part of the RXRa promoter in umbilical cords of 292 children from the
Southampton Women's Survey, and related these findings to their bone
mass at 4 years old, assessed by DXA (Hologic Discovery).

Results: There was a wide range of percentage methylation. After
taking account of age and sex, for three of the six CpG sites, there
was a strong negative association between the RXRa promoter
methylation status and the child's whole body percentage bone
mineral content ($r_p=-0.2$ to $-0.13$, $p=0.002$ to 0.046), and estimated
volumetric BMD ($r_p=-0.18$ to $-0.13$, $p=0.003$ to 0.032). Similar
relationships were observed for estimated volumetric BMD at the hip
($r_p=-0.133$ to $-0.125$, $p=0.025$ to 0.035).

Conclusions: We have demonstrated that percentage bone mineral
content and estimated volumetric BMD in childhood are negatively
associated with perinatal methylation status within the RXRa promoter.
Methylation usually leads to reduced gene expression, suggesting that
levels of RXRa in utero may be positively related to these bone indices in
childhood, possibly suggesting novel mechanisms whereby maternal
factors may influence offspring skeletal development.

Disclosure of Interest: None declared.

OC23
RISK FACTORS PREDICTIVE OF JOINT REPLACEMENT IN
A TWO-YEAR MULTICENTRE CLINICAL TRIAL IN
KNEE OSTEOARTHRITIS USING MRI: RESULTS FROM
OVER SIX YEARS OF OBSERVATION
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Objectives: To identify predictive factors for total joint replacement (TKR)
using data from MRI of knee OA patients in a Phase III multicentre DMOAD study.

Materials/Methods: Knee OA patients from a 2-year clinical trial
evaluating leflunomide vs. naproxen were investigated for the incidence
of TKR of the study knee. Patients ($n=161$) who completed the study
according-to-protocol were selected. Incidence of TKR was assessed
blindly to the treatment following telephone interviews ($n=123$).

Results: A total of 18 TKRs (14.6%) were performed in the time
frame of 4-7 years following enrolment in the original study. More
TKRs were performed within the naproxen than the leflunomide group
(61% vs. 39%). Furthermore, baseline score of bone narrow lesions
(BMLs) in the medial compartment ($p=0.0001$), medial joint space
width ($p=0.0008$), presence of severe medial meniscal tear ($p=0.004$),
meniscal meniscus ($p=0.013$), and C-reactive protein level ($p=
0.049$) were strong predictors of TKR. Changes at the end of the study
also yielded strong predictors: change in cartilage volume of the
medial compartment ($p=0.005$), global knee ($p=0.034$), and
WOMAC pain ($p=0.009$) and function ($p=0.023$) scores. Multivariate
analysis showed that baseline severe medial meniscal tear ($p=0.023$)
and presence of a medial BML ($p=0.025$) were the strongest
independent long-term predictors of TKR.

Conclusions: This study shows that in the context of OA clinical trials,
clinical data and structural changes identified by MRI allow prediction of
a "hard" outcome such as TKR. The findings support the usefulness and
predictive value of MRI in defining study outcome in DMOAD trials.

Disclosure of Interest: The original study was supported by Merckle
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ArthroLab Inc., JMP and JPP are consultants for and shareholders in
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from ArthroLab Inc. FA is an employee of ArthroVision Inc.

OC24
SCLEROSTIN PLAYS A KEY ROLE IN ABNORMAL WNT/
β-CATENIN SIGNALING IN HUMAN OSTEOARTHRITIC
SUBCONDRAL OSTEOBLASTS LEADING TO REDUCED
MINERALIZATION
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Objectives: Clinical and in vitro studies suggest that subchondral bone
cancer due to abnormal osteoblast (OB) function, is involved in the
progression and/or onset of osteoarthrosis (OA). Moreover, human OA
subchondral Ob show a phenotype of very differentiated cells, however
they fail to mineralize normally in vitro as in vivo. Wnt signaling plays a
key role in osteogenesis by promoting the differentiation and minerali-
zation of OB mainly via the canonical Wnt/β-catenin (eWnt) signaling
pathway. Sclerostin (SOST) has been shown to alter eWnt signaling,
however the regulation of SOST in OA OB remains unknown. Here we
investigated the role of SOST in OA OB.

Materials/Methods: We prepared primary human subchondral Ob using
the sclerotic median portion of the tibial plates of OA patients undergoing
knee arthroplasty, or from tibial plateaus of normal individuals at
autopsy. SOST expression and production was evaluated by qRT-PCR
and WB analysis. The regulation of SOST expression was determined in
response to transforming growth factor-B1 (TGF-B1) and as a function of
the growth of OA OB. SOST inhibition was performed using siRNA
techniques. eWnt signaling was evaluated by measuring target gene
expression using the TOPFlash Tcf/lef luciferase reporter assay and
intracellular β-catenin levels by WB. Mineralization was evaluated by
Alizarin red staining. TGF-B1 levels were determined by ELISA.

Results: SOST expression and production were elevated in OA
comparing to normal Ob. TGF-B1 expression was high in OA Ob and
stimulated SOST expression and production in Ob. eWnt signaling was
reduced in OA compared to normal Ob. Inhibiting SOST expression by
siRNA increased eWnt signaling using the TOPflash reporter assay and
also increased β-catenin levels in OA Ob. Mineralization of OA Ob was
reduced compared to normal Ob and was inversely related to SOST
expression in Ob. SOST inhibition corrected eWnt signaling pathway
and abnormal mineralization in OA Ob.

Conclusions: This is the first demonstration that elevated SOST levels
in OA OB are responsible, at least in part, for their reduced eWnt
signaling and abnormal mineralization. As SOST is a secreted soluble
protein, this could lead to potential new avenues of treatment of OA to
correct their abnormal bone phenotype and mineralization.

Disclosure of Interest: None declared.

OC25
FIVE-YEAR DENOSUMAB TREATMENT
OF POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS:
RESULTS FROM THE FIRST TWO YEARS
OF THE FREEDOM TRIAL EXTENSION
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Objectives: The FREEDOM trial open-label extension is designed to evaluate the long-term efficacy and safety of denosumab for up to 10 years. We report the results from the first 2 years of the extension, representing up to 5 years of denosumab exposure.

Materials/Methods: Postmenopausal women enrolled in the extension previously completed FREEDOM. During the extension, all women received denosumab (60 mg) every 6 months and calcium and vitamin D daily. For the FREEDOM denosumab group, the data reflect 5 years of denosumab treatment (long-term group). For the FREEDOM placebo group, the data reflect 2 years of denosumab treatment (de novo group). P-values are descriptive.

Results: There were 4550 (70.2%) FREEDOM women enrolled in the extension (2343 long-term, 2207 de novo). During the 4th and 5th years of denosumab treatment, the long-term group had further 1.9% and 1.7% increases in lumbar spine BMD and further 0.7% and 0.6% increases in total hip BMD (all P<0.0001 compared with extension baseline). Total BMD increases with 5-year denosumab treatment were 13.7% (lumbar spine) and 7.0% (total hip). In the de novo group, BMD increased during the first 2 years of denosumab treatment by 7.9% (lumbar spine) and 4.1% (total hip) (all P<0.0001 compared with extension baseline). After denosumab administration, serum CTX was rapidly and maximally reduced in both groups with the characteristic attenuation observed at the end of the dosing interval, as previously reported. Incidences of new vertebral and nonvertebral fractures were low and below rates observed in the FREEDOM placebo group. Adverse event reports were similar for both groups: in the long-term group, 83.4% reported AEs and 18.9% were serious. In the de novo group, the percentages were 82.8% and 19.4%, respectively. In FREEDOM, the respective percentages were 92.8% and 25.8% in the denosumab group, and 93.1% and 25.1% in the placebo group. Two subjects in the de novo group had AEs adjudicated to ONJ, which healed without further complications; one resolved within the 6-month dosing interval and denosumab was continued. There were no atypical femoral fractures.

Conclusions: Denosumab treatment for 5 years was well-tolerated and continued to significantly reduce CTX and significantly increase BMD.

Reference: 1 Cummings; NEJM 2009; 361:756. 2 Eastell; JBMR, 2010; doi:10.1002/jbmr.251

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OC27

POOR CORRECTAL BONE STATUS IN MEN WITH ELEVATED CONCENTRATIONS OF OSTEOPROTEGERIN—THE STRAMBO STUDY

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Objectives: Osteoprotegerin (OPG) strongly inhibits bone resorption; however, its relationship to bone microarchitecture remains unclear. Our aim was to study cross-sectionally the association between the OPG concentration and bone microarchitecture in men.

Materials/Methods: The study was performed in a population-based cohort of 1149 men aged 20 to 87. Bone microarchitecture at distal radius andibia was assessed by high resolution peripheral QCT (XtremeCT Scanco) and we measured serum OPG concentration and bone turnover markers: osteocalcin (OC), bone-specific alkaline phosphatase (BSAP), PINP, C-terminal type I collagen telopeptide (CTX-I), urinary deoxypyridinoline (DPD). Differences in bone microarchitectural parameters across the quartiles of OPG concentration were assessed in the models adjusted for age, weight, height, physical activity, ischemic heart disease, diabetes, calcium intake, serum levels of free testosterone, bioavailable 17βestradiol, parathyroid hormone, 25-hydroxycholecalciferol, and creatinine.

Results: After adjustment for the confounders, men in the highest (fourth) quartile of OPG levels (≥455 pmol/L) had higher total cross-sectional area and trabecular area at the diastal radius and distal tibia (3.6–6.0%, p<0.05). At the distal radius and tibia, the highest OPG quartile was associated with lower cortical thickness (8.2%, p<0.001 and 3.7%, p<0.05) and volumetric bone mineral density (vBMD, 2.7%, p<0.001 and 1.6%, p<0.05) compared with the three lower quartiles combined. Association of the OPG level with trabecular microarchitecture (trabecular vBMD, number, thickness and distribution) was not significant. Men in the fourth OPG quartile had higher levels of bone resorption markers (DPD - 13.1%, 0.41 SD, p<0.001; CTX-I - 11.8%, 0.19 SD, p<0.01) in comparison with the three lower quartiles combined. Among the bone formation markers, OC (but not BSAP and PINP) remained higher in the fourth OPG quartile (7.7%, 0.19 SD, p<0.005).

Conclusions: Thus, in men, high serum OPG concentration is associated with poor cortical bone status, which is most likely due to accelerated bone turnover.

Disclosure of Interest: None declared.

OC27

IN BALLOON KYPHOPLASTY FOR OSTEOPOROTIC VERTEBRAL BODY FRACTURES, THE POTENTIAL OF REDUCTION IS DEPENDING ON THE TIME TO SURGERY

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