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SHORT COMMUNICATIONS

1. Short communications preclinical

New cartilage quality evaluation using cyclic nano indentation: case study with a tool DMOAD compound active in the rat MNX model

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Measurement of cartilage material level properties are lacking in small osteoarthritis (OA) animal model. We evaluated an indentation technique allowing cartilage depth dependant quality in femurs from SHAM and meniscectomized (MNX) rats treated with vehicle and a disease modifying osteoarthritis drug (DMOAD) selected on its in vivo efficacy.

Surgical joint destabilization was performed in 10-week-old female Lewis rats. DMOAD was delivered by oral dosage (20 mg/kg/d) until sacrifice (21 days post-surgery). Femur was used for phase-contrast micro-computed tomography allowing determination of hyaline cartilage thickness of each condyle as well as trabecular and cortical subchondral bone (SB) morphometric parameters. The quality (indentation depth and Young's modulus) of each condyle of the femoral cartilage was evaluated through bioindentation. Cartilage of proximal tibia was evaluated and scored using the OARSI method.

MNX animals showed higher tibial OARSI score and a deterioration of the trabecular SB and to more mineralized SB bone plate. In MNX, depth of indentation increased and Young's modulus decreased at each cartilage depth investigated in the medial condyle (respective average +74% and -35%), indicating softening of the cartilage, while μ CT analysis showed increased hyaline cartilage thickness. At the lateral condyle indentation depth and Young's modulus also respectively increased and decreased without morphologic alteration. DMOAD prevented OA progression in the femur and tibia and normalized femoral biomechanical and trabecular SB alterations without SB bone plate mineralization.

This technique generated data on cartilage quality which were correlated to well-validated readouts and allows to differentiate OA and DMOAD effects.

Osteocyte-specific ablation of Ppar γ improves energy metabolism and prevents fat accumulation but not bone loss in response to a high fat diet

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Ppar γ is a master transcriptional regulator of energy metabolism. We demonstrated that Dmp1-Cre/Lox-mice (KO) have increased bone mass and improved energy metabolism. Here we investigated if Ppar γ -deficiency in Dmp1 cells can prevent high fat diet effects on these parameters. For this purpose, WT and KO male mice aged of 16 weeks received a high fat or chow diet (HF 60% vs CD 10% of fat) for 12 weeks. Lean and fat, bone structure, metabolic rate and tissue temperature were evaluated respectively by echoMRI, microCT, labmaster and infrared camera.

As expected vertebral BV/TV was higher in KO (+39% vs WT, $p < 0.01$) and lower in HF (-12% vs CD) mainly due to an effect on thickness (-17% vs CD, $p < 0.01$) but there was no interaction between diet and genotype. Cortical structure was not affected by diet. Under HF, movement, VO₂ and heat were higher in KO (+41%, +13%, +13% vs WT, $p < 0.05$). Body temperature was also higher, particularly in the BAT-neck region (+1.5% vs WT, $p < 0.01$). UCP1&3 and PPAR β & γ expression in BAT was higher in KO (84%, 139%, 125% and 167% vs WT, $p < 0.01$). Histology and UCP1 expression indicate a browning of the WAT. As a result, glucose and insulin tolerance test were improved in the KO (AUC -22% and -9% vs WT, $p < 0.05$). Finally, HF induced fat mass increase was prevented in KO (+17% vs CD and +44% vs CD in WT, $p < 0.05$) whereas increased in lean mass was greater (+14.2% vs CD and +9.6% vs CD in WT).

In conclusion, ablation of Ppar γ by Dmp1-Cre improves bone mass but does not prevent the deleterious effects of HF on bone. In contrast, it improves BAT activity and insulin sensitivity, preventing fat accumulation and improving glucose homeostasis. How bone regulate energy metabolism under the control of Ppar γ remains to be determined.

Fracture repair in bisphosphonate-treated osteoporotic bone

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Post-menopausal osteoporosis, which is characterized by an increase in bone resorption and high bone turnover, is treated with bisphosphonates to block osteoclast activity. Since bone remodelling is a critical step in fracture healing, it is hypothesized that bisphosphonate therapy may impair the bone's ability to repair fractures.

Ovariectomy (OVX)-induced oestrogen deficiency is used as a model for post-menopausal osteoporosis. Twelve week old mice were OVX and 8 weeks later, the bisphosphonate Alend-

ronate was injected 2x/week until sacrifice. After 5 weeks of Alendronate treatment, a 0.2 mm osteotomy was introduced into the femora and the defect was stabilized with non-rigid and rigid plates, respectively. Animals were sacrificed 1 and 5 weeks after the osteotomy for histological and MicroCT analysis.

A 2-fold increase in BV/TV of lumbar vertebral bodies was observed in Alendronate treated sham and OVX animals compared to controls. Treatment with Alendronate preserved or augmented BV/TV by reducing the bone loss in OVX animals and increasing the BMD in sham animals. Although callus formation could be seen only 5 weeks post implantation in the non-rigid fixation system in all experimental conditions, osteotomized femora stabilized with non-rigid fixations and treated with Alendronate formed a large callus with a decreased degree of mineralization compared to animals treated with vehicle.

The increased callus in bisphosphonate-treated animals might be a consequence of the insufficient primary stability at the defect site coupled with an inhibition of the resorption activity of osteoclasts and may suggest that the remodeling process required for normal bone healing is impaired.

The efficacy of local bisphosphonate and BMP-2 delivery in improving bone mass and mechanical implant stability

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Because of low bone mass and reduced mechanical properties, fixation in osteoporotic patients is still challenging. In the present study, our aim was to improve implant stability in osteoporotic bone using a hyaluronan hydrogel for local delivery of bisphosphonates (BP) and bone morphogenetic protein 2 (BMP-2). The hypothesis was that BP would prevent early resorption in response to interventional trauma and BMP-2 would support bone formation, which is impaired in osteoporotic bone.

41 adult female wistar rats were divided into 7 groups: groups 1 and 2 were the healthy controls, groups 3 to 7 were ovariectomized at 13 weeks. All animals received a BaSO₄-PEEK miniscrew in the proximal tibia at 25 weeks. In groups 2 and 4, pure hydrogel was pipetted into the drill hole before screw insertion. ZOL-BMP2 loaded hydrogel was given in group 5. Group 6 received zoledronate systemically, group 7 zoledronate systemically and BMP-2 peri-locally (sub-cutaneous).

Bone mineral density (at 12, 24 and 29 weeks) and implant osseointegration (0, 3, 6, 9, 14, 20 and 28 days post-op) were monitored using in vivo microCT. Post mortem, samples underwent histological examinations.

Our data showed that pure gel is bioinactive in terms of implant fixation. ZOL-BMP2-gel induces significant increase of bone-implant contact and peri-implant bone fraction, mostly

through reduced resorption. In our model, systemic administration did not induce better fixation.

In conclusion, local ZOL-BMP2 delivery with a hyaluronan hydrogel to improve implant stability in osteoporotic bone is a potent alternative to systemic drug administration at significantly lower doses.

2. Short communications clinical

Risk and predictors of subsequent fractures after an atypical femoral fracture

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Objective: Fracture risk after an atypical femoral fracture (AFF) in patients discontinuing or pursuing anti-resorptive drugs (AR) is unknown. The objective of this study was to investigate the incidence and predictors of new fragility fractures and second AFF after an AFF.

Methods: In a longitudinal case-control study, incidence and predictors of subsequent fragility fractures and of second AFF were assessed in 50 subjects with AFF compared to 50 subjects with typical femoral fracture (TFF) matched by age (± 1 year) and gender, and 50 previous or current bisphosphonate users (BP) matched for gender from the Geneva Retired Cohort.

Results: Twenty one patients (42%) with previous AFF sustained a new fragility fracture, compared with 30 (60%) in the TFF group and 7 (14%) in the BP. The risk of a new fracture in the AFF group was similar to the TFF ($p=0.553$), but higher than in BP users ($p=0.003$). AFF predicted subsequent fragility fracture independently of age, BMI, prior fractures history, osteoporosis status, duration of AR drugs and continuation of AR drugs during follow-up (HR 2.88, CI 95% 1.20–6.94, $p=0.018$). Second AFF occurred in 23 subjects with AFF (46%), more frequently in subjects with low BMI and longer duration of AR treatment prior to the initial AFF. Second AFF were more frequent in subjects who continued AR drugs after first AFF (83% vs 35%, $p=0.030$).

Conclusions: AFF is an independent predictor of subsequent fragility fractures. A bone anabolic agent may be considered after an AFF as AR treatments prior to the AFF or continued thereafter is a risk for a second AFF.

Rebound-associated vertebral fractures after denosumab discontinuation: A series of 8 women with 42 spontaneous vertebral fractures

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Osteoporosis (OP) treatments are given for a limited period of time because of a risk/benefit balance. Reversibility of OP treatment is observed by the measurements of bone markers turnover (BMTs) and bone mineral density (BMD). The effect on vertebral fracture (VFX) is difficult to evaluate. The OP treatment discontinuation is associated with an increase of BMTs and a more or less rapid decrease of BMD. Denosumab (Dmab) discontinuation is associated with a severe rebound effect on BMTs and BMD for near 24 months. A recent publication suggests an increase of VFX (Osteoporos Int 2015 Oct 28).

We report the cases of 8 postmenopausal women. They received Dmab 60 mg every 6 months for 2 to 8 doses. The 8 women were on calcium and vitamin D. A wide biological assessment excluded a secondary cause of OP. VFX were documented by MRI.

Five OP women without any prior fragility fracture were treated every 6 months with 4 to 6 Dmab doses. Dmab was stopped because there was no more OP on BMD (3 women 55, 56 and 59 y old), the aromatase inhibitors were stopped (77 y old) and according to the wish of the patient (77 y old). 9 to 16 months after Dmab discontinuation, they presented respectively 5 (D11, D12, L2-L4), 9 (D7-D9, D12-L5), 2 (D11 and D12), 5 (D12-L2) and 9 (D5-D9 and D11-L2) symptomatic spontaneous (SS) VFX.

A 65 y old woman with osteoporosis and 1 prevalent VFX was treated every 6 months with 8 Dmab doses. Ten months after Dmab discontinuation she presented 6 SSVFX (D5, D8, D12, L2-L4).

These 62 y old woman (osteopenia, treated with aromatase inhibitors) received 2 Dmab doses every 6 months. The subsequent Dmab dose was forgotten. Twelve months after the last Dmab dose she presented a D10 SSFx.

A 71 y old woman (one prevalent VFX and one hip fracture) received 2 Dmab doses with a delay of 11 months because of a lack of compliance. Eleven months after the last Dmab dose she presented 5 SSVFX (D12, L2-L5).

These 8 cases show a severe increased risk of vertebral fractures in the 9 to 16 months after the last injection of Dmab. The occurrence of these fractures can be explained by the severe rebound effect observed after denosumab discontinuation. It is urgent to: 1) inform the health authorities and patients of this risk; 2) determine treatment regimens before or at the time of denosumab discontinuation.

Prior exposure to bisphosphonates prevents the rebound of bone turnover markers after denosumab therapy

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Cessation of denosumab (Dmab) treatment is followed by a transient rebound of bone turnover markers (BTM), with an accelerated bone loss and the possibility of a transient increase in bone fragility and fracture risk. We investigated whether bisphosphonate (BPs) therapy prior to Dmab could attenuate this rebound.

In a retrospective longitudinal study, we assessed changes in serum CTX levels in 35 patients (31 women, 4 men, mean age 68.6 years [range 50–84]) up to 17 months after Dmab cessation. Of them, 18 patients had received BP prior to Dmab (mean exposure 6.7 years, range 1–13; mean gap time between BPs exposure and Dmab initiation 3.2 years, range 0–14).

Dmab treatment lasted from 6 months to 4.5 years. In subjects who received only one Dmab injection (n=8), CTX did not rebound after cessation. In 7 out of 9 patients treated with Dmab (mean 5 injections, range 3–8) and without prior exposure to BPs, CTX increased +117% (range 36–233) above the upper limit of premenopausal range by 12 months (range 6–18) after Dmab. In contrast, in 15 out of 18 patients treated with Dmab (mean 3.7 injections, range 3–7) and previously exposed to BPs, CTX remained in the normal range.

This study indicates that the rebound in bone turnover markers occurring after cessation of denosumab in patients who have received multiple injections may be prevented by prior exposure to BPs, likely related to the persistence of BPs in bone. Thus, in the patients with prior long acting BPs exposure, denosumab cessation may not be a concern.

Is there an optimal Trabecular Bone Score (TBS) lumbar spine vertebrae combination to predict Major Osteoporotic Fracture (MOF)? The OsteoLaus Cohort Study

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Guidelines recommend to use the average bone mineral density (BMD) over L1 to L4 for osteoporosis diagnosis and prediction of fracture. Exclusion of vertebrae is recommended according to specific rules (ISCD position). Optimal combination is unknown for TBS, a surrogate of bone micro-architecture. The aim of this study is to test several TBS vertebrae combinations in regard to MOF prediction.

The OsteoLaus cohort included 1500 women 50 to 80 years old. All women had a detailed questionnaire, BMD and TBS

	OR (95 % CI)	AUC (95 % CI)	p < 0.05 vs L14TBS	p < 0.05 vs L12TBS
L1–2 TBS	2.16 (1.80–2.58)	0.73 (0.69–0.76)	ns	–
L1–3 TBS	2.09 (1.74–2.50)	0.72 (0.68–0.75)	ns	ns
L1–4 TBS	1.98 (1.65–2.36)	0.71 (0.67–0.75)	–	ns
L2–3 TBS	1.92 (1.61–2.29)	0.70 (0.66–0.74)	ns	0.04
L2–4 TBS	1.81 (1.52–2.17)	0.69 (0.65–0.73)	0.001	0.001
L3–4 TBS	1.53 (1.29–1.82)	0.68 (0.65–0.72)	0.0002	0.0002

Table 1

Adjusted (age and glucocorticoid status) OR and area under the curve of different combination of vertebrae for TBS

measurements and vertebral fracture assessment. The primary outcome was the prevalence of MOF according to TBS per-vertebral combination. L1–L4 TBS was used as reference value.

Out of 1466 women included in the study (mean age 64.5 ± 7.6 years), 12.7% suffered from MOF. The odd ratios per standard deviation decreased (OR) were 1.53 (1.29–1.80) and 1.80 (1.50–2.15) for the spine and total femur BMD respectively. Adjusted (age and glucocorticoids status) OR and area under the curve of different combination of vertebrae can be found in ► Table 1 for TBS.

It seems that excluding L4 improves the fracture risk prediction. Further prospective studies are needed to confirm these results.

POSTER SESSION

Associations between TBS and BMD, trabecular microstructure and fat mass in the Geneva Retirees Cohort

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Background: A high proportion of fracture occurs in osteopenic subjects. Trabecular Bone Score (TBS) is a texture parameter obtained from the spine DXA image which predicts fractures. The objective of this study was to investigate the associations between TBS, trabecular (Tb) bone microstructure and fat mass in postmenopausal women.

Methods: Seven hundred forty five women (age 65.0 ± 1.4 years) enrolled in the Geneva Retirees Cohort with areal BMD and TBS data were included in the study. Trabecular (Tb) volumetric bone density (vBMD) and microstructure at the distal radius and tibia were assessed by HR-pQCT (Xtreme CT, Scanco Medical, Bassersdorf, Switzerland). Body composition was assessed by DXA.

Results: TBS was positively correlated with lumbar spine aBMD ($r=0.49$), radius and tibia Tb vBMD ($r=0.35$ and 0.29 , respectively) and Tb number ($r=0.29$ and 0.23 , respectively), $p < 0.001$ for all. TBS was negatively correlated with trunk fat mass

($r=-0.19$, $p < 0.001$). In 431 women (58%) with osteopenia (at least one T-score at the spine, hip or femoral neck between -2.5 and -1 , with none ≤ -2.5), 91 (21%) had low TBS (≤ 1.2). Osteopenic women with low TBS (≤ 1.2) had lower lumbar spine aBMD (-3.9% , $p < 0.001$); a trend for lower distal radius Tb vBMD and number (-3.8% for both, $p=0.060$ and 0.144 respectively); and higher trunk fat mass ($+37\%$, $p < 0.001$) compared to osteopenic women with TBS > 1.2 .

Conclusion: These data suggest that lower TBS values compared to BMD observed in some osteopenic patients are mainly related to fat mass rather than to trabecular microstructure.

Monitoring live human mesenchymal stem cell differentiation and subsequent selection using fluorescent RNA-based probes

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Investigating mesenchymal stem cell differentiation requires time and multiple samples due to the destructive endpoint assays performed. Osteogenesis of human bone marrow derived mesenchymal stem cells (hBMSCs) has been widely studied for bone tissue engineering. Recent studies show that the osteogenic differentiation of hBMSCs can be assessed by quantifying the ratio of two important transcription factors (Runx2/Sox9). In previous studies, these transcription factors can only be detected via destructive methods, either intra-cellular immunostaining or PCR. Here we demonstrate a new technique to observe mRNA expression of two genes in individual live cells using two fluorescent probes specific for Runx2 or Sox9 mRNA. The changes of mRNA expression in cells with or without osteogenic induction can be observed in a non-destructive manner. In addition, the osteogenic hBMSCs can be separated based on the relative intracellular fluorescence of Sox9 in relation to Runx2 using fluorescence activated cell sorting (FACS). The isolated cells show different proliferate rates and osteogenic differentiation potential. Relatively homogeneous cell populations with high osteogenic potential can be isolated from the original heterogeneous osteogenically induced hBMSCs within the first week of induction. This offers a more detailed analysis of the ef-

fectiveness of new therapeutics both at the individual cell level, e.g. number of responding cells, and the response of the population as a whole. By identifying and isolating differentiating cells at early time points, prospective analysis of differentiation is also possible, which will lead to a greater understanding of MSC differentiation.

Tissue mechanics of piled critical size biomimetic and biominerizable nanocomposites: formation of bio-reactor-induced stem cell gradients under perfusion and compression

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Perfusion bioreactors are used to solve problems in bone tissue engineering with respect to sufficient nutrient and oxygen supply especially in critical size bone grafts. Biominerizable and biocompatible nanocomposite materials are attractive and suitable scaffold materials for bone tissue engineering because they offer mineral components in organic carriers. Human adipose derived stem cells (ASCs) can potentially be used to increase bone healing, especially when seeded onto a porous electrospun scaffold.

Electrospun nanocomposite disks of poly-lactic-co-glycolic acid and amorphous calcium phosphate nanoparticles (PLGA/a-CaP) were seeded with ASCs and eight disks were stacked in a bioreactor running with normal culture medium (no differentiation supplements). Under continuous perfusion and uniaxial cyclic compression, load-displacement curves as a function of time were assessed during 9 days. Stiffness and energy dissipation were recorded. Moreover, stem cell densities in the layers of the piled scaffold were determined as well as their morphologies and differentiation status (endothelial cell differentiation, chondrogenesis and osteogenesis).

While the stiffness of the cell free constructs increased over time based on the transformation of the a-CaP nanoparticles into flake-like apatite, ASC-seeded constructs showed a constant stiffness. Stem cell density gradients were histologically determined with a linear increase from the bottom to the top of the pile ($r^2 > 0.95$) [1]. Cell morphology was influenced by the flow rate, with stem cells getting more roundish at higher flow rates. Some osteogenesis was found upon osteopontin immunostaining, while no endothelial cell differentiation and no chondrogenesis was triggered.

The fabrication of a critical size bone graft is presented based on a biominerizable bone-biomimetic nanocomposite with preserved stiffness when seeded with ASCs. The cell densities of ASCs inside the piled construct varied with a linear gradient.

Beginning osteogenesis was triggered by the dynamic culture conditions including perfusion and compression.

References: [1] Baumgartner W et al. J Mech Behav Biomed Mater 2015; 47: 124–134.

BMP antagonists modulate RANKL dependent osteoclast formation

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Osteoinductive growth factors, including BMP2 are used in bone regenerative medicine. Induction of antagonists may be the cause for the need of supraphysiological amounts of BMP2 and for BMP2-associated osteolysis. Herein, we hypothesize that antagonists not only limit BMP efficacy but also mediate effects like osteoclastogenesis.

Primary murine OB (2-days old *C57BL/6J* mice) were cultured in media containing $1,25(\text{OH})_2\text{D}_3$ (0/10–8/10–9 M) \pm BMP2 (33/166 nM). Transcript levels of BMP3, Noggin and Gremlin-1 were analyzed by qRT-PCR. M-CSF dependent *Osteoclast Precursor Cells* (*C57Bl/6J*) were grown in media containing M-CSF (30 ng/ml) and RANKL (2.5/20 ng/ml) \pm Noggin, Gremlin-1 and BMP3 (33 nM). Effects of antagonists on OC development were assessed by adding the proteins at days 0–6, 0–3 (proliferation), 4–6 (differentiation). OCs were visualized by TRAP staining, multinucleated ($n \geq 3$) cells were counted.

BMP2 dose-dependently increased mRNA levels of Noggin and Gremlin-1 and decreased BMP3 mRNA in OBs. Noggin and Gremlin-1 with 2.5 ng/ml RANKL enhanced OC formation 10-fold as compared to RANKL alone. Addition of antagonists increased OC formation 3-fold when added during days 0–3, as compared to days 4–6.

OBs exposed to BMP2 express increased levels of mRNA encoding BMP antagonists Noggin and Gremlin-1. The increase in the synthesis of antagonists may account for the low bioefficacy of exogenously added BMP2. Furthermore, the antagonists synergize with RANKL in increasing OC formation when added early in OC development. Consequently, increased expression of antagonists in response to BMP2 may account for the risk of BMP2-associated osteolysis.

An organ-on-chip model of the endothelial barrier to study the role of perivascular cells in bone regeneration

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The identification of mesenchymal stem cells at perivascular sites of the endothelial barrier, suggests that pericytes have a role as multipotent progenitors. Microfluidic technologies have shown the potential to closely mimic the vascular micro-environment and represent an alternative to animal models. The aim of this project was to develop a microfluidic system comprised of a 3D microvascular network embedded in a hydrogel enabling the investigation of perivascular cells in a physiologically relevant context.

A microfluidic mold was fabricated out of polycarbonate and comprises 3 different layers creating an empty chamber upon assembly. A removable microcapillary placed within the chamber enables creation of a microchannel within the gel. Collagen type I was injected into the chamber and polymerized at 37 °C for 60 min. Microchannels were created by careful retraction of the capillary. The chip was connected to a reservoir of endothelial growth medium and perfused using a micro pump. Microchannels were seeded with human umbilical vein endothelial cells (HUVECs) and observed by time-lapse microscopy.

Regular channels (diameter 150 µm) could be created. Time-lapse microscopy revealed efficient cell attachment and complete coverage of the surface of the microchannel. Good viability of HUVECs was observed and vessel sprouting occurred 28 h after initiation of perfusion.

We have successfully developed a perfused microvascular model. The embedding of microchannels within a hydrogel matrix will enable to study cellular cross-talk and cell migration.

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The positive effect of hormone replacement therapy on bone mineral density and trabecular bone score persists after its withdrawal: the OsteoLaus Cohort

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Hormone replacement therapy (HRT) increases BMD but controversy exists regarding residual effect after withdrawal. We aimed to explore the effect of HRT on BMD and bone micro-architecture, assessed by TBS.

The OsteoLaus study included 1,500 women (50–80 years). BMD at lumbar spine (LS), femoral neck (FN) and total hip (TH) as well as TBS were measured. After exclusion of women with current or past anti-osteoporotic treatments, the remain-

ing women were classified according to HRT status as: Never (NU, n=617), Current (CU, n=282) and Past (PU, n=380) Users.

The 3 groups differed in age: 67.4±6.8, 64.0±6.8 and 62.1±8.0 years for PU, CU and NU respectively (p<0.001). After adjustment for age and BMI, BMD and TBS values decreased significantly according to HRT status (CU>PU>NU, p<0.01) with significant between-groups difference for all BMD LS and TH values. BMD FN and TBS differed only when CU were compared to PU or NU (PU vs NU for TBS: p=0.066). TBS was negatively associated with age: BMI-adjusted slopes for 10-year increment were -0.051 (-0.060; -0.041), -0.032 (-0.048; -0.017) and -0.022 (-0.038; -0.005) in NU, PU and CU respectively (p<0.05). Similar pattern was seen for adjusted slopes of BMD with age except for the comparison between PU and NU at FN.

We show for the first time that current HRT use is associated with a significantly better preservation of TBS. The benefits of HRT use for the TBS and the BMD at LS and TH, seem to persist in PU.

An innovative formulation of alendronic acid 70 mg weekly: a buffered effervescent tablet

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Alendronate is still considered as a gold-standard therapy for the treatment of osteoporosis.

The aim is to present an innovative formulation, a buffered effervescent tablet containing an equivalent of 70 mg alendronate.

A bioequivalence study vs alendronate 70 mg weekly tablet as well as a scintigraphic study investigating the effect of the new formulation on gastric emptying and gastric pH are presented. Data from post-marketing experience are given.

A bioequivalence study was conducted in 70 female and 45 male subjects aged 45 to 73 years. Bioequivalence was assumed if the 90% CI of both the treatment ratio T/R of Ae_{0-48} (cumulative amount excreted into urine during the entire period of sample collection) and of E_{max} (maximum excretion rate) were within 80%–125%. For Ae_{0-48} , T/R was 88.14% (82.92–93.69) and for E_{max} , T/R was 90.44% (84.85–96.41), allowing to conclude that both formulations are bioequivalent and thus therapeutically equivalent.

The scintigraphic study showed that gastric pH after ingestion of the buffered solution was immediately buffered to levels above pH 3 meaning that the risk of exposing the stomach and oesophageal lining to acidified alendronate is negligible.

Post-marketing experience since the launch of the buffered alendronate 70 mg effervescent tablet in the US and in EU supports a very promising tolerability profile.

The buffered alendronate 70 mg effervescent tablet is therapeutically equivalent to alendronate 70 mg weekly tablet and it

presents advantages which could result in increased compliance and persistence in osteoporosis treatment.

M-CSF- and GM-CSF-dependent haematopoietic progenitor cells give rise to osteoclasts

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Levels of circulating cytokines are elevated in inflammatory diseases. In synergism with $1,25(\text{OH})_2\text{D}_3$, TNF α and IL-17A induce the release of GM-CSF by murine osteoblasts *in vitro*, resulting in a change in the haematopoietic microenvironment of osteoclasts (OC) and osteoclast progenitor cells (OPC). Herein, the effects of GM-CSF on OC development were further studied.

Non-adherent M-CSF dependent OPC obtained from bone marrow cells were grown for 3 days in media supplemented with M-CSF, with GM-CSF or M-CSF/GM-CSF. The potential of the three OPC pools to develop into OC was assessed by subsequent culture with M-CSF/RANKL.

OPC precultured with M-CSF, GM-CSF and M-CSF/GM-CSF all gave rise to OC. In GM-CSF and M-CSF/GM-CSF treated OPC, levels of transcripts encoding dendritic cell marker CD11c, DC-STAMP and OC-STAMP were 100x higher than those in M-CSF treated OPC. After starting M-CSF/RANKL-treatment, transcripts for CD11c, DC-STAMP and OC-STAMP decreased gradually. In progressing cultures, DC-STAMP/OC-STAMP transcripts increased again along with OC development, as also observed in M-CSF treated OPC. Levels of transcripts encoding OC markers NHA2, CTR and Acp5 increased with OC formation in all OPC pools and correlated with number of OC.

GM-CSF treated OPC express dendritic markers but upon removal of GM-CSF and stimulation with M-CSF/RANKL they reverse their phenotype and give rise to OC with similar resorption activity as OC generated from M-CSF treated OPC. Progenitors generated in presence of GM-CSF have a high potential to form OC and may lead to an increased number of OC upon homing to bone, causing accelerated bone resorption.

The BMP2 variant L51P rescues bone formation of human mesenchymal stem cells in the presence of intervertebral disc cells

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The intervertebral disc (IVD) is an avascular tissue with a nearly absent self-healing potential. While the clinical gold stan-

dard treatment of disc-related degeneration is spinal fusion, minimally invasive surgical options such as laparoscopic anterior spinal fusion exists and results in an incomplete discectomy of the disc. We previously showed that IVD cells hinder the osteogenic differentiation of mesenchymal stem cells (MSC) *in vitro* (1). Within the present study, we aimed to investigate the contribution of bone morphogenetic proteins (BMP) in bone formation of MSC.

Human bone marrow-derived mesenchymal stromal cells were co-cultured with IVD cells in the presence of L51P, a BMP2 variant with osteoinductive potential via inhibition of noggin (2). The osteogenic differentiation was evaluated by gene expression, alkaline phosphatase (ALP) activity and histology.

IVD cells expressed BMP antagonists, namely noggin, gremlin and chordin as measured by transcript and protein levels. The osteogenic differentiation of MSC was hindered by IVD cells as detected by Alizarin red staining and ALP activity. L51P added to the cultures induced bone formation by interfering with the IVD cells' secreted BMP antagonists.

Conclusions: The IVD cells secrete BMP antagonists, which are responsible for bone non-fusion. The concept of antagonizing endogenous BMP inhibitors with L51P may represent a promising clinical option to augment bone regeneration during spinal fusion.

References: [1] Chan SC, Tekari A, Benneker LM, Heini PF, Gantenbein B. Osteogenic differentiation of bone marrow stromal cells is hindered by the presence of intervertebral disc cells. *Arthritis Res Ther* 2015; 18: 29. [2] Keller S, Nickel J, Zhang JL, Sebald W, Mueller TD. Molecular recognition of BMP-2 and BMP receptor IA. *Nat Struct Mol Biol* 2004; 11: 481–488.

Zehnjährige Denosumab-Behandlung bei postmenopausalen Frauen mit Osteoporose: Ergebnisse der FREEDOM-Erweiterungsstudie

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Osteoporose ist eine schwere chronische Erkrankung, die eine langfristige Behandlung erfordert. Daher sind langfristige Wirksamkeits- und Sicherheitsdaten von großer Bedeutung. Denosumab (DMAb) wird weltweit in über 80 Ländern zur Behandlung von postmenopausalen Frauen mit Osteoporose angewandt. Die Wirkung der DMAb-Behandlung über bis zu 10 Jahre wurde in der 3 Jahre dauernden FREEDOM-Studie

und in der 7 Jahre dauernden Verlängerung dieser Studie untersucht. Im vorliegenden Beitrag stellen wir die Ergebnisse des letzten Verlängerungsjahres vor, die auf einer bis zu 10 Jahre langen, durchgängigen DMAB-Behandlung beruhen.

Während der Verlängerung nahmen die Probandinnen 60 mg DMAB alle 6 Monate sowie Kalzium und Vitamin D täglich. Für diese Analyse erhielt die Langzeitgruppe eine 10 Jahre lange DMAB-Therapie (3 Jahre im Rahmen der FREEDOM-Studie und 7 Jahre im Rahmen der Verlängerung); die Cross-over-Gruppe erhielt eine 7 Jahre lange DMAB-Behandlung (3 Jahre Placebo im Rahmen der FREEDOM-Studie und 7 Jahre DMAB im Rahmen der Verlängerung).

Von den 4550 Probandinnen, die in die Verlängerungsphase eintraten, nahmen 2784 (61%) zu Beginn von Jahr 10 weiterhin an der Studie teil. Von diesen Probandinnen nahmen 2212 (80%) ihren Abschlusstermin nach 10 Jahren wahr, 120 (4%) brachen ab, und 452 (16%) befanden sich zum Zeitpunkt der Einreichung des vorliegenden Beitrags noch in der Studie. In der Langzeitgruppe traten weitere signifikante Knochendichte-Zugewinne auf; die durchschnittlichen 10-Jahres-Steigerungen gegenüber den FREEDOM-Ausgangswerten betrugen 21,6% für die Lendenwirbelsäule und 9,1% für den gesamten Hüftbereich. Die Crossover-Gruppe wies kumulative 7-Jahres-Zugewinne von 16,3% (Lendenwirbelsäule) und 7,3% (gesamter Hüftbereich) gegenüber den Ausgangswerten der Verlängerungsstudie auf (▶ Abb. 1; alle $p < 0,0001$ im Vergleich zu den Ausgangswerten von FREEDOM, zu den Ausgangswerten der Verlängerung und zur vorherigen Messung). In beiden Gruppen wurden vergleichbare, anhaltende Rückgänge bei den Knochenumsatzmarkern beobachtet. Zum Ende des Verabreichungszeitraums schwächte sich die Wirkung auf charakteristische Weise ab. Die Jahresraten neuer vertebraler und nicht-vertebraler Frakturen blieben niedrig. Insgesamt entsprachen die Inzidenzraten unerwünschter Ereignisse und schwerer unerwünschter Ereignisse den zuvor in der Verlängerungsstudie gemeldeten Daten.

Die DMAB-Behandlung für bis zu 10 Jahre ging mit einer anhaltenden Verringerung des Knochenumsatzes und mit einem

anhaltenden Zugewinn der Knochendichte einher. Das Nutzen-Risiko-Profil von DMAB blieb in dieser alternden Population von postmenopausalen Frauen unverändert.

Corrélation entre le score T de la hanche totale (HT) lors de la DMO et l'incidence des fractures non vertébrales (NVFX) sous traitement par dénosumab (DMAB) pendant 10 ans maximum

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Objectif : Etudier la relation entre le score T obtenu pour la DMO de la HT et l'incidence de la NVFX pendant un traitement de 10 ans par DMAB.

Matériels et méthodes: Les femmes ont reçu du DMAB pendant 3 ans au cours de l'essai FREEDOM (N=3902); une grande partie d'entre elles (N=2343) a été recrutée pour la phase d'extension et a ainsi continué à prendre du DMAB pendant 7 années supplémentaires, soit 10 ans au total de traitement ininterrompu. Un modèle fondé sur des mesures répétées a été utilisé pour estimer les scores T lors de la DMO pour chaque sujet pendant tout le suivi, en particulier à chaque estimation de la NVFX parmi tous les sujets à risque au moment de la FX. Le modèle à risques proportionnels de Cox a été ajusté en fonction du délai avant NVFX, marquant la réponse au traitement, et de l'évolution dans le temps du score T de HT lors de la DMO comme covariable variant dans le temps.

Résultats: L'incidence des NVFX a été moindre avec un score T de HT lors de la DMO plus élevé (▶ Fig. 1). Par exemple, des

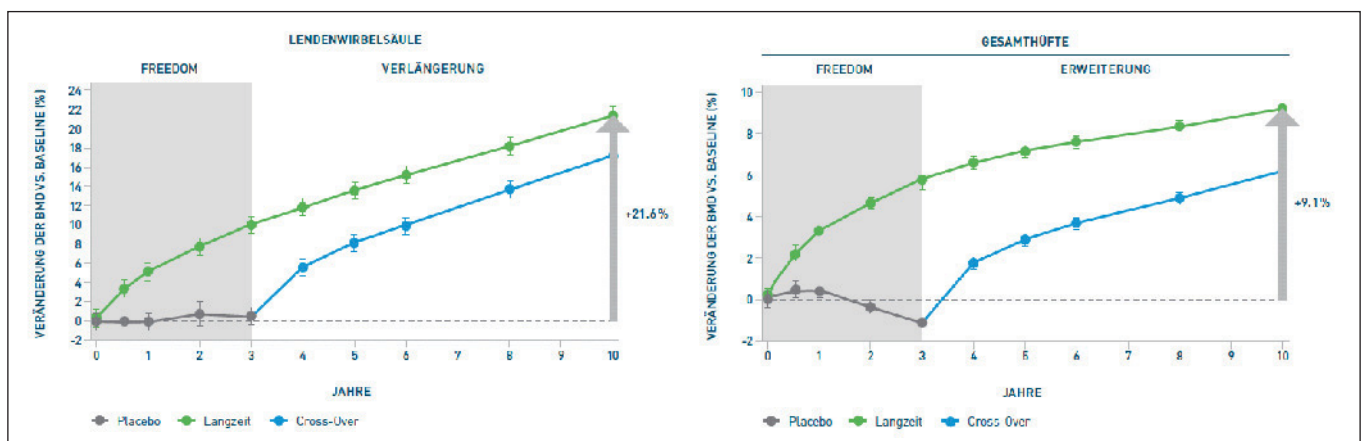


Abb. 1 Die durchschnittlichen 10-Jahres-Steigerungen gegenüber den FREEDOM-Ausgangswerten

scores T de HT de $-2,5$ et $-1,5$ lors de la DMO ont été associés à une incidence des NVFX à 1 an d'environ 3,0% et 2,0%. Les scores T supérieurs à $-1,5$ semblent avoir un impact minime sur la réduction de l'incidence des NVFX, de façon analogue à ce qui est constaté chez les sujets non traités. Cette corrélation inverse entre le score T de HT lors de la DMO et l'incidence des NVFX existe quel que soit l'âge et les FX antérieures (données non présentées).

Conclusion: Des scores T de HT plus élevés lors de la DMO, sous traitement par DMAB, sont associés à une plus faible incidence des NVFX, au même titre que la corrélation déjà établie chez les patients naïfs de tout traitement. Toute amélioration de la DMO de même ampleur aboutirait à des réductions différentes du risque de FX en fonction de la DMO initiale. Nos recherches confirment l'importance des mesures de la DMO chez les patients suivant un traitement contre l'ostéoporose pour disposer d'un élément prédictif du risque de FX et étaye notre hypothèse selon laquelle l'évaluation d'un score T spécifique doit faire partie des objectifs thérapeutiques.

The role of iron in the development of osteoclasts

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Introduction: Iron is the most abundant trace metal in humans. To avoid iron metabolism disorders such as anemia, iron homeostasis must be tightly regulated. Membrane iron transporters, such as ferroportin and DMT1, are critical proteins for the regulation of systemic and cellular iron homeostasis. Recently we found an increase in transcript levels of DMT1, a membrane transporter for iron uptake, during the in vitro development of osteoclasts from progenitor cells. We therefore wish to investigate the direct effects of iron on the development of osteoclast lineage cells focusing on one target, DMT1.

Methods: M-CSF-dependent, non-adherent osteoclast progenitor cells derived from C57Bl/6J mice were grown in culture medium supplemented with two DMT1 inhibitors (AE147 and MPO11A1) and a reference compound (CISMBI) at concentrations of 0, 1, 3, 10, 30, and 60 μM . AE147 and MPO11A1 were previously synthesized and tested by the groups of Rey-

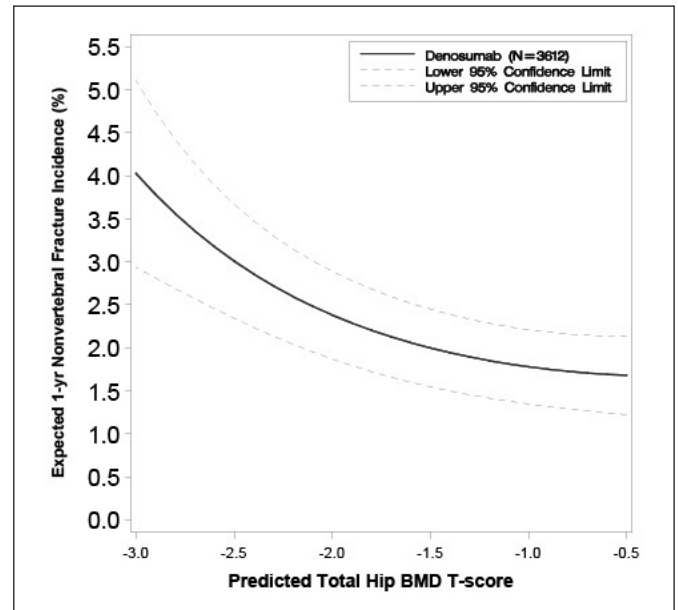


Fig. 1 Relation entre risque de fracture non vertébrale et score T de hanche totale attendu lors de la DMO (analyse finale à 84 mois). Inclut des sujets avec fractures, randomisés dans le bras dénosumab, issu de l'étude FREEDOM, depuis la phase initiale jusqu'au mois 84 de la phase d'extension; N=nombre de sujets randomisés dans le bras dénosumab dans l'étude FREEDOM dont le score T de hanche totale lors de la DMO a été mesuré au début de l'étude FREEDOM puis évalué au moins une fois lors de l'étude FREEDOM ou la phase d'extension, y-axis: Incidence à un an de fracture non vertébrale attendue (%), x-axis: Score T attendu pour la HT lors de la DMO

mond and Hediger, which are part of the NCCR TransCure network. After cultures of 3 and 5 days, osteoclastogenesis was assessed by the activity of the osteoclast marker enzyme TRAP in cell lysates. Cell viability was determined using an XTT-Assay.

Results: Cell viability and osteoclastogenesis decreased dose-dependently in the presence of both competitive inhibitors, with MPO11A1 exerting stronger inhibition than AE147. In contrast, CISMBI did not affect cells viability yet fully blocked osteoclastogenesis at 60 μM .

Conclusion: Specific DMT1 inhibitors appear to negatively affect osteoclastogenesis. However, whether this is a consequence of a specific effect of perturbed iron transport or of unspecific toxic effects requires further studies.

■ Programm (Stand bei Drucklegung)

Annual Meeting SVG0/ASCO und SBMS 2016

12. Mai 2016, Inselspital Bern (Auditorium Ettore Rossi)			
08.45 Uhr	Registrierung		
09.00 Uhr	Begrüßung Präsidenten SVG0 und SBMS		
09.05 Uhr	„State of the Art“-Lecture Preclinical Evolution of bone tissue engineering strategies Prof. Ivan Martin, Basel Chair: Prof. D. Pioletti		
09.40 Uhr	Short communications preclinical Vorsitz: P. Richards, P. Ammann		
10.30 Uhr	Kaffeepause		
10.50 Uhr	Short communications clinical Vorsitz D. Frey, K. Lippuner		
11.40 Uhr	„State of the Art“-Lecture Translational Hypophosphatasia: From Bench to Bedside Prof. Franz Jakob, Würzburg Chair: O. Lamy		
12.15 Uhr	Lunch		
SVG0/ASCO (Auditorium Ettore Rossi)		SBMS (Kursraum 1)	
Chair: C. Meier, M. Birkhäuser		Chair: D. Pioletti	
<i>Update Metabolic Bone Disease</i>		<i>„State of the art“-Lecture Preclinical</i>	
13.00 Uhr	Prise en charge des patients souffrant de maladie rare en Suisse: du changement en 2016 Dr. med. Bérengère Aubry-Rozier, Lausanne	13.00 Uhr	Mineral disorders in teeth and potential strategies for their repair: the „genetics/stem cells/tissue engineering“ amalgam Prof. Thimios Mitsiadis, Zürich
13.30 Uhr	Nouveautés dans les traitements de l'ostéoporose Prof. Serge Ferrari, Geneva	13.40 Uhr	<i>Poster presentations preclinical</i> Chair: D. Pioletti
14.00 Uhr	Prévention de la perte osseuse lors du traitement du cancer du sein par anti-aromatases Dr. med. Emmanuel Biver, Geneva		
<i>Update Guidelines/Research</i>			
14.30 Uhr	HRT: Neue Empfehlungen SMG, NICE und Endocrine Society Priv.-Doz. Dr. Petra Stute, Bern		
15.00 Uhr	Einfluss der Sarkopenie auf das Frakturrisiko Prof. Heike Bischoff-Ferrari, Zürich	15.00 Uhr	Assemblée Générale SBMS
15.30 Uhr	Kaffeepause		
16.00 Uhr	Prize Session		
16.20 Uhr	„State of the Art“-Lecture Clinical Identification of patients at high fracture risk Frau Dr. med. Karine Briot, Paris Chair: S. Ferrari		
16.45 Uhr	Assemblée Générale SVG0/ASCO		