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EndoCompass project: research roadmap for calcium and bone endocrinology

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Abstract

Background: Endocrine science remains underrepresented in European Union research programmes despite the fundamental role of hormone health in human well-being. Analysis of the CORDIS database reveals a persistent gap between the societal impact of endocrine disorders and their research prioritization. At national funding level, endocrine societies report limited or little attention of national research funding towards endocrinology. The EndoCompass project—a joint initiative between the European Society of Endocrinology and the European Society of Paediatric Endocrinology—aimed to identify and promote strategic research priorities in endocrine science to address critical hormone-related health challenges.

† W.H. and P.K. contributed equally.

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Methods: Research priorities were established through comprehensive analysis of the EU CORDIS database covering the Horizon 2020 framework period (2014–2020). Expert consultation in bone and calcium endocrinology was conducted to identify key research priorities, followed by broader stakeholder engagement including society members and patient advocacy groups.

Results: Research priorities encompass primary hyperparathyroidism, chronic hypoparathyroidism, and rare calcium–phosphate disorders. Key areas include bone as endocrine organ, bone mass acquisition, secondary osteoporosis, and skeletal dysplasias. Special emphasis is placed on cellular senescence, sex-specific differences in disease manifestation, and development of novel diagnostic tools for bone quality assessment.

Conclusions: This component of the EndoCompass project provides an evidence-based roadmap for strategic research investment. This framework identifies crucial investigation areas into metabolic bone disease pathophysiology, prevention, and treatment strategies, ultimately aimed at reducing the burden of these disorders on individuals and society. The findings support the broader EndoCompass objective of aligning research funding with areas of highest potential impact in endocrine health.

Keywords: calcium, phosphate, parathyroid hormone, vitamin D, bone, primary hyperparathyroidism, hypoparathyroidism, hypophosphataemia, inactivating PTH/PTHrP signalling disorders, bone mass acquisition, bone mineralization, skeletal dysplasia, cellular senescence, diagnostic technologies, bone quality, osteocytes, osteoporosis, targeted treatments

Introduction

The area of calcium and bone covers a broad spectrum of common and rare calcium–phosphate metabolic disorders and of bone diseases, which are seldom overlapping and hence inevitably have 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, fibroblast growth factor-23 (FGF23), and renal metabolism, as well as with PTH resistance in inactivating PTH/PTH-related protein (PTHrP) signalling disorders (iPPSDs).⁴ In recent years, interest in some rare calcium and phosphate metabolism disorders increased among the medical community managing adults, because of targeted therapies that significantly improved patient outcomes.

The skeleton performs multiple functions, including acting as an endocrine organ, in addition to its mechanical, haematopoietic, and metabolic functions. In this way, secreted factors regulate distant tissue functions via 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 unravelled 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 (eg, 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 document provides future research priorities and healthcare 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 its scope. 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 for Paediatric Endocrinology (ESPE), and 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 document is subdivided into 3 main sections. The first is related to the disorders of calcium and phosphate metabolism; the second relates to disorders of the skeleton, and the third discusses overarching 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 healthcare needs from each of the chapters is listed.

Calcium and phosphate metabolic disorders

Clinical spectrum of PHPT

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

It 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 normocalcaemic PHPT, ionized calcium and 25-hydroxyvitamin 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 is required, or whether a few patients may benefit from early surgery.⁶ However, robust selection criteria are still missing.⁷ Normocalcaemic PHPT 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, males and children can also be affected.⁹ A younger 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 1 of 10 genes, most commonly those causing multiple endocrine neoplasia. A 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 promote 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 patients where no mutation can be identified.

It is the case that PHPT most often arises from a single parathyroid adenoma, while multiple adenomas, parathyroid hyperplasia, and carcinoma can also cause increased aberrant PTH secretion. The prognostic relevance of atypical parathyroid adenomas remains uncertain, and the areas of pathogenesis, diagnosis, and therapy of parathyroid carcinoma 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 action need to be considered.⁷ In the surgical treatment of multigland and hyperplastic disease, ongoing research is required to define the optimal strategy (total, subtotal, or less than–subtotal parathyroidectomy), depending 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

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 centres, are essential to reduce the prevalence of iatrogenic hypoparathyroidism and other complications. In children, non-surgical forms prevail, including genetic and autoimmune causes.¹⁴ However, the underlying genetic causes remain 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, or residual PTH secretion) favouring, 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 help develop 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 upcoming¹⁸ replacement therapies using 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 for 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 currently relies 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 immunotherapy²¹ is a promising novel approach. It also sheds new light on pathogenesis of the disease but requires further research.

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 are observed in hypophosphatasia (HPP), chronic hypophosphataemia related to FGF23 excess in X-linked hypophosphatasia (XLH) or other mechanisms,²² or end-organ resistance to PTH in iPPSDs.²² Alterations in activation of the calcium-sensing receptor (CaSR), or in calcitriol synthesis and signalling, can cause life-threatening deviations in serum calcium levels.

The development of consensus guidelines^{23,24} and continuous efforts to analyse data in registries of patients with rare diseases contribute to 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 FGF23-neutralizing antibodies (burosumab) in XLH or bone-targeted recombinant alkaline phosphatase (in the form of asfotase alfa) in HPP, could profoundly improve outcomes in specific conditions. Pharmacotherapies that are not specifically designed for rare disorders extend the spectrum of therapeutic options in PTH-related disorders. These include calcimimetics (cinacalcet) in neonatal severe hyperparathyroidism and the above-mentioned PTH analogues for the treatment of hypoparathyroidism, including its rare inherited forms. Calcilytic CaSR modulators (encaleret) for autosomal dominant hypocalcaemia look very promising²⁵ and could be tested in other forms of non-surgical hypoparathyroidism. Disorders such as iPPSDs 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 optimization of existing therapeutic agents, extending their label to other indications, such as burosumab in tumour-induced osteomalacia or autosomal dominant hypophosphatasia from *FGF23* gene mutations, as well as the development of new targeted drugs and repurposing of drugs. Optimization of different management strategies is 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 XLH²⁶ and HPP²⁷ and could potentially mark a new era in the future treatment of rare diseases. Until then, non-pharmacologic treatments have to be optimized and evaluated, including functional therapy,

psychosocial support, and multidisciplinary patient care, including the involvement of patient advocacy groups. These rare disorders require prospective multicentre registries to assess outcomes of therapies far beyond paediatric age.

Bone health and pathology

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

Advances in bone biology research during the past 2 decades have highlighted the importance of bone as potential regulator of metabolic processes that are independent of mineral metabolism. It has been shown that bone cells express and bone matrix releases various bioactive factors (eg, prostaglandin E₂, Wnt signalling molecules, nitric oxide, RANK ligand, and many more). These factors act locally in a para- and autocrine manner to regulate skeletal development, biomechanical adaptation, and mineral metabolism. Furthermore, these factors allow communication with more distant tissues, such as skeletal muscles and fat, through the circulatory system.^{28,29}

The recently developed, bone-targeted therapies that use antibodies, for both common and rare bone diseases, highlight the important future opportunities presented by discovery of bone-secreted factors. For example, romosozumab, a monoclonal antibody targeting osteocyte-secreted sclerostin, increases bone formation, decreases bone resorption, and effectively reduces fractures in postmenopausal osteoporosis.³⁰ As already mentioned above, burosumab, a monoclonal antibody targeting FGF23 (a factor mainly produced by osteocytes), improves phosphate homeostasis in both genetic XLH and acquired tumour-induced osteomalacia.³¹ In addition, novel studies have indicated that elevated levels of FGF23 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 FGF23 and degenerative brain diseases (ie, increased risk of dementia and Alzheimer's disease).³⁴

The multifunctional osteocyte, with its intricate network of osteocyte cell body–housing lacunae and dendrite-containing canaliculi, appears of central importance in the endocrine communication of bone tissue.³⁵ Novel factor identification strategies, including microRNAs and molecule-containing extracellular vesicles, will provide novel insights into osteocyte-mediated communication. Furthermore, investigations that focus on osteocyte network properties, which include advanced imaging modalities and 3D analysis, will aid our understanding of osteocyte communication on a different level.^{36,37} Using these tools, network disruptions via a loss of canalicular or dendrite connectivity with ageing-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 mineralization—micropetrosis.³⁹ Further research in this area is needed to fully understand the pathophysiology and to design therapeutic interventions.

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, the function of all organs, and 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 undertaking dual-energy X-ray absorptiometry (DXA), age- and sex-specific reference data (accounting for ethnicity, height, and pubertal status) still need to be accumulated for novel imaging modalities, such as high-resolution peripheral quantitative computed tomography (HRpQCT), trabecular bone structure, or finite element analysis. Also, there is a need to systematically study the influence on bone mass acquisition of conditions that, for limited or prolonged periods of time, either accelerate it (precocious puberty/early-onset sustained obesity) or delay it (delayed puberty/growth, nutritional impairment and chronic disease, hypogonadism), as well as their long-term consequences for bone health.⁴²

In addition to imaging modalities, various bone material properties 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 the mechanistic pathways involved.⁴³ This 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 a transient or permanent nature) may or may not cause sustained deleterious effects on bone mass acquisition. Therefore, the assessment of a patient's potential for recovery has become standard of care in secondary osteoporosis⁴⁶ and requires collaborative research efforts. Analysis of the mechanisms determining impairment of bone mass acquisition by chronic medications (ie, 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 paediatric bone and DNA samples from patients affected by rare bone diseases (ideally in the context of society-driven international registries) will facilitate diagnostic and therapeutic studies.

Secondary osteoporosis and bone quality

Secondary osteoporosis, caused by underlying disease (specifically inflammation, toxins, medications, hypogonadism, sarcopenia, or immobility), occurs in up to 30% of postmenopausal women, > 50% of premenopausal women, and between 50% and 80% of men diagnosed as osteoporotic. It 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 in type 2 diabetes mellitus (T2DM).^{49–51} 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 is a metabolic disease of pandemic dimensions and the most common endocrine contributor to osteoporosis development. Both T1DM and 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 features of compromised bone quality have been discovered in diabetes mellitus, 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 mineralization 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, as well as 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 by which thyroid hormones influence osteoblasts and osteoclasts have been the focus of recent research, whereby the Wnt signalling 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. 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 Glucocorticoid-induced osteoporosis 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 The risk of fracture and re-fracture increases with higher/supraphysiological corticosteroid dosage or a treatment duration of more than 3-6 months.⁷¹ The pathophysiological mechanisms involve various effects on bone cells (ie, altered osteocyte signalling and apoptosis, increased longevity of osteoclasts, and reduction of calcium absorption).⁷²⁻⁷⁴ The changes in bone quality are complex and most probably depend on the variety of treatment methods. For example, bone loss in glucocorticoid-induced osteoporosis is characterized by an initial rapid, profound decrease in bone mineral density (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

Immobility is a largely neglected, but by far the most common form of secondary osteoporosis, demonstrating the mechanical necessity of muscle pull for bone health. It appears to affect bone geometry and quality, distinctly differently from 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 favoured for specific types of secondary osteoporosis. Multidisciplinary care focuses on 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 both to identify systematic gaps and to design and implement therapeutic solutions.

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 to decrease the need for interpretational manpower, the development of deeper molecular genetic analysis and faster interpretation using technology associated with artificial intelligence is required.⁸² Improvement in the understanding of predicted and functionally tested disease mechanisms will allow development of precision treatments at the DNA, mRNA, and protein levels.

This requires in-depth training of bone specialists and tertiary medicine in specialized centres 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 ageing population, will prevent significant morbidity and improve quality of life. These are therefore a research priority.

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

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), they result in significant morbidity. The underlying pathology remains inadequately understood and the optimal therapy is often undefined, with 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 into 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 osteoporosis⁸⁶ 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, for example, 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 and quality of life, enable smooth transition from paediatric to adult care, and help in establishing management guidelines.

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 (eg, using enzyme replacement, such as asfotase alfa in HPP⁸⁸; neutralizing an elevated hormone, such as burosumab in XLH⁸⁹ or denosumab in RANKL-mediated disorders⁹⁰; and receptor inhibition or upregulating an alternative compensatory pathway in achondroplasia^{46,91}).

The current nosology of genetic skeletal disorders⁸⁵ 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.⁹² 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 pre-clinical interventions. Strategies to develop precision therapies for rare diseases involve not just targeting proteins (drug targets), but also mRNAs (eg, anti-sense oligonucleotides) and gene therapy.⁹³

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 also be applicable to more common disorders. Partnering with pharmaceutical companies and scientific engagement in every part of the process are 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 (eg, the use of carbamazepine, which stimulates intracellular proteolysis and alleviates endoplasmic reticulum stress, in metaphyseal chondrodysplasia or other conditions with similar cellular pathology⁹⁴). Future research should focus on elucidating which drug may be effective and which biomarker(s) may be useful in this setting.

Overarching topics

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 by developmental signals. It has been considered an underlying mechanism for multiple pathologies, including bone loss and fragility associated with ageing and metabolic bone diseases. Thereby, the accumulation of senescent cells in the 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 tumour suppressor, mTOR and NFκB pathways, and senescence-associated β-galactosidase plays a central role in regulating senescence.⁹⁵ The current senolytic drugs, including rapamycin, ruxolitinib, fisetin, navitoclax, and metformin, are designed to target a specific secretory phenotype (so-called senescence-associated secretory phenotype [SASP]) consisting of bioactive molecules that affect cell function.^{96,97} Thus, SASP inhibitors address the inflammatory signal that is sent off by senescent cells. However, when administered systematically, these drugs 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,⁹⁸ or combination with other drugs to increase the effectiveness of the removal of the senescent cells only in damaged tissue, as these cells manifest a heterogeneous cellular phenotype.

Animal studies focused on eliminating senescent cells by targeting specific pathways: genetically with selective ablation of p16^{INK4A}-positive senescent cells or pharmacologically using intermittent treatment with the senolytics dasatinib plus quercetin. They reported promising results on prevention of age-related bone loss by promoting bone formation while inhibiting bone resorption.⁹⁹ Despite negative effects reported by some animal studies,¹⁰⁰ a phase 2, open-label, randomized, controlled clinical trial is being undertaken to determine if the senolytics dasatinib, quercetin, and fisetin improve skeletal health in older humans.¹⁰¹ Therefore, more translational research is needed to specify the conditions and effectiveness of senolytic drugs for long treatment. In addition, it would be worth including in the study design a comparison of senolytic with classical anti-osteoporotic drugs in terms of prevention of bone loss. As ageing causes accumulation of senescent cells in other organs besides bone, the effectiveness of senolytic drugs is a very attractive area of drug development, targeting multiple age-related complications, including bone loss and fragility.

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.^{102,103} The prevalence in women further increases to 1%-3% after menopause, suggesting that the development of oestrogen deficiency in postmenopausal women plays a role in unmasking hypercalcaemia.^{104,105} Exactly how oestrogens and other hormones lead to differences in the occurrence of PHPT requires further investigation. This difference also underlines 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 to express a functional PHEX protein, leading to a milder phenotype compared with male patients. However, such a gender-specific difference in disease severity is observed in some¹⁰⁶ but not all studies.¹⁰⁷ This 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 (iPPSDs) types 2 and 3 (previously referred to as pseudohypoparathyroidism type 1a and 1b) are caused by inactivating variants of the maternal allele of the *GNAS* gene within exons 1-13 or by methylation abnormalities in the *GNAS* locus. They are a typical example of imprinting disorders.²⁴ In iPPSD type 3 in particular, the molecular events and their pathogenetic effects need to be further studied.

Bone growth and the attainment of peak bone mass, as well as the rate of bone loss during ageing, are profoundly influenced by sex. This is exemplified by the lifetime risk of fractures for women which approaches 50%, in comparison with only 25% in men. Oestrogen has been shown to be one of the main hormones regulating bone metabolism, and loss of oestrogen action—either through menopause or genetic mutations affecting the oestrogen receptor—leads to bone loss. In addition, testosterone, either directly or by conversion to oestradiol, also influences bone metabolism.¹⁰⁸ More recently, the gonadotrophic hormone follicle-stimulating hormone has also been linked to changes in bone metabolism, independently of oestrogen.¹⁰⁹ This shows that the endocrinology underlying the sex differences in bone mass accrual and bone loss is incompletely understood and warrants further investigation to improve skeletal health across the lifespan.

From a clinical point of view, most studies for diagnosis, treatment, and outcomes have been performed in women. 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.¹¹⁰
2. In comparison with women, men more often suffer from secondary osteoporosis (a prevalence of 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.¹¹¹ Although anti-resorptive 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.¹¹²

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.

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.^{113,114} Additionally, no tools are available for fracture risk prediction in children with bone fragility. 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 (eg, trabecular bone score,¹¹⁵ hip structure analysis, 3D DXA,¹¹⁶ and vertebral fracture assessment¹¹⁷). These offer additional risk detection and 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 scans are also emerging. These techniques could be expanded to include bone marrow changes related to impaired bone quality in some individuals, for example, with diabetic bone disease with spectral and photon-counting applications.^{118,119} New generations of HRpQCT are increasingly used in some countries for detailed assessment of 3D bone microarchitecture (eg, trabecular thickness and cortical porosity) at an ultra-high resolution (less than 50 µm) at peripheral sites (distal radius, distal tibia) and predict major osteoporotic fractures.^{120,121}

Applying finite element modelling or radiomics approaches based on machine learning to different imaging data sets may bring greater breakthroughs in this field, comparable with the advances in the field of cancer imaging.¹²²

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-spectrometry¹²³ and quantitative methods based on magnetic resonance imaging,^{124,125} 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 spectroscopy¹²⁶ can evaluate volume of bone marrow fat fraction and saturation index of the lipids in bone as novel parameters for fracture risk. It would be useful if other spectral approaches (ie, Raman spectroscopy) could be employed on a

larger scale to provide information on the organic part of the bone matrix, given the implications of advanced glycation end products and others affecting bone quality.

The interesting developments in the field of non-imaging methods (biomarkers, biosensors) rely on the identification¹²⁷ of the following:

1. New biomarkers, including microRNAs¹²⁸ and other omics-detected candidate biomarkers that could provide complementary data for timely diagnosis of bone fragility
2. Types of invasive or non-invasive biosensors that could allow quicker, cheaper, more reliable, and real-time assessment of bone status to monitor bone mechanical competence, remodelling, or healing
3. Biosensors for point-of-care testing of capillary calcium or phosphate for a variety of conditions such as hypoparathyroidism, iPPSD, XLH, or renal failure^{129,130}

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 paediatric 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 centres, 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 cells 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 as treatment for use in other, 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 socio-economic 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 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 favoured for certain types of secondary osteoporosis.
- Implementation of investigations for early detection of bone fragility disorders at different stages of life requires advanced diagnostic techniques, more sophisticated monitoring, and tertiary training of medical and radiology staff in specialist centres.

- 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 in most 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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