



Special Issue: “X-Linked Hypophosphatemia”

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Rickets and osteomalacia are associated with impaired mineralization in growth plate cartilage and the bone osteoid. Many cells and factors are involved in this complex process of mineralization (Hasegawa et al. in this Special Issue, Contribution 1). Historically, vitamin D was discovered as an anti-rachitic factor [1], and it cured vitamin-D-deficient rickets/osteomalacia. However, vitamin D deficiency is one of the causes of rickets/osteomalacia, and vitamin-D-resistant rickets was later reported [2]. An investigation of a large family with vitamin-D-resistant rickets indicated the X-linked dominant inheritance of this disease [3].

There were some controversies regarding terminology before the cloning of *X-linked phosphate-regulating endopeptidase homolog (PHEX)* [4]; hypophosphatemic rickets and vitamin D-resistant rickets had been used almost synonymously with X-linked hypophosphatemia. Indeed, XLH, which is caused by inactivating mutations of *PHEX*, is the most common type of hypophosphatemic or vitamin D-resistant rickets in which the excessive actions of FGF23 [5] lower serum phosphate by suppressing the expression of sodium-phosphate cotransporters in proximal tubules (Koike et al. in this Special Issue, Contribution 2). In addition, several other diseases have similar clinical and biochemical findings to XLH (Nakanishi et al. in this Special Issue, Contribution 3), indicating the importance of genetic testing in achieving a definite diagnosis of XLH (Ohata et al. in this Special Issue, Contribution 4). However, depending on the methods used, genetic testing cannot detect some mutations.

Since the primary pathophysiology of XLH is due to excessive actions of FGF23 and subsequent chronic hypophosphatemia, patients with XLH present various symptoms and signs involving bone, cartilage, ligament, joint, tooth, and muscle which significantly affect QOL in both child- and adulthood (Ikegawa et al., Contribution 5, Ito, and Okawa et al. in this Special Issue, Contributions 6, 7). Because of this multiorgan involvement and life-long burden, multidisciplinary team management and an appropriate transition are essential issues in managing patients with XLH (Kubota in this Special Issue, Contribution 8).

Patients with XLH have conventionally been treated with phosphate and active vitamin D, which effectively correct some but not all abnormalities (Tajima et al., Imanishi et al. in this Special Issue, Contributions 9,10). This conventional treatment also has some limitations, such as adverse events and poor adherence (Zukeran et al. in this issue, Contribution 11). Recently, burosumab, an anti-FGF23 monoclonal antibody, was approved for XLH in several countries. While burosumab improves some features, it is not known whether burosumab can correct all the abnormalities in XLH (Tajima et al. and Imanishi et al. in this Special Issue, Contributions 9,10). The long-term efficacy and safety of burosumab also require further study, as do the indication of this new therapy. When medical therapy cannot correct bone deformities, various orthopedic approaches remain an option (Higuchi in this Special Issue, Contribution 12).

In this Special Issue concerning X-linked hypophosphatemia, the above-mentioned basic and clinical topics are discussed by several experts in this field. Still, several important



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questions remain, as discussed in the following papers, such as the physiological function of the PHEX protein, the mechanism of FGF23 overexpression via inactivating mutations in *PHEX*, and the pathogenesis of enthesopathy. Furthermore, it is largely unknown whether all the clinical features, including the response to treatment described in patients with XLH, can be similarly observed in other patients with hypophosphatemia caused by FGF23 excess. We hope that this Special Issue, which summarizes up-to-date knowledge concerning XLH, will be helpful not only for clinicians caring for patients with rickets/osteomalacia but also as an inspiration to scientists for future research.

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List of Contributions

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