KEYWORDS: osteoporosis, antiresorptive drugs, denosumab, PTHrP analogs.

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DIABETES AND BONE

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Diabetes mellitus type 1 and 2 (T1DM and T2DM) are associated with increased fracture risk in both male and female individuals. The relative risk (RR) of hip fractures in patients with T1DM ranges from 1.7 to 12.3, and increases with age, particularly after the age of 40. The outcome of a single study showed that the prevalence of morphometric vertebral fractures was higher in young (30 year old) patients with T1DM (24%) than in a control population (6%). Patients with T2DM in general have a moderately increased risk of hip fractures (RR 1.7, 95% CI 1.3—2.2). However, when restricting the analysis to the cohorts with more than 10 years of follow-up observation, the RR of hip fractures increased to 2.7 (95% CI 1.7—4.4). Fractures of the wrist and the foot also appeared to be more frequent in patients with T2DM than in healthy individuals. A single study conducted in Japan found that T2DM was associated with an increased risk of vertebral fractures in women (OR 1.9; 95% CI 1.11—3.12) and men (OR 4.7; 95% CI 2.19—10.20). Drs. Albright and Reifenstein first suggested that there was a link between BMD loss and T1DM over 50 years ago. Nowadays, it has been proven that individuals with T1DM have 22—37% less BMD than the non-diabetic control. The effects of T2DM on bone metabolism have remained less clear. Many studies have found a 5-10% increase in BMD above an age-matched non-diabetic population. By contrast, the trabecular bone score (TBS) at the lumbar spine decreased in patients with T2DM. It appeared that fracture risk in T2DM is higher for a given BMD T-score and age or for a given FRAX score (a web-based tool for estimating the 10-year probability of bone fracture risk). Both MRI and high-resolution peripheral quantitative CT revealed an increase in cortical porosity and trabecularization of the bone cortex. Bone material strength (assessed by *in vivo* microindentation) appeared to be lower in T2DM patients compared with non-diabetic controls, which is consistent with the alteration in collagen structure induced by hyperglycemia. The cellular and molecular mechanisms of increased bone fragility are rather complicated and probably not fully understood yet. At the tissue level, a decreased number of osteoblasts and diminished quantities of osteoid have been documented in patients with T2DM. The activation frequency of the bone remodeling units is decreased in diabetic patients. At the same time, the degree of bone mineralization and of non-enzymatic collagen crosslinking by pentosidine increased and positively correlated with HbA1c levels. These findings are consistent with a relatively low bone turnover state. Other determinants of bone fragility include Wnt dysregulation and increased marrow fat, adipokine alterations, oxidative stress, inflammation, use of thiazolidinediones or some SGLT2 inhibitors. Complications of diabetes mellitus increase the risk of falls and risk of fracture. In addition to this, recent investigations have identified the crucial role of osteocalcin in regulating insulin metabolism in a hormonal manner. The use of osteoblast-specific knockout mice produced a strong body of evidence that glucose homeostasis is controlled by the amount of osteocalcin in the circulation. Observational data in humans has provided strong evidence of a link between the levels of circulating osteocalcin and type 2 diabetes mellitus, although clinical trials of osteocalcin have not been initiated. In conclusion, patients with diabetes have an increased risk of low-traumatic fracture, particularly with hip fractures, yet the common approach to osteoporosis diagnostics appears to be inefficient. The mechanism of bone fragility in patients with diabetes is not fully understood, but it certainly related to hyperglycemia and the consequent changes in bone tissue and bone remodeling regulation. The role of osteocalcin on glucose metabolism and its potential therapeutic advantages in diabetic patients remains to be investigated.

KEYWORDS: FRAX score, bone fragility, vitamin D deficiency.

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RARE BONE DISEASE WITH ABNORMAL BONE MASS

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The group of genetic skeletal disorders comprises a total of almost 500 entities. Obviously this a very heterogeneous group with a clinical picture ranging from lethal over (very) severe to almost asymptomatic. Also the mechanisms that are disturbed vary, depending on the time, the skeletal sites as well as the cell types being affected. Despite the fact that these monogenic conditions are in general very rare, they can provide us with nice models for more complex, multifactorial diseases that are more common in the population. This is definitely the case for osteoporosis and a subset of the genetic skeletal disorders. For many of the latter, the disease causing genes have been identified and the underlying pathogenic mechanisms provided novel insights with relevance towards understanding and treatment of osteoporosis. Some monogenic conditions present with an increased fracture rate as seen in osteoporosis. This can be due to structural abnormalities within the bone matrix as is the case in some forms of osteogenesis imperfecta or osteopetrosis. But in other conditions the increased fracture risk is simply caused by a reduced bone mass, as seen in osteoporosis pseudoglioma syndrome. Also the pathogenic mechanisms of sclerosing bone dysplasias associ-

ated with an increased bone mass and in some cases protection against fracturing, are of relevance for osteoporosis. One of the major breakthroughs in the field of bone metabolism has been the role of canonical Wnt signaling in bone formation. The unraveling of several sclerosing bone dysplasias have been instrumental for this. Furthermore, in other conditions the regulation of this pathway turned out to be disturbed resulting in an increased bone formation rate. This is nicely exemplified in sclerosteosis and Van Buchem disease lacking sclerostin, a bone specific inhibitor of canonical Wnt signaling. Finally, the study of monogenic skeletal diseases not only contributed towards the understanding of mechanisms and regulation of bone homeostasis but also provided some novel targets for drug development for the treatment or prevention of osteoporosis. For example, monoclonal antibodies against sclerostin and cathepsin K are currently under development. This supports the idea that the study of rare monogenic conditions has important implications also for more common related conditions.

KEYWORDS: genetic skeletal disorders, Wnt signaling, sclerostin, cathepsin K.

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PRIMARY HYPERPARATHYROIDISM: CHALLENGES IN NORMOCALCEMIC AND MILD CASES

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The clinical presentation of primary hyperparathyroidism (PHPT) has changed dramatically in Western societies after increased accessibility to biochemical analyses. Thus, the diagnosis is today often made by change in patients without specific symptoms. Operative treatment is always an option and recommended in patient with markedly increased calcium levels or typical symptoms. However, the vast majority of patients in the modern Western clinic do not present organ related symptoms and their calcium levels are only slightly increased, or even within the upper limit of normal. Several consensus development conferences have discussed management of these patients with mild, borderline PHPT during the last twenty years. In developing countries in The Middle East, Asia and Latin America, patients still present with classical symptoms, severe hypercalcaemia, osteitis fibrosa and prevalent fractures. The female preponderance is much less pronounced in these areas and the presentation and severity of the disease related to vitamin D deficiency. With the recent change in socio-economic status in these areas, the clinical presentation of PHPT has drifted towards the more non-classical presentation with non-specific symptoms raising the same discussion on treatment indications. As disease severity in PHPT seems to be related to vitamin D deficiency and as the true calcium level might be masked by low levels, patients might be repleted with vitamin D during work-up and in preparation for surgical treatment. Only few studies have so far addressed this question, however based on recent randomized and controlled studies, pre-surgical Vitamin D treatment in PHPT seems to be safe and beneficial regarding PTH levels and BMD. Thus, in the modern clinic, most patients will present with few if any symptoms, high normal or slightly increased calcium levels with only slightly or moderately elevated PTH. Differential diagnoses must be ruled out and familiar or syndromic forms identified. Before decision for active treatment or observation is made, the patient should be handled to optimize vitamin D levels and ensure that no medical treatment is interfering with calcium levels.

KEYWORDS: primary hyperparathyroidism (PHPT), hypercalcaemia, vitamin D.

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GENETIC CAUSES OF HYPERPARATHYROIDISM

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Primary hyperparathyroidism (PHPT) is caused by autonomous hypersecretion of parathyroid hormone (PTH) by solitary parathyroid adenoma (~85%), parathyroid hyperplasia/multiple adenomas (~15%) or less frequently by parathyroid carcinoma (~1—5%). The majority of cases of PHPT are sporadic. Only 10—20% occur as a part of one of familial syndromes which include multiple endocrine neoplasia type 1, type 2A, type 4, hyperparathyroidism-jaw tumour syndrome, familial hypocalciuric hypercalcemia and familial isolated hyperparathyroidism, and has specific features in each of them. To date only two genes (tumor suppressor gene *MEN1* and oncogene *CCND1*) have been proven to play a role in tumorigenesis of sporadic parathyroid adenomas. Somatic *CDC73* mutations are frequently associated with parathyroid carcinomas. The role of somatic mutations in other genes in parathyroid tumorigenesis remains controversial.

KERWORDS: hyperparathyroidism, genetics, adenoma.

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SECONDARY HYPERPARATHYROIDISM DUE TO CHRONIC KIDNEY DISEASE. THE MANAGEMENT OF CALCIUM — PHOSPHOROUS DISTURBANCE

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Chronic kidney disease (CKD) is a widespread disease, which is characterized by progressive deterioration of kidney function. CKD is not only limited to negative effects on the kidney but is associated with a multifactorial dysregulation of bone and vascular calcification and is closely linked to increased cardiovascular disease and concomitant bone disease. These comorbidities are responsible for increased and premature mortality in CKD pa-