Endocrinologists and orthopedic surgeons in rare bone diseases: an important synergy

Laura Masi [1], Domenico Campanacci [2]

[1] Metabolic Bone Diseases Unit; Musculoskeletal and Rehabilitation Department – Careggi University Hospital, Florence, Italy; [2] Orthopedic Oncology Unit, Musculoskeletal and Rehabilitation Department – Careggi University Hospital, Florence, Italy

ABSTRACT

Collectively, metabolic skeletal diseases—particularly the rare forms—are frequently associated with severe clinical outcomes. Given the inherent interconnectedness of bone metabolism and bone structure, a single-specialty approach is insufficient for comprehensive care in this setting, which instead requires a holistic understanding and effective management based on expertise spanning both the underlying metabolic processes and the resulting structural and mechanical aspects. This fundamental need for a combined approach is the main driver of interdisciplinary collaboration.

Opinions differ on the ideal organizational structure to facilitate successful cooperation among professionals from widely differing disciplines.

Recognition of the specific and complementary skills of each individual team member is crucial. It is increasingly recognized that teams with mutual and aligned interests can provide the basis for efficient and fruitful and collaboration.

KEYWORDS

Rare bone diseases, multidisciplinary approach.

Introduction to rare bone diseases

Collectively, metabolic skeletal diseases – particularly the rare forms – are frequently associated with severe clinical outcomes. Important molecular pathways implicated in the regulation of bone and mineral metabolism have been identified in recent years, coinciding with descriptions of the clinical manifestations and radiographic characteristics of a number of genetic bone diseases. On the basis of their functionally diverse phenotypes, numbering 116, rare skeletal diseases [1] are divided into four major groups: due to altered osteoclast, osteoblast, or osteocyte activity; due to altered bone matrix proteins; due to altered bone microenvironmental regulators; and due to deranged calciotropic hormonal activity. These conditions result in short stature, bone deformities, dental abnormalities, pain, fractures, and disability, and they can negatively affect neuromuscular function and hematopoiesis [1].

In addition, bone tissue constitutes a major systemic compartment of the human body, and its active metabolism regulates the deposition and resorption of minerals. Since these processes can be influenced by various factors, even non-skeletal diseases can affect bone metabolism [2]. This knowledge has enabled the development of specific therapies that have significantly changed the quality of life of patients with rare bone diseases (RBDs). Both genetic and acquired pediatric bone diseases can compromise bone strength, leading to fractures during childhood. If left untreated, these conditions lead to reduced bone mass, deformities, and impaired quality of life, with potential long-term consequences [3-5].

This report explores the complex landscape of RBDs, emphasizing their profound impact on patients. It highlights the indispensable roles of endocrinologists and orthopedic surgeons, whose distinct yet complementary expertise is crucial for optimal patient outcomes.

Article history

Received 15 Nov 2025 – Accepted 19 Nov 2025

Contact

Laura Masi; masilau@aou-careggi.toscana.it

Metabolic Bone Diseases Unit, Musculoskeletal and Rehabilitation Department, University Hospital of Florence (AOUC), Florence, Italy

Phone: +39 328 4124427

While the synergy between endocrinologists and orthopedic surgeons is pivotal, the holistic management of RBDs requires a multidisciplinary network, including geneticists, radiologists, and rehabilitation specialists, to address the systemic and multi-organ nature of these conditions. This synergistic approach addresses both the underlying metabolic/genetic dysregulations and the resulting structural/mechanical complications. Such collaboration leads to improved diagnostic accuracy, tailored treatment plans, and enhanced patient quality of life. It also facilitates care during the crucial transition from pediatric to adult services.

Physiology of bone

Bone formation, which begins *in utero*, occurs through two major mechanisms: endochondral and intramembranous ossification. Also called modeling, this process continues throughout

childhood and adolescence until skeletal maturity is reached. Thereafter, bone continues to be broken down and rebuilt (remodeling) throughout life, adapting to mechanical demands. The function of remodeling is to regulate mineral homeostasis and maintain the biomechanical competence of the skeleton [1]. The cells involved in skeletal metabolic activity are osteoclasts, osteoblasts, and osteocytes [1,6]. The bone extracellular matrix, or osteoid, is a complex of self-assembled macromolecules composed predominantly of collagens (~90% of the matrix proteins), non-collagenous glycoproteins, hyaluronan, and proteoglycans. The osteoid and its local modulating factors are also primary factors in the metabolic activity of bone tissue, with minerals constituting another key component of its metabolic machinery. This activity is regulated by systemic and local factors, as well as mechanical signals [1].

Bone plays a crucial role in providing structural support to the body, protecting organs, and facilitating locomotion and sensory perception [7,8]. But it also serves additional functions [9], acting as a storage site for vital minerals and essential ions [10]. Additionally, bone is a source of stem cells, and bone marrow provides an ideal environment for the process of hematopoiesis.

Approximately 95% of skeletal size and bone and muscle mass is acquired before the age of 18 years [11], making childhood a critical period for building a strong musculoskeletal system. Bone structure and quality are influenced by various factors: genetic background, organ function, chronic systemic illnesses, medications, and muscular diseases, as well as metabolic diseases. Rare bone diseases can be classified based on their underlying pathophysiology, which may encompass altered activity of osteoclasts, osteoblasts, or osteocytes, as well as issues with bone matrix proteins, microenvironmental regulators, or calciotropic hormone activity [1].

Primary osteoporosis is usually caused by an underlying genetic defect. It is characterized by fragile bones and deformities, requiring both orthopedic support to treat fractures and deformities, and endocrinological support to manage any metabolic aspect.

Given the inherent interconnectedness of bone metabolism and bone structure, a single-specialty approach is insufficient for comprehensive care in RBDs, which instead require a holistic understanding and effective management based on expertise spanning both the underlying metabolic processes and the resulting structural and mechanical aspects. This fundamental need for a combined approach is the main driver of interdisciplinary collaboration.

It is strongly recommended that patients with rare skeletal diseases be managed at highly specialized centers, such as those belonging to the European Reference Network on Rare Bone Diseases [12,13]. Patients and their families should have better access to high-quality healthcare, while greater availability of reliable information on rare skeletal diseases might allow the development of better treatment plans in the future [14].

In recent years, specific treatments have been developed for a small number of skeletal diseases [12,14,15]. For most, however, current treatment options still consist of symptomatic approaches and monitoring for treatable complications.

Several fundamental characteristics of RBDs highlight the crucial importance of multidisciplinary collaboration in this setting:

a) RBDs are a very diverse group of conditions, each characterized by distinct issues related to bone development, structure, or metabolism. Because they are so complex, specialized multidisciplinary care is often needed to treat all their different symptoms [16].
b) A significant challenge with RBDs is their low individual prevalence. Most healthcare professionals, even those specializing in bone health, do not see enough cases to build critical expertise in specific conditions [17]. Limited exposure often leads to low awareness, which contributes to delayed or incorrect diagnoses [17].
c) Given the often extreme and pervasive manifestations of RBDs, a collaborative approach involving dedicated specialists and researchers with diverse expertise is essential to improve clinical care. This collaborative model ensures the provision of comprehensive, holistic, continuous, patient-centered, and participative care, addressing all aspects of a patient's condition [18]. In addition to these considerations, a combined approach also lays the groundwork for interdisciplinary research, particularly important in view of the frequent risk of misdiagnosis.

The role of the endocrinologist in rare bone disease management

The endocrinologist's role is paramount in addressing the biological mechanisms that often drive RBDs. In clinical practice, endocrinologists conduct thorough assessments of bone health, which extend to evaluating bone density levels and pinpointing areas of concern that may indicate underlying metabolic imbalances. Hormones are fundamental to maintaining robust bone health, influencing myriad processes from the rate of bone growth to the precise amount of calcium and phosphate incorporated into bone tissue.

Endocrinologists have a deep understanding of the biochemical processes governing bone health, and may thus be considered the "metabolic architects" of bone. Their primary expertise is centered on the cellular and molecular pathways that regulate bone formation, resorption, and mineralization, rather than solely on its macroscopic physical structure. Crucially, this deep understanding of bone biology at a microscopic level allows endocrinologists to identify the root metabolic or genetic causes of rare bone diseases – knowledge that can guide systemic medical therapies directly addressing these dysfunctions. Their diagnostic work-up of RBDs often begins with a comprehensive evaluation of metabolic and hormonal markers. Knowledge of the metabolic pathway underlying a given disorder may help in the management of affected patients. However, the bone remodeling phenotype is not fully known for all metabolic bone diseases, and disease-targeted therapies are not yet available for most conditions. Consequently, the treatment options for patients – often children – with these complex syndromes are restricted to antiresorptive or anabolic agents. Nonetheless, the patient's metabolic profile may help in selecting the most appropriate pharmacological treatment [1].

The role of the orthopedic surgeon in rare bone disease management

The orthopedic surgeon's expertise, especially in the setting of RBDs, is centered on the structural, mechanical, and biological aspects of bone health. These specialists therefore play an essential role in addressing the physical manifestations and complications of these diseases. Beyond pathological fracture fixation, they are trained to restore axial and rotational limb alignment, address joint mobility issues, and correct acquired bone deformities. The diagnostic work-up of bone diseases by orthopedic surgeons is comprehensive, integrating a complete health history, a thorough physical examination, and advanced imaging techniques. A wide variety of management and treatment strategies are employed to correct structural abnormalities, stabilize fragile bones, and enhance physical function in patients with RBDs. These methods frequently combine highly specialized surgical procedures with nonsurgical interventions.

Orthopedic interventions are often critical for enabling mobility, preventing severe disability, and improving daily function, especially in conditions that cause significant skeletal deformities or fragility. The collaborative work of these specialists directly impacts the patient's ability to perform daily activities, thereby enhancing their quality of life.

Orthopedic surgeons therefore play an indispensable role in managing the immediate and long-term physical challenges posed by RBDs, ensuring that patients maintain as much mobility and function as possible, often through complex surgical and rehabilitation strategies.

The essential contribution of the multidisciplinary network

While endocrinologists and orthopedic surgeons, dealing with metabolic and structural aspects, form the backbone of care, the complexity of RBDs necessitates the involvement of a broader spectrum of specialists to provide truly comprehensive management:

- **Clinical geneticists:** Essential for the diagnostic work-up. Given that most RBDs have a genetic etiology, geneticists are crucial for identifying specific gene mutations, providing genetic counseling to families, and guiding reproductive choices. Their role is increasingly vital in the era of precision medicine and gene-targeted therapies.
- **Radiologists and neuroradiologists:** Specialized imaging is the cornerstone of diagnosis and monitoring. Radiologists with expertise in skeletal dysplasia are needed to interpret complex bone phenotypes, while neuroradiologists monitor complications such as basilar invagination or spinal stenosis, which are common in several rare syndromes.
- **Physiatrists and physical therapists**: These specialists focus on functional recovery and the maintenance of muscle strength. They design personalized rehabilitation programs that are critical post-surgery and for preventing the loss of mobility associated with progressive skeletal deformities.
- **Odontologists and maxillofacial surgeons**: Many rare bone diseases, e.g., osteogenesis imperfecta, X-linked hypophosphatemia (XLH) significantly affect dental health and craniofacial development. Regular monitoring of dentition and specialized surgical interventions are often required to maintain oral function and quality of life.
- **Pain management specialists and psychologists**: Chronic pain is a debilitating feature of many RBDs. A specialized approach to pain management, combined with psychological support, is essential to address the emotional and social burden of living with a rare, chronic disability.
- **Pathologists**: In cases requiring biopsy, specialized bone pathologists are indispensable for the histological differential diagnosis between rare metabolic conditions and primary bone tumors or other forms of skeletal dysplasia.

This integrated network ensures that every facet of the patient's health – from molecular diagnosis to functional rehabilitation – is addressed. The specific clinical contributions of these additional specialists are summarized in Table I.

Rare bone diseases at the University Hospital of Florence (Azienda Ospedaliero Universitaria Careggi-AOUC)

Opinions differ on the ideal organizational structure to facilitate successful cooperation among professionals from widely differing disciplines.

Table I Clinical roles and contributions of multidisciplinary specialists in rare bone disease management.

SPECIALIST	ROLE AND KEY CONTRIBUTION
Clinical geneticist	Essential for the initial diagnostic work-up; identifies specific gene mutations and provides genetic counseling to patients and their families.
Radiologist / Neuroradiologist	Crucial for the interpretation of complex skeletal phenotypes and for monitoring complications such as spinal stenosis or basilar invagination.
Physiatrist / Physical therapist	Focuses on functional recovery and maintenance of muscle strength, designing personalized rehabilitation programs, particularly after orthopedic surgery.
Odontologist / Maxillofacial surgeon	Monitors and treats dental anomalies and craniofacial development issues common in conditions such as osteogenesis imperfecta and XLH.
Pathologist	Indispensable for the histological differential diagnosis between rare metabolic conditions and primary bone tumors in cases requiring a biopsy.
Pain management specialist / Psychologist	Manages chronic pain and provides psychological support to address the emotional and social burden of living with a rare, chronic disability.

Recognizing the specific and complementary skills of each team member is essential. It is increasingly understood that teams with shared and aligned interests create a strong foundation for effective collaboration across various expertise areas. This collaboration, which also involves orthopedic surgeons with their well-balanced expertise, is vital for addressing specific clinical and research questions, ultimately aiming to improve patient care and foster innovation [19]. Two key figures in managing RBDs are the endocrinologist and the orthopedic specialist experienced in these conditions. For many years, a multidisciplinary group focusing on the diagnosis and treatment of RBDs has been active at the University Hospital of Florence (AOUC). Over time, close collaboration between endocrinologists from the hospital's Metabolic Bone Diseases Unit and orthopedic surgeons from its Orthopedic Oncology Unit has led to the development of a structured model for managing patients with various diseases, including RBDs. This collaboration has also resulted in the publication of scientific papers [20-22] and the sharing of various diagnostic and therapeutic care pathways (PDTA) for RBDs [23-26].

Since 2021, the AOUC has run monthly outpatient clinics in which patients with RBDs are assessed by an endocrinologist from the Metabolic Bone Diseases Unit working in conjunction with an orthopedic surgeon from the Orthopedic Oncology Unit.

During the examination, the specialists determine which tests are required. Some of them (radiological examination and evaluation of bone mineral density) can be performed the same day, with the orthopedic specialist's evaluation therefore available immediately, while biochemical tests at the Metabolic Bone Diseases Unit must be scheduled and performed at a later date. Follow-up visits to review the final report can be conducted either in person or remotely via telemedicine.

Scheduled remote consultations between the specialists and the patient's general practitioner can also be arranged to discuss specific cases. To date, a total of 686 patients have been seen in the clinic since its establishment.

Table II Rare bone disease types assessed (2021–present), including initial and follow-up visits.

RARE BONE DISEASES	TOTAL NUMBER OF VISITS (INITIAL AND FOLLOW-UP VISITS)
Bone fibrous dysplasia	302
Osteogenesis imperfecta	667
Tumoral calcinosis	26
Hypophosphatemic rickets (XLH)	121
Hypophosphatasia	15
Cystic angiomatosis	1

Table II lists the different RBDs assessed over this period, showing the total number of visits.

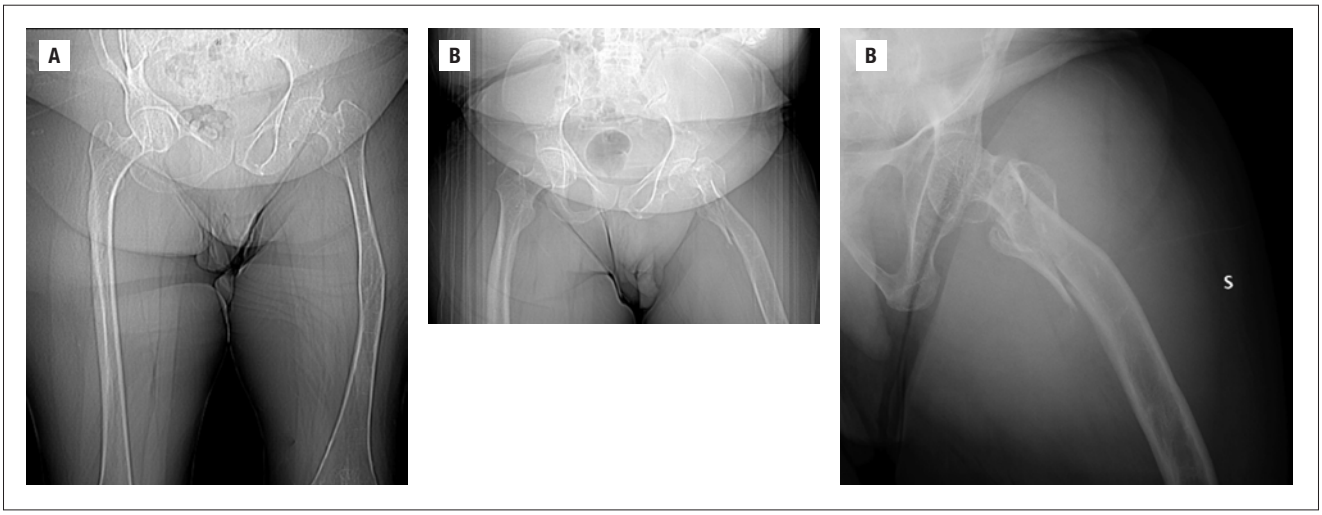
In some cases, prompt orthopedic surgery was required and arranged. Brief descriptions of several surgically treated patients are given below.

Case 1

A 43-year-old male patient affected by osteogenesis imperfecta, presenting with coxa vara and procurvatum deformity of the left femoral shaft, sustained – due to the underlying pathology – a femoral fracture following a fall from his wheelchair. In agreement with the doctors in the patient's hometown, a transfer to the University Hospital of Florence (AOUC) was promptly planned and the patient underwent successful surgery within 48 hours. An osteosynthesis with plate, screws, and cerclage for a peritrochanteric fracture of the left hip was performed. The surgery was performed in 2023 and follow-up X-ray showed the fixation devices in place and intact, with no signs of loosening. The baseline findings were essentially unchanged, particularly the bone curvatures.

Figure 1 shows an X-ray prior to the femoral fracture (A), revealing pelvic dysmorphism and rotation. There is a bilateral bowing deformity of the femoral diaphyses, more pronounced

Figure 1 X-ray prior to femoral fracture. **A**: pelvic dysmorphism and rotation. There is a bow-shaped deformity of the femoral diaphyses bilaterally, more pronounced on the left. On the left side, there is evidence of previous midshaft fractures and an exostosis measuring approximately 0.76 cm on the medial margin of the distal third. A significant reduction in bone mineral density is noted in the visualized bone segments. **B** and **C**: left per-subtrochanteric fracture and a non-displaced fracture of the ipsilateral iliac wing.



on the left. On the left side, there is evidence of previous midshaft fractures and an exostosis measuring approximately 0.76 cm on the medial margin of the distal third. A significant reduction in bone mineral density is noted in the visualized bone segments. B and C: Left per- and subtrochanteric fracture and a non-displaced fracture of the ipsilateral iliac wing. Figure 2 shows: (A) surgical fixation of a left per-and subtrochanteric fracture with plate and screws; (B) follow-up of a procurved left per-and subtrochanteric femoral fracture treated with plate and screws, demonstrating near-complete consolidation, hardware *in situ* and intact; and (C) 18-month follow-up after osteosynthesis with plate, screws, and cerclage for left proximal femur fracture in this patient with osteogenesis imperfecta, hardware *in situ* and intact.

Case 2

A 53-year-old patient with severe tumoral calcinosis due to homozygous 4bp deletion in exon 3 of the *GANT3* gene initially showed improvement with intravenous bisphosphonates. Nevertheless, the substantial calcinosis in the right hip (about 20 cm in diameter) continued to cause significant discomfort and poor quality of life, prompting the decision, after careful consideration, to proceed with surgical management. The patient presented with an ulcerated calcinosis in the proximal lateral region of the right thigh. Joint examination revealed a large mass in the posterolateral region extending to the anteromedial region. The skin of the proximal lateral region of the right thigh showed multiple ulcerations.

The necessary surgical treatment, which was first discussed with the patient, included excision of the ulcerated skin with debulking of the anteromedial portion of the mass. After joint evaluation, reconstruction of the defect was performed by plastic surgeons.

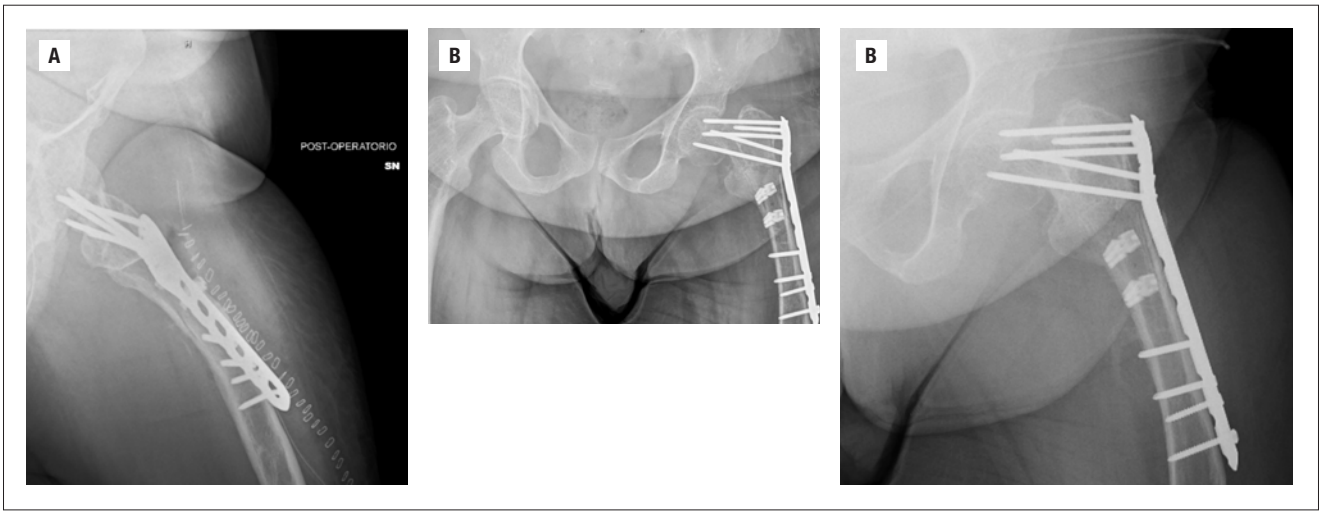
A gross examination revealed a subcutaneous mass measuring 21 x 13 x 5 cm with a raised, whitish lesion and an ulcerated area measuring 11 x 9 cm over a previous 5 cm linear scar. Histological examination showed massive deposition of calcium salts in the dermal and hypodermic stroma (calcinosis), inflammation-associated sclerotic changes, hemosiderin deposits, and giant cell foreign body reactions of the stroma.

This patient, regularly followed up at our center, is currently doing well.

Cases 3 and 4

Due to a *GALNT3* gene mutation inherited from consanguineous parents, two brothers developed tumoral calcinosis. The first is a 33-year-old man with a history of tumoral calcinosis. In 2021, he was in good health except for clearly visible calcification of the right shoulder, measuring approximately 1.5-2 cm, with red, warm skin. An ultrasound of the right shoulder revealed large deposits of calcium in the soft tissues of the posterior and lateral deltoid bundles, along with a strong Power Doppler signal (matching what was observed on a CT scan in 2018). Despite the lack of vascular signal, tiny calcifications of up to 8–9 mm were observed inside the supraspinatus fibers. The rotator cuff tendon fibers appeared continuous, the long head of the biceps muscle tendon was normal, and there was no intra-articular effusion in the glenohumeral or acromioclavicular region. The forced position of the arm significantly reduced the subacromial space for sliding of the rotator cuff tendon, resulting in severe functional limitation of the upper limb. The patient underwent MRI evaluation followed by an orthopedic consultation. MRI of the right shoulder showed a gross abnormal signal formation measuring 9 x 6.5 x 5 cm (CC x AP x LL) extending posteroinferiorly deeply into the triceps muscle and superficially into the superficial subcutaneous tissue. Concomitant perilesional edematous imbibition was observed. The width of the subacromial sliding space was reduced. The patient underwent an orthopedic examination and subsequently surgery to remove a calcified mass from the right shoulder. Histological examination was compatible with calcinosis: fibroadipose and muscular stromas with inflammation-associated sclerotic changes, and widespread dystrophic calcifications. Furthermore, given the presence of small calcifications on the left shoulder that did not warrant surgical intervention, it was decided to perform percutaneous lithochlasia, which led to a

Figure 1 2 X-ray after surgical procedure. **A**: surgical fixation of a left per-subtrochanteric fracture with plate and screws. **B**: follow-up demonstrating near-complete consolidation, hardware in situ and intact. **C**: 18-month follow-up after osteosynthesis with plate, screws, with hardware in situ and intact.



significant clinical improvement.

His 23-year-old brother underwent surgery to remove a calcified lesion on the right hip measuring approximately 15 cm in diameter. Both brothers are currently under regular orthopedic and endocrinological follow-up.

Case 5

A patient with cystic angiomatosis consulted his doctor due to pain in the lumbar spine, sometimes causing difficulty even sitting. The patient was referred for an orthopedic oncology consultation, and a biopsy was scheduled. A computed tomography scan, used to guide the biopsy, revealed that the skeletal segments examined—particularly L5, the sacrum, and the remaining pelvic bones—showed mixed structural changes, predominantly lytic in nature. Histological examination revealed the presence of rare polymorphonuclear inflammatory cells and blood material.

Case 6

In a further patient with cystic angiomatosis, who also consulted the doctor due to pain in the lumbar spine, sometimes causing difficulty even sitting, MRI of the lumbar spine was performed, revealing diffuse involvement of the spine, particularly at the sacrum, with the presence of newly formed extra skeletal tissue. Multiple angiomatous formations were documented at the level of the sternal manubrium, the heads of the humeri bilaterally, both scapulae, affecting the somata and pedicles of T1, T4, T5, T6, T8, T9, T10, T12, L2, L3, L4, and L5, and the anterior portion of the somata of T7 and T11.

Following a review by the Multidisciplinary Oncology Groups—GOM, the patient was evaluated at our Metabolic Bone Diseases Unit. The patient had osteomalacia due to very low levels of vitamin D, with baseline biochemical profile revealing severe vitamin D deficiency and secondary hyperparathyroidism (Table III, column A), confirming the diagnosis of concomitant osteomalacia. The management of cystic angiomatosis remains challenging; however, the use of zoledronate is increasingly reported as an effective strategy for controlling bone pain and limiting lesion progression [27,28]. After correction of vitamin D levels (Table III, column B), the patient started therapy with zoledronate, 4 mg i.v. per month. After 1 year of treatment, the patient is clinically improved, without chronic pain. On MRI, the affected areas remain unchanged, showing the same signal characteristics on T1-weighted sequences, and moderate hyperintensity on T2-weighted and STIR sequences. Our findings align with the literature, demonstrating that initiation of targeted antiresorptive therapy can significantly improve the quality of life in these patients [27].

In conclusion, combining the expertise of the endocrinologist and orthopedic specialist is helpful in many ways and improves the care of people with RBDs. A multidisciplinary (endocrinology and orthopedics) outpatient clinic exclusively dedicated to RBDs offers a comprehensive, coordinated, patient-centric approach that significantly enhances diagnostic accuracy, treatment efficacy, and the quality of life of individuals living with these complex conditions.

Table III Biochemical parameters before (Column A) and after (Column B) correction of secondary hyperparathyroidism.

PARAMETER	PATIENT VALUE JULY 2024 (A)	PATIENT VALUE OCTOBER 2024 (B)	REFERENCE RANGE
Complete blood count (CBC)	Normal	Normal	–
e-GFR	78	79	>60 mL/min/1.73m²
Creatinine	1.18	1.10	0.8-1.2 mg/dL
Creatinine clearance	139	129	70–140 mL/min
Calcium	9.9	9.5	8.5–10.1 mg/dL
Phosphorus	3.1	3.2	2.5–4.9 mg/dL
25-OH Vitamin D	14*	31	30–100 ng/mL
Bone alkaline phosphatase	12.5	13.2	<22.4 mcg/L
Alkaline phosphatase	89	78	40-150 U/L
Total protein	7.17	7.10	6.4–8.2 g/dL
Protein electrophoresis	Normal	Normal	–
Calciuria (24h urine calcium)	89*	148	100–300 mg/24h
Phosphaturia (24h urine phosphorus)	789	846	400–1300 mg/24h
TSH	2.34	–	0.4–4.0 mIU/L
PTH	71.40*	38.1	<36.80 pg/mL

* = Out of range

References

1. Masi L, Agnusdei D, Bilezikian J, et al. Taxonomy of rare genetic metabolic bone diseases. Osteoporosis Int. 2015;26(10):2529-58.
2. Masi L, Ferrari S, Javaid MK et al. Bone fragility in patients affected by congenital diseases non-skeletal in origin. Orphanet J Rare Dis. 2021;16(1):11.
3. Boyce AM, Gafni RI. Approach to the child with fractures. J Clin Endocrinol Metab 2001; 96(7):1943-52.
4. Gordon CM, Zemel BS, Wren TA, et al. The determinants of peak bone mass. J Pediatr. 2017;180:261-9.
5. Ciancia S, van Rijn RR, Högler W, et al. Osteoporosis in children and adolescents: when to suspect and how to diagnose it. Eur J Pediatr. 2022;181(7):2549-61.
6. Boyce BF, Zuscik MJ, Xing L (2013). Biology of bone and cartilage. In: Thakker RV, Whyte MP, Eisman JA, Igarashi T (eds) 1 ed. Genetics of bone biology and skeletal diseases. Ch. 1 pp. 3-24.
7. Choi IA, Umemoto A, Mizuno M, Park-Min KH. Bone metabolism – an underappreciated player. NPJ Metab Health Dis. 2024;2(1):12.
8. Florencio-Silva R, Sasso GR, Sasso-Cerri E, Simões MJ, Cerri PS. Biology of bone tissue: structure, function, and factors that influence bone cells. Biomed Res Int. 2015;2015:421746.
9. Karsenty G, Ferron M. The contribution of bone to whole-organism physiology. Nature. 2012;481(7381):314-2.
10. Peacock, M. Calcium metabolism in health and disease. Clin J Am Soc Nephrol. 2010;5 Suppl 1:S23-30.
11. Baxter-Jones AD, Faulkner RA, Forwood MR, Mirwald RL, Bailey DA. Bone mineral accrual from 8 to 30 years of age: an estimation of peak bone mass. J Bone Miner Res. 2011;26(8):1729-39.
12. Walleczek NK, Förster K, Seyr M, et al. Rare skeletal diseases: a multidisciplinary postnatal approach to diagnosis and management. Wien Med Wochenschr. 2021;171(5-6):94-101.
13. European Reference Network on rare bine diseases (ERN BOND). Available at: https://ernbond.eu/. Accessed, October 2, 2025.
14. Semler O, Rehberg M, Mehdiani N, Jackels M, Hoyer-Kuhn H. Current and emerging therapeutic options for the management of rare skeletal diseases. Paediatr Drugs. 2019;21(2):95-106.
15. Sabir AH, Cole T. The evolving therapeutic landscape of genetic skeletal diseases. Orphanet J Rare Dis. 2019;14(1):300.
16. Grasemann C, Wernsmann J, Appelman-Dijkstra NM, et al. Transition care for young persons with rare bone mineral conditions: a Consensus Recommendation from the ECTS Rare Bone Disease Action Group 6. Calcif Tissue Int. 2025;116(1):73.
17. Chandran M, Alves I, Carpenter T, et al. Improving care pathways for people living with rare bone diseases (RBDs): outcomes from the first RBD Summit. Osteoporos Int. 2023;34(8):1301-10.
18. Casareto L, Appelman-Dijkstra NM, Brandi ML, et al.; European Reference Network on rare BONe Diseases. ERN BOND: the key European network leveraging diagnosis, research, and treatment for rare bone conditions. Eur J Med Genet. 2024;68:104916.
19. Eekhoff EMW, Micha D, Forouzanfar T et al. Collaboration around rare bone diseases leads to the unique organizational incentive of the Amsterdam Bone Center. Front Endocrinol (Lausanne). 2020;11:481.
20. Masi L, Beltrami G, Ottanelli S, et al. Human preosteoblastic cell culture from a patient with severe tumoral calcinosis-hyperphosphatemia due to a new GALNT3 gene mutation: study of in vitro mineralization. Calcif Tissue Int. 2015;96(5):438-52.
21. Donati S, Palmini G, Aurilia C, et al. Establishment and molecular characterization of a human stem cell line from a primary cell culture obtained from an ectopic calcified lesion of a tumoral calcinosis patient carrying a novel GALNT3 mutation. Genes (Basel). 2025;24:16(3):263.
22. Masi L, Gozzini A, Franchi A, et al. A novel recessive mutation of fibroblast growth factor-23 in tumoral calcinosis. J Bone Joint Surg Am. 2009;91(5):1190-8.
23. DD 5607/2023 Rete Toscana Malattie Rare PDTA X-Linked Hypophosphoremic Rikets. Available at: https://malattierare.toscana.it/media_rtmr_pub/filer_public/PDTA/allegatiDecreto/all7-dd-5607-2023-Rachitismo.pdf. Accessed, October 2, 2025.
24. DD 11505 Rete Toscana Malattie Rare PDTA Tumoral Calcinosis. Available at: https://malattierare.toscana.it/media_rtmr_pub/filer_public/PDTA/allegatiDecreto/all5-dd-11505-2020_pdta_calcinosi_tumorale.pdf. Accessed, October 2, 2025.
25. DD 11505 Rete Toscana Malattie Rare PDTA Bone Fibrous Dysplasia. Available at: https://malattierare.toscana.it/media_rtmr_pub/filer_public/PDTA/allegatiDecreto/all10-dd-11505-2020_pdta_displasia_fibrosa.pdf. Accessed, October 2, 2025
26. DGR N.36 del 21.01.2013 Rete Toscana Malattie Rare PDTA Osteogenesis Imperfecta. Available at: https://malattierare.toscana.it/media_rtmr_pub/filer_public/atti/PercorsiAssistenziali/2013_DGR_36_PercorsiAssistenzialiAll1.pdf. Accessed, October 2, 2025.
27. Marcucci G, Masi L, Carossino AM, et al. Cystic bone angiomatosis: a case report treated with aminobisphosphonates and review of the literature. Calcif Tissue Int. 2013;93(5):462-71
28. Dwivedi PC, Borde C, Yasam RV, Nagarkar R. A rare case of cystic angiomatosis involving the bones: our experience and review of literature. World J Nucl Med. 2025;24(2):173-6.