Osteoporosis and other musculoskeletal disorders—treatment is challenging!

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Osteoporosis is a major public health concern with heightened fracture risk, affecting a high number of people regardless of sex and age. This issue focusses on pathological states and diseases of bone, cartilage and mineral metabolism as well as a novel therapeutic approach for postmenopausal osteoporosis.

The manuscript by Wolfgang Högler and Leanne Ward focusses on achondroplasia. This is the most common form of disproportionate short stature. A dominantly inherited FGFR3 mutation permanently activates the fibroblast growth factor receptor 3 (FGFR3) and its downstream MAPK signalling pathway. Inhibited chondrocyte differentiation causes serious medical complications such as foramen magnum and spinal stenosis and upper airway narrowing. Various substances with target elements in molecular disease mechanism are described by the authors.

Hypophosphatasia, a rare disorder with perinatal, infancy, childhood and adult presentations, is the topic of Sebastian Simon and Heinrich Resch. Severe forms are autosomal recessive with an early onset, whereas milder forms have a later onset. Symptoms like nontraumatic and nonhealing fractures, musculoskeletal pain, chondrocalcinosis, seizures, loss of fully rooted teeth and respiratory insufficiency occur. A causal enzyme therapy replacement with asfotase-alfa was approved by the US Food and Drug Administration in 2015. Asfotase-alfa improves respiratory insufficiency, bone mineralisation and long-time survival in combination with a good safety profile.

Adalbert Raimann and colleagues describe X-linked hypophosphatemic rickets, a rare genetic metabolic disorder caused by dysregulation of fibroblast-like-growth factor 23 (FGF23) leading to a profound reduction in renal phosphate reabsorption. Various symptoms can occur in both children and adults with severe impairment of quality of life. Coordination of patient management within the major medical disciplines is a mainstay to optimize treatment and reduce disease burden.

The Wnt signaling pathway in bone metabolism identified the negative regulator of bone mass sclerostin as a potential target for the treatment of osteoporosis. Katharina Kersch-Schindl describes pre-clinical and clinical studies in the development of the novel antibody romosozumab, a potent inhibitor of sclerostin (“inhibiting the inhibitor”). Biochemical analyses of clinical studies showed a significant increase in bone formation markers, which then slowly decreased within a year. This was accompanied by a particularly initially pronounced decrease in bone resorption. This dual mechanism of action led to an increase in bone mineral density and a significant reduction in fracture risk. In Japan, South Korea, Canada, and the USA osteoporotic patients at high risk for fracture may already be treated with romosozumab. In the European Union, the European Medicines Agency published a positive vote in December 2019.

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