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ABSTRACT

World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (WCO-IOF-ESCEO 2020): Oral Communications Abstracts

OC1

EFFICACY AND SAFETY OF ROMOSOZUMAB AMONG POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS AND MILD-TO-MODERATE CHRONIC KIDNEY DISEASE

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Objective: To determine if baseline (BL) renal function affects the efficacy and safety of romosozumab (Romo).

Materials and Methods: We performed post hoc analyses of 2 Romo trials in postmenopausal women with osteoporosis. In ARCH, 4,093 patients (pts) were randomized 1:1 to Romo 210 mg monthly or alendronate (ALN) 70 mg weekly for 12 months (mean age, 74.3; 96.1% with prevalent vertebral fractures [VFx]). In FRAME, 7,180 pts were randomized 1:1 to Romo 210 mg or placebo (Pbo) monthly for 12 months (mean age, 70.9; 18.3% with prevalent VFx). For these analyses, pts were categorized by BL eGFR (mL/min/1.73m^2): normal renal function (eGFR ≥ 90), mild renal insufficiency (eGFR 60–89), or moderate renal insufficiency (eGFR 30–59). Least squares mean (LSM) % change from BL in BMD at the lumbar spine, total hip, and femoral neck; incidence of new VFx and adverse events (AEs); and changes in renal function were assessed for each eGFR category at month 12 of the double-blind treatment period.

Results: At BL, most pts had mild/moderate renal insufficiency: 84% in ARCH, 88% in FRAME. In both studies, change from BL in BMD was significantly higher in the Romo group across BL eGFR categories (Figure). There was an interaction between BMD increase and renal function, and although BMD increase was less in women with impaired renal function, differences between Romo and control groups remained significant (Figure). Among pts with eGFR ≥ 90, 60–89, and 30–59, the incidence of new VFx (Romo vs ALN or Pbo) at month 12 was 3.3% vs 7.3%, 3.2% vs 3.9%, and 3.4% vs 6.2% in ARCH and 0.5% vs 3.0%, 0.4% vs 1.5%, and 0.6% vs 2.1% in FRAME. In both studies, the incidences of AEs and serious AEs were similar in both treatment groups within and across eGFR categories. AEs of mild-to-moderate hypocalcemia (investigator reported) occurred in 2 pts (1 Romo [eGFR 60–89], 1 ALN [eGFR ≥ 90]) in ARCH and 1 pt (Romo [eGFR 60–89]) in FRAME. Five pts (0 Romo, 5 ALN) in ARCH and 19 pts (14 Romo, 5 Pbo) in FRAME had decreases in serum Ca levels (albumin adjusted); in the Romo group all were mild (< LLN–8.0 mg/dL) or moderate (< 8.0–7.0 mg/dL). Similar % of pts in each group had changes in renal function over 12 months of treatment.

Conclusion: The efficacy and safety of Romo vs ALN or Pbo was similar among postmenopausal women with osteoporosis and different levels of renal function.

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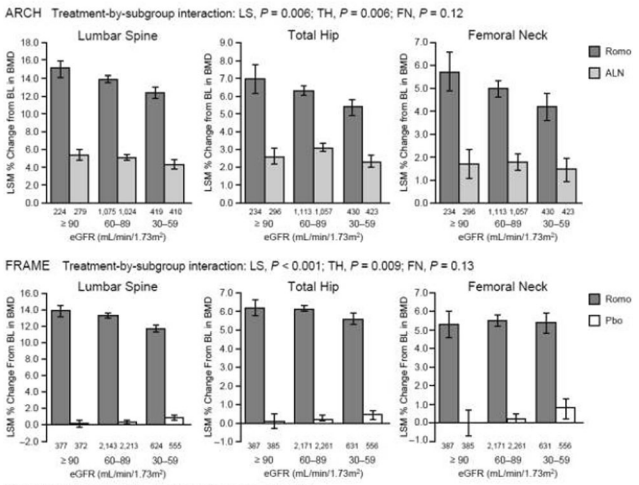
Disclosures: PM reports consultant/advisory activities for Amgen and Radius Health and has received grants from Amgen, Radius Health, and Ultragenyx; JA is a consultant and speaker for Amgen; BHA has received speaking and consultation fees from Eli Lilly and Amgen; AMC has received honoraria/consultation fees from Eli Lilly and Amgen; AC, MO, NRS, WY, and ZY are employees and stockholders of Amgen; EG reports consultant/speaker's bureau/advisory activities for Amgen, Takeda, Sandoz, and UCB Pharma; BL is on advisory boards for Amgen, UCB Pharma, and Eli Lilly and has received research grants from Amgen and Novo Nordisk; AM has received consulting fees from Amgen, Astellas BioPharma K.K., and Teijin Pharma; IRR has received speaking and consultation fees from Eli Lilly and Amgen; MV is an employee of UCB Pharma.

Figure. LSM (95% CI) % Change in BMD From Baseline to Month 12



Number of pts are shown below each bar. Error bars represent 95% CIs.
In FRAME, change in BMD from baseline for the eGFR 15–29 mL/min/1.73m² subgroup is not reported: there were only 7 patients in the placebo group for each of the measured sites and only 7, 8, and 8 patients in the romosozumab group for LS, TH, and FN, respectively.
Abbreviations: ALN, alendronate; BL, baseline; BMD, bone mineral density; CI, confidence interval; eGFR, estimated glomerular filtration rate; FN, femoral neck; LS, lumbar spine; LSM, least squares mean; Pbo, placebo; Romo, romosozumab; TH, total hip.

OC2

ROMOSOZUMAB AFTER DENOSUMAB IMPROVES LUMBAR SPINE AND MAINTAINS TOTAL HIP BONE MINERAL DENSITY IN POSTMENOPAUSAL WOMEN WITH LOW BONE MASS

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Objective: Romosozumab (Romo), an anti-sclerostin antibody that increases bone formation while decreasing bone resorption, reduces fracture risk within 12 months. Here we evaluate the effects of transitioning from denosumab (DMAb) to Romo in treatment-naïve patients.

Materials and Methods: This phase 2 trial (NCT00896532) enrolled postmenopausal women with a lumbar spine (LS), total hip (TH), or femoral neck T-score ≤–2.0 and ≥–3.5. Patients were randomized to placebo (Pbo) or various doses of Romo monthly or every 3 months from baseline (BL) to month (M) 24, were rerandomized to 12 months of DMAb or Pbo (M24-36), and then all were to receive Romo 210mg monthly for 12 months (M36-48). Results for the overall population have been previously published (1,2). Here we present data from a subset of patients who were randomized to Pbo for 24 months, DMAb (n=16) or Pbo (n=12) for 12 months, and then Romo for 12 months.

Results: In patients who were randomized to Pbo followed by DMAb, Romo treatment for 12 months maintained bone mineral density (BMD) gained during DMAb treatment at the TH (mean change from end of DMAb treatment, 0.9%) and further increased BMD gains at the LS (mean change from end of DMAb treatment, 5.3%) (Table). As expected, P1NP and β-CTX levels decreased with DMAb. Upon transition to Romo (M36-48), P1NP levels initially increased and gradually returned to BL by M48 while β-CTX gradually increased to BL levels.

In patients who transitioned to Romo after 36 months of Pbo, BMD increased at the LS and TH (Table). P1NP levels initially increased with Romo and gradually returned to BL by M48 while median β-CTX level remained below BL with Romo treatment.

Conclusions: BMD response in the Pbo to Romo group was similar to that observed in other studies. Transitioning to Romo after 12 months of DMAb further improves LS BMD and maintains TH BMD.

References: 1) McClung MR, J Bone Miner Res 2018;33:1397-1406. 2) Kendler DL, Osteoporos Int 2019;30:2437-2448.

Table

Treatment from M0–24:	Pbo	Pbo
Treatment from M24–36:	Pbo	DMAb 60 mg Q6M
Treatment from M36–48:	Romo 210 mg QM	Romo 210 mg QM
	N = 12	N = 16
BMD, mean % change (95% CI)		
Lumbar spine		
M0–24	2.7 (0.2, 5.1)	−0.8 (−2.8, 1.1)
M24–36	−0.4 (−2.1, 1.4)	5.5 (3.6, 7.4)
M36–48	9.1 (6.1, 12.1)	5.3 (3.2, 7.4)
M24–48	8.9 (5.5, 12.4)	11.5 (8.8, 14.3)
Total hip		
M0–24	−2.2 (−3.6, −0.8)	−1.6 (−2.7, −0.5)
M24–36	−0.3 (−1.4, 0.8)	2.8 (2.1, 3.6)
M36–48	4.6 (2.7, 6.4)	0.9 (−0.1, 1.8)
M24–48	4.7 (2.7, 6.7)	3.8 (2.6, 5.0)
BTM, median (Q1, Q3)		
P1NP, µg/L		
M0	37.0 (33.8, 41.0)	52.4 (44.9, 59.2)
M24	38.2 (30.0, 55.6)	50.0 (40.0, 56.0)
M36	35.9 (30.3, 55.5)	17.4 (11.2, 21.4)
M39	49.5 (36.3, 79.9)	43.1 (31.6, 55.6)
M48	36.2 (29.2, 48.2)	64.6 (54.2, 72.5)
β-CTX, ng/L		
M0	372.0 (306.0, 415.5)	503.5 (392.5, 635.5)
M24	534.0 (433.5, 692.0)	626.0 (466.0, 833.0)
M36	376.0 (305.0, 533.5)	162.5 (95.5, 268.0)
M39	348.0 (282.0, 438.5)	311.0 (239.0, 385.0)
M48	321.0 (276.5, 407.0)	532.0 (378.0, 661.0)

β-CTX, β-isomer of the C-terminal telopeptide of type I collagen; BMD, bone mineral density; BTM, bone turnover marker; CI, confidence interval; DMAb, denosumab; M, month; P1NP, procollagen type 1 N-terminal propeptide; Pbo, placebo; Q1, quartile 1; Q3, quartile 3; QM, monthly; Q6M, every 6 months; Romo, romosozumab.

Disclosures: This study was sponsored by Amgen, Astellas, and UCB Pharma. MR McClung received consulting fees and honorarium from Amgen. MA Bolognese received contract fees from Amgen and was a speaker for Amgen. JP Brown received research support from Mereo, Radius, and Servier; received consulting fees from Amgen, Eli Lilly, and Servier; and was on the speakers' bureau for Amgen and Eli Lilly. J-Y Reginster received research funding from IBSA-Genevrier, Mylan, CNIEL, and Radius Health; received lecture fees from IBSA-Genevrier, Mylan, CNIEL, and Dairy Research Council; and received consulting fees or participated in paid advisory boards for IBSA-Genevrier, Mylan, Radius Health, and Pierre Fabre. BL Langdahl received research support from Amgen and Novo Nordisk and was on the speakers' bureau for UCB, Amgen, and Eli Lilly. N Ruiz-Santiago, Y Shi, M Rojeski, H Kassahun, and M Oates are employees of and own stock in Amgen. J Timoshanko and C Libanati are employees of and own stock in UCB.

OC3

VERTEBRAL FRACTURES BEFORE, DURING AND AFTER DENOSUMAB. A RETROSPECTIVE STUDY OF 858 CASES

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OBJECTIVE: Evaluate subject characteristics and risk factors associated with the occurrence of vertebral fractures (VF) after treatment with Denosumab (DMAB).

METHODS: Among a network of 22 bone consultants from different parts of Switzerland, we collected the clinical history of 858 randomly chosen women, in whom treatment with DMAB was interrupted, 172 of them having breast cancer. Our questionnaire documented age, BMI, Bone Mineral Density (BMD), life style, family history, bone related diseases and treatments, fractures, bone resorption markers, and treatments for breast cancer. Data for these variables were recorded for the periods before, during and after DMAB treatment.

RESULTS: The mean age was 65 years [range 27 – 92]. Bisphosphonates had been administered before DMAB in 46%, and after in 64.5% (76.4% of them with Zoledronate). The mean duration of DMAB treatment was 35 months [6-96]. Follow-up, starting 6 months after the last dose, was 28 months (1 -107). In 96.5% the follow-up lasted > 6 months. The mean T-score of lumbar spine BMD was -2.55 (SD 0.97) before, -1.90 (1.11) during, and -2.15 (1.16) after treatment. The T-score at femoral neck was -2.06 (SD 0.78) before, -1.45 (0.83) during, and -1.93 (0.76) after treatment. Trabecular Bone Score (TBS) was measured among 95 patients in each period, and was 1.22 before, 1.27 during, and 1.29 after DMAB treatment; with significant increases ($p<0.001$ for trend). The percent of patients with osteoporotic fractures was 36.1% before, 5.2% during and 12.5 % after DMAB treatment; and that of patients with vertebral fractures (VF) was 20.4 % before (2.9 % with multiple VF), in 2.1% during (0.5 % with multiple VF), and in 11.0 % after treatment (6.4 % with multiple VF, with a mean of 2.9 VF per fractured patient). Hip fractures were observed in 3.5 % before, 0.7% during and 0.6% after treatment. The numbers of humerus, pelvis and rib fractures were similar.

The influence of each parameter mentioned above on the occurrence of fractures will be evaluated.

CONCLUSION: Treatment with Denosumab in 858 women led to an increase in BMD and TBS, and to a decrease in fractures. In the ± 28 months following treatment cessation, vertebral fractures increased. The occurrence of fractures will be analyzed in respect to case history, clinical characteristics, risk factors as well as evolution of BMD and resorption markers.

OC4

DIFFERENTIAL EFFECTS OF ABALOPARATIDE AND TERIPARATIDE ON CORTICAL VOLUMETRIC BMD AND BONE STRENGTH INDICES IN THE PROXIMAL FEMUR BY DXA-BASED 3D MODELING

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Objectives: To estimate changes in bone strength indices in the proximal femur over 18 months of treatment with placebo (PBO), abaloparatide (ABL), or teriparatide (TPTD) using a 3D modeling approach applied to DXA images from the ACTIVE trial.

Materials and Methods: A subset of 750 pts from the ACTIVE trial, 250 from each treatment group (PBO, ABL, TPTD) were randomly selected with data stratified by study site and patient race/ethnicity. Using Hip DXA scans at baseline and months 6 and 18, DXA-based 3D modeling (3D-SHAPER v2.10.1, Galgo Medical, Spain) was performed to evaluate cortical volumetric BMD (vBMD) and geometric parameters. Density-weighted cross-sectional moment of inertia (CSMI*) and section modulus (Z*) were generated at the femur neck (FN) and intertrochanteric (IT) regions as indices of bone strength. Pairwise group comparisons were made for % change from baseline data using P-values derived from contrast tests based on an MMRM model.

Results: After 18 months of treatment, ABL and TPTD similarly increased cortical thickness in the total hip (+1.5%) (both P<0.001 vs PBO). However, only ABL significantly increased hip cortical vBMD (+1.3%) vs PBO (-0.2%) and did so to a significantly greater extent than TPTD (0.4%) (both P<0.05 vs ABL). After 18 months, the increases from baseline in CSMI* and Z* were significantly greater in both the ABL and TPTD groups vs PBO in the FN and IT regions (P<0.0001 for all; Table). The increases with ABL were significantly greater than with TPTD for both CSMI* and Z* in the FN region (P<0.001 for both).

Conclusion: Both ABL and TPTD resulted in increased hip bone strength indices by DXA-based 3D modeling after 18 months. ABL significantly increased CSMI* and Z* to a greater extent than TPTD at the femur neck, consistent with its greater increase in hip cortical vBMD. Further studies may be warranted to investigate how these differences in clinically important regions impact hip strength.

Table: Changes in Hip Bone Strength Indices at 18 Months

% Change from Baseline	PBO	ABL	TPTD
FN CSMI*	0.5 ± 0.4	7.2 ± 0.6#^	4.5 ± 0.5 #
FN Z*	0.2 ± 0.3	7.7 ± 0.5 #^	5.0 ± 0.4 #
IT CSMI*	0.7 ± 0.5	6.6 ± 0.5 #	5.6 ± 0.5 #
IT Z*	0.7 ± 0.6	7.3 ± 0.6 #	6.4 ± 0.6 #

Mean ± SE; #p<0.0001 vs PBO; ^p<0.001 vs TPTD

OC5

FRACTURE RISK REDUCTION BY ANTI-OSTEOPOROSIS PHARMACOTHERAPY ACCORDING TO BASELINE RISK FACTORS AMONG POSTMENOPAUSAL WOMEN: METAREGRESSION ANALYSES OF RANDOMISED TRIALS

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Objectives: To synthesise the evidence on the effect of anti-osteoporosis pharmacotherapy according to baseline variables known to influence fracture risk among postmenopausal women; and to critically appraise internal validity of RCTs.

Materials and Methods: Meta-regression analysis was based on restricted maximum likelihood (mixed) models. We included 143 references representing 69 distinct trials that examined the effect of bisphosphonates [BP], denosumab [DMAB], selective oestrogen receptor modulators [SERM], parathyroid hormone receptor [PTHR] agonists and romosozumab, either compared to placebo or head-to-head. The baseline covariates were: fracture history, age, lumbar spine T-score and BMI. The Cochrane risk of bias tool was used to evaluate the RCTs. Data sources were MEDLINE, EMBASE and Cochrane Library from Jan 1996 to Nov 2019.

Results: Antiresorptive treatment (BP, SERM and DMAB) is more efficient compared to placebo in reducing vertebral fractures [VF] (RR= 0.59, 95% CI: 0.51, 0.69), with improved efficacy following increasing age (trial average range: 50-85 years): k=25; β: 0.96, 95% CI: 0.93, 0.99, but irrespective of the other baseline covariates. Regardless of the baseline covariates there was an effect of antiresorptive treatment compared to placebo on non-VF (RR= 0.82, 95% CI: 0.76, 0.89). Compared to either placebo or BP, anabolic treatment (PTHR, romosozumab) reduced the risk of both VF and non-VF irrespective of any of the baseline covariates. The certainty of the evidence was moderate; due to the apparent risk of bias related to the internal validity (incl. reporting bias).

Conclusions: Antiresorptive and anabolic treatment were beneficial in fracture risk reduction among postmenopausal women mostly independently of baseline risk. Since anabolic treatment was more effective than BP irrespective of baseline risk, there is no trial evidence to support the notion that anabolic treatment should be limited for the very high-risk patients.

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OC6

BUROSUMAB IMPROVES BIOCHEMICAL, SKELETAL, AND CLINICAL FEATURES OF TUMOR-INDUCED OSTEOMALACIA (TIO) SYNDROME

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Objective: Evaluate the efficacy and safety of burosumab, a fully human monoclonal antibody to FGF23, in adults with TIO.

Materials/Methods: In an ongoing open-label Phase 2 study (NCT02304367), 17 adults with TIO or cutaneous skeletal hypophosphatemia syndrome (CSHS) were enrolled and received burosumab. Key endpoints were changes in serum phosphorus and osteomalacia as assessed from trans-iliac crest bone biopsies. This report excludes 3/17 subjects who did not have TIO: 2 subjects diagnosed with X-linked hypophosphatemia post-enrollment and 1 subject with CSHS.

Results: Serum phosphorus increased from baseline (BL; 1.60 mg/dL) and was maintained after titration, from Week (W) 22 (2.85 mg/dL, dose cycle midpoint) to W144 (2.56 mg/dL, dose cycle endpoint, $p<0.0001$). Serum TmP/GFR and $1,25(OH)_2D$ also increased with burosumab. 11 subjects underwent paired bone biopsies at BL and W48. Osteoid volume/bone volume decreased from a mean ± SE of 17.6% ± 5.9% at BL to 12.1% ± 4.7% at W48 ($p=0.086$). Mean ± SE osteoid thickness decreased from 16.5 ± 3.6 μm to 11.3 ± 2.8 μm ($p<0.05$). Using imputation, mineralization lag time decreased from a mean ± SE of 1598 ± 420 days to 1032 ± 712 days ($p=0.41$). Osteoid surface/bone surface showed no change from BL (mean ± SE BL: 57% ± 9%, W48: 57% ± 7%). Of 249 areas identified with increased uptake on bone scan at BL, 68 (27%) and 81 (33%) were fully healed at W96 and W144, respectively; 56 (23%) and 32 (13%) were partially healed at W96 and W144, respectively. There were significant improvements in patient-reported outcomes of fatigue and pain as well as measures of physical functioning and proximal muscle function with burosumab. All subjects had ≥1 adverse event (AE). Two subjects discontinued: 1 to undergo chemotherapy to treat an AE of neoplasm progression and 1 failed to meet serum phosphorus dosing criteria (receiving minimal burosumab dosing). There were 16 serious AEs in 7 subjects, all unrelated to drug. Of the 6 subjects with a serious AE of tumor progression/compression, 5 had a history of tumor progression prior to enrollment. There was 1 death, considered unrelated to treatment.

Conclusions: In adults with TIO Syndrome, burosumab was associated with improvements in phosphate metabolism, osteomalacia, skeletal metabolism, physical functioning, fatigue, pain, and quality of life.

OC7

TEMPORAL TRENDS AND FACTORS ASSOCIATED WITH BISPHOSPHONATE DISCONTINUATION AND RESTART

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Background: Adverse events related to long-term use of bisphosphonates have raised interest in temporary drug discontinuation. Trends in bisphosphonate discontinuation and restart, as well as factors associated with these decisions are not fully understood at a population level.

Methods: We investigated temporal trends of bisphosphonate discontinuation from 2010 to 2015, and identified factors associated with discontinuation and restart of osteoporosis therapy. Our cohort consisted of long-term bisphosphonate users identified from 2010-2015 Medicare data. We defined discontinuation as ≥ 12 months without bisphosphonate prescription claims. We used conditional logistic regression to compare factors associated with alendronate discontinuation or osteoporosis therapy restart in the 120-day period preceding discontinuation or restart referent to the 120-day preceding control periods.

Results: Among 73,800 long-term bisphosphonates users, 59,251 (80.3%) used alendronate, 6,806 (9.2%) risedronate, and 7,743 (10.5%) zoledronic acid, exclusively. Overall 26,281 (35.6%) discontinued bisphosphonates for at least 12 months. Discontinuation of bisphosphonates increased from 1.7% in 2010, reaching a peak of 14% in 2012 with levels plateauing through 2015. The factors most strongly associated with discontinuation of alendronate were: benzodiazepine prescription (aOR = 2.5, 95% CI [2.1, 3.0]), having a dual-energy X-ray absorptiometry (DXA) scan (aOR = 1.8, 95% CI [1.7, 2.0]) and skilled nursing facility care utilization (aOR = 1.8, 95% CI [1.6, 2.1]). The factors most strongly associated with restart of osteoporosis therapy were: having a DXA scan (aOR = 9.9, 95% CI [7.7, 12.6]), sustaining a fragility fracture (aOR = 2.8, 95% CI [1.8, 4.5]), and an osteoporosis or osteopenia diagnosis (aOR = 2.5, 95% CI [2.0, 3.1]).

Conclusions: Our national evaluation of bisphosphonate discontinuation showed that an increasing proportion of patients on long-term bisphosphonate therapy discontinue medications. The factors associated with discontinuation of alendronate were primarily related to worsening of overall health status, while traditional factors associated with worsening bone health were associated with restarting osteoporosis medication.

OC8

MACROBIOTIC DIETS, PLANT-BASED DIETS, VEGETARIANISM, VEGANISM AND BONE HEALTH: A SYSTEMATIC REVIEW AND META-ANALYSES

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Abstract

Objectives: Despite the benefits that vegetarian and vegan diets have on cardiovascular diseases, such as obesity, hypertension, type 2 diabetes mellitus, and ischemic heart disease, vegetarians and vegans have a lower bone mineral density (BMD) and vegans seem to have, in addition to some adverse nutritional consequences, higher levels on fractures compared to omnivores. Nevertheless, the effect that less restrictive options like plant-based diets (defined in terms of low frequency of animal food consumption) and macrobiotic diets (a diet that consists of cereals, pulses, and vegetables with small additions of seaweeds, fermented food, nuts, and seeds avoiding animal products but fish may be taken occasionally) can have on bone health is still unknown. The objective of this systematic review and meta-analyses is to evaluate possible benefits/risks that macrobiotic and plant-based diets can have on bone health and to update new information of vegetarian and vegan diets regarding bone status.

Material and methods: A systematic search was conducted in PubMed, Scopus, and Science Direct, covering the period from the respective start date of each database to January 2020. Inclusion criteria (original studies in children and adults, written in English or Spanish comparing those following macrobiotic, plant-based diets, vegetarian or vegan diets with omnivores as controls, with BMD information for the whole body, lumbar spine, or femoral neck and/or the number of fractures as the outcome). Following a diet for less than six months was an exclusion criteria. The quality assessment tool for observational cohort and cross-sectional studies is used to assess the quality of the studies.
Results: Preliminary results show that macrobiotic, vegetarian and vegan diets have a negative impact on BMD. Conversely, those following a plant-based diet seem to have better bone health outcomes. Nevertheless, most of the studies did not include important confounders such as calcium intake, body mass index, physical activity, hormone use, sunlight exposure, consumption of alcohol, and smoking behavior.
Conclusions: Vegetarians, vegans and those following macrobiotic diets have a lower BMD compared to omnivores. Well-planned plant-based diets however seem to be a good choice to build and maintain good bone health. More studies including important confounders are needed to draw appropriate conclusions.
The authors declare no conflicts of interest.

OC9

DISEASE PHENOTYPE AS A PREDICTOR OF TREATMENT RESPONSE IN OSTEOARTHRITIS: RESULTS FROM A PHASE II CLINICAL TRIAL OF THE FIRST-IN-CLASS IMIDAZOLINE-2 RECEPTOR LIGAND CR4056

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Objective: CR4056 is a novel imidazoline-2 receptor (I_2R) ligand endowed with potent analgesic activities in animal pain models, by innovative modulation of the monoaminergic descending inhibitory pathway [1]. The present proof-of-concept study tested the short-term efficacy and safety of CR4056 in patients with knee osteoarthritis (OA) pain with different disease phenotypes.
Methods: This multicenter, prospective, randomized, placebo-controlled, double-blind trial (EudraCT n. 2015-001136-37) enrolled patients with different OA phenotypes, including patients with a neuropathic pain component (painDETECT questionnaire ≥19), inflammatory OA (flares) or metabolic OA (BMI ≥27.5 kg/m^2, the WHO threshold for pre-obesity). Patients with knee OA (ACR clinical/radiological criteria, K-L grade 2/3) and moderate/severe pain (score ≥50 on 0-100 WOMAC pain subscale) received oral CR4056 (100 mg bid in women and 200 mg bid in men) or placebo (both genders) for 14 days. Intention-to-treat (ITT: Worst-Case approach for non-completers) changes in WOMAC pain (primary endpoint) were analyzed by the Wilcoxon test.
Results: 213 patients were treated with CR4056 (92 women, 52 men) or placebo (69 overall). CR4056 decreased WOMAC pain vs. placebo after only 14 days and with a similar pattern in the overall population and the investigated OA phenotypes. In the metabolic OA phenotype (BMI ≥27.5, N=156), all CR4056-treated groups showed a statistically and clinically significant improvement vs. placebo in WOMAC pain of 12-18 points. Secondary pain and function outcomes followed a pattern consistent with the primary endpoint. There were too few patients with a neuropathic or inflammatory phenotype for a meaningful analysis. There were no serious adverse events and CR4056 was well tolerated: the most common AE was mild headache.
Conclusions: CR4056 is the first I_2R ligand showing analgesic activity in humans. The compound was safe and effective in reducing knee OA pain in this short phase II trial, especially in overweight patients representing the metabolic OA phenotype. This observation prompts longer-term evaluation of the analgesic activity of CR4056 and the exploration of possible links between the I_2 pathway and altered pain perception in the metabolic OA phenotype.
Reference: [1] Li JX. Imidazoline I(2) receptors: An update. Pharmacol Ther 2017;178:48-56.

OC10

THE NOVEL, INTRA-ARTICULAR CLK/DYRK1A INHIBITOR LORECIVIVINT (SM04690), A WNT PATHWAY MODULATOR, IMPROVED RESPONDER OUTCOMES IN SUBJECTS WITH KNEE OSTEOARTHRITIS: A POST HOC ANALYSIS FROM A PHASE 2B TRIAL

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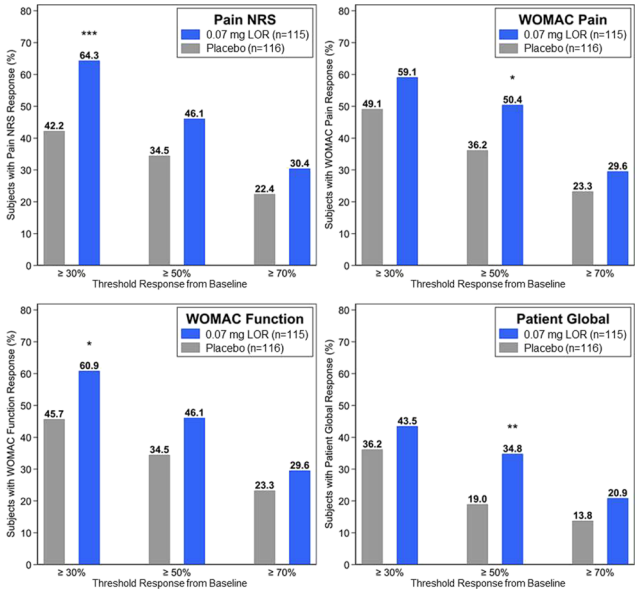
Objectives: Lorecivivint (LOR; SM04690) is a small-molecule, intra-articular (IA) CLK/DYRK1A inhibitor that modulates the Wnt pathway and has demonstrated beneficial effects on patient-reported outcomes (PROs) relative to placebo (PBO) in two Phase 2 knee OA trials. Representing PROs as discrete threshold responses instead of as changes in mean point estimates may more meaningfully evaluate clinical benefits experienced by trial subjects. This post hoc analysis was conducted to measure the proportion of LOR-treated subjects in a 24-week Phase 2b study who achieved 30%, 50%, or 70% threshold responses over baseline in Pain Numeric Rating Scale (NRS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) subscores, and Patient Global Assessment (PtGA). Results from the Phase 3 selected dose of 0.07 mg LOR are presented here.
Material and Methods: Subjects had ACR-defined knee OA, Kellgren-Lawrence (KL) grades 2–3, and Pain NRS scores ≥4 to ≤8 in the target knee and <4 in the contralateral knee. A single 2mL IA injection of 0.03 mg, 0.07 mg, 0.15 mg, or 0.23 mg LOR, or vehicle PBO was given in the target knee at baseline. The proportion of subjects meeting 30%, 50%, or 70% threshold responses over baseline in the weekly average of daily Pain NRS [0–10], WOMAC Pain [0–100], WOMAC Function [0–100], and PtGA [0–100] at Week 12 was determined. The odds ratios (OR [95%CI]) of achieving each threshold response level were calculated.
Results: 635 subjects (91.4%) completed the study. Treatment with 0.07 mg LOR versus PBO at Week 12 led to
1. Significantly ($P<0.05$) increased odds of achieving a 30% threshold response in Pain NRS (OR 2.47 [1.45, 4.19]) and WOMAC Function (OR 1.86 [1.10, 3.12])
2. Significantly increased odds of achieving a 50% threshold response in WOMAC Pain (OR 1.79 [1.06, 3.03]) and PtGA (OR 2.28 [1.25, 4.16])
3. Numerically, but not significantly, more subjects achieving a 70% threshold response in all PROs
Improvements were maintained through Week 24.
Conclusions: LOR, in development as a potential disease-modifying knee OA drug, demonstrated significantly higher odds ratios of achieving and maintaining clinically relevant improvements in PROs compared with placebo from Week 12 through Week 24. Phase 3 studies are ongoing.
Figure: Responder outcomes from a Phase 2b trial of LOR: Pain NRS, WOMAC Pain, WOMAC Function, and Patient Global Assessment at Week 12.



Logistic regression of LOR versus placebo using the FAS (Full Analysis Set, all dosed subjects) and non-responder imputation. *P<0.05, **P<0.01, ***P<0.001

Logistic regression of LOR versus placebo using the FAS (Full Analysis Set, all dosed subjects) and non-responder imputation. *P<0.05, **P<0.01, ***P<0.001

OC11

EFFICACY AND SAFETY OF AN INTRA-ARTICULAR INJECTION OF JTA-004, A NOVEL ENHANCED PROTEIN SOLUTION, IN KNEE OSTEOARTHRITIS PAIN: A RANDOMISED, DOUBLE-BLIND CONTROLLED PHASE II/III STUDY

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Objective: The objective was to assess the efficacy and safety of a single intra-articular administration of JTA-004, a novel protein solution in development for the treatment of knee osteoarthritis (OA) pain. 3 JTA-004 formulations were tested and compared to Hylan G-F 20 during a 6-month period.

Material and methods: In this prospective, multicentre, double-blind phase II/III trial (NCT02740231), 164 patients were randomly assigned to one of the three JTA-004 formulations or the reference treatment (Hylan G-F 20) in a 1:1:1:1 ratio. Patients were evaluated using Western Ontario McMaster Universities (WOMAC®) scores and Short-Form health survey (SF-12). The primary efficacy endpoint was the change from baseline at 6 months in WOMAC® VA3.1 Pain Subscale. Safety was assessed by monitoring and reporting vital signs, physical examination, adverse events and concomitant medications throughout the study.

Results: At 6 months, patients in the three JTA-004 groups showed a better improvement in pain compared to patients in the reference group. The between-group difference (between each JTA-004 test group and reference group) in adjusted (adapted to difference in baseline values) mean change in WOMAC® Pain Subscale Score from baseline ranged between -9.49 mm and -11.63 mm at 6 months post-injection. Statistical superiority of each JTA-004 formulation over Hylan G-F 20 was however not demonstrated (p-value between 0.052 and 0.141). As the three JTA-004 formulations had a similar efficacy in terms of pain reduction, a *post hoc* analysis was subsequently performed between the pooled JTA-004-treated patients and the reference group. This analysis showed a 26.1 ± 2.4 (adjusted mean ± SE) mm improvement in pain in the pooled JTA-004 group vs. 15.6 ± 4.1 mm in the reference group at 6 months, demonstrating a statistically significant superiority of JTA-004 over the reference (between-group difference = -10.57; p = 0.030).

All JTA-004 formulations were shown to be well tolerated and had a clinically acceptable safety profile.

Conclusions: This study provides a first evidence of efficacy and safety of JTA-004 in the treatment of knee OA pain. A subsequent larger pivotal phase III study involving 676 patients will be conducted to further confirm these promising findings.

OC12

CONFIRMED AND SEVERE SARCOPENIA BY EWGSOP2 PREDICT 10-YEAR FRACTURE RISK INDEPENDENT OF FRAX, FALLS AND BMD IN THE OSTEOPOROTIC FRACTURES IN MEN (MROS) STUDY: A META-ANALYSIS

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Aims

Having demonstrated that measures of physical function, but not DXA appendicular lean mass (ALM), are predictive of incident fracture, we

investigated the predictive value of confirmed and severe sarcopenia, using the recent European Working Group on Sarcopenia in Older People (EWGSOP2) recommendations, for incident fracture, independent of femoral neck bone mineral density (FNBMD), FRAX 10-year fracture probability and prior falls.

Methods

In USA, Sweden and Hong Kong (HK) MrOS cohorts, we used an extension of Poisson regression to investigate relationships between sarcopenia (y/n) and incident major osteoporotic fracture (MOF: clinical vertebral, hip, wrist or proximal humerus). Confirmed sarcopenia was based on low DXA ALM/height^2 in combination with high chair stand time or low grip strength. Additional low gait speed constituted severe sarcopenia. Associations were adjusted for age and follow-up time, reported as hazard ratio (HR) for first incident MOF. Further analyses adjusted additionally for FRAX MOF probability, prior falls (y/n) or FNBMD T-score. Results were synthesized by meta-analysis.

Results

We studied 5660 men in USA, 2764 in Sweden and 1987 in HK; (mean ages 73.5, 75.4 and 72.4 years; mean follow-up time 10.9, 8.7 and 9.9 years; mean % incident MOF 10%, 16%, 7% respectively). Confirmed sarcopenia (prevalence=5.5% USA; 2.9% Sweden; 10.1% HK) was associated with incident MOF [HR: 1.82 (95%CI: 1.46, 2.27)]. Associations remained after adjustment for prior falls or FRAX probability. Adjustment for FNBMD T-score led to attenuation of the relationship: (HR:1.39; 95%CI:1.11, 1.75). In addition, severe sarcopenia (prevalence 0.5% USA; 0.6% Sweden; 3.6% HK) appeared more robustly associated with incident MOF [HR: 2.07 (95%CI: 1.28, 3.33)], and remained associated after each adjustment [e.g. with BMD T-score, HR: 1.80 (95%CI: 1.12, 2.91)].

Conclusions

The predictive value for fracture of EWGSOP2 sarcopenia definitions is reduced by inclusion of FN BMD T-score, but addition of low gait speed as the marker of severe sarcopenia yields a more robust predictive measure, albeit with lower prevelance. These findings further support the importance of physical performance measures in defining sarcopenia.

OC13

MUSCLE DENSITY, BUT NOT SIZE, CORRELATES WELL WITH MUSCLE PERFORMANCE

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OBJECTIVE: To determine the associations of handgrip strength (HGS) and the Timed Up and Go test (TUG) with muscle size and density of different muscle levels in healthy controls.

METHODS: 301 controls were enrolled in this study and recruited for QCT imaging of the lumber, hip and mid-thigh. We also test muscle strength (HGS) and physical performance (TUG). Gluteus maximus muscle(GMaxM) and gluteus medius/minimus muscle(GM/MinM), trunk muscle at vertebrae L2 level and mid-thigh muscle were measured for cross-sectional areas and attenuations. Health-related covariates included blood pressure, diabetes mellitus, fracture history, fast serum glucose and the EuroQol five-dimension score (EQ-5D).General linear models were fitted using method of least squares to evaluate associations of TUG and handgrip strength with muscle CSA and density.

RESULTS: None of the associations between muscle area and TUG was significant after adjustment for age, height and weight. The same result was observed in men for associations between muscle density and TUG. In contrast, in women gluteus maximus and trunk muscle density showed a significant association with TUG even after adjustment for age, height and weight, although slopes were rather small. Interestingly the slope was even negative in females (β -0.06, p =0.001, adjusted). In men but not in women muscle area of the gluteus maximus and of the mid-thigh were significantly associated with HGS but results were not significant for the trunk muscle. Gluteus maximus and trunk muscle density were significantly associated with HGS in men and women. Mid-thigh muscle density was significantly associated with HGS in men only.

CONCLUSION: Our study results show that muscle density performs better than muscle size in associating with muscle performance and seems to be as a surrogate for the role of physical performance as hip fracture risk factors.

OC14

THE MULTIDIMENSIONAL PROGNOSTIC INDEX PREDICTS FALLS IN OLDER PEOPLE: AN 8-YEAR LONGITUDINAL COHORT STUDY OF THE OSTEOARTHRITIS INITIATIVE

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OBJECTIVES: Falls are associated with several negative outcomes. Early identification of those who are at risk of falling is of importance in geriatrics, and comprehensive geriatric assessment (CGA) seems to be promising. Therefore, the present study investigated whether the multidimensional prognostic index (MPI), based on a standard CGA, is associated with falls in the Osteoarthritis Initiative (OAI).

MATERIALS AND METHODS: A standardized CGA including information on functional, nutritional, mood, comorbidities, medications, quality of life, and cohabitation status was used to calculate a modified version of the MPI, categorized as MPI-1 (low), MPI-2 (moderate), and MPI-3 (high risk). Falls were self-reported and recurrent fallers were defined as ≥2 in the previous year. Logistic regression was carried out and results are reported as odds ratio (ORs) with their 95% confidence intervals (CIs).

RESULTS: The final sample consisted of 885 older adults (mean age 71.3 years, female = 54.6%). Recurrent fallers showed a significant higher MPI than their counterparts (0.46 ± 0.17 vs 0.38 ± 0.16; P < .001). Compared with those in MPI-1 category, participants in MPI-2 (OR 2.13; 95% CI 1.53–2.94; P < .001) and in MPI-3 (OR 5.98; 95% CI 3.29-10.86; P < .001) reported a significant higher risk of recurrent falls over the 8-years of follow-up.

CONCLUSIONS: Higher MPI values at baseline were associated with an increased risk of recurrent falls, suggesting the importance of CGA in predicting falls in older people.

OC15

5-YEAR ADVERSE OUTCOMES OF SARCOPENIA DIAGNOSED ACCORDING TO SIX DIFFERENT DEFINITIONS

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Introduction: Six operational definitions are proposed by different working groups for the diagnosis of sarcopenia. We have previously shown, out of our SarcoPhAge study, that most of the sarcopenia definitions were significantly associated with deaths over a 3-year period, but not with physical disabilities and institutionalizations. Our aim is to compare, in the same cohort, the impact of using the 6 definitions on the prevalence and on the 5-years follow-up consequences of sarcopenia.

Methods: Sarcopenia was diagnosed according to: EWGSOP 1, IWGS, SSCWD, AWGS, FNHI and EWGSOP 2. Muscle mass was measured with DXA, muscle strength by hand dynamometer and physical performance by 4-m gait speed or the SPPB. Cox Proportional Hazard ratios were calculated for 5-year incidence of mortality, institutionalization, fracture, fall, or hospitalization during the 5-year follow-up period. Analyses were adjusted for age, sex, number of drugs and comorbidities, cognitive status and physical activity level.

Results: 534 older subjects were included at baseline (73 (68-78) years, with 321 (60.1%) women). The prevalence of sarcopenia differed depending on the definition used: 13.9% with EWGSOP1, 17.6% with IWGS, 8.6% with SSCWD, 7.9% with AWGS, 5.6% with FNHI and 4.5% with EWGSOP 2. A total of 481 participants were included in the analyses on the 5-year mortality and institutionalizations, 463 on fractures, 465 on hospitalizations and 459 on falls. Among them, 65 died, 10 were institutionalized, 54 had fractures, 240 were hospitalized and 191 fell. In multivariate analysis, a higher risk of mortality is observed when the diagnosis of sarcopenia was made with the EWGSOP 1 [HR of 2.12 (95% IC 1.12-4.03)] and the AWGS definitions [HR of 3.43 (95% IC 1.72-6.86)]. For EWGSOP 2, the smaller sample of sarcopenic individuals identified have impacted the statistical power of the study, and consequently the association was not significant [HR of 1.42 (95% IC 0.59-3.42)] but remained in the same range of those observed using the EWGSOP1. In subjects diagnosed with severe sarcopenia with EWGSOP 2, the association with 5-year mortality was not significant in the multivariate fully-adjusted model [HR of 2.18 (95% IC 0.88-5.40)], probably because of low statistical power, but these participants were at higher risk of experiencing at least one fracture at 5 years [3.76 (95% IC 1.08-13.05)]. Sarcopenia was not significantly associated with the 5-year incidence of institutionalization, fall and hospitalization regardless of the definition chosen.

Conclusion: In this sample, we found that sarcopenia diagnosed with EWGSOP 1 and AWGS and severe sarcopenia diagnosed with EWGSOP2 are associated with mortality and fracture respectively. However, the various definitions are leading to significantly different prevalences of sarcopenia, within the same population. This has to be taken into account in future researches.

OC16

LEVEL AND CHANGE IN SARCOPENIA COMPONENTS PREDICT ADVERSE HEALTH OUTCOMES: FINDINGS FROM THE HEALTH, AGING AND BODY COMPOSITION STUDY

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Objective

To examine level and change in muscle mass, strength and function in relation to risk of mortality, minor trauma fracture, hospital admission and falls among older people participating in the Health, Aging and Body Composition Study (USA).

Material and Methods

Analyses were based on 2902 men and women, aged 70-79 years at baseline (1997-8). Appendicular lean mass (ALM) was ascertained using DXA; muscle strength by grip dynamometry; and muscle function by gait speed. Exposures were mean level of each characteristic and change in age-specific z-scores (characterised by linear mixed models) between baseline and 5-year follow-up. These were examined as predictors of mortality, self-reported and adjudicated hospital admission and minor trauma fracture, and self-reported falls in the subsequent decade using sex-adjusted time-to-first event Cox regression with or without adjustment for potential confounders.

Results

Mean(SD) baseline grip strength, gait speed and ALM was 32.7(10.6) kg, 1.1(0.2) m/s and 20.1(5.0) kg respectively; annual percentage declines were 1.3(3.4), 1.3(3.8) and 0.7(1.1). The proportion experiencing each outcome was: death (64%), minor trauma fracture (15%); hospital admission (83%); and falls (71%). Lower grip strength and gait speed were associated with increased risk of all outcomes ($p<0.03$); lower ALM only predicted mortality and minor trauma fracture ($p<0.03$). Greater declines in grip strength, gait speed and ALM were related to increased risk of mortality and hospital admission ($p<0.01$); declines in gait speed and ALM also predicted falls ($p<0.01$). Hazard ratios for mortality, hospital admission and falls per SD greater decline in gait speed, adjusted for sociodemographic and lifestyle factors, were 1.18(95%CI:1.13,1.24), 1.15(1.11,1.21) and 1.12(1.07,1.18) respectively. Sex-adjusted models for level and change in grip strength and ALM each explained 4% of the variation for mortality; values for gait speed level and change were 12% and 4% respectively.

Conclusion

Lower levels and greater declines in muscle mass, strength and function were associated with increased risk of adverse health outcomes. This suggests that interventions to maximize peak levels in earlier life, and to reduce rates of age-related decline, may reduce the burden of disease in this age group.

OC17

RELATIONSHIP BETWEEN OBESITY AND RISK OF MAJOR OSTEOPOROTIC FRACTURE IN POSTMENOPAUSAL WOMEN: TAKING FRAILTY INTO CONSIDERATION

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Background: The role of obesity in fracture risk remains to be uncertain and inconclusive in postmenopausal women. Our study aimed to assess the relationship between obesity and risk of major osteoporotic fracture (MOF; i.e., a clinical fracture of upper arm or shoulder, hip, spine, or wrist) in postmenopausal women, after taking frailty into consideration.

Methods: We used the data from the Global Longitudinal Study of Osteoporosis in Women (GLOW) 5-year Hamilton cohort for this study. Frailty was measured by a frailty index (FI) of deficit accumulation at baseline. We incorporated an interaction term (obesity x FI) in the Cox proportional hazards regression model.

Results: We included 3985 women (mean age: 69.4 years) for analyses, among which 29% were obese (n = 1118). There were 200 (5.02%) MOF events documented during follow-up: 48 (4.29%) in obese women and 152 (5.65%) in the nonobese group. Significant relationships between obesity, frailty and MOF risk was found: HR = 0.72 (95% CI: 0.67 - 0.78) for obesity, and HR = 1.34 (95% CI: 1.11 - 1.62) per-SD increase

in the FI. The interaction term was also significant: HR = 1.16 (95% CI: 1.02 - 1.34) per-SD increase. Increased HRs were found with higher FIs regarding the relationship between obesity and MOF risk, indicating increasing frailty attenuated the protective effect of obesity (Figure 1 below).

Conclusions: After taking frailty into consideration, obesity was significantly associated with decreased risk of MOF in postmenopausal women, but frailty modifies the propensity of obesity towards decreased fracture risk. Evaluating frailty status may aid in understanding of the complex relationship between obesity and fracture risk.

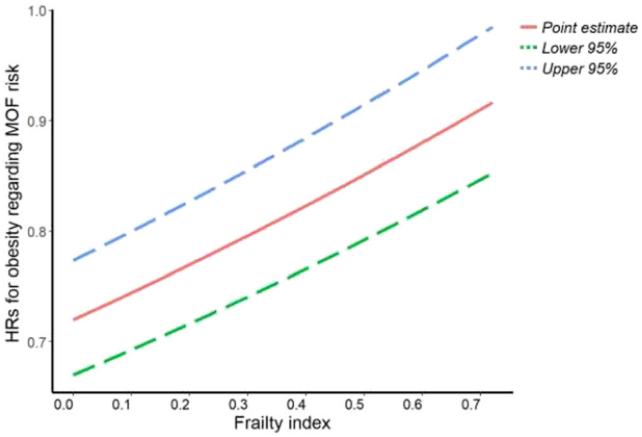

Figure 1. Different HRs for obesity regarding the MOF risk at different levels of the FI

OC18

IDENTIFICATION OF THE MOST IMPORTANT FEATURES OF KNEE OSTEOARTHRITIS PROGRESSORS USING MACHINE LEARNING METHODS

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ABSTRACT

Objective: We still lack robust prediction models that are able to guide clinical decisions and stratify osteoarthritis (OA) patients according to risk of disease progression. This study aimed at identifying the most important features of knee OA progressors. To this end, we used machine learning (ML) algorithms on a large set of subjects and features to develop advanced prediction models that provide high classification and prediction performance.

Methods: Participants, features and outcomes were from the Osteoarthritis Initiative. Features were from baseline (1107), including articular knee tissues (135) assessed by quantitative MRI. OA progressors were ascertained by four outcomes: cartilage volume loss in medial plateau at 48 and 96 months (Prop_CV_48M, 96M); Kellgren-Lawrence (KL) grade ≥2; and medial joint space narrowing (JSN) ≥1 at 48 months. Six feature selection models were used to identify the common features in each outcome. Six classification methods were applied to measure the accuracy of the selected features in classifying the subjects into progressors and non-progressors. Classification of the best features was done using auto-ML interface and the area under the curve (AUC). To prioritize the top features, Sparse Partial Least Square (sPLS) method was used.

Results: For the classification of the best common features in each outcome, Multi-Layer Perceptron (MLP) achieved the highest AUC in Prop_CV_96M, KL, and JSN (0.80, 0.88, 0.95), and Gradient Boosting Machine (GBM) for Prop_CV_48M (0.70). sPLS revealed that the baseline top five features to predict knee OA progressors are the joint space width (JSW), mean cartilage thickness of peripheral, medial, and central tibial plateau, and JSN.

Conclusion: This is the first time that such a comprehensive study was performed for identifying the best features and classification methods for knee OA progressors. Data revealed that early prediction of knee OA progression can be done with high accuracy and based on only a few features. This study identifies the baseline X-ray and MRI-based features and the most important for predicting knee OA progressors. These results could be used for the development of a tool enabling prediction of knee OA progressors.

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OC19

RESVERATROL BENEFITS BONE HEALTH IN POSTMENOPAUSAL WOMEN – OUTCOMES OF THE TWO-YEAR RESHAW TRIAL

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Objective: To evaluate the effect of 12 months of resveratrol (RES) supplementation on bone mineral density (BMD) in postmenopausal women.

Methods: RESHAW (Resveratrol Supporting Healthy Ageing in Women) is the largest (146 participants) and longest (2 years) trial of RES supplementation undertaken in postmenopausal women (mean age 64 years). Participants were randomised to RES (75mg twice daily, >98% *trans*-resveratrol) or placebo for 12 months, after which they crossed over to the alternate supplement for a further 12 months. Before and after each phase, we assessed bone mineral density in the hips and lumbar spine (by DEXA) and the bone resorption marker, C-terminal telopeptide type-1 collagen (CTX).

Results: Following 12 months of RES, lumbar spine BMD increased by 1.5% compared to placebo, equating to an 18% improvement in t-score (P=0.005). RES reduced the loss of BMD in the femoral neck, resulting in a 12% improvement in FRAX t-score (P<0.001), a 36% reduction in hip fracture risk (P=0.040) and a 9% reduction in the 10-year risk of a major osteoporotic fracture (P=0.052). These results were confirmed by the within-individual comparisons from the 2 x 12-month analysis wherein BMD increased in both the femoral neck (P=0.040) and total femur (P=0.035) compared to placebo, and this was accompanied by a 7.3% reduction in plasma CTX (P=0.025). Our sub-analysis of responses to RES supplementation revealed a relative increase of BMD in the femoral neck and reduction in CTX levels in older women (≥65 years) compared to women at mid-life (45-64 years).

Conclusion: This is the first study demonstrating benefits of RES supplementation for older women at least 10 years postmenopausal who are at heightened risk of osteoporotic fractures and for whom the health risks of initiating hormone replacement therapy outweigh any bone protective benefits.

OC20

GEOGRAPHICAL ASSESSMENT OF BONE MINERAL DENSITY WITH RELUGOLIX COMBINATION THERAPY: RESULTS FROM THE PHASE 3 LIBERTY PROGRAM

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Objectives

In phase 3 LIBERTY 1 and 2 studies, once-daily relugolix combination therapy (Relugolix-CT [relugolix 40 mg, estradiol (E2) 1.0 mg, norethindrone acetate (NETA) 0.5 mg]) significantly reduced menstrual blood loss (MBL) in women with heavy menstrual bleeding associated with uterine fibroids (UF).[1] We assessed whether there was geographical variation in skeletal response to Relugolix-CT.

Materials and Methods

Premenopausal women (age 18–50 years) with heavy menstrual bleeding (MBL volume ≥ 80 mL/cycle) were randomized (1:1:1) to receive Relugolix-CT for 24 weeks, relugolix 40 mg alone for 12 weeks followed by Relugolix-CT for 12 weeks (delayed Relugolix-CT), or placebo for 24 weeks. Randomization was stratified by geographical region (North America vs Rest of World) and baseline MBL volume (< 225 vs ≥ 225 mL). Bone mineral density (BMD) by dual energy X-ray absorptiometry of the lumbar spine (LS) (L1–4) was assessed at screening and Weeks 12 and 24. Percent change in BMD from baseline was summarized by treatment group.

Results

In pooled LIBERTY studies (N: 768), mean % changes from baseline at 24 weeks in LS BMD for Relugolix-CT, placebo, and delayed Relugolix CT were -0.233, 0.184, and -1.972%, respectively. When evaluated by region, results were consistent in EU/ South America/ South Africa: -0.346, 0.088, and -2.707% and in North America: -0.192, 0.164, and -1.844%, respectively (Table).

		Changes in lumbar spine BMD at 12 and 24 weeks	
	N	12 weeks	24 weeks
Total Cohort			
Placebo	256	0.342%	0.184%
Relugolix + E2/NETA	254	-0.626%	-0.233%
Relugolix → Relugolix + E2/NETA	258	-1.961%	-1.972%
EU, South American, South Africa			
Placebo	46	0.492%	0.088%
Relugolix + E2/NETA	51	-0.054%	-0.346%
Relugolix → Relugolix + E2/NETA	49	-2.070%	-2.707%
North American (United States)			
Placebo	161	0.262%	0.164%
Relugolix + E2/NETA	153	-0.888%	-0.192%
Relugolix → Relugolix + E2/NETA	149	-1.965%	-1.844%

Conclusions

Compared to relugolix alone, Relugolix-CT preserves bone mass in the lumbar spine over 24 weeks. Geographic differences in skeletal response were not observed, demonstrating consistent results across different ranges and populations. Initiating treatment for UF with relugolix combined with E2/NETA represents a potential method for preserving BMD while providing therapeutic benefit over the long-term.

Reference

1. Al-Hendy et al., ASRM 2019

Disclosures

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OC21

VITAMIN D SUPPLEMENTATION IN PREGNANCY RESULTS IN GREATER OFFSPRING BONE MASS AT 4 YEARS: FINDINGS FROM THE MAVIDOS TRIAL

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Objectives: In the multi-centre MAVIDOS trial, pregnancy vitamin D supplementation increased neonatal bone mass amongst winter-born babies. We aimed to ascertain whether this effect is sustained into later childhood, and have now assessed bone indices at 4 years old in the Southampton participants.

Materials and Methods: In Southampton, Oxford and Sheffield, in a double-blind design, 1134 pregnant women were randomised to 1000 IU/day cholecalciferol or matched placebo from 14 weeks gestation to birth. At age 4 years (Southampton participants only, n=723 births), offspring assessments included anthropometry, whole-body dual-energy x-ray absorptiometry (DXA) [Hologic Horizon, yielding whole body less head (WBLH) bone mineral content (BMC), bone mineral density (BMD), bone area (BA) and lean mass (LM)], and a maternal questionnaire. Linear regression was used to estimate the mean difference (represented by β) in outcomes between the two randomisation arms, adjusted for sex, and age at DXA. Additional adjustment for gestational age, maternal early pregnancy BMI and the child's milk intake was performed in further models. Outcomes were standardised to a standard deviation scale, for ease of comparison.

Results: 564 children attended the 4-year visit; 452 had a useable DXA with minimal movement artefact. Maternal pregnancy vitamin D supplementation led to greater offspring indices of bone mass compared with placebo, irrespective of season, for example WBLH BMD at age 4 years, [supplemented group, 0.477 (95% CI: 0.472,0.481) g/cm^2; placebo group 0.470 (0.466,0.475) g/cm^2; β=0.18 (0.00,0.35) SD p=0.047], and evidence of associated greater LM [supplemented group, 9.25 (9.08,9.42) kg; placebo group 9.01 (8.83,9.18) kg; β=0.15 (-0.02, 0.31) SD p=0.081]. Associations were consistent for lumbar spine indices, for BA and BMC, and in the fully adjusted models. No differences in child height, weight or BMI were observed between groups.

Conclusions: This is the first ever demonstration, in a large placebo-controlled, double-blind randomised trial, that maternal pregnancy vitamin D supplementation leads to sustained improvement in offspring bone and muscle mass, informing public health approaches for the prevention of fractures.

OC22

SUPERIOR EFFICACY OF CALCIFEDIOL SOFT GELATIN CAPSULES VS CHOLECALCIFEROL FOR THE MANAGEMENT OF VITAMIN D DEFICIENCY IN POSTMENOPAUSAL WOMEN: A TREATMENT TO BE CONSIDERED IN THERAPEUTIC GUIDELINES

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Objective

To assess the efficacy of calcifediol in the treatment of vitamin D deficiency, compared with therapeutic guidelines recommendations for cholecalciferol in postmenopausal women.

Material and Methods

Phase III-IV, double blind, randomised, controlled, multicentre superiority clinical trial. Postmenopausal women with baseline levels of 25(OH)D < 20 ng/mL were randomised to three arms: 266 mcg of calcifediol/month for 4 or 12 months (standard and test regime), or to cholecalciferol 25000 IU/month for 12 months (as per therapeutic guidelines).

Results from an interim analysis - performed upon completion of month 4 visit by 100% of evaluable patients - are presented and reported without unblinding the study treatments. Both calcifediol groups are summarised for analysis.

The trial has been approved by the corresponding ethics committees and national competent authorities.

Results

298 women were included in the ITT analysis. The average age was 63.4 ± 8.2 years, 10.7% had osteoporosis and received treatment, mean BMI was 29.3 ± 6 kg/m^2, 25% of the population had basal 25(OH)D levels <10ng/mL. All demographic characteristics and risk factors for osteoporosis were balanced amongst groups.

When analysing per treatment group,13.5% and 35% of women in the calcifediol group reached values of 25(OH)D > 30ng/mL at 1 and 4 months when compared to 0% and 8.2% respectively in the cholecalciferol group (p<0.01).

The mean change in ng/mL (Table 1) when compared to baseline was 14.9 ± 8.1 with calcifediol and 9.9 ± 5.7 with cholecalciferol (p<0.01).

No relevant safety issues were reported for the present analysis.

Table 1: Variation of mean 25(OH)D levels

	Calcifediol (n= 200)	Cholecalciferol (n = 98)	p
Baseline	12.8 ± 3.9	13.2 ± 3.7	-
Month 1	22.6 ± 7.8	18.4 ± 4.0	<0.001
Month 4	27.8± 9.0	23.1 ± 5.4	<0.001

Conclusions

Calcifediol shows a greater efficacy than cholecalciferol regime (as recommended in therapeutic guidelines), for the treatment of vitamin D deficiency in postmenopausal women. Cholecalciferol fails to achieve recommended levels in a significant proportion of this population.

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OC23

PERIOSTEAL EXPANSION DOES NOT COMPENSATE LOSS OF BONE STRENGTH CAUSED BY ENDOSTEAL RESORPTION WITH AGING: A LONGITUDINAL HR-PQCT STUDY WITH 3D-REGISTRATION FROM THE GERICO COHORT

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Introduction: Age-related bone loss is classically associated with accelerated bone resorption at the trabecular and endocortical bone surfaces. Meanwhile, periosteal expansion has been proposed as a mechanical compensation to increase bone strength in response to endosteal bone loss. However, this concept has never been investigated in longitudinal studies, neither has the association with changes in bone strength.

Methods: Bone mineral density and microstructure at distal radius and tibia were assessed by high resolution peripheral quantitative computed tomography (HR-pQCT), and bone strength by micro-finite element analysis, at baseline and after 3.2 ± 0.4 years, in 303 postmenopausal women (80%) and men (20%) (age 65.0 ± 1.4 years) from the Geneva Retirees Cohort. An advanced 3D rigid registration technique was used to obtain a highly sensitive quantification of the net periosteal and endosteal volumes changes between the two HR-pQCT assessments.

Results: Cortical volume (Ct.V) and failure load (FL) decreased over time both at the radius and tibia (Ct.V, -3.0 ± 3.4% and –1.7 ± 3.4%; FL -3.0 ± 5.0% and -0.6 ± 4.6% , respectively). Changes in failure load were negatively correlated with net endocortical resorption at the radius (r=-0.23, p<0.001) and tibia (r=-0.36, p<0.001). In contrast, net periosteal apposition was positively associated with net endocortical resorption at the radius (r=0.62, p<0.001) and tibia (r=0.33, p<0.001), but not with changes in failure load (r=0.02, p=0.688; r=0.03, p=0.584, respectively).

Conclusion: Periosteal and endocortical changes with aging are partially correlated, but changes of bone strength with ageing result predominantly from endocortical bone loss which is only partially compensated by periosteal expansion. These new data on the respective contribution of bone modeling and remodeling on changes in bone strength with ageing need to be confirmed in larger cohorts.

OC24

MEASURES OF MUSCLE ADIPOSITY, BUT NOT MUSCLE CROSS-SECTIONAL AREA, PREDICT FRACTURES INDEPENDENT OF FRAX, FALLS AND BMD IN THE OSTEOPOROTIC FRACTURES IN MEN (MROS) STUDY

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Aims

DXA appendicular lean mass (as an estimate of muscle mass) is poorly associated with incident fractures after adjustment for bone mineral density (BMD). We investigated the predictive value of muscle measures from peripheral quantitative (pQ)CT for incident fractures, controlling for BMD, FRAX 10-year fracture probability or prior falls.

Methods

In the US MrOS cohort, we used an extension of Poisson regression to investigate relationships between muscle measures from pQCT at the 66% tibia (Stratec XCT2000/3000; muscle cross-sectional area (CSA), muscle density and intramuscular fat area) and incident major osteoporotic fracture (MOF: clinical vertebral, hip, wrist or proximal humerus). Associations were adjusted for age and follow-up time, reported as hazard ratio (HR/SD increase in the exposure) for first incident MOF. Further analyses adjusted additionally for FRAX MOF probability, prior falls (y/n) or femoral neck BMD T-score.

Results

We studied 1008 men [mean (SD) age: 77.0 (5.1) years], followed for a mean(SD) 7.1(2.8) years until MOF (n=68 fractures). In models adjusted for age and follow-up time, there were no statistically significant associations between muscle CSA, density or intramuscular fat area, and risk of MOF. The pattern of relationships was not materially changed by adjustment for prior falls or FRAX probability. In contrast, after inclusion of femoral neck BMD T-score, greater intramuscular fat area was predictive of greater MOF risk [HR/SD: 1.49 (95%CI:1.17,1.90)], and higher muscle density was associated with lower MOF risk [HR/SD: 0.76 (95%CI: 0.59,0.98)].

Conclusions

pQCT measures of muscle adiposity [intramuscular fat area (positive) and muscle density (negative)], but not muscle cross-sectional area, were associated with an increased risk of incident major osteoporotic fractures only after adjustment for femoral neck BMD T-score. These findings demonstrate the complex interplay between muscle, fat and bone tissue in fracture risk.

OC25

A NEW PREDICTION TOOL BASED ON ELECTRONIC MEDICAL RECORDS DATA TO ASSESS IMMINENT HIP FRACTURE RISK IN SECONDARY FRACTURE PREVENTION: A COHORT ANALYSIS INCLUDING OVER 700,000 PATIENTS FROM DENMARK, SPAIN AND THE UK

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Objective

There is a scarcity of clinical tools to estimate imminent (1-year) Fx risk amongst recently fractured subjects. We have developed and externally validated a tool to predict the imminent hip Fx risk in the year following a first fragility Fx.

Methods

Patients with a first recorded Fx at age 50 or over were identified in primary care records from Catalonia (SIDIAP) and the UK (CPRD), and in the Danish Health Registers (DHR). SIDIAP participants were split in a training (80%) and test (20%) datasets. A total of 46 potential predictors were identified from previous literature. LASSO was used to select key predictors, and combined in a prediction tool using logistic regression. The model was internally (test set) and externally (CPRD and DHR) validated in terms of discrimination (area under ROC curve [AUC]) and calibration (observed vs predicted stratified by age and gender). Intercepts were recalibrated in CPRD and DHR to account for differences in baseline risk.

Results

The SIDIAP training/test datasets included 39,282/9,820 patients, with 310 (0.8%)/80 (0.8%) sustaining a hip Fx in the following year. CPRD and DHR contributed 148,077 and 509,551 participants and 10,814 and 12,713 hip Fx, respectively.

The final validated tool included 7 predictors (Table 1) and had an AUC of 0.78 with good calibration. External validation in CPRD and DHR showed AUC of 0.71 and 0.70, respectively.

Conclusions

We have developed and validated a prediction tool for the estimation of imminent hip Fx risk amongst patients who have just suffered their first Fx. The resulting tool has great predictive validity (discrimination and calibration) in three large real-world European populations.

Disclosures: all disclosures are outside the submitted work.

Table 1. Predictors (OR (95% CI)) for the Imminent Hip Fx tool

Variables	OR	Low 95%CI	High 95%CI
Age (years)	1.08	1.07	1.09
Sex (Male)	0.73	0.55	0.96
Dementia diagnosis	1.53	1.14	2.06
Diabetes without complications	1.29	1.01	1.66
Proton pump inhibitors use	1.21	0.96	1.53
Renal disease	1.18	0.86	1.62
Cardiovascular disease	1.11	0.85	1.44

Abbreviations: OR, Odds Ratio; CI, Confidence interval.

OC26

THE POTENTIAL FOR OPPORTUNISTIC IDENTIFICATION OF VERTEBRAL FRACTURES IN PATIENTS UNDERGOING A CT SCAN AS PART OF DAILY CLINICAL PRACTICE: A DESCRIPTIVE STUDY USING REGISTRY DATA

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Objective

The individual and societal benefits of opportunistic screening for vertebral fractures using CT scans performed as part of daily clinical practice (*routine CT*) will be dependent not only on the diagnostic performance of the method but also on the proportion of referrals who have already been diagnosed with vertebral fractures and/or treated for osteoporosis. The purpose of this scoping analysis was to assess the potential for opportunistic screening for vertebral fractures in patients undergoing a routine CT.

Materials and methods

2,000 consecutive men and women, aged ≥50 years, undergoing a CT of the thorax, abdomen and/or pelvis from 1st January 2010 at Holbæk Hospital, Denmark. These patients were matched 1:3 on age and gender against a randomly drawn background population cohort from the same geographic region and year. Data were retrieved from Danish health and prescription registers.

Results

	CT scan population (n=2,000)	Background population controls (n=5,923)
Age, mean (years)	70.2	70.3
Gender, % men	51.6	51.5
Medical history, %[1]		
Vertebral fracture	1.5	0.6
Major osteoporotic fracture	14.2	11.7
Osteoporosis	3.5	3.0
Medications, %		
Current AOM[2]	6.1	4.0
Prior AOM[3]	14.0	10.8
Current corticosteroids[2]	14.6	6.9

AOM, anti-osteoporosis medication. [1)] using hospital ICD-10 diagnosis codes from 1994 or later; [2)] in the year prior to the year of the index scan; [3)] from 1995 or later

Conclusion

Patients undergoing a routine CT scan of the thorax, abdomen and/or pelvis have a low prevalence of already recognized prior vertebral fractures, diagnosed osteoporosis, and current AOM treatment, although higher than in a matched background population comparator cohort. With vertebral fractures estimated to be prevalent in up to 1 in 4 men and women aged 50 years or older[1], these results indicate a significant potential for opportunistic identification of vertebral fractures using routine CT scans.

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OC27

A CLINICAL TOOL FOR AUTOMATED PREDICTION OF HIP AND MAJOR OSTEOPOROTIC AT FIVE- AND ONE-YEARS FRACTURES USING ELECTRONIC MEDICAL RECORDS DATA: THE EPIC STUDY

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Objectives: Increasing availability of patient data in healthcare is an unprecedented opportunity for creating prediction tools that can be automatically implemented in electronic medical records system. We aimed to develop and validate a fracture prediction tool that leverages patient data as routinely available in primary care computerized records.

Methods: Population-based cohort study. Data was extracted from all subjects ≥ 50 years old registered in the SIDIAP database on 1/1/2012, with data for 1+ years. SIDIAP contains primary care records linked to pharmacy dispensations for >6 million people (>80% Catalonian population). Participants were followed up until the earliest of death, transfer out/migration, or end of 2017.

A model was developed to predict hip fracture and major osteoporotic fracture risk at 1 and 5 years. Potential predictors were pre-specified based on previous literature and combined in Cox models to derive prediction tools. Bootstrapping methods were used to select key predictors to be combined in the final resulting models. Internal validation was performed on a reserved 20% random sample, using c-statistic for discrimination, and observed vs predicted plots for calibration.

Results: A total of 1.76 million people were included (1.41M development cohort and 0.35M validation cohort), 50.7% women, of average age 65.4 years.

Fracture rates were 3.57/1,000 person-years for hip and 11.61 for major fracture. Key predictors of increased fracture risk included age, female gender, history of falls or previous fractures, specific medication/s use (insulin, GnRH inhibitors, anticonvulsants, sedatives, SSRI, antipsychotics), and a history of diabetes mellitus (type 1>type 2), cerebrovascular disease, ischemic heart disease, COPD and anorexia nervosa. Variables associated with lower fracture risk included use of statins, thiazide diuretics, and overweight/obesity.

Combined, these resulted in a c-statistic of 85% for hip and 84% for major fracture at 5 years and 85% and 72% at one year. Calibration was excellent for both outcomes and time points.

Conclusions: We have developed and validated a clinical prediction tool for hip and major osteoporotic fracture risks, with an excellent performance. This tool can be installed in electronic primary care records systems for automated risk calculations at the population level. More research is needed on the transportability and external validity of this tool.

OC28

HIGH RISK OF HIP FRACTURE AND HIP FRACTURES SAVED IN THE SCOOP STUDY

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Objective: The SCOOP study compared usual care to a FRAX-based screening strategy, whereby anti-osteoporosis treatments were targeted to women age 70-85 years at high risk of hip fracture. In the screening arm, 14.6% of the women were allocated to the high risk group. Over the course of 5 years, screening prevented 54 hip fractures compared with usual care (p=0.002). The present analysis examined the pattern of prevented hip fractures using observed (O) and expected (E) hip fracture rates.

Materials and Methods: Five-year probabilities of hip fracture were calculated, without the inclusion of femoral neck BMD, using an adaptation of the FRAX UK model.

Results: In the 6250 women in the usual care arm, a total of 212 women with incident hip fractures were expected, with a total of 218 fractures actually observed (O/E 1.03, 95% 0.90-1.18). In the 6233 women in the screening arm, 212 women with incident hip fractures were also expected, but only 164 were observed (O/E 0.77, 95% 0.66-0.90), a reduction of 48 hip fractures. Within the screening arm alone, 142 hip fractures were expected in the 5335 women (rate 2.7%) deemed not to be at high risk of hip fracture, with 125 hip fractures observed (O/E 0.88, 95% 0.73-1.05). In contrast, in the 898 women categorised at high risk and recommended for treatment, 70 hip fractures were expected (rate 7.8%) but only 39 were observed ((O/E 0.56, 95% 0.40-0.77).

Conclusion: Screening by FRAX hip fracture probability is associated with a significant reduction in hip fractures. The trend for a small non-significant reduction in those not deemed at high risk may infer an independent effect of screening on hip fracture risk, though this requires further exploration. However, the majority of hip fractures prevented in SCOOP arose from the women designated to be high risk and recommended for anti-osteoporosis treatment. These results support the use of FRAX as a gateway for screening in women age 70 years or more.

OC29

BONE MICROARCHITECTURE OR AREAL BONE MINERAL DENSITY FOR DISCRIMINATION OF VERTEBRAL DEFORMITY IN OLDER ADULTS: A CROSS-SECTIONAL STUDY

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Background: Both areal bone mineral density (aBMD) and bone microarchitecture have been associated with vertebral deformity (VD), but there are limited data on the utility of bone microarchitecture measures in combination with aBMD in discriminating VD. Objective: This study aimed to describe whether bone microarchitecture measures alone or in combinations with aBMD can improve discrimination of VD in older adults.Material and Methods: Data on 196 subjects (mean age (standard deviation, SD) =72 (7) years, female 46%) were utilized. VD of T4-L4 and spine aBMD were measured using dual-energy X-ray absorptiometry. VD was defined if anterior to posterior height ratio (Ha/Hp) was more than 3-SD, 4-SD below, or >25% decrease compared with the sex-matched normal means. Bone microarchitecture parameters at distal radius were collected using high-resolution peripheral computed tomography (HRpQCT) and analyzed using StrAx. Results: The strongest associations were seen for the cortical thickness (odds ratios (ORs): 2.63/SD decrease for 25% and 2.38/SD decrease for 3-SD criterion) and compact cortical area (OR: 3.33/SD decrease for 4-SD criterion). The area under the curve (AUC) for spine aBMD for VD was 0.594, 0.597 and 0.634 for 25%, 3-SD and 4-SD criteria, respectively (all $P<0.05$). Compact cortical area, cortical thickness and compact cortical thickness alone had the largest AUCs for VD (0.680-0.685 for 25% criterion, 0.659-0.674 for 3-SD criterion and 0.699-0.707 for 4-SD criterion). Adding spine aBMD or radial volumetric bone mineral density (vBMD) to each cortical measure did not improve VD discrimination (ΔAUC 0.8% to 2.1%). Conclusions: Cortical measures had the best utility for discriminating VD when used alone. Somewhat surprisingly, adding either spine aBMD or radial vBMD did not improve the utility of cortical measures.

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OC30

NO NEGATIVE ASSOCIATIONS, AND EVEN SOME POSITIVE ONES, BETWEEN BONE MASS, MICROSTRUCTURE AND STRENGTH, AND DIETARY ACID LOAD IN A PROSPECTIVE COHORT OF COMMUNITY-DWELLING WOMEN AND MEN

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Background: According to the debated acid-ash theory, dietary acid load (DAL) may be a risk factor for osteoporosis. Studies on the association of DAL with bone mineral density (BMD) have, however, yielded inconclusive results. Bone microstructure (MS) and strength have not yet been evaluated in relation to DAL. In this cross-sectional and longitudinal study conducted in the Geneva Retirees Cohort (GERICO), we explored the associations between BMD, bone MS and strength, fracture risk, and DAL in postmenopausal women and men.

Methods: GERICO comprised healthy women and men aged 65±1 years at baseline. Potential renal acid load (PRAL) (mEq/d) was calculated as a DAL proxy from 3-day food records to characterise participants' diet as alkaline (ALK-D) (PRAL<-5), neutral (NEUT-D) (-5≤PRAL≤5) or acidic (ACID-D) (PRAL>5). Volumetric BMD and bone MS at the distal radius and tibia, and areal BMD (aBMD) were assessed by peripheral high-resolution quantitative computed tomography and dual-energy X-ray absorptiometry, respectively, at baseline (n=853, 79% women) and

after 6.1±1.4 years of follow-up (n=695). Bone strength was assessed by micro-finite element analysis at baseline (n=850) and after 3.0±0.5 years (n=613). Prevalent and incident fractures were recorded.
Results: Fifty-nine, 23 and 18% of the participants had ALK-D, NEUT-D and ACID-D, respectively. Baseline BMD, bone MS and strength were non-different or even better in those with an ACID-D as compared with those with ALK and NEUT-D. Indeed, women with ACID-D had higher values of tibia trabecular MS, while men had greater hip and radius aBMD and bone strength. Women, but not men, with an ACID-D had lower cortical, endocortical and trabecular bone loss at the radius compared to those with ALK and/ or NEUT-D, even after adjustment for covariates. In both sexes, the changes of peripheral bone strength and of bone traits at the tibia and spine did not differ in the 3 PRAL groups. There was no difference in prevalent and incident fractures.
Conclusions: The null or even positive associations observed between BMD, bone MS and strength, fractures, and DAL in this cohort of healthy individuals, do not support the hypothesis of DAL-mediated negative effects on bone as postulated by the acid-ash theory.

OC31
FREQUENCY OF NORMAL DXA AND T-SCORE OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN WITH FRACTURE: A REGISTRY-BASED COHORT STUDY

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Purpose: Some women who sustain osteoporotic fracture have normal BMD and the majority do not have T-score osteoporosis. We hypothesized that adding trabecular bone score (TBS) to DXA would: 1) demonstrate that few women with fracture have normal bone, (normal T-score AND TBS) and 2) increase the proportion of women with fracture that have abnormal bone (T-score ≤ -2.5 or low TBS).
Methods: In Manitoba a public healthcare system anonymously links DXA data to population-based databases. This study included all women age 50+ with a 1st DXA from 2/1999 to 3/2018 for whom valid spine and hip DXA, TBS and fracture data were available. Abnormal vertebrae were excluded from T-score calculation following ISCD guidance. Fractures were defined as any fracture (excluding head/neck, hands/feet, ankle and those from high-trauma) within 5 years before (prior) or 5 years after DXA (incident). Bone status was defined as: Normal = T-score of spine, femoral neck and total femur ≥ -1.0 AND TBS >1.31; Abnormal = T-score ≤ -2.5 OR TBS < 1.23; and borderline = all others.Analyses were stratified by age decade, (50-59, 60-69, 70-79 and 80+ years).
Results: 4649 women fractured prior to index DXA; only 261 (6%) had normal bone. The prevalence of normal bone in those with prior fracture declined with age from 11% age 50-59 to 1% age 80+ (Cochran-Armitage p-trend <0.001). Of the 451 women with prior hip fracture, bone was normal in 4 (<1%). In those with incident fracture (2547 any, 391 hip) only 4% and 1% respectively had normal bone. In those with any incident fracture an age-related decline in normal bone (9% age 50-59 to 1% age 80; p-trend <0.001) was observed. T-score osteoporosis was present in 40% with any prior and 46% with any incident fracture (65% and 60% for prior and incident hip fracture, respectively). Including TBS increased the proportion with abnormal bone to 61% and 68% for any prior or incident fracture, and to 80% and 81% for prior or incident hip fractures, respectively (all $p < 0.001$).
Conclusion: Normal bone by DXA is rare in women with fracture when both BMD and TBS are considered. Including TBS increases identification of abnormal bone compared to BMD alone. Most fractures occur in postmenopausal women without T-score osteoporosis. Treating only those women with a T-score ≤-2.5 will result in many with subsequent fractures not receiving therapy.

OC32
THE RISK OF HIP AND NON-VERTEBRAL FRACTURES IN PARKINSON'S DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Objectives: Parkinson's disease (PD) is a neurodegenerative disorder that is more prevalent in older individuals. Previous studies have suggested that PD patients have an increased risk of fractures compared to the general population, mainly due to falls. However, the risk has not been fully assessed. To assess the impact of PD on the risk of hip and non-vertebral fractures, we conducted a systematic review and meta-analysis.
Materials and methods: Comprehensive searches of three key bibliographic databases (Medline, Embase and Cochrane) were conducted to identify reviews and primary studies relating to the risk of fractures in patients with PD. An initial search (December 2017) was conducted to identify relevant systematic reviews as a source of primary data. Further focused searches were undertaken to identify additional primary studies published since the most recent systematic review conducted their searches on hip fractures. The searches for primary studies were performed in March 2018 with an update in 2019 (Medline only) and supplemented with additional search techniques. Search terms were based around Parkinson's disease and fractures. We selected observational studies with data on the risk of fractures in adults with PD compared to controls without a diagnosis for this disorder. Study quality was assessed using the Newcastle Ottawa Scale. We used the random-effects model to pool the results.
Results: Seventeen independent studies (14 cohorts and 3 case-controls), that involved 2,337,184 participants were included in the hip fracture analysis. Nine studies (all cohorts), that involved 1,363,910 people were included in the non-vertebral fracture analysis. Study quality was judged to be moderate to good. Overall, PD patients have an increased risk for both hip fractures (RR 2.40, 95% CI 2.04 to 2.82) and non-vertebral fractures (RR 1.80, 95% CI 1.60 to 2.01) compared to controls. The relative risk for hip fractures is higher in men (RR 2.93, 95% CI 2.05 to 4.18) than in women (RR 1.81, 95% CI 1.61 to 2.04). There were no effects of the study design, geographical region, or criteria for diagnosing Parkinson's disease on the hip fracture rate.
Conclusions: There is an increase in the risk of hip and non-vertebral fractures in patients with Parkinson's disease, with male patients with PD being more at risk of hip fractures than female patients.

OC33
MUSCLE DENSITY IS BETTER THAN BONE DENSITY IN THE DISCRIMINATION OF INCIDENT HIP FRACTURE: A PROPENSITY SCORE MATCHING STUDY

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Objective To explore the value of muscle parameters for the discrimination of acute hip fractures and to compare discriminating capabilities with bone variables.

Methods 438 low-energy acute hip fracture cases and 316 healthy controls from the China Action on Spine and Hip Status (CASH) study were included in the study. Muscle cross sectional area (CSA) and density were measured for the gluteus maximus (G.max) and gluteus medius and minimus (G.med/min). Areal BMD (aBMD) of the femoral neck (FN) and total hip (TH) were measured. Using propensity score matching (PSM), we generated two samples with cases and controls matched for age, BMI and sex. Logistic models were used to evaluate the odds ratio (OR) of fracture per SD increase of muscle and bone parameters.

Results After PSM, 159 femoral neck fracture cases were matched with 159 non-fracture controls, and 101 intertrochanteric fracture cases with 101 controls. G.max muscle Hounsfield unit (HU) value (FN fracture: OR 0.39, CI% 0.28-0.54, TR fracture: OR 0.23, CI% 0.13-0.39) and G.med/min muscle HU value (FN fracture: OR 0.11, CI% 0.07-0.19, TR fracture: OR 0.05, CI% 0.02-0.13) were strongly associated with hip fracture after adjustment for FN aBMD. At both fracture sites G.med/min muscle density showed the best discrimination (AUC 0.882 for FN fractures, 0.945 for TR fractures) while G.max muscle density was equivalent to FN aBMD in discrimination of fractures and G.max muscle CSA was poorer than the other indices.

Conclusion Muscle density performs better than aBMD and muscle size in the discrimination of hip fracture.

OC34

EFFICACY OF SYMPTOMATIC TREATMENTS FOR KNEE OA: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS WITH A 6-MONTH TIME-HORIZON

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Introduction: Several pharmacological options claim their ability to better control the symptoms of knee OA but their respective efficacy is still debated. The purpose of this network meta-analysis (NMA) is to assess and to compare the potential benefit of different pharmacological treatments (given for at least 6 months) on pain and function, in patients suffering from knee OA

Methods: Studies were retrieved through a systematic review process in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA). Medline (via Ovid), Scopus, and Cochrane database of systematic reviews (via Ovid) were searched for RCTs published up to August 2018, performed in adults (18 years and over) and which assess the efficacy of knee OA treatments. All pharmacological treatments, commonly prescribed or currently reviewed by the regulatory authorities, for the symptomatic relief of knee OA, including all routes of administration, were considered, providing they were given for at least 6 consecutive months. The primary outcomes were pain and function changes from baseline. A Bayesian network meta-analysis combining direct and indirect comparisons was run and Standardized mean differences (SMDs) and mean differences with 95% credibility intervals (95%CrIs) were calculated. A hierarchy of the competing interventions using the surface under the cumulative ranking curve (SUCRA) and mean ranks was obtained.

Results: 9349 references were identified from the search strategy and 92 were concordant with our inclusion criteria. Among them, 83 interventions were studied for pain and 59 for function. More than half of the studies were performed on participants aged 60 years and older and the mean duration of treatment across studies was 50 months. A significant association with decreased pain was found for Hyaluronic Acid (SMD -0.28, 95%CrIs -0.39;-0.17), Crystalline Glucosamine Sulfate (SMD -0.29, 95%CrIs -0.57;-0.01), the combination of Hyaluronic acid and Triamcinolone (SMD -0.39, 95%CrIs -0.75;-0.04), Vitamin D (SMD -0.31, 95%CrIs - 0.55;- 0.06) and pharmaceutical-grade Chondroitin Sulfate (SMD -0.23, 95%CrIs -0.39;-0.07). For pain, the combination Hyaluronic Acid + Triamcinolone had the highest probability of being the most effective long- term treatment (SUCRA value of 0.79). Moreover, a significant improvement in physical function was observed following treatment with Crystalline Glucosamine Sulfate (SMD -0.44, 95%CrIs -0.66;-0.22), Tanezumab (SMD -0.39, 95%CrIs -0.73,-0.05, Acetaminophen (SMD -0.34, 95%CrIs -0.69,0.00), Vitamin D (SMD -0.30, 95%CrIs -0.84,-0.24) and Hyaluronic Acid (SMD -0.21, 95%CrIs -0.44,0.01). For function, Crystalline Glucosamine Sulfate has the highest probability of being the most effective long-term treatment (SUCRA value of 0.91).

Conclusion: A minimum of 6-month treatment with Hyaluronic Acid, Crystalline Glucosamine Sulfate, pharmaceutical- grade Chondroitin Sulfate, Tanezumab, Vitamin D, Acetaminophen or the combination of Hyaluronic Acid and triamcinolone, was shown, in this NMA, to improve pain and/or physical function in patients suffering from knee OA.

OC35

OSTEOGENESIS IMPERFECTA: FRACTURE CHARACTERISTICS DURING PREGNANCY AND POST-PARTUM

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Objectives. Pregnancy and post-partum are conditions associated with bone loss. Fracture occurrence during pregnancy and post-partum, and the determinants of these fractures, are not well known in Osteogenesis imperfecta (OI). The aim of this study was to characterize the fractures that occurred during pregnancy and the post-partum period in a cohort of women suffering from OI followed in Cochin Hospital or recruited through the French GRIO study group.

Materials and methods. Retrospective multicentric study including 29 OI patients from the Reference Center for Rare Bone Diseases of Cochin Hospital, Paris, and 21 patients included from other French Centers via the GRIO. A total of 50 patients, and 83 pregnancies, were included.

Results. Among the 50 OI patients included, 12 patients (24%) (14 pregnancies/83) had a fracture during pregnancy or in the 6 months following delivery. Among these patients, 2 presented fractures for 2 consecutive pregnancies, and 2 other patients presented fractures during pregnancy and also during the post-partum period. Therefore 16 pregnancy-related fracture events were analyzed. The localization of fractures were: spine (4/16), proximal femur (6/16), pelvis or ribs (3/16), ankle (1) and wrist (1). The mechanisms of fractures were: spontaneous (10/16), low trauma (3/16) and traumatic (3/16). Fractures during pregnancy occurred during the third trimester and those that occurred in the post-partum period occurred with a mean delay of 2 months from delivery.

Patients characteristics: OI women from this cohort had had 1 pregnancy in 52% of cases, 2 pregnancies in 34% and 3 pregnancies or more in 14%.

Mean age was 32,7±3,1 in the fracture group, compared with 29,3±5,0 years-old in the non-fractured group (p=0.002). Patients had OI type 1 in 77.1% of cases, type III in 14.3% of cases, and other OI subtypes in 8.6%. All patients that displayed fractures in the post-partum period were breastfeeding, compared with 47% of patients with no fractures (p=0.03). Fracture during pregnancy or post-partum was not associated with the severity of OI including number of fractures during childhood, number of fractures after puberty, scoliosis or orthopedic surgery. Bisphosphonates had been administered in 17% of patients with fractures compared with 24% with no pregnancy-related fractures (non significant). Bone mineral density was lower in patients with pregnancy-related fractures compared with other patients : spine Z-score -2.9±1.6DS vs -1,48±1,67 (p=0.03), and total hip Z-score -2,05 ±0,74 vs -0,53±1,36 (p=0.04). At least one concomitant osteoporosis inducing disease or risk factor was identified in 81.8% of fractured patients: smoking, spondyloarthritis, Crohn's disease, low vitamin D level, anorexia nervosa, or immobilization.

Conclusion. OI management during pregnancy and post-partum should aim for the optimal control of modifiable risk factors. Breastfeeding should be avoided especially in women with low bone mass or other risk factors.

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OC36

TREATMENT INITIATION RATE POST HIP FRACTURE AS A KEY INDICATOR IN AN ORTHOPAEDIC FRACTURE LIAISON SERVICE.

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Objectives

One of the major key indicator of Fracture Liaison Services (FLS) success is initiation/continuation of anti-osteoporosis treatment (Osteoporosis Canada Guidelines). These clinical indicators have been proposed to help assess the performance of FLS for the secondary prevention of fragility fractures (FF). Our objective was to assess the success of the Lucky Bone^{TM} FLS in the management of hip fractures.

Methods

A FLS was implemented in our orthopaedic wards for the management of men and women ≥ 50 years that sustained a hip fracture. Data was obtained from patients that were admitted for a hip fracture between April 1 st, 2019 and September 30th, 2019. Key indicators of efficiency were measured as proportions of patients with treatment initiation and continuation. Xrays were also screened for atypical femoral fractures (AFF).

Results

Sixty three subjects sustained a hip fracture during this time period (mean age of 82.4 (±10.3), 30.2% male). Fifty-six (56) of the hip fractures were FF (88.9%) and 2 were AFF (3.5%). Only 15 out of the 56 subjects were already under bisphosphonates treatment (26.8%), including both AFF patients. Twelve out of 15 (80%) were switched to denosumab. The combined treatment initiation or continuation rate was 71.4%. Both AFF were identified during the review, not at the time of the fracture.

Conclusion

The combined treatment initiation or continuation rate of the hip fracture patients in our FLS was 71.4%. These results demonstrate that our FLS is efficient. Most FLS on hip fractures are reporting a 60 to 80% FF identification rates and ≈ 46% treatment initiation rate. We also noted that the ≈30% of patients that were not initiated on treatment were the most at-risk for a subsequent fracture, including the oldest old, suffering of dementia or were polymedicated. Finally, AFF is still underdiagnosed in our orthopaedic department.

OC37

PHYSICAL PERFORMANCE TRAJECTORIES AND MORTALITY AMONG NURSING HOME RESIDENTS: THE RESULTS OF THE SENIOR COHORT

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Objectives: This study aimed to identify physical performance (PP) trajectories and their association with mortality among nursing home residents who were followed up for 3 years.

Material and Methods: A longitudinal analysis of the data from the SENIOR (Sample of Elderly Nursing home Individuals: an Observational Research) cohort was conducted. Baseline clinical characteristics (i.e., age, sex, body mass index, medical history, medication, civil status, educational attainment, cognitive status, depressive symptoms) and the date of death were collected from the medical records. PP was assessed annually by the Short Physical Performance Battery (SPPB) test. Multiple imputations were performed to manage the missing data. PP trajectory groups were estimated using latent growth curve analysis. The association between the baseline characteristics and trajectory groups was evaluated with multinomial logistic regressions. Cox proportional hazard regression models were applied to examine the risk of mortality according to the PP trajectory groups after adjustments were made for all baseline characteristics.

Results: A total of 604 nursing home residents with a mean age of 82.9 ± 9.1 years were included. Three PP trajectory groups were identified: slow decline (N=96), moderate decline (N=234) and fast decline (N=274). Subjects in the fast decline trajectory group were more likely to be older, female and widow(er)s, to have cognitive impairment, take more medications and have a more involved medical history. After adjustments were made for potential confounding variables and the baseline SPPB scores, the residents in the fast decline and moderate decline trajectory groups had an increased risk of mortality compared to those in the slow decline trajectory group, with HR values of 1.78 (95% CI=1.34-2.26) and 1.37 (95% CI=1.10-1.66), respectively.

Conclusions: PP trajectories provide value-added information to baseline geriatric assessments and could be used for predicting 3-year mortality among nursing home residents. It may be important to regularly monitor the SPPB score and signal an alert when a fast decline in PP is detected in older people.

OC38

LIFESTYLE, ANTHROPOMETRY, AND BONE HEALTH ACROSS THREE GENERATIONS OF THE HERTFORDSHIRE COHORT STUDY

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Objectives

The aim of this study was to explore associations between lifestyle, anthropometry, and bone density across three generations of the Hertfordshire Cohort Study (HCS).

Materials and Methods

Data from three generations of participants in the HCS [grandparents (F0), parents (F1), and children (F2)] were utilized to assess associations

between lifestyle, BMI, and bone health across these generations. Questionnaire data were used to run linear regressions in generational pairs (n=461 from F0 to F1, n=188 from F1 to F2, and n=273 from F0 to F2) examining prudent diet score, alcohol consumption, smoking behaviour, and adult BMI. A subset of participants had dual-energy x-ray absorptiometry (DXA) scans, and to increase statistical power, these data were collapsed into parent and child pairs (n=60). Linear regressions examining parent-child associations in femoral neck and lumbar spine bone mineral density (BMD) z-scores were run, with adjustment for parent-child prudent diet score and adult BMI residuals. Results are presented B (95% confidence interval).

Results

Prudent diet score and adult BMI were significantly positively associated in all three generational pairs: F0 to F1 (Prudent diet score: 0.188 (0.079, 0.298); BMI: 0.316 (0.193, 0.439), F1 to F2 (Prudent diet score: 0.198, (0.004, 0.391); BMI: 0.217, (0.093, 0.341), and F0 to F2 (Prudent diet score: 0.376, (0.205, 0.546); BMI: 0.222, (0.105, 0.339). Generational associations were reported for alcohol consumption (F0 to F1) and smoking behaviour (F0 to F1 and F1 to F2). Femoral neck and lumbar spine BMD z-scores were significantly associated between parents and children, with associations remaining robust after adjustment (Femoral neck adjusted for diet: 0.400, (0.037, 0.764); Lumbar spine adjusted for diet: 0.553, (0.359, 0.747); Lumbar spine adjusted for BMI: 0.433, (0.173, 0.692).

Conclusion

Some, but not all, lifestyle factors were associated across three generations of the HCS. Significant associations of femoral neck and lumbar spine BMD between parents and children were robust to adjustment for lifestyle. Future studies in larger groups are now warranted.

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THE DIFFERENT DIAGNOSIS CRITERIA OF THE EWGSOP2 DEFINITION AND THEIR RELATIONSHIP WITH 5-YEAR ADVERSE CONSEQUENCES

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Introduction: The new definition of the EWGSOP (2019) offers several diagnostic criteria for assessing muscle mass, muscle strength, and physical performance. We aimed to measure the impact of using one or other criteria on the prevalence of sarcopenia.

Methods: We included participants of the SarcoPhAge (Sarcopenia and Physical Impairments with Advancing Age) study, a population-based Belgian cohort involving 534 participants aged 65 years and older. Muscle mass was measured with Dual-Energy X-Ray absorptiometry (we compared ASM with ASM/height^2), muscle strength was measured both by Grip Strength using Jamar hydraulic hand-held dynamometer and the 5-times Chair Stand test, physical performance was measured by the 4-meter gait speed test, the Short Physical Performance Battery test (SPPB) and the Timed up and Go (TUG) test. Cox Proportional Hazard ratios were measured for 5-year incidence of mortality, institutionalization, and incidence of at least one fracture, fall, or hospitalization during the 5-year follow-up period. Analyses were adjusted for age, sex, number of drugs and comorbidities, cognitive status and physical activity level.

Results: The following prevalence of sarcopenia was found: 4.5% using ASM/height^2 + Grip Strength, 8.2% using ASM + Grip Strength, 9.0% using ASM/height^2 + Chair Stand and 14.2% using ASM + Chair Stand. The prevalence of severe sarcopenia varied from 1.1% (using the combined criteria of Chair Stand + ASM/height^2 + TUG) to 8.1% (using the combined criteria of Chair Stand + ASM + SPPB). Mortality data was analysed on 481 participants (53 lost-to-follow-up). Sarcopenia appears to be significantly associated with 5-year mortality only when the Grip Strength is considered as muscle strength measurement and nor with the Chair Stand test criteria. However, this relationship was no more significant in the multivariate fully-adjusted model. Regarding severe sarcopenia criteria, significant fully-adjusted HR of 3.01 (95%CI 1.7-6.60) was found for mortality using Grip Strength + ASM + gait speed criteria, HR of 2.87 (95% CI 1.23-6.68) was found using Grip Strength + ASM + SPPB criteria, HR of 2.61 (95% CI 1.09-6.25) was found using Grip Strength + ASM/heigt^2 + gait speed criteria and finally, HR of 2.68 (95% CI 1.04-6.93) was found using Grip Strength + ASM/heigt^2 + SPPB criteria. We never highlighted any predictive power of mortality when the Chair Stand test is used as measure of muscle strength or when the TUG is used as measure of physical performance. Regarding muscle mass, the use of ASM or ASM/height^2 seems however to have no specific impact on the predictive value of mortality. We did not find any association between one of the diagnostic criteria employed and 5-year incidence of fractures, hospitalization, institutionalization and falls.

Conclusion: Within a diagnosis of sarcopenia/severe sarcopenia, highlighted by our results, it could be justify to privilege Grip Strength to measure muscle strength and gait speed or SPPB test to measure physical performance. Indeed, as compared with Chair Stand test and TUG test, those former criteria seem more related to 5-year incidence of mortality.

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COST-EFFECTIVENESS OF BINOSTO (BUFFERED SOLUBLE ALENDRONATE 70 MG) EFFERVESCENT TABLET FOR THE TREATMENT OF POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS IN ITALY

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Objective: To estimate the cost-effectiveness of Binosto (buffered soluble alendronate 70 mg) effervescent tablet compared to relevant alternative treatments for postmenopausal women with osteoporosis in Italy.

Methods: A previously validated Markov microsimulation model was adjusted to the Italian healthcare perspective to estimate the lifetime costs (expressed in €2019) per quality-adjusted life-years (QALY) of Binosto compared with generic alendronate, denosumab, zoledronic acid and no treatment. Pooled efficacy data for bisphosphonates derived from the NICE meta-analysis were used for bisphosphonate treatments and 1-year persistence of Binosto and alendronate was derived from a prospective observational study. Analyses were conducted for high-risk women 60-80 years of age with a bone mineral density (BMD) T-score ≤-3.0 or with existing vertebral fractures.

Results: In all of the simulated populations, Binosto was dominant (more QALYs, less costs) compared to denosumab. The cost per QALY gained of Binosto compared to generic alendronate and no treatment fall always below €20,000 per QALY gained. In women aged 75 years and older with prevalent vertebral fractures and in women aged 65 years and older with T-score ≤-3.0, Binosto was even shown to be dominant (more QALYs, less costs) compared to generic alendronate and no treatment. Zoledronic acid was associated with more QALY than Binosto but the cost per QALY gained of zoledronic acid compared to Binosto was always higher than €70,000 per QALY gained and thus not cost-effective.

Conclusion: This study provides the first economic analysis of an alendronate effervescent tablet, suggesting that Binosto represents a cost-effective strategy compared with generic alendronate, zolderonic acid and no treatment, and a dominant strategy compared to denosumab for the treatment of postmenopausal women with osteoporosis in Italy aged 60 years and over.

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