in the Netherlands and 62 years in the US population.[19,20]

Standardized morbidity ratios

In the Dutch cohort (5464 person-years), the SMR for the risk of developing breast cancer was 3.4 (95% CI: 1.6–5.9) compared to the general Dutch population.[19] The SMR

Table 6.1 Cohort characteristics

	LUMC	NIH	PALGA
Number of female patients	134	121	645
Median age at diagnosis of FD (years)	25.5 (0–70)	13.0 (1–80)	-
Median age at last follow-up (years)	40.5 (3–79)	19.0 (4–100)	-
Type FD			
Monostotic	94	5	-
Polyostotic	27	9	-
McCune-Albright	13	107	-
Mazabraud's syndrome	9	2	-
Thoracic FD lesions	27 (20%)	70 (58%)	-
Breast Cancer	10 (7.4%)	5 (4.1%)	42 (6.5%)
Carcinoma	4	0	26
DCIS	5	5	9
Both	1	0	7
Age at diagnosis (years)	46.0	36.6	51.1

Characteristics of the Dutch and US cohorts and of the PALGA cohort.
FD = Fibrous Dysplasia; DCIS = ductal carcinoma in situ; NIH = National Institutes of Health; PALGA = Dutch National Pathology Registry.

for breast cancer in patients with lesions localized in the thoracic region was even higher showing a 13.2-fold increased malignancy risk (95% CI: 6.2–22.8). Despite an overall lower incidence rate of breast cancer in the US cohort compared to the Dutch cohort (4.1% vs. 7.4%), the SMR was similarly increased in the US cohort (3053.5 person-years) showing a 3.9-fold increased risk for breast cancer (95% CI: 1.2–8.2) compared to the general US population, and a 5.7-fold increased risk (95% CI: 1.4–13.0) in the presence of thoracic lesions.[20]

Breast cancer characteristics in the combined Dutch and US cohorts (Table 6.2)

A total of 15 patients were diagnosed with breast cancer in the combined cohorts, 10 with a ductal carcinoma in situ (DCIS) and 5 with an invasive adenocarcinoma, No Special Type, one of which had histological evidence for mucinous differentiation. In none of the 15 patients who developed breast cancer was this diagnosed by the physician who was treating their fibrous dysplasia. The diagnosis was based on the discovery of a painless swelling, which was further investigated by a general physician or by detection of features suspicious of malignancy on routine mammography performed in the context of a national screening program. All 15 patients had polyostotic fibrous dysplasia, and 9 had McCune-Albright syndrome, all with a history

Table 6.2 Patient and tumor characteristics

Patient ID	Age at diagnosis of FD	FD type[A]/ MZB	Localization of FD lesions[B]	Age at diagnosis of breast cancer	Side of breast cancer	Type of breast cancer[C]	Stage of breast cancer	Receptor status in breast cancer[D]	Identified genes and type of mutation in breast cancer[E]	Reads GNAS/ frequency in breast cancer	GNAS mutation in bone
1	16	PFD	Skull, Humerus (R), Ulna (R), Ribs (L+R), Sternum, Pelvis (L+R), Femur (R), Tibia (R), Fibula (R) Metatarsal (R)	52	Right	Invasive Carcinoma NST Mucinous diff + DCIS gr III[F]	T3N1M0	ER/PR + Her2/ neu -	NA		R201H
2	49	PFD	Ribs (L+R), Thoracic and Lumbar Spine	52	Right	Invasive Carcinoma NST	T1N0M0	ER/PR + Her2/ neu +	PIK3CA: H1047A	11.356 0.243	NA
3	58	PFD	Ribs (L), Sternum, Thoracic and Lumbar Spine, Pelvis (L), Femur (L), Tibia (L), Fibula (L)	50	Left	DCIS	DCIS gr III	ER/PR + Her2/ neu -	**GNAS**: R201C	1.416 0.210	R201C
4	24	PFD+ MZB	Skull, Sternum, Pelvis (R), Femur (R), Tibia (R), Fibula (R), Calcaneus (R), Metatarsal (R)	54	Left	DCIS	DCIS gr III	ER/PR - Her2/ neu +	PIK3CA: G545G	8.746 0.060	R201H
5	0	MAS+MZB	Skull, Humerus (L+R), Radius (L+R), MCP (L+R), Ribs (R+L), Sternum, Thoracic and Lumbar Spine, Pelvis (L+R), Femur (L+R), Tibia (L+R), Metatarsal (L+R)	37	Right	DCIS	DCIS gr II	ER/PR + Her2/ neu -	**GNAS**: R201C AKT1: G17L	7.610 0.347 0.499	R201C

Table 6.2 *Continued*

Patient ID	Age at diagnosis of FD	FD type[A]/ MZB	Localization of FD lesions[B]	Age at diagnosis of breast cancer	Side of breast cancer	Type of breast cancer[C]	Stage of breast cancer	Receptor status in breast cancer[D]	Identified genes and type of mutation in breast cancer[E]	Reads GNAS/ frequency in breast cancer	GNAS mutation in bone
6	2	MAS	Skull, Humerus (L+R), Ulna (L+R), Radius (L+R), Ribs (L+R), Sternum, Thoracic + Lumbar Spine, Pelvis (L+R), Femur (L+R), Tibia (L+R)	48	Left	Invasive Carcinoma NST	T2N1M0	ER/PR +; Her2/ neu -	PIK3CA: G545L	7.882 0.257	R201C
7	48	MAS+ MZB	Radius (R), Ribs (R), Pelvis (L), Femur (R), Tibia (R)	48	Right	Invasive Carcinoma NST	T2N1M0	ER/PR +; Her2/ neu -	**GNAS**: R201H PIK3CA: H1047A	12.013 0.348 0.030	NA
8	3	PFD	Thoracic and Lumbar Spine, Femur (L)	37	Right	DCIS	DCIS gr III	ER/PR -; Her2/ neu +	ERBB2: L755S PIK3CA: H1047A TP53: A248G	16.584 0.701 0.258 0.547	NA
9	56	PFD	Cervical Spine, Humerus (R)	50	Left	Invasive Carcinoma NST	T2N1M0	ER/PR +;	-		NA
10	0	MAS+MZB	Skull, Cervical + Thoracic Spine, Ribs (R), Humerus (R), Femur (R), Tibia (R)	32	Right	DCIS	DCIS	NA	NA	NA	NA
11	27	MAS	Skull, Ribs (R), Cervical and Thoracic Spine, Tibia (L), Fibula (L)	41	Right	DCIS	DCIS	ER/PR +; Her2/ neu -	NA	NA	NA

Table 6.2 continues on next page

Table 6.2 *Continued*

Patient ID	Age at diagnosis of FD	FD type[A]/ MZB	Localization of FD lesions[B]	Age at diagnosis of breast cancer	Side of breast cancer	Type of breast cancer[C]	Stage of breast cancer	Receptor status in breast cancer[D]	Identified genes and type of mutation in breast cancer[E]	Reads GNAS/ frequency in breast cancer	GNAS mutation in bone
12	3	MAS	Skull, Clacicle (L), Scapula (R), Humerus (L+R), Radius (L+R), Ulna (R), Ribs (L), Pelvis (L+R), Femur (L+R), Tibia (R), Fibula (L+R)	27	Right	DCIS	DCIS	ER/PR +;	NA	NA	NA
13	14	MAS	Skull, Pelvis (L+R)	40	Left	DCIS	DCIS	NA	NA	NA	NA
14	2	MAS	Skull, Scapula (R), Humerus (L+R), Radius (L+R), Hands (L+R), Sternum, Ribs (L+R), Cervical, Thoracic and Lumbar Spine, Femur (L+R), Tibia (L), Fibula (R), Foot (L)	46	Right	DCIS	DCIS	NA	**GNAS:** R201H	NA	NA
15	4	MAS	Skull, Humerus (L+R), Radius (L+R), Ulna (L+R), Hands (L+R), Thoracic Spine, Ribs (L+R), Pelvis (L+R), Femur (L+R), Tibia (L+R), Fibula (L+R)	29	Left	DCIS	DCIS	NA	NA	NA	NA

Characteristics of patients with breast cancer
[A] PFD = polyostotic fibrous dysplasia; MAS = McCune-Albright syndrome; MZB = Mazabraud syndrome.
[B] R = right; L = left.
[C] DCIS = Ductal carcinoma in situ; NST = no special type.
[D] ER = estrogen receptor; PR = progesterone receptor.
[E] NA = Not Available.
[F] Patient has two breast tumours (bilateral).

of precocious puberty and three with documented growth hormone (GH) excess. Thirteen of the 15 patients (87%) had lesions localized in the thoracic region: 11 (73%) in the ribs, 4 (27%) in the sternum and 9 (60%) in the thoracic vertebrae. The thoracic lesions were ipsilateral to the breast cancer in 10 patients (77%), were located in the midline in one case and were contralateral in 2 cases. Traditional risk factors for breast cancer were assessed in 13 of the 15 patients and could not been documented in two patients who were lost to follow up. The most consistent risk factor for breast cancer was prolonged exposure to gonadal hormones because of precocious puberty in patients with McCune-Albright syndrome (n = 9). One patient had a first degree relative (mother) with breast cancer diagnosed at the age of 84 years. Nine of eleven patients had positive expression of both estrogen (ER) and progesterone receptors (PR), and two patients with negative PR and ER had positive HER2-neu receptors. None of the 11 patients with receptor data had triple-negative receptor status. Survival was 100% and none of the patients had developed local recurrence or distant metastases after a median follow-up of 8.6 years (range 2–15 years).

Mutation analysis

Targeted next-generation-sequencing was performed to determine the presence of a *GNAS*-mutation in 8 of the 10 patients from the Dutch cohort using libraries of Life Technology's Ion AmpliSeq™ Cancer Hotspot Panel v2 (supplemental data). Mutation analysis of one of the 5 patients from the US cohort was performed with Sanger sequencing (Table 6.2). NGS revealed a *GNAS*-mutation in three of 8 patients (38%) from the Dutch cohort in whom this could be evaluated. In two of these patients, the same *GNAS*-mutations were detected in fibrous dysplasia lesions, and in one patient the mutation was also detected in a myxoma (patient 7). Sanger sequencing revealed a *GNAS*-mutation in the pathological DCIS specimen of one US patient, resulting in a total prevalence of *GNAS*-mutations of 44% in the combined cohorts. *PIK3CA*-mutations were additionally identified in most patients with NGS (n = 6, 75%). All *GNAS*-positive tumors were ER and PR positive and HER2-Neu negative.

DISCUSSION

In this study we demonstrate a more than three-fold increased risk for developing breast cancer at a younger age in women with the more severe forms of fibrous dysplasia compared to the general population.[19,20] Although an element of selection bias is inherent to the study of patients from cohorts from tertiary referral centers,

we believe that combining the Dutch and US cohorts minimized this potential bias because of the different distribution of FD type and thus severity in the respective cohorts. In the Dutch cohort 72% of patients had monostotic fibrous dysplasia whereas in the US cohort 88% of patients had McCune-Albright syndrome. Standardized morbidity ratios for breast cancer were, however, very similar between cohorts: 3.4 (95% CI: 1.6–5.9) for the Dutch cohort and 3.9 (95% CI: 1.2–8.2) for the US cohort. In both cohorts, most recent data on national incidence ratio of breast cancer were used. The high incidence rate of breast cancer in women with FD and the young age at diagnosis of breast cancer were both confirmed in the national pathology registry of the Netherlands (PALGA), median age 51 years (range 27–75 years) and histological diagnosis of breast cancer (6.5%).

Patients with fibrous dysplasia were clearly younger than members of the general population at the time of diagnosis of breast cancer. While the median age at diagnosis of breast cancer was similarly above 60 years of age both for the Netherlands (61 years) and the United States (62 years), all patients in our combined cohort were younger than sixty years of age at the time of diagnosis of breast cancer, with a respective median age of 46 and 36 years for the Netherlands and the US. In addition to the median age, there is an increasing trend in breast cancer incidence in both countries in the past decades and both countries have their care similarly organized with national screening programs from the age of 50 years.[19,20]

Data on a possible association between breast cancer and fibrous dysplasia are scarce, restricted to 4 case reports which suggested the association to be potentially related to hormonal disturbances commonly observed in McCune-Albright syndrome such as prolonged exposure to gonadal hormones associated with precocious puberty or GH-excess although the mechanism by which GH-excess may increase the risk of developing breast cancer remains speculative.[10-13] Whereas data from a large meta-analysis of epidemiological studies on the relevance of circulating IGF-1 for breast cancer risk suggests a potential role for IGF-1 in the development of breast cancer, a further study from Brazil showed no correlation between IGF-1 and risk for breast cancer development.[21,22] Breast cancer risk was also shown not to be increased in patients with true GH-excess in acromegaly.[23,24] Notwithstanding, our finding of GH excess in 3 out of 15 patients with breast cancer suggests that perhaps we should not entirely exclude excess GH/IGF-1 as a potential risk factor for breast cancer in fibrous dysplasia. While endocrinopathies may be a potentially contributory factor, we did also observe a *GNAS*-positive cancer in a patient without endocrine disease.

We identified *GNAS*-mutations in pathological specimens of breast tumors in 4 out of 9 patients with fibrous dysplasia (44%), compared with less than 1% reported incidence of *GNAS*-positive breast cancer in the general population.[25-29] Since several other mutations, including the high prevalence of *PIK3CA*-mutations, 75%, were detected, we do not feel that there was a technical or material quality issue explaining the lack of *GNAS*-mutations in the breast cancer tissue of 6 patients, especially since targeted next generation sequencing is very sensitive and has a detection limit of < 1%. This might be due to intra-tumoral mosaicism of the *GNAS*-mutation in fibrous dysplasia, where a mixture of *GNAS*-mutated cells and wild type cells are needed to develop a neoplasm this has been described in other rare benign bone tumors, including enchondromas and osteochondromas, explaining the reported detection rates (range 36–82%) of *GNAS*-mutations in bone and in myxomas of fibrous dysplasia patients and thus the detection rate for *GNAS*-mutations in the breast cancer tissue of our patients.[26,27]

It might be also possible that *GNAS*-mutated cells are capable of creating an environment in which mutations occur more easily in wild type cells. The creation of an oncogenic niche by mesenchymal cells has been described in combination with the development of myelodysplastic syndrome and secondary leukemia as well as in the development of secondary peripheral chondrosarcoma from osteochondroma.[30,31]

The prevalence of *GNAS*-mutations in the breast cancer tissue of fibrous dysplasia patients and the association between breast cancer and thoracic localization of FD lesions supports, in our view, a role for the *GNAS*-mutation in the pathophysiology of breast cancer in these patients. In addition to the increased prevalence of endocrinopathies, the increased prevalence of breast cancer provides further evidence that in fibrous dysplasia the role of *GNAS*-mutations extends beyond the scope of skeletal manifestations to a more systemic expression of the disease, including carcinogenesis.

Our findings from this study hold important implications for the follow up of FD patients. Although this is the first study addressing the prevalence of breast cancer in fibrous dysplasia, we believe our results to be substantial enough to enable us to recommend screening for breast cancer in women with fibrous dysplasia, especially those with thoracic lesions, at a younger age than currently advocated by national guidelines. Further research is required to unravel the exact mechanism by which a *GNAS*-mutation may be responsible or contribute to the development of breast cancer in patients with fibrous dysplasia.

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SUPPLEMENTAL DATA

Immunohistochemistry of breast cancer receptor status

All samples were deparaffinised with xylene and rehydrated in alcohol before being washed in deionised water and phosphate buffered saline (PBS). Envision FLEX Target Retrieval Solution, High pH was performed for ER and PR and Envision FLEX Target Retrieval Solution, Low pH, was performed for Neu. Slides were washed and followed by 5 min incubation with Envision Flex peroxidase-blocking reagent. The samples were washed again and incubated for 20 min with 1/20 mouse-anti human estrogen receptor monoclonal antibody (Dako, EP1); 1/400 mouse-anti human progesterone receptor monoclonal antibody (Dako, PGR636) and 1/200 mouse-anti human Neu receptor monoclonal antibody (Dako). Staining was performed automatically (Dako Autostainer Link 48). After 3 washes the slides were incubated with Envision Flex/HRP for 20 min. After 3 washing steps, slides were incubated for 10 min with Envision Flex DAB+ Chromogen and after another rinsing the samples were stained with hematoxylin (Klinipath 4085.9002). Tumor receptor status was assessed by an author with wide experience with the method (VTHBMS). http://www.agilent.com/en/products/immunohistochemistry/antibodies-controls/primary-antibodies/estrogen-receptor-a-(dako-omnis). http://www.agilent.com/en/products/immunohistochemistry/antibodies-controls/primary-antibodies/progesterone-receptor-pgr636.

Next-generation sequencing

Libraries were generated using Life Technology's Ion AmpliSeq™ Cancer Hotspot Panel v2. This panel consists of 207 amplicons covering over 20,000 bases of 50 genes with known cancer associations, including the *GNAS* gene. Other genes from this panel are *KRAS* (exon 2–4); *NRAS* (exon 2–4); *HRAS* (exon 2–3); *BRAF* (exon 11,15); *EGFR* (exon 3,7,15,18–21); *GNAQ* (exon 5); *GNAS* (exon 8–9); *IDH1* (exon 4); *IDH2* (exon 4); *KIT* (exon 2, 9–18); *PDGFRA* (exon 12,14,15,18,23); *PIK3CA* (exon 2,5,6–10,14,18,21); *RET* (exon 10–12,15,16); *TP53* (exon 4–8,11) including the hotspots of the following genes: *ABL1*; *AKT1*; *ALK*; *APC*; *ATM*; *CDH1*; *CDKN2A*; *CSF1R*; *CTNNB1*; *ERBB2*; *ERBB4*; *EZH2*; *FBXW7*; *FGFR1*; *FGFR2*; *FGFR3*; *FLT3*; *GNA11*; *HNF1A*; *JAK2*; *JAK3*; *KDR*; *MET*; *MLH1*; *MPL*; *NOTCH1*; *NPM1*; *PTEN*; *PTPN11*; *RB1*; *SMAD4*; *SMARCB1*; *SMO*; *SRC*; *STK11* and *VHL*. The unaligned bam files generated by the Proton sequencer were mapped against the human reference genome (GRCh37/hg19) using the TMAP 5.0.7 software with default parameters (https://github.com/iontorrent/TS). Subsequently variant calling was performed using the Ion Torrent specific caller, Torrent Variant Caller (TVC)-5.0.2,

using the recommended Variant Caller Parameter for Cancer Hotspot Panel v2. Variant interpretation was undertaken using Geneticist Assistant which assigns Functional Prediction, Conservation scores and Disease associated information to each variant (http://softgenetics.com/GeneticistAssistant_2.php). Once a pathogenicity is assigned to a variant, the same pathogenicity is automatically attributed to the next time the variant is observed. CHPv2 is regularly used in the Pathology Department LUMC of the LUMC, so that virtually all CHPv2 variants have been previously observed and annotated. Integrative Genomics Viewer (IGV) was used for visually inspecting the observed variants.


FIBREUZE DYSPLASIE
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PART III

Surgical treatment

Chapter 7

The role of cortical allogeneic strut grafts in the treatment of fibrous dysplasia of the proximal femur

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ABSTRACT

Background: Fibrous dysplasia of the proximal femur is a progressive, often recurrent condition of bone that can cause skeletal deformity, fractures, and pain. Allogeneic cortical strut grafting to minimize the risk of fracture or as part of fracture treatment is a promising treatment option, but evidence is scarce on the intermediate-to long-term results of this procedure and there are no data on factors associated with graft failure.

Questions/purposes: The purposes of this study were (1) to evaluate the revision-free survivorship; (2) radiographic findings; (3) factors associated with failure; and (4) complications associated with cortical strut allograft to prevent or treat fractures of the proximal femur in patients with fibrous dysplasia.

Methods: Between 1980 and 2013 we performed cortical strut allografting in 30 patients for impending or actual fractures of the proximal femur, of whom 28 (93%) were available for follow-up at a minimum of 2 years (mean, 13 years; range, 4–37 years) and of whom 22 (73%) had also been evaluated within the last 5 years. During that time, the indications for cortical strut allografting were an impending fracture of the proximal femur, persistent pain, or an actual nondisplaced femoral fracture. In patients who presented with a diaphyseal fracture, a fracture with severe dislocation of severe varus deformity, which required an osteotomy, placement of a blade plate was instead performed and these patients are not included here. During that time, for patients with diaphyseal fractures, and in patients with a displaced femoral fracture of the proximal femur, placement of a blade plate without strut grafting was instead performed; these patients are not included here. The primary outcome was the success rate of allogeneic cortical strut grafting surgery as assessed by the absence of revision surgery for a newly sustained fracture, resorption of the graft, or progressive deformity of the proximal femur. The association of possible contributing factors to graft failure such as gender, age at surgery, preoperative fracture, and anchoring distances of the graft in healthy bone was also evaluated using Cox regression analysis.

Results: Revision surgery was performed in 13 patients, resulting in a mean survival time of 13 years (Kaplan-Meier 95% confidence interval [CI] 10–16). Radiological resorption of the graft was observed in 15 of 28 patients (54%). However, revision surgery was not performed in all patients who developed graft resorption, because of the absence of a risk for fracture on the basis of the anatomical site of resorption. Identified risk factors for graft failure included preoperative fractures (hazard ratio [HR] 4.5; 95% CI 1.2–17.2; p = 0.028) and insufficient proximal anchoring of the graft in healthy bone (HR 6.02; 95% CI 1.3–27; p = 0.02). One patient sustained a refracture after surgery resulting from an in-hospital fall. The fracture was treated without further surgery, and it healed.

Conclusions: Our findings from this study suggest that cortical strut allografting may be a viable option for treatment of fibrous dysplasia of the proximal femur without a previous pathological fracture. Surgeons should pay particular attention to the proximal fixation point of the allograft to decrease the risk of failure. Patients with a fracture have an increased risk of failure and reoperation and so should be treated with an osteosynthesis.

INTRODUCTION

Fibrous dysplasia is a rare benign bone disease caused by a postzygotic, activating mutation of the GNAS gene, which alters the signaling of G-protein at the cellular level. The bone lesions are characterized by local replacement of healthy bone by fibrous tissue, which is produced by poorly differentiated osteoblasts, osteoclast activation, and local increase in bone turnover. Clinical manifestations include pain, deformities, and increased risk for fractures. The spectrum of fibrous dysplasia includes single lesions (monostotic fibrous dysplasia), multiple lesions (polyostotic fibrous dysplasia), and the combination of polyostotic disease with extraskeletal manifestations such as precocious puberty, hormonal dysregulation, and cafe´-au-lait skin patches as observed in McCune-Albright syndrome. Although lesions may occur in any bone, the proximal femur and craniofacial bones are the predominant localizations of fibrous dysplasia.[1] As a result of the weightbearing properties of the proximal femur, lesions at this site are vulnerable to microfractures, which may be associated with pain, pathological fractures, and ultimately a varus deformity of the femoral neck, leading to the "shepherd's crook deformity" characteristic of fibrous dysplasia lesions at this site. Lesions of the proximal femur historically have been treated with curettage and cancellous bone grafting.[2]

However, these procedures were associated with a high risk of local recurrence, and the use of cortical grafts subsequently was proposed as a preferable alternative on the basis that cortical bone may be less prone to replacement by dysplastic tissue.[3,4] In 2005 DiCaprio and Enneking[3] suggested that allogeneic cortical strut grafting should be used instead of autogenous cortical bone in fibrous dysplasia because they would be less likely or at least slower to be replaced by dysplastic tissue, therefore providing better material for grafting. Whereas failure rates were reported to be lower in allogeneic cortical strut grafting compared with cancellous bone grafting, it has so far been difficult to anticipate which patients are more likely to benefit from allogeneic cortical strut grafting and which factors are associated with graft failure.[2,5] In addition, to our knowledge, there are few reports on long-term follow-up of patients treated with cortical strut allografting; because fibrous dysplasia has a propensity to recur, this is an important gap in knowledge. We therefore sought (1) to evaluate the revision-free survivorship; (2) radiographic findings; (3) factors associated with failure; and (4) complications associated with cortical strut allograft to prevent or treat fractures of the proximal femur in patients with fibrous dysplasia.

PATIENTS AND METHODS

Data on all patients who received an allogeneic cortical strut graft for fibrous dysplasia of the proximal femur from 1980 to 2013 at the Orthopaedic Department of the Leiden University Medical Center were evaluated in a retrospective study design. In The Netherlands, this kind of research does not need approval of the ethical committee.

Patient population

Between 1980 and 2013 we performed cortical strut allografting in 34 patients for impending or actual fractures of the proximal femur or for persistent pain nonresponsive to medical treatment. Patients who underwent additional valgus osteotomy (n = 4) were excluded from the study, because the aim of our study was to evaluate the efficacy of allogeneic cortical strut grafting in preventing varus deformity rather than to correcting it. Another two patients were excluded because follow-up was below the minimum of 2 years. This left 28 patients (82%) available for follow-up at a minimum of 2 years (mean, 13 years; range, 4–37 years), of whom 22 (73%) had also been evaluated within the last 5 years. Sixteen of the 28 patients studied (57%) had monostotic disease, 11 (39%) had polyostotic disease, and one patient had McCune-Albright syndrome (Table 7.1). Gender was evenly distributed (15 female, 13 male). Median age at the time of allogeneic cortical strut grafting was 23 years (range, 5–50 years), and mean follow-up after surgery was 13 years (range, 4–37 years). Four patients had surgery of the proximal femur before allogeneic cortical strut graft surgery and 11 patients had a preoperative fracture (for details, see Table 7.1). Of the 28 patients who were treated with allogeneic cortical strut grafting, 27 received a fibular strut graft and one patient received a tibial strut graft (seven dual struts and 21 single). Twenty-one patients were additionally treated with curettage and placement of allogeneic cancellous bone during the allogeneic cortical strut grafting procedure.

Treatment algorithm

The indications (Fig. 7.1) for cortical strut allografting during the follow-up period were agreed on by all participating surgeons. They included impending fracture of the proximal femur, persistent pain, or an actual nondisplaced femoral fracture. During that time, for patients with diaphyseal fractures, patients who were treated with an osteotomy and in patients with a displaced fracture of the proximal femur, placement of a blade plate without strut grafting were instead performed (nine patients); these patients are not included in the current study. Curettage in combination with

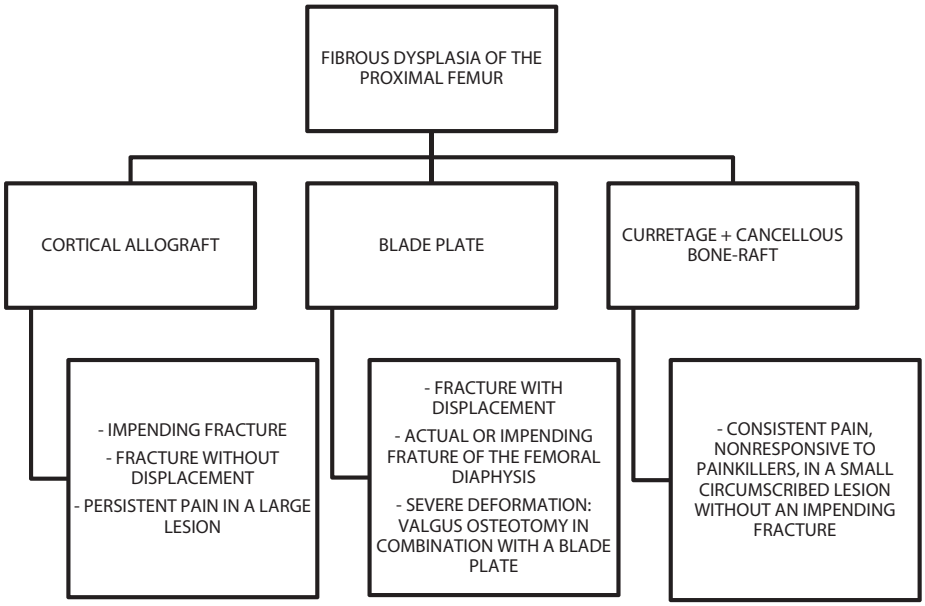


Fig. 7.1 The protocol for surgical treatment of fibrous dysplasia of the proximal femur in our center is shown.

cancellous bone grafting was performed occasionally (five patients) in individuals presenting with pain but with a small, circumscribed lesion and whose images did not suggest a risk of pathological fracture; likewise, those patients are not included in this study.

Allogeneic cortical strut grafting technique

The patient was placed in a supine position and a straight lateral incision was made to expose the greater trochanter and diaphysis; the femur was reached posteriorly to the vastus lateralis. A Kirschner wire was introduced in the fibrous dysplasia lesion under guidance of fluoroscopy by passing it through the lateral cortical bone at the level of the lesser trochanter, pushing it through the fibrous dysplasia lesion to the end in the femoral head, specifically aiming for the tip of the Kirschner wire ending in vital cancellous bone while evading the physis if still open. A cannulated reamer was then placed over the Kirschner wire to create a fitting tunnel for the allogeneic cortical strut grafting. Material was obtained from the lesion if biopsy had not been performed before the procedure. Curettage of the defect was not routinely performed but particularly in cases with scalloping and thinning of the cortex in which case it was necessary to partially fill the lesion with cancellous bone graft. The diameter of

Table 7.1 Patient characteristics

Patient ID	Gender	Type of FD	Age at surgery	Prior surgery	Preoperative fracture	Type of graft	Curettage + cancellous graft	Number of struts	Proximal anchoring ratio	Failure mechanism	Reoperation	Follow-up (years)
1	F	Polyostotic	48	CBG	No	Fibula	No	1	13%	-	No	19
2	F	Monostotic	31	No	No	Fibula	No	1	19%	-	No	4
3	F	Monostotic	39	No	No	Fibula	Yes	1	-	-	No	20
4	M	Polyostotic	10	No	No	Tibia	No	2	3%	Resorption	Yes	26
5	M	Polyostotic	12	No	No	Fibula	No	1	9%	-	No	25
6	M	Monostotic	10	No	Yes	Fibula	No	1	3%	Fracture	Yes	14
7	F	Monostotic	27	CBG	Yes	Fibula	Yes	2	3%	Resorption	Yes	28
8	M	Monostotic	37	No	No	Fibula	Yes	1	10%		No	7
9	M	Monostotic	12	No	Yes	Fibula	Yes	1	7%	Resorption	Yes	5
10	F	Polyostotic	17	No	Yes	Fibula	Yes	2	3%	Resorption	Yes	12
11	F	Polyostotic	45	No	No	Fibula	Yes	1	8%	-	No	7
12	M	Polyostotic	5	No	Yes	Fibula	Yes	1	3%	Fracture	Yes	9
13	F	Polyostotic	22	No	Yes	Fibula	Yes	1	4%	Deformity	Yes	25
14	M	Monostotic	24	No	No	Fibula	Yes	1	6%	-	No	6
15	F	Monostotic	23	CBG	Yes	Fibula	Yes	2	3%	Fracture	Yes	9

Table 7.1 *Continued*

Patient ID	Gender	Type of FD	Age at surgery	Prior surgery	Preoperative fracture	Type of graft	Curettage + cancellous graft	Number of struts	Proximal anchoring ratio	Failure mechanism	Reoperation	Follow-up (years)
16	F	Polyostotic	27	No	No	Fibula	Yes	1	17%	-	No	6
17	F	Monostotic	15	No	No	Fibula	Yes	2	20%	-	No	6
18	M	Monostotic	8	No	Yes	Fibula	Yes	1	6%	-	No	4
19	M	Polyostotic	27	No	No	Fibula	Yes	1	5%	Resorption	Yes	25
20	M	Monostotic	9	No	No	Fibula	Yes	1	10%	-	No	11
21	F	Monostotic	18	No	No	Fibula	Yes	2	6%	Fracture	Yes	4
22	M	Monostotic	50	No	No	Fibula	Yes	1	8%	-	No	11
23	F	Monostotic	21	No	No	Fibula	Yes	1	17%	-	No	8
24	M	Monostotic	24	No	No	Fibula	Yes	2	4%	Resorption	Yes	7
25	F	MAS*	14	Osteosynthesis	Yes	Fibula	Yes	1	8%	-	No	37
26	F	Polyostotic	44	No	No	Fibula	No	1	19%	-	No	10
27	F	Monostotic	10	No	Yes	Fibula	No	1	5%	Resorption	Yes	5
28	M	Polyostotic	25	No	Yes	Fibula	Yes	1	1%	Resorption	Yes	13

* CBG = Cancellous Bone Grafting.
** MAS = McCune-Albright Syndrome.

the strut graft was compared with the drilled tunnel to secure smooth insertion of the allogeneic cortical strut grafting. Under fluoroscopy a Kirschner wire was introduced into the center of the allogeneic cortical strut grafting for more accurate docking. The cortical allograft was then placed over the Kirschner wire and the lateral protruding graft was leveled with the femoral cortex. An additional allogeneic cortical strut graft was inserted in lesions that involved more than three-fourths the diameter of the femoral neck. Patients were encouraged to mobilize postoperatively using two crutches and partial weightbearing (up to a maximum of 15 kg). Gradual increase in weightbearing was allowed after 6 weeks if increasing consolidation of the graft was observed on plain radiographs.

Outcomes assessment

The primary outcome of our study was the proportion of patients undergoing revision surgery as a result of fracture, progressive deformity, and/or progressive resorption of the graft with return of pain. Resorption of the graft was determined by evaluation of consecutive, yearly radiographs undertaken by one of the authors (BCJM). Grafts were scored as "totally resorbed" if over 50% of the graft was resorbed or if resorption extended to the full diameter of the graft. Potential risk factors for revision surgery were also assessed, including gender, age at the time of surgery, a preoperative fracture, proximal and distal anchoring of the graft in healthy bone, concurrent curettage of the fibrous dysplasia lesion during allogeneic cortical strut grafting surgery, and concurrent placement of cancellous bone during allogeneic cortical strut grafting surgery. Proximal and distal anchoring was assessed by measuring the length of both the proximal and distal parts of the graft that were anchored in vital bone (Pa and Da in Fig. 7.2) and the length of the femoral neck (LFC in Fig. 7.2). We then calculated the ratio of the proximal and of the distal length of the graft in vital bone to the length of the femoral neck. The ratio had to be used because old radiographs were used without calibrated measuring options.

Statistical analysis

Statistical analysis was performed with the use of SPSS for Windows, Version 23.0 (SPSS, Inc, Chicago, IL, USA). Survival analysis was performed with the use of the Kaplan-Meier method. Risk factors were assessed with use of the log-rank test and/or with a univariate Cox regression model and results are presented as mean ± SD. The influence of continuous data, for example age at the time of surgery, was analyzed with the use of a linear regression model.

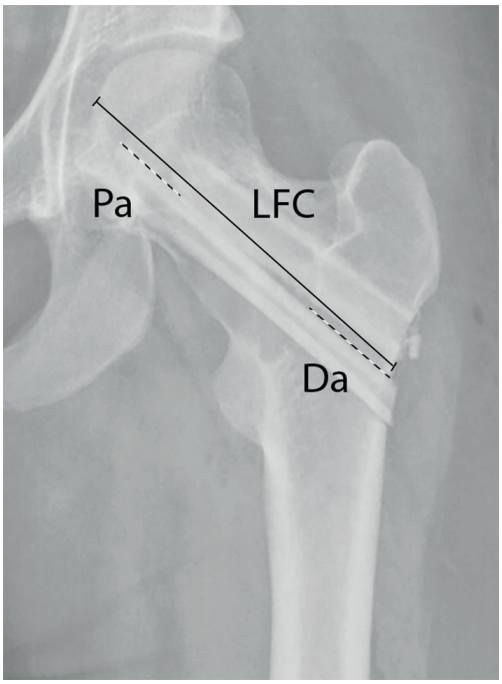


Fig. 7.2 Assessment of the anchoring ratio of the graft in vital bone. The proximal anchoring (Pa) and distal anchoring (Da) parts of the graft were measured and divided by the length of the femoral collum (LFC) to obtain the ratio. In case two grafts were used, we chose the measurement with the deepest anchoring. LFC was defined by as the length between the lateral cortex and femoral head in alignment with the graft.

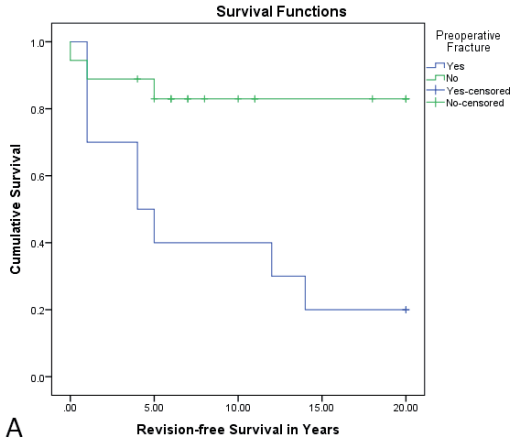
RESULTS

Revision-free survivorship

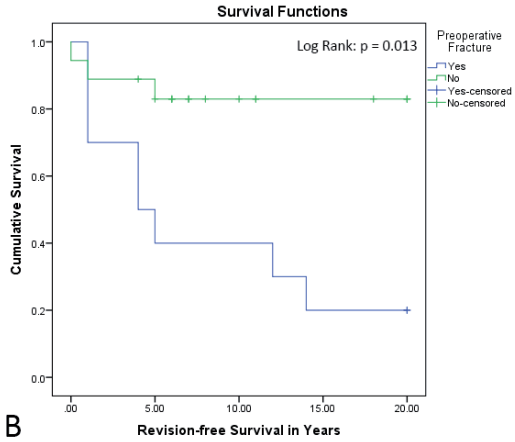
Overall revision-free survival was 54% after 20 years and mean survival time in Kaplan-Meier (Fig. 7.3) was 13 years (95% confidence interval [CI] 10–16). Thirteen of 28 patients (46%) underwent a reoperation as a result of resorption of the graft (61%), a fracture (31%), or as a result of progressive deformation of the proximal femur (8%). Mean time to graft failure was 7 ± 8 years.

Radiological appearance of grafts

Radiological resorption of the graft (Fig. 7.4) was observed in 15 patients (54%). However, revision surgery was not performed in all patients who developed graft resorption, because according to the treatment protocol in our center, surgery is only required in case of an impending or actual fracture and/or persistent pain. The other 13 patients showed full incorporation of the bone graft (Fig. 7.5).



A



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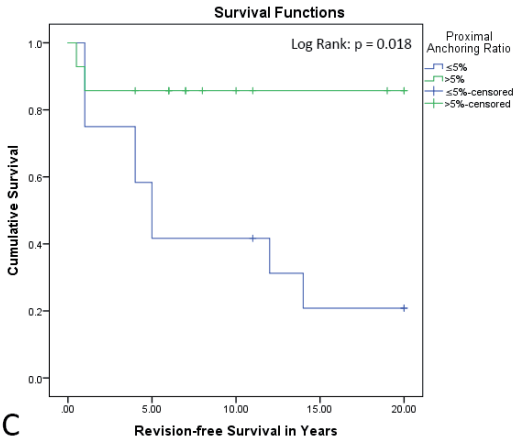

C

Fig. 7.3A–C The Kaplan-Meier curve for revision-free survival (A) indicates that most failures occur in the first 5 years after surgery. The Kaplan-Meier curves (B–C) illustrate the role of a preoperative fracture and insufficient proximal anchoring on revision-free survival.

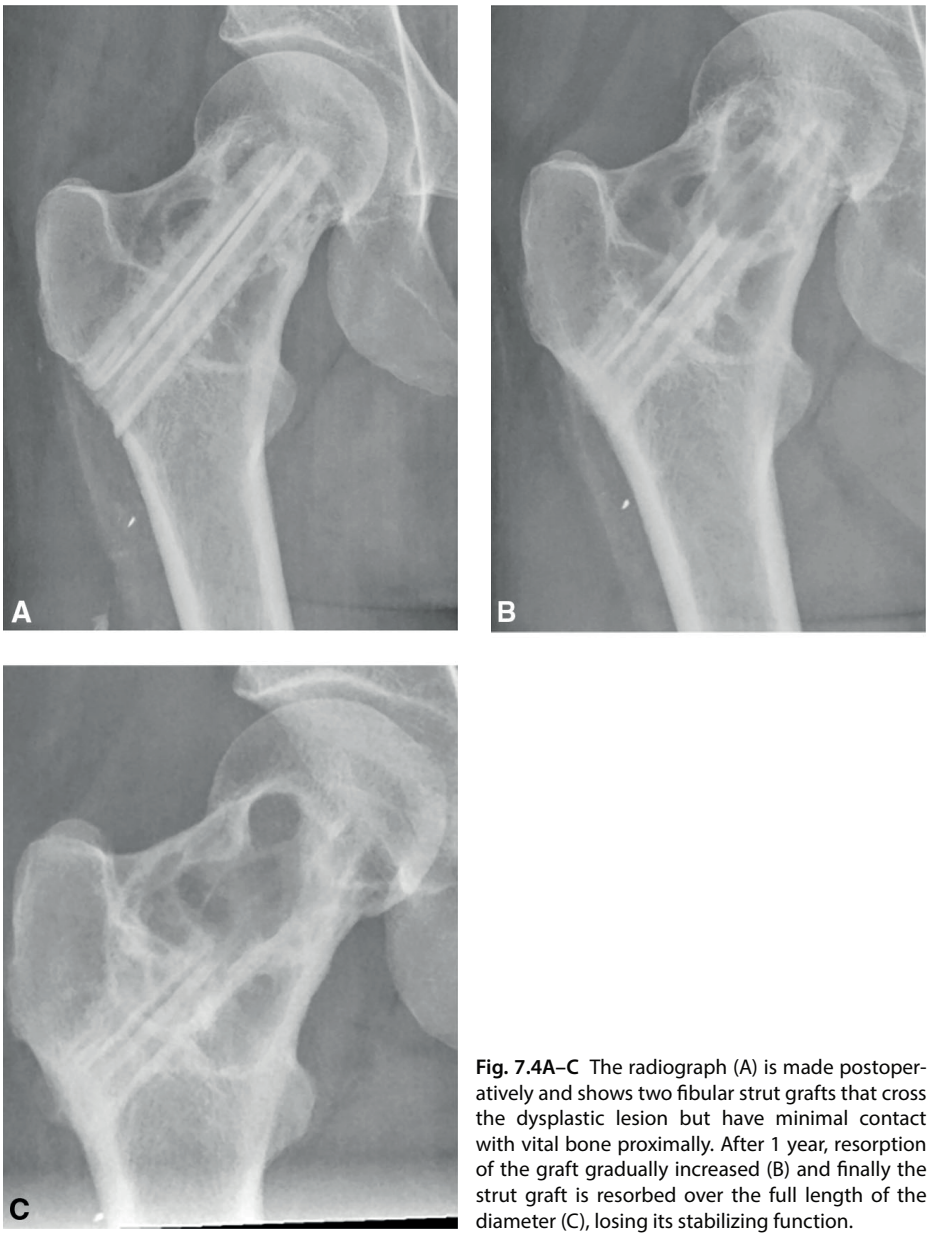

Fig. 7.4A–C The radiograph (A) is made postoperatively and shows two fibular strut grafts that cross the dysplastic lesion but have minimal contact with vital bone proximally. After 1 year, resorption of the graft gradually increased (B) and finally the strut graft is resorbed over the full length of the diameter (C), losing its stabilizing function.

Factors associated with survivorship of grafts

Preoperative fracture was associated with increased risk for revision surgery (hazard ratio [HR] 4.5; 95% CI 1.2–17.2; p = 0.028; Table 7.2) as was insufficient proximal anchoring of the graft in vital bone (HR 6.0; 95% CI 1.3–27.0; p = 0.020), although this was not the case for insufficient distal anchoring (HR 1.4; 95% CI 0.5–4.2; p =

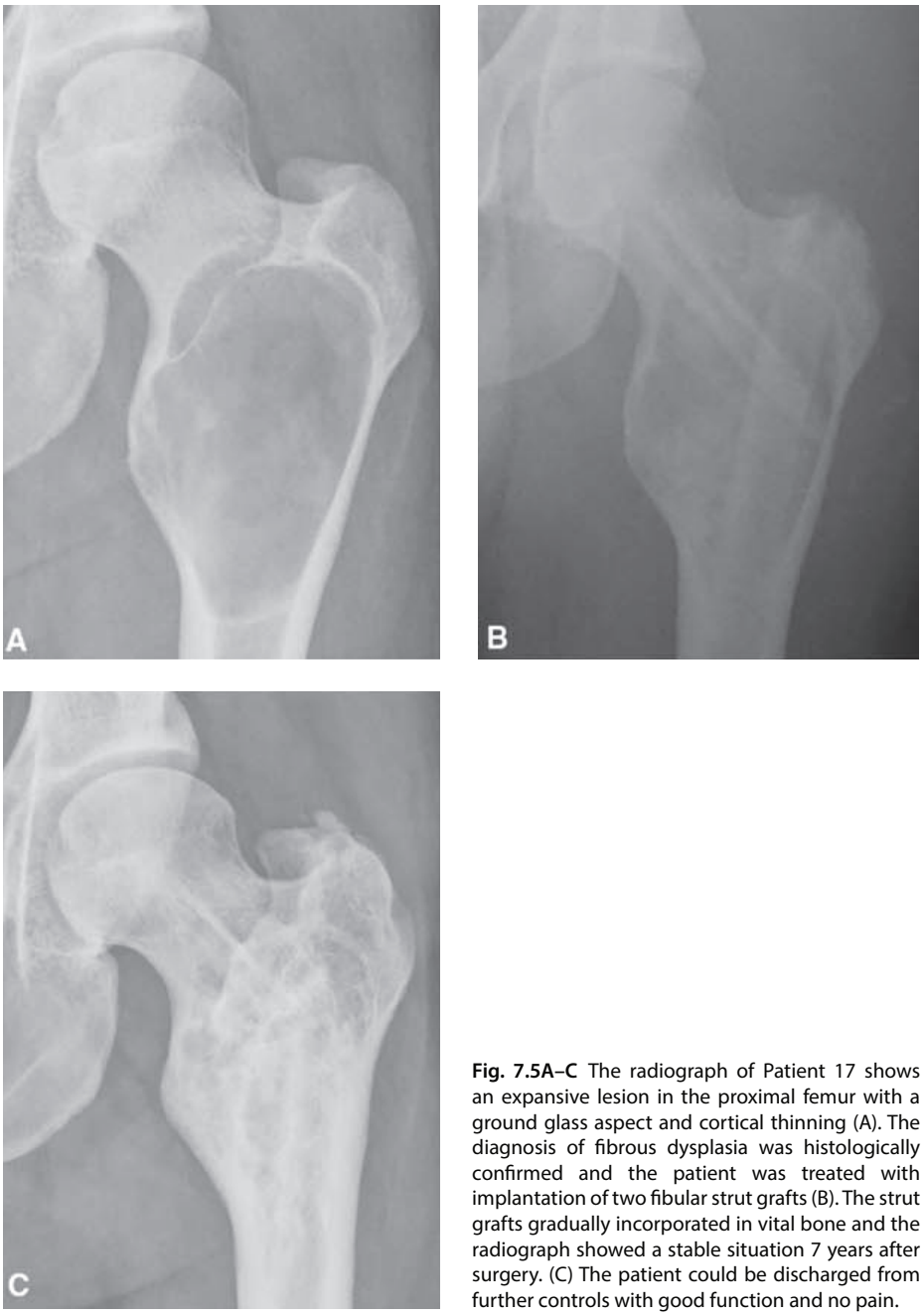

Fig. 7.5A–C The radiograph of Patient 17 shows an expansive lesion in the proximal femur with a ground glass aspect and cortical thinning (A). The diagnosis of fibrous dysplasia was histologically confirmed and the patient was treated with implantation of two fibular strut grafts (B). The strut grafts gradually incorporated in vital bone and the radiograph showed a stable situation 7 years after surgery. (C) The patient could be discharged from further controls with good function and no pain.

0.543) with the numbers available. Revision-free survival curves of the risk factors confirmed the results of the Cox regression analysis (Fig. 7.3). Gender, type of fibrous dysplasia, additional curettage and/or cancellous bone grafting, and previous surgery

Table 7.2 Risk factors for failure of ACSG surgery (univariate Cox regression analysis)

Risk factor	Hazards ratio	95% confidence interval	P-value
Monostotic fibrous dysplasia	0.50	0.2–1.6	.230
Previous surgery	0.79	0.2–3.6	.756
Additional curettage + CBG*	1.34	0.4–4.9	.657
Distal anchoring ratio ≤ 5%	1.40	0.5–4.2	.543
Gender (male)	1.40	0.5–4.2	.543
Preoperative fracture	4.50	1.2–17.2	.028
Proximal anchoring ratio ≤ 5%	6.02	1.3–27.0	.020
Age at surgery	1.05/year	1.0–1.1	.087

* CBG = Cancellous Bone Grafting.

before allogeneic cortical strut graft surgery did not appear to be associated with reoperation after allogeneic cortical strut graft surgery with the numbers available. Although patients who received cortical allografts at a young age appeared to have an increased risk of reoperation compared with older patients, age was not associated with revision surgery (HR 1.05/year; 95% CI 1.0–1.1; p = 0.087).

Complications

One patient sustained a refracture after surgery resulting from an in-hospital fall. The fracture was treated without further surgery, and it healed. No other complications of surgery were observed.

DISCUSSION

Despite progress in understanding the pathogenesis of fibrous dysplasia, its treatment has been subject to controversy ever since the first reports of Lichtenstein on management of the disease, emphasizing its notorious recurrent character, the wide variations in phenotype, and the lack of a successful treatment strategy.[6,7] Over the past few decades many surgical approaches have been proposed and discarded in the management of fibrous dysplasia ranging from particular forms of grafting to a variety of types of implants or a combination of both.[3] Although curettage and bone grafting using cancellous bone have been historically the treatments of choice, the perspective of the value of this treatment in fibrous dysplasia lesions of the proximal femur has altered over the last decades as a result of increasing reports on the marginal

outcome of the procedure (Table 7.3).[2,8-12] We theorized that allogeneic cortical strut grafting might improve the outcome of fibrous dysplasia lesions of the proximal femur, arguing that cortical allografts would be less prone to be affected by pathological fibrous dysplasia bone and therefore less prone to resorb and fail. We found that allogeneic cortical strut grafting has a survivorship of 54% after long-term follow-up and that patients who presented with fracture (as opposed to impending fracture) and patients whose grafts lacked sufficient proximal fixation were at increased risk of undergoing reoperation.

This study had a number of limitations. First, the small number of patients included in our study reflects the low prevalence of symptomatic fibrous dysplasia, although our series of patients was larger than any reported thus far of which we are aware. Because of a small study size, it is possible that we were unable to detect the less common complications of allogeneic cortical bone grafting. Furthermore, we have to

Table 7.3 Previous studies into surgical treatment of fibrous dysplasia of the femoral neck

Study	Number	Type of graft	Mean follow-up	Failure graft	Clinical outcome
Harris et al. (1962) [8]	10	Cancellous autograft	Unknown	5/10	Five of 10 had a poor outcome
Nakashima et al. (1984) [10]	8	Autograft	Unknown	2/8	25% had a poor outcome
Enneking and Gearen (1986) [3]	15	Cortical autograft	6 years	2/15	Two of 15 had a poor outcome (reoperation)
Stephenson et al. (1987) [12]	18	Cancellous autograft	10.4 years	25/31	81% had a poor outcome
Guille et al. (1998) [2]	22	Cancellous autograft	15 years	22/22	100% had resorption
Ippolito et al. (2003) [9]	5	Cancellous autograft	Unknown	3/5	Three of 5 patients had a poor outcome (reoperation)
George et al. (2008) [4]	8	Cortical autografts	4.1 years	1/8	One patient had a poor outcome (recurrence)
Tong et al. (2013) [22]	15	Cancellous autograft with internal fixation	12–32 months	0/15	No patients needed a reoperation
Nishida et al. (2015) [11]	8	Cortical autograft with internal fixation	75 months	0/8	No patient had a poor outcome

take into account the possibility that some of the risk factors that were not associated with treatment outcome in our study might show an association in larger studies. Second, the long span of time over which this retrospective study's procedures were performed saw many changes in patient care. Although the indications were generally consistent over time at the study site, it is impossible to know with certainty that they were applied with precision over the nearly 35-year timeframe. Also, many of these procedures were performed before patient-reported outcomes tools came into wide use, and so we could not report patient-reported outcomes here. It is our impression based on chart review and patient surveys done after surgery that pain improved in most of these patients. Furthermore, we appreciate that the variability in treatment options for fibrous dysplasia of the proximal femur, which is no doubt the result of the heterogeneity of the disease, makes it difficult to compare different patients. Although the use of multiple trajectories, additional cancellous bone grafting, and additional curettage were taken into account in our analysis, these different approaches within the treatment with cortical allografts might affect the outcome in larger studies. Finally, although the treatment of fibrous dysplasia is centralized in The Netherlands, it is common in long-term studies that some patients were lost to follow-up.

Although a large proportion of patients in this study (nearly half of them) underwent revision at some point during the follow-up period, we consider the fact that more than half of the patients did not undergo further surgery actually a reasonably good result. The reason for this is that the condition recurs so commonly, and other described approaches actually reported even more frequent failures than we observed here.[2,12] Most previous studies were restricted to limited follow-up and are therefore likely to overestimate the therapeutic effect of bone grafting, a fact that is further emphasized by studies with long-term follow-up generally, suggesting a poorer outcome (Table 7.3). Because of its mean follow-up of 13 years, our study gives a fair representation of the long-term effects of allogeneic cortical strut graft treatment in fibrous dysplasia lesions of the proximal femur. However, Kaplan-Meier survivorship analysis (Fig. 7.3A) showed that most reoperations were performed within 5 years after the primary surgery, indicating that after 5 years, failure of allogenous cortical strut grafts leading to reoperation is less likely to be expected. In addition, besides being biologically preferable to prevent graft resorption, the use of allogeneic bone has the advantage of no additional surgery being required to retrieve autogenous bone.

Slightly more than half of our patients experienced radiographic evidence of graft resorption. Again, however, we consider this a reasonably good result considering the problems reported using other techniques when dealing with proximal femoral

lesions in patients with fibrous dysplasia, especially in studies addressing cancellous bone grafting in which recurrence is reported in nearly all patients.[2,12] Although the indication for reoperation was graft resorption in the majority of the cases (61%), graft resorption was not an indication for reoperation per se, because we would only perform a reoperation in case graft resorption led to an impending or an actual fracture.

We identified several risk factors for failure of allogeneic cortical strut graft surgery in this study. In patients undergoing cortical strut allografting, we found a minimal proximal anchoring ratio in vital bone of 5% is required to enable the graft to be incorporated in the proximal femur. Therefore, proper evaluation of proximal placement preoperatively and intraoperatively should be mandatory, whereas this is not so for distal anchoring in which case anchoring in the cortex will generally suffice. Although it has previously been reported that insufficient proximal docking in healthy bone might have played a role in failure of allogeneic cortical strut grafting in two patients in the Enneking/Gearen study,[3] our study is the first to clearly identify insufficient proximal anchoring of the graft and preoperative fractures as risk factors for failure of allogeneic cortical strut graft surgery. Our data also demonstrate a higher risk of revision in patients with a preoperative fracture. Patients who sustained a fracture of the proximal femur at some point before surgery have thus a high risk of failure of allogeneic cortical strut grafting by either resorption or a consecutive fracture. We suspect that a pathological fracture is only the endpoint of a sliding scale. Guille et al. already identified involvement of the calcar femorale as a risk factor for failure.[2] If the calcar is involved, the proximal femur will considerably lose stability by loss of redistribution of stress forces.[13] Subsequently the proximal femur will be more prone to fractures. A cortical strut graft will very likely not be able to address the extensive forces applied on the proximal femur without this form of stability. Based on the results with internal fixation in other studies and the findings from our present study, we recommend primary internal fixation in patients with extensive lesions that threaten to fracture or have already induced a fracture, because this approach has shown promising results in several studies.[2,9,12,14-23] More importantly, although only the combination of internal fixation and autografts has so far been studied, there might be an important role for implantations in combination with cortical allografts in patients with preoperative risk factors.

Although the polyostotic form of fibrous dysplasia is generally associated with a worse outcome compared with monostotic disease, we were not able to identify polyostotic fibrous dysplasia as a risk factor for graft failure.[2,5] This may be explained by the fact that polyostotic fibrous dysplasia can be profoundly variable in its course and in the

extent of lesions. Patients with extensive lesions, both monostotic and polyostotic fibrous dysplasia, were primarily treated with internal fixation, because a strut graft would not properly bridge the lesion and therefore local expansion and not the type of fibrous dysplasia would be a risk factor. Furthermore, we expected that young age at the time of surgery would be a risk factor based on the hypothesis that fibrous dysplasia tends to be more active and aggressive during childhood and because patients with extensive disease are generally diagnosed at a younger age.[24] However, we were unable to demonstrate this in the present study, perhaps because of the statistical limitations imposed on our statistical analysis by the sample size. Although this procedure can be technically challenging, we were gratified by the relative rarity of complications in this series. This compares favorably to bone grafting with autogenous bone, which can be accompanied by complications at the donor site.[25,26]

Our findings from this study suggest that cortical strut allografting may be a viable option for treatment of fibrous dysplasia of the proximal femur who have not already experienced a fracture. Surgeons should pay particular attention to the proximal fixation point of the allograft to decrease the risk of failure. Patients with a fracture have an increased risk of failure and reoperation and so should be treated with osteosynthesis.

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Chapter 8

Individualized approach to the surgical management of fibrous dysplasia of the proximal femur

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ABSTRACT

Background: Fibrous dysplasia of the proximal femur presents with heterogeneous clinical manifestations dictating different surgical options. However, to date there are no clear recommendations to guide the choice of surgical approach and no general guidelines for the optimal orthopedic management of these lesions. The objective of this study was to evaluate treatment outcomes of both angled blade plates and intramedullary nails, using as outcome indicators revision-free survival, pain, function and femoral neck-shaft angle. Based on published literature, we also propose a treatment algorithm, taking into account different factors, which may play a role in the selection of one surgical approach over another.

Methods: Data were evaluated in thirty-two patients (18 male) from a combined cohort from the Netherlands and Austria who had a surgical intervention using an angled blade plate (n = 27) or an intramedullary nail (n = 5) between 1985 and 2015, and who had a minimal follow-up of one year. The primary outcome was success of the procedure according to the revised Henderson classification. Secondary outcomes, which were assessed at one year and at the end of follow-up included: function (as measured by walking ability), pain and change in femoral neck-shaft angle over time.

Results: Analysis of data showed that revision-free survival was 72% after a median follow-up of 4.1 years. Revision was necessary in two patients for structural failure due to a fracture distal to an angled blade plate and in 7 patients due to angled blade plate-induced iliotibial tract pain. At the end of follow-up 91% of all patients had good walking ability and 91% were pain free. There was no significant postoperative change observed in femoral neck shaft angle.

Conclusion: Our data show that fibrous dysplasia of the proximal femur can be adequately and safely treated with angled blade plates or intramedullary nails, provided that these are used according to specific characteristics of the individual patient. Based on published literature and our own experience, we propose an individualized, patient-tailored approach for the surgical management of fibrous dysplasia of the proximal femur.

BACKGROUND

Fibrous dysplasia is a genetic, not inheritable, rare bone disorder that was first described in the late nineteen-thirties.[1-3] The disorder is due to a post-zygotic activating mutation of the GNAS-gene that decreases the GTPase activity of the stimulatory G-protein (Gsα).[4,5] This results in increased intracellular levels of cAMP in bone forming cells, leading to replacement of lamellar bone with ill-woven, under mineralized (fibrous) tissue of poor quality, associated with clinical manifestations of pain, deformity and pathological fractures. The clinical spectrum of fibrous dysplasia varies widely, including single lesions (monostotic), multiple lesions (polyostotic), and the combination of polyostotic fibrous dysplasia with extra-skeletal manifestations such as café-au-lait patches and/or endocrinopathies such as precocious puberty and growth-hormone excess in the McCune-Albright Syndrome or intramuscular myxomas in the Mazabraud's syndrome.[6,7] The bony lesions are predominantly localized in the proximal femur and craniofacial bones.[8] Because of the weight-bearing forces acting on the lower extremities, the femur is most prone to deformities and fractures, ultimately resulting in the pathognomonic feature of fibrous dysplasia of the proximal femur; the 'shepherds crook' deformity.[9]

The surgical management of fibrous dysplasia of the proximal femur has been particularly challenging due to the high load of mechanical forces acting on this bone.[10] A number of surgical options have been initially proposed, including different types of bone grafting, various osteosynthesis, with or without additional osteotomy or a combination of these modalities. Over the past decade, however, there has been a reported increasing preference for the use of intramedullary nails and angled blade plates due to better treatment outcomes with these procedures.[11-16] In this study, we assess the clinical outcome of both angled blade plates and intramedullary nails in fibrous dysplasia of the proximal femur, using as outcome indicators implant function, revision-free survival and pain relief, in a combined cohort of patients from the Leiden University Medical Center (LUMC) in the Netherlands and the Medical University of Graz (MUG) in Austria. We also perform a review of published literature on available surgical options in the management of fibrous dysplasia of the proximal femur, specifically focusing on the heterogeneity of the features of fibrous dysplasia at this site, and on the factors potentially affecting outcomes using different procedures. Finally, based on our collective experience and on findings from published literature, we set out to propose a patient-tailored approach for the surgical management of fibrous dysplasia of the proximal femur.

METHODS

Patient selection

Ninety-six patients with an established diagnosis of fibrous dysplasia of the proximal femur who underwent surgery at the Orthopaedic Department of the LUMC or of the MUG between 1985–2015 were identified from the two hospitals' registries. Included in the study were 32 patients who were treated with either an angled blade plate or an intramedullary nail and were followed-up for at least one year after surgery. Sixty-four patients in whom other surgical interventions were undertaken such as different types of grafting or other types of osteosyntheses were excluded from the study. Data from the 32 patients included in the study were retrieved from their medical records. Ethical approval was obtained from the Medical Ethics Committee of both centers.

Treatment protocol

According to the treatment protocol for fibrous dysplasia of the proximal femur followed at both the LUMC and the MUG, patients received an angled blade plate in case of a fracture with displacement, an (impending) fracture with involvement of the femoral shaft or in case of severe deformity of the proximal femur, in which case a valgus osteotomy was performed prior to implantation of the angled blade plate.[17] Only one patient from the LUMC received an intramedullary nail because the fibrous dysplasia lesion could not be bridged with an angled blade plate as the whole femur was affected (ID 17). Patients from the MUG were all initially treated with an angled blade plate as first choice, but the policy was changed to the use of intramedullary nails as first choice due to recurrent blade plate-induced pain of the iliotibial tract. The choice of additional bone grafting was based on the surgeon's preference, particularly in the presence of relatively large lesions, although realizing that these would be likely to undergo resorption in time.

Assessment of outcomes of surgical interventions

In this study the primary outcome of surgery using blade plates was success of the procedure, as defined by the modified Henderson classification for reconstructive surgery with endoprosthesis for bone tumours.[18] Secondary outcomes consisted of functional outcomes, pain and continuous femoral bowing and these outcomes were measured at three time points: directly after surgery (< 2 months), one year after surgery and at the end of the follow-up period. Data on functional outcome and pain were retrieved from electronic medical records. Functional outcome was evaluated by walking ability and categorized as good (walking a normal distance unaided and

without complaints); moderate (able to walk only short distances) and severe (walking with the help of an aid (crutches/frame) or using a wheelchair). An increase of femoral deformity was judged by measured changes in the Femoral-Neck-Shaft-Angle (FNSA) of the femur on conventional radiographs.

Statistical analysis

Statistical analysis was performed with the use of SPSS for Windows, Version 23.0 (SPSS, Inc, Chicago, IL, USA). Results are presented as median and intermediate range or mean ± SD. FNSAs were analysed at different time-points using a general linear model for repeated measurements. Differences in FNSA-change between angled blade plates and intramedullary nails were analysed using an independent T-test.

RESULTS

Patient characteristics

Individualized patients' data and cohort characteristics are respectively shown in Tables 8.1 and 8.2. Thirty-two patients from our combined cohort were included in

Table 8.1 Cohort characteristics

	LUMC	MUG	Total
N	17	15	32
Male:Female	9:8	9:6	18:14
Median age at diagnosis (years (range))	9 (3–42)	23 (0–51)	12 (0–51)
Type of fibrous dysplasia			
Monostotic	3	12	15
Polyostotic	10	2	12
McCune-Albright	4	1	5
Type of surgery			
Angled blade plate	16	11	28
Intramedullary nail	1	4	5
Median age at surgery (years (range))	19 (11–67)	23 (6–51)	20 (6–67)
Preoperative fracture	77%	13%	47%
Characteristics of surgery			
Osteotomy	35%	13%	25%
Custom made	53%	0%	28%
Additional cancellous bone grafting	18%	53%	34%
Additional cortical strut grafting	53%	0%	28%
Median follow up after surgery (years)	4.1 (1–31)	4.7 (1–18)	4.1 (1–31)

Table 8.2 Individual patient characteristics

Patient ID	Gender/ age at surgery	Type of fibrous dysplasia*	Prior surgery of the proximal femur	Indication for surgery	Type of implant†	Osteotomy	Cancellous bone grafting	Cortical bone grafting	Follow-up in years	Failure
1	M/16	MAS	TEN Nails	Deformity	Custom made ABP	Yes	No	No	1,4	No
2	M/17	MAS	TEN Nails	Fracture	Custom made ABP	No	No	Yes	1,3	No
3	F/67	PFD	Fibular graft	Fracture	Custom made ABP	No	No	No	1,8	No
4	F/58	MAS	-	Fracture	Custom made ABP	No	No	Yes	2,0	No
5	M/12	PFD	Fibular graft, TEN Nails, external fixture	Fracture	Custom made ABP	No	No	No	4,1	No
6	M/29	PFD	Fibular graft (2x)	Pain	Custom made ABP	No	No	Yes	3,8	No
7	M/20	PFD	CBG, Plate osteosynthesis	Deformity	ABP	Yes	No	No	6,7	Yes
8	F/45	PFD	Fibular graft	Pain	Custom made ABP	No	Yes	No	4,1	No
9	F/19	MFD	Fibular graft	Fracture	ABP	No	No	No	4,7	No
10	F/18	PFD	Fibular graft (3x)	Deformity	ABP	Yes	Yes	Yes	9,4	No
11	M/16	MFD	-	Deformity	ABP	Yes	No	Yes	14,8	No
12	M/14	PFD	-	Deformity	ABP	Yes	No	Yes	17,3	Yes
13	M/11	PFD	-	Deformity	ABP	Yes	No	Yes	31,1	No
14	F/26	MFD	-	Fracture	ABP	No	Yes	Yes	1,8	No
15	F/40	MAS	Plate osteosynthesis, Fibular graft	Fracture	Custom made ABP	No	No	Yes	4,3	No
16	M/14	PFD	-	Fracture	ABP	No	No	No	1,0	No
17	F/30	PFD	Fibular graft	Pain	Custom made IMN	No	No	No	1,1	No
18	M/16	MFD	TEN Nails	Impending fracture	IMN	No	No	No	1,0	No
19	F/15	MFD	TEN Nails	Deformity	IMN	Yes	Yes	No	1,1	No
20	M/15	MAS	-	Deformity	IMN	Yes	No	No	1,4	No

Table 8.2 *Continued*

Patient ID	Gender/ age at surgery	Type of fibrous dysplasia*	Prior surgery of the proximal femur	Indication for surgery	Type of implant†	Osteotomy	Cancellous bone grafting	Cortical bone grafting	Follow-up in years	Failure
21	M/51	MFD	-	Pain	ABP	No	No	No	7,4	No
22	F/21	MFD	-	Pain	ABP	No	Yes	No	7,8	Removal (irritation)
23	M/43	MFD	-	Impending fracture	ABP	No	Yes	No	3,6	Removal (irritation)
24	F/50	MFD	-	Impending fracture	ABP	No	No	No	4,0	Removal (irritation)
25	M/33	MFD	-	Pain	ABP	No	No	No	2,2	Removal (irritation)
26	F/29	MFD	-	Impending fracture	ABP	No	No	No	10,1	No
27	M23	PFD	-	Pain	ABP	No	Yes	No	15,9	No
28	M23	MFD	-	Pain	ABP	No	Yes	No	3,3	No
29	M14	MFD	-	Fracture	ABP	No	Yes	No	9,3	Removal (irritation)
30	F/46	MFD	-	Impending fracture	ABP	No	Yes	No	4,7	Removal (irritation)
31	F/6	MFD	-	Impending fracture	ABP	No	Yes	No	17,7	Removal (irritation)
32	M/13	PFD	Nancy Nails	Impending fracture	IMN	No	No	No	16,4	No

* MAS = McCune-Albright Syndrome; PFD = Polyostotic Fibrous Dysplasia; MFD = Monostotic Fibrous Dysplasia.
† ABP = Angled blade plate; IMN = Intramedullary nail.

the study. There was a slight predominance for the male gender (18 vs. 14). Median age at diagnosis was 12 years (range 0–51) and median age at time of surgery was 20 years (range 6–67 years). Fifteen patients had monostotic fibrous dysplasia, 12 had polyostotic fibrous dysplasia, 5 had McCune-Albright syndrome and one had Mazabraud's syndrome. Fifteen patients (47%) had a preoperative fracture at a median of 3 years prior to surgery (range 0–43 years). Fourteen patients had surgery of the proximal femur prior to implantation of the angled blade plate or of the intramedullary nail, most commonly in the form of an allogeneic strut graft (n = 6) or of fixation using Titanium-Elastic-Nails (TEN) (n = 5). Primary indication for surgery included a disabling varus deformity (n = 8), fractures (n = 9), pain symptoms (n = 8) and impending fractures (n = 7). Twenty-seven patients received an angled blade plate compared to 5 patients who received an intramedullary nail. Eight patients (25%) needed an additional osteotomy. In 11 cases (34%) the lesion was additionally filled with cancellous bone grafting or in 9 cases (28%) with allogeneic strut grafts. In 9 cases a custom-made titanium implant (8 blade plates and 1 intramedullary nail) was used. The procedure for implanting an angled blade plate was shorter in case an osteotomy was not required, compared to the time taken for implantation of an intramedullary nail (146 ± 46 vs. 230 ± 78 minutes). Procedures requiring an additional osteotomy took slightly longer to perform (respectively 182 ± 67 vs. 246 ± 85 minutes). Median follow-up after surgery was 4.1 years (range 1–31 years) for the whole cohort.

Revision-free survival

Two patients needed revision surgery 3 and 4 years after initial surgery due to structural failure of the implant (Henderson type 3B), both caused by a fracture distal to the implanted angled blade plate (Fig. 8.1). None of the other 30 patients included in this study sustained a fracture after surgery. Seven patients with monostotic fibrous dysplasia who were primarily treated with an angled blade plate in combination with cancellous bone grafting had soft tissue failure (Henderson type 1A) in the form of persistent iliotibial tract complaints requiring removal of the angled blade plate in all after a median of 3.0 (range 0–5) years after initial surgery. All 7 patients became pain free after removal of the endoprosthesis and none had recurrence of pain, fractures, or required further surgery for the duration of follow-up. Furthermore, there were no neurovascular complications, no complications related to the osteosyntheses and no infections. Revision-free survival was thus 97% for the whole cohort after 1 year and 72% at the end of follow-up after a median of 4.1 years (range 1–31 years).

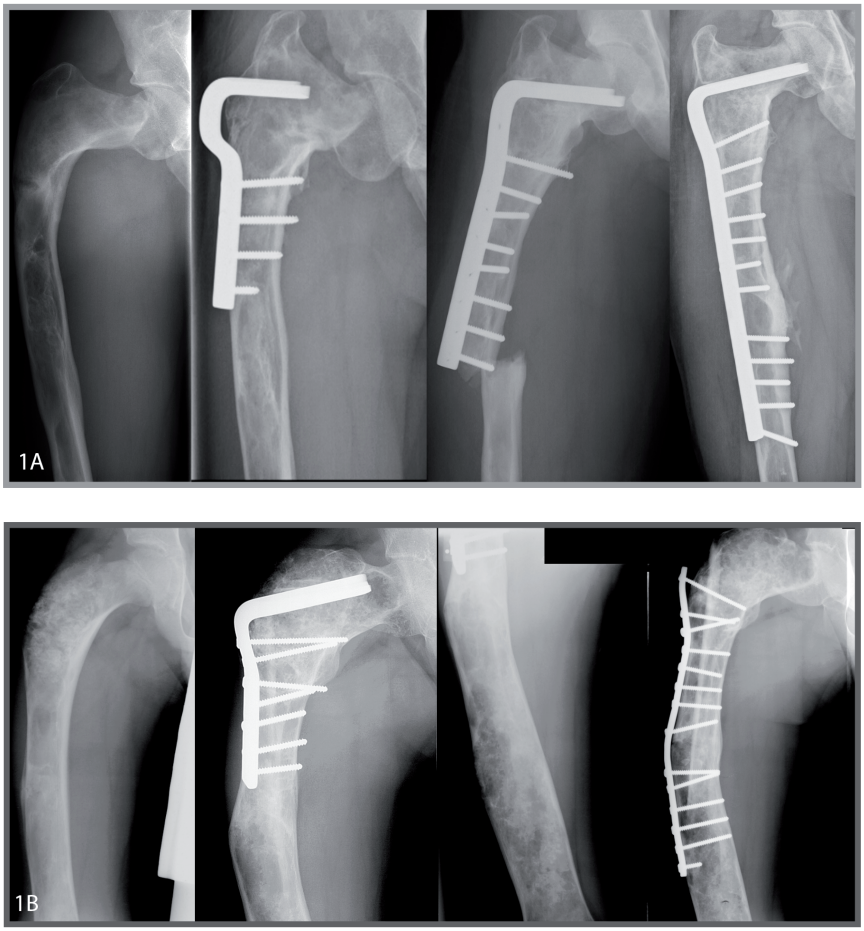

Fig. 8.1 Structural failures after angled blade plate endoprosthesis. The first patient that needed revision surgery (ID 7) was a male with shepherd's crook deformity of the femur and was previously treated elsewhere for a pathological femoral fracture by means of a valgus osteotomy combined with a short angled blade plate (Fig. 8.1A). The coxa vara persisted however (FNSA 67º), associated with severe pain complaints for which he was referred to the LUMC, 8 years after his first surgery. A subtrochanteric osteotomy was performed and fixation was undertaken using a larger blade plate and a temporary external fixator, which resulted in improvement of the coxa vara (FNSA 97º) and good functional outcome. Pain was adequately controlled with additional bisphosphonate therapy. Four years later the patient unfortunately sustained a fracture of the femoral diaphysis, distal to the angled blade plate. This part of the femur was also affected with fibrous dysplasia and together with the stress riser of the distal angled blade plate formed a weak location in the femur, prone to fracturing. The angled blade plate was removed and a longer angled blade plate was inserted to cover the whole area of the affected femur. This procedure was followed by a good functional outcome and disappearance of pain symptoms lasting to the end of follow up. The second patient who needed revision surgery (ID 12) was a male with a fracture through a fibrous dysplasia lesion of the proximal femur who was treated with a correction osteotomy and fixation with an angled blade plate in combination with a allogeneic strut graft at the age of fourteen (Fig. 8.1B). He unfortunately sustained a stress fracture distal to the blade plate, 3 years after the initial surgery. The angled blade plate was removed during revision surgery and a long femoral plate was used to stabilize the femoral shaft. The patient was able to walk with crutches and had no more pain complaints. However, his severe coxa vara (FNSA 69º) remained unchanged.

Pain symptoms and functional outcome

Thirty out of 32 patients had pain at the site of the fibrous dysplasia lesions of the proximal femur prior to surgery. One year after surgery only 6 patients had persistent pain at this site so that 81% of the patients were pain free. This figure further increased to 91% at the end of follow-up. Prior to surgery only 16% of the 32 patients had a good function (walking a normal distance unaided and without complaints), 66% had a moderate function (able to walk for a small distance) and 18% could only mobilize with the help of crutches or frame or by being wheelchair bound. One year postoperatively 88% had good function and at the end of follow-up 29 out of 32 (91%) of patients could walk a normal distance unaided. Three patients still needed crutches at the end of follow-up and one patient with mental retardation was wheelchair bound.

Femoral Neck-Shaft-Angle

In the group of patients who required an additional valgus osteotomy, average FNSA was corrected from 89° ± 20 to 118° ± 13 directly after surgery. In the whole cohort, mean FNSA was 123.1° ± 11 after implantation of an angled blade plate and 131.3° ± 1 after implantation of an intramedullary nail. FNSA did not significantly change one year after surgery or at the end of follow-up ($p = 0.129$). There was no significant difference between patients who received an angled blade plate compared to those receiving an intramedullary nail regarding change of FNSA after one year ($p = 0.541$) or at the end of follow-up ($p = 0.591$).

DISCUSSION

In this study we evaluated the clinical outcome of two types of surgical interventions for fibrous dysplasia of the proximal femur using angled blade plates and intramedullary nails. Our findings demonstrate that both modalities adequately maintained postsurgical FNSA, resulted in good clinical outcome regarding function and pain and generally prevented fractures although two patients still developed a pathological fracture distal to the angled blade plate. This was likely to be due to a stress riser effect in a fibrous dysplasia lesion, most probably as a result of the blade being too short to cover the whole area of the lesion. Angled blade plate implants were also associated with persistent complaints of the iliotibial tract in 7 patients with monostotic disease and relatively small fibrous dysplasia lesions, which necessitated removal of the angled blade plate with no further complications and good outcome at the end of follow-up.

Ever since the disease was first described, the management of fibrous dysplasia has been very challenging, not the least because of its wide and heterogeneous clinical spectrum and variable associations with extraskeletal manifestations.[1-3,10] Nowhere is this more true than in the management of fibrous dysplasia of the proximal femur. A fibrous dysplasia lesion of the proximal femur is thus known to cause more pain, fractures and especially deformity than any other disease localization.[9,10,19,20] Surgical treatment of a fibrous dysplasia lesion of the proximal femur must therefore not only treat and prevent pathological fractures, but also aim at preventing progressive varus deformity. Similar to the case with other rare diseases, the low incidence of fibrous dysplasia has resulted in the outcome of treatment modalities being evaluated in only small and often heterogeneous patient cohorts in which various surgical interventions have been performed usually at treating physician's discretion rather than according to high level evidence or to consensus guidelines. A number of surgical interventions have thus been performed over the past few decades, some subsequently discarded because of failure of the procedure or high rates of complications. We review here the outcomes of most of the surgical interventions reported in the literature which have been used in the management of fibrous dysplasia of the proximal femur, including bone grafting, intramedullary nails, angled blade plates and dynamic or compression hip screws. We also review the treatment of fibrous dysplasia of the proximal femur in pediatric patients.

LITERATURE REVIEW OF SURGICAL PROCEDURES USED IN FIBROUS DYSPLASIA OF THE PROXIMAL FEMUR

Curettage and bone grafting

Historically, fibrous dysplasia lesions of the proximal femur were treated by curetting the lesion, with or without filling of the emptied cavity with cancellous bone grafts. This technique was soon found to be highly inefficient due to high recurrence rates and is therefore no longer used (Table 8.3).[10,11,13,21-25] In 1986 Enneking and Gearen[26] suggested the use of allogeneic strut grafts instead of cancellous bone grafts, arguing that cortical allogeneic bone was less likely to be resorbed than cancellous bone and would therefore offer more efficient and especially long lasting stability to fibrous dysplasia lesions of the proximal femur. Despite good outcomes in the series they reported, there has been discrepancy with the outcome of cortical allografts reported by others (Table 8.3).[17,25,27,28] Different factors may play a role in the between studies discrepancy in results of graft survival. Patients with no fracture preoperatively have

Table 8.3 Overview of the literature on surgical treatment of fibrous dysplasia of the proximal femur

Type of surgery	Author/year	N	Type of surgery	Mean follow-up	Failure	Outcome
Grafts	Harris et al. (1962)	10	Cancellous Autograft	Unknown	5/10	Poor in 50%
	Nakashima et al. (1984)	8	Autograft (unknown origin)	Unknown	2/8	Poor in 25%
	Enneking er al. (1986)	15	Cortical Autograft	6 years	2/15	Poor in 2out of 15 (revision surgery)
	Stephenson et al. (1987)	18	Cancellous Autograft	10.4 years	25/31	Poor in 81%
	Guille et al. (1998)	22	Cancellous Autograft	15 years	22/22	Resorption of graft in 100%
	Ippolito et al. (2003)	5	Cancellous Autograft*	Unknown	3/5	Poor in 60% (revision surgery)
	George et al. (2008)	8	Cortical Autografts	4.1 years	1/8	Poor in 12.5% (recurrence)
	Tong et al. (2013)	13	Cancellous Autograft with internal fixation	12–32 months	0/13	No patients required revision surgery
	Kushare et al. (2014)	8	Various Grafts	3 years	Unknown	Unclear
	Nishida et al. (2015)	8	Cortical Autograft with compression hip screw	75 months	0/8	No patient had poor outcome
	Leet et al. (2016)	46	Various Grafts	19.6 years	39/52	KM-survival: 50% survival at 14.5 years
	Majoor et al. (2016)	28	Cortical Allograft	13 years	13/28	Good outcome in patients without a preoperative fracture and adequate proximal anchoring
Intramedullary Nail	Harris et al. (1962)	3	Single intramedullary rod	Unknown	1/3	The only patient with fibrous dysplasia of the collum developed a severe varus deformity
	Freeman et al. (1987)	6	Multiple osteotomies with a Zickel Nail	34.5 months	2/6	Two patients needed revision surgery

Table 8.3 *Continued*

Type of surgery	Author/year	N	Type of surgery	Mean follow-up	Failure	Outcome
	Keijser et al. (2001)	5	Intramedullary nails, additional multiple osteotomies in one patient	19.4 years	3/5	Three patients needed at least one revision surgery after the first IMN
	O'Sullivan et al. (2002)	10	Bilateral osteotomies and Sheffield rods	18 months	3/10	Three femurs needed revision surgery. 4/5 patients had a bad functional outcome due to severe coxa vara.
	Ippolito et al. (2003)	19	Interlocking cephalomedullary nails	Unknown	0/19	All patients had a good outcome with no worsening of deformities
	Jung et al. (2006)	7	Multiple osteotomies with intramedullary nails	30 months	0/7	No patients needed a revision surgery and good functional outcome in all patients
	Yang et al. (2010)	14	Valgus osteotomy with intramedullary nails	75.3 months	0/14	No patient needed revision surgery
	Zhang et al. (2012)	28	IMN, additional osteotomy in 8 patients	50 months	0/28	No patients needed revision surgery. Good functional outcome in the majority.
	Kushare et al. (2014)	16	Intramedullary nails	3 years	1/16	One patient required further surgery and 5 had pain at last follow-up
	Ippolito et al. (2015)	11	Two stage coxa vara correction and definitive fixation with an interlocking nail	4.7 years	4/11	Four patients had complications after the first surgery and another four needed further surgery after the second implant
	Benedetti Valentini et al. (2015)	8	Customized adult humeral nail in children (4-7 years)	2.9 years	3/8	Three patients required revision surgery as an adult. One patient required distal screw removal and acquired nail breakage

Table 8.3 continues on next page

Table 8.3 *Continued*

Type of surgery	Author/year	N	Type of surgery	Mean follow-up	Failure	Outcome
	Present study	5	Intramedullary nails, one of which was customized	4.1 years	0/5	All patients had a good outcome with no worsening of deformities
Angled Blade Plate	Ippolito et al. (2003)	2	Angled blade plates after valgus osteotomy	4.5 years	1/2	One failed due to cutting out of the plate. The other ABP had a good outcome.
	Leet et al. (2016)	2	Angled Blade Plates	Unknown	Unknown	Outcome of ABP not described
	Ippolito et al. (2015)	8	Angled Blade Plates	Unknown	1/8	One patient had screw loosening with lateralization of the plate
	Present study	28	Angled Blade Plates, 8 of which were customized	4.1 years	2/28	Two failures, in 7 patients ABP removed due to complaints of the iliotibial tract
Dynamic/ Compression Hip Screw	Li et al. (2012)	21	Valgus osteotomy with DHS fixation	19–128 months	2/21	One patient revision surgery with an intramedullary nail after a fracture and one had a loose lag screw
	Tong et al. (2013)	2	Valgus osteotomy with DHS fixation	12–32 months	0/2	No patient needed revision surgery
	Nishida et al. (2015)	8	Cortical Autograft with compression hip screw	75 months	0/8	No patient needed revision surgery

thus been shown to have a good prognosis with allogeneic strut grafts, providing that there is sufficient healthy bone proximally in the femoral neck for the strut graft to be anchored and grown into.[17] Putting these findings together, it may be concluded that there is a place for allogeneic strut grafts in the management of impending fractures and of pain due to fibrous dysplasia of the proximal femur in selected cases in which there is no history of a pathological fracture of the proximal femur, there is enough bone stock proximal in the femoral neck to anchor the strut graft, there is no indication for a valgus osteotomy and the fibrous dysplasia lesion does not extend to the femoral shaft. Based on experience in the LUMC (unpublished data), revision surgery with a second allogeneic strut graft in a previously treated femur should not be recommended as prone to fail (Supplemental File). A number of studies have reported the use of different types of bone grafts combined with internal fixation.[11,25,28,29] To our knowledge, the advantage of additional bone grafting has never been analyzed in detail, and it is difficult to interpret whether the good outcomes in some of these studies were due to the additional bone grafting or were solely due to the beneficial stabilizing effect of the mechanical implant.

Intramedullary nail

Over the past decade there has been a preference for using intramedullary nails in the management of fibrous dysplasia of the proximal femur.[10,11,12,14-16,20,24,30-33-34] Despite apparent consensus in the literature about this surgical modality, there is still much debate on the type of intramedullary nail that should be used. Solitary rods, lacking proximal and distal locking and therefore failing to offer sufficient support, frequently lead to persistent coxa vara deformity and poor functional outcome, suggesting they should not be used in fibrous dysplasia of the proximal femur (Table 8.3). However, cephalomedullary nails with bipolar fixation of both the proximal and distal end of the implant have demonstrated good outcomes in terms of low failure rates and good function in patients with severe forms of fibrous dysplasia, as they provide sufficient support to the proximal femur.[11,13,14,16,31,33] Compared to angled blade plates, intramedullary nails offer the advantage of being minimally invasive and being more frequently used in general trauma units, which generates more experience with their use, providing an osteotomy is not required. Although fractures have also been reported after treatment with intramedullary nails, they are generally believed to associated with a lower risk of developing fractures compared to angled blade plates.[16,24] In the current study, we also demonstrate a good functional outcome in 5 patients who were treated with an intramedullary nail, with no revision surgery required, good walking ability and complete relief of pain after up to 16 years of

follow-up (Fig. 8.2). Based on these findings, intramedullary nails appear to be a sound treatment option for fibrous dysplasia of the proximal femur, providing that a bipolar proximal and distal fixation of the nail can be performed and that the femoral neck screw does bridge the lesion in the metaphysis.

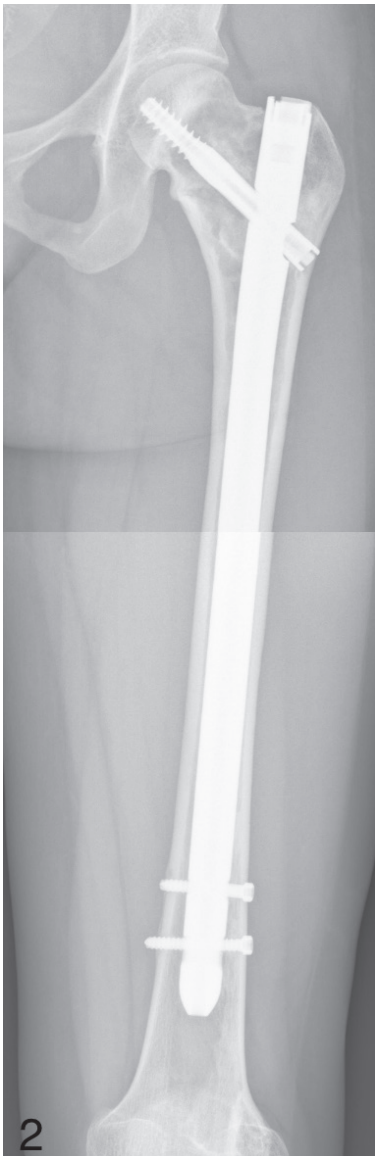

Fig. 8.2 Customized intramedullary nail. A customized intramedullary nail with a HA-coated proximal screw was used in one patient (ID 18), in order to ensure ingrowth in the femoral neck. The nail had an enlarged diameter because this particular patient had severe cortical thinning throughout the length of the femur, providing insufficient structural support for a standard sized intramedullary nail intramedullary.

Angled blade plates

The use of angled blade plates in the management of fibrous dysplasia of the proximal femur has been reported in a number of studies, all conducted in small numbers of patients, almost always using different types of implants and lacking reporting on functional outcomes.[11,16,25] This scarcity of reported data with the use of this implant modality precludes the drawing of any firm conclusion on the use of the angled blade plates in fibrous dysplasia of the proximal femur. In the present study we demonstrate that angled blade plates have a good outcome in the majority of cases of fibrous dysplasia of the proximal femur with a low postoperative fracture rate and arrest of progressive varization of the femur. In our series only two out of the 27 cases (7%) treated with an angled blade plate developed a fracture. In both cases the fracture occurred distal to the angled blade plate, probably because of failure of the angled blade plate to completely cover the fibrous dysplasia lesion. Because the distal part of the plate may function as a stress riser, which may in itself increase fracture risk in the presence of a fibrous dysplasia lesion, we do recommend that to avoid this complication, the angled blade plate is positioned to bridge the entire fibrous dysplasia lesion. The implant positioning should also ensure that both proximal and distal ends are anchored into healthy bone. To avoid these complications we have been recently using customized angled blade plates in the LUMC. These customized blade plates can be designed to cover the whole of the affected part of the femur and thus more efficiently prevent fractures. Based on published literature and on our two centers' experience, it is our opinion that angled blades plates hold an advantage over intramedullary nails in patients with severe deformities of the femur shaft and thus of the intramedullary canal. Severe deformity often necessitates performing multiple difficult osteotomies, which precludes the introduction of an intramedullary nail, while an angled blade plate can still be easily positioned to ensure stability of the fibrous dysplasia lesion as customized angled blade plates in these cases accurately follow the curves of the deformed femur and this provides adequate fitting and stability to the femur. Angled blade plates do also hold an advantage over intramedullary nails in patients with previous metaphysical cortical grafts, as the partially resorbed cortical bone often does not allow placement of the proximal screws of an intramedullary nail while the angled blade plate can still be implanted with relative ease thus providing adequate mechanical support. A possible downside of the angled blade plate that has come to light in our study is the possibility of developing complaints of the iliotibial tract such as pain and associated difficulty in walking. Because the 7 angled blade plate recipients who developed these complaints in our study originated from the same center, the question arises whether the surgical technique used differed between our

two centers. A closer look revealed that in the LUMC, where none of these patients developed complaints of the iliotibial tract, an additional step in the procedure was for the 95-degree angle in the cortex to be milled out to ensure submerging of the plate into the bone. In the MUG, removal of the hardware in patients with complaints of the iliotibial tract resulted in good functional outcome in all with no reported (new) pathological fractures. Notwithstanding these outcomes may have also be due to the fact that these cases had mild fibrous dysplasia and it is likely that the femur in more severe types of fibrous dysplasia will not be so forgiving after removal of any form of supporting hardware. Based on published literature and data from our combined cohort we can conclude that angled blade plates can be effectively and safely used in fibrous dysplasia of the proximal femur, providing that the lesion can be adequately bridged by the implant with proximal and distal locking of the angled blade plate into healthy bone. Based on the LUMC experience, we also recommend that the surgeon should ensure submerging of the plate into the bone, as this appears to prevent complaints of the iliotibial tract.

Dynamic/Compression Hip Screw

A number of studies have reported the use of dynamic hip screws (DHS), either after a valgus osteotomy or for stabilization of a pathological fracture of the proximal femur.[29,35] Nishida et al. used a compression hip screw (CHS) in combination with an allogeneic strut graft in 8 patients, which led to similar results after a mean follow-up of 75 months.[28] However, studies addressing the use of these devices in the treatment of pathological fractures show that they have a high failure rate compared to angled blade plates and intramedullary nails.[36,37] Additionally, the short stem of the DHS and of the CHS does not seem to be able to protect the distal part of the femur, which is often affected in fibrous dysplasia, from fracturing. We would therefore not advocate the use of the DHS or CHS in fibrous dysplasia of the proximal femur.

Pediatric patients

Treatment of pediatric patients with fibrous dysplasia of the proximal femur calls for a different surgical approach to that of adults with this disease localization, as the growth of the femur has to be accounted for in the placement of internal fixation to avoid to the growth plate or to the pediatric vascular circulation of the proximal femur.[9,11,38] Moreover, standard intramedullary devices used in adults will not generally fit into the small femoral shaft of children, ruling out their use in most young children, especially in growing patients with an open physis.[15] Titanium elastic nails (TEN) have frequently

been used to address fractures, and although most fractures show good healing, the TENs will not prevent any subsequent fracture or the progression of deformities and should therefore not be used in the proximal femur of young patients with fibrous dysplasia.[11,15] Different intramedullary devices have been proposed, among which humeral nails and a new small diameter pediatric interlocking intramedullary device.[15,25] However, there are to date scarce data on the use of these devices and it has been associated with a number of drawbacks such as continuous deformation of the femur and introduction of the nails into the apophysis of the greater trochanter in growing children. To address the problem of the small femoral shaft in children it has been suggested to use an angled blade plate (Table 8.3). This is supported by our findings of a good outcome of this procedure in the 3 patients who were treated with angled blade plates before the age of 12 in the current study. An allogeneic allograft may also be considered in pediatric patients with lesions of the femoral neck and no other risk factors. Regardless of the choice of treatment, it is important to realize that the risk of failure or recurrence and the need for revision surgery is high in young and growing patients and that in pediatric patients there is a clearly unmet need for a tailored device providing stability and preventing further deformation of the femur.

Proposed surgical treatment algorithm for the management of fibrous dysplasia of the proximal femur

Based on published literature, our decades of experience in the LUMC and MUG centers and data from studying our combined cohort, we propose the following algorithm for the surgical management of fibrous dysplasia of the proximal femur (Fig. 8.3). In this proposed treatment algorithm there is a place for allogeneic strut grafting, albeit limited to cases without a previous fracture, without a fibrous dysplasia lesion extending to the femoral shaft, without a deformity of the femur requiring a valgus osteotomy and with adequate bone-stock proximally in the femoral neck.[17] In case of failure of the allogeneic strut graft, revision surgery with an angled blade plate is preferred over the placement of an intramedullary nail, as the introduction of a blade is easier to perform in a femoral neck with remnants of strut grafts. Internal fixation with either an intramedullary nail or an angled blade plate is preferred in patients with risk factors associated with the placing of an allogeneic strut graft. Using either of these devices, it is imperative that the fibrous dysplasia lesion is completely bridged especially in the femoral head, with adequate, bipolar fixation of the implant ends in healthy bone with either the blade of the angled blade plate or the screw of the intramedullary nail. Angled blade plates should also be adequately submerged into the cortex to prevent the development of complaints of the iliotibial tract. In case

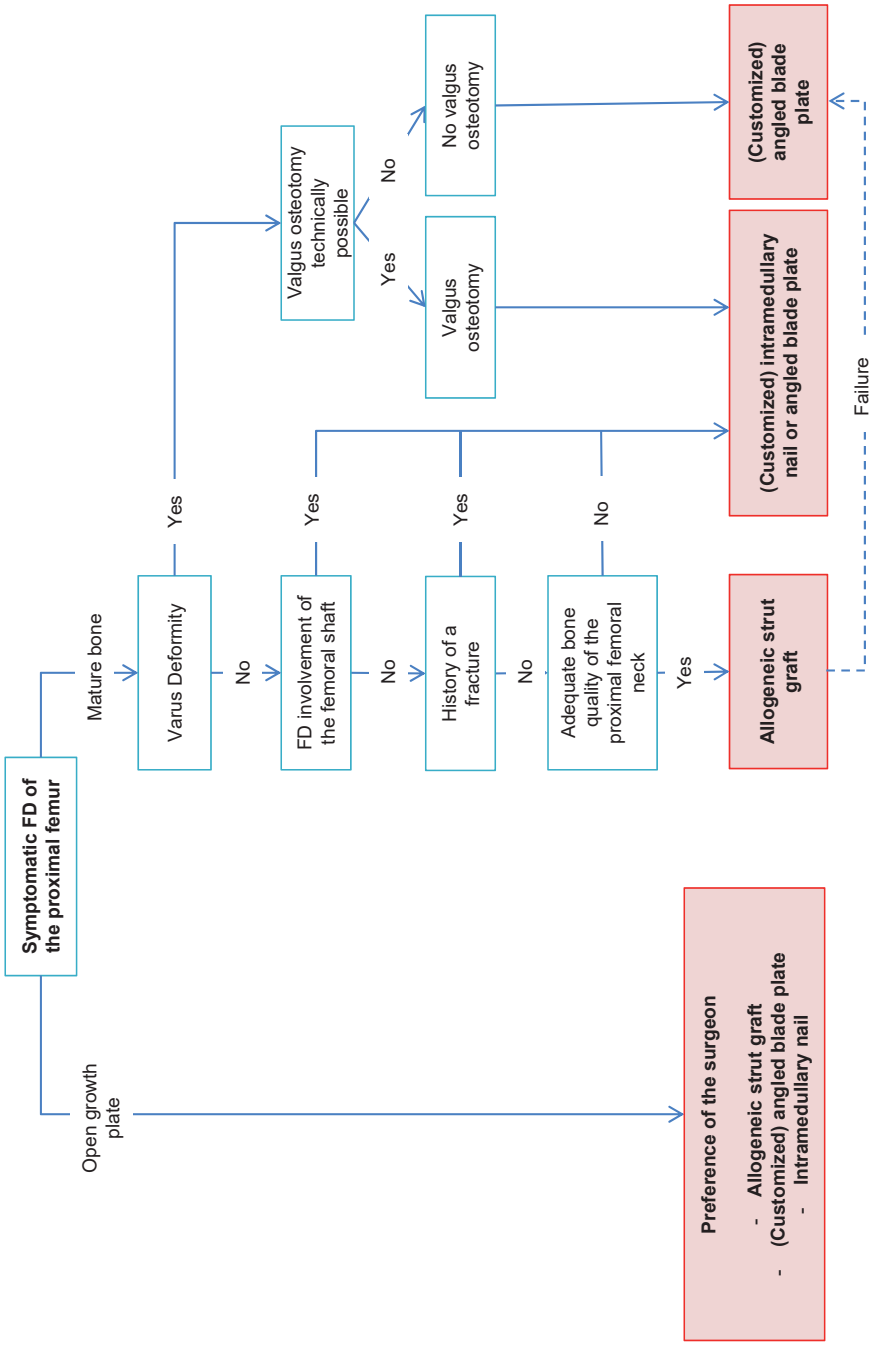

Fig. 8.3 Proposed individualized, patient-tailored algorithm for the surgical management of fibrous dysplasia of the proximal femur.

of severe deformity of the femur without the possibility of a valgus osteotomy, a customized blade plate is the implant of choice. The use of dynamic or compression hip screws and TENs is not recommended in fibrous dysplasia of the proximal femur.

CONCLUSION

Fibrous dysplasia of the proximal femur can be adequately and safely treated with angled blade plates, intramedullary nails or allogeneic strut grafts, provided that these are used according to the specific characteristics of the individual patient. Fibrous dysplasia of the proximal femur remains a challenging entity, but continuous improvements in a variety of treatment options have paved the way towards a more favorable clinical outcome. Based on published literature, decades of experience from 2 expert centers in Austria and the Netherlands and data from a combined cohort in this study we propose an individualized, patient-tailored algorithm for the surgical management of fibrous dysplasia of the proximal femur, taking into account different treatment modalities and associated factors that play a role in the outcome of the different implants. Future research should focus on the development of implants that meet the specific needs of the challenging pediatric and adult patients with fibrous dysplasia of the proximal femur.

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SUPPLEMENTAL FILE

Allogeneic cortical strut grafts represent an attractive option for the treatment of fibrous dysplasia lesions of the proximal femur, provided that patients dot not have any of the previously described risk factors for failure of the procedure.[17] There are scarce data on possible treatment options after failure of allogeneic strut grafts in fibrous dysplasia of the proximal femur. We evaluated our cohort of 29 patients who were treated with these types of grafts for failure rates after consecutive different surgical interventions.

Patients and methods

In a retrospective study design, we included 29 patients (15 male) with allogeneic strut grafts without osteotomy and/or osteosynthesis between 1980–2013 and with a minimal follow-up of two years after surgery. Mean age a time of surgery was 22.9 years (5–50 years) and the primary outcome of this study was failure, measured as revision surgery for fracture, progressive deformity or progressive resorption of the graft.

Results

After a median follow up after surgery of 9 years (2–37 years) 14 patients (48%) needed a reoperation after the first ACGS. Patients presenting with a pathological fracture before index ACGS had an increased risk for failure ($p < 0.05$). Mean age at time of failure was 27 years (14–42), median time to failure was 4.5 years (0–20 years) and gender was evenly distributed. Failure mechanisms were resorption (50%), fracture (43%) and one patient needed a reoperation as a result of progressive deformity of the proximal femur. On average patients with a reoperation had 1.9 reoperations (± 1.4 SD) compared to 0.9 (± 1.4 SD) reoperations in the whole group of FD patients. Seven patients were treated again with allogeneic strut grafts, two with intramedullary nails, four had severe bowing of the femur and received a blade plate (3 custom made) and one patient was treated with prevot pins. Four out of seven patients with consecutive allogeneic strut grafts and the patient with prevot pins needed at least one more revision surgery as a result of consecutive failure. All patients who received a blade plate (4) or intramedullary nail (3) had improvement of pain and mobility and did not need another reoperation.

Conclusion

These data show that failure after allogeneic strut grafts in general occurs in the first three years after surgery. Failure of allogeneic strut grafts in fibrous dysplasia of the proximal femur appears to be a risk factor for failure of a consecutive intervention with the use of these grafts. We therefore recommend treating patients with primary failure of allogeneic strut grafts with an additional osteosynthesis of the proximal femur.

Chapter 9

Clinical course and management of fibrous dysplasia of the humerus

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Submitted

ABSTRACT

Background: Fibrous dysplasia (FD) is a rare bone disorder that can cause pain, deformity and fractures at the site of lesions. Although the humerus is often affected, evidence on the clinical course and treatment of FD lesions located at the humerus is scarce.

Purposes: In this retrospective study we evaluated (1) the clinical characteristics of FD of the humerus; (2) risk factors for pathological fractures; and (3) outcomes of conservative treatment, surgery and sclerosing injections of cystic lesions at this site, with a good outcome being defined as revision-free follow-up with no recurrent fracture, delayed union or complications.

Methods: Out of the 255-strong cohort of patients with FD, treated at the Leiden University Medical Center between 1990–2015, 50 had FD of the humerus (57 humeri) and were included in the study. Data were collected from medical records on age at diagnosis, sex, type of FD, clinical features including pain and fractures, endocrinopathies, and history of surgical interventions. Potential risk factors for a fracture were analysed on conventional radiographs and MR-imaging of FD lesions and included anatomical localization of the lesions, involvement of the cortex and the presence of cysts. Primary outcomes of surgery and of injections of the cysts with sclerosing agents were the absence of newly sustained fractures and/or need for revision surgery.

Results: Thirty-one of the 50 patients (62%) had monostotic FD, 11 (22%) had polyostotic FD and 8 (16%) had McCune-Albright syndrome. Mean follow-up after diagnosis was 9.4 years (± 12.5 SD) and 27 patients (54%) had sustained at least one pathological fracture at a mean age of 19.1 years (± 15 years SD). A fracture was the presenting symptom in 22 patients (44%). The presence of cystic degeneration in an FD lesion was identified as a risk factor for fracture in logistic regression analysis (OR 4.1, p = 0.033, 95% CI 1.1–14.9). Conservative treatment of fractures resulted in a good outcome in 70% of patients. Three of five patients who were treated with cancellous allogeneic bone grafting had a good outcome, with the other two needing revision surgery. Two of three patients who had cortical bone grafting had a good outcome and one sustained a fracture, which successfully healed on conservative treatment. Three of five patients who received sclerosing injections of cystic lesions had good outcomes, one sustained a subsequent fracture and one required additional surgery.

Conclusion: FD of the humerus is associated with a relatively mild course. Although pathological fractures occur in half of patients, two third of these heal successfully on conservative treatment. Cystic degeneration of an FD lesion represents a risk factor for fractures. Surgical treatment with a view to decrease pain or stabilize impending fractures appears to be more beneficial with the use of cortical rather than cancellous bone grafting, although definite recommendations on this type of treatment should await results of studies performed in larger cohorts.

INTRODUCTION

Fibrous dysplasia (FD) is a rare bone disorder in which healthy bone is locally replaced by fibrous tissue of poor quality. The lesions can be present in a single bone (monostotic FD) or several bones (polyostotic FD), and in combination with a number of endocrinopathies in the context of the McCune-Albright Syndrome (MAS), which include precocious puberty, growth-hormone and prolactin excess and hyperthyroidism and with café-au-lait skin lesions. FD is caused by a missense mutation of the GNAS-gene that occurs post-zygotically and results in a net increase of intracellular cAMP in affected cells.[1] The mosaic distribution of the mutation causes a wide variation in clinical expression of FD, varying from completely asymptomatic patients, to patients with severe pain, deformities, and fractures. Although FD is predominantly localized in the proximal femur and craniofacial bones, the bones of the upper extremity, especially the humerus, may also be affected.[2] Literature on the natural history and treatment of FD of the humerus is scarce, with reports on the management of FD generally focusing on the lower extremities, which are more prone to complications because of their weight-bearing properties.[3,4] In our experience, FD lesions of the humerus may also be symptomatic, although behaving differently from FD lesions of the lower extremities. This led us to retrospectively evaluate (1) the clinical characteristics of FD of the humerus; (2) risk factors for pathological fractures; and (3) the surgical and non-surgical treatment of FD lesions at this site.

PATIENTS AND METHODS

Study design

Our FD database consists of 255 patients with different types of FD, evaluated and followed-up at our tertiary referral centre for rare bone diseases between 1990–2015. From this cohort, we identified from medical records 50 patients (male/female ratio 25:25) with an FD lesion at 57 humeral sites. The diagnosis of FD was established on the basis of clinical and radiological features, with conventional radiographs being available in all patients, and MR imaging performed as required. In case of doubt about the diagnosis, this was confirmed on the basis of histological evaluation of a biopsy of the lesion and/or the case was referred for evaluation to the National Netherlands Committee for Bone Tumours. All patients had to have a minimum follow-up of 1 year to be included in the study. The study was approved by the Medical Ethical Committee of the Leiden University Medical Center.

Data collection

Data retrieved from patients' medical records included age at diagnosis, sex, type of FD (e.g., monostotic, polyostotic or McCune-Albright syndrome), clinical features including pain, endocrinopathies in the context of MAS such as precocious puberty, GH-excess, presence of café-au-lait patches, prevalence of pathological fractures of the affected humerus, and history of surgical interventions. The radiological studies were evaluated by an experienced skeletal radiologist (HMK).

Potential risk factors for pathological fractures (Fig. 9.1) were assessed according to the findings of a previous study on the risk of pathological fractures in patients with femoral metastasis and included: 1) Localization of the lesions (metaphysis, epiphysis, diaphysis or a combination); 2) Cystic degeneration of the FD lesions on MR imaging (yes/no); 3) Maximal length of the (biggest) lesion in mm. 4); Circumferential cortical involvement (> 50%); 5) Transverse cortical involvement (> 50%); 6) Axial cortical involvement (> 30 mm).[5] Evaluation of the presence of cystic components in a

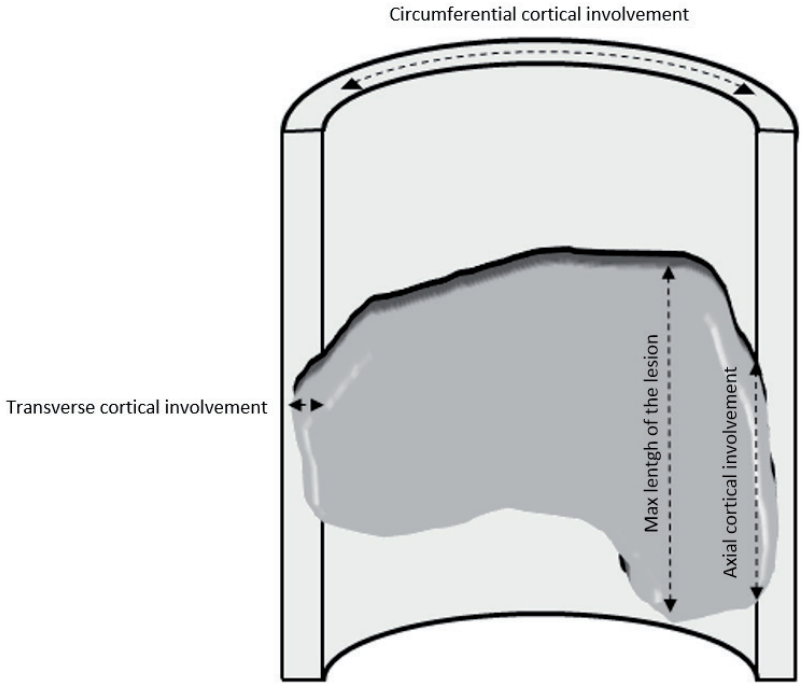


Fig. 9.1 Potential risk factors for fractures in fibrous dysplasia of the humerus. Schematic drawing of potential risk factors for fractures in fibrous dysplasia of the humerus, including maximal length of the lesion, circumferential extent of cortical involvement (> 50%), transverse cortical involvement (> 50%), axial cortical involvement (> 30 mm), anatomical localization of the lesion (metaphysis, epiphysis, diaphysis) and presence of cystic degeneration.

fibrous dysplasia lesion could only be reliably performed by MR imaging, including T2-weighted and T1-weighted post-contrast fat suppressed sequences, and was, therefore, solely conducted in patients with available MR scans (n = 19).

Different surgical and non-surgical interventions were evaluated and categorized as follows: 1) Fracture treatment; 2) Surgical treatment of FD of the humerus for various indications; 3) Minimally invasive injections of cystic FD lesions with sclerosing agents to prevent pathological fractures. A good outcome was defined as no need for reoperation, no (re)fracture and no delayed union or non-union. All interventions were further evaluated for complications.

Statistical analysis

Statistical analysis was performed using SPSS for Windows, version 23.0 (SPSS, Inc., Chicago, IL, USA). Unless stated otherwise, results are presented as mean ± SD, or as a percentage in case of categorical data. Clinical predictors for pathological fractures were assessed in a univariate logistic regression analysis and subsequently in a multivariate logistic regression analysis to correct for age and sex.

RESULTS

Patients characteristics (Table 9.1)

Out of the 255 patients from our FD cohort, 50 (19.6%) patients (25 male and 25 female) had FD lesions of the humerus, with 7 having bilateral lesions, totalling 57 humeral lesions for study. Thirty-one patients (62%) had monostotic FD, 11 (22%) had polyostotic FD and 8 (16%) had MAS. Mean age was 35.7 ± 18.8 years, and mean age at diagnosis was 22.7 ± 16.7 years in MFD patients, 26.4 ± 16.6 years in PFD patients and was significantly lower in MAS patients at 4.1 ± 4.6 years (p = 0.002). Mean follow-up after diagnosis was 9.4 years (± 12.5 SD).

Humeral fibrous dysplasia lesions

Humeral FD lesions were generally large with a mean length of 143 mm (± 82.5 SD) and the cortex was often involved (95%). In 37% of lesions, only the diaphysis was affected, in 20% the diaphysis and metaphysis, in 11% only the metaphysis and the whole of the humerus was affected in 33% of humeral lesions. Over half of the cortical circumference of bone was affected in 87% of cases, and more than half of the transverse width of the cortex was affected in 84%. Mean axial cortical involvement was 99.1 mm (± 60.0

Table 9.1 Patient characteristics

Patient ID	Gender	Side	Age at diagnosis (years)	Type of fibrous dysplasia*	Fracture of the humerus	Age at time of first fracture (years)	Cystic deformation**	Follow-up in years
1	Female	Left	13	MFD	Yes	13	Yes	4
2	Male	Right	9	PFD	No	-	NA	26
3	Female	Left	8	MFD	Yes	8	NA	1
4	Female	Both	3	MAS	No	-	NA	19
5	Female	Left	4	MAS	No	-	NA	39
6	Male	Right	13	MFD	Yes	10	NA	3
7	Female	Right	24	MFD	Yes	24	Yes	1
8	Female	Right	31	MFD	Yes	31	Yes	4
9	Male	Left	16	MFD	Yes	13	NA	11
10	Male	Right	7	MFD	Yes	8	NA	36
11	Female	Left	29	MFD	Yes	29	NA	7
12	Male	Left	29	MFD	No	-	NA	15
13	Female	Left	19	PFD	No	-	No	3
14	Female	Left	38	MFD	No	-	No	1
15	Female	Both	0	MAS	Yes	28	NA	50
16	Male	Right	9	MFD	Yes	10	No	3
17	Male	Left	59	MFD	No	-	NA	1
18	Female	Left	10	MFD	Yes	11	NA	2
19	Female	Both	0	MAS	No	-	NA	41
20	Male	Right	11	MFD	Yes	11	No	8
21	Female	Left	5	MFD	Yes	5	NA	8
22	Male	Right	31	PFD	Yes	27	NA	18
23	Male	Left	7	MFD	Yes	7	NA	7
24	Male	Right	14	MFD	Yes	15	Yes	1
25	Female	Left	30	MFD	Yes	31	Yes	1
26	Female	Right	57	MFD	Yes	57	Yes	2
27	Male	Left	10	MFD	Yes	10	Yes	5
28	Female	Right	4	PFD	No	-	NA	32
29	Female	Left	5	PFD	No	-	No	13
30	Female	Right	21	PFD	No	-	NA	32
31	Female	Both	6	MAS	No	-	NA	2
32	Female	Both	1	MAS	Yes	62	NA	61
33	Male	Left	12	MFD	Yes	13	NA	13
34	Male	Left	11	PFD	No	-	NA	1
35	Male	Left	10	MFD	Yes	11	Yes	1
36	Female	Left	49	PFD	No	-	NA	1
37	Male	Left	60	MFD	No	-	NA	1
38	Male	Right	12	MFD	Yes	12	NA	10
39	Male	Right	20	MFD	No	-	Yes	1
40	Male	Left	10	MFD	Yes	11	Yes	2

Table 9.1 continues on next page

Table 9.1 *Continued*

Patient ID	Gender	Side	Age at diagnosis (years)	Type of fibrous dysplasia*	Fracture of the humerus	Age at time of first fracture (years)	Cystic deformation**	Follow-up in years
41	Male	Right	50	PFD	No	-	NA	3
42	Female	Right	63	MFD	No	-	No	1
43	Male	Right	16	MFD	Yes	16	NA	6
44	Female	Right	29	MFD	Yes	29	Yes	1
45	Female	Left	35	PFD	No	-	No	5
46	Female	Left	32	MFD	No	-	NA	11
47	Male	Right	24	PFD	No	-	NA	5
48	Male	Right	32	MFD	No	-	Yes	11
49	Male	Both	5	MAS	Yes	16	NA	12
50	Male	Both	14	MAS	No	-	NA	11

* MFD = monostotic fibrous dysplasia; PFD = polyostotic fibrous dysplasia; MAS = McCune-Albright syndrome.
** NA = Not analysed (no MRI).

SD) and in 81% axial cortical length was over 30 mm. Cystic degeneration of humeral FD lesions was observed in 74% of cases in which an MRI had been performed and the cystic component comprised more than half of the lesion in 64% of these. In 77% of patients with cystic degeneration of the FD lesion and a fracture, this ran through the cystic part of the lesion (Fig. 9.2).

Clinical predictors for pathological fractures

Twenty-seven patients (54%) had sustained at least one pathological fracture at a mean age of 19.1 years (± 15 years SD) and a fracture was the presenting symptom in 22 patients (44%). None of these patients were using crutches at the time of the fracture. In univariate logistic regression analysis (Table 9.2) only the presence of cysts was predictive for a pathologic fracture (OR 3.5, p = 0.027, 95% CI = 1.6–10.8). This was still significant after correction for age and sex (OR 4.1, p = 0.033, 95% CI 1.1–14.9). No other factors were found to be significantly associated with a fracture at the site of a humeral FD lesion, although there was a trend for circumferential cortical involvement to do so (OR 8.3, p = 0.064, 95% CI 0.9–78.3).

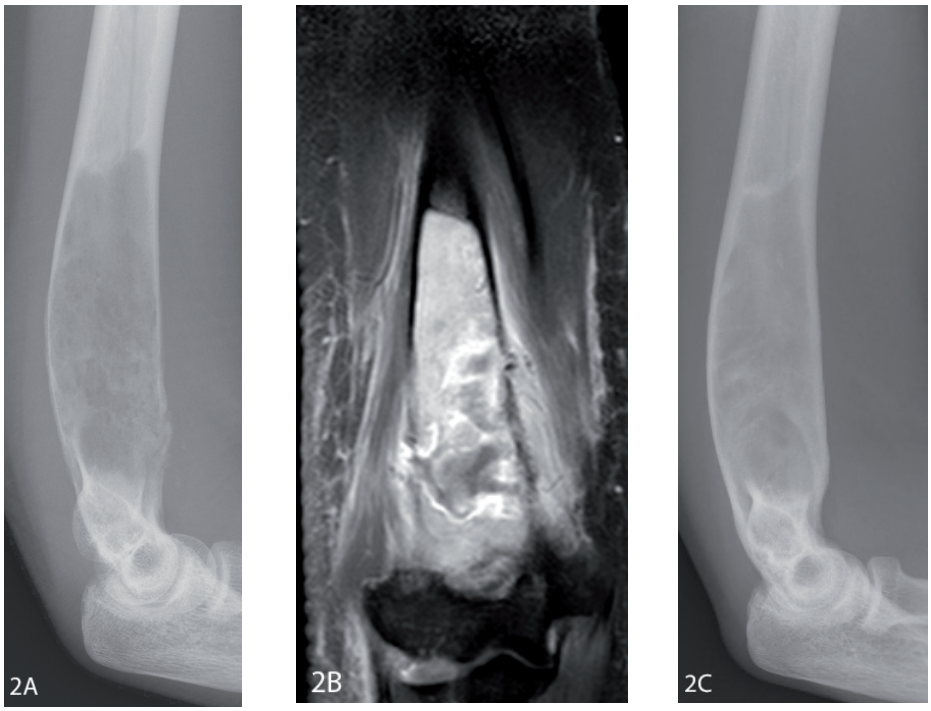


Fig. 9.2 Cystic degeneration of a fibrous dysplasia lesion of the humerus. Patient nr. 8 with an osteolytic lesion in the distal part of the humerus with evident cortical thinning and a fracture on the anterior side of the humerus (2A). Formation of cysts visible in the fracture area on T1-weighted fat supressed post-contrast MR-images, (2B). The fracture was treated with a cast resulting in good healing and no recurrent fractures. Conventional radiographs 6 years after the fracture showing increased cortical thickening and slightly increased sclerosis of the lesion compared to radiographs at diagnosis (2C).

Table 9.2 Logistic regression

	Factor	Odds ratio	Sig.	95% CI
Univariate	Age	1.03	0.100	0.99–1.07
	Gender	2.47	0.189	0.77–7.92
	Length of the lesion (mm)	1.00	0.764	0.99–1.01
	Transverse cortical involvement (> 50%)	2.10	0.377	0.41–10.80
	Circumferential cortical involvement (> 50%)	8.33	0.064	0.89–78.31
	Axial cortical involvement (> 30 mm)	3.43	0.116	0.74–15.91
	Cyst in the lesion	*3.54*	*0.027*	*1.16–10.81*
After correction for age and gender	Length of the lesion (mm)	1.00	0.731	0.99–1.01
	Transverse cortical involvement (> 50%)	2.56	0.292	0.45–14.66
	Circumferential cortical involvement (> 50%)	7.28	0.089	0.74–71.87
	Axial cortical involvement (> 30 mm)	2.84	0.195	0.59–13.81
	Cyst in the lesion	*4.08*	*0.033*	*1.12–14.89*

Conservative treatment

All 27 humeral fractures were primarily treated conservatively using a cast, a sling, or a brace, which resulted in a good outcome (no recurrent fracture, no non-union or delayed union and no indication for further surgery) in 16 patients (59%). Three patients sustained at least one recurrent fracture (two patients had 1 recurrent fracture and one patient had 2 recurrent fractures), prior to a good outcome using repetitive conservative treatment of the fracture. Eight patients eventually required at least one further intervention after a median of 13 months (range 1–100 months) following the primary fracture, including allogeneic graft surgery in 4 patients and sclerosing injections in cystic FD lesions of 5 patients.

Surgical treatment

Eight patients underwent 10 surgical interventions (Table 9.3). Primary indication for surgery was pain (n = 4), or an impending fracture after conservative treatment of an initial fracture (n = 4). Five patients were treated with allogeneic cancellous bone grafting (CBG). Three of these had a good outcome, but two patients required additional surgery due to continuous pain (n = 1) or continuous risk of an impending fracture (n = 1). The second intervention consisted of cryosurgery in the patient with persistent

Table 9.3 Surgical treatment

Patient ID	Gender/age at first surgery (years)	History of a fracture	Indication	Type of surgery**	Failure mechanism	Second intervention
9	M/17	Yes	Impending fracture*	CBG		
20	M/11	Yes	Impending fracture*	Cortical allograft	Fracture	Cast
22	M/35	Yes	Impending fracture*	Cortical allograft		
29	F/4	No	Pain	CBG	Pain	Cryosurgery
38	M/11	Yes	Impending fracture*	CBG	Impending fracture	Cortical autograft
45	F/37	No	Pain	Cortical allograft + nail		
46	M/32	No	Pain	CBG		
48	M/13	No	Pain	CBG		

* Impending fracture after a previous fracture with insufficient healing.
** CBG = cancellous bone grafting with allografts.

pain, which failed to decrease pain levels, and a cortical allograft in the patient with a continuous risk of a pathological fracture that resulted in a good outcome. Three patients were primarily treated with cortical allografts (Fig. 9.3), supplemented with a titanium nail in one patient. Two patients had good outcomes with no further complaints of pain and no need for additional surgery, and one patient sustained a fracture at the site of the reconstruction after a traumatic injury. The fracture was treated conservatively and showed good healing with no further intervention necessary.

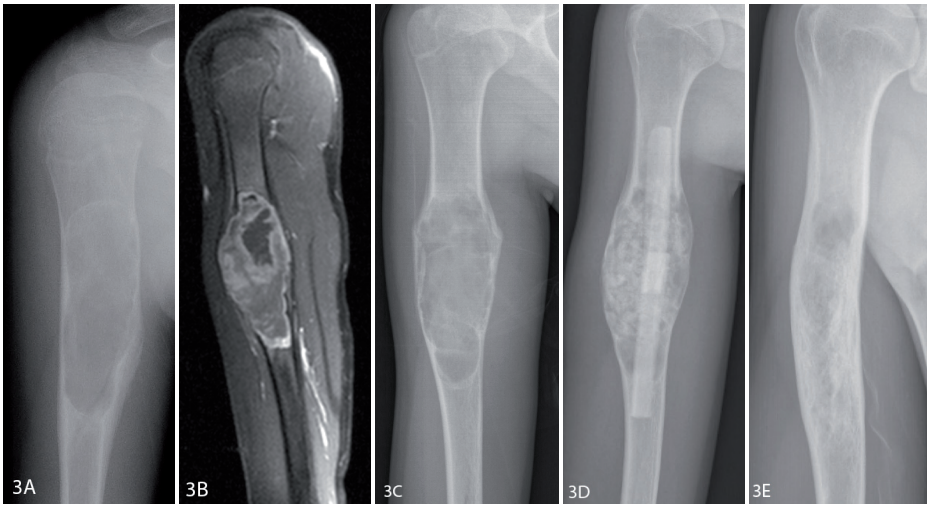
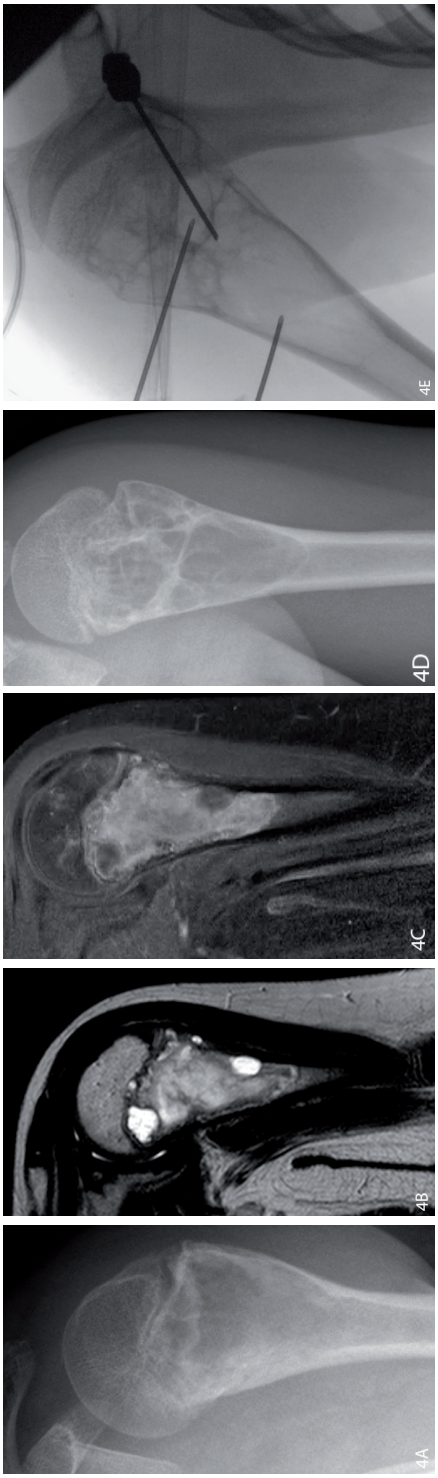


Fig. 9.3 Allogeneic strut grafting in fibrous dysplasia of the humerus. Patient nr. 20 presented with a fracture of the humerus. The fracture healed after conservative treatment with a cast (3A). Two years later, the patient sustained a recurrent fracture. After initial immobilization using a cast, he was treated with injection of a sclerosing agent. However, pain persisted and three years later a coronal T1-weighted fat suppressed post contrast MR images showed a fibrous dysplasia lesion with cystic degeneration (3B). Histologic evaluation confirmed the diagnosis. A repeat MRI scan performed a year after diagnosis showed increased cortical thinning (3C). Two cortical allografts were placed in the lesion, which was additionally filled with autogenous iliac crest bone (3D), which resulted in complete relief of his pain and full restoration of function of the right arm. Control radiographs 9 years later show largely resorbed strut grafts, but also evident cortical thickening, well-mineralized bone and no suggestion of an impending fracture (3E).

Injections

Five patients received injections in the cystic part of the FD lesion using different sclerosing agents, including aethoxysclerol 3% (8–15 ml), depomedrol (120 mg) or ethibloc (7.5 ml) to prevent impending fractures and decrease pain (Table 9.4). Four patients received multiple injections. Three patients had a good outcome, with disappearance of pain complaints, no fractures and progressive filling and cortical thickening of the lesion on conventional X-rays (Fig. 9.4). One patient sustained



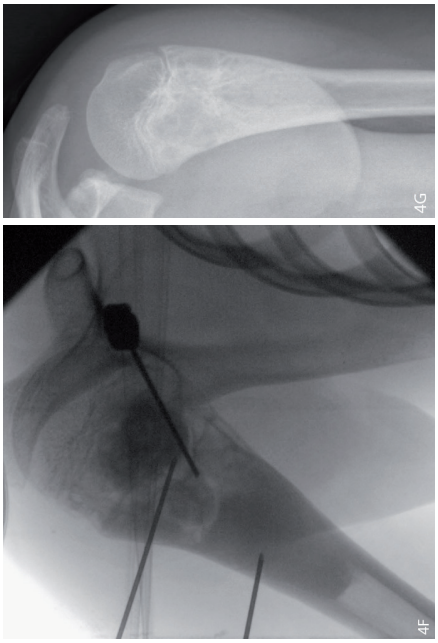


Fig. 9.4 Cystic embolization in fibrous dysplasia of the humerus. Patient nr. 40 presented with a pathologic fracture of the humerus after a minor trauma. Radiographs showed an osteolytic lesion of the diaphysis and metaphysis with cortical thinning (4A). Sagittal MR imaging showed a lesion with intermediate signal intensity on T1-weighted images (4B) in combination with focal islands with high intensity, a high signal on coronal T2-weighted images and inhomogeneous signalling after administration of contrast (4C). A diagnosis of fibrous dysplasia with cystic degeneration was made. Two years later further cortical thinning indicative of an impending fracture was seen on conventional radiographs, (4D). This was treated with an injection of aethoxysclerol in order to prevent recurrent fractures (4E and F) resulting in complete relief from pain, free range of motion of the upper arm and good mineralisation of bone on a control radiograph 1 year after treatment (4H).

Table 9.4 Embolic injection of the cysts

Patient ID	Gender/age at first injection (years)	Indication	Number of injections	Agent(s)	Failure
1	F/13	Impending fracture Growth plate at risk	2	Depomedrol	No
20	M/11	Impending fracture	3	Depomedrol (2) & Ethibloc (1)	Reoperation with cortical allograft due to an impending fracture
23	M/7	Impending fracture	2	Depomedrol	Fracture
33	M/14	Impending fracture	3	Depomedrol	No
40	M/12	Impending fracture	1	Polidocanol (3)	No

Five patients received injections in the cystic part of the FD lesion with different embolic agents, including depomedrol (120 mg), aethoxysclerol 3% (8–15 ml) or ethibloc (7.5 ml).

several fractures after treatment with sclerosing injections and one patient required additional surgery.

DISCUSSION

In this study we evaluated clinical features, management and prognosis of FD lesions of the humerus in a relatively large cohort of 50 patients with predominant monostotic FD. In our 255-strong FD cohort, the prevalence of FD of the humerus was 20%, and as previous reported, we also observed a higher prevalence of humeral lesions in polyostotic and MAS patients.[2,6] More than half of the patients with humeral FD (53%) developed a fracture at the affected humeral site, and the majority had a good outcome after initial conservative treatment (59%) or conservative treatment in recurrent fractures (n = 3, 11%). Surgical treatment failed in two out of five patients with allogeneic cancellous bone grafting and in one out of three patients with cortical bone grafting. Sclerosing injections of cysts adequately prevented pathological fractures in three out of five patients, which is an important finding as cysts were identified as risk factors for pathological fractures of the humerus.

Fibrous dysplasia is a heterogeneous disorder and its clinical course appears to be significantly different in lesions of the humerus compared to the more commonly situated lesions of the lower extremity, in which weight-bearing forces give cause

to a high incidence of deformities and fractures, often associated with pain and ultimately with more impaired Quality of Life (QoL).[2,3,7-9] Although FD of the humerus is believed to run a milder course than that of the lower limbs, our findings from this study suggest that the majority of the patients with humeral lesions had sustained at least one fracture at the site of the lesion. Importantly, none of these patients were using crutches at the time of their fracture, which is especially relevant in polyostotic patients with lesions of the lower extremity, as the use of crutches would put weight-bearing forces on the humerus. In a study on fractures in 35 patients with polyostotic FD, Leet et al. reported that fractures of the humerus accounted for 19% of a total of 172 fractures.[10] In our Leiden FD cohort, we observed that phosphaturia and a high skeletal burden score were associated with high fracture rates at a younger age. As all three of these factors are related to disease severity in FD, it is likely that patients with extensive disease are more prone to sustain pathologic fractures. Our current study is the first to address fracture risk in FD based on radiologic characteristics of the lesion. Our findings are in keeping with those of a study of fracture risk in femoral bone metastases, in which both axial cortical involvement > 30 mm and circumferential cortical involvement > 50% were identified as risk factors for pathological fractures.[5] Despite the common assumption that larger lesions are more prone to fractures, the length of a humeral FD lesion was not associated with an increased risk of developing a fracture. However, in contrast to the study on femoral metastases, in which circumferential cortical involvement of more than 50% was significantly associated with pathological fractures, in our study, we only found a non-significant trend for this ($p = 0.064$), possibly because of the relatively small number of patients studied. The only factor that was significantly associated with fractures in the current study was cystic degeneration of the FD lesions. The development of cysts in FD has been specifically reported in the humerus, although these cysts have never been associated with an increased risk of fractures.[6,11-13] It appears that the presence of cysts may further weaken bone and decrease its stability, thereby increasing the risk of fracture, whereas the size of a lesion or involvement of the cortex may not. These findings suggest that routine MRI should be advocated in FD of the humerus to assess the risk of developing a fracture, as cystic degeneration cannot be reliably evaluated on conventional plain radiographs. Our findings of promising outcomes of specifically targeting humeral cysts with injections of sclerosing agents suggest that this intervention may represent a minimally invasive method to reduce the risk of fractures in cystic FD lesions of the humerus.[14,15] However, it is of note that two of the five patients in our series who underwent sclerosing therapy of FD lesions still fractured their humerus or needed surgery after multiple injections with sclerosing agents.

Despite the relatively high fracture rate in the current study, patients with humeral FD are reported to have fewer deformities, less pain and better QoL compared to those with FD lesions of the lower extremities.[7,16,17] Due to the lack of weight-bearing forces acting on the humerus, conservative treatment of these fractures appears to be on the whole adequate in the majority of the patients. Our results are in keeping with those of a number of studies reporting good outcomes conservative treatment of pathological fractures of humeral FD lesions, with success rates of 93% and 94%.[10,18] No cases of delayed union or non-union were reported in any of the published studies, suggesting that bone healing is not impaired in FD of the humerus.

In FD there is a difference in outcome between cancellous and cortical allogeneic bone grafting, with the latter believed to being superior due to better mechanical loading and lower resorption rates.[4,19,20] In keeping with our results, Stephenson et al. reported failure of two out of four CBG procedures in FD of the humerus.[18] However, failure rates of this procedure in the lower extremity have been reported to be up to 100%, suggesting that outcomes of graft surgery are better in FD lesions of the humerus compared to those of the femur.[21] Although low numbers preclude any firm conclusions on this, cortical bone grafting does appear to be associated with a slightly better outcome, as four studies that reported on outcomes of this procedure in a total of 14 patients with humeral FD reported no reoperations, no graft resorption, and good functional outcomes.[22-25] In contrast to the case in femoral localisations, reconstruction with osteosynthesis is sporadically used in humeral FD, with additional benefit in specific cases with the use of devices such as Prevot pins.[26]

Our study has some limitations. Although we were able to study FD of the humerus in a relatively large cohort, we also appreciate the small number of patients included in the study, may have precluded the identification of factors other than cystic degeneration for increased fracture risk in this FD localization. A further limitation of our study may be the potential of a selection bias in our inclusion of symptomatic patients, whereas FD of the non-weight bearing bones is often asymptomatic, possibly explaining the relatively high fracture-rate observed in our study, with true fracture-rate being possibly lower. As the majority of patients included in the study presented with a fracture, there were no available MR images prior to the fracture. Hypothetically cystic degeneration might develop after a fracture, instead of being a risk factor for it. However, there are to our knowledge no data supporting this premise in FD lesions of the humerus. Lastly, due to the low number of interventions of different types performed over time, we were only able to use descriptive statistics in the evaluation of treatment of FD of the humerus.

In conclusion, FD of the humerus is associated with a relatively mild course despite the development of pathological fractures in 50% of patients, although two third of these can be successfully treated with conservative measures. Whereas the size of an FD lesion of the humerus does not appear to influence the risk of developing a fracture, we identified cystic degeneration within a humeral FD lesion as a significant risk factor for developing pathological fractures, suggesting that routine MR-scanning should be advocated in FD at this localization to allow the timely management of these lesions, which holds a generally good outcome. Surgical interventions aiming at decreasing pain or stabilizing impending fractures should include the use of cortical rather than cancellous bone grafts, although definite recommendations relating to the choice of surgical interventions should await results from larger studies.

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FIBREUZE DYSPLASIE
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PART IV

Medical treatment

Chapter 10

Outcome of long-term bisphosphonate therapy in McCune-Albright syndrome and polyostotic fibrous dysplasia

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ABSTRACT

Introduction: McCune-Albright syndrome (MAS) is a rare bone disorder characterized by fibrous dysplasia (FD), endocrinopathies, and café-au-lait patches. FD patients have been shown to respond favorably to treatment with bisphosphonates, but data are scarce in the more severe polyostotic form (PFD), including MAS, and factors determining treatment outcome are not known, particularly in the long-term.

Methods: We evaluated the biochemical (bone turnover markers [BTMs]) and clinical (pain reduction) outcome of bisphosphonate therapy in 11 patients with MAS and 30 patients with PFD: median duration of treatment 6 years (range, 2 to 25 years). Prognostic factors for treatment outcome were identified in both groups.

Results: Patients with MAS were younger at diagnosis ($p < 0.001$), all had precocious puberty, and four (36%) had additional growth hormone (GH) excess associated with severe craniofacial FD. Extent of skeletal disease was more severe in MAS compared to PFD. MAS patients had higher serum alkaline phosphatase (ALP) concentrations ($p = 0.005$), higher skeletal burden scores ($p < 0.001$), and more fractures ($p = 0.021$). MAS patients had also higher levels of FGF-23 ($p = 0.008$) and higher prevalence of hypophosphatemia ($p = 0.013$). Twenty-four of 30 PFD patients (80%) demonstrated a complete clinical and biochemical response within a year of starting treatment ($p = 0.015$), compared to only four of 11 MAS patients (36%). There were no nonresponders. In the whole group, FGF-23, total ALP, P1NP, and CTX positively correlated with skeletal burden scores (all $p < 0.001$), which was the only significant risk factor for an incomplete response to bisphosphonate therapy ($p < 0.01$).

Conclusion: Our data suggest a beneficial and safe outcome of long-term bisphosphonate therapy in the majority of patients with PFD, although response to therapy was limited by the higher skeletal disease burden in MAS patients. In the PFD/MAS population studied, the only identified prognostic factor that influenced the outcome of bisphosphonate therapy was a high skeletal burden score.

BACKGROUND

Fibrous dysplasia (FD) is a rare genetic, non-inheritable bone disorder in which a single bone (monostotic form [MFD]; 70% of patients) or several bones (polyostotic form [PFD]; 30% of patients) may be affected by replacement of normal bone by fibrous tissue of poor structure and quality.[1] In McCune-Albright Syndrome (MAS), PFD is associated with endocrinopathies, primarily precocious puberty, and with cutaneous café-au-lait patches.[2,3] The various forms of FD are caused by a missense mutation of the GNAS1-gene in chromosome 20q13, leading to activation of the stimulatory a-subunit of the G-protein Gs, resulting in the activation of cAMP in mutated cells.[4,5] The mutation occurs postzygotically, resulting in a somatic mosaic state, and thus in a wide spectrum of clinical expression of the disease.[4] Because of the highly variable number of FD lesions and therefore of disease severity, clinical manifestations range from the completely asymptomatic patient with an incidentally discovered radiological lesion, to the patient with extensive skeletal disease who is crippled by severe bone pain, deformities, and fractures. Diagnosis of MAS is primarily clinical and radiological, and although bone histology and genetic analysis do confirm the diagnosis, these are seldom required to establish it. Patients with PFD often display a less severe disease pattern than those with MAS, with less extensive skeletal disease and generally less marked increases in bone turnover. However, the natural history of the various forms of FD remains elusive, and prognostic factors for outcome of therapeutic interventions remain to be identified, particularly in the more severe forms of the disorder.[6]

Therapeutic options for FD have so far been mainly surgical, aiming at reducing fractures, stabilizing impending fractures, and correcting deformities. Medical options consist primarily of treatment with bisphosphonates. The rationale for using these antiresorptive agents in FD is based on the increased bone resorption observed in and around FD lesions.[7] A positive outcome of treatment with bisphosphonates in the form of reduction in bone pain and arrest of expansion of fibrous lesions, was first reported by Liens and colleagues in 1994.[8] A number of reports on the potential beneficial effect of bisphosphonates on bone pain in FD have been published since.[9-14] However, all these publications reported on results of open studies, and the only recently conducted randomized, double-blind, placebo-controlled study of oral alendronate administered in adults and children at doses of 10 to 40 mg daily in cycles of 6 months on/off for 2 years failed to demonstrate a beneficial effect of alendronate over placebo, although a reduction of the bone resorption marker urinary NTx and an increase in areal BMD was observed in the actively treated group.[9]

Several factors such as high skeletal burden, increased serum concentrations of FGF-23, and the presence of endocrinopathies, particularly growth hormone (GH) excess, have been shown to predict poor prognosis in FD patients.[15] However, there are no published data on the long-term outcome of treatment with bisphosphonates or on prognostic factors influencing treatment outcome, particularly in patients with PFD, with or without endocrinopathies in the context of MAS. We speculated that because of their high skeletal disease burden, presence of endocrinopathies, and the often documented FGF-23–induced renal phosphate wasting, MAS patients may respond less well to bisphosphonate therapy than patients with PFD without endocrinopathies.

PATIENTS AND METHODS

We searched our hospital records for all patients with PFD and MAS from our cohort of 255 patients with FD, who were evaluated and followed at our Outpatient Clinic between 1990 and 2014. The diagnosis of PFD was established on the basis of clinical and radiological features, with occasional histological and genetic confirmation where required. The extent of bone involvement was determined by imaging using 99mTechnetium skeletal scintigraphy, and skeletal burden scores (SBSs) were calculated as described by Collins and colleagues.[6] Scoring was undertaken by two independent observers (BCJM and NMA-D), and differences between scores were resolved by consensus.

The diagnosis of MAS was established on the basis of PFD associated with endocrinopathies in the form of precocious puberty, with occasional additional endocrinopathies such as growth hormone or prolactin excess or hyperthyroidism. The presence of cafe-au-lait patches was recorded, but not considered essential for the diagnosis of MAS. Sixty-two patients with PFD, 13 of whom had endocrinopathies in the context of MAS, were identified from hospital records (Fig. 10.1). Twenty patients with PFD and one with MAS were excluded from analysis, as they did not require treatment with bisphosphonates because of absence of pain symptoms and/or in the presence of normal bone turnover (n.18), refusal of therapy (n.1), long-term treatment with bisphosphonates for osteoporosis (n.1), and inclusion in the on-going Profidys Eurocores study (http://clinicaltrials.gov/show/NCT00445575;n.1). Compared to bisphosphonate-treated patients, the 21 untreated patients (13 male and 8 female; 20 PFD and 1 MAS) were older at the time of diagnosis with a mean age 48 years ± 19.5 SD compared to 18.6 ± 16 years in treated patients. Analysis of the long-term effect of bisphosphonate treatment was thus conducted in 11 patients with MAS and 30

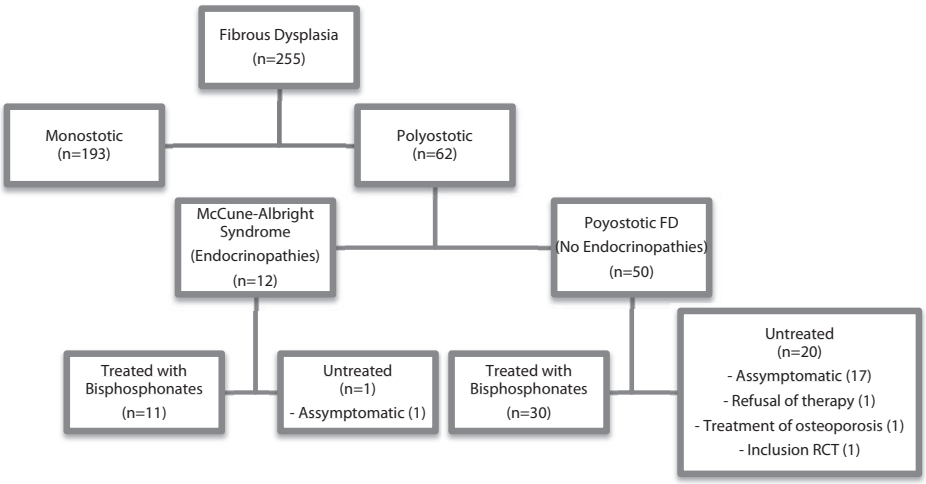

Fig. 10.1 Patient study flowchart.

patients with PFD without endocrinopathies. The study was approved by the Medical Ethical Committee of the Leiden University Medical Centre.

Data collection

Data of identified patients with PFD/MAS were retrieved from their hospital records about age, gender, and clinical and laboratory features in all patients studied. Data had been collected during outpatient visits at baseline (after an overnight fast) and at each subsequent outpatient visit at 3-month to 6-month intervals after start of treatment with bisphosphonates. These included data on pain (using verbal assessment that consisted of the same questions at each visit: Did the patient have pain or not? Was it mild, moderate, or severe? Was it better, worse, or unchanged since the previous visit?), presence of deformities, fractures, cafe-au-lait-patches, a history of precocious puberty, and confirmed additional endocrinopathies including GH excess, prolactin excess, hyperthyroidism, and FGF-23–induced renal phosphate wasting. Data were also retrieved about other laboratory parameters, including serum concentrations of creatinine, calcium, phosphate, albumin, 25-OH vitamin-D (RIA Incstar; DiaSorin, Stillwater, MN, USA), and intact PTH. Data on serum total alkaline phosphatase (ALP) (colorimetric method on the Roche Modular P800 analyzer; Roche Diagnostics, Almere, The Netherlands) were available in all patients. From 2006 onward, data on procollagen 1 aminoterminal propeptide (P1NP) and beta crosslaps (CTX) were also available as measured using an electrochemiluminescent immunoassay with a Modular Analytics

E-170 system (Roche Diagnostics, Almere, The Netherlands), but by then, treatment with bisphosphonates had been initiated in a number of patients so that baseline values before start of treatment were not available in all patients. The C-terminal FGF-23 (Immutopics, San Clemente, CA, USA) was randomly collected during medical care, off phosphate supplementation in ethylenediamine-tetraacetic acid (EDTA) plasma, and measured after short storage at –20°C prior to analysis using the BioTek ELx50 Washer (BioTek, Bad Friedrichshall, Germany).[16] All analyses were performed according to the manufacturer's protocol. Renal phosphate wasting was defined by the presence of two documented consecutive measurements of serum phosphate below the lower limit of normal (0.90 mmol/L) combined with a low tubular reabsorption of phosphate (TRP) (< 80%) as determined by the fractional TRP as measured by serum and urine concentrations of phosphate and creatinine in samples obtained after an overnight fast.[17] Data from the endocrinologic screening were collected in all MAS patients, including GH, IGF-1, prolactin, thyroid-stimulating hormone (TSH), and cortisol, with all blood samples collected after an overnight fast. Values for bone turnover markers (BTMs) and GH and IGF-1 were adjusted for age in all pediatric patients.[18,19]

Treatment protocol

In the early 1990s our center chose to treat FD patients requiring bisphosphonate therapy with the then newly developed nitrogen-containing bisphosphonate olpadronate, obtained by the dimethylation of the nitrogen molecule of the backbone structure of pamidronate. This dimethylation process was shown in our laboratory to increase the specificity of olpadronate toward bone resorption in vitro and vivo and to reduce its cellular toxicity.[20] The fivefold to 10-fold increase in potency of olpadronate compared to pamidronate was confirmed in a dosefinding study in patients with Paget's disease of bone, and its efficacy in achieving long-term remission and decrease in pain in > 89% of patients was further established in a long-term study in a cohort of 157 patients with this disease.[21,22] An advantage of olpadronate was that it could be used both orally and intravenously, and that its oral use provided more flexibility than the then-available bisphosphonate preparations by the availability of a 5-mg tablet for pediatric use for children 6 years or older, and of a 50-mg tablet for adult use. The maximumoral adult daily dose of 200 mg, and pediatric daily dose of 20 mg were very well tolerated, with only occasionally reported mild gastrointestinal side effects, which did not require discontinuation of the drug in most cases. The intravenous preparation of olpadronate was administered in doses of 4 or 8 mg as loading dose before starting oral olpadronate or as daily doses for 3 to 5 consecutive days at 3-month to 6-month intervals in the most severe cases with very high bone

turnover. The tablet and intravenous formulations of olpadronate were prepared and supplied by our hospital pharmacy for the whole period covered by this study. Treatment was administered in all forms of FD on the basis of increased bone turnover regardless of presence or absence of pain, but all patients with PFD and MAS analyzed in this study had pain of variable severity at one or more FD sites. Treatment was exceptionally administered in the presence of normal bone turnover in two patients who demonstrated rapid postoperative resorption of a recent fibula strut graft, and in one who was using high-dose inhalation corticosteroids for asthma, but all three did have bone pain. Olpadronate was administered orally at a starting dose of 200 mg/day, tapering to 50 mg/day and stopping 3 to 6 months after normalization of BTMs. The drug was administered intravenously as loading dose before starting oral treatment in case of very high bone turnover, in the rare case when oral medication was not well tolerated, or when oral use of maximum doses failed to normalize bone turnover after 12 months of treatment.

Ten of the 11 MAS patients and 28 of the 30 PFD patients were primarily treated with olpadronate in different doses and schedules orally and/or intravenously. Two patients with PFD were treated exclusively with oral risedronate or alendronate and one child with MAS did not tolerate oral olpadronate and was treated exclusively with i.v. pamidronate. Another eight patients temporarily received, at the discretion of their treating physician, oral or intravenous nitrogen-containing bisphosphonates other than olpadronate. These were in the form of daily 30 mg oral risedronate or daily 10 mg, or weekly 70 mg oral alendronate; 3 monthly cycles of intravenous pamidronate at doses of 15 mg daily for 3 consecutive days in adults, and 1 mg/kg body weight for 3 consecutive days in children older than 6 years, as recommended by Glorieux in osteogenesis imperfecta; or 6 to 12 monthly single infusions of 4 mg intravenous zoledronate.[23] The bisphosphonate preparations used, and cumulative doses of each preparation, are shown for MAS and PFD patients, in Tables 10.1 and 10.2, respectively. Relative potencies of all bisphosphonates used in this study have been reported.[24]

The aim of treatment with bisphosphonates, regardless of type of preparation, dosage, or schedule of administration, was to normalize bone turnover, hoping to achieve a consequent reduction in pain symptoms and to prevent the progression of FD lesions, thereby potentially decreasing the risk of complications such as deformities and fractures. Treatment was discontinued 3 to 6 months after normalization of bone turnover, and restarted as required when this was documented to increase again. The choice of high bone turnover to start and restart of therapy with bisphosphonates was based on the known FD temporal sequence of flare and remission, suggested

Table 10.1 Characteristics of patients with McCune-Albright Syndrome and cumulative dose of various nitrogen-containing bisphosphonates used

Patient ID	Gender/age at diagnosis (years)	Symptoms	Average FGF-23 (N < 125 U/ml)	Skeletal burden score	Age at start of therapy	Cumulative dose of Bisphosphonates**
1	F/3	Café-au-lait spots, precocious puberty and hypophosphatemia	NA*	59.66%	7	Olp 100 mg iv + 27375 mg oral, Zol 20 mg iv and Ris 5475 mg oral
2	F/4	Precocious puberty, hypophosphatemia and ovarian cysts	200 U/ml	26.08%	22	Olp 32 mg iv and 300000 mg oral, APD 1680 mg, Zol 20 mg iv
3	F/15	Café-au-lait spots, precocious puberty and hypophosphatemia	174 U/ml	25.28%	45	Olp 240 mg iv and 109500 mg oral
4	F/1	Café-au-lait spots, precocious puberty, hypophosphatemia, hyperthyroidism and GH-excess	274 U/ml	64.69%	45	Olp 720 mg iv and 365000 mg oral
5	F/0	Café-au-lait spots, precocious puberty and hypophosphatemia	161 U/ml	44.02%	19	Olp 764 mg iv and 144000 mg oral
6	F/3	Precocious puberty, hypophosphatemia and ovarian cysts	168 U/ml	9.77%	46	Olp 16 mg iv and 63250 mg oral
7	F/1	Café-au-lait spots, precocious puberty, hypophosphatemia, hyperthyroidism, GH-excess, hyperprolactemia and ovarian cysts	277 U/ml	42.63%	7	APD 360 mg iv
8	F/2	Café-au-lait spots, precocious puberty and hyperthyroidism	131 U/ml	56.46%	46	Olp 20 mg iv and 730000 mg oral, APD 900 mg iv
9	M/5	Café-au-lait spots, precocious puberty, hypophosphatemia, GH-excess, hyperprolactemia and autonomous testosteron production	180 U/ml	31.27%	13	Olp 20 mg iv and 328500 mg oral
10	M/10	Café-au-lait spots, precocious puberty, hypophosphatemia and hyperprolactemia	316 U/ml	64.26%	16	Olp 73000 mg oral
11	F/12	Café-au-lait spots, precocious puberty and hypophosphatemia	162 U/ml	38.70%	28	Olp 116 mg iv and 621975 mg oral, Ale 10500 mg, Ris 4200 mg, Zol 4 mg

* NA = not available.
** Olp = Olpadronate; Zol = Zolendronate; Ris = Risedronate; Ale = Alendronate.

to be associated with phases of expansion and consumption of mutated skeletal progenitor cells as mechanisms underlying the development, maintenance, and burning out of individual lesions.[25-27] It has been suggested that during skeletal growth the development and maintenance of a lesion would be associated with high bone turnover, and periods of remission would be associated with normal bone turnover, during which normal remodeling of FD bone may take place. However, the concept of the association between clinical flares and the level of BTMs has never been formally addressed. There are thus no direct studies examining the mechanism(s) that drive skeletal pain in FD. A number of observational studies, but not all, have shown the ability of antiresorptive therapy to relieve FD pain, suggesting that increased bone turnover may contribute to the mechanism of pain in FD.[8,9,11,13,14,28] However, other studies including ours here reported, fail to demonstrate a correlation between FD pain and disease burden.[29] The ultimate objective of the use of bisphosphonate therapy would thus be to normalize bone turnover with a view to prevent the development and/or expansion of FD lesions as well as to allow for normal remodeling to take place in FD lesions, theoretically aiming at improving bone quality and strength, although this is as yet to be formally demonstrated. All patients were prescribed calcium and vitamin D supplements concomitant to starting treatment with bisphosphonates, and serum 25-hydroxy-vitamin D level was controlled 3 months after start of therapy and supplementation adjusted accordingly. Active metabolites of vitamin D and phosphate supplements were additionally prescribed as required, predominantly in children, prior to start treatment with bisphosphonates, to correct moderate to severe hypophosphatemia associated with FGF-23–induced renal phosphate wasting. The decision not to treat FGF-23–induced mild hypophosphatemia in the absence of overt osteomalacia was based on published histomorphometry data in FD (albeit in children and adolescents), suggesting that although low serum phosphate may be associated with a mild systemic mineralization defect in PFD, it was debatable whether this warranted treatment in the absence of signs of rickets, as the more severe mineralization defect observed in dysplastic lesions was independent of serum phosphate levels.[30] Clinical and biochemical response to treatment in the form of verbal assessment of pain and biochemical markers of bone turnover and recurrence of FD activity after discontinuation of treatment were evaluated during outpatient clinic visits at start of treatment and at 3-month to 6-month intervals thereafter. Adverse effects were carefully documented at each outpatient visit.

Outcome of treatment with bisphosphonates was determined primarily by biochemical outcome as judged by normalization of serum values of the BTM (total) ALP (complete

Table 10.2 Characteristics of patients with polyostotic fibrous dysplasia and cumulative dose of various nitrogen-containing bisphosphonates used

Patient ID	Gender/age at diagnosis (years)	Extraskeletal symptoms	Average FGF-23 (N < 125 U/ml)	Skeletal burden score	Age at start of therapy	Cumulative dose of bisphosphonates**
12	F/5	Hypophosphatemia	133 U/ml	16.70%	35	Olp 68 mg iv and 146000 mg oral
13	F/9	-	160 U/ml	24.89%	22	Olp 124 mg iv and 219000 mg oral
14	F/5	-	134 U/ml	16.68%	39	Olp 91250 mg oral
15	F/45	-	100 U/ml	4.04%	51	Olp 60833 mg oral
16	M/9	Café-au-lait spots, hypophosphatemia	152 U/ml	17.10%	19	Olp 282875 mg oral
17	M/11	-	126 U/ml	24.78%	20	Olp 12 mg iv and 109500 mg oral
18	F/16	Café-au-lait spots	132 U/ml	15.30%	38	Olp 40 mg iv and 282875 mg oral
19	F/11	-	115 U/ml	15.75%	50	Olp 12 mg iv and 30417 mg oral
20	F/24	Hypophosphatemia	139 U/ml	15.80%	30	Olp 109500 mg oral
21	F/20	-	91 U/ml	7.13%	20	Olp 12mg iv and 27375 mg oral
22	F/8	-	166 U/ml	7.92%	19	Olp 20 mg iv and 27375 mg oral + Zol 8 mg iv
23	M/60	Hypophosphatemia	114 U/ml	13.74%	60	Olp 82125 mg oral
24	M/27	Hypophosphatemia	79 U/ml	7.65%	42	Olp 118692 mg oral
25	M/39	Café-au-lait spots	133 U/ml	24.96%	44	Olp 24 mg iv, Ale 900 mg, Ris 900 mg, Zol 48 mg iv
26	M/4	-	134 U/ml	23.90%	48	Ris 1800 mg
27	M/27	-	103 U/ml	2.05%	50	Olp 436 mg iv and 261583 mg oral, APD 360 mg iv, Zol 19 mg iv

Table 10.2 *Continued*

Patient ID	Gender/age at diagnosis (years)	Extraskeletal symptoms	Average FGF-23 (N < 125 U/ml)	Skeletal burden score	Age at start of therapy	Cumulative dose of bisphosphonates**
28	M/14	-	101 U/ml	16.42%	36	Olp 96 mg iv and 6083 mg oral
29	M/16	-	116 U/ml	NA	22	Olp 42583 mg oral
30	M/25	-	NA	15.80%	35	Olp 56 mg iv and 155125 mg oral
31	M/31	Hypophosphatemia	NA	7.07%	31	Olp 48 mg iv and 73000 mg oral
32	M/25	-	81 U/ml	7.93%	40	Olp 73000 mg oral
33	F/32	-	NA	16.26%	50	Olp 12 mg iv and 146000 mg oral
34	F/44	Café-au-lait spots, hypophosphatemia	112 U/ml	NA	51	Olp 100375 mg oral
35	F/24	-	107 U/ml	10.65%	55	Ale 3640 mg
36	M/8	Hypophosphatemia	195 U/ml	18.53%	12	Olp 28 mg iv and 360974 mg oral, Zol 12 mg
37	F/58	-	82 U/ml	16.12%	58	Olp 205313 mg oral
38	M/3	-	432 U/ml	15.75%	7	Olp 140 mg iv
39	F/35	-	131 U/ml	7.13%	37	Olp 4563 mg oral, Zol 8 mg iv
40	F/19	-	NA	15.75%	43	Olp 20 mg iv and 104938 mg oral
41	F/24	Hypophosphatemia	198 U/ml	17.87%	41	Olp 16 mg iv and 705667 mg oral, Ale 89180 mg, Zol 6 mg, Ale 114975 mg

* NA = not available.
** Olp = Olpadronate; Zol = Zolendronate; Ris = Risedronate; Ale = Alendronate.

response), decrease but no normalization of its value (incomplete response), or no change in its value (nonresponder). Clinical outcome was judged to be complete in case of disappearance or significant reduction in the severity of bone pain (complete response) and judged to be incomplete in the event of insufficient reduction in pain symptoms (incomplete response), usually coupled with non-normalization of ALP. In this study, time to normalization of bone turnover was evaluated using serum concentrations of ALP because this is a marker of bone formation, the prime defect in FD, and data on this marker were available at baseline and at each 3-month to 6-month outpatient clinic visit thereafter. Data were also retrieved for serum P1NP and CTX measurements but these were only available from 2006 onward, when they became available for use in the clinic, by which time a number of patients had already started treatment with bisphosphonates, so that these measurements are reported but not included in the analysis of primary outcome of treatment.

Statistical analysis

Statistical analysis was performed using SPSS for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA). Unless otherwise stated, results are presented as mean ± SD, or as a percentage in case of categorical data. We identified prognostic factors influencing the response of bone turnover to bisphosphonate treatment by incorporating gender, age at start of treatment, GH excess, phosphate level, and FGF-23 in a logistic regression model. We used Spearman's rank correlation coefficient to correlate serum levels of FGF-23 and ALP with SBS values.

RESULTS

Patients' characteristics

MAS patients

Data on MAS patients are shown in Table 10.1. Eleven patients had MAS (9 female and 2 male) with a median age at diagnosis of 3.0 years (range, 0 to 15 years). All MAS patients had precocious puberty, 5 (45%) had at least one or more additional endocrinopathies including growth hormone excess (n = 4; all associated with extensive craniofacial disease), prolactin excess (n = 3), and hyperthyroidism (n = 3). Not all patients had the characteristic cafe-au-lait patches (n = 9; 82%). Ten of the 11 MAS patients in whom it was measured (91%) had increased FGF-23 levels, with a median of 174 U/mL (range, 131 to 316 U/mL; normal range < 125 U/mL), and FGF-23 levels were significantly higher in MAS patients with GH excess, with a median serum concentration of 277

U/mL (range, 274 to 316 U/mL) compared to MAS-patients without GH excess: 165 U/mL (range, 131 to 200 U/mL), $p < 0.0001$. Despite the documented increased FGF-23 levels in all MAS patients, only eight (73%) developed age- and gender-adjusted low serum phosphate levels, and four of those required phosphate supplementation at some stage during childhood and adolescence. At the time of starting bisphosphonate therapy, only one of these four patients, an adolescent of 16 years with extensive skeletal involvement including craniofacial localization, treated excess prolactin and GH, corrected severe vitamin D deficiency, and inappropriately low serum phosphate due to FGF-23-induced renal phosphate wasting still required maximum doses of active metabolites of vitamin D and phosphate supplementation, which he had been using for 18 months prior to starting treatment to maintain his serum phosphate at 0.85 mmol/L (normal, 0.90 to 1.5 mmol/L). The mean lifetime number of fractures sustained by MAS patients was 3.6 (range, 0 to 13) and they required a mean of 2.4 surgical interventions per patient (range, 0 to 7). The lesions were bilaterally distributed in all MAS patients and all but one had craniofacial disease, particularly severe in the presence of GH excess. The mean ± SD SBS was 42.1% ± 18.0%. Scores were particularly high in patients with craniofacial disease and GH excess, with maximal scores of 75% in the craniofacial region in all patients with GH excess, compared with a mean score of 37.5% ± 30.6% in patients without GH excess ($p < 0.040$). The two patients with MAS but no cafe-au-lait patches had significantly lower SBS values (17.92% ± 11.54%) than those with cafe-au-lait patches (47.44% ± 14.47%), $p = 0.026$. Histological confirmation of the disease was available from specimens obtained at surgery for fractures and/or correction of deformities in six MAS patients, two of whom had genetic confirmation of the pathognomonic GNAS mutation.

PFD patients

Data on PFD patients are shown in Table 10.2. Thirty patients with PFD (15 female and 15 male), with a mean ± SD age at diagnosis of 23.5 ± 15.8 years were studied. None had laboratory evidence for endocrinopathies on endocrinology screening, but five (16%) had cafe-au-lait patches. The five patients with PFD and cafe-au-lait patches had higher SBS values (19.12% ± 5.13%) than the ones without pigmented skin lesions (13.29% ± 5.63%), although the difference was not statistically significant, $p = 0.115$. Fifteen of the 26 patients in whom it was measured (58%) had increased serum FGF-23 levels with an overall median of 128 U/mL (range, 79 to 432 U/mL), only two of whom had FGF-23–induced mild hypophosphatemia, which did not require treatment with active metabolites of vitamin D or phosphate supplementation prior to starting bisphosphonate therapy. Lateralization of the FD lesions was present in

18 patients (60%). The mean lifetime number of fractures sustained by PFD patients was 1.3 (range, 0 to 11) fractures and it was necessary to undertake a mean of 2.0 (range, 0 to 10) surgical interventions per patient. The mean SBS was 14.3% ± 6.5%. Twenty PFD patients had histological confirmation of the disease and in none was the disease genetically confirmed.

MAS versus PDF patients

Data on MAS versus PFD patients are shown in Table 10.3. There was no significant difference in gender distribution between PFD and MAS patients. Diagnosis was made at a significantly younger age in MAS compared to PFD (5.1 versus 23.5 years; p = 0.001), and disease was bilateral in all MAS patients compared to 67% of patients in the PFD group. MAS patients had more extensive skeletal disease compared to PFD patients with significantly higher ALP concentrations (a median of 257 U/L [range, 102 to 1782 U/L] versus 115 U/L [range, 72 to 604 U/L]; p = 0.002), significantly higher SBS values (42.1% versus 14.3%; p < 0.001), and they had sustained significantly more fractures (p = 0.024; 95% CI 0.37 to 4.26). MAS patients had also higher FGF-23 levels (a median of 174 U/mL [range, 131 to 316 U/mL] versus 128 U/mL [range, 79 to 432 U/mL]; 95% CI 19.7 to 123.7 U/mL; p = 0.008), and more frequent episodes of FGF-23–induced hypophosphatemia (81% versus 36%; p = 0.013), but did not significantly require more surgery than PFD patients (2.36 ± 2.6 versus 2.0 ± 2.5; 95% CI –2.15 to 1.42; p = 0.68).

Table 10.3 Comparative clinical, laboratory and disease burden characteristics between MAS and PFD

	McCune-Albright syndrome		Polyostotic fibrous dysplasia			
Factor	Mean	Standard deviation	Mean	Standard deviation	Mean difference	p-value
Alkaline phosphatase	499.6	± 619.0	144.1	± 116.3	355.5	0.005
Average FGF-23	207.1	± 64.9	135.4	± 66.9	71.7	0.008
Skeletal burden score	42.1%	± 18.0	14.3%	± 6.5	28.0	0.000
Age at diagnosis	5.1	± 5.0	23.5	± 15.8	18.4	0.001
Number of fractures	3.64	± 3.9	1.32	± 2.3	2.3	0.021
Number of surgeries	2.36	± 2.6	2.0	± 2.5	0.4	0.682
Hypophosphatemia	81.8%	-	35.5%	-	46.3	0.013

Correlates of SBS values

FGF-23 levels positively correlated with the extent of the skeletal lesions as measured by SBS values in the whole PFD/MAS group studied (Fig. 10.2A), as did serum ALP, P1NP, and CTX concentrations prior to starting bisphosphonate therapy (Fig. 10.2B for ALP) ($p < 0.001$ for all three BTMs). Spearman's rank correlation coefficient (SRCC) of SBS values and average serum FGF-23 levels was 0.620 ($p < 0.001$), and SRCC of SBS and serum ALP levels was 0.562 ($p < 0.001$). Serum FGF-23 also inversely correlated with serum phosphate levels, SRCC –0.426 ($p < 0.014$), but increased FGF-23 levels were not necessarily associated with hypophosphatemia in regression analysis.

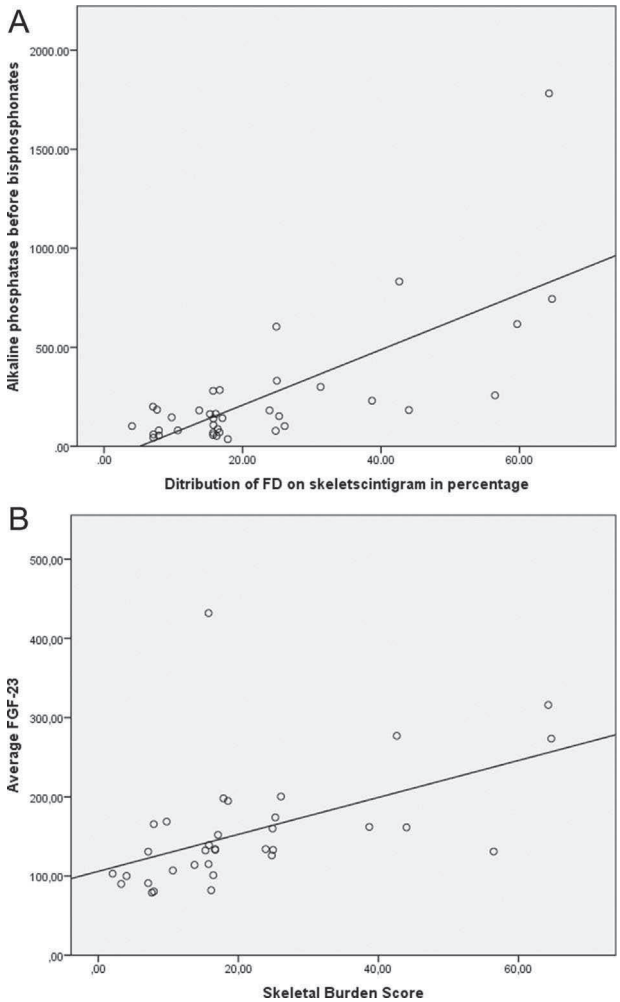

Fig. 10.2 (A) Positive relationship between skeletal burden scores and bone turnover as judged by total ALP concentrations prior to treatment with bisphosphonates. (B) Positive relationship between skeletal burden scores and average FGF-23 levels.

Outcome of bisphosphonate therapy

Mean age at start of bisphosphonate therapy was 27 ± 16.1 years in MAS patients compared to 37 ± 14.0 years in PFD patients ($p = 0.057$). There were six children who started therapy at age 16 years or less: two in the PFD group, both male, aged 7 and 12 years (Table 10.2), and four in the MAS group, three females and one male, aged 7, 7, 13, and 16 years (Table 10.1). Mean duration of follow-up after start of therapy was 12.3 ± 7.6 years in MAS patients, and 5.8 ± 6.4 years in PFD, with periods of discontinuation of treatment lasting between 6 and 12 months in the majority of PFD patients but not the majority of MAS patients. Bone turnover was significantly higher at start of treatment in MAS patients with a median serum ALP of 257 U/L (range, 102 to 1782 U/L) compared to 115 U/L (range, 72 to 604 U/L) in PFD patients (95% CI 139.1 to 541.3 U/L; $p = 0.002$). In the subgroup of patients in whom serum levels of P1NP and CTX were available at start of treatment with bisphosphonates and during follow-up (3 MAS and 22 PFD patients), median P1NP values were 960 ng/mL in MAS compared to 73.5 in PFD ($p < 0.0001$) and median CTX was 1.550 ng/mL in MAS compared to 0.360 ng/mL in PFD ($p = 0.001$). In both groups, serum ALP, P1NP, and CTX concentrations before starting bisphosphonate therapy were positively correlated with SBS (respectively, SRCC 0.72, $p < 0.001$; SRCC 0.87, $p < 0.001$; SRCC 0.71, $p < 0.001$) and with average FGF-23 levels (respectively, SRCC 0.588, $p = 0.001$; SRCC 0.671, $p = 0.001$; SRCC 0.663, $p = 0.001$).

Twenty-four of the 30 patients with PFD (80%) demonstrated a complete clinical and biochemical response to bisphosphonate therapy, with relief of pain symptoms and normalization of serum ALP concentrations, compared to only four of the 11 MAS patients (36%), of whom only one (of four) with GH excess demonstrated a similar complete response despite adequate suppression of GH excess in all patients ($p = 0.019$; Fig. 10.3). Patients with MAS required significantly higher cumulative doses of bisphosphonates to demonstrate a biochemical effect on ALP and to maintain it than patients with PFD (2696 mg versus 1470 mg, respectively; $p = 0.019$). In the subset of patients in whom data on P1NP and CTX were available before starting bisphosphonate therapy and sequentially thereafter, normalization of these markers was observed, in keeping with changes in ALP, within a year of starting treatment in 83% of PFD patients and in one of the three MAS patients. In patients in whom these markers did not normalize, maximum decrease in serum values was also observed, in keeping with changes in ALP, within the first year of treatment and stabilized thereafter. In complete responders, biochemical response in the form of normalization of ALP was observed within the first year of treatment in the majority of PFD and MAS patients except for one PFD patient in whom ALP normalized after 42 months of treatment, and one MAS

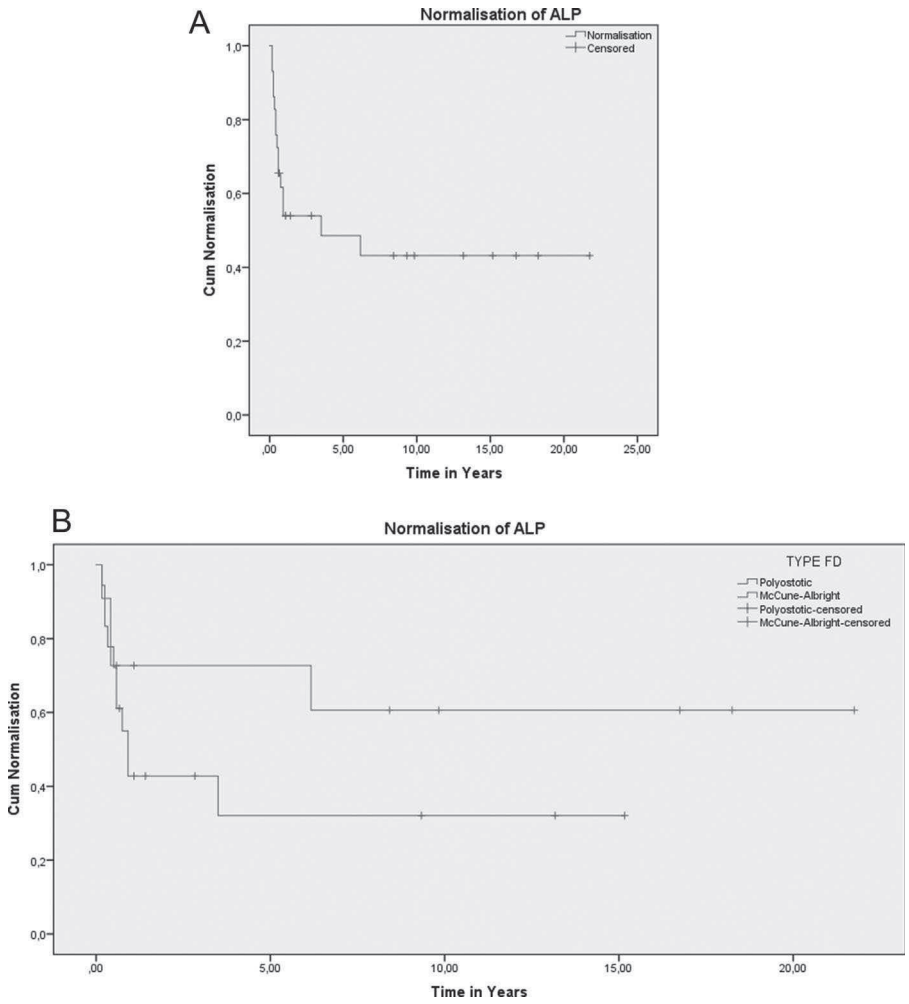

Fig. 10.3 Kaplan-Meier survival curves showing normalization of total ALP concentrations within the first year after starting treatment with bisphosphonates in the majority of complete responders with PFD or MAS (A), and similar course to normalization of ALP concentrations in patients with PFD or MAS with high ALP concentrations prior to starting bisphosphonate therapy (B).

patient in whom ALP normalized after 74 months of treatment (Fig. 10.3). Interestingly, the late normalizing PFD patient had a higher SBS than the mean for the PFD group (18.5% versus 14.3%), and the late and only MAS patient in whom ALP normalized had a lower SBS than the mean of the generally poorly-responding group of MAS patients (31.3% versus 42.1%). There were no absolute nonresponders, and all patients not showing a complete response (6/30 PFD and 7/11 MAS) demonstrated some decrease in severity of pain and a decrease in serum levels of ALP with a median decrease of

41% ranging from a minimum of 14% to a maximum of 78%. Treatment could not be discontinued in the long term, particularly in patients with MAS but also in patients with PFD with high SBS values, who required long-term bisphosphonate therapy to maintain the complete or incomplete suppression of increased bone turnover.

Factors affecting outcome of bisphosphonate therapy in PFD and MAS

In our series of patients, the only factor identified as affecting outcome of treatment with bisphosphonates in PFD after correction for age and gender was a high SBS ($p = 0.015$) independently of the presence or absence of endocrinopathies. A more limited response was consequently observed in patients with MAS who exhibited the highest SBS values because of more extensive skeletal disease. Neither serum concentrations of FGF-23 nor hypophosphatemia correlated with outcome of treatment with bisphosphonates either in PFD or in MAS patients. GH excess did not appear to influence outcome of treatment, although analysis was precluded by the limited number of patients with this endocrinopathy.

Safety issues with the long-term use of bisphosphonates in PFD and MAS

Ten of the 41 patients with PFD or MAS (24%) reported minor adverse effects, in the form of mild gastrointestinal complaints, headaches, and/or nausea with the use of oral medication. Only in one child with MAS did treatment need to be discontinued. In 38 patients who received one or more courses of olpadronate intravenously, only two had a severe acute phase reaction after the first course of treatment. Despite the high mean cumulative dose and long-term use of bisphosphonates, there was maintenance

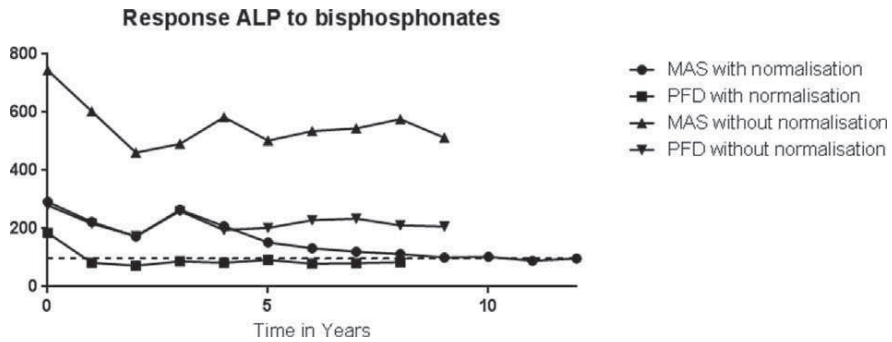

Fig. 10.4 Changes in serum total ALP concentrations in four individual patients illustrating similarities in complete and incomplete response to bisphosphonate therapy in PFD and MAS. The graphs also illustrate the maintenance of ALP activity with repeated treatment as required in complete responders, and no further suppression of the decreased bone turnover attained beyond 2 years of treatment, despite longer-term use of these agents in incomplete responders.

of normal BTMs with repeated treatment as required in complete responders, and no further suppression of the decreased bone turnover attained beyond 2 years of treatment despite longer-term use of these agents in incomplete responders (Fig. 10.4). There were no reports of osteonecrosis of the jaw or of atypical femoral fractures in any of the patients in our series. In children between the ages of 7 and 16 years treated long term for up to 9 years, there was no disturbance in linear growth.

DISCUSSION

In this study, we retrospectively evaluated the outcome and safety of long-term treatment with nitrogen-containing bisphosphonates in a case series of patients with the more severe polyostotic forms of FD, including those with endocrinopathies in MAS. Our findings demonstrate a beneficial effect of bisphosphonate therapy primarily on bone turnover and secondarily on pain symptoms in the majority of patients with PFD (80%), with a more limited response observed in patients with MAS (36%), likely due to their more extensive skeletal disease. In keeping with this premise, we further identify SBS as the only prognostic factor influencing the outcome of bisphosphonate therapy.

Over the past 25 years it has been the policy of our center to treat all patients with FD who demonstrated increased bone turnover, which with a few exceptions was associated with pain in all patients with PFD or MAS, with nitrogen-containing bisphosphonates, aiming at normalizing bone turnover, and hoping in the process for an associated reduction in pain symptoms, arrest of expansion of individual FD lesions, and prevention of debilitating complications such as deformities and fractures encountered in progressive disease, particularly of the growing skeleton. The lack of correlation between skeletal pain and disease burden in FD, is analogous to the highly variable frequency and severity of skeletal pain observed within and between individual patients suffering from the same metastatic tumor burden.[31] This analogy has led to the hypothesis that it is not just bone remodeling, but also a neuropathic component, possibly related to abnormal remodeling of the sensory innervation of bone, that may drive bone pain in FD.[32] This has been shown in animal models of skeletal cancer pain that effectively mirror the clinical picture observed in humans with bone cancer pain.[33] Whereas a neuropathic component to FD pain could not be excluded in our patients, our data based on long-term follow-up of a relatively large cohort of PFD and MAS patients with moderate to severe FD, support the association of clinical flares with increased BTMs, and the abatement of pain with normalization of these markers in the majority of patients, thus providing justification for the use

of antiresorptive agents in FD in the presence of high bone turnover. The hypothesis is further supported by the persistence of pain, albeit of lesser severity, in patients in whom these agents fail to normalize BTMs.

We chose to primarily use the nitrogen-containing bisphosphonate olpadronate in the medical management of these patients, because of its proven efficacy in Paget's disease of bone and its excellent track record for gastrointestinal tolerance, allowing the safe administration of high oral doses for longer periods of time in adult and pediatric patients with severe disease.[22] Its dosage flexibility in the pediatric population also represented a clear advantage. However, other bisphosphonates, albeit all nitrogen-containing, were also mostly temporarily prescribed during the course of the disease at the treating physician's discretion.

Our primary outcome measure was the effect of bisphosphonate therapy on parameters of bone turnover, regardless of preparation, mode of administration, or schedule of treatment. In this study, we used serum ALP as marker of bone turnover because this is a marker of bone formation and mineralization, and it was the marker with the most complete set of available data before treatment and at regular intervals thereafter for the duration of follow-up across the 25-year span of our study. We also chose ALP as bone turnover marker because of its significant correlation with SBS values, a specific marker of skeletal disease severity in FD, and because cells in the endosteal fibrosis of FD lesions have been shown to exhibit strong ALP activity.[6,7] We did not use the markers of bone turnover P1NP and CTX in our analysis because data on these were only available from 2006 onward when the measurements were first made available for use in the clinic, and a number of patients had by then already started treatment with bisphosphonates, so that a number of baseline values for these markers were consequently missing.

Our secondary outcome measure related to the effect of bisphosphonate therapy on bone pain, a vexing and often debilitating clinical feature of FD, particularly in the presence of extensive skeletal disease. A caveat about the data regarding this measure in our study is that although data on bone pain were documented in all patients at nearly all outpatient visits, which were at short intervals of 3 to 6 months, these consisted of recording the presence or absence of pain, its severity, and changes in the pattern of pain rather than the data being systematically obtained with the use of validated pain questionnaires such as a visual analogue score (VAS), which does represent a limitation of our study. Notwithstanding, there was a clear trend for reduction or disappearance of pain symptoms on bisphosphonate therapy, which

paralleled the normalization of bone turnover, and interestingly a beneficial effect on reducing pain symptoms was also observed in MAS patients with extensive skeletal disease even when bisphosphonate therapy was not able to sufficiently decrease bone turnover. FD is a disorder of bone growth, with excessive and abnormal bone of poor quality being formed instead of normal bone at one or more skeletal sites. In these sites, mutated cells of the osteogenic lineage at various stages of maturation are exposed to the effects of excess endogenous cAMP production, which is due to the inappropriate stimulation of adenylate cyclase by the mutated Gsa, leading to a spectrum of dysfunctional and architecturally imperfect bone growth, particularly in the growing skeleton.[34-38] As a result of the abnormal chemical composition and mineral content of the deposited matrix, the abnormal bone is mechanically unsound and fragile and at the same time more compliant than normal bone, leading to increased risk for deformities and insufficiency fractures with debilitating consequences particularly in the presence of high skeletal burden. The problem is further compounded by the increased production of FGF-23, leading to renal phosphate wasting, which has been documented in variable degrees in some 50% of patients with PFD/MAS, and may result in severe cases in further demineralization, osteomalacia, and further increased risk for deformities and fractures.[39] Increased expression of IL-6 from mutated mesenchymal precursor cells stimulates local osteoclast recruitment and activity, leading to increased bone resorption in and around FD lesions, associated with a local increase in bone remodeling.[7,40] However, increased bone resorption is not the prime pathophysiologic mechanism for an FD lesion so that it seems counterintuitive to use bisphosphonates, the most widely used antiresorptive agents, to treat a disorder of primarily disturbed bone formation. On the other hand, the use of bisphosphonates in such a disorder is supported by their successful use in osteogenesis imperfecta, in which they have been shown to significantly decrease skeletal morbidity.[23,41,42] Notwithstanding, the local increase in bone remodeling may contribute to the expansion of an FD lesion, particularly in the growing skeleton. The question arises whether a bisphosphonate-induced decrease in bone remodeling in an FD lesion may be beneficial on the natural history of the disorder by potentially halting the expansion or resulting in the regression of an FD lesion. There is some evidence for this from open studies, but because the natural history of the disorder remains elusive, more evidence from randomized, placebo-controlled trials is required to identify which patients respond best and should thus be targeted for therapy.

Available evidence for a beneficial effect of bisphosphonates in FD

Surgical interventions, successful in reducing pain, correcting deformities, and treating and preventing fractures have been the mainstay of treatment of FD since the disease was first described in the late 1930s.[43] Several publications, particularly using intravenous pamidronate in open studies, have shown the ability of this nitrogen-containing bisphosphonate to improve bone turnover and to decrease bone pain in adults and children with FD.[8,11,44-47] Some studies have also shown beneficial radiological changes potentially associated with improved bone quality and decreased risk of complications.[10,14,48] However, the only randomized controlled trial (RCT) using the nitrogen-containing bisphosphonate alendronate in daily oral doses ranging from 10 to 40 mg daily in 6-month cycles for 2 years failed to demonstrate any significant beneficial effect in FD patients compared to placebo. Notwithstanding, the lack of decrease in ALP in this study suggests that the dose and schedule of alendronate used may not have been adequate to efficiently decrease bone turnover in the severely affected treated patients. Longer-term treatment and higher cumulative doses may have been needed to significantly decrease bone turnover, although this would have been precluded by the use of the oral formulation of alendronate. Results of an ongoing RCT using risedronate 30 mg daily for 2 months every 6 months – the Profidys study – are eagerly awaited, but children, who probably represent the most important target group for bisphosphonates, have unfortunately not been included in this study. Moreover, it has also been suggested that the disease continues to progress with lesions expanding under bisphosphonate treatment,[49] and a direct beneficial effect of bisphosphonates on the characteristic abnormal structure of bone of an FD lesion has so far not been demonstrated.[13] Opinion is thus divided on the beneficial effect of bisphosphonates in FD, and their use in the management of patients with this disorder remains, therefore, a topic of debate.

Potential mechanism underlying the beneficial effect of bisphosphonates in FD

Bisphosphonates so far used in the management of FD have all been nitrogen-containing bisphosphonates, the antiresorptive effect of which is mediated by the inhibition of protein prenylation resulting in inactivation of osteoclasts.[50] Protein prenylation is a type of posttranslational modification critical to a variety of GTP binding proteins, including Gsg. A potential mechanism of action of bisphosphonates in FD besides its antiosteoclastic effect is a possible additional effect of the inhibition of prenylation of Gsg on Gsa mutated cells of the osteogenic lineage, which may potentially decrease the endogenous overexpression of cAMP and thus the potential development and expansion of an FD lesion.[51]

Concerns with long-term use of bisphosphonates in FD

A general concern with the use of bisphosphonates in any skeletal disorder is the potential consequences of continuing suppression of bone remodeling by the longer-term use of these agents. In patients with FD, the spectrum of clinical expression of the disease is wide and the skeletal burden variable. We have addressed this concern by individually tailoring treatment to bone turnover status, an approach which has allowed the possibility of "drug holidays" for a maximum duration of a year in most PFD patients, but not MAS patients. A second concern in the management of these patients is the use of bisphosphonates in MAS patients with untreated GH excess, in which case, the stimulatory effects of GH excess on bone turnover will compete or negate the inhibitory effects of bisphosphonates, calling for higher doses of bisphosphonates, and longer-term usage, with potential development of associated complications. A third concern is the use of these agents in the presence of FGF-23–induced renal phosphate wasting, a relatively common finding, although in variable degrees, in the more severe cases of PFD and MAS, because of the potentially associated disturbance in mineralization.[39,52] A last concern is the potential lack or curtailed skeletal uptake in predominantly sclerotic lesions such as those observed in craniofacial FD, but beneficial effects of these agents have also been reported particularly in isolated craniofacial (CF) FD.[53-55]

In our study, treatment with bisphosphonates was well tolerated in adults as well as in children except for one young MAS patient, and only mild side effects were documented despite the high cumulative dose required to achieve an effect in the more severely affected cases of FD described here. We believe our specific individually tailored treatment protocol, based on maintaining a normal bone turnover status, was probably instrumental in the prevention of potential complications such as atypical fractures and osteonecrosis of the jaw. Attention to correction of metabolic abnormalities such as vitamin D deficiency and hypophosphatemia, which could have worsened mineralization of FD lesions, has also helped in the prevention of further complications such as insufficiency fractures and associated increased pain symptoms. In our cohort, long-term bisphosphonate therapy was not associated with deleterious effects on linear growth in treated children, as also previously demonstrated by our group in bisphosphonate-treated children with severe osteoporosis.[56]

Factors influencing outcome of bisphosphonate therapy in FD

High SBS, GH excess, and high FGF-23 levels have been previously found to predict poor prognosis in FD.[6] However, in our cohort, we identified high skeletal burden as

the only prognostic factor influencing outcome of bisphosphonate therapy. Although GH excess has been shown to be associated with higher skeletal burden, and three of our four patients with GH excess did have an incomplete clinical and biochemical response to treatment, we could not demonstrate a significant impact of GH excess on outcome of treatment, probably because of the small number of patients with this endocrinopathy in our MAS series. FGF-23 has been shown to be expressed throughout the osteogenic lineage in osteoblasts, osteocytes, and stromal cells, as well as in the vascular walls in FD lesions.[57] The positive correlation of FGF-23 with SBS, as shown by Collins and colleagues and confirmed in our study, is thus not surprising.[39] However, neither FGF-23 levels nor phosphate levels predicted treatment outcome. This finding is in line with recent reports suggesting that the FGF-23 secreted by the FD lesions is not active FGF-23 but consists largely of the inactive form of the peptide.[57]

Strengths and limitations of the study

Our study has strengths as well as limitations. Its main strength is the inclusion of a relatively large number of patients with the more severe forms of FD, its novel treatment protocol choosing high bone turnover rather than bone pain to determine start and restart of therapy, and aiming at normalizing bone turnover thus permitting drug holidays as required and precluding unnecessary long-term treatment with bisphosphonates. A further strength is the close monitoring and long-term follow-up of these patients for the duration of treatment. The study has also limitations. Its main limitations are the limitations inherent to a retrospective study as well as the limitations resulting from the use of verbal assessment data rather than data derived from formally validated tools such as VAS for evaluation of the clinical outcome of pain. However, all patients had pain symptoms and data on pain were not randomly obtained in our study, but were consistently enquired about at each outpatient visit that took place at short intervals of 3 to 6 months for the duration of treatment. A last potential limitation of our study is the possibility that the progressive improvement in bone pain may not have been due to the use of bisphosphonates, but were at least in part due to the natural course of FD. In conclusion, our data from this retrospective study suggest a beneficial and safe outcome of long-term bisphosphonate therapy in the majority of patients with PFD, although response to therapy was limited in MAS patients by their higher skeletal disease burden. In our patients with high skeletal burden, who do demonstrate a complete response to treatment, maximum response is observed with few exceptions after 1 year of treatment. In the population studied, the only identified prognostic factor that influenced outcome of bisphosphonate therapy was a high SBS.

We believe our findings carry significant clinical implications, because they justify an attempt to treat patients with the more severe forms of FD with bisphosphonates, particularly in view of the demonstrated safety of the strictly monitored long-term administration of these agents and the as-yet-scarce evidence for the efficacy and safety of alternative therapeutic options such as denosumab or oral tocilizumab. Which bisphosphonate should be used, at which dose, at which dosing interval, and for which duration of treatment remains to be established. Whether bisphosphonates have also an antinociceptive effect independently of their antiresorptive effect in FD certainly warrants further investigation. Consensus over these issues should be reached in the design of future large-enough multicenter studies, conducted for long enough, in order to definitively establish the position of bisphosphonates in the armamentarium of therapeutic options used in the treatment of the ubiquitous skeletal disorder of FD.

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Chapter 11

Denosumab in bisphosphonate-refractory fibrous dysplasia: a case series

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Submitted

ABSTRACT

Fibrous dysplasia (FD) is a rare bone disorder due to an activating mutation of the *GNAS*-gene. The effectiveness of denosumab, a monoclonal antibody to RANKL has been recently reported in case studies of FD. We present a case series of 12 patients (9 female), with FD treated with denosumab for at least a year at the Leiden Center for Bone Quality between May 2013 and May 2016. All patients had been previously treated with bisphosphonates at high cumulative doses for a mean of 8.8 years. One patient had monostotic craniofacial FD, 7 polyostotic FD and 4 McCune-Albright syndrome, 2 with growth hormone excess. Median Skeletal Burden Score was 20.8 (range 0.3–64.7). Denosumab was administered at a dose of 60 mg 3–6 monthly for a median of 14.5months (range 13–29M) on the basis of increased bone turnover markers (BTM) and pain. At baseline, mean±SD serum ALP was 226 ± 152 U/L, P1NP 369 ± 385 ng/mL and CTX 393 ± 257 ng/mL. Patients receiving denosumab at 3-monthly intervals demonstrated more significant decreases in BTM at 6 months in the 3 monthly compared to 6 monthly schedules of denosumab: ALP ($p = 0.007$) and P1NP ($p = 0.025$) but not CTX (NS). BTM normalized in 8 of the 12 treated patients after a median time of 4.7 months (range 2.1–24.0), 5 of whom had not reached normalisation of BTM after long-term treatment with bisphosphonates. Denosumab was well tolerated and no side effects were reported, particularly no hypocalcaemia, for the duration of treatment. Our data show that denosumab at a dose of 60 mg three-monthly is effective in significantly decreasing BTM and pain and is well-tolerated and safe in patients with severe FD, representing a promising therapeutic option in those refractory to treatment with bisphosphonates. Longer-term studies in larger number of patients are warranted to confirm these findings.

INTRODUCTION

Fibrous dysplasia is a rare bone disorder characterized by replacement of bone by highly vascularized fibrous tissue in one (monostotic) or more bones (polyostotic) that may be associated with significant skeletal morbidity.[1,2] The disorder is due to activating mutations of the *GNAS*-gene leading to overproduction of cyclic AMP and abnormal cellular responses, such as increased production of the bone resorbing factors IL-6 and RANKL.[3-5] Broader distribution of the *GNAS*-mutation may be associated with extraskeletal manifestations, particularly endocrine glands, such as endocrinopathies in the McCune-Albright Syndrome (MAS) and intramuscular myxomas in Mazabraud's syndrome.[6]

Although there is as yet no approved medical treatment for fibrous dysplasia, several studies have reported clinical and biochemical improvement in patients treated with variable bisphosphonate regimens.[7-14] However, response to bisphosphonates may be incomplete and inadequate in decreasing pain symptoms, particularly in patients with polyostotic disease and high skeletal burden.[12,13] Recent case reports suggest successful treatment of patients with fibrous dysplasia with the RANKL inhibitor, denosumab.[15-18] We have treated bisphosphonate-refractory patients with denosumab and here we describe the clinical and biochemical outcomes of 12 consecutively treated patients with this agent.

PATIENTS AND METHODS

Patients

Included in this retrospective study were adult patients with fibrous dysplasia attending the Outpatient Clinic of the Center for Bone Quality of the Leiden University Medical Center (LUMC) who fulfilled the following criteria: a. Previous treatment with bisphosphonates with incomplete biochemical and/or clinical responses defined as failure to achieve normal values of total serum alkaline phosphatase (ALP) activity, in the absence of liver disease, and/or of serum amino-terminal propeptide of type 1 procollagen (P1NP) levels and persistence of skeletal pain; b. To have received 3 or 6 monthly treatment with denosumab, with at least 4 administrations with this agent.

In our center, management of patients with fibrous dysplasia is conducted following a standard care trajectory that includes collection of data about type and extent of disease, extent of skeletal involvement as calculated by the skeletal burden score on

technetium-99 bone scans, screening for endocrinopathies, history of previous medical or surgical treatment and evaluation of laboratory and clinical parameters of disease activity (particularly pain) at predefined time intervals. Retrospective analysis of the collected data were approved by the Medical Ethics Committee of the LUMC and informed consent was obtained from all patients for the off label use of denosumab.

Treatment protocol

Treatment with denosumab was initially initiated at 6-monthly intervals in 6 patients, according to the regimen used in osteoporosis. As it became apparent that the biochemical response with this interval failed to sustain the initial decrease in bone turnover markers, the interval was reduced to 3 monthly administration of denosumab. All selected patients received subcutaneous injections of denosumab 60 mg every 3 or 6 months and daily calcium and vitamin D supplements. The primary outcomes of treatment were normalization of biochemical markers of bone turnover and reduction in skeletal pain. Patients were seen in the clinic every 3 months during which blood samples were collected for evaluation of bone and mineral metabolism and data on change in pain and potential adverse effects of treatment were obtained.

Radiological and biochemical investigations

The extent of bone involvement was determined by skeletal scintigraphy using the validated skeletal burden score (SBS).[19] Non-fasting blood samples were collected from all patients and measured for calcium, albumin, phosphate, creatinine and γ-GT by semiautomated techniques. Alkaline phosphatase was measured by a fully automated P800 modulator system (Roche BV, Woerden, The Netherlands). Parathyroid hormone (PTH) and 25-OH vitamin D (25-OHD) were measured using the Immulite 2500 assay (Siemens Diagnostics, Breda, The Netherlands) and the LIAISON® 25-OH Vitamin D TOTAL assay (DiaSorin S.A./N.V., Brussels, Belgium), respectively. P1NP and β C-terminal telopeptide of type 1 collagen (CTX) were determined by the E-170 system (Roche BV, Woerden, Holland). The C-terminal of Fibroblast Growth Factor 23 (FGF-23) (Immutopics, San Clemente, CA, USA) was measured after short storage at -20°C prior to analysis using the BioTek ELx50 Washer (BioTek, Bad Friedrichshall, Germany). All analyses were performed according to the manufacturer's protocol.

Statistical analysis

Statistical analysis was performed using SPSS for Windows, version 23.0 (SPSS, Inc., Chicago, IL, USA). Unless otherwise stated, results are presented as median (range or

IQ), or as a percentage in case of categorical data. A linear mixed model was used to assess the subtypes of FD and dose intervals as attributive factors for the response to treatment with denosumab over time. A paired sample t-test was used to compare bone markers before and after treatment.

RESULTS

Twelve patients (9 women) who received at least 4 injections of denosumab (range 4 to 9) with a median follow-up of 18 months (range 14–30) were studied (Table 11.1). Seven patients had polyostotic fibrous dysplasia, 4 had MAS and one had severe monostotic craniofacial disease. All were previously treated with bisphosphonates predominantly olpadronate for a median period of 8.7 years (range 0.7–22.1) and their median SBS was 20.8 (0.3–64.7). Previous treatment with bisphosphonates had led to temporary normalisation of ALP in 3 patients (33%), temporary normalisation of P1NP in 3 patients (33%) and temporary normalisation of CTX in all patients. Serum values of biochemical markers of bone turnover (BTM) varied markedly among patients (see Table 11.1). At time of first denosumab initiation serum ALP activity was increased in 11/12 patients (median 191 U/L, range 75–538 U/L), serum P1NP in 12/12 patients (median 241 ng/ml, range 73–1235 ng/ml) and serum CTX in 3/12 patients (median 375 ng/ml, range 114–999 ng/ml). CTX values should be interpreted with caution because blood was obtained in the non-fasting state that can affect measured values of CTX, however, blood samples were always taken in the morning and therefore comparable to one another. Median time between the last bisphosphonate treatment and first denosumab injection was 4.0 months (range 0–103 months).

Serum calcium, adjusted for albumin, phosphate, creatinine and 25-OHD vitamin D concentrations and plasma PTH levels were within their respective reference ranges in all studied patients and despite absence of hypophosphatemia, plasma FGF-23 levels were elevated in 9/12 patients and correlated with the Skeletal Burden Score

Biochemical response to treatment

Treatment with denosumab was initially administered at 6 monthly intervals in six patients, which was not sufficient to retain serum levels of BTM below baseline values. For example, in 6 patients with 6 monthly intervals serum ALP activity, although significantly decreased at 3 months after a singe denosumab injection, was only 13% lower compared to the basal values after 6 months, while this was 50.8% lower in 6

Table 11.1 Patient characteristics

Patient ID	Gender/ age at start denosumab	Type of fibrous dysplasia	Skeletal Burden Score	Average FGF-23	Duration & cumulative dose of bisphosphonates	Follow-up (months)	Denosumab scheme	Bone turnover markers prior to denosumab treatment
1	F/36	PFD	16.70	133.00	1.7 yrs/ 1528 mg	14	60 mg sc/3 mo	ALP 183; P1NP 290; CTX 347
2	F/33	PFD	24.89	160.00	11.84 yrs/ 2314 mg	26	60 mg sc/3 mo	ALP 183; P1NP 290; CTX 347
3	M/52	PFD	24.96	133.00	9.52 yrs/ 24 mg	12	60 mg sc/3 mo	ALP 330; P1NP 354; CTX 548
4	F/50	MAS	64.69	273.50	8.9 yrs/ 4370 mg	20	60 mg sc/3 mo	ALP 503; P1NP 812; CTX 999
5	F41	MAS	44.02	161.40	22.1 yrs/ 2204 mg	11	60 mg sc/6 mo	ALP 161; P1NP 198; CTX 333
6	M/33	MAS	31.27	173	11.8 yrs/ 3305 mg	12	60 mg sc/3 mo	ALP 144; P1NP 124; CTX 604
7	F/46	MAS	38.70	162.00	18.5 yrs/ 6336 mg	9	60 mg sc/6 mo	ALP 203; P1NP 208; CTX 148
8	F/41	PFD	0.26	116	2.47 yrs/ 316 0mg	19	60 mg sc/6 mo	ALP 75; P1NP 73; CTX 241
9	F/35	PFD	0.58	71	4.7 yrs/ 570 mg	14	60 mg sc/6 mo	ALP 94; P1NP 80; CTX 114
10	F/68	PFD	5.60	159	0.7 yrs/ 600 mg	11	60 mg sc/3 mo	ALP 198; P1NP 864; CTX 403
11	F/28	MFD	13.80	202	8.6 yrs/ 4740 mg	15	60 mg sc/3 mo	ALP 135; P1NP 109; CTX 166
12	M/28	PFD	7.77	115	5.0 yrs/840 mg	11	60 mg sc/6 mo	ALP 275; P1NP 273; CTX 443

patients who received injections of denosumab at 3 monthly intervals. Changes in serum P1NP levels were very similar (Fig. 11.1). Linear mixed model analysis (Table 11.2 and Fig. 11.1) revealed a significant difference over time between patients who received denosumab at 3-monthly intervals compared to those who received the agent a 6-monthly intervals for ALP ($p = 0.007$) and P1NP ($p = 0.025$), but not for CTX ($p = 0.162$). There was no significant difference in biochemical response between subtypes of fibrous dysplasia. These results suggest that the denosumab regimen used in the treatment of osteoporosis is inadequate for the treatment of fibrous dysplasia and all patients were subsequently treated with a 3 monthly schedule of 60 mg denosumab. A single patient with a still modest biochemical response after 4 denosumab injections of 60 mg was further treated with 120 mg every 3 months.

Outcomes of denosumab treatment

Compared to pretreatment ALP levels, mean serum ALP levels after 12 months were significantly reduced from 237 ± 150 IU/L to 104 ± 59 IU/L ($p < 0.01$), reflecting a 51.5 ± 16.2% decrease in this bone turnover marker. P1NP also decreased, albeit not statistically significant, from 385.0 ± 76 ng/ml to 233.8 ± 505.4 ng/ml ($p = 0.146$). CTX decreased 23.5%, from 412 ± 251 to 315 ± 318 pg/ml, which was not significant ($p = 0.403$). At the end of the study at a mean of 18 ± 5 months after the start of treatment, serum ALP values were significantly decreased by 48% to 98 ± 50.3 IU/l ($p < 0.01$). P1NP levels similarly remained lower with a 48% decrease at 213.7 ± 35.7 ng/ml, albeit not significant ($p = 0.07$).

Of the 11 patients with increased serum ALP activity at baseline, values normalized in 9 (82%) whereas serum P1NP levels which were increased in all patients, reached the normal range in 9/12 (75%) at the end of follow up.

Biochemical response to treatment generally stabilized after the second injection of denosumab, with no further decrease observed at subsequent injections at (Fig. 11.1). This is illustrated in the patient shown in Fig. 11.2 in whom serum ALP activity decreased from 538 IU/l reaching a plateau of still inadequately high ALP at 321 IU/l after 18 months of treatment with denosumab given at 6-monthly and later 3-monthly intervals. Continuation of treatment at a dose of 120 mg denosumab 3-monthly resulted in a further decrease of serum ALP activity within the normal lab range to 100 IU/l.

A number of factors known to affect response to bisphosphonates did not appear to affect response to denosumab. Serum P1NP levels decreased by 66.5% in patients

Table 11.2A Results linear mixed model: polyostotic vs McCune-Albright

BTM	Subtype	Time	Mean	95% confidence interval	Sig.
ALP	Polyostotic	T1	228.5	130–327	0.083
		T2	172.6	73–272	
		T3	138.0	40–236	
	McCune-Albright	T1	252.8	113–392	
		T2	95.7	-48–237	
		T3	167.8	28–307	
P1NP	Polyostotic	T1	409.8	138–682	0.110
		T2	380.0	103–657	
		T3	230.6	-46–507	
	McCune-Albright	T1	335.5	-50–721	
		T2	42.0	-343–427	
		T3	223.0	-162–608	
CTX	Polyostotic	T1	357	143–572	0.010
		T2	511	287–736	
		T3	292	67–516	
	McCune-Albright	T1	521	217–825	
		T2	129	-206–464	
		T3	603	300–907	

Table 11.2B Results linear mixed model: 3-monthly vs 6-monthly doses

BTM	Dosis	Time	Mean	95% confidence interval	Sig.
ALP	3-monthly	T1	270.7	163–378	0.007
		T2	173.5	66–281	
		T3	118.5	11–226	
	6-monthly	T1	202.5	95–310	
		T2	116.7	6–228	
		T3	177.3	70–285	
P1NP	3-monthly	T1	450.3	144–757	0.025
		T2	319.7	13–626	
		T3	91.4	-222–404	
	6-monthly	T1	319.7	13–626	
		T2	175.1	-149–499	
		T3	342.7	36–649	
CTX	3-monthly	T1	484	238–731	0.162
		T2	555	308–801	
		T3	375	106–643	
	6-monthly	T1	339	93–586	
		T2	129	-170–428	
		T3	431	185–678	

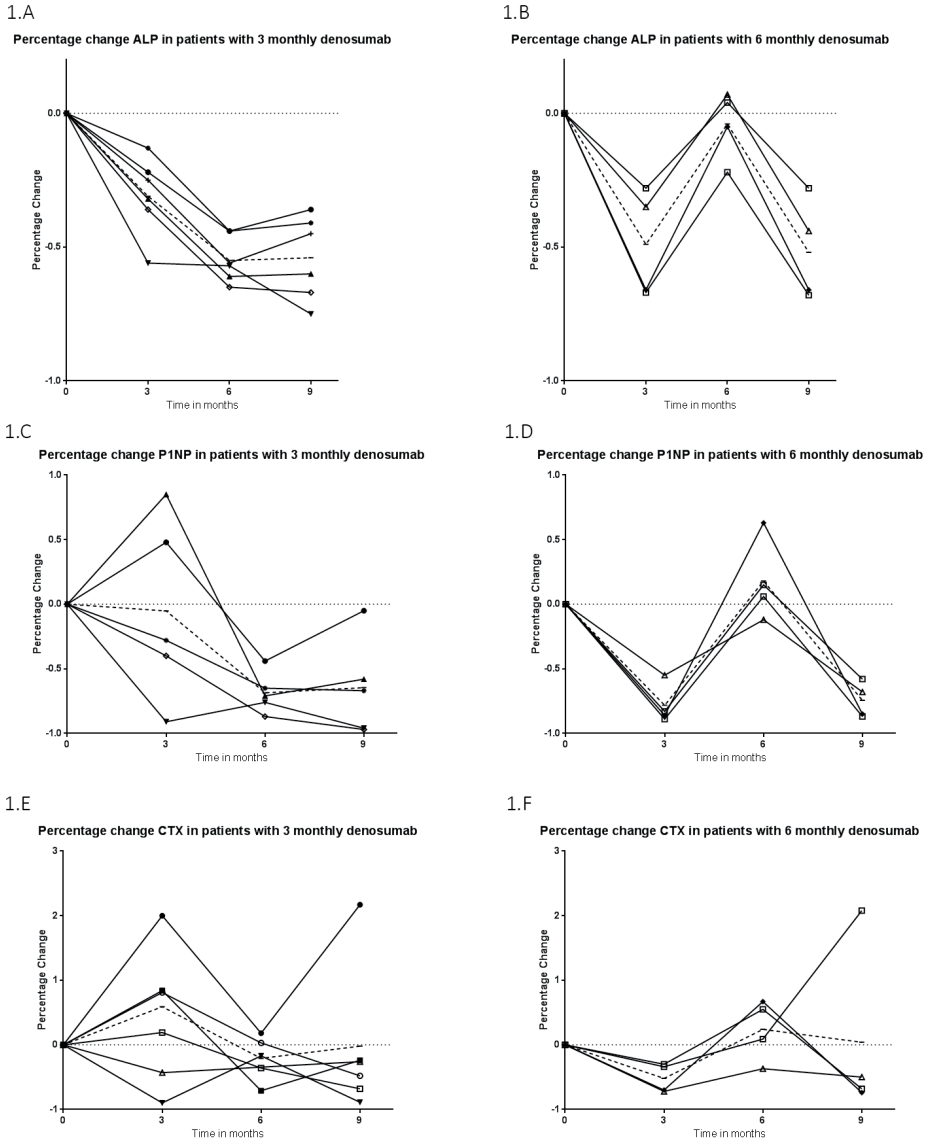
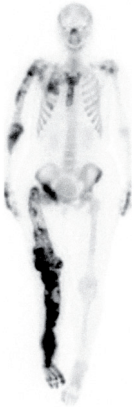
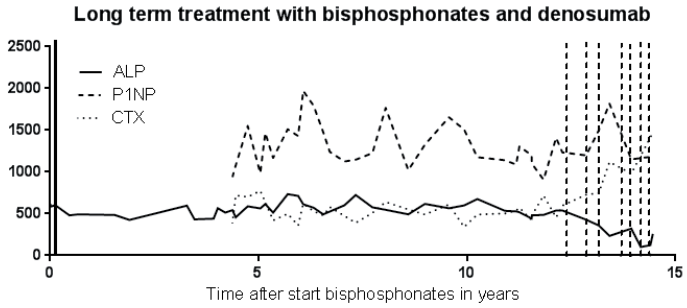


Fig. 11.1 Graphs showing the percentage change of ALP, P1NP and CTX after 9 months of treatment with 3-monthly or 6-mothly doses of denosumab. The dotted line indicates mean percentage change. The graphs clearly show an increase in ALP and P1NP levels after 3 months in the group with 6-monthly treatment with bone turnover returning to pre-treatment levels (ALP) or even higher (P1NP). The graphs regarding the group with 3-monthly doses however, show an increase decline in ALP and P1NP levels with stabilization after 6 months. Graphs on CTX do not show a clear pattern, which might be due to the fact that blood samples in our patients were taken in a non-fasting state, which might decrease the reliability of the samples. Another explanation for this unclear pattern of CTX levels might be based on the hypothesis that responses on CTX are generally more acute compared to those of P1NP and ALP, however, this remains to be shown.





2A 2B

Fig. 11.2 One of our patients (nr. 2, Fig. 11.2), diagnosed with polyostotic FD after a pathologic fracture of the right femur at the age of 3 years, has had denosumab injections for almost 3 years after she had previously been treated with bisphosphonates for over 12 years, mainly with olpadronate, orally (cumulative dose 146,000 mg) and IV (cumulative dose 68 mg) and twice with alendronate IV 5mg. Her femur was severely affected resulting in reduced mobility and pain, not only form her femur but due to the FD changes in the right side of the body with involvement of the complete upper and lower right extremity, several ribs, the sternum, the pelvis and in a lesser form the left upper extremity (2A). Although bisphosphonate treatment initially decreased ALP serum levels (2B) and subsequently resulted in a decrease in pain; bone turnover remained high during the treatment with bisphosphonates. Due to consistent high bone turnover in combination with increasing pain levels, she was started on 60mg denosumab injections 6-monthly. After 6 months but she had a notable decrease in pain, an increase in mobility and P1NP and ALP had both decreased, although CTX levels had increased, probably as a result of a rebound effect, and after 13 months P1NP levels had also increased. Due to an additional increase in pain, she was switched to 60 mg denosumab 3-monthly and later to 120 mg denosumab 3-monthly doses. P1NP levels dropped to baseline levels prior to denosumab and ALP even normalised two years after start of denosumab treatment. The decrease in bone turnover went hand in hand with a decrease in pain symptoms and increased mobility. During treatment she had muscle pains of the lower legs, possibly as a side effect of denosumab. Phosphate, calcium and PTH levels remained normal during treatment.

with skeletal bone score above the median value and by 46.5% in those with skeletal bone score below the median value. Similarly, serum P1NP levels decreased by 60.8% in patients with serum FGF23 levels above the median value and by 51.2% in those with levels below the median value.

Clinical response to treatment

Ten patients of the 12 patients reported significant improvement of pain. In some patients the response was remarkable, occurring early after the first injection with denosumab and two patients remained pain-free for the duration of the follow up period. In one patient with severe disease of the right lower limb, in addition to the

reported reduction in pain, local tenderness and skin temperature over the affected femur were also reduced. One patient reported no change in pain complaints while another experienced a transient increase in pain after initiation of treatment.

Safety aspects of treatment with denosumab

In two patients with MAS, treatment was associated with a mild decrease in serum phosphate concentrations to nadir values of 0.63 mmol/l (normal range: 0.8–1.5) while no decrease in serum calcium concentrations was observed but intact plasma PTH levels did increase to 11.2 and 20.7 pmol/l, respectively. Increases in the dose of vitamin D supplementation corrected these biochemical abnormalities. Except for the transient increase in bone pain in the patient described above, no other adverse events were observed in any of the patients and there was no incidence of symptomatic or asymptomatic hypocalcaemia.

DISCUSSION

Our findings from this retrospective study in 12 patients with mostly severe polyostotic fibrous dysplasia suggest that treatment with denosumab is effective, safe and well tolerated, and may provide an attractive option in patients who demonstrate resistance to treatment with bisphosphonates. Six-monthly intervals of 60 mg denosumab were not sufficient to sustain the initial effect on bone turnover markers, whereas bone turnover makers remained low in 3-monthly intervals of denosumab injections.

While there is currently no approved treatment of the disease, various regimens of different bisphosphonates are commonly used in the management of patients with fibrous dysplasia with skeletal complaints and/or high rates of bone turnover. Several open studies, mostly with pamidronate and olpadronate, have demonstrated reduction of bone turnover and bone pain in adults and children with fibrous dysplasia.[7,9-12,14,20] Some studies also reported beneficial radiological changes.[21-23] The only RCT study with daily oral alendronate in 6 monthly cycles for 2 years failed to demonstrate a significant beneficial effect compared to placebo.[13] However, in this study ALP failed to decrease, perhaps suggesting that higher doses or shorter interval schedules may have been required.[12] Despite success of bisphosphonate treatment, in some patients symptoms persist and bone turnover remains high necessitating alternative treatment options. The finding of upregulation of RANKL in skeletal lesions of patients with fibrous dysplasia provided the rationale for exploring the use of the

Table 11.3 Previous studies into denosumab treatment in fibrous dysplasia

Study	Number	Duration & cumulative dose of bisphosphonates	Mean follow-up (months)	Dose denosumab	Markers	Clinical outcome
Ganda and Seibel (2013)	2	8 years/45 mg zoledronic acid	8	60 mg	P1NP; uDPD; Ca; PO4; PTH	BTM's normalized in 1 month (P1NP 164* -> 15; uDPD 11.2 -> 3.5). Hip pain from 7/10 to 4/10.
		2.5 years/20 mg zoledronic acid	20	60 mg		Adverse event: asymptomatic hypocalcaemia and increased again after +- 3 months after injections.
Boyce et al. (2012)	1	1 year/unknown pamidronate	7	Start 1 mg/kg monthly; 0.25 mg/kg 3-monthly	P1NP; CTX; Ca; Phos;	BTM's normalized in 5 weeks (b-ALP 452->65; uDPD 15.3 -> 6.1). Pain not described. Adverse event: asymptomatic hypocalcaemia.
Eller-Vainicher et al. (2016)	1	> 9 years/81 mg pamidronate	20	60 mg	Osteocalcin, ALP (start 75), CTX	Dramatic reduction in BTM's (CTX 2000 dropped till 250; P1NP 1300 dropped till 100), pain -> no painkillers) and arrest tumor growth. Adverse event: hypophosphatemia and secondary hyperparathyroidism. Dramatic rebound in BTM's and severe hypercalcaemia.
Benhamou et al. (2014)	1	> 10 years/3600 mg pamidronate	35	60 mg	CTX	Pain response after a few hours and after 4 weeks normalization of BTM's (osteocalcin 55 to 10; ALP 75 to 42; BTX 1190 to 100). After 3 months accumulation of pain until next administration.

RANKL inhibitor denosumab in the management of severely affected patients with inadequate responses to bisphosphonates.[4]

Reports of 5 patients described early clinical improvements and dramatic reductions in biochemical markers of bone turnover with denosumab.[15-18] Different treatment schedules were used ranging from 120 mg once every 6 months to 60 mg one-monthly (Table 11.3).

We addressed the issue of denosumab dosing in our study and we showed that the dose of denosumab as used in the treatment of osteoporosis (60 mg once every 6 months) is insufficient for the treatment of patients with fibrous dysplasia. In contrast, 60 mg 3-monthly led to a significant decrease in the levels of bone turnover markers by more than 50% of baseline values leading to their normalization in a substantial number of patients, in contrast to failure of bisphosphonates to do so in these patients, some even after long term use and high cumulative doses. The relationship between baseline and final values of serum ALP activity indicated further that some patients, particularly those with extensive disease, may require higher doses in order to normalize bone turnover as illustrated in the patient who required 120 mg once every 3 months to achieve normalisation of bone turnover markers. It should be mentioned that in this patient 12 years of bisphosphonate treatment failed not only to normalize bone turnover markers but the lowest level ever achieved was still 4.5 times the upper limit of the reference range. Important for clinical practice is the observation that the decrease in biochemical markers of bone turnover reached usually their nadir values within the first 6 months of treatment with denosumab and, thus, a decision about changing the dose regimen can be made early in the course of treatment. Patients with high SBS scores responded to the 60 mg 3 monthly as well therefore we would suggest this as a starting regiment, which can be tailored to the individual patient.

Remarkable was the clinical response with reduction of bone pain very early after the start of treatment in all but one of our patients, as also reported in 4/5 previously described patients.[15-18] With the 3-monthly treatment regimen, the effect on pain persisted for the whole observation period up to 24 months. Our protocol with blood sampling every 3 months does not allow any conclusion about an association between the decrease of bone resorption and the improvement of bone symptoms. Earlier, pharmacodynamic studies of denosumab have shown dramatic reductions of serum CTX within days after a subcutaneous injection and there is no reason to believe that the response would be different in patients with fibrous dysplasia.[24,25] This remains, however, to be shown.

The clinical profile of our patients is similar to that described in the literature as most the likely to show an inadequate response to bisphosphonates because of severity of disease; 11 patients had polyostotic disease, 4 of whom had MAS, FGF23 was increased in 7/12 patients and the majority had a high skeletal burden score.[19,26] The latter has been recently identified by our group as the only prognostic factor influencing the outcome of bisphosphonate therapy.[12] Our results from this study demonstrated however that none of these factors influenced the response of the patients to denosumab, including the skeletal burden score.

We believe that the data presented in this case-series together with those of previous case reports provide sufficient rationale for the design of a controlled study on the efficacy and tolerability of denosumab in patients with severe fibrous dysplasia and inadequate response to bisphosphonates for whom no alternative treatment is currently available. Treatment was well tolerated and except for the non-symptomatic changes in phosphate and PTH which could be easily addressed with increasing vitamin D supplements.

An important question that this study does not address is the duration of the therapy and the management of patients once a clinical and biochemical remission is achieved. It is well known that the action of denosumab, in contrast to that of the bisphosphonates, is quickly reversible following discontinuation of treatment with transient increases in BTM above pretreatment levels, described also as "rebound phenomenon" that is thought to be due to a rapid, synchronous upregulation of osteoclastogenesis as also reported in the treatment of a child with fibrous dysplasia.[15,27] This response is intriguing because it was recently reported that patients treated with bisphosphonates followed by denosumab do not show a rebound of BTM following discontinuation of the latter.[28] Before additional data from a controlled study become available, physicians using denosumab to treat patients with fibrous dysplasia should be aware of this potential reaction to stopping denosumab treatment and emphasize treatment adherence. However the results of this study show that in certain patient groups denosumab may provide a well-tolerated alternative in patients resistant to treatment with bisphosphonates.

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FIBREUZE DYSPLASIE
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Summary and general discussion

Chapter 12

Summary of this thesis

Fibrous dysplasia (FD) is a rare and ubiquitous disorder, with a very wide clinical spectrum, not only related to the different distribution and evolution of skeletal lesions over time, and the variable related symptoms and impairment in function and quality of life, but also to the wide potential range of extra-skeletal manifestations possibly present in these patients: no two fibrous dysplasia patients are alike. This thesis addresses the heterogeneity of FD, grouping the study of interesting and important topics and issues related to this disorder in four parts: Pain and quality of life; Extra-skeletal manifestations, Surgical treatment and Medical treatment.

Part I: Pain and quality of life in fibrous dysplasia

Part I of this thesis addresses the consequences of having fibrous dysplasia on various aspects of quality of life. In **Chapter 2** FD-associated pain symptoms were evaluated in a collaborative study between the Medical University of Graz and the Leiden University Medical Center. A total of 197 patients with FD completed a survey about the presence and severity of pain at the site of their FD lesions. Mean reported pain score on a scale of 1–10 was 1.9 in the whole group and 4.1 in patients who reported having pain. The severity of pain was significantly higher in patients with lesions of the lower extremities or ribs compared to patients with lesions of the upper extremity or with craniofacial lesions. The presence of pain did not significantly differ between localizations of FD lesions. Severe subtypes of FD (polyostotic/McCune Albright) were associated with both presence and severity of pain. Although less than 50% of patients with FD reported pain at the site of their lesions, pain represented a major clinical manifestation of the disorder, also in limited monostotic disease. These results provide new insights in our appreciation of pain in FD.

In **Chapter 3** quality of life and pain levels were evaluated in 97 patients with FD, using the Short Form-36 and the Brief Pain Inventory questionnaires. Data were compared with those of the general Dutch population. Fibrous dysplasia patients had significantly lower quality of life outcome scores compared to the general Dutch population in all tested domains of the Short Form-36 except for the "Mental health" and the "Role emotional" domains. Severe type of FD was associated with more impaired quality of life outcomes. There was no significant difference in Brief Pain Inventory domains between FD subtypes. Quality of life was lower in patients with high skeletal disease burden, as reflected by high skeletal burden scores and high levels of the bone turnover marker P1NP. We demonstrated impairments in quality of life across the wide spectrum of FD, which importantly also includes its milder monostotic forms. These findings hold significant clinical implications as they draw attention to the clinically

unmet need to address Quality of Life issues in the management of patients with all types of FD, including its monostotic forms.

In **Chapter 4**, Illness Perceptions were studied in our cohort of FD patients. Illness perceptions are patients' cognitions and emotions about their illness and its treatment, which may importantly impact on Quality of Life. Illness perceptions were compared between patients with FD and those with other disorders; factors associated with illness perceptions were identified and their relationship with Quality of Life evaluated. A difference in illness perceptions was observed between FD subtypes and interestingly, patients with craniofacial lesions reported perceiving more consequences of their illness than those with other FD localizations. High skeletal burden score was associated with perceiving more negative consequences of the disease and attributing the cause of FD to psychological factors. High FGF-23 levels were associated with attributing more symptoms to the disease and perceiving more consequences. The majority of IPQ-R domains were associated with impairments in Quality of Life. Our results demonstrate that in patients with FD illness perceptions importantly relate to Quality of Life, differ from those in patients with other disorders, and are associated with disease severity. Identifying and addressing maladaptive illness perceptions may improve the quality of life in patients with FD.

Part II: Extra-skeletal manifestations of fibrous dysplasia

Part II of this thesis addresses extraskeletal manifestations in patients with FD, which are important to screen for the full evaluation of the spectrum of the disorder. Intramuscular myxomas in the context of Mazabraud's syndrome represent a rare, but one of the most well-known non-endocrinological manifestations of *GNAS*-mutations outside the skeleton in FD. In **Chapter 5**, the clinical course, treatment outcomes and role of *GNAS*-mutations was evaluated in patients with the Mazabraud's syndrome in a multi-centre study conducted under the auspices of the European Musculo-skeletal Oncology Society (EMSOS). In a combined cohort of 32 patients a prevalence of Mazabraud's syndrome of 2.2% was observed among all types of FD patients, including those with monostotic disease. However, this may still be an underestimate of the true prevalence of myxomas in FD due to the often-asymptomatic nature of intramuscular myxomas. Patients with disproportional complaints or persistent resistance to treatment of pain symptoms should therefore undergo further evaluation, preferably with MR-imaging as these symptoms might be soft tissue related. We also demonstrated that although surgical resection results in satisfactory outcomes, a quarter of the patients require further surgery despite

free resection margins. High cellularity of the myxomas was identified as a risk factor for recurrence after resection. Finally, *GNAS*-mutations were identified in 83% of the resected myxomas tested, emphasising the shared origin of FD and myxomas and the fact that the *GNAS*-mutation is capable of causing lesions outside the skeleton in patients with FD. Specific attention was also reserved for the role of *GNAS*-mutations in **Chapter 6**, addressing the finding of an increased risk in women with FD to develop breast cancer. In a combined study with the National Institutes of Health in Bethesda (US), the incidence of breast cancer was shown to be higher in women with FD compared to the incidence in the respective national populations of the Netherlands and the US, and women who developed breast cancer were shown to develop the malignancy at a younger age than that of the general population. These findings were confirmed by data from the National Dutch Pathology Registry. Data from this study further showed that the risk of developing breast cancer in FD was especially increased in women with FD lesions of the thoracic region, in the proximity of the breast. This was emphasized by the finding of a *GNAS*-mutation in 44% of the breast cancers studied, while these mutations are normally found in less then 1% of breast cancers in the general population. Although this is the first study addressing the prevalence of breast cancer in FD, we believe our results to be substantial enough to recommend early screening for breast cancer in women with FD, especially in those with thoracic FD lesions.

Part III: Surgical treatment of fibrous dysplasia

In **Chapter 7** the role of allogeneic strut grafts was evaluated in patients with FD lesions of the proximal femur. In a series of 28 patients we showed that revision surgery was indicated in 46% of the patients, mainly because of resorption of the graft. However, we were able to identify specific risk factors for failure of allogeneic graft surgery, including a preoperative fracture of the proximal femur and insufficient proximal anchoring of the graft in healthy bone. In patients without these risk factors, allogeneic strut grafting offers a viable option with good outcomes. Patients who do have risk factors for failure should be treated with osteosynthesis instead of grafting. This was further evaluated in **Chapter 8**, where the outcomes of intramedullary nailing and angled blade plates were evaluated in 32 patients from a combined cohort of the Leiden University Medical Center and the Medical University of Graz. Revision-free survival was 72% after a median follow-up of 4.1 years, and only two patients had structural failure, both having been treated with an angled blade plate and having developed a fracture below the angled blade plate in the area of an FD lesion. Seven patients with complaints of the iliotibial tract had their angled blade plates removed without further complications.

The majority of the patients showed good outcomes regarding levels of pain, function and femoral-neck-shaft-angle. It was therefore concluded that FD of the proximal femur can be adequately and safely treated with angled blade plates or intramedullary nails, provided that these are used according to specific characteristics of the individual patient. On the basis of these results combined with data from published literature, an individualized, patient-tailored approach to the surgical management of FD of the proximal femur was proposed taking into account different treatment modalities and associated factors potentially playing a role in the outcome of the different implants. In the last chapter on the surgical management of FD, **Chapter 9**, findings from a study of 50 patients with FD lesions of the humerus are reported. Data showed that although FD of the humerus generally runs a mild course, over half of the patients had sustained a fracture. Interestingly, cystic degeneration, and not the size of the lesion, was identified as a risk factor for fractures. As cystic degeneration of FD appears to have a direct effect on its course, further evaluation of lesions at this site should be performed using MR-imaging, as cysts cannot be reliably evaluated on conventional radiographs. We stated that pathological fractures of the humerus may be safely treated conservatively in FD, as we demonstrated good outcomes in two thirds of patients who had conservative treatment of these fractures. Outcome of surgical treatment in an attempt to decrease pain or stabilize impending fractures might benefit from the use of cortical grafting instead of cancellous bone grafting, although definitive recommendations on the best surgical interventions should await results of future studies conducted in larger cohorts.

Part IV: Medical treatment of fibrous dysplasia

In **Chapter 10** the results of long-term treatment of patients with polyostotic FD with or without additional endocrinopathies in the context of McCune-Albright syndrome (MAS) with bisphosphonates are presented. Outcomes of treatment with these agents including biochemical outcome (change in bone turnover markers) and clinical outcome (pain reduction) of bisphosphonate therapy were evaluated in 11 patients with MAS and 30 patients with polyostotic FD after a median duration of treatment of 6 years. Twenty-four of 30 patients with polyostotic disease (80%) demonstrated a complete clinical and biochemical response within a year of starting treatment, compared to only four of 11 MAS patients (36%). There were no non-responders. In the whole group, FGF-23, total ALP, P1NP, and CTX positively correlated with skeletal burden scores, which was the only significant risk factor for an incomplete response to bisphosphonate therapy. Our data suggest a beneficial and safe outcome of long-term bisphosphonate therapy in the majority of patients with polyostotic FD, although

response to therapy was limited by the higher skeletal disease burden in MAS patients. In the population studied, the only identified prognostic factor that influenced the outcome of bisphosphonate therapy was a high skeletal burden score, suggesting that in more severely affected patients, the effect of bisphosphonates might be insufficient. In **Chapter 11**, treatment outcomes of denosumab, a monoclonal antibody to RANK-L were evaluated in 12 bisphosphonate-refractory patients with a median follow-up of 14.5 months. This is the first report of denosumab outcomes in a series of patients with FD. Denosumab was administered by subcutaneous injections of 60 mg 3–6 monthly on the basis of high bone turnover with associated complaints of pain. Patients with a 3-monthly treatment schedule had significantly more decrease in bone turnover markers compared to patients on a 6-monthly treatment schedule. BTM normalized in 8 of the 12 patients, 5 of whom had not reached normalisation of BTM after long-term treatment with bisphosphonates. Denosumab was well tolerated and no side effects were reported. Our results show that denosumab may provide a well-tolerated and effective therapeutic option in patients with severe FD refractory to treatment with bisphosphonates. Three-monthly 60 mg dosage schemes appear to have the most promising effect on bone turnover markers and pain.

Chapter 13

General discussion

The findings from this thesis were instrumental in shedding new light on various important aspects of the rare bone disease fibrous dysplasia (FD). The role of *GNAS*-mutations in the development of pathologic changes in tissues other than the skeleton was explored, current treatment modalities, both medical and surgical, were evaluated and discussed, and the impact of fibrous dysplasia on the quality of life of patients affected with this disorder was systematically addressed. This Discussion chapter addresses remaining knowledge gaps, new questions generated by our findings, as well as future research perspectives.

Pitfalls and challenges in the diagnosis of fibrous dysplasia

An important challenge in the management of FD is the avoidance of delayed diagnosis. As nearly universal in the case of rare diseases, there is a lack of knowledge about the clinical presentation of fibrous dysplasia among non-specialists in the field of bone diseases, and among general practitioners. This often leads to problems in recognizing the manifestations of the disease resulting in diagnostic delay.[1] The wide clinical spectrum of fibrous dysplasia and heterogeneity of disease manifestations represent an even greater challenge for early diagnosis.[1-4] Early recognition of fibrous dysplasia in primary care and in secondary non-bone specialised care institutions may be very difficult. Case examples are that of an elderly patient with a pathological fracture of the humerus, but without ever having had complaints; a young patient with facial deformities, precocious puberty and GH-excess in the context of McCune-Albright syndrome, or a patient with a shepherd's crook deformity of the femur and severe mobility problems which all have fibrous dysplasia but associated with very different clinical presentations. In order to prevent diagnostic delay, specialist centres should aim at increasing awareness not only among general practitioners which are likely to be the first health care professionals to see the patient at presentation, but also among colleagues not familiar with rare bone diseases such as endocrinologists, rheumatologists, ENT surgeons, ophthalmologists and orthopaedic surgeons. Information about fibrous dysplasia should be made available and be easily accessible to both treating physicians and patients on reliable websites in order to facilitate a shorter diagnostic process. Guidelines should also be developed for further investigation of the extent and severity of the skeletal and non-skeletal manifestations of FD, and for best standard of care in its management.

Another pitfall in the early diagnosis of fibrous dysplasia is the variation in diagnostic approach between institutions, and also between different specialisms. Fibrous dysplasia represents the multidisciplinary disease par excellence, but it remains to

date often diagnosed and treated by a single medical specialty. Historically, fibrous dysplasia has been diagnosed on the basis of clinical and radiographic features, but today we have access to a wide range of diagnostic tools to aide this process. Clinical presentation remains, however, the most important tool for diagnosis, with the classical skeletal manifestations of fibrous dysplasia consisting of pain at the site of a lesion, deformity of affected bones and pathological fractures. In case of the McCune-Albright syndrome, these symptoms are usually more severe and associated with endocrinological abnormalities such as precocious puberty, GH-excess or hyperthyroidism. Next to evaluation of clinical characteristics, conventional X-rays should be evaluated for the characteristic features of fibrous dysplasia such as a ground glass effect, endosteal scalloping, well-circumscribed borders, possible cortical thinning and absent periosteal reaction, and the pathognomonic shepherd's crook deformity in severe cases of fibrous dysplasia of the proximal femur.[3-6] Evolution of fibrous dysplasia lesions has been reported on radiographic imaging, with lesions observed to become more sclerotic and less homogenous over time.[4,7] A technetium-99 skeletal scintigraphy should be performed to establish the extent and type of FD (monostotic vs. polyostotic, and craniofacial involvement), and skeletal burden scores (SBS) should be calculated.[8-10] The use F-NaF bone PET/CT scanning appears promising,[11-13] with possible advantages over technetium-99 skeletal scintigraphy including a more quantitative evaluation of the activity of fibrous dysplasia lesions and readily available 3D images that may aid in determining fracture risk and help with planning of surgical interventions. The evaluation of the potential of F-NaF bone PET/CT scanning in fibrous dysplasia represents an interesting topic for future research in this field.

Next to plain radiography and whole body scan imaging, computed tomography scans (CT-scans) of FD lesion(s) can be a helpful tool for orthopaedic surgeons to plan an intervention and for the development of a custom-made implant as demonstrated in Chapter 5 of this Thesis.

Magnetic Resonance scanning (MR-scanning) is also valuable in the evaluation of fibrous dysplasia.[14-16] It has been shown in this thesis that cystic changes represent a risk factor for fractures in FD of the humerus, thus providing the rationale for an increased role for MR-imaging in FD at this localisation as cystic changes are most sensitively assessed using MR-imaging. The advantage of MR-scans over conventional radiographs or CT-scans is their detailed imaging of soft tissue. MR-scans are thus also indicated in case of suspicion for intramuscular myxomas in the context of Mazabraud's syndrome, especially in the presence of unexplained complaints of the upper leg.[17]

Both CT-and MR-scans may be used to assess a rare possible malignant transformation of an FD lesion.[18] Both CT- and MRI-scans are important imaging techniques to evaluate the extent of affected bone in patients with craniofacial FD, as well as to assess the risk of compression of cranial nerves.[19,20]

Currently, bone markers such as ALP, P1NP and CTX are mostly used to monitor disease activity and response to medical therapy in a variety of bone diseases, including osteoporosis. It would be of interest to investigate a potential role for these markers in the diagnosis and differential diagnosis of FD, for instance simple bone cysts or a Paget lesion, which may present with similar radiographic features as an FD lesion.[21-24] Serum levels of FGF-23, that are often increased in polyostotic fibrous dysplasia, and shown to be related to extent and severity of FD lesions, could also help to discriminate fibrous dysplasia from other bone disorders, although little is so far known about levels of FGF-23 in simple bone cysts, morbus Paget or osteosarcomas.[25,26]

Next to bone markers, serum levels of calcium, phosphate, vitamin D, and intact PTH should be determined in patients with FD as these are known to be associated with mineralisation defects and are at risk of further impairment in mineralisation of bone in case of vitamin D deficiency or hypophosphatemia, which would in turn increase the risk of pain, deformity and fracture.[27,28] Extraskeletal manifestations of FD should be evaluated by an endocrinology screen in which serum levels of growth hormone and IGF-1 (especially in craniofacial FD), prolactin, TSH, cortisol are elevated. Serum levels of FGF-23 and phosphate should also be determined and TMP/GFR calculated to screen for possible renal phosphate wasting. Non-endocrine manifestations of FD, such as intramuscular myxomas, should be screened for on the basis of symptoms. Lastly, an increased risk of developing breast cancer in relatively young women with fibrous dysplasia was demonstrated in this thesis, as described in Chapter 3. On the basis of these findings early screening for breast cancer from the age of 35 was recommended in women with FD, particularly those with thoracic FD lesions.

In case the diagnosis of FD is still in doubt, especially in case of a possible malignant bone tumour, it is advisable to perform a biopsy of the lesion with additional *GNAS*-mutation analysis.[29-31] It is important to realize, however, that a *GNAS*-mutation might not be identified in all patients with FD, as identification rates vary widely, even in patients with evident polyostotic distribution of FD lesions.[32-34] These false negative results might be at least partially related to the mosaic distribution of the GNAS-mutation, which can lead to sampling errors. However, an important further factor for false negative results is the type of mutation analysis conducted on the

pathologic specimens. Next-generation sequencing is thus more likely to accurately identify a mutation in mosaic disorders than Sanger sequencing, and would provide more information about the frequency of the mutation in the sampled region. The process of decalcification of the samples also appears to play a role in the reliability of the outcomes of genetic analysis in FD.[35]

Impaired Quality of Life in fibrous dysplasia

The wide clinical spectrum in FD translates in a wide spectrum of impairment in QoL among patients with FD. Although we have shown that extensive disease and the presence of endocrinopathies are associated with more severe impairment in quality of life and negative illness perceptions, it is critical to realize that a number of additional factors may play a negative role on QoL in an FD patient.

Definition of disease activity in FD

One of the as yet to be unravelled aspect of FD is how to define disease activity. Pain is believed to be associated with active disease and it has been suggested that the latter may be associated with increased bone turnover as identified by increased circulating levels of bone turnover markers, but this premise remains to be conclusively established. Notwithstanding, the presence of pain symptoms and/or increased bone turnover markers have been used as indications for treatment with antiresorptive agents, in the hope that decreasing bone turnover would be associated with a decrease in pain symptoms as a result of decreasing FD disease activity. However, in two of our studies addressing pain in patients with FD (Chapter 9 and 10), none of the bone markers studied was associated with pain levels, and this was also true for serum levels of FGF-23. This finding suggests that a metabolically active lesion is not necessarily painful. It has also been suggested that some radiographic features may suggest activity or quiescence of a fibrous dysplasia lesion. Sclerotic rimming is thus believed to reflect quiescence of a lesion, typically in older patients with an incidental diagnosis of FD, whereas cortical thinning and a ground glass appearance are believed to be associated with active disease and also with a risk of developing deformities and pathological fractures.[4,7,36] Whereas extent and metabolic activity of FD lesions can be assessed by skeletal scintigraphy, activity of these lesions does not appear to change significantly over time, even after intensive treatment with antiresorptive agents and significant decreases in bone turnover, precluding the use of this imaging technique for monitoring changes in disease activity. The ability of NaF-PET scans to demonstrate reliable changes following treatment remains to be established.

The need for a multidisciplinary approach in the management of fibrous dysplasia

In this thesis the benefits and limitations of a number of available surgical and medical options for the treatment of FD have been discussed. The surgical treatment of FD has historically focused on lesions of the lower, weight-bearing extremities as these have the higher likelihood of being associated with pain, deformities and (recurrent) fractures, with resulting impairment of function and associated impairment in quality of life.[37-39] In contrast to fractures of the lower extremities, fractures of the upper extremities tend to be more forgiving and heal properly in the majority of cases after conservative treatment with immobilization of the fracture site with a cast or sling as has demonstrated in Chapter 6.[38] In Chapter 5 of this thesis an individualized, patient-tailored approach is proposed for the management of FD of the proximal femur, based on our own experience and that reported in published literature. The proposed algorithm should be considered as best clinical practice surgical treatment strategy based on our clinical experience and that of others, rather than being a strict guideline on the basis of hard evidence, which remains to date rather scarce. Well-established (international) studies conducted in a large number of patients and addressing outcome of various available interventions are required to confirm the validity of the proposed algorithm in the management of FD of the proximal femur. Although surgery has been the main treatment option for patients with FD until the early nineties, medical treatment options using antiresorptive agents such as bisphosphonates and more recently denosumab and tocilizumab are gaining increasing popularity, although opinions are still divided on indications for treatment and type, optimal dose and interval of use of these agents, mainly as existing studies have largely been conducted in small and heterogenic cohorts, and relatively low administered doses, raising questions about the reliability of reported outcomes and the implication of these results for current clinical practice.[21-24,40-44] In Chapter 7 of this thesis treatment with mainly the oral bisphosphonate olpadronate was evaluated in patients with polyostotic FD and various disease severity and activity as evaluated by serum levels of bone turnover markers and calculated skeletal burden score (SBS). Our data from this study suggest that whereas the majority of patients responded to a certain extent to treatment with bisphosphonates, a high SBS was associated with relative resistance to treatment. Interestingly, the majority of patients who had an incomplete response to long-term treatment with bisphosphonates, demonstrated a surprisingly swift and complete response to treatment with the RANK-Ligand antibody denosumab with normalisation of bone turnover markers and disappearance or significant decrease in pain levels as reported in Chapter 8. No side-effects were observed with treatment with either bisphosphonates or up to 1 year treatment with

denosumab. Our findings suggest that patients with symptomatic FD and increased bone turnover may be safely treated with bisphosphonates, also in the long-term with a potential beneficial switch to three-monthly denosumab injections in those with an unsatisfactory response to at least one year of treatment with appropriate doses of bisphosphonates. Caution should be however, exerted with the use of denosumab, based on recent reports of deleterious rebound effects on discontinuation of treatment in patients with osteoporosis as well in 2 cases of FD.[24,45-47]

Another suggested therapeutic agent in the management of symptomatic FD is tocilizumab, an inhibitor of IL-6, an interleukin that has been reported to be one of the driving factors for increased osteoclastogenesis in FD.[48] Apart from a single case report there are to date no reports on outcomes of treatment with tocilizumab in patients with FD.[44] Future studies are required to establish the role of each of these antiresorptive agents in the management of patients with FD, particularly addressing specific hard outcome measures such as prevention of progression of lesions, deformity and fractures, but also control of pain and improvement of function and quality of life.

In this thesis we addressed the use of both medical and surgical options but did not specifically look at the outcomes of a combined approach, which might be a particularly interesting and to date unexplored field in the management of fibrous dysplasia. As shown in Chapter 4 and 5, recurrence of activity of FD lesions is responsible for failure of a number of surgical interventions, especially relating to bone grafting interventions where grafts partially or fully resorb after implantation in the pathological FD tissue. It could be speculated that pre- and postoperative treatment with antiresorptive agents may improve outcomes of these procedures by decreasing the activity of FD lesions thus precluding recurrence of curetted lesions or resorption of implanted bone grafts. Although not specifically studied in FD, bisphosphonates have been shown to be able to reduce resorption rates of bone grafts in basic studies.[49,50] A hypothetical downside of combining bone grafting with antiresorptive treatment might be that bone grafts might take longer to anchor in healthy bone as a result of the decreased bone turnover, although this has not been studied in FD.[51,52] Lowering recurrence and resorption rates could improve the outcomes of bone graft surgery in FD, allowing for a single biological reconstruction instead of repeatedly undergoing surgery, as is now often the case in patients with severe lesions of the lower extremities, particularly of the proximal femur. Because antiresorptives agents have been suggested to have a thickening effect on the often thinned cortex of FD affected long bones, the outcome of metallic implants might also potentially improve by pre- and post-operative treatment with antiresorptive agents by decreasing the risk of (repetitive) fractures or breaking out of implants.[53,54]

Data on outcome of combined medical and surgical treatment are very scarce to non-existent in FD. One of the major reasons for the lack of studies addressing combined treatment options is probably the heterogeneity of FD phenotypes, the different types of surgery performed and the variety of medical agents administered. This makes it nearly impossible to draw any firm conclusions regarding the possible synergetic effect of antiresorptive treatment with surgical procedures on various outcomes, including pain and function, using retrospective data. Prospective studies are thus warranted but unfortunately difficult to perform in the currently sized cohorts due to the rarity of FD, especially as you would want to specifically look at subgroups of patients, surgical interventions and medication used. International collaboration would provide a basis to perform these much-needed studies to further improve and individualize the various treatment options in patients with FD.

Future perspectives in the management of fibrous dysplasia

More and more studies are now focusing on unravelling the pathophysiologic mechanism of the various manifestations of FD, aiming at developing novel approaches for its treatment with the ultimate goal being the definitive cure of the disease. Many of the limitations in current treatment options are due to our lack of full understanding the pathophysiology of FD. In spite of the discovery of *GNAS*-mutations as the cause for the development of FD, we do not as yet fully understand the mechanism by which these mutations lead to the different pathognomonic features of FD, nor do we comprehend what exactly causes the wide differences between FD phenotypes.[29,30,55,56] An example of this is our failure to understand why full excision of monostotic lesions is associated in almost all cases with recurrence of the lesions, despite securing free resection margins, suggesting that even very few residual undetected GNAS-mutated bone cells are capable of resulting in recurrence of an FD lesion.[3,57] A possible explanation for this phenomenon might lie in the mosaic pattern of the causative *GNAS*-mutation. It would be interesting to study this hypothesis by performing genetic analysis of bone biopsies of FD lesions sampled at different distances from the radiographic and histological visible margins of an FD lesion and determining the frequency of the *GNAS*-mutation in these samples using Next-Generation-Sequencing. A promising new FD mouse models could aid in answering these questions.[58,59] If we could determine what kind of resection margin would be appropriate, we could hypothetically be able to cure monostotic patients from FD by resecting the whole of FD affected bone, although we have to bear in mind that a large resection might have serious disadvantages depending on what reconstruction is possible after resection. Another interesting starting point in trying to develop a

cure for FD is the notion that FD can be seen as a disease of pluripotent cells mutating during embryonic development, in other words considering FD as a stem cell disease.[60] This means that the disorder could theoretically be systemically treated with a form of genetic therapy by silencing the mutated allele.[61] Ex vivo experiments have already demonstrated that it is possible to revert the FD phenotype with the use of lentivirally-expressed shRNAs.[62] However, in vivo experiments, let alone implementation of this kind of therapy in clinical practice are currently precluded by the lack of possibilities to restrict delivery of healthy stem cells to specific skeletal sites.[61]

Another potentially attractive option for the treatment of fibrous dysplasia might be local injection of anti-resorptive agents. Hypothetically, higher doses of these agents might be locally administered without an increased risk for systemic side effects. The possibility of injecting local agents has so far only been explored in cystic degeneration of humeral FD lesions, but might potentially be interesting as future treatment option of symptomatic lesions in other anatomical localisations.

While awaiting the discovery of a definitive cure for FD, which may take decades, we should continue to further explore the added benefits of a multidisciplinary approach in the management of FD.

Fibrous dysplasia as a systemic disease

Historically, FD was first described as a disease of bone. Whereas still mainly considered to be a rare disease of bone, more systemic effects of the GNAS mutation are represented in the extraskeletal manifestations of patients with FD as endocrinopathies in the context of the McCune-Albright syndrome (less than 5% of all patients with FD) or intramuscular myxomas in the context of Mazabraud's syndrome (less than 1% of all patients with FD).[4,63] Interestingly, the *GNAS*-mutation that is responsible for this disease is not only found in the bony lesions of patients with FD, but also in the thyroid tissue of patients that develop associated hyperthyroidism, in the pituitary tissue of patients with associated GH-excess or prolactin excess and in associated intramuscular myxomas.[29,64-67] It is of note that in the absence of FD, solitary pituitary adenomas, solitary thyroid adenomas and solitary intramuscular myxomas may also carry *GNAS*-mutations.[56,68-70] These findings suggest that *GNAS*-mutations do not only affect skeletal tissue but also, albeit to a lower extent, other tissue types. This might be explained by the function of the *GNAS* complex locus and its encoding of the stimulatory G protein (Gsα). Gsα plays a key role in the osteoblastic lineage and in the differentiation of bone marrow stromal cells, providing the explanation for the formation of FD lesions by

stimulation of Gsα and therefore cAMP, resulting in enhanced commitment of stromal cells but also an inhibition of their further differentiation into osteoblasts.[71,72] Next to skeletal tissue, Gsα is expressed in a large number of tissues from ectodermal, endodermal and mesodermal origin. These tissue types include the proximal renal tubules, neonatal brown fat, thyroid tissue, gonads and the paraventricular nucleus of the hypothalamus and pituitary.[64,72] The majority of these tissue types have been described as possibly malfunctioning in patients with McCune-Albright syndrome.[67]

With this knowledge we can probably explain why patients with a wide distribution of GNAS-mutations are at risk of developing extraskeletal manifestations, as they have the increased risk of these mutations being also present in tissue types other than bone. It is thus not surprising that intramuscular myxomas in the context of Mazabraud's syndrome are often found in patients with McCune-Albright syndrome, or that we found an increased risk of developing breast cancer in women with polyostotic FD, with lesions at thoracic sites.[73] It is however essential to realize that this hypothesis does not preclude the possibility of extraskeletal manifestations occurring in patients with monostotic disease. The finding of Mazabraud's syndrome related myxomas in patients with monostotic fibrous dysplasia underlines this, and it is likely that this also applies for other extraskeletal manifestations such as GH-excess, precocious puberty or even breast cancer. This also raises the possibility of the detection of (many) more *GNAS*-linked extraskeletal manifestations of FD, in the coming years, as have new extraskeletal manifestations such as thyroid carcinoma and in this thesis breast cancer been linked to FD in recent years.[66] It is therefore essential that we change the general perspective of FD from being only a disorder of bone to a broader view that the skeletal manifestations of FD may represent only part of the systemic manifestations of *GNAS* mutations and that these systematic manifestations may not be precluded by the monostotic or less severe forms of skeletal disease.

Conclusion

Fibrous dysplasia is a heterogeneous genetic but non-inherited rare bone disorder that is caused by the mosaic distribution of a postzygotic mutation of the *GNAS*-gene. Although its predominant features are the characteristic bony lesions, there is a wide spectrum of FD phenotypes that include a continuously expanding list of extraskeletal manifestations, underlining the systemic aspect of this *GNAS*-related disease. In line with its wide range of phenotypes, FD is associated with a wide clinical spectrum of symptoms, with pain, deformity, and fractures, leading not only to decreased mobility and function but also significantly impairing Quality of Life. Available surgical and

medical therapeutic options should be delivered in a patient-tailored, individualized manner, with full knowledge of their limitations and complications to ensure their most optimal outcome of the various modalities used, singly or in combination. FD is often a multisystemic disease, particularly its most severe forms, so that a multidisciplinary approach is mandatory to achieve the best life-long outcomes. The rarity of the disease dictates that all health care professionals involved in the care of FD should invest in international collaboration to provide the necessary power of numbers that can only be provided from large multicentre studies to address the several unanswered questions posed by this ubiquitous disorder, and fulfil the clinical unmet need of developing best clinical practice guidelines for its management.

Key findings

- Fibrous dysplasia is a systemic, *GNAS*-related disease, with characteristic bony lesions as its key feature.
- Pain symptoms are common in fibrous dysplasia, particularly in lesions of the weight-bearing lower extremities and ribs and generally in the more severe types of fibrous dysplasia.
- Quality of Life is impaired throughout the wide spectrum of fibrous dysplasia, including its milder forms, with severity of impairment being related to disease extent and severity as evaluated on skeletal scintigraphy by skeletal burden scores.
- Illness perceptions are altered leading to impaired Quality of Life in patients with fibrous dysplasia.
- Mazabraud's syndrome is more prevalent than previously suggested, and surgical resection of symptomatic myxomas has a good functional outcome, although recurrence may occur.
- Women with FD have an increased risk of developing breast cancer at a younger age than the general population, particularly those with thoracic FD lesions.
- Fibrous dysplasia lesions of the humerus with cystic deformation are associated with increased fracture risk, although these fractures can be safely treated conservatively in the majority of the patients.
- Cortical allografts, angled-blade plates and intramedullary nails are adequate and safe treatment options for fibrous dysplasia of the proximal femur, provided they are tailor-designed according to individual patient specifications.
- Long-term bisphosphonate therapy is associated with beneficial and safe outcomes in the majority of patients with polyostotic fibrous dysplasia, although response to therapy is limited by the higher skeletal disease burden in the more severely affected patients, particularly those with McCune-Albright syndrome.

- In patients with incomplete response or resistance to long-treatment with bisphosphonates, treatment with denosumab is associated good clinical and functional outcomes in the majority of the patients.
- FD should be treated by multidisciplinary teams in dedicated centres ideally collaborating with national and international centres with expertise in this disorder and other rare bone diseases.

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Chapter 14

Fibreuze dysplasie: een heterogeen ziektebeeld

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DAMES EN HEREN,

Fibreuze dysplasie (FD) is een zeldzame chronische aandoening waarbij fibreus weefsel wordt gevormd in één of meerdere botten. Hoewel sommige patiënten nooit klachten zullen krijgen, zijn er andere die al op jonge leeftijd uitgebreide morbiditeit hebben. De ziekte wordt vaak pas laat herkend, terwijl het risico op ernstige deformiteiten en fracturen juist in een vroeg stadium nog beperkt kan worden. Aan de hand van 3 casussen laten wij de diversiteit in het klinisch beeld van FD zien.

Patiënt A, een sportieve, 46-jarige vrouw met een blanco medische voorgeschiedenis, werd vanuit een perifeer centrum verwezen naar de afdeling Orthopedie vanwege sinds 1 jaar bestaande progressieve pijn in de linker heup, die verergerde bij hardlopen. Stoppen met hardlopen en fysiotherapie hadden geen effect gehad op de pijn. De orthopedisch chirurg aldaar vermoedde een chondroïde afwijking van het linker femur en besloot patiënte door een specialistisch centrum te laten beoordelen.

Bij lichamelijk onderzoek zagen wij een niet-zieke vrouw met geringe drukpijn over de trochanter major. De heupfuncties waren niet-afwijkend. Laboratoriumonderzoek liet een ongestoorde botombouw zien (Tabel 14.1). Op basis van conventioneel röntgenonderzoek en MRI stelden we de diagnose 'FD' (Fig. 14.1). Op een skeletscintigram was een licht verhoogde botactiviteit zichtbaar ter hoogte van de afwijking in het linker femur; in de rest van het skelet waren geen afwijkingen aanwezig. Het ging hier dus om een monostotische vorm van FD.

Op basis van het klinisch beeld, de ongestoorde botombouw en het ontbreken van een duidelijk verhoogde botactiviteit op het skeletscintigram concludeerde

Tabel 14.1 Laboratoriumuitslagen van patiënt A, B en C*

Uitslag	Patiënt A	Patiënt B	Patiënt C	Referentiewaarde
Alkalische fosfatase	42	123	197	0–98 U/l
P1NP	27	101	333	< 59 ng/ml
Anorganisch fosfaat	1.30	1.50	1.03	0.90–1.50 mmol/l
Parathyreoïdhormoon	1.9	9.0	2.3	0.7–8.0 pmol/l
25-hydroxyvitamine D	73	29	49	50–240 nmol/l

* Verhoogde waarden zijn weergegeven in rood. Verhoogde waarden van alkalische fosfatase en procollageen-type 1-N-'terminal'-propeptide (P1NP, marker voor botaanmaak) duiden op een verhoogde botombouw. Hierbij moeten ook de waarden van anorganisch fosfaat, parathyreoïdhormoon en vitamine D bepaald worden, omdat verstoringen hierin ook kunnen leiden tot een verhoogde botombouw.

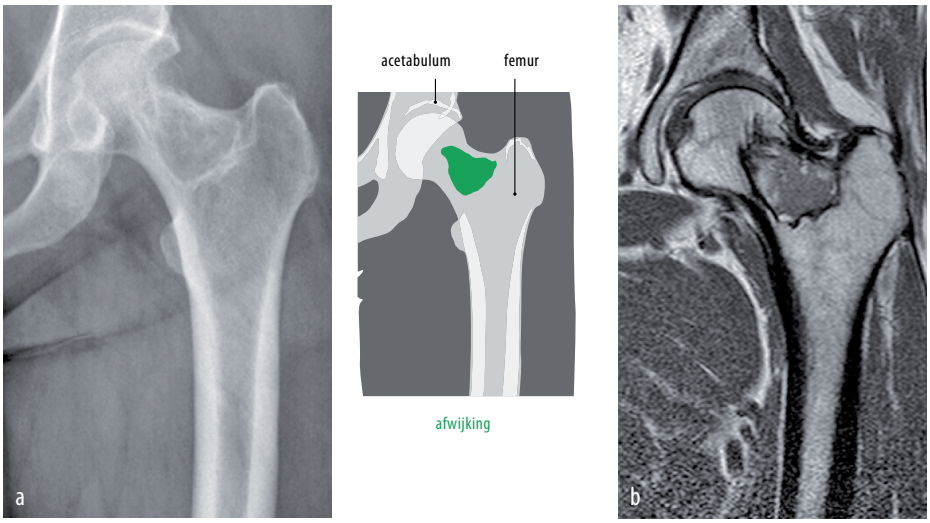

Fig. 14.1 (a) Anterieur-posterieure rontgenfoto van het proximale deel van het linker femur van patient A, met een scherp en sclerotisch begrensde lucente afwijking met een matglasaspect in het collum femoris. (b) Coronale T1-gewogen MRI-scan toont een afwijking in het femur zonder deformatie, corticale aantasting of uitbreiding naar de weke delen.

de endocrinoloog dat er op dat moment geen indicatie was voor behandeling met bisfosfonaten. De orthopedisch chirurg constateerde dat er geen aanwijzingen waren voor een dreigende pathologische fractuur. We stelden daarom een conservatief beleid voor, zonder restricties in de dagelijkse belasting van de linker heup. De komende 10 jaar zullen wij patiënte klinisch en radiologisch vervolgen.

Patiënt B is een 25-jarige man met een blanco voorgeschiedenis. De huisarts had hem naar onze afdeling Orthopedie verwezen wegens klachten van de rechter heup sinds de kinderleeftijd, waarbij er geleidelijk een afwijkend looppatroon was ontstaan. De reden om nu een orthopedisch chirurg te raadplegen was dat de pijn in de heup was toegenomen, uitstraalde naar de rechter lies en verergerde bij rotatie.

Bij lichamelijk onderzoek zagen wij een niet-zieke man met pijn bij flexie, abductie en rotatie van de heup. De heupfuncties waren duidelijk beperkt. Radiologisch onderzoek toonde osteolytische, expansieve afwijkingen met deels een matglas-achtig aspect in het acetabulum en proximaal in het rechter femur die pasten bij FD; daarnaast was er een pathologische fractuur van het collum, die waarschijnlijk de toename van de heuppijn verklaarde (Fig. 14.2a). Op het skeletscintigram zagen we een toegenomen botactiviteit in de femurschacht en de rechter tibia. We stelden daarop de diagnose 'FD'.

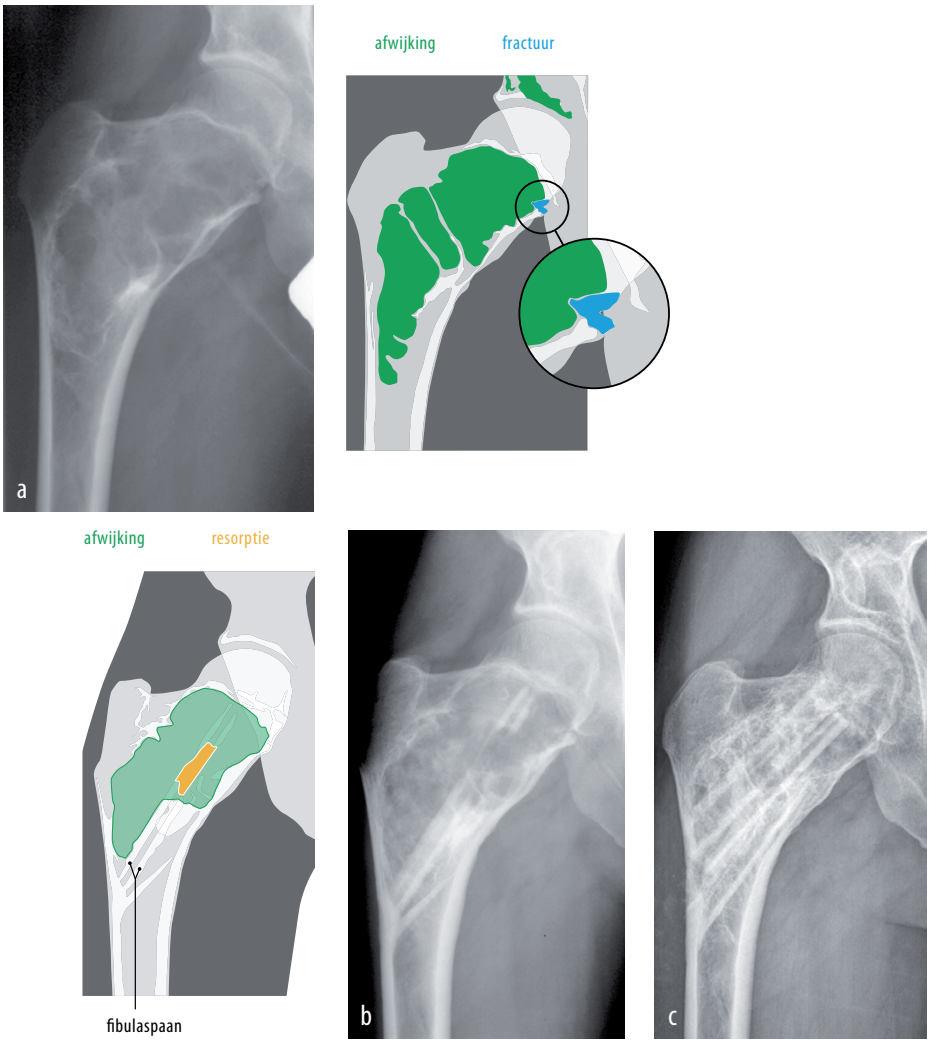

Fig. 14.2 Anterieur-posterieure rontgenfoto's van de rechter heup van patient B. (a) Er zijn osteolytische, expansieve afwijkingen in het acetabulum en proximaal in het femur met deels een matglas-achtig aspect die passen bij fibreuze dysplasie. Ook is een discrete pathologische fractuur van het mediale collum femoris zichtbaar. (b) Na het plaatsen van allogene fibulaspanen in het collum trad tot 3 keer toe resorptie van deze fibulaspanen op door activiteit van de ziekte, waarvoor patient steeds opnieuw werd geopereerd. (c) Na de vierde operatie is er een stabiele situatie waarin de spanen goed geincorporeerd zijn in het gezonde botweefsel proximaal in de femurkop.

Patiënt onderging een operatie, waarbij we 2 allogene fibulaspanen van een donor inbrachten in het collum femoris om de fractuur te overbruggen en stevigheid te bieden. Door de actieve ziekte trad echter grotendeels resorptie op van deze fibulaspanen (Fig. 14.2b), waardoor er wederom een risico was op het optreden van

een pathologische fractuur. Na 2 jaar voerden we daarom een revisieoperatie volgens dezelfde procedure uit; een dergelijke revisieoperatie was nog 2 keer nodig. Na de vierde operatie, 6 jaar na de eerste, waren de fibulaspanen adequaat in het omliggende botweefsel geïncorporeerd en werd zodoende een succesvolle biomechanisch stabiele situatie bereikt (Fig. 14.2c).

Op basis van de aanhoudende pijn, de persisterend verhoogde botactiviteit op het skeletscintigram en de verhoogde botmarkers in het bloed (zie Tabel 14.1), besloten we patiënt te behandelen met het bisfosfonaat olpadronaat 50–200 mg/dag per os. Hij had echter ook een secundaire hypoparathyreoïdie bij een vitamine D-deficiëntie (zie Tabel 14.1), en daarom behandelden we hem eerst met calcium 500 mg en vitamine D_3-preparaten (400 IE).

Na aanvang van de bisfosfonaattherapie nam de pijn sterk af en normaliseerde de botombouw. Op dit moment heeft patiënt minimale heupklachten. Hij krijgt bisfosfonaattherapie als hij een recidief van de pijn heeft die gekoppeld is aan een verstoring van het botmetabolisme zoals blijkt uit laboratoriumonderzoek.

Patiënt C werd als 7-jarig meisje gezien in een perifeer centrum vanwege een pathologische fractuur van het rechter femur. Enkele weken na haar geboorte had patiënte pubertas praecox ontwikkeld, die werd gekenmerkt door mammavorming, geslachtsbeharing en een anovulatoire cyclus.

Bij lichamelijk onderzoek werd aldaar een niet-ziek, pijnlijk meisje gezien, met meerdere café-au-lait-vlekken op de huid. Skeletscintigrafie toonde op meerdere plaatsen een toegenomen botactiviteit, en een CT-scan van de schedel liet uitgebreide craniofaciale afwijkingen zien (Fig. 14.3). Op basis van de opvallende combinatie van pubertas praecox, café-au-lait-vlekken en de uitgebreide distributie van afwijkingen die bij FD pasten, werd de diagnose 'McCune-Albright-syndroom' gesteld. In de loop der jaren onderging patiënte meerdere operaties, waaronder chirurgische correctie van een coxa vara, plaatosteosynthese in beide bovenbenen, opvulling van een FD-afwijking in de radius, en 4 operaties voor decompressie van de N. opticus rechts, gevolgd door reconstructieve chirurgie van craniofaciale FD met periorbitale lokalisaties. Daarnaast werden verscheidene fracturen conservatief behandeld.

Vanwege de complexiteit van de aandoening werd patiënte op 19-jarige leeftijd naar ons centrum doorverwezen. Op basis van de multipele fracturen, de progressie van de FD-afwijkingen en de pijn bij een hoge botombouw (zie Tabel 14.1), besloten wij patiënte te behandelen met olpadronaat in verschillende doseringen: 50–200 mg/

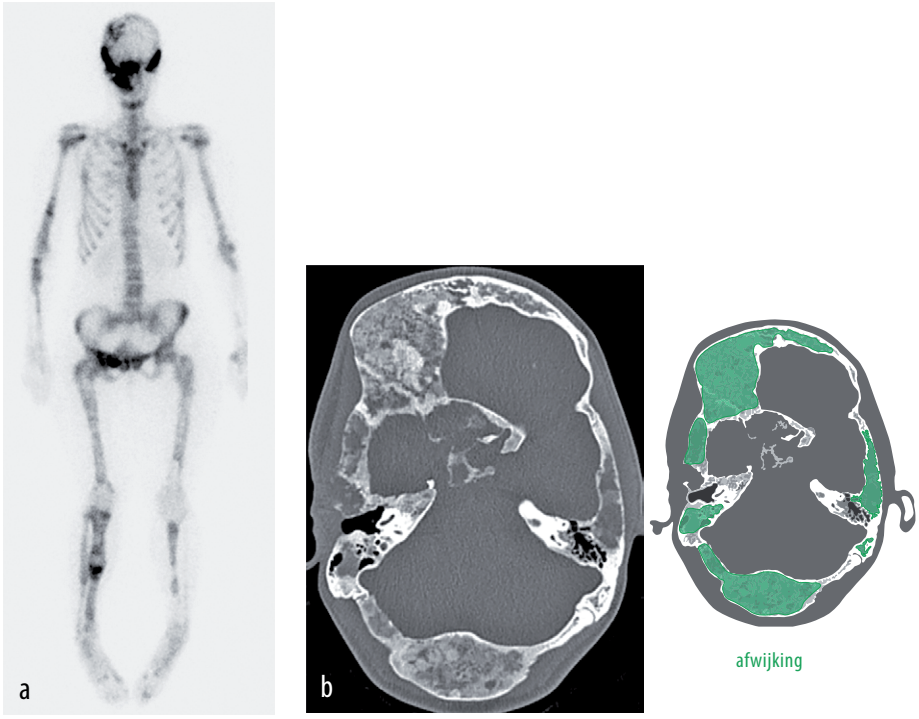

Fig. 14.3 (a) Skeletscintigram van patient C met een verhoogde botactiviteit craniofaciaal, in alle extremiteiten, meerdere ribben, het bekken en in de wervelkolom. (b) Transversale CT-scan van de schedel met afwijkingen in vrijwel alle ossale structuren van het neurocranium.

dag oraal, en 8 mg/dag i.v. in kuren van 4–5 dagen op geleide van het klinisch beeld. Hierop verminderde de pijn, normaliseerde de botombouw nagenoeg en traden geen fracturen meer op. We behandelen patiënte momenteel met tussenpauzes met bisfosfonaten om de botombouw op peil te houden.

BESCHOUWING

In 1891 beschreef Von Recklinghausen voor het eerst een ziektebeeld waarbij intra-ossale afwijkingen resulteerden in ernstige skeletdeformiteiten.[1] In de jaren 30 rapporteerde Albright over een gecombineerd beeld van benigne botafwijkingen, café-au-lait-vlekken en pubertas praecox. Dit zou later bekend komen te staan als het McCune-Albright-syndroom. In 1938 werd het ziektebeeld zónder de hormonale stoornissen uiteindelijk fibreuze dysplasie genoemd.[2,3]

Tabel 14.2 Klinische typen van fibreuze dysplasie

Type	Kenmerk	Frequentie
Monostotische FD	1 FD-afwijking	circa 80%
Polyostotische FD	> 1 FD-afwijking	circa 15%
McCune-Albright syndroom	> 1 FD-afwijkingen in combinatie met pubertas praecox, en daarnaast mogelijk: • café-au-lait-vlekken • groeihormoonoverproductie prolactineoverproductie • hyperthyreoïdie • Cushing-syndroom	circa 4%
Mazabraud syndroom	≥ FD1 -afwijking in combinatie met myxomen in weke delen*	< 1%

* Vaak in combinatie met polyostotische fibreuze dysplasie (FD) of met McCune-Albright-syndroom, zelden bij monostotische FD.

FD bestrijkt een heterogeen ziektebeeld (Tabel 14.2). Ongeveer 80% van de patiënten heeft 1 botafwijking (monostotische vorm); de overige hebben meerdere botafwijkingen (polyostotische vorm). De polyostotische vorm kan ook voorkomen in combinatie met extraskeletale afwijkingen. Patiënten met het McCune-Albright syndroom hebben naast botafwijkingen ook endocriene afwijkingen en café-au-lait-vlekken. Het Mazabraud syndroom is een combinatie van botafwijkingen en myxomen in de weke delen, meestal intramusculair.

Omdat een groot aantal van de FD-afwijkingen geen klachten geeft, is de wereldwijde incidentie van FD onbekend. Wel wordt FD bij ongeveer 5–7% van alle benigne bottumoren gezien.[4] De afwijkingen kunnen in elk bot voorkomen, maar hebben een voorkeur voor het proximale deel van het femur en het aangezicht.[5]

Etiologie

FD ontstaat door een postzygote mutatie in het *GNAS*-gen.[6] Doordat deze mutatie in het postzygote stadium ontstaat, is de ziekte niet erfelijk en bestaat er een verband tussen het tijdstip van het optreden van de mutatie en het fenotype van FD. De *GNAS*-mutatie leidt bij FD tot lokale productie van fibreus weefsel door afwijkende osteoblasten op de plaats van gezond botweefsel. Zowel het McCune-Albright als het Mazabraud syndroom is onderdeel van het spectrum van FD (zie Tabel 14.2). Bij deze syndromen lijkt de *GNAS*-mutatie ook een rol te spelen in niet-ossale structuren.[6]

Klinisch beeld

Een groot deel van de patiënten heeft geen klachten. Vaak wordt een FD-afwijking dan ook per toeval ontdekt bij radiologisch onderzoek, wat grotendeels het hiaat in de incidentiecijfers verklaart. Dit asymptomatische type komt aanzienlijk vaker voor bij patiënten met monostotische FD.

Bij patiënten die wel klachten hebben, komen deze vaak tot uiting op de kinderleeftijd. Gedurende deze periode treden dan ook de meeste – al dan niet pathologische – fracturen op, vaak in gewichtsdragende botten zoals de lange pijpbeenderen van de benen. Ook na de adolescentie kunnen de FD-afwijkingen blijven toenemen in grootte en activiteit. Dit resulteert in ernstige deformiteiten, waarbij het vaak gaat om ernstige varisatie van het collum femoris, en blijvende invaliditeit; bij varisatie gaat de infantiele valgusstand over in een varusstand. Bij een klein aantal patiënten (< 1%) treedt maligne ontaarding op.[7]

Daarnaast kunnen patiënten met het McCune-Albright syndroom klachten ontwikkelen op basis van endocriene disfunctie, zoals pubertas praecox, groeihormoon- en prolactineoverproductie, en hyperthyreoïdie. Overproductie van de hypofysehormonen is gekoppeld aan uitgebreide craniofaciale distributie van de FD-afwijkingen. Deze lokalisatie kan ook resulteren in blind- en doofheid wanneer hersenzenuwen worden gecomprimeerd.

Patiënten met het Mazabraud-syndroom krijgen vaak mechanische klachten, pijn of beide door wekedelenzwellingen, die bijna altijd gelokaliseerd zijn rond de fibreuze afwijkingen in het bot.

Bij een deel van de patiënten 'dooft' een FD-afwijking in het verloop van enkele decennia uit, waarna bij beeldvormend onderzoek een scherp en sclerotisch begrensde, deels ingevulde afwijking wordt gezien.

Diagnostiek

Vanwege de zeldzaamheid van de ziekte treedt regelmatig aanzienlijke vertraging op in de diagnostiek en behandeling, zoals bij alle 3 onze patiënten. Vaak is het mogelijk de diagnose te stellen op basis van het klinisch beeld en de bevindingen bij conventioneel radiologisch onderzoek; als er twijfel is over de diagnose of als er aanwijzingen voor een maligniteit zijn, kan dit worden aangevuld met MRI. Bij lichamelijk onderzoek kunnen afwijkende heupfunctietesten, en dan met name afwijkende rotatie-uitslagen, een aanwijzing vormen voor afwijkingen in het proximale deel van het femur.

Bij conventioneel radiologisch onderzoek wordt een scherp en soms sclerotisch begrensde osteolytische afwijking gezien, vaak met een typisch matglasaspect. Soms is sprake van een expansieve afwijking. Bij actieve FD-afwijkingen kan de cortex verdund of onderbroken zijn. Inactieve of weinig actieve afwijkingen hebben vaak een duidelijke sclerotische begrenzing. Om te beoordelen of het gaat om één of meerdere FD-afwijkingen en om de activiteit van de afwijking of afwijkingen te bepalen dient een skeletscintigram gemaakt te worden.

Bij alle symptomatische patiënten moeten de bloedwaarde van alkalische fosfatase en van procollageen-type 1-N-'terminal'-propeptide (P1NP; een marker voor botaanmaak) worden bepaald om de mate van botombouw te kunnen beoordelen. Een verhoogde botombouw kan namelijk gerelateerd zijn aan de hoeveelheid pijn, en verscheidene medicamenten grijpen aan op de botombouw. Daarnaast worden de vitamine D- en de fosfaatwaarde bepaald, omdat een slechte mineralisatie van het bot gekoppeld is aan pijn en aan een hoger fractuurrisico. Andere oorzaken van een verhoogde botombouw, zoals hyperthyreoïdie, hypoparathyreoïdie en – bij het McCune-Albright syndroom – overmatige groeihormoonproductie, dienen uitgesloten te worden.

FGF-23 is een fibroblastgroeifactor die door osteocyten geproduceerd wordt bij gezonde personen en die de fosfaathuishouding nauwkeurig controleert. Bij FD produceren de aangetaste osteocyten met een *GNAS*-mutatie deze factor echter overmatig, vooral bij polyostotische FD en het McCune-Albright-syndroom. De FGF-23-productie correspondeert met de ernst van de activiteit van de botafwijkingen en kan hypofosfatemie induceren door verhoogde fosfaatexcretie in de proximale niertubulus.[8] Bij patiënten met polyostotische FD en een verlaagde fosfaatwaarde raden wij daarom aan om de FGF-23-waarde te bepalen; voor het gebruik van FGF-23 als prognostische marker is momenteel geen plaats.

'FD' is voornamelijk een radiologische diagnose. Bij twijfel over de aard van een afwijking kan histopathologisch onderzoek van een weefselbiopt worden verricht. Ook kan een eventuele *GNAS*-mutatie worden onderzocht, maar door mozaïcisme bewijst afwezigheid van deze mutatie niet dat er geen sprake is van FD.6

Therapie

Bij asymptomatische patiënten met een kleine – en dus inactieve – FD-afwijking zonder fractuurrisico is een conservatief beleid gerechtvaardigd en geldt het advies om terug te komen bij klachten. Symptomatische patiënten worden in de jaren na

de diagnose gecontroleerd, wisselend van 3-maandelijkse tot 2-jaarlijkse controles. Voor patiënten met pijn, een fractuur of dreiging daarvan, of een deformiteit zijn er verschillende therapeutische opties, zowel chirurgisch als medicamenteus. Hierbij is het zaak tijdig met de behandeling te beginnen om ziekteprogressie en complicaties te voorkomen. Bij symptomatische patiënten, ongeacht het aantal afwijkingen, wordt een multidisciplinaire benadering sterk aanbevolen, het liefst in een gespecialiseerd centrum.

Chirurgie

Deformiteiten, pathologische fracturen of dreiging daarvan, en pijn ondanks medicamenteuze behandeling vormen een indicatie voor chirurgisch ingrijpen. De keuze voor het soort interventie is sterk afhankelijk van de lokalisatie, de kwaliteit van het omliggende bot, de uitgebreidheid van de FD-afwijking en de leeftijd van de patiënt. Bij een dreigende fractuur van een gewichtsdragend pijpbeen is bottransplantatie een optie. Hierbij gaat de voorkeur uit naar het gebruik van corticaal donorbot, bijvoorbeeld fibulaspanen, omdat dit minder risico geeft op resorptie dan transplantatie van spongieus, autoloog bot.[4,9]

Bij ernstige deformiteit van het proximale deel van het femur, bijvoorbeeld bij een coxa vara of een zogenaamde 'herdersstafdeformiteit', wordt het bot verstevigd met een hoekplaat of intramedullair implantaat, eventueel in combinatie met een correctie-osteotomie om de deformiteit op te heffen. Soms moet gezien de ernst van de deformiteit osteosynthesemateriaal worden geplaatst dat op maat is gemaakt met een 3D-printer.

Bij compressie van hersenzenuwen bij patiënten met craniofaciale FD moet het betreffende fibreuze botweefsel verwijderd worden.

Medicatie

Bij patiënten met een vitamine D-deficiëntie moet allereerst deze vitamine gesuppleerd worden. Bisfosfonaten kunnen de botombouw remmen en verlichting van de pijn geven, en kunnen zowel oraal als intraveneus worden gegeven.[10] Voorspellers van een matige respons op bisfosfonaattherapie zijn overproductie van groeihormoon en uitgebreide distributie van de FD-afwijkingen; daarom moet voorafgaand hieraan de groeihormoonconcentratie worden bepaald en is skeletscintigrafie noodzakelijk. Bij aanvang van de bisfosfonaattherapie is adequate suppletie van calcium in combinatie met vitamine D3 belangrijk.

Dames en Heren, fibreuze dysplasie is een zeldzame chronische botaandoening met een breed klinisch spectrum. Patiënten met ernstige FD moeten in een vroeg stadium behandeld worden om uitgebreide complicaties op latere leeftijd te beperken of te voorkomen. Kenmerkende symptomen zijn pijn, fracturen en deformiteiten. Bij de diagnostiek moeten extraskeletale afwijkingen zoals die voorkomen bij het verwante McCune-Albright en Mazabraud syndroom, worden uitgesloten. De behandeling van symptomatische patiënten is multidisciplinair en er zijn zowel chirurgische als medicamenteuze opties. Op basis van het klinisch beeld, bevindingen bij beeldvormend onderzoek en botmarkers kunnen de therapierespons en de prognose goed worden vervolgd.

LEERPUNTEN

- Fibreuze dysplasie (FD) geeft een heterogeen ziektebeeld, dat varieert van de asymptomatische patiënt tot de patiënt met een ernstig klinisch beeld en uitgebreide beperkingen in het dagelijks leven.
- Bij asymptomatische patiënten met een kleine FD-afwijking zonder fractuurrisico is een conservatief beleid gerechtvaardigd; voor symptomatische patiënten is multidisciplinaire behandeling nodig.
- Door vroege opsporing en tijdige behandeling van FD kan de pijn worden verminderd en kan het optreden van complicaties op latere leeftijd, zoals fracturen en deformiteiten, deels of geheel worden voorkomen.
- Craniofaciale FD dient tijdig herkend te worden om complicaties als blind- en doofheid te voorkomen.
- Bij symptomatische patiënten en bij patiënten met polyostotische FD moeten de waarde van vitamine D en van fosfaat worden bepaald, omdat deze patiënten een hoger risico hebben op pathologische fracturen.
- De behandeling van patiënten met FD bestaat uit chirurgie en bisfosfonaattherapie.

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Chapter 15

Nederlandse samenvatting

Fibreuze dysplasie (FD) is primair een heterogene botziekte. Of het nu gaat om de distributie van laesies, het beloop over de tijd, de grote verscheidenheid in symptomen en dagelijkse belemmeringen of de verscheidenheid aan manifestaties buiten het skelet, geen enkele FD patiënt is hetzelfde. In dit proefschrift hebben we gekeken naar de verschillende aspecten van deze interessante aandoening, welke zijn onderverdeeld in vier onderdelen: 1. Pijn en kwaliteit van leven in FD; 2. Extra-skeletale manifestaties in FD; 3. De chirurgische behandeling van FD; 4. De medicamenteuze behandeling van FD.

Pijn en kwaliteit van leven in fibreuze dysplasie

Hoofdstuk 2 beschrijft de pijnklachten van patiënten met FD in een gezamenlijke studie van de Medische Universiteit van Graz en het Leids Universitair Medisch Centrum. In totaal 197 patiënten vulden een vragenlijst in over de aanwezigheid en ernst van pijnklachten ter hoogte van hun FD laesies. De gemiddelde pijnscore op een schaal van 1 tot 10 was 1.9 in de gehele groep en 4.1 in de groep patiënten die daadwerkelijk pijn hadden. Patiënten met laesies van de onderste extremiteit of van de ribben rapporteerden significant meer pijn ten opzichte van patiënten met laesies van de bovenste extremiteit of van het hoofd. De aanwezigheid van pijn verschilde niet per lokalisatie. Een ernstiger type FD, zoals de polyostotische vorm of het McCune-Albright syndroom, was geassocieerd met zowel de aanwezigheid van pijn als de ernst van de pijn symptomen. Deze resultaten bieden nieuwe inzichten in onze evaluatie van pijn in patiënten met FD. Hoewel minder dan 50% van de patiënten met FD pijn rapporteren, blijven pijnsymptomen een van de belangrijkste manifestaties van FD, ook bij de patiënten met milde (monostotische) ziekte.

Hoofdstuk 3 vergelijkt de kwaliteit van leven en pijnsymptomen van 97 patiënten met FD met cijfers van de Nederlandse bevolking. Patiënten met FD hadden een significant lagere kwaliteit van leven in vergelijking met de algemene Nederlandse bevolking voor alle domeinen van de SF-36 op de domeinen 'Mentale gezondheid' en 'Rolbeperkingen door een emotioneel probleem' na. Het hebben van een ernstigere vorm van FD was geassocieerd met een lagere kwaliteit van leven, maar had geen invloed op gemeten pijnscores. De kwaliteit van leven was ook lager in zowel patiënten met een meer uitgebreide verspreiding van de laesies welke werd gemeten met de 'skeletal burden score', als bij patiënten met hogere bloedwaarden van de botturnover marker P1NP. De resultaten van dit hoofdstuk laten duidelijk zien dat de kwaliteit van leven is aangedaan in patiënten met FD, en hoewel een lagere kwaliteit van leven geassocieerd was met een ernstigere vorm van FD, gelden de

beperkingen in kwaliteit van leven ook voor de minder ernstig aangedane patiënten. Het laatste hoofdstuk over de consequenties van FD, **Hoofdstuk 4**, schetst een beeld van de ziektepercepties (Illness perceptions) van patiënten met FD. Ziektepercepties zijn de gedachten en emoties van patiënten met betrekking tot hun aandoening of de behandeling hiervan. Deze ziektepercepties kunnen echter gevolgen hebben voor de kwaliteit van leven. Daarom hebben we de ziektepercepties van patiënten met FD vergeleken met die van patiënten met andere aandoeningen, keken we naar factoren die van invloed zijn op deze ziektepercepties en hebben we het effect van ziektepercepties op de kwaliteit van leven geëvalueerd. Er waren significante verschillen in ziektepercepties tussen de verschillende typen FD, waarbij patiënten met een craniofaciale vorm van FD meer consequenties ervoeren dan patiënten met een andere vorm van FD. Uitgebreide skeletale betrokkenheid was geassocieerd met het ervaren van meer negatieve consequenties en het toeschrijven van de oorzaak van FD aan psychologische factoren. Hoge bloedwaarden van FGF-23 waren geassocieerd met het toeschrijven van meer klachten aan de aandoening en met het ervaren van meer consequenties. Daarnaast waren negatieve ziekte percepties duidelijk geassocieerd met verminderde kwaliteit van leven. We concluderen dan ook dat ziektepercepties in FD beïnvloed worden door de ernst van de aandoening en een belangrijke associatie hebben met de kwaliteit van leven. Het herkennen en adresseren van negatieve ziektepercepties kan daarom een positief effect hebben op de kwaliteit van leven van patiënten met FD.

Extra-skeletale manifestaties in fibreuze dysplasie

Deel II van dit proefschrift behandeld de manifestaties van FD buiten het skelet, een aspect van FD dat steeds relevanter wordt en waar steeds meer nadruk op komt te liggen. Het Mazabraud's syndroom, een combinatie van fibreuze dysplasie en intramusculaire myxomen, representeert een zeldzame, maar een van de bekendste niet-endocrinologische manifestaties van *GNAS*-mutaties buiten het skelet in FD. **Hoofdstuk 5** beschrijft het klinische beloop, de uitkomsten van behandelingen en de rol van GNAS-mutaties in 32 patiënten met het Mazabraud syndroom die werden geëvalueerd in een multicenter studie van de Europese Musculo-skeletale Oncologie Vereniging (EMSOS). De prevalentie van Mazabraud's syndroom in FD werd berekend op 2.2%, waarbij interessant genoeg ook myxomen werden gevonden in patiënten met de monostotische vorm van FD. Desondanks representeren deze prevalentiecijfers waarschijnlijk slechts het topje van de ijsberg, en is het aannemelijk dat myxomen vaker voorkomen in FD maar asymptomatisch blijven. Patiënten met disproportionele klachten of persisterend falen van behandeling zouden daarom verdere evaluatie

moeten ondergaan middels een MRI-scan om eventuele weke delen pathologie, zoals myxomen, aan het licht te brengen. Uit onze studie bleek ook dat, ondanks goede functionele uitkomsten van de resectie van de myxomen, een kwart van de patiënten opnieuw een resectie nodig heeft op basis van een recidief, ondanks vrije resectie marges bij de eerste operatie. Een hoge cellulariteit van de myxomen werd geïdentificeerd als een risicofactor voor een recidief na resectie. Ten slotte werden er *GNAS*-mutaties gevonden in 83% van de geteste myxomen, wat de gedeelde origine met ossale FD laesies onderschrijft, evenals de mogelijk belangrijke rol van *GNAS*-mutaties buiten het skelet.

Een belangrijke rol was tevens weggelegd voor *GNAS*-mutaties in **Hoofdstuk 6**, waar de bevindingen zijn beschreven van een studie waarin werd gekeken naar een mogelijk verhoogd risico op borstkanker in vrouwelijke patiënten met FD. In samenwerking met de National Institutes of Health in Bethesda (Verenigde Staten) toonden we aan dat de incidentie van borstkanker hoger is in vrouwen met FD in vergelijking met de respectievelijke nationale populaties in de VS en in Nederland, en dat deze vrouwen borstkanker ontwikkelen op een zeer jonge leeftijd. Deze bevindingen werden bevestigd in de Nederlandse Nationale Pathologie Database (PALGA). Interessant genoeg was het risico op borstkanker met name verhoogd in vrouwen met thoracale FD laesies, oftewel FD laesies in de buurt van de mammae. Ten slotte werd het vermoeden op een link tussen borstkanker en FD verder kracht bijgezet door het aantonen van *GNAS*-mutaties in 44% van de onderzochte borstkankers in ons FD cohort, terwijl deze mutatie wereldwijd in minder dan 1% van de borstkankers wordt gevonden. Hoewel dit de eerste studie is waarbij wordt gekeken naar het voorkomen van borstkanker in FD, geloven wij dat de resultaten van deze studie substantieel genoeg zijn om vroege screening voor borstkanker te adviseren in vrouwen met FD, met name in vrouwen met FD laesies van de thorax.

Chirurgische behandeling van fibreuze dysplasie

Hoofdstuk 7 beschouwt de rol van het gebruik van allogene botspanen, een vorm van bottransplantaties, in FD patiënten met laesies van het proximale femur. In een serie van 28 patiënten toonden we aan dat revisie-chirurgie geïndiceerd was in 46% van de patiënten, met name als gevolg van resorptie van het donorbot. Echter, konden we in deze studie duidelijke risicofactoren voor het falen van een allogene spaanplastiek identificeren, te weten een fractuur van het proximale femur in de voorgeschiedenis en onvoldoende gezond bot aan de proximale zijde van de spaanplastiek waar de botspaan in verankerd kan worden. In patiënten zonder deze risicofactoren is een

allogene spaanplastiek een goede en veilige behandeloptie. Patiënten mét een risicofactor voor falen zouden daarentegen behandeld moeten worden met een metalen implantaat.

In **Hoofdstuk 8** werd daarom gekeken de resultaten van behandeling met intramedullaire pennen en hoekplaten in 32 patiënten uit een gecombineerd cohort van het Leiden Universitair Medisch Centrum en de Medische Universiteit van Graz. Revisie-vrije overleving was 72% na een mediane follow-up van 4.1 jaar. In slechts 2 patiënten was er sprake van structureel falen van het implantaat, in beide gevallen doordat er een fractuur was ontstaan onder de hoekplaat in een gebied met FD. Zeven patiënten klaagden over klachten van de tractus iliotibialis na het plaatsen van een hoekplaat, welke zodanig belemmerend waren dat de hoekplaat verwijderd moest worden. Geen van deze patiënten ontwikkelde echter complicaties of een fractuur na verwijdering van de hoekplaat. De meerderheid van de patiënten had een goede uitkomst wat betreft pijn, functie en de hoek tussen het collum en de femurschacht. We concludeerden dan ook dat FD van het proximale femur adequaat en veilig behandeld kan worden met hoekplaten of intramedullaire pennen, mits deze worden geplaatst op basis van de specifieke karakteristieken van de patiënt. Op basis van deze resultaten in combinatie met gepubliceerde literatuur ontwierpen we daarom een geïndividualiseerd, op maat gemaakt werkschema voor de behandeling van FD van het proximale femur, welke de verschillende factoren die effect kunnen hebben op de uitkomst van een type operatieve ingreep meeneemt in de keuze voor een behandeling.
In het laatste hoofdstuk over de chirurgische behandeling van FD, **Hoofdstuk 9**, wordt gekeken naar 50 patiënten met FD laesies van de humerus. Hierin toonden we aan dat hoewel FD van de humerus over het algemeen een mild beloop heeft, meer dan de helft van de patiënten een fractuur oploopt. Cysteuze degeneratie van de FD laesie in de humerus was geassocieerd met een verhoogd risico op een fractuur, terwijl de grootte van de laesie geen invloed had op dit risico. Omdat cysteuze degeneratie van een FD laesie invloed heeft op het beloop, is verdere evaluatie van laesies in de bovenarm middels een MRI-scan aanbevolen, aangezien cysteuze degeneratie niet goed beoordeeld kan worden op conventionele röntgen opnames. Mocht er een fractuur ontstaan in een FD laesie van de bovenarm dan geneest deze over het algemeen goed. Fracturen van de humerus kunnen daarom in eerste instantie conservatief behandeld worden met immobilisatie, aangezien tweederde van de patiënten daarbij een goede uitkomst heeft. Chirurgische behandeling om pijnsymptomen te verhelpen of om dreigende fracturen te voorkomen kan theoretisch gebaad zijn bij het gebruik van corticale bottransplantaties in plaats van

het implanteren van spongieus bot, echter definitieve aanbevelingen met betrekking tot de chirurgische behandeling van FD van de humerus kunnen pas gedaan worden aan de hand van resultaten van grotere cohorten in de toekomst.

Medicamenteuze behandeling van fibreuze dysplasie

Hoofdstuk 10 illustreert onze resultaten van een lange termijnstudie naar het effect van bisfosfonaten in patiënten met polyostotische FD of het McCune-Albright syndroom (MAS). We evalueerden de biochemische respons (botturnover markers) en klinische uitkomsten (pijn) van behandeling met bisfosfonaten in 11 patiënten met MAS en 30 patiënten met polyostotische FD, met een mediane behandelduur van 6 jaar. Vierentwintig van de 30 patiënten met polyostotische ziekte (80%) lieten een complete biochemische en klinische respons zien binnen een jaar na het starten van de behandeling, terwijl slechts 4 van de 11 patiënten met MAS (36%) een complete respons hadden. Er waren geen patiënten die helemaal niet reageerden op de behandeling. De markers FGF-23, AF, P1NP en CTX correleerden met de 'skeletal burden' scores. Een hoge skeletal burden score was de enige statistisch significante risicofactor voor het hebben van een incomplete respons op bisfosfonaten. Onze data impliceert een voordelige en veilige uitkomst van (langdurige) behandeling met bisfosfonaten in de meerderheid van de patiënten met de polyostotische vorm van FD. De te verwachten respons is echter minder goed in patiënten met uitgebreidere ziekte zoals bij MAS. In deze ernstiger aangedane patiënten zijn bisfosfonaten mogelijk niet afdoende in staat om de verhoogde botstofwisseling en pijnklachten te verbeteren.

In **Hoofdstuk 11** hebben we daarom gekeken naar de resultaten van behandeling met denosumab, een monoklonaal antilichaam voor RANK-L, in 12 patiënten met een incomplete respons op behandeling met bisfosfonaten. De mediane follow-up was 15 maanden. Dit is de eerste studie waarbij gekeken wordt naar het effect van de behandeling met denosumab in een serie patiënten met FD. Patiënten met een verhoogd botmetabolisme met daarbij pijnsymptomen werden 3–6 maandelijks behandeld met subcutane injecties met 60 mg denosumab. Patiënten die volgens een 3-maandelijks schema werden behandeld hadden significant betere biochemische uitkomsten dan patiënten met een 6-maandelijks schema. In 8 patiënten normaliseerden de bot turnover markers, terwijl dat in 5 van deze 8 patiënten niet was gelukt na langdurige behandeling met bisfosfonaten. Er werden geen bijwerkingen gezien van de behandeling met denosumab. Deze resultaten suggereren dat in specifieke patiëntgroepen, behandeling met denosumab een goed alternatief is wanneer behandeling met bisfosfonaten faalt. Driemaandelijkse behandelschema's

met 60 mg denosumab lijken een veelbelovend effect te hebben op bot turnover markers en pijn.


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CURRICULUM VITAE

Bas Majoor was born on January 7th 1988 in Laren (Noord-Holland). He lived with his family in Bennekom, and graduated from the Atheneum of the Pantarijn in Wageningen in 2006.

In 2006 he started medical school at the Leiden University Medical Center. Between 2009–2010 he paused his study for one year to take place in the board of the student society Minerva. In 2013 he did his Gynecology internship in Paramaribo, Suriname. During his internships he started an enterprise, Knoet&Wood, for which he manufactured wooden furniture. In 2012 he gained his first experience in research at the Old Road Campus of the Oxford University (UK) as part of his research internship, looking at the link between the *P21*-gene and colorectal cancer under the supervision of prof. dr. I. Tomlinson.

After graduating cum laude from medical school in 2014, he started his PhD on fibrous dysplasia, under supervision of prof. dr. P.D.S. Dijkstra, dr. N.A.T. Hamdy and dr. N.M. Appelman-Dijkstra, of which the results are presented in this thesis. During his PhD, Bas was involved in the organization of the first national patient day for fibrous dysplasia, resulting in the establishment of the Patient Foundation for fibrous dysplasia in the Netherlands, and he was able to set up an international collaboration with the Medical University of Graz (Austria), where he performed research under supervision of prof. dr. A. Leithner.

In 2017 he started working as a resident not in training at the Surgery Department of the Haaglanden Medical Center in The Hague, where he started his residency training in Orthopaedic Surgery in January, 2018.

Bas currently lives with Evelien Sandberg in Amsterdam, and they will both defend their thesis on April 25th 2018.