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-

tients. Therefore, an early detection of bone related and cardiovascular problems in this patient group will help to improve the therapeutic approach. Secondary hyperparathyroidism due to CKD is possibly one of the most important and most frequent comorbidities which is associated with CKD and a multifactorial dysregulation of bone and mineral metabolism. The respective systemic disorder has been named chronic kidney disease-mineral bone disorder (CKD-MBD), associated with increased cardio- and cerebrovascular calcification in this group of patients. Disturbances of mineral metabolism including parathyroid hormone (PTH), calcium, phosphorus, vitamin D, acidosis, and alkaline phosphatase (AP) are increasing during CKD, abnormalities in bone turnover, mineralization, volume, linear growth, or strength and vascular or other soft tissue calcifications contribute to the clinical outcomes. Bone biomarkers, e.g. PTH and isoforms of AP are increasingly important to generate diagnostic information independently of kidney function to predict underlying bone turnover and fracture risk, as well as diagnostic bone biopsies, which are underutilized. The KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD–MBD) has focussed on the specific problems in CKD patients with regard to their mineral metabolism first in 2009. Since then, not only the attention of clinical doctors and scientists for CKD-MBD patients has increased, there is a number of new insights into bone regulation and its importance via therapy options. Hemodialysis systems, kidney transplantation as well as nutrition and hydratation balance have a large impact on mineral and bone metabolism, but also a large number of medications e.g. phosphate binders and vitamin D supplements, or calcimimetic drugs, based on allosteric activation of the calcium-sensing receptor expressed in various human tissues. Future developments include more sensitive biomarkers to define disease risks in CKG patients and new therapeutic options, e.g. via molecular modulations of new metabolic targets.

KEYWORDS: hyperparathyroidism, chronic kidney disease, diagnosis.

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ACROMEGALY AND MULTIPLE TUMORS

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Acromegaly is associated with increased growth hormone (GH) and insulin-like growth factor-1 (IGF-1) levels which, in addition to the characteristic signs, symptoms and complications of acromegaly, may support tumor development and growth. In 1993 a 52 year old female patient was operated due to a medulla oblongata tumor (no histopathology available). In 2012, aged 71 years she was diagnosed with acromegaly due to typical clinical and hormonal characteristics (IGF-1 586 ng/mL, GH in OGTT 2.38, 3.48, 1.96 ng/mL). However, contrast-enhanced MRI did not reveal a pituitary adenoma. The rest of the pituitary function was normal. We have started to search for ectopic source of GH/GHRH. Firstly, we made abdominal and chest CT (June 2012), which revealed three tumors: solid stomach tumor located on the border of the gastric cardia and corpus, right adrenal gland tumor and right lung tumor, communicating with pleura and lymphatic nodes up to 1.5 cm, located in the mediastinum. The CT also showed hypodense lesion in liver (segment IV b, 1.6 cm in diameter) and heterogeneous echostructure of thyroid gland with right lobe enlargement and left lobe solid-cystic tumor (2.6 cm in diameter). Somatostatin receptor scintigraphy revealed increased tracer accumulation in the right thyroid lobe. No tracer accumulation was noted in the location of the lungs and stomach. Circulating GHRH levels were assessed 3 times with normal values. All tumors were radically resected. The histopathological examination of these neoplasms did not reveal GH secretion. The repeated MRI pituitary gland revealed hypodense lesion 5 mm in diameter, could represent microadenoma. Revision of first MRI pituitary gland showed also this small adenoma on first pituitary MRI imaging. We also made control abdominal CT which showed left kidney tumor: 1.7×1.6×2.0 cm, with clear border, showing a strong contrast enhancement. Patient refused pituitary and kidney surgery. Acromegaly is well-controlled with monthly somatostatin analogue therapy (Octreotide LAR 30 mg i.m.). Despite of numerous further tests, the cause of the disease remains unknown. AIP and MEN1 mutations were excluded. Next-generation cancer panel containing 99 cancer genes did not identify possible unifying gene abnormality in her germline DNA. **Conclusions.** Coexistence of acromegaly and occurring tumours suggests a common aetiology of these disorders. To this time, no genetic abnormality could be identified with the tests that have performed. Whole exome or genome sequencing using germline and tumor sample DNA might further help the identification of a tumour-predisposing genetic alteration.

KEYWORDS: acromegaly, growth hormone, somatostatin, tumors.

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ALCOHOL-INDUCED PSEUDO-CUSHING SYNDROME WITH CHRONIC HYPOKALEMIA CAUSED BY DIURETIC ABUSE: CLINICAL CASE REPORT

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Background. Diagnosis of Cushing's syndrome often remains a challenge, as well as distinction between Cush-