ABSTRACT

World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (WCO-IOF-ESCEO 2021): Meet-The-Experts Abstracts

MTE1
TRANSGENDER MEDICINE: BONE AND MUSCLE
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Worldwide, the number of transgender persons receiving gender-affirming hormonal treatment has been steadily increasing. Hormonal treatment (HT) in transgender women (male-to-female transgender people) usually consists of the combination of an estrogen and an androgen-lowering drug, whereas in transgender men (female-to-male transgender people) HT consists of testosterone. Taken that sex steroids are major players both in acquisition and maintenance of bone mass and skeletal musculature, it is relevant for the care of transgender people to understand what the effects are of the profound hormonal changes they undergo for their bone and muscle health. Moreover, the study of these effects may allow to gain some further insights in the role of sex steroids in bone and muscle physiology. As to bone health, transgender women tend to have a lower bone mineral density (BMD) than cisgender men, possibly because of lower level of physical activity. Transfeminine HT results in a decrease of bone turnover, a modest short- and longer-term increase of lumbar spine BMD and no change to limited increase of hip BMD. HT decreases lean mass and muscle strength while increasing fat mass. In transgender men BMD before initiation of HT is not different from cisgender women. Testosterone treatment results in increased bone turnover, except in transgender women older than 50y (i.e., postmenopausal) in whom testosterone reduces bone turnover. Testosterone treatment appears able to preserve BMD both in the shorter- and longer- term. Furthermore, cortical bone size and cortical thickness are increased in transgender men compared to cisgender women. Reliable data on fracture risk are not available. Testosterone treatment reduces fat mass and induces a substantial increase of skeletal muscle mass and associated muscle strength. As will be discussed, the whole of these findings reflects the predominant role of estrogens in the regulation of bone homeostasis in both the female and male skeleton and the role of androgens on muscle mass and strength and, directly or indirectly, on cortical bone apposition.

MTE2
IMPACT OF GLUCOCORTICOIDS ON BONE AND MUSCLE
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Glucocorticoids are effective immunomodulatory drugs used for many inflammatory disorders as well as transplantation. However, glucocorticoids are associated with several side effects including an increased risk of osteoporosis and fractures. Glucocorticoid-induced osteoporosis (GIOP) is a common cause of secondary osteoporosis in adults. The pathophysiology of GIOP is multifactorial, with both direct effects on bone cells (decreased osteoblastogenesis, decreased lifespan of osteoblasts and osteocytes, and an increased number of osteoclasts) and indirect effects through suppression of the somatotropic and gonadotropic axes as well as altered intestinal and renal calcium handling, resulting in a negative calcium balance. In addition, glucocorticoids induce loss of muscle mass and strength (glucocorticoid-induced myopathy) leading to an increased risk of falls. The combined effect on bone and muscle accounts for the higher fracture risk in patients on glucocorticoids.

In patients starting glucocorticoids, there is a rapid phase of bone loss, followed by a slower decline. This bone loss is most pronounced in regions of the skeleton with abundant trabecular bone, such as the lumbar spine. Although vertebral fractures are particularly characteristic of GIOP, the risk of nonvertebral and hip fractures is also increased. Fracture

risk increases within 3 to 6 months after the start of gluco-corticoid therapy and fractures occur at higher BMD than in postmenopausal osteoporosis. Despite availability of clear evidence and international guidelines for the prevention of GIOP, a large treatment gap remains. Nonpharmacological measures include physical exercise, smoking cessation, and avoidance of alcohol abuse, in addition to sufficient calcium intake and avoidance of vitamin D deficiency. Randomized controlled trials have demonstrated the efficacy of alen-dronate, risedronate, zoledronate, denosumab, and teripara-tide in GIOP. Zoledronate and denosumab have shown supe-rior effects on BMD than risedronate. In head to head trials, patients on teriparatide had fewer new vertebral fractures as compared with alendronate. In 2021, the Belgian Bone Club conducted an umbrella systematic review to update its 2006 consensus recommendations for the prevention and treat-ment of GIOP in adults.

Patients with glucocorticoid-induced myopathy present with gradual onset of proximal muscle weakness, with lower extremity weakness usually occurring before upper extremity weakness and being more severe. The glucocorti-coid dose that induces glucocorticoid-induced myopathy as well as the time to onset of symptoms varies widely among patients. Treatment consists of reduction and, if possible, discontinuation of glucocorticoids. Fluorinated glucocor-ticoids can be replaced with nonfluorinated glucocorti-coids. In addition, physical therapy should be considered for the prevention and treatment of glucocorticoid-induced myopathy.

MTE3
HIV AND BONE
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Life expectancy of people living with HIV (PLWH) is reach-ing similar length as in the general population. Accord-ingly, age-related comorbidities, including osteoporosis, are increasing in PLWH. Fracture risk is higher and increases approximately 10 years earlier as compared to the HIV-negative population. Classical risk factors of bone fragility are highly prevalent in PLWH but HIV infection itself and the type of antiretroviral therapy (ART) regimen (especially tenofovir and protease inhibitors) also contribute to bone loss. The majority of bone loss occurs during virus replica-tion and at initiation of ART (immune reconstitution), and is associated with an increase of bone resorption (upregulation RANKL). Periodic assessment of fracture risk is indicated in PLWH, but FRAX underestimates fracture probability in these patients. Measurement of bone mineral density is recommended in patients at increased fracture risk, and in

all postmenopausal women and men above 50 years of age. General preventive measures (promotion of physical activity, discontinuation of toxic habits, nutritional counseling, and supplementation) should be implemented. Calcium and vita-min D supplements provided as ART initiation lower BMD loss. Bisphosphonates have been shown to increase bone den-sity in PLWH but fracture outcomes are not available. In case of osteoporosis or high fracture risk, review of ART regimen in favor of more bone-friendly options should be discussed. The reduction of tenofovir plasma concentrations with tenofo-vir alafenamide attenuates BMD loss but it remains unknown whether it contributes to fracture risk reduction.

MTE4
IS SCREENING FOR OSTEOPOROSIS USEFUL?
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Osteoporotic fractures present a major public health prob-lem, for individuals, healthcare systems, and society. Current estimates suggest that, in developed countries, around one in three women and one in five men aged 50 years or older will have a fragility fracture during their remaining lifetime. While, in the last four decades, remarkable progress has been made in terms of our understanding of osteoporosis (we have a definition, diagnostic test (DXA), comprehensive risk assess-ment tools and affordable, effective treatments), but many indi-viduals with osteoporosis are not recognized or treated – there is a huge treatment gap. Would screening for osteoporosis in the general population help to reduce fracture rates?

In this session, we will discuss the current evidence for and against population based screening for high fracture risk. A large UK randomized trial of fracture risk screening using FRAX in primary care (SCOOP) demonstrated a reduction in hip fracture risk consequent to the screening intervention, and meta-analysis with two other screening trials from Denmark and the Netherlands has confirmed this effect. We will con-sider the evidence provided by these studies and how they may inform the practical implementation of osteoporosis screening. With a screening program comes a variety of challenges. It is cost-effectiveness must be proven and it must be accept-able to patients, doctors, and politicians alike—implement-ing change in overburdened healthcare systems with aging populations and in the wake of the COVID-19 pandemic is difficult. We will discuss how screening can be made eco-nomically viable, and present approaches to automated case-finding which will require minimal input from clinicians in primary care. We all want the best for our patients—we know that many are suffering fractures which could have been prevented through appropriate risk assessment and treatment—but is screening the most useful approach?

MTE5

CALCIUM-VITAMIN D: STILL A ROLE IN OSTEO-POROSIS MANAGEMENT?

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Supplementary calcium and vitamin D are often prescribed alongside antiosteoporosis medication, and may play an important role in the management of older institutionalized adults. In the first randomized controlled trial to consider the efficacy of these agents, a daily dose of calcium (1200 mg) and vitamin D3 (800 IU) in community dwelling elderly women normalized serum parathyroid hormone and 25(OH)D levels and apparently led to a reduced bone loss and decreased risk of hip fracture but in a subsequent study which used a 400 IU daily vitamin D dose, a nonsignificant reduction in hip fractures was observed, possibly as a consequence of the lower doses used. In recent years, calcium supplementation has been controversial, with some but not all studies suggesting that there may be an increased risk of cardiovascular disease among women prescribed therapy. However recent studies show no association between risk of cardiovascular diseases and calcium supplementation in physiological doses, which can be considered safe. The most recent systematic review of the effectiveness of calcium and vitamin D combined supplementation observed a reduction in hip and total fracture which appeared more marked in the elderly, patients with low body weight and increased fracture risk and concluded that the minimum effective dose of calcium is 1200 mg while vitamin D should not be below 800 IU. Previous studies, including previous systematic reviews, have yielded conflicting results; methodological factors may be the explanation for these differing results, highlighting the need to look at the details of each study. In general, the combination of calcium with vitamin D is well tolerated, although increased frequency of urinary and renal tract stones has been reported and many patients report mild gastrointestinal irritation with calcium supplementation. This workshop will discuss the available literature, and consider how we can incorporate current knowledge into clinical practice.

Conflict of interest

ED has received honoraria from UCB, Lilly, and Pfizer.

MTE6

REHABILITATION AFTER FRAGILITY FRACTURE

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Fragility fractures are associated with pain, loss of bone mineral density and muscle mass, disability, reduced quality of life, increased risk of subsequent fracture, and death. Guidance for the prevention, management, and treatment of osteoporosis has been developed by multiple national and regional organizations, and international campaigns exist to reduce the morbidity and mortality associated with osteoporosis. The treatment of individuals post fracture is multifactorial. Moreover, other risk factors exist for future fractures, such as sarcopenia, frailty, low supply of dietary protein, poor muscle strength and power, inadequate dynamic balance, and environmental risks such as safe walking environments. The management of most of these risk factors falls broadly within the scope of rehabilitation. Multimodal exercise post fragility fracture to the spine and hip is strongly recommended to reduce pain, improve physical function, and improve quality of life. Outpatient physiotherapy post hip fracture has a stronger evidence base than outpatient physiotherapy post-vertebral fracture. Appropriate nutritional care after fragility fracture provides a large range of improvement in morbidity and mortality. Education increases understanding of osteoporosis which in turn increases utilization of other rehabilitation services. Education may improve other health outcomes such as pain and increase a patient's ability for self-advocacy. Rehabilitation interventions are inter-reliant and research investigating these relationships may increase the relevance of rehabilitation research to clinical care.

MTE7

FRACTURES DURING CHILDHOOD AND ADOLESCENCE

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Growth during early life, through childhood and adolescence is an important determinant of peak bone strength, and thus, risk of later-life osteoporosis. During adolescence, individuals gain 20% of their adult height, 50% adult weight, and 40% of their peak bone mass. During childhood, fractures peak during infancy and in early adolescence. In contrast to later life, males tend to fracture more than females during infancy and adolescence. Data from longitudinal studies show there is an offset in peak growth rates, where height and lean mass occur first, followed by bone area and finally a period of consolidation where bone mineral continues to be accrued. The peak period of fractures occurs after peak height growth and while bone mineral consolidation occurs. The timing of puberty, and rate of both height and weight growth impact peak bone mass and later life fracture risk. Genetics account for ~ 60–85% of variation in peak bone mass, with environment contributing the remainder.

Modifiable environment, such as nutrition status and physical activity, play an important part in determining healthy growth with maternal and paternal environment also playing important roles. Further to this, there is impact of epidemiological transition on pubertal timing, body composition; how this might impact childhood and later fracture risk in transitioning populations is also an important area of focus. The etiology and impact of acute and chronic childhood diseases on current and future fracture risk is also an extremely important area for clinical and research fields, with a growing body of evidence and guidelines for assessment, treatment, and monitoring.

Key evidence will be reviewed from across the globe, drawing from randomized controlled trials, longitudinal cohort data, and meta-analyzes. The session will also include considerations for the assessment of the skeleton using bone densitometry during the growing years.

MTE8
DISCUSSION OF COMPLEX BONE DISORDER CASES
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Skeletal Rare Diseases: Case discussions with members of the IOF SRD Academy International Osteoporosis Foundation Skeletal Rare Diseases Academy.

Although individually rare, the health burden consequent to Skeletal Rare Diseases as a whole is substantial and there are critical nuances to diagnosis, management, and therapy which are often missed or neglected at presentation. In order to raise awareness and provide education in this important area of clinical practice, the International Osteoporosis Foundation has established the IOF Skeletal Rare Diseases (SRD) Academy.

This session will showcase key aspects of the SRD Academy, focusing on case presentations that demonstrate important clinical aspects of skeletal rare diseases including McCune Albright Syndrome and Tumor-Induced Osteomalacia. The aspiration is to provide a valuable learning opportunity for clinicians working in osteoporosis and metabolic bone disease, but who may not be experts in skeletal rare diseases.

MTE9
CAN WE INFLUENCE FRACTURE REPAIR?
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Introduction: Fracture repair involves bringing damaged tissue back to a cellular and structure normality to restore its biomechanical function. Only a fraction of these fractures will not heal properly. We will discuss immune and inflammatory factors of the injury response to bone and surrounding tissues. We'll discuss current research and clinical strategies for fracture repair. We will focus on specific local and systemic therapies which enhance fracture repair.

General Overview: We will present the potential role of the immune system in fracture healing, including T-cells, inflammatory cytokines, and impact of unresolved inflammation on fracture repair. The role of mesenchymal stem cells in callus formation will be presented.

Fracture Repair enhancement therapy: *Focal Therapy*: Biophysical intervention such as local pulsed electromagnetic fields (PEMF) and low-intensity pulsed ultrasonography (LIPUS) are currently available for clinical use. Biological enhancement such as autologous platelet-rich plasma (PRP) and bone marrow-derived cell therapies, extracellular signaling molecules (platelet-derived growth factors—PDGF—and Fibroblast growth factor—FGF-2), TGF-b superfamily (bone morphogenetic protein BMP-2 and -7) and Wnt signaling proteins. *Systemic Therapy*: Current and future systemic biological fracture repair enhancements include antiinflammatory cytokines such as IL4, IL10, and IL13, recombinant Parathormone (rPTH), and antisclerostin, anti-IL-20 and anti-DKK1 monoclonal antibodies. Future gene therapy applications will also be discussed.

Conclusion: No specific, enhanced fracture repair therapy presents a significant clinical impact as of today. Nevertheless, future therapeutics for enhanced fracture repair are being developed to improve tissue composition and structure, along with clinically significant shorter fracture repair time. Genome editing and gene therapy strategies will also become available in the not-so-distant future.

MTE10
FLS AND FRACTURE RISK REDUCTION
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Even though it is established that adults suffering a fracture after a fall from standing height or less are at increased risk of another fracture, few patients receive effective management. This is despite the availability of validated fracture risk assessment tools and a range of antiosteoporosis treatments that can rapidly reduce a patient's fracture risk. Closing the secondary fracture prevention gap has been highlighted as a priority for policymakers globally. The key steps for the key components for the patient pathway include identification, investigation, treatment recommendation,

and monitoring to ensure early initiation of treatment and longer-term adherence. A number of reviews have now demonstrated positive effects on treatment recommendation and fracture reduction from studies using different designs.

A major challenge faced by clinicians is policy prioritization so a local FLS can be sufficiently funded to benefit patients. An FLS benefit and budget impact model has been developed to describe the expected number of fractures avoided, impact on healthcare use and costs, as well as describe the costs of fracture prevention program for staffing, investigations, and medications. The inputs are adapted for each country from the published literature, government data, and expert opinion. The results of this model can be applied at the national, regional or local hospital level to inform policy decision-making and plan services.

MTE11

HOW TO WARRANT RELIABLE DATA FOR CALCIOTROPIC HORMONES AND BONE TURNOVER MARKERS ASSAYS?

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Determination of biomarkers is of paramount importance in clinical practice and millions of tests are daily performed worldwide. Yet, even if automated, biomarker determination remains a challenge. Indeed, as in any other analytical process, different variations in the process can lead to an unexpected wrong result, potentially leading to erroneous medical decisions. Traditionally, three types of errors can occur can happen during the whole process of biomarker determination, namely, the pre-analytical, the analytical, and the postanalytical error.

Biomarkers of bone turnover (BTM) and calciotropic hormones are not free from these potential errors. Preanalytical errors are the most frequently observed in daily practice. They encompass errors like the use of wrong sampling tube, the fasting status, the time of sampling, the presence of fractures or the stability of the analytes. These conditions can differently affect BTM, parathyroid hormone (PTH), FGF23, and vitamin D (VTD) metabolites—even if these latter are less influenced by preanalytical conditions.

One of the major issues of the analytical phase is probably linked to standardization—or rather to the lack of standardization of analytical methods, which really complicates the follow-up of patients. Indeed, some assays can provide very discrepant results, sometimes by several magnitudes, because of this lack of standardization. Standardization—or harmonization—of biochemical assays necessitate the identification of the analyte of interest (the measurand), a commutable standard recognized by the scientific community, the presence of reference method procedures (RMPs), and

that all manufacturers use these tools to calibrate the assays accordingly. Standardization efforts are however, undertaken by the Vitamin D Standardization Program (VDSP) and the International Federation of Clinical Chemistry (IFCC). Yet, to date, 25(OH)D is the only analyte for which the prerequisites are present and the efforts have lead to improved situation. PINP assays are not standardized but, in patients who do not suffer from chronic kidney diseases (CKD) the results are quite homogenous. True bone markers (bone alkaline phosphatase and Tartrate resistant acid phosphatase, type 5b) also show more coherent results. Improvement is still needed for β-CTX, FGF23, and other VTD metabolites.

Finally, regarding the postanalytical phase, the need of good reference ranges is mandatory.

In conclusion, reliable data can be obtained for BTM and calciotropic hormones, but important efforts, especially on standardization of the assays and on the implementation of good standard operating procedures (SOPs) for blood sampling and transportation are needed.

MTE12

MANAGEMENT OF MEN WITH OSTEOPOROSIS

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Male osteoporosis is clearly under-estimated, under-diagnosed, and under-treated. The diagnosis is often made late or even after a fracture event, also because guidelines on screening politics do not agree whether and when men should be considered. Furthermore, not only fewer men receive a correct and timely diagnosis, but also fewer men receive adequate treatment. Clinical trials are far less performed in men with respect to women, and we tend simply extrapolating from the female counterpart our clinical management. Since male osteoporosis is frequently secondary to other conditions and often associated with comorbidities, the identification of specific causes of male osteoporosis is essential to drive a correct and personalized treatment and should follows careful diagnostic approach. Very few studies assessed the effect of antiosteoporotic treatments in men and most of them considered only bone mineral density (BMD) as primary endpoint. However, BMD alone is not sufficient to clearly define osteoporosis in men and should not be considered the only target of treatments. A more integrated approach should be assessed, including for example vertebral morphometry, evaluation of sarcopenia and measures of bone and skeletal muscle strength.

Adequate management of male osteoporosis requires life style interventions and treatment of underlying conditions as first step, and decision on which specific antiosteoporotic drug to use as second step. According to guidelines,

pharmacological therapy is recommended for men with hip and/or vertebral fragility fracture, men with a T-score (spine, hip) lower than –2.5 S.D., and men with T-score between − 1 and − 2.5 (spine, hip) and fracture risk over 20% or hip fracture risk in 10 years ≥ 3% according to FRAX. However, national guidelines and rules might differ in the different countries. Men receiving chronic therapy with high dosage glucocorticoids and men receiving androgen deprivation therapy for prostatic cancer are also candidates to anti-osteoporotic drugs. Supplement with calcium and vitamin D should always be considered, and replacement therapy with testosterone is fundamental in men diagnosed with hypogonadism.

The antiresorptive and anabolic drugs approved for osteo-porosis in men are represented by bisphosphonates, denosumab, and teriparatide, but the data are incredibly few compared to osteoporosis in the female. Furthermore, no study, except one with zoledronic acid, had fracture risk as primary end point. Only few, preliminary data are available for romosozumab. There is also need for clinical trials assessing the efficacy of multistep therapeutic approach, that is, for example, antiresorptive drugs plus testosterone in hypogonadal men, and combination therapy (e.g., antiresorptive plus anabolic drugs).

Finally, it is fundamental to note that male osteoporosis is not simply a disease related to aging. Many conditions acting before and during puberty might compromise the bone health for the rest of the life. Nevertheless, the early identification of these conditions (such as, for example, the Klinefelter syndrome, malabsorption diseases, and vitamin D deficiency) might allow for better management of fracture risk.

MTE13
UCB SPONSORED MEET-THE-EXPERT SESSION - BUILDINGBONE, IMPROVING OUTCOMES: MEET THE EXPERTS

UCB[1]
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This highly interactive session will showcasereal-life clinical cases from Dr Andrea Singer (MedStar Georgetown University Hospital,USA) and Dr Ralf Oheim (University Medical Center Hamburg UKE, Germany) toinitiate discussion on the optimal therapeutic management of postmenopausalwomen with severe osteoporosis at very high fracture risk. The experts willprovide a background to their patient cases, before opening the floor to theaudience to share their opinions on the optimal treatment strategy for eachcase. The actual course of action taken by each expert, along with theresultant clinical outcomes, will then be discussed, with audience invited toask questions and, again, share their opinions.