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Management of X-Linked Hypophosphatemia in adults

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Abstract

X-linked hypophosphatemia (XLH) is caused by mutations in the *PHEX* gene which result in Fibroblast Growth Factor-23 (FGF23) excess and phosphate wasting. Clinically, XLH children present with rickets, bone deformities and short stature. In adulthood, patients may still be symptomatic with bone and joint pain, osteomalacia-related fractures or pseudofractures, precocious osteoarthritis, entesopathy, muscle weakness and severe dental anomalies. Besides these musculoskeletal and dental manifestations, adult XLH patients are also prone to secondary and tertiary hyperparathyroidism, cardiovascular and metabolic disorders. Pathophysiology of hyperparathyroidism is only partially understood,..... Similarly, the pathophysiological mechanisms of potential cardiovascular and metabolic involvements are not clear, but FGF-23 excess may play an essential role. Treatment should be considered in symptomatic patients, patients undergoing orthopedic or dental surgery and women during pregnancy and lactation. Treatment with oral phosphate salts and active vitamin D analogs has incomplete efficacy and potential risks. Burosumab, a recombinant human monoclonal antibody against FGF 23, has proven its efficacy in phase 2 and phase 3 clinical trials in adult patients with XLH, but currently its position as first line or second line treatment differ among the countries.

Keywords

X-linked hypophosphatemia, FGF-23, hyperparathyroidism, phosphate supplementation, active vitamin D derivatives

1. Introduction

X-linked hypophosphatemia (XLH) is a rare inherited form of renal phosphate wasting disorder caused by loss of function mutations in the *PHEX* gene, located on the X chromosome, which is expressed in osteocytes and odontoblasts [1]. These mutations result in increased circulating concentrations of FGF-23 [2]. Excess FGF-23 inhibits the renal reabsorption of phosphate, suppresses 1-hydroxylation of 25-hydroxyvitamin D (25(OH)D) in the kidney and stimulates the 25-vitamin D-24 hydroxylase [3]. XLH is thus characterized by renal phosphate wasting with reduced TmP/GFR (tubular maximal reabsorption of phosphate adjusted for glomerular filtration rate), and inappropriately low 1,25(OH)₂D serum concentrations, responsible for decreased intestinal phosphate absorption, both resulting in chronic hypophosphatemia.

Clinically, rickets and growth retardation in childhood are the main features of XLH and appear during the first or second year of life [4]. Subjects with XLH can develop bone deformities (especially of the lower extremities), that may require corrective surgical treatment [5]. In adulthood, patients are prone to osteomalacia which, together with abnormal mechanical stress linked to leg deformities, predisposes to fractures and pseudofractures. Patients further present with degenerative joint disease, enthesopathy, muscle weakness, dental disease such as tooth decay and dental abscesses and hearing loss [4,5]. The rheumatologic manifestations are responsible for bone and joint pain, stiffness, decreased joint mobility and decreased physical function which may considerably alter quality of life [6]. Fatigue is also a main symptom in adults and contributes to alteration of quality of life. However, many adult patients do not have clinical manifestations at all.

This review focuses on the endocrine and metabolic complications that may be encountered in XLH adult patients besides the “classic” musculoskeletal and dental manifestations, and on the therapeutic options available for these patients. Other clinical features and complications of adult XLH patients will be discussed elsewhere in this review.

2. Endocrine and metabolic complications in adult XLH patients

2.1 Hyperparathyroidism

The primary pathophysiological basis for renal phosphate wasting in XLH is the *PHEX* mutation-related FGF-23 excess. Renal phosphate wasting can be however accentuated by concomitantly increased PTH action. Indeed, patients with XLH frequently present with (moderately) increased plasma PTH concentrations.

Secondary and tertiary hyperparathyroidism have been repeatedly reported in XLH patients [7–26]. The precise prevalence and pathophysiology of secondary hyperparathyroidism, which

is defined by low to normal calcemia and increased PTH concentrations, in adult XLH patients is not known. Definition of PTH normal values is frequently inaccurate because elaborated from vitamin-D deficient populations, with consequently increased PTH values considered as the upper limit of normal [27]. Therefore, the prevalence of secondary hyperparathyroidism in XLH patients may be underestimated in studies lacking appropriate control population. In these patients, insufficient correction of 1,25(OH)₂vitamin D deficiency by use of too low doses of active vitamin D analogs seems to be associated with the occurrence of secondary hyperparathyroidism, this effect being exacerbated by chronic phosphate supplementation.

Some patients with XLH develop tertiary hyperparathyroidism defined by hypercalcemia and inappropriate (normal or elevated) PTH concentrations. Parathyroid autonomy (**Figure 1**), especially develops in patients with earlier onset of the disease, longer duration of the treatment (> 10 years in all cases, between 15 and 20 years for the majority), higher doses of oral phosphate salts and longer periods of treatment with very high phosphate doses [20].

Parathyroid autonomy further complicates XLH by worsening hypophosphatemia, causing hypercalcemia and hypercalciuria that may contribute to renal complications such as nephrocalcinosis and, at least in theory, by raising the risk of skeletal involvement. Again, the precise prevalence of tertiary (hypercalcemic) hyperparathyroidism in adult XLH patients, based on prospective evaluation, is not known.

From the pathogenetic point of view, hyperparathyroidism in XLH patients is classically attributed to recurrent stimulation of parathyroid glands by oral phosphate boluses resulting in intermittent supraphysiological serum phosphate concentrations [10,13,20]. However, cases of secondary and tertiary hyperparathyroidism have been documented in XLH patients who never received phosphate therapy, arguing against a role of intermittent hyperphosphatemia [13,26,28–32]. Actually, deficient production of calcitriol induced by FGF23 excess is very likely the main factor involved in the development of hyperparathyroidism as calcitriol is a known inhibitor of parathyroid cell proliferation [33]. In addition to calcitriol-suppressing effect of FGF23, altered PTH secretory dynamics, and loss of PHEX function in the parathyroid gland leading to abnormal PTH mRNA cleavage or degradation have been suggested to play a role in the occurrence of hyperparathyroidism [25,29].

2.2 Metabolic and cardiovascular complications

Cardiovascular complications have been described in XLH patients, even at a very young age. Hypertension has been reported in small series of children with XLH (aged 8-20 years) with a need for anti-hypertensive treatment for some of them and left ventricular hypertrophy (LVH), mostly concentric, on echocardiogram for almost half of them [34,35]. Most of these patients had normal ECG. In a recent report of 22 XLH patients, 6 had hypertension with an average age of onset of 29 years [36].

Three other studies have evaluated the prevalence of LVH among XLH patients giving contradictory results since no left ventricular dysfunction was found in the 45 patients evaluated [37–39]. To date, descriptions of cardiac structure and function in XLH patients have been limited to 2D echocardiography and restricted to the left ventricle. One important limitation of these echo-based studies is that the measurement of LV volumes and mass by 2D echocardiography requires assumptions to be made concerning LV geometry, introducing a source of inaccuracy and variability [40], especially in patients with short stature, in whom normative data for LV mass are lacking. Cardiac magnetic resonance imaging (CMR) provides a highly accurate and comprehensive assessment of cardiac geometry and function. CMR provides regional myocardial wall thickness, myocardial mass and atrial and ventricular volumes based on precise delineation of myocardial borders without the need for geometric assumptions [41,42] and would be the appropriate tool to precisely assess cardiac structure and function in XLH patients.

The pathophysiology of these cardiovascular complications is not known. The role of nephrocalcinosis and hyperparathyroidism in the development of hypertension and LVH has been suggested since almost all affected patients presented also with nephrocalcinosis and/or secondary hyperparathyroidism [34–36]. Further, participation of high FGF-23 levels seems more than likely. Indeed, *in vitro* and *in vivo* in wild-type and *klotho*-deficient mice, FGF-23 is able to induce LVH and to increase blood pressure [43]. Finally, in *Hyp* mice, which are a model of human XLH, chronically elevated circulating FGF-23 is associated with increased heart-to-body weight ratio and increased blood pressure [44].

Altogether, few studies with limited sample size indicate increased cardiovascular risk in XLH patients. There is therefore an urgent need for larger prospective studies assessing the cardiovascular involvement in adult XLH patients, to tailor the appropriate clinical management. To date, we propose in adult XLH patients to monitor blood pressure and to perform LV mass evaluation at least once at the transition period, with further evaluation according to the findings and the clinical context.

Regarding other cardiovascular risk factors such as dyslipidemia, hyperglycemia and obesity, no study has evaluated their prevalence in adult XLH patients. Yet, several arguments from the literature suggest that XLH patients may be prone to such metabolic disorders, particularly through the elevation of FGF-23. FGF-23 shares structural similarities with FGF-19 and FGF-21 which are involved in the regulation of glucose and lipid metabolism [45]. In cohorts of elderly Swedish men and women, serum FGF-23 levels was found to be associated with higher body mass index (BMI), larger waist circumference, elevated triglycerides, lower HDL cholesterol and apoA1, and increased total and trunk fat mass [46]. The subjects with higher FGF-23 levels had an increased risk of metabolic syndrome. Impaired glucose metabolism has

also been described in *Hyp* mice with reduced serum insulin and increased glycemia [47]. These mice have also a greater food consumption [48]. The elevation of PTH concentrations often seen in XLH patients could also play a role in the occurrence of metabolic disorders. Plasma PTH has been positively correlated to waist circumference, BMI, systolic and diastolic blood pressure, plasma triglycerides, HOMA of insulin sensitivity, cardiovascular mortality and negatively correlated to HDL-cholesterol in elderly Swedish men and women [49,50]. Another study in 52 normotensive, glucose-tolerant, healthy subjects found that plasma PTH level was inversely correlated with insulin sensitivity index [51]. Hyperparathyroidism is also associated with dyslipidemia, obesity, hypertension and insulin resistance [52–54]. Finally, chronic hypophosphatemia and vitamin D deficiency could also be involved. Serum phosphate concentrations correlated negatively with blood pressure, triglyceride, glucose values, waist circumference, HOMA index values and insulin in healthy subjects [55–60] and lower phosphate levels have been reported in subjects with metabolic syndrome. Vitamine D deficiency increased insulin resistance, decreased insulin production and was associated with metabolic syndrome [61,62].

However, these studies are mainly observational and describe associations and not causal relationships between these parameters. Thus, direct implication of these factors in the pathogenesis of metabolic syndrome still needs to be proved.

3. Treatment

3.1 Indications

In childhood, early treatment with oral phosphate and active vitamin D supplements has been shown to have beneficial effects on linear growth, rachitic bone deformations and dental abnormalities [5]. Once growth is complete, adolescents or young adult XLH patients often stop the burdensome treatment, no longer seeing its benefits. The taste of oral phosphate supplements clearly contributes to the low therapeutic adherence and frequent treatment arrest at this transition period. However, chronic phosphate wasting has also consequences in adulthood such as osteomalacia-related fractures and pseudofractures, fatigue, muscle involvement or dental problems, that can be improved by treatment [4]. Collaboration between adult and pediatric specialists is thus crucial to avoid loss of follow-up during the transition period.

There is no consensus regarding indications of treatment in adult patients since its efficacy has not been precisely evaluated, and it may be source of renal and endocrine complications. Oral phosphate salts and active vitamin D derivatives can be maintained or reintroduced in symptomatic patients. This treatment can reduce bone pain and improve osteomalacia, muscle strength and physical function in some patients [63]. However, the benefit of treatment should be discussed again with the patient in the absence of improvement in symptoms.

Spontaneous insufficiency fractures are more likely to heal faster with therapy [4]. It is also recommended before and 3-6 month after surgical orthopedic or dental interventions to promote bone mineralization [4]. The treatment does not prevent the occurrence of enthesopathy, which is also source of pain in these patients [64] and it does not modify osteoarthritis-related pain. Phosphate and vitamin D treatment is also beneficial for dentin mineralization and dental health, especially if it has been started in early childhood [65,66] but has not been well evaluated in periodontal defects. Hearing difficulties and metabolic complications (*cf. supra*) can appear during adulthood but it is not known if treatment with phosphate and active vitamin D derivatives can prevent their occurrence [5].

Finally, phosphate and vitamin D treatment could help to prevent osteomalacia in menopausal women at risk of osteoporosis.

In asymptomatic patients, the lack of knowledge about the long-term consequences of chronic hypophosphatemia and the efficacy of the therapy made the treatment even more debated.

3.2 Phosphate and active vitamin D derivatives

Transition from childhood to adulthood, which is a period of high growth velocity, is marked in XLH patients by a decrease in calciuria, a raise in PTH levels and a decrease of phosphatemia. It is therefore important in these patients to diminish phosphate intakes from 4 times daily to 3 times daily and to increase 1,25(OH)₂D supplementation to avoid growth failure and bone deformities. Once growth is complete, vitamin D analogs are decreased to maintenance doses and phosphate doses are further decreased to twice-daily administration.

In adult XLH patients, when indicated, oral phosphate salts are given usually at 700-1200 mg/day in two divided doses. Alfacalcidol should be preferred to calcitriol and is given at a dose of 0.75 to 1.5 µg once daily. This dose should be individually titrated in order to avoid hypercalcemia, hypercalciuria while keeping PTH concentrations in normal range [67]. There is no evidence to recommend monitoring calcitriol concentrations for adjustments of the dose of active vitamin D derivatives. Any 25(OH)D deficiency should be corrected.

The aim of treatment is to release symptoms, not to normalize serum phosphate levels. Unlike the childhood period, serum alkaline phosphatase activity is not a major marker of treatment efficacy but abnormal levels, in particular of the bone specific isoenzyme, could indicate extensive osteomalacia in adult patients.

Since inappropriate or excessive treatment may result in hyperparathyroidism and hypercalciuria with nephrocalcinosis and renal insufficiency, plasma calcium, PTH, creatinine and 24-h urinary calcium excretion need to be carefully monitored [4]. Increasing PTH levels may be corrected by increasing the calcitriol dose or by reducing the phosphate dose and, in case of hypercalcemia or hypercalciuria, the active vitamin D derivative dose must be reduced [4]. Renal ultrasonography or, preferably, renal CT scan should be performed at the transition

period to detect nephrocalcinosis and/ or nephrolithiasis. Ultrasound monitoring can be then performed in adult patients on treatment.

Despite the benefits of this treatment, it tends to increase FGF-23 in both the *Hyp* mouse and humans with XLH [68,69] and the clinical consequences of this rise in FGF-23 concentrations are uncertain. High FGF-23 levels may have deleterious effects on health, in particular on metabolism and cardiac functions (*cf supra*).

3.3 Burosumab

After the identification of the role of FGF-23 excess in the pathophysiology of XLH, much effort has been directed to develop new pharmacological strategies targeting the FGF-23 pathway.

A recombinant human monoclonal IgG1 antibody (burosumab, formerly KRN23) directed against FGF-23 has been developed and is now licensed for children older than 1 year of age in Europe and for both children and adults in the US. It binds the amino-terminal domain of FGF-23 and prevents FGF-23 from binding to its receptor [70]. In preclinical studies in *Hyp* mice, a reduction of phosphaturia and an improvement of phosphatemia and 1,25(OH)₂D levels have been observed along with improved growth and muscle strength [71,72]. In randomized double-blinded phase 1 and 2 trials, once monthly subcutaneous administration of burosumab in XLH adults increased serum levels of phosphate, TmP/GFR, and 1,25(OH)₂D [73,74]. Burosumab administration was also associated with significantly improved patient perception of their physical functioning and stiffness due to their disease [75].

This efficacy and safety profile has been recently confirmed in a large, double-blind, placebo-controlled, phase 3 trial of burosumab in 134 symptomatic adults with XLH [76]. Participants were assigned to burosumab 1 mg/kg or placebo subcutaneously every 4 weeks for 24 weeks, followed by an open-label phase on burosumab during further 24 weeks. Across midpoints of dosing intervals, 94% of burosumab-treated participants attained mean serum phosphate concentration above the lower limit of normal as compared to 7.6% of those receiving placebo. Burosumab significantly reduced the WOMAC Index stiffness subscale compared with placebo and was associated with better active fracture healing (**Figure 2**)[76]. Recently, an open-label, single-arm, phase 3 study demonstrated the efficacy of subcutaneous burosumab, 1.0 mg/kg administered every 4 weeks, in improving osteomalacia in 14 adults with XLH, with significant amelioration of osteomalacia-related histomorphometric measures at Week 48 of treatment [77].

In parallel, in an open-label phase 2 trial, burosumab administered sub-cutaneously at 2-week intervals in children aged 5 to 12 years improved renal tubular phosphate reabsorption, serum phosphate levels, linear growth, physical function and reduced the pain [78].

In the United States (US), burosumab is indicated for the treatment of XLH in adult and pediatric patients 1 year of age and older [79]. In Europe, burosumab therapy is authorized

only for treatment of XLH with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeletons [80]. It is currently considered as second line therapy for children who fail to respond to optimal treatment with phosphate and vitamin D derivatives and as first line for children with a severe form of rickets with complications.

In US, the recommended starting dose regimen is ~~0.8 mg/kg of body weight every two weeks in children and~~ 1 mg/kg body weight every four weeks in adults. ~~In Europe, starting dose regimen is 0.4 mg/kg of body weight.~~ Fasting serum phosphate needs to be reassessed every 4 weeks to adjust the dose, at least for the first 3 months of treatment. Burosumab should be used only at referral centers. The most common adverse reactions observed under treatment are back pain, headache, restless leg syndrome, decreased vitamin D, dizziness, constipation, injection site reaction, vomiting, and fever. No immunogenicity has been associated with burosumab treatment so far.

3.4 Future therapeutic strategies in adult patients

3.4.1 Inhibitors of FGF-23 effects

Several other treatments are being studied that alter FGF-23 production or degradation, or block the negative effects of FGF-23. FGF-23 receptor antagonists (NVP-BGJ398) aiming at inhibiting effects of high FGF-23 levels are under development [81]. A number of other potential pharmacological targets have been identified, including antagonizing peptides known to inhibit bone mineralization as well as the regulation of FGF-23 protein expression. Treatment of *Hyp* mice with Hexa-D-Arginine enhanced bone 7B2•PC2 activity, normalized FGF-23 degradation and rescued the *Hyp* phenotype [82].

3.4.2 Calcitonin

Subcutaneous administration of calcitonin has been suggested to increase phosphatemia and $1,25(\text{OH})_2\text{D}$ and decrease FGF-23 levels in patients with XLH [83,84]. In a recent double-blind study, 21 adults with XLH were randomized to nasal calcitonin 400 IU/day or placebo for 3 months. No effects on serum phosphate, serum calcium, circulating levels of PTH, TmP/GFR, $1,25(\text{OH})_2\text{D}$ and FGF-23 levels have been shown at the end of the 3 months [85]. Moreover, uncertainties on whether treatment with calcitonin may increase risk of malignant disease will perhaps limit its use.

3.4.3 Inhibition of CYP24A

CYP24A1 is an enzyme involved in the inactivation of vitamin D metabolites and its renal expression is increased in renal phosphate wasting disorders due to high levels of FGF23. Loss of *Cyp24* in murine models of human XLH disease resulted in near-complete recovery of rachitic/osteomalacic bony abnormalities without any improvement in the serum biochemical profile. Treatment of these mice with a CYP24 inhibitor also ameliorated their rachitic bones

[86]. Pharmacologic CYP24 inhibition could thus represent a future therapeutic strategy for XLH patients.

3.5 Multidisciplinary care

Enthesopathy and osteoarthritis need to be taken care of by rheumatologic teams. Treatment aims to release the pain and to improve stiffness, joint mobility, muscle weakness and physical function. It relies on analgesics, non steroidal anti inflammatory drugs, physiotherapy and physical exercise recommendations, in addition to treatment with phosphate and active vitamin D derivatives or with burosumab. Dental, orthopedic and neurosurgical care are also often needed and must be provided in expert centers. General recommendations should be given to encourage lifestyle changes for cardiovascular and obesity prevention. Therapeutic patient education is crucial for a better treatment adherence. Patients can get information during workshop organized in reference centers or by self-help groups.

4. Treatment of endocrine complications

4.1 Hyperparathyroidism

The prevention or correction of hyperparathyroidism is an important goal in management of adult XLH patients. The phosphate supplementation should not be given without active vitamin D metabolites! If secondary hyperparathyroidism developed, phosphate doses should be decreased, and the doses of the active vitamin D metabolite increased. In a prospective, randomized, placebo-controlled, double-blind, 1-year trial, paricalcitol (a vitamin D analog) was shown to suppress PTH secretion in XLH patients with previous evidence of secondary hyperparathyroidism [87]. Thus, paricalcitol appears to be an effective adjunct to standard therapy to prevent progression of hyperparathyroidism in these patients. However, urinary calcium excretion must be carefully monitored as hypercalciuria developed in some treated subject [87].

The standard surgical approach to patients with tertiary hyperparathyroidism has been either subtotal parathyroidectomy or total parathyroidectomy with autotransplantation. Preoperative evaluation with Technetium-99 m Sestamibi SPECT and ultrasound imaging, as well as the use of intraoperative parathyroid hormone measure, are effective in guiding surgical resection [88]. As these patients are susceptible to severe postoperative bone hunger, appropriate supplementation with oral calcium can minimize hypocalcemic symptoms [88]. Tertiary hyperparathyroidism is in theory the result of hyperplasia of all four (or more) glands. However, several reports indicate that up to 29% of patients with tertiary hyperparathyroidism may have disease limited to one or two glands [9,20,21,25,88,89], allowing selective adenectomy.

A single dose of cinacalcet, an allosteric modulator of the calcium sensing receptor, prevented the phosphate-induced increase in PTH concentrations in 8 XLH patients aged 6 to 19 yrs [90].

Analogical data in adult populations are lacking. In a recent case report, cinacalcet was also shown to reduce the serum FGF-23 levels [24], which remained stable after six months of therapy. Long-term clinical studies in pediatric and adult XLH patients are needed to investigate the usefulness of cinacalcet as adjuvant therapy preventing hyperparathyroidism. A future tool to manage hyperparathyroidism could be burosumab. In the phase 3 trial on adults, PTH concentrations decreased in the burosumab-treated group and increased at week 24 in the placebo group, suggesting that burosumab could improve hyperparathyroidism in these patients [76].

4.2 Cardiovascular and metabolic disorders

The effect of treatment with phosphate and active vitamin D derivatives or with burosumab on prevention of these complications is currently unknown. Given the potential role of FGF-23 excess in the pathogenesis, the new pharmacological strategies targeting the FGF-23 pathway may be useful to prevent hypertension, LVH and metabolic syndrome. To date, current recommendations about the prevention and treatment of metabolic syndrome should be followed.

5. Pregnancy and lactation

Since pregnancy is a condition where calcium and phosphate demands are increased, treatment with active vitamin D derivatives and oral phosphate salts can be proposed to prevent mineralization defect of the fetal skeleton, especially during the third trimester [5]. However, skeletal complications have not been reported in genetically unaffected infants born to mothers with XLH [91]. Follow-up of XLH pregnant women in maternity hospitals for high-risk pregnancy is recommended even without need for special treatment or monitoring.

During lactation, regulation of calcium and phosphate metabolism enables sufficient galactopoiesis [5]. Low milk phosphorus content has been reported in an untreated XLH mother [92] but lactating Hyp mice seem to have normal milk composition despite hypophosphatemia [93]. Therefore treatment with active vitamin D derivatives and oral phosphate salts can also be proposed to lactating XLH women but is not mandatory.

Genetic counseling for the woman and her partner is required before considering pregnancy and should be performed by a physician expert in the field. Parents need to be informed about the risk of transmitting the disease and about the management strategy for affected neonates. Eighty-five to 90% of patients with genetic hypophosphatemia have an identified germinal *PHEX* mutation [94], which can be inherited or *de novo*. Mosaicism can also be observed for *de novo PHEX* mutations. However, no genetic defect is found in around 10% of patients. Pre-implantation genetic diagnosis in seriously affected patients who ask for it is technically

feasible when a genetic defect has been identified but it should be discussed case by case in reference centers.

Screening of hypophosphatemia needs to be performed in new borns. The familial *PHEX* mutation can be searched in a cord blood sample and/or the neonate be tested for serum phosphate, creatinine, alkaline phosphatase and urine phosphate excretion.

6. Conclusion

The main clinical feature of XLH remains the bone deformities and growth retardation in children, focusing the attention of physicians on legs straightening and growth. However, adults should be regularly monitored for the prevention and limitation of bone pain, stiffness and extra-osseous complications, in particular hyperparathyroidism and metabolic disorders. Current therapy with phosphate supplements and vitamin D analogs (partly) corrects osteomalacia but requires an adequate balance between the benefits derived from treatment and the potential risks, and has low therapeutic adherence. Outcomes of therapy are still not optimal and therapies targeting the pathophysiology of the disease are required. Agents able to decrease FGF-23 expression or its activity open the way for other successful therapeutic approaches. Finally, prevention and correction of hyperparathyroidism is an important goal in management of adult XLH patients.

Contributors

ALL and PK: wrote the manuscript.

MLB: Critical reading of the paper and construction of the paper.

AL: Critical reading of the paper, construction of the paper and the associated figures.

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Conflicts of interest

ALL has no conflict of interest to declare.

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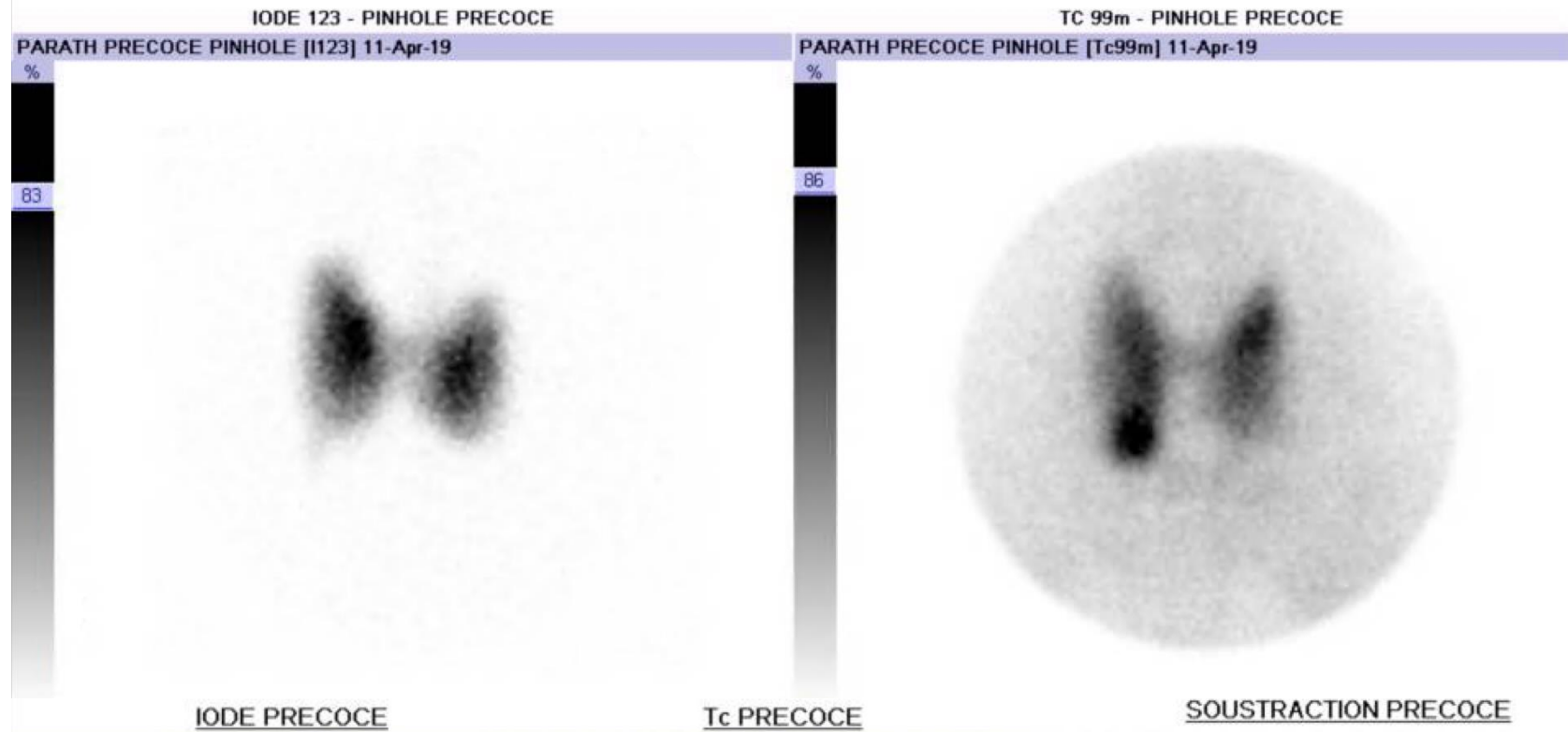
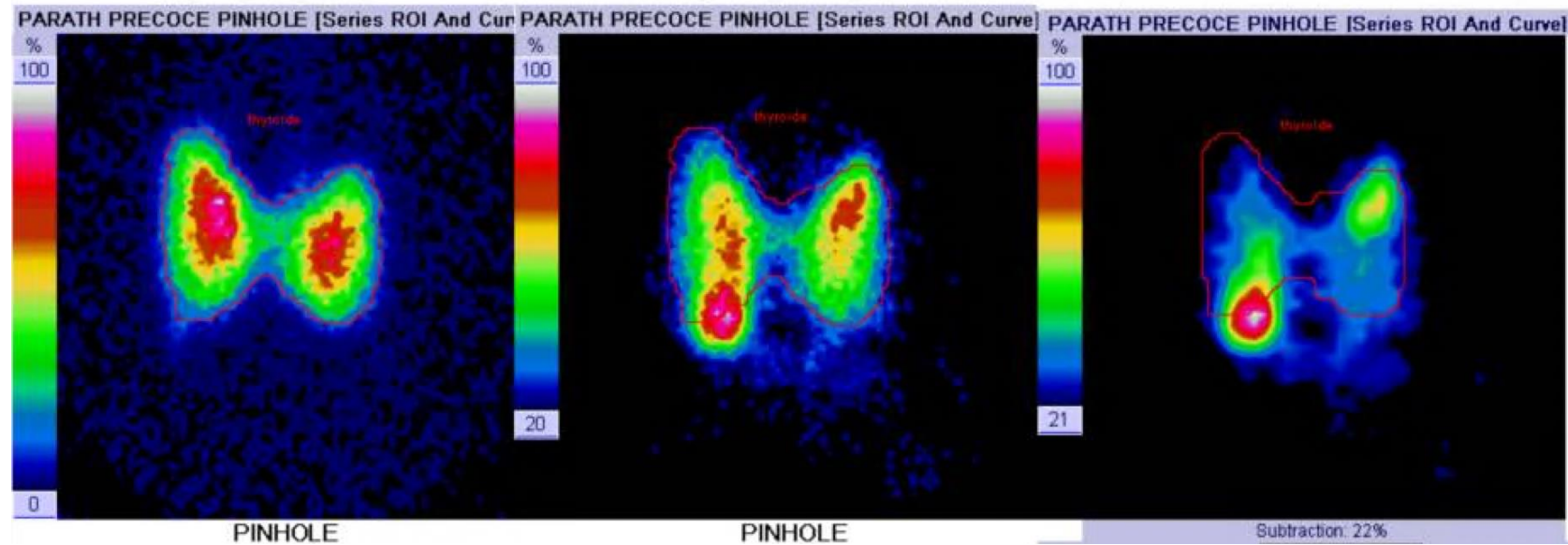
Legends of figures

Figure 1: Imaging of a parathyroid adenoma

A and B : (99m)Technetium Sestamibi-(123)Iodine Scintigraphy images showing the thyroid (left panels) and one right inferior parathyroid adenoma in a 16-years old XLH patient presenting with hypercalcemia and elevated PTH levels upon phosphate supplements and vitamin D analogs.

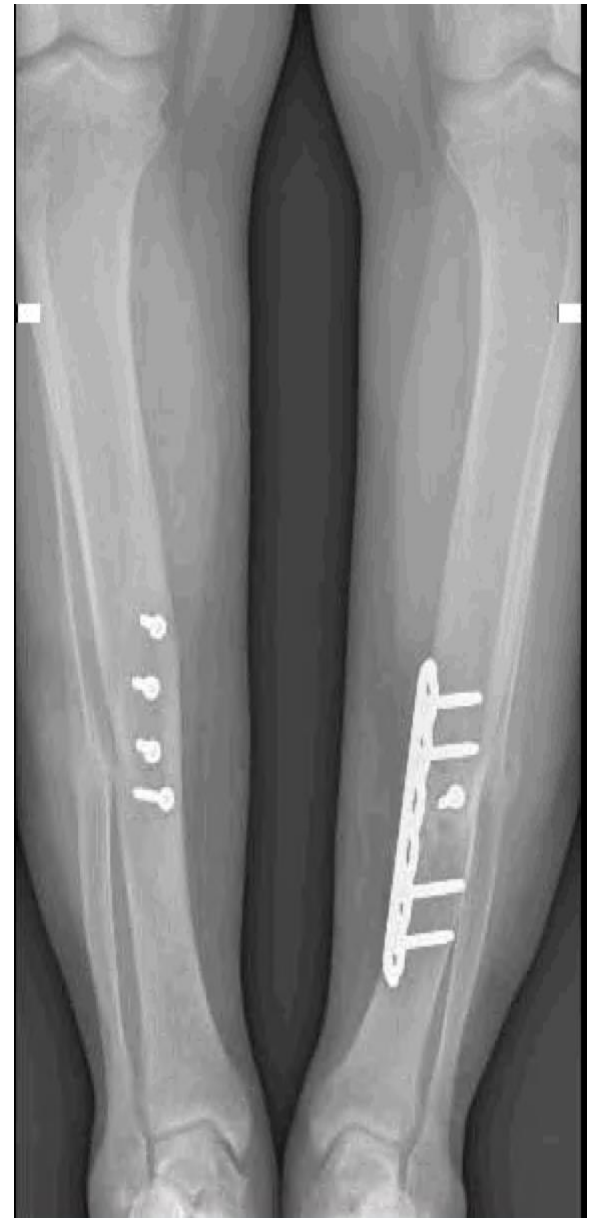
Figure 2: Fracture healing in a 19 years old patient affected with XLH

Before (A) and after (B) one year of burosumab treatment once a month.

A**B****Figure 1**



A



B

Figure 2