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ORAL POSTERS – CLINICAL

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OP1 (P16)

HR-pQCT and DXA Changes in Bone Density and Microarchitecture Over Two Years in Young Adults

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Timing of peak bone microarchitecture parameters measured with high-resolution peripheral quantitative computed tomography (HR-pQCT) may differ from dual x-ray absorptiometry (DXA) due to resolution or skeletal site differences. We aimed to assess differences in timing of peak values for microarchitecture and bone density using HR-pQCT and DXA. Females (n=42, 21.5 yrs) and males (n=33, 21.6 yrs) from the Calgary youth cohort of the Canadian Multicentre Osteoporosis Study (CaMos) participated in a 2-year follow-up study. DXA (Hologic, USA) scans of the left hip provided areal bone mineral density (aBMD) of femoral neck (FN) and total hip (TH). Non-dominant radius and left tibia were scanned using HR-pQCT (Scanco Medical, Switzerland). To compare repeat scans, automated 3D image registration was conducted (IPL software). Total volumetric BMD (Tt.BMD), cortical BMD (Ct.BMD), trabecular BMD (Tb.BMD) and cortical porosity (Ct.Po) were assessed. Repeated measures ANOVA determined age-related bone change. DXA-derived aBMD decreased at the hip for females and males by 0.5-1.0% per year ($p<0.01$). At the radius, volumetric BMD increased by 0.6-1.0% per year for males and females ($p<0.01$). There were no significant changes in Ct.Po at the radius ($p>0.05$). At the tibia, there were no significant changes in volumetric BMD; however, Ct.Po increased 7% for females and 10% per year for males ($p<0.01$). Our findings are consistent with known DXA peaks occurring before 20 years at the hip. An increase in HR-pQCT-derived BMD parameters at the radius, suggests peak density at the radius occurs at an age >22 years. At the tibia, all HR-pQCT-derived BMD parameters remained stable, suggesting peak density may occur before 22 years. Like DXA, timing of peak HR-pQCT values differ according to skeletal site (radius vs. tibia). Cohorts used for HR-pQCT normative data should include recruitment of subjects <22 years of age to capture peak measurements for all sites.

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OP2 (P48)

A New Method for 3D-QCT of the Distal Forearm Using Clinical Whole-Body CT Scanners

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Introduction: For peripheral QCT usually dedicated scanners like the XtremeCT (ScancoMedical AG, Switzerland) are used. However, scan times are long and only small volumes or single slices can be acquired. In contrast, with widely available clinical whole-body CT scanners, 10 to 20cm long scans of both distal forearms can be acquired in seconds. We developed a 3D analysis method using 3D segmentation and an automatic placement of analysis volumes of interest (VOIs) for determining bone mineral density (BMD), content (BMC) and cortical thickness.
Methods: 23 datasets of both distal forearms of young professional male climbers (n=11) and age and BMI matched healthy controls (n=12) were acquired on a SIEMENS VolumeZoom (80kV, 122mAs, 24cm FOV, 15cm scan, 1.0mm slice thickness, kernel B60s, Siemens Osteo Phantom for BMD calibration). Endosteal and periosteal surfaces of radius and ulna were segmented using a multi-step local adaptive thresholding procedure. Four anatomically adapted VOIs (ultra-distal, distal, mid, proximal) were automatically defined in the radius.
Results: Integral, cortical and trabecular BMD and BMC and cortical thickness were measured in each VOI (results are denoted as: climbers, controls, p-value). Young adult climbers showed significantly increased integral and cortical BMD (ultra-distal: 762±50mg/cm³, 653±48mg/cm³, $p<0.001$; distal: 1074±35mg/cm³, 1018±59mg/cm³, $p<0.05$) and BMC as well as cortical thickness (ultra-distal: 0.97±0.08mm, 0.87±0.06mm, $p<0.001$; distal: 1.2±0.1mm, 1.1±0.1mm, $p<0.05$) in both distal VOIs. Trabecular BMD (170±18mg/cm³, 142±36 mg/cm³, $p<0.05$) and BMC was significantly higher in the ultra-distal VOI. Results for mid and proximal VOIs were not significantly different.
Conclusion: A new 3D-QCT analysis program for the distal forearm was developed specifically exploiting advantages of whole-body CT scanners. It can be used to determine BMD, BMC and cortical thickness at any position along the radius included in the scan. The study showed that climbing predominantly affects bone parameters in the most distal regions of the forearm.

OP3 (P391)

Increased Cortical Porosity in Women and Men with Diabetes: the Framingham Osteoporosis Study

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Although type 2 diabetes mellitus (DM) patients have normal or increased BMD as determined by DXA, risk of fracture is greater in DM than non-DM. This paradox has led to investigation of deficits in skeletal microarchitecture that may be responsible for increased fracture risk in DM. We conducted a community-based study of women and men to compare bone microarchitecture by DM status. Participants included 627 members (367 women, 260 men) of the Framingham Osteoporosis Study, mean age 65 yrs (range, 45-84). We defined DM as fasting glucose (FG) $\geq$126 mg/dl or use of DM medication and pre-DM as FG=100-125 mg/dl. Bone microarchitecture and density of the tibia and radius were measured by HR-pQCT (XtremeCT, SCANCO). Linear regression was used to calculate means (± SEs) for HR-pQCT bone indices according to DM status, adjusted for age, sex, and weight. 71 (40 men, 31 women) cohort members had DM (11%). At the tibia, persons with DM had significantly higher cortical porosity (11.17% ± 0.38 vs. 10.03% ± 0.13, p<0.01) and lower cortical vBMD (796.74 ± 8.02 vs. 814.00 ± 2.76, p=0.04) compared with non-DM. In contrast, trabecular vBMD and trabecular number were higher in DM, although differences were not statistically significant. Further, cortical porosity in the tibia was highest in DM (11.19% ± 0.38), intermediate in pre-DM (10.10% ± 0.19), and lowest in the non-DM group (9.95% ± 0.18); trend, p=0.02. HR-pQCT measures at the radius were not associated with DM. Results were similar when stratified by sex. In this community-based study, we found that women and men with DM had deficits in cortical bone at the tibia. To reduce the burden of skeletal fragility in DM, it will be important to determine whether deficits in cortical bone explain increased fracture risk observed in older adults with DM.

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OP4 (P218)

Serum Sclerostin is Associated with Impaired Insulin-Induced Whole-Body Glucose Uptake in Obesity

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Background: Disturbed Wnt signalling has been implicated in numerous diseases, including type 2 diabetes and the metabolic syndrome. Wnt and insulin signalling pathways exhibit cross-talk at multiple levels. Wnt proteins enhance phosphorylation of insulin signaling molecules in skeletal muscle cells. Sclerostin is a bone-derived circulating inhibitor of the Wnt signalling pathway and is increased in obesity. Obesity is also characterised by defects in insulin signalling in muscle cells resulting in peripheral insulin resistance. It is hitherto not reported whether circulating Wnt signalling inhibitors are related to impaired insulin-induced effects on glucose uptake in lean and/or obese individuals. To examine whether serum sclerostin is associated with insulin-induced whole-body glucose uptake and whether this association differs between obese and lean individuals.

Methods: Whole-body glucose uptake (WBGU) was assessed by a hyperinsulinaemic euglycaemic clamp and expressed per lean body mass in lean and obese healthy women (BMI$\leq$25 vs. BMI$\geq$30 kg/cm^2). Serum sclerostin was measured using the MesoScale Discovery chemiluminescence assay.

Results: Twenty-one lean and 21 obese women were included (mean±SD; age 37±11 years, BMI 22.0±2.0 kg/cm^2 and n=21; age 39±12 years; BMI 34.8±4.9 kg/cm^2, respectively). Serum sclerostin was higher in obese as compared with lean women (123±33 vs. 93±33 ng/L, p=0.006). Insulin infusion did not affect serum sclerostin. Due to interaction for obesity in the relationship between serum sclerostin and WBGU (p=0.014), further analyses were stratified for obesity. In obese but not lean women serum sclerostin was related to WBGU (-0.089±0.028 mg•kg^{-1}•min^{-1}, p=0.005) after adjustment for age. Further adjustment for BMI attenuated the association (-0.067±0.028 mg•kg^{-1}•min^{-1}, p=0.026). This relationship was not confounded by renal function, blood pressure or lipid levels.

Conclusion: Serum sclerostin is inversely related to insulin-induced whole-body glucose uptake in obese but not lean women. Further studies after direct effects of sclerostin on insulin action are warranted.

Disclosure: The authors declared no competing interests.

OP5 (P392)

The Effect of Treatment with Intact PTH on Undercarboxylated Osteocalcin and Measures of Energy Metabolism in Hypoparathyroidism: a Randomised, Placebo-Controlled Trial

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Osteocalcin (OC) is produced by osteoblasts in an undercarboxylated form (ucOC). Recently ucOC has been shown to influence energy metabolism in mice. In hypoparathyroidism (HPT) secretion of parathyroid hormone (PTH) is decreased or absent suppressing bone turnover. We recently randomised patients with HPT to treatment with PTH or placebo and demonstrated a marked increase in bone turnover. In particular, OC increased by more than 800%. We therefore investigated in the same cohort if there was a similar increase in ucOC and if that increase affected energy metabolism. 62 patients with HPT were randomised to treatment with either 100 µg PTH1-84 (Preotact®, Nycomed, Denmark) or placebo for 24 weeks. We measured fat mass using DXA at baseline and after 24 weeks. We took fasting blood samples at baseline and after 24 weeks. Fasting plasma glucose was measured using standard

techniques and. By using ELISA we determined ucOC, leptin, adiponectin, and insulin. As a measure of insulin resistance we calculated HOMA-IR. During treatment ucOC increased by 1185.0±814.4% in the PTH treated group and by 69.3±79.4% in the placebo group ($p<10^{-50}$). In addition, body weight decreased by 1.1±4.0% in the treatment group and increased 0.8±2.5% in the placebo group (p=0.04). Glucose, adiponectin, leptin, HOMA-IR, total body fat mass, or truncal fat did not change significantly. Moreover, there was a significant and negative correlation between change in ucOC and change in body weight (p=0.004) or change in total body fat mass (p=0.03). Change in ucOC did not significantly correlate with changes in other parameters. In conclusion PTH treatment significantly increased ucOC and decreased body weight, however, insulin resistance or adipokines were unaffected. An explanation for the weight loos may be subtle hypercalcaemia in PTH treatment inhibiting appetite. Our data do not support a role for ucOC in energy metabolism in humans.
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OP6 (P274)

Routine Laboratory Examination in Osteoporosis in Primary Care: Uncertainty About the Benefits

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Background: Primary osteoporosis is the main cause of reduced quality of bone. In some cases however, osteoporosis is caused by an underlying disease. For this reason routine laboratory examination is advised in most guidelines. The prevalence of laboratory abnormalities in clinical setting has been established in previous studies. There is a lack of similar data in primary care populations, nor are there studies that have evaluated the medical benefit of routine laboratory examination. The goal was assessment of the prevalence and practical consequences of abnormalities in routine laboratory examination in osteoporosis in primary care.
Method: In a population study of women≥65 years with clinical risk factors for osteoporosis (n=2320), and in a population (n=2699) of persons referred for bone densitometry by GPs, we collected blood samples (including: ESR, TSH/T4, Calcium, Albumin, Creatinine and 25-hydroxyvitamin D) regardless if there was osteoporosis or not. Of all participants with one or more abnormalities, we collected data from the GPs about already existing diagnoses and previous laboratory abnormalities and the consequences for treatment in one year follow up.
Results: The prevalence of laboratory abnormalities in participants with osteoporosis (n=1334) except for 25-hydroxyvitamin D was 4.9%, which was a new finding in 1.8%. In 0.7% this influenced treatment or led to new diagnoses connected with osteoporosis. The prevalence of 25-hydroxyvitamin D≤50nmol/L was 50%. There was no association between the presence of osteoporosis or (recent) fractures and laboratory abnormalities (OR 1.00, 95%CI: 0.92-1.08, respectively OR 1.28, 95%CI: 0.88-1.87).
Conclusion: In these primary care populations the prevalence of relevant laboratory abnormalities was limited and there was no association with osteoporosis. Since all patients with osteoporosis are treated with vitamin D supplementation, the need for measurement of 25-hydroxyvitamin D is debatable. The results of this study should be a reason to reconsider the advice for routine laboratory examination in osteoporosis guidelines.
Disclosure: The authors declared no competing interests.

OP7 (P49)

Low Body Mass Index in Young Women Affects BMD and Bone Bending Strength

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Background: Adolescence and young adulthood is a critical period for the development of peak bone mass. In addition, low bone mineral density (BMD) is a frequently overlooked consequence of eating disorders in this population. Thus, bone loss that leads to fracture in the young women represents an area of active research and clinical investigation. The purpose of this study is t**o** investigate whether low BMI is associated with low bone mineral density (BMD) and bone bending strength in young women, and whether any such association could be explained by low levels of habitual physical activity, bone turnover markers or low percent body fat. The secondary purpose of this study is to examine the difference in mean BMD and bone bending strength between underweight body mass index (BMI) ≤ 18.9 kg/m^2 and normal and overweight BMI 19.0 to 29.9 kg/m^2 in young females. We hypothesised that young women with low BMI is associated with low BMD and low tibial bending strength, such association may be explained by low levels of habitual physical activity, low bone turnover marker activity or low percent body fat.
Method: Thirty females, age 18-30 years, with a BMI ≤18.9 kg/m^2 (n=15) and a BMI between 19–29.9 kg/m^2 (n=15) served as study subjects. The dependent variables are BMD and bone bending strength. BMD values were expressed as Z-score units and in absolute values for femoral neck, lumbar spine, forearm, and leg obtained with a dual-energy X-ray absorptiometry (DXA, Hologic Discovery-W scanner, Bedford, MA, USA). Bone bending stiffness of the tibia and ulna were determined using a Mechanical Response Tissue analyzer called MRTA (NASA, Mountain View, CA, USA) and bone turnover markers by ELISA using bone biomarker kits (Quidel Corporation, San Diego, CA, USA).
Results: Weight, height, FM, LBM, Body Fat % and tibia length were significantly lower (all p<0.05) in the low BMI group compared with the normal+high BMI group. Relative to the normal+high BMI group, the low BMI group also exhibited significantly lower tibial bending strength (TEI) (148 vs. 195 Nm^2, p<0.05), Femoral neck (FN) BMD (z-score -2.44 vs. 0.15), lumbar spine (LS) 1-4 BMD (z-score -2.08 vs. 0.09), whole body (WB) BMD (z-score = -0.50 vs. 0.53), forearm BMD (z-score -0.5 vs. 6.2), total hip (z-score -0.89 vs. 0.2) (all p<0.05). Multiple regression results show that significant independent predictors of TEI are total hip BMD (β = 2.51) and LS1-4 BMD (β = -1.40) (R^2 = 0.367, p<0.05). Simple correlation coefficient between ulnar bending strength (UEI) and ulna BMD (r=0.25, p=0.27) and between TEI and hip BMD (r=0.29, p=0.12) were low.

Conclusion: We concluded that young women with BMI <18.9 kg/m^2 have significantly low tibial bending strength, and low BMD for whole body, distal arm, hip, FN, and LS1-4 with z-scores ranging from -0.5 to -2.44. Total hip BMD and LS1-4 BMD were significant determinants of tibial bending strength in young females. (Funded by RSCA Mini Grant Award, Cal Poly Pomona, CA).
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OP8 (P275)

The Fracture Patient Phenotype: Bone and Fall-Related Risk Factors in Patients at the Fracture Liaison Service

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Background: Fractures are the result of bone- and fall-related risk factors. We evaluated the prevalence of both bone- and fall-related risk factors in patients visiting the Fracture Liaison Service (FLS).
Methods: A retrospective chart review was performed of all consecutive patients with a recent fracture visiting the FLS for fracture risk evaluation.
Results: Out of 3,057 patients aged 50-90 years, 1,111 consecutive patients who were able and willing to be evaluated at the FLS, were included (71% women, mean age 65.2 yrs.), 8% with a hip, 29% with a major, 57% with a minor and 6% with a finger or toe fracture. At least one bone- or fall-related risk factor was present in respectively 90% and 83% of the total population. At least one fall-related risk factor was more frequently present in women (women vs. men: 86% vs. 78%, p=.002) and at higher age (80-89 vs. 50-59 yrs.: 100% vs. 76%, p=<.001). At least one bone-related risk factor was more frequently present in women (women vs. men: 91% vs. 87%, p=.043), with lower BMD (osteoporosis vs. normal BMD: 94% vs. 83%, p=<.001), with more severe fx (hip vs. finger or toe fx: 90% vs. 88%, p=.016) and with higher age (80-89 vs. 50-59 yrs.: 100% vs. 83.7%, p=<.001). Most patients had a combination of bone- and fall-related risks (77%), 12% had only bone-related risks, 6% had fall-related risks and only 4% had no bone- or fall-related risk.
Conclusion: Four out of five patients with a recent fracture presenting at the FLS have a combination of bone- and fall-related risk factors. Therefore, careful evaluation of both bone and fall-related risk factors at the FLS will contribute to optimal fracture risk evaluation and to decisions about further fall and fracture prevention.
Disclosure: The authors declared no competing interests.

OP9 (P276)

Roux-en-Y Gastrectomy Results in Greater Increase in Bone Turnover after Surgery than Sleeve Gastrectomy in Morbidly Obese Patients

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Bariatric surgery for severe obesity results in a rapid weight loss and beneficial metabolic effects, but may have negative effects on the skeleton. We evaluated the changes in bone turnover in response to bariatric surgery with two surgical techniques, Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG). Forty-six morbidly obese subjects (mean age 44.9 yrs, BMI 42.1) were operated with RYGB (n=21) or SG (n=25). Twenty-five healthy subjects with normal body weight (mean age 45.8 yrs, BMI 23.0) were recruited as controls. Fasting serum samples were collected before and 6 months after the operation and bone turnover markers (CTX, PINP, TRAcP5b, osteocalcin) were analysed. Volumetric bone mineral density (vBMD) was measured by quantitative computed tomography in a subset of 21 subjects. Both RYGB and SG resulted in a significant weight loss and decrease in fasting plasma glucose and insulin (p<0.001 for all). At baseline, obese subjects had significantly lower levels of bone markers than the healthy subjects (p<0.05). Levels of bone markers increased significantly 6 months after surgery (p<0.001 for all). The median increases in CTX, PINP, TRAcP5b and osteocalcin were greater (p<0.01) after RYGB (303, 162, 72 and 141%, respectively) than after SG (106, 59, 27 and 60%). In the subset with vBMD analysis, vertebral vBMD increased in obese subjects without DM2 (N=13) (p=0.055), while there was no change in obese subjects with DM2 (N=8). Bone markers increased in all obese subjects irrespective of their DM2 status (p<0.05 for all). The surgical method did not affect the change in vBMD (p=0.60). Bone turnover is increased in response to bariatric surgery but is affected by the surgical technique. In contrary to previously published data on areal BMD by DXA, vBMD does not decrease, but may even increase at short term, in non-diabetic patients after bariatric surgery.
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OP10 (P304)

The Association between Serum Uric Acid, Bone Mineral Density, Hip Bone Geometry and Fracture Risk: the role of Age and Vitamin C

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Background: We prospectively investigated the association between uric acid (UA), bone mineral density (BMD) at femoral neck (FN-BMD), hip bone geometry (HBG) parameters and incident fracture risk in elderly men and women and if these associations were modified by age and vitamin C intake.
Methods: Data of 5,074 participants of the Rotterdam Study (RS), a prospective population based cohort, were available (mean follow-up 9,9 years). Serum UA was assed at baseline. FN-BMD was measured at baseline and the 2nd, 3rd and 4th visit of the RS, whereas HBG parameters were measured at baseline and the 2nd and 3rd visit. We fitted linear regression models in generalized estimated equations to study UA in relation to FN-BMD and HBG. Cox proportional hazard regression models were used to look at the association of serum UA with fracture risk. All associations were corrected for age, gender, and confounders.
Results: Serum UA levels (per SD increase) were associated with higher FN-BMD (β=0.007, *P*=0.0002), thicker cortices (β=0.002, *P*=0.014) and lower bone width (β=-0.013, *P*=0.008). Also, UA was related to lower cortical buckling ratio (β=-0.19, *P*=0.005). Hazard Ratios (HRs) per SD increase of baseline UA levels for the development of any type of incident fractures, non-vertebral fractures and osteoporotic fractures were 0.93 (95%CI=0.86-0.995), 0.92 (95%CI=0.86-0.998) and 0.91 (95%CI=0.84-0.977), respectively. All associations were more prominent in older individuals and in participants with high intakes of vitamin C (>median) (interactions with age or vitamin C both *P*<0.05).
Conclusion: Higher levels of serum UA are associated with higher BMD (at expense of thicker cortices and narrower bone diameters) and could be a protective factor in bone metabolism among men and women. However, interactions with age and vitamin C may be present.
Disclosure: The authors declared no competing interests.

OP11 (P305)

SSRIs and Change in Bone Mineral Density in a Population-Based Study of Middle-Aged and Older Men and Women

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Selective serotonin inhibitors (SSRIs) are assumed to play a role in bone metabolism via the modulation of serotonin levels. Several cross-sectional studies reported an association between SSRI use and lower bone mineral density (BMD). However, longitudinal studies showed conflicting results and had limited longitudinal exposure information. Therefore, our objective was to investigate the association between SSRIs and BMD, and changes in BMD in a longitudinal study with 14 years of follow-up. Our study was embedded in the population-based Rotterdam Study cohort. SSRI use was based on pharmacy dispensing records. Femoral neck BMD was measured using dual-energy X-ray assessment (DXA) at minimal 1 and up to 4 visits between 1991-2004. The annual percentage change in BMD was calculated between 2 consecutive visits. Multivariate linear mixed models were applied to examine the association between SSRI use and repeated measurements of BMD, and changes in BMD, stratified by sex, in comparison to non-users. Analyses were adjusted for time-varying covariates; age, body mass index, lower limb disability, smoking, alcohol intake, medication use and depressive symptoms. The study population included 2,568 men and 3,484 women, with in total 14,488 BMD measurements and 7,212 BMD change values. At baseline, the mean age was 68.1 years (standard deviation [SD] 7.7), and 68.9 years (SD 8.3), respectively, with a median of 3.9 years between BMD measurements (interquartile range 1.8–4.6). In women, the mean BMD of SSRI users was 0.840 g/cm^2 (n=78), versus 0.831 g/cm^2 for non-users (n=6739, p=0.194). The annual decline in BMD in women was not significantly stronger in SSRI users (n=117) than in non-users (N=3086, beta= -0.093%, p=0.152). Similarly, no significant association was observed for men. Therefore, our study indicated that use of SSRIs is not associated with lower BMD, and a stronger decline in BMD in middle-aged and older men and women.
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OP12 (P339)

Safety and Efficacy of Odanacatib in the Treatment of Men with Osteoporosis: a Randomised Placebo-Controlled Trial

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Osteoporosis in men is an important clinical problem, associated with significant morbidity, mortality and societal expense. Odanacatib (ODN), a selective oral inhibitor of cathepsin K, is currently being investigated as a treatment for osteoporosis. This Phase III, double-blind, randomised, placebo-controlled, 24-month study investigated the safety and efficacy of ODN for the treatment of men with osteoporosis. Eligible patients were men 40–95 years of age with idiopathic osteoporosis or osteoporosis due to hypogonadism, who had a lumbar spine (LS), femoral neck (FN), or total hip (TH) T-score of ≤–2.5 to ≥–4.0 without prior vertebral fracture, or ≤–1.5 to ≥–4.0 with one prior vertebral fracture. Participants were randomised (1:1) to ODN 50 mg weekly or placebo. All received vitamin D (5600 IU/week) and calcium up to 1200 mg/day, if required. The primary efficacy outcome measure was the percent change from baseline in LS BMD. Secondary outcomes included changes in BMD at the FN, TH, and trochanter, bone turnover markers, and safety and tolerability. In total, 292 men were randomised and treated (mean age 68.8 years; 5.8% total testosterone levels <250 ng/dL). Compared with placebo, treatment with ODN for 24 months increased BMD at the LS and all 3 hip sites (TH, FN and trochanter) by 5.6%, 2.0%, 1.7%, and 2.1%, respectively (LS, TH, and trochanter $p<0.001$; FN $p=0.008$) and decreased the bone resorption marker u-NTx/Cr (–68%, $p<0.001$). Bone formation markers initially decreased with ODN, then returned towards levels found with placebo by Month 24. ODN was associated with an incidence of adverse events similar to placebo. In this study in men with osteoporosis, ODN increased spine and hip BMD, and decreased bone resorption with a smaller effect on bone formation. ODN is a promising potential therapy for the treatment of osteoporosis in men. (ClinicalTrials.gov number NCT01120600.)

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OP13 (P340)

Abstract not available

OP14 (P341)

Intranasal Administration of PTH(1-34) for the Treatment of Osteoporosis - Equivalence to Subcutaneous Injection at the Neck of Femur in the Food and Drug Administration (FDA) Mandated Preclinical Model

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Background: Osteoporosis affects 200 million people worldwide, it is characterised by low bone mass and micro-architectural deterioration, increasing risk of fracture. PTH(1-34) is a proven anti-osteoporotic drug, self-administered by subcutaneous (SC) daily injection. Patient compliance to PTH(1-34) therapy can be sub-optimal for some patients. There is therefore an urgent unmet clinical need to offer alternative administration regimens. Intranasal (IN) delivery of PTH(1-34) offers an attractive non-invasive approach to improve compliance. We show, for the first time, using a proven intranasal nano-enabled delivery system, an equivalent anabolic effect on bone with the same dose of PTH(1-34) administered either SC or IN. The aim was to determine the anabolic effect of PTH(1-34) delivered intranasally in the US FDA pre-clinical model for research into osteoporosis.

Methods: PTH(1-34) liquid formulations for IN delivery were analysed for stability. Following ethical approval, ovariectomised (OVX) rats were randomly divided into groups receiving an equal dose of SC or IN PTH(1-34). Bone tissue was assessed using micro computed tomography following ovariectomy or SHAM and treatment with PTH(1-34) IN or SC, or no PTH(1-34) IN and SC controls. Data were subject to Kolomogorov-Smirnov tests for normality followed by ANOVA.

Results: Stability of formulations was confirmed using HPLC analysis >12 months. Ovariectomy induced bone loss was confirmed in neck of femur (NOF) trabeculae: 50% reduction in bone volume, 51% reduction in trabecular number and 37% increase in trabecular porosity ($p<0.05$). Post treatment NOF trabecular bone volume significantly increased 58% (OVX 21.22±1.6% vs IN 33.5±2.5%) trabecular number significantly increased 50% (OVX 3.27±0.2mm^{-1} vs IN 4.91±0.29mm^{-1}) and trabecular porosity significantly decreased 16% (OVX 78.78±1.6% vs IN 66.50±2.5%) ($p<0.05$). There was no significant difference in bone microarchitecture between SC and IN administration of PTH(1-34) at equivalent doses ($p>0.05$).

Conclusion: Intranasal delivery of PTH(1-34) is a viable alternative to subcutaneous injection to improve patient compliance.

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OP15 (P342)

Early Changes in Bone Turnover Markers are Associated with Increases in BMD During Treatment with Blosozumab in Postmenopausal Women with Low BMD

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Background: A randomised, blinded study evaluated the effect of treatment with blosozumab, a humanised monoclonal antibody targeted against sclerostin, on BMD and bone turnover markers (BTMs) in postmenopausal women with low BMD. The objectives of these analyses are to determine the 1) relationship between change in BTMs (PINP, BALP, OC, and CTX) at 2, 4, and 12 weeks and change in BMD after 1 year of treatment; 2) BTM and time point most strongly associated with 1-year change in spine, hip, and total body BMD; 3) proportion of patients responding to treatment based on change in BTMs.
Method: Multiple regression models with applied forward selection identified the strongest association between change in BTM and change in spine, hip, and total body BMD after 1 year of treatment. Least significant change (LSC) in BTM was determined from within subject variability of repeated measures to define proportion of responders.
Results: A strong association was observed between early change in BTMs reflecting bone formation and BMD increases with 1-year of blosozumab treatment. In a model considering treatment effect and BTMs reflecting bone formation, changes in PINP at 2 and 4 weeks were significantly correlated with changes in spine ($p<.01$) and hip BMD ($p<.02$) at 1 year. When treatment and PINP increases are considered, CTX decrease at 2 weeks was also significantly correlated with change in hip ($p=.04$) but not spine BMD. In the highest dose group, PINP at 4 weeks was correlated ($p<.01$) with BMD at 52 weeks (spine $r=.51$, hip $r=.56$, whole body $r=.62$). The LSC from post-baseline PINP measurements in the placebo group was 10 ng/mL; response rates were >95% with Q2W dosing, 52% with Q4W dosing, and 8% with placebo.
Conclusion: We conclude change in PINP by 4 weeks of treatment with blosozumab identifies later BMD response at 1 year of treatment.
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OP16 (P393)

Osteoblasts from Type V OI Patients Demonstrate Gain-of-Function for Mineralisation Despite Decreased *COL1A1* Expression

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Osteogenesis imperfecta (OI) is a genetically heterogeneous disorder characterised by bone fragility. Most cases result from dominant mutations in type I collagen, while recessive OI is caused by defects in genes whose products interact with type I collagen. Type V OI has dominant inheritance, with characteristic skeletal findings and mesh-like lamellation on bone histology. It is caused by a unique heterozygous mutation in *IFITM5* (c.-14C>T), which encodes BRIL, a transmembrane protein expressed in osteoblasts. The mutation generates a start codon in the 5'-UTR, adding five residues to the BRIL N-terminus. However, the mechanism of type V OI and its relationship with type I collagen is unknown. We identified 8 patients with the *IFITM5* (c.-14C>T) mutation. Using cultured osteoblasts from patients with characteristic type V OI, we verified expression and stability of mutant *IFITM5* transcripts. In differentiated type V OI primary osteoblasts in culture, *IFITM5* expression and BRIL protein level is comparable to control. Both early (*ALPL* and *IBSP*) and late (osteopontin and osteocalcin) markers of osteoblast differentiation are increased in type V OI osteoblasts. Mineralisation, assayed by alizarin red staining, was increased in type V OI osteoblasts compared with control. In contrast to other differentiation markers, type V OI osteoblasts have less than half the level of *COL1A1* transcripts found in control in mid to late differentiation, with concomitantly decreased collagen protein secretion. Decreased secreted type I collagen underlies decreased crosslinked collagen in matrix, and altered appearance of fibrils deposited in culture. The increased mineralisation and advanced differentiation of type V OI osteoblasts likely underlie the overactive tissue calcification and hypertrophic callus formation seen in affected individuals and demonstrates that type V OI has a gain-of-function mechanism. Decreased type I collagen expression, secretion and matrix incorporation establish type V OI as a collagen-related defect.
Disclosure: The authors declared no competing interests.

OP17 (P394)

Non-Surgical Hypoparathyroidism in Denmark – Epidemiology, Mortality and Complications

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Background: Non-surgical hypoparathyroidism (NS-HypoPT) is a rare disease, characterised by low levels of calcium and PTH. A number of genetic variants have been shown to cause inadequate PTH secretion, although the aetiology often remains unknown. It may also appear on autoimmune basic, either isolated, as a part of the autoimmune polyendocrine syndrome, associated with APS-1, or as acquired antibodies that activate the calcium sensing receptor (CaSR). Autosomal dominant hypocalcaemia (ADH) is caused by an activating mutation (gain-of-function) in the CaSR. Little is known about this group of patients, including their mortality and morbidity. The aim was to identify all patients diagnosed with NS-HypoPT in Denmark and assess their mortality and risk of complications.
Methods: Cases (patients with NS-HypoPT) were identified through registers and review of their individual hospital charts. To access their mortality and morbidity we compared the cases with a group of age-and gender matched population based controls.
Results: In a population of 5.336.394 persons, a total of 180 cases with NS-HypoPT were identified, among whom 123 (68%) were alive at the day of follow-up, equal to a prevalence of 2.3/100,000 inhabitants). Only 38 were genetic verified. Compared with controls, mortality was not increased, but patients had a significantly increased risk of seizures (Hazard ratio [HR] 10.05) renal insufficiency (HR 6.01), cataract (HR 4.21), neuropsychiatric complications (HR 2.45), infections (HR 1.94), cardiovascular diseases (HR 1.91) and fractures at the upper extremities (HR 1.93). In contrast, patients had significantly reduced risk of malignant diseases (HR 0.44).
Conclusion: NS-HypoPT is a rare disease associated with a number of complications that should be considered when taking care of these patients.
Disclosure: The authors declared no competing interests.

OP18 (P395)

Baseline Characteristics of the ZIPP Study Cohort Provide a Unique Insight into the Evolution of *SQSTM1* Mediated Paget's Disease

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Paget's disease of bone (PDB) is a common disorder with a strong genetic component. The most important susceptibility gene is SQSTM1. Mutations of this gene are found in about 40% of patients with familial and 10% of those with sporadic PDB but there is limited information on the early characteristics of disease evolution in *SQSTM1* mutation carriers Here we report on the baseline clinical characteristics of participants of the ZIPP study - a multinational randomised trial of genetic testing and targeted intervention with Zoledronic acid in asymptomatic subjects who carry *SQSTM1* mutations. The study group comprised 203 *SQSTM1* mutation positive subjects of mean (±SD) age 49.2 ± 9.0 years of whom 110 (54.4%) were female. The most common mutation was P392L (63.5%) followed by M404V (12.3%), G425R (9.9%), A390X (3.9%), G411S (3.4%), Glu396X (1.5%), Thr350GlnfsX28 (1.5%), Gln371X (1%), F406V (1%), K378X (1%), E396X (0.5%) and I424S (0.5%). Analysis of radionuclide bone scan images at baseline revealed abnormalities that were thought to represent early PDB-like lesions in 31 subjects (15.2%). The commonest sites were the spine (48%), pelvis (35%), femur (12%) and tibia (6.4%). About 30% of subjects had multiple lesions. All subjects were asymptomatic. Serum total alkaline phosphatase (ALP) concentrations were elevated in 10 subjects (5%). Subjects with PDB-like lesions were marginally older than those without lesions 51.1 ± 9.4 *vs.* 49.2 ± 8.9 and lesions were significantly more common in men (20.6% vs. 10.9% (p=0.02). Elevated ALP concentrations were found in 16% of subjects with lesions and 3% of subjects without lesions (p=0.002). There was no association between *SQSTM1* mutation type and the presence of lesions. This study demonstrates that by the age of 50 about 15% of *SQSTM1* mutation carriers have asymptomatic PDB-like bone lesions. Lesions occur more commonly in men, which is consistent with the fact that PDB affects men more frequently than women. The study confirms that PDB is a clinically silent disease in its early stages and shows that measurements of total ALP are not a sensitive means of detecting early lesions. Further follow up of this cohort will provide a unique insight into the evolution of PDB with age and into the effects of zoledronic acid in modifying the natural history of this condition.
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