Future research strategies and health care needs in calcium and phosphate metabolism disorders and bone disorders

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Abstract:
This manuscript provides future research priorities and specifies health care needs in the fields of calcium and phosphate metabolic disorders and bone diseases, which are associated with significant disease burden and great societal impact. Specified areas of interest and unmet needs were identified by 16 European experts – members of the Calcium and Bone Focus Area of the European Society of Endocrinology (ESE), of the Bone and Growth Plate Working Group of the European Society of Paediatric Endocrinology (ESPE) and of the ESE Young Endocrinologists and Scientists committee (EYES). Priority topics were further developed in working groups with expertise in these specified areas. In the field of calcium and phosphate metabolism, topics included the clinical spectrum of primary hyperparathyroidism, the pathogenesis and management of chronic hypoparathyroidism, and the molecular basis of, and targeted treatments in, rare calcium and phosphate disorders. In the field of bone disorders, selected topics included the role of bone as an endocrine organ and action of hormones on bone development, bone mass acquisition in children and adolescents and the impact of chronic illness on this process, the frequently encountered secondary osteoporosis, the management of bone fragility disorders throughout life, the molecular basis and health implications of skeletal dysplasias, and targeted treatments in rare bone disorders. Some topics concerning both areas are discussed separately, including cellular senescence in bone heath and beyond, the molecular underpinnings of the sex bias in some calcium, phosphate and bone diseases as well as the development of novel diagnostic tools for bone quality assessment.

Introduction:

The calcium and bone focus area covers a broad spectrum of common and rare calcium-phosphate metabolic disorders and of bone diseases, which are rarely overlapping, hence have inevitably an inherent duality. However, both groups of disorders are associated with significant burden and are of great societal importance.

Disturbances in calcium and phosphate metabolism in adults are most often related to excessive or deficient secretion of parathyroid hormone (PTH), as in primary hyperparathyroidism (PHPT) and chronic hypoparathyroidism (1-3). In children, both rare heritable and common acquired calcium and phosphate disorders are seen. Heritable mineralization disorders are caused by gene defects in calcium sensing, in vitamin D, PTH, FGF-23 and renal metabolism, as well as with PTH resistance in inactivating PTH/PTHrP signaling disorders (iPPSDs) (4). In recent years, some rare calcium and phosphate metabolism disorders gained interest also in the adult medical community because of targeted therapies that significantly improved patients' outcomes.

The skeleton performs multiple functions including acting as an endocrine organ in addition to its mechanical, hematopoietic, and metabolic functions. Thereby secreted factors regulate distant tissue functions in a biochemical crosstalk and contribute to overall health and well-balanced homeostasis. The drugs used today in some rare bone diseases have improved the outcomes of affected patients and changed the paradigm from treating the symptoms of the disease to correcting the molecular defect or its direct consequences. Based on the unraveled mechanisms of rare diseases, some targeted therapies have been developed and implemented in clinic, not just for individual rare diseases but also for common disorders such as osteoporosis, for example anti-sclerostin therapy for the treatment of postmenopausal osteoporosis. However, a targeted therapy / cure is not available for most of the 771 rare and complex bone diseases (5).

This manuscript provides future research priorities and health care needs in the fields of calcium and phosphate metabolic disorders and of bone diseases. Calcium-phosphate disorders and bone diseases resulting from organ failure (such as kidney, heart or gut) or electrolyte disturbances (such as in sodium or magnesium) are beyond the scope of the present manuscript. Prioritized areas of interest and unmet needs were identified by 16 European experts – members of the Calcium and Bone Focus Area of the European Society of Endocrinology (ESE), of the Bone and Growth Plate Working Group of the European Society of Pediatric Endocrinology (ESPE) or of the ESE Young Endocrinologists and Scientists (EYES) committee. These priority topics were discussed and further developed in working groups including both basic researchers and clinicians with expertise in these specific areas. The manuscript is subdivided in 3 main sections, the first of which is related to the disorders of calcium and phosphate metabolism, the second to disorders of the skeleton, and the third to transversal topics such as cellular senescence, sex differences, and novel diagnostics tools used in these fields. As a conclusion, the summary of key research actions and health care needs from each of the chapters is presented in bullet points.

I/ Calcium and phosphate metabolic disorders

1. Clinical spectrum of primary hyperparathyroidism

Primary hyperparathyroidism (PHPT) is a disorder caused by an overactivity of one or more parathyroid glands, leading to excessive secretion of PTH, hypercalcemia and target organ (bone and kidney) involvement.

PHPT can present as a symptomatic form with overt skeletal and kidney complications. In addition to these classical complications, neurocognitive, cardiovascular, metabolic, and gastrointestinal functions,

as well as quality of life, can be compromised (2). More research is needed to understand how PHPT and hypercalcaemia affect the heart, blood vessels and brain, whether such effects are reversible following parathyroidectomy, and to translate the accumulated knowledge into clinical recommendations. Asymptomatic PHPT is characterized by the lack of symptoms or signs regardless of the presence of target organ involvement. In normocalcemic primary HPT (nHPT) ionized calcium and 25OH vitamin D are normal with elevated levels of PTH while target organ involvement might or might not be present. For this more recently defined entity, research is required to determine whether active monitoring of this conditions is required, or whether a few patients may benefit from early surgery (6). However, robust selection criteria are still missing (7). nPHPT may also represent an early precursor of PHPT (8). National, European or international registries from large patient longitudinal cohorts will be useful to better describe the wide range of clinical presentation of PHPT and treatment outcomes.

While PHPT is more prevalent in elderly females. but males and children can also be affected (9). The younger the age at presentation, and a positive family history or dysmorphic features should raise the suspicion of a heritable form. More than 10% of patients with PHPT will carry a pathological variant in one of 10 genes, most commonly those causing multiple endocrine neoplasia. The genetic diagnosis has clinical consequences, as the management of these disorders can differ from sporadic PHPT and investigation of other family members is required. Endocrine societies should establish education on the availability and clinical utility of genetic tests (10). Nationwide, European, and international genetic databases, including data from whole-genome sequencing of early onset or familial PHPT are needed to make a step forward in understanding the underlying genetic (or epigenetic) causes in those where no mutation can be identified.

PHPT most often arises from a single parathyroid adenoma, while multiple adenomas, parathyroid hyperplasia and carcinoma can also cause increase aberrant PTH secretion. The prognostic relevance of atypical parathyroid adenomas remains uncertain, and the areas of pathogenesis, diagnosis and therapy of parathyroid carcinoma pathogenesis are hot topics of current research.

Parathyroid surgery remains the only definitive treatment for PHPT, and recently updated consensus criteria for surgery have been published (7). Pharmacological therapy with calcimimetic agents and/or bone antiresorptive medications may be appropriate for selected patients, however the different mechanisms of actions need to be considered (7). In the surgical treatment of multigland and hyperplastic disease, ongoing research is required to define optimal strategy (total, subtotal or less than subtotal parathyroidectomy) depending i.e. on the age of the patient, and the potential efficacy of radiofrequency therapy. When PHPT is diagnosed during pregnancy, management guidance should be followed (11).

2. Pathogenesis and management of chronic hypoparathyroidism

Chronic hypoparathyroidism is a lifelong disorder that significantly decreases the quality of life of affected individuals and represents an important healthcare problem with non-negligible societal costs (1, 12). Many patients in low- and middle-income countries worldwide are not properly diagnosed and treated. The most common form of hypoparathyroidism in adults is iatrogenic, acquired following neck surgery in approximately 75% of cases (13). Therefore, actions to limit unnecessary thyroid surgery, and centralization of cervical surgery in high-volume expert centers, are essential to reduce the prevalence of iatrogenic hypoparathyroidism and other complications. In children, non-surgical forms prevail, including genetic and autoimmune causes (14). The underlying genetic causes remain, however, unidentified in some cases. In patients without genetic abnormalities in Sanger sequencing or in

targeted next generation sequencing, discovery of novel genes, deep intronic variations, epigenetic abnormalities or chromatin reorganization should be a priority for future research in familial or sporadic forms of the disease.

Complications of chronic hypoparathyroidism are highly variable. For instance, a minority of patients with persistent hypercalciuria will develop nephrolithiasis or nephrocalcinosis. To provide adequate personalized management, it is crucial to identify factors (metabolic, renal, genetic, residual PTH secretion) favoring, or protecting from, development of disease-related complications. National and international registries and genetic databases from large cohorts will facilitate identification of such disease modifying factors and developing efficient tools for precision medicine.

The main goals of treatment of chronic hypoparathyroidism are to avoid hypocalcaemia, control hyperphosphataemia, reduce disease-related complications and improve quality of Life. The existing (15-17) and upcoming (18) replacement therapies by PTH analogues represent a major step forward in the management of the disease. However, these replacement practices do not fully restore the physiological state of PTH secretion but are pharmacological approaches whose long-term repercussions - particularly on bone and kidney remain unknown and need to be carefully monitored (19). Continuous point-of-care capillary calcium monitoring with the option to adapt PTH replacement therapy would improve patients' biochemical control, which is currently relying on random serum calcium assessment every 3 - 6 months and not allowing adaption of daily calcium fluctuation. Similar to diabetes mellitus (20), replacement of parathyroid cells derived from human stem cells, permitting calcium sensing and restoring regulated PTH secretion, could be the future in the treatment of hypoparathyroidism. In autoimmune causes of hypoparathyroidism, especially those linked to *AIRE* gene mutations, JAK inhibition-based immunotherapy (21) is a novel promising approach, shedding also new light on the disease pathogenesis but requires further research.

3. Molecular mechanisms and targeted treatments in rare calcium and phosphate disorders

Disorders of mineral metabolism can result in profound morbidity involving both the skeleton and non-skeletal organs. Pathophysiologic mechanisms involve direct impairment of mineralization such as observed in hypophosphatasia (HPP), chronic hypophosphatemia related to fibroblast growth factor 23 (FGF-23) excess in X-linked hypophosphatemia (XLH) or related to other mechanisms (22), or end-organ resistance to PTH in iPPSDs (22). Alterations in the CaSR activation or in calcitriol synthesis and signaling can cause life-threatening deviations of serum calcium levels.

The development of consensus guidelines (23), (24) and continuous efforts to analyse data in rare disease patient registries contribute to an improved state-of-the-art management and understanding of this heterogeneous family of disorders. Deep phenotyping including both skeletal and non-skeletal tissues should be more precisely performed in the coming years and constitute a priority for research. Recent advances in targeted treatments, such as FGF-23-neutralizing antibodies (burosumab) in XLH or bone-targeted recombinant ALP (asfotase alfa) in HPP could profoundly improve outcomes in specific conditions. Pharmacotherapies not specifically designed for rare disorders, including calcimimetics (cinacalcet) in neonatal severe hyperparathyroidism and the above-mentioned PTH analogues for the treatment of hypoparathyroidism including its rare inherited forms extend the spectrum of therapeutic options in PTH-related disorders. Calcilytic calcium sensing receptor (CaSR) modulators (encaleret) for autosomal dominant hypocalcemia looks very promising (25). Disorders such as iPPSD still await causal treatments targeting the specific molecular defects and should be the focus of research due to the high burden of disease.

Future research efforts should involve both optimization of existing therapeutic agents, extending their label to other indications such as burosumab in tumor induced osteomalacia or autosomal dominant hypophosphataemia from FGF23 gene mutations, as well as the development of new targeted drugs and re-purposing of drugs. Optimization of different management strategies are also an important area for future research. Alternative therapeutic concepts for rare diseases including gene therapy have shown promising results in preclinical models for mineralization disorders including XLH (26) or HPP (27) and could potentially mark a new era in the future treatment of rare diseases. Until then, non-pharmacologic treatment including functional therapy, psychosocial support and multidisciplinary patient care including the involvement of patient advocacy groups have to be optimised and evaluated. These rare disorders require prospective multicenter registries to assess outcomes of therapies far beyond pediatric age.

II/ Bone health and pathology

1. The role of bone as an endocrine organ, hormones and bone development

Advances in bone biology research during the past two decades highlighted the importance of bone as potential regulator of metabolic processes that are independent of mineral metabolism. Bone cells are found to express and bone matrix to release various bioactive factors e.g. prostaglandin E2, Wnt signalling molecules, nitric oxide, receptor activator of nuclear factor kappa-B ligand and many more. These factors act locally in a para- and autocrine manner to regulate skeletal development, biomechanical adaptation and mineral metabolism. Further, these factors allow to communicate with more distant tissues i.e. skeletal muscles, fat and other distant organs through the circulatory system (28), (29).

Highlighting the important future opportunities for discovery of bone-secreted factors, are the recently developed bone targeted therapies using antibodies, both for common and rare bone diseases. For example, romosozumab, a monoclonal antibody targeting osteocyte secreted sclerostin, increases bone formation and decreases bone resorption and effectively reduces fractures in postmenopausal osteoporosis (30). As already mentioned above, burosumab, a monoclonal antibody targeting FGF-23 - a factor mainly produced by osteocytes - improves phosphate homeostasis in both genetic XLH and acquired tumor-induced osteomalacia (31). In addition, novel studies have indicated that elevated levels of FGF-23 are associated with cardiovascular diseases (32), and FGF23-lowering therapy was associated with a reduction in the incidence of cardiovascular events (33). Some recent data also report possible links between FGF-23 and degenerative brain diseases, i.e. increased risk of dementia and Alzheimer's disease (34).

The multifunctional osteocyte with its intricate global network of osteocyte cell body housing lacunae and dendrite containing canaliculi appears of central importance in the endocrine communication of the bone tissue (35). Novel factor identification strategies including micro-RNAs and molecule-containing extracellular vesicles will provide novel insight into osteocyte-mediated communication. Furthermore, investigations that focus on osteocyte network properties that include advanced imaging modalities and 3D-analysis will aid our understanding of osteocyte communication on a different level (36), (37). With these tools, network disruptions via loss of canalicular or dendrite connectivity with aging-induced bone pathologies have been documented (38). Disruption in osteocyte communications may include osteocyte apoptosis or other forms of cell death together with the potential endpoint seen

in osteocyte lacunar mineralisation – micropetrosis (39). Further research in this area is needed to fully understand the pathophysiology and design therapeutic interventions.

2. Bone mass acquisition in children and adolescents, and impact of chronic illness

Childhood and adolescence are crucial lifetime stages for bone mass acquisition. Specific to bone development in children are the relatively higher remodelling rate and the influence of nutrition, function of all organs, locomotion, growth and puberty on the amount of natural mass bone acquisition (40). Correct evaluation of bone strength in young people who have not yet achieved peak bone mass is essential to diagnose bone fragility (41). As opposed to dual-energy x-ray absorptiometry (DXA), age and sex specific references data (accounting for ethnicity, height and pubertal status) still need to be developed for novel imaging modalities such as high-resolution peripheral quantitative computed tomography (HRpQCT), trabecular bone structure (TBS) or finite element analysis (FEM, FEA). Also, the influence on bone mass acquisition of conditions that, for limited or prolonged periods of time, either accelerate (precocious puberty/early onset sustained obesity) or delay bone mass acquisition (delayed puberty/ growth, nutritional impairment and chronic disease, hypogonadism) and their long-term consequences on bone health should be systematically studied (42).

In addition to imaging modalities, various bone material properties as assessed by histomorphometry determine and characterize bone strength. Based on existing bone biopsy data, rare bone and growth disorders should be better characterized from a bone material perspective (static and dynamic cortical and trabecular structures, material densities, matrix composition) to elucidate mechanistic pathways involved (43). Such information will help to develop targeted treatments to maximize bone strength in young patients with specific chronic illnesses, depending on their cause (44). Acquired osteoporosis may have a biomechanical (neuromuscular), inflammatory (cytokines), cytotoxic (medication, environment), autoimmune or endocrine basis (45). The timing, duration and progressivity of these factors during growth, be they of transient or permanent nature, may or may not cause sustained deleterious effects on bone mass acquisition. Therefore, the assessment of a patient's recovery potential has become standard of care in secondary osteoporosis (46) and requires collaborative research efforts. Analysis of the mechanisms determining bone mass acquisition impairment by chronic medications (i.e., glucocorticoids) and development of targeted therapeutic agents to be used simultaneously to prevent bone health impairment should be a priority (47).

Coordinated efforts to collect pediatric bone and DNA samples of patients affected by rare bone diseases (ideally in the context of society-driven international registries) will facilitate diagnostic and therapeutic studies.

3. Secondary osteoporosis and bone quality

Secondary osteoporosis, caused by underlying disease, specifically inflammation, toxins, medications, hypogonadism, sarcopaenia or immobility, occurs in up to 30% of postmenopausal women, > 50% of premenopausal women, and between 50% and 80% of men diagnosed as osteoporotic and is associated with an increased risk of fracture (48). The standard fracture risk assessment tool (FRAX) underestimates fracture risk in people with secondary osteoporosis, such as type 2 diabetes (49), (50), (51). Most systemic diseases and organ dysfunctions can lead to osteoporosis. Research on mechanistic understanding of the different causes of secondary osteoporosis will provide new insights into bone quality parameters relevant to bone strength/bone homeostasis and guide more targeted, and thus more effective, treatment modalities.

Diabetes mellitus (DM) is a metabolic disease of pandemic dimensions and the most common endocrine contributor to osteoporosis development. Both type 1 (T1DM) and type 2 DM (T2DM) are associated with a higher risk of fracture (52). The formation of advanced glycation end products in the bone matrix associated with high blood glucose contributes to impaired biomechanical properties (53). More recently, additional compromised bone quality features have been discovered in DM, such as high cortical porosity in a subgroup of individuals with T2DM (54), lower local microhardness at the femoral neck in T2DM, and microcrack accumulation associated with osteocyte lacunar mineralisation in T1DM (55). The presence of vascular complications in T2DM leads to structural and mechanical deterioration of the trabecular bone at the femoral neck (56), (57). Therefore, it may be clinically useful to identify signs of vascular disease in individuals with T2DM to assess fracture risk beyond the results of DXA and FRAX (57).

Thyroid hormones influence skeletal development and linear growth in childhood and bone turnover and bone mass (58). Overt and subclinical hyperthyroidism, if left untreated, causes reduced bone mass, poor bone quality and increased fracture risk (59), (60). The molecular mechanisms of how thyroid hormones influence the osteoblasts and osteoclasts are the focus of recent research, whereby the Wnt-signaling pathway has been implicated (61). Future research should further focus on unravelling these, and other thyroid hormone induced pathways.

Chronic liver disease also has a negative effect on the skeleton and recent studies on the femoral neck and/or lumbar spine have provided evidence of stage-dependent microstructural bone changes in various liver diseases, including alcohol-related liver disease, metabolism-associated fatty liver disease, cholestatic hepatopathy, primary biliary cholangitis and liver cirrhosis (62-67). Much more evidence needs to be acquired to understand which biochemical changes cause impairment in biomechanical bone properties.

Drug treatment /pharmaceutical agents may also lead to bone loss (68) and glucocorticoid-induced osteoporosis (GIOP) is certainly the most common medication-induced cause of secondary osteoporosis (69). About 1% of the population is treated with glucocorticoids on a long-term basis due to various inflammatory conditions (70), and the risk of fracture and re-fracture increases with higher/supra-physiological corticosteroid dosage or a treatment duration of more than 3-6 months (71). The pathophysiological mechanisms involve various effects on bone cells, i.e. altered osteocyte signaling and apoptosis, increased longevity of osteoclasts and reduction of calcium absorption (72), (73), (74). The changes in bone quality are complex and most likely depend on the variety of treatment methods. For example, bone loss in GIOP is characterized by an initial rapid, profound decrease in BMD and a continuous annual loss of smaller magnitude thereafter (75). However, the risk of fracture increases even faster, so that an additional determination of bone quality should be considered (76).

A largely neglected, but the by far most common form of secondary osteoporosis, which demonstrates the mechanical necessity of muscle pull for bone health, is immobility which appears to affect bone geometry and quality distinctly different to primary osteoporosis (40, 77-79). Future research should address the muscle-bone interplay (80), medical and biomechanical therapeutic interventions for bone mass acquisition, fracture reduction and quality of life in children and adults with reduced mobility.

Early detection of the cause of secondary osteoporosis is extremely important and necessary to improve bone health and prevent further bone loss. Therapy is primarily focused on treating the underlying cause, where possible. Research is needed to clarify whether individual types of osteoporosis medication should be favored for specific types of secondary osteoporosis. Multidisciplinary care is the basic principle of preventing osteoporosis-related fractures. However, there are still considerable deficits in the healthcare system concerning the early recognition, diagnosis,

treatment, and follow-up of patients with secondary osteoporosis (81). Future investigations will help to identify systematic gaps and help design and implement therapeutic solutions.

4. Management of bone fragility disorders in different periods of life:

Improved management of bone fragility disorders in all periods of life involves earlier and more accurate detection of skeletal disease, more sophisticated and targeted treatment options, and advanced technology to monitor treatment effects.

To improve detection rates of genetic and epigenetic causes of skeletal disease and decrease the need for interpretational manpower, the development of deeper molecular genetic analysis and faster interpretation using AI technology is required (82). Improvement in the understanding of predicted and functionally tested disease mechanisms will allow development of precision treatments on DNA, mRNA and protein level.

This requires in depth training of bone specialists and tertiary medicine in specialized centers that work together to ensure collective learning (83),(84). Large European grants should be made available to support these rare disease research networks demonstrating translational research from bedside to bench to bedside. To enable faster development of and early access to new precision therapies for rare disease, regulators need to simplify legislative procedures around clinical trials.

More detailed natural history data in secondary bone fragility will enable preventive measures and early treatment. Establishment of effective fracture liaison services will further refine secondary prevention of fragility fractures. Novel, non-invasive, readily available and cost-effective diagnostic and monitoring tools to reduce falls and fracture risk in the aging population will prevent significant morbidity, and improve quality of life, and is therefore a research priority.

In both the pediatric and adult setting, research into the long-term outcomes of skeletal disease-specific complications, such as growth, mobility, quality of life and societal participation should be conducted, and registries will help to achieve this.

5. Molecular basis and major health implications of skeletal dysplasias:

Skeletal dysplasias encompass a large spectrum of genetic disorders of the skeleton with abnormal bone growth, structure, or strength (85). Individually, they are rare but collectively, due to the large number of skeletal dysplasias (>700), result in significant morbidity. Underlying pathology remains inadequately understood and optimal therapy often undefined, and precision drug treatment targeting the underlying molecular mechanism not available for most skeletal dysplasias. Gene discoveries have increased exponentially, demonstrating the value of advanced genetic tools, and motivating further research to the complex pathogenesis of skeletal dysplasias.

However, further basic research is required to uncover the cellular pathology and implicated molecular pathways in various forms of skeletal dysplasia. Understanding the pathophysiology of skeletal dysplasias may also benefit a larger patient population. This is evidenced by anti-sclerostin treatment for osteoporosis (86), which at present is in clinical trials for osteogenesis imperfecta; preclinical data show positive effects on bone mass and strength (87).

The spectrum of disease manifestations of various skeletal dysplasias in different phases of life and health projections across the life course remain inadequately studied. Research on therapeutic approaches needs to focus not only on correcting the pathophysiology but also more broadly on surgical approaches, rehabilitation, functional / environmental adaptations, preventative measures, pain management, psychological support, and quality of life. Patient groups must be involved in

identifying these research goals. International registries should be utilized to collect and analyse such data.

A multidisciplinary approach is of particular importance in genetic skeletal disorders, to enable cohesive care throughout the life course. The patients have a range of physical impairments due to their skeletal disorder, but also a disease-specific spectrum of extraskeletal manifestations requiring medical attention. These may include e.g., dental and oral health problems, immune deficiency, impaired hearing, and neurological or ophthalmologic manifestations. Research on multidisciplinary management by medical specialties, adequate personnel resources, and allied health professionals is likely to greatly improve patient care, quality of life, enable smooth transition from pediatric to adult care, and help in establishing management guidelines.

6. Targeted treatments in rare bone disorders

During the past decade treatment of some rare disorders has shifted from symptom-based management to targeted treatments which aim to resolve or negate the underlying molecular defect. In the bone field targeted therapies have been successfully implemented in a small number of disorders, as previously mentioned, e.g., using enzyme replacement such as asfotase alfa in hypophosphatasia (88); neutralizing an elevated hormone such as burosumab in XLH (89); and receptor inhibition or upregulating an alternative compensatory pathway in achondroplasia (46, 90).

The current nosology of genetic skeletal disorders (85) includes 771 conditions, most of which lack targeted treatment. These conditions are rare and complex as they affect bone development and homeostasis through multiple genes and pathways (91). Understanding the clinical manifestations and molecular and biochemical pathophysiology is a prerequisite for developing targeted therapies. Genetic animal models are also necessary for molecular characterization and testing preclinical interventions. Strategies to develop precision therapies for rare diseases involve not just targeting proteins (drug targets) but also mRNAs (e.g. anti-sense oligonucleotides) and gene therapy (92).

Despite some successes, much work is warranted to obtain targeted therapies in most rare bone diseases. This is a major research priority, with the aspiration that treatment strategies in rare skeletal disorders will be applicable also to more common disorders. Partnering with pharmaceutical companies and scientific engagement in every part of the process is important to enable realization of new therapies.

Expansion of the application profile for bone-targeted treatments, such as the use of burosumab in tumour-induced osteomalacia or achondroplasia drugs in hypochondroplasia and other growth failures, will increase the availability of therapeutic options for a broader range of conditions. Another more cost-effective approach may be in repurposing existing medications for alternative uses e.g., the use of carbamazepine, which stimulates intracellular proteolysis and alleviates Endoplasmatic Reticulum stress, in metaphyseal chondrodysplasia or other conditions with similar cellular pathology (93). Future research should focus on elucidating which drug may be effective and which biomarker(s) may be useful in this setting.

III/ Overarching topics

1. Cellular senescence and bone health

Cellular senescence is an irreversible cell arrest caused by several triggers including DNA damage, oxidative stress, telomere dysfunction or oncogenic stress, which cause tissue impairment. Cellular senescence can be triggered in normal cells in response to various intrinsic and extrinsic stimuli, as well as developmental signals and has been considered an underlying mechanism for multiple pathologies, including bone loss and fragility associated with aging and metabolic bone diseases. Thereby, the accumulation of senescent cells in bone microenvironment in various conditions has been considered as one of the possible triggers and has thus become an interesting target in the development of anti-senescence strategies in musculoskeletal diseases, known as senolytics.

Activation of the p53/p21$^{WAF1/CIP1}$ and p16^{INK4A}/pRB tumor suppressor, mTOR, NFkB pathways and senescence-associated-beta-galactosidase (SA-β-gal) activity play a central role in regulating senescence (94). The current senolytic drugs including rapamycin, ruxolitinib, fisetin, navitoclax or metformin are designed to target a specific secretory phenotype (so-called senescence associated secretory phenotype, SASP) consisting of bioactive molecules that affect cell function (95), (96). Thus, SASP inhibitors address the inflammatory signal being sent off by senescent cells. However, these drugs administered systematically exhibit a variety of "off-target" effects because of tissue and cell specificity and their continuous use is not advised. Therefore, short term treatment to alleviate some SASP induced effects might be considered in future use (97) or combination with other drugs to increase the effectivity of the removal of the senescent cells only in damaged tissue as these cells manifest heterogeneous cellular phenotype. Animal studies focused to eliminate senescent cells targeting specific pathways - genetically with either using a selective ablation of p16^{Ink4a}-positive senescent cells or pharmacologically using an intermittent treatment of the senolytics dasatinib plus quercetin, reported promising results on prevention of age-related bone loss by promoting bone formation while inhibiting bone resorption (98). Despite negative effects reported by some animal studies (99), a phase 2, open-label, randomized controlled clinical trial is currently undertaken to determine if the senolytics dasatinib, quercetin and fisetin would improve skeletal health in older humans (100). Therefore, more translational research is needed to specify the condition and effectivity of senolytic drugs for a long treatment. In addition, it would be worthy to include in the study design the comparison of senolytic with classical anti-osteoporotic drugs in terms of prevention of bone loss. As aging is causing accumulation of senescent cells in other organs besides bones, the effectiveness of senolytic drugs is a very attractive area of drug development targeting multiple-age related complications, including bone loss and fragility.

2. Sex differences in calcium and bone metabolism and diseases

The molecular mechanisms behind sexual dimorphism in some disorders of calcium and phosphate metabolism may be related to hormones, genetic or epigenetic factors. Primary hyperparathyroidism is one of the most common endocrine diseases in adults and is more common in women than in men (101), (102). The prevalence in women further increases to 1-3% after menopause, suggesting that the development of estrogen deficiency in postmenopausal women plays a role in unmasking hypercalcaemia (103, 104). Exactly how estrogens and other hormones lead to differences in the occurrence of primary hyperparathyroidism requires further investigation. This difference also underlined the importance of including both males and females in animal and clinical studies. X-linked hypophosphataemia is a well-known genetic disease. X-linked dominant inheritance means that male patients have a complete loss of PHEX function in all body cells, whereas in female patients, random inactivation of the X chromosome causes approximately 50% of the cells should express a functional PHEX protein, leading to a milder phenotype compared to male patients. However, such a gender-

specific difference in disease severity is observed in some (105) but not all studies (106) which could be due to biased inactivation of the X chromosome in female patients and requires further studies including allele-specific expression analyses. The inactivating PTH/PTHrp signalling disorders (iPPSD) type 2 and 3 (previously referred to as pseudohypoparathyroidism type 1a and 1b) are caused by inactivating variants on the maternal allele of the GNAS gene within exons 1–13 or by methylation abnormalities in the GNAS locus and are a typical example of imprinting disorders (24). In iPPSD3 in particular, the molecular events and their pathogenetic effects need to be further studied.

Both bone growth and the attainment of peak bone mass as well as the rate of bone loss during aging are profoundly influenced by sex, exemplified by the lifetime risk of fractures for women approaching 50% in comparison to only 25% in men. Estrogen has been shown to be one of the main hormones regulating bone metabolism and loss of estrogen action either through menopause or genetic mutations affecting the estrogen receptor led to bone loss. In addition, testosterone, either directly or by conversion to estradiol, also influences bone metabolism (107). More recently, also the gonadotrophic hormone follicle stimulating hormone (FSH) has been linked to changes in bone metabolism independent of estrogen (108), showing that the endocrinology underlying the sex differences in bone mass accrual and bone loss are incompletely understood and warrant further investigation to improve skeletal health during the life span.

From a clinical point of view, most studies for diagnosis, treatment and outcomes have been performed in women and studies investigating the generalizability to men have shown mixed results; 1) fracture prediction tools to identify the need for BMD measurement and osteoporosis treatment are less accurate in men than in women (109) 2)in comparison to women, men more often suffer from secondary osteoporosis (prevalence up to 30% in postmenopausal women, > 50% in premenopausal women, and between 50% and 80% in men) (48) 3) the clinical trials of anti-osteoporosis drugs have been much smaller in men than in women and usually use BMD rather than fracture as an outcome (110) and although antiresorptive treatments are licensed for both women and men with osteoporosis, romosozumab is only approved for the treatment of postmenopausal osteoporosis in women 4) the male gender is an independent factor associated with mortality after a hip fracture (111). To ensure optimal diagnosis and treatment of osteoporosis and bone disease in both women and men, awareness of these differences is important for the design of future studies, including those on transgender bone health.

3. Novel diagnostic technologies for bone quality assessment

The lack of accuracy in fracture risk prediction via DXA in a large proportion of adult individuals creates the need for the development of novel approaches and the optimization of existing methods to ensure improved and personalized assessment of bone strength and metabolism (112), (113). Additionally, no tools for fracture risk prediction in children with bone fragility are available. Their development should also be a priority. Given the availability, low cost, and low radiation of DXA, several DXA add-ons are increasingly applied to improve its diagnostic performance (e.g., trabecular bone score [TBS] (114), hip structure analysis [HSA], 3D DXA, (115), Vertebral Fracture Assessment [VFA]) (116), which offer additional risk detection and the distinction between fracture and non-fracture groups. Considering that many individuals never receive a DXA scan but various routine clinical scans for other health reasons, studies examining the potential of opportunistic screening for osteoporosis using spine, chest, or abdomen X-rays or routine computed tomography (CT) scans are also emerging. These techniques could be expanded to include bone marrow changes related to impaired bone quality in some

individuals e.g., with diabetic bone disease with spectral and photon-counting applications (117), (118). New generations of high-resolution peripheral quantitative computed tomography (HRpQCT) are increasingly used in some countries for detailed assessment of 3D bone microarchitecture (e.g., trabecular thickness, cortical porosity) at an ultra-high resolution (less than 50 micrometers) at peripheral sites (distal radius, distal tibia) and predict major osteoporotic fractures (119), (120).

Applying finite element modelling or radiomics approaches based on machine learning on different imaging datasets may bring greater breakthroughs in this field, comparable to the advances in the field of cancer imaging (121).

While imaging methods provide surrogate indicators of bone strength, application of microindentation testing in clinical settings could offer more direct information on the mechanical competence of cortical bone.

Non-X-ray–based methods such as radiofrequency echographic multi-spectrometry (REMS) (122) and quantitative methods based on magnetic resonance imaging (MRI) (123) are particularly promoted given their lack of X-ray exposure and promising initial results that may outperform DXA in prediction of osteoporotic fracture risk. Single-voxel proton MR spectroscopy (1H-MRS) (124) can evaluate volume of bone marrow fat fraction and saturation index of the lipids in bone as a novel parameter for fracture risk. It would be useful if other spectral approaches, i.e., Raman spectroscopy, could be employed on a larger scale to provide information of the organic part of the bone matrix, given the implications of advanced glycation end products and others inflicting bone quality.

The interesting developments in the field of non-imaging methods (biomarkers, biosensors) rely on the identification (125) of i) new biomarkers, including micro-RNAs (126) and other omics-detected candidate biomarkers that could provide complimentary data for timely diagnosis of bone fragility; ii) types of invasive or noninvasive biosensors that could allow quicker, cheaper, more reliable, and real-time assessment of bone status to monitor bone mechanical competence, remodelling, or healing; and iii) biosensors for point-of-care testing of capillary calcium or phosphate for a variety of conditions such as hypoparathyroidism, iPPDS, XLH or renal failure (127, 128). Further studies are warranted to clarify the applicability and usefulness of these developments in the context of bone and calcium metabolism.

Key future actions:

- Regular clinical updates should aid the education of both pediatric and adult endocrinologists on the uncertainties and advancements in the management of patients affected by PHPT at different stages of life.
- Actions to limit unnecessary thyroid surgery, and to centralize neck surgery in high-volume expert centers, are essential to reduce the prevalence of post-surgical hypoparathyroidism.
- Point-of-care calcium monitoring for treatment adjustment and clinical trials on therapeutic modalities approaching the physiologic state of regulated PTH secretion, including replacement of parathyroid cell derived from human stem cells, are the key future steps to improve treatment of chronic hypoparathyroidism.
- Advances in the targeted treatment of some rare calcium and phosphate disorders are leading to better outcomes and have potential for treatment for use in other, both common and rare, conditions. Many rare disorders in the field are still awaiting causal treatment and should be the focus of research due to the high socioeconomic and medical disease burden. Patient registries are required to better understand this heterogeneous group of disorders and the effect of interventions.

- Future research should aim to decipher novel underlying mechanisms in trans-tissue crosstalk.
- Age- and sex-specific reference data for novel imaging modalities are required to facilitate the assessment of the impact of conditions that either accelerate, delay or impair bone mass acquisition and bone fragility.
- Further research on secondary osteoporosis shall clarify whether specific types of drugs or interventions should be favored for certain types of secondary osteoporosis.
- Implementation of early detection investigations of bone fragility disorders at different stages of life requires not just advanced diagnostic techniques, more sophisticated monitoring and tertiary training of medical and radiology staff in specialist centers.
- The treatment of skeletal dysplasia requires a multidisciplinary team effort and should include functional and environmental adaptations, psychological support, and quality of life aspects. Further genetic and epigenetic research will expand our molecular understanding of bone homeostasis.
- The precision treatments applied today to some rare diseases need to be tested in other rare and common disorders. Massive research efforts are needed to identify disease mechanisms inmost genetic skeletal diseases.
- Cellular senescence is a characteristic of aged, damaged cells that secrete bioactive molecules to promote a vicious inflammatory environment driving disease states. A more detailed mechanistic understanding in relation to bone homeostasis remains necessary and requires collaborative research strategies. Senolytics targeting senescent cells in the body might be potential candidates in the treatment of bone pathologies (osteoporosis, diabetic bone disease).
- Sex differences in various common or rare calcium & phosphate and bone diseases can be attributed to hormonal, genetic or epigenetic factors. For example, men suffer more frequently from secondary osteoporosis, clinical studies are less developed, fracture prediction tools are less accurate, and the male sex has a higher mortality rate after hip fracture. Research needs to be transparent and inclusive to allow for detailed investigations including sex-specific mechanisms.
- With new insights into the quality of bone (material) and the role of new factors contributing to bone strength, imaging techniques are being developed, optimized and repurposed to enable personalized medical diagnosis.

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