Osteoporosis International (2022) 32 (Suppl 1):S37-S39
https://doi.org/10.1007/s00198-021-06111-1

ABSTRACT

# World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (WCO-IOF-ESCEO 2021): Plenary Lecture Abstracts



## PL1
## MANAGEMENT OF MUSCULOSKELETAL DISEASE FROM CRADLE TO GRAVE

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Osteoporosis (reduced bone density) constitutes a major public health problem through its association with age-related fractures. These fractures typically occur at the hip, spine and wrist. Our research into osteoporosis at the MRC Lifecourse Epidemiology Unit over three decades has characterised the epidemiology of these fractures and contributed to the generation of preventive strategies against them throughout the lifecourse. Around 1 in 2 women and 1 in 5 men in the UK will sustain an osteoporotic fracture from age 50 years onwards. Incidence rates rise with age, and rates in women are around double those in men above age 50 years (in large part due to the accelerated bone loss after the menopause among women). The rates are generally higher in Caucasian than in Asian and Afro-Caribbean populations. Life expectancy is increasing around the globe, and the number of elderly individuals is rising in every geographic region. Assuming constant age-specific incidence rates for fracture, the number of hip fractures occurring worldwide among people aged 65 years and over will rise from 1.7 million in 1990 to 6.3 million in 2050. In addition to this demographic trend, studies between 1930 and the late 1980s consistently reported increases in the age-adjusted incidence of hip fractures among men and women; these now appear to have levelled off in Europe and North America, due to both period and birth cohort effects. Risk factors for osteoporosis in later life include low body mass index, cigarette smoking, alcohol consumption, physical inactivity and poor dietary calcium and vitamin D status; developmental factors include genetic constitution, diet and exercise. Examples of preventive strategies against fracture resulting from our work range from maternal vitamin D supplementation during pregnancy (which enhances childhood bone mineral accrual) as well as primary and secondary preventive strategies involving risk assessment and treatment during later adult life. Together, these well-validated strategies will assist in reducing the burden of this major contributor to musculoskeletal ageing.

## PL2
## BUILDING BONE STRENGTH WITH ANABOLIC AGENTS

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Osteoporosis is a condition characterized by both low bone mass and deteriorated skeletal architecture. The ideal therapy, then, would be one that increases bone mass and improves skeletal structure. Anti-remodeling agents strengthen the skeleton by decreasing the number and depth of bone remodeling units. However, because they inhibit bone formation as well as resorption, they do not restore bone structure. In contrast, osteoanabolic agents, by activating bone formation by osteoblasts, improve both trabecular and cortical bone structures.
Three anabolic agents are now available. The PTH receptor agonists, teriparatide and abaloparatide, activate remodeling-based bone formation but also, to a lesser extent, increase bone resorption. Romosozumab, a sclerostin inhibitor, activates remodeling- and especially modeling-based bone formation while decreasing bone resorption. This dual effect results in a very positive bone balance during the first few months of therapy. Each of these agents has been shown to improve skeletal architecture and to increase bone strength in preclinical studies.
Recent clinical studies have documented that osteoanabolic agents induce larger, faster gains in bone mineral density (BMD) than do anti-remodeling agents. In head-to-head trials in patients at very high risk of fracture, teriparatide and romosozumab reduce fracture risk more effectively than do oral bisphosphonates. Transition to an anti-remodeling drug after a course of anabolic therapy is necessary to prevent the rapid loss of BMD upon discontinuation of an anabolic drug. Importantly, the fracture risk reduction achieved with 12–18 months of anabolic therapy persists for at least 2 years after patients are transitioned to an anti-remodeling drug. Bone density responses to teriparatide and romosozumab are less when administered to patients who have received a bisphosphonate or denosumab than when given to treatment-naïve patients. Based on these results, coupled with the knowledge that on-treatment BMD correlates with current fracture risk, the IOF and several national societies now recommend that anabolic agents be the initial therapy in patients at very high risk of fracture. Issues of safety, evaluating the benefit–risk profiles of individual patients, and matters of cost and reimbursement need to be considered in selecting patients for anabolic therapy.

## PL3
## MANAGEMENT OF BONE DISEASE IN CANCER

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The introduction of bone-targeted treatments has transformed the clinical care of patients with bone metastases from solid tumors or myeloma bone disease. Both bisphosphonates and denosumab have a major beneficial impact on skeletal morbidity, leading to improved quality of life and physical functioning and reduced demands on expensive interventions and hospital care. International guidelines recommend the use of a bone-targeted agent for all patients with metastatic bone disease (and multiple myeloma) throughout the course of the disease alongside sequential systemic anticancer treatments. Denosumab has

been shown in large, well-controlled clinical trials to have the greatest activity and has some tolerability and convenience advantages over the bisphosphonates. Treatment should be initiated at diagnosis of bone metastases and, due to the ongoing risk of skeletal morbidity, usually continued indefinitely.

Bone targeted treatments can also modify the process of metastasis and in breast cancer have important effects on disease outcomes as well as on bone health. The effects of adjuvant bisphosphonates in early breast cancer were demonstrated in a meta-analysis of individual patient data from all available randomized trials. In postmenopausal women, bisphosphonates (zoledronate or daily oral clodronate/ibandronate) prevented about 1 in 4 bone recurrences and 1 in 6 breast cancer deaths; no effects on disease outcomes could be identified in premenopausal women. Somewhat surprisingly, these effects could not be reproduced with denosumab. The biologic basis of the discordance in results between bisphosphonates and denosumab and biomarkers that can predict treatment efficacy will be discussed.

## PL4
## THYROID, BONE AND CARTILAGE

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Thyroid hormones are essential for skeletal development and are important regulators of bone maintenance in adults. I will discuss the skeletal consequences of thyroid dysfunction and disease, resistance to thyroid hormone (RTH) resulting from dominant-negative mutations of the thyroid hormone receptors, and variations in normal thyroid status. Childhood hypothyroidism results in delayed skeletal development, retarded linear growth, and impaired bone mineral accrual. Epiphyseal dysgenesis is evidenced by classic features of stippled epiphyses on x-ray. In severe cases, post-natal growth arrest may result in a complex skeletal dysplasia. Thyroid hormone replacement results in catch-up growth and enhanced bone maturation, but recovery may be incomplete dependent on the duration and severity of hypothyroidism prior to treatment. Childhood thyrotoxicosis is rare and accelerates linear growth. Advanced bone age and premature closure of the growth plates result in short stature, and craniosynostosis may occur in severe cases.

A severe skeletal phenotype characteristic of congenital hypothyroidism occurs in children with RTH due to mutations affecting thyroid hormone receptor TRα. Mutations of TRβ, however, disrupt the hypothalamic–pituitary–thyroid axis and increase thyroid hormone levels causing a variable skeletal phenotype.

In adults, hypothyroidism inhibits bone turnover, but identification of the effects on bone mass requires long-term follow-up of untreated patients. Thyrotoxicosis is well-known to cause severe osteoporosis and fracture, but cases are rare because of prompt diagnosis and treatment. Nevertheless, recent data indicate that subclinical hyperthyroidism, in which the serum TSH concentration is suppressed but circulating thyroid hormones are normal, is associated with low bone mineral density and an increased risk of incident fracture. Similar studies have shown that variation in thyroid status within the reference range in post-menopausal women is associated with bone loss and an increased risk of fracture.

In summary, euthyroid status is required for normal post-natal growth and bone mineral accrual and is fundamental for maintenance of the adult skeleton.

## PL5
## BONE AND CARTILAGE TALK TOGETHER

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The bone–cartilage interface is an important synergistic unit consisting of the area between the deep layers of articular cartilage and the underlying subchondral bone. Cross-talk between the bone and cartilage occurs during embryonic development and skeletal growth. During embryonic development, the processes of osteogenesis and chondrogenesis are closely linked and do not occur independently. Paracrine mechanisms are important for the biological actions of trophic factors involved in the development of the cartilage and bone and the maintenance and structural integrity of the interface between them. The close physical association between the bone and cartilage allows biological interaction and suggests that biochemical and molecular cross-talk may contribute to the development of musculoskeletal diseases such as osteoarthritis (OA), osteoporosis (OP) and osteochondritis dissecans (OCD). This presentation will focus on the role of the cartilage and bone cross-talk and the key biological mediators that are involved in the pathogenesis and progression of arthritic diseases, focusing on OA and OP. OA is a slow growing and progressing condition that accumulates pathology and symptoms over time, with features that are much closer to OP than rheumatoid arthritis (RA). Of course, the cross-talk between the bone and cartilage is implicated in all these diseases, but there are likely to be important mechanistic similarities between OA and OP. Although cartilage degradation and loss are one of the key hallmarks of OA, it is now recognized that the whole joint is involved in the progression of OA and cross-talk between cartilage and subchondral bone is thought to be a central feature of this process. In OA, cross-talk is elevated at the bone–cartilage interface due to osteochondral angiogenesis and bone remodelling. Vascular invasion from the bone into the cartilage and development of microcracks and fissures provide additional pathways for diffusion of biological molecules and cells and thus increased communication between the tissues. Alterations in either bone or cartilage can modulate signalling pathways including HIF-2α, OPG/RANK/RANKL, TGF-β and Wnt/β-catenin. These pathways in turn may alter the physiological homeostasis of neighbouring tissues and affect the structural integrity and biomechanical function of the joint unit as a whole. The role of the cross-talk in the progression of bone and joint diseases requires further investigation using high-throughput omics technology platforms including genomics, epigenetics, proteomics and metabolomics approaches and integration of the data obtained into a unified framework that emphasises spatio-temporal relationships between the key mediators and the cells and tissues involved. The Human Cell Atlas initiative has been established to create comprehensive reference maps of all human cells as a basis for understanding human health and diagnosing, monitoring and treating disease. These efforts will contribute to a deeper mechanistic understanding of the cellular taxonomy in the cross-talk between bone and cartilage and may reveal novel therapeutic targets or highlight opportunities for drug repurposing.

## PL6
## ARE THERE TREATMENTS FOR SARCOPENIA?

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Sarcopenia, or muscle failure, often occurs in later life. One of its key characteristics is low muscle strength. As low muscle strength is associated with many relevant clinical outcomes, including falls, fractures, and disability, effective prevention and treatment of sarcopenia in older adults are of utmost importance. Several randomized controlled clinical trials have been performed to test the effect of exercise and nutritional interventions, or their combination, in older adults with sarcopenia or

those at high risk. These trials often used different definitions for sarcopenia or also included those with frailty (an aging concept different from sarcopenia), which hampers the interpretation of the results. In the current lecture, several relevant studies will be discussed focusing on the evidence of exercise and dietary protein in the prevention and treatment of sarcopenia.

## PL7
## GUT MICROBIOME, BONE AND JOINT

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While it is known that microbial dysbiosis is associated with the onset of arthritis and bone disease, mechanistic insights on how it facilitates the development of arthritis and bone loss remained largely elusive. We speculated that a breakdown of intestinal barrier function caused by microbial dysbiosis and changed microbial metabolites allows immune cells to shuttle from the gut to the joints and trigger arthritis as well as bone loss. We have previously shown that short-chain fatty acids (acetate, propionate, butyrate), which are built by the fermentation of dietary fibres through intestinal microbiota, are not only powerful anti-inflammatory mediators but also protect the bone by inhibiting the formation of bone-resorbing osteoclasts. To test the role of gut microbiome changes in arthritis and arthritis-related bone loss, we tested whether intestinal barrier function is impaired before the onset of human RA and experimental arthritis. Of note, zonulin, a potent inhibitor of intestinal tight junctions, thereby increasing gut leakiness, was elevated in autoimmune mice and men even before the onset of arthritis and predicted the onset of human RA. Intestinal barrier function and expression of epithelial tight junctions were decreased before the onset of experimental arthritis and at onset of human RA. Photoconvertible mice induced for arthritis showed that barrier dysfunction is associated with the shuttling of immune cells from the gut to the joints during this process. Furthermore, intestinal dysbiosis preceded gut leakiness and arthritis. Restoration of the intestinal barrier in the pre-phase of arthritis using the short-chain acid butyrate or zonulin antagonist larazotide inhibited the development of arthritis and bone loss. In summary, these data show that microbial dysbiosis and intestinal barrier dysfunction precede the onset of arthritis and allows the trafficking of immune cells from the gut to the joints, which results in inflammation and bone destruction. Modification of intestinal dysbiosis and improving intestinal barrier function may therefore be important for preventing arthritis and bone loss associated with arthritis.

## PL8
## IS GENETICS HELPING TO IMPROVE OSTEOPOROSIS MANAGEMENT?

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The genetics revolution has led to a profound effect on our understanding of pathophysiology of both common and rare diseases, including osteoporosis and skeletal dysplasias. The challenge now is translating this knowledge into clinical benefit. Genetics and genomics could improve management for osteoporosis in multiple ways:

1. Disease prediction, through development and application of polygenic risk scores for osteoporosis and fracture — knowing who is or is not at high-risk, allowing targeting of resources and screening towards high-risk individuals and avoiding unnecessary tests and interventions in low-risk individuals
2. Pharmacogenomics: predicting who might be at risk of adverse drug reactions and/or who might benefit from personalised dosing regimens
3. Screening for rare genetic disorders of bone fragility — identifying individuals with forme fruste of osteogenesis imperfecta, hypophosphasia, or other skeletal dysplasias in whom alternative therapeutic approaches should be considered
4. Informing therapeutics: drugs that target genes identified through human genetic studies are more likely to pass through development pipelines; moreover, genetic data can help predict potential toxicities

These are not just theoretical prospects or hopeful aims: all these components have already been demonstrated in the literature, and it is likely that more is to come. Certainly functional genomics in the bone is at early stage, and we have a wealth of genetic data to explore for novel therapeutics, particularly novel anabolic agents.

## PL9
## REHABILITATION OF MENOPAUSAL HORMONE THERAPY IN OSTEOPOROSIS MANAGEMENT

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Menopausal hormone therapy (MHT) is the treatment of choice for the management of bothersome menopausal symptoms and symptoms of vulvovaginal atrophy. MHT increases bone mineral density and reduces the risk of both vertebral and non-vertebral fractures up to 40% in both high- and low-risk postmenopausal populations. The initial publication of the two WHI trials has cast doubts as to the safety of MHT with regard to the breast and the cardiovascular system. Subsequent data indicate that the efficacy and safety of MHT depend on the age of initiation, the dose and the type of hormones, as well as the route of administration. In perimenopausal and postmenopausal women within the first decade after their last menstrual period, MHT has a favorable benefit–risk ratio and prevents the menopause-associated bone loss with additional benefits on quality of life and on cardiometabolic parameters. Women who stop MHT and are still at risk for fracture should be switched to another anti-resorptive medication.

## PL10
## NEW APPROACHES OF RARE SKELETAL DISEASES (SRD) MANAGEMENT

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There are approximately 500 rare skeletal diseases, over 100 of these are metabolic in nature, and pharmacological interventions are being applied to treat some of them.
The experience clearly indicated the need for a broad care team of specialists to care about SRD patients within a collaborative organizational model.
The importance that the bone doctor becomes aware about the off-label use of drugs for bone fragility, the novel therapies, and the organizational models is paramount.
For this reason the IOF SRD Academy is implementing programs of education and of information about new discoveries in the field of targeted pharmacols in SRD.
Examples of new drugs for the cure of SRD and of the developmental pipeline of the future pharmacological intervention will be presented and discussed.