JBMR Plus, 2024, **9**, ziae165
https://doi.org/10.1093/jbmrpl/ziae165
Advance access publication: December 17, 2024
Editorial

Special Collection on Rare Musculoskeletal Diseases 2024

Eva S. Liu[1,*] **and Maegen J. Wallace**[2]

[1]Division of Endocrinology, Diabetes, and Hypertension, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, United States
[2]Department of Pediatric Orthopedic Surgery, Phoenix Children's Hospital, Phoenix, AZ 85016, United States

*Corresponding author: Eva S. Liu, Division of Endocrinology, Diabetes, and Hypertension, Brigham and Women's Hospital, 221 Longwood Ave 2nd Floor, Boston, MA 02115, United States (esliu@bwh.harvard.edu).

Keywords: alkaline phosphatase, hypophosphatasia, X-linked hypophosphatemia, osteogenesis imperfecta

There has been increasing focus on the characterization of rare musculoskeletal disorders, with investigations spanning from "bench to bedside." Over 55 manuscripts were submitted to this special collection on rare musculoskeletal disorders. Submitted manuscripts included a diverse range of topics, including dissection of the molecular pathophysiology underlying these disorders, clinical studies investigating their genetic causes, treatment options, phenotypes, and studies examining the impact of rare musculoskeletal disorders on quality of life. Invited reviews on palovarotene treatment for fibrodysplasia ossificans progressiva (FOP), melorheostosis, the role of peripheral nerves in trauma-induced heterotopic ossification, and the muscle phenotype in osteogenesis imperfecta summarized how both basic and clinical translational studies have contributed to our current understanding of these rare disorders.

Several of the rare musculoskeletal disorders discussed highlight that ectopic ossification/calcification, characterized by pathological tissue mineralization, is an important consequence of these diseases. Hypophosphatasia (HPP) is characterized by mutations in the gene that encodes tissue-nonspecific alkaline phosphatase (*ALPL*), leading to increased plasma pyrophosphate (PPi) levels and decreased skeletal mineralization. High PPi levels can result in pyrophosphate dihydrate crystal deposition, leading to chondrocalcinosis or arthritis. The study by Tornero et al[1] reports that chondrocalcinosis is more prevalent than arthritis in patients with HPP. It is also more prevalent in patients with a confirmed genetic mutation in *ALPL* compared with those with low alkaline phosphatase (ALP) levels and a negative genetic test. Moreover, within the group with *ALPL* mutations, patients with chondrocalcinosis have lower ALP levels compared with those without this complication. In contrast to HPP, the mouse model for craniometaphyseal dysplasia (CMD) is characterized by a knock-in in-frame deletion of phenylalanine 377 in the ankyrin (*Ank*) gene ($Ank^{KI/KI}$), leading to high serum levels of ALP, low plasma levels of PPi, and ectopic joint mineralization. Reichenberger et al[2] reported that treating $Ank^{KI/KI}$ mice with recombinant human ENPP1-Fc protein, which catalyzes the production of PPi from adenosine triphosphate (ATP), decreased the volume of ectopic mineralization at the base of the skull and in the foot joints but did not normalize skeletal deformities.

Clinically, ectopic ossification and joint pathology, like osteoarthritis reported in patients with rare musculoskeletal disorders, can result in significant morbidities, including pain and impaired quality of life. X-linked hypophosphatemia (XLH) is characterized by mutations in the phosphate-regulating endopeptidase homolog X-linked (*PHEX*) gene, leading to high circulating levels of fibroblast growth factor 23 (FGF23) and hypophosphatemia. Khan et al[3] reported that at least 50% of adults with XLH develop joint complications like osteoarthritis and enthesopathy, the pathologic mineralization of the bone–tendon attachment site. Their study showed that, in a cohort of 281 adult patients with XLH followed in the XLH Disease Monitoring Program, just slightly over half are employed full time, while the PROMIS Physical Function assessment demonstrated that patients had the greatest difficulty in running short distances and climbing stairs. In particular, those who had undergone fewer orthopedic surgeries were more likely to be employed full time or to be engaged in medium-activity work vs light/sedentary work. In another study examining quality of life, Dahir et al[4] investigated patient-reported outcomes on quality of life in a cohort of adults with pediatric-onset HPP who had been treated with the ALP replacement therapy asfotase alfa from baseline through 12 months of therapy. This study found that, following asfotase alfa initiation, significant improvements were seen in score assessments of depressive symptoms, physical function, work productivity, pain, and fatigue.

Research in the field of osteogenesis imperfecta (OI) has been increasing in recent years. Congruent with this growth, many interesting OI manuscripts are included in this collection, which range from basic science to improved phenotype correlations to clinical trials. Although correlations between genotype and phenotype in OI have been previously published, the study by Byrd et al[5] extends previous work in 294 pediatric patients to highlight that more than 90% of cases are due to collagen type 1 alpha1/type 1 alpha2 (COL1A1/1A2) variants and that the rare variants are associated with higher rates of scoliosis and expressive-language delay. From a translational perspective, Aksornthong et al[6] performed a meta-analysis to assess osteoclast indices in humans and mice with OI. The study showed that changes in osteoclast indices are similar, findings that will be important to consider for future studies.

Received: December 10, 2024. **Accepted:** December 16, 2024

The collection also includes many studies on ultra-rare musculoskeletal diseases. As an example, Barbato et al[7] described a pilot study in patients with type I Gaucher disease evaluating enzyme-replacement therapy, cholecalciferol, and dietary changes. The authors found positive bone health changes in 25 patients treated with their protocol. Another ultra-rare condition, Jansen metaphyseal chondrodysplasia, was investigated by Obiezu et al[8] in terms of ocular findings. The authors found common ocular features in 6 patients, including widely spaced eyes and down-slanted palpebral fissures, with 4 of 6 patients having decreases in the ganglion cell layer of the eye, indicating subclinical optic nerve atrophy. They also showed that ocular findings increase as these patients age, and therefore recommend routine ophthalmic examinations into adulthood.

Collectively, this Special Collection on Rare Musculoskeletal Diseases 2024 highlights our expanding knowledge of many rare diseases and the musculoskeletal and extra-skeletal features of these diseases. These studies highlight the importance of a thorough "bench to bedside" approach in the rare disease world. They also emphasize how each researcher, from those performing basic-science mouse research to those working as clinician scientists, adds value and differing perspectives in order to advance the science and ultimately clinical care of individuals affected by rare musculoskeletal diseases.

Author contributions

Eva S. Liu (Supervision, Writing—original draft, Writing—review & editing), Maegen J. Wallace (Supervision, Writing—original draft, Writing—review & editing).

References

1. Tornero C, de Miguel E, Navarro-Compan V, Balsa A, Aguado P. Prevalence of chondrocalcinosis and calcium pyrophosphate deposition disease in a cohort of adult patients with low alkaline phosphatase levels and a positive versus negative genetic ALPL study. *JBMR Plus*. 2024;8(11). https://doi.org/10.1093/jbmrpl/ziae124
2. Reichenberger EJ, O'Brien K, Hatori A, et al. ENPP1 enzyme replacement therapy improves ectopic calcification but does not rescue skeletal phenotype in a mouse model for craniometaphyseal dysplasia. *JBMR Plus*. 2024;8(9). https://doi.org/10.1093/jbmrpl/ziae103
3. Khan A, Johnson B, Nixon A, et al. Association between work productivity and characteristics of adults with X-linked hypophosphatemia: an analysis of the XLH disease monitoring program. *JBMR Plus*. 2024;8(11). https://doi.org/10.1093/jbmrpl/ziae102
4. Dahir KM, Ing SW, Deal C, Messali A, Bates T, Rush ET. Improvement in quality of life after asfotase alfa treatment in adults with pediatric-onset hypophosphatasia: data from 5 patient-reported outcome measures. *JBMR Plus*. 2024;8(8). https://doi.org/10.1093/jbmrpl/ziae062
5. Byrd J, White AC, Nissen CG, et al. Genotype-phenotype correlations in 294 pediatric patients with osteogenesis imperfecta. *JBMR Plus*. 2024;8(11). https://doi.org/10.1093/jbmrpl/ziae125
6. Aksornthong S, Patel P, Komarova SV, et al. Osteoclast indices in osteogenesis imperfecta: systematic review and meta-analysis. *JBMR Plus*. 2024;8(11):ziae112. https://doi.org/10.1093/jbmrpl/ziae112
7. Barbato A, Vergatti A, Giaquinto A, et al. Imiglucerase, cholecalciferol, and bone-diet in skeletal health management of type I Gaucher disease patients: a pilot study and systematic review. *JBMR Plus*. 2024;8(8):ziae071. https://doi.org/10.1093/jbmrpl/ziae071
8. Obiezu F, Costa MTMDQ, Huryn LA, et al. Ocular findings in Jansen metaphyseal chondrodysplasia. *JBMR Plus*. 2024;8(9):ziae089. https://doi.org/10.1093/jbmrpl/ziae089