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ABSTRACTS

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P173

Far upstream element binding protein 3 expression is associated with bone formation

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Genome-wide association studies (GWAS) are one of the most powerful approaches to identify genetic loci that are associated with bone mineral density (BMD). GWAS have identified hundreds of associations with BMD; however, only few have been functionally evaluated, and functional characterization remains a challenge. One of the loci significantly associated with femoral neck BMD at genome-wide level ($p = 3.4 \times 10^{-22}$) is SNP rs7851693 from the intron of far upstream element binding protein 3 (FUBP3) gene. Here, we investigated a functional role of FUBP3 in bone remodelling. Variants mapping to FUBP3 were prioritized using GCTA and FINEMAP. Expression of FUBP3 in 47 osteoporotic and osteoarthritic human bone tissue samples was compared to healthy controls. The expression of FUBP3 was significantly decreased (p = 0004) in bone tissues from osteoporotic patients as compared to healthy controls. Furthermore, we examined FUBP3 expression in whole fish during zebrafish development and adulthood, and fin regeneration, by in situ hybridisation and Q-PCR. Two fold increase in FUBP3 expression (p = 0,003) in the newly formed zebrafish fins suggests that FUBP3 is involved in tissue regeneration and formation of bone tissues. Moreover, we also investigated expression of FUBP3 during osteogenic, adipogenic and myogenic differentiation of human mesenchymal stem cells. Indeed, silencing of FUBP3 inhibited osteogenic differentiation confirming the involvement of FUBP3 in the formation of osteoblasts. Altogether, our results suggest that FUBP3 plays an important role in bone biology and osteoporosis susceptibility in humans.

P174

Leveraging unconfounded genetic risk scores to stratify fracture risk by age at onset

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Aim: Increasing age is the strongest and most recognized risk factor of osteoporosis and fracture risk in both sexes. GWAS have identified up to 1103 independent genetic variants associated with bone mineral density estimated from heel ultrasound (eBMD). Under the principle of Mendelian Randomization, estimates derived from genetic risk scores (GRS) are robust against confounding across strata. We investigated in a population-based setting whether a GRS constructed from eBMD variants is a robust predictor of incident fractures and their age at onset.

Methods: We included in this study 11,351 participants of the Rotterdam Study with GWAS data and up to 20 years of fracture follow-up. Incident non-vertebral fractures were confirmed in 2153 (19%) individuals using GP records and hospital registries. GRS was constructed as a weighted sum of the number of eBMD-decreasing alleles at 1031 genetic variants. Cox regression and Weibull survival analyses were implemented to determine the association of the GRS and fracture risk and event time ratio (ETR) adjusting for sex.

Results: Every GRS standard deviation (SD) increment was associated with 20% increased risk (HR 1.20 95%CI 1.15–1.25; $P < 2x10^{-16}$) of fracture. When analyzed across GRS quintiles, non-skeletal anthropometric characteristics were randomized across strata. As compared to individuals in the middle GRS quintile who hold the mean population BMD and fracture risk, individuals in the highest GRS quintile had 1.5 increased risk of fracture (HR 1.52 95%CI 1.09–2.11; P = 0.01). Also, fractures occurred significantly earlier in individuals with the largest number of BMD-decreasing alleles (ETR = 0.95, 95%CI 0.91–0.99).

Conclusions: GRS are increasingly accessible tools providing robust and interpretable fracture risk estimates that are not prone to confounding and allowing risk stratification capturing age at fracture. We show how a sub-optimal epidemiological tool for fracture prediction (heel ultrasound) is leveraged by using a genetic framework.

Keywords: Genetic risk scores; BMD; Fracture

P192

Mid1 is a novel mediator of subchondral bone resorption in antigen-induced arthritis

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Introduction: Rheumatoid arthritis (RA) is a chronic autoimmune joint disease characterized by subchondral bone destruction not reversible by currently available therapeutics. We have shown that mice deficient for Fas gene (Fas-/-) are protected from local bone resorption in antigen-induced arthritis (AIA), a murine model of RA, and have a lower frequency of synovial myeloid cells, which down-regulate *Mid1* gene. The objective of the study was to evaluate the role of *Mid1* in bone resorption in AIA.

Materials and methods: After receiving ethical approval, arthritis was induced by immunization of mice with methylated bovine serum albumin (mBSA) with subsequent intra-articular injection of mBSA. Synovial myeloid (CD11b + Gr− 1 +) cell transcriptome was analyzed by Affymetrix ST 2.0 arrays. Bioinformatics analysis was performed using Bioconductor. Differences in gene expression were confirmed by qRT-PCR. WT-AIA mice were treated in vivowith metformin, which inhibits proinflammatory effect of Mid1, at daily dose 1 g/kg, to assess effects on arthritis development.

Results: *Mid1* gene was up-regulated in myeloid cells (logFC = 2.01, p(BH-adjusted) = 0.0003, limma + BH-adjustment) and bulk joint tissue (logFC = 8.74, p = 0.02, Welch-test) of WT mice in comparison to Fas-/- mice with non-resorptive arthritis. Despite its position on X chromosome *Mid1* expression in joints was not sexually dimorphic and was up-regulated in WT-AIA in both male (logFC = 1.92, p = 0.006, T-test) and female mice (logFC = 8.74, p = 0.02, Welch-test). Furthermore, expression positively correlated with knee

diameter (r = 0.68, p = 0.03, Spearman´s rank correlation) and levels of pro-inflammatory cytokines in arthritis joints (IL-1: r = 0.78, p = 0.008; IL-6: r = 0.70, p = 0.025; TNF:r = 78, p = 0.008, Spearman´s rank correlation). Metformin treatment of WT-AIA mice ameliorated the severity of arthritis assessed by knee diameter (3.69 ± 0.21 mm WT-AIA vs. 3.36 ± 0.12 mm WT-AIA + metformin, p = 0.008, T-test).

Conclusions: Mid1 is a novel mediator of subchondral bone destruction in arthritis and its inhibition might present a new therapeutic target for inflammation-mediated joint destruction.

Keywords: Mid1, Bone resorption, Arthritis

P207

Impaired muscle fiber morphology in the Chihuahua zebrafish model of classical dominant osteogenesis imperfecta

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Muscle and bone build a powerful unit to facilitate movement, to provide structure and to protect organs. In disease states, both types of tissue may be compromised individually. While the genetic disorder of classical dominant osteogenesis imperfecta (OI) leads to brittle bones and increased fracture risk, patients may also present lower muscle mass and function. Although positive bone-muscle effects following exercise are likely, the exact link between bone quality and muscle function remains understudied. Elucidating the specific mechanisms in the bone-muscle unit is thus essential to pave the way for new treatment strategies of OI. The Chihuahua zebrafish (*Chi/+*) carrying a heterozygous glycine substitution in collagen I is an interesting model of OI showing drastically impaired bone structure, mechanical properties, and cellular indices. The aim of this study is to assess whether muscle tissue in the *Chi/+* model is similarly affected as the compromised bone.

Chi/+ and wild-type (WT) zebrafish (2 months old) were used for muscle characterization (N = 6/group). Histomorphometry was performed on 4 µm-thin transversal whole-body sections stained with H&E. Fiber morphology was assessed in the trunk muscles where fast- and slow-twitch fibers are located in the central and lateral sides, respectively. Two regions of interest per section were evaluated.

Results clearly point to smaller muscle fiber cross-sectional area in *Chi/+* mutants with 204 ± 37 µm^2 vs. 280 ± 18 µm^2 (p = 0.05) and higher fiber density in *Chi/+* with 464 ± 70 fibers/mm^2 vs. 360 ± 22 fibers/mm^2 (p = 0.05). Similar to human OI, *Chi/+* zebrafish show substantially altered muscle function besides impaired mineralized hard tissue indices.

This study highlights that understanding the bone-muscle interaction in physiological and pathological conditions is important for improving OI disease management and further underlines the use of biomechanical loading regimes for zebrafish to investigate the response of the whole musculoskeletal system to both conventional and pharmaceutical treatment.

Keywords: Bone-muscle axis, Osteogenesis imperfecta, Zebrafish

P282

The bone biomechanical response during sclerostin-neutralizing antibodies treatment is maintained in periostin knockout mice

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Sclerostin neutralizing Ab (Scl-Ab) potently stimulates bone formation but these effects are not sustained. Periostin (Postn), a matricellular protein, mediates the anabolic response to mechanical loading and is a Sost inhibitor[1]. We previously observed that Postn expression is repressed by Scl-Ab in mice but that mechanical loading is able to reactivate bone formation in these conditions, concomitant to increased Postn expression. We hypothesized that Postn expression levels play a direct role in the bone biomechanical response during treatment with Scl-Ab.

Sixty-five four month-old Postn$^{-/-}$ and Postn$^{+/+}$ mice received Scl-Ab (50 mg/kg/w) or veh for 4 to 6 weeks. At week 4, axial compression was applied on the left tibia 3 days per week for 2 weeks at 16 N. The right tibia served as non-loaded control. P1NP level was monitored every 2 weeks to assess bone formation and bone microarchitecture was evaluated by µCT on femur, tibiae and L3 vertebra.

With Scl-Ab, P1NP levels peaked at week 2 and declined thereafter in both genotypes. Scl-Ab increased Tb.BV/TV at femur and vertebrae as well as Ct.Th similarly in Postn$^{+/+}$ (+145%, +204%, +37%, respectively vs Veh, $p < 0.001$) and Postn$^{-/-}$ (+252%, +306%, +40%, respectively vs Veh; $p < 0.001$). Loading during Scl-Ab treatment further increased tibia Tb.BV/TV and diaphysis Ct.Th, without interaction by genotypes (Postn$^{+/+}$ +22% and +7%; Postn$^{-/-}$ +12% and +8% vs nonloaded tibia, $p < 0.01$). However a significant interaction between loading and genotype was noted for Ct.Th at tibia metaphysis (Postn$^{+/+}$ +15%, Postn$^{-/-}$ +4%, p Int < 0.05).

In conclusions, periostin is not required for the overall bone anabolic response to Scl-Ab nor its reactivation by mechanical loading. These results suggest that increasing strain could sustain Scl-Ab bone forming effects by further suppressing Sost expression, rather than stimulating Postn expression, allowing for an improved Scl-Ab/target ratio.

Reference: [1]Bonnet N. et al., JBC, 2009.

Concurrent Oral Poster Presentations 2—Clinical/Public Health

P236

The fracture predictive ability of lumbar spine BMD and TBS as calculated based on different combinations of the lumbar spine vertebrae

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Trabecular bone score (TBS), a surrogate of bone microarchitecture, is an independent predictor of osteoporotic fractures. It is measured in the lumbar spine (LS) DXA scans in the same regions of interest as BMD, L1-L4. We aimed to study whether different combinations of the lumbar vertebrae in the calculations of LS TBS and BMD perform differently in major osteoporotic fractures (MOF) prediction.

Study comprised 1475 postmenopausal women (mean age = 64.5y) of the Swiss population-based study, who had undergone questionnaires, vertebral fracture assessments, LS DXA scans (Hologic) and TBS (Medimaps, v4.0) measurements. T-tests were ran to test the differences in general characteristics between women who fractured and those who did not; binary logistic regressions adjusted for age + BMI or for age + BMI + LS BMD were performed to