Osteoporosis International (2018) 29:1815–1825
https://doi.org/10.1007/s00198-018-4552-3

ORIGINAL ARTICLE

Subtrochanteric and diaphyseal femoral fractures in hypophosphatasia—not atypical at all

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Received: 23 October 2017 / Accepted: 25 April 2018 / Published online: 17 May 2018

Abstract

Summary Risk for subtrochanteric and diaphyseal femoral fractures is considered increased in patients with hypophosphatasia (HPP). Evaluating a large cohort of HPP patients, we could for the first time quantify the prevalcence and identify both morphometric features as well as predisposing factors for this complication of severe HPP.

Introduction Subtrochanteric and diaphyseal femoral fractures have been associated with both, long-term antiresorptive treatment and metabolic bone disorders, specifically Hypophosphatasia (HPP). Building on a cross-sectional evaluation of real-world data, this study reports risk factors, prevalence, treatment outcome and morphometric particularities for such fractures in HPP as compared to Atypical Femoral Fractures (AFF) in long-term antiresorptive treatment.

Methods For 15 out of 150 HPP patients identified with having experienced at least one such fracture, medical records were reviewed in detail, extracting medical history, genotype, lab assessments, bone mineral density (DXA), radiographic data on femoral geometry and clinical aspects of fracture etiology and healing.

Results Bilateral fractures were documented in 10 of these 15 patients, yielding a total of 25 fractures for evaluation. Disease-inherent risk factors included autosomal-recessive, childhood onset HPP, apparently low alkaline phosphatase (ALP) ≤ 20 U/l and substantially elevated pyridoxal 5′-phosphate (PLP) > 3 times upper limit of normal as well as high lumbar spine BMD. Fracture morphology met definition criteria for AFF in 88% of cases. Femoral geometry revealed additional risk factors previously described for AFF, including decreased femoral neck-shaft angle and increased femoral offset. Extrinsic risk factors include Hypovitaminosis D (80%) and pre-treatment with bisphosphonates (46,7%) and Proton-Pump Inhibitors (40%).

Conclusions Increased risk for subtrochanteric and diaphyseal femoral fractures in HPP appears to result from both compromised bone metabolism as well as disease-associated bone deformities. In severe HPP, generous screening for such fractures seems advisable. Bisphosphonates and Hypovitaminosis D should be avoided. Healing is compromised and requires mindful consideration of both pharmacological and surgical options.

Keywords Atypical femoral fractures · Bisphosphonates · Femoral geometry · Hypophosphatasia

Introduction

Over recent years, so-called atypical femoral fractures (AFFs) have gained increasing attention specifically in the context of long-term antiresorptive treatment [1–3]. Additional risk factors assumed to predispose to these kinds of fractures include female gender and glucocorticoid use [4], obesity and dementia [5], age, diabetes mellitus, hypocalcemia, use of proton pump inhibitors, and low total hip bone mineral density (BMD) [6, 7]. The clinical significance of vitamin D deficiency in this context is controversial and more often declined [8] than confirmed [9]. In more detail, a dichotomous location pattern of AFF has been confirmed, differentiating between more proximal, subtrochanteric, and more distal, diaphyseal fractures. It is not clear, yet, if these two represent distinct fracture entities and if so, what factors like, e.g., femoral bowing, patient age, bone mineral density, or cultural differences predispose to these fracture types, respectively [10, 11].

Even though the pathophysiologic mechanisms underlying atypical femoral fractures have not been completely elucidated, current considerations include suppressed bone remodeling and associated accumulation of microdamage as well as

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aspects of predisposing femoral geometry [1]. Overall, incidence rates for these fractures in the general population are very low, particularly when compared to typical osteoporotic fractures. In a large cohort study, the incident rate for atypical femoral fractures (AFFs) was calculated to be 5.9 in 100,000 person-years [12].

Following the ASBMR second task force report [1], the case definition for AFF includes localization along the femoral diaphysis, distal to the lesser trochanter and proximal to the condylar area plus at least four out of the following five so-called major criteria: (1) association with minimal or no trauma; (2) origin from the lateral cortex with a transverse orientation; (3) incomplete fractures only affecting the lateral cortex, complete bicortical fractures can involve a medial spike; (4) the fracture is not/minimally comminuted; and (5) endosteal/periosteal thickening at the fracture site (beaking/flaring). By definition "pathological fractures associated with primary or metastatic bone tumors and miscellaneous bone diseases (e.g. Paget's bone disease, fibrous dysplasia)" are excluded.

According to a comprehensive review article covering 834 AFF, treatment of these fractures regularly mandates surgical stabilization, preferentially by intramedullary nailing [13], even though literature on healing potential of these fractures is controversial. Based on registry data, Schilcher et al. in 2015 reported a high surgical revision rate specifically in case of complete AFF [14]. Similarly, healing of incomplete femoral fractures seems to be hampered in many instances eventually requiring surgical stabilization [13]. Several case reports suggest beneficial effects of osteoanabolic treatment on bone healing in AFF [15–17].

Femoral fractures similar to AFF have been reported in different rare metabolic bone disorders, e.g., osteopetrosis, osteogenesis imperfecta, pycnodysostosis [18–21], and particularly HPP, marked by deficient alkaline phosphatase (ALP) activity, impaired bone mineralization, and increased fracture risk [22–25].

Based on these considerations, we performed this cross-sectional evaluation aimed at identifying risk factors, prevalence, treatment outcomes, and morphometric aspects for both, subtrochanteric and diaphyseal femoral fractures in hypophosphatasia (HPP) as well as commonalities with AFF associated with long-term antiresorptive treatment.

Material and methods

This is a single-center, cross-sectional analysis in order to evaluate prevalence, risk factors, and characteristic features of subtrochanteric and diaphyseal femoral fractures in patients with HPP. Diagnosis of HPP was established by the presence of HPP-related clinical signs, symptoms, or complications in all patients plus two out of the following three criteria

- Persistently low ALP levels in serum below age- and gender-adjusted lower normal range (at least two measurements with an interval of > 4 weeks)
- Documented genetic mutation in the ALPL gene
- Serum PLP and/or urine phosphoethanolamine (PEA) above upper normal range

Screening medical records of 150 HPP patients, we identified $n = 15$ (10%) with a previous diagnosis of a subtrochanteric or diaphyseal femoral fracture. For those patients who have had at least one such fracture, further data acquisition included fracture specific information on morphology and underlying fracture mechanism, diagnosis and treatment, limb/bone geometry as well as medical history comprising concomitant medication, HPP genotype, lab reports on ALP activity and ALP-substrate levels (PLP, PEA), vitamin D, PTH, and bone mineral density (DXA).

X-ray analysis was based on plain radiographs available in the hospital's database. Subtrochanteric fractures were defined as fractures located in the proximal area from the distal margin of the lesser trochanter to 5 cm below the lesser trochanter [10, 26, 27]. Diaphyseal femoral fractures were defined as fractures extending from below the subtrochanteric region to the supracondylar metaphyseal flare [10].

Quantification of the femoral neck shaft angle (FNSA) and femoral shaft bowing angle were determined as previously described [28]. Briefly, horizontal lines bisecting the femur at 0 and 5 cm distal to the lesser trochanter and at 5 and 10 cm above the distal articular surface, respectively, were projected onto the radiographs. Vertical connecting lines were drawn between these points bisecting the femur proximally and distally. The angle between these connecting lines on anteroposterior radiographs defines the lateral femoral bowing angle (lat. FBA/lFBA). Similarly, anterior bowing (ant. FBA/aFBA) was determined using lateral projections [10]; FNSA is the angle between proximal connection line and a line drawn from the femoral head through the center of the femoral neck. Cortical thickness index and canal to calcar ratio as well as lateral to medial cortex ratio were quantified using previously established methodology. Briefly, canal-to-calcar ratio is determined dividing intramedullary femoral canal width (FW) by calcar width (CW), cortical thickness index is calculated dividing femoral diaphysis width (DW) minus FW divided by DW, and lateral-to-medial cortex ratio is determined using lateral cortex width (LW) divided by medial cortex width (MW) [29]. Anterior/posterior thickness ratio was determined analogously using lateral projections of the femoral bone. Cortical femoral thickness was assessed using a simple femoral cortical thickness index at 10 cm below the lesser trochanter [29]. Fracture height was measured as described by Saita et al. [30]. Geometrical measurements are illustrated in Fig. 1.

Statistical analysis was set up to determine absolute frequencies and corresponding proportions, arithmetic means,

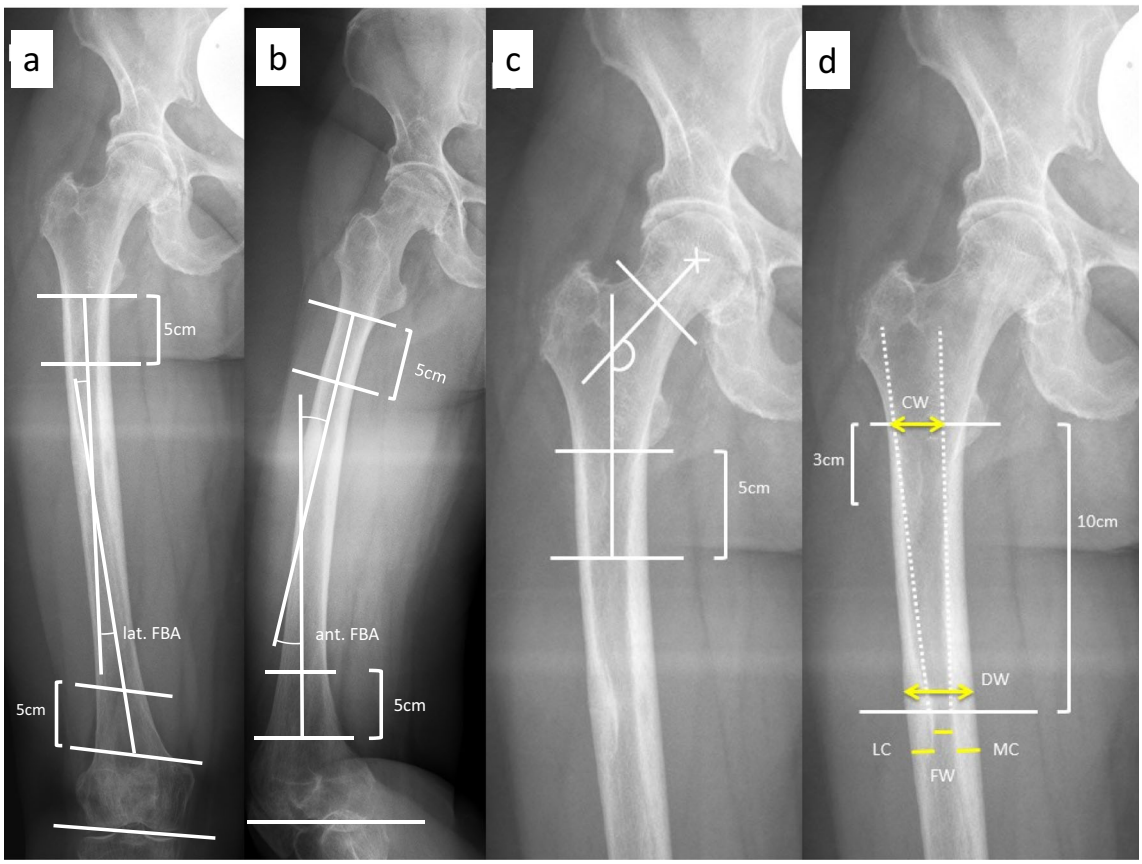

Fig. 1 Graphical depiction of assessment of femoral geometry [28, 29]. Details are given in the "Materials and methods" section. **a** Lateral femoral bowing angle (lat. FBA/lFAB) determined on anteroposterior radiographs. **b** Anterior femoral bowing angle (ant FBA/aFBA) determined on lateral radiographs of the femur. **c** Assessment of the femoral neck shaft angle (FNSA) on anteroposterior radiographs. **d** Measurement of femoral canal width (FW), calcar width (CW), femoral diaphysis width (DW), lateral cortex width (LW) and medial cortex width (MW)

and median and respective variation measures for patient inherent data, main disease symptoms, and associated risk factors. Exploratory correlation analyses were calculated using Pearson's and Spearman's correlation coefficient. Between-group differences were assessed using independent samples *t* tests in case of normally distributed data. Otherwise, Mann-Whitney *U* test was applied. *P* values of less than 0.05 were considered statistically significant. All statistical analyses were performed using SPSS ver. 24 statistical software package (SPSS Inc. Chicago IL).

Results

Demographics and patient characteristics

Out of $n = 15$ individuals identified with a history of at least one femoral fracture in the area from distal to the lesser trochanter to proximal to the supracondylar flare, 12 were women. Mean age was 54.7 years (range 39–76), and mean age at the time their first diaphyseal femoral fracture was diagnosed was 45.9 years (range 30–62). Mean BMI was 28.3 kg/m^2 (21.2–46.7) with 13 patients exhibiting values between 20 and 30 and only two patients being severely obese (BMI 35.8 and 46.7). Individual patients' characteristics are given in Table 1.

Retrospectively, all 15 individuals had various clinical signs and symptoms related to HPP in early childhood. Premature loss of deciduous teeth was reported in 10 patients, bone deformities (scoliosis, knock knees, bowing of long bones) were present in 11 patients, a history of craniosynostosis was documented in 5 of them, and delayed gross motor development was reported for 8 patients. Retrospectively, all these patients have to be classified as having some form of pediatric onset HPP. However, none of them was appropriately diagnosed until adulthood. Owing to limited availability of medical records from childhood age, further sub-classification in terms of perinatal, infantile, or childhood onset was not reliably possibly in the retrospect.

Genotyping was available for $n = 14$ patients with all of these patients harboring mutations in both alleles suggesting recessive disease with a compound heterozygous constellation in $n = 13$ patients while one patient was homozygously affected. Details are given in Table 1.

Table 1 Individual patient characteristics including BMD, fracture types, and mutational analysis. *D* diaphyseal, *S* subtrochanteric, *n.a.* not available

ID no.	Age (year)	Gender	Weight (kg)	Height (cm)	BMI (kg/m^2)	LS T-score	LS Z-score	Fracture side		Exon	cDNA	Protein	Exon	cDNA	Protein
								Right	Left						
01	44	Female	57	160	22.3	+ 3.3	+ 3.7	D	D	6	c.530C > T	p.Ala177Val	6	c.530C > T	p.Ala177Val
02	54	Female	85	154	35.8	+ 0.2	+ 1.2	D	D	6	c.526G > A	p.Ala176Thr	7	c.661G > T	p.Gly221Cys
03	55	Female	82	166	29.8	+ 0.9	+ 2.0	S	D	6	c.571G > A	p.Glu191Lys	10	c.1001G > A	p.Gly334Asp
04	71	Female	69	158	27.6	n.a.	n.a.	S	S	6	c.526G > A	p.Ala176Thr	6	c.535G > A	p.Ala179Thr
05	62	Female	68	160	26.6	− 0.2	+ 1.4	S	S	6	c.571G > A	p.Glu191Lys	12	c.1354G > A	p.Glu452Lys
06	39	Male	64	160	25.0	− 0.6	− 0.5	S	–	4	c.211C > A	p.Arg71Ser	6	c.571G > A	p.Glu191Lys
07	46	Female	115	157	46.7	+ 7.0	+ 7.5	S	D	5	c.379A > G	p.Thr127Ala	6	c.526G > A	p.Ala176Thr
08	51	Female	48	134	26.7	+ 3.8	+ 4.7	D	D	5	c.382G > A	p.Val128Met	11	c.1276G > A	p.Gly426Ser
09	45	Female	51	155	21.2	+ 1.0	+ 1.5	S	–	10	c.1009G > A	p.Asp337Asn	12	c.1363G > A	p.Gly455Ser
10	76	Female	53	152	22.9	+ 3.5	+ 5.9	S	D	6	c.500C > T	p.Thr167Met	6	c.571G > A	p.Glu191Lys
11	55	Male	78	175	25.5	− 0.8	− 0.3	–	D	6	c.571G > A	p.Glu191Lys	10	c.1001G > A	p.Gly334Asp
12	73	Female	63	146	29.6	+ 3.1	+ 5.4	–	S	6	c.571G > A	p.Glu191Lys	10	c.1001G > A	p.Gly334Asp
13	56	Male	83	168	29.4	+ 0.5	+ 1.1	D	–	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
14	43	Female	65	160	25.4	+ 1.3	+ 1.6	S	S	3	c.119C > T	p.Ala40Val	7	c.746G > T	p.Gly249Val
15	50	Female	80	160	29.7	− 0.6	0.0	D	D	6	c.571G > A	p.Glu191Lys	12	c.1354G > A	p.Glu452Lys
Mean	54.7		70.7	157.9	28.3	+ 1.6	+ 2.5								

Fracture history

Ten out of the 15 patients (66.6%) exhibited bilateral fractures summing up to 25 fractured femora accessible for evaluation. Taking into account that four patients reported recurrent fractures of the same femur at different positions over time, altogether, a minimum of $n = 33$ diaphyseal femoral fractures occurred in these 15 subjects. For those patients with multiple fractures of one femur, evaluations were focused on the most recent fracture. None of these fractures was caused by an adequate trauma. All subjects had experienced between 2 and 51 additional fractures in locations other than the femoral diaphysis. Five individuals had suffered at least one additional pseudofracture of another long bone, specifically the tibia ($n = 5$) and the humerus ($n = 2$).

In 13 patients, all their femoral fractures originated from the lateral cortex, in one patient with bilateral fractures (no. 07), both fractures initiated from the medial cortex. Later in life, this same patient experienced another femoral fracture initiating from the lateral cortical bone (Figs. 2 and 3). One patient (no. 15) showed pseudofractures originating from the lateral cortex on one femur and from the medial cortex at the other femur (Fig. 4). In $n = 23$ fractures, cortical beaking or flaring could be seen. Four fractures occurred in a periprosthetic setting. Based on retrospective evaluation of available documentation, at the time when treatment was initiated, $n = 17$ out of the 25 femoral fractures were incomplete, i.e., affecting only one cortex in the anteroposterior radiographs while $n = 8$ fractures were complete, i.e., bicortical. Of these complete fractures, two were diagnosed only after the patients fell and experienced a fracture dislocation. However, in the retrospect, both these patients with displaced fractures had prodromal symptoms beforehand, suggesting that local destabilization had already started earlier. Out of the 25 fractures, $n = 12$ were located in the subtrochanteric region, i.e., within the area 5 cm below the lesser trochanter while $n = 13$ were diaphyseal fractures. Seven patients retrospectively reported long-standing prodromal symptoms and thigh pain over the time before the fracture was diagnosed while in eight patients, clinical manifestation was with acute pain and disability.

Risk factors

A total of seven out of the 15 patients (46.7%) were diagnosed with having osteoporosis in the past and thus were treated with one or more bisphosphonates prior to their femoral fractures. Antiresorptive treatment modalities included alendronate ($n = 3$), pamidronate ($n = 4$), and zoledronic acid ($n = 2$). Mean total treatment duration with bisphophonates was 5.33 years (range 1–11 years). In addition to bisphosphonate exposure, one individual had also received both strontium ranelate for 2 years and fluorides for several years in the past (no. 10). No previous treatment with denosumab or teriparatide was documented in these patients before onset of their first femoral pseudofracture. A history of hypovitaminosis D without supplementation was documented for $n = 12$ patients (80%), suggesting that this also applied at the time of fracture. Six patients (40%) reported long-term treatment with proton pump inhibitors for a mean duration of 10 years (range 4–18 years). Two patients were active smokers; one patient had type II diabetes mellitus.

Lab evaluations

Bone turnover markers and substrate levels were not consistently available for the time of fracture. To get an overall impression about bone and mineral metabolism in these patients, evaluations were done based on most recent lab results. Mean ALP level of the patients was 10.5 U/l (SD 5.0; range 4–22 U/l) and 14 out of 15 had values below 20 U/l (normal range for adult men 40–129 U/l, for adult women 35–104 U/l) with none of the patients receiving bisphosphonates during the last 12 months. Substrate levels were considerably elevated in

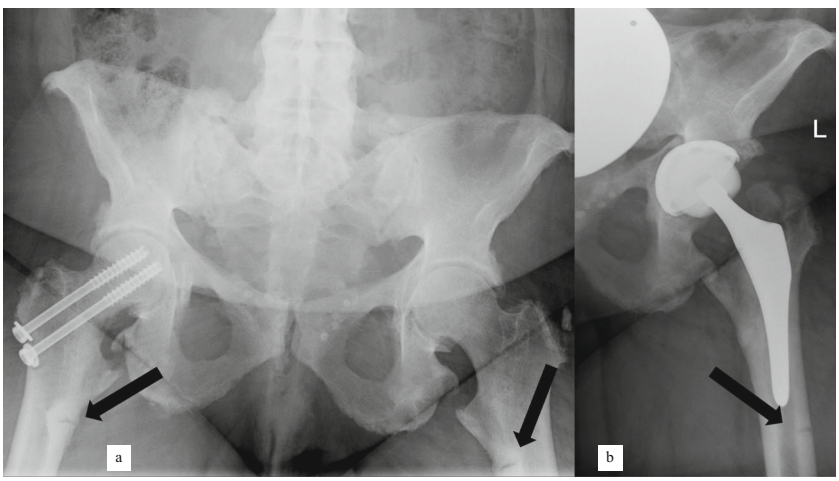

Fig. 2 Patient with femoral fractures originating from the medial cortex on both sides (**a**). Following total hip replacement, she experienced another femoral fracture originating from the lateral cortex (**b**)

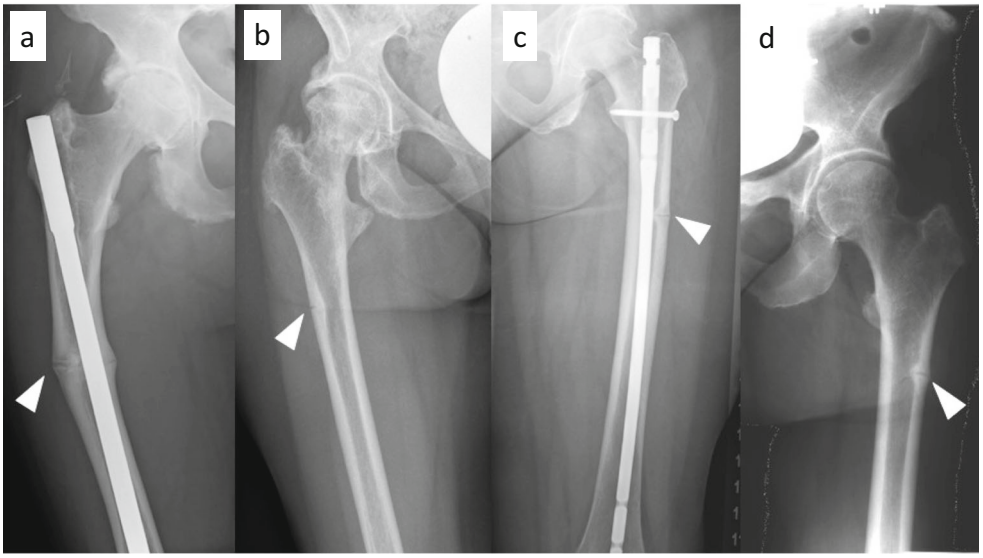

Fig. 3 Examples of femoral fractures considering ASBMR case definition of AFF, i.e., fractures are located along the femoral diaphysis distal to the lesser trochanter and meet at least four of the five major features, i.e., (1) all fractures represented were associated with minimal or no trauma; (2) the fracture line originates at the lateral cortex and is substantially transverse in its orientation; (3) complete fractures (**a**) extend through both cortices, incomplete fractures (**b**–**d**) involve only the lateral cortex; (4) the fracture is non-comminuted or minimally comminuted and (5) fractures show localized periosteal or endosteal thickening of the lateral cortex

all patients. Mean PLP level was 585.4 ng/ml (normal range 7–30 ng/ml) with all PLP values being above 100 ng/ml. Similarly, individual PEA levels in urine available for 12 patients were in between 21.7 and 180 mmol/mol creatinine (normal range 2.3–11.3) with a mean value of 79.3 mmol/mol creatinine.

Serum-phosphate levels tended to be in the upper normal range or slightly elevated. Calcium levels were essentially

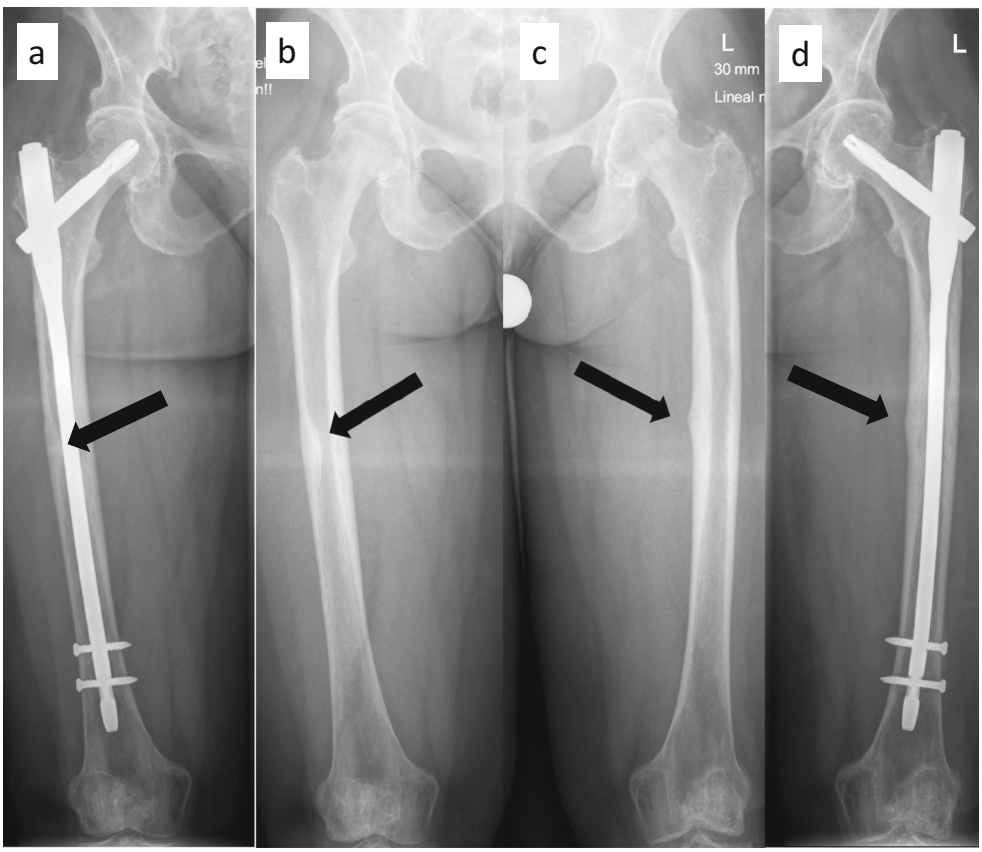

Fig. 4 Patient with bilateral femoral fractures associated with seriously limited mobility for several years. Fractures originating from the lateral cortex at the right femur (**b**) and from the medial cortex on left femur (**c**). Patient was treated with reamed intramedullary nailing and enzyme replacement therapy (ERT) was started. At follow up 4 months after surgery and initiation of ERT, osseous consolidation and remodeling was obvious (**a**, **d**) and full weight bearing was possible

normal with a tendency to higher normal values. NTX values as a marker of bone resorption and turnover tended to be in the lower normal range or even reduced. No abnormalities were found regarding excretion of calcium and phosphorus in the urine.

Bone mineral density DXA

Lumbar spine bone mineral density results were available for $n = 14$ patients. BMD was remarkably high with an average T-score of + 1.6 (SD 2.2, range − 0.8 to + 7.0) and a mean Z-score of + 2.5 (range − 0.5 to + 7.5). Individual values are given in Table 1. Owing to metal implants, femoral BMD was available for only five patients. Mean T-score was − 2.0 (SD 0.8; range − 2.9 to − 0.9) for total femur and − 2.0 (SD 1.2; range − 3.5 to − 0.4) at the femoral neck. Mean Z-score for total femur was − 1.5 (SD 0.9; range − 2.5 to − 0.1) and − 1.1 (SD 1.3; range − 2.7 to + 0.3) for the neck area.

Fracture/bone geometry

Mean femoral neck shaft angle (FNSA) could be assessed for 24 fractured femora and was 122.34° (SD 12,29; range 97.9–145.7). Lateral femoral bowing angle (lFBA) could be assessed in 17 out of the 25 fractures. Mean lFBA was 8.23° (SD 5.63; range 0.4–21.9°). Thirteen femora exhibited an lFBA > 3° which is usually considered increased. Mean cortical thickness index was 0.57 (SD 0.09; range 0.27–0.67); Analogously, the canal-to-calcar ratio was increased to 0.74 (range 0.58–1.11), both values indicating cortical osseous thickening. For evaluating medial vs. lateral proportion of cortical thickening, the lateral-to-medial cortex ratio was used. With a mean of 1.24, this was substantially elevated implicating preferentially lateral cortical thickening. Calculating fracture height, values ranged between 6.7 and 150 mm, i.e., all fractures were located along the proximal half of the femoral diaphysis. For those 10 patients with bilateral fractures, both were on the same level, i.e., subtrochanteric/diaphyseal in seven and on different height in only three, supporting the idea of a relevant causative role of an individual's anatomy and femoral geometry. Femoral offset was increased in most of the patients with an average value of 54.1 mm (range 27.6–87.9 mm). Details are given in Table 2.

Using inferential analyses, there was a significant correlation of serum-PLP levels with lateral cortical thickening ($p = 0.032$), i.e., higher PLP levels were associated with increased lateral cortical thickness. In line with that, patients with higher PLP levels had a higher lateral to medial cortex ratio ($p = 0.047$). Moreover, patients with lower serum ALP had a significantly lower fracture height ($p = 0.027$), i.e., in patients with lower serum-ALP, fractures were located more distally towards the disphyseal part of the femur. Accordingly, ALP levels were significantly lower in patients with diaphyseal fractures as compared to patients with subtrochanteric fracture localization ($p = 0.04$). Patients with higher PEA levels had significantly higher lumbar T- and Z-scores ($p = 0.044$ and $p = 0.030$, respectively). In terms of predisposing medical treatment, there was a significant correlation between bisphosphonate treatment duration and lateral cortical thickness, i.e., longer BP exposure was associated with thicker lateral cortex ($p = 0.045$). In addition, the younger the age at fracture, the longer the proton pump inhibitor therapy was going on ($p = 0.033$).

Table 2 Radiographic measures of femoral geometry

	Min	Max	Mean	SD
Femoral neck shaft angle/FNSA (°)	97.90	145.70	122.34	12.29
Femoral width (mm)	10.60	23.70	14.11	3.34
Diaphyseal width (mm)	25.50	38.00	32.59	3.76
Cortical thickness index	0.27	0.67	0.57	0.09
Canal to calcar ratio	0.58	1.11	0.74	0.13
Lateral cortex width (mm)	5.60	16.90	10.43	2.03
Medial cortex width (mm)	3.10	15.70	9.22	3.12
Lateral to medial cortex	0.69	1.89	1.24	0.38
Fracture height (mm)	6.70	150.00	64.43	41.14
Femoral offset (mm)	27.6	87.9	54.11	13.53

Treatment

The majority of fractures ($n = 23$) required surgical intervention at some instance. Only two fractures were solely treated with conservative methods. Taking into account both primary and revision surgeries, most frequent surgical intervention consisted of intramedullary rodding ($n = 17$). While 9 out of these 17 cases showed osseous consolidation at final evaluation, radiographs of 8 fractures did not exhibit complete healing. Still, all of these patients are clinically stable and thus neither require nor request additional surgical procedures. Altogether, $n = 3$ intramedullary rodding procedures had to be revised due to implant failure, persistent instability, or novel fractures. Other surgical procedures accomplished to manage these fractures included total hip replacement (THR) in 5 cases, and plating in 5 patients. Four out of the five plating approaches had to be revised due to implant failure ($n = 2$) and new fractures adjacent to the implant ($n = 2$), and only one healed appropriately. In total, $n = 9$ surgeries required revision for instability, loosening, and new fractures and were eventually treated with rodding or THR requiring revision implants. Delayed fracture healing was reported for $n = 23$ fractures (92%).

Pharmacological treatment with teriparatide in addition to surgical intervention was initiated in four patients following diagnosis of the fracture. In two patients, femoral fractures were diagnosed after approval of Asfotase Alfa. One of these

latter patients was started on enzyme replacement therapy without additional surgery and exhibited initial signs of consolidation at 3 months and complete osseous bridging at 6 months follow-up. The second patient exhibiting bilateral fractures received simultaneous intramedullary rodding and initiation of enzyme replacement therapy after surgery. Follow-up at 4 months showed complete clinical and radiographic healing on both sides.

Discussion

The work presented here aimed at evaluating key aspects of subtrochanteric and diaphyseal femoral fractures in HPP based on clinical routine data. This approach has certain limitations which should be kept in mind when interpreting these findings. Analysis is based on retrospective evaluation of data obtained from medical records, including reports from different hospitals and primary care facilities with heterogeneous data quality. Considering the observational nature of this evaluation, explanatory power of this data is limited. Specifically, this approach cannot provide desirable data for an age-/gender- and ideally disease severity/genotype-matched control group or accordingly matched pairs for the femoral geometric measures and has to rely on literature data in that respect.

Still, available data strongly supports that the risk for subtrochanteric and diaphyseal femoral fractures appears to be increased in hypophosphatasia [22, 23, 31]. In the large cohort assessed for this evaluation, the combined prevalence of both subtrochanteric and diaphyseal fractures was as high as 10%. Since many individuals experienced bilateral and/or recurrent fractures, a total of 33 femoral fractures occurred in these 150 persons. Importantly, even though the underlying cohort of 150 HPP patients screened covered the complete spectrum of disease severity, all these fractures occurred in patients harboring mutations in both alleles. This again is in line with the notion that all individuals with these fractures retrospectively had symptoms in early childhood and have to be considered some form of pediatric onset disease.

Reflecting that these 150 individuals cover about 7500 lifetime years, this equals to an incidence rate of 33 fractures in 7500 person-years, i.e., 44/10,000 person-years. For comparison, the incidence rate in the general population of Sweden was recently supposed to be 0.09/10,000 person-years with an increase to up to 8.4/10.000 person-years for those with ≥ 2 years of bisphosphonate use [2].

Clinical and radiographic features of subtrochanteric and diaphyseal fractures in HPP appear similar to what is known for AFF in the setting of long-term antiresorptive treatment, suggesting similarities of the underlying pathophysiology. Indeed, 22 out of the 25 fractures met established ASBMR criteria for AFF (Fig. 3). Three fractures differed, essentially because they initiated from the medial cortex. Even though initiation of these fractures from the medial cortex is more frequently seen in different forms of osteomalacia like, e.g., X-linked hypophosphatemia (XLH) and as stress fractures in athletes [23, 32, 33], our findings support the notion that medial fractures can also occur in HPP, with one patient coincidently exhibiting both, one lateral and one medial fracture.

Speculating on the underlying pathophysiology, one obvious commonality of HPP and long-term antiresorptive treatment is reduced bone turnover. This would feed into the idea of low bone turnover and impaired remodeling, i.e., deficient healing capacity and accumulation of microcracks as a causative factor in both these situations. Accordingly, this risk might accumulate in HPP patients exposed to additional risk factors, particularly bisphosphonates. Indeed, a history of previous treatment with bisphosphonates was found in 6 out of the 15 patients evaluated. Bisphosphonates have already been deemed inappropriate for HPP patients in the past even though there were only few documented cases demonstrating negative impact of such treatment [22, 34]. Taking up on this thought, this current analysis now provides compelling evidence that bisphosphonates can be harmful particularly in severe HPP and should essentially be avoided. Moreover, other supposed risk factor like long-term treatment with proton-pump inhibitors or hypovitaminosis D [9] should be taken into account and—if possible—precluded when treating HPP patients at risk.

Elevated levels of circulating PLP have been identified as a hallmark of hypophosphatasia decades ago [35], and it appears that PLP might also be a suggestive marker in order to identify patients at risk for these fractures, considering that all assessed in this study exhibited values > 3 times the upper normal limit. Concurrently, PEA levels in urine were remarkably high in those patients. In this context, it would have been interesting to know levels of inorganic pyrophosphate (PPi) since this might be both, a potential candidate to reflect disease severity and a causative agent in fracture pathophysiology. However, approved assays for reliably testing PPi levels in clinical routine are not available at this point.

Data presented here confirms cortical thickening being an indicator of developing diaphyseal femoral fractures even in HPP, since this was observed in the majority (91.7%) of cases. Findings also confirm previous observations suggesting low FNSA being a risk factor for this kind of fractures since varus hip geometry with an FNSA below 128° was seen in 15 affected hips. Along with varus conformation of the proximal femur, increased femoral offset appears a predisposing factor. Mean offset in the current cohort was 54.1 mm, considerably exceeding the value of 43.1 mm, recently reported as being a threshold predisposing to AFF [36]. In line with literature data [10], these current findings in HPP also confirm increased bowing as a risk factor for femoral fractures in HPP. Looking at this from a different perspective, these pathological deformities eventually predisposing to such fractures in

HPP, specifically decreased FNSA and increased femoral bowing, could be considered a sequelae of childhood rickets, i.e., a sign of pediatric onset HPP.

Structural aspects appear to be in line with what is seen in AFF, including presence of cortical flaring/beaking and increased cortical thickening (Fig. 3). Again, this appears even more pronounced in HPP. Cortical thickness index, the canal-to-calcar ratio, and the medial-to-lateral cortex ratio were repeatedly demonstrated to be increased in AFF [29]. However, in the cohort under investigation, all these three parameters were even beyond those reported in studies for AFF [10].

BMD values for the proximal femur were available only for few patients owing to metal implants in most of the hips. However, lumbar-spine BMD values available for the majority of patients were remarkably high in HPP patients with subtrochanteric or diaphyseal femoral fractures. It was reported earlier for children with HPP that individual lumbar spine BMD Z-scores are significantly higher than those measured at the hip [37], and disease-associated inappropriately structured mineralization of bone tissue [38] and ligamentous structures at the spine resembling a DISH-like phenotype can be considered to contribute to erroneously high lumbar spine BMD values [39, 40]. Otherwise, to the best of our knowledge, there is no systematic evaluation of LS-BMD in patients with AFF following long-term antiresorptive treatment for osteoporosis, and considering the underlying disease, BMD would probably be low in most of them. Still, AFF do not appear to be associated with particularly low BMD as this is the case for typical femoral fractures [7]. It remains speculative if—potentially together with high PLP—this could be a marker of flawed mineralization and deposition of inappropriately structured mineral.

From a clinical perspective, persisting thigh pain appears to be the most prevalent symptom to identify patients at risk for femoral (pseudo-) fractures and HPP patients reporting thigh pain should further be evaluated radiologically, specifically considering the high proportion of bilateral manifestations. This is of particular importance since these fractures appear to develop progressively in most instances, and we identified two patients in whom prodromal sigs eventually culminated in a fall with seriously displaced.

The question of a potential association between HPP and AFF has recently been addressed in a case-control study [41]. Evaluating a series of 10 patients with AFF following bisphosphonates and 13 control patients on bisphosphonates without femoral fractures, no coding mutations in the ALPL gene were found in these patients. Hence, the authors concluded that there is no evidence of HPP as a risk factor for atypical femur fractures. In clear contrast, our results confirm an increased risk of subtrochanteric and diaphyseal femoral fractures in HPP. Accordingly, in osteoporosis patients experiencing AFF, a mindful look for low ALP values—ideally before antiresorptive treatment is initiated—appears reasonable in order not to miss a case of HPP [42]. Vice versa, supposed osteoporosis patients should be evaluated for low ALP activity before starting antiresorptive treatment.

Building on the findings of these analyses, surgical treatment with load-bearing implants, typically intramedullary rodding appears advisable while inferior results were seen with plate fixation. Considering the fact that new fractures occurred in four patients after removal of the internal fixation and in line with previously reported experience [43]. Implants should not be removed if there is no urgent medical need and if so, they should be replaced within the same surgical approach. In line with what has been reported in the literature, osteoanabolic treatment with teriparatide was used as additional treatment in four of the patients included in this analysis. Eventually, all these fractures healed at least partially but it remains elusive to what extent this is due to osteoanabolic intervention, specifically when considering recent data questioning a substantial positive effect of TPTD in AFF [44]. Similarly, there was a positive course of treatment in those two patients receiving enzyme replacement therapy following diagnosis of a femoral fracture but it would be premature to draw any final conclusions. Data seem encouraging but the clinical impact of enzyme replacement therapy in terms of fracture prevention and improved healing of these fractures remains to be elucidated.

Notwithstanding aforementioned limitations of this study, data appear appropriate to confirm an increased prevalence of subtrochanteric and diaphyseal femoral fractures in adult HPP patients specifically in case of recessive disease, i.e., in patients bearing two mutations on different alleles. The risk for these fractures appears to be driven by disease-inherent alterations of bone metabolism, bone quality, and associated geometrical particularities. Additional potential risk factors that warrant further attention include previous treatment with bisphosphonates and proton pump inhibitors as well as hypovitaminosis D. Still, more detailed, ideally prospective data would be helpful for both understanding the pathophysiology of these fractures in HPP as well as supporting recommendations in terms of clinical management. Until additional data is available, treatment should preferentially be conducted at centers that have experience with both current recommendations on the treatment of AFF and the specific metabolic setting in hypophosphatasia.

Acknowledgements We thank Jasmin Baumann, Silke Achtziger, Ursula Hellwich, and Nicole Luksche for their highly valued assistance with data collection and archiving.

Compliance with ethical standards

Conflicts of interest FG reports personal fees from Lilly during the course of the study.

LS reports grants and personal fees from Novartis and Alexion and personal fees from Lilly and Amgen during the course of the study.

Statement This study is a retrospective evaluation of clinical routine data. For this type of study, formal consent is not required.

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