ECTS CONGRESS

10 MAY PRE CONGRESS
11-14 MAY 2019
BUDAPEST
HUNGARY

CONGRESS REPORT

www.ects2019.org

ECTS
European Calcified Tissue Society

Foreword from Anna Teti, ECTS president

The ECTS 2019 Congress was held in Budapest 11-14 May 2019, preceded by an interesting and well attended pre-congress day that allowed networking and interactions in a lively and friendly atmosphere. The main programme included various update and educational sessions, along with interactive industry symposia, meet the expert sessions and poster fora. Proudly, our meeting had a rich programme for the next generation of scientists entirely organised by the ECTS Academy, which is extending their interactions with national academies and with young scientists outside Europe. Among them, the Asian new investigators are enriching the tight relationships established over the years between the ECTS and the Japanese, Chinese and South Korean societies of musculoskeletal research.

A total of 415 abstracts, including regular abstracts and new data abstracts, were submitted, from which 138 oral presentations were selected. The congress was attended by 1178 participants, with top 5 countries represented by the UK, Germany, South Korea, Greece and Hungary. In addition to plenary symposia and thematic workshops, the ECTS/ASBMR clinical debate was held, this year won by the ASBMR speaker, along with the Big 50 session dedicated to the 50th anniversary from the discovery of bisphosphonates as antiresorptive drugs.

The ECTS 2019 Congress Report summarises the congress highlights and walks readers throughout the new discoveries in the calcified tissue and related research fields. If you missed any sessions, many of them are recorded and available online. Simply click on the link and you will be returned to the lively atmosphere of the congress.

Thanks to the Editorial Board members for their effort, and all of you for trusting and supporting the ECTS.

See you next year in Marseille, France, 16-19 May 2020, with the pre-congress day on 15 May.

Professor Anna Teti, ECTS President

Contents

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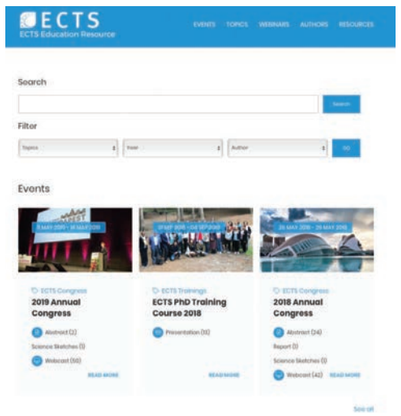

ECTS celebrates 50 years of bisphosphonates

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It is now 50 years since the first papers on bisphosphonates were published. ECTS congress 2019 celebrated this Big 50 milestone with a special session considering the impact of this most widely used class of anti-resorptives.

HIGHLIGHTS

- 50 years after their first application for treatment of Paget's disease of bone, bisphosphonates are now widely used for treatment of osteoporosis, cancer-induced bone disease, and rare bone diseases
- Potential anti-ageing, cardiovascular and anti-cancer effects are now being investigated
- Novel bisphosphonate structures can improve potency and enable drug delivery to bone

Graham Russell (Oxford) started the session by explaining how bisphosphonates, originally invented as industrial water softeners, were identified as a major new group of medicines.

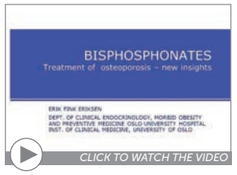
There was some serendipity in this discovery! Working in Berne in the 1960s, Herbert Fleisch discovered that inorganic pyrophosphate was a natural inhibitor of mineralization in blood and urine. He then worked with Graham Russell to find enzymatically stable analogues of pyrophosphate, and bisphosphonates were thus identified.

Initial pharmacological work was performed with Marion Francis from Procter & Gamble. The first clinical work was done with etidronate in Paget's disease of bone. Clinical uses were then particularly developed in the "bone and cancer" field, with bisphosphonates used in imaging agents for bone scintigraphy, and in treatment of osteolytic lesions and ectopic calcifications.

Osteoporosis arrived late in the clinical development of bisphosphonates, because of limitations to assess their efficacy on BMD, but are now widely used (see below).

Bisphosphonates do much more than inhibiting mineralization. During the 1990s it was determined in Sheffield that bisphosphonates inhibit bone resorption through acting on the mevalonate pathway. However, their mechanism of action is probably even more complex, and recent data indicate that bisphosphonates are active on common mechanisms of ageing ("senolytics").

Erik Eriksen (Oslo) discussed further the use of bisphosphonates in the clinic for treatment of osteoporosis and other musculoskeletal disorders.



Yearly infusions of zoledronic acid constitute a standard therapy for osteoporosis. An infusion every 18 months has also recently been shown to be effective in osteopenic patients. Dr Eriksen now bases his frequency of infusions on yearly assessment of bone turnover. Using this approach, most patients just need new infusions every three years, which is in accordance with recent studies showing preservation of antifracture efficacy with infusion period of 1.5 to 3 years.

In recent years, there has been too much focus on very rare side effects (osteonecrosis of the jaw) and atypical femoral fracture) and use of bisphosphonates has declined, with a parallel increase in fracture rate, e.g. in the USA.

Interestingly, users of bisphosphonates for osteoporosis appear to derive another major benefit, namely reduced mortality, which has been demonstrated in a total of 8 studies including two randomized, controlled bisphosphonate trials after hip fracture (e.g. see Beaupre LA, *et al*. 2011, Lyles KW, *et al.* NEJM 2007). The mechanism involved is currently unknown, but several possibilities have been suggested. Zoledronic acid protects against radiation damage and prolongs life span of mesenchymal cells. However, increased survival due to use of bisphosphonates could be mediated via effects on fractures, cardiovascular system, anti-cancer effects, DNA stability, and anti-angiogenic effects demonstrated in other studies. There could also be additive effects where statins are also used, as both classes of drugs act on the mevalonate pathway.

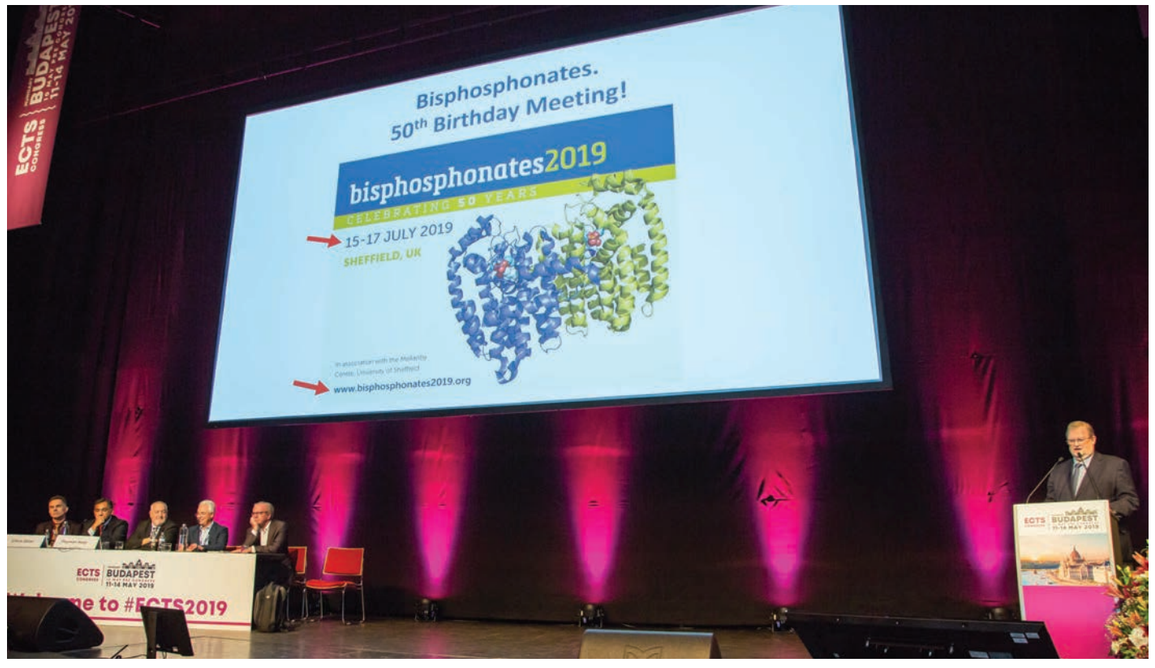
Local transient osteoporosis is often associated with bone marrow lesions (edema) found in many inflammatory and non-inflammatory musculoskeletal diseases. Bisphosphonates ibandronate and zoledronic acid can reduce this edema and pain. Interestingly, neridronate has been shown to decrease pain and improve function in osteoarthritis. This is a quite interesting current area of research.

Robert Coleman (Sheffield, UK) discussed the use of bisphosphonates for the treatment and prevention of bone metastasis.

Bisphosphonates are commonly used to reduce bone resorption and the risk of skeletal complications in patients with bone metastases. However, it is their potential to modify the disease processes involved in cancer metastasis that has attracted recent attention.

The use of bisphosphonates in patients with early cancer builds on Paget's classic "seed and soil hypothesis" from the 19th century, a concept developed further by Gregory Mundy and colleagues in the 1980s. Cancer cells can remain dormant for many years in the bone marrow before forming bone metastases and are interdependent with the bone microenvironment. Early metastasis prevention studies with clodronate were conducted by Ingo Diel and Trevor Powles. These suggested treatment benefits in preventing metastasis and breast cancer deaths, but other trials gave conflicting results and the treatment approach was not adopted by the oncological community.

Beneficial effects of bisphosphonates in the adjuvant setting gained much attraction around 10- years ago, thanks to the ABCSG-12 trial led in Austria by Michael Gnant, in which zoledronic acid improved disease-free survival in early breast cancer patients receiving ovarian suppression with goserelin and either anastrozole or tamoxifen. However, the AZURE study of adjuvant zoledronic acid in a broader population of breast cancer patients indicated that the whole situation is more complex. Long-term disease-free survival was increased only in postmenopausal women and there were even possible detrimental effects in premenopausal women. These findings were confirmed by an EBCTCG individual patient meta-analysis that included around 29,000 women in randomised trials. Benefits were limited to postmenopausal women and appeared to be a class effect, with similar findings in trials that included intravenous zoledronic acid, oral clodronate or oral ibandronate.



In other news...

Bliuc D, et al. published a prospective cohort study in 6,120 patients showing that treatment with amino-bisphosphonates (alendronate and risedronate) is associated with 34% lower mortality compared to no treatment. In contrast, use of etidronate has not shown any significant association with reduction of mortality.

Sing CW, et al. reported data from a retrospective study in 34,991 patients with newly diagnosed hip fracture. This showed how treatment with alendronate was associated with 1-year reduction in cardiovascular mortality and incident myocardial infarction, and with a slightly significant reduction in the risk of stroke at 5 and 10 years.

As a result of the EBCTCG findings, several guidelines in both North America and Europe now recommend adjuvant use of bisphosphonates in postmenopausal women with early breast cancer.

In contrast, no beneficial effects of anti-resorptive denosumab have been shown in the adjuvant setting. The D-CARE trial found no effect on breast cancer recurrence or mortality, despite the known powerful effects of the agent on reducing bone turnover (manuscript under review at Lancet Oncology, published abstract: Coleman RE, *et al*. J Clin Oncol 2018). The differences in activity between denosumab and the bisphosphonates suggest that the beneficial effects of bisphosphonates in the adjuvant setting are due to more than inhibition of bone resorption alone. Osteoclast inhibition is only part of the story!

Hal Ebetino (Rochester, USA), then closed with an assessment of future directions for bisphosphonates.

Bone mineral binding of bisphosphonates (alendronate > zoledronic acid > ibandronate > risedronate) is not directly correlated to their potency for inhibiting bone resorption, which is greatest for zoledronic acid.

Hal Ebetino and collaborators are designing novel bisphosphonate compounds to explore their structure-activity relationships. They have designed a new bisphosphonate analogue with a lower affinity for mineral than risedronate but still with a high antiresorptive capacity, which may have eventual clinical application. They also are developing fluorescent bisphosphonates to unravel their mechanism of action.

Bisphosphonates may be conjugated to various drugs as a targeting platform technology. Such "conjugates" are more stable *in vivo*, but the technology also allows drug releasing linkages for bone targeted therapeutics.

This concept of "target and release" is very promising. For example, etidronate has been linked to cytarabine. Along the same line, bortezomib linked to bisphosphonate has increased the efficacy of bortezomib in an animal model of multiple myeloma and reduces its toxicity. There are also bisphosphonate-prostaglandin conjugates recently reported. Hal Ebetino's group has used this technology for bisphosphonate linkage to fluoroquinolone, to treat osteomyelitis in animal models.

Q&A SESSION

Among several questions, the panel Q&A session discussed more about the potential of bisphosphonates for treating osteoarthritis, their observed beneficial effects on bone pain, and the dosing levels appropriate in various settings to obtain positive results while avoiding adverse effects. Please see the online video.

ECTS WORKING GROUPS

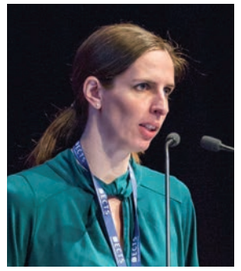
Our pre-congress Working Groups covered diverse topics in a format designed for interactive and lively discussions.

- WG1 Animal models in bone research (see page 48)
- WG2 Rheumatic Diseases and Bone
- WG3 Bone bioengineering, regeneration and implants
- WG4 Non mammalian models – fish models of rare skeletal disorders
- WG5 Osteoclasts – novel fundamental insights
- WG6 Rare disorders with increased/ectopic bone formation
- WG7 Cancer and primary bone tumours (see page 57)
- WG8 Cartilage pathophysiology
- WG9 Imaging bone strength (see page 56)
- WG10 Paget Disease of Bone
- WG11 Epigenetic regulation of bone formation – non-coding RNAs

Reports from selected Working Groups are included elsewhere in the congress report.

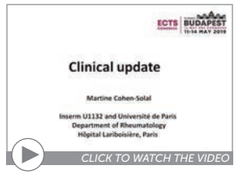
What is new in musculoskeletal research around the world

Since last ECTS in May 2018, over 2000 manuscripts were published on bone. Of those, about 50 papers were published in Cell, Nature and Science journals.



Martina Rauner covered the year's high-impacting publications in basic research, including the discovery of new stem cell populations, a new type of blood vessel in bone, and new insights into the origin and maintenance of osteoclasts.

Martine Cohen-Solal reviewed the year's clinical research publications related to the epidemiology of osteoporosis, bisphosphonates, biotherapies, calcium and vitamin D, and other bone diseases.



In other news... See "In other news..." throughout the report for various highlighted publications.

Osteoporosis

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HIGHLIGHTS

- 50th anniversary of bisphosphonates celebrated with keynote speakers involved in the bisphosphonates story (see above)
- East meets West symposia on mobility and longevity, and osteoporosis drug dosing
- Updates on latest RCTs of osteoporosis treatments
- Passive smoking in childhood associated to higher osteoporosis risk later in life

Osteoporosis clinical update

The first clinical update of ECTS 2019 reviewed the latest developments in osteoporosis treatment, and vitamin D supplementation.

Juliet Compston (Cambridge, UK) discussed the current evidence and concerns regarding bone anabolic agents teriparatide, abaloparatide and romosozumab.

Of these three treatments, only teriparatide is currently approved for clinical use in Europe, abaloparatide has been rejected and a decision on romozosumab is pending*.

Both teriparatide and abaloparatide bind to the PTH/PTHrP receptor, with abaloparatide giving a more transient cAMP signal, in theory leading to a higher ratio of bone anabolic to catabolic pathways than teriparatide. Romosozumab binds to sclerostin, both stimulating bone formation and inhibiting bone resorption.

The pivotal RCTs performed for each agent produced quite large reductions in vertebral fracture, and significant reductions in non-vertebral fractures were demonstrated for teriparatide and abaloparatide.

Comparisons between anabolic agents have so far only analysed BMD and bone strength as primary end points. The ACTIVE trial showed abaloparatide was superior to teriparatide in increasing BMD at all time points. However, the limited data obtained so far suggest this does not translate into a greater efficacy for reducing fractures. McClung MR, et al. found romosozumab produced significantly greater improvements in BMD than both teriparatide and alendronate in 419 postmenopausal women with low BMD. More recent QCT measurements and FEA estimated bone strength in small groups of postmenopausal women with low bone mass show that romosozumab is superior to teriparatide for improving bone mass and strength, especially at the hip. This year, Ken Poole (WCO-IOF-ESCEO) has presented data at the 2019 World Congress on Osteoporosis showing significantly greater changes in vertebral cortical thickness after one year of treatment with romosozumab, compared to teriparatide.

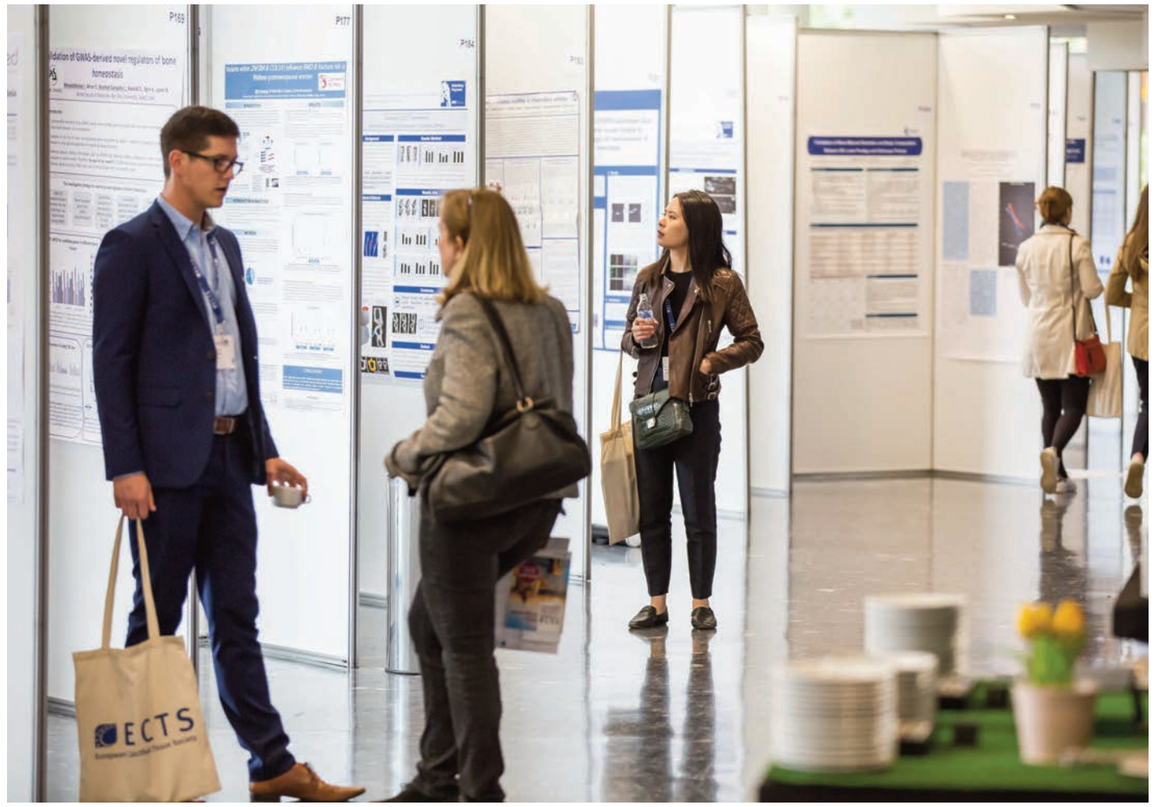
Data providing a direct comparison of anabolics and antiresorptive therapies has been obtained in the ARCH and VERO studies in postmenopausal women with severe osteoporosis. ARCH found romosozumab significantly reduced vertebral, non-vertebral and hip fractures compared to alendronate, and the VERO study showed significantly lower incidences of vertebral and clinical fractures after 24 months with teriparatide compared to risedronate.

MOOT our local hosts in Budapest

The Hungarian Society of Osteology and Osteoarthrology (MOOT) were the local hosts for ECTS 2019. Since its founding in 1990, MOOT has been active in raising the standards for osteoporosis care in Hungary. The society supports health care professionals with recommendations and training, and its annual meeting is attended by 300-400 participants. An educational conference for osteoporosis centres and symposium on metabolism and bone diseases are also organised annually.

As well as providing the local organising committee, MOOT organised the national day during the pre-congress. This featured sessions on secondary osteoporosis, and evaluations of the osteoporosis treatment gap in seven different central and eastern European countries.

Welcoming speech from István Takács, MOOT President, and chair of the ECTS 2019 local organising committee.



Previously published trials of romosozumab showed a reversal of its effects on P1NP and bone density after cessation of treatment. However, the ACTIVE EXTEND, FRAME and ARCH trials have also suggested that beneficial effects of anabolics on fracture can be maintained by subsequent antiresorptive therapy.

There are some safety concerns with anabolic therapy, particularly an excess of cardiovascular events in study participants treated with romosozumab. Amgen has provided data to the FDA concerning major adverse cardiovascular events in the FRAME and ARCH studies, showing no significant increases in risk compared to alendronate during the double blind and overall study periods, except for a small but statistically significant increase in the risk of stroke.

In conclusion, anabolic therapy can be considered more effective than oral bisphosphonates in preventing fractures in high-risk individuals, especially when combined with subsequent antiresorptive therapy to maintain the benefits after treatment has ended.

**Stop press: the approval in Europe of romosozumb for use in treatment of severe osteoporosis is now in question due to a negative opinion given by CHMP.*

Bente Langdahl (Aarhus, Denmark) then discussed antiresorptive treatment with denosumab, and especially management of the patient after discontinuation of treatment.

The fracture risk efficacy of denosumab has been clearly demonstrated in the FREEDOM trial. This trial was extended and showed a sustained effect on BMD, hip and vertebral fractures for up to 10 years. A "virtual twin" statistical modelling approach to obtain virtual placebo data was presented by Ferrari SL, et al. at ASBMR 2018, supporting these findings as well as showing a very low ratio of adverse effects (ONJ, AFF) compared to prevented fractures. Furthermore, the risk of second fracture appears reduced with denosumab and further analysis of FREEDOM data this year has shown BMD improvements relating to reduced fracture risk.

Bente Langdahl then discussed studies comparing denosumab to bisphosphonates (e.g. Miller PD, *et al.*), which have shown potential benefits especially for those patients not responding well to an oral bisphosphonate.

Data from several studies indicate a reversal of denosumab benefits after cessation of treatment, with patients from the FREEDOM trial occasionally experiencing multiple vertebral fractures, with identified risk factors of a prior vertebral fracture, off-treatment duration and off-treatment total hip BMD loss. Potential mechanisms could include high RANKL/OPG after clearing of denosumab, and an increased pool of activated osteoclast precursors.

The most recent osteoporosis treatment guidelines from the Endocrine Society (2019) recommend giving bisphosphonate after cessation of denosumab before a treatment holiday. A current clinical trial ZOLARMAB (NCT03087851) is evaluating three transition options for bisphosphonate treatment following denosumab, giving zoledronic acid to postmenopausal women, and men above 50 years, at 6 or 9 months following the last denosumab injection or when bone turnover markers have increased significantly. This study should report later this year, but early results suggest a highly individual response.

Finally, Carola Zillikens (Rotterdam) reviewed the latest discussion concerning vitamin D and bone health.

Vitamin D deficiency has long been known to cause bone mineralisation disturbances (rickets, osteomalacia) or osteoporosis and fractures. However, meta-analyses of clinical studies (e.g. Zhao JG, et al. 2017) suggests no significant benefit of vitamin D supplementation in reducing risk of fractures. Analysis in a recent Mendelian Randomisation study assessed genetic variants related to specific clinical risk factors. Genetic variants related to low BMD were found associated to fracture risk, but not the variants associated with low vitamin D status.

A further question has been whether combined vitamin D and calcium supplementation might reduce fracture risk. A modest reduction of risk has been shown in some studies, but meta-analyses have given conflicting results, the most recent not finding any meaningful effect. Debate continues concerning the methodology of these studies and several trials had few patients with severe vitamin D deficiency. There are 8 ongoing clinical trials of vitamin D supplementation in community dwelling adults, for example the US Vital study which has investigated if large doses of vitamin D can reduce risk of cancer, heart disease and stroke, showing mainly negative results. Ancillary studies will look at fractures and falls.

Carola Zillikens also reviewed the evidence concerning vitamin D effects on falls risk and functional decline, which might affect fracture rates. In fact, high doses of vitamin D may be associated with an increased risk of falls. A further concern are the potential side effects of calcium and vitamin D supplementation, such as hypercalcuria and kidney stones.

Does this mean that the debate concerning vitamin D supplementation is now over? Measurement of vitamin D levels in the European population using carefully standardized LC-MS/MS protocols showed that around 40% of the population are vitamin D deficient (serum 25(OH)D < 50 nmol/L). There are differing recommendations of vitamin D levels sufficient for bone health (20-75 nmol/L), but it is clear that a large proportion of the population has an underlying vitamin D deficiency that could contribute to bone and other health problems. Carola Zillikens concluded that any strategy for vitamin D supplementation should be targeted on specific sub-groups, institutionalised or house-bound elderly, people at high risk of vitamin D deficiency, and patients treated with osteoporosis drugs.

In other news...

Desai RJ, et al. reported a low rate of initiation of osteoporosis therapy after hip fracture among 97169 patients aged 50 years or older, from analysis of data retrieved from US health insurance companies covering the period 2004-2015. Rate of initiation of osteoporosis treatment showed a continuous decrease in the period of interest from 9.8% of patients in 2004 to 3.3% in 2015.

McClung M, et al. showed the efficacy in terms of BMD increase of 24-month therapy with romosozumab followed by 12-month treatment with denosumab, vs placebo in postmenopausal women. No significant higher incidence of adverse events was recorded.

Another paper on romosozumab was published by Lewiecki EM, et al. presenting data from a phase 3 RCT in men with osteoporosis treated for 12 months. BMD increased significantly by 12% in the lumbar spine and by 2.5% at the hip, regardless baseline BMD, age and FRAX.

Kahwati LC, et al. published a systematic review of 11 RCTs and showed that vitamin D alone reduces total fracture incidence compared to placebo, with no effect on hip fracture, while vitamin D and calcium was not associated with fracture reduction. Supplementation with vitamin D alone or with calcium has no effect on mortality, cardiovascular disease or cancer.

Firanescu C, et al. examined the efficacy of verteboplasty vs sham procedure in pain relief in a RCT involving 180 patients with acute osteoporotic vertebral compression fractures. Data have shown a significant reduction in VAS score during the 12-month follow-up in both groups without any between-group difference.

From fetus to old age

This Sunday morning clinical workshop on clinical and public health discussed how factors affecting the development of the skeletal tissues in the fetus can have long term effects into old age.

The first presentation by Jonathan Tobias (Bristol, UK) showed how certain factors during the fetal phase and in early life influence bone accrual and geometry development.

Optimization of nutrition through supplementation has been shown in some studies to be favourable to bone health, but not all studies have shown consistent effects. On the other hand, a suboptimal intrauterine environment, as is the case in pre-eclampsia, has been linked to adverse long-term bone health effects.

A second example is the breech position during pregnancy, in which the range of fetal movement and limb joint stresses are different. Breech presentation at birth had previously been associated with lower neonatal bone mineral content and area, and recently it has been demonstrated that these associations even persist into later life and that also periosteal circumference is altered. Negative external environmental influences were touched upon briefly, but will require further studies.

The next presentation by Ola Nilsson (Örebro, Sweden) explained the development of the growth plate chondrogenesis clearly using animations and provided an overview of the different categories of influential factors.

Endocrine factors, inflammatory cytokines, paracrine factors, the matrix, and intracellular processes are of importance. A number of syndromes with short stature and their corresponding underlying genetic mutations were shown in detail. Intriguingly, the mutations often map to loci identified previously in musculoskeletal genome-wide association studies. These recent discoveries have immediate clinical diagnostic implications, and hopefully near-future therapeutic studies will follow.

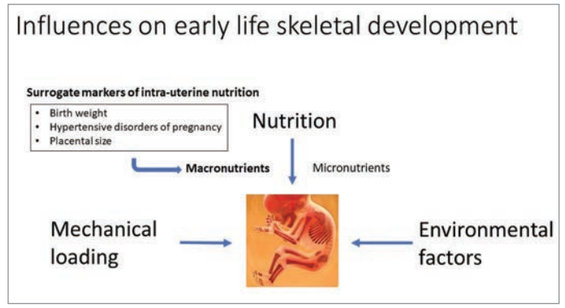


Figure 1. *Influences on early life skeletal development (Jonathan Tobias)*

HIGHLIGHTED ORAL POSTER PRESENTATION

Astrid Kamilla Stunes (Trondheim, Norway, P162) studied 47 mothers in the second and third trimester of pregnancy and offspring pairs at 8-9 years of age and observed a positive association between second trimester 25(OH)D levels and offspring lumbar spine BMD, while no association with BMD measured at other sites and TBS was seen. They conclude that offspring whose mothers is vitamin D deficient are at higher risk of having reduced bone mass at 8-9 years and suggest the need for monitoring vitamin D levels during pregnancy and eventually correct any deficiency. Currently, number of patients in the study is too low to assess which percentage of BMD change in offspring could be explained by vitamin levels in mothers. There is no clear explanation of why the significant association was found only at the lumbar spine.

Oral presentations on osteoporosis and risk predictors

Tilen Kranjc (Rotterdam) has used a "machine learning approach" (Black Box) to predict non-vertebral fracture risk from DXA images that contain much more information than just BMD. This study included femoral neck DXA images of 3824 participants from the Rotterdam study. In ROC curves, the model showed AUC of 0.75 on the training set and 0.70 on the test set, performing definitely better than BMD alone (AUC 0.50). However, BMD was not evaluated as a continuous variable, which could exaggerate the advantage of the new method. Further validation is ongoing on two additional independent cohorts and the authors will take into account other clinical risk factors for fracture.

SCOOP was a randomized controlled trial showing that screening using the FRAX score (with or without DXA) reduced the incidence of hip fractures by 28%. **Eugene McCloskey** (Sheffield, UK) reported that the positive findings of the SCOOP trial were not due to a difference in falls rate between both study groups. This was a valid objection since subjects were aware of their high-risk status and could have modified their behaviour during the trial. Several risk factors for falls were identified but they were well balanced between both groups. There was no significant interaction between falls and study group as shown by the absence of significant differences in falls incidence between both study groups. The positive effect of screening on fracture rate is thus likely mediated by osteoporosis treatment and is not attributable to a reduction in falls.

Serge Ferrari (Geneva), presenting on behalf of Cesar Libanati, explained how their group used the 12-month data of the ARCH trial (romosozumab vs alendronate) to show that the T-score after one year of therapy is an indicator of subsequent fracture risk during the second year of the trial, when all patients were on open alendronate treatment. These findings confirm previous data obtained with zoledronic acid or denosumab therapy. Using the ARCH trial, they could indeed show that total hip T-score at 1 year was associated with subsequent 1-year vertebral and nonvertebral fracture rate, regardless of therapy previously received. Vertebral T-score at the lumbar spine was not related to subsequent non-vertebral fracture risk but only to vertebral fracture risk. These findings support the concept of T-score targets in osteoporosis treatment, independently of treatment received.

Nathalie Bravenboer (Amsterdam) investigated the clinical value of bone biopsy performed 1 year after renal

transplantation in 33 non-diabetic subjects. Bone biopsy could detect otherwise unsuspected delayed mineralization, and preliminary data suggest bone histology could be predictive of future vertebral fractures. Full histomorphometry appears to be required to confirm this.

Xavier Nogués (Barcelona) reported results from a large Spanish observational study in breast cancer patients on aromatase inhibitors (AIs), confirming that bisphosphonate treatment reduces clinical fracture incidence (HR 0.69; 95% CI, 0.49-0.99). "Real world" data thus confirm the positive effects of randomized controlled trials in the setting of AI-induced fragility fractures.

Katerina Trajanoska (Rotterdam) reported that genetic factors substantially explain the phenotypic variance of serum osteocalcin levels using genome wide association data. Her group found that 4 novel genetic variants (SNPs) are associated with serum osteocalcin levels in elderly people. Initial data suggest some relationship between these variants and bone pathways.

Steven Boonen Clinical Research Award

SPONSORED BY: AMGEN

The recipient of the 2019 Steven Boonen Clinical Research award is **Professor Roger Bouillon**, Professor Emeritus in Endocrinology at KU Leuven, Belgium.

Roger Bouillon was the mentor of Steven Boonen, was a founding member and the president of European Board of Endocrinology, and was also president of the International Bone and Mineral Society. He has published more than 700 papers on various aspects of bone and calcium homeostasis. Vitamin D is a major focus of his research. He organized the workshop on vitamin D in Bruges, Belgium.

The topic of Prof Bouillon's Steven Boonen award lecture was "Two billion years of evolution of vitamin D". He started from the role of vitamin D in zebrafish and chickens. Evidence of rickets was found in approximately 6% of ancient Roman skeletons of less than 18 years of age. During the Renaissance period in Florence the Medici family had several cases of rickets. Even now, rickets is still present across the world, and the World Health Organisation aims to eradicate rickets before 2030.

Prof Bouillon also explained that, based on evidence from basic and preclinical studies, vitamin D has a broad spectrum of biological actions. Observational studies have linked low vitamin D levels with many major human diseases. Mendelian randomization studies suggested that low vitamin D values are related to multiple sclerosis and type 1 diabetes. Randomized control trials and meta-analysis also showed a role of vitamin D in upper respiratory infections, blood pressure and more importantly in mortality.

Prof Bouillon is lead author of the 2019 ECTS position statement "Management of endocrine disease: Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency" which advises to improve vitamin D status in risk groups, and recommends further genetic research to investigate individual vulnerability to vitamin D deficiency. Concerning finally who should be treated with vitamin D, Prof Bouillon's answer is "it should be given to those who need it".

Secondary osteoporosis

In our ECTS 2019 clinical update on secondary osteoporosis, Andrea Palermo (Rome) reviewed the main endocrine factors known to be involved, while Stuart Ralston (Edinburgh) discussed non-endocrine factors.

Endocrine factors

Thyroid Hormones

Receptors for T3, the active thyroid hormone, are present on all types of bone cells and on chondrocytes. Both hypo-and hyperthyroidism increase the fracture rate (a U-curve).

The deleterious effects of thyroid-stimulating hormone (TSH) suppressive L-T4 therapy for thyroid cancer on fracture rate are underestimated. C. Aubert *et al*. recently demonstrated that there was a progressive increase in hip fracture rate with the degree of lowering of TSH levels, even within the euthyroid range. The rate of vertebral fractures for TSH levels consistently below 0.05 microIU/ml is increased by 3-fold, which is equivalent to a decrease in BMD of 1 T-score unit.

Cushing's Disease

The deleterious effects of hypercortisolism on bone are well known. Pathological fractures can be the presenting sign of Cushing's disease and the fracture rate is increased even in subclinical hypercortisolism.

Bone-active therapy is recommended if surgery is impossible or delayed, at least in postmenopausal women.

Growth Hormone

For thyroid hormones, there is also a U-curve relationship between growth hormone (GH) levels and fracture risk.

Patients with GH deficiency have a low bone turnover and a mild PTH resistance. The increased fracture risk is dependent on the delay between diagnosis of GH deficiency and initiation of GH replacement therapy. BMD can still be increased by alendronate in GH-treated patients.

Testosterone

Hypogonadism is an essential cause of male osteoporosis. Decreased testosterone levels lead to low bioavailable estradiol levels and increase the risk of falls. The estradiol / testosterone ratio is lower in men who fracture, compared to men who do not have a fracture. Andrea Palermo recommends to start testosterone therapy in men with testosterone levels below 200 ng/dl and an increased risk of fracture (see also page 13).

Primary Hyperparathyroidism

Primary hyperparathyroidism impairs cortical and trabecular compartments.

Surgery is the best way to improve BMD and reduce the fracture risk in osteopenic and osteoporotic women with primary hyperparathyroidism.

Non-endocrine factors

Genetic Factors

Firstly, Stuart Ralston pointed out that osteoporosis is always secondary considering the key roles of age, sex and genetic factors. JA Morris et al. recently showed that 20% of BMD variance is explained by 518 genome-wide significant loci, underlying the importance of genetic factors in the pathogenesis of osteoporosis.

Coeliac Disease

Malabsorption, inadequate calcium intake, and the presence of other autoantibodies, notably against OPG, are all reasons why coeliac patients are at increased risk of osteoporosis.

When patients follow a gluten-free diet, the increase in BMD will often plateau after 2 years and antiresorptive drugs are recommended if patients are still osteoporotic.

Inflammatory Bowel Diseases

An increased risk of fracture has been demonstrated in patients with Crohn's disease, with a relative risk (RR) of 1.2. The pathogenesis is uncertain: chronic inflammation, malabsorption and treatment of the disease all play a contributory role.

Cirrhosis

The RR of fracture in patients with primary biliary cholangitis is 3.0 and raised sclerostin secretion could be a key pathogenic factor. In patients with non-alcoholic fatty liver disease (NAFLD), the RR of osteoporosis is increased to 1.5.

Neurological Diseases

RR of fractures is increased to 1.9 in Parkinson's disease, 2.0 in multiple sclerosis (key contribution of corticosteroid treatment), 3.3 (data for hip fractures only) in dementia, 2.8 (data for hip fractures only) after stroke, and 2.2 in epilepsy. These data come from the SIGN 142 systematic review.

Drugs

RR of fractures is increased to 1.6 in corticosteroid users (as an average since the increased risk is highly dependent on the dose), 1.4 in SSRIs users, 2.0 in patients on AIs and 1.7 in patients under GnRH agonists therapy.

When stopping such "osteotoxic" drugs, a decrease in fracture rate has been well shown for corticosteroid therapy, but there are very little data for other drugs.

Rheumatoid Arthritis

The RR of fracture is increased to 1.3. All disease-modifying antirheumatic drugs (DMARDs) used for treatment of rheumatoid arthritis prevent bone erosions, but there is no good evidence that they can prevent osteoporosis. Conversely, there is little evidence that drugs used for the treatment of osteoporosis prevent bone erosions.

Ankylosing Spondylitis

The RR of fracture is also increased to 1.3. Here, the pathogenesis of osteoporosis is multifactorial, including the deleterious effects on bone of IL-17 and TNF, the presence of OPG antibodies and the use of corticosteroids. Infliximab, a TNF inhibitor, increases BMD but there is only anecdotal evidence for IL-17 blockade.

MGUS

The RR of fracture in cases of MGUS (monoclonal gammopathy of unknown significance) is increased to 1.4. Pathogenic factors are probably similar to osteoporosis in multiple myeloma, including DKK-1, MIP1-alpha and possibly RANKL.

HIV

The RR of fracture is increased to 1.5 and the pathogenesis is multifactorial, including the RANKL/OPG system and immune reconstruction after therapy.

Effects of low testosterone on bone density and quality

The main sex steroid regulating bone turnover in men is 17-beta-estradiol (17-β-E2), synthesized from testosterone by aromatase. Estrogens and androgens reduce the birth rate of osteoclasts and osteoblasts. They decrease the lifespan of osteoclasts, but prolong that of osteoblasts and of osteocytes. Although low estrogen levels in older men are associated with impaired bone microarchitecture, data on androgens are discordant.

At ECTS 2019, Anne Piot (left), a resident in Rheumatology practicing in Lyon, presented results from two separate studies investigating the link between sex steroids levels and prospectively evaluated changes in bone microarchitecture.

The first presentation given in the plenary oral presentations on Osteoporosis and Bone Loss (PLO18), described results obtained in the STRAMBO (Structure of the Aging Men's Bones) study. This is a single center cohort study of 820 older men followed up for 8 years, involving collaboration between Inserm (French National Institute of Health and Medical Research) and Mutuelle des Travailleurs de la Région Lyonnaise, a complementary health insurance company. The study has found that low levels of Apparent Free Testosterone Concentration (AFTC) and bioavailable 17-β-E2 are associated with accelerated deterioration of cortical bone, while total testosterone and 17-β-E2 are weakly associated. The study is now published in JBMR.

A second presentation (ND-P036), for which Anne Piot was awarded an on site oral presentation, was on the effect of testosterone treatment on bone microarchitecture in patients with Klinefelter syndrome. In this rare condition, an additional X chromosome is associated with low testosterone levels. Men with Klinefelter syndrome were recruited to the KLINOS study from a research fertility program conducted by Ingrid Plotton (University of Lyon, Hôpital Femme-Mère-Enfant, Lyon). The study has found they have reduced BMD and several alterations of bone microarchitecture, notably decreased cortical thickness at the tibia. Patients were reassessed after 30 months testosterone therapy and there was an improvement in several parameters of trabecular and cortical bone at both radius and tibia.

The mechanisms underlying androgen deficit in each group are different (additional X chromosome in the Klinefelter syndrome, progressive decrease in androgen secretion in older men). A further difference is the period of life when the androgen deficit operates. For Klinefelter syndrome, the main effect is during growth and peak bone mass formation, while in older men, bone loss is clearly occurring later in life. Bone mass deficit and microarchitectural deterioration are proportional to the sex steroid deficit, which is more severe in Klinefelter syndrome.

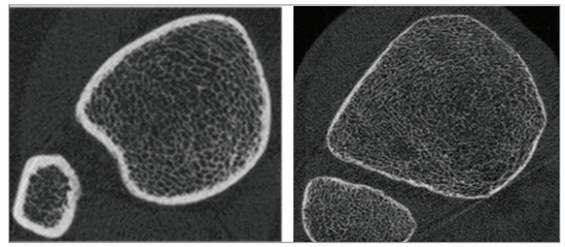


figure 2. *HR-pQCT at the tibia: control (left) and Klinefelter syndrome (right)*

Both studies employed HR-pQCT for bone imaging. Anne Piot told us "The excellent resolution of HRpQCT (82µm) provides more accurate measurement of bone microarchitecture (e.g. cortical thickness, trabecular number). In longitudinal studies, it allows more accurate assessment of average yearly changes in the investigated variables." Quite typically for longitudinal studies, the main challenge was dropout of participants, mainly a risk among the elderly men in the STRAMBO study, due to diseases, poor mobility, or loss of interest. The Lyon group offered free transport by a taxicab to their department, which made it easier for participants to attend the visit.

Follow-on studies are planned. Results from the KLINOS study clearly indicate that testosterone treatment would improve bone microarchitecture and, consequently, may increase bone strength, in hypogonadal patients with Klinefelter syndrome. To build on the results from the KLINOS study, a multicenter study could assess of the effect of the improvement of bone microarchitecture obtained by testosterone therapy on the incidence of fractures.

Results from the STRAMBO study suggest that eventually, older men with low serum testosterone concentration could also benefit from an assessment of bone status, with a view to anti-osteoporosis treatment if required. An analysis is planned with new software to allow a better assessment of the changes in the trabecular compartment, and the impact of the sex steroid deficit on the loss of bone strength.

HIGHLIGHTED ORAL POSTER PRESENTATION

Although individuals with suffering from chronic obstructive pulmonary disease (COPD) have increased risk of osteoporosis and osteoporotic vertebral fractures (OVF), the role of smoking in this relationship has not been elucidated. Fjorda Koromani (Rotterdam, P260) has estimated the risk the risk of OVF in subjects with COPD and the role of smoking in a population-based cohort of elderly men and women, using sex-specific logistic regression models. They found that in men COPD is associated with increased risk of OVF independent of smoking status.

ECTS ASBMR debate

The prevention of osteoporotic fractures

Our traditional Saturday evening debate between representatives of ECTS and ASBMR was on the motion: **This house believes that intervention to increase peak bone mass rather than targeting bone loss would be more effective in reducing the osteoporotic fracture.**

The ECTS congress cast its vote before the debate: FOR: **46%** AGAINST: **29%** UNDECIDED: **25%**

ECTS/ASBMR Debate

For the Motion

FOR THE MOTION on behalf of ECTS: Nicholas Harvey, Professor of Rheumatology and Clinical Epidemiology within Medicine at the University of Southampton, UK

Nicholas Harvey started by stating that the debate concerned the "increase in peak bone mass (PBM)" per se, and not any specific intervention to achieve this objective.

His main points:

- Osteoporosis has such a huge impact that it needs to be addressed at a population level and not at the individual level.
- Indirect evidence supports the notion that PBM is a major determinant of later fracture risk. These studies demonstrate tracking of BMD through childhood, predictive value of baseline BMD for later BMD over 10 years, and modelling of the effect of PBM on development of osteoporosis.
- In the large US Health ABC cohort, in older age BMD after 10 years follow up is largely explained by BMD at baseline. In the US SOF study, baseline rather than changes in BMD predicted fracture risk.
- In a population the majority of fragility fractures occur in non-osteoporotic individuals, so are missed by targeted approaches.
- Nicholas Harvey favours a population rather than a targeted (high-risk) approach because targeted therapy can only ever reach a small proportion of the population, and has major limitations (insufficient diagnosis, undertreatment, poor adherence to therapy), whereas a "population strategy" improves BMD in all, through intervention or behavioural changes that later become a normal "part of life", leading to a healthier population.
- Such a strategy avoids problems in detection, risk stratification and medicalization.

ECTS/ASBMR Debate

Against the Motion

AGAINST THE MOTION on behalf of ASBMR: Benjamin Leder (Boston, USA), Professor of Medicine at Harvard Medical School, and practicing endocrinologist at Massachusetts General Hospital.

Benjamin Leder first stated that 60-90% of PBM depends on genetic factors. Moreover, increasing PBM needs sustainable efforts.

His main points:

- Targeting bone loss is effective: e.g., bisphosphonate prescription rate has changed over time, followed a few years later by an inverse change in hip fracture rate.
- There is evidence that an increase in PBM is not sustainable. Exercise increases BMD but this gain progressively decreases when sustained exercise is stopped. There are no data on the effects of sustained exercise on bone quality, nor on fracture rate. Bone area is increased in the throwing arms of baseball players, but the effects are gradually lost when the players end their careers.
- In general, behavioural interventions are not sustainable.
- What about scalability? Consider childhood obesity: despite large campaigns, much expense and intervention of famous people... childhood obesity continues to increase. In contrast, targeting bone loss is effective, sustainable and scalable.

In the rebuttals:

Nicolas Harvey argued that:

- Whilst population variance in PBM has a genetic contribution, it is clear that environmental factors may move the overall distribution (for example secular increase in height observed in many populations in recent decades), demonstrating capacity to alter PBM.
- Food fortification would be simpler to implement than sustained exercise.
- Limitations of the "targeted approach" include the treatment gap, the necessity to detect cases for therapy and the known poor adherence to treatment.
- A good example of sustainability is the persisting effect of gestational vitamin D supplementation, since the increase in BMD in offspring is still present 4 years after birth in the MAVIDOS RCT.

Benjamin Leder argued that:

- There are other observational studies showing a lack of effect of gestational Vitamin D supplementation on BMD in the offspring.
- There are NO studies showing that increasing PBM will reduce fracture rate in later life.

In the vote after the debate, Benjamin Leder won with 51%, and thus was the winner of the Golden Femur on behalf of ASBMR!

Real world epidemiology for the bone researcher

Daniel Prieto-Alhambra (Oxford) led an interactive session exploring the use of real-world evidence (RWE) in bone research and the challenges that might be faced.

The session began with an extensive overview of data resources that can be used as the basis for studies. With the increased digitisation of modern healthcare, increasing sources of Big Data are available, including hospital and outpatient data, primary care records, registries, drug utilization data, patient and device generated data. These can be used in studies designed to investigate characterization, causality and prediction of disease, drug safety and other questions. Among these, causality and prediction are the more difficult to assess. However, highly developed online R-software based research portals are available to assist data analysis.

Working groups were then tasked to design a RWE study to characterize the use of anti-osteoporosis drugs in Europe, study their safety profiles, and to predict who is at risk of adverse effects. The groups had to discuss the data sources of interest, study design, study population and exposure of interest, the analytical approach, and strengths and limitations of their study.

Ling Oei, who attended this session, told us "This was a nice way to get to know some participants and their fields of expertise. Attendees were well-balanced with representation including epidemiologists, clinicians, basic scientists, health scientists, etc. Teamwork brought some attractive research ideas forward!"

Osteoporosis and bone loss

Six oral presentations at a plenary session of ECTS2019 presented latest findings on various mechanisms and factors that contribute to osteoporosis and bone loss.

Periodontitis is a highly prevalent disease that results in loss of connective tissue and bone support and can progress to bone destruction, tooth mobility and finally, tooth loss. Persistent inflammation causes alveolar bone loss not only by stimulating osteoclast activity, but also by directly suppressing bone formation via increasing the expression of Dickkopf-1 (Dkk-1). **Paula Goes** (Dresden) investigated whether Dkk-1 is a main contributor to periodontitis-induced alveolar bone loss (ABL), using a murine model with a specific deletion of Dkk-1 in osteocytes (Dkk-1;Dmp1-Cre mice). Periodontitis was induced by ligature around the upper 2nd left molar, the contralateral side was used as control. She reported that the deletion of Dkk-1 on osteocytes prevented bone loss compared to Cre negative mice with periodontitis (control). Histological analysis displayed a significant reduction in osteoclast number as well as an increase in osteoblast and osteocyte numbers when compared to control. There was no change of P1NP serum levels between the groups, however, a significant reduction of CTx serum levels was observed in Dkk-1;Dmp1-Cre mice compared to control. She concluded that Dkk1 derived from osteocytes plays a crucial role on alveolar bone loss in periodontitis.

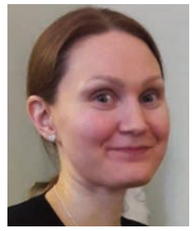
Osteocytes respond to local mechanical inputs by modulating secretion of the Wnt-antagonists sclerostin (SOST) and Dkk-1. A small amount of sclerostin and Dkk-1 are to be found in circulation and have been shown to correlate with bone mineral density (BMD). Nevertheless, it is not clear whether circulating Wnt-antagonists contribute to bone anabolism at distant sites or are biomarkers of localised effects. **Paul Baldock** (Sydney) has employed conditional mouse models of Sost and Dkk-1 to delineate their local and endocrine effects on bone tissue. In an elegant study using limb-specific Sost or Dkk-1 null mice which retained expression and secretion in the axial skeleton, they could show that local sclerostin and Dkk-1 production is fundamental to the stimulation of bone accrual, but that both Wnt-antagonists lack an endocrine function in the regulation of bone accrual.

Activation of T cells has been found to contribute to bone loss in the setting of postmenopausal osteoporosis. In this study, **Juliane Colditz** (Dresden) *et al*. showed that Dkk-1 is expressed in T cells and that T cell-derived Dkk-1, rather than osteoblast-derived Dkk-1, mediates estrogen deficiency-induced bone loss, providing new insights into the disease mechanisms of estrogen-deficiency-induced bone loss.

See Juliane's excellent Science Sketch on her Dkk-1 study here.

Fjorda Koromani (Rotterdam) and colleagues have previously shown that the prevalence of true osteoporosis vertebral fractures (OVF) significantly differs across the quantitative morphometry (QM) and algorithm-based qualitative (ABQ) definitions. In this study they compared the ability of the two OVF definitions to predict skeletal fragility outcomes, including future non-vertebral (NVF), osteoporotic fracture (OV) and mortality in a population-based cohort of men and women 55 years and older. They concluded that ABQ-defined OVFs seem to pick up operational characteristics of bone fragility better than QM.

Passive smoke exposure has been linked with the risk of osteoporosis in adults



As part of the longitudinal Cardiovascular Risk in Young Finns Study, Sanna Tolonen (Helsinki) and colleagues examined the independent effects of exposure to passive smoking in childhood on adult bone health.

They found that parental smoking in childhood was associated with lower pQCT derived bone sum index (-0.064 ± 0.023 per smoking parent, P = 0.004) and a higher incidence of low-energy fractures in adulthood (OR 1.28, 95% CI 1.01–1.62). This data provides more evidence that children of parents who smoke have impaired bone health in adulthood. This study has been published in JCEM.

After the congress we asked Sanna Tolonen (left) some more questions about her research on exposure to passive smoking and adult bone health.

Please tell us about your research interests and current professional activities?
I finished my PhD at the University of Helsinki in 2019 and at the moment I´m working as a dietitian. However, I'm planning to continue research work and will surely apply funding for it. My research interests are mostly related to bone health and different lifestyle habits, particularly on food and exercise.

What is the Cardiovascular Risk in Young Finns Study, and how does this relate to bone health?
The Cardiovascular Risk in Young Finns Study is a prospective longitudinal cohort study which was launched in 1980 with 3596 girls and boys aged 3-18-years and born in Finland. After the initiation year, several follow-ups have been conducted, and in the latest study even the children and parents of the participants were invited to the health examinations. The first bone measurements were done in 1991 with DXA for a subpopulation of the original cohort which were later repeated. In 2008, approximately 50% of the Young Finns cohort participated in the peripheral quantitative computed tomography (pQCT) and heel ultrasound bone measurements.

Why was it particularly decided to do the smoking association study?
We wanted to study if passive smoking was an independent risk factor for children's bone health later in life. Previously, this was studied mostly in adults, although, the effects of passive smoking in childhood may be even more harmful than to adults.

How were pQCT measurements performed in the study?
In 2008, pQCT bone measurements were performed with 1884 subjects from the original Young Finns cohort when they were 31-46 years old. Two functionally different bones, radius and tibia, were measured from the distal and shaft sites with computed tomography device (XCT 2000R, Stratec Medizintechnik GmbH). The same pQCT device was used in all five study centers. The lengths of ulna and tibia were measured with a tape measure and the measurement lines of distal radius and tibia were defined as 4% and 5% from the cortical endplate. The shaft sites were 30% for both studied bones. The in vivo precision of the pQCT measurements varied between 0.5-4.4%. Written informed consent was obtained from all participants.

Do you anticipate any impacts of this study in public health, policy, public attitudes? Has there been any response already, or interest in the media?
Results of the present study have been published this year in the Journal of Clinical Endocrinology and Metabolism and also in the local media in Finland. I think that the awareness of how bad passive smoking can be has increased. Even though, smoking is now prohibited in many public places in Finland, children and others too may still be exposed to passive smoke, which should be minimized in the future.

Are there some next steps planned for further research building on this study? Or other bone-related questions in the data from the Young Finns study?
Yes, I have been planned to continue to work with the Young Finns study in the future. Particularly, I would be interested to investigate if different nutritional factors are associated with bone health in the present population. And if only possible, I would like to perform some additional examinations either with DXA or pQCT in the upcoming years. In addition, we have discussed that fracture data could be studied more carefully for instance with the national health care registers.

What did you think about the ECTS congress? Was there interest in your presentation?
I would like to thank the organisers for the ECTS 2019 congress which was a nice experience for me. I have attended the ECTS congress only once before, so it was nice to be back and hear the latest research news in the bone area. After my presentation I got a few questions, for example did we take account physical activity and passive smoking during pregnancy in the statistical models. In fact, physical activity was recorded and taken into account from the beginning of the study.

In other news...

Hansen L, et al. published a population-based case-control study reporting data from the Danish patient registry whose aim was to evaluate the association between risk for major osteoporotic fractures and social inequality. Authors demonstrated that income, marital status and area of residence were significant risk factors for fractures by studying a total of 189,838 fractured patients.

A systematic review and meta-analysis published by de Souto Barreto, et al. showed the efficacy of exercise in reducing falls and fractures, though no significant reductions in multiple falls, hospitalization or mortality.

A study by Buehring B, et al. reported data from 5834 men enrolled in the "Osteoporotic Fractures in Men" study (MrOS) and proposed the concept of "dysmobility syndrome", that may increase the risk of falls and fractures, based on a score for impaired musculoseketal strength (see also page 21). The authors showed the incidence of major osteoporotic fractures increases in association with dysmobility syndrome. The addition of the dysmobility syndrome to high FRAX score increases the fracture risk, compared to the presence of just one of the two.

When might there be an imminent risk of fracture?

The ECTS 2019 workshop on osteoporosis treatment reviewed the data on imminent risk of fracture in osteoporosis patients.

Serge Ferrari (Geneva) discussed imminent risk associated with prior fracture.

The risk of a recurrent fracture is essentially observed during the first two years after the index fracture, reaching up to 20%. It is a function of the site of the index fracture, i.e. maximal after a vertebral fracture. After a first hip fracture, the risk is increased 11.8-fold in the first month and 2.2-fold at the end of the first year. The increased risk of falls after a first hip fracture also contributes to this specific risk. After one of the four classical MOFs, the risk also increases about 4-fold during the first year.

Recently obtained long-term data comes from the Icelandic experience. Up to 49% of the patients who have a first fracture refracture within 10 years. It is "only" 35% after a hip fracture but this apparently lower risk is due to an increase in mortality and the competing effect of death on future fractures. The risk depends on age and is more visible in older patients, at least during the first 5 years.

The site of a second fracture is relatively independent of the site of the index fracture, underlying the fact that there is no innocent fracture.

The FRAX score underestimates the "imminent" risk of fracture. This tool can give the 10-year risk of a new fracture in patients who have had a first fracture but the increase in the risk is not linear and 20% refracture within 2 years. An early treatment will thus avoid a higher number of fractures.

There is only one trial that has specifically included patients with a recent fracture. Lyles, *et al*. showed more than 10 years ago in patients with a recent hip fracture that 5 mg of zoledronic acid decreases the subsequent risk of fracture.

Two recent trials compared an antiresorptive with an anabolic agent in high risk patients, including some with recent fractures: the VERO trial compared teriparatide with risedronate and the ARCH trial compared romosozumab with alendronate. Both anabolic agents rapidly reduce the risk of fracture compared to antiresorptives. A subgroup analysis of the VERO trial showed that the superior efficacy of the anabolic agent is even more obvious in subjects with a recent clinical fracture.

Anna Nilsson (Gothenburg) then covered imminent risks associated with other clinical risk factors.

This is a relatively new concept and data on the effect of other clinical risk factors (CRFs) than a prior fracture is sparse.

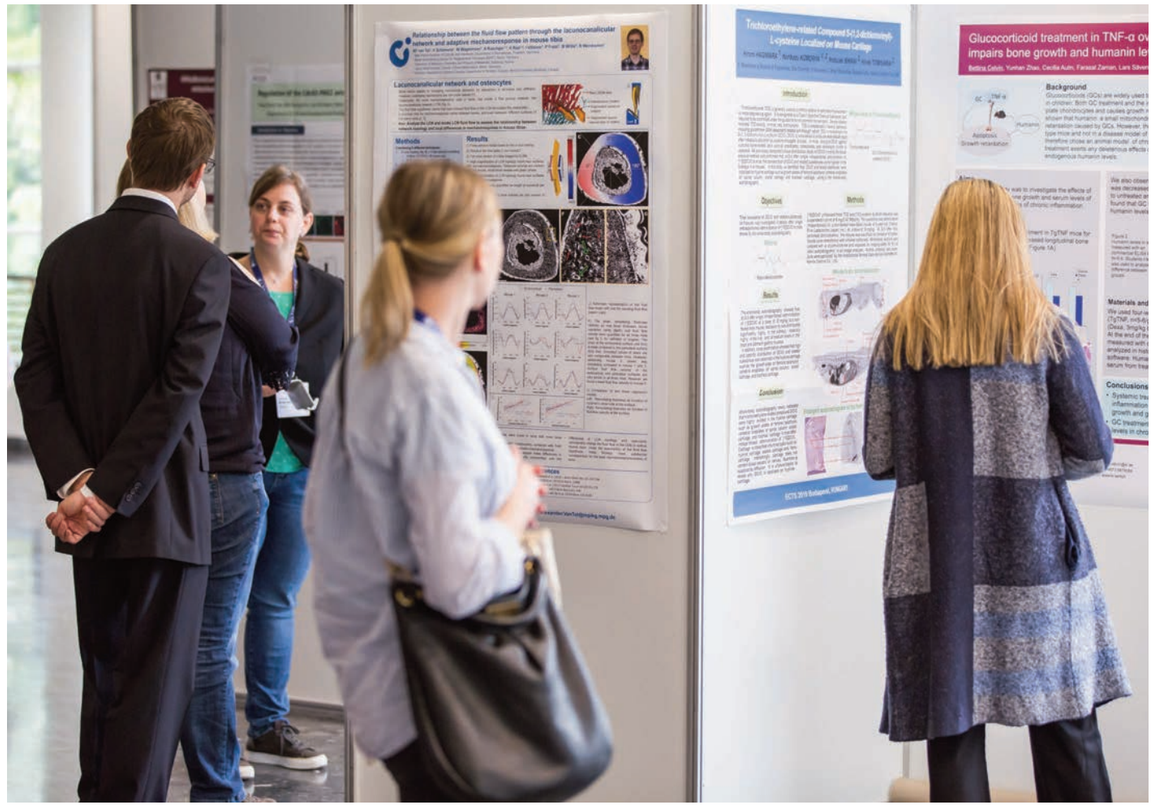
A low BMD is a major determinant of fracture risk; for example, for every SD decrease in bone mass, the risk of fracture increases by about 3-fold. Advanced age is an important CRF per se and there are several other CRFs independent of BMD, such as smoking, alcohol abuse and a family history of hip fractures. These factors are part of the FRAX prediction tool, but they are not CRFs for imminent fractures.

Secondary osteoporoses are also part of the FRAX tool, as is rheumatoid arthritis, which increases the risk of fracture independently of BMD. This is much less demonstrated for other causes of secondary osteoporosis.

It is probably only for glucocorticoid-induced osteoporosis that the risk of imminent fractures has been clearly demonstrated. Glucocorticoids lead to an accelerated bone loss up to 12% during the first year. Fracture risk increases sharply, already within 3 months after starting therapy. It has been known for a long time that there is a major increase in fracture rate during the first 6 months of glucocorticoid therapy, even if the risk is dose-dependent.

In other news...

A cohort study by Prieto-Alhambra, D et al. reported data from 997 patients aged 50 years or older, admitted for hip fracture in 45 Spanish hospitals. The authors showed as the most frequent in-hospital complications were delirium (36.1%) and kidney failure (14.1%). In hospital mortality was 2.1%, while the 4-month mortality was 11%. The analysis of data stratified by age and sex showed that survival depends on age and sex (lower in men).



East meets West

ECTS CONGRESS HUNGARY BUDAPEST 10 MAY PRE CONGRESS 11-14 MAY 2019

East-West symposium on Mobility and Longevity

The East meets West Symposium took place on the Pre-congress day. This Symposium represents a continuation of long-standing relationships between our Society and Eastern countries, initiated by Claus Glüer and with special guidance by Steven R. Cummings.

The topic of this year was "Mobility and Longevity", an issue important not only for scientific aspects but also from a socio-economical point of view.

Firstly, **Steven Cummings** (San Francisco) discussed the essential issues to be addressed, as seen from a Western perspective. In particular, he emphasized the role of muscle mass and its quality, highlighting that a clinical diagnosis of "sarcopenia" may also include consideration of functional limitation (slow walking, rising from a chair without hands and walking upstairs). Techniques well validated for the assessment of bone, specifically Dual X-Ray Absorptiometry, may be less suited for the evaluation of muscle.

The Eastern perspectives were illustrated by **Weibo Xia** as representative of China, **Yuuki Imai** as representative of Japan and **Kwang Joon Kim** as representative of South Korea.

The speakers emphasized the rapid ageing of the population (China), the fact that 36 % of the population requiring long-term support have osteoarthritis disease (Japan) and the role of jump power measurement as a predictor of dysmobility syndrome (South Korea). Dysmobility syndrome, a proposed new classification analogous to metabolic syndrome, considers interactions between musculo-skeletal disorders, increasing prevalence of obesity and neurological disorders such as Parkinson's disease that can increase the risk of falls. All of these factors affect the risk of fracture and along with this mobility and quality of life, and ultimately longevity.

The symposium was well attended and the discussion was very friendly and instructive.

Several of the Eastern and Western cultural and practical approaches in these countries are quite different; however, the mission of these symposia, as well as the Meet-the-Professor sessions (this year including "Optimising drug dosing" and "How to efficiently run a Fracture Liaison Service") and the Next-Gen Synergy Session organized by the ECTS Academy is intended to fill the gap, bridging different visions of the problems and emphasizing common challenges and solutions.

East-West experts compare osteoporosis drug dosing

Yoshiya Tanaka and Erik Eriksen discussed the optimization of osteoporosis drug dosing from the eastern and western perspectives.

Yoshiya Tanaka (Fukuoka, Japan) explained the current practice in Japan for treatment of osteoporosis with antiresorptive and anabolic therapies.

As in western countries, alendronate, risedronate, minodronate, ibandronate and zoledronate are among the bisphosphonates used in Japan, but often with different doses.

Yoshiya Tanaka explained that variations between countries in the dosing of bisphosphonates effective for bone health relate to differences in BMI, body weight, and renal function. For example, Fogelman I, *et al.* demonstrated significant changes in BMD at lumbar spine in postmenopausal women treated with risedronate 5 mg in USA and Europe, while the same efficacy has been demonstrated with half of the dose by Japanese studies. Indeed, Shiraki M, *et al.* showed the efficacy and safety of the 2.5 mg daily dose for osteoporosis treatment in Japanese patients.

For treatment with romosozumab, the largest gain in lumbar spine BMD was observed with a 210 mg monthly dose, in a multicenter study performed in USA, South America and Europe. This same result was observed also by a phase 2 trial performed in Japan. This study in Japanese patients with osteoporosis reported a similar higher increase in lumbar spine BMD with the 210 compared to the 140 mg monthly dose. Yoshiya Tanaka also underlined that reductions in vertebral fractures are reported in Japan with this treatment, similar to those observed in Western clinical trials.

Teriparatide is available in Japan with a weekly administration at the dose of 56.5 µg/week. Studies with the weekly dosing of teriparatide have been performed in Japanese patients, but there are no data in Western countries. Clinical trials are ongoing in Korea and China. A study by Fujita T, et al. published in 1999 showed significant increases in lumbar spine BMD at 48 weeks, while serum bone-type alkaline phosphatase increased at 4 weeks. In a phase 3 study by Nakamura T, et al., a weekly injection of 56.5 mcg reduced the incidence of new vertebral fracture vs placebo in a 72-week observation period.

For denosumab, data have shown that administration of 60 mg every 6 months has similar efficacy in vertebral fracture risk reduction in Japanese postmenopausal women with osteoporosis, compared to what has been observed in the FREEDOM trial.

In Japan, denosumab was approved in 2017 for inhibition of progression of bone erosions in patients with rheumatoid arthritis. Data from a phase II clinical trial of administration of 60 mg denosumab every 6 months in patients with rheumatoid arthritis also on methotrexate, reduces erosion score at 12 months. Dr Tanaka pointed out that discontinuation of denosumab in these patients is associated with BMD decrease but no changes in bone erosions.

Discussing the western perspective, Erik Eriksen (Oslo) focused on the utility of bone turnover markers during osteoporosis treatment with various agents.

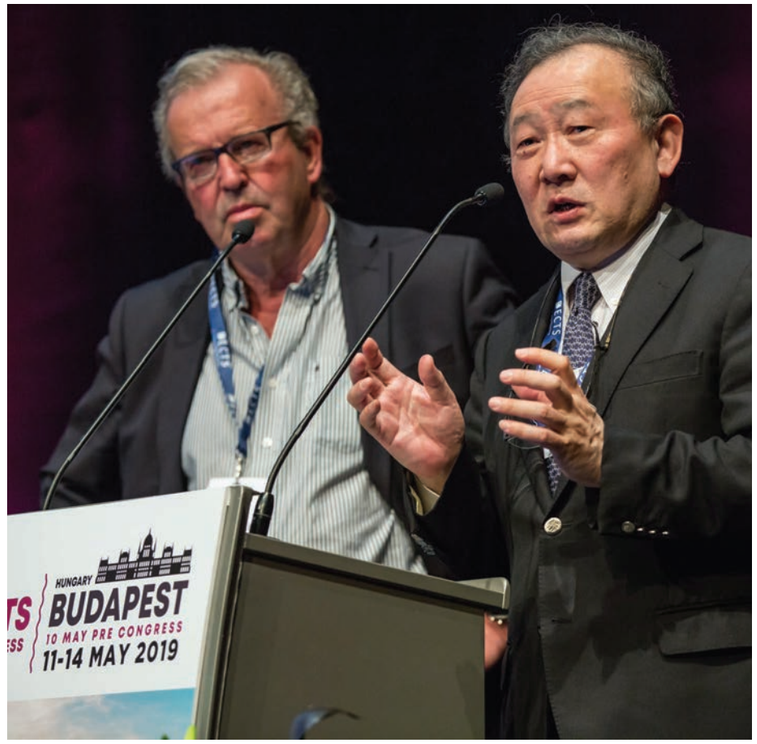
In his presentation, he highlighted that a decrease in bone turnover markers during antiresorptive therapy precedes changes in BMD and correlates with fracture reduction. A recent paper by Naylor KE, et al. showed that measuring bone turnover markers after bisphosphonate discontinuation may be useful in identifying patients who need to re-start treatment. High levels of P1NP and CTX were indeed associated with decrease in total hip BMD in 50 postmenopausal women assessed at 2 years after bisphosphonate discontinuation. Dr Eriksen pointed out that P1NP has minimal diurnal variation and is an optimal tool for monitoring osteoblast activity. Therefore, P1NP should be assessed for monitoring of antiresorptive therapy in the future.

A relevant question is the type of osteoporosis treatment to be used after denosumab discontinuation. Horne AM, *et al*. published data on the use of zoledronate after denosumab. Intravenous zoledronate was administered after a mean of 65 days and results have shown that gain in BMD is mostly maintained with this particular regimen. However, in 2019, Lamy O, et al. reported two cases of postmenopausal women previously treated with bisphosphonates in which alendronate, administered after denosumab discontinuation, was ineffective in preventing fractures. Clearly, we need more data to help determine which dose of bisphosphonates should be used. A likely relevant factor is that patients metabolize bisphosphonates in different ways.

Dr Eriksen also discussed how to manage therapy with zoledronate. There is evidence that the effect of zoledronate, usually administered at the dose of 5 mg intravenously once a year, could last more than a year.

Reid I, et al. published interesting data in 2014 on the effect of a single infusion of zoledronate on the occurrence of clinical fracture. They found a significant reduction of clinical fractures and in new morphometric vertebral fractures at three years after one infusion vs placebo. This reduction was not different comparing patients receiving single infusion vs those receiving three or more annual infusions. P1NP reduction was not different between the two groups.

Based on these data, Dr Eriksen suggests to measure P1NP annually after the first infusion of zoledronate and evaluate whether or not patient needs more infusion. In his experience, the yearly dosing is not needed in the majority of patients. He suggests this approach as the best way to manage zoledronate therapy in clinical practice, even in light of the data that demonstrated as the risk of atypical femur fracture is minimal if zoledronate is not administered once a year.



As far as management of zoledronate therapy, Dr Eriksen showed other interesting data on how to decide to stop treatment. Cosman F, et al. have shown that after 3 years of treatment with zoledronate, the low T-score at neck or total femur and incident vertebral fracture during the 3 years of treatment course were predictive of new vertebral fractures. Conversely, prevalent vertebral fractures did not influence subsequent (after 3 years of treatment) vertebral fracture risk, but predicted the risk of new non-vertebral fractures. Hence, after 3 years of zoledronate treatment, in women with femur T-score > 2.5 and no new fracture during the treatment period, it is reasonable to discontinue treatment.

With reference to teriparatide, there is no reason for optimization of the dose or for making changes in the time course. Daily 20 mcg administration for a 2-year period has given the best results in terms of fracture reduction. In particular, the best fracture reduction is seen for treatment lasting longer than 14 months. There are rare cases of patients, described in the pivotal trial with teriparatide, that did not respond to the drug in terms of increase of P1NP, and Dr Eriksen suggested to take into account the BMD response in these patients to make decisions in clinical practice. He suggested monitoring of P1NP every at 6 months during teriparatide treatment, because it is the best reflection of PTH effects at the cellular level.

Concerning therapy with denosumab, Dr Eriksen stated that the role of bone turnover markers is of value and shows less of the variation seen with bisphosphonates.

Estrogen therapy, in Dr Eriksen's view, once started, should be continued as long as possible. Data from a Danish study has shown that BMD continues to increase at the spine and the femur, cardiovascular protection was demonstrated for 18 years with no increase in risk of breast cancer, and a concomitant reduction was observed in mortality. The recent 18 year reassessment of the Women's Health initiative study also showed reduced all-cause mortality in women starting HRT below the age of 60.

In conclusion, Dr Eriksen strongly agrees with the use of bone turnover markers (particularly P1NP) for monitoring osteoporosis therapy with bisphosphonates, denosumab and teriparatide, and suggests the use of DXA for diagnosis and for decision on when to take a drug holiday during treatment with bisphosphonates. In this latter setting bone markers are very useful with respect to re-initiation of therapy, because they show reduced effects of previous antiresorptive therapy at least one year before any decrease in BMD is detectable.

The session also included a discussion of the experiences in running of Fracture Liaison services in East and West. See videos of presentations by **Yong-Chan Ha** (South Korea) and **Kristina Akesson** (Sweden).

Our Eastern partner societies

Chinese Society of Osteoporosis and Bone Mineral Research (CSOBMR)

FOUNDED: 2001
CURRENT MEMBERSHIP: Approximately 2,000
OFFICIAL PUBLICATION: Chinese Journal of Osteoporosis and Bone Mineral Research
WEBSITE: http://www.csobmr.org.cn/

PAST PRESIDENT:
Weibo Xia
(Peking Union Medical College and Hospital)

Each year, CSOBMR runs one national and one international meeting (International Conference on Osteoporosis and Bone Research). They also hold an annual young investigator meeting, and an advanced clinical training course held in a different part of China each year. CSOBMR is associated with the Chinese Medical Association and is an important contributor to Chinese health policy consultations. They are also active on Chinese social media (WeChat).

Japanese Society for Bone and Mineral Research (JSBMR)

FOUNDED: 1982
CURRENT MEMBERSHIP: Approximately 2,200
OFFICIAL PUBLICATION Journal of Bone and Mineral Metabolism
WEBSITE: http://jsbmr.umin.jp

CURRENT PRESIDENT:
Sakae Tanaka
(University of Tokyo Hospital)

The Society was founded at first as a research cooperative meeting in 1967, and developed to the JSBMR in 1982. It runs an annual meeting (next in Kobe, October 12-14 2019) and Skeletal Science Restart, an annual training activity for about 30 young members every year. JSBMR has published several clinical guidelines in Japan, including on the management and treatment of osteoporosis (revised 2015), and diagnostic criteria for rickets and osteomalacia (2015) and spine fracture (2012).

Korean Society for Bone and Mineral Research (KSBMR)

FOUNDED: 1989
CURRENT MEMBERSHIP: 1,572
OFFICIAL PUBLICATION Journal of Bone Metabolism
WEBSITE: http://www.ksbmr.org

CURRENT PRESIDENT:
Ho-Yeon Chung
(Kyung Hee University Hospital)

KSBMR runs two academic conferences: one in Korean each autumn and an international meeting each spring (Seoul Symposium on Bone Health). They also organise a clinical osteoporosis update for primary care physicians twice a year, a clinical densitometry course, an advanced program for metabolic bone disease, and a Young Leader's Camp for basic researchers. They have published a textbook of osteoporosis every 4-5 years, a clinician's guide every 1-2 years and three fact sheets. KSBMR collaborates with the Korean health system and is proposing improvements to national health insurance policy through contacts with the government.

Korean Society of Osteoporosis (KSO)

FOUNDED: 1998
CURRENT MEMBERSHIP:: 2665
OFFICIAL PUBLICATION Osteoporosis and Sarcopenia
WEBSITE: http://www.koreanosteoporosis.or.kr

CURRENT PRESIDENT:
Chang-Hee Suh
(Ajou University School of Medicine)

KSO organises alternating national and international meetings each autumn, instructional lecture courses for clinicians and paramedics, and two positional meetings each year. They work with "Korea Women's Health and Ostoeporosis Foundation", a subordinate organization of The Ministry of Gender Equity and Family and have run several policy forums with the National Assembly. As well as their website, KSO are also active on Facebook.

After the congress we asked representatives of the four Eastern partner societies a few questions:

What do you think about the ECTS congress this year? Were there any particular highlights for you?

Weibo Xia (CSOBMR President): *This ECTS congress was very well organized. I was deeply impressed by all the rare bone disease sessions and the mobility and longevity symposium.*

Ho-Yeon Chung (KSBMR President): *The ECTS 2019 congress was well prepared and organized. I was happy to see working groups and symposia on rare bone diseases.*

Yoshiya Tanaka (JSBMR Vice-president): *The annual meeting of ECTS is always very well organised and the programme has been improved every year. We are particularly impressed by the ECTS Academy and New Investigator programme, and the reviewing of practice guidelines which is very useful and valuable for international participants. The East meets West activities have become substantial and fruitful.*

Chang-Hee Suh (KSO President): *This year's ECTS meeting was great. It had an excellent schedule. My highlights were the pre-congress programme, especially the East-meets-West program. However, it would have been even more fabulous if it was held in a regular schedule, not in the pre-congress.*

What recent advances in bone research do you think are particularly important, in your own countries?

Weibo Xia: *We have conducted a national osteoporosis prevalence study.*

Ho-Yeon Chung: *Numerous studies of clinical research in the Republic of Korea have been developed using national epidemiologic data. In basic research, many good studies on cartilage have been published recently.*

Yoshiya Tanaka: *Clinical medicine has developed significantly in the field of bone/mineral metabolism. This new development was based on the results of many basic research investigations in Japan, including RANKL and cathepsin K, which were discovered by JSBMR members.*

Chang-Hee Suh: *In Korea, an interest about "the Dysmobility Syndrome" has rapidly grown. Many researchers are focusing on it.*

How could bone research benefit from more collaboration between researchers in the East and West? What are the challenges involved in achieving more collaboration?

Weibo Xia: *There are many collaboration networks on different bone diseases in the EU. Perhaps some Asian countries could be involved in these networks in future?*

Ho-Yeon Chung: *It would be good to have the opportunities to collaborate on clinical studies that may show differences between ethnic groups or countries.*
Yoshiya Tanaka: *It is important to perform more collaboration in the global level, in fact not limited in the East and West. If we get appropriate grants, we will be able to perform in the field of bone and mineral research among your communities and ours. Accelerating medicines partnership (AMP RA/SLE) funded by NIH is a good example. At the single cell level this project is analysing tissue and blood samples from people with rheumatoid arthritis and systemic lupus erythematous to pinpoint genes, proteins, biological pathways, and signaling networks.*
Chang-Hee Suh: *Because the genetic and environmental fundamentals are so different between the two parts of the world, every collaboration can bridge a gap of knowledge of each of them. The primary challenges are funding and reachability. If every society can open their chance of research fund or opportunity to participate in a multi-centre study, the benefit of collaboration can be amplified.*

Cooperation with ECTS has been active for a few years now. How would you like cooperation between our societies to develop in the future?
Weibo Xia: *CSOBMR treasures our past good cooperation. We hope ECTS will continues this special session for East meets West. We may establish a new training course between our two societies.*
Ho-Yeon Chung: *It would be good to share a common educational program with each other. It is desirable that each society increase the opportunity for participation by increasing travel grant. It would be nice to keep a joint session to increase interest and participation.*
Yoshiya Tanaka: *We are discussing several ideas with ECTS, including joint sessions and new investigators educational sessions in the annual meetings of each society, expanding travel grants, interaction between the ECTS academy and its JSBMR counterpart, a training course or international school, and an ECTS-JSBMR exchange programme to organise long stays in centres of excellence in Europe and Japan.*
Chang-Hee Suh: *I believe that both societies have to find a way to provide the opportunity for cooperative research to the young generation. It may start from a simple international poll for finding consensus. Giving a chance for the younger generation is the best thing that we can do for the future.*

Rare Bone Disease

ECTS CONGRESS HUNGARY BUDAPEST 10 MAY PRE CONGRESS 11-14 MAY 2019

HIGHLIGHTS
- New treatments for skeletal dysplasias in development
- Transition from pediatric to adult care receiving increasing attention
- Perspectives from Hypophosphatasie Deutschland a Rare Disease Patient Organisation
- Latest results from clinical trials of burosumab, a promising treatment for X-linked hypophosphatemia

ECTS/ICCBH Workshop on Rare Bone Disease Pathophysiology, Manifestation and Treatment from Childhood to Adulthood

The ECTS-ICCBH Workshop on Rare Bone Diseases was supported by Inozyme and Kyowa Kirin. The scientific content has not been influenced in any way by its sponsor.

This pre-congress workshop, chaired by Carola Zillikens, Outi Mäkitie and Nick Bishop, was focused on rare bone diseases affecting bone mineralization and fragility in children and adults.

The morning session was started by **Uwe Kornak** (Berlin) who talked about the spectrum of skeletal dysplasias and their diagnostic challenges. He described several different skeletal dysplasias in more detail, and potential therapeutic approaches.

The second speaker was **Antonella Forlino** (Pavia, Italy) who spoke about the model systems of skeletal fragility, focusing on osteogenesis imperfecta (OI). She described the potential of *in vitro* and *in vivo* models to dissect pathways involved in the OI pathogenesis (such as unfolded protein response) making a comparison among the different models. In particular, she talked about the use of zebrafish as model for OI VIII that was generated using CRIPR/Cas9-based gene editing. This model has been used to test FDA-approved drugs such as the chemical chaperone 4PBA.

The last speaker of the morning session was **Melita Irving** (London) who talked about the emerging new treatments for skeletal dysplasia.

The talk started with a "simple" question: "Who are we treating?" – the need to know our patients better, in order to treat them more effectively. To answer to this question, Melita Irving emphasised the importance of the natural history of the patients (pain, obesity, sleep disorder, etc) and of the scientific rigor (i.e. establish clear end-points). She also described the emerging treatments for hypophosphatasia (strensiq), osteochondromas (palovarotene), achondroplasia (vosoritide, TA46, TransCon-CNP and infagratinib) and metaphyseal chondrodysplasia (carbamazepine).

Klaus Mohnike (Magdeburg, Germany) started the afternoon session with a talk on the multidisciplinary management of patients with rare bone disease.

He reported on the experience of the Magdeburg Centre for Rare Bone Diseases, one of few centres dedicated to skeletal dysplasias in Germany.

Genetic skeletal disorders are now classified into 42 groups. Diagnosis is initially based on clinical/auxological symptoms before any genetic analysis. Diagnosis and subsequent care of patients should involve a multidisciplinary team including geneticists, medical specialists, psychologists, and others. Case studies were given from the aggrecan group of disorders, SHOX deficiency and hypochondroplasia. These showed how growth hormone treatment, if given with a sufficiently early diagnosis, may be beneficial for these particular disorders. However, a one-year growth target is defined to evaluate if treatment is beneficial or should be stopped.

Prof Mohnike also discussed the Magdeburg experience in caring patients with hypophosphatemic rickets, and the higher incidence of sudden infant death syndrome among people with achondroplasia. This is currently unexplained, but foramen magnum stenosis is a likely cause. Beside MRI studies, clinical and neurophysiological tests have been performed to determine how to identify children at risk, and who should receive corrective surgery. An international registry led by BOND-ERN will evaluate standard of care in infants with achondroplasia.

Martine Cohen-Solal (Paris) then discussed the transition from paediatric to adult care for rare bone diseases.

There is a strong need to provide age-appropriate services to young adults, with a purposeful and planned transition to adult care, particularly focused on preparing the patient to become responsible for their health in the most independent manner. The transition from pediatric to adult care for patients with rare bone diseases has been hardly studied. An Italian study set up a registry of 30,000 rare disease patients in the Veneto region, which showed a relative increase in prevalence of musculoskeletal disorders in adults, compared to the pediatric patients.

In most countries, adult health services are not adapted very well for rare diseases, for example equipment is not suited for patients with a low height. More generally, transition can also present challenges for parents and siblings, and concerns about the future. A US initiative Got Transition to support patients at this stage in their life was highlighted. In France, the National Reference Centre for Rare Bone Disorders supports health care providers working locally with patients and their families, providing tutorials, guidelines and communication tools. The BOND European Reference Network is taking a similar approach for rare bone diseases at the European level. Patient organisations such as OIFE can also assist during the transition period. A recently identified challenge in France is a drop in the attendance of transition visits after the first visit. However, involvement of a dedicated transition coordinator can really help a successful transition.

Gerald Brandt (President of Hypophosphatasie Deutschland (HPP) e.V) spoke via video link about the patient perspective on hypophosphatasia and osteogenesis imperfecta.

People with these disorders need multidisciplinary care, for example both need genetic counselling, specialist orthopedic, physiotherapy, dental care, psychology and speech therapy. Subtypes can be quite different and so individual, holistic care is essential. Larger clinical centres are generally better suited to providing this kind of multidisciplinary care. These naturally attract more rare disease patients, feeding back to enhanced clinical experience, data collection and excellence in patient care.

Mr Brandt talked especially about the challenges of transition, drawing on his own experience of experiencing new symptoms at adulthood and changing his care team. There is still a lack of experienced clinical centers for adults, but the large clinical centers should be the best places to organize this, assisting a smooth transition from pediatric to adult care. The emphasis in adults with hypophosphatasia (and also for osteogenesis imperfecta) is on maintaining rather than improving health. Support for leading a normal adult life, for example entering employment, is also an essential goal.

Patient organisations also play a key role in empowering and educating young adult patients as they become their own case manager. They also increasingly connect patients directly with each other, and the relevant medical disciplines, to discuss new insights and ideas.

To finish the workshop, two posters were selected for a presentation.

Timur Yorgan (Hamburg, P200) presented his study in mice lacking Plastin-3, mutations of which are involved in rare X-linked osteoporosis. The bone phenotype of these mice, analysed by microCT, showed they recapitulate the changes in cortical bone observed in the human disease, but not the changes in trabecular bone. Ex vivo study of the mouse osteoblasts suggests the cortical thinning could be due to significant downregulation of Sfrp4.

Yiming Feng (Beijing, P334) presented a case of a 40-year-old female presenting with 7 years of back pain. Radiology confirmed diffused osteosclerosis, and DXA measurements showed high bone density affecting the vertebrae, though no syndactyly was observed. Bone turnover markers were in the normal range, except beta-CTX was increased. A next generation sequencing analysis found a novel LRP4 mutation (c.1601G>C;p.R534T). Functional *in vitro* studies confirmed impaired sclerostin inhibition of Wnt signaling. Much more needs to be done to understand the mechanisms of this novel mutation, that led to the atypical features occurring in this case.

The workshop was supported by educational grants from industry.

Plenary oral presentations on rare musculoskeletal disorders

Celia Gregson (Bristol, UK) explained how a rare mutation in SMAD9 associated with high bone mass has identified the BMP signalling pathway as a potential osteo-anabolic target for osteoporosis. Her group studied a large cohort with unexplained high bone mass characterised by high bone strength and low/normal bone turnover, and without fractures or nerve compression. Whole exome sequencing identified a rare heterozygous missense mutation in SMAD9 (c.65T[C, p.Leu22Pro) segregating with high bone mass across three generations. In-silico protein modelling predicts the mutation severely disrupts the structure of the MH1 DNA-binding domain of SMAD9.

High SMAD9 expression was recorded in mouse osteocytes and zebrafish pre-osteoblastic cells, and SMAD9 variants were found strongly associated with eBMD in the UK Biobank population. SMAD9 is therefore proposed as a potential osteo-anabolic target for the treatment of osteoporosis. The preprint paper is available.

Procollagen protein misfolding in the Endoplasmic Reticulum (ER) leads to osteoblast malfunction in severe osteogenesis imperfecta. Sergey Leikin (Bethesda, USA) is investigating new therapeutic strategies for severe osteogenesis imperfecta, particularly by enhancing the autophagic degradation of procollagen by lysosomes at osteoblast ER exit sites. In a mouse model of severe osteogenesis imperfecta, his group found that knockout of ATG5, which is required for required for LC3 lipidation at the ER exit sites, only marginally affects procollagen degradation and ER stress, though significant growth retardation was still observed. Osteoblast-specific genetic manipulation of ATG5 produced a more severe phenotype. The results suggest that enhancing autophagic degradation of procollagen is a potential therapeutic strategy for osteogenesis imperfecta.

Marco Ponzetti (L'Aquila, Italy) reported some latest data on the role of lipocalin-2 (Lcn2) in Duchenne muscle dystrophy. Serum levels of Lcn2 directly correlate with mechanical unloading and inflammation, and both conditions are found in DMD patients. The MDX model of Duchenne muscle dystrophy also has increased Lcn2 serum levels. These mice were crossbred with Lcn2 knockout mice, and at 6 months of age the crossed mice had higher muscle strength, reduced muscle fibrosis, increased intact muscle fibres and higher BV/TV compared to the MDX mice. Comparable results were obtained by treating MDX mice with Lcn2-blocking-antibody. These results point to Lcn2 as a key determinant of the phenotype of the MDX mouse model.

Burosumab is a fully human monoclonal antibody to FGF23 approved for X-linked hypophosphatemia (XLH). **Ola Nilsson** (Stockholm) presented results from a phase 3 trial involving 61 children treated with burosumab vs. oral phosphate and active vitamin D. Burosumab gave significantly greater improvements in phosphate metabolism, rickets and bowing (see Figure 3). No one discontinued the treatment and adverse events related to treatment were mild to moderate in severity. See also pages 31-32 for updates on other clinical trials of burosumab.

Frank Rutsch (Muenster) reported on two global retrospective studies to describe the natural history of generalized Arterial Calcification of Infancy (GACI), due to ENPP1 or ABCC6 deficiencies. GACI is often fatal due

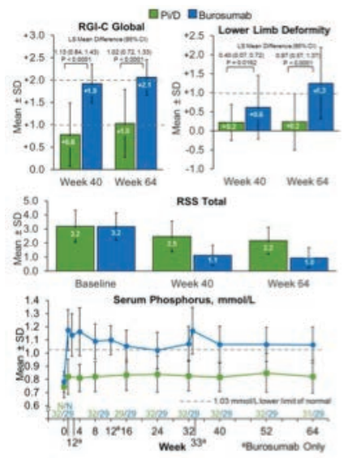


Figure 3. *Changes in serum phosphorus, rickets and lower limb deformity with burosumab vs oral phosphate and active vitamin D*

to myocardial infarction, and a majority of GACI survivors develop Autosomal Recessive Hypophosphatemic Rickets type 2 (ARHR2). There are currently no approved treatments. The studies enrolled 42 patients, of which 37 had GACI and 17 developed ARHR2. Of the 37 patients with GACI, 87% had arterial calcification and 30 had cardiac dysfunction, with 14 of the subjects dying during the study at a media age of 1.3 years. Patients with ARHR2 experienced pain (72%), bowing (53%) and short stature (29%). Data from this study will aid the design of clinical trials for an ENPP1-Fc enzyme replacement therapy.

Ulrike Baschant (Dresden) and colleagues have identified transferrin receptor 2 (Tfr2) as a regulator of osteoclastogenesis and differentiation of hematopoietic stem cells. This iron-sensing receptor which is essential for iron homeostasis, was previously identified by the Dresden group as a regulator of bone homeostasis that inhibits bone turnover by interacting with BMP signaling. Now, they have studied $Tfr2^{-/-}$ mice and found a 66% increase in the number of osteoclast precursors in the bone marrow, compared to wild type mice. Osteoclast precursors also showed increased differentiation capacity, early stage viability and reduced apoptotic events, suggesting an increased lifespan. Short-term and long-term HSC populations were also reduced in the $Tfr2^{-/-}$ mice, and competitive *in vivo* HSC transplantations showed a reduced ability for engraftment by $Tfr2^{-/-}$ cells.

Oral presentations on rare bone diseases and early onset osteoporosis

Xiang Li (Beijing) presented a retrospective study of 249 patients affected by tumour-induced osteomalacia (TIO) that were enrolled in China from 2004 to 2018. Among the patients, 14.6% had refractory disease (24 with persistent TIO, and 18 with recurrent disease). Half of the participants with refractory disease had tumours located in the lower extremities. Risk factors associated with refractory disease were determined in a multivariate model as: being female, having had a spine tumour and bone involvement, and having had lower phosphorus values.

Riikka Mäkitie (Helsinki) aimed to find new bone markers in two forms of early-onset osteoporosis associated to mutations in PLS3 and WNT1. Currently used bone biomarkers are reported as normal in the affected patients. The authors measured DKK1, sclerostin and FGF23 in 17 subjects with WNT1 osteoporosis, 14 with PLS3 osteoporosis and compared them to 39 negative control subjects. DKK 1 values were higher in PLS3 subjects, while they were normal in WNT1 subjects. FGF23 was higher in WNT1. However, it is not yet established if these markers are related to the severity of the diseases.

Tom Thacher (Mayo Clinic, Rochester) has evaluated the rickets severity score (RSS) using data obtained in a phase II clinical study of burosumab in children with X-linked hypophosphatemia. He examined the relationship of RSS with the biochemical parameters and anthropometric characteristics of the disease. He explained how RSS is obtained from radiological images of wrists and knees. The worst side is scored. Inter- and intra-operator reliability was good. Height, function (six-minute walk test), alkaline phosphatase and radiological function were also assessed at baseline, and after 40 weeks. RSS corresponded to anthropometric, biochemical and functional impairment in these subjects. Thus, it can potentially be used to monitor XLH therapy.

Demetros Braddock (Yale) described new observations of early onset osteoporosis due to heterozygous ENPP1 loss of function mutations. Three adult male patients presenting at UKE Hamburg with early onset osteoporosis and already some fractures, combined with elevated FGF23 levels and phosphate wasting, reduced BMD and trabecular and cortical thickness of the tibia and radius. All three were found to have heterozygous missense mutations in ENPP1. All these observations were recapitulated in Enpp1asj/asj mice, with changes in bone morphology apparent by 10 weeks and osteopenia developing by 23 weeks of age, along with a reduced mineral apposition rate and increased mineralisation lag time. ENPP1 deficiency therefore results in decreased bone formation, and undermineralised bone matrix, and human heterozygous ENPP1 deficiency could be clinically significant.

Melissa Formosa (Malta) has used exome sequencing to analyse the genetic mutation involved in familial osteoporosis diagnosed in a Maltese family. A novel variant p.Q287X within the KIF26B gene was identified. This was functionally studied in a zebrafish knockout model which showed reduced numbers of mineralised vertebrae compared to the wild type, decreases in BMD, bone volume/tissue volume, and higher osteoclast activity. KIF26B is involved in intracellular transport and cell division, and further study might identify novel targets for osteoporosis treatment.

Parveneh Ebrahimi (Malmo, Sweden) has performed a pilot study to compare DNA methylation in blood and bone. This approach may provide a more accessible way to study the epigenetics of bone strength. Blood and bone samples were analysed from 12 elderly females undergoing hip replacement surgery and were analysed for DNA methylation across 850 k CpG sites. Over 29,000 similar methylation levels (SMPs) were identified across 7000 genes, including ESR1, EN1 and WNT16 previously identified in large GWAS, and 12,000 SMPs located near SNPs associated with bone phenotypes. This approach may be useful for larger cohort studies of skeletal strength in the future.

Expert forum focuses on X-linked hypophosphatemia

The XLH Expert Forum was supported by Kyowa Kirin in the form of an educational grant. The scientific content has not been influenced in any way by its sponsor.

In the ECTS 2018 congress, exciting results were presented from clinical trials of burosumab, a new therapy for rare inherited bone disease X-linked hypophosphatemia (XLH). In ECTS 2019, an expert forum was convened to discuss the clinical diagnosis and management of XLH.

Signe Sparre Beck-Nielsen (Aarhus, Denmark) explained that XLH is a rare congenital disease (prevalence 1:21000) linked to chromosome X that can affect children and adults.

XLH is caused by a PHEX mutation. The absence of active PHEX induces an increase in local mineralization inhibitors and an increase in FGF-23 levels.

Increased FGF23 will decrease calcitriol levels and phosphate (Pi) absorption. FGF23 also increases urinary Pi excretion, both effects leading to profound hypophosphatemia. Moreover, autocrine/paracrine actions of FGF23 induce an increase in mineralization inhibitors.

The consecutive decrease in chondrocyte formation and hydroxyapatite synthesis will lead to severe rickets in children and osteomalacia in adults.

Diagnosis of XLH is confirmed by identification of an inactivating mutation in PHEX. However, XLH patients may go undiagnosed. In a relatively large Danish study, 20% of XLH patients were identified after family screening. Usually, a history of rickets, dental abscesses and serum/urine abnormalities led to the diagnosis after testing for the XLH mutation.

Typical clinical characteristics in children consist of severe skeletal deformations, short stature and spontaneous dental abscesses. Symptoms in adults can consist of genu varus/valgus, tibial and femoral bowing, coxa vara, intoeing and osteoarthritis/joint pain.

When BMD is measured by classical DXA, lumbar values are often surprisingly increased. This is because DXA measures areal BMD, explaining why BMD can be artificially increased because of enthesopathies/ calcifications and an increase in bone size. BMD measurement by HRpQCT shows that volumetric BMD is actually decreased.

Surprisingly, the risk of fractures appears to be reduced. In the Danish study, the RR was 0.46. This reduction in the risk of fractures is probably a consequence of significantly wider bones.

Conventional treatment consists of oral phosphate supplements and calcitriol administration. A close follow-up is mandatory. The introduction of burosumab, an antibody against FGF23, is evidently a more specific therapy. This has already been shown to be more efficient in children and also probably in adults. It is not recommended to treat adult patients without overt symptoms. Treatment could reduce the occurrence of dental abscesses, but it increases the risk of secondary hyperparathyroidism (HPT).

For clinical practice recommendations for the diagnosis and management of XLH, please refer to the recently published consensus paper.

Peter Kamenicky (Paris) then discussed how XLH is a multifaceted metabolic disorder.

XLH is frequently associated with secondary and sometimes tertiary hyperparathyroidism (HPT), due to "overtreatment" with phosphate salts.

Parathyroid hyperplasia is due to low calcitriol levels and phosphate therapy, although the exact pathophysiology is unknown. In a study at his centre (Lecoq, *et al*. manuscript in preparation), Peter Kamenicky found that 17/68 (25%) of the XLH patients had biochemical secondary HPT. There was a positive relationship between calcium and PTH levels, which is evidently abnormal. 10% of the patients were hypercalcemic and there was an increased incidence of nephrocalcinosis. Parathyroid hyperplasia appeared to be as frequent as parathyroid adenomas at surgery.

FGF23 itself has also several metabolic effects. Higher FGF23 levels correlate with increased fat mass, larger waist circumference and an adverse lipid profile. Two thirds of adults with genetic hypophosphatemia are overweight or obese.

Lastly, FGF23 induces left ventricular hypertrophy in mice, but this possible effect has not been adequately studied in man.

Working Group on Rare Disorders with Increased/ Ectopic Bone Formation

This Working Group was supported by Inozyme. The scientific content has not been influenced in any way by its sponsor.

This pre-congress Working Group provided a comprehensive overview of the many rare disorders involving increased or ectopic bone formation.

Gretl Hendrickx (Hamburg) described the most important cranial hyperostosis disorders. Previously these were characterised mostly according to their radiological/ phenotypic characteristics, but there is now a shift to gene-based diagnostics, including prenatal screening.

In particular, Gretl Hendrickx discussed disorders with significant cranial hyperostosis and impaired bone resorption. Calvarial hyperostosis leads to prominent frontotemporal bones, mostly a cosmetic issue, and the molecular basis of this disorder remains unknown. In contrast, the very rare condition of hyperostosis cranialis interna has been described in only 14 individuals and is caused by mutation of SLC39A14, which encodes a Zn transporter. Cranial hyperostosisis also observed in osteopetrosis and pycnodysostosis.

Lothar Seefried (Wuerzburg, Germany) then described the various focally sclerosing bone disorders, including osteochondromas and Camurati-Engelmann disease.

Corinna Grasemann (Essen, Germany) presented two cases of juvenile Paget's Disease of Bone, an extremely rare form of the disease involving overstimulated osteoclasts. Treatments include pamidronate to help reduce ALP levels and denosumab to reduce osteoclast activity.

Finally, **Martina Rauner** gave an update on fibrodysplasia ossificans progressiva, where the body becomes entombed by extreme ectopic bone formation. There are no effective treatments, but trials with palovarotene are giving very promising results, and a phase 3 study is due to start at the end of 2019 (see ECTS congress 2018 report).

HIGHLIGHTED ORAL POSTER PRESENTATION

Ludovic Martin (Paris, P132) has screened natural compounds *in vitro* in order to identify new drugs able to interact with the FGFR3 signalling pathways, especially for treatment of achondroplasia. Among the compounds studied, Theobroma cacao extracts were active and after further purification the flavanol epicatechin is identified as the most relevant compound. This has been further studied in human chondrocytes, mouse cells expressing normal or mutant Fgfr3, and ex vivo Fgfr3 mouse femur cultures. The results suggest epicatechin acts mostly on proliferative chondrocytes inside the femoral growth plate.

In other news...

Results from two phase 2 trials performed in children and one phase 3 RCT in adults with X-linked hyposphosphatemia treated with burosumab were published. The two phase 2 studies published by Carpenter TO, et al. and Whyte MP, et al. showed efficacy of burosumab in improving serum phosphate, tubular phosphate reabsorption, rickets and physical function and preventing growth decline in children. Insogna KL, et al. published the 24-week results from a phase 3 RCT in adults, showing that burosumab treatment is associated with increase in serum phosphate, and with a higher fracture healing vs placebo.

Ralston SH, et al. published a clinical guideline on the diagnosis and management of Paget's disease of bone. They performed a systematic review on the diagnosis and treatment of Paget and made recommendations on the main laboratory and imaging exams to be performed and on pharmacological and surgical treatment of the disease. The guidelines have been endorsed by ECTS, IOF, ASBMR, the UK Bone Research Society and the British Geriatric Society.

ECTS 2019 Supported Charity

The Hungarian Federation of People with Rare and Congenital Diseases (HUFERDIS, in Hugarian RIROSZ) is our supported charity this year at ECTS 2019.

HUFERDIS is a network of 55 Hungarian rare disease patient organisations and individuals active in the field of rare diseases. There are around 700,000 rare disease patients in Hungary. HUFERDIS activities include support for patients, organization of common programmes and events, supporting research and patient advocacy, and public awareness campaigns. Rare Disease Days are organized each year and in 2016 HUFERDIS established the "Lifebelt" Information Centre and Helpline for Rare Disease Patients.

The ECTS 2019 indoor soccer tournament raised almost €1300 for HUFERDIS. Well done!

Bone and Cartilage Biology

ECTS CONGRESS | HUNGARY BUDAPEST 10 MAY PRE CONGRESS 11-14 MAY 2019

HIGHLIGHTS

- Progress on understanding the trans-differentiation of hypertrophic chondrocytes to osteoblasts
- The role of senescent cells in delayed cartilage healing
- Big Data's Secret – large phenotyping and clinical research projects yielding massive datasets for the research community

Basic science update on bone biology

Annegreet Veldhuis-Vlug (Amsterdam) described the most recent advances in our understanding of the role of bone marrow adiposity (BMA) during ageing, and in bone disease.

During ageing, BMA increases as BMD decreases, gradually in men and accelerating at menopause in women. Similar changes are observed in other conditions with high fracture risk, such as osteoporosis, anorexia nervosa and following bariatric surgery.

The current hypothesis of the mechanism behind this inverse balance in bone marrow adiposity and bone mass is a shift in the differentiation of the skeletal stem cell from the osteoblastic to the adipogenic lineage.

Several studies have already identified gene expression changes in skeletal stem cells that would affect their differentiation to bone cells or adipocytes. For example, a reduced *Pgc1a* expression was found in ageing mice, which increases adipogenesis in the skeletal stem cells of knockout mice.

Hormonal changes during ageing certainly contribute to these changes. Postmenopausal estrogen treatment has been shown to decrease BMA, even after just two weeks of treatment. Similarly blocking FSH decreases reduces BMA. This year, PTH treatment was also shown to change the balance from adipogenesis to osteoblastogenesis, and also induce lipolysis of mature adipocytes, which is evident from their reduced size. Annegreet Veldhuis-Vlug also discussed studies investigating how high fat diets might affect BMA, and how the response of BMA to a high fat diet differs compared to visceral fat, in terms of inflammation and insulin resistance.

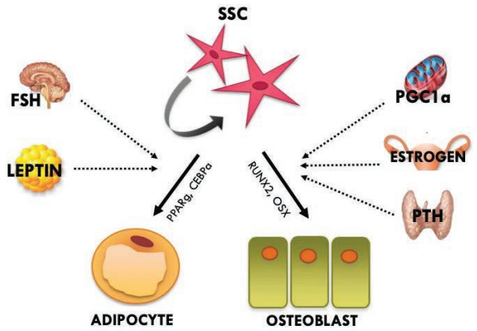


Figure 4. *Factors influencing differentiation of skeletal stem cells (SSC) to an osteoblastic or adipocyte lineage*

The talk concluded with some interesting questions for future research, including whether adipocytes can de-differentiate and re-differentiate, as revealed in a recent study of mammary gland adipocytes. Finally, from a clinical perspective, targeting lineage allocation to shift the balance of adipocytes and osteoblasts in bone marrow could be an interesting therapeutic approach for osteoporosis in future.

Laurent Beck (Nantes, France) aimed to answer three simple questions in his talk on this very broad subject: why should phosphate (Pi) sensing exist, how is this achieved, and what are the Pi sensor candidates?

Pi has several essential biological functions and 85% within the human body is found in the skeleton. The main pathological issues with Pi in mammals are in fact due to overload or Pi toxicity, causing for example vascular calcifications or chronic kidney disease in humans. Pi sensing helps an organism maintain balanced Pi levels, and mammals can take advantage of bone as a Pi storage organ.

Pi itself is a signaling molecule, regulating osteoblasts, chondrocytes and processes in other organs apart from bone. Pi sensing mechanisms can involve binding of Pi on a membrane receptor, Pi transport into the cell and/or activation of Pi-dependent intracellular signaling pathways. While it is clear that Pi sensing is taking place, the sensors involved are only beginning to be identified. While CaSR was recently described to bind Pi at the membrane, and IP6K2 suggested as being an intracellular Pi sensor, Laurent Beck's group has demonstrated that PiT1 and PiT2, the two high-affinity Pi transporters that are expressed in bone, are involved in phosphate sensing, modulating by Pi binding rather than Pi transport, and are involved in Pi-dependent FGF23 secretion *in vivo*.

Christine Hartmann (Muenster, Germany) then explained how hypertrophic chondrocytes can develop a "second career" as osteoblasts.

Hypertrophic chondrocytes were previously thought to undergo cell death, following their contribution to endochondral ossification in the cartilage growth plate. However, it was first observed in 1875 that chondrocytes can potentially become osteoblasts. Genetic studies by ablation of Sox9 have shown that Sox9 can inhibit this process. Lineage tracing studies by a number of labs in the more recent years have demonstrated that hypertrophic chondrocytes can differentiate into cells expressing osteoblast markers. These studies have found the trans-differentiated osteoblast- and osteocyte marker expressing cells in trabecular and endosteal bone, but never in the periosteal bone.

So far, this process is thought to be important for embryonic bone development, and in fracture healing. Christine Hartmann's group has investigated the role of β-catenin in the differentiation of chondrocyte-derived osteoblasts. Mouse models have been developed with deleted or stabilised β-catenin in the hypertrophic zone. In each case an extreme phenotype is generated, either a severe loss of trabecular bone or blockage of bone marrow cavity formation, respectively. These phenotypes are in part due to changes in osteoclastogenesis at the chondro-osseous front, via negative regulation of Rankl by β-catenin. Manipulation of the Rankl/Osteoprotegerin system in hypertrophic chondrocytes partially reverses these respective phenotypes. Yet, trabecular bone formation is still compromised by deletion of Rankl in hypertrophic chondrocytes and lineage tracing experiments showed that β-catenin is required for the chondrocyte to osteoblast trans-differentiation process.

It is a current hot research topic to determine exactly how the trans-differentiation process occurs, for example whether this is via a stem cell-like state, if a specific subpopulation is involved, and the precise molecular mechanisms by which β-catenin controls the trans-differentiation. It will also be of interest to determine to what extent this process is involved in diseases such as osteoarthritis (OA) and osteoporosis. If this process is involved in the remodelling of the articular chondrocytes during OA, then drugs modulating this process may be useful tools for treating OA.

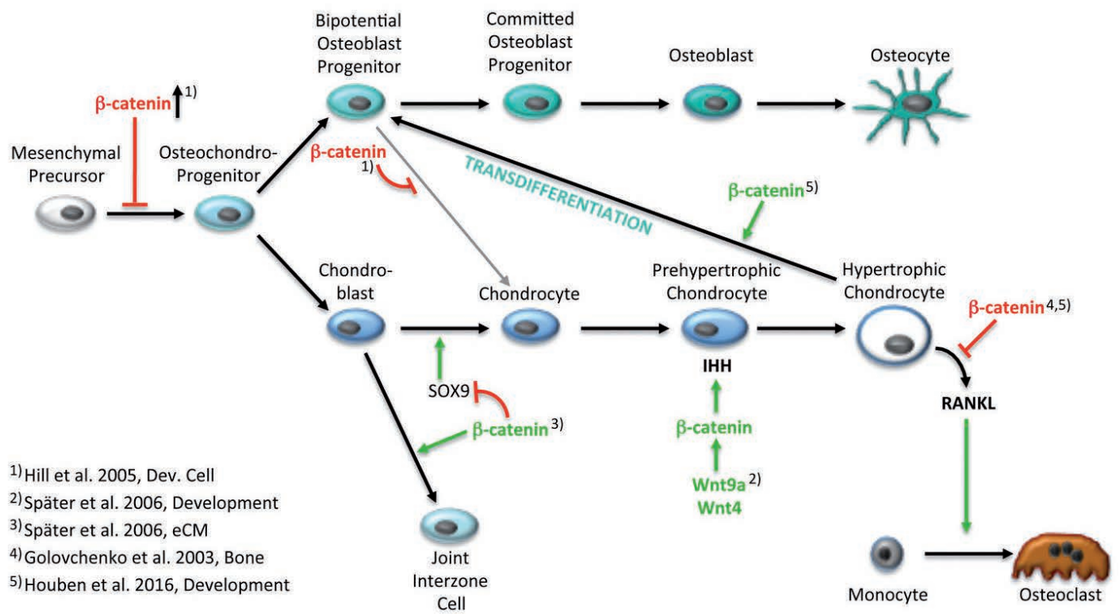


Figure 5. *Roles of Wnt/β-catenin signalling during skeletal lineage differentiation (Christine Hartmann)*

After the congress we asked Christine Hartmann more about her research and thoughts about progress in this field.

Please tell us more about your research group at the University of Münster

Since 2012 I am a full professor at the University of Münster. I am part of the medical faculty and work at the Institute of Musculoskeletal Medicine, heading the group of Bone and Skeletal Research.

The general research interest of my group is understanding the role of primarily Wnt-signalling in skeletal development during embryogenesis. Over the past years we have made major contributions in this research field and showed that β-catenin the central player of the Wnt/β-catenin pathway is playing a role at multiple steps within the mesenchymal lineages (osteoblast-, chondrocyte- and joint-lineage) of the skeleton. One of its main functions appears to act in a permissive way suppressing chondrogenesis with in the precursors of the osteoblast- and synovial joint lineage thereby enabling their differentiation, as loss of β-catenin results in a differentiation of precursors of these two lineages into chondrocytes.

In addition, β-catenin plays multiple roles in differentiated chondrocytes: it is involved in the regulation of Indian hedgehog (Ihh), a molecule that plays a central role in skeletogenesis. Amongst others, Ihh links chondrocyte maturation to perichondrial osteoblastogenesis. In hypertrophic chondrocytes, β-catenin has dual functions; on the one hand it negatively regulates RANKL thereby controlling osteoclastogenesis locally at the chondro-osseous border. On the other hand, it is required for the differentiation of chondrocyte-derived osteoblasts. Currently, we are also studying the role of certain Wnt ligands degenerative and inflammatory diseases of the joint and in bone homeostasis.

How did you become interested in this area of research?

I did my undergraduate and graduate work in a Drosophila lab, studying early patterning events and organogenesis. It was then that I discovered my interest in developmental biology. As a post doc I moved to the US and joined the laboratory of Cliff Tabin at Harvard Medical School. His lab was at that time well known for their work on the molecular signals involved in vertebrate limb development. One of my original projects was to look at Wnt signalling in proximal-distal and dorso-ventral patterning of the limb. Yet, my experimental results were pointing into another direction – a role for Wnt signalling in skeletogenesis. By chance, this work led to the discovery of the role of Wnt9a (also known as Wnt14) in joint development and maintenance. When I started my own lab at the Institute of Molecular Pathology in Vienna, we moved from using the chick as a model system, to mouse.

What particular challenges were involved in progressing these studies and obtaining the findings so far?

These in vivo studies require complex breeding steps which are fairly time-consuming as they involve many different genetic alleles, a Cre-allele, a knock-out and a floxed allele for β-catenin, and a reporter allele, allowing to trace the progeny of β-catenin deficient cells.

Your presentation highlighted that we still don't understand the actual trans-differentiation mechanism. What new kinds of tools or studies could really help make progress on this question?

An in vivo live tracking system, allowing to follow the fate of a particular cell as it differentiates, would be a fantastic tool. Single-cell analysis of hypertrophic chondrocytes may also be an interesting tool to study whether distinct populations of hypertrophic chondrocytes exist, and to identify candidates regulating this process.

What might be the eventual translational impact of this research?

Currently, we know that this process of chondrocyte trans-differentiation is relevant during embryonic development and also for repair processes such as fracture healing. Yet, this process could also play a role in diseases such as osteoporosis or osteoarthritis. Particularly, in the latter it is still not clear how the articular cartilage gets replaced by bone. Drugs stimulating this process of chondrocyte-to-osteoblast transition may potentially be useful in combination with other drugs as therapeutics in fracture healing, while those preventing such a transition may be useful therapeutics in preventing osteoarthritis progression.

How often do you come to ECTS congress, and how did you find the congress this year?

This is my first time at an ECTS congress this year in Budapest, but it will certainly not be the last ECTS congress that I attend. A few years back, I attended the ECTS PhD training course as a lecturer and very much enjoyed it, and I have sent my PhD students to these courses since. What I enjoyed most about the ECTS congress is that it combines clinical and basic research in an excellent way. The organizing committee did an excellent job, putting an interesting program together and inviting superb speakers.

HIGHLIGHTED ORAL POSTER PRESENTATION

Ingvild Kristine Blom-Hogestol (Oslo, Norway, P161) studied 30 patients undergoing Roux-en-Y gastric bypass at baseline and 1 year after surgery in order to evaluate changes in bone marrow adipose tissue (BMAT) by performing bone marrow biopsy at the iliac spine. Total tissue volume of the BMAT was evaluated. BMAT was positively associated with HbA1C and negatively with lumbar spine and femoral neck BMD. BMAT significantly decreased one year after surgery, with a more pronounced decrease in patients with more weight loss, and in females compared males (females were all pre-menopausal).

In other news...

Its reported that osteoclasts are more long lived than previously thought. During embryonic development, osteoclasts form from the erythroid-myeloid progenitors and continue to live for a long time via fusion with other monocytic precursors. On average, about 1% of osteoclasts take up one nucleus per day, and osteoclasts only take up one nucleus at a time. As osteoclasts on average have about 5 nuclei, it takes about half a year to renew the nuclei of one osteoclast. Finally, osteoclasts also lost nuclei during the experimental period, suggesting that there is a constant turnover of nuclei in osteoclasts. These new insights into osteoclast origin and maintenance also proposed a new treatment strategy for osteopetrosis, suggesting that possible transfusion of monocytes would suffice to reduce bone mass. This was demonstrated in a model of cathepsin K-based pycnodysostosis, in which pycnodysostotic mice gained osteoclasts after transfusion of monocytes.

In a recent report from Japan, a new feature of RANKL was identified: its function as a receptor. These studies have identified that RANKL can signal via its intracellular domain upon activation of RANK, which is presented on secreted vesicles from osteoclasts. Thus, this provides a possible explanation of the suppressed bone formation observed when suppressing osteoclast function. Separating RANKL forward (osteoclast) and reverse (osteoblast) signalling could provide a new treatment modality suppressing osteoclast activity, but maintaining osteoblast function.

Oral presentations on metabolism, diabetes and bone quality

Type 2 diabetes (T2D) is associated with higher fracture risk, yet patients have a normal to high BMD making it hard to identify those at risk. **Eva Maria Wölfel** (Hamburg) has characterised post-mortem femoral cortical bone samples from 12 T2D cases, and 11 age-matched controls, by 3D micro-CT and Fourier-transform infrared spectroscopy. This analysis identified a sub-group of T2D individuals with exceptionally high cortical porosity compared to the other T2D and control samples. These individuals also had areas of low calcium content and low Young's modulus in the endocortical region.

Patients with type 2 diabetes (T2D) experience increased fracture risk despite presenting with normal or high BMD pointing towards impaired bone quality. Eva Maria Wölfel (Hamburg) characterized post-mortem femoral cortical bone from individuals diagnosed with T2D and age-matched controls with micro-CT, backscattered electron imaging and Fourier-transform infrared spectroscopy. Analyses revealed a high cortical porosity subgroup with a changed mineralization pattern compared to T2D cases with no morphology phenotype and controls. In the T2D cases with high porosity, resorption was initiated in the endocortical cortex. In this compartment, a lower degree of mineralization, higher mineral heterogeneity and reduced stiffness was observed.

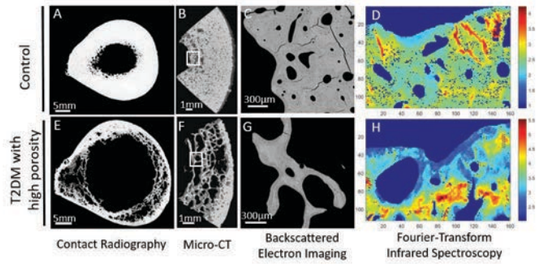


Figure 6. *Multi-length scale analysis of cadaveric human femoral cortical bone from control and T2D cases*

As discussed in a workshop in the ECTS 2018 congress, Roux-en-Y gastric bypass (RYGB) used to treat obesity and T2D typically induces a decrease in aBMD and increases the fracture rate. **Ingvild Kristine Blom-Hogestol** (Oslo) has studied the changes bone material strength in 34 individuals before and after RYGB, using impact microindentation. Of these, 13 individuals were diagnosed with T2D. In fact, one year after surgery, bone material strength index was found to improve by around 6% in all participants. Still, aBMD was found to decrease at the lumbar spine, femoral neck, hip and total body, and bone turnover markers increased.

There is evidence from animal studies that GLP-1 receptor agonist Liraglutide, used to treat T2D, might

increase BMD by suppressing bone resorption. **Katrine Hygum** (Aarhus, Denmark) has investigated this effect in 56 T2D patients receiving Liraglutide therapy or placebo over 26 weeks. Bone turnover marker P1NP decreased significantly in the Liraglutide group for the first 4 weeks but then increased to elevated levels by week 13. This was accompanied by a decrease in body weight, but no change in total hip BMD. In contrast, body weight did not change, and hip BMD decreased in the placebo group. No change in CTX was measured in either group. Therefore, no effect of Liraglutide was found on bone resorption, but treatment may preserve hip BMD, mediated by changes in body weight.

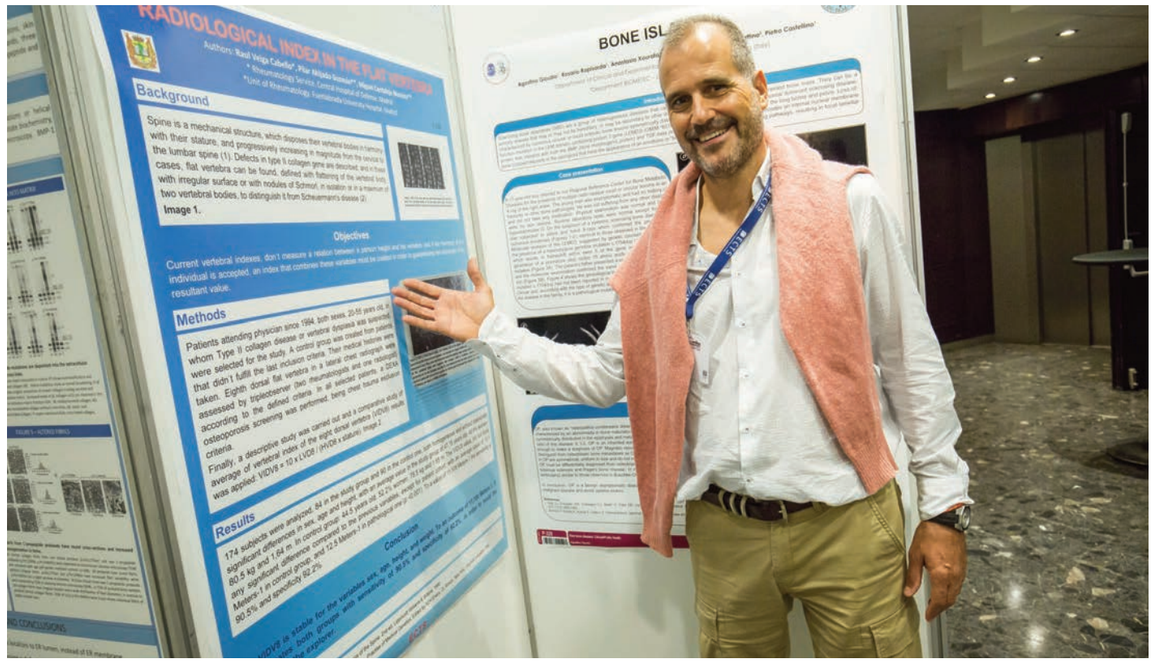
Natalia Campos-Obando (Rotterdam) has investigated whether coronary artery calcification (CAC) has an association with serum phosphate (Pi) levels. Using the Mendelian Randomization approach, analysis of data obtained within the Rotterdam study I population cohort (n=1693) has determined that Pi is causally related to CAC, including in individuals without hyperphosphatemia or chronic kidney disease, and with a stronger effect in men. Further research into the sex difference and mechanisms is required.

Nicolas Bonnet (Geneva) has previously demonstrated in mouse models that cathepsin-K dependent periostin degradation limits the increase of periosteal bone formation induced by RANKL. This observation has now been investigated in 695 post-menopausal women of the GERICO cohort, with circulating levels of cathepsin-K digested periostin measured by ELISA, and trabecular and cortical bone parameters measured by HR-pQCT. Subgroups received treatment with denosumab (n=19) and bisphosphonates (n=20). Overall, an inverse association between periostin degradation and periosteal diameter was found, as observed in the mouse model. Inhibition of RANKL by denosumab reduced periostin degradation and limits the reduction in cross sectional areas.

Jens-Jacob Lindegaard Lauterlein (Odense, Denmark) and colleagues aimed to determine if the high bone mass phenotype due to gain of function mutations in LRP5 progresses with age. The study involved bone phenotyping of 15 LPR6-HBM patients by DXA and HR-pQCT, with follow-up after an average 5.8 years later. No significant differences in BMD or HR-pQCT were observed between the two time points, except for increased trabecular vBMD and BV/VT. It appears that in adulthood, the LRP5-HBM phenotype stabilises.

HIGHLIGHTED ORAL POSTER PRESENTATION

Janina Vavanikunnel (Basel, Switzerland, P001) examined the association between bone turnover markers and parathyroid function in a cohort of 110 patients with type 2 diabetes. They found lower P1NP, CTX, magnesium and PTH compared to controls. The only independent predictor of bone turnover in the multivariate analysis was PTH and hypomagnesemia was associated with hypoparathyroidism; serum phosphorus was slightly higher in diabetes patients, while calcium, creatinine and vitamin D levels were not different. Authors conclude that low bone turnover is associated with functional hypoparathyrodism in type 2 diabetes.



Update on Big Data projects

ECTS CONGRESS HUNGARY BUDAPEST 10 MAY PRE CONGRESS 11-14 MAY 2019

An ECTS-IFMRS session "Big Data's Secret" updated us on the latest progress of major research initiatives exploiting Big Data, low cost gene sequencing and standardised mouse phenotyping.

Graham Williams (Imperial College London, recipient of ECTS Steven Boonen award 2018) reported on the recent achievements of the International Mouse Phenotyping Consortium (IMPC).

IMPC builds on the efforts of the International Knockout Mouse Consortium (IKMC), which aims to mutate all protein-coding genes in C57Bl/6 mouse embryonic stem cells as a global research resource. To date, over 20,000 mouse embryonic stem cell lines, 28,000 targeting constructs and 7980 knockout lines have been generated.

The IMPC involves 19 centres in 11 countries who perform phenotype analysis of the mouse lines generated by IKMC, using standardised protocols, in a collaboration that will continue at least until 2030. Detailed Bone phenotype analysis is being performed by the Origins of Bone and Cartilage Diseases (UK) project using a standardised phenotyping workflow involving digital X-ray microradiography, micro CT for bone microarchitecture, and 3-point bending and compression testing. Complementary studies are undertaken by the KOMP BoneBase (USA) project.

To date, almost 1000 knockout mouse lines have been phenotyped by the OBCD project, with approximately 11% displaying significant abnormalities affecting bone structure and strength. Up to 55% of deleted genes have not previously been annotated to have a function in bone and have not been associated with abnormal skeletal phenotypes.

For example, the *Creb3l1 KO* mouse line has one of the most severely abnormal bone phenotypes and this gene was found to be associated with BMD in GWAS analyses. Furthermore, a mutation in *CREB3L1* has recently been identified in a patient with osteogenesis imperfecta confirming the concordance between mouse and human genetic data, whilst *Creb3l1* expression was also enriched in osteocytes.

Further new genes of interest include *DAAM2*, which is involved in canonical and non-canonical Wnt signalling, and *SLC20a2*, which encodes a transporter essential for phosphate-mediated regulation of FGF23 secretion. Deletion of *Daam2* and *Slc20a2* resulted in bone fragility with a disproportionately mild effect on BMD, indicating these genes may represent novel determinants of bone strength via their effects on bone quality.

19 phenotype parameters
(Reference data from >350 female 16 week-ol C57BL/6N wild-type mice

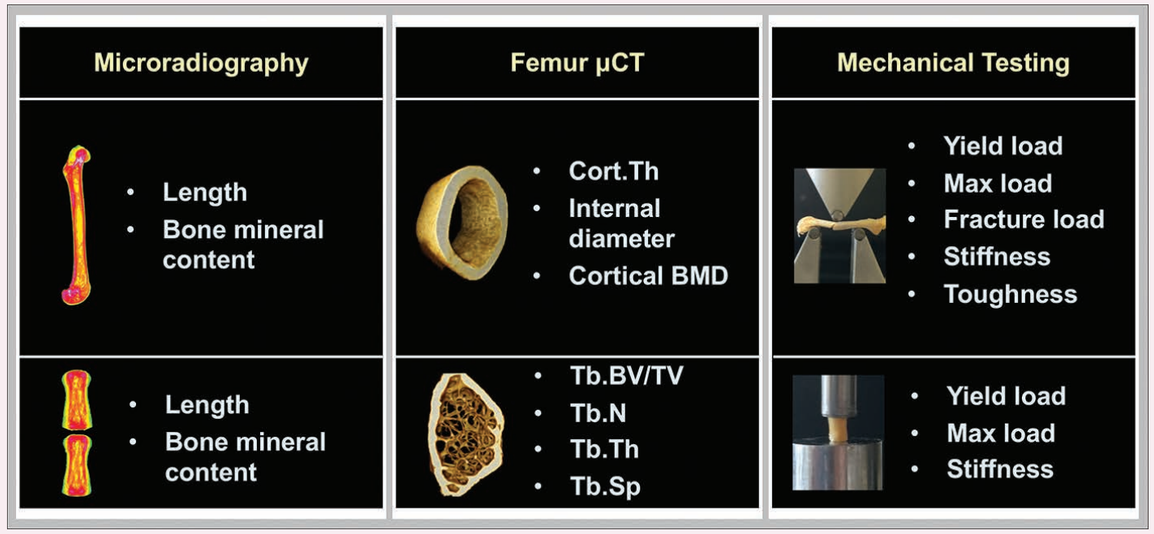


Figure 7. *OBCD bone phenotyping parameters (Graham Williams)*

Jonathan Tobias (Bristol, UK) then updated us on the latest activities of the UK Biobank related to the musculoskeletal field.

The UK Biobank has around 500,000 participants aged 40-69. A standard set of clinical measurements and genotyping has been performed in all participants, as well as collection of lifestyle data and linkage to electronic health records.

Subsets of the population have undergone more specialised measurements. For example, in 100,000 subjects, DXA imaging has been performed of the whole body, hips, knees, lumbar spine and lateral thoracolumbar spine has been performed, to obtain multiple data related to musculoskeletal disorders. This data is being further analysed in the UK AUGMENT study, to identify novel genetic determinants, especially for spinal fractures, joint shape and scoliosis.

Several important studies have already been published using UK Biobank data. A recent study revealed 518 loci associated to BMD as estimated by ultrasound measurements of the heel (eBMD), of which 301 were novel. In terms of functional follow up of newly identified genes, as reported at ECTS 2019, a *SMAD9* mutation is associated with high bone mass, and genetic variation in *B4GALNT3* influences circulating levels of sclerostin, both of which were identified as eBMD loci in UK Biobank.

Genome wide association studies (GWASs) in UK Biobank have also been used to identify novel genetic influences on osteoarthritis, suggesting potentially novel therapeutic targets. One of the new OA hits identified was in SOX9, recently found to be associated with hip shape in a separate GWAS, pointing to a potentially novel pathogenic pathway for OA.

HIGHLIGHTED ORAL POSTER PRESENTATION

Elizabeth Curtis (Southampton, UK, P220) investigated the association between birthweight (self-reported), limb muscle mass and abdominal adiposity (assessed by MRI) in 1513 men and 2286 women aged 40-69 years form the UK Biobank. Birthweight was significantly associated only with high muscle volume and not with measures of adiposity. These data suggest that interventions for optimizing birthweight are warranted for preventing future sarcopenia. There are no data on the gestational age and future analyses will clarify whether birthweight could be considered a major or minor factor influencing muscle strength in the middle age.

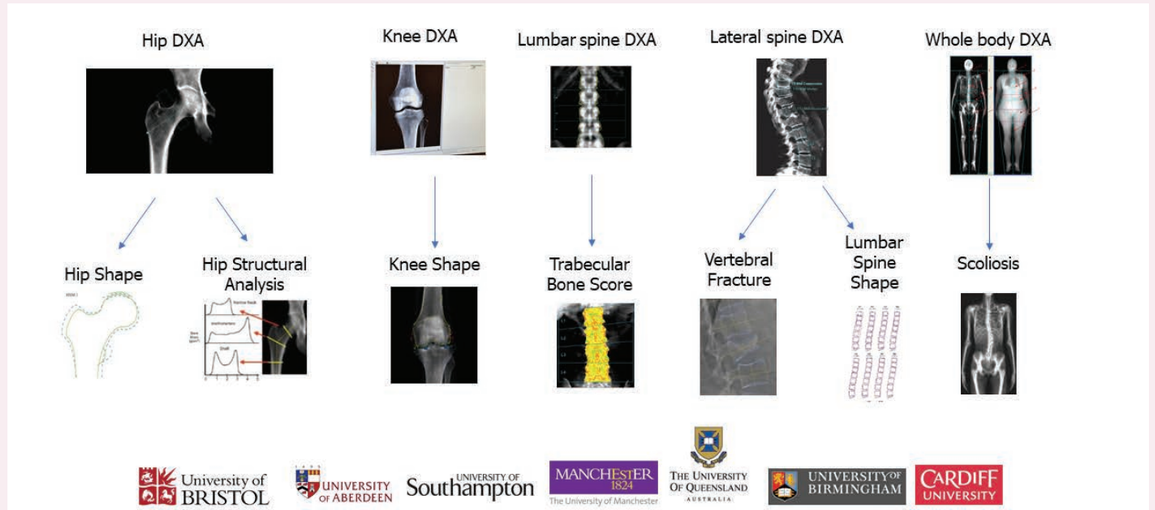


Figure 8. *AUGMENT study: generation of DXA endophenotypes for n=100,000 in the UK Biobank (Jonathan Tobias)*

Oral presentations on bone pathophysiology

It has been previously shown that osteoclasts have a role in inflammatory response. **Maria-Bernadette Madel** (Nice, France) presented new data from transcriptomic profiling of two osteoclast subsets. This identified an absence of expression of the fractalkine receptor CX3CR1 in 75% of inflammatory osteoclasts. Transgenic CX3CR1 knockout mice were found to have higher BV/TV and cortical thickness than wild type mice, and reduced differentiation of inflammatory osteoclasts. Expression of CX3CR1 in inflammatory osteoclasts reduced their ability to induce TNFα-producing $CD4^+$ T-cells. Planned RNAseq analysis aims to identify the pathways involved in immunomodulation by osteoclasts, shedding more light on the mechanisms of inflammatory bone destruction.

Alfredo Cappariello (L'Aquila, Italy) reported that breast cancer-derived extracellular vesicles (EVs) suppressed osteogenic markers but promoted a pro-inflammatory profile in osteoblasts. Further, they stimulated osteoclastogenesis as well as the angiogenic potential of endothelial cells *in vitro* and *in vivo*. Thus, EVs are important communication tools between tumour and bone cells.

Jie Zheng (Bristol, UK) presented results of a Mendelian randomization analysis of GWAS data (10,584 individuals), which reveals a causal influence of circulating sclerostin on BMD and fractures. Two novel plasma sclerostin loci, B4GALNT3 and GALNT1, which encode glycosylation enzymes, were identified. This data suggests that strategies targeting these enzymes to reduce circulating sclerostin may be useful for the treatment of osteoporosis.

Komal Waqas (Rotterdam) has investigated the association of advanced glycation end products in the skin to fractures, BMD, and trabecular bone score (TBS). AGEs form during life as pathological collagen crosslinks making skin (and bone) less flexible. This study performed in the Rotterdam study cohort with almost 3,000 participants showed that skin AGEs are associated with vertebral fractures, but not BMD or TBS. Surprisingly, skin AGE content also did not associate with type 2 diabetes, which has been shown in other studies. Thus, more research is required to address this discrepancy.

Liliana Mellor (Madrid) previously generated a mouse model of psoriatic arthritis which has elevated levels of the S100A9, as found in human psoriatic skin samples. Neutrophils and keratinocytes are the main cell types expressing S100A9. To investigate the mechanisms involved, two further mouse models were developed, with global or inducible epidermal deletion of S100A9. The global knockout mice developed more severe inflammatory skin disease compared to the other two models, however their joints were protected from psoriatic arthritis. These results indicate that neutrophil-derived S100A9 could play a protective role in psoriasis, while keratinocyte-derived S100A9 could be detrimental to synovial joints and bone.

Natalie Butterfield (Imperial College London) has developed a new method to quantitatively assess osteoarthritis. So far, only OARSI histological scoring systems were used. Their group has now combined several approaches that assess articular cartilage volume and subchondral bone, and on top are feasible in a high-throughput context. After validation of this approach using a DMM model of osteoarthritis, they have phenotyped 50 knock-out lines from the International Mouse Phenotyping Consortium and identified several novel genes that may be associated with OA.

Oral presentations on local and systemic regulators of bone turnover

Michael Thelen (Berlin) has investigated whether the loss of response to mechanical unloading observed in aged bone tissue is also found in disorders of premature ageing. This has involved studies of the GorabPrx1 mouse model of the progeroid rare disorder gerodermia osteodysplastica, using microCT, histomorphometry and imaging of the osteocyte lacuna-canicular network.

Upon loading, control mice developed a bone anabolic response with greater cortical area and a doubling of the trabecular bone volume fracture. This anabolic response was not observed under the same loading conditions in the GorabPrx1 mouse model. Osteocyte numbers were found roughly doubled in these mice, and displayed a lower canalicular density and

connectivity. This altered lacuna-canicular network may prevent proper strain amplification through the bone and therefore an anabolic response, so contributing to bone fragility under loading in gerodermia osteodysplastica.

Maaike Schilperoort (Leiden, Netherlands) presented data from an investigation in mice to determine if bone health could be affected by disturbances to the circadian clock. Tibiae were obtained from mice sacrificed at different times over a 24-hour time period. Gene expression analysis found diurnal variations of clock-related genes, as well as genes involved in osteoclastogenesis, osteoblast proliferation and function, and osteocyte function.

Subsequently, mice were subjected to weekly 12-hour disruptions to their normal light-dark cycle over 16 weeks. In these mice, clock gene expression was disrupted or attenuated, and serum markers of bone formation and bone resorption were reduced. Significant changes to trabecular bone structure were determined by microCT. Together these results suggest that circadian disruption negatively affects bone turnover and bone structure.

Melanie Haffner-Luntzer (Ulm, Germany) has previously demonstrated the effect of chronic psychosocial stress on bone growth, and has now investigated the role of the gut microbiome in mediating this effect. Fecal transplantation was performed from non-stressed mice (single housed) to mice subjected to the chronic-subordinate-colony-housing (CSC) paradigm, and from single housed mice to a CSC group. Saline was used as an additional control. Serum markers of immunological activation KC, IL-6 and MCP-1 were found increased in CSC mice receiving saline or CSC fecal transplant, and bone phenotyping revealed disturbed long bone growth. However, CSC mice receiving donations from non-stressed mice showed no increase of KC and IL-6 levels, and the previously observed effects of stress on bone parameters were abolished. These results indicate the gut microbiome does have a role in the consequences of chronic social stress, with immune activation being at least partly responsible.

Lucie Bourgeoin (Geneva) has investigated the hypothesis that type 2 diabetes increased bone fragility via a downregulation of periostin. Her group has previously reported that periostin expression in osteocytes and lining cells is required to decrease sclerostin and stimulate of bone formation. The study analysed female Postn-/- mice subjected to a high fat or normal diet, and Db/Db mice with overexpression of Postn. Bone phenotyping of each group has confirmed that type 2 diabetes decreases periostin expression. A high fat diet induced a deterioration in bone quality in wild type mice, which was not observed in the Postn-/- mice on the same diet. However, bone structure and strength were rescued in the Db/Db mice with Postn overexpression.

Antonia Sophocleous (Nicosia, Cyprus) has obtained evidence that the gut microbiome regulates the susceptibility to osteoarthritis in mice. Mice had the original microbiome removed by antibiotics and were then subjected to destabilisation of medical meniscus (DMM), as a model of osteoarthritis. Mice then received a reconstitution of their microbiome using a mixture of probiotic strains, or vehicle and the progression of osteoarthritis was then measured by microCT and histology. The study found significantly less cartilage damage at the medial femoral condyle in treated mice compared to controls, though no difference in osteoarthritic progress in the tibial plateau and no significant impact on subchondral bone indices. Nevertheless, this interesting result warrants further study on the potential of probiotics for osteoarthritis treatment.

While low phosphate is implicated in reduced muscle function in hypophosphatemic disorders, the precise mechanisms are not yet known, and particularly if a mechanism independent of hormonal changes exists. **Sampada Chande** (New Haven, USA) has generated conditional knockout mice lacking one or two copies of the phosphate tranporters Pit1 and Pit2 in their skeletal muscle. This allowed a reduction of phosphate supply without causing hypophosphatasia and hormonal changes. All mice were found to have reduced running activity, indicative of impaired endurance. Mice with conditional deletion of both transporters experienced a lethal phenotype with severe skeletal muscle degeneration. These results show that Pit1 and Pit2 are essential for normal myofiber development and survival, and that the reduced endurance observed with hypophosphatemia may be independent of homeostatic hormonal changes.

HIGHLIGHTED POSTER PRESENTATIONS

Franziska Lademann (P139) has created a great Science Sketch to explain her work on thyroid hormone transporter Mct8 as a negative regulator of trabecular bone mass in male mice. She also gave a SNAPs presentation of her poster.

Simone Bianciardi (P261) reported on a preliminary analysis of gut microbiome in a restricted sample of postmenopausal women and elderly men from an ongoing prospective population-based study. They observed trends for different proportions of Bacteroidaceae and Prevotellaceae between osteoporotic patients and controls, as well as a statistically significant increase in Enterobacteriaceae in patients with osteoporosis.

Molecular Biology of Fracture Healing

Mechanisms of fracture healing were discussed in an ECTS 2019 workshop.

Anita Ignatius (Ulm, Germany) presented novel insights about the involvement of inflammatory components in fracture healing.

Fracture healing is impaired in around 10% of patients due to ageing, concurrent inflammatory disorders or additional severe injuries. It is a complex process with closely linked phases of inflammation, repair and remodelling. The early inflammatory phase of fracture healing is regarded to be critical for the healing process by initiating down-stream responses inducing tissue regeneration. Disturbances to the finely tuned immune response may lead to disturbed fracture healing.

In this context, Anita Ignatius is particularly interested in the role of the complement system, a crucial arm of innate immunity, which is rapidly activated by danger associated molecular pattern being released from injured tissues.

To study the influence of posttraumatic inflammation on bone healing, the Ignatius group established an experimental model of severe trauma in rodents by combining a blunt chest trauma with a femur fracture. The severe trauma induces acute systemic inflammation (complement activation, IL-6 increase) and disturbs the immune response at the site of fracture (e.g. increased neutrophil recruitment). Fracture healing is severely impaired reflecting the situation in polytrauma patients. Notably, the blockade of the receptor of the complement anaphylatoxin C5a (C5aR) completely abolished the negative effects of severe trauma on bone healing.

In subsequent studies, the Ignatius group unravelled C5a effects on bone. They showed that C5aR is strongly upregulated by osteoblasts in response to bone injury, indicating that osteoblasts might serve as effector cells for C5a under inflammatory conditions. C5a/C5aR signalling mediates the secretion of inflammatory cytokines (e.g. IL-6, IL-8) and of RANKL, the key stimulator of osteoclastogenesis. Moreover, C5a was able to stimulate osteoclast formation directly. Confirming C5aR knockout mice display increased bone mass due to reduced bone resorption, indicating that the C5a/C5aR axis induces an immune response in osteoblasts and activates osteoclast formation.

This is relevant for bone healing. Bony callus formation is crucially disturbed in mice with an osteoblast specific overexpression of C5aR suggesting that C5a induces bone erosion under inflammatory conditions by its direct action on bone cells. Notably, fracture healing is also disturbed in C5aR knockout mice, possibly due to a strong suppression of early inflammation. Thus, a balanced complement activation is crucial for bone healing.

Finally, a transcriptome analysis published last year has identified about 600 genes, which were differentially regulated upon C5a treatment. Many were related to TLR-signalling, what could be relevant in infectious bone disorders, and with insulin signalling and glucose metabolism, suggesting that the C5a/C5aR axis may also regulate osteoblast functions beyond their inflammatory response.

Celine Colnot (Paris) then discussed bone regeneration mechanisms and the role of periosteal stem cells in the regeneration of fracture healing.

Skeletal stem cells have multiple origins. Bone marrow stromal cells have a local osteogenic potential within the bone marrow compartment during bone repair. Periosteum, located at the outer surface of the bone, is another local source of skeletal stem cells for bone repair.

Celine Colnot's group has used genetically engineered mice expressing GFP (PrxCre) to label all the mesenchymal lineage and osteoprogenitors. By sorting GFP+ cells from periosteum and bone marrow cells, it was shown that they could differentiate into osteoblasts, adipocytes and cartilage ex vivo. The regenerative function of the cells *in vivo* was shown by their integration in callus and bone when transferred in tibial fractures.

Through periosteum transplantation, it was shown that periosteum has a stem cell subpopulation. Comparative expression analysis studies between periosteum cells and bone marrow cells at the third day after fracture identified differentially expressed genes, including an increase in periostin in the activated periosteum. Periostin is an extracellular matrix protein that mediates mechanic stimulation of osteoblasts.

Periostin knockout mice displayed impaired fracture healing. They also failed to maintain the periosteal stem cell population after injury, suggesting a role of periostin in the renewal of periosteal stem cells. Although bone marrow and periosteal cells derive from mesenchymal lineage, they establish bone compartments with completely different environments. Periosteal cells have a higher capacity to respond to injury and contribute to periosteum activation and bone healing. Clinically, in children there is high regenerative potential upon bone fracture when periosteum is intact.

In a mouse model of achondroplasia due to a gain of function mutation in FGFR3, the fracture healing process is impaired with defective transition from hypertrophic chondrocytes to bone. There is also formation of fibrotic tissue. Transplantation of mutant periosteal cells in wild type fractures caused the same pseudoarthrosis, while the opposite transfer rescued the phenotype. This indicates the intrinsic role of periosteal cells in the transition phase from cartilage to bone.

To conclude, periosteum is responsive to injury by expressing genes involved in extracellular matrix and bone deposition. In the cartilage to bone transition in callus, FGFR signaling regulates cartilage-to-bone transition. At the end of the repair process the new periosteum is formed, and periosteal stem cells self-renewal depends on periostin.

HIGHLIGHTED ORAL POSTER PRESENTATION

Extracellular vesicles derived from mesenchymal stem cells may offer an alternative to cell-based regenerative therapies. Andrew Stone (York, P030) has identified a biomarker (CD317) that discriminates human MSC subpopulations suitable for regenerative applications, from those with a pro-inflammatory profile, and has analysed the extracellular vesicle protein and miRNA cargo of the CD317 positive cells.

Workshop on Articular Cartilage

Andrei Chagin (Stockholm, Moscow) gave an overview of our latest understanding of articular cartilage stem cells and processes of cartilage renewal.

While articular cartilage is considered a non-regenerating tissue, neonatal cartilage can heal without a scar and microfracture is used in orthopaedic surgery to repair small cartilage defects. This observation is likely due to stem cell activities.

Cells with progenitor-like characteristics have been previously observed in the superficial zone and more recent Cre mouse model studies have observed in vivo differentiation of the superficial cells to chondrocytes. Andrei Chagin has built on these studies using lineage tracing (Prg4+ cells) and various new or established fluorescent reporter systems (generating amazing 3D images shown in his talk) to observe more details of the cell behaviour.

These studies have shown that superficial cells are slow dividing, and again confirmed as chondrocyte progenitors. Positive of stem cell markers including Notch1 and CD73 was found, and they can divide symmetrically along the cartilage surface. Around 20% of the cells do not differentiate and appear to maintain their own population. All this points to the superficial cells being self-renewing chondro-progenitors, fulfilling all the criteria for being classified as adult stem cells.

To support the renewal of articular cartilage, mouse embryonic chondrocytes were labelled, but by 30 days of age were found absent, probably due to cell death or trans-differentiation (see also Basic Science Update on Bone Biology and interview with Christine Hartmann, pages 35-36), fully substituted by those chondrocytes generated from the superficial cells. In fact, this experiment showed that superficial cells were responsible for constituting the mouse adult articular cartilage. On the other hand, ablating this cell population have given conflicting reports of the eventual osteoarthritis phenotype (Zhang M, *et al.* 2016), which may be due to incomplete ablation and re-population of the superficial cells. Others (e.g. Decker RS, *et al.* 2017) have suggested that *Prg4+* cells involved in healing of cartilage defects originate in the synovium, but interpretation of this data is difficult and it is still possible that these cells originate in the cartilage surface.

Jennifer Elisseeff (Baltimore, USA) then discussed senescence in articular cartilage.

Progress towards repair of cartilage defects in the field of tissue engineering has been slow. For cartilage, the paradigm is to redirect healing processes rather than develop a scaffold for cells to populate and regenerate tissue. Inflammation can prevent cartilage regeneration, and so the tissue immune environment is now being targeted.

For wound healing in other tissues (e.g. muscle), biological scaffolds have been designed that can generate a pro-regenerative immune environment. A likely factor for the differences in healing between muscle and cartilage is the new concept of senescent cells. The senescence-associated secretory phenotype (SASP) has been associated both to tissue repair and implicated in chronic disease and regulation of immune cells, particularly macrophages and T cells. Dr Elisseef's group are studying the changes in the macrophage phenotype in response to SASP depending on their environment, which in combination with single cell analysis is generating some new classifications of macrophage cells.

Studies in a mouse model of ACL injury have observed that expression of senescence cell marker P16+ increases after the injury. Dr Elisseeff's group have isolated and analysed secretory exosomes produced by the cells, finding evidence of a bystander effect where senescence is transferred to neighbouring cells. Use of a "senolytic" drug to remove senescent cells reduced inflammation and repaired cartilage tissue. Repeating the experiment in older animals, high P16 expression in the joint was found even prior to the injury, but only limited tissue repair after treatment. Nevertheless, their inflammation and pain levels improved. A phase 1 clinical trial of this senolytic drug is currently in progress.

HIGHLIGHTED POSTER PRESENTATION

Nina Lukač (Zagreb, Croatia, P192) has studied antigen-induced arthritis in wild type mice, and Fas$^{-/-}$ mice, which are protected from local bone resorption normally observed. Mid1 expression was found upregulated in the myeloid cells and bulk joint tissue of the wild type mice in comparison to Fas$^{-/-}$ mice. Treatment with metformin ameliorated the severity of arthritis assessed by knee diameter. This study raises interesting questions about potential protective benefits of metformin against antigen-induced arthritis in diabetic patients receiving treatment with metformin.

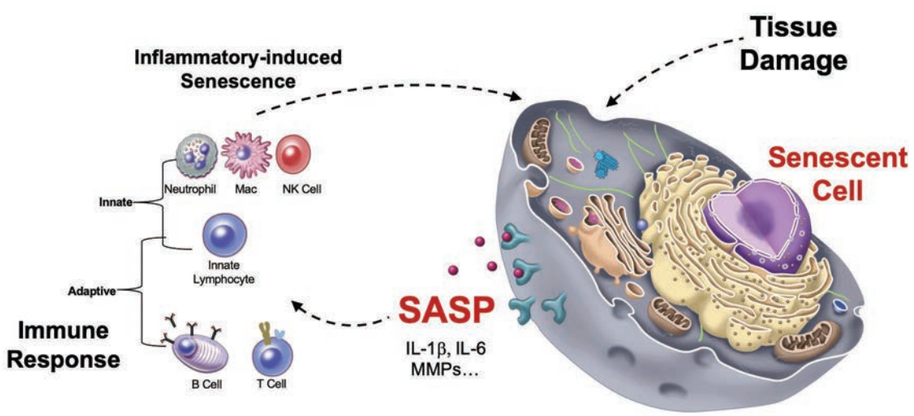


Figure 9. *Interactions of the senescence-associated secretory phenotype (SASP) with immune cells (Jennifer Elisseeff)*

Sclerostin: bone speaking to the body

This excellent plenary symposium focused on the role of sclerostin beyond its well-established effect on bone remodeling.

Ryan Riddle (Baltimore, USA) presented a comprehensive overview of the role of sclerostin in metabolism.

Circulating sclerostin levels are positively correlated with fat, raising the question whether sclerostin exerts effects outside the skeleton.

- *Sost*$^{-/-}$ mice have smaller adipocytes due to reduced fatty acid synthesis
- *Sost* overexpression increases fat
- *Sost*$^{-/-}$ mice have improved glucose metabolism and are resistant to high fat diet

Therefore, sclerostin regulates adipocyte metabolism and increases fatty acid synthesis.

These findings raise the question whether pharmacological inhibition of sclerostin using the anti-sclerostin antibody (Scl-Ab) affects body composition and metabolism. Indeed, Scl-Ab reduces adipose accumulation and protects mice from high fat diet.

In addition, expression of Lrp4 by both the adipocyte and osteoblast is required for normal sclerostin endocrine function.

The main conclusion of this talk was that sclerostin has an endocrine function, that facilitates communication between bone and adipose tissue.

The second talk by Natasha Appelman-Dijkstra (Leiden, Netherlands) focused on clinical aspects of sclerostin deficiency.

Sclerosteosis and van Buchem disease are two rare bone dysplasias caused by genetic defects in sclerostin synthesis. These patients have increased bone mass with intact bone quality. In addition, they often suffer from various complications, including hearing loss, increased intracranial pressure and increased mortality.

Beyond bone, the role of sclerostin in vascular calcification was discussed. Circulating sclerostin levels are also associated with cardiovascular disease, diabetes and insulin resistance. Interestingly, sclerostin is also expressed in the articular cartilage and alterations in sclerostin expression have been observed in arthritis patients. The main conclusion of this presentation was that more investigations are needed to understand extraskeletal effects of sclerostin.

Working group on animal models in bone research

This working group provided an overview of available models for bone research, and practical tips.

Firstly, **Aymen Idris** (Sheffield) discussed animal models for cancer, especially the various models for cancers that metastasize to bone. His recent work on the cannabinoid pathway and the evaluation of inhibitor JZL184 has involved evaluation of many different models.

The second speaker **Reinhold Erben** (Vienna) considered the advantages and disadvantages of bone histomorphometry, a long established but still useful technique for studies in pre-clinical mouse models. This covered the most suitable bone segments to analyse, and how to most effectively analyse bone formation rate as a functional parameter for bone turnover.

Jan Tuckermann (Ulm) then discussed pros and cons of using mouse Cre-lines for osteoblast-conditional gene knockouts. He presented Runx2-Cre and Dmp1-Cre mice as examples.

Finally, **Ester Wehle** (Zurich) presented her poster P201 on the use of CRISPR/CAS9 to generate dual fluorescent reporter mouse models. This should allow the rapid identification of osteoblasts and osteoclasts for single cell mechanomics in samples from *in vivo* experiments.

Oral presentations on the molecular basis of bone pathology

Andrew Chantry (Sheffield, UK) has investigated how bone recovers after chemotherapy for multiple myeloma, and if this is enhanced by bone anabolic therapy. His study demonstrated in a multiple myeloma mouse model, that a bone anabolic treatment (a TGF receptor I kinase inhibitor) with chemotherapy improved the healing of myeloma bone disease, and fracture resistance.

Ciro Menale (Milan, Italy) showed that deletion in mice of antioxidant protein dipeptidyl peptidase 3 leads to increased oxidative stress, bone loss and increased osteoclastogenesis, accompanied by increased expression of inflammatory pro-osteoclastogenic cytokines. This result supports a role for oxidative stress in bone pathology and that DPP3 may be identified as a new osteoimmunological player in bone disease.

Eleni Douni (Vari, Greece) demonstrated that transgenic models of osteoporosis expressing human RANKL (TgRANKL) progressively develop bone marrow adiposity (BMA), while inhibition of osteoclast activity and bone resorption upon treatment with alendronate dramatically decreased BMA. This result indicates a possible involvement of osteoclasts and bone resorption in BMA development.

Heike Weidner (Dresden, Germany) showed that the mouse analog of luspatercept, a novel erythroid-stimulating agent, improves the bone phenotype of myelodysplastic mice (NUP98-HOXD13 transgenic mice, NHD13) and protects from bone loss induced by estrogen withdrawal.

Antonio Maurizi (L'Aquila, Italy) has conducted a transcriptomic study in soft tissues from a mouse model of autosomal dominant osteopetrosis type 2 (ADO2). This has identified common multiorgan alterations characterized by an increase in the pro-fibrotic TGFβ pathway, which was confirmed by perivascular fibrosis.

Aymen Idris (Sheffield, UK) has investigated inhibition of monoacylglycerol lipase (MAGL), an enzyme of the endocannabinoid system, in animal models of primary sarcoma. and secondary prostate and breast cancer. In these mouse models, MAGL inhibition reduced osteolytic bone metastasis and skeletal tumour growth. However, in wild-type mice, reduced bone volume was obtained, indicating a limited usefulness of MAGL as a therapeutic target.

Oral presentations on osteoblasts and bone formation

Wnt1 was previously identified as a potent bone anabolic Wnt ligand. Julia Luther (Hamburg) has investigated this potential therapeutic target in a doxycycline-inducible mouse model with Wnt1 overexpressed in osteoblasts when doxycycline is withdrawn. This latest study has shown increased bone formation in aged mice within 3 weeks of the transgene induction, but normalization to the level of control mice by reintroducing doxycycline to the diet, expected due to increased osteoclast activity. Thus targeting Wnt1 could be a rapid bone anabolic strategy for osteoporosis, but would need to be combined with subsequent antiresportive treatment.

Alasdair Kay (York, UK) has obtained a low-serum adapted human mesenchymal stem cell line Y101.5, with enhanced osteogenic potential *in vitro* and *in vivo*. Conditioned medium from Y101.5 induced a similar pro-osteogenic phenotype in the parental Y101 cells, which appears partly mediated by extracellular vesicles. RNAseq has identified significantly upregulated lipid/cholesterol metabolism pathways in the compared with the Y101 cells, and modifications to the secretome and EVome of the cells have been determined by mass spectrometry.

Parathyroid hormone is an osteoanabolic treatment, and **Carole Le Henaff** (New York) and other US colleagues have investigated the hypothesis that increasing PKA activity in osteoblasts will have a similar effect. The PKA regulatory subunit 1A was inducibly deleted in mice of 1 month or 5 months of age, to increase PKA activity, with the mice then subjected to bone phenotyping. In both groups of mice, a decrease in whole body, femoral and tibial BMD was measured, and the activity of both osteoblasts and osteoclasts was increased. microCT showed an increase in trabecular bone mass and reduction of cortical bone in vertebrae and femurs. The expression of PTH-regulated genes was also changed, confirming that high PKA activity mimics hyperparathyroidism.

FGFR3 mutations result in craniofacial defects (e.g. craniosyntosis, wormian bones formation), but such defects are absent in *Fgfr3* mouse models. **Emilie Dambroise** (Paris) has investigated FGFR3 function in zebrafish models. Firstly, larvae expressing mCherry in osteoblasts were treated with an FGFR inhibitor. These developed a large fontanel area, indicating disturbed cranial vault formation. A *fgfr3*$^{-/-}$ zebrafish line was then established. Analysis of 3-month old *fgfr3*$^{-/-}$ showed reduced overall size and significant changes to craniofacial bone morphology. Crossing of this line with the mCherry labelled line showed that deletion of *fgfr3* prevented osteoblast expansion.

While sclerostin inhibits bone formation mostly via antagonism of LRP5/6, **Cyril Thouvery** (Geneva)

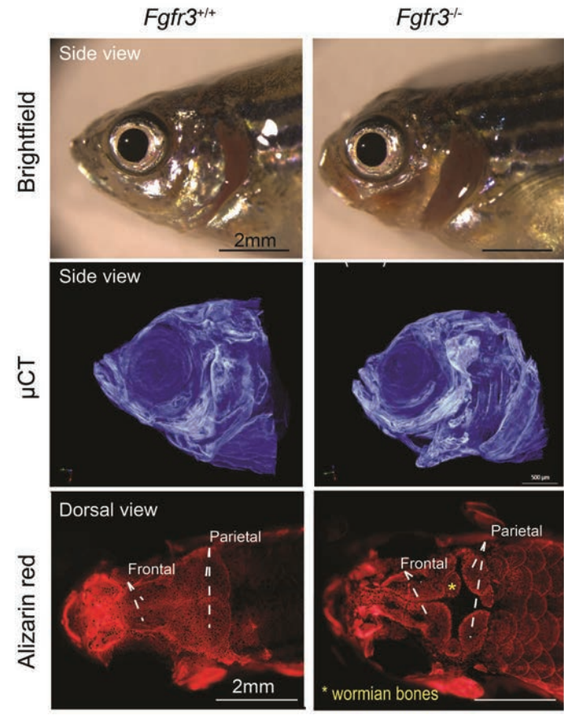


Figure 10. *Fgfr3 mutants present drastic craniofacial defects*

previously found an independent mechanism via platelet-derived growth factor receptor (PDGFR). The physiological relevance of this crosstalk between sclerostin and PDGFR has now been investigated further in 4-month old mice with inducible suppression of PDGFRα and PDGFRβ in osteoblasts. Treatment with anti-SOST antibody was found to give a higher increase in trabecular bone volume in the *Osx-Cre; Pdgfraf/f; Pdgfrbf/f* mice, compared to controls, while cortical bone increased similarly in both. *Ex vivo* analysis also found higher expression of *Wisp1*, a Wnt target gene in response to antibody treatment, and PDFGR inhibition of osteoblast cells increased Wnt3a-induced β-catenin transcriptional activity. PDGFR signaling is therefore involved in potentiating the bone-anabolic effects of anti-SOST antibody treatment.

Impaired bone anabolism in osteoporosis involves reduced osteoblast differentiation, mediated by transcription factors. **Camille Blandin** (Paris) has investigated the role of transcription factors Dlx5 and Dlx6 in the differentiation of murine osteoblastic progenitors, where the absence of Dlx5/6 was found to decrease levels of osteocalcin and alkaline phosphatase. Analysis of mice with osteoblast-specific deletion of Dlx5/6 found a lethal phenotype in *Dlx5/6* $^{fl/fl}$*Osx-Cre*, but the heterozygous mutation showed impaired bone formation during growth, including a lower cortical thickness, lower BMD at 3 months, lower periosteal volume, unclosed skull sutures and dental abnormalities.

Communication between cells and bone environment

This basic/translational workshop at ECTS 2019 focused on interactions between bone and the vascular system.

Anjali Kusumbe (Oxford) presented recent developments concerning the role of blood vessels and vascular niches in ageing and bone metastasis.
Her previous research established high-resolution techniques to image vasculature in bone, identifying different subsets of vessels.

A specialized blood vessel subtype, type H, which expresses high levels of the endothelial markers CD31 and endomucin is in close proximity to osteoprogenitors. Age-associated decline in bone mass is associated with the loss of these specialized blood vessel capillaries, while an increase in type H vessels in aged mice leads to proliferation of osteoprogenitors and higher bone mass.

They further investigated how heterogeneity in vasculature and bone affects metastatic cell reactivation. To understand age-associated signals, breast cancer cells expressing luciferase and GFP were injected into young and aged mice.

In aged mice, the expansion of injected cells was higher showing less quiescence compared to young recipients, suggesting that the young niche promotes quiescence. RNA sequencing of whole bone of the aged mice showed increases in immune system processes, T cell proliferation, and cytokines that promote proliferation, but downregulation of secreted factors related to quiescence and dormancy, compared to young mice.

Injection of the bone secretome together with cancer cells into the tibias showed that the secretome was sufficient to trigger the expansion of cancer cells in young mice.

The same set of experiments performed following irradiation or chemotherapy showed an increase in the quiescent fraction, while RNA sequencing confirmed downregulation of cancer cell proliferation.

Further analysis showed that pericytes were the source of secreted factors promoting quiescence, while pericytes specifically in the bone were expanded post irradiation via PDGF signalling. This could explain why cancer cells stay dormant and are protected in bone, compared to other organs.

Inhibition of blood flow decreases pericyte expansion following irradiation or chemotherapy, and could render cancer cells more susceptible to cancer treatment, as fewer cancer cells will remain dormant in bone marrow.

Matthew Greenblatt (New York) then spoke about the targeting of skeletal endothelium to counteract bone loss.
His group has investigated how vascular endothelium regulates skeletal mesenchymal cells and ultimately drives anabolic bone formation. They have utilized mice with an osteoblast-specific deletion of *Shn3*, resulting in markedly elevated bone formation, as a tool to probe the mechanisms by which osteoblasts shape their supporting cell types in bone, including vascular endothelium.

Mice with this conditional Shn3 deletion also demonstrated an increase in skeletal vascular endothelium, showing that osteoblasts actively and continuously regulate vascular endothelium in bone.

To uncover the mediator of this angiogenic effect of SHN3 deficiency, transcriptomic analysis of SHN3-deficient osteoblasts identified SLIT3 as an osteoblast-derived pro-angiogenic factor.

Genetic deletion of Slit3 reduced skeletal vascular endothelium, resulting in low bone mass because of impaired bone formation, thus partially reversing the high bone mass phenotype of *Shn3*$^{-/-}$ mice.

This coupling between osteoblasts and vascular endothelium is essential for bone healing, as shown by defective fracture repair in SLIT3-mutant mice and enhanced fracture repair in SHN3-mutant mice.

Finally, administration of recombinant SLIT3 both enhanced bone fracture healing and counteracted bone loss in a mouse model of postmenopausal osteoporosis. This suggests that vascular endothelial cells can join osteoblast and osteoclast-lineage cells as cellular targets for the treatment of disorders of low bone mass or impaired skeletal healing.

In other news...

A highlight in last year´s bone research was the identification of a new vessel, the transcortical vessel. These transport the vast majority of blood into bone and transport cells (such as neutrophils) and nutrients into bone. The authors in Germany also found that osteoclasts are necessary to direct the direction of vessel growth. This was independently confirmed by a group at Imperial College London, who also found osteoclasts to be important for vessel growth

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FGF23, a phosphotropic hormone... and beyond

This Educational Symposium was supported by Kyowa Kirin in the form of an educational grant. The scientific content has not been influenced in any way by its sponsor.

An educational symposium at ECTS 2019 gave us an update on the latest understanding of FGF23 as a phosphotropic hormone affecting phosphate metabolism in multiple skeletal disorders.

Reinhold Erben (Vienna) gave the first talk of the symposium on FGF23-induced hypophosphatemias.
He started by illustrating the skeletal consequences of hypophosphatemia in a mouse model with mutations of the phosphate regulating gene with homologies to endopeptidases on the X chromosome (PHEX). The model shows a disorganized growth plate, and cartilage abnormalities. Studies published in the early 2000s eventually implicated the hormone FGF23 in the pathogenesis of rickets in these abnormalities. Shimada T, *et al.* proved that overproduction of FGF23 causes tumour-induced osteomalacia (TIO) and genetic studies showed that gain-of-function mutations in the FGF23 gene cause autosomal dominant hypophoshatemic rickets (ADHR).

FGF23 is essential for protection against hyperphosphatemia and for regulation of the 1-alpha-hydroxylase function. However, excessive production of FGF23 is associated with phosphate wasting in patients with normal renal function.

DEFINITIONS:

Phosphotropic – targeting phosphate metabolism

Phosphaturic – stimulating renal phosphate excretion

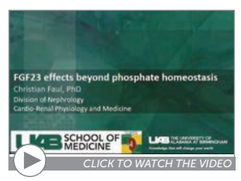
After identification of FGF23, it took about 10 years to find out how FGF23 functions. It requires the FGF receptor (FGFR) and its co-receptor, Klotho, to exert its phosphaturic function. Andrukhova O, *et al.* showed that Klotho is expressed in the proximal tubule, as well as the FGFR. At this level, FGF23 downregulates expression of the sodium-phosphate co-transporter NaPi2a, thus exerting its phosphaturic effect. Due to its additional effects in the distal nephron, FGF23 is not only a phosphaturic, but also a sodium and calcium-conserving hormone.

Increased secretion of FGF23 causes renal phosphate wasting and is seen in tumor-induced osteomalacia (ectopic secretion), X-linked hypophosphatemia (XLH), autosomal dominant hypophosphatemic rickets (ADHR), autosomal recessive hypopohosphatemic rickets 1 and 2 (ARHR1 and ARHR2), Raine syndrome, and osteoglophonic dysplasia (OGD).

Dr Erben described the regulation of FGF23 production in osteocytes: 1,25(OH)2D is the major regulator at the transcriptional level, and other regulating factors are PTH, phosphorus, calcium, but also inflammation, erythopoietin and iron deficiency.

Apart from its endocrine function, FGF23 has paracrine/autocrine activity. Increased FGF23 secretion in bone inhibits mineralization through systemic (hypophosphatemia) and local (increased pyrophosphate - PPi concentration through inhibition of the alkaline phosphatase in the osteocytes) mechanisms. In a mouse model of XLH (Hyp mice), Murali SK, *et al.* showed that these autocrine/paracrine functions of FGF23 is responsible, together with accumulation of ASARM peptides and osteopontin, of the mineralization defects characteristic of the disease and may be of help for targeting therapies.

It remains to be determined if FGF23 has additional functions in other organ systems, for example the heart. Dr Erben concluded that "There is still a lot of things we do not understand about FGF23!"



Christian Faul (Birmingham, Alabama) then spoke about "FGF23 effects beyond phosphate homeostasis".
He started by referring to chronic kidney disease (CKD) and how it is highly associated with elevated prevalence of cardiovascular disease, which is in fact the leading cause of death in CKD. The pathogenesis is complex and involves several mechanisms. Among them, cardiomyocyte hypertrophy, fibrosis, inflammation, cell death, and several metabolic abnormalities play a central role in the pathogenesis of uremic cardiomyopathy. Apart from traditional factors (such as diabetes, hypertension, etc.), risk factors for cardiovascular disease in CKD include anemia, inflammation, oxidative stress, endothelial dysfunction, and metabolic changes, including perturbation of phosphate metabolism,

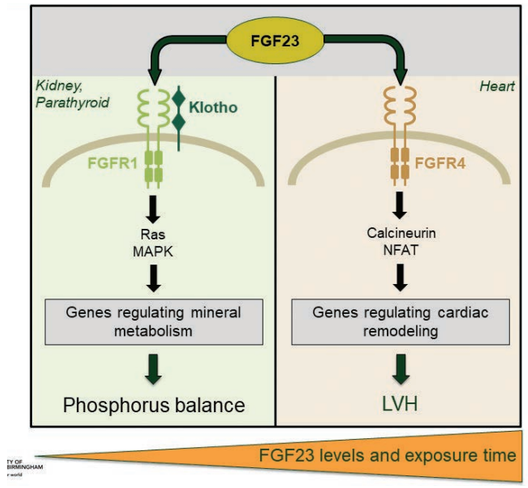


Figure 11. *FGFR4 mediates Klotho-independent FGF23 signaling in the heart (Christian Faul/UAB)*

elevated FGF23 levels, reduction in Klotho, reduction of 1,25(OH)2D, and elevated PTH.

FGF23 is elevated in CKD patients and represents an independent risk factor of cardiovascular disease. It is also strongly associated with increased mortality. Faul C, et al. found in 2011 that elevated FGF23 levels are directly and independently associated with cardiac hypertrophy in CKD patients. They also showed that treatment of cardiomyocytes with FGF23 in animal models induces hypertrophic growth of isolated cardiomyocytes. Additionally, blocking FGF receptors (FGFR) may prevent cardiac hypertrophy with no effect on blood pressure in an animal model of CKD.

Christian Faul discussed the mechanisms of FGF23 action on cardiomyocytes. Klotho is not expressed in healthy or injured heart tissues, and FGF23 acts through a Klotho-independent signaling pathway in the heart involving FGFR isoform 4 and the calcineurin/nuclear factor of activated T cells (NFAT) pathway in cultured cardiomyocytes. In particular, the duration of FGF23 elevation rather than the degree of elevation predicts the development of pathological cardiac remodeling. Hence while the FGFR1/Klotho pathway is essential for FGF23-regulated phosphate homeostasis in the kidney, FGFR4 mediates FGF23-regulated cardiac remodeling in the absence of Klotho.

Therapeutic options targeting FGF23 signaling are now being investigated to prevent cardiovascular disease in CKD. Pharmacological blockade of FGFR4 by specific antibody protects against FGF23-induced cardiac hypertrophy and fibrosis in a rat model of CKD, without affecting kidney function, FGF23 levels or blood pressure.

Dussold C, *et al*. recently published the first study showing that lowering FGF23 in a CKD model can attenuate cardiac injury. They observed that DMP1 reduction contributes to elevation of FGF23 in CKD, and that genetic or pharmacological supplementation of DMP1 in a mouse model of CKD prevents FGF23 elevation and pathologic cardiac remodeling without effect on kidney functions.

One unresolved question is whether serum phosphate can have direct effects on the heart, and could contribute to any pathological perturbation of cardiac remodeling.

Apart from patients with end-stage renal disease, FGF23 levels are also higher in patients with genetic, FGF23-dependent, hypophosphatemic disorders, such as X-linked hypophosphatemia (XLH). However, patients with XLH do not develop cardiac hypertrophy.

In a murine model of XLH, the presence of elevated FGF23 levels was not associated with cardiac hypertrophy or perturbation of cardiac function in the absence of altered kidney function. Many experimental studies have been developed to address these issues and it is possible that other factors altered in CKD but not in XLH promote the cardiac effects of FGF23. For example, in CKD serum FGF23 levels are much higher than in XLH; in CKD serum phosphate levels are elevated while in XLH they are reduced; in CKD the blood pressure is high, while in XLH it is normal.

Finally, Christian Faul showed that surprisingly the kidneys appear to be resistant to heart-derived FGF23. Additionally, extrarenal effects of high FGF23 levels should be considered. FGF23 has effects on the endothelial function, development of atherosclerosis, hippocampal neurons, and the immune system (polymorphonuclear leukocytes and macrophages).

He proposed that a potential explanation of the above observations is the relationship between FGF23 and inflammation, that could theoretically form a vicious inflammatory cycle. Inflammatory cytokines can elevate FGF23 and FGF23 may increase inflammatory cytokine production. This would result in uncontrolled local and systemic inflammation and FGF23 excess and eventually in spread tissue damage, including cardiovascular disease and worsening of the initial injury.

There was more on FGF23 in health and disease in an ECTS 2019 clinical workshop with **Seiji Fukumoto** (Tokishima, Japan) and **Alison Boyce** (Bethesda, USA). Please click below to view the videos from this workshop online.

Bone Imaging

ECTS CONGRESS HUNGARY BUDAPEST 10 MAY PRE CONGRESS 11-14 MAY 2019

HIGHLIGHTS

- Bone cryo-sectioning, a powerful approach for histology, including quantitative studies
- Insights into the visco-plastic deformation behaviour of bone and the potential of non-collagen protein phosphorylation for prediction of fracture risk
- HR-pQCT clinical imaging innovations improving prospects for fracture risk prediction

Advances in preclinical bone imaging

The ECTS 2019 basic science update on Technology focused this year on bone imaging.

David Rowe (Farmington, USA) presented a new high-throughput method for bone cryosectioning using a tape-transfer system.

Using this method, various fluorescent labels of bone formation, bone resorption, and other markers of interest can be combined, thus, allowing the extraction of several data at once. Combining high-throughput imaging with the International Mouse Phenotyping Consortium may provide plenty of novel information on bone regulators in the future.

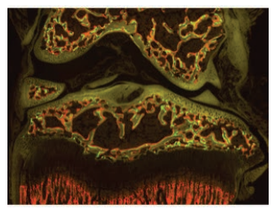


Figure 12. *Frontal section of a growing knee showing the mineralization labels (alizarine complexion and calcein) overlaid onto the fluorescence image of a safranin-O/fast green stain. (David Rowe)*

In the second talk, Michelle McDonald (Sydney, Australia) explained how her group has used intravital 2-photon imaging to observe osteoclast fusion and fission *in vivo*, previously only possible to observe *in vitro*.

This method was originally developed to assess how osteoclasts remodel the myeloma metastatic niche in bone, releasing tumour cells from dormancy. However, have also observed rare events of osteoclast fission and re-fusion, which could be promoted to more frequent events after RANKL treatment. Thus, these novel insights into osteoclasts *in vivo* show, once again, that osteoclasts may be longer lived cells than previously expected and that they recycle nuclei, possibly for rejuvenation purposes.

Meet the Expert

In his Meet the Expert session, David Rowe explained further the protocols for tape-stabilized cryosectioning.

Existing histological analyses of skeletal tissues have a number of limitations. They are time consuming and semi-quantitative, requiring subjective interpretation of slides from trained individuals.

Tape-stabilized cryosectioning preserves the morphology of mineralized tissues. Tissue sections are adhered rigidly to glass slides and imaged repeatedly over several rounds of staining. The resultant images are then aligned either manually or via computer software to yield composite stacks of several layered images. The protocol allows for co-localization of numerous molecular signals to specific cells within a given section. In addition, these fluorescent signals can be quantified objectively via computer software.

Specific examples of implementation are:

- Sexual dimorphism in the dynamic mineralization and cellular activities that are used in the histomorphological assessment of the vertebrae and femur.
- Models of cell based regenerative medicine in which the histology can distinguish the contribution of the host and donor to the repair process.
- Models of postnatal knee development and the earliest phases of osteoarthritis.

The presentation of the protocol provoked a very stimulating discussion, with many scientific groups expressing interest to incorporate this method in their ongoing programmes of rapid bone phenotyping. To date these mostly consist of conventional X-ray, DXA, micro-CT and biochemistry.

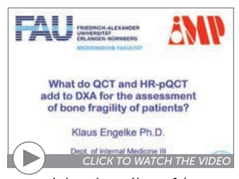
Advances in clinical imaging of bone quality

A plenary symposium at ECTS 2019 focused on bone quality as determinant of bone fragility, and the added value of QCT and HR-pQCT for characterising bone fragility in the clinic.

Philipp Thurner (Southampton, UK), a biomechanical engineer, discussed whether complementary techniques and approaches for assessing bone quality can improve on the current capabilities for prediction of femoral neck fracture risk.

For assessing fracture risk, it is relevant to characterise the geometry and the material properties of cortical and trabecular bone. Bone is not just a mineral, it is a viscous-plastic solid containing also non-collagen proteins (NCP). If we assess bone failure from a nanosocale model, we see that bone fails between the NCP and the mineral. NCP quantities and distribution may be a function of age and pathology. It is not yet clear if there is a hierarchy, but osteopontin and osteocalcin are both important. Phosphorylation levels of NCP change with age in males and females. Damage seems linked to the inelastic nature of bone hydration. NCP phosphorylation could be of diagnostic value.

Klaus Engelke (Erlangen, Germany) then explained how QCT and HR-pQCT can add to DXA for the assessment of bone fragility and bone quality of patients.



in vivo bone fragility is not fully captured by bone mass measurements by DXA. Both QCT and HR-pQCT are able to detect separately trabecular and cortical bone, and both can have finite element (FEA) analysis applied. HR-pQCT can also measure porosity to provide details of bone microarchitecture.

Several *in vitro* studies have shown that QCT-based FEA correlates very well with hip strength, and is superior to DXA hip aBMD, QCT hip vBMD and bone mineral content for predicting the failure load at the hip. However, a combination of trabecular and cortical parameters obtained by QCT allows a prediction of hip fracture similar to FEA. *in vivo* validation of QCT vs DXA has been conducted in several prospective studies, so far showing broad comparability.

Only two prospective studies have so far investigated FEA *in vivo* compared to BMD. The Bone Microarchitecture International Consortium has recently published its latest results showing HR-pQCT bone indices improved prediction of fracture over femoral neck aBMD or FRAX scores alone. The main data providing a direct comparison of QCT vs DEXA is from the Osteoporotic Fractures in Men (MrOS) study. For incident vertebral fracture assessment, FEA was found to provide a better prediction than BMD.

Future DXA based technologies may have a large clinical impact. Important new developments for DXA are trabecular bone score, FEA and 3D-DXA. FEA adds independent information compared to BMD and FRAX, and finite element models can explain 90-100% of bone strength. However, it increasingly appears that bone fragility and fracture risk is not simply about bone strength and other factors must be considered, for example muscle condition.

Klaus Engelke was recipient of the Excellence in Research Award at ECTS 2019.

In his Meet the Expert session "Bone imaging beyond DXA", Andrew Burghardt (University of California, San Francisco) discussed the available bone imaging techniques useful for assessment of bone fragility and fracture risk, changes in bone strength and therapy monitoring.

MRI images the general bone structure but is expensive and takes 7-15 minutes to obtain images. CT gives more detail of bone geometry, QCT obtains also data on BMD, and finally bone microarchitecture can be resolved by HR-pQCT. CT does have superior contrast for calcified tissue, and with software to simulate compression, can generate FEA models . It does require radiation exposure, but there is potential to utilise CT data obtained for other patient measurements to analyse bone fragility. Major trials on osteoporosis treatment now use HR-pQCT. HR-pQCT is also feasible for growth development. But it is difficult to follow patients because the regions-of-interest (ROI) may change.

The discussion in this session covered potential application of HR-pQCT for osteogenesis imperfecta, where it could potentially fill a gap between DXA and biopsy. No data is available so far, but a study is ongoing on osteogenesis imperfecta HR-pQCT data in adults.

In other news...

Due to the progress in sectioning and imaging bone, several new stem cells were identified in various niches, as for example stem cells in the jaw, the growth plate, and the periosteum. Also, advances in single cell sequencing now make it possible to discriminate between subpopulations within a putative stem cell population, and link these subpopulations to certain functions, for example hematopoietic stem cell support.

Working Group on Imaging of Bone Strength

This Working Group was supported by Scanco. The scientific content has not been influenced in any way by its sponsor.

Our pre-congress Working Group on Imaging Bone Strength discussed in more detail the tools available for HR-pQCT and its application for studying bone loss and rare diseases.

Bert van Rietbergen (Eindhoven) discussed micro finite element (micro-FE) analysis and 3D rigid image registration. These tools allow the assessment of bone strength and the observation of temporal bone loss and formation changes.

Ellouz *et al*. used 3D registration to improve the reproducibility of cortical indices by selecting the exact same analysis volume in repeated measurement. It can be used as well for detecting periosteal and endosteal resorption or expansion. The latter was demonstrated for the Geneva Retirees Cohort study for two timepoints, up to 3.5 years apart. This data has revealed significant endosteal expansion, which was elevated in females compared to males.

3D registration can also be used to assess local bone adaptation. In the first bedrest study to employ 3D assessment of bone microstructure, increased cortical porosity was found prominent after 60 days of unloading, but recovered to baseline after one year follow up (see Figure 13). It was also used to measure spaceflight-induced bone loss in cosmonauts, which was found highly variable between subjects, and not restored to pre-flight levels, even after several months after their return.

Van Rietbergen *et al*. reported that micro-FE parameters measured at the distal radius had similar associations with fracture risk as DEXA parameters in retrospective studies. This year, however, an international study in eight prospective cohorts (the Bone Microarchitecture International Consortium) found that analysis of HR-pQCT indices by micro-FE is better at predicting bone fracture risk than areal BMD measured by DEXA. Although, micro-FE is not for screening, it might be useful for drug studies.

The use of micro-FE seems to be promising for improving our understanding of fracture healing. While BMD and bone microarchitecture recovers over 2 years, bone stiffness has been found to increase steadily at the fracture site to a level above the contralateral site. However, plaster casts and metals may interfere in micro-FE analysis.

For rare diseases the use of HR-pQCT is just starting, validation is difficult, but 3D registration may nicely show the effect of a treatment.

Regarding rare diseases, only a few papers have looked at biomechanical read-outs. Potential flaws are other consequences of the disease, such as abnormal tissue mineralization, and experimental validation.

Florian Barvencik (Hamburg) then gave an overview on recent examples of HR-pQCT used to study rare bone diseases.

Previously, the study of rare diseases has led to the development of new bone disease therapies for more general application, examples of rare diseases leading to therapies include hypophosphatasias (for bisphosphonates) and sclerosteosis (SOST antibody). HR-pQCT has been recently used to characterise the bone microarchitecture of a child with a rare, de novo mutation in SCN8A, that was experiencing early onset osteoporosis and fractures. This analysis assisted selection of a bisphosphonate therapy, which was successful in preventing further fractures in the next 23 months. The combined trabecular and cortical bone loss, replicated in Scn8a-deficient mice, has confirmed that SCN8A mutations negatively affect bone mass.

HR-pQCT has also been applied for autosomal dominant osteopetrosis (ADO2). High density islands occur in the diseased bone and Butscheidt, *et al*. investigated identification of these islets with DEXA and HR-pQCT. The use of HR-qPCT allowed quantifiable data to be obtained on these bone structural alterations, though these were not found correlated to fracture risk. For osteogenesis imperfecta (OI), HR-pQCT has characterised alterations in trabecular bone microstructure, which was found worse in the patients with severe forms of OI.

Hypophosphatasia (HPP) patients, who experience accumulation of phosphate, inhibited bone mineralization and hypercalciuria, have also been studied by HR-pQCT. Using HR-pQCT, it is possible to follow changes in the bones, and this study found a good comparison with conventional histology of a biopsy. With the HR-pQCT analysis, it was possible to distinguish HPP patients with fractures compared to those without.

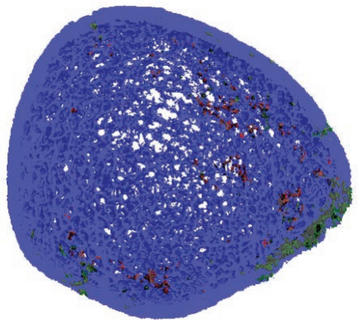


Figure 13. *A cross-sectional image of the tibia measured* in vivo. *3D registration was used to reveal microstructural changes in the bone during a one-year period after long term bedrest. Red: bone loss, green: bone gain, blue: bone that remained during the recovery period (Bert van Rietbergen)*

Bone and Cancer

ECTS CONGRESS HUNGARY BUDAPEST 10 MAY PRE CONGRESS 11-14 MAY 2019

HIGHLIGHTS

- Targeting the bone microenvironment now considered essential for prevention of metastasis to bone
- Tgif1 involved in the promotion of breast cancer metastatic progression by osteoblasts

Insights from outside: cancer dormancy

A plenary symposium in the ECTS 2019 Insights from Outside strand focused on the interesting, timely and clinically relevant topic of cancer dormancy.

During the first presentation, Jürgen Dittmer (Halle, Germany) discussed the mechanisms underlying cancer dormancy by focussing mainly on breast cancer.

He emphasized the heterogenous nature of breast cancer themselves as well as the complexity of tumour microenvironment. Metastasis is a multistep cascade initiated by cancer stem cells. After extravasation to distant organs, cancer cells can expand to form metastases or acquire a dormant state. Several factors can induce cancer cell dormancy/quiescence for instance TGF-β2 in the bone and BMP-4 in the lung. Similarly, various signalling molecules have been shown to promote homing and survival of dormant cells including c-Src, JAG1, CXCR4 and E-cadherin. Thus, the interaction between the cancer cells and the microenvironment is crucial for the determination of cancer cell behaviour at the metastatic site.

The second presentation by Caroline Wilson (Sheffield, UK) focused on the clinical aspects of cancer dormancy and how bone targeted agents influence the bone environment and consequently dormancy.

Caroline Wilson discussed the role of circulating tumour cells (CTCs) and disseminated tumour cells (DTCs) as well as the establishment of the pre-metastatic niche. The presence of DTCs in the bone marrow predict poor prognosis. However, bisphosphonates that induce osteoclast apoptosis and are often used as a bone targeted therapy reduce the number of DTCs.

She also highlighted several important clinical studies concerning bone targeted agents as adjuvant treatment in breast cancer patients. Adjuvant zoledronic acid had no survival benefit in the entire patient group. However, in post-menopausal patients, adjuvant zoledronic acid significantly reduced bone relapse. Related to these findings, the challenge of clinically determining menopausal status was discussed. Finally, two recent studies using anti-RANKL antibody in adjuvant setting were presented. In the ABCSG-18 study, adjuvant denosumab significantly reduced fractures in postmenopausal women with hormone receptor-positive, early-stage breast cancer. In the D-CARE study, adjuvant denosumab did not reduce breast cancer recurrence or deaths in early stage breast cancer patients. These results suggest that only inhibiting osteoclast activity is not sufficient to prevent metastases, but that the entire bone microenvironment should be considered.

Working group on cancer and bone

The Cancer and Bone working group was chaired by Nadia Rucci (L'Aquila, Italy) and contained 4 presentations covering basic and clinical aspects of primary bone tumours.

The first talk by **Dominique Heymann** (Sheffield, UK) provided a comprehensive introduction to the topic with a focus on osteo-, chondro- and Ewings sarcoma. An important message was that primary bone tumours are very heterogenous and prognosis of patients is often poor. In addition, he discussed how genetic and epigenetic events contribute to primary bone tumours as well as the importance of tumour microenvironment and cancer stem cells. Finally, therapeutic strategies to target tumour intrinsic and extrinsic properties were discussed.

The second speaker **Miklos Szendröi** (Budapest) presented a surgeon's point of view. He discussed the

HIGHLIGHTED ORAL POSTER PRESENTATION

Marie-Therese Haider (Hamburg, P074) has conducted *in vivo* and *in vitro* studies to show that osteoblasts promote breast cancer cell migration, but that metastatic breast cancer burden is reduced in a Tgif1-deficient bone microenvironment.
In Tgif1$^{-/-}$ mice, bone mass was reduced, but also tumour incidence and metastasis. RNAseq analysis identified Sema3E to be abundantly expressed and secreted by Tgif1$^{-/-}$ osteoblasts, and treatment with Sema3E inhibits tumour growth.

decision making when surgeons select the operation in patients with primary bone tumours. There are various options for reconstruction, including allografts and vascularized and vascular free autographs. All approaches have benefits and disadvantages and the choice depends on various factors including the age and activity of the patient and the location and grade of the tumour.

Georges F. Carle (Nice, France) then focused on the role of autophagy in the crosstalk between osteosarcoma and the bone microenvironment. The presentation highlighted the complex role of autophagy in cancer with stage-dependent anti- tumoral and pro-tumoral effects. In addition, autophagy modulates microenvironment and autophagy-deficient bone microenvironment promotes osteosarcoma growth and increases bone metastases.

The fourth talk was selected from the conference abstracts. **Joelle Tchicaya Bouanga** (Paris) presented how cancer stem cells contribute to metastasis of osteosarcoma. Specifically, the role of Calpain-6 as a stimulator of metastatic potential was discussed.

In other news...

A prospective cohort study by Ramin C, *et al.* has shown that breast cancer survivors have higher risk of osteopenia/osteoporosis during a mean follow up of 5.8 years compared to cancer-free women. Women at higher risk of osteopenia/osteoporosis were those aged 50 years or less, with estrogen-positive tumours, those treated with aromatase inhibitors or chemotherapy and hormonal therapy.

Another interesting study in breast cancer patients has been published by Gnant M, *et al.* on adjuvant denosumab treatment of postmenopausal patients with hormone receptor-positive breast cancer. The study reported a higher disease-free survival in the denosumab group vs the placebo group at 5 years.

ECTS Academy networking for New Investigators

The goal of the New Investigator Seminar and Gathering, organized by the ECTS Academy was to give new investigators a chance to present their work in a relaxed environment. The presentations were selected from the abstracts submitted by New Investigators and the best presentation was selected by the audience.

The first presentation by **Stephanie Thiele** (Dresden, Germany) showed the bone marrow phenotype of HLA-B27 transgenic rats (B27-Tg) which is an established model of spondyloarthritis, a group of inflammatory diseases that primarily affects the axial joints but affects also other tissues. Chronic inflammation was shown to reduce subcutaneous and gonadal fat as well as decreased bone marrow fat. As a consequence, adipocyte-derived cytokines and triglycerides were reduced in the serum of transgenic rats. In contrast, IL-17, which was shown to reduce adipocyte differentiation *in vitro* was elevated, indicating that chronic inflammation decreases body and bone marrow fat possibly via IL-17.

In the second presentation **Claudia Camerino** (Bari, Italy) demonstrated how oxytocin affects bone, brain and soleus muscle in response to cold stress. Oxytocin was shown to have a protective effect towards slow-twitch muscle and induce a switch of soleus towards a slow-twitch phenotype. Furthermore, oxytocin was shown to regulate the inter-organ communication between brain and soleus muscle.

The third presentation by **Vincent Ka Fai Cheng** (Hong Kong) showed the effect of AKAP11 on osteoblast differentiation and mineralization. AKAP11 has been identified in a GWAS study to be close to RANKL, a susceptibility locus for bone mineral density. AKAP11 deletion in MC3T3-E1 osteoblastic cells resulted in reduced alkaline phosphatase activity and impaired matrix mineralization. Furthermore, expression of several bone matrix genes was decreased while no difference was observed in early osteoblast marker genes. Consistently, RNA sequencing results revealed significant enrichment of pathways related to matrix organization, suggesting that AKAP11 plays an important role in matrix mineralization.

Thiberiu Banica (Ghent, Belgium) presented how Wnt-signaling parameters in the serum reflect bone mass and metabolism in healthy boys and men. DKK-1 concentration was shown to be higher in peri-pubertal boys than in adult men. OPG and sclerostin levels were not statistically different between the two groups. No association were found between any of the Wnt signalling components and bone turnover markers P1NP, CTX or osteocalcin. Furthermore, no association between Wnt signalling components and lumbar or whole-body BMC were found. These results indicate that serum levels of sclerostin, OPG and DKK-1 are not related to bone mass in healthy peri-pubertal boys or adult men.

The last presentation of the session by **Syazrah Salam** (Sheffield, UK) introduced the relationship between vascular calcification and bone microstructure in advanced chronic kidney disease. Ankle vascular calcification was shown to negatively correlate with distal tibia cortical thickness and positively with cortical porosity. No correlation was found with distal radius microstructure and bone mineral density T-score. The main conclusion of the results was that ankle vascular calcification was associated with worse cortical microstructure of distal tibia.

After all presentations, the audience voted for their favourite one. The recipient of the Best Presentation Award was Vincent Ka Fai Cheng.

Next Generation Synergy

The first Congress night finished with the Next Generation Synergy Session - Most Exciting Developments in the Musculoskeletal Field. Young delegates from several global networks gave us insights into their activities. Speakers presented many successful recently published and ongoing research results from the MusculoSkeletal Interdisciplinary Translational Young Researchers (MuSkITYRs) from Germany; Bone Research Society (BRS) from the United Kingdom; Emerging EUropean league against rheumatism NETwork (EMEUNET); Korean Society for Bone and Mineral Research (KSBMR); Chinese Society of Osteoporosis and Bone Mineral Research (CSOBMR).

Discussion followed on how more intensive partnering of these societies with the ECTS could be enhanced. The event was concluded with informal networking enjoying colourful sandwiches (of which some were topped by Hungarian paprikas), soft drinks and beer.

NI Mentoring Session

The NI Mentoring Session is becoming an established activity of the ECTS Academy. This year as well it met with a very high level of attendance and enthusiasm. Starting off with drinks, finger-food and networking, the participants were then introduced to the format by Chair **Hermann Agis** (Vienna). The participants had the opportunity to discuss various topics with an array of experienced and well-established academic and industrial professionals in an analogy of a 'speed-dating session': 15 minutes each session and then it is time to move along!

Duncan Bassett (Imperial College London), who shared his invaluable experience on 'How to write a successful grant' ('start very early, have a brilliant innovative idea, concentrate on hypothesis and aims of the grant, be a perfectionist!'),

Carola Zillikens (Rotterdam) shared her views on 'How to balance life and work ('no one size fits all rule, important to define goals and priorities, allow for different priorities at different phases of one's life')

Andrea Burden (Zurich) gave her insight about 'How to transition to independence' ('be frank and sincere to your mentors and establishment, prepare very thoroughly for upcoming interviews, believe in your own value and don't be discouraged').

Other exceptional mentors were **Michelle McDonald** (Darlinghurst, Australia), who gave important advice on 'How to image'; **Nicholas Bonnet** (University of Geneva, and Nestlé), who shared personal experience on 'How to combine academia and industry'; and **Johannes Grillari** (Evercyte GmbH) who gave a vibrant account of 'How to start a spin-off'.

The session was very well-managed and interactive and all mentees were given the opportunity to give their contact details so that they could be matched-up with experienced professionals in the setting of the *ECTS Academy Mentor Scheme*. This Scheme provides a unique opportunity to enhance an individual's skills, knowledge and performance through one-to-one meetings with a series of experienced professionals from a wide range of sectors and professions.

Recipients of ECTS grants and awards at ECTS 2019

ECTS CONGRESS HUNGARY BUDAPEST 10 MAY PRE CONGRESS 11-14 MAY 2019

ECTS STEVEN BOONEN CLINICAL RESEARCH AWARD
Supported by Amgen (Europe) GmbH
Roger Bouillon

ECTS IAIN T BOYLE AWARD
Björn Busse

ECTS EXCELLENCE IN RESEARCH AWARD
Klaus Engelke

ECTS MIKE HORTON BASIC/ TRANSLATIONAL AWARD
Miep Helfrich

ECTS PHILIPPE BORDIER CLINICAL AWARD
Christian Meier

ECTS 2019 FELLOWSHIP AWARDS
Valentina Capo
Elena Tsourdi

ECTS-AGNOVOS NEW INVESTIGATOR AWARDS
Supported by AgNovos Healthcare
Marco Ponzetti
Gretl Hendrickx
Juliane Colditz
Melanie Haffner-Luntzer
Mylène Zarka
Imke A. K. Fiedler
Fjorda Koromani

ECTS-BONE REPORTS NEW INVESTIGATOR AWARDS
Supported by Elsevier Bone Reports
Annika vom Scheidt
Franziska Lademann
Yasmine Hachemi

ECTS TRAVEL AWARDS
Carolina Medina-Gomez
Maria-Bernadette Madel
Liliana Mellor
Ciro Menale
Antonio Maurizi
Heike Weidner
Patricia Das Neves Borges
Riikka Mäkitie
Eleonora Palagano

ECTS EAST-MEETS-WEST RESEARCH AWARD
Xiang Li
Vincent Ka Fai Cheng
Gen Matsumae
Saori Kunii
Young Jun Won
A-Sol Kim
Kwangkyoun Kim
Amit Saraf
Rekha Ramot
Rajesh Khadgawat

ECTS EAST-MEETS-WEST RECOGNITION AWARD
Chang Suk Suh
Ho-Yeon Chung
Weibo Xia
Yoshiya Tanaka

ECTS ALLIED HEALTH PROFESSIONAL AWARD:
Mehdi Alrubayee

ECTS-ICCBH AWARDS:
Sara Penna
Gali Guterman-Ram
Luciano Colangelo
Lujiao Li
Lidiia Zhytnik
Adalbert Raimann

ECTS ACADEMY-IBI POSTER FOCUS AWARD:
Supported by Industrie Biomediche Insubri SA
Olja Grgic
Cornelia Bratengeier

ECTS ACADEMY-IBI NEW INVESTIGATOR SEMINAR AWARD:
Supported by Industrie Biomediche Insubri SA
Vincent Ka Fai Cheng

CLINICAL WEBINAR AWARD:
Emmanuel Biver

BASIC WEBINAR AWARD:
Leonor Cancela

ECTS-ASBMR GOLDEN FEMUR AWARD:
Benjamin Leder

ECTS RECOGNITION AWARD:
Istvan Takacs

ONSITE SELECTED ORAL PRESENTATIONS

Basic/Translational award won by **Maura Strigini** (Saint-Etienne, France, P189). In her work, she showed an improvement of osteoarthritis in an animal model when using a ketogenic diet. Cartilage degrading enzymes, such as MMP13, could be blocked by beta-hydroxy-butyrate induced by ketogenic diet. Nutrition could thus impact inflammation, notably by epigenetic effects, and improve osteoarthritis.

Clinical award won by **Anne Piot** (Lyon, France ND-P036). See page 13

ECTS through the year

ECTS CONGRESS HUNGARY BUDAPEST 10 MAY PRE CONGRESS 11-14 MAY 2019

ECTS is the main organisation in Europe for researchers and clinicians working in the musculoskeletal field, and in addition to the annual congress there is a busy programme of activities through the year.

ECTS Educational activities include the ECTS PhD training course (*next one* is September 7th-10th 2019 in Bologna), webinar series' "Bone, Muscle and Beyond" and "ERC grant winners" and online resources including webcasts from our past congresses, presentations, webinar recordings, abstracts and many other e-learning tools.

The Society also provides a range of travel awards, grants and fellowships for young investigators.

ECTS is also active in promoting the field of bone research in cooperation with other national societies worldwide and there is an ongoing publication of position and policy papers on relevant topics.

Members of the ECTS receive benefits including reduced registration fees for ECTS events and enhanced access to online resources. For more details on how to join, please *see our website.*

Feedback on ECTS 2019

From twitter

@RNOHMBDCentre A tour de force session on FGF23 at #ECTS2019 Just when you think you've understood it there is always more to learn!

@andystone93 Pleasure to present to #ECTS2019! Some great talks in this session so far! #extracellularvesicles

@RyanCRiddle More great bone biology at #ects2019 this morning and sightseeing this afternoon.

@michbal19 Thanks @karl_j_lewis glad you enjoyed the movies. Always exciting to see biology happen in real time! So pleased to have had the opportunity to present this work @ #ECTS2019 in beautiful Budapest. @GarvanInstitute

From congress delegates

Since I am a master student in Medicine, ECTS 2019 was the first congress I attended. I really enjoyed both the clinical and basic science presentations, and especially the New Investigator Mentoring Session and Meet the Expert sessions. It was an amazing experience to present the research that I conducted under supervision. (Master student)

I have been to ECTS for a few years now and take interest in both clinical and basic scientific sessions. It is the best venue to present your bone research results and the formal and informal interactions are really good. It feels like coming home every time at a different place in Europe meeting old and new friends. (Post-doctoral clinical fellow)

I always really enjoy going to ECTS to meet friends and colleagues from Europe and elsewhere to discuss developments in (bone) research and life in general. The atmosphere is always one of cutting edge science, but also of friendship and warm hospitality, and taking place at the most wondrous locations highlighting the impressive history of Europe. (Professor)

From the survey of congress delegates

A great place to hear the latest result in a casual atmosphere

A high level congress

A highly interactive meeting with an excellent level of new information

An excellent chance to interact with top people working in the bone field and know some of the latest in this area

The conference was well organized and different fields were covered. I think this is the best conference in the bone field.

It covers everything new on the bone health/osteoporosis/research

You can discuss the latest advances in research and clinical practice.

Beneficial for research and networking

Best European bone meeting

Best networking in bone in Europe

Broad interest for all in the field, good networking opportunity, collaborative

Comprehensive & well-organised update on basic & clinical research

ECTS Academy

ECTS CONGRESS HUNGARY BUDAPEST 10 MAY PRE CONGRESS 11-14 MAY 2019

The daughter society of ECTS started in 2016 and supports new investigators in developing their careers in the musculoskeletal field, including both basic and clinical researchers.

As well as organising its own programme during the annual congress, the ECTS Academy (*now with their own website*) organises networking and mentoring, and benefits include free registration at the ECTS annual congress and a personal research grant.

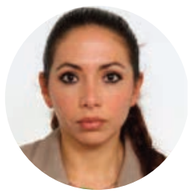
Membership lasts 5 years and is awarded through an annual application process. Profiles of the current members can be *viewed here.*

Congratulations to the latest members (pictured right) of ECTS Academy who were announced in Budapest!

Applications will next be open in autumn 2019, see here for more details.

Ursula Heilmeier

Alex Ireland



Carolina Medina-Gomez

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