1

Spine Imaging, Aortic Calcification, and Bone Health

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Prevalent vertebral fracture has for decades been recognized as a biomarker of bone fragility and fracture risk, and has been shown to be an important predictor of incident fractures after accounting for bone mineral density, age, and other risk factors. However, over the past two decades research has now shown that the same images that capture prevalent vertebral fracture also detect moderate to severe abdominal aortic calcification (AAC), and that AAC is a biomarker of multisite atherosclerosis that predicts incident cardiovascular disease (CVD) events after accounting for other clinical CVD risk factors. Moreover, recent studies in two cohorts have shown prevalent vertebral fracture also predicts incident CVD events, and that AAC predict incident fractures accounting for each other. However, prevalent vertebral fracture and AAC frequently are unrecognized in clinical practice. Efforts to opportunistically use radiographs and computed tomography images in clinical practice, as well as dedicated use of lateral spine imaging as part of bone densitometry combined with artificial intelligence to close this health care gap will also be discussed.

2

Strong Bones and Healthy Hearts: Common Pathways, Shared Risk factors, and the role of Movement in Healthy Aging

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When you ask an older adult about their personal goals you often hear that I just want to "be able to run around with my grandkids" or "keep living in my own home". While for some, these goals can be a reality, often, these expectations can be unrealistic or can be taken away very quickly particularly if a fall and/or fracture occurs "*she had a fall, and that was the beginning of the end*" Consumer 71 years.

Osteoporosis and cardiovascular disease (CVD) are common in older adults. Historically they were viewed as two separate diseases, CVD being a disease affecting mainly men, and osteoporosis seen as a disease of women. Mounting evidence links the two diseases, not just though shared risk factors but a complex interplay of various mechanisms. Those with CVD have a higher prevalence of osteoporosis and fracture risk, while people with osteoporosis (or fracture) have an increased risk for cardiovascular events.

This presentation will leverage my 14 years as a clinical Accredited Exercise Physiologist, focusing on the importance of bone and cardiovascular health for healthy ageing. The talk will briefly overview the epidemiology linking osteoporosis and CVD and novel markers identifying CVD risk in patients attending routine DXA scans.

The talk will conclude with key, practical take-home messages for clinicians to optimise lifestyle approaches in their patients. Specifically, through providing an overview of the evidence of available exercise programs and guidelines for bone and cardiovascular health benefits and, to prevent falls and fractures. Emphasis will be placed on how this can be safely achieved in patients who may present with osteoporosis with/without CVD. My talk will draw on the perspectives and preferences of the community, and those with lived experience, to ensure lifestyle approaches are both effective, and relevant to those they serve.

3

Diabetes and its effect on bone health

Morten Frost[1]

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4

Bisphosphonates or Denosumab after Fracture? Real-World Evidence from a Target Trial Emulation in Multimorbid Adults

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Background: Multimorbidity is prevalent in fracture populations and increases refracture and mortality risk [1-3]. However, multimorbid individuals are often excluded from RCTs, leaving the comparative effectiveness of antiresorptives uncertain. Target trial emulation (TTE) provides a framework for estimating causal effects from observational data [4]. We compared bisphosphonates with denosumab in reducing refracture and all-cause mortality across multimorbidity clusters.

Methods: Whole-population linked data identified treatment-naïve adults aged 50 years and above in New South Wales, Australia, who sustained low-trauma fractures requiring emergency or hospital admission (2010-2018). Exclusions included prior osteoporosis treatment, previous fractures, metastatic cancer and other metabolic bone disorders. Clone-censor-weight approach was applied comparing treatment strategies of initiating bisphosphonate (alendronate, risedronate, zoledronic acid) versus denosumab within a 12-month grace period, with time zero defined as the index fracture and follow-up for 4 years for refracture and mortality outcomes. Individuals were cloned, assigned to bisphosphonate or denosumab, and censored if observed treatment deviated from assigned treatment. Inverse probability of censoring weights addressed informative censoring. Latent class analysis (LCA) classified individuals into multimorbidity clusters based on baseline comorbidities. Estimated treatment effects were stratified by sex and multimorbidity clusters.

Results: Among 117,031 eligible individuals, 5,917 initiated bisphosphonate and 2,661 initiated denosumab within the grace period. LCA identified five clusters: four multimorbidity clusters (complex cardiovascular, cardiometabolic, geriatric, mental health; median comorbidity count: 4-12) and one healthy cluster (median: 1). Compared with denosumab, bisphosphonate use was associated with lower all-cause mortality overall (HR 0.79 men, HR 0.71 women) and across most multimorbidity clusters (HR 0.74-0.94). Refracture risk was comparable between groups (HR 0.88-1.52) (figure).

Conclusion: In this real-world TTE, bisphosphonate initiation after fracture was associated with lower mortality compared with denosumab in both healthy and multimorbid populations, with comparable refracture risk. These findings suggest bisphosphonates have non-skeletal benefits that warrant further investigation.

Table. Adjusted Hazard Ratios (HR) Comparing Bisphosphonates to Denosumab, by Sex and Multimorbidity cluster [1]

Multimorbidity cluster	Men – Mortality HR (95%CI)	Women – Mortality HR (95% CI)	Men – Refracture HR (95%CI)	Women – Refracture HR (95%CI)
Overall	0.79 (0.74 - 0.85)	0.71 (0.67 - 0.76)	0.96 (0.86 - 1.09)	1.01 (0.94 - 1.10)
Healthy	0.74 (0.65 - 0.84)	0.60 (0.53 - 0.67)	1.02 (0.84 - 1.23)	0.99 (0.88 - 1.10)
Cardiometabolic	0.74 (0.63 - 0.87)	0.70 (0.61 - 0.82)	0.88 (0.69 - 1.14)	0.96 (0.80 - 1.14)
Complex cardiovascular	0.82 (0.70 - 0.95)	0.81 (0.69 - 0.94)	1.10 (0.78 - 1.63)	1.13 (0.89 - 1.46)
Geriatric	0.94 (0.83 - 1.06)	0.84 (0.74 - 0.97)	0.93 (0.70 - 1.23)	0.96 (0.78 - 1.20)
Mental Health	0.84 (0.59 - 1.11)	0.82 (0.60 - 1.12)	1.01 (0.63 - 1.84)	1.52 (1.02 - 2.25)

[1] Hazard ratios <1 indicate low risk with bisphosphonates compared to denosumab; values >1 indicate a lower risk with denosumab. All models were adjusted for age, Charlson comorbidity index, fracture site, hospitalisations, prior falls, prior osteoporosis diagnosis, prior DXA scan, prior steroids, socioeconomic disadvantage and educational/occupational status. Abbreviations: HR, hazard ratio; CI, confidence interval.

5

Oxr1-Dependent Autophagy Drives Osteoclastogenesis by Mitigating ROS-Induced Mitochondrial Damage

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Publish consent withheld

6

Tissue-specific knockdown of the vitamin D receptor in mice via muscle- and bone-targeted rAAV vectors

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Background: Vitamin D regulates calcium homeostasis via the vitamin D receptor (VDR), which has well-established roles in bone and underappreciated functions in muscle development. Previous studies using conditional *VDR* knockouts in embryonic muscle and bone progenitors could not distinguish developmental roles from postnatal functions.

Methods: Postnatal targeting of the VDR^{flox} allele was performed using custom muscle- and bone-targeting adeno-associated viral vectors (AAVs) to express Cre recombinase. 8-week-old $Vdr^{fl/fl}$mice received a single i.p. injection of either AAVMYO-tMCK63-Cre (Vdr_{muscle}^{AAV}) or AAV8-Sp7-Cre (Vdr_{bone}^{AAV}) at $5x10^{11}$ vg/mouse, or saline (controls). Allele-specific PCR was used to confirm recombination in target tissues. Functional outcomes were assessed via grip strength, treadmill running, histology, 3D bone imaging, and biomechanical testing.

Results: Targeted *VDR* deletion resulted in tissue-specific recombination and associated functional changes. Vdr_{muscle}^{AAV} mice showed reduced grip strength (**Figure 1A**), greater reduction in running speed and distance compared to baseline (**Figure 1B-C**) and altered muscle gene expression. Vdr_{bone}^{AAV} mice exhibited increased cortical

thickness (**Figure 1D)** and vertebral stiffness. In a parallel mouse study, Ai9 reporter mice confirmed efficient, tissue-specific recombination with both vectors.

Conclusion: This study demonstrates proof-of-principle for AAV-mediated postnatal gene targeting of musculoskeletal tissues. Our findings highlight postnatal roles for *VDR* in muscle and bone, separating them from developmental effects and offering a platform for future functional dissection.

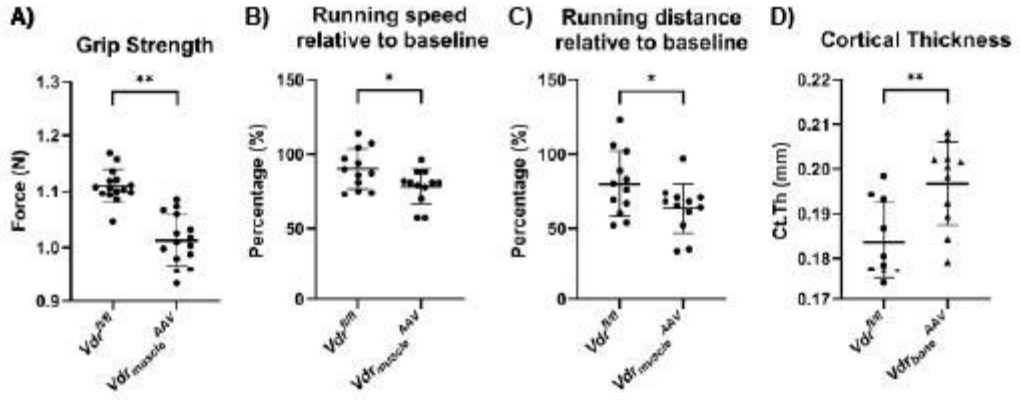

Figure 1. AAV-mediated knockout of VDR impairs muscle function and alters bone architecture. A. Vdr_{muscle}^{AAV} mice displayed significantly reduced grip strength compared to saline controls. **B.** Running speed and **C.** distance were significantly reduced relative to baseline in Vdr_{muscle}^{AAV} mice. **D.** Vdr_{bone}^{AAV}mice exhibited increased cortical bone thickness. (* p<0.05, ** p<0.01)

7

MMP-9 has a sex-specific role in the anabolic effects of intermittent parathyroid hormone in trabecular bone

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Intermittent parathyroid hormone (iPTH), an anabolic osteoporosis treatment, induces bone formation, but with limited efficacy and duration. Since the proteolytic enzyme matrix metalloproteinase (MMP)-9 mediates angiogenesis and osteogenesis during bone development and repair, we investigated whether iPTH's anabolic actions require MMP-9.

In 8-week-old wild-type (WT) mice treated with iPTH (80μg/kg, 10 days), osteoblast numbers (histomorphometry) and trabecular bone mass and thickness (micro-CT) were increased. MMP-9 transcripts were significantly elevated (qRT-PCR) in male femurs (+47%, $P<0.05$, n=6), but not in females.

Administration of iPTH to WT and MMP-9 knockout (KO) mice (n=8-10/group, 80μg/kg, 5x/week, 5 weeks) elevated serum P1NP levels in male (3-fold) and female (2-fold) mice, both WT and KO, confirming increased bone formation. In the tibial diaphysis, iPTH led to greater cortical thickness (micro-CT) in all groups, indicating that the cortical response did not require MMP-9 in either sex. However, a sex-difference was observed in the effect of iPTH: multiple level thresholding along the metaphysis revealed that, in WT mice, the iPTH-induced increase in low- and medium-density bone was greater and extended further along the bone in female mice than male. Additionally, the iPTH effect on low-density bone was less in male MMP-9 KO mice than WT, whereas this genotype-difference was not observed in females. In the metaphysis, iPTH increased trabecular thickness, number, and volume similarly in female WT and KO mice. In contrast, in male WT mice, iPTH induced an increase only in trabecular thickness (+20%), which was completely blocked in MMP-9 KO mice ($P<0.001$).

In summary, the anabolic impact of iPTH on trabecular bone differs between sexes and is mediated, at least in part, by MMP-9 in male, but not female mice. This suggests MMP-9-mediated matrix turnover and/or angiogenesis might accompany PTH's bone building actions in a sex-specific way, and that anabolic therapies may have sex-specific mediators.

8

Women produce bone with less carbonate substitution than men, and exhibit a sex-specific difference in collagen deposition with age

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Both men and women exhibit increased bone fragility with ageing, but older women have greater fragility than men, including greater cortical porosity. Older women also exhibit increased mineralisation and collagen maturity compared to younger women. Whether this reflects degeneration of existing bone or a modification in how new material is deposited by osteoblasts during remodelling is not known. We sought to determine whether defects in mineral and collagen emerge in newly formed bone deposited in older people, and whether there are sex differences in bone composition between men and women.

Cadaveric femoral midshaft samples from 10 healthy younger men and women (aged 20-40) and 10 older men and women (aged 77-95) were obtained from the Melbourne Femur Research Collection. 5 recently formed osteons per subject were analysed by synchrotron-based Fourier-transform infrared microspectroscopy in the cortex of the posterior octant (which exhibits the greatest age-related increase in porosity). Mineral accrual, collagen compaction and carbonate substitution were measured.

In both younger and older individuals, mineral accrual, carbonate substitution and collagen compaction all increased significantly with increasing distance from the osteonal pore, reflecting secondary mineralisation. In older women, mature regions of the osteon exhibited collagen fibres that were more compact than in younger women (mean ratios ±SEM: 1.68±0.14 vs 1.63±0.10; $p<0.01$). Men did not exhibit this age-related difference. However, male bone in both age groups had greater carbonate substitution than female bone at the same age (0.0081±0.03 vs 0.0076±0.02; $p<0.001$).

Overall, women and men produce bone with different material composition: men have a higher degree of bioapatite carbonate substitution throughout adult life. In addition, as women (but not men) age, new bone deposited during remodelling has more compact collagen than when younger. This suggests two sex-dependent material differences in bone composition that may contribute to the greater bone fragility of older women.

9

In vivo micro-computed tomography imaging allows tracking of bone remodelling activity with progression of osteoarthritis

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Objective: Degenerative musculoskeletal diseases can be characterized by abnormal bone remodelling. In mouse models of osteoarthritis (OA), elevated bone resorption activity has been reported as early as two weeks post OA induction. A recent study highlighted the necessity of early and frequent quantification of bone alterations in early-stage OA. This proof-of-concept study aims to establish a time-lapse *in vivo* imaging protocol with high temporal resolution to longitudinally track abnormal bone remodelling activity in a mouse OA model.

Methods: Eight ten-week-old C57BL/10 mice were assigned to control (CT) and OA groups. Four mice from the OA group received intra-articular injection of collagenase on the right knee to induce OA. Longitudinal *in vivo* micro-computed tomography (microCT) scans (10.4 μm, 70 kVp, 114 μA; vivaCT80, Scanco Medical AG) were performed one day before collagenase injection and then weekly for eight weeks in total, resulting in nine scans for each animal. To visualize bone remodelling activity, image registration was performed on serial microCT scans. Bone resorption rate, BRR (%/day), and bone formation rate, BFR (%/day), were measured to quantify bone remodelling activity. To test the differences between CT and OA group at each time interval, a one-way analysis of covariance was used.

Results: Representative 3D visualization of bone formation and bone resorption are shown in **Fig.1 A-B**. Abnormal bone remodelling activities were observed in osteoarthritic femur. When compared to control femur, significantly larger bone resorption rate ($p < 0.01$) was observed in the first week post collagenase injection in both the lateral and medial femur, as shown in **Fig.1 C-D**.

Conclusion: This study, for the first time, demonstrated that abnormal bone remodelling could be detected as early as one week post OA induction using longitudinal *in vivo* microCT, offering a promising approach for earlier diagnosis, intervention and treatment evaluation of musculoskeletal disorders.

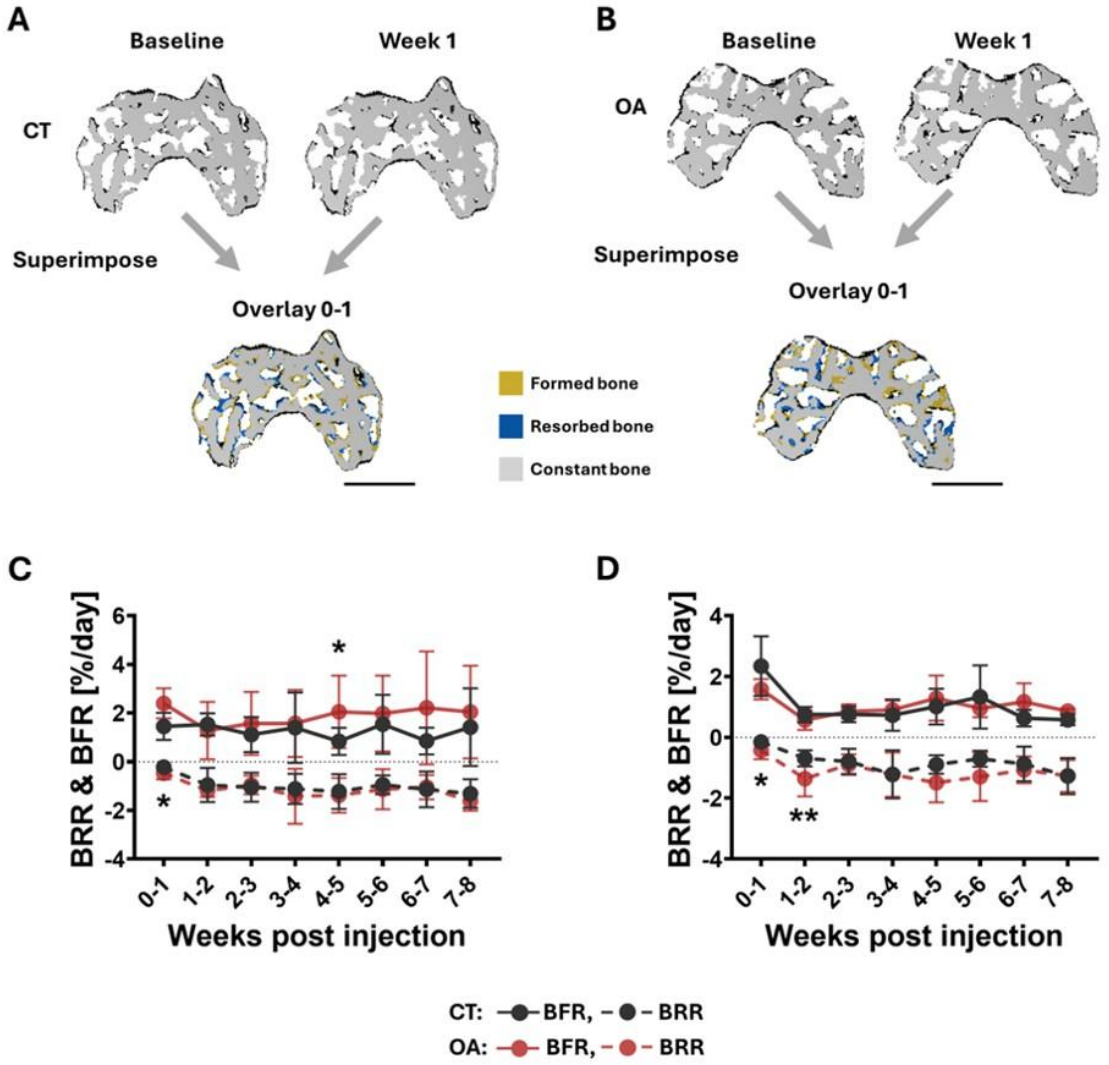

Fig. 1. Representative 3D visualization of segmented trabeculae in femur after collagenase injection from (A) CT and (B) OA groups. Within each treatment group, the top row shows the registered segmented trabecular bone at two consecutive time points, i.e., baseline (week 0), and week 1 after collagenase injection. The image at the bottom - within each treatment group - shows the formed and resorbed bone between baseline (week 0) and week 1. Yellow: formed bone; blue: resorbed bone; grey: constant bone. Bar = 1.0 mm. Bone resorption rate (BRR), and bone formation rate (BFR) from CT and OA group at (C) lateral side, and (D) medial side. *, $p < 0.05$; **, $p < 0.01$.

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Genome wide association analysis of volumetric bone mineral density phenotypes: the Vietnam Osteoporosis Study

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Objective

Volumetric bone mineral density (vBMD), measured via peripheral quantitative computed tomography (pQCT), captures site-specific cortical and trabecular bone features, offering improved assessment of bone quality over areal BMD. This study performs a genome-wide association study (GWAS) of vBMD at the radius and tibia (4% distal and 66% proximal sites) to investigate the genetic architecture underlying skeletal microstructure and strength.

Methods

A total of 3,190 men and women (mean age 52 years) from the Vietnam Osteoporosis Study (VOS) were included. Participants underwent peripheral QCT (pQCT) scans using the XCT2000 (Stratec, Germany), capturing vBMD—cortical, trabecular, and total—at the 4% distal and 66% proximal radius and tibia. Genotyping was conducted using the Illumina Infinium Global Screening Array (>700,000 SNPs). We applied standard quality control thresholds (MAF >1%, call rate >98%, HWE P $>1\times10^{-4}$). A genome-wide association study (GWAS) was performed using a mixed linear model approach, adjusting for age and sex to identify loci associated with vBMD.

Results

Several genome-wide significant associations ($P < 5\times10^{-8}$) were detected at chromosome 7 for vBMD at the 66% proximal sites of both the tibia and radius. These SNPs were located near *WNT16* and *FAM3C*, genes previously associated with osteoporosis. For the 4% distal site, a distinct genome-wide signal was identified on chromosome 10, near *FRMD4A*, which has been linked to skeletal and craniofacial abnormalities. These findings highlight site-specific genetic architecture underlying volumetric bone density.

Conclusion

We identified genome-wide significant loci for vBMD at both proximal and distal skeletal sites, including variants near known bone genes (WNT16, FAM3C) and a novel locus near FRMD4A. These findings may reflect diverse biological mechanisms influencing trabecular and cortical bone. Further work may uncover biomarkers and therapeutic targets to improve risk prediction and new therapeutic strategies for osteoporosis.

11

Effects of a Smartphone App–Delivered Exercise Intervention on Musculoskeletal Health in Older Adults with Sarcopenic Obesity Undergoing Caloric Restriction: A 6-Month Randomised Controlled Trial

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Abstract

Objective: To compare the effects of a 6-month home-based functional and impact training (FIT) intervention delivered by a smartphone application versus aerobic exercise on vertical jump, physical function, and body composition in older adults with sarcopenic obesity undergoing caloric restriction.

Material and Methods: A total of 116 community-dwelling adults aged 60-89 years with self-reported obesity (BMI≥30 kg/m^2) and a SARC-F screening score ≥2 were randomised to FIT (3-5 sessions/week of home-based resistance, balance, and impact exercise) or control (150 min/week walking/jogging) delivered via the Physitrack® app. All participants commenced a 6-month caloric restriction (750-1000 kcal/day from habitual intake, delivered by an Accredited Practicing Dietitian using Physitrack® and telephone consults). Vertical jump power and physical function (stair climb power, 5x sit-to-stand time, gait speed, and Short Physical Performance Battery [SPPB]), and dual X-ray absorptiometry-determined body composition and areal bone mineral density (aBMD).

Results: At baseline, mean±SD age was 66.5±4.0 years and mean BMI was 35.8±4.4 kg/m^2;74% were female. A 37% FIT and 32% control participants withdrew or were lost to follow-up. Mean weight loss was -2.1 kg (95%CI: -3.4, -0.9) for FIT and -1.7 kg (95%CI: -3.0, -0.5) for control, with no significant difference between groups. Vertical jump and stair climb power significantly improved in FIT but not control, while chair stand time

and SPPB significantly improved in both groups (P<0.05), with no difference between groups). Total fat mass and appendicular lean mass significantly decreased in both, with no significant differences. Lumbar spine and total hip aBMD did not change in either group.

Conclusions: FIT and control experienced similar weight loss, body composition improvements and functional gains, with no significant differences between groups, although lower-limb muscle power improved only in FIT. High attrition rates in both groups suggest intervention adaptations may be necessary to increase acceptability in this population.

12

Determinants of refracture and mortality in patients managed by a secondary fracture prevention program: insights from over a decade of follow-up

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Aims: Minimal trauma fractures (MTFs) increase the risk of subsequent fractures. This risk is reduced if patients are managed within a Secondary Fracture Prevention Program (SFPP). We examined the predictors of refracture and mortality in a long-term prospective study of the Concord SFPP.

Methods: 562 patients with incident MTFs were enrolled between 2005-2010 and managed according to SFPP standards. Follow-up data for 543 patients was obtained. Predictors of refracture and mortality were analyzed using Cox proportional hazards models, adjusted for competing risk of death.

Results: Baseline mean age of the cohort was 66.2±10.9 years (range 39-92) and 80% were female. Index fractures comprised of 36% wrist, 20% lower limb, 12% hip, 12% humerus, 2% vertebral and 18% other fractures. During a median follow-up of 15.2 years (IQR 11.1-17.3, range 0-19.4), 39% had died, and 31% refractured within 10 years. 38% of patients who were initiated on pharmacotherapy refractured, compared to 17% not on pharmacotherapy. 22% of refractures were hip and 15% were vertebral fractures.

Independent predictors of refracture on multivariate analysis included index vertebral fracture (HR 2.87; 95% CI:1.14-7.21), maternal hip fracture (HR 3.09;1.31-7.26), each additional prevalent fracture (HR 1.15;1.01-1.29), corticosteroid use (HR 2.21;1.28-3.82), each additional fall <12 months (HR 1.73;1.41-2.12), ≥3 comorbidities (HR 1.52;1.01-2.29) and lower LS BMD (HR 1.05 per 0.1g/cm^2 decrease;1.01-1.09). Age, sex, BMI, initial hip fracture, Vitamin D, calcium level and hip BMD were not predictive. Independent predictors of mortality included increasing age (HR 3.00 per 10-year

increase;2.49-3.62), male sex (HR 1.97;1.32-2.94), smoking (HR 2.61;1.57-4.34), lower FN BMD (HR 1.16 per 0.1g/cm^2 decrease;1.07-1.26) and refracture event (HR 1.48;1.01-2.18).

Conclusion: In this long-term prospective cohort study, several clinical risk factors are associated with high refracture and mortality rates, despite pharmacotherapy. Higher risk groups require more intensive monitoring and management, and further analysis on pharmacotherapy adherence is underway.

13

Influence of Non-Skeletal Input Parameters on REMS BMD Assessment

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Background: Radiofrequency Echographic Multi Spectrometry (REMS) is an emerging, radiation-free ultrasound technology used for assessing bone mineral density (BMD), T-score, Z-score, and a derived 'Fragility Score'. While published studies indicate high precision, REMS assesses BMD indirectly by analysing raw backscattered ultrasound signals through a database of spectral models matched against gender, age, site, and BMI. We hypothesized that REMS BMD assessments could be influenced by variations in operator-entered patient age and BMI, even with unchanged bone structure.

Methods: Four volunteers were scanned up to 20 times on the same day. Initially, operator-entered age input was progressively increased. Scans were then repeated at a fixed age input with varying weight and height inputs to manipulate BMI.

Findings: Calculated REMS BMD consistently decreased with increasing age input; a 10-year age increase correlated with an approximate 7% BMD decrease. Similarly, a 10kg weight decrease led to an approximate 8% decrease in derived BMD, in a linear pattern from 110 to 40 kg. REMS BMD also progressively increased with varied BMI inputs, plateauing at BMI ≥ 40 kg/m^2. The Fragility Score showed a weak relationship to BMD from different data inputs, with age being a major determinant.

Conclusions: Our findings demonstrate that REMS BMD estimates can vary significantly based on input patient age or weight, independent of actual changes in underlying bone. This has important implications for both diagnosis and precision of repeat measurements over time. These insights are crucial for optimizing REMS application and ensuring accurate clinical interpretation. A deeper understanding of how non-skeletal determinants impact derived BMD, in conjunction with clarifying the

specific skeletal components predominantly assessed, is essential for advancing its utility and reliability in clinical practice.

14

Identification of novel *GCM2* and *AIRE* mutations in sporadic and seemingly idiopathic hypoparathyroidism by whole-exome sequencing

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Publish consent withheld

1. 1. Sahoo SK, Zaidi G, Srivastava R, et al. Identification of autoimmune polyendocrine syndrome type 1 in patients with isolated hypoparathyroidism. Clin Endocrinol (Oxf). 2016 Oct;85(4):544-50. 2. Abbott JK, Huoh YS, Reynolds PR, et al. Dominant-negative loss of function arises from a second, more frequent variant within the SAND domain of autoimmune regulator (AIRE). J Autoimmun. 2018 Mar;88:114-120. 3. Oftedal BE, Assing K, Baris S, et al. Dominant-negative heterozygous mutations in AIRE confer diverse autoimmune phenotypes. iScience. 2023 May 5;26(6):106818.

15

Using multi-omics to discover new molecular determinants of skeletal health and disease.

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Multi-omics refers to the analysis of multiple layers of molecular information to better understand complex biological systems. By combining information from genomics, transcriptomics, proteomics and others; researchers can glean complex biological insights that might be undetectable using a single approach. In my presentation I will describe some of these approaches and then demonstrate how information from transcriptomics can provide a biological context to skeletal disease-associated genetic variation.

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Romosozumab for patients with multiple myeloma with skeletal events on zoledronic acid

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Myeloma bone disease (MBD) affects ~80% of patients with multiple myeloma (MM) and contributes significantly to morbidity and mortality. Zoledronic acid and denosumab inhibit bone resorption in MM patients but do not restore lost bone, consequently ~45% of patients still experience skeletal-related events (SREs). Sclerostin, a Wnt antagonist suppresses bone formation. Sclerostin inhibition prevents MBD in mouse models. Romosozumab, an anti-sclerostin antibody, reduces fractures in osteoporosis but effects on MBD are unknown. We hypothesise that romosozumab would increase bone formation and restore bone mass in patients with MM.

Firstly, the effect of romosozumab on MBD was tested in the 5TGM1 mouse model of MM. Secondly, we developed a phase II, single arm, pilot study of romosozumab in MM patients with SREs despite bisphosphonate therapy. Patients receive 210mg romosozumab subcutaneously monthly for 12 months (n=12). Primary outcomes include safety and changes in bone turnover markers; secondary endpoints include changes in bone mineral density (BMD) and SRE. Bone marrow biopsies were collected for single-cell RNA-seq (scRNA-seq) analysis.

Romosozumab stopped MBD and reduced morbidity in myeloma-bearing mice. In patients (n=9 enrolled), the number of lytic lesions at baseline on skeletal survey was none (n = 2), 1 (n = 1), 1-3 (n = 1) or >3 (n = 5). Bone formation marker P1NP increased (median change of 107%) and bone-resorption marker beta-CTX decreased (54%) at three months relative to baseline. Lumbar spine BMD increased at six (8%) and twelve months (19%) of treatment. No safety concerns or new SREs were observed. scRNA-seq revealed expansion of osteoblasts and upregulation of bone formation and mineralisation genes post-treatment.

In conclusion, romosozumab prevented MBD in a MM mouse model and increased bone formation and BMD in MM patients. These findings support the potential of romosozumab to rebuild bone and address a key therapeutic gap in MM.

17

Circulating Tumour and Bone Marrow Microenvironment Derived Factors Distinguish MGUS from Multiple Myeloma

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Multiple myeloma is a haematological cancer characterised by proliferation of clonal plasma cells (PC) in the bone marrow (BM) that is proceeded by a precursor stage, monoclonal gammopathy of undetermined significance (MGUS). The BM plays a role in supporting myeloma PC and in MGUS to myeloma progression. It is difficult to clinically differentiate MGUS patients who will rapidly progress to myeloma (3-5 years) compared with those likely to remain stable. We aimed to discover blood-based factors that could differentiate myeloma and MGUS and to determine the source of these proteins.

Olink Explore HT that allows relative quantitation of up to 5000 proteins was performed on peripheral blood plasma from MGUS and myeloma patients (n=9/group). Single-cell RNA sequencing (scRNAseq; 10xGenomics Chromium [V3.1]) was performed on bone marrow cells isolated from 2 myeloma trephine biopsies (n=2 newly diagnosed, n=2 treated), and 1 non-cancer control.

Proteomic analysis identified 516 proteins that were significantly correlated with BM PC% in MGUS and myeloma patients (Spearman $p < 0.05$), including 89 significantly upregulated proteins (FDR $p < 0.05$; LIMMA) and 10 significantly downregulated in myeloma compared with MGUS patients. To identify the source of these proteins scRNA was performed on 45,863 BM cells. The analyses revealed that factors dysregulated in the blood of myeloma patients include 75 PC derived factors (eg. BCMA, SLAMF7) and 24 proteins that are never or rarely expressed by myeloma PCs, including those expressed by BM osteoblasts (eg. VIT) and adipocytes (eg. CCL14).

We have discovered both plasma cell derived factors and microenvironment derived factors significantly upregulated in peripheral blood plasma from myeloma compared

with MGUS samples. Future studies will investigate these factors in progressing MGUS compared to those with stable MGUS (>5years). The ability to discover blood-based factors associated with progression will provide opportunities to identify individuals with high-risk MGUS.

18

Disorganization of Bone Components in Metabolic and Genetic Bone Disorders such as Hypophosphatasia: Emerging Insights into Pathogenesis and Clinical Assessment

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Background – In metabolic and genetic bone diseases, bone cell function may be impaired or cells may receive incorrect matrix components. As a result, inappropriate components may be deposited within the matrix or in incorrect locations, leading to a disorganized bone matrix—a serious clinical and biomechanical abnormality. As we reported, such misorganization disrupts load and energy transfer, causing damage, deformities, and fractures, independent of bone mineral density (BMD). Hypophosphatasia (HPP) exemplifies this process.

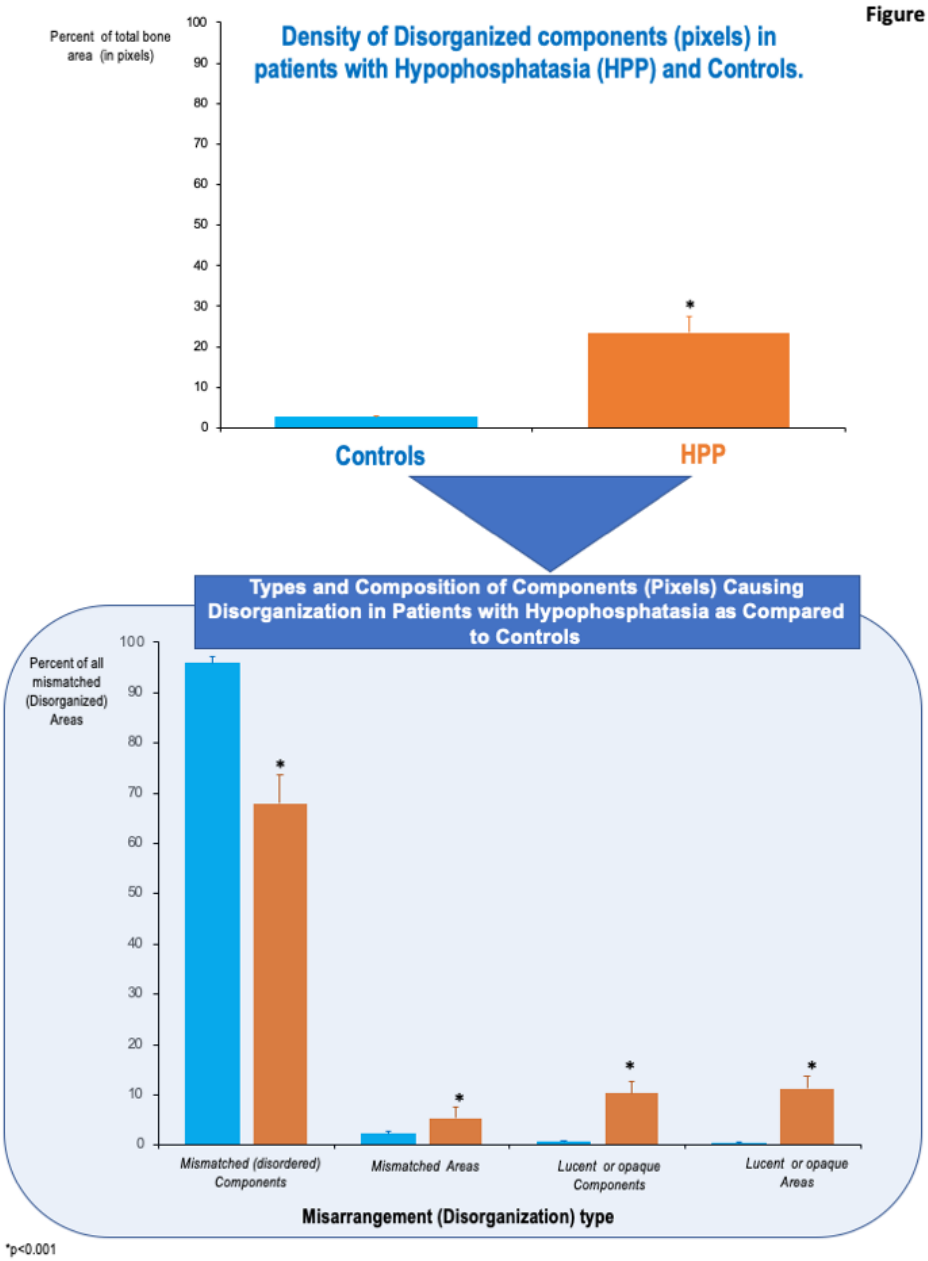
In HPP, deficiency or dysfunction of tissue-nonspecific alkaline phosphatase (TNSALP) leads to the accumulation of abnormal matrix components and a disorganized bone matrix. We therefore hypothesized that quantifying matrix misarrangement could provide a robust tool for identifying and assessing and identifying patients with HPP.

Methods- We studied 29 patients with adult-onset hypophosphatasia (HPP) and 103 age-and sex-matched controls. The extent of bone matrix disorganization and the characteristics of the most disorganized areas were assessed on femoral X-rays using a novel, validated tool (ALIGNOGRAM).

Findings- In patients with HPP, 235.48±3.97 out of 1,000 matrix components (pixels) were disorganized, compared to 27.85±0.27 in controls ($p<0.0001$)—representing an 8.45-fold greater degree of misarrangement.

Remarkably, in all patients with HPP, disorganization was attributable to the presence of lucent (hypodense) or opaque (hyperdense) components—a feature observed in less than 1% of controls. In contrast, among controls, disorganization was predominantly due to mismatched or disorderly arranged components (pixels), which represented the sole abnormality in 95.7% ± 1.26 of them (Figure).

Figure



Interpretation– Disorganized bone matrix with lucent (hypodense) and/or opaque (hyperdense) elements should alert health professionals to the presence of an underlying genetic or metabolic disease like hypophosphatasia (HPP). This biomarker, quantifiable on plain X-rays available worldwide, offers a widespread and affordable method for early detection, routine monitoring, and therapy response assessment—especially in patients suffering from metabolic, genetic and other rare bone diseases such HPP.

19

Spatial Mapping of Glucose-to-Fat Conversion in Bone Marrow: Implications for Therapeutic Targeting

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Publish consent withheld

1. 1. Rosen, et al., Nat Rev Endocrinol. 2023;19(11):626-38.
2. 2. Yu, et al J Clin Invest. 2021;131(2).
3. 3. Zou W et al. Cell Metab. 2020;32(5):801-13 e6.

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Accurate Identification of High-risk Individuals for Imminent Subsequent Fractures: A Deep Learning Approach using Administrative Data

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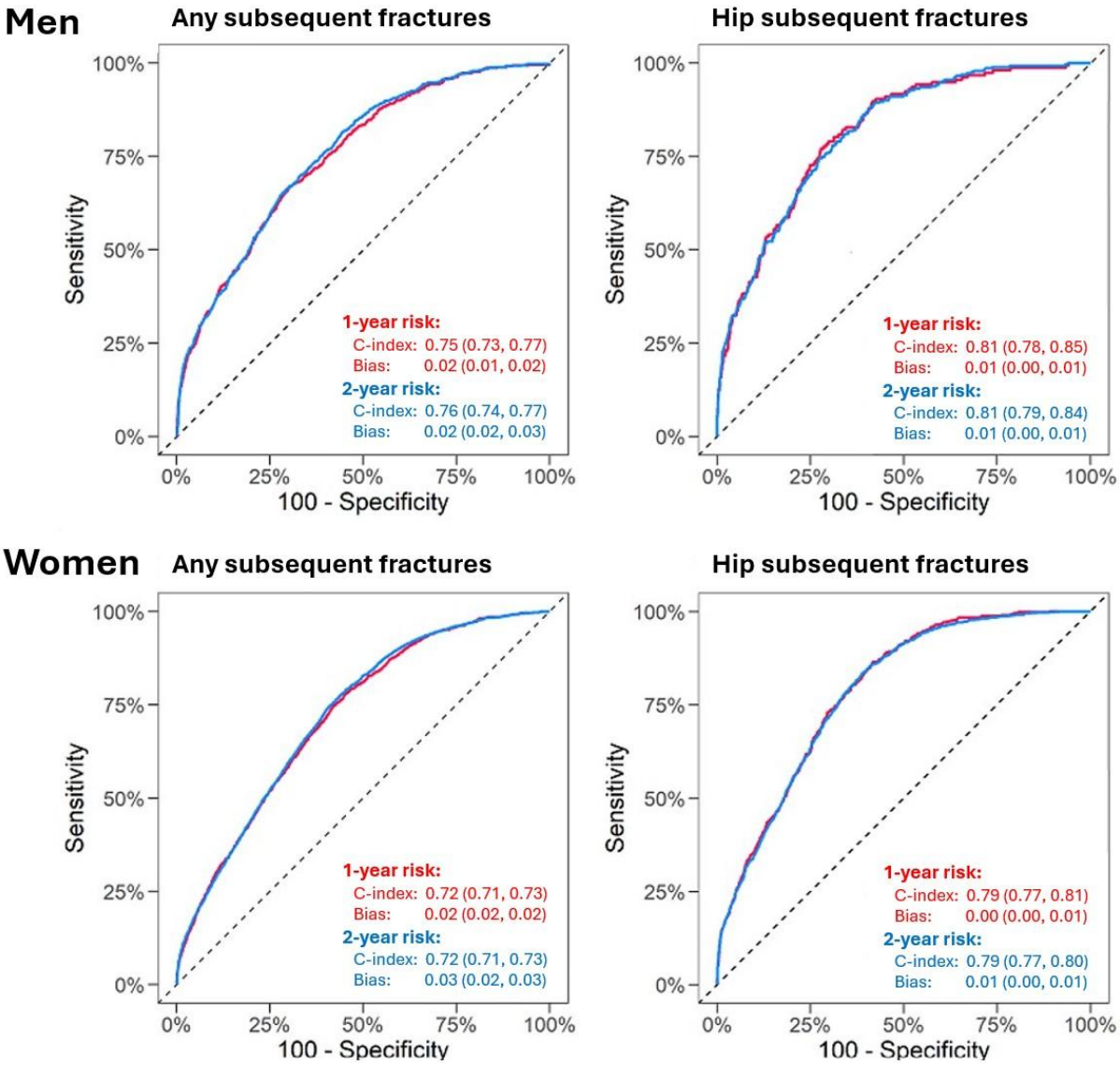
Early identification of patients at risk of subsequent fractures is crucial for optimizing post-fracture care given the evidence on imminent fracture risk. We developed and validated a deep learning model to predict the 1- and 2-year risks of subsequent hospitalized fractures using routinely collected administrative data.

This statewide population-based cohort study included 269,294 adults in NSW, born on or before 01 January 1950, who sustained an incident fracture between 2005 and 2017 and were followed through 2022. Fractures and 65 predefined chronic diseases related to fractures and mortality were identified using ICD-10 codes recorded within 5 years of the index fracture. We used *DeepHit*, a robust deep learning model to account for complex non-linear data and competing mortality risks, to predict subsequent fracture risk. Performance was assessed using discriminative and calibration analyses, and SHAP quantified predictor importance.

Over a median follow-up of 5 years (IQR: 1.5-8.6), 13,358 men and 46,222 women were admitted for a subsequent fracture, yielding the incidence of 31.2 (95% CI: 30.6-31.7) and 42.9 (42.5-43.3)/1,000 person-years, respectively. Subsequent hip fracture incidence was 5.3 (5.1-5.4) and 8.0 (7.9-8.1)/1,000 person-years in men and women, respectively. Predictors included age, index fracture site, prior fractures or falls, and

1,870 ICD-10 codes. Neither BMD nor weight was included. The model showed strong discrimination and calibration for predicting subsequent fractures at any site and hip (Figure). For 1-year risk of subsequent hip fractures, C-index was 0.81 (95% CI: 0.78-0.85) in men and 0.79 (0.77-0.81) in women; and bias was 0.01 (0.00-0.01) in both sexes. Important predictors included age, index fracture site, prior fractures or falls, and comorbidities such as hypertension, heart failure, chronic lung diseases, cataracts, renal failure and cancer.

Our findings support the use of routinely collected administrative data and deep learning for automated risk stratification within the healthcare system.



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Bioengineering of novel bone-grafting materials for oral applications

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Introduction

Dentistry utilises bone grafts tailored as granules, blocks or hydrogels in the challenging environment of the oral microbiome. We aimed to produce dual-functional novel antimicrobial bone grafting materials for both intra-oral and orthopaedic applications.

Methods

Antimicrobial lipoic-acid-capped silver nanoparticles (AgNPs) were synthesised in the laboratory and incorporated into novel bone granules produced under pressure/heat and a range of hydrogel systems. The composites were tested for their MIC and MBC against six key oral pathogens, stability, release, topography, FITR, x-ray diffraction, EDS-SEM, compressive testing and biological response to osteoblasts and osteoclasts. *In vivo* analysis utilised a rabbit cranial model of bone regeneration.

Nisin Z, mānuka oil and purified β-triketones were nanoencapsulated and investigated alone and in conjunction with other delivery polymers. Antimicrobial MIC, MBC and disc diffusion were conducted, rheometry, incorporation efficiency, release profiles, SEM, TEM, FTIR, DLS, x-ray diffraction, *in vitro* biocompatibility and large animal testing were conducted.

Results

AgNP synthesis produced particles of 1-12 nm which were effective against a wide range of bacteria with MIC <12.5 µg/ml. Stability of the AgNPs was confirmed on bone processed at 160℃ and GelMA crosslinked with Ru/SPS but not with other hydrogel system. Bone regeneration in the rabbit cranial model was better than control and comparable to BioOss®.

Nanospheres between 100-300 nm were produced that enhanced the antimicrobial activity of the encapsulated active on oral bacteria. The nanospheres were used alone or incorporated in GelMA, collagen or PVA. Release profiles and biocompatibility studies showed tailorable release, biocompatibility and bone regeneration.

Conclusion

Nanotechnology can be utilised to produce graft materials with dual functionality, enhancing bone regeneration and providing antimicrobial protection.

22

Parathyroid hormone actions in bone and mineral metabolism

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Parathyroid hormone is a critical regulator of organismal calcium homeostasis. PTH exerts its physiologic and pharmacologic actions by binding to its cell surface receptor and initiating intracellular signaling cascades that leads to changes in target gene expression. We have identified salt inducible kinases as critical mediators of the intracellular actions of parathyroid hormone in bone and kidney. PTH-induced increases in intracellular cyclic AMP levels lead to protein kinase A activation. PKA then phosphorylates salt inducible kinases and inhibits their cellular activity. Thus, direct small molecule SIK inhibitors mimic the actions of PTH. In this presentation, we will discuss translational research regarding the development of SIK inhibitors to treat osteoporosis, CKD-MBD, and hypoparathyroidism

23

Cell metabolism in skeletal cells: bystander or driver?

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Circadian glucocorticoid rhythm *timing* and *amplitude* regulate bone remodeling

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Background

Synthetic glucocorticoids increase fracture risk. Beyond elevated glucocorticoid levels, loss of circadian rhythmicity may contribute, as flattened glucocorticoid rhythm induces osteoporosis in mice. This study investigated how glucocorticoid rhythm *amplitude* and *timing* affect bone health.

Methods

We implanted 7.5% corticosterone (CORT) pellets in female C57Bl/6J mice. This blunts the natural circadian CORT rhythm without elevating CORT exposure. To assess the role of glucocorticoid troughs and peaks, we injected CORT pellet-implanted mice with glucocorticoid receptor (GR) antagonist RU486 timed at the natural glucocorticoid trough (p.m.), or with CORT at the natural glucocorticoid peak (a.m.) for one week. To examine the importance of trough-timing, CORT pellet-implanted mice received daily a.m. or p.m. RU486 injections for 7 weeks. We analyzed plasma bone formation marker P1NP levels (ELISA), gene expression profiles (qPCR), and bone microarchitecture (micro-CT).

Results

Flattening the CORT rhythm for one week reduced plasma P1NP by -38%, compared to vehicle ($p<0.01$). Reinstating a trough normalized P1NP (+2% ns), whereas reinstating a peak did not (-57% $p<0.001$). After 7 weeks, P1NP peaked at the time of RU486 injection, regardless of injection timing, indicating that GR-signaling troughs drive bone formation. Mechanistically, CORT pellets flattened the diurnal expression amplitude of circadian regulation gene *Bmal1* (morning vs evening, ns), which was restored by RU486 at either time point (morning vs evening, $p<0.05$). Regarding bone microarchitecture, 7 weeks of flattened CORT rhythm reduced cortical bone thickness (-13% $p<0.001$) and trabecular bone volume (-32% $p<0.05$). RU486 injection at either timepoint rescued cortical thinning (a.m. -2% ns; p.m. -1% ns). Notably, a.m. RU486 injections preserved trabecular bone volume (+3% ns), while p.m. injections failed to prevent loss (-31% $p<0.05$), demonstrating that trough-timing matters.

Conclusion

Reinstating a well-timed GR trough prevents osteoporosis in mice. Thus, maintaining GC withdrawals during glucocorticoid-treated patients may be promising to prevent osteoporosis.

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Implementing dietary improvements to reduce fracture risk in aged care residents

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Protein and calcium intakes in older adults in aged care remain below recommended levels, despite correction of these inadequacies using high-protein, high-calcium foods being associated with reduced fractures. To upscale the potential anti-fracture benefits of this dietary improvement we developed a training program to upskill food service staff to deliver foods in line with this intervention. We aim to determine if this staff training would result in increased protein and calcium intakes in residents.

This 12-week cluster randomised trial involved 12 aged care homes; 6 randomised to intervention (staff training) and 6 to control (residents consume from regular menus). Residents consented to food intake (plate waste analysis), nutritional status (mini nutrition assessment tool) and quality of life (EQ-5D-5L) assessments at baseline and week 12 with medical records reviewed at baseline. Staff were interviewed before and after training and intervention to determine barriers to implementation. Analysis of dietary outcomes was performed using a linear mixed effects model, with home entered as a random intercept, and baseline values entered as covariates.

Data was obtained from 78 residents (median age 84.5 years; IQR: 80-89, 85% female, n=52 intervention). Baseline protein (65g/day; IQR 53-78, 0.9 g/kg body weight; IQR:0.7-1.1) and calcium (773 mg/day; IQR: 605-982) intakes were below the respective recommended levels of 1g/kg body weight and 1100mg/day. Following intervention group differences were observed for daily intakes of protein (16g/day; 95%CI: -3, 35), calcium (302mg/day; 95%CI: 117, 486) and dairy servings (0.9s/day; 95%CI: 0.3, 1.5). Staff provided insights into implementation barriers.

While improvements to protein and calcium intakes in residents were observed, operational constraints may have impeded intervention efficacy and detection of anti-fracture efficacy limited by the short study duration. A potential solution is mandating food standards in aged care to ensure nutritional adequacy in residents.

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Ten years of research in practice confirms high intensity exercise as first line therapy for osteoporosis

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BACKGROUND: We have previously reported high intensity resistance and impact training (HiRIT, aka. ONERO™) reduces risk for osteoporotic fracture by improving bone, muscle, posture and functional performance, both in clinical trials and clinical practice. A full ten years of rigorous research monitoring of the effects of ONERO™ in a real-world osteoporosis clinic setting, has now provided sufficient data to examine the factors that influence patient responses to ONERO™.

AIM: To determine factors influencing the effect of ONERO™ on bone mineral density (BMD) in older women undertaking ONERO™.

METHODS: In this longitudinal clinical intervention project, 1020 women (age=61.7±7.9yrs, Ht=163.2±6.7cm, Wt=63.0±10.8kg, total hip T-score -1.6±0.7), attending a specialised osteoporosis service, were examined for change in BMD after up to 24 months exposure to ONERO™. Attendance (adherence) and exercise load (i.e. weight lifted) were monitored. The relationships between exercise load (kg), moderating variables, and magnitude of change in BMD were determined.

RESULTS: Older adult women consistently undertaking ONERO™ classes exhibit significantly improved femoral neck BMD (+0.6%, $P<0.001$), lumbar spine BMD (+1.1%, $P<0.001$) and whole body BMD (+1.0% $P<0.001$) compared with women not doing ONERO™.

There were positive dose-response relationships between exercise load and improvements in hip and spine BMD (0.15 to 0.21 mg/cm^2 per kg lifted). The exercise loading dose-response was positively moderated by weekly exercise frequency (up to 2.5 times per week). Taking osteoporosis medicine ($p<0.027$), older age ($p<0.002$), and higher daily calcium consumption ($p<0.009$) were also associated with greater ONERO™-related changes in BMD.

CONCLUSION: Supervised ONERO™ improved BMD in older women at risk of osteoporotic fracture with a dose-response effect of exercise loading and training frequency. Presence of osteoporosis medication, older age, and daily calcium consumption were positively related to the bone response. This unique real-world data continues to endorse supervised ONERO™ exercise for the prevention of osteoporotic fracture.

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Timed glucocorticoid treatment prevents cartilage degeneration driven by chronic disruption of circadian rhythms in C57BL/6J mice

Eugenie Macfarlane[1], Lauryn Cavanagh[1], Joseph Tannous[1], Colette Fong-Yee[1], Caitlyn Massarotti[1], Markus Seibel[1], Hong Zhou[1]

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Chronic disruption of circadian rhythms (CR) from shift work increases the risk of osteoarthritis. We have previously found in mice that chronic CR disruption induces cartilage loss and accelerates the development of knee osteoarthritis. We further discovered that the diurnal rhythmicity of circulating glucocorticoids is abolished during chronic disruption of CR, characterized by a loss in the normal daily peak of serum corticosterone. When we blocked abnormal rhythmic glucocorticoid signaling in $Col2a1Cre^{T2}/GR^{flox/flox}$ mice, cartilaginous circadian gene expression maintained intrinsic rhythmicity and cartilage loss was mitigated during chronic CR disruption. We therefore hypothesized that the detrimental effects of CR disruption on the skeleton would be mitigated by restoring the normal daily peak of serum corticosterone.

To test this hypothesis, 8-week-old C57BL/6J male mice were exposed to an established model of chronic CR disruption. Mice were maintained on either a normal 12:12hr light-dark cycle (non-shifted) or exposed to weekly 12hr phase-shifts, equivalent to spending alternate weeks in London and Sydney for 10-weeks (shifted). A third group of mice were shifted but received daily corticosterone at a dose mimicking endogenous glucocorticoid levels without inducing hypercortisolism. Paraffin-embedded knee joints were cut, stained with toluidine blue/fast green and scored according to Osteoarthritis Research Society International recommendations.

Histological analysis revealed that chronic CR disruption caused pronounced cartilage damage in shifted compared to non-shifted mice ($p=0.009$, Fig1), characterized by proteoglycan loss, superficial fibrillations and damage that extended to some of the calcified cartilage. In shifted mice treated with corticosterone, cartilage damage was significantly reduced compared to untreated shifted mice ($p=0.03$).

Our results provide compelling in vivo evidence that loss of the diurnal peak in glucocorticoid signaling drives cartilage damage during chronic CR disruption. Treatments that aim to restore peak physiological glucocorticoid levels in shift workers may mitigate the detrimental effects of CR disruption on skeletal health.

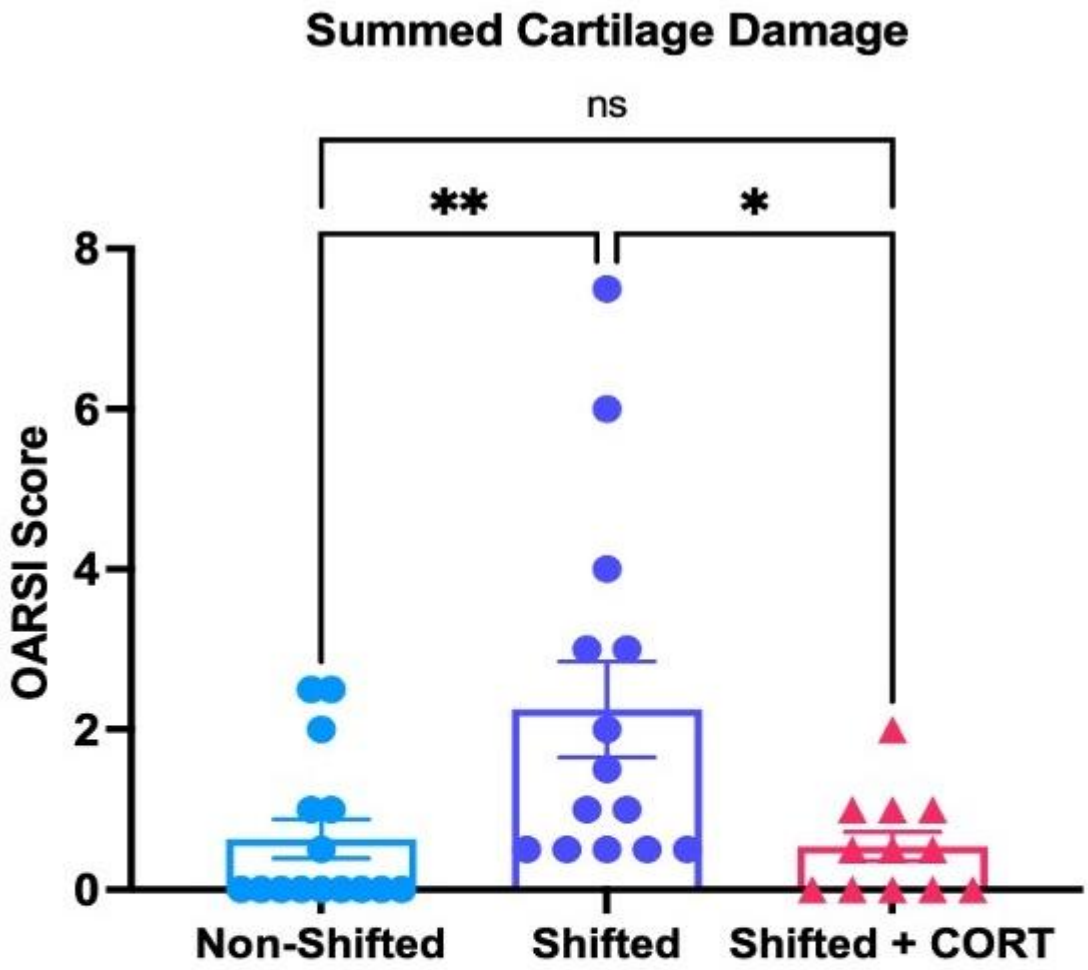

Figure 1. Treatment with corticosterone mitigates cartilage damage induced by chronic circadian rhythm disruption in shifted mice. CORT, corticosterone; OARSI, Osteoarthritis Research Society International. Analysed by one-way ANOVA Kruskal-Wallis test n=12-15/group.

29

Progressive Decline in Nonvertebral Fracture Incidence with Zoledronate Use >3 Years: Post Hoc Analysis of an RCT

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The anti-fracture efficacy of most osteoporosis drugs is assessed in trials over three years. However, treatment of osteoporosis is required long-term, so it is important to know whether effectiveness of treatment changes over time. To-date, this information has only been available from open extensions of the treatment groups from clinical trials. Such data are subject to selective loss of frailer patients from the cohort, and no placebo comparator group is available to permit reliable measurement of anti-fracture efficacy.

Our 6-year RCT of zoledronate or placebo every 18 months in 2000 osteopenic women aged >65 years is longer than most other trials of osteoporosis drugs, and only 3.6% of participants withdrew or were lost to follow-up (Reid IR et al, NEJM 379:2407, 2018). Therefore, anti-fracture efficacy can be validly compared between the first and second halves of this study.

There were 178 non-vertebral fractures in the placebo group and 108 in the zoledronate group (excluding fractures of the hands, feet and face). Fracture rates per 1000 women-years in the placebo group were 28 (95%CI 23,35) and 32 (26, 40) in years 1-3 and years 4-6, respectively. In the zoledronate group, fracture rates were 23 (18, 30) and 13 (9, 18) per 1000 women-years in the first and second halves of the study. The rate ratios for non-vertebral fractures were 0.83 (0.60, 1.14) in years 1-3, and 0.40 (0.27, 0.58) in years 4-6 (between-period comparison, $P<0.05$). Rates ratios for total fragility fractures, which included vertebral fractures also, showed a similar pattern: years 1-3, 0.72 (0.54, 0.97); years 4-6, 0.37 (0.28, 0.50).

These findings suggest that the efficacy in non-vertebral fracture prevention of anti-resorptive drugs has been underestimated because of the short-term evaluation of their effects. Further, it indicates that longer term treatment with these drugs may yield greater benefit to patients.

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Gender Affirming Hormone Therapy (GAHT) and Bone Health: Insights from a Preclinical Model of Feminising Hormone Therapy

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The impact of gender-affirming hormone therapy (GAHT) on bone health in transgender people remains poorly understood. Puberty suppression with gonadotropin-releasing hormone analogues (GnRHa) impairs peak bone mass accrual, and while GAHT can partly restore bone density, recovery to cisgender levels may not be complete. Data on bone health in trans women are also conflicting, and only one retrospective cohort study has examined fracture risk following GAHT. This study showed that older trans women had a higher fracture risk compared with age-matched healthy cis men, whereas no increase in fracture risk was observed in trans men compared with cis male controls.

To address this gap, our research uses preclinical mouse models to isolate the skeletal effects of estradiol during puberty and adulthood, which is difficult to achieve in human studies. These models allow us to explore how estradiol dose, timing, and local bone concentrations affect bone microstructure, cell metabolism and strength following pubertal suppression.

Our findings offer new insights into how estradiol supports bone integrity and highlight the potential for optimising GAHT regimens to better protect skeletal health in transfeminine individuals. The presentation will discuss how these models reveal the mechanisms by which estradiol protects bone and how this knowledge could inform strategies to improve bone health in trans girls and women.

31

Menopausal hormone therapy for fracture prevention

Bronwyn Stuckey[1]

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The trend in clinical practice has been to use menopausal hormone therapy (MHT) for management of menopausal symptoms and to reserve other agents – bisphosphonates, RANK-L inhibitors, and SERMs – for the prevention of osteoporotic fracture. Perhaps this is because there is a dearth of randomised controlled studies of MHT with fracture prevention as the primary end-point. However, there is ample epidemiological evidence for the role of oestrogen depletion leading to loss of bone density and osteoporotic fracture and, conversely, for MHT in preventing a rise in bone resorption and bone loss. To cement a role for MHT in fracture prevention, clinicians will

require an understanding of the mechanism by which oestrogen protects bone, evidence for the relative efficacy of oestrogen in comparison to bone-specific agents, a level of comfort in MHT prescribing, and an awareness of the long term risks and benefits of each therapeutic option.

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Macrophage iron overload as a driver of bone marrow dysfunction and skeletal aging

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Publish consent withheld

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Perimenopausal bone mineral density but not rate of bone loss is associated with incident fracture

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Aim

Bone loss following menopause has been well described. There are fewer studies examining associations between bone mineral density (BMD) around the time of menopause, and incident fracture. This study investigated associations between BMD values, BMD loss around menopause, and fracture.

Methods

Participants (n=287, aged 50-56yr) were women who self-reported recent menopause (≥12 months to <5yr since last menstrual period) for at least one assessment phase of the Geelong Osteoporosis Study. BMD was measured at the femoral neck, lumbar spine, ultra-distal forearm and mid-forearm using Lunar DPX-L and GE-Prodigy densitometers. Incident fractures were ascertained by examination of radiological reports.

Cox proportional hazard models were used to examine associations between BMD and incident fracture. BMD was assessed as: i) T scores and ii) percentage change in BMD per year from first report of menopause to the next follow-up phase attended (median 2.1, IQR 1.9-3.3 yr). Models were adjusted for anthropometric measurements, lifestyle factors and medication use including menopausal hormone therapy.

Results

Mean(±SD) age at menopause was 50.3±4.5 years. During a median of 16.1 (IQR 8.7-21.7) years follow-up, 71 women sustained at least one fracture. Sites of fracture included forearm n=14, spine n=10, ankle n=10, rib n=8, humerus n=8, foot n=7, hand n=4, scapula n=3, hip n=2, tibia/fibula n=2, pelvis n=1, clavicle n=1 and patella n=1.

In adjusted models, greater femoral neck and lumbar spine BMD T scores around menopause were associated with a lower risk of incident fracture (HR 0.78; 0.62, 0.98, p=0.031 and 0.79; 0.65, 0.97, p=0.024, respectively).

No other associations were observed.

Conclusion

Greater BMD T scores at the femoral neck and lumbar spine around the time of menopause were associated with a lower risk of incident fracture. No associations were observed for BMD measurements at the forearm, or for bone loss around the time of menopause.

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Cortical bone in older women has greater collagen compaction and less osteocyte connectivity at the time of deposition

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Bone fragility increases with age and fractures are common even with normal bone mineral density. Poor bone composition, including reduced osteocyte connectivity, may contribute, but whether it occurs by gradual degradation of pre-existing bone, or by deposition of compromised bone during remodelling is not known. Here, we tested the hypothesis that older women have an intrinsic defect in bone production.

Osteons from mid-diaphyseal femoral cortex of healthy younger (19–40 years) and older (77–95 years) women (10 women / group, Melbourne Femur Collection) were imaged by synchrotron-based Fourier-Transform Infrared Microspectroscopy (FTIRM), quantitative backscattered electron imaging (qBEI), and high-resolution confocal microscopy. Since these archived samples lacked timed fluorochrome labels, we developed a method to identify four stages of osteonal bone maturation (early, mid, late, and stable) based on histology (complete osteons uninterrupted by more recent remodelling), calcium content (qBEI), and phosphate:amide I gradient across the osteon wall (FTIRM).

The mineralisation process did not differ between the two age groups; older and younger women showed similar increases in phosphate, calcium, and carbonate from the Haversian canal to the cement line at all osteon maturation stages. However, in mid, late, and stable osteons from older women, collagen was more compact than in younger women: amide I:II ratio was ~5% lower (mean ratios ±SEM: 1.72±0.14 *vs* 1.63±0.06; $p<0.001$). While osteocyte lacunar density (osteocyte cell number) did not differ, osteocyte connectivity (canalicular density) was ~40% lower in new osteons of older women (0.088±0.011 vs 0.053±0.009; $p<0.0001$, $\mu m/\mu m^3$). This indicates that the disconnected network originates during new bone formation.

Our classification method enables stage-specific identification of unlabelled osteons and suggests that bone fragility in older women originates as it forms during cortical remodelling. The more compact collagen and poorly connected osteocyte network may be a bone mass-independent contributor to age-related bone fragility in women.

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Osteoclast recycling as a potential mechanism driving rebound bone loss following denosumab withdrawal

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Discontinuation of denosumab (Dmab), results in a severe rebound increase in osteoclast formation and bone resorption, increasing risk of multiple vertebral fractures. We determined the temporal changes in osteoclast formation following the removal of the RANKL decoy receptor osteoprotegerin (OPG:Fc) in mice, demonstrating early elevations in local and systemic RANKL, and a subsequent overshoot in serum TRAP as osteoclasts rapidly re-formed. More recently, accumulation of osteoclast precursors has been demonstrated to contribute to this rapid rebound in osteoclast formation. Previously, our group characterised a novel osteoclast lineage cell arising from osteoclast fission, osteomorph, which is capable of re-fusing to form osteoclasts. We sought to determine whether OPG:Fc leads to increased osteoclast fission and an accumulation of osteomorphs, providing evidence that osteomorphs may contribute to enhanced osteoclast formation following withdrawal of Dmab.

Treatment of primary murine osteoclasts with OPG:Fc (250ng/ml) for 30 hours led to a 70% reduction in total osteoclasts ($p<0.01$). Interestingly, a reduction in apoptotic osteoclasts ($p<0.01$), and a 2-fold increase in total cell number were demonstrated ($p<0.02$). Live-cell imaging of OPG:Fc treated LysM-TdTomato-expressing primary multinucleated osteoclasts over a 30-hour period, demonstrated a significant increase in fission events compared to control (Figure 1a). These data indicate that osteomorphs, in addition to osteoclast precursors, accumulate during anti-RANKL treatment.

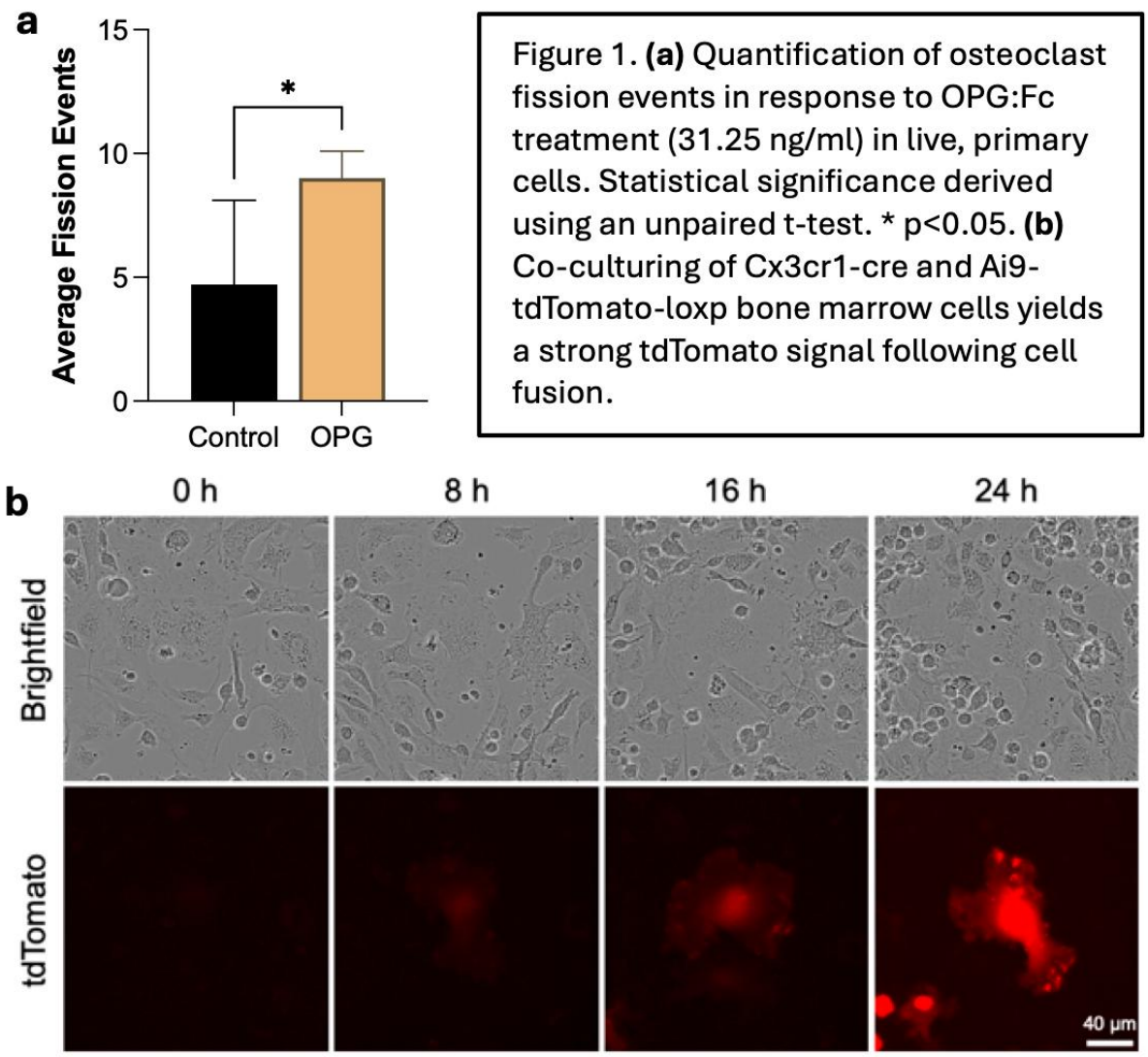

Figure 1. **(a)** Quantification of osteoclast fission events in response to OPG:Fc treatment (31.25 ng/ml) in live, primary cells. Statistical significance derived using an unpaired t-test. * $p<0.05$. **(b)** Co-culturing of Cx3cr1-cre and Ai9-tdTomato-loxp bone marrow cells yields a strong tdTomato signal following cell fusion.

We recently developed a novel osteoclast lineage tracing system whereby, upon fusion of pre-osteoclasts from CX3CR1-cre and Ai9-tdTtomato mice, cytoplasmic tdTomato expression initiates. This system allows, for the first time, fate-tracking of osteoclast fusion and fission products in real time (Figure 1b). We will utilise this system to investigate fission and importantly re-fusion of osteomorphs into osteoclasts to demonstrate their role in bone loss following withdrawal of anti-RANKL treatment. This innovative approach will provide opportunities to interrogate osteomorph biology and develop new insight into advancing sequential therapy approaches for osteoporosis.

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Sex- and compartment-specific deficits in volumetric bone mineral density (vBMD) and estimated bone strength among older people living with HIV (PLWH).

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Background: People living with HIV (PLWH) are living longer due antiretroviral therapy (ART) but chronic-HIV increases the risk of age-associated diseases including osteoporosis. Data suggest that HIV infection and ART exposure increase fracture-risk though quantitative bone data from older PLWH are few.

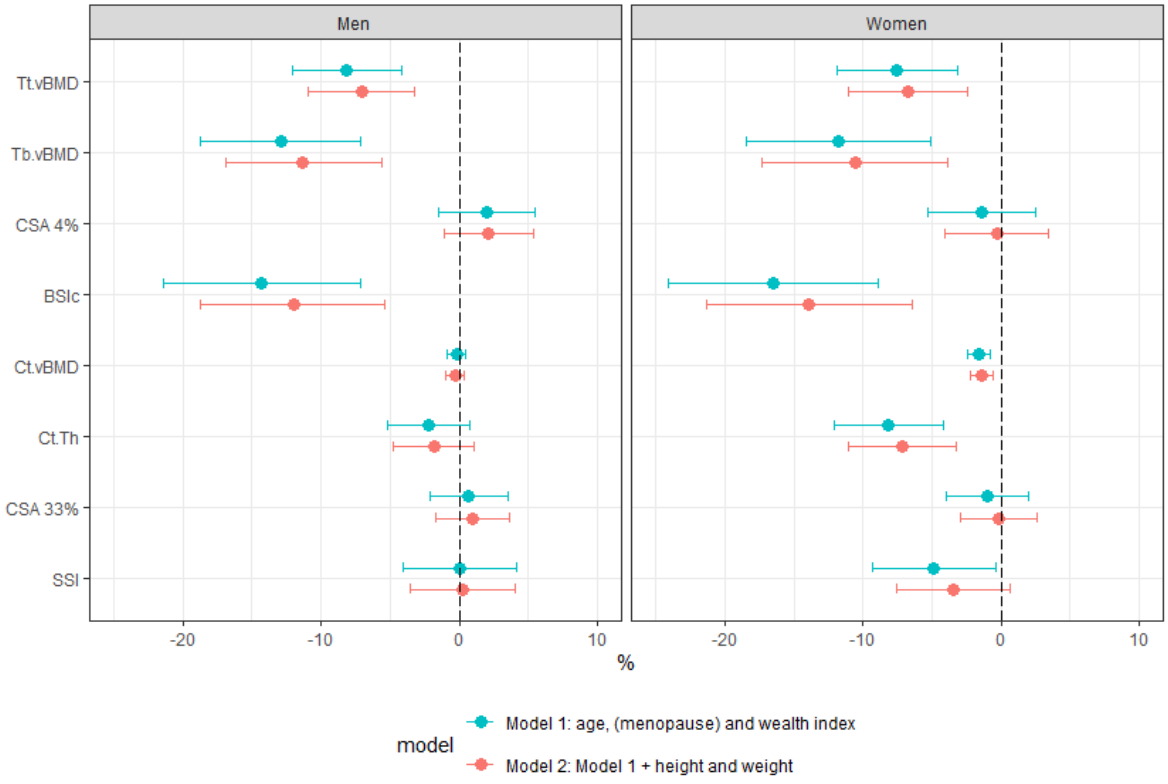
Methods: A cross-sectional study of men and women ≥40 years (20.3% PLWH) was conducted in Harare, Zimbabwe. Sociodemographic data, menopause status, HIV status and treatment, and anthropometry were collected. Outcomes from radial peripheral quantitative computed tomography (pQCT) were: total volumetric bone mineral density (Tt.vBMD), trabecular vBMD (Tb.vBMD), cross-sectional area (CSA), compressive bone strength (BSIc), cortical vBMD (Ct.vBMD), cortical thickness (Ct.Th), proximal CSA, and stress-strain index (SSI). Sex-stratified linear regression determined differences by HIV status, minimally adjusted for age, wealth index, and menopause

status, and further adjusted for height and weight. Linear regression assessed associations between HIV and ART durations on bone.

Results: 1101 participants had pQCT data (Male:48.6%) and were mean(SD) age 62.4(14.1) years. PWLH were a decade younger, and had lived with HIV for a median[IQR] of 9.3[4.8;12.9] years. HIV-related bone deficits, robust to full adjustment were observed. Men with HIV had lower radial Tt.BMD, Tb.BMD, and BSIc than HIV-negative men of -7.1 [-10.9;-3.2]%, -11.3 [-16.9;-5.6]%, and -12.0 [-18.7;-5.4]%, respectively. Deficits of similar magnitude were seen in women with HIV (Figure), who also had lover Ct.vBMD and Ct.Th by -1.4 [-2.3;-0.6]% and -7.2 [-11.1;-3.3]%, respectively compared with HIV-negative women (Figure 1). In women with HIV, longer HIV duration was associated with lower radius Tt.BMD, Tb.BMD, BSIc and Ct.Th, independent of age and ART.

Conclusions: Trabecular deficits predominate in PWLH, though in women cortical deficits were evident. This is important as post-menopause, most bone loss is cortical in nature and suggests women with HIV may be at increased risk of age-associated fragility fracture earlier in their lifecourse.

Figure 1. Sex-stratified radial pQCT differences by HIV status



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Generation of an osteocyte-specific Cre mouse model reveals distinct roles of osteocytes

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Recent advances have greatly expanded our understanding of osteocytes, the cells embedded within the bone matrix. These cells are now recognized as central regulators of skeletal homeostasis, with critical roles in mechanotransduction, bone remodeling, mineral metabolism, and hematopoiesis. However, achieving specific in vivo targeting of osteocytes has remained a major challenge. We generated a novel Cre mouse line that enables osteocyte-specific targeting. Remarkably, ablation of osteocytes using these Cre mice led to increased bone mass in both young and aged mice. Single-cell RNA sequencing further identified distinct osteocyte subpopulations and age-related compositional shifts. These findings provide new insights into the role of osteocytes and establish a tool for advancing osteocyte research.

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Bone Health in Microgravity: Tracking Bone Remodelling in Spaceflight and Recovery

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Bone remodelling is driven by mechanical signals, with bone formation and resorption tightly coordinated to maintain skeletal integrity. When loading increases, bone mass and strength generally rise to meet higher demands. In contrast, disuse leads to bone loss, typically beginning in trabecular-rich regions, but it remains unclear how these changes progress and whether they can be effectively reversed once loading is restored. The goal of this talk is to show how high-resolution peripheral quantitative computed tomography imaging allows us to study bone microstructure at a level of detail where individual sites of formation and resorption can be identified. Using spaceflight as a unique model of disuse and recovery, we can investigate how bone adapts to the absence of mechanical loading and how it responds once mechanical cues are reintroduced. By combining imaging with computational modeling, we can relate local remodeling activity to mechanical stimuli and begin to define the limits of recovery. These insights not only inform astronaut health during and after long-duration missions but also shed light on the fundamental processes by which bone structure is maintained, lost, and potentially regained under mechanical challenge.

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Time-lapse *in vivo* contrast-enhanced micro-computed tomography uncovers structural disease patterns of early post-traumatic osteoarthritis in a DMM mouse model

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Publish consent withheld

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Longitudinal associations of multimorbidity with physical function and risk of falling in middle-aged adults

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Background: Few studies have evaluated the longitudinal associations of multimorbidity with physical function in middle-aged adults. In 3,272 participants (1,812 females, aged 45-69 years) from the Busselton Healthy Ageing Study, we studied the associations of baseline multimorbidity count and patterns with physical function and the risk of falls at year 6.

Method: At baseline, 21 morbidities were assessed and four multimorbidity patterns were identified using latent class analysis. Physical function tests including hand grip strength, timed up and go (TUAG) and five times sit to stand (5TSTS) were performed,

and falls occurring in the previous 12 months were captured through self-report at year 6. General linear models and logistic regression were used to evaluate associations, accounting for sex, and baseline age, BMI, smoking status, physical activity, and alcohol consumption.

Results: The mean age at baseline was 57.9 ± 5.7 years. At 6 years, 877 (26.8%) participants reported at least one fall, and 350 (10.7%) reported two or more falls. Increasing multimorbidity count or being in the "Predominantly mental health & musculoskeletal" or "Predominantly cardiometabolic" multimorbidity classes were associated with greater risk of falling, lower grip strength and slower TUAG and 5TSTS performance at year 6 (**Table**). Among fallers, increases in multimorbidity count (odds ratio 1.15 [95% CI 1.07, 1.25]) and being in the "Predominantly mental health & musculoskeletal" class (OR 1.98 [1.36, 2.88] vs "Relatively healthy") were associated with greater risk of multiple falls. In addition, increasing multimorbidity remained risk factor for falling adjusting for participants' lower physical function.

Table Associations of baseline multimorbidity count and patterns with physical function and the risk of self-reported falls at year 6

	Risk for falling	**Grip strength (kg)**	**TUAG (seconds)**	**5TSTS (seconds)**
Multimorbidity patterns	OR (95% CI)		Estimated mean (SEM)	
Relatively healthy	Ref.	31.6 (0.2)	7.3 (0.1)	12.7 (0.1)
Predominantly respiratory & atopy	1.06 (0.83, 1.37)			
		31.6 (0.3)	7.2 (0.1)	12.9 (0.2)
Predominantly mental health & musculoskeletal	1.78 (1.41, 2.24)			
		30.8 (0.3)	7.7 (0.1)	13.5 (0.2)
Predominantly cardiometabolic	1.47 (1.01, 2.14)			
		29.2 (0.5)	8.0 (0.2)	14.5 (0.3)
Multimorbidity count	OR (95% CI)		Regression coefficient (SE)	
Per unit increase	1.13 (1.08, 1.18)	-0.23 (0.06)	0.11 (0.02)	0.24 (0.03)

Conclusion: Our study showed that increasing multimorbidity count and certain morbidity patterns are associated with lower physical function and greater risk of falling in middle-aged adults. Lower physical function only partially explains the increased risk of falling conferred by multimorbidity, suggesting this risk could also be mediated through other mechanisms.

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Bone regeneration using iPS cell-derived immortalized mesenchymal stem cells

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Publish consent withheld

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Postponement of fracture as a novel metric for expressing anti-fracture efficacy: An IPD meta-analysis

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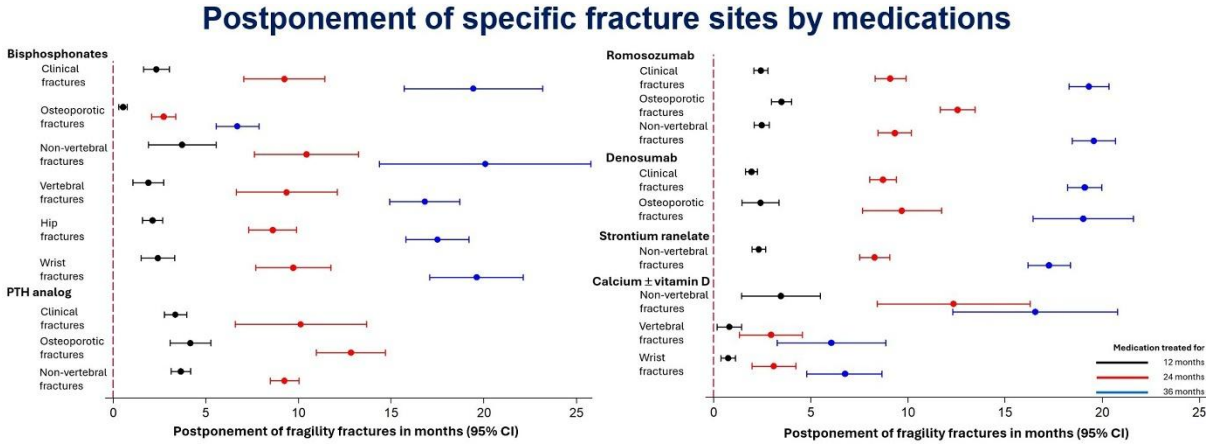
The interpretation of osteoporosis treatment effects remains challenging, contributing to its global undermanagement crisis. We propose the *"Postponement of Fracture"* as a novel and intuitive metric to express anti-fracture efficacy.

"Postponement of Fracture" is defined as the gain in fracture-free survival time attributable to osteoporosis treatment, calculated as the difference in restricted mean fracture-free survival time (RMST) between the intervention and control groups. We conducted a two-stage individual patient-level data meta-analysis, including randomized controlled trials (RCTs) in high-impact journals that assessed anti-fracture efficacy, used a 1:1 allocation ratio, and reported at least one statistically significant result with Kaplan-Meier curves. First, we reconstructed individual patient-level data using the *IPDfromKM* application, and then calculated RMST differences at 12, 24, and 36 months post-intervention for each analysis result included in the meta-analysis. Secondly, a random-effects meta-analysis was performed to pool RMST differences by specific medications and fracture sites.

The meta-analysis included 32 analysis results from 18 RCTs (median size: 1776 participants; IQR: 1085–4093), with 78% of trials having a maximum follow-up of 24 or

36 months. Osteoporosis treatment, treated for 12, 24, and 36 months, postponed fractures on average by 2.6 (95% CI: 2.2–2.9), 9.1 (8.1–10.0), and 16.7 months (14.1–18.6), respectively. Parathyroid hormone analogs and romosozumab yielded the longest postponement for osteoporotic fractures, while calcium supplementation (± vitamin D) was associated with the shortest postponement for wrist fractures. *"Postponement of Fracture"*-related advice, such as *"a 3-year treatment would give you 17 extra months of health, and only 8 out of 100 people like you will fracture, compared to 20 without treatment"* is more intuitive and informative than the conventional *"the treatment would reduce fracture risk from 20% to 8%"*.

"Postponement of Fracture" offers a complementary, patient-centered metric for interpreting treatment effects, thus improving doctor-patient risk communication and treatment uptake.



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Nano-encapsulation of mānuka oil for bone loss associated with microbial Infection

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Aims

Microbial infection contributes to the progressive absorption and destruction of bone, as well as the formation of aberrant bone structures. Pathogenic bacteria can colonise the bone cells, leading to bone degradation. Also, bacterial cytokines and toxins trigger the host's immune response, further disrupting bone homeostasis. Periodontal disease is a common and serious condition which originates from dental plaque formation and ultimately leads to alveolar bone loss.

Mānuka oil is an essential oil with strong anti-microbial properties when extracted from the foliage, bark, and seeds of *Leptospermum scoparium*, a native shrub in both New Zealand and Australia. This research aims to develop an antimicrobial gel with the encapsulation of mānuka oil-loaded nanospheres for the treatment of bacterial-induced bone loss associated with periodontal diseases.

Methods:

Mānuka oil or purified β-triketones were nanoencapsulated using a microfluidics platform and were characterised with DLS, FTIR and fluorescence labelling. Antimicrobial efficacy and biocompatibility were then quantitated. Nanospheres were further incorporated into a biogel for prolonged and controlled release. The nanosphere-gel composite was assessed for morphology by SEM, rheological properties, syringe-ability, antimicrobial effects against oral-related bacteria, and biocompatibility evaluated *in vitro*. *In vivo* therapeuticeffects were investigated in a rat periodontitis model through micro-CT analysis of alveolar bone loss and histological evaluation.

Results:

Nano-encapsulation provided sustained release of the mānuka oil/purified β-triketones and spheres exhibited strong antimicrobial properties against oral pathogens. Further, formulation of nanosphere-gel composites was achieved with comparable viscosity and syringe-ability to commercial products used for periodontal treatment, while ensuring good biocompatibility and antimicrobial release. *In vivo* application in the rat periodontitis model showed a significant decrease in alveolar bone loss and results were significantly better than a commercial product.

Conclusion:

The Biogel containing mānuka oil-loaded nanospheres demonstrates strong antimicrobial activity and shows promise in reducing alveolar bone loss associated with periodontal disease.

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Air pollution and bone health outcomes: Periods of susceptibility from pregnancy to childhood

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Abstract coming soon.

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A First Nations Woman's Health Journey

Agnes Mosby[1]

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Consumer Advocate Presentation

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Bone health perspectives among Aboriginal and Torres Strait Islander people

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Bone health is an under-researched area, with scarce data available in the Aboriginal and Torres Strait Islander population. Aboriginal and Torres Strait Islander people have a greater fracture risk than non-Indigenous Australians. In addition, hip fractures occur at younger ages in Aboriginal and Torres Strait Islander people compared with non-Indigenous Australians: 65 versus 81 years in men and 74 versus 83 years in women. Prevalence of chronic disease, such as cardiovascular disease, type 2 diabetes and kidney disease, is higher among Indigenous adults and associated with increased risk of osteoporosis, falls and fracture. Despite the impact of falls on Indigenous health, current policy lacks focus on bone conditions, and pain is often a pertinent finding to establish underlying fracture and disease. Understanding perspectives and beliefs about bone health in the Aboriginal and Torres Strait Islander population is essential for designing effective, culturally safe programs and services. Sparse data exist about knowledge, attitudes and service preferences relating to bone health among Aboriginal and Torres Strait Islander people. In this study, we explored the perspectives, beliefs and knowledge on bone health among Aboriginal and Torres Strait Islander adults in Victoria, and topics considered essential to increase Community health literacy by co-creating an educational program for Community members.

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A heartbreaking case of hypocalcaemia

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Case

Mr. G, a 35-year-old man with class III obesity and no prior medical history, was admitted with decompensated heart failure. He was a non-smoker, did not use alcohol/recreational drugs, and took no regular medications. Cardiomyopathy workup, echocardiogram and coronary angiogram confirmed non-ischemic cardiomyopathy [left ventricular ejection fraction(LVEF) 31%] of unclear aetiology.

Biochemistry showed hypocalcaemia [corrected calcium(cCa) 1.8mmol/L, ionized calcium(iCa) 0.86mmol/L], hyperphosphataemia (2.25mmol/L), low 25-hydroxyvitamin D [25(OH)D 19nmol/L], inappropriately-normal parathyroid hormone (PTH 6.8pmol/L), and normal renal function. Following intravenous calcium gluconate, oral calcium carbonate, calcitriol and colecalciferol supplementation, his cCa levels normalised, though phosphate remained elevated(2.26mmol/L). After stabilization post-diuresis, he was discharged on colecalciferol 2000IU, calcium carbonate 1000mg, aspirin 100mg, atorvastatin 80mg, bisoprolol 5mg, eplerenone 12.5mg, esomeprazole 20mg and frusemide 80mg daily.

On further assessment in Endocrinology clinic, Mr G exhibited no signs/symptoms of hypocalcaemia. History was unremarkable in regards to potential aetiologies, except for a family history of symptomatic hypocalcaemia in his younger sister and his brother, who had Angelman syndrome and a history of hypocalcaemic seizures. Historical biochemistry revealed chronic hypocalcaemia (cCa 1.9mmol/L, age 31). 24-hour urine collection demonstrated inappropriate hypercalciuria (11.7mmol/day), raising suspicion for Autosomal Dominant Hypocalcaemia (ADH). Screening for autoimmune and infiltrative causes of hypoparathyroidism, including neck ultrasound were unremarkable. Brain CT showed calcifications in multiple subcortical regions. Renal imaging revealed no nephrocalcinosis/nephrolithiasis.

Managing Mr. G's hypocalcaemia was challenging, as calcium and calcitriol supplementation worsened hyperphosphataemia and hypercalciuria, increasing the risk of renal complications and progressive basal ganglia calcification. As such, we

ensured normal vitamin D levels, and accepted mild asymptomatic hypocalcaemia. Calcium carbonate was prescribed with meals as a phosphate binder, and a low-phosphate diet was initiated with good effect.

Mr G's heart failure improved rapidly with correction of calcium and 25(OH)D levels alongside initiation of heart failure therapy, including empagliflozin and sacubitril/valsartan. At 6 months, LVEF had recovered to 53%. Frusemide and eplenerone were eventually ceased, allowing safe initiation of hydrochlorothiazide for hypercalciuria management.

Mr. G later discovered that his older maternal cousins had ADH-1. Following genetic counselling, he was diagnosed with the same, confirmed by a heterozygous mutation in the calcium-sensing receptor (CASR) gene. He was unfortunately deemed ineligible for the CALIBRATE trial for Encaleret due to recent heart failure.

Discussion

Hypoparathyroidism affects 37 per 100,000(1), majority are iatrogenic following neck surgery/irradiation or drug-related. Evaluation for non-iatrogenic hypoparathyroidism should include autoimmune, genetic and infiltrative conditions. Assessing family history can be pivotal to diagnosis. ADH is a rare genetic condition with a prevalence of 3.9 per 100,000(2).

Calcium homeostasis is regulated by PTH, vitamin D, and CaSR-mediated auto-regulation. A fall in iCa activates CaSR in the parathyroids and kidneys, stimulating PTH release and increasing urinary calcium reabsorption. PTH release restores normal calcium levels through promoting bone resorption, renal activation of 1,25 dihydroxyvitamin D, and gastrointestinal calcium absorption.

ADH-1 is caused by a gain-of-function mutation in the CaSR gene, increasing the receptor's sensitivity to calcium and suppressing PTH at lower levels of serum calcium. It is characterized by hypocalcaemia, inappropriately low PTH and hypercalciuria.

Calcium plays a key role in myocardial excitation-contraction coupling and relaxation. Meta-analysis of 43 studies(n=47 cases) showed significant association between hypocalcaemia and reduced LVEF(3). In hypocalcaemic heart failure, 48% of cases are caused by idiopathic hypoparathyroidism(4). Multiple case reports on hypocalcaemic heart failure have described rapid LVEF improvement with calcium correction(5, 6). Interestingly, two unrelated families with ADH and concomitant cardiomopathy share the same activating mutation P221L in the CASR gene(4, 7).

While our case also demonstrated LVEF recovery once calcium improved, the relative contribution of heart failure therapy versus calcium correction is unclear. It is possible his 25(OH)D deficiency resulted in acute worsening of chronic hypocalcaemia, precipitating his cardiac presentation.

Conventional therapy for hypoparathyroidism involves calcium and calcitriol supplementation, aiming to keep patients asymptomatic, calcium levels slightly below/in the lower range of normal, phosphate normal, avoid hypercalciuria, and prevent renal/extra-skeletal complications(1). In our case, this approach is limited by worsening hyperphosphataemia, hypercalciuria, and high pill burden. Ultimately, it fails to address the underlying pathophysiology of PTH deficiency in hypoparathyroidism, or the low calcium set-point in ADH.

Encaleret, a novel oral calcilytic and negative allosteric modulator of the CaSR, aims to reset the pathologically low calcium set-point in ADH. In a Phase 2b trial on 13 patients with ADH-1, it increased corrected calcium and PTH, reduced phosphate and urinary calcium, and maintained stability in pre-existing renal calcifications(8). It is currently undergoing phase 3 clinical trial (CALIBRATE).

PTH analogues, including PTH1-34/teriparatide, recombinant human PTH [rhPTH(1-84)], and Palopegteriparatide, have shown promising results in trials which included a small number of patients with ADH-1(9). Palopegteriparatide consists of PTH(1-34) transiently conjugated to methoxypolyethylene glycol, which is cleaved under physiological pH and temperature, allowing for sustained release of PTH(1-34). Compared to teriparatide, it has a longer half-life, and once-daily administration achieved stable PTH levels. In the phase 3 PaTHway trial (n=84 cases), 93% achieved independence from conventional therapy(10), though only one patient had ADH-1. While PTH replacement does not address the underlying CaSR overactivation in ADH and may worsen hypercalciuria, a case series reported reduced calciuria in three ADH-1 patients treated with rhPTH(1-84) monotherapy(9). Although rhPTH(1-84) is no longer commercially available, Palopegteriparatide remains a promising treatment option for ADH.

In summary, our case illustrates a rare genetic cause of hypoparathyroidism in a young man, presenting with non-ischemic cardiomyopathy in the setting of severe hypocalcaemia. While standard workup for cardiomyopathy remains essential, this case adds to the limited literature on hypocalcaemic heart failure. It also illustrates the limitations of conventional therapy and draw attention to the emerging therapies that target the pathophysiology of hypoparathyroidism and ADH.

Take home messages

- Causes of non-iatrogenic hypoparathyroidism including genetic, infiltrative, and autoimmune diseases
- Assessment of family history is important in the evaluation of non-iatrogenic hypoparathyroidism
- Hypocalcaemic heart failure is a rare but reversible cause of HFrEF, although it remains a diagnosis of exclusion after cardiomyopathy workup

- Conventional therapy with calcium/calcitriol supplementation is often limited by hypercalciuria/hyperphosphataemia/renal complications
- Novel therapies target the underlying pathophysiology of autosomal dominant hypocalcaemia/hypoparathyroidism

1. 1. Bilezikian JP. Hypoparathyroidism. J Clin Endocrinol Metab. 2020;105(6):1722-36.
2. 2. Roszko KL, Stapleton Smith LM, Sridhar AV, Roberts MS, Hartley IR, Gafni RI, et al. Autosomal Dominant Hypocalcemia Type 1: A Systematic Review. J Bone Miner Res. 2022;37(10):1926-35.
3. 3. Newman DB, Fidahussein SS, Kashiwagi DT, Kennel KA, Kashani KB, Wang Z, et al. Reversible cardiac dysfunction associated with hypocalcemia: a systematic review and meta-analysis of individual patient data. Heart Fail Rev. 2014;19(2):199-205.
4. 4. Guarnieri V, Valentina D'Elia A, Baorda F, Pazienza V, Benegiamo G, Stanziale P, et al. CASR gene activating mutations in two families with autosomal dominant hypocalcemia. Molecular Genetics and Metabolism. 2012;107(3):548-52.
5. 5. Kharel M, Subedi A, Hossain MF. Hypocalcemic cardiomyopathy with heart failure: A rare Case report. Clin Case Rep. 2024;12(9):e9463.
6. 6. Mapelli M, Nepitella AA, Ferdico S, Formenti A, Baggiano A, Campodonico J, et al. Hypocalcaemic cardiomyopathy presenting as heart failure exacerbation due to untreated primary hypoparathyroidism. ESC Heart Fail. 2025;12(1):708-16.
7. 7. Chikatsu N, Watanabe S, Takeuchi Y, Muraosa Y, Sasaki S, Oka Y, et al. A family of autosomal dominant hypocalcemia with an activating mutation of calcium-sensing receptor gene. Endocr J. 2003;50(1):91-6.
8. 8. Gafni RI, Hartley IR, Roszko KL, Nemeth EF, Pozo KA, Lombardi E, et al. Efficacy and Safety of Encaleret in Autosomal Dominant Hypocalcemia Type 1. N Engl J Med. 2023;389(13):1245-7.
9. 9. De Coster T, David K, Breckpot J, Decallonne B. Management of autosomal dominant hypocalcemia type 1: Literature review and clinical practice recommendations. J Endocrinol Invest. 2025;48(4):831-44.
10. 10. Khan AA, Rubin MR, Schwarz P, Vokes T, Shoback DM, Gagnon C, et al. Efficacy and Safety of Parathyroid Hormone Replacement With TransCon PTH in Hypoparathyroidism: 26-Week Results From the Phase 3 PaTHway Trial. J Bone Miner Res. 2023;38(1):14-25.

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'Too hard to ignore – an unusual case of Osteosclerosis'

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Clinical Record

A 31-year-old woman presented with acute-on-chronic abdominal pain, flushing, and watery diarrhoea. Her medical history was significant for polycystic ovarian syndrome, bipolar affective disorder (on lithium) and hidradenitis suppurativa.

Physical examination revealed a generally tender abdomen, with no skin rashes or lymphadenopathy identified. Stool cultures were unremarkable, and a computerised tomography (CT) scan of her abdomen did not demonstrate radiological evidence of colitis, but revealed diffuse, mottled bone sclerosis. This was found to involve the entirety of her axial and appendicular skeleton. There was no evidence of hepatosplenomegaly. She was discharged with a presumed diagnosis of infective colitis and followed up in the Endocrinology Metabolic Bone Clinic.

A subsequent nuclear medicine whole body bone single-photon emission CT (SPECT)/CT scan demonstrated the neck-tie sign of the sternum (Figure 1) and diffuse crisp radiotracer uptake throughout the rest of the skeleton consistent with a Superscan pattern, an image appearance representing intense osteoblastic activity (Figure 1)(1). The neck-tie sign is thought to represent expansion of the manubrium and sternal marrow without concurrent expansion of the manubriosternal joint, with increased tracer uptake on bone scintigraphy giving an appearance of a neck-tie(2).

Investigations for diffuse osteosclerosis ruled out malignancy (electrophoresis, flow cytometry and mammography) and urine fluoride was not elevated (1.2mg/L, ref <2.0), but revealed an elevated tryptase level of 126ug/L (reference range <11.4ug/L). Bone marrow biopsy yielded a "dry tap" aspirate with trephine demonstrating abnormal aggregates of spindle-shaped mast cells >15 in a group, with positive staining for tryptase and CD25. (Figure 2). No other haematological malignancy was

identified. Peripheral blood c-KIT D816V testing and all-haem NGS yielded no somatic variants. A diagnosis of systemic mastocytosis (SM) was made.

In the absence of 'B and C' findings, her disease was classified as indolent SM(Table 1,2). A bone mineral density scan revealed a significantly elevated Z-score of 2.9 at the left hip, and elevated bone formation maker [Procollagen type 1 N-terminal propetide 95mcg/L (ref 15-70mcg/L)], but normal bone resorption marker [C-terminal Telopeptide 480ng/L (ref 150-800ng/L)]. Treatment with a histamine type-2 receptor antagonist provided mild symptomatic relief.

Discussion:

In contrast to osteoporosis, osteosclerosis refers to abnormal hardening and progressive increase in skeletal bone mass either secondary to increased bone formation or decreased resorption(3). Although uncommon, it is an important clinical finding most often secondary to an underlying disease process – some with severe consequences if not appropriately investigated and diagnosed.

The most significant are of malignant (infiltrative lymphoma or leukaemia, osteoblastic metastases from solid tumours such as prostate and breast) or haematological (myelosclerosis, mastocytosis) origins(4). Other causes include congenital (osteopetrosis) and metabolic (hypoparathyroidism) [Table 3]. Given our patient's young age, it was imperative to exclude malignancy.

SM is an uncommon neoplastic disease of mast cells characterised by proliferation and accumulation in skin and other organs. It is diagnosed based upon minor and major criteria, and associated with a (5). Mast cells in bone marrow may secrete mediators that promote osteoclastic or osteoblastic activity. It should be considered as a differential diagnosis in any individual presenting with atopic symptoms and unexplained osteoporosis/osteosclerosis. Management of indolent and smouldering mastocytosis is aimed at symptom control, with cytoreductive therapies generally reserved for advanced SM to mitigate organ damage and extend survival(10).

Bone disease in mastocytosis is relatively common, with the understanding that proinflammatory mediators cause an imbalance of osteoclastic (histamine, heparin, tumour necrosis factor, and interleukin-6) or osteoblastic activity(6). Osteoporosis is more common (up to 50% total SM cases) (6), although osteosclerosis is reported in up

to 75% of cases with aggressive SM, which carries a poorer prognosis (median life expectancy of 41 months)(7). The pathophysiology for osteosclerotic development is thought to be due to an imbalance towards elevated IFN-Significantly elevated tryptase levels are also reported in association with osteosclerosis. In our patient, her lack of end-organ involvement classified her as indolent SM. However, regular surveillance is highly recommended to monitor for transformation.

Althought treatment of the underlying pathology remains key to reversing or preventing progression of other causes of osteosclerosis, published literature is limited in the context of A case report demonstrated resolution of osteosclerosis after allogenic stem cell haematopoetic stem cell transplant and subsequent cytoreductive therapy after one year (8). However, studies have predominantly addressed osteoporosis associated with SM. Review of the literature has suggested improved BMD and suppression of bone turnover markers after use with bisphosphonates, as well as Denosumab once alternative causes for osteoporosis have been considered(9). , evidence for anabolic agents is limited and not recommended due to the theoretical risk of worsening mast cell proliferation(6).

Currently, this patient's findings have remained stable on serial CT imaging over 14 months. It remains uncertain if osteosclerosis will reverse on her current . Further observational studies and outcomes from case reports of mastocytosis-induced osteosclerosis would be useful to better understand the disease trajectory and long-term complications.

Lessons from Practice:

- Osteosclerosis is an uncommon but important clinical finding to investigate given the wide array of differential diagnoses, some of which are associated with a poor prognosis
- Systemic mastocytosis should be considered in anyone with atopic symptoms and unexplained osteoporosis/osteosclerosis
- Treatment options for osteosclerosis are limited and current advice is to treat the underlying pathology
- Further studies are required to better understand the trajectory of bone density and long-term complications once osteosclerosis is identified

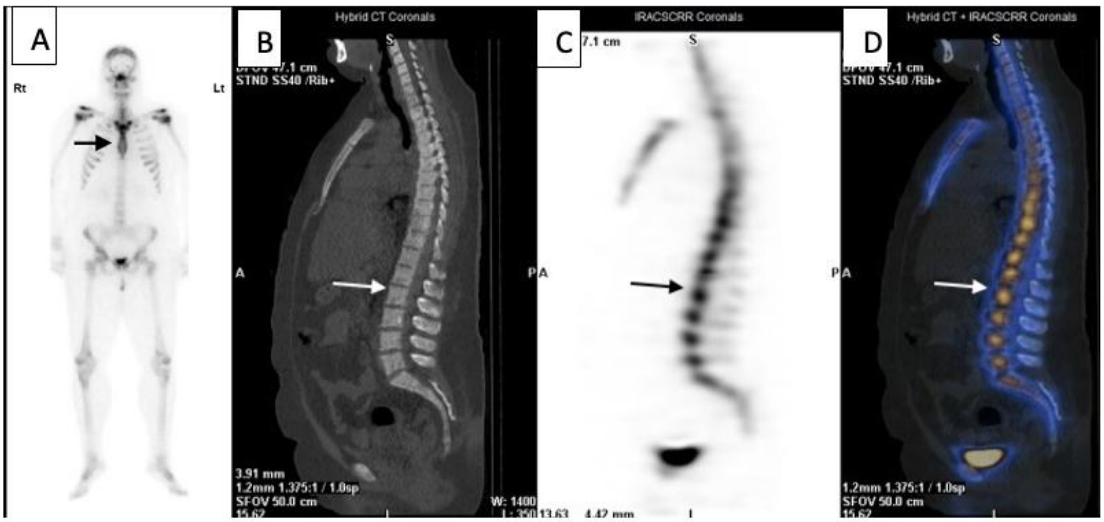

Figure 1:
Panel A: Neck-tie sign on bone scintigraphy; Panel B-D: diffuse crisp radiotracer uptake throughout the spine

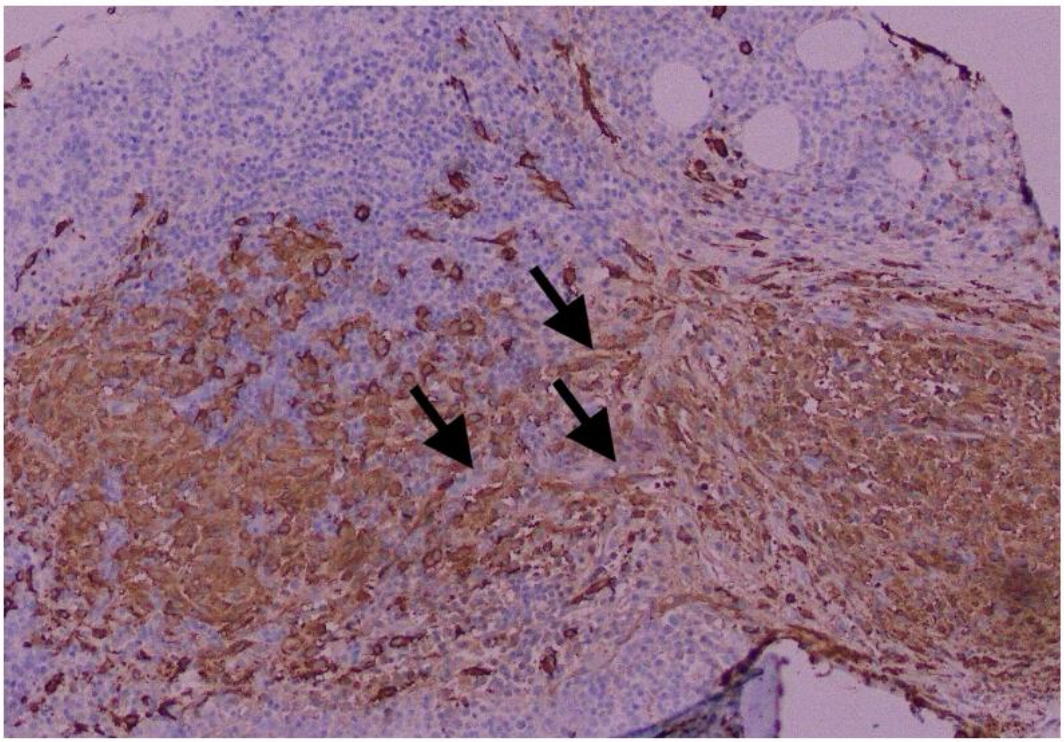

Figure 2: Trephine sample demonstrating spindle-shaped mast cells, with positive staining for tryptase

Table 1: WHO diagnostic criteria for systemic mastocytosis (SM)(10)

Major criterion
• Multifocal dense infiltrates of mast cells (≥15 mast cells in aggregates) in bone marrow biopsies and/or in sections of other extracutaneous organ(s)
Minor criteria
• ≥25% of all mast cells are atypical cells (type I or type II) on bone marrow smears or are spindle-shaped in mast cell infiltrates detected in sections of bone marrow or other extracutaneous organs
• KIT-activating KIT point mutation(s) at codon 816 or in other critical regions of KIT in bone marrow or another extracutaneous organ
• Mast cells in bone marrow, blood, or another extracutaneous organ express one or more of: CD2 and/or CD25 and/or CD30
• Baseline serum tryptase concentration > 20 ng/mL (in the case of an unrelated myeloid neoplasm, an elevated tryptase does not count as an SM criterion. In the case of a known HαT, the tryptase level should be adjusted
The diagnosis is SM if at least 1 major and 1 minor or 3 minor criteria are fulfilled

Table 2: 'B' and 'C' symptoms of mastocytosis (10)

B-findings
• High MC burden: Infiltration grade (MC) in BM ≥30% in histology (IHC) and/or serum tryptase ≥200 ng/mL and/or KIT D816V VAF ≥10% in BM or PB leukocytes
• Signs of myeloproliferation and/or myelodysplasia: Hypercellular BM with loss of fat cells and prominent myelopoiesis ± left shift and eosinophilia ± leukocytosis and eosinophilia and/or discrete signs of myelodysplasia (2 cm) C-findings
• Organomegaly: Palpable hepatomegaly without ascites or other signs of organ damage or/ and palpable splenomegaly without hypersplenism and without weight loss or/and lymphadenopathy palpable or visceral LN-enlargement found in ULS or CT (>2 cm)
C-findings
• Cytopenia/s: ANC <1 x 10^9/L, Hb<10g/dL, PLT<100 x 10^9/L (one or more found)
• Hepatopathy: Ascites and elevated liver enzymes ± hepatomegaly or cirrhotic liver ± portal hypertension
• Spleen: Palpable splenomegaly with hypersplenism ± weight loss ± hypalbuminemia
• GI tract: Malabsorption with hypoalbuminemia ± weight loss
• Bone: Large-sized osteolysis (≥2 cm) with pathologic fracture ± bone pain

Table 3: Differential diagnoses for osteosclerosis

Differential Diagnoses
Haematological disorders
Myelofibrosis
Sickle cell disease
Osteosclerosing multiple myeloma
Mastocytosis
Malignancy – osteoblastic metastases
Prostate and Breast
Lymphoma: infiltrative
Leukaemia: infiltrative
Metabolic
Renal osteodystrophy
Hyperthyroidism
Hypoparathyroidism
Poisoning
Fluorosis
Idiopathic
Paget disease
Congenital: sclerosing bone dysplasias
Osteopetrosis
Pyknodysostosis
Osteomesopyknosis
Other
Hepatitis C associated osteosclerosis (HCAO)

1. Askari E, Shakeri S, Roustaei H, Fotouhi M, Sadeghi R, Harsini S, et al. Superscan Pattern on Bone Scintigraphy: A Comprehensive Review. Diagnostics (Basel). 2024;14(19).

2. Buckley B, Chan VO, Mitchell DP, McDermott S, Eisenberg RL, Heffernan EJ, et al. The clothes maketh the sign. Insights Imaging. 2016;7(4):629-40.

3. Rama TA, Henriques AF, Matito A, Jara-Acevedo M, Caldas C, Mayado A, et al. Bone and Cytokine Markers Associated With Bone Disease in Systemic Mastocytosis. J Allergy Clin Immunol Pract. 2023 May;11(5):1536-1547. doi: 10.1016/j.jaip.2023.02.007.

4. Al Salam H YJ, Jones J. Generalized increased bone density in adults 2010 [Available from: https://radiopaedia.org/articles/12115.

5. Pardanani A. Systemic mastocytosis in adults: 2015 update on diagnosis, risk stratification, and management. Am J Hematol. 2015;90(3):250-62.

6. Wang M, Seibel MJ. Skin and bones: systemic mastocytosis and bone. Endocrinol Diabetes Metab Case Rep. 2023;2023(2).

7. Riffel P, Schwaab J, Lutz C, Naumann N, Metzgeroth G, Fabarius A, et al. An increased bone mineral density is an adverse prognostic factor in patients with systemic mastocytosis. J Cancer Res Clin Oncol. 2020;146(4):945-51.

8. Ustun C, Courville EL. Resolution of osteosclerosis after alloHCT in systemic mastocytosis. Blood. 2016 Apr 7;127(14):1836. doi: 10.1182/blood-2016-01-690669. PMID: 27512733.

9. Degboé Y, Nezzar C, Alary P, Maëva M, Bulai Livideanu C, Laroche M. Management of Bone Health in Adult Mastocytosis. Curr Osteoporos Rep. 2025 Feb 13;23(1):10. doi: 10.1007/s11914-025-00901-w. PMID: 39946039; PMCID: PMC11825596.

10. Pardanani A. Systemic mastocytosis in adults: 2023 update on diagnosis, risk stratification and management. Am J Hematol. 2023 Jul;98(7):1097-1116. doi: 10.1002/ajh.26962.

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When Hormones Meet Hypophosphatemia: the complex relationships of Iron, Phosphate, Periods, and Pregnancy in Autosomal Dominant Hypophosphataemic Rickets

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Autosomal dominant hypophosphatemic rickets (ADHR) is a rare disorder caused by heterozygous mutations in *FGF23*, resulting in a cleavage-resistant protein. Ongoing FGF23 signalling subsequently causes renal phosphate wasting and reduces $1,25(OH)_2D_3$ production, resulting in hypophosphatemia, secondary hyperparathyroidism, and osteomalacia. Iron deficiency worsens ADHR by upregulating *FGF23* expression, and the biochemical and clinical phenotype of ADHR can worsen at times of increased iron demand, such as menarche and pregnancy. Conversely, iron infusions (particularly iron carboxymaltose) can further lower phosphate levels. Clinically, ADHR manifests with bone pain, muscle weakness, skeletal deformities, and fractures; and, in contrast to X-linked hypophosphataemic rickets, is often worse in women.

Here we describe a family with three sisters with ADHR, and the pregnancies of two of these sisters. The family lives at substantial distance from the caring hospital.

The eldest has had three pregnancies, in addition to ADHR, an eating disorder, poor medication compliance, and chronic iron deficiency. During her first pregnancy, managed elsewhere, an iron infusion caused severe hypophosphataemia (0.19mmol/L) requiring admission and intravenous replacement. An emergency caesarean was performed at 36 weeks for foetal growth restriction. Her second pregnancy, managed collaboratively with our team and the obstetric physicians, was complicated by stress fractures in her tibia and metatarsals in her second trimester. Ongoing worrying severe hypophosphataemia was managed with oral phosphate (up to 6-8 Sandoz tablets/day), alfacalcidol (8 mcg/day); simultaneously, iron-deficiency anaemia was managed with oral iron (400 mg ferrous sulphate/day). Serum phosphate, adjusted-calcium and ferritin remained poorly responsive; however, the baby grew well and was delivered close to term, again by caesarean. Post-pregnancy, she was found to have multiple pseudofractures on bone scan. Treatment compliance was intermittent. She recently represented at four weeks' gestation, with phosphate 0.35mmol/L, ferritin 17µg/L, and 25(OH)D 22nmol/L and acknowledged she had not been taking any replacement. Treatment has been restarted.

The middle sister also had a recent pregnancy. Prior to this she had had multiple pseudo- or frank fractures, particularly of her metatarsals (she chose her school subjects according to classroom location to avoid stairs). During her pregnancy, she presented at 11 weeks' gestation with hypophosphatemia (0.6 mmol/L), low ferritin (16 µg/L), and 25(OH)D of 41 nmol/L. She was advised to take low doses of phosphate and alfacalcidol, cholecalciferol, and a combined iron/folate preparation (Fefol). However, compliance was tenuous. She reported unexplained 'blackouts' and was found to have phosphate <0.3mmol/L, the obstetric team hospitalised her for intravenous replacement. Her baby was delivered at term. Subsequently the baby has been found to have ADHR also.

The youngest sister also has classical biochemical and clinical features of ADHR, with phosphate levels 0.5-0.6mmol/L. Their father, the proband in this family, has low BMD (t-scores around -2.5 to -3) but has never fractured or had pseudofractures. His phosphate is typically low normal, or just below the reference range (0.6-0.8mmol/L).

These cases illustrate the challenges of managing ADHR in women, particularly in the context of nutritional deficiencies, eating disorders, and iron deficiency, all of which exacerbate phosphate wasting; and the impact of increased iron demands of menstruation and pregnancy. They also highlight the complexities of coordinating care across multiple clinical teams.

In the longer term, burosumab a monoclonal antibody targeting FGF23, might be considered. However, it is licensed for X-linked hypophosphataemic rickets in (non-pregnant) adults but not ADHR. The long-term bone health and future pregnancy outcomes for this family remain uncertain.

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Phenotypic primary hyperparathyroidism cured after focused parathyroidectomy in a patient with familial hypocalciuric hypercalcaemia

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Introduction

Familial hypocalciuric hypercalcemia (FHH) is an autosomal dominantly inherited condition which occurs secondary to inactivating mutations in the calcium sensing receptor (*CASR*) gene. The usual biochemical manifestations are mild elevations in the serum calcium and parathyroid hormone (PTH), resulting from alternation in the set point in CaSR to extracellular calcium level. It is a close differential diagnosis of primary hyperparathyroidism (PHPT) and is not amenable to surgical cure in contrast to that of PHPT. Hence, it is imperative to differentiate FHH from PHPT, typically by measurement of calcium creatinine clearance ratio (CCCR).

We here describe a patient harboring a *CASR* mutation, who presented with a PHPT phenotype: moderate-severe hypercalcemia, hypercalciuria, and imaging evidence of a solitary parathyroid adenoma. The hypercalcemia resolved after removal of the parathyroid adenoma and the patient is still in remission 16 months after the parathyroidectomy.

Case description

A 44-year female presented in April 2023 with incidentally detected hypercalcemia on routine blood testing. She had low mood, constipation, and polyuria, but without a history of kidney stones, fracture, or peptic ulcer disease. Her mother also had hyperparathyroidism with kidney stones and had undergone neck surgery; but the details were not available. There was no personal or family history of pituitary or pancreatic tumors. Biochemistry revealed PTH-medicated hypercalcemia with hypercalciuria confirming a diagnosis of PHPT (albumin adjusted serum calcium 3.07 [reference range 2.20-2.60] mmol/L, serum phosphorous 0.73 [reference range 0.8-1.5] mmol/L, plasma intact PTH 14.1 [reference range1.6-6.9] pmol/L, serum creatinine 51 [reference range 45-90] mmol/L, 24-hour urinary calcium 7.9 [age-specific normal <6.5] mmol, calcium creatinine clearance ratio 0.04).

Complication screening was negative for nephrolithiasis, nephrocalcinosis, and osteoporosis (Z-score at lumbar spine, femoral neck, and distal third radius were -1.2, -1.6, and -0.5 respectively). Localization studies using both ultrasonography and parathyroid-SPECT computed tomography revealed a concordant lesion suggestive of right superior parathyroid adenoma, with a maximum diameter of 24 mm. In view of the positive family history, genetic testing was done using a targeted next-generation sequencing, which revealed a known pathogenic heterozygous mutation in the *CASR* gene: c.73C>T, p.Arg25*. In view of moderate-severe hypercalcemia, hypercalciuria, and localization of a parathyroid adenoma, a decision for removal of right superior parathyroid adenoma was made in the multidisciplinary meeting.

While waiting for the surgery, she needed cinacalcet 60 mg/day for control of her symptomatic hypercalcemia. She was also treated for her vitamin D deficiency. A focused parathyroidectomy was done in March 2024 which led to normalization of her serum calcium (2.60 nmol/L) and PTH (7.0 pmol/L), in the immediate postoperative period. Histopathology confirmed a parathyroid adenoma. At the time of last follow up in July 2025, both her blood calcium and PTH were in the normal reference limits (2.56 mmol/L and 5.3 pmol/L respectively).

Conclusion and discussion

Patients with *CASR* mutations with a phenotype of PHPT have been rarely reported in the literature. These patients especially with moderate-severe hypercalcemia and hypercalciuria as in our patient, may benefit from a parathyroidectomy. Life-long monitoring is possibly needed to rule out future recurrence of hypercalcemia, which in turn may reveal a phenotype of FHH. The exact pathophysiology behind development of parathyroid adenoma in patients carrying *CASR* mutations is not known and needs further studies.

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Cardiovascular and Infectious Diseases are Key Drivers of Mortality After Fracture in Rheumatoid Arthritis

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Aim

Rheumatoid Arthritis (RA) has been associated with elevated post-fracture mortality, potentially due to its associated comorbidities. This study aimed to identify specific comorbidities driving post-fracture mortality in RA patients.

Methods

This case-control matched study was conducted using the West Australian Rheumatic Disease Epidemiological Registry (WARDER). 1075 RA patients with a potential fragility fracture presenting to WA hospitals between 1996 and 2010 were matched to 1156 rheumatic disease-free controls using age, year of first fracture, Accessibility Remoteness Index of Australia, sex, and the rheumatic disease version of the Charlson Comorbidity Index (CCI). Patients were followed for up to five years with COD categorised by system according to the International Classification of Disease.

Findings

RA was associated with significantly reduced survival post-fracture due to cardiovascular disease (CVD; HR 1.35, 95% CI 1.13–1.61, p=0.001) and infectious diseases (ID; HR 1.58, 95% CI 1.02–2.45, p=0.04). CVD mortality risk were elevated in patients with prior myocardial infarction (HR 1.46, 95% CI 1.09–1.97, p=0.01), while ID-mortality was increased in remote patients (HR 2.00, 95% CI 1.10–3.66, p=0.02) with chronic renal disease (HR 2.82, 95% CI 1.61–4.96, p<0.001).

Conclusion

RA patients experiencing fractures face a heightened risk of death from CVD and ID. Implementing strategies such as more intensive CVD surveillance in RA patients with a history of myocardial infarction or consideration of antibiotic prophylaxis in RA patients from remote regions with a history of chronic renal disease could reduce post-fracture mortality.

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A Robust SEM-BSE Workflow for Large-Field and High-Resolution Imaging of Skeletal Tissues

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Publish consent withheld

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Influence of initial fracture site on subsequent fracture at an Australian tertiary health service

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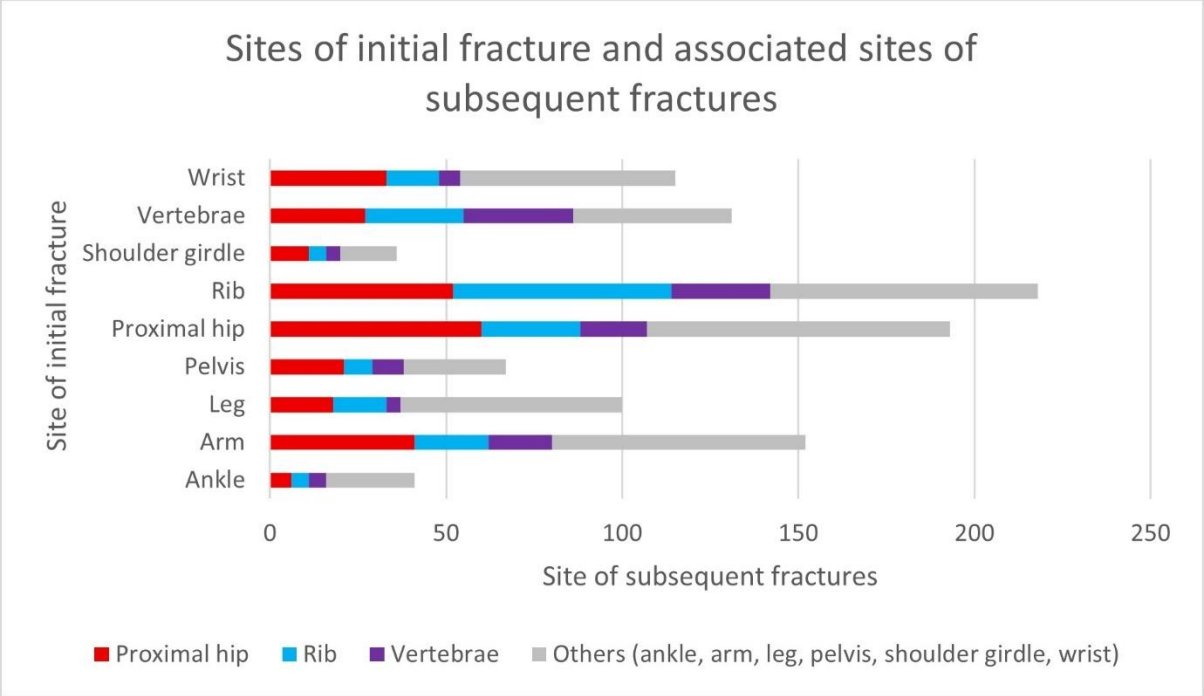

Aim

A fragility fracture is associated with high risk of subsequent fractures, and increased morbidity/mortality. This study aims to evaluate the predictors of re-fracture presentations at an Australian tertiary hospital.

Method

Adults(age>50 years) presenting with fractures to Western Health between 2018-2022 were identified through emergency department and hospital ICD-10-AM codes. Fractures of skull/hands/feet, and ICD-10-AM trauma codes were excluded. Re-fracture group was defined by fracture re-presentations until the year 2024. Data regarding demographics, fracture site, osteoporosis treatment, and osteoporosis clinic follow-up were extracted. Baseline characteristics between Re-fracture and Single-fracture cohort were compared, and predictors of re-fracture presentations were investigated.

Results

8462 cases sustained 9386 fractures over the study period. Hip fractures were the most common(n=1991), followed by rib(n=1428). 860(10.2%) re-presented with a subsequent fracture(Re-fracture group). Re-fracture group were older [median(range)age: 79(69 – 86) vs. 74(63 – 84), $p<0.0001$], with higher mortality rate (23.3% vs. 17.4%, $p<0.0001$) than Single-fracture group. Fractures were two-fold higher in females, although sex distribution was similar between groups. Highest rates of re-fracture were seen in European-born cases(12.4%). While incident vertebral, rib and pelvic fractures had the highest rates of re-fracture (14.1%, 13.9%, 12.6%, respectively), incident rib(n=218) and

hip fractures(n=193) accounted for the highest number of re-fracture presentations(Figure1). Most common sites of subsequent fractures were proximal hip(25.5%) and rib(17.8%). At subsequent fracture, 68% of Re-fracture cases were not on osteoporosis therapy, and 87% had not received osteoporosis specialist follow-up.

Conclusion

Traditionally, hip and vertebral fractures were considered the highest-risk sites for re-fracture. In our cohort, rib fractures were found to have one of the highest burdens of re-fracture hospital presentations. Osteoporosis treatment gap may differ between incident fracture site. Further investigations into determinants for re-fracture may assist healthcare services deliver targeted, timely interventions.

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Lactoferrin acts synergistically with flucloxacillin against mature *Staphylococcus aureus* biofilm in vitro

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Background: Biofilm formation is one of the primary pathogenic mechanisms of staphylococcal osteomyelitis, contributing significantly to the chronicity and recurrence of the infection. However, there is currently no effective treatment specifically targeting biofilm-associated infections. Lactoferrin, an 80-kDa iron-binding glycoprotein, possesses broad-spectrum antimicrobial and bactericidal activities. The aim of this study is to investigate the efficacy of lactoferrin in combination with flucloxacillin in eradicating staphylococcal biofilms.

Methods: A CDC Biofilm Reactor was utilized to cultivate mature *Staphylococcus aureus* Xen-36 biofilms on implant-grade stainless steel coupons for 3 days. Structurally stable biofilms were obtained through continuous replacement of nutrient-rich media and saline wash. The coupons were then randomly placed into treatment solutions of the control group, lactoferrin group, flucloxacillin group, and flucloxacillin–lactoferrin group for a 3-day synergy assay. Fresh treatment medium was replaced daily, and bacterial cells from both the culture media and coupons were collected and quantified using serial dilution plating to determine colony-forming units (CFUs). On this basis, a biodegradable Hydrogel-Niosome system was prepared to achieve

sustained drug release from a single application. Biofilm eradication of flucloxacillin and lactoferrin under this local delivery system was evaluated by CFU counting.

Results: The findings showed that the combination of flucloxacillin and lactoferrin significantly enhanced biofilm eradication efficacy. Co-administration of 80 mg/mL lactoferrin with flucloxacillin at concentrations of 20 µg/mL and 200 µg/mL resulted in a >6-log reduction in media CFU within two days, and mature biofilms on the metal coupon surfaces were almost completely eradicated after 3 days. This enhanced biofilm killing was observed in subsequent experiments with the Hydrogel-Niosome delivery system ($P < 0.05$), providing an effective approach for delivering lactoferrin and flucloxacillin to biofilms in vivo.

Conclusion: Lactoferrin can significantly enhance biofilm eradication in synergy with flucloxacillin, highlighting its potential in treating staphylococcal osteomyelitis.

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Knowledge, attitudes and intentions towards osteoporosis and other health conditions among older Australians

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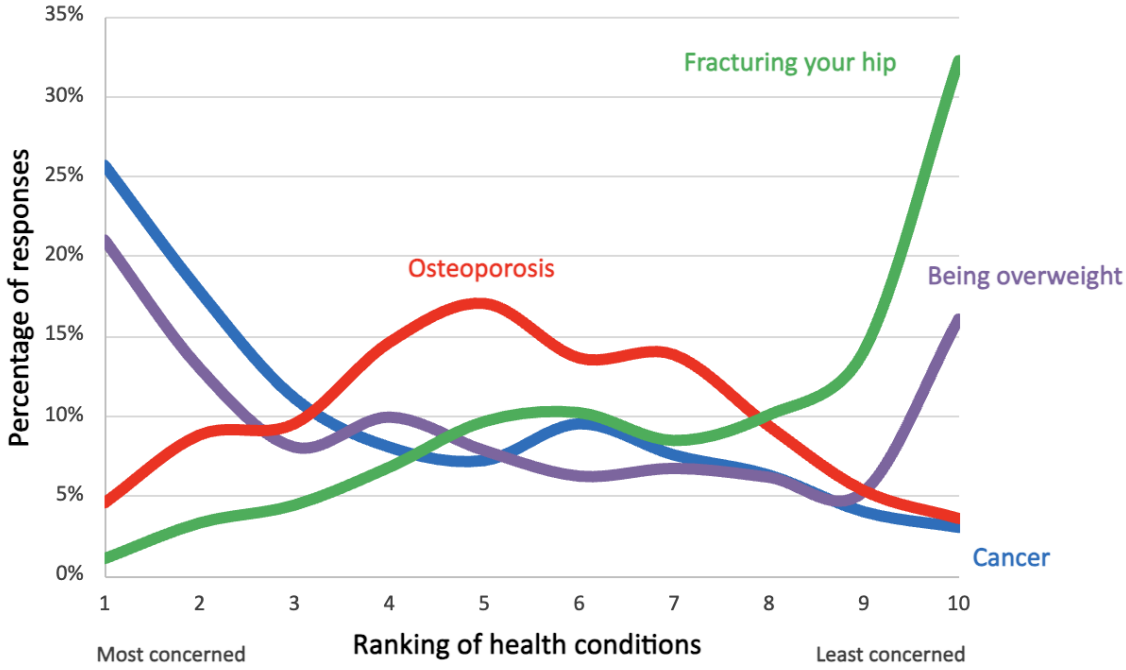

Background and Aims:

Osteoporosis burden is underdiagnosed and undertreated [1]. Increasing community awareness and education are recognised as priorities but there are limited studies assessing how older Australians view in relation to other health conditions. This study aimed to assess knowledge, attitudes and intentions towards osteoporosis in adults aged over 50 years.

Methods:

A validated online questionnaire, developed with an expert panel, was administered to 1460 healthy volunteers, aged 64.1 ± 9.6 years. The questionnaire assessed knowledge of osteoporosis risk factors (exercises, calcium sources, vitamin D deficiency, balance and falls) using a Likert scale. Attitudes and intentions to reduce their risk of osteoporosis and other health conditions were also assessed. Respondents were asked to rank health conditions from 1 (most concerned) to 10 (least concerned). Distinct rating responses for health conditions are displayed in Figure 1.

Results:

Correct responses to knowledge questions were highest for good sources of calcium (45%) and lowest for improving balancing and reducing fall exercises (17%). Misconceptions were common, with 54% and 49% of participants identifying walking and swimming respectively as beneficial for preventing osteoporosis. Cancer (25.7 %) and being overweight (21.0 %) were ranked as the primary health condition they were most concerned about, while only 4.5% ranked osteoporosis and 1.0% ranked fracturing a hip as their health condition most concerned about. When asked how they felt about osteoporosis, only 17.6% (n=252) ‘pay a lot of attention’ to reduce risk of

osteoporosis. Only 21.2% (n=310) were aware of Medicare rebates for bone density testing.

Conclusions:

The study identifies a concerning lack of awareness and knowledge about osteoporosis among older adults. These findings are consistent with a recent report recommending increased funding on public awareness [1]. ANZBMS should consider health promotion strategies to target discrete behaviours and address barriers and promoters for osteoporosis prevention.

1. [1] Bohingamu Mudiyanselage S, Watts JJ, Gebremariam K, Abimanyi-Ochom J, Osteoporosis and fractures in Australia. A burden of disease analysis, 2023 to 2033. Healthy Bones Australia 2024.

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Investigation on the permeability of 3D printed zirconia bone implants

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Bone tissue engineering has become a prominent research field in regenerative medicine attributed to the staggering frequency of bone disease, particularly in the ageing demographic. Excess overhead and risks of autoimmune responses to invasive surgeries are primary drivers of research into temporary three-dimensional structures for orthopaedics. The efficacy of these scaffolds is characterised by a combination of mechanical and biological behaviours correlated to their topological and material properties. However, current literature lacks consideration of critical mass transport quantified as permeability, and its effectiveness on tissue regrowth and cell infiltration. In response, this study developed four TPMS gyroid designs using Gaussian curvature as a design tool to encompass surface curvature and pore interconnectivity. The samples were designed at ~65% porosity with internal curvatures of 0 mm-2, -2 mm-2, -4 mm-2, and -6 mm-2 characteristic of trabecular bone. Experimentation involved zirconia partially stabilised (3Y-TZP) samples additively manufactured via stereolithography. Results indicated scaffolds of higher internal curvature performed the greatest over the range of experiments. Human osteoblast cells were observed to prefer concave and hyperboloid surfaces during in vitro testing. Proliferation of the -6mm-2 Gyroid (G6) scaffold were found comparable to the control scaffold (0 mm-2) over ten days. While all scaffolds emphasised shearing patterns during compression, the G6 exhibited superior compressive strength of 134 MPa, and a Young's Modulus of 0.7GPa associated with struts arched profiles that minimised stress concentrations. Permeability testing using viscous fluids established a distinctive

inverse relationship between scaffold fluid ingress and internal pore curvature. Increased fluid ingress was identified in -2mm-2 Gyroid (G2) and correlated to a decrease in curvature, improving free fluid flow through the scaffold. Overall, the findings presented critical relationships between permeability and scaffold efficacy, offering insights into Gaussian curvature as an effective design method.

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Reversible impact of cumulative cigarette smoking exposure and cessation on fragility fractures in older men

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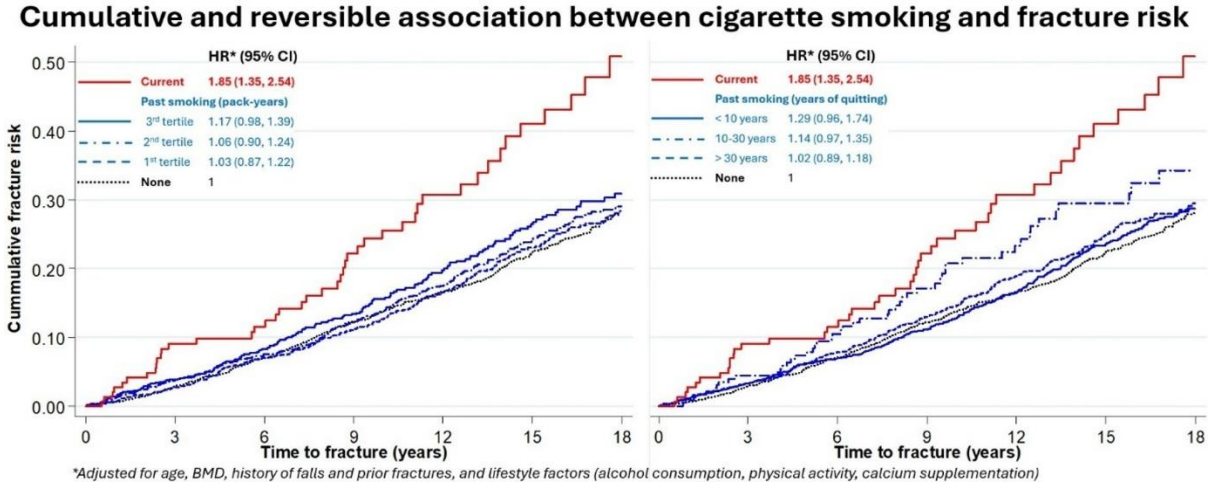
Regardless of the reported negative association between cigarette smoking and fragility fractures, the reversibility of this effect remains unclear. We determined the cumulative and reversible effects of cigarette smoking on fracture risk.

We analysed data of 5992 men (average age: 74± 5.9 years) from the Osteoporotic Fractures in Men Study in the USA. Smoking status (current, past, or never), cumulative smoking exposure (tertiles of pack-years) and time since cessation (<10, 10-30, >30 years) were self-reported, and fractures were radiologically confirmed. The main smoking exposure was categorised as current, past (by pack-years or time since quitting) or never. A Cox regression was used to estimate adjusted hazard ratios (aHRs) for incident fractures, adjusting for age, BMD, history of falls or prior fractures and lifestyle factors.

During a median follow-up of 12.4 years (IQR: 7.0-18.2), 1,084 participants sustained a fragility fracture (~14.5 fractures/1,000 person-years), including 237 hip fractures (3.2 hip fractures/1,000 person-years). At recruitment, 3.4% men currently smoked, while 59% were past smokers. Cigarette smoking had a dose-response association with fracture risk (Figure). Compared with nonsmokers, current smokers were independently associated with two-fold greater fracture risk (aHR: 1.85, 95% CI: 1.35-2.54). Among past smokers, those in the highest pack-year tertile or who had quit within the past 10 years tended to have 20-30% greater risk of fractures (1.17, 0.90-1.39, and 1.29, 0.96-1.74, respectively). However, past smokers with lower cumulative exposure or cessation beyond 10 years were not associated with fracture risk. A sensitivity analysis, accounting for competing mortality risks yielded similar, though attenuated, results. A

similar dose-response relationship was also found between smoking conditions and hip fractures.

The negative impact of cigarette smoking on bone fragility is reversible, suggesting that quitting smoking could substantially lower fracture risk. This underscores the importance of smoking cessation interventions for preventing fragility fractures in the community.



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An AI-Agent for Personalized Time to Repeat Bone Mineral Density measurement

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Background and Aim: The optimal interval for repeating bone mineral density (BMD) assessments remains unclear, contributing to global osteoporosis under-management. We developed the *Time to Osteoporosis* algorithm to personalize BMD reassessment intervals based on individual risk profiles. This model was integrated into **BONEcheckGPT**, an AI-powered conversational agent designed to facilitate clinical implementation and patient communication.

Methods: We used online data of participants from the Osteoporotic Fracture in Men Study in the USA (MrOS) and the Study of Osteoporotic Fractures (SOF) who had 2+ BMD measurements. The current analysis included 5298 men and 5169 women with an average age of 73.5 (±5.8) and 73.0 (±4.7) years, respectively. We developed a multistate Markov-Cox model to quantify individual transition risks toward osteoporosis or fragility fractures, accounting for confounders and competing mortality risks. Personalized "Time to Osteoporosis" was determined as the point when the predicted cumulative risk surpassed a clinical threshold, guiding optimal timing for repeat BMD assessment. This

algorithm was integrated into BONEcheckGPT, an AI agent that autonomously interprets user inputs and provides individualized risk estimates through prompt interactions.

Results: During a median follow-up of 14.1 years, 29.8% of participants developed osteoporosis or fragility fractures, and 41.7% died. Our predictive algorithm incorporates sex, age, baseline BMD, fracture history after age 50, and recent falls to estimate personalized intervals for repeat BMD measurements. For example, a 70-year-old woman with a T-score of –2.2 and a recent fall has a 23.6% predicted risk within 2 years, suggesting a repeat BMD in 1.3 years. Doctors and patients can easily obtain these personalized estimates using BONEcheckGPT[**https://bonecheck.org/ChatGPT**]; a demo is available here [**https://youtu.be/4il9pH-4rO4**].

Conclusions: We developed an AI agent for predicting osteoporosis risk and an optimal time to repeat BMD. The tool empowers informed decision-making and enhances doctor-patient risk communication, improving osteoporosis-related outcomes.

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Bone health outcomes in patients transitioning off denosumab therapy

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We conducted a retrospective audit at St Vincent's Hospital, Sydney, of all patients who attended the Bone and Calcium Clinic between January 2022-2025 and discontinued denosumab therapy.

Data collected included treatment duration, bone mineral density (BMD) at denosumab initiation and discontinuation, 1-year post-discontinuation BMD, and reason for cessation. Of the 40 patients included, 22 transitioned to non-anabolic agents, mainly due to lower fracture risk (younger age and/or BMD level) or treatment duration, while 18 switched to anabolic therapy, often after sustaining a fracture while on denosumab. All patients transitioning received at least 12 months of follow-up therapy or a single dose of zoledronic acid timed either with the next scheduled denosumab dose or three months prior.

Among patients transitioning to romosozumab, BMD changes were similar whether therapy overlapped with denosumab by 3 months (n=5) or not (n=12) (LS:4.62±7.72% vs 3.95 ± 5.81%;TH:-1.23±1.89 vs-1.03±4.18%). Elevated CTx >800 ng/L within 2 months of stopping denosumab, were associated with hip BMD loss (≥3%) in three patients transitioned to romosozumab. In contrast, two patients with CTx >800 ng/L later in therapy (8 months) who received immediate treatment with zoledronic acid or denosumab experienced smaller hip BMD declines (-1.3% and -2.4%).

Among 23 patients who discontinued denosumab due to age or treatment duration, one-year post-discontinuation BMD changes did not differ significantly between those treated with denosumab for >3.5 years and those treated for ≤3.5 years (LS -2.02±2.89% vs 3.62±2.08%;TH -1.60±1.38% vs-2.03±2.88%). Similarly, among 17 patients who ceased therapy following a fracture, total hip BMD changes were comparable between the >3.5- and ≤3.5-year groups (-0.45±3.07% vs -0.99 ±4.41%). Lumbar spine BMD was not assessed due to degenerative changes.

Although the sample size was small, bone loss appeared to be less in patients transitioning from denosumab to romosozumab compared to those transitioning to bisphosphonates.

Table 1: Clinical Characteristics and Outcomes

	Non-Anabolic (n=22)	Anabolic (n=18)	p value
Age	69.8 ± 8.0	81.2 ± 8.4	< 0.001
BMI	22.7 ± 3.3	23.7 ± 3.1	0.169
Female	21 (95%)	17 (94%)	-
Denosumab duration (years)	4.5 ± 2.5	5.3 ± 3.3	0.184
Fracture on denosumab	0	17	-
Transitional therapy	Risedronate n = 12 Alendronate n = 5 Zoledronic Acid n = 3 Oestradiol gel = 1	Romosozumab = 17 Teriparatide = 1	-
Baseline BMD prior to commencement of denosumab			
Lumbar Spine	0.91 ± 0.16	0.89 ± 0.15	0.359
Total Hip	0.77 ± 0.11	0.72 ± 0.11	0.103
Femoral Neck	0.73 ± 0.08	0.71 ± 0.07	0.218
% BMD change following treatment with denosumab (mean BMD change in g/cm²)			
Lumbar Spine	+9.8% (0.08 ± 0.06)	+9.9% [a] (0.08 ± 0.10)	0.387
Total Hip	+5.6% (0.04 ± 0.02)	+8.6% (0.06 ± 0.07)	0.175
Femoral Neck	+4.5% (0.03 ± 0.04)	+6.5% (0.04 ± 0.04)	0.284
% BMD change following transition from denosumab (mean BMD change in g/cm²)			
Lumbar Spine	-1.8% (-0.02 ± 0.03)	+3.1% [b] (0.03 ± 0.05)	0.001
Total Hip	-1.6% (-0.01 ± 0.01)	-0.3% (-0.00 ± 0.02)	0.071
Femoral Neck	-2.3% (-0.01 ± 0.02)	+0.8% (0.01 ± 0.02)	0.004
Individuals with clinically significant (≥3%) changes in site-specific BMD			
≥3% LS increase	1 (4.5%)	2[c] (11%)	-
≥3% TH increase	0 (0%)	3 (16.6%)	-
≥3% FN increase	1 (4.5%)	3 (16.6%)	-
≥3% LS decrease LS	7 (31.8%)	1 (4.5%)	-
≥3% TH decrease	4 (18.1%)	4 (18.1%)	-
≥3% FN decrease	7 (31.8%)	2 (11.1%)	-

a - 14/18 individuals had degenerative changes.
b - 14/18 individuals had degenerative changes. Excluding 1 individual who showed a 13% increase, the remaining 3 individuals demonstrated a mean increase of 2.6%.
c - Only 2/9 individuals LS BMD improvement ≥3% did not have degenerative changes.

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Disease burden and treatment patterns in adult patients with X-linked hypophosphataemia: results from an Australian clinician survey

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X-linked hypophosphataemia (XLH) is a hereditary FGF-23-mediated renal phosphate wasting syndrome. Adults with XLH experience progressive musculoskeletal/dental complications with substantial disease burden. Local data on disease prevalence, burden and treatment patterns in Australian adults with XLH are lacking.

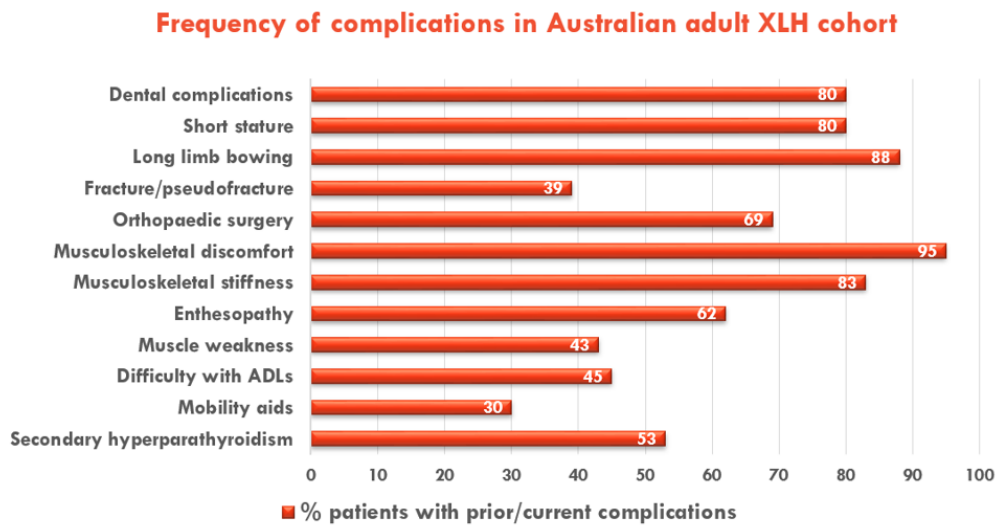
Australian clinicians who managed at least one adult (≥18yrs) with XLH in the past 10-years were invited to complete an online survey (REDCap) via society e-newsletters (e.g. ANZBMS, ESA) or direct invitation. XLH cases were defined as i) radiological evidence of

rickets and ii) fasting serum hypophosphataemia and iii) renal phosphate wasting (low TmP/GFR) and iv) any of *PHEX* pathogenic mutation, inappropriately elevated iFGF-23, or supportive family history.

Between August 2024-April 2025, data for 109-patients were recorded by 26-clinicians, including 55-patients with comprehensive clinical data. Patients were mean 45-years-old, mostly female (69%) and majority (75%) were diagnosed in infancy/childhood (≤5-years). Patients frequently suffered dental complications (abscess and/or extraction; 80%) (Fig1) however <50% had current dentist involvement. Musculoskeletal complications and functional limitations were common (Fig1), including difficulty performing ADLs (45%) and use of mobility aids (30%). However, only 11% accessed physio/occupational therapy. Majority (87%) received >5-years conventional therapy (phosphate and/or calcitriol), frequently limited by poor adherence and/or intolerance (30%). Forty-five patients received burosumab treatment (anti-FGF-23) which was discontinued in six patients due to restless legs (n=2), poor adherence (n=2), constipation (n=1) and pregnancy (n=1). Most patients (>80%) on burosumab had a global clinician assessment of "marked" or "moderate" improvement in physical function and quality-of-life.

Australian adults with XLH are frequently burdened by dental/musculoskeletal complications and functional limitation, however multidisciplinary care may be under-utilised. In this real-world cohort, burosumab is well-tolerated and associated with meaningful improvement in clinician-assessed physical function and quality-of-life. Further ascertainment of prevalence, disease burden and treatment patterns will facilitate more informed treatment strategies for our national adult XLH cohort.

Figure 1 – Frequency of complications in Australian adult XLH cohort



XLH = X-linked hypophosphataemia; ADLs = activities of daily living.

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Determinants of REMS Femoral Neck Fragility Score

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2. St Vincent's Hospital, Sydney

Background: Radiofrequency Echographic Multi Spectrometry (REMS) is a radiation-free ultrasound technology that assesses bone mineral density (BMD), T-score, Z-score, and a derived 'Fragility Score' (FS). REMS analyses reflected backscattered ultrasound signals through a database of spectral models matched by gender, age, site, and Body Mass Index (BMI). The FS estimates skeletal fragility and is derived from analyses of REMS spectra in segmented bone regions of interest (ROI). Each radiofrequency segment is classified as 'frail' or 'non-frail' based on the similarity to the frequency spectrum of two age-matched frail and non-frail data sets. For each ROI, the FS value is defined as the percentage of the analysed RF portions that were classified as 'frail'. The FS value for the patient is the average of the FS in all the ROI values of the bone scanned.[1]

Methods: Forty participants were scanned using REMS. The femoral neck (FN) FS (FNFS) was analysed in linear and multiple regression with age, weight, height and REMS FN BMD (REMS-FNBMD) as the independent variables. FNFS was also compared with FRAX estimate derived using the REMS-FNBMD.

Findings: Age was the strongest predictor of FNFS. Polynomial regression of degree two best fitted the relationship, with age accounting for 98% of the observed variance. In multiple regression analysis, age, weight, height, and REMS-FNBMD were weak independent predictors of FNFS. FNFS was positively correlated with FRAX. However, as FRAX is also strongly age-dependent, further analyses are necessary to determine the age-independent relationship.

Conclusions: REMS FNFS is strongly dependent on age. Weight, height and REMS-FNBMD are weak independent predictors. These findings underscore the necessity of a clearer understanding of how skeletal and non-skeletal factors influence REMS-derived scores. Further prospective studies are required to assess the utility of Fragility Score in fracture prediction.

1. Pisani, P., Conversano, F., Muratore, M., Adami, G., Brandi, M. L., Caffarelli, C., Casciaro, E., Di Paola, M., Franchini, R., Gatti, D., Gonnelli, S., Guglielmi, G., Lombardi, F. A., Natale, A., Testini, V., & Casciaro, S. (2023). Fragility Score: a REMS-based indicator for the prediction of incident fragility fractures at 5 years. Aging Clinical and Experimental Research. https://doi.org/10.1007/s40520-023-02358-2

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Calcium Isotope Markers (CIM): A Novel Tool for Early Detection and Monitoring of Osteoporosis

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Osteoporosis diagnosis and monitoring are still constrained by diagnostic methods that assess bone mineral density (DXA) or infer bone turnover through indirect biochemical markers. We present an emerging biomarker based on naturally occurring stable calcium (Ca) isotopes in blood and urine that provides a direct, sensitive, and non-invasive indicator of bone calcium balance .

This method avoids the use of radioactive tracers. Instead, it relies on high-precision measurement of the ratio of stable Ca isotopes ($\delta^{44/42}$Ca). Because lighter isotopes (e.g., ^{42}Ca) are preferentially incorporated into bone during mineralisation, bone formation results in higher $\delta^{44/42}$Ca values in extracellular fluids, while bone resorption leads to lower $\delta^{44/42}$Ca values in serum and urine. These values are compared to established threshold levels to determine whether an individual is in a state of net bone gain or loss.

Recent clinical studies demonstrate that Ca isotope ratios, known as Calcium Isotope Markers (CIM), correlate with established bone turnover markers (e.g., P1NP, β-CTX-I) and respond rapidly to treatment with antiresorptives such as denosumab. Changes in CIM values can be detected within 1 to 2 weeks, enabling earlier insight into treatment response than either DXA or common BTMs, which typically require 8 to 12 weeks to reflect changes.

This presentation will outline the physiological principles of Ca isotope fractionation, analytical workflow, and clinical data demonstrating its clinical relevance. CIM offers a robust, minimally invasive, and reproducible method that is not influenced by peptide degradation or short-term variability.

By capturing real-time shifts in skeletal Ca metabolism, Ca isotope analysis has the potential to significantly improve the diagnosis and monitoring of osteoporosis, allowing earlier intervention, personalised treatment adjustment, and improved long-term outcomes for patients at risk of fracture or suboptimal therapeutic response.

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Decoupling calcified cartilage from cortical bone reveals distinct mineralisation patterns in an osteoarthritis mouse model

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Introduction: Cortical thickening and calcified cartilage enlargement are hallmark features of osteoarthritis (OA)[1]. Conventional microCT systems lack a monochromatic beam and use energy integrating detectors which makes it challenging to delineate calcified cartilage from cortical bone. In this study, we apply contrast-enhanced synchrotron-radiation micro-computed tomography (SR-microCT) with articular cartilage staining, to delineate cortical bone and calcified cartilage and quantify their structural and compositional change across disease stages in a murine model of spontaneous OA.

Methods: Tibiae from STR/ort (OA, n = 16) and CBA/1 (control, n = 16) mice were obtained from a previous study[3]. Samples were incubated in an anionic contrast agent solution (Hexabrix™) and imaged in a humidity chamber[4] using SR-microCT (X02DA-TOMCAT beamline, Switzerland[5]) at 3 µm voxel size. Articular cartilage and subchondral mineralised tissues were segmented. Calcified cartilage was defined as low-attenuating mineralised tissue beneath articular cartilage and separated from underlying cortical bone using a dual-thresholding approach. Three-dimensional morphometric and attenuation-based compositional metrics were extracted. Group comparisons were performed using generalised least squares (GLS) regression with ANOVA-style post-hoc tests.

Results: Representative SR-microCT image (Fig.1a) illustrates clear delineation of the osteochondral interface, including a distinct calcified cartilage layer (Fig.1b). Quantitative analysis revealed that mean X-ray attenuation in cortical bone (Fig.1c,e) is approximately twice that of calcified cartilage (Fig.1d,f), suggesting lower mineralisation in the latter and contrary to results suggested by Raman spectroscopy[6]. Notably, calcified cartilage showed significant, stage-dependent increases in attenuation, consistent with increasing mineralisation previously reported using X-ray scattering[7]. In contrast, cortical bone attenuation showed minimal sensitivity to age and disease progression.

Conclusion: Delineating calcified cartilage using SR-microCT enabled assessment of its mineral content, revealing distinct mineralisation patterns from cortical bone during OA progression.

Acknowledgement: We thank the TOMCAT beamline staff for their support. This project received funding from several schemes[8,9,10].

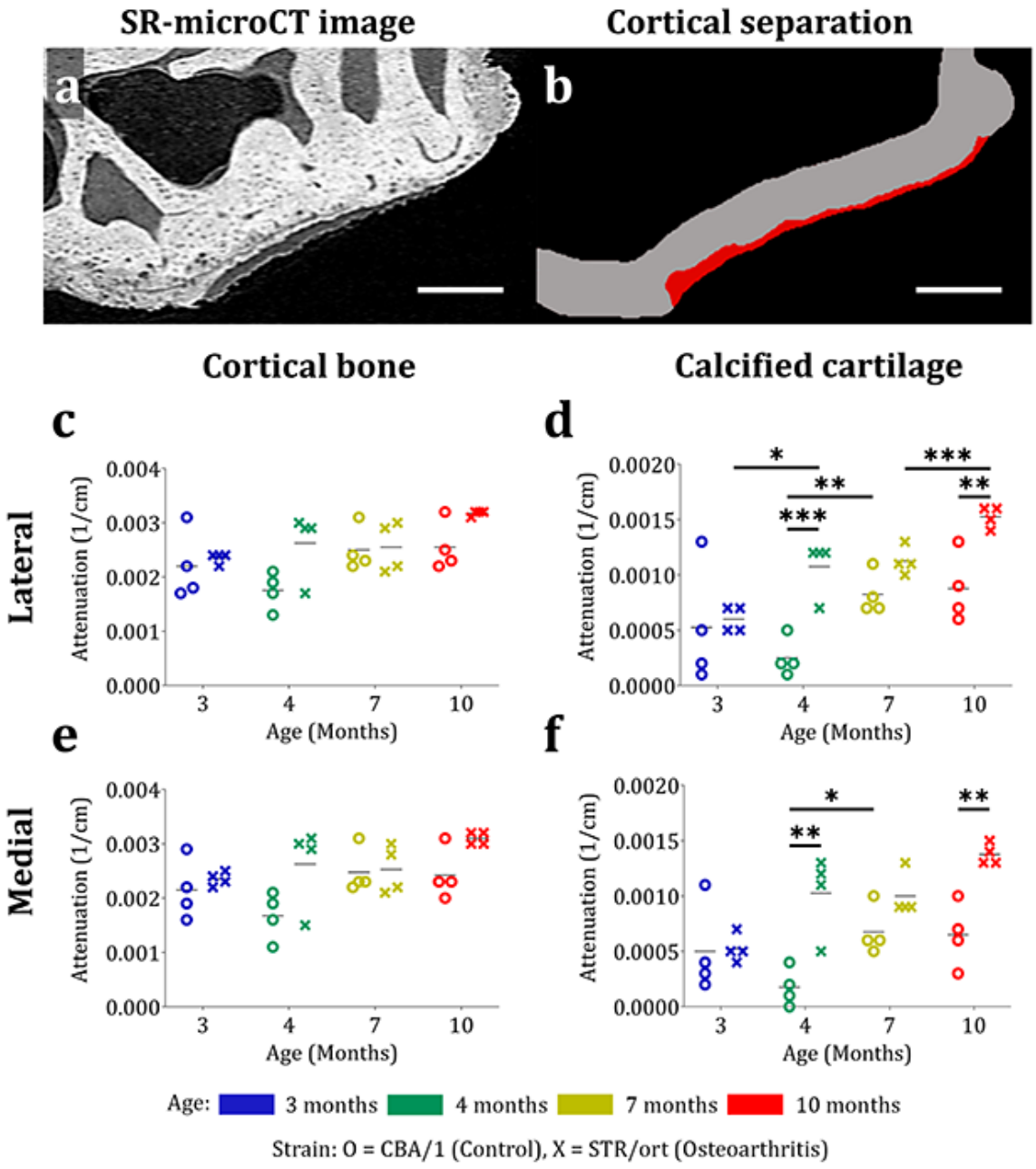

Figure 1: *(a) Representative contrast-enhanced SR-microCT image of a 3-month-old CBA/1 (control) mouse tibia showing the medial epiphyseal region. (b) Calcified cartilage (red) and cortical bone (gray) masks extracted using a dual-thresholding approach. (c–f) Extracted mean attenuation values for cortical bone and calcified cartilage, across lateral (c-d) and medial (e-f) compartments. Scale bar: 200 µm.*

1. Goldring, S. R. Therapeutic Advances in Musculoskeletal Disease 4, 249–258 (2012).

2. Madi, K. et al. Nature Biomedical Engineering 4, 343–354 (2019).
3. Stok, K. S. et al. Bone 45, 414–422 (2009).
4. Choo, R. J. et al. Review of Scientific Instruments 84, (2013).
5. Stampanoni, M. et al. Developments in X-Ray Tomography V vol. 6318 (2006).
6. Das Gupta, S. et al. Acta Biomaterialia 106, (2020).
7. Finnilä, M. A. J. et al. Journal of Bone and Mineral Research 37, 1700–1710 (2022).
8. FWO and F.R.S.-FNRS under the Excellence of Science program (EOS-No.40007553).
9. EU Shared-Cost RTD Action (QLK3-CT-2002-02039).
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Automated abdominal aortic calcification and trabecular bone score independently predict incident fracture during routine osteoporosis screening

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Publish consent withheld

1. 1.Gebre et al. Abdominal Aortic Calcification, Bone Mineral Density, and Fractures: A Systematic Review and Meta-analysis of Observational Studies. J Gerontol A Biol Sci Med Sci. PMID 36000920.

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Regulation of Bone and Cartilage Metabolism by Supersulfides and Their Therapeutic Potential

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Background:
Polysulfides, a class of molecules containing multiple sulfur atoms, have recently been identified as biologically active species involved in alternative sulfur respiration and other physiological functions. This study aimed to investigate the role of cysteinyl-tRNA synthetase 2 (CARS2), a key enzyme for polysulfide production, in bone and cartilage metabolism.

Methods:
We employed a tibial fracture model using *Cars2* mutant mice (*Cars2*$^{AINK/+}$) and wild-type littermates (*Cars2*$^{+/+}$). Histological analysis, bulk RNA-seq, and qRT-PCR were performed on the fracture callus at 2 weeks post-operation. In an osteoarthritis (OA) model, histological evaluation was conducted 16 weeks after surgery, and intra-articular administration of the polysulfide molecule GSSSG was assessed. In vitro, primary mouse synovial fibroblasts were treated with IL-1β and polysulfides, followed by qRT-PCR. Sulfur metabolomics using LC-ESI-MS/MS was performed on synovial and cartilage tissues from both genotypes. Uptake of GSSSG was evaluated in ATDC5 cells using stable isotope-labeled GSSSG.

Results:
Cars2$^{AINK/+}$ mice showed delayed callus formation in the fracture model. Transcriptomic analyses revealed upregulation of inflammatory SASP-related genes and downregulation of endochondral ossification markers. In the OA model, disease progression was significantly accelerated in *Cars2*$^{AINK/+}$ mice. Conversely, administration of 30 μM GSSSG significantly suppressed OA progression in wild-type mice. GSSSG also reduced IL-1β-induced inflammatory gene expression in synovial fibroblasts. Sulfur metabolomics indicated decreased levels of reactive sulfur species and polysulfide metabolites in *Cars2*$^{AINK/+}$ synovium and cartilage. In ATDC5 cells, only GSSSG treatment elevated intracellular reactive sulfur levels, with isotope tracing confirming cellular uptake of exogenous sulfur from labeled GSSSG.

Conclusion:
CARS2-derived polysulfides, particularly GSSSG, may suppress OA-related inflammation and lipid peroxidation, potentially by inhibiting ferroptosis. This study highlights the anti-inflammatory and antioxidant roles of polysulfides in the musculoskeletal system and suggests their therapeutic relevance in fracture healing and OA treatment.

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Bone health in heart transplantation: a Melbourne perspective revealed a higher rate of post-transplant fractures in females which occurred earlier than in males despite antiresorptive therapy and preserving bone density those who received it.

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To evaluate bone health outcomes of cardiac transplant recipients given the known bone density loss and fragility fractures in this cohort (1). The primary outcome was effect of antiresorptive therapy (treatment) on incidence of post-transplant fragility fractures. Secondary outcomes included the treatment impact on bone mineral density (BMD) and adverse events.

This retrospective cohort study included 196 adult patients (mean age 48 ± 12.9 years; 30.1% female) who underwent heart transplantation between 2012 and 2021 at the Alfred Hospital in Melbourne. Patient data were extracted from medical records.

Fragility fractures occurred in, 21 patients (10.7%) with a post-transplant fracture rate of 9.2% (18 patients).

Those treated had significantly lower baseline BMD (Table 1a). Treatment attenuated BMD loss at 12- and 24-months post-transplant at all sites (Table 1b) but fracture rates were equal in both treatment-naïve (9.2%, 7/76) and treatment-exposed (9.4%, 11/117) groups. Treatment naïve patients lost BMD most significantly in the first 12 months after transplant, with 4% BMD loss in the spine (figure 1), 7% in total hip (figure 2) and 5% in femoral neck (figure 3) compared with those treated (95% CI 0.26 range, $p<0.001$).

Females fractured significantly more often and earlier than males (19.0% vs 5.2%, $p = 0.006$) (mean fracture-free survival 3,295 vs 3,918 days, $p=0.001$) even after adjusting for age, rejection rates and treatment.

In this real-world cohort, antiresorptive therapy attenuated BMD loss but did not reduce fracture incidence in adult heart transplant recipients, likely due to selection bias where high risk patients were preferentially treated. Female recipients had a higher and earlier risk of fractures.

These findings support a need for proactive bone health management in cardiac transplant recipients, particularly for female patients who represent a vulnerable and

high-risk group. This is in line with international guidelines' recommendations for an individualised approach (2).

Table 1a	Mean ± Standard Deviation		P Value
	Antiresorptive therapy naïve	Antiresorptive therapy exposed	Antiresorptive naïve vs exposed
Baseline BMD Spine (g/cm2)	1.09 ± 0.172	0.88 ± 0.187	<0.01
Baseline BMD Femoral Neck (g/cm2)	0.911 ± 0.183	0.722 ± 0.140	<0.01
Baseline BMD Hip (g/cm2)	0.994 ± 0.148	0.829 ± 0.157	<0.01
Table 1b			
Change in lumbar spine BMD at 12 months	-0.044 ± 0.078	0.007 ± 0.082	0.004
Change in lumbar spine at 24 months	-0.055 ± 0.111	0.024 ± 0.096	<0.001
Change in femoral neck at 12 months	-0.722 ± 0.083	-0.031 ± 0.067	0.01
Change in femoral neck at 24 months	-0.087 ± 0.092	-0.027 ± 0.074	0.003
Change in total hip at 12 months	-0.072 ± 0.072	-0.02 ± 0.050	<0.001
Change in total hip at 24 months	-0.064 ± 0.099	-0.009 ± 0.075	0.014

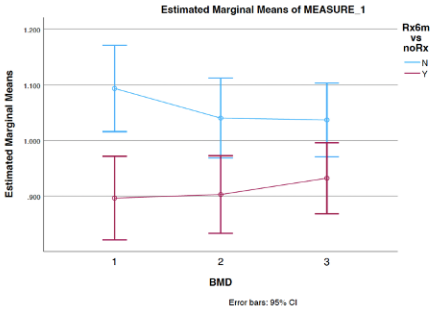

Figure 1: BMD Spine at baseline, 12mo and 24mo post-transplant

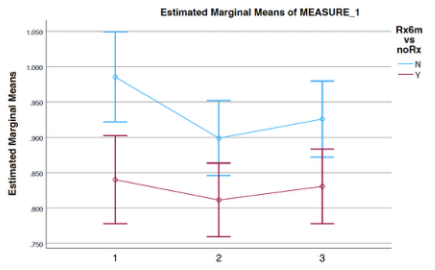

Figure 2: BMD total hip at baseline, 12moand 24mo post-transplant

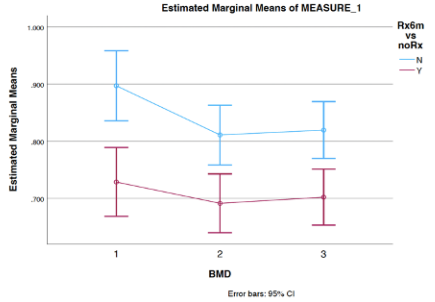

Figure 3: BMD Femoral neck at baseline, 12mo and 48h post-transplant

1. Leidig-Bruckner G, Hosch S, Dodidou P, Ritschel D, Conradt C, Klose C, et al. Frequency and predictors of osteoporotic fractures after cardiac or liver transplantation: a follow-up study. The Lancet. 2001;357(9253):342-7.

2. Velleca A, et al. The International Society for Heart and Lung Transplantation (ISHLT) guidelines for the care of heart transplant recipients. J Heart Lung Transplant. 2023 May;42(5):e1-e141. doi: 10.1016/j.healun.2022.10.015. Epub 2022 Dec 20. PMID: 37080658.

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In Vivo Profiling of Osteoclast Gene Expression Using a Novel Binary Cre - RiboTag System

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Osteoclasts are multinucleated cells that resorb bone and contribute to bone remodeling and skeletal diseases. Although comprehensive functional analysis of osteoclasts is highly desired, their multinucleated nature and strong adherence to the bone surface make it technically challenging to isolate them from tissue for transcriptomic analyses. To overcome this limitation, we developed a novel strategy that enables osteoclast-specific gene expression profiling without requiring cell isolation.

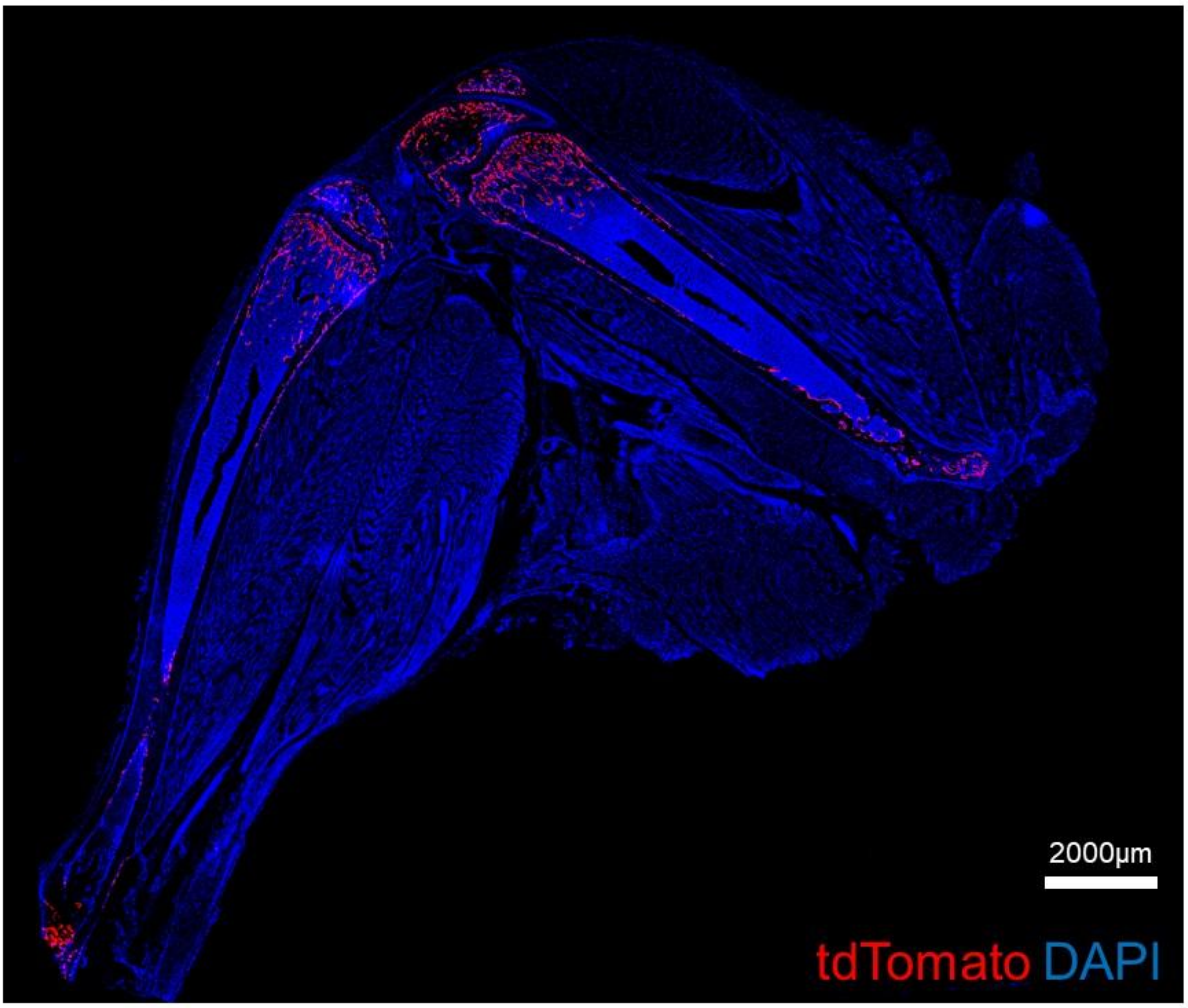
We generated a binary Cre recombinase system by splitting Cre into N-terminal (nCre) and C-terminal (cCre) fragments and knocking each into the *Ctsk* and *Acp5* gene loci, respectively. This design ensures Cre activity only in mature osteoclasts co-expressing both genes. These mice (Binary Cre) were crossed with $Rosa26^{tdTomato}$ mice to validate tissue specificity (Fig.1) and with $Rpl22^{HA}$ (RiboTag) mice to enable HA-tag labeling of ribosomes specifically in osteoclasts. Immunohistochemistry confirmed tdTomato expression exclusively in $TRAP^{+}$ multinucleated osteoclasts, with negligible signal in non-skeletal tissues. Using bone tissue from Binary Cre; RiboTag mice, we isolated HA-labeled ribosomes via anti-HA immunoprecipitation and extracted mRNA for bulk RNA-seq analysis. The results revealed highly enriched expression of canonical osteoclast markers including *Ctsk* and *Acp5*. RNA integrity numbers (RIN) were consistently in the range of 6–7, supporting the feasibility of transcriptomic analysis from bone tissue.

Conventional Cre lines frequently used in osteoclast research, such as $Rank^{Cre}$, $LysM^{Cre}$, and $Ctsk^{Cre}$, exhibit substantial off-target activity in non-osteoclastic cells, making them unsuitable for transcriptomic applications requiring high cell-type specificity. In

contrast, the newly developed Binary Cre system achieves stringent osteoclast specificity, thereby enabling precise mRNA isolation from osteoclasts in vivo.

This system enables high-fidelity, in vivo transcriptomic profiling of osteoclasts under physiological and pathological conditions. Our method represents a powerful new platform to explore osteoclast behavior and to identify novel therapeutic targets for skeletal disorders.

(Fig.1)



$Ctsk^{nCre/+}; Acp5^{cCre/+}; R26^{tdTomato/+}$

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Meclozine and growth hormone ameliorate bone length and quality in experimental models of achondroplasia

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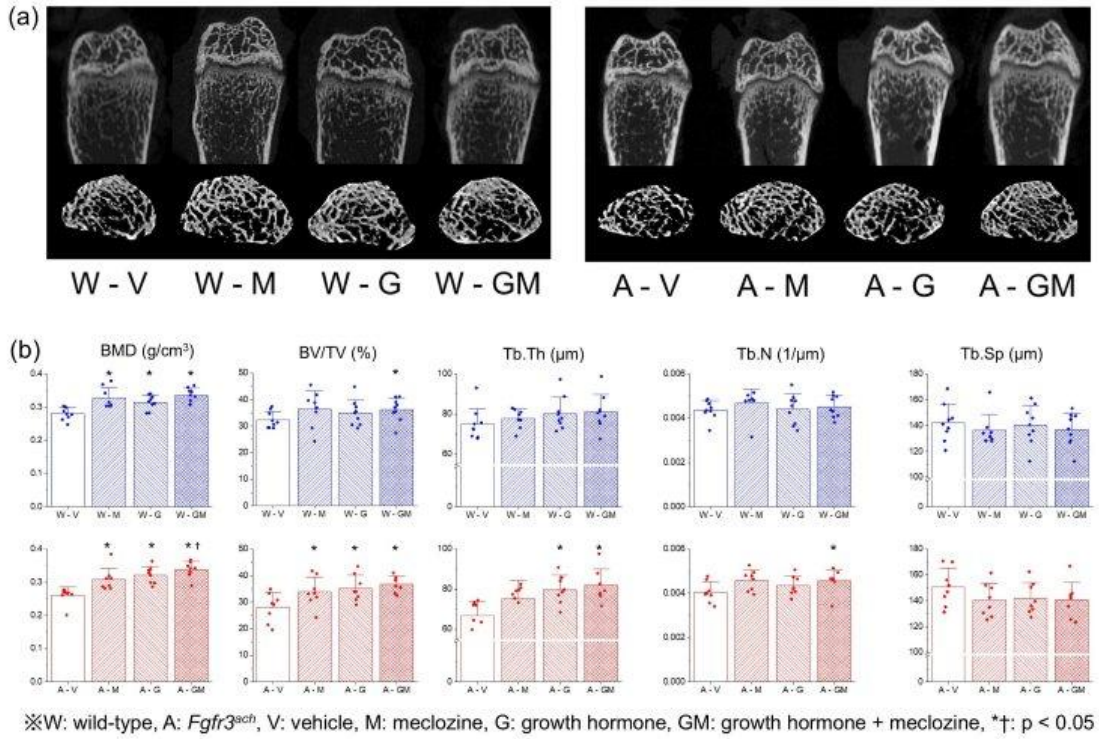
Introduction Achondroplasia (ACH) is a common skeletal dysplasia associated with short-limbed short stature caused by gain-of-function mutations in the fibroblast growth factor receptor 3 (*FGFR3*) gene. Meclozine was found to inhibit FGFR3 signaling using a drug repositioning strategy. In some countries, growth hormone (GH) has been employed to ameliorate short stature in children with ACH. This study aims to investigate the effects of meclozine and GH on bone growth and quality using an experimental model of ACH.

Materials and methods Meclozine (2 mg/kg/day) and/or GH (0.35 mg/kg/day) were administered to a mouse model of ACH from the age of 7 to 56 days. Body length and body weight of each mouse were measured during these treatments. At the end of treatments, these mice were subjected to microcomputed tomography (μCT) scans to measure the lengths of long bones and bone mineral density (BMD). The width of growth plate was quantified by histological analysis.

Results The body and bone length of transgenic mice significantly increased after treatment with meclozine and GH, although there was no additive effect of the combination therapy on promoting bone growth. In contrast, BMD was additively increased by the combination therapy. The width of the growth plate in transgenic mice was significantly increased by both treatments, although the hypertrophic zone was enlarged by meclozine but not by GH.

Conclusion Meclozine or GH may be an option for treating children with ACH to ameliorate bone length and quality, but the additive effect would be limited.

Figure legends Microstructure analysis of the distal femur in each mice after combination treatment. (a) Representative μ-CT images of the trabecular bone at the end of treatment. (b) Bar charts with plots of the trabecular bone parameters.



※W: wild-type, A: *Fgfr3*^{ach}, V: vehicle, M: meclozine, G: growth hormone, GM: growth hormone + meclozine, *†: $p < 0.05$

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3D Shaper in Monitoring Bone Loss in Lung Transplant Patients

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Background: Bone loss is a well-recognized complication in lung transplant recipients, primarily due to immunosuppressive therapy which often includes long-term corticosteroid therapy. Standard clinical assessment of proximal femoral bone loss currently relies on dual-energy X-ray absorptiometry (DXA) to measure areal bone mineral density (aBMD), particularly at the total proximal femur (TPF; considered the optimal site to monitor hip aBMD). However, DXA provides limited information about bone geometry and volumetric bone mineral density (vBMD), potentially underestimating early or subtle bone loss.

Objective: This study investigates the utility of 3D-Shaper, a software tool that reconstructs 3D femoral models from standard DXA scans, to estimate vBMD in transplant patients on corticosteroids. We hypothesize that 3D-Shaper-derived vBMD is a more sensitive indicator of steroid-induced bone loss in the proximal femur compared to conventional aBMD at the TPF.

Methods: A longitudinal analysis was conducted on a cohort of 216 (M 120, F96) lung transplant recipients. All participants underwent serial hip DXA scans (maximum 20) between 2008 to 2024, pre- and post-transplantation. Subjects ranged in age from 17 to 74 years (mean 53.4, SD 0.99) with a mean weight 69kg (SD 1.15). Rate of loss in TPF aBMD was compared to the derived rate of loss in trabecular and cortical vBMD, estimated using 3D shaper, using linear mixed models analysis.

Results: Analysis of proximal femoral bone loss, using 3D-Shaper-derived vBMD, showed statistically significant earlier and more rapid rate of loss, particularly in trabecular vBMD, compared to the gold standard TFP aBMD measures.

Conclusion: 3D-Shaper volumetric analysis of the proximal femur may provide a more sensitive and clinically informative measure of bone loss in lung transplant patients on corticosteroids than conventional aBMD. These findings support the possible integration of 3D modelling tools into routine bone health assessment for solid organ transplant recipients

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DXA-measured visceral adipose tissue and accelerated biological ageing in middle-aged adults

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Background: Ageing is a major risk factor for morbidity and mortality. Obesity, particularly excess visceral adipose tissue (VAT), may accelerate the rate of ageing process, however few studies investigated the relationship of VAT and biological ageing in middle-aged adults. In 4,799 participants (2,614 females, aged 45-69 years) from the Busselton Healthy Ageing Study, we studied the associations of dual-energy X-ray

absorptiometry (DXA)-derived VAT with two markers of biological ageing, Phenotypic Age Acceleration (PhenoAgeAccel) and leukocyte telomere length (LTL).

Method: Whole body DXA (GE Lunar) was used to estimate VAT mass. Phenotypic Age was calculated using nine standard clinical biomarkers. A subsample of 1,221 randomly selected participants had LTL measured via multiplex quantitative PCR. Sex-stratified linear regression assessed VAT associations with PhenoAgeAccel and LTL, adjusting for chronological age and lifestyle covariates including smoking history, physical activity, education level and alcohol consumption.

Results: The mean DXA-VAT mass was 1677±873 g in males and 882±598 in females. PhenoAgeAccel (median [IQR]) was +0.56 [-1.95, 3.30] and -1.75 [-4.37, 1.11] years, and mean LTL, expressed as the T/S ratio, was 1.69±0.35 and 1.79±0.35 for males and females, respectively. Higher VAT was associated with increased PhenoAgeAccel in both sexes, and each 100g increase in VAT associated with 0.145 (95% CI 0.123, 0.166) and 0.305 (0.277, 0.334) years more advanced PhenoAgeAccel in males and females, respectively. In females, but not males, increased VAT was associated with reduced LTL T/S ratio (-0.007 [-0.011, -0.002] per 100g increase in VAT). All associations remained significant after further adjustment of BMI and waist circumference in the models.

Conclusion: In middle-aged adults, DXA-measured VAT is associated with accelerated ageing beyond traditional anthropometric measures of obesity. These findings support VAT as a potentially modifiable risk factor for ageing, allowing the potential development of VAT reduction strategies to promote healthy ageing.

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Associations between “peak bone mass” and later life bone density: Data from the Geelong Osteoporosis Study

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Purpose

Bone mass is accrued during childhood and adolescence until “peak bone mass” is achieved during early adulthood. It is presumed that attaining greater peak bone mass will result in better bone health in later life, but few studies have been capable of directly assessing this relationship. This study aimed to explore associations between bone mineral density (BMD) in young adulthood and later life in a representative cohort of Australian women.

Methods

Dual x-ray absorptiometry (Lunar DPX-L, then later Prodigy) was measured at two time-points (baseline and 25yr follow-up) of the Geelong Osteoporosis Study. BMD T-scores for L2-L4 lumbar spine, femoral neck and total hip were calculated using local reference data. Participants aged between 20-30y at baseline and who returned at follow-up were included. Pearsons correlations between BMD T-scores at each time point were calculated and linear regressions modelled including age, height, weight and other clinical confounders. Each site was modelled separately.

Results

Participants were 61 women (median age 25.9y, IQR 23.6-28.6), followed for a median 28.4y (IQR 28.0-28.5). Baseline BMD was strongly correlated with follow up BMD at all sites (spine: r=0.763; femoral neck: r=0.649; total hip: r=0.678, all p<0.001). Baseline lumbar spine T-score predicted follow-up T-score, independent of age and height (β=0.938, p<0.001). Trends were similar for femoral neck (β=0.665, p<0.001) and total hip (β=0.710, p<0.001), but age and height did not reach significance in these models.

Conclusions

This work confirms theoretical understandings of the relationship between peak bone mass and bone health in older life and supports future research targeting interventions at young adults.

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Concomitant spinal cord injury and traumatic brain injury impact bone remodelling, understanding the molecular changes through proteomic analysis.

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Publish consent withheld

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Effects of A Digital Voice Assistant-Delivered Osteoporosis Self-Management Program on Diet in Postmenopausal Women with Osteoporosis: A 12-Month Randomised Controlled Trial

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Abstract

Objective: To determine the effects of a digital voice assistant (DVA)-delivered self-management program on intakes of nutrients and foods recommended for supporting musculoskeletal health in postmenopausal women with osteoporosis.

Methods and Materials: Fifty postmenopausal women with osteoporosis were randomly assigned to a DVA intervention (N=25) or control group (N=25) for a 6-month intervention and an additional 6-month maintenance period. During the intervention period, the DVA group received three videos per month containing information on nutrition, exercise, and medication for osteoporosis via a provided DVA device located in their home. Dietary videos focused on dairy, dairy alternatives, protein, calcium and vitamin D. The control group received six emails with weblinks to osteoporosis information. Participants completed 24-hour food recalls on two weekdays and one weekend day at baseline, 6 and 12 months.

Results: Participants (mean age 64.3 ± 6.1 years) accessed approximately 80% of prescribed videos during the intervention. At 6 months, mean protein intake increased by 5.2 g/day (95%CI: -7.1, 17.6) for DVA and reduced by -4.4 g/day (95%CI: -16.5, 7.7) for control. Mean calcium intake changes were 88 mg/day (95%CI: -78, 254) and -66 mg/day (95%CI: -229, 97) for the DVA and control group, respectively. 12 months, there were no significant within the group changes in protein or calcium intakes, nor any between-group differences at either time point. However, daily low-fat milk and egg servings increased in the DVA group compared with controls from baseline to 12 months (P=0.02).

Conclusions: A DVA-delivered intervention including osteoporosis-related nutrition information, did not increase habitual protein or calcium intake however, there was increased consumption of low-fat milk and eggs in women with osteoporosis. Larger trials are required to determine whether similar interventions are effective for improving osteoporosis-focused diet.

Keywords: digital health, osteoporosis, diet, postmenopausal women

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Genome-wide association study meta-analysis identifies association of a locus containing the vitamin D 24-hydroxylase gene (*CYP24A1*) with bone mineral density

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Background: Femoral neck bone mineral density (FN-BMD) is used to diagnose osteoporosis and assess risk of fracture. FN-BMD is highly heritable, yet the underlying genetic mechanisms are not fully understood.

Aims: Conduct a new and larger genome-wide association study (GWAS) meta-analysis to identify genetic determinants of FN-BMD.

Methods: GWAS meta-analysis included 13 cohorts comprising 139,811 individuals with FN-BMD measurements. Genetic associations were identified using GCTA-COJO and considered novel if located >1Mb from known BMD-associated loci. Genetic colocalization was performed on novel loci using *coloc* to detect evidence of shared genetic effects on related traits.

Results: We identified 194 independent associations for FN-BMD ($P_{cojo}<5\times10^{-8}$), of which 5 were novel. One novel locus on chromosome 20q13.2 was located downstream of *CYP24A1* (Fig.1A). This gene encodes vitamin D 24-hydroxylase, a mitochondrial enzyme expressed in the kidney that mediates inactivation of 1,25-dihydroxyvitamin D3 ($1,25(OH)_2D_3$) and precludes activation of its prohormone 25-hydroxyvitamin D (25OHD). *CYP24A1* loss-of-function mutations in humans cause increased $1,25(OH)_2D_3$, hypercalcaemia, hypercalciuria and nephrolithiasis. Follow-up of the lead variant within the *CYP24A1* locus revealed evidence of pleiotropy with key components of the PTH-calcium-vitamin D axis (Fig.1B). The *A* allele (frequency=0.72) of rs6127099 was associated with higher FN-BMD, 25OHD, calcium and phosphate, but lower PTH and renal function (eGFR). Strong evidence of colocalization (posterior probability >0.99) was detected among variants associated with FN-BMD, serum 25OHD, PTH, calcium, and eGFR. Intermediate evidence of colocalization was detected with phosphate (PP=0.47).

Conclusions: We report a novel genetic association with FN-BMD in a locus containing *CYP24A1* that is robustly associated with several traits related to the PTH-calcium-vitamin D axis. Further research is necessary to better understand the significance of these findings, especially considering that there is a lack of evidence

supporting an effect of vitamin D supplementation on BMD and fracture in vitamin D sufficient individuals.

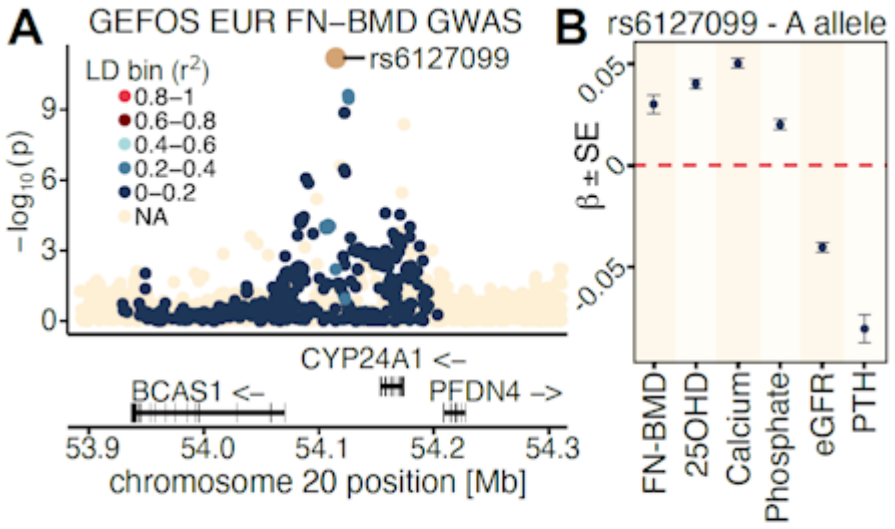

Figure 1. (A) Regional association plot showing the FN-BMD GWAS association signal downstream of CYP24A1. (B) Forest plot showing the estimated association between the A allele of rs6127099 on FN-BMD, 25OHD, calcium, phosphate, eGFR and PTH.

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Hard tissue-forming ability of alpha-smooth muscle actin-positive cells in dental pulp

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Although dental pulp forms hard tissues in response to external stimuli, the distribution and properties of mesenchymal stem cells that differentiate into hard tissue-forming cells remain unclear. α-smooth muscle actin (SMA) localizes in undifferentiated cells to be involved in tissue repair. Therefore, in this study, the differentiation ability of α-SMA-positive cells in dental pulp was analyzed during pulp injury healing using a lineage-tracing analysis. Four-week-old α-SMA-CreERT2/ROSA26-loxP-stop-loxP-tdTomato (iα-SMA/Tomato) mice were administrated Tamoxifen for 2 days. At 0–14 days after the final administration, the localization of α-SMA/Tomato-positive cells in the molar dental pulp

was analyzed. In addition, iα-SMA/Tomato mouse molars were extracted and immediately transplanted into the subcutaneous tissues of wild-type mice. The expression of Runx2 and Osterix in α-SMA/Tomato-positive cells was examined immunohistologically at 3 and 14 days posttransplantation. In 4-week-old iα-SMA/Tomato mice, α-SMA/Tomato-positive cells were localized around the dental pulp blood vessels. The distribution pattern and number of these positive cells hardly changed from days 0 to 28, indicating the non-proliferation of most α-SMA-positive cells. In the transplanted teeth, since most cells in the upper dental pulp are necrotic at 3 days, there is no reaction for α-SMA, Runx2, and Osterix in the coronal pulp. At 14 days posttransplantation, reparative dentin was observed in the root pulp adjacent to the original dentin. Bone tissue with numerous locular structures was also formed apart from the dentin in the coronal pulp. α-SMA/Tomato-positive cells were discerned on the surface of these hard tissues and colocalized with Runx2 and Osterix. These results suggest that α-SMA-positive cells in the dental pulp were quiescent under physiological conditions but proliferated and differentiated into odontoblasts and osteoblasts after pulp injury.

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Making the first fracture the last fracture Examining the efficacy of the Westmead Hospital Fracture Liaison Service in reducing re-fractures over 3 years

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Background

Prevention of the next fracture after a sentinel minimal trauma fracture (MTF) brings benefits for patients, clinicians and healthcare systems. While fracture liaison services (FLS) are established models of care to prevent refractures, recent work has questioned the efficacy of hospital-based services. We sought to determine the impact of Westmead FLS on refractures.

Methods

In 2019, Westmead Hospital implemented an FLS which detects fractures based on ICD-10/SNOMED coding and provides multidisciplinary care for patients to prevent

refractures. This study sought to compare one and three-year refracture rates in FLS patients and a control group, defined as patients approached by FLS but were lost to follow-up, did not attend or refused treatment. Age, gender, index-fracture location and Charlson Comorbidity Index (CCI) were included as baseline characteristics for Cox regression.

Results

There were 279 and 127 in the patient and control group respectively who sustained a MTF between 2019 and 2022. Both groups had similar baseline characteristics. A statistically significant decrease in three-year refracture rates in FLS patients vs control (10.4% vs 23.6%, p<0.001) was observed, although there was no difference at one year (4.3% vs 5.5%, p=0.61). FLS patients had an overall ~55% reduction in three-year refracture risk (HR 0.413, p<0.001). A similar reduction in three-year refracture risk was observed in patients with CCI range of 1-3 vs 4+ (HR 0.434, p=0.002) across both groups.

Conclusions

Patients who attend the FLS have a statistically significant reduction in refractures, with less than half the risk of refracture, at three years. This was not seen after one year, suggesting evaluation of FLSs requires a latency review period of at least three years. Patients with CCI 1-3 have less than half the risk of refracture compared to CCI 4+ patients over a three-year period, highlighting the impact of comorbidities on refracture.

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Feasibility, safety and efficacy of OsteoStrong® in postmenopausal women with low bone mineral density

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Background: OsteoStrong® is a membership-based musculoskeletal strengthening program. Over 10 million OsteoStrong® sessions have been completed worldwide, but evidence on adherence, safety, and efficacy is limited. We aimed to determine the feasibility of OsteoStrong® for postmenopausal women with low bone mineral density

(BMD), and measure 8-month changes in BMD, bone microarchitecture, and physical function.

Methods: In this single-arm trial, 44 postmenopausal women with low BMD (dual-energy x-ray absorptiometry-determined T-score <-1.0 but >-3.0 at total hip and/or lumbar spine) attended once-weekly OsteoStrong® sessions for 8 months. We calculated 8-month changes in areal BMD (primary outcome: total hip areal BMD [aBMD]), trabecular bone scores (TBS), high-resolution peripheral quantitative computed tomography-determined bone microarchitecture, and physical function.

Results: A total of 769 women were screened to recruit 44 eligible participants (conversion rate 6%; mean age 61.2±5.5 years), and 38 (86%) completed follow-up. Mean±SD OsteoStrong session adherence was 83±28% and two possibly intervention-related adverse events were recorded. At 8 months, there were no changes in total hip, femoral neck, and lumbar spine aBMD (all P>0.05; Figure), while TBS decreased (P<0.05). At the distal radius, total, trabecular and cortical volumetric BMD (vBMD; Figure), and cortical thickness (mean change: -0.007mm [95%CI: -0.012, -0.002]), decreased. At the distal tibia, cortical vBMD decreased (Figure), and trabecular separation (mean change: 0.007mm [95%CI: 0.001, 0.012]) increased. Chair stand (mean change: -0.8 sec [95%CI: -1.2, -0.5]) and stair climb (mean change: -0.1 sec [95%CI: -0.2, -0.002]) times decreased, while Short Physical Performance Battery scores increased (mean change: 0.2 [95%CI: 0.03, 0.38]).

Conclusion: In postmenopausal women with low BMD, OsteoStrong® was safe, and achieved good adherence and some improvements in physical function. However, 8 months of OsteoStrong® did not result in significant improvements in BMD or bone microarchitecture, suggesting it should not replace proven effective treatments for people with osteoporosis.

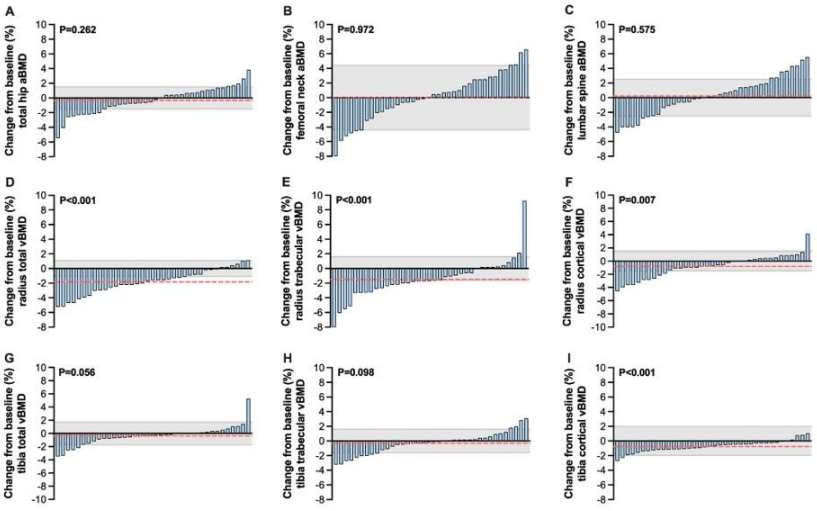

Figure. Individual (blue bars), mean (dotted orange lines) and least significant (grey shading) changes for dual-energy X-ray absorptiometry- and high-resolution peripheral quantitative tomography-determined bone parameters. P-values <0.05 indicate a significant mean change.

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"Skeletal Age" for cumulative impact of cigarette smoking on post-fracture mortality

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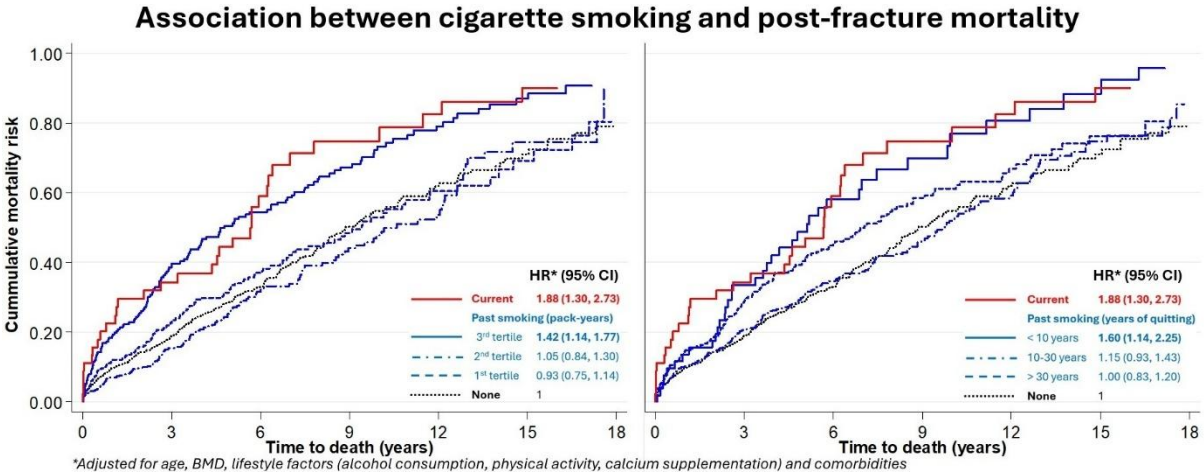
Cigarette smoking is associated with an increased mortality risk, though its impact on post-fracture mortality remains unclear. We determined the association between cigarette smoking and post-fracture mortality risk and proposed the *"Skeletal Age"* metric to communicate the risk of cigarette smoking on post-fracture mortality.

We analysed data of 1084 fracture patients (average age at fracture: 82.6±6.6 years) from the Osteoporotic Fractures in Men Study in the USA. Cigarette smoking status (current, past or never), cumulative smoking exposure (tertiles of pack-years) and time since smoking cessation (<10, 10-30 or >30 years) were self-reported, and deaths were confirmed via death certificates. A Cox regression was used to quantify the association between smoking conditions and post-fracture mortality, accounting for known confounders. *"Skeletal Age"* is the sum of chronological age and the number of years of life lost associated with a risk factor or fracture.

Over a median follow-up of 5.1 years (IQR: 2.1-9.3), 639 fracture patients died (~10.2 deaths/100 person-years). Current and past smokers with the highest tertiles of smoking exposure or <10 years of smoking cessation were independently associated with 90%, 42% and 60%-greater risk of post-fracture mortality than non-smokers, respectively (Figure). Past smokers who had smoked less or quit for >10 years were not associated with mortality risk, suggesting smoking's impact on post-fracture mortality was reversible. Notably, a 60-year-old fracture patient who was currently smoking had a *"Skeletal Age"* of 65.1 years, suggesting current smoking was associated with 5 years of life lost post-fracture. Similarly, those who had either smoked heavily or quit within 10 years would lose 3 and 4 years of life (~*"Skeletal Age"* of 62.9 and 63.8 years), respectively.

The association between cigarette smoking and post-fracture mortality is reversible, indicating the benefits of smoking cessation on mortality. *"Skeletal Age"* can be employed to improve doctor-patient communication.



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Genetic differences between abdominal aortic and coronary artery calcification and implications for vascular disease and adverse health outcomes

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Knowledge gap: Calcification in the coronary and abdominal aortic arteries is associated with adverse health outcomes. However, it isn't known whether pathophysiological influences of abdominal aortic calcification (AAC) differ from coronary artery calcification (CAC).

Aims: 1: Identify genetic determinants of AAC and establish if they influence CAC. **2:** Contrast effects of genetically determined AAC and CAC on different forms of vascular disease and their corresponding sequelae.

Methods: AAC was quantified in 49,271 UK-Biobank study participants using a lateral spine dual energy X-ray absorptiometry-based machine-learning algorithm. Genetic determinants of AAC were identified by genome-wide association study analyses (GWAS). Genetic similarity of AAC and CAC was estimated by LD-score regression using a published CAC GWAS (N~35,776). Mendelian Randomization (MR) estimated the effect of higher AAC and CAC on coronary artery disease and its primary clinical outcome - myocardial infarction, carotid artery disease and stroke, peripheral artery disease and critical limb ischemia.

Results: AAC and CAC were moderately genetically correlated (r_g=0.6, $CI_{95\%}$=0.47-0.70) indicating they are influenced by a mixture of shared and unique genetic mechanisms. GWAS of AAC detected genome-wide significant associations ($p<5\times10^{-8}$) at 15 genomic regions, including 5 novel regions. 11 were associated with CAC in the same direction ($p<0.05$), whereas four were not associated ($p>0.05$, Fig.1A). MR showed that higher AAC and CAC was associated with increased risk of coronary artery disease and myocardial infarction (Fig.1B). In contrast, higher AAC, but not CAC was associated with carotid artery disease [proxied by increased carotid plaques and carotid intima media thickness (Fig.1C)], and stroke. Likewise, peripheral artery disease was associated with increased AAC, but not CAC. Critical limb ischemia was not available for testing.

Conclusions: AAC and CAC are partially influenced by distinct genetic mechanisms. A better understanding of these differences may uncover new pathophysiological

mechanisms that contribute to adverse health outcomes.

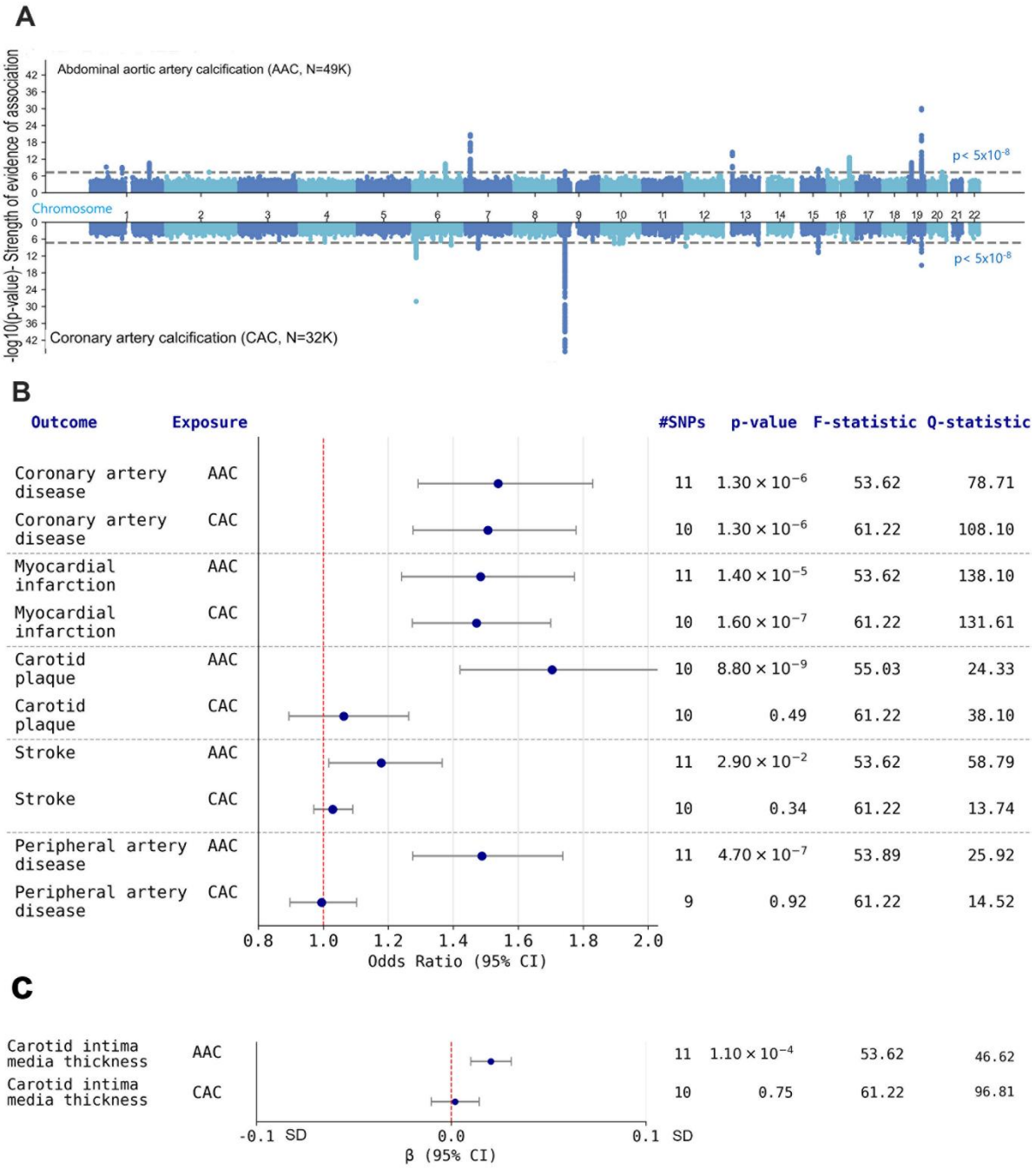

Fig 1A: Miami plot contrasting genetic associations of AAC and CAC across the genome. **Fig 1B:** Estimated effect of genetically determined AAC and CAC on different vascular disease outcomes using a two-sample inverse-variance weighted MR. Odds ratios are presented with their 95% confidence intervals and are expressed per 1 standard deviation (SD) increase in AAC / CAC. **Fig 1C:** Estimated effect of genetically determined AAC and CAC on carotid intima-media thickness. The effect (β) is expressed in SD per 1SD increase in AAC /CAC.

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Melatonin Promotes Osteogenesis but Activates TLR4-Mediated Osteoclastogenesis in a Dose-Dependent Manner

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Publish consent withheld

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Incidence of vertebral fracture in a cohort of Australian women: Data from the Geelong Osteoporosis Study

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Purpose

Vertebral fractures are a common outcome of osteoporosis, yet these skeletal injuries are often asymptomatic and undiagnosed. Studies to assess the rate of incident fractures are often limited by their study design (e.g. clinical trials with strict inclusion and exclusion criteria, opportunistic clinical samples). This study aimed to assess the incidence of vertebral fracture in a representative cohort of Australian women.

Methods

Lateral vertebral assessment (Lunar Prodigy) was obtained at two time points for participants of the Geelong Osteoporosis Study. Incident vertebral fractures were defined by the software according to Genant semi-quantitative criteria where the fracture was new at follow-up. Baseline characteristics, including age, height, weight and other clinical confounders, were compared between those with and without incident fracture. Incidence rate was calculated as number of participants with incident

fracture over the total number of person-years (p-y) of observation, and subsequently age-standardised to the Australian population.

Results

Participants were 701 women (ages 21-86y), 19 of whom experienced an incident vertebral fracture. The standardised incidence rate was 31.88 (19.69-44.07) fractures per 1000p-y. Individuals who fractured were older (70.1 vs 48.7, $p<0.001$) and shorter (158.1 vs 163.0cm, $p=0.001$), than those who did not. They were more likely to be fallers (52.6% vs 24.5%, $p=0.005$), smokers (42.1% vs 12.8%, $p<0.001$), to have lower mobility (42.1% vs 13.5%, $p<0.001$), and have an existing vertebral fracture at baseline (10.5% vs 1.6%, $p=0.005$). They also had lower femoral neck bone mineral density (BMD) ($p=0.001$). No associations were observed between incident fracture and back pain (prevalent or onset), self-rated health or height loss at follow-up.

Conclusions

Incident fracture was associated with older age, shorter height, smoking, low mobility, and previous falls, as well as prior vertebral fracture and lower bone mineral density, but not associated with back pain, self-rated health or height loss.

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Collagen-based constructs for periodontal disease and bone regeneration

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Introduction

As the main matrix component of bone, collagen has played a critical role in the fabrication of synthetic bone substitutes. However, poor mechanical properties, fast resorption and lack of antimicrobial activity can result in inefficient treatment outcomes. Hence, this project aims to syntheses collagen constructs with antimicrobial properties by nanoencapsulation of mānuka oil and β-triketones for bone regenerative applications.

Methods

Mānuka oil or β-triketones oils were nanoencapsulated using ionic gelation, and the morphology and average size were characterised by dynamic light scattering (DLS), scanning electron microscopy (SEM) and fluorescent staining. Antimicrobial activity was assessed against gram-positive and gram-negative species. Nanospheres biocompatibility was evaluated on human gingival fibroblasts. Nanosphere stability, oil

encapsulation efficiency and oil-release profiles were measured *in vitro*. Nanospheres were incorporated into collagen constructs, and the nanospheres distribution, construct structure and porosity investigated. Biocompatibility, mechanical strength and antimicrobial properties against relevant pathogens were evaluated *in vitro*. While *in vivo* biocompatibility and regenerative properties were investigated in a cranial bone defect model in New Zealand white rabbits, assessed via micro-CT analysis of new bone formation, and histological evaluation of inflammatory response.

Results

DLS, SEM and fluorescent staining results showed successful production of nanospheres with an average size of 300-500 nm, with a stable structure and oil release. Antimicrobial efficiency was obtained against gram-positive and gram-negative bacterial species. *In vitro* experiments demonstrated the construct's biocompatibility, high porosity, thermal stability and a satisfactory level of structural integrity. Further discussion of the *in vivo* results to follow, including the micro-CT and histological analysis of new bone formation and inflammatory response.

Conclusion

The study concludes with an overview and perspectives for developing novel biocompatible, antimicrobial collagen-based constructs which could provide potential treatment options for guided tissue/ bone regeneration in periodontal or orthopedic applications.

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Rural-urban differences in osteoporosis and sarcopenia prevalence among Gambian older adults: A pilot study

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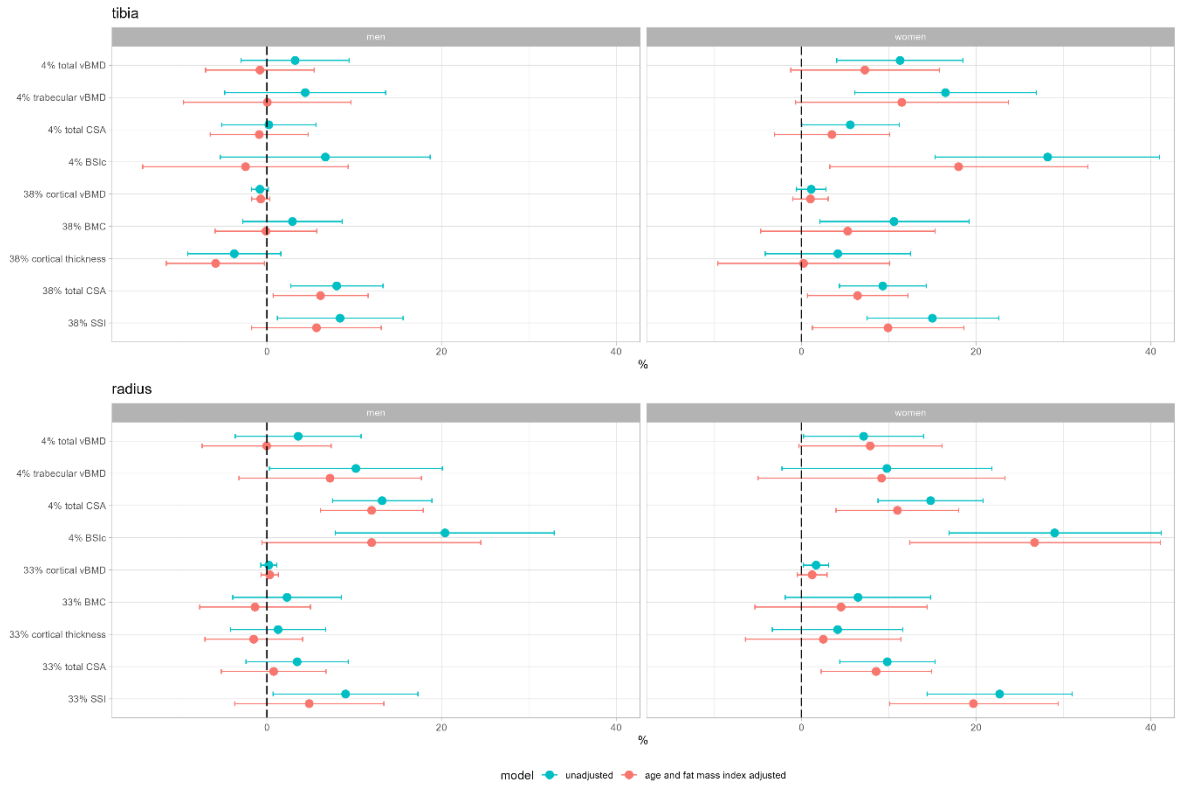
Background: Rural-urban differences in osteoporosis and fracture prevalence are well-described in high-income countries, with rural bone mineral density (BMD) generally higher. Despite rapid urbanization and increasing longevity Africa data are

scarce. Thus, we investigated rural-urban differences in bone and muscle health in older Gambian adults.

Methods: Participants aged ≥55 years from rural (n=209) and urban communities (n=101) had dual-energy X-ray absorptiometry (DXA: total hip [TH], femoral neck [FN], and lumbar spine [LS]) and peripheral quantitative computed tomography scans (pQCT: diaphyseal and epiphyseal radius and tibia). Outcomes were: DXA areal BMD (aBMD), bone mineral content (BMC), bone area (BA); pQCT total volumetric BMD (vBMD), trabecular vBMD, bone strength indices, cross-sectional area (CSA), BMC, and cortical vBMD. Osteoporosis (NHANES III, T-score <-2.5) and sarcopenia (EWGSOP2 ALM and HGS) prevalence were computed. Linear regression was used to describe rural-urban differences in DXA and pQCT outcomes unadjusted (model 1) and age and fat mass index (FMI) adjusted (model 2).

Results: Osteoporosis at either FN or TH was more prevalent in urban men (20% vs rural 10%) and rural women (45% vs urban 31%). LS T-scores <-2.5 were more common in rural participants (M:27% vs 14%; F:61% vs 35%). Sarcopenia was higher in rural participants (M:30% vs. 18%; F:18% vs. 15%). When fully adjusted (model 2) urban Gambians had lower BMC but greater BA at the FN and TH, while aBMD differed little. Urban men had lower adjusted tibial cortical vBMD but greater tibial diaphyseal and radial epiphyseal CSA (Figure). After adjustment urban women had greater radial CSA and estimated strength (Figure).

Conclusions: Our findings highlight that osteoporosis and sarcopenia are highly prevalent in older Gambians, with rural-urban differences influenced by sex. Given ongoing nutrition transition and urbanization across Africa, larger population-based studies are urgently required to better inform targeted prevention strategies and interventions.



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Myeloma screen has poor yield as part of secondary osteoporosis screen

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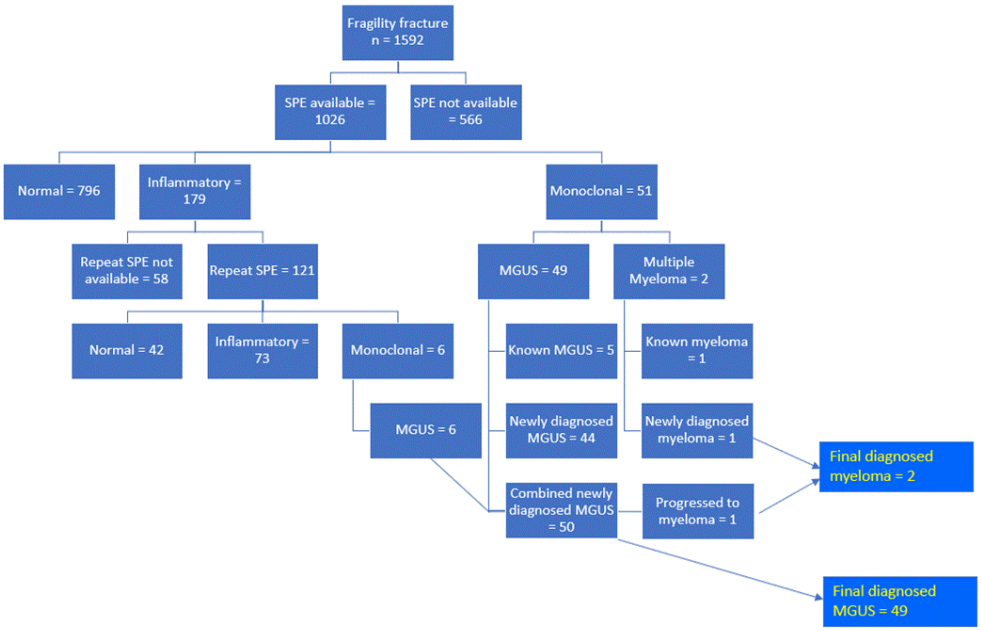
Multiple myeloma (MM) is a secondary cause of osteoporosis and universal screening has been recommended post fragility fracture. However, the longitudinal yield of this approach has not been evaluated. We aim to assess the yield of myeloma screen in the

Austin Fracture Liaison Service database between 1/6/2009 and 1/6/2014. Patient demographics, fragility fracture type, bone density, pathology results including serum protein electrophoresis (SPE), urine Bence Jones protein were extracted. SPE were classified as normal, inflammatory (which prompted repeat SPE) or monocloncal (Monoclonal Gammopathy of Unknown Significance (MGUS) or MM).

1026 SPE were available for 1592 confirmed fragility fracture in 1589 patients over 5 years, median age was 72 years (IQR 62, 81), 26% were men, and 24% sustained hip or pelvic fracture. Initial myeloma screen performed 3 days (IQR 7, 35) post admission revealed 796 (78%) normal, 179 (17%) inflammatory, and 51 (5%) monoclonal results. After excluding 6 subjects with known MM and MGUS, repeat SPE for 121 subjects in the inflammatory category yielded an additional 6 monoclonal results. Final cohort with confirmed categorisation after repeat SPE (n = 455) found 838 normal, 73 inflammatory, and 51 monoclonal results. The monoclonal cohort was followed for a median of 4.4 years (IQR 2.4, 7.5), with 49 MGUS and 2 MM diagnosis (n = 1 progressed to MM after 11 years). Both cases had elevated globulin and anaemia at time of diagnosis.

Although monoclonal gammopathy increases fracture risk and high dose anti-resorptive agents are used therapeutically in MM, diagnosis alone does not alter osteoporosis management. Performing SPE acutely post fracture returned 17% inflammatory results requiring further testing. At a testing cost of $71,388.40 and 4.4 years of follow-up, 2 cases of MM were diagnosed. The yield of universal myeloma screen was low as both cases were already flagged by routine pathology.



1. Royal Osteoporosis Society. Effective secondary prevention of fragility fractures : clinical standards for fracture liaison services. R. Osteoporos. Soc. (2019)
2. Veronese N et al. Monoclonal gammopathy of undetermined significance and bone health outcomes: a systematic review and exploratory meta-analysis.2018 J Bone Miner Metab 36:128–132

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Negative impact of pelvic radiotherapy on bone mineral density in women treated with gynaecological malignancies

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Background: Reduced bone mineral density (BMD) and pelvic insufficiency fractures (PIFs) are well-documented complications of external beam radiotherapy (EBRT) for gynaecological malignancies and contribute to significant post-treatment morbidity and mortality. Prevalence of PIFs post EBRT vary from 7.8-14% with most occurring within 2 years after treatment. The underlying pathogenesis is thought to be related to microvascular occlusion and impaired osteoblast function.

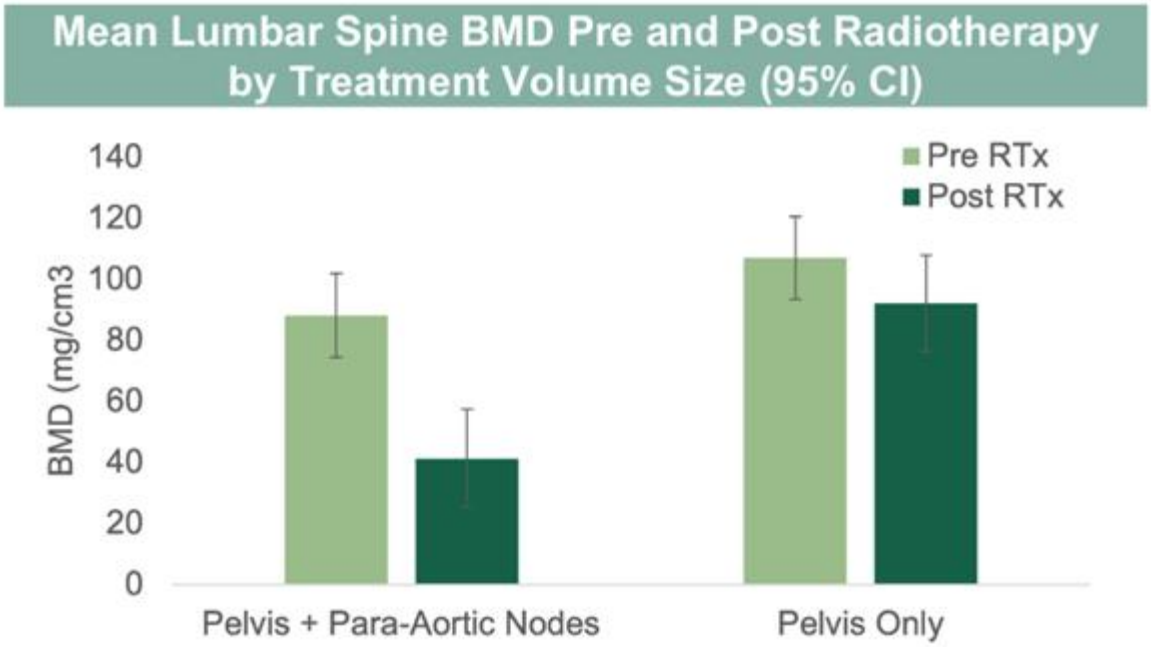
Objectives: Minimal evidence is available on the relationship between radiotherapy volumes, doses and impact on BMD loss. This retrospective study will analyse the effects of the radiotherapy on site-specific BMDs.

Methods and Materials: Data was reviewed for 135 patients who received EBRT for gynaecological malignancies at a single Sydney hospital. 28 were identified as having completed a lumbar spine and left femoral neck BMD measured by Quantitative Computed Tomography (QCT) at baseline and within 18 months post treatment. Their treatment volumes and approximate doses of radiation to the lumbar spine (L2-4, L3) and left femoral head were recorded from treatment plans and correlated with changes in BMD.

Results: Patients were predominantly post-menopausal, mean age 63.3 and ECOG 0-1. Mean radiotherapy dose of 49.9 Gy, with 21 receiving pelvic only and 7 extended nodal radiation. 21/28 received adjuvant chemotherapy. Mean time of completion of radiotherapy to follow-up QCT was 6.1 months. 23/26 patients experienced a decline in BMD, with BMD decreasing by -24.5%, 95% CI [-14.6% to -34.3%] in lumbar spine and by -3.6%, 95% CI [-0.5% to -7.6%] in femoral neck. Lumbar spine bone loss was more pronounced when the treatment field extended above L4 to incorporate the pelvis and

para-aortic nodes (-52.9%) compared to pelvis alone (-9.9%), t(8) = 3.673, p = 0.006) (Fig). A significant correlation was demonstrated between radiotherapy dose and BMD loss at the L3 vertebrae but not at the femoral neck.

Conclusion: This study provides evidence that pelvic radiotherapy for gynaecological malignancies contributes to significant bone loss and that this effect is most pronounced within the treatment field. Further research is required to develop strategies to mitigate against this bone loss.



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Evaluating the utility of zebrafish scales to model cellular and genetic determinants of human bone health

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Knowledge gap: Zebrafish scales are composed of mineralized collagen plates that remodel and regenerate. The cells and genes that regulate these processes have not been characterised at single cell level, nor has their utility for modelling human skeletal disease been fully explored.

Aims: (1) Define the landscape of cells in zebrafish scales, (2) identify cells and genes involved in scale regeneration, and (3) determine if they have defined roles in human skeletal disease.

Methods: Scales from 1 year old wild-type male zebrafish were harvested and dissociated. Cell clusters, and their differentially expressed genes were defined by single-cell RNA sequencing. Transgenic fluorescent zebrafish lines were used to validate cell type predictions and compare their spatial distribution within the scale. Cell clusters involved in scale regeneration were identified based on enrichment of genes known to be upregulated during scale regeneration[1]. The nosology and classification of genetic skeletal disorders database[2] was used to define cell clusters that were enriched with genes involved in human skeletal disease.

Results: 26 clusters of cells encompassing haematopoietic and non-haematopoietic lineages were defined. The haematopoietic group was made up of B-cells, T-cells, macrophages, macrophage-osteoclast-like cells, and granulocytes. The non-haematopoietic group comprised of epithelial cells, melanocytes, fibroblasts, and several osteoblast clusters at different stages of differentiation. Immunofluorescence revealed that haematopoietic and non-haematopoietic cells exhibited distinct spatial localizations within the scale (Fig.1A and B). Multiple clusters of the osteoblast lineage, fibroblasts and neuronal cells were enriched with scale regenerating genes (Fig.1C). In contrast, osteoblasts, fibroblasts, but not neuronal cells were enriched with genes involved different skeletal disorders, and particularly those with high/low bone mass (Fig.1D).

Conclusion: Our study defines the repertoire of cells found in zebrafish scales and shows that cells involved in scale regeneration express many evolutionarily conserved genes with defined roles in human bone health and disease.

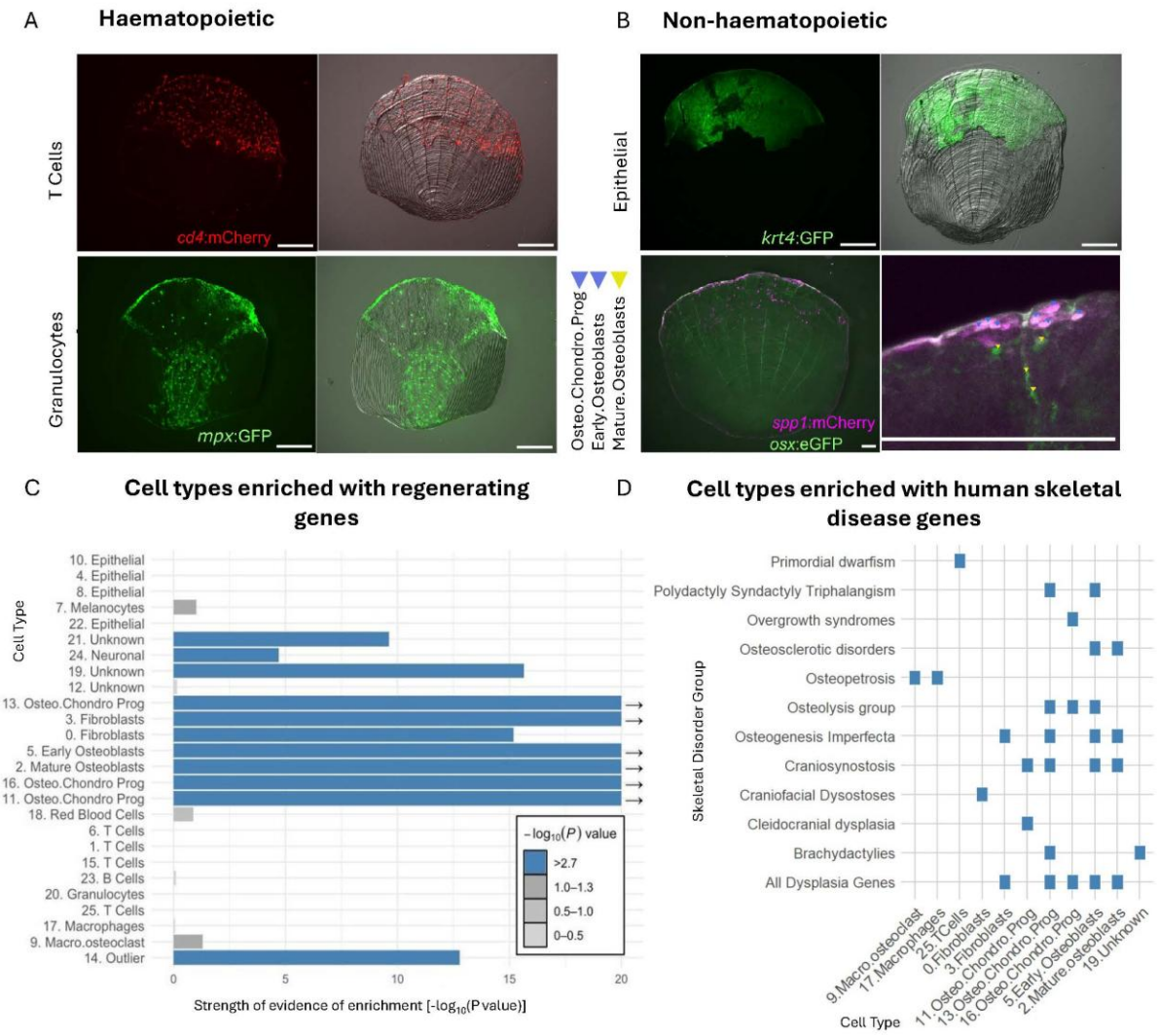

Figure 1.A. Ontogenetic scales of transgenic zebrafish expressing markers for haematopoietic cell types. **B.** Ontogenetic scales of transgenic zebrafish expressing markers for non-haematopoietic cell types. **C.** Bar plot showing strength of evidence of enrichment (x-axis) of different cell types (y-axis) for genes that are over-expressed during scale regeneration from Bergen et al., 2022. (Bonferroni correction: $0.05/26_{CellTypes} = 1.9\times10^{-3}$, 'Osteo.Chondro Prog' = osteoblast-chondrocyte progenitors, 'Macro.osteoclast' = macrophage-osteoclast-like cells). **D.** Tile Plot showing cells for which robust evidence of enrichment was observed for genes that cause different groups of human skeletal disorders (Unger et al., 2023. Blue tiles have a p-value < 1.19×10^{-3}). Enrichment analyses were conducted using hypergeometric tests.

1. 1.Bergen DJM, Tong Q, Shukla A, Newham E, Zethof J, Lundberg M, Ryan R, Youlten SE, Frysz M, Croucher PI, Flik G, Richardson RJ, Kemp JP, Hammond CL, Metz JR. Regenerating zebrafish scales express a subset of evolutionary conserved genes involved in human skeletal disease. BMC Biol. 2022 Jan 21;20(1):21. doi: 10.1186/s12915-021-01209-8. PMID: 35057801; PMCID: PMC8780716.
2. 2. Unger S, Ferreira CR, Mortier GR, Ali H, Bertola DR, Calder A, Cohn DH, Cormier-Daire V, Girisha KM, Hall C, Krakow D, Makitie O, Mundlos S, Nishimura G, Robertson SP, Savarirayan R, Sillence D, Simon M, Sutton VR, Warman ML, Superti-Furga A. Nosology of genetic skeletal disorders: 2023 revision. Am J Med Genet A. 2023 May;191(5):1164-1209. doi: 10.1002/ajmg.a.63132. Epub 2023 Feb 13. PMID: 36779427; PMCID: PMC10081954.

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Developing a preclinical model to distinguish inflammation- and glucocorticoid-driven bone loss in the context of arthritis

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Background
Synthetic glucocorticoids suppress inflammation in arthritis. However, long-term use induces osteoporosis (GIOP), as does inflammation itself. To support future studies on glucocorticoid therapy, we developed a preclinical GIOP model in arthritis that distinguishes between inflammation- and glucocorticoid-driven bone loss.

Methods
To assess long-term bone effects of glucocorticoids and transient arthritis, we used the collagen antibody-induced arthritis (CAIA) model in 8-week-old male Balb/c mice. Collagen-II antibodies were administered (day 0), followed by LPS (day 4); controls received saline. From day 7 to 49, mice received daily methylprednisolone (MP). Arthritis was scored from day 5 to 21 based on paw redness and swelling. On day 49, mice were sacrificed to analyze white blood cell counts (WBC), bone remodeling markers (ELISA), femoral bone microarchitecture (microCT), and tibial gene expression (qPCR).

Results
At treatment onset (day 7), all CAIA groups showed elevated arthritis scores. By day 21, vehicle-treated CAIA mice sustained arthritis (+10% vs day 7, $p<0.05$), while MP fully resolved arthritis (-100%). At endpoint, arthritis had resolved in all groups. WBC in vehicle-treated CAIA mice matched controls (ns), but were reduced by MP (-48% vs CAIA-vehicle, $p<0.01$). CAIA did not affect serum P1NP (ns), while MP reduced P1NP (-46% vs CAIA-vehicle, $p<0.05$). In line, MP suppressed *Bglap* expression (-81% vs CAIA-vehicle, $p<0.01$). Serum TRAP and *Trap* expression were similar across groups. Furthermore, CAIA did not alter bone shaft length or cortical microarchitecture (ns), while MP reduced shaft length (-5%, $p<0.001$) and cortical thickness in diaphysis and metaphysis (-10%, $p<0.001$), compared to CAIA-vehicle. Conversely, CAIA reduced trabecular bone volume (-23% vs control, $p<0.001$), which was rescued by MP (+24%, $p<0.01$).

Conclusion
Treating CAIA mice with glucocorticoids restores inflammation-driven trabecular bone loss, while causing cortical bone loss and suppressing bone formation. These site-specific effects make CAIA a valuable model for studying GIOP in arthritis.

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Early Trabecular Bone Microarchitecture Deficits in a Female Mouse Model of Parkinson's Disease.

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Women with Parkinson's disease (PD) are at elevated risk of osteoporosis and fracture, yet the mechanisms linking neurodegeneration and skeletal fragility, particularly in the context of oestrogen status, remain poorly defined. This study aimed to investigate the early effects of dopaminergic neurodegeneration on trabecular bone in female mice, as part of a broader design that will also assess the impact of oestrogen depletion via ovariectomy (OVX).

Here, we report findings from ovary-intact female mice treated with intrastriatal 6-hydroxydopamine (6OHDA) to model PD-related neuronal loss. Six weeks after lesioning, femoral trabecular bone was analysed by micro-computed tomography (micro-CT). Compared to controls, 6OHDA-treated mice exhibited significantly reduced bone volume ($p = 0.015$), trabecular connectivity ($p = 0.038$), and intersection surface ($p = 0.0015$), alongside increased variability in trabecular thickness ($p = 0.020$), indicating

early microarchitectural compromise. Trends toward reduced bone volume fraction (%BV/TV, p = 0.054) and connectivity density (p = 0.071) were also noted. In contrast, trabecular thickness, number, spacing, and structural model index were unaffected.

These data suggest that PD-like neurodegeneration alone is sufficient to disrupt trabecular bone quality in ovary-intact females. Ongoing analyses will evaluate whether oestrogen deficiency exacerbates these effects, providing new insight into the sex-specific skeletal vulnerability observed in PD.

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Revision Risk Following Primary Total Hip Arthroplasty in Australian Rheumatoid Arthritis Patients

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Purpose: To compare the risk of total hip arthroplasty (THA) revision between patients with rheumatoid arthritis (RA) and patients with osteoarthritis (OA), using data from the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR).

Methodology: This cohort study analysed 3,269 RA and 389,450 OA patients undergoing primary THA recorded in the AOANJRR, from 1999 to 2023. Cumulative percent revision (CPR) rates were calculated using Kaplan-Meier methods. Hazard ratios (HRs) were determined through Cox proportional hazard models adjusted for age and sex. Outcomes included all-cause revision and revision for dislocation, infection, aseptic loosening, and periprosthetic fracture (PPF).

Results: RA is associated with a higher all-cause revision (HR 1.26; 95% CI 1.08–1.48; p=0.004), revision for infection (HR 1.38; 95% CI 1.00–1.89; p=0.047), early aseptic

loosening (0-3 months; HR 2.66; 95% CI 1.37–5.15; p=0.003), and dislocation (HR 1.78; 95% CI 1.35–2.33; p<0.001). However, no differences were observed in revision for PPF.

Conclusion: RA is a complex multisystem disease that, despite therapeutic advances, continues to be associated with serious adverse post-operative risks including revision for infection, aseptic loosening, and dislocation. Increased risk of revision for infection emphasises the importance of multidisciplinary team involvement to optimise the balance between disease control and infection risks in RA patients on potentially immunosuppressant therapies. An absence of current strategies to prevent early aseptic loosening in RA highlights a need for further research. Increased risk of revision for dislocation suggests surgeons should consider dual mobility THR in RA patients to improve post-operative outcomes.

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Prevalence and Incidence of Vertebral Fractures in Middle-aged and Older Working Men: A Cross-sectional and Longitudinal Study

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Introduction:
Most epidemiological studies on vertebral fractures (VFs) in the general population have focused on elderly women. This study conducted a cross-sectional analysis targeting a population that included many middle-aged and older working men, aiming to investigate the prevalence of existing VFs, including asymptomatic cases, and to analyze its associated factors. In addition, a longitudinal study was conducted to investigate the incidence of new VFs and identify related risk factors.

Methods:
The study included 5,509 participants (4,872 men; mean age 56.2 ± 10.4 years) who underwent low-dose chest CT as part of a lung cancer screening program during health check-ups in 2018. Using our proprietary AI-based automated vertebral fracture detection system (sensitivity 86.7%, specificity 98.4%), VFs from T1 to L2 were classified according to the Genant semi-quantitative (SQ) grading system. SQ grade ≥1

was defined as VF, and SQ ≥2 as severe VF. Frequencies were calculated, and multiple regression analysis was performed to identify factors associated with existing VFs.

A total of 4,560 individuals (4,099 men; mean age 56.3 ± 10.1 years) who underwent at least one follow-up examination after 2019 were observed until 2021. The incidence of new severe VFs was evaluated, and multivariate regression analysis was used to identify risk factors.

Results:
The prevalence of existing VFs and severe VFs was 1.94% and 1.09%, respectively. The three-year incidence of new severe VFs was 0.68%. Factors associated with existing VFs were older age ($p < 0.01$) and alcohol consumption ≥3 units/day ($p = 0.02$). Risk factors for new severe VFs were older age ($p = 0.01$) and existing severe VF ($p < 0.01$).

Conclusion:
In a large population including many middle-aged and older men, older age and alcohol consumption were associated with existing VFs, and older age and existing severe VFs were risk factors for new severe fractures.

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Fracture rates decline during COVID-19 lockdowns

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Purpose

Nationwide lockdowns to address the rise of COVID-19 in Australia during 2020 restricted public gatherings, work movements and outdoor activities. These changes may have influenced the presentation of injuries, including fractures. This study aimed to investigate fracture rates at a major regional tertiary hospital in Victoria during this time in comparison to respective dates in 2019 and explores emerging trends.

Method

This retrospective cohort study assessed radiological reports of women attending Barwon Medical Imaging, which directly services the University Hospital Geelong, during the initial COVID-19 lockdown from 31 March to 8 July 2020, and comparable dates in 2019. Information was collected regarding patient age, fracture site date and cause of fracture. Rates per 1,000/person-years (py) in each age group were calculated and age-standardised to the broader Australian population. The overall percentage change in fracture rates across both years was also determined.

Results

Fracture rates were lower in 2020 across all age groups except ages 60-69 and 70-79 years. Ages 80+ years had the highest fracture rates with 47.8 (95% confidence interval [CI]: 42.8-65.8) in 2019 and 36.1 fractures per 1,000/py (95% CI: 31.8-40.3) in 2020. Ages 30-39 years, however, had the lowest fracture rates in both years with rates of 6.4 (95% CI: 5.2-7.6) and 4.4 (95% CI 3.4-5.3), respectively. Overall, fracture rates reduced by 10.9% during the pandemic ($p<0.01$), with age-standardised rates decreasing from 14.6 (95% CI: 13.9-15.2) to 12.7 (95% CI: 12.1-13.3) fractures per 1,000/py ($p<0.01$).

Conclusion

Fracture rates declined during the COVID-19 lockdowns, likely due to the strict lockdown restrictions placed on public mobility. Further research is needed to determine whether the decrease in fracture rates is applicable to the whole Australian population, including men.

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Advanced Paternal Age and Offspring Bone Health in Adulthood; Do Associations Reported in Childhood Persist?

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Aims: There is growing evidence supporting paternal contributions to child health. Previous findings from the Vitamin D In Pregnancy study suggested that advanced paternal age was associated with lower bone measures of offspring at age 11 years. However, whether these associations are evident when peak bone mass is attained remains unknown. This study aimed to investigate associations between paternal age and offspring bone health at age 20 years.

Methods: Data from the Raine study, a multigenerational cohort, were used. Among 1183 offspring with total body DXA (GE Lunar) data at the 20-year follow up, 1142 had information on their father's age and were included in analysis. Linear regression models were developed to examine associations of outcome of interest (offspring parameter of bone and body composition) and paternal age during pregnancy (16-18 weeks' gestation), with the final models adjusted for maternal age and offspring sex, gestational age, birthweight, and height, weight and age at DXA assessment. Bone mineral content models were also adjusted for bone area and fat and lean mass models were additionally adjusted for each other.

Results: Fathers' median age was 31 years (IQR 27-35, range 15-58). In final models, advanced paternal age was not significantly associated with offspring total body bone mineral density (β: -0.00036; 95% CI: -0.0013, 0.00061 g/cm^2; p=0.46) or bone mineral content (β: -0.90; 95% CI: -3.60, 1.79 g; p=0.51). Paternal age was also not significantly associated with total body fat mass (β: -0.0042; 95% CI -0.011, 0.028 kg; p=0.24) or lean mass (β: -0.0040; 95% CI -0.011, 0.0028 kg; p=0.25).

Conclusions: Previous inverse associations reported were not detected in this cohort. This may suggest that early life effects are attenuated at peak bone mass. Further research is needed to assess this association in clinically relevant DXA sites such as the hip and spine.

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Fracture Prophylaxis for Adult Lung Transplant Recipients: a clinical audit of fracture risk identification and prevention

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BACKGROUND: As life expectancy following lung transplantation (LT) improves, and age of lung transplant recipients increases vulnerability to glucocorticoid-induced osteoporotic fractures is increased [1,2]. Our institution offers LT recipients protocolized antiresorptive therapy, with zoledronic acid (ZA) used first line.

METHODS: Adults who underwent LT from January 2012 to December 2018 and survived at least 6 months were retrospectively studied. Coprimary outcomes were incidence, prevalence, and predictors of osteoporotic fractures and major osteoporotic fractures post-LT.

RESULTS: Four hundred and five LT recipients (41% female, median age 59 years) had a median follow-up of 4.9 years (interquartile range 3.4-6.7). Osteoporotic fracture prevalence was 12% (n = 49) pre-LT and 15% (n = 60) post-LT. Major osteoporotic fracture post-LT occurred in 11% (n = 45). Antiresorptive therapy was received by 47% pre- and 89% post-LT. On multivariate analysis, risk factors for osteoporotic fracture were pre-LT osteoporotic fracture (hazard ratio (HR) 2.32 (95% confidence interval (CI) 1.09-4.96)), female sex (HR 2.08 (95% CI 1.09-3.94)), glucocorticoid use pre-LT (HR 2.08

(95% CI 1.09-3.99)), and time (months) to first ZA infusion post-LT (HR 1.04 (95% CI 1.01-1.06)). Risk factors for major osteoporotic fracture were pre-LT osteoporotic fracture, female sex, age, and time to first ZA infusion.

Risk of fracture also varied depending on pre-existing lung disease. Prevalence of fracture were 3% (2/58) for those with Cystic Fibrosis (CF), 16% (32/194) for patients with Obstructive Lung Disease, 17% (19/114) for those with Interstitial Lung Disease, 8% (2/26) for pulmonary hypertension, and 23% (3/13) of those with non-CF Bronchiectasis.

CONCLUSION: LT recipients receiving protocolized antiresorptive treatment post-LT had a low incidence of osteoporotic fracture.

1. Chambers DC, Cherikh WS, Harhay MO, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: thirty-sixth adult lung and heart-lung transplantation Report-2019; Focus theme: Donor and recipient size match. J Heart Lung Transplant 2019;38:1042-55. https://doi.org/10. 1016/j.healun.2019.08.001.
2. Wigfield CH, Buie V, Onsager D. "Age" in lung transplantation: factors related to outcomes and other considerations. Curr Pulmonol Rep. 2016;5:152-158. doi: 10.1007/s13665-016-0151-y. Epub 2016 Aug 13. PMID: 27610336; PMCID: PMC4992499.

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Psychotropic medication use and bone loss in men

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Psychotropic medication use has been shown to be associated with decreased bone mineral density (BMD), quality and increased fractures. Less is known about psychotropic use and associated bone loss over time. Data from 941 men (≥20 years) participating in the Geelong Osteoporosis Study were used in this longitudinal study. BMD (g/cm^2) at the spine and hip were measured using dual-energy X-ray absorptiometry at baseline, 5 and 15-years post-baseline. Body mass index (BMI) was

calculated, lifestyle factors and medication use self-reported and socioeconomic status was determined. Mood and anxiety disorders were identified using a clinical interview (SCID-I/NP). Multivariable linear regression was used to determine the association between psychotropic medication use and change in BMD over time, before and after adjusting for potential confounders. Over the study period (median 13.2yrs), psychotropic use was adversely associated with change in BMD at the spine (unadjusted mean difference -0.065g/cm^2, 95% CI -0.097, -0.032, p<0.001) and hip (-0.038g/cm^2, 95% CI -0.059, -0.011, p=0.001). BMI was identified as an effect modifier. Psychotropic use was associated with spine and hip bone loss at the 25th (adjusted mean difference -0.079g/cm^2, 95% CI -0.124, -0.035, p<0.001 and -0.059g/cm^2, 95% CI -0.085, -0.033, p<0.001, respectively) and 50th percentile (adjusted mean difference -0.055 g/cm^2, 95% CI -0.124, -0.035, p=0.002 and -0.038g/cm^2, 95% CI -0.059, -0.017, p<0.001, respectively), but not the 75th percentile of BMI. Our data indicate that psychotropic use is associated with bone loss in non-obese men.

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Hypercalcaemia in a tiger man

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Hypercalcaemia is attributable to primary hyperparathyroidism or malignancy in up to 90 percent of cases.[1] Less common aetiologies include granulomatous disorders such as sarcoidosis that lead to increased gastrointestinal absorption of calcium driven by elevated 1,25-dihydroxyvitamin D (calcitriol) levels due to increased 1-α-hydroxylase activity.[1, 2] Whilst it is estimated that sarcoidosis-related myopathy occurs subclinically in up to 50-80 percent of patients with sarcoidosis, symptomatic skeletal muscle involvement is considered to be rare.[3] Furthermore, hypercalcaemia has generally not been associated with sarcoid-related myopathy[3]. We report on an unusual case of parathyroid hormone (PTH) independent hypercalcaemia associated with imaging features highly suggestive of sarcoid-related myopathy.

An 87-year-old man was referred with severe hypercalcaemia (corrected calcium 3.47 mmol/L). His only symptoms were of proximal lower limb myalgia over several months, postural palpitations and dizziness. His past medical history was significant for treated localised prostate cancer and colorectal adenocarcinoma, osteoporosis, stage 3B chronic kidney disease, paroxysmal atrial fibrillation, stroke and hypertension. His salient regular medications included colecalciferol and denosumab. Examination was unremarkable without any evidence of obvious proximal muscle weakness, bony

tenderness or lymphadenopathy. Initial investigations confirmed severe hypercalcaemia with a corrected calcium of 3.22 mmol/L (ionised calcium 1.65 mmol/L) with an accompanying phosphate of 1.60 mmol/L and 25-vitamin D of 53 nmol/L. He was treated with intravenous fluids, calcitonin and denosumab 60mg subcutaneously. Further investigations revealed a suppressed PTH level of 1.2 pmol/L, normal thyroid function tests, mildly elevated creatine kinase (429 U/L), normal serum ACE level (41 IU/L), and an elevated lactate dehydrogenase (370 IU/L) and erythrocyte sedimentation rate (14 mm/h). Cancer, including myeloma, screening markers were unremarkable. A whole-body technetium-99m bone scan yielded no abnormal focal uptake and a non-contrast CT brain, chest, abdomen and pelvis was unrevealing. Following a hospital re-presentation with hypercalcaemia, previously pending results revealed a markedly elevated 1,25-dihydroxy Vitamin D level at 350 pmol/L with no known exogenous calcitriol intake. Unfortunately, no PTH-related peptide level was available. An F-18 FDG -PET/CT was performed and found a highly abnormal distribution of FDG avidity with predominant appendicular muscular uptake described as 'tiger-stripes' which are suggestive of muscular sarcoidosis with nil uptake elsewhere. Anti-nuclear matrix protein 2 (NPX2) myositis antibody positivity was equivocal in subsequent testing, but other rheumatological and infective screening tests were unremarkable. Unilateral muscle biopsy was eventually performed however suffered from a significant delay of 16 days since PET/CT imaging. In contrast to findings from PET/CT imaging, biopsy of skeletal muscle in the right thigh supported a diagnosis of an NXP2/paraneoplastic myositis with no evidence of granulomas. Interestingly, whilst awaiting muscle biopsy, the patient developed hypocalcaemia requiring calcium supplementation during outpatient follow up and remained normocalcaemic. Steroid treatment and further investigation and surveillance was considered however the patient opted for a watchful waiting approach given his comorbidities and minimal symptomatic burden.

Hypercalcaemia in sarcoidosis is well-recognised however this is rarely observed in those with isolated muscular involvement[2]. Nevertheless, there have been several case reports describing this clinical association.[4,5] A case series of 3 hypercalcaemia cases with muscular FDG uptake and non-caseating granulomas on muscle biopsy was described in 2016[3]. Subsequently, several similar cases have been reported[6-11], with most reporting on marked clinical and biochemical recovery following steroid therapy. The term 'tiger-man sign', which describes the diffuse muscle FDG uptake as seen in our present case, was first utilised by Wieërs et al.[5] however use of this terminology in cases of hypercalcaemia with similar FDG PET/CT imaging findings seems to be non-universal despite descriptions of imaging features being quite similar. In our present case, NXP2-related myositis posed a potential differential aetiology for hypercalcaemia

however dermatomyositis-related hypercalcaemia has been related to regression of calcific deposits rather than increased 1,25-dihydroxyvitamin D[13-15].

This case highlights the potential challenges in establishing underlying processes driving PTH-independent hypercalcaemia. Testing in a concurrent, rather than stepwise, approach in severe hypercalcaemia has been suggested unless there are suspicions for a specific underlying aetiology[1]. In the present case, perhaps a more expeditious approach to FDG-PET/CT imaging may have led to timelier biopsy. It is well recognised that sarcoidosis can resolve spontaneously or display a waxing and waning picture.[16] Given the significant delay to biopsy, coupled with self-resolution and development of hypocalcaemia, and the potential for sampling error with a unifocal biopsy, it is possible that a histological diagnosis had been missed. Whilst remaining a rare cause of hypercalcaemia, timely investigations including FDG-PET/CT imaging following negative initial investigations may allow for earlier institution of effective aetiology-directed therapy in similar unusual cases of PTH-independent hypercalcaemia.

Take home messages:

- In severe PTH-independent hypercalcaemia, a concurrent, rather than stepwise, testing approach to elucidate the underlying aetiology should be considered unless there are strong suspicions for a specific cause.

- The 'tiger man sign', which describes diffuse muscular uptake on FDG-PET/CT often involving appendicular musculature, is suggestive of muscular sarcoidosis.

- Although unusual, hypercalcaemia related to muscular sarcoidosis appears to respond well to steroid therapy.

- Delays in appropriate investigations may impact diagnostic yield and therefore limit formulation of optimal surveillance and therapeutic strategies.

1. Walker MD, Shane E Hypercalcemia: A Review. Jama 2022; 328: 1624-36.
2. Gwadera Ł, Białas AJ, Iwański MA, Górski P, Piotrowski WJ Sarcoidosis and calcium homeostasis disturbances-Do we know where we stand? Chronic respiratory disease 2019; 16: 1479973119878713.
3. Mageau A, Rigolet A, Benali K et al. Life-Threatening Hypercalcemia Revealing Diffuse and Isolated Acute Sarcoid-Like Myositis: A New Entity? (A Case-Series). Medicine 2016; 95: e3089.

4. Kallas M, Green F, Hewison M, White C, Kline G Rare causes of calcitriol-mediated hypercalcemia: a case report and literature review. The Journal of clinical endocrinology and metabolism 2010; 95: 3111-7.
5. Wieërs G, Lhommel R, Lecouvet F, Van den Bergh P, Lambert M A tiger man. Lancet (London, England) 2012; 380: 1859.
6. Orandi AB, Eutsler E, Ferguson C, White AJ, Kitcharoensakkul M Sarcoidosis presenting as granulomatous myositis in a 16-year-old adolescent. Pediatric rheumatology online journal 2016; 14: 59.
7. Caré W, Blanc E, Cournac JM, Doutrelon C, Aletti M, Lecoules S Hypercalcemia revealing diffuse granulomatous myositis. European journal of nuclear medicine and molecular imaging 2017; 44: 1413-4.
8. Dierks A, Kircher M, Schmid SJ, Kramer D, Buck AK, Lapa C Tiger man sign in sarcoid myopathy. European journal of nuclear medicine and molecular imaging 2019; 46: 1039-40.
9. Uslar T, Olmos R, Godoy-Santin J, Mellado P, Gonzalez G Sarcoid-like granulomatous myositis-associated hypercalcemia. An infrequent case to consider. Medicina 2021; 81: 462-6.
10. Muse A, Cates M, Rogers P, Evans M, Walker J 'Tiger woman sign' hypercalcaemia: a diagnostic challenge. Clinical medicine (London, England) 2021; 21: 73-5.
11. Karthik V, Roshan R, Jabbar PK, Nair A Isolated muscular sarcoidosis presenting as hypercalcaemic renal failure. BMJ case reports 2023; 16.
12. Milojevic IG, Sobic-Saranovic D, Milojevic B, Artiko VM Muscular sarcoidosis in the eyes of (18) F-FDG PET/CT. Journal of clinical ultrasound : JCU 2022; 50: 399-404.
13. Wilsher ML, Holdaway IM, North JD Hypercalcaemia during resolution of calcinosis in juvenile dermatomyositis. British medical journal (Clinical research ed) 1984; 288: 1345.
14. Ostrov BE, Goldsmith DP, Eichenfield AH, Athreya BH Hypercalcemia during the resolution of calcinosis universalis in juvenile dermatomyositis. The Journal of rheumatology 1991; 18: 1730-4.
15. Chiu HH, Remalante PP, Nacianceno P, Velasco R, Larrazabal R, Zamora G Dermatomyositis Presenting as Life-threatening Hypercalcemia. J Rheum Dis 2020; 27: 285-9.

16. Chiu HH, Remalante PP, Nacianceno P, Velasco R, Larrazabal R, Zamora G Dermatomyositis Presenting as Life-threatening Hypercalcemia. J Rheum Dis 2020; 27: 285-9.

17. Drent M, Crouser ED, Grunewald J Challenges of Sarcoidosis and Its Management. The New England journal of medicine 2021; 385: 1018-32.

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Title: Menopause-related bone loss in women living with HIV: A systematic review

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Background: Improved life expectancy due to antiretroviral therapy (ART) means women living with HIV (WLH) are increasingly at risk of age-related diseases such as osteoporosis. While HIV and its treatment can negatively impact bone health, data from WLH across menopause, when bone losses are already high, are limited.

Methods: We systematically searched five electronic databases (MEDLINE, Embase, Global Health, Scopus, and Web of Science) up to April 22, 2025, using a search strategy combining terms related to HIV, menopause, and bone measurements. Cross-

sectional and longitudinal studies assessing bone measures in mid-life WLH, and their comparators without HIV, were included. Quality assessment was performed using the Joanna Briggs Institute Critical Appraisal tools.

Results: After deduplication, 1,057 articles were screened, with 17 records included following full-text review. The majority (9/17) were from North America, with the remainder from Africa (5/17) and South America (3/17). Dual-energy X-ray absorptiometry-based cross-sectional studies consistently found WLH had lower areal bone mineral density (aBMD) than peers without HIV at a similar menopause stage. Longitudinal studies also suggested that WLH experience greater menopause-related bone loss than those living without HIV. Computed Tomography-based studies (3/17) reported trabecular compartment-specific bone deficits in WLH, relative to women without HIV. Associations between ART use, particularly tenofovir disoproxil fumarate (TDF), and bone outcomes were conflicting, possibly driven by the ubiquity of TDF as a first-line therapy across Africa. Overall, study quality was high in most domains, though longitudinal studies suffered from incomplete follow-up (**Figure**).

Conclusion: This systematic review highlights that WLH have poorer bone-related outcomes, including lower BMD, during all stages of menopause transition, experience greater menopause-related bone losses, predominantly in trabecular-rich sites compared to women without HIV. These findings highlight the need for context-specific targeted bone health assessment and management strategies for this underserved population with elevated fracture risk.

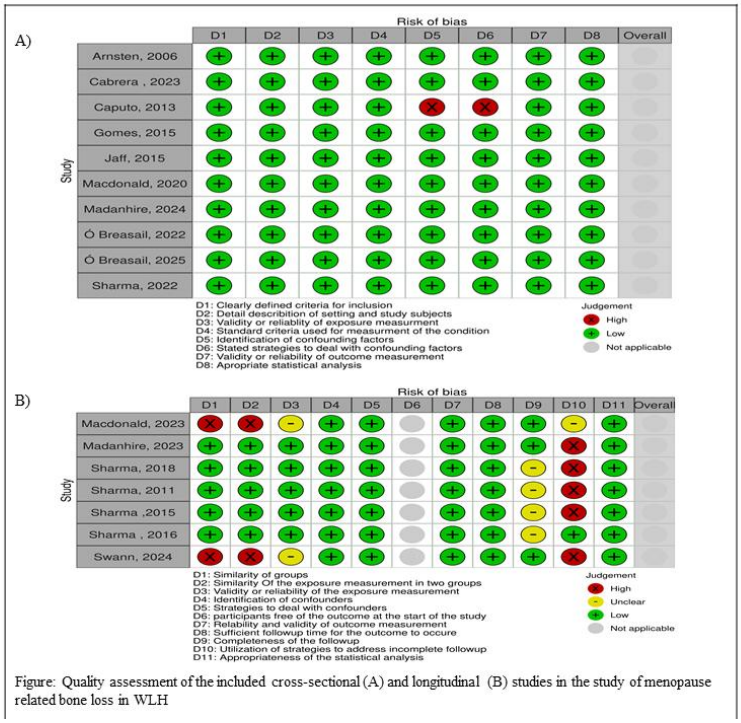

Figure: Quality assessment of the included cross-sectional (A) and longitudinal (B) studies in the study of menopause related bone loss in WLH

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Challenges in management of low bone density in a young man with malabsorption and recurrent iron infusions

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Hypophosphataemia and osteomalacia after recurrent intravenous iron infusions (IVI) are a known phenomenon[1-3]. However, the best treatment approach for patients with established osteomalacia who require repeated infusions and at high risk for osteoporosis remains unknown.

We present the case of a 23-year-old male referred to metabolic bone clinic with reduced bone density without fracture. The patient has a history of idiopathic megarectum with chronic constipation and pseudo-obstruction with recurrent iron deficiency anaemia requiring repeated IVI. There is also a history of mild asthma treated with oral glucocorticoids in childhood, mild intellectual disability, and ureteric obstruction. He receives Ferric Carboxymaltose (FCM) infusions every three months. Hypophosphataemia (0.5-0.55mmol/L, reference 0.8-1.5mmol/L) occurred frequently two weeks post-FCM infusion. Screening DEXA showed reduced Z scores of -2.5 at the femoral neck and -2.6 at the lumbar spine. ALP and hormonal profiles, including total testosterone and thyroid stimulating hormone, were normal. C-telopeptide levels were elevated (720ng/L, ref 170-600ng/L[4]). Concurrent Vitamin D deficiency (17nmol/L, reference 50-250nmol/L) was addressed. Parathyroid hormone was mildly elevated (9.6pmol/L, ref 1.6-6.9pmol/L). A clinical diagnosis of osteomalacia secondary to recurrent hypophosphataemia post IVI was made without bone biopsy. Conservative management of idiopathic megarectum has been unsuccessful. Surgical management is being considered which may worsen malabsorption and increase IVI requirements.

This case presents an ongoing management challenge as consensus guidelines for managing hypophosphataemia post IVI are not available. The treatment of hypophosphataemia and the timing and duration of monitoring post infusion are unclear. The use of iron formulations with a lower risk of hypophosphataemia, such as Ferric Derisomaltose[2, 5], particularly in patients with demonstrated hypophosphatemia, should be first line. Although BMD can improve with treatment of osteomalacia[6], there is no clear guidance to support when it is safe to initiate osteoporosis treatment. Anti-resorptive therapy in patients with untreated osteomalacia may be harmful[7].

1. Vilaca, T, Velmurugran N, Smith C, et al. Osteomalacia as a complication of Intravenous Iron Infusion: A Systematic Review of Case Reports. Journal of Bone and Mineral Research. 2022;37(6):1188-1199.
2. Schaefer B, Tobiasch M, Wagner S, et al. Hypophosphatemia after intravenous iron therapy: Comprehensive review of clinical findings and recommendations for management. Bone. 2022;154:116202.
3. von Brackel F, Grambeck J, Barvencik F, et al. In-depth clinical characterization of intravenous iron infusion-induced hypophosphatemic osteomalacia and its resolution. JBMR Plus. 2025;9(1):139.
4. Jenkins N, Black M, Paul E, et al. Age-related reference intervals for bone turnover markers from an Australian reference population. Bone. 2013;55(2):271-6.
5. Zoller H, Wolf M, Blumenstein I, et al. Hypophosphataemia following ferric derisomaltose and ferric carboxymaltose in patients with iron deficiency anaemia due to inflammatory bowel disease (PHOSPHARE-IBD): a randomised clinical trial. Gut. 2023;72(4):644.
6. Guo Y, Zhou YH, Wu XP, et al. Changes in Bone Mineral Density Following Conventional Oral Phosphonate Treatment of Hypophosphatemic Osteomalacia: A Non-Randomized Controlled Study. Int J Gen Med. 2021;14:7925-31.
7. Arboleya L, Braña I, Pardo Eet al. Osteomalacia in Adults: A Practical Insight for Clinicians. Journal of Clinical Medicine. 2023; 12(7).

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[4-(Methylthio) phenylthio] methane bisphosphonate (MPMBP) prevents deterioration of bone microarchitecture, reduction of soleus muscle mass, and increase of visceral fat in elastase-induced emphysema mice

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Introduction:
Chronic Obstructive Pulmonary Disease (COPD) cause disorders of bone, muscle and lipid metabolism as extrapulmonary lesions. The disorders are likely due to systemic inflammation and oxidative stress underlying the pulmonary emphysema. [4-(Methylthio) phenylthio] methane bisphosphonate (MPMBP) is a novel bisphosphonate with anti-inflammatory and antioxidant properties that has the potential to prevent COPD-related complications. The aim of this study is to examine whether MPMBP prevents disorders of bone, muscle and lipid metabolism in elastase-induced emphysema mice.

Methods:
Twelve-week-old male C57BL/6J mice received intratracheal saline (S group) or porcine pancreatic elastase (E group), and from 16 weeks weekly subcutaneous injections of vehicle (V group) or 2.4 mg/kg MPMBP (M group), forming four groups (SV, SM, EV, EM). At 24 weeks, micro-CT (μCT) assessed fat volume. Then bilateral femur and tibia, lungs, lower limb muscle tissue, gonadal fat tissue, inguinal fat tissue, and dorsal brown adipose tissue were collected. The weights of the muscle and fat tissues were measured using a scale. Bone microarchitecture was analyzed by μCT and histomorphometry.

Results:
The E group had emphysematous lungs.The EV group showed a significant decrease in bone formation and bone volume compared to the SV group, whereas the EM group maintained these parameters at levels comparable to the SV group. Furthermore, no significant reduction in bone resorption parameters was observed in the EM group. Regarding muscle and fat tissues, the EV group exhibited an increase in visceral fat and a decrease in soleus muscle tissue mass compared to the SV group, while the EM group was rescued from these changes.

Conclusion:

MPMBP prevents disorders of bone, muscle and lipid metabolism in elastase-induced emphysema mice, suggesting its potential to rescue extrapulmonary lesions s of COPD.

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Rock solid but fragile: a case of autosomal dominant osteopetrosis

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We describe the case of a woman in her late 30s presenting with autosomal dominant osteopetrosis (ADO). Her disease course has been complicated by more than 22 fractures across her life. Although our patient has declined to undergo genetic testing, the diagnosis has been made based on clinical features, in addition to a history of the same condition in her mother and grandmother. Her mother passed away in her 50s from complications after hip fracture.

The patient became known to our health service after requiring medical repatriation from Central America following a fall while travelling in 2019. During this fall she sustained right humerus and left femoral fractures, both of which required surgical management with open reduction and internal fixation (ORIF). These fractures were complicated by issues with fracture non-union, wound infection, and chronic osteomyelitis requiring long-term antibiotic suppression. She does not have evidence of dental involvement, cranial nerve compromise or bone marrow failure. Her predominant management issues relate to her frequent fractures, poor fracture and wound healing, and the impact on her mobility and functional status. Her management has required a multidisciplinary team approach, involving the Orthopaedic team, Endocrinology team, and allied health, in particular physiotherapy. She participates in a variety of different exercise modalities to maintain muscle strength and mobility, and engages with physiotherapy regularly to assist with injury recovery and pain management.

With respect to investigations, her calcium, phosphate and parathyroid hormone levels are within normal limits, and she is vitamin D replete at 86nmol/L. She has a mild normocytic anaemia. X-rays of the long bones demonstrate diffuse sclerosis, while ‘Erlenmeyer flask deformity’ of the distal femur is also seen, consistent with osteopetrosis (Figure 1). Bone mineral densitometry shows an abnormally elevated T-score of 20.9 at the AP spine and 13.4 at the right femoral neck.

Osteopetrosis encompasses a group of conditions characterised by reduced bone resorption by osteoclasts, resulting in highly dense bone that is structurally weak and prone to fracture (1). Other than increased fracture risk, abnormal bone remodelling

can lead to skeletal deformity, which may result in neurological compromise if involving the cranial nerve foramina. Affected individuals can also have dental abnormalities or cytopaenias from bone marrow compromise related to bone expansion into marrow cavities (2). The most common form of osteopetrosis seen in adults is autosomal dominant osteoporosis (ADO), with an estimated incidence of 1 in 20,000 (2). The majority of cases have mutations in CLCN7, which encodes the chloride channel 7 on the osteoclast vesicular membrane (2).

Fracture risk is mediated by the uneven formation of poor-quality bone, and typically fractures occur under tensile stress, generally occurring at right angles to the cortex (1). The unique bone architecture makes operative management of fractures challenging, as the bone is resistant to drilling or holding screws, and is prone to iatrogenic fracture. Post-operatively, defective remodelling can result in non-union and implant failure, and repair can be complicated by osteomyelitis, as in our patient (1).

At present, there are no disease-modifying treatments for non-infantile autosomal dominant osteopetrosis. Management focuses on managing and preventing complications, and a multidisciplinary team approach to management is essential (3). Adequate calcium intake and vitamin D exposure should be ensured. Surgical management of fractures requires specialist expertise, due to the procedural challenges with fracture repair and the risk of complications. ORIF is favoured over intramedullary nail (IMN) for fixation of long bone fractures, as narrowing of the medullary canals limits use of IMN. However, limited intramedullary haematopoeisis in these patients can delay fracture healing due to poor periosteal blood supply (4). Pain management is also an important consideration, however studies into optimal treatment modalities are lacking. A French survey of 16 patients with ADO found that 86% patients reported pain as a feature of their disease, both from acute fractures and generalised pain in non-fractured bones (3). 66% of participants reported the disease impacts their professional life (3).

Our patient has a particular focus on maintaining her functional independence and mobility in the context of this condition, as well as managing her pain with non-pharmacological strategies where possible. In the absence of disease-modifying treatments, our current management strategies focus on preventing further falls and fractures, as well as supporting maintenance of mobility and function. This case illustrates the substantial impact ADO can have on quality of life, while also highlighting the need for further research into the optimal approaches to pain management, physiotherapy and exercise.

Take home messages:

- Osteopetrosis is a lifelong condition, with the management focussed on preventing and treating the complications
- Issues with recurrent fractures, poor fracture and wound healing, and chronic infection are common, and require specialist Orthopaedic input
- Acute and chronic pain management is an important aspect of care
- A multidisciplinary team approach with medical and surgical specialists, as well as allied health, is essential to manage this complex and heterogenous condition

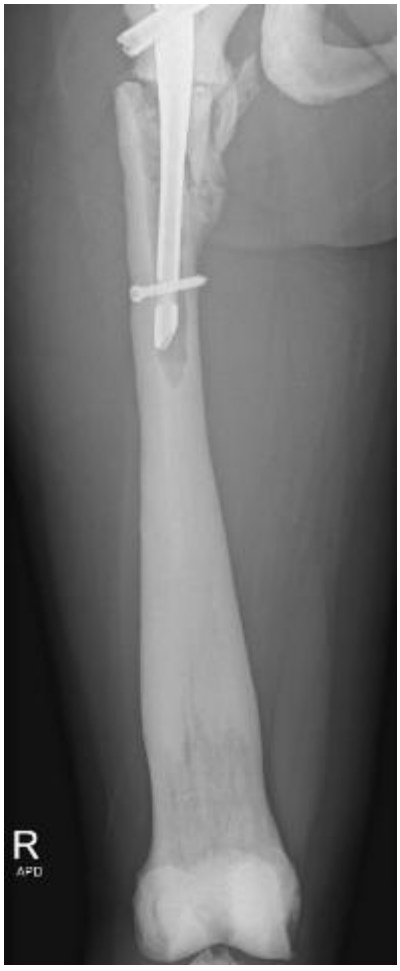

Figure 1. X-ray of right femur

1. 1. Wu, C., Econs, M., DiMeglio, L., Insogna, K., Levine, M., Orchard, P., Miller, W., Petryk, A., Rush, E., Shoback, D., Ward, L., Polgreen, L. 2017, 'Diagnosis and Management of Osteopetrosis: Consensus Guidelines From the Osteopetrosis Working Group', J Clin Endocrinol Metab, vol 102(9), pp3111-3123.

2. 2. Funck-Brentano, T., Zillikens, M., Clunie, G., Siggelkow, H., Appelman-Dijkstra, N., Cohen-Solal, M. 2024, 'Osteopetrosis and related osteoclast disorders in adults: A review and knowledge gaps On behalf of the European calcified tissue society and ERN BOND', European Journal of Medical Genetics, vol 69.

3. 3. Cohne-Solal, M., Collet, C., Bizot, P., Pavis, C., Funck-Brentano, T. 2023, 'Osteopetrosis: the patient point of view and medical challenges', Bone, vol 167.

4. 4. Yang H, Shao GX, Du ZW, Li ZW 2021, 'Treatment for subtrochanteric fracture and subsequent nonunion in an adult patient with osteopetrosis: A case report and review of the literature', World J Clin Cases, vol 9(35), pp11007-11015.

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Anabolic effects of romosozumab in an Australian context with notable prior anti-resorptive treatment

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Background: Romosozumab has shown strong efficacy in trials, but real-world evidence, especially in Australian populations with significant prior anti-resorptive use, is limited. Evaluating its effectiveness and identifying predictors of response in these complex patients is essential to guide treatment selection.

Aim: This study evaluated real-world outcomes of romosozumab in an Australian cohort with significant prior anti-resorptive therapy and identified factors predicting an optimal bone mineral density (BMD) response.

Method: This retrospective cohort study included 53 patients from two Australian tertiary hospitals who received 12 months of romosozumab between 2021 and 2023, all with baseline and follow-up DXA scans. Most patients (~85%) had considerable prior anti-resorptive treatment. Comparative data from Australian cohorts treated with teriparatide (n=54) or anti-resorptive treatments (n=60) were also included. Linear regression analysis explored the relationship between potential confounders and changes in lumbar spine (LS) BMD.

Results: Significant BMD increases were observed in the romosozumab group at the lumbar spine, total hip, and femoral neck ($p<0.05$). LS BMD gains were substantially higher in the romosozumab group compared to both teriparatide (11.3±8.2% vs. 5.0±8.6%, $p<0.001$) and anti-resorptive treatments (11.4±8.6% vs. 6.6±6.1%, $p=0.004$). Treatment-naïve patients trended towards greater LS BMD improvements (14.0±6.6%) compared to those previously treated (10.7±8.5%, $p=0.220$). Linear regression showed lower baseline LS BMD ($\beta=-13.14$, $p=0.001$), more prior vertebral fractures ($\beta=-1.38$, $p=0.004$), and longer prior anti-resorptive treatment duration ($\beta=-0.36$, $p=0.003$) were independently associated with smaller LS BMD gains. Despite this, romosozumab still conferred significantly higher LS BMD gains compared to both teriparatide and anti-resorptive treatments ($\beta=-4.18$, $p<0.001$).

Conclusion: These Australian real-world findings confirm romosozumab's effectiveness even with significant prior anti-resorptive use. While prior exposure can moderate anabolic effects, romosozumab remains superior, with baseline characteristics providing useful predictors to optimise outcomes.

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Patients With Chronic Kidney Disease Have Accelerated Microarchitectural Bone Deterioration

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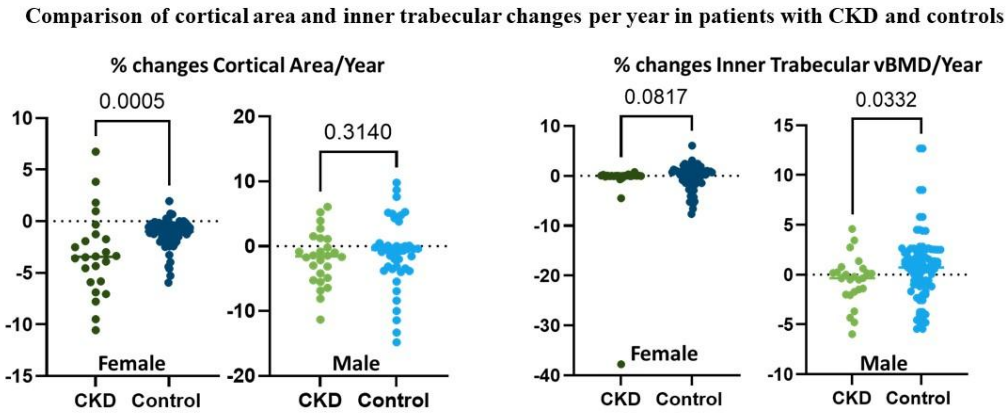

Background:

Unbalanced remodelling upon intracortical and medullary canal surfaces of cortical bone enlarge these surfaces facilitating more frequent unbalanced remodelling events that erode the ever-decreasing cortical bone volume. By contrast, unbalanced remodelling upon surfaces of trabecular plates perforate and remove them with their surfaces. We therefore hypothesised that CKD accelerates cortical bone loss, but trabecular bone loss eventually ceases as trabeculae disappear; particularly in postmenopausal women.

Methods:

Distal radius microarchitecture was quantified using serial High Resolution peripheral Quantitative Computed Tomography (HR-pQCT) scans in patients with CKD (24F, age 62.0 [52.6-68.8]), (26M, age 54.8[53.2-58.1]) followed for a median of 4.6(2.9–7.2) years, and controls (67F, 45M) followed for 3.7(1.4–7.9) years.

Results:

Respective changes (%/yr) in microarchitecture relative to changes in controls were: in women, cortical area decreased faster (-3.4[-5.9 to -1.4] vs -0.99[2.0 to -0.46], p=0.0005); change in cortical volumetric bone mineral density (vBMD) (-1.38[1.29] vs -1.06[0.69] was not significant (p=0.14). Inner trabecular vBMD was unchanged (0.0[-0.1 to 0.05) vs 0.68[-0.19 to 1.2], p=0.08). In men, greater decreases in cortical area (-1.6[-4.9 to 1.1] vs -0.56[-3.5 to 0.29] did not achieve significance (p=0.31) but cortical vBMD decreased (-0.96[-1.4 to -0.04] vs 0.06[-0.82 to 1.6], p=0.024). However, unlike in women, there was a greater decrease in inner trabecular vBMD relative to controls (-0.35[-1.85 to 0.43] vs. 0.72[0-0.1to 2.5], p=0.03)

Conclusion:

Within the constraints imposed by the small sample, we infer that microarchitectural deterioration is severe in CKD and continues, particularly in cortical bone, signaling the need for antiresorptive therapy to slow bone loss and anabolic therapy to reconstruct the skeleton.

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The interplay between histone/DNA modifying enzymes and metabolites in regulating bone aging and metabolism

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Epigenetic enzymes act as crucial conduits allowing environmental and diet cues to transmit their effect on to the genome and have emerged as critical regulators of bone marrow stromal cell (BMSC) function and skeletal integrity. We have began deciphering the function of histone and DNA modifying enzymes such as Enhancer of Zeste homologue 2 (Ezh2) and the TET DNA dioxygenases 1 and 2 on bone development and aging. Our studies have revealed essential functions in bone development and deregulation during osteoporosis and general aging leading to trabecular bone loss, reduced osteoblast numbers, and lineage skewing favouring the adipocyte lineage at the expense of osteoblasts. Transcriptomic analyses has revealed pathways that are important for osteogenesis and fat metabolism including Wnt/Bmp signalling, novel zinc finger and homeobox transcription factors and novel mediators of IGF-1 signalling / mTOR pathway whose dysregulation contributes to the skeletal phenotypes. In parallel, we are investigating the impact of diet on BMSC biology utilising the high fat diet induced diabetes model and hyperglycaemic conditions showing drastic effects on lineage determination, oxidative stress, senescence, and DNA damage. We have utilised metabolomic profiling to uncover metabolites that are regulators of BMSC function and deregulated by hyperglycaemia. Together, these findings reveal converging epigenetic, transcriptomic and metabolic pathways that govern BMSC fate, bone integrity, and aging uncovering potential new future strategies for age- and diabetes-related bone loss.

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What outcomes matter to people living with or at risk of minimal trauma fracture? Findings from the 'Measures that Matter' survey

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Background and Aim

To meet patient needs, we must understand the therapeutic outcomes that are meaningful and valuable to them. Few studies have explored the outcomes that really matter to patients living at increased risk of minimal trauma fracture (MTF). The aim of the 'Measures that Matter' survey was to determine and rank the outcomes that are important to this population.

Methods

A survey of outcomes related to the diagnosis and management of conditions and sequelae of low BMD, and other outcomes typically included in musculoskeletal research, was developed through an iterative process with consumer advocates and clinicians. It was pilot tested in postmenopausal women with low BMD (n=5) and wording adjusted for clarity. The final survey included 1 open- and 27 closed-ended (3 using Likert scale scoring and ranking) questions delivered online (LimeSurvey, Version 5.6.7) for 11 weeks (Aug-Oct 2023). Men and women over 45 at risk of MFT were recruited through university-based email broadcasts, social media advertising, community groups, and Healthy Bones Australia subscriber invitation.

Results

A total of 533 respondents (66.8±7.6yrs, 94.6% female) completed the survey. Overall, 97.4% self-reported undergoing a diagnostic test (DXA) of BMD, and 37.7% reported a previous MTF. Almost half (45.2%) were taking vitamin D and calcium, and 59.0% reported never having taken anti-osteoporosis medicines. The top five rated items were 'level of independence', 'quality of life', 'confidence in movement and mobility', 'mental

health and wellbeing', and 'ease of bones breaking' (>90% surveyed respondents rated these as 'most important').

Conclusions

By listening to the lived experiences of people at risk of MTF, researchers, health-care providers, and policy makers can focus therapeutic strategies on outcomes that truly matter to patients. Our survey findings suggest outcomes other than BMD per se are the most important to people living with or at increased risk of MTF.

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Systemic mastocytosis and osteoporosis - a clinical case and review of the literature

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Background: Although systematic mastocytosis (SM) is uncommon with a prevalence of 1 in 10,000, osteoporosis is present approximately 22% of cases (1, 2). The objective of this report is to describe a case of SM associated with osteoporosis and review the current management strategies.

Case report: We describe a 41-year-old man referred for management of Type 1 Diabetes Mellitus. He had a history of a previous vertebral fracture with dual-energy X-ray absorptiometry (DEXA) scan showing spinal osteoporosis (L1-4 BMD 0.856g/cm^2, T-score -3.0, left femoral neck BMD 1.031g/cm^2, T-score -0.3 and left total femur BMD 1.016g/cm^2, T-score -0.6). Clinically, he demonstrated pigmented macules, papules and dermatographism. Investigations showed multiple elevated serum tryptase levels and subsequent bone marrow biopsy confirmed SM, the latter of which was complicated by right sacral alar fracture, without any associated lytic lesions. Osteoporosis and cutaneous lesion were the sole features, with a subtype diagnosis of indolent systemic mastocytosis (ISM) for which he was commenced on oral risedronate therapy and has ongoing surveillance with a multidisciplinary team.

Discussion: Osteoporosis secondary to SM involves several mediators, including tryptase, histamine, heparin and multiple inflammatory cytokines. There is preferential trabecular bone involvement, likely due to the increased clonal mast cells colonising the bone marrow (3, 4). Skin lesions are detected in less than half of patients with osteoporosis caused by ISM and thus, clinicians need a low threshold for suspicion as osteoporosis may be the only presenting feature (5). Additionally, observational data has demonstrated ISM in 0.5% of cases of osteoporosis, however in young men this proportion increased up to 5.8%. Bisphosphonates are the main treatment of choice, however this is mainly based on low quality evidence and expert opinion (6).

Conclusion: This case reinforces the need for increased vigilance of SM as an uncommon and potential differential for unexplained osteoporosis.

1. 1. Orphanet: an online rare disease and orphan drug data base [Internet]. 1999 [cited 12th June 2025]. Available from: https://www.orpha.net/en/disease/detail/2467.
2. 2. Ungerstedt J, Ljung C, Klimkowska M, Gülen T. Clinical Outcomes of Adults with Systemic Mastocytosis: A 15-Year Multidisciplinary Experience. Cancers (Basel). 2022;14(16).
3. 3. McKenna MJ. Histomorphometric study of mast cells in normal bone, osteoporosis, and mastocytosis using a new stain. Calcified Tissue International. 1994;55(4):257-9.
4. 4. Jankovski L, Rakusa M, Koceva A, Janež A, Kopač P, Jensterle M. Indolent Mastocytosis and Bone Health: Molecular Mechanisms and Emerging Treatment Options. Int J Mol Sci. 2025;26(12).
5. 5. Gehlen M, Schmidt N, Pfeifer M, Balasingam S, Schwarz-Eywill M, Maier A, et al. Osteoporosis Caused by Systemic Mastocytosis: Prevalence in a Cohort of 8392 Patients with Osteoporosis. Calcif Tissue Int. 2021;109(6):685-95.
6. 6. Degboé Y, Nezzar C, Alary P, Maëva M, Bulai Livideanu C, Laroche M. Management of Bone Health in Adult Mastocytosis. Curr Osteoporos Rep. 2025;23(1):10.

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Bone health screening in patients with type 2 diabetes mellitus - a single-centre retrospective audit

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This retrospective audit examines bone mineral density (BMD) screening practices in patients with type 2 diabetes mellitus (T2DM) at St Vincent's Hospital, Sydney. T2DM represents a significant health burden, particularly among older adults, with substantial morbidity and mortality (1). Skeletal fragility is increasingly recognised as a complication of T2DM(2). However, BMD screening using dual-energy X-ray absorptiometry (DXA) underestimates fracture risk in T2DM patients, as BMD is often normal/elevated due to concomitant obesity(3,4). Despite being associated with

elevated fracture risk, there is no current Medicare-funded reimbursement for screening DXA(5) and it is unclear what proportion of T2DM patients undergo bone health assessment, including a BMD scan.

This study aims to evaluate the frequency of bone health assessment (new fractures, back pain, anti-resorptive use or DXA scans) and investigate associations between diabetes-related metabolic factors (glycaemic control, renal function and other diabetes-associated complications) with BMD. Data will be retrospectively collected from approximately 300 patients attending the diabetes clinics between July-December 2023.

In a preliminary analysis of an initial 50 patients, mean age was 70±11.5years, with a mean T2DM duration of 21±12 years. Ten (20%) had a BMD scan within the last 5 years (mean total hip T-score -1.2 ± 1.49) and 6 (12%) had bone health assessment during the consultation, with a documented history of osteoporosis being the predominant rationale. Total hip BMD was positively correlated with BMI, after adjusting for age and T2DM duration. There was no significant association found between total hip BMD and the presence of diabetes complications, insulin use and glycaemic control.

Findings from this audit highlight that bone health is not routinely assessed in T2DM management, potentially related to a lack of guidelines. Further research to establish how metabolic markers can predict poor bone health are required to improve the clinical management of bone health in T2DM.

1. Diabetes: Australian facts, Summary. (2023). Australian Institute of Health and Welfare. https://www.aihw.gov.au/reports/diabetes/diabetes/contents/summary.
2. Janghorbani, M., Van Dam, R. M., Willett, W. C., & Hu, F. B. (2007). Systematic review of type 1 and type 2 diabetes mellitus and risk of fracture. American journal of epidemiology, 166(5), 495–505. https://doi.org/10.1093/aje/kwm106
3. Vestergaard P. (2007). Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes--a meta-analysis. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA, 18(4), 427–444. https://doi.org/10.1007/s00198-006-0253-4
4. Ahmad O.S., Leong A., Miller J.A., Morris J.A., Forgetta V., Mujammami M., Richards J.B. (2017) A Mendelian Randomization Study of the Effect of Type-2 Diabetes and Glycemic Traits on Bone Mineral Density. Journal of bone and mineral research, 32(5): 1072-1081.

5. Bone Density Testing in General practice Healthy Bones Australia (2022) https://healthybonesaustralia.org.au/wp-content/uploads/2023/07/hba-gp-bone-density-brochure-2023-v10.pdf

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Unexplained Fragility Fractures and Elevated IgE: Two Cases Suggesting Hyper-IgE Syndrome and a Novel Adverse Reaction to Romosozumab

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Severe, treatment-refractory or early-onset osteoporosis should prompt evaluation for secondary causes. Causes include endocrine, inflammatory, gastrointestinal, and genetic conditions, among others. Hyper-IgE syndrome (HIES) is a rare primary immunodeficiency disorder characterised by markedly elevated serum IgE, recurrent infections and skeletal anomalies, including osteoporosis and increased fracture burden. We describe two cases of severe osteoporosis in post-menopausal women, both with markedly elevated IgE levels, raising the possibility of underlying HIES.

Case 1, a 56-year-old woman, experienced extensive fragility fractures despite anabolic (teriparatide) and anti-resorptive treatment with fracture burden out of keeping with bone mineral density [baseline bone mineral density (BMD): left femoral neck (LFN) T score -1.5, left total hip (LTH) TS -1.8 and left distal radius (LDR) TS -1.6]. An elevated serum IgE level of 1225 kU/L (<100) was first noted in 2024.

Case 2, a 56-year-old woman with severe osteoporosis [baseline BMD: total lumbar spine (LS, L1-L4) TS -3.5 and LFN TS -2.4] did not respond to bisphosphonate therapy and developed a severe erythematous skin reaction following the fourth dose of romosozumab therapy (Figure 1). Elevated eosinophils 4.5 x 10^9/L (0-0.5) and serum IgE 21,608 kU/L (0-200) were noted. Previous IgE results were also found to be elevated in 2016: 11,704 kU/L (<100). Histology revealed a spongiotic dermatitis with features favouring a drug eruption. She was successfully treated with prednisolone and cyclosporin for four weeks.

This case report highlights two rare but important clinical observations: elevated serum IgE levels in two post-menopausal women with severe osteoporosis raising the possibility of underlying HIES, and an unexpected severe erythematous drug reaction to romosozumab. Ongoing management includes formal genetic testing to confirm the diagnosis, as well as comprehensive evaluation of family members. Further research is

needed to understand the safety profile of anabolic agents like romosozumab in patients with immune dysregulation.

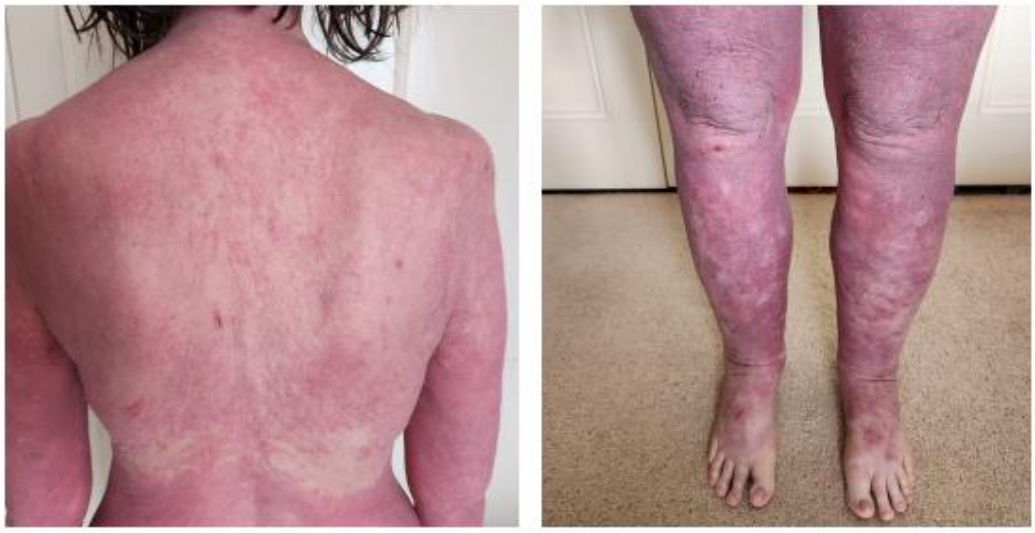

Figure 1. Clinical photographs demonstrating the severe widespread erythematous skin reaction following romosozumab (Case 2)

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The reliability of neonatal screening for developmental dysplasia of the hip in a regional service: How many cases are we not capturing?

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Introduction: Developmental dysplasia of the hip (DDH) represents a spectrum of issues influencing the development of the hip joint. In Australia, it is standard practice to combine universal hip examination in conjunction with selective ultrasound screening to at-risk risk infants soon after birth. However recent evidence in metropolitan Melbourne reported that approximately 50% of cases may not be captured by such protocols. Thus, this project aims to evaluate the how many cases are captured by the neonatal screening program at a regional service in Geelong, Victoria. **Methods:** A retrospective review of medical records was conducted and all new patients that presented to University Hospital (UHG) for screening and/or diagnosis for DDH between January 1st 2015 to December 31st 2017 were included. Only those

that were born at UHG with details on neonatal hip screening results were included. The sensitivity and specificity of the neonatal screening program to detect DDH were employed as measures of diagnostic accuracy. **Results:** There were 1,207 infants of 7367 live births at UHG, of whom 90 were diagnosed with DDH. Of those 40 (44.4%) were captured by neonatal screening and 50 (55.6%) were missed resulting in a 44.4% sensitivity and 94.1% specificity. Those who were born breech were more likely to be captured by neonatal screening (12/40 [30.0%] captured vs 1/50 [2.0%] missed, p>0.001) and those with asymmetrical skin creases were more like to be missed (2/40 [5.0%] captured vs 33/50 [66.0%] missed, p>0.001). **Conclusion:** While neonatal screening has high specificity, however like studies in metropolitan services, more than half of the DDH cases presenting at UHG had negative screening results at birth. This highlights the potential need for a more targeted approach in risk-based screening and the necessity for continued surveillance throughout infancy to account for the developmental nature of this condition.

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Co-designing a digital health tool to support self-management of hypophosphatasia in adults

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Publish consent withheld

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Running on empty: assessing the cost of low energy availability on female athlete bone health through quantitative ultrasound

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An imbalance between energy intake and expenditure, termed low energy availability (LEA), is associated with a 3-5-fold increase in fracture risk. The impacts of LEA are felt heavily by young female athletes, where a period of LEA can threaten both long-term bone health and career longevity. As such, the need for adequate and safe tools to pre-emptively assess and monitor bone health in female athletes is clear. Therefore, this study aimed to apply the radiation free and portable technology of quantitative ultrasound (QUS) to estimate bone health status of subadult female athletes, and understand how personal and athletic attributes, alongside risk of LEA, impacts bone elasticity and architecture.

Method: Twenty female athletes, aged 14 to 30 years, were recruited from the sports of netball and swimming. A contact QUS device was applied to the calcaneus monthly for four months. At each data point, frequency dependent attenuation (FDA), heel velocity, training volume and risk of low energy availability were recorded and analysed.

Results: Group mean relative change was low across all parameters (1.16% FDA, 1.26% normalised FDA, 0.25% velocity), with heel velocity the only parameter to significantly differ between groups based on LEA risk ($p < 0.05$). A significant positive relationship between changes in heel velocity and changes in training was observed only amongst athletes of low risk of LEA ($p = 0.015$). Least significant change (27%) was met positively in four participants, and negatively in one participant.

Conclusion: An elevated risk of LEA minimises the positive effects of exercise load on bone health; bone elasticity (velocity) more so than bone architecture (FDA). This data emphasises the importance of individualised longitudinal assessments of bone health, and highlights QUS as a useful tool to be able to detect individualised changes in bone status over a four-month period.

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B6 toxicity: an important hypocalcaemia mimic

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A 22 year-old male presented with symptomatic hypocalcaemia in the setting of known primary hypoparathyroidism due to Autoimmune Polyendocrine Syndrome type 1 and a concurrent infectious diarrhoeal illness. His symptoms were notable for paraesthesia, weakness, brain fog and atypical chest and limb pain. There was no demonstrable tetany nor muscle spasms. His biochemistry on presentation demonstrated an adjusted calcium level of 1.78mmol/L and an ionised calcium level of 0.96mmol/L.

His remaining manifestations of APS Type 1 were hypoadrenalism, oral candidiasis and emerging hypogonadism. His baseline prescribed medications were 0.75microg Calcitriol BD, 600mg Calcium Carbonate QID, Hydrocortisone 16mg mane, 6mg midi, fludrocortisone 100mcg daily. He was also taking BioMag up to three tablets daily to aid in maintaining an appropriate serum calcium, ashwagandha and intestaselect supplements to aid in his gut health and general wellbeing.

Whilst maintaining a corrected calcium level in the range of 2.0-2.15mmol/L proved difficult with his ongoing diarrhoea and probable malabsorption, it was notable that our patient had persistent symptoms of brain fog, and intermittent paraesthesias despite relative correction of his calcium level. Due to his persistent symptoms, a vitamin B6 level was ordered, returning a value of 709 nmol/L (normal range 35-110). He was subsequently diagnosed with vitamin B6 toxicity and the offending agents; BioMag and ashwagandha were ceased.

Whilst there is an increasing awareness of vitamin B6 toxicity with nutraceuticals[1], this case demonstrates a specific risk in patients with known hypocalcaemia. Currently there are no published case reports of B6 toxicity in persons with a known calcium disorder.

Acute hypocalcaemia typically presents with neuromuscular irritability, peripheral and perioral paraesthesia. Severe acute hypocalcaemia (Corrected Calcium <1.9mmol/L) presents with muscular spasm or tetany[2]. Confusion and agitation may also be present. Profound hypocalcaemia can also lead to QT prolongation and seizure, these signs however, are not relevant to our case.

Vitamin B6 toxicity typically presents as a sensory neuropathy, with a glove and stocking distribution. Additionally, a “disequilibrium syndrome” consisting of hyperaesthesia,

bone pain and muscle weakness has also been described[3]. These symptoms develop secondary to neuronal cell death, which occurs in a dose dependant fashion[4]. Vitamin B6 is abundant in both plant and animal products, with no reported cases of B6 toxicity from diet alone. Toxicity has been shown to develop at high doses acutely (>1000mg/day) and with chronic over supplementation[5]. BioMag supplementation is commonly utilised in persons with hypoparathyroidism due to this tablet containing 301.5mg of Magnesium to aid in maintaining a normal serum magnesium, whilst also containing 50mg calcium ascorbate dihydrate, and 100IU of vitamin D. However, it also contains 50mg of Vitamin B6[6], which is twenty-five times the recommended daily intake of B6 at 1.7mg per day, whilst also 50% of the recommended upper safe limit of 50mg per day[7,8].

Current guideline-directed management for hypoparathyroidism consists of calcium and Active Vitamin D (calcitriol) replacement, taken multiple times per day, which can lead to pill burden and non-adherence. In addition to the acute presentations, prolonged under-replacement leads to sequelae of chronic hypocalcaemia with brain fog, basal ganglia calcification, extrapyramidal symptoms. Over-replacement results in hypercalcaemia and the development of complications of therapy with hypercalciuria, nephrocalcinosis, chronic kidney disease basal ganglia calcification and neuromuscular excitability. [2,9]. The development of a Parathyroid hormone replacement has been long sought after, and whilst the clinical trial data of the new agent; palopegteriparetide is promising, real world data is required to truly change practice.

This case demonstrates the need to consistently re-evaluate the presumptive diagnosis when a person is not responding to the prescribed treatment. It is important to be aware of rare and common conditions that share symptomatology, and to investigate appropriately.

Conclusion

Vitamin B6 toxicity can mimic the symptomatology of hypocalcaemia. This case highlights the need for a thorough drug history, noting the branding and dosages of nutraceutical supplements. Well-intentioned and appropriate use of supplements may cause harm if not administered correctly.

Take home points

Vitamin B6 toxicity is a rare but under-recognised condition
Symptomatology of B6 toxicity overlaps with those of hypocalcaemia and may co-exist
A thorough drug history, including nutraceuticals is required, including branding and dosages in the management of hypocalceamia, as many patients may unintentionally be on offending agents at inappropriate doses

If clinical improvement is not seen as expected, continue to re-evaluate your differentials and management

1. 1. Hartley, T. (2025, June 27). Australia's TGA issues interim report to remove supplements high in B6 from shelves as toxicity cases rise. ABC News. https://www.abc.net.au/news/2025-06-28/tga-takes-action-over-b6-toxicity/105470210 Accessed 29/6/2025
2. 2. Schafer, A. L., & Shoback, D. M. (2016, January 3). Hypocalcemia: diagnosis and treatment. Endotext - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK279022/
3. 3. Dalton, K., & Dalton, M. J. (1987). Characteristics of pyridoxine overdose neuropathy syndrome. Acta neurologica Scandinavica, 76(1), 8–11. https://doi.org/10.1111/j.1600-0404.1987.tb03536.x
4. 4. Vrolijk, M. F., Opperhuizen, A., Jansen, E. H. J. M., Hageman, G. J., Bast, A., & Haenen, G. R. M. M. (2017). The vitamin B6 paradox: Supplementation with high concentrations of pyridoxine leads to decreased vitamin B6 function. Toxicology in vitro : an international journal published in association with BIBRA, 44, 206–212. https://doi.org/10.1016/j.tiv.2017.07.009
5. 5. Bender D. A. (1999). Non-nutritional uses of vitamin B6. The British journal of nutrition, 81(1), 7–20.
6. 6. Blackmores Bio magnesium. (n.d.). https://www.blackmores.com.au/products/bio-magnesium?srsltid=AfmBOoo6VD0uQey5jhx-hPWYuwX4evzO8XChelgXJhWdCytHhw3yaZH2. Accessed 29/6/2025
7. 7. Otten JJ, Hellwig JP, Meyers LD (Eds) (2006) Dietary Reference Intakes: The Essential Guide to Nutrient Requirements. The National Academies Press, Washington, DC 2006. pp.530-541
8. 8. EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA), Turck D, Bohn T, et al. Scientific opinion on the tolerable upper intake level for vitamin B6. EFSA J. 2023;21(5):e08006. Published 2023 May 17. doi:10.2903/j.efsa.2023.8006
9. 9. Khan AA, Bilezikian JP, Brandi ML, et al. Evaluation and Management of Hypoparathyroidism Summary Statement and Guidelines from the Second International Workshop. J Bone Miner Res. 2022;37(12):2568-2585. doi:10.1002/jbmr.4691

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Bone Mineral Density Changes After Liver Transplantation: Experience from A Tertiary Transplant Unit

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Publish consent withheld

1. 1. Rodríguez-Aguilar, E.F., Pérez-Escobar, J., Herrera, D.S., García-Alanis, M., Toapanta-Yanchapaxi, L., Gonzalez-Flores, E. and García-Juárez, I., 2021, September. Bone disease and liver transplantation: a review. In Transplantation Proceedings (Vol. 53, No. 7, pp. 2346-2353). Elsevier. 2. Li, X.Y., Lew, C.C.H. and Kek, P.C., 2021. Bone mineral density following liver transplantation: a 10-year trend analysis. Archives of Osteoporosis, 16(1), p.169.
2. 2. Li, X.Y., Lew, C.C.H. and Kek, P.C., 2021. Bone mineral density following liver transplantation: a 10-year trend analysis. Archives of Osteoporosis, 16(1), p.169.

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Assessing Protocolisation of Hypophosphataemia Screening in High-Risk Patients Receiving Parenteral Iron

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Background

Intravenous iron formulations, particularly ferric carboxymaltose, iron polymaltose and iron sucrose, can cause hypophosphataemia, potentiated by factors such as vitamin D deficiency, malabsorption, or recurrent infusions. Concord Hospital published a protocol in February 2023 to guide risk stratification and monitoring for hypophosphataemia following parenteral iron.

Aim

Assess adherence to hypophosphataemia screening guidelines before and after publication of a local protocol.

Methods

A retrospective audit was conducted of individuals receiving ferric carboxymaltose, iron polymaltose or iron sucrose from February 2022 to August 2023. Individuals were classified as high-risk if they received recurrent infusions, had vitamin D deficiency, had pre-existing hypophosphataemia, documented malabsorption syndromes or malnutrition. Appropriate screening was defined as a documented phosphate level on the electronic medical record 1-4 weeks post-infusion. Rates of screening for hypophosphataemia were compared before and after the protocol implementation. Descriptive statistics and chi-squared analysis were utilised to evaluate changes in screening rates.

Results

Of 426 encounters reviewed, 186 were identified as high-risk, involving 79 individuals. Among these, 182 infusions were ferric carboxymaltose and 4 were iron sucrose. High-risk encounters occurred due to recurrent infusions (n=158), vitamin D deficiency (n=6), malabsorption syndromes (n=15), and malnutrition (n=7). There were 99 high-risk encounters prior to protocol implementation and 87 following. Screening was performed appropriately in 20.2% of pre-protocol encounters (n=12) and 12.6% post-protocol (n=8) ($p = 0.168$). Among pre-protocol encounters, 6 patients developed post-infusion hypophosphataemia, 4 met criteria for phosphate replacement, and 2 were appropriately treated. Post-protocol, 4 patients developed hypophosphataemia, with 1 requiring and receiving appropriate replacement.

Conclusions

Despite protocolisation, adherence to hypophosphataemia screening in high-risk patients remained low. The incidence of hypophosphataemia following parenteral iron in this group was substantial, underscoring the need for routine monitoring. Enhanced dissemination, education, and system-level strategies are required to promote protocol adherence and ensure safe intravenous iron practices

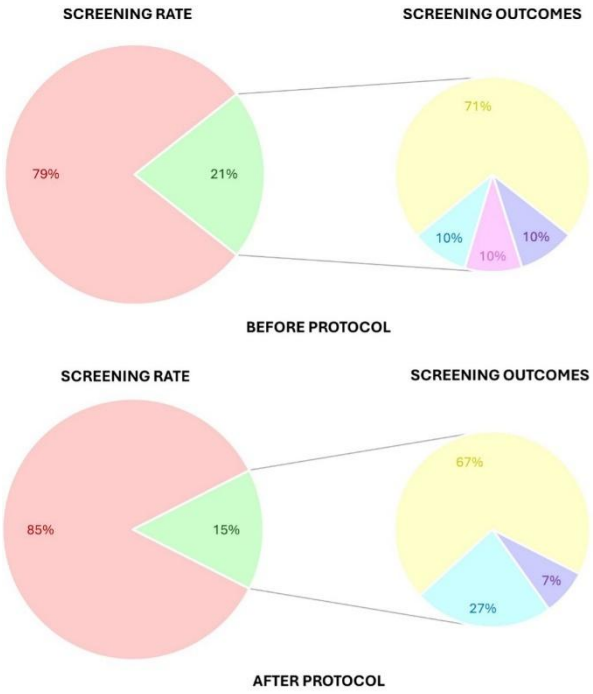

FIGURE 1: Representation of Screening Rates and Screening Outcomes

This figure breaks down the rates of screening in individuals identified as high-risk (left) and outcomes for screened individuals (right). This is compared from before the protocol was implemented (upper chart) to after the protocol was implemented (lower chart).

FIGURE LEGEND

LEFT

RED – Not screened

GREEN – Screened

RIGHT

YELLOW – Normal Phosphate

BLUE – Hypophosphataemia NOT requiring replacement

PINK – Hypophosphataemia requiring replacement NOT replaced

PURPLE – Hypophosphataemia requiring replacement APPROPRIATELY REPLACED

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Giant Cells, Giant Questions: Denosumab Therapy in Central Giant Cell Granuloma

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Summary

A 22-year-old male was referred to endocrinology for assessment and management of a right-sided mandibular lesion diagnosed as a central giant cell granuloma (CGCG) on biopsy. The patient first noticed a painless swelling in 2020, initially attributed to possible trauma. His medical history included eczema, treated with fortnightly dupilumab. Additional regular medications included cholecalciferol 1000 IU daily. He was otherwise well, a non-smoker, and living with his family while working in a warehouse.

There was no relevant family history.

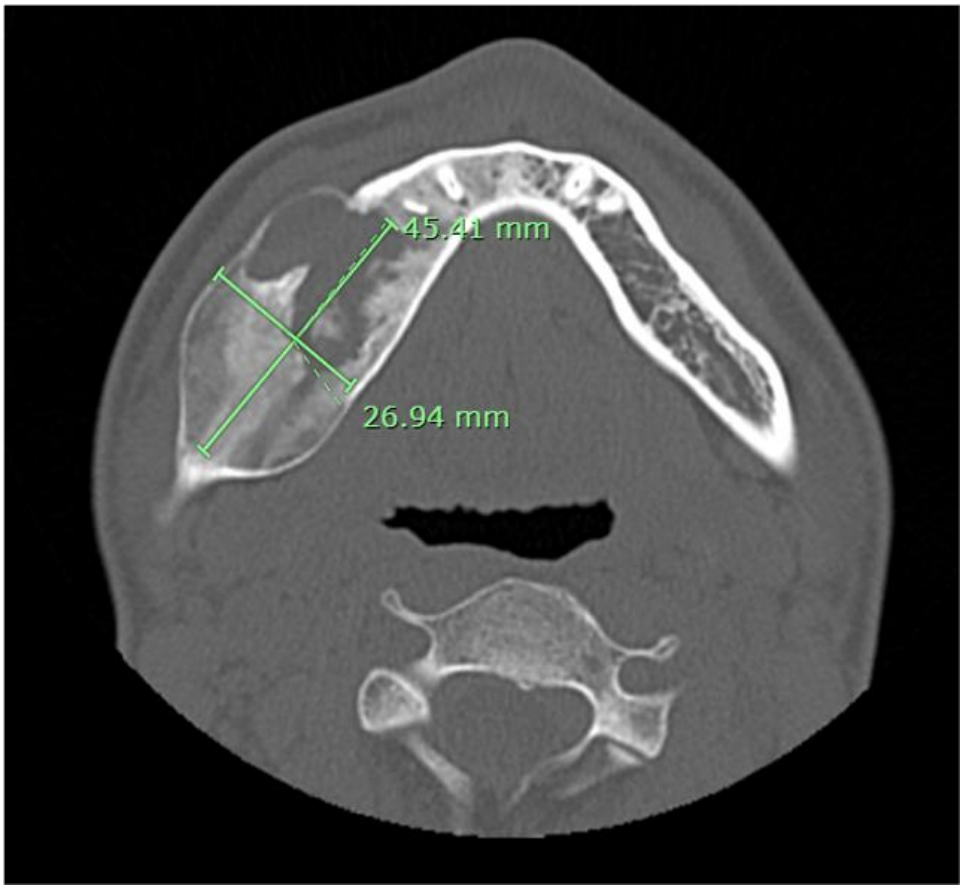
Given the lesion size and location, oral and maxillofacial surgery (OMFS) colleagues had concerns that enucleation could result in a mandibular discontinuity defect associated with significant morbidity. Due to this, medical management of the large mandibular CGCG was deemed most appropriate.

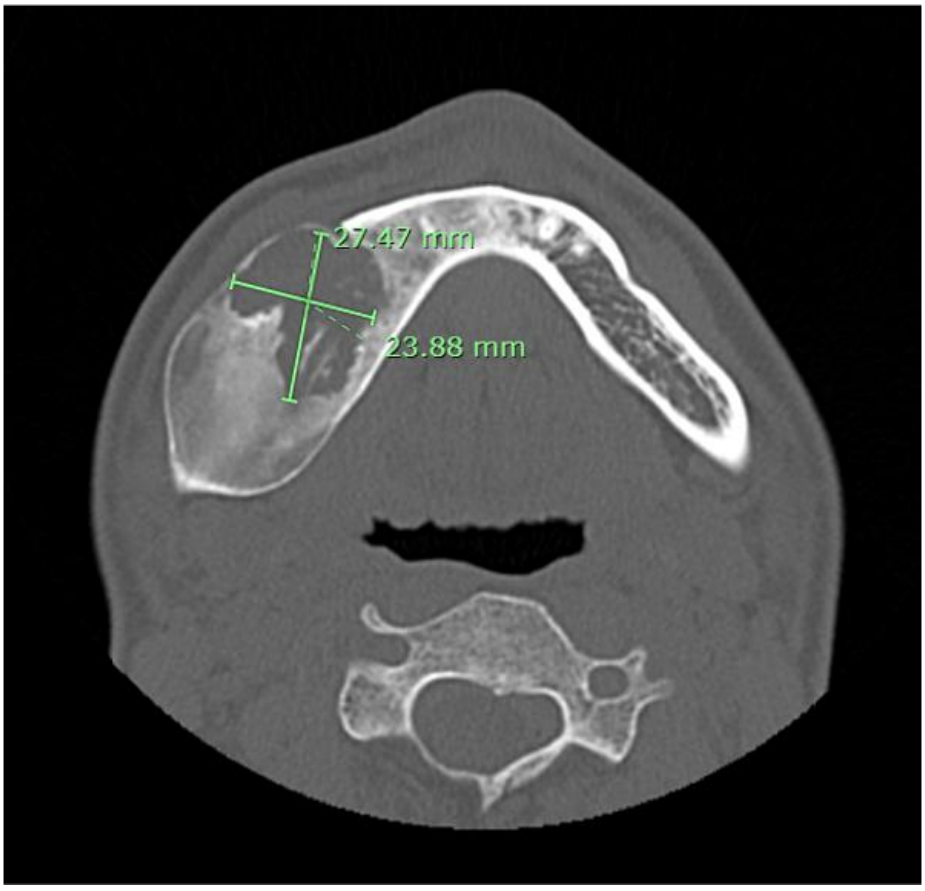
Investigations

Histopathology of mandibular lesion (October 2024): stroma is comprised of ovoid to spindle cells with scattered giant cells. There is mild chronic lymphocytic inflammatory infiltrate. No nuclear atypia or microorganisms are seen. No evidence of malignancy - consistent with giant cell granuloma.

Biochemistry (November 2024): Serum phosphate 1.47 mmol/L (0.75-1.50 mmol/L), corrected calcium 2.37 mmol/L (2.15-2.65 mmol/L), 25-hydroxyvitamin D (25(OH)D) 41 nmol/L (>50 nmol/L), parathyroid hormone (PTH) 5.6 pmol/L (2.0-8.5 pmol/L), estimated glomerular filtration rate (eGFR) >90 mL/min.

Imaging (computed tomography (CT) September 2024): No cortical perforation, however thinning of the cortex. Mixed sclerotic/ lytic lesion. Total length ~45.41mm, width ~26.94mm. Lytic lesion 27.47mm x 23.8mm.


45.41 mm
26.94 mm


27.47 mm
23.88 mm

Discussion

CGCG is a benign but sometimes locally aggressive intraosseous lesion of the jaw, typically affecting young adults, with a predilection for females [1]. The incidence is approximately one per million [2]. It most commonly involves the anterior mandible and may present with painless swelling, though ~20-30% behave aggressively, with pain, tooth absorption, invasion of perignathic tissues and higher chance of recurrence [1]. Differential diagnoses include Brown tumour of hyperparathyroidism, aneurysmal bone cyst, osteosarcoma, and giant cell tumour of bone (GCTB), which it histologically resembles [3].

Histologically, both CGCG and GCTB possess many overlapping similarities [4]. Both contain spindle-shaped mononuclear cells overexpressing Receptor Activator of Nuclear factor kB Ligand (RANKL), which recruit osteoclast-like giant cells. While surgical resection is the traditional first line treatment, their shared pathophysiology has led to interest in the use of denosumab, a monoclonal antibody against RANKL.

While denosumab is an established therapy for GCTB, evidence in CGCG is limited to case reports and small series [5]. Pogrel *et al.* described 8 patients with biopsy-proven mandibular CGCG who received denosumab 120 mg monthly (plus loading doses). Radiological evidence of calcification was observed within 3 months and no recurrences were noted at 5-year follow-up [6]. However, a key limitation of this case series is the lack of detail regarding lesion size and aggressiveness. Other series have demonstrated mixed outcomes, including recurrence after cessation of therapy, particularly in aggressive lesions which are often defined as those exhibiting size of greater than 5 cm or lesions demonstrating rapid growth, root resorption, tooth displacement, cortical bone thinning, cortical bone perforation or recurrence after curettage.

Rhou *et al.*, in the most comprehensive study to date, reported recurrence rates up to 50%, often within 12 months of denosumab cessation [7]. Their 6-year prospective observational study followed 8 patients (median age of 20.5 years, all mandibular lesions) who received standardised, time-limited courses of denosumab 120mg, with stepwise increase in dosing interval based on response. This protocol was selected in recognition of the less aggressive nature of CGCG compared to GCBT, where loading doses of denosumab and more intensive regimens are typically used. Larger baseline size, aggressive subtype and fewer than 12 initial doses were more common in the recurrence group. In contrast, the case series by Kim *et al.* included 5 patients with CGCG but provided limited follow-up data [8]. Both high- and low-dose denosumab

regimens were employed, further limiting the ability to evaluate the optimal denosumab dose and most effective treatment strategy for CGCG.

Potential complications of denosumab therapy include hypocalcaemia, rebound hypercalcaemia, and rare cases of osteonecrosis of the jaw (ONJ). In a paediatric series by Vanderniet *et al.*, 100% of patients developed symptomatic hypercalcaemia post-treatment despite prophylactic zoledronic acid, highlighting the challenge of denosumab cessation in younger patients [9]. This rebound phenomenon is thought to result from high baseline bone turnover markers during childhood before skeletal maturity is reached.

While a meta-analysis published in 2020 suggested a possible increase in recurrence risk when denosumab is used preoperatively in GCTB [10], the included studies were small, non-randomised, and confounded by lesion aggressiveness. There is insufficient evidence to definitively conclude that neoadjuvant denosumab increases recurrence risk in CGCG.

Management plan

Given the lesion's size and OMFS concern regarding upfront surgical resection, a shared decision was made to trial denosumab 120 mg monthly for 3–6 months with close monitoring and without a loading dose. A dental review was arranged prior to treatment to assess the risk of ONJ and consider prophylactic extractions as required. Biochemical monitoring (serum calcium, phosphate, alkaline phosphatase (ALP), PTH, 25(OH)D, C-terminal telopeptide of type 1 collagen (CTX) and procollagen type 1 amino-terminal peptide (P1NP)) and serial imaging (orthopantomogram (OPG)) were planned every 3 months. If medical therapy reduces the lesion burden, OMFS may consider surgical intervention.

Take home messages

- CGCG is a rare jaw lesion that can mimic GCTB histologically and radiologically.
- Denosumab may be a useful treatment in selected cases of CGCG where surgery carries high morbidity.
- There is limited evidence guiding optimal dosing and duration of denosumab in CGCG, particularly how to minimise the risk of recurrence in aggressive lesions.
- Risks of denosumab therapy include hypocalcaemia, ONJ, and rebound hypercalcaemia after cessation.
- Thorough dental evaluation and biochemical monitoring are essential prior to and during denosumab therapy.

1. [1] Lee J-C, Huang H-Y (2020) Soft Tissue Special Issue: Giant Cell-Rich Lesions of the Head and Neck Region. Head and Neck Pathology 14(1): 97-108. 10.1007/s12105-019-01086-2
2. [2] de Lange J, van den Akker HP, Klip H (2004) Incidence and disease-free survival after surgical therapy of central giant cell granulomas of the jaw in The Netherlands: 1990–1995. Head & Neck 26(9): 792-795. https://doi.org/10.1002/hed.20069
3. [3] Rosenberg AE, Nielsen GP (2001) Giant cell containing lesions of bone and their differential diagnosis. Current Diagnostic Pathology 7(4): 235-246. 10.1054/cdip.2001.0080
4. [4] Auclair PL, Cuenin P, Kratochvil FJ, Slater LJ, Ellis GL (1988) A clinical and histomorphologic comparison of the central giant cell granuloma and the giant cell tumor. Oral Surg Oral Med Oral Pathol 66(2): 197-208. 10.1016/0030-4220(88)90094-1
5. [5] Abu-Zaid A, Alaqaili SI, Ahmad SO, Bin Hazzaa I, Alharbi H (2019) Preoperative Denosumab plus Surgery in the Management of Giant Cell Tumor of Bone: A Comprehensive Narrative Literature Review. Gulf J Oncolog 1(30): 67-75
6. [6] Pogrel MA, Hossaini-Zadeh M (2021) Denosumab for the management of central giant cell granuloma of the jaws-a case series. Int J Oral Maxillofac Surg 50(8): 1019-1022. 10.1016/j.ijom.2020.12.013
7. [7] Rhou YJJ, Wang CJ, Nguyen M, et al. (2022) Clinical and Radiologic Response of Central Giant Cell Granuloma to Denosumab: A 6-Year Prospective Observational Study. Calcif Tissue Int 110(4): 464-474. 10.1007/s00223-021-00935-z
8. [8] Kim TS, Usera GL, Ruggiero SL, Weinerman SA (2017) Improvement of Giant Cell Lesions of the Jaw Treated With High and Low Doses of Denosumab: A Case Series. JBMR Plus 1(2): 101-106. 10.1002/jbm4.10010
9. [9] Vanderniet JA, Wall CL, Mullins A, et al. (2022) Denosumab for central giant cell granuloma in an Australian tertiary paediatric centre. Bone 159: 116395. 10.1016/j.bone.2022.116395
10. [10] Chen X, Li H, Zhu S, Wang Y, Qian W (2020) Pre-operative denosumab is associated with higher risk of local recurrence in giant cell tumor of bone: a systematic review and meta-analysis. BMC Musculoskelet Disord 21(1): 256. 10.1186/s12891-020-03294-2

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Risk of fracture in adulthood is associated with childhood fracture history independent of bone mineral density in women: The Geelong Osteoporosis Study

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Aims: Fractures during childhood are increasingly prevalent, however the relationship with fracture and bone mineral density (BMD) into adulthood remains to be fully elucidated. Therefore, this study aimed to determine the association between fracture and BMD in adulthood and fracture history in childhood.

Methods: Data pertain to the 15-year follow-up of the Geelong Osteoporosis Study. There were 635 women with complete information on fractures in childhood and adulthood. Fracture in childhood (<20 years) was documented by self-report and in adulthood (≥20 years) was self-reported and confirmed from radiological reports where possible. BMD at the hip and spine were determined using a Lunar Prodigy Pro (GE Madison, USA). Chi square and Mann-Whitney U tests were used to evaluate univariate associations between childhood fracture and adult bone measures, and logistic and linear regression models were used to evaluate multivariate associations (adjusted for current age, mobility, height and weight).

Results: In univariate models those with adulthood fracture were more likely to have had a fracture in childhood (yes adulthood fracture: 35/168 [20.8%] vs no adulthood fracture: 67/437 [14.3%], p=0.05). There was borderline significance with mean BMD at the neck of femur (no childhood fracture: 0.872g/cm^2 [IQR:0.795,0.985] vs yes childhood fracture: 0.913g/cm^2 [IQR:0.815,1.010], p=0.08) but no other site. In adjusted models, childhood fracture remained a significant predictor of adulthood fracture (OR:1.92 95% CI:1.18,3.13) and was not attenuated by inclusion of current BMD. The association between childhood fracture and femoral neck BMD was attenuated after adjustment (p=0.55).

Conclusion: In this cohort of women, childhood fracture was associated with occurrence of fracture in adulthood, but no relationship with adult BMD was detected. Given these observed associations were independent of BMD, it is plausible that the mechanism behind the association is behavioural (e.g. increased risk taking) or explained by changes in bone not detectable by DXA.

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Ten years clinical experience of bone health in aging transgender women from a single practice

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Introduction: The management of bone health in older transwomen receiving long-term gender-affirming hormone therapy (GAHT) remains poorly characterized. This study aims to examine the clinical characteristics and bone health profiles of older transwomen presenting to a single endocrinology practice.

Methods: A retrospective review was conducted on transwomen aged ≥50 years seen from 2015 to present. Demographic, treatment, and bone health data were collected.

Results: Twelve transwomen were identified, with a mean age of 61.8 years (±1.75, range 51–72) and mean GAHT duration of 25.6 years (±4.9, range 4–46). Topical oestrogen was the most common formulation (80%). Six participants (50%) had undergone bilateral orchidectomy at a mean age of 39.5 years (±6.4); three of these also had vaginoplasty. None were current smokers. Mean body weight was 85.6 kg (±6.3, range 54–121), and mean BMI was 30.0 kg/m^2 (±2.1, range 24–42). All patients underwent bone densitometry at presentation to the practice; four of whom were prior to GAHT. One participant already showed osteoporosis in the lumbar spine and osteopaenia in the hip. Among the eight with post-GAHT scans (mean 32 years on GAHT, ±3.8, range14-44),), osteopaenia was observed in one spine and three hips, based on both biological and affirmed gender reference ranges. One patient developed a sacral fracture; no other osteoporotic fractures were reported.

Conclusion: There is ongoing need to address bone health in older transwomen on long-term GAHT. Although most patients did not exhibit clinically significant bone loss or fractures, isolated findings of osteoporosis and osteopaenia warrant proactive screening and tailored management. Collaborative, longitudinal care strategies are essential to optimize musculoskeletal outcomes in this population.

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Multiple paragangliomas and osteoporosis in a patient with DNMT3A mutation: a new association

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Introduction: DNA methyltransferase 3 alpha (*DNMT3A*) gene mutation is a novel mutation associated with paraganglioma and pheochromocytoma (PPGL). We report a patient with *DNMT3A* mutation with multiple paragangliomas (PGs) and severe osteoporosis.

Case Summary: A 41-year-old white male patient with short stature, microcephaly, intellectual impairment and sparse hair has a history of norepinephrine-producing multiple PGs initially diagnosed at 29 years. His serum normetanephrine and dopamine levels were raised [normetanephrine: 1180 (<670pmol/L), 3-methoxytyramine 300 (<181pmol/L)] without significant hypertension. He initially underwent excision of carotid tumours when first diagnosed however subsequent structural imaging investigation showed metastatic PGs with intracardiac lesionsHe partially responded to LuTATE therapy. The most recent Ga-TATE scan showed stable metastatic PGs with no suspicious DOTATE avid bony lesions. He also has osteoporosis with multiple low trauma fractures including fractured tibia and fibula at age of 3 years after jumping off a bed in two separate incidents and a low traumatic humeral fracture. His last fracture was in his 20s. A DEXA scan at age 38 years was consistent with osteoporosis (lumbar T score -3.1, Z score -2.1 and left hip T score -2.9, Z score -2.0). A genetic test (BluePrint panel) was done to search for the genetic cause of his PGs which showed heterozygous mutation in *DNMT3A* c.899T>C.p.(Leu300Pro0), a variant of unknown significance (VUS).

Discussion: The patient's clinical features are consistent with Heyn-Sproul-Jackson syndrome, a condition caused by gain-of-function mutations in the highly conserved PWWP domain of *DNMT3A*. Mutations in this domain can also cause PGs.. Catecholamine excess from secreting PPGL can lead to secondary osteoporosis. In our case, the patient has had multiple low-trauma fractures since childhood; therefore, the potential association between the *DNMT3A* mutation and osteoporosis should be considered. DNMT3A regulates osteoblasts but the role of this mutation in osteoporosis requires further investigation.

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The impact of metabolic syndrome on changes in trunk muscle cross-sectional area: a 10-year longitudinal study.

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Background:
Sarcopenia, a major contributor to locomotive syndrome, involves progressive loss of skeletal muscle mass and strength. Reduced strength in the psoas major and erector spinae muscles is linked to gait disturbances, falls, and low back pain. Metabolic syndrome, characterized by obesity, hypertension, hyperglycemia, and dyslipidemia, is increasingly prevalent among Japanese men. Insulin resistance, central to the pathophysiology of metabolic syndrome, may also be associated with sarcopenia. However, few studies have explored this relationship, particularly from a long-term perspective in working-age individuals. This study aimed to evaluate the area of the psoas major and erector spinae muscles in a large working-age population and examine the effects of metabolic syndrome on trunk muscle area changes.

Methods:
We included 1,504 working-age men who met the following criteria: ① Underwent health checkups at the HITACHI Health Care Center between 2004–2006, including CT-based visceral fat measurement, and repeated the same exam 10 years later; ② Male; ③ Had baseline data for metabolic syndrome-related factors (age, BMI, visceral fat area(VFA), blood pressure, HbA1c) and respiratory factors(%VC, FEV1.0). We performed multiple regression analysis to identify baseline predictors of 10-year changes in psoas major and erector spinae muscle area.

Results:The 10-year change rates in psoas and erector spinae muscle areas were -6.7 ± 10.3% and -4.8 ± 11.4%, respectively. Multiple linear regression analysis identified VFA and HbA1c as significant predictors of psoas major area loss, and %VC also predicted erector spinae area loss.

Conclusion:
Among metabolic syndrome-related factors and respiratory factors, visceral fat obesity, hyperglycemia and low vital capacity influenced the long-term trunk muscle loss in working-age men.

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"Deadly double-trouble" – life-threatening hypocalcaemia following denosumab and parenteral iron administration

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Case Study

A sixty-two-year-old gentleman presented with peripheral and perioral paresthesia, and a subsequent generalised tonic-clonic seizure due to severe hypocalcaemia. Initial ionised calcium (iCa) was undetectable <0.61mmol/L (1.15-1.33 mmol/L) with a nadir phosphate of 0.57 mmol/L (0.75-1.50 mmol/L) and hypomagnesemia 0.46 mmol/L (0.70-1.10 mmol/L). Parathyroid hormone (PTH) was elevated at 95.7pmol/L (1.5-7.0 pmol/L). Eighteen days prior, he had received his first denosumab 60mg dose for osteoporosis diagnosed on dual-energy x-ray absorptiometry bone densitometry imaging (left femoral neck T-score -3.6, right femoral neck T-score -3.0).

This occurs on a background of complex Crohn's disease. Our patient had previously undergone multiple ileocolonic resections, resulting in short-gut-syndrome and malabsorption. Body mass index was 18.3 kg/m^2 and he required high micronutrient supplementation including Vitamin D 30,000 IU weekly and monthly ferric carboxymaltose (FCM) infusions. His last FCM infusion was one week prior to denosumab. The timeline of FCM infusion, denosumab administration and resultant hypocalcaemia is summarised in Figure 1.

Baseline investigations two weeks prior to denosumab and FCM infusion demonstrated Vitamin D replete at 84 nmol/L (50-200nmol/L), stable chronic kidney disease (CKD) with eGFR 37mL/min (>90mL/min) and creatinine 168 mcmol/L (60-110 mcmol/L). Corrected calcium was 2.21 (2.10-2.60mmol/L), but may not have been an accurate reflection given his low albumin of 22g/L (32-47g/L). Phosphate level was normal at 0.83mmol/L. Alkaline phosphatase (ALP) was elevated at 174 U/L (30-110 u/L).

Unfortunately, during the seizure, our patient sustained bilateral neck of femur fractures (Figure 2) requiring sequential hip arthroplasties. Hypocalcaemia management required high dose and protracted use of intravenous calcium to maintain iCa level above 1.0mmol/L (Figure 1). Whilst doses have been weaned, the requirement for oral calcitriol and calcium carbonate supplementation five months following his denosumab dose remains (Figure 1).

Discussion

We describe an extreme case of life-threatening hypocalcaemia following denosumab and FCM administration within a seven-day interval. The effect was pronounced in the setting of chronic malabsorption and CKD.

Denosumab binds to receptor activator of nuclear factor kappa-B ligand (RANKL) to prevent osteoclast mediated bone resorption. This reduces calcium and phosphate liberation from bone (1). Hypocalcaemia can result in at-risk individuals including those with CKD, pre-existing hypocalcaemia, other electrolyte abnormalities such as hypophosphatemia and hypomagnesemia, vitamin D deficiency, malabsorption and a high bone turnover state (2). In response to hypocalcaemia, a compensatory rise in PTH is expected to stimulate 1,25-dihydroxyvitamin D mediated gastrointestinal calcium absorption (1,3). However, this was impaired in our patient due to short-gut-syndrome and CKD leading to reduced production of 1-α-hydroxylase (1). Ultimately, intractable hypocalcaemia occurred due to blunting of usual compensatory mechanisms. Even prior to his iron infusion, our patient was at a higher risk of hypocalcaemia post denosumab given baseline elevated ALP and probable unrecognised pre-existing hypocalcaemia in the setting of low albumin. In patients with low albumin levels (<25g/L), use of corrected calcium may be unreliable, and ionised calcium represents a more accurate reflection of serum calcium levels (4).

The interaction between parenteral iron formulations and denosumab can cause significant disruption to the calcium-phosphate homeostasis and has only recently come to light (1,3). Parenteral iron associated hypophosphatemia occurs due to reduced degradation of biologically active fibroblast-growth-factor 23 (FGF-23) (1,3). Elevated FGF-23 results in renal phosphate wasting and reduces activation of Vitamin D (1,3). This is named the 6H syndrome – *h*yperphosphaturia and *h*ypophosphataemia, due to *h*igh FGF-23 with secondary effects of *h*ypovitaminosis 1-25$(OH)_2$D, *h*ypocalcaemia and secondary *h*yperparathyroidism (1). Frequent iron infusions and co-administration with denosumab can therefore amplify and prolong hypocalcaemia and hypophosphataemia (Figure 3). Of available preparations in Australia, FCM (*Ferinject*®) appears to have the highest risk of 6H syndrome, with rates up to 51.0%, and ferric derisomaltose (*Monofer*®) appears to be least implicated (5-7).

Thus far, case reports of calcium and phosphate abnormalities from denosumab and parenteral iron (FCM and iron polymaltose) range from same day administration to seven weeks apart (1,3). Consensus on safe dosing intervals is lacking (1,3).

A management dilemma arises in patients already on long-term denosumab therapy who also require iron infusions (1). Denosumab doses cannot be delayed or abruptly discontinued due to rebound fracture risk (1,3). Intravenous iron formulations with

reduced risk of hypophosphatemia, such as ferric derisomaltose, should therefore be considered (5). Where ongoing risk factors for hypocalcaemia persist or switch to Monofer is insufficient, transition from denosumab to zoledronic acid, where appropriate, may decrease, but not eliminate, the risk of electrolyte disturbance. While most reported cases implicate denosumab, given its high potency and rapid onset, there is one case report of interaction with zoledronic acid, indicating that the pathophysiology is not unique to denosumab (1).

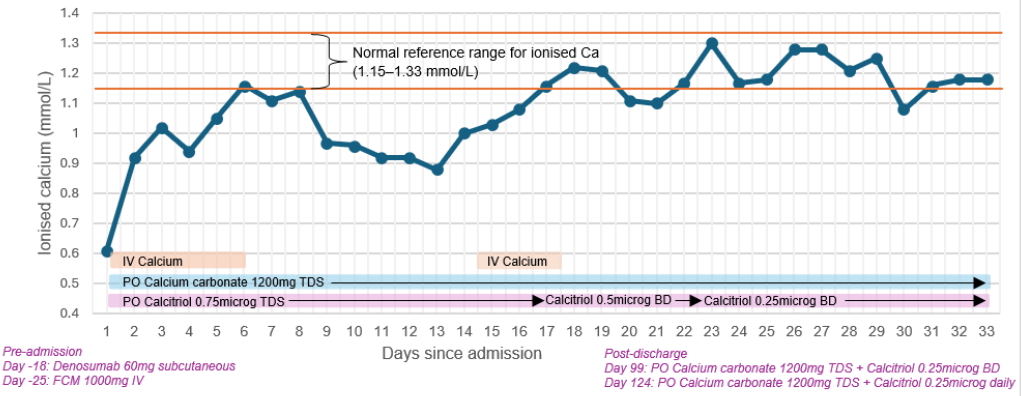
If co-administration has occurred, close electrolyte monitoring should be undertaken at 7, 14 and 28 days post denosumab administration as this has typically been the highest risk period (1,3). Where strong risk factors for hypocalcaemia are present, prophylactic calcitriol, alongside calcium and phosphate replacement may be required (1,3). Notably, patients with inflammatory bowel disease are more likely to develop hyperoxaluria and the risk of calcium oxalate renal calculi should be considered in prolonged calcitriol supplementation (2). Magnesium deficiencies should also be corrected to reduce functional hypoparathyroidism (8).

Clinicians should be aware of the risk of severe hypocalcaemia with denosumab, especially in individuals whose compensatory mechanisms are diminished, as previously described. In patients requiring iron infusions, especially in the setting of malabsorption, denosumab should be used judiciously due to the risk of prolonged and serious electrolyte disturbance. Our case illustrates that even a single dose can be deadly with long-lasting morbidity.

Takeaway messages

- The use of denosumab in patients with risk factors such as established malabsorption can lead to severe hypocalcaemia. This is exacerbated in patients who also receive parenteral iron.
- Where co-administration cannot be avoided, lower risk parenteral iron formulations such as ferric derisomaltose should be considered. Close electrolyte monitoring for at least four weeks following denosumab is recommended to enable early intervention.
- Clinician awareness and a careful drug history is vital to reduce chances of interactions. The ideal dosing interval between the two drugs remains to be elucidated.

Figure 1 - Timeline of FCM infusion, denosumab dose and trend in ionised Ca during admission



Pre-admission
Day -18: Denosumab 60mg subcutaneous
Day -25: FCM 1000mg IV

Post-discharge
Day 99: PO Calcium carbonate 1200mg TDS + Calcitriol 0.25microg BD
Day 124: PO Calcium carbonate 1200mg TDS + Calcitriol 0.25microg daily

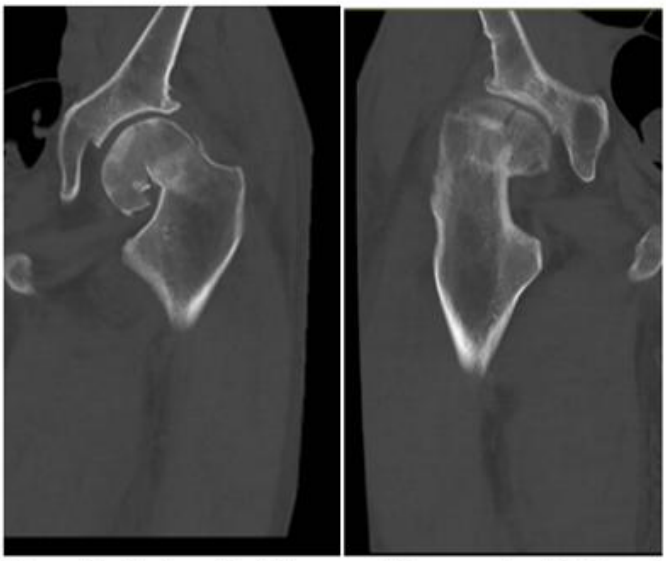


Figure 2 – (Left to right) Computed Tomography (CT) imaging of the left and right hip respectively demonstrating bilateral impacted neck of femur fractures.

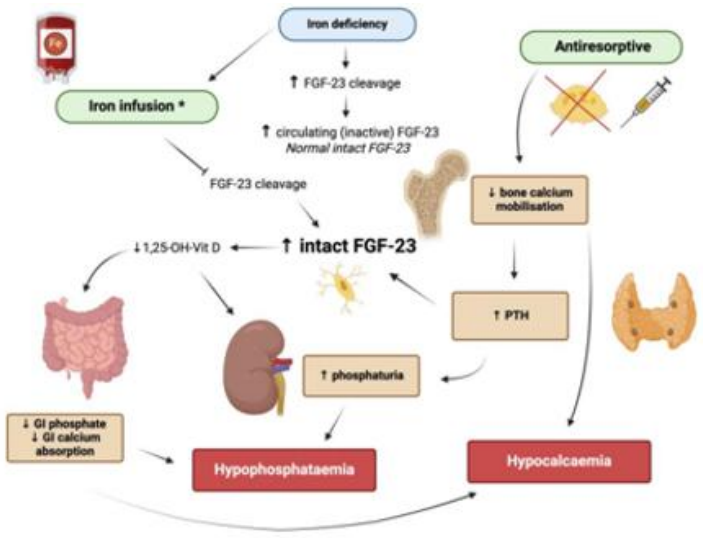


Figure 3 – Image courtesy of Stokes et. al (2025) demonstrating the interaction between parenteral iron and anti-resorptive therapies.

1. Gabrielle Stokes, Angela Sheu, Christian M Girgis, Christopher P White, “Double Trouble” – the impact of iron infusion and antiresorptive therapy on calcium-phosphate homeostasis, JBMR Plus, 2025;, ziae177, https://doi.org/10.1093/jbmrpl/ziae177
2. Spångeus A, Rydetun J, Woisetschläger M. Prevalence of denosumab-induced hypocalcemia: a retrospective observational study of patients routinely monitored with ionized calcium post-injection. Osteoporos Int. 2024
3. Ye S, Grill V, Luo J, Nguyen HH. Concurrent Denosumab and Parenteral Iron Therapy Precipitating Severe Hypocalcemia and Hypophosphatemia. JCEM Case Rep. 2024 Feb 1;2(2). doi: 10.1210/jcemcr/luae005
4. Desgagnés N, King JA, Kline GA, Seiden-Long I, Leung AA. Use of Albumin-Adjusted Calcium Measurements in Clinical Practice. JAMA Netw Open. 2025;8(1):e2455251. doi:10.1001/jamanetworkopen.2024.55251
5. Bellos I, Frountzas M, Pergialiotis V. Comparative risk of hypophosphatemia following the administration of intravenous iron formulations: a network meta-analysis. Transfus Med Rev. 2020;34(3):188-194.
6. Blumenstein I, Shanbhag S, Langguth P, Kalra PA, Zoller H, Lim W. Newer formulations of intravenous iron: a review of their chemistry and key safety aspects - hypersensitivity, hypophosphatemia, and cardiovascular safety. Expert Opin Drug Saf. 2021 Jul;20(7):757-769. doi: 10.1080/14740338.2021.1912010
7. Zoller H, Wolf M, Blumenstein I, Primas C, Lindgren S, Thomsen LL, Reinisch W, Iqbal T. Hypophosphataemia following ferric derisomaltose and ferric carboxymaltose in patients with iron deficiency anaemia due to inflammatory bowel disease (PHOSPHARE-IBD): a randomised clinical trial. Gut. 2023 Apr;72(4):644-653. doi: 10.1136/gutjnl-2022-327897.
8. Florentin M, Elisaf MS. Proton pump inhibitor-induced hypomagnesemia: A new challenge. World J Nephrol. 2012 Dec 6;1(6):151-4. doi: 10.5527/wjn.v1.i6.151.

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Profiling Tibial Cortical BMD Gradients: Associations with Body Composition in Childhood Cancer Survivors and Controls

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Background:
Cortical bone mineral density (BMD) varies across its cross-section and axial length, reflecting adaptations to mechanical loading. However, the utility of cortical BMD profiles in characterising skeletal adaptation remains unexplored. This study compared cortical BMD distribution patterns between childhood cancer survivors (CCS), a population at risk of BMD deficits, and healthy controls, and examined associations between density gradient profiles and body composition.
Methods:
Cortical BMD was assessed at the 38% and 66% tibial sites using pQCT in CCS (n=8) and healthy controls (n=10) aged 6-12. Differences in BMD across cortical divisions (endocortical, midcortical, pericortical) and between groups were examined using mixed-design repeated-measures ANOVA. Individual cortical BMD profiles were characterised using quadratic regression. Hierarchical linear models assessed associations between BMD profile shape parameters (linear and quadratic) and DXA-derived lean mass index (LMI) and fat mass index (FMI), adjusting for age and sex.
Results:
Significant variation in BMD was observed across cortical divisions at both tibial sites ($p < 0.001$), with no group or group × division interactions. At the 66% site, higher LMI was associated with positive linear and quadratic coefficients from fitted regression models ($p=0.048$ and 0.039, respectively). These coefficients reflect a cortical BMD profile with higher periosteal BMD density and a more convex curvature. Conversely, at the 38% site, higher LMI was associated with negative linear and quadratic coefficients ($p=0.023$ and 0.011, respectively), indicating a concave BMD profile with a midcortical density peak. These shape parameters suggest that lean mass is linked to distinct BMD distribution patterns depending on the tibial site. FMI was not significantly associated with cortical BMD profiles at either site.
Conclusions:
Cortical BMD varies significantly across concentric divisions, with distinct distribution patterns at proximal and distal tibial sites in relation to lean mass. Profiling cortical BMD may enhance understanding of skeletal adaptation and guide targeted osteogenic strategies in at-risk populations.

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Laxative misuse resulting in hypercalcaemia with inappropriately normal parathyroid hormone levels and digital clubbing: A case series

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Table 1: Summary of patient characteristics and results.

Case	Laxative Misuse	Calcium, PTH and acid-base pattern	Digital Clubbing
Case 1 34-year-old female	Up to 400 Coloxyl with Senna tablets daily	Peak Ca 5.30 mmol/L; chronic ~3.0 mmol/L over 10 years PTH not fully suppressed 1.8-3.1 pmol/L Bicarbonate 51 mmol/L at time of peak Ca, subsequently normal.	Present
Case 2 24-year-old female	Up to 100 tablets daily	Intermittent Ca up to 2.93 mmol/L over 2 years PTH not fully suppressed 1.8-12.5 pmol/L Bicarbonate normal.	Present
Case 3 30-year-old female	50–100 tablets daily since mid 20s	Intermittent Ca up to 2.81 mmol/L over 4 years PTH not fully suppressed 1.8-2.3 pmol/L Bicarbonate normal.	Absent

Abbreviations: Calcium (Ca), parathyroid hormone (PTH)

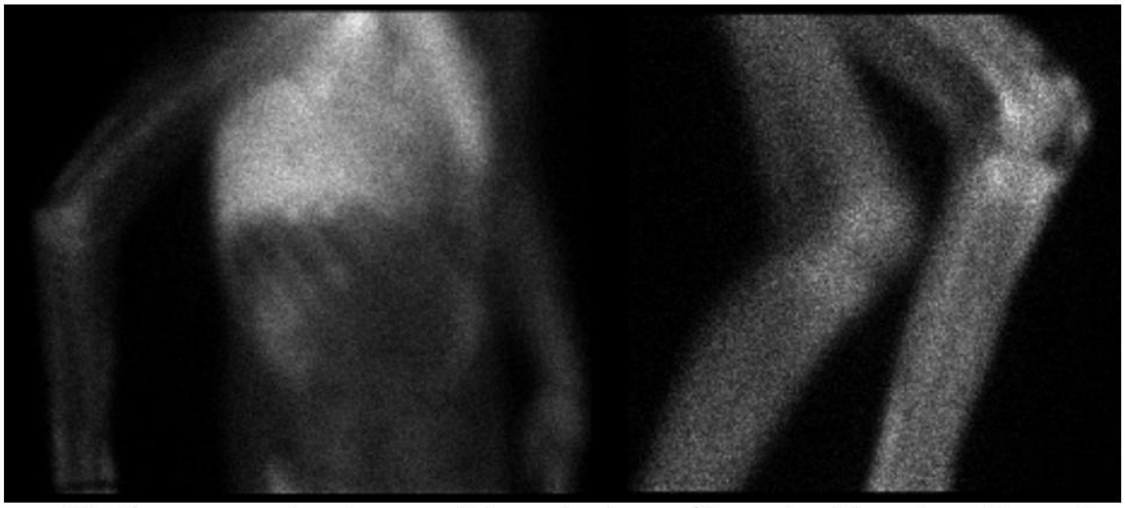

Figure 1A: Bone scan showing possible early signs of hypertrophic osteoarthropathy

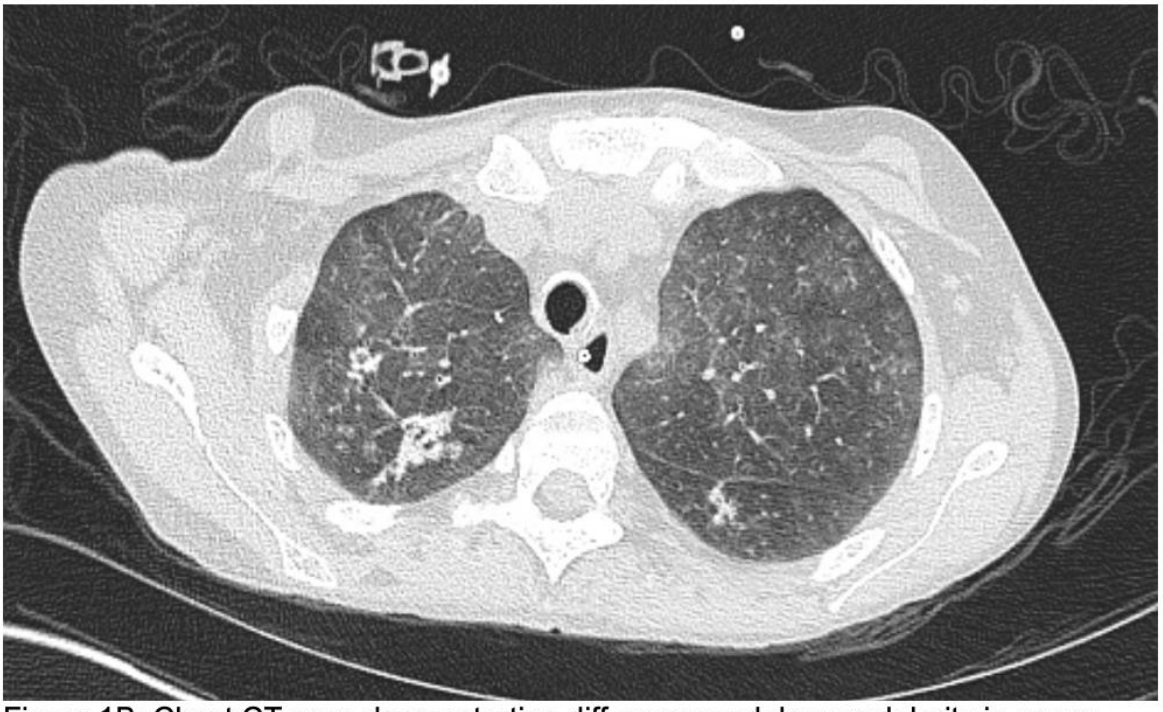

Figure 1B: Chest CT scan demonstrating diffuse groundglass nodularity in upper lobes and metastatic pulmonary calcifications, calcification of the trachea and left main coronary artery.

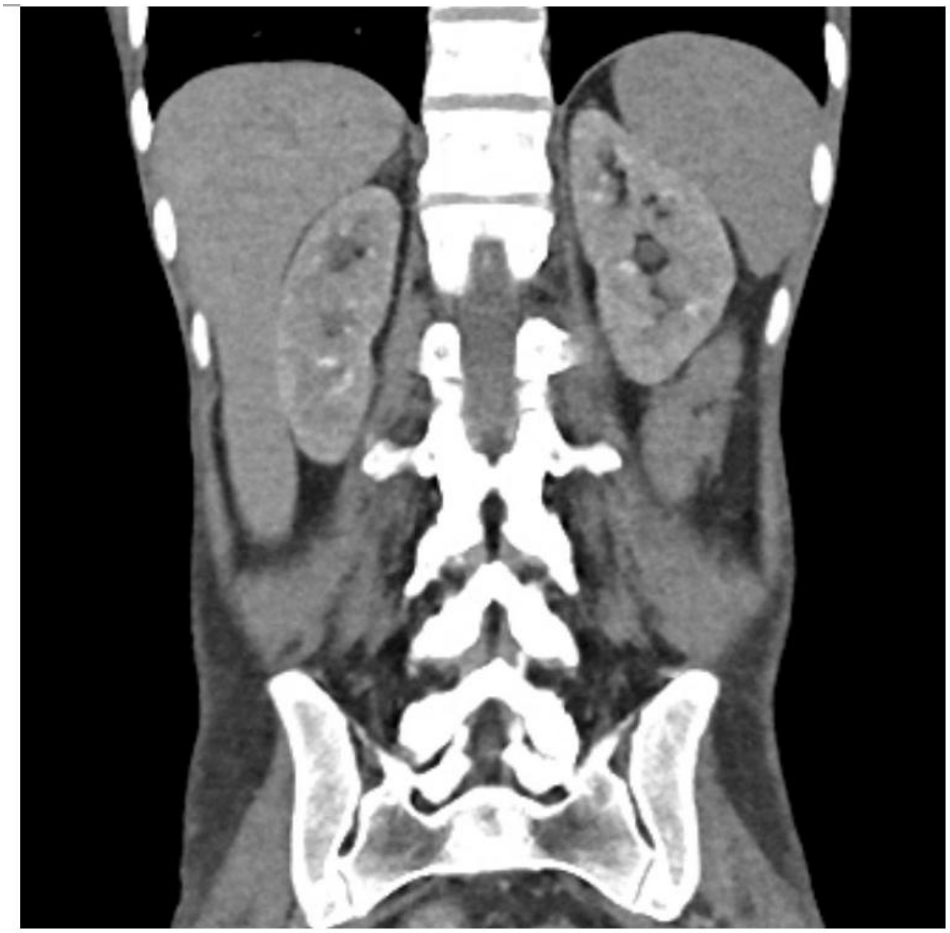

Figure 1C: Bilateral medullary nephrocalcinosis

Case 1

A 34-year-old woman with restrictive anorexia nervosa (AN) since adolescence had over ten admissions for severe hypercalcaemia since age 23. At first presentation, corrected calcium was 5.30 mmol/L (2.1-2.6), ionised calcium 2.68 mmol/L, and bicarbonate 51 mmol/L. At presentation, she was taking oral sodium bicarbonate for unclear reasons. Later calcium levels ranged 3.5-4.5 mmol/L with normal bicarbonate. She was suspected of using up to 400 Coloxyl with Senna tablets daily. Parathyroid hormone (PTH) was not suppressed at 2.6 pmol/L (2.0-6.0), even at peak calcium. Sestamibi scan was normal; 4D-CT was not performed due to renal impairment. Urine studies excluded familial hypocalciuric hypercalcaemia; no other PTH-independent cause was found. She remained chronically hypercalcaemic (~3.0 mmol/L) over 10 years, likely due to ongoing laxative misuse. PTH remained low-normal. Cinacalcet (up to 60 mg twice daily) reduced calcium from 2.84 to 2.63 mmol/L. She developed digital clubbing, multi-organ damage from metastatic calcifications (Figure 1A-C), and is planning dialysis for advanced kidney disease.

Case 2

A 24-year-old woman with AN and misuse of up to 100 Coloxyl with Senna tablets daily had intermittent hypercalcaemia over two years, peaking at 2.93 mmol/L. PTH ranged

from 1.8-12.5 pmol/L on eight occasions. Vitamin D was normal. She had digital clubbing. Other causes of hypercalcaemia were excluded.

Case 3

A 30-year-old woman with AN and 50-100 Coloxyl with Senna tablets daily for four years had corrected calcium between normal and 2.81 mmol/L. PTH was consistently low-normal (1.8-2.3 pmol/L). Vitamin D was normal. No clubbing was present. Workup is ongoing.

Patient details and results are summarised in Table 1.

Discussion

AN affects approximately 30,000 Australians annually (1), with rising incidence and earlier onset (2). Stimulant laxative misuse is estimated to affect one in three patients with AN, though true prevalence is difficult to determine (3). Coloxyl with Senna, a commonly misused over-the-counter product, contains calcium-based stabilisers. Overconsumption can cause hypercalcaemia, as seen in these cases.

These cases highlight a distinctive biochemical pattern of hypercalcaemia with inappropriately normal PTH levels. This contrasts with classical calcium excess syndromes, such as milk-alkali syndrome, which typically show suppressed PTH. The classic syndrome - originally linked to the Sippy regimen combining calcium carbonate and dairy - presents with hypercalcaemia, metabolic alkalosis, and renal impairment (4). Although there has been a resurgence in calcium-induced hypercalcaemia due to supplement use (5), most modern cases still demonstrate PTH suppression. In one series, 11 of 15 patients with supplement-induced hypercalcaemia had suppressed PTH (5). Earlier reports of non-suppressed PTH likely reflected outdated assays measuring C-terminal fragments, which accumulate in renal impairment. Current assays measure the N-terminal region, unaffected by renal function (6). The lack of suppression in our patients, including one with calcium >5 mmol/L, is unusual and may reflect altered calcium sensing from the episodic nature of calcium excess and dehydration, which may affect temporal PTH regulation.

Laxative induced hypercalcaemia is likely multifactorial. Each Coloxyl with Senna tablet contains 69 mg calcium hydrogen phosphate dihydrate and 93 mg calcium phosphate (Aspen Pharmaceuticals, personal communication, July 2025), totalling 52 mg elemental calcium (7). Our patients were each taking at least 50 tablets daily; approximately 2,600 mg elemental calcium. The threshold for calcium-induced hypercalcaemia is unclear and likely affected by renal function and vitamin D status, with cases reported at "safe" doses (6). Dehydration from laxative-induced fluid loss likely exacerbates hypercalcaemia. If vomiting is present as a purging method, alkalosis may also reduce renal calcium excretion, mimicking milk-alkali physiology. Of our

patients, only Case 1 had alkalosis (bicarbonate 51 mmol/L) due to concurrent sodium bicarbonate ingestion, resulting in marked hypercalcaemia to 5.3 mmol/L.

Digital clubbing was noted in two of three cases, a rare but reported feature of laxative misuse (8). Clubbing is hypothesised to result from altered vascular dynamics and megakaryocyte bypass of pulmonary filtration (9). Its occurrence in inflammatory bowel disease suggests gastrointestinal dysfunction may play a role (9), which may partly explain its presence in laxative misuse. Clubbing may be a clinical clue to covert stimulant laxative use in patients with AN.

Management differs from classic calcium excess syndromes. Patients may be psychologically dependent on laxatives, complicating withdrawal. Rebound oedema and constipation are common and may result from persistent hyperaldosteronism, typically resolving within weeks (3). These symptoms are distressing and can trigger relapse. Inpatient management is often required. In Case 1, despite extensive efforts, the patient was unable to cease laxative misuse and developed irreversible complications including metastatic calcifications and end-stage kidney disease.

Coloxyl with Senna misuse should be suspected in patients with anorexia nervosa and unexplained hypercalcaemia, particularly when accompanied by digital clubbing. These cases highlight distinctive biochemical features, including the absence of alkalosis and inappropriately normal or elevated PTH levels, distinguishing them from classic calcium-excess syndromes. Laxative withdrawal is often difficult due to psychological dependence and requires coordinated medical and psychiatric care. Further case reports are needed to better understand the underlying pathophysiology and guide management. Given the potential for severe complications, regulatory measures to restrict excessive over-the-counter access to stimulant laxatives should be considered.

Take Home Messages

1. Coloxyl with Senna contains calcium, and misuse can cause hypercalcaemia, exacerbated by dehydration.
2. PTH was not fully suppressed in any case, suggesting an unusual pathophysiology.
3. Digital clubbing may be a clinical clue to stimulant laxative misuse.
4. Laxative withdrawal is difficult due to dependence and rebound symptoms and requires multidisciplinary care.
5. Regulatory limits on stimulant laxative sales should be considered.

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Education of Junior Medical Officers Improves Identification and Accurate Coding of Osteoporotic Fractures

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Official government statistics and population-based estimates of osteoporotic fractures in Australia are highly discordant. These discrepancies are in part due to inaccuracies in clinical coding, a process used to translate hospital-related healthcare information into standardised codes and Diagnosis Related Groups (DRG). Most medical staff have limited understanding of the requirements for accurate clinical coding. Thus, incomplete documentation and missed diagnoses result in glaring inaccuracies, including in coding of osteoporotic fractures, which in turn leads to under-reporting of such fractures and eventually significant consequences for resource allocation for osteoporosis and fracture prevention services.

We performed an audit of all inpatient fracture admissions in patients aged 50 years or above, reviewing the accuracy of clinical diagnosis and associated coding. Of 216 admissions reviewed between July and November 2024, 94 cases were found to be due to osteoporosis. However, only a single admission received the correct DRG. Post audit adjustment of DRGs to reflect the correct diagnosis resulted in $190,000 of additional funding.

To improve medical documentation and thus coding of osteoporotic fractures, an education program was delivered in February 2025 to train junior doctors in the definition of osteoporosis and medical documentation requirements for accurate coding of osteoporotic fractures. Following the education session, a further 10-week audit was conducted. This demonstrated a significant overall improvement in the accuracy of coding from 1% to 36%. This effect was most pronounced in the first 5 weeks post education (42% accuracy) as compared to the following 5 weeks (27% accuracy). Documentation for hip fracture improved to 77% coding accuracy, while radius and humerus fracture documentation was accurate in only 10% and 13%, respectively.

This study demonstrates that the coding accuracy of osteoporotic fractures can be improved through targeted education. However, the effect varies by fracture site and diminishes over time.

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Challenges in managing hypercalcaemia in pregnancy: two case reports

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Background

Hypercalcaemia during pregnancy is rare, affecting approximately 0.03% of women of reproductive age, and causing maternal and foetal complications. Primary hyperparathyroidism is the most common cause, accounting for up to 90% of cases of hypercalcaemia during pregnancy. Hypercalcaemia of malignancy in pregnancy is extremely rare.

Case 1

A 32 year-old woman presented at 22 weeks' gestation with new onset progressive back pain and severe symptomatic hypercalcaemia to 4.2 mmol/L. She had a history of hormone positive breast cancer. MRI showed innumerable liver metastases and extensive spinal lesions, including a pathological T4 fracture. Her hypercalcaemia improved following acute hypercalcaemia management, including aggressive IV fluids, calcitonin and frusemide, but remained elevated around 2.9 mmol/L. However, her calcium level gradually normalised after commencing doxorubicin and cyclophosphamide treatment. Caesarean section was performed at 26 weeks' gestation due cancer progression and need to escalate cancer treatment.

Case 2

A 30 year-old woman was incidentally found to have moderate PTH-dependent hypercalcaemia at 3.48 mmol/L in her third trimester at 30 weeks' gestation. She had a known history of mild hypercalacemia but no previous imaging. Hypercalcaemia was acutely managed with IV fluids, calcitonin and cinacalcet, achieving a nadir calcium of 2.88 mmol/L. A neck ultrasound showed a right sided parathyroid adenoma although further localisation studies were contraindicated. She underwent a four-gland exploration with removal of a right superior parathyroid adenoma and resolution of her hypercalcaemia.

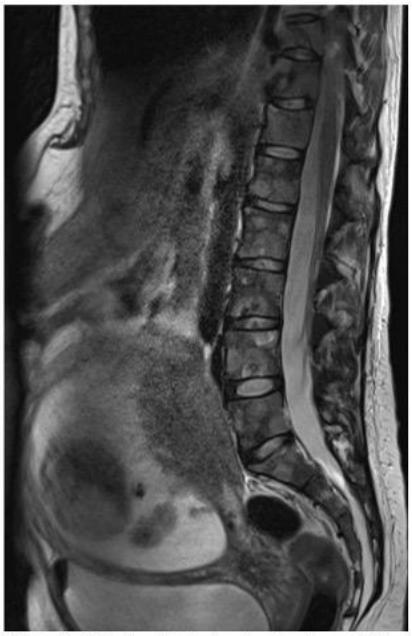

Figure 1. MRI showing spinal metastases of Case 1

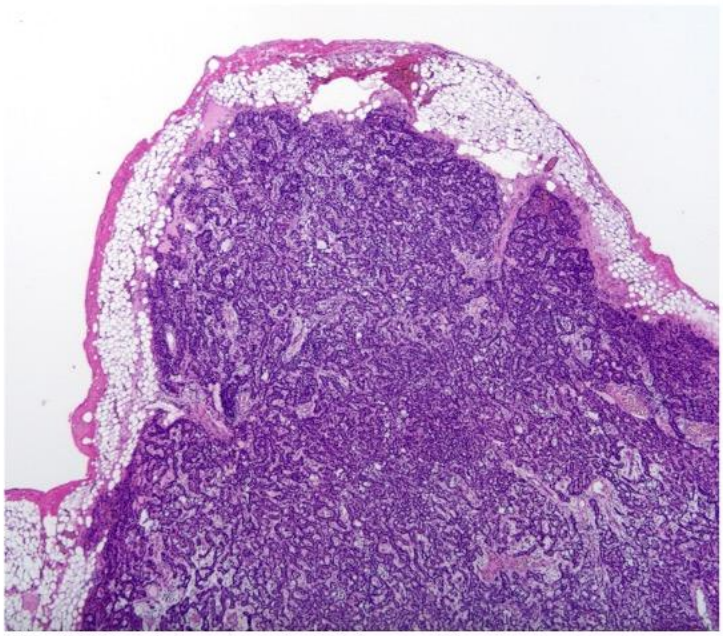

Figure 2. Histopathology of parathyroid adenoma of Case 2

Learning points

Our cases highlight the challenges of managing hypercalcaemia in pregnancy with different aetiologies requiring distinct management strategies. For our first case, chemotherapy treatment of the underlying malignancy was key to controlling the patient's hypercalcaemia. Our second case had a successful four-gland exploration during her third trimester without maternal or foetal complications, and neck exploration and parathyroidectomy should be considered where hypercalcaemia is refractory to medical therapy.

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Denosumab followed by romosozumab significantly improved bone density but did not prevent rebound vertebral fractures – A Case Report

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Denosumab discontinuation is associated with rapid bone loss and increased risk of rebound vertebral fractures. The optimal transition from denosumab to romosozumab to mitigate this risk, enhance bone mineral density (BMD), and reduce fracture risk remains unclear. We describe a 72-year-old gentleman with severe osteoporosis who sustained vertebral fractures following transition from denosumab to romosozumab.

Six-monthly denosumab was commenced in 2019 following a humeral fracture. After two years of therapy, bone turnover markers (BTMs) were suppressed [CTx 160 ng/L (100-750), P1NP 24 mg/L (15-115), ALP 48 U/L (30-110)] (Table 1) and BMD had improved but remained in the severe osteoporotic range at the hip (LS T score -2.2 [+6.5% since baseline], LFN TS -3.1 [+9.8%], LTH TS -3.1 [+8.3%], RFN TS -3.4 [+5.6%] and RTH TS -2.9 [+9.1%]). After three years of denosumab, a spontaneous T8 vertebral fracture occurred in 2023. Monthly romosozumab (210mg) was commenced in September 2023, five months after the last denosumab injection, and continued for 12 months. BTMs rose during romosozumab treatment (CTx 300 ng/L, P1NP 55 mg/L, ALP 128 U/L) (Table 1).

Despite eight months of romosozumab, and 12 months after denosumab cessation, spontaneous new T4 and T6 vertebral fractures developed. BTMs at romosozumab completion were not suppressed [CTx 614 ng/L, P1NP 95 mg/L, bsALP 42.6 mg/L (3.7-20.9)] (Table 1). Following 12 months of romosozumab, intravenous zoledronic acid (5mg) (ZA) was administered in August 2024, with successful BTM suppression after three months (CTx 126 ng/L, P1NP 15 mg/L, ALP 75 U/L) (Table 1). BMD significantly improved (LS TS -1.3 [+10.9% since 2022], LFN TS -2.7 [+7.5%], LTH TS -2.7 [+9.1%], RFN TS -2.4 [+20.3%] and RTH TS -2.6 [+5.5%]). Six months following ZA, BTMs remain low (CTx 234 ng/L, P1NP 28 mg/L and ALP 66 U/L) (Table 1), and no further fractures have occurred.

Table 1. Bone turnover markers

	C-terminal telopeptide of type 1 collagen (CTx), ng/L (reference range 100-750)	Procollagen type 1 amino-terminal peptide (P1NP), µg/L (15-115)	Alkaline phosphatase (ALP), U/L (30-110)	Bone specific alkaline phosphatase (bsALP), µg/L (3.7-20.9)
August 2020	86	18	48	-
January 2023	160	24	48	-
January 2024	300	55	128	-
July 2024	-	-	170	-
August 2024	614	95	136	42.6
November 2024	126	15	75	-
March 2025	234	28	66	-

Denosumab Romosozumab Zoledronic Acid

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Zoledronic Acid in Pediatric Acute Lymphoblastic Leukemia Management: A Case Report of Region-Specific Bone Recovery

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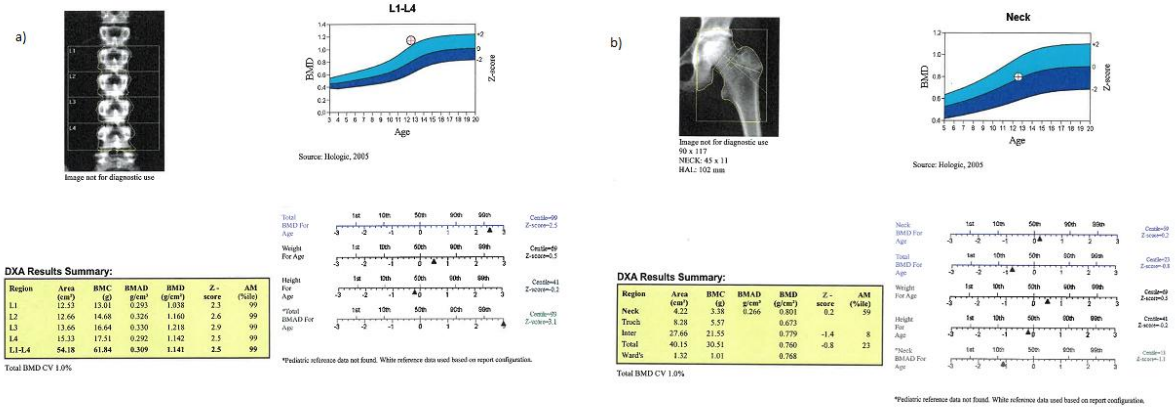
Background: Skeletal morbidity is a common yet often under-recognized complication in children with acute lymphoblastic leukemia (ALL). Bisphosphonates are frequently used to manage skeletal complications in children with secondary osteoporosis; however, evidence on region-specific and long-term skeletal responses, particularly following zoledronic acid (ZA), a third-generation bisphosphonate, remains limited. Case Presentation: We report the case of an 8-year-old girl with standard-risk ALL who developed vertebral fractures during maintenance chemotherapy and received a single intravenous dose of ZA (0.0275 mg/kg). At 1-year follow-up, dual-energy X-ray absorptiometry (DXA) revealed a markedly elevated lumbar spine bone mineral density (BMD) (Z-score +2.60), which was sustained at 4 years (Figure 1a). In contrast, femoral

neck BMD showed delayed but progressive recovery, improving from a low Z-score of -3.40 to +0.20 (Figure 1b). Peripheral quantitative computed tomography (pQCT) one year post-ZA revealed low tibial cortical and trabecular volumetric BMD (Z-scores -1.80 and -3.00, respectively), with marked improvement by year four (Z-scores +0.96 and -0.47, respectively). Further assessments at 4-year follow-up revealed increased trabecular bone score (Z-score +1.40) and tibial cortical thickness (Z-score +1.73). Bone turnover markers were within normal pediatric ranges.
Conclusion: This case illustrates the region- and time-dependent skeletal response to ZA in a pediatric oncology patient. It underscores the importance of site-specific imaging in long-term monitoring and highlights the limitations of systemic bone turnover markers in capturing localized skeletal changes. Until controlled trials provide clearer guidance, we recommend incorporating serial, site-specific imaging, including bone geometry and microarchitecture assessments, into follow-up care for children receiving bisphosphonates.



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Mood disorder and Bone Material Strength Index in women

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Introduction: Mood disorder has been shown to be associated with reduced bone mineral density and increased fracture risk but whether other properties of bone are impacted is yet to be determined. Therefore, the aim of this study was to investigate the association between mood disorder and Bone Material Strength Index (BMSi) in a population-based sample of women.

Method: Data were derived from the first 177 women participating in the 25-year follow-up of the Geelong Osteoporosis Study (ages 38-91 years). Lifetime history of mood disorder was assessed using semi-structured clinical interviews (SCID-I/NP). BMSi was measured using a handheld impact microindentation device (OsteoProbe® RUO, Active Life Scientific, CA, USA) on the anterior surface of the mid-tibia. Anthropometric measurements were performed and education, medication use and lifestyle factors were self-reported. Multivariable linear regression models were used to determine associations between mood disorder and BMSi while testing for potential confounding.

Results: Seventy-two women meet criteria for a lifetime history of mood disorder. Those with a lifetime mood disorder had a lower BMSi, were less active and more likely to use antidepressants compared to those with no lifetime mood disorder; otherwise the groups were similar in age, education, body mass index (BMI), smoking status and alcohol consumption. After adjustment for age and BMI, mean BMSi was 3.3% lower [73.7 (95% CI 71.9-75.5) vs. 76.2 (95% CI 74.6-77.9), p=0.04] compared to women without a mood disorder. Education, activity level, alcohol consumption, smoking status and medication use did not contribute to the model.

Conclusion: In this preliminary analysis, BMSi was lower in women with a history of mood disorder suggesting bone material properties may also be contributing to previously observed increased fracture risk in this population. Following replication in larger samples including men, bone impact microindentation may be a promising new measurement method for the clinic.

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Out of the shadow: Transforming care for people living with hypophosphatasia

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Background: Hypophosphatasia (HPP) is a rare, inherited metabolic condition caused by variations in the alkaline phosphatase liver/bone/kidney (ALPL) gene. These variations result in low alkaline phosphatase activity, leading to impaired mineralisation of bones and teeth. Although rare, HPP can be severely disabling. Its variable presentation often leads to under-recognition and delayed diagnosis, with many individuals navigating fragmented care and limited access to appropriate treatment. The challenges faced by people living with HPP are not unique - they reflect broader issues experienced by many Australians with rare diseases. Australia's health system is not designed to meet the needs of people with rare and complex conditions.

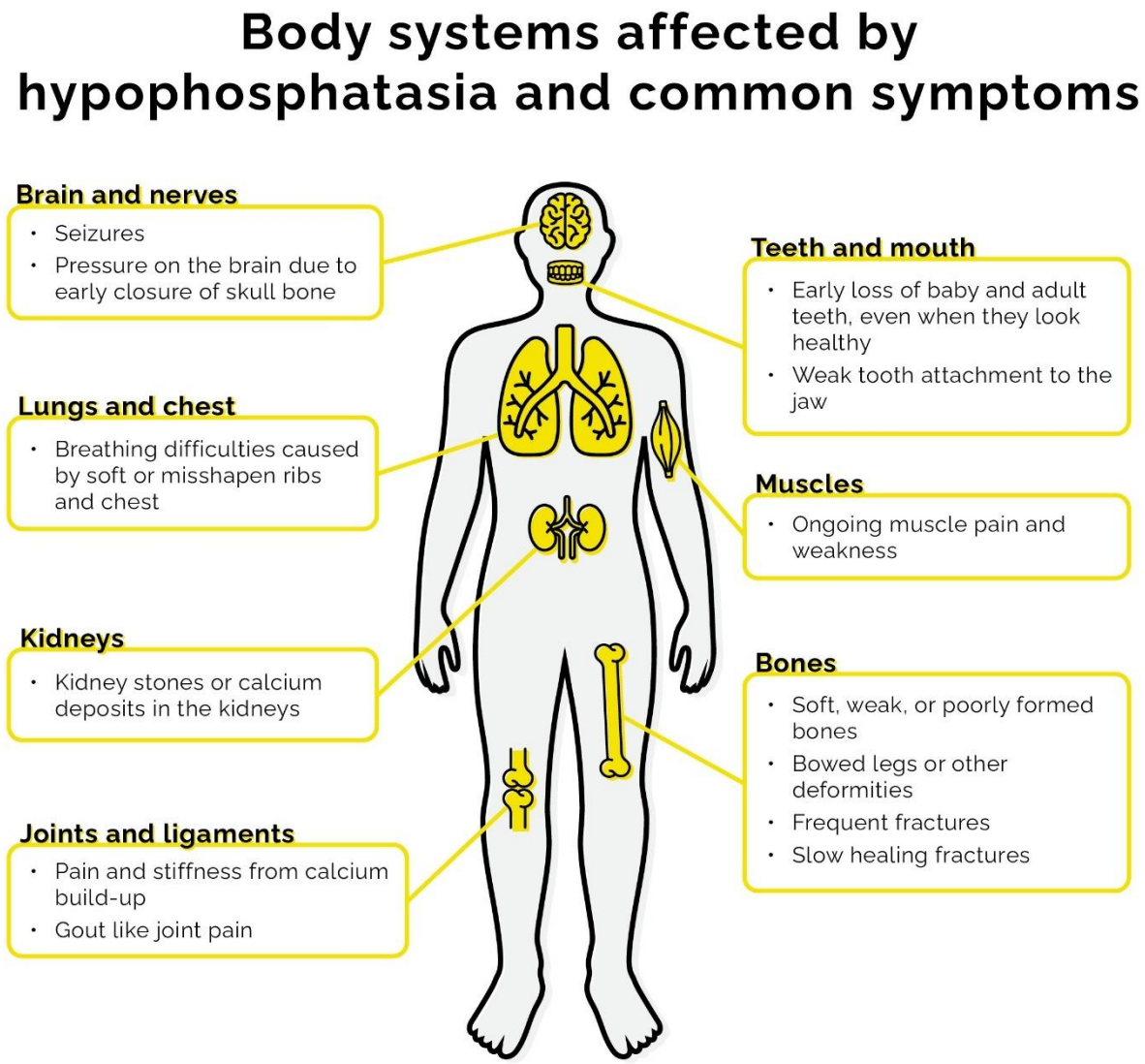
Objective: To examine the barriers to timely diagnosis, treatment access and coordinated care for HPP, and identify practical opportunities for improving care - both for HPP and the wider rare disease community.

Methods: An evidence-based report was developed using literature reviews, health system analysis, and interviews with clinicians, researchers, advocates and people living with HPP. The process aimed to combine evidence and lived experience to identify key system gaps and solutions.

Results: Diagnosis is often delayed, sometimes by decades, due to limited awareness and missed recognition of hallmark features, such as persistently low alkaline phosphatase levels. Treatment access is constrained, and there is no consistent model of care. Many individuals report significant physical, emotional and financial burden. These challenges are not unique to HPP; they reflect broader gaps in how Australia supports people with rare conditions, particularly those outside well-established treatment pathways.

Conclusion: Improving care for HPP offers a model for broader rare disease reform. Priority actions include increasing clinical awareness, fit-for-purpose treatment assessment and access pathways, and nationally coordinated multidisciplinary care models. While HPP affects a small population, strengthening systems to better support

it may yield wider benefits for Australians with rare and under-recognised conditions.



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Beyond the jaw: teriparatide in the management of bilateral external auditory canal osteonecrosis

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Introduction

Bisphosphonates and denosumab are among the most prescribed therapies for osteoporosis, supported by extensive evidence demonstrating favourable skeletal benefit-risk profile. It is essential to remain vigilant for emerging or under-recognised complications associated with these agents. We present an unusual case of bilateral

external auditory canal (EAC) osteonecrosis in a 62-year-old woman with long-standing osteoporosis treated with long-term zoledronic acid complicated by previous radiotherapy exposure, subsequently managed with teriparatide.

Case Summary

A 62-year-old woman was commenced on annual intravenous zoledronic acid in 2009 for osteoporosis, with baseline lumbar spine BMD 0.75 g/cm2 (T-score -2.6) and left hip BMD 0.57 g/cm2 (T-score −2.9). Total antiresorptive therapy duration was nine years. Her background includes acute lymphoblastic leukemia treated with allogeneic bone marrow transplantation and radiotherapy (25 Gy in 12 fractions, Dec 2007; 12 Gy in 6 fractions, Jun 2008), as well as membranous glomerulonephritis in remission and hyperlipidaemia. Between 2021 and 2023, she presented with a two-year history of bilateral otorrhoea, otalgia, and severe mixed hearing loss. Otoscopy revealed exposed bone in both EACs confirming osteonecrosis, supported by non-contrast CT petrous bone imaging showing bilateral bony erosion of the anterior and inferior EAC floors, more pronounced on the left side (Figure 1).

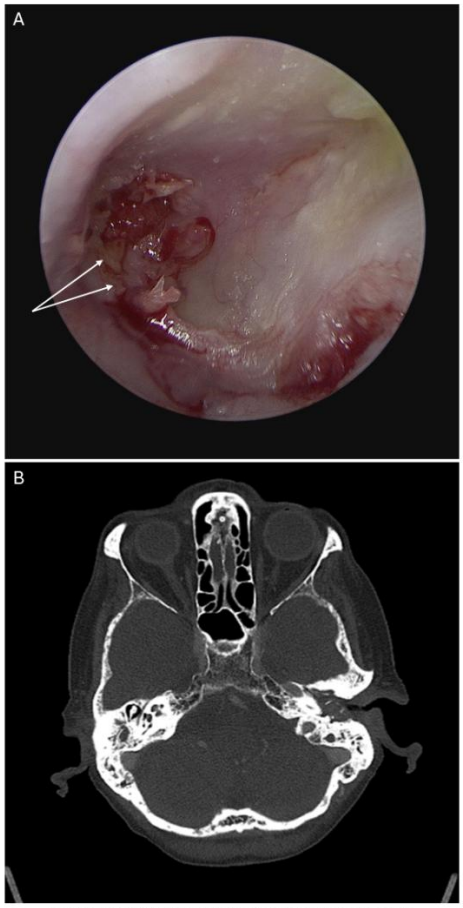

Figure 1: Right EAC examination under anaesthesia demonstrating exposed bone (white arrows) consistent with EAC osteonecrosis **(A)**. Axial section of CT petrous temporal bones showing erosion of the floors of the EACs mainly anteriorly and inferiorly, with changes more marked on the left side supportive of bilateral EAC osteonecrosis **(B)**.

Her case was reviewed with the Radiation Oncology team, who noted that the prior radiotherapy was delivered at a dose unlikely to be the sole contributor to osteonecrosis, suggesting that additional risk factors were likely involved. Other risk factors include previous bisphosphonate exposure as outlined, previous temporomandibular joint septic arthritis treated with drainage and antibiotics, prior glucocorticoid exposure for graft versus host disease and smoker status with over 20 pack/year history. She had no history of diabetes, alcohol excess, or habitual cotton bud use. Repeat BMD scan in 2023 demonstrated ongoing low lumbar spine BMD 0.90 g/cm2 (T-score −2.3) and left hip BMD 0.68 g/cm2 (T-score −3.1). She had no history of minimal trauma fractures with previous bilateral rib fractures found incidentally in 2023.

Initial management included aural toileting, curettage, and topical therapy through Ear/Nose/Throat (ENT) clinic. In view of her diagnosed EAC osteonecrosis, further antiresorptive therapy was contraindicated. In view of her underlying osteoporosis with high fracture risk and supported by its role in promoting bone remodelling and treating other forms of osteonecrosis, teriparatide was considered as a therapeutic option. Following multidisciplinary discussion with her haematologist and radiation oncologist, teriparatide was commenced in April 2024. Prescribed teriparatide dose was 20 micrograms daily via subcutaneous route, tolerated without significant side effects. Of note, later in the year, she suffered from a cerebrovascular event resulting in hemiparesis requiring rehabilitation with good functional recovery. She currently remains on teriparatide with progress BMD scan after 12 months of teriparatide revealing improvement in lumbar BMD to 0.95 g/cm2 (T-score −2.0) despite her neurological setback. She also achieved reduction in otological symptom burden and stable radiographic changes on serial CT petrous temporal bone imaging with ongoing regular ENT follow-up.

Discussion:

Complications such as osteonecrosis of the jaw (ONJ) and atypical femoral fractures have been associated with prolonged antiresorptive therapy. Heightened recognition of these risks has led to more judicious prescribing practices and the adoption of recommended treatment duration limits. The pathogenesis of ONJ remains incompletely understood. Risk factors include intravenous bisphosphonate use, oncological indications for antiresorptive use, prolonged antiresorptive exposure, diabetes, tobacco use, excessive alcohol intake, and glucocorticoid therapy.[1] In addition to its potent bone-forming effects for treatment of osteoporosis, teriparatide (recombinant human parathyroid hormone 1-34) has been shown to be an effective and well-tolerated therapeutic option that promotes bone remodelling and improves healing in established cases of medication-related ONJ (MRONJ).[2] EAC osteonecrosis is infrequently reported in literature but is believed to share a similar pathophysiological mechanism and risk profile to MRONJ. Diagnosis is primarily clinical, with exposed necrotic bone typically identified on otoscopic examination. While working definitions

typically require the presence of clinical signs for at least eight weeks in the absence of significant prior radiotherapy, our case is notable for its presumed multifactorial aetiology contributing to the development of osteonecrosis.[3] Radiographical and histopathological findings can be supportive of the diagnosis but are not essential.

We carried out a literature review using PubMed combinations of search terms "osteonecrosis", "ear canal", "auditory canal", "ear", "bisphosphonate", and "denosumab" expanding on the last published literature review by Kumar et al.[4] Including our case, we identified 28 cases of EAC osteonecrosis potentially related to antiresorptive use.[3-9] Most occurred in women over 65 with prolonged exposure, consistent with the postmenopausal osteoporotic population. Clinical presentations ranged from asymptomatic to severe otalgia, otorrhoea, and hearing loss, with less than half of reported cases demonstrating bilateral involvement. Management ranges from conservative topical therapy and antiresorptive cessation to surgical debridement or resection with reconstruction. There is currently no guidance on reintroducing antiresorptives following resolution. To our knowledge, this is the first case of teriparatide use in EAC osteonecrosis.

Conclusion:
While EAC osteonecrosis is an uncommon complication of antiresorptive therapy, this case highlights the need for a high index of suspicion due to its morbidity and impact on quality of life. Localised ear symptoms in patients with prior antiresorptive exposure should prompt consideration of this diagnosis and early ENT referral. Stable disease was achieved with teriparatide; however, further research is needed to clarify its role in EAC osteonecrosis.

Learning Points:
• EAC osteonecrosis is a rare but serious complication of long-term antiresorptive therapy.
• In patients receiving antiresorptive agents who develop new or persistent otological symptoms, clinicians should maintain a high index of suspicion and exercise caution before continuing therapy.
• Prompt ENT referral is essential to ensure timely diagnosis via otoscopy and to initiate appropriate management, including surgical intervention if required.
• Bilateral EAC osteonecrosis is less common than unilateral disease; bilateral ear evaluation is essential, particularly in patients with systemic risk factors such as antiresorptive use or prior radiotherapy.
• Although teriparatide was well tolerated and associated with clinical improvement in this case, its role in the treatment of EAC osteonecrosis remains undefined, and further studies are needed to assess its efficacy and long-term safety.

1. AlDhalaan NA, BaQais A, Al-Omar A. Medication-related Osteonecrosis of the Jaw: A Review. Cureus. 2020 Feb 10;12(2):e6944. doi: 10.7759/cureus.6944. PMID: 32190495; PMCID: PMC7067354.

2. Sim IW, Borromeo GL, Tsao C, Hardiman R, Hofman MS, Papatziamos Hjelle C, Siddique M, Cook GJR, Seymour JF, Ebeling PR. Teriparatide Promotes Bone Healing in Medication-Related Osteonecrosis of the Jaw: A Placebo-Controlled, Randomized Trial. J Clin Oncol. 2020 Sep 10;38(26):2971-2980. doi: 10.1200/JCO.19.02192. Epub 2020 Jul 2. PMID: 32614699.

3. Peřina V, Salzman R, Treglerová J. Denosumab-related osteonecrosis of the external auditory canal-benefit of the early surgical management. Ear Nose Throat J. 2024 May;103(5):277-281. doi: 10.1177/01455613211053389. Epub 2021 Oct 21. PMID: 34672841.

4. Kumar S, Diamond T, Walton J. Two Cases of External Auditory Canal Osteonecrosis in Patients on Antiresorptive Therapy for Osteoporosis. JCEM Case Rep. 2023 Feb 27;1(2):luad021. doi: 10.1210/jcemcr/luad021. PMID: 37908466; PMCID: PMC10580658.

5. Mayer AW, Oladokun D, Mistry D. Recognizing bisphosphonate-induced ear osteonecrosis in primary care: a case report. Fam Pract. 2024 Apr 15;41(2):219-222. doi: 10.1093/fampra/cmae012. PMID: 38413046.

6. VanDolah H, Crossley JR, Kim HJ. Three cases of uncommon medication-associated osteonecrosis of temporal bone. World J Otorhinolaryngol Head Neck Surg. 2023 Dec 3;10(3):237-240. doi: 10.1002/wjo2.146. PMID: 39233865; PMCID: PMC11369790.

7. Yamaguchi S, Mori T, Asano N, Susa M, Oishi N, Ozawa H, Nakayama R. Bilateral osteonecrosis of the external auditory canal caused by bone-modifying agents for cancer bone metastases. Int Cancer Conf J. 2025 May 27;14(3):311-318. doi: 10.1007/s13691-025-00772-z. PMID: 40625758; PMCID: PMC12229342.

8. Petersen LØ, Johansen IR. Osteonecrosis of the ear canal in a patient treated with bisphosphonate. Ugeskr Laeger. 2023 Jun 5;185(23):V02230076. Danish. PMID: 37325983.

9. Polizzotto MN, Cousins V, Schwarer AP. Bisphosphonate-associated osteonecrosis of the auditory canal. Br J Haematol. 2006 Jan;132(1):114. doi: 10.1111/j.1365-2141.2005.05833.x. PMID: 16371027.

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Intrinsic capacity and sarcopenia: data from the Geelong Osteoporosis Study

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Background: Intrinsic capacity (IC), proposed by the WHO as the overall combination of an individual's physical and mental abilities, has been identified as a key indicator of healthy ageing. While the Integrated Care for Older People (ICOPE) framework focuses on overall IC, it includes aspects of ageing which are also relevant to sarcopenia. The aim of this cross-sectional study was to explore the IC-sarcopenia relationship in older women.

Methods: Composite IC scores were calculated for 191 women (60-90y), with higher scores reflecting greater capacity, based on five domains: vitality (repeated chair stands, perceived energy, weight loss), cognition (Mini-Mental State Examination), psychological wellbeing (Hospital Anxiety and Depression Scale), locomotion (timed Up-&-Go) and sensory abilities (vision, hearing). Scores for each domain ranged from 0 (unhealthy) to 3 (healthy). Low appendicular lean mass (ALM/h^2<5.5kg/m^2) was measured by DXA and low handgrip strength (HGS<16kg) by dynamometry. Education, physical activity (inactive/sedentary/active/very-active), smoking and alcohol use were self-reported. Linear regression modelling was used to determine associations of IC with components of sarcopenia and lifestyle factors.

Results: Median IC score=12 (range 4-14). In separate models, low-HGS (β= -2.178, se 0.547, p<0.001) and low-ALM/h^2 (β= -1.242, se 0.464, p=0.008) were negatively associated with IC scores. In a multivariable model, independent associations with IC included low-HGS (β= -1.379, se 0.463, p=0.003), low-ALM/h^2 (β= -1.180, se 0.373, p=0.002), age (β= -0.074, se 0.017, p<0.001), smoking (β= -1.318, se 0.494, p=0.008) and physical activity: with 'inactive' as reference, sedentary (β=2.305, se 0.434), active (β=2.676, se 0.419) and very-active (β=3.000, se 0.464) groups showed a dose-related association with IC (all p<0.001).

Conclusion: The association between IC scores and components of sarcopenia, independent of age and movement, suggest that further research should investigate the ICOPE framework as a screener for functional deterioration, psychological decline and energy imbalance, all of which contribute to sarcopenia.

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DXA based 3-dimensional (3D) modelling technology to examine differential bone loss following heart transplantation

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Background:Bone mineral density (BMD) loss following heart transplantation is common. Areal BMD (aBMD) measurements using 2-dimensional (2D) dual-energy X-ray absorptiometry (DXA) cannot differentiate between cortical and trabecular compartments and may not fully reflect bone fragility, particularly early post-transplantation. DXA-based three-dimensional (3D) modelling (3D-Shaper) calculates volumetric BMD (vBMD) and may be more informative.

Aims: To determine compartmental vBMD loss following heart transplantation using 3D-Shaper and to identify clinical factors associated with greater bone loss. Secondary outcome was to compare aBMD loss by DXA versus 3D-Shaper.

Methods: Single centre, retrospective cohort study of heart transplant recipients, within 4-13 months post-transplant.

Results: In thirty-six subjects, greater mean vBMD loss occurred in the trabecular (-6.93% ± 8.90) than in the cortical compartment (-3.20% ± 4.70, p = 0.03). Loss of total hip aBMD with DXA was strongly correlated with cortical (r2=0.76, p=<0.001), trabecular (r2=0.82, p=<0.001) and integral (r2=0.86, p=<0.001) vBMD loss. Compartmental bone loss was not associated with bone specific or glucocorticoid pulse therapies.

Conclusions: There was two-fold greater vBMD loss in the trabecular, compared to cortical compartment within 13 months post-transplantation. Total hip aBMD decline correlated strongly with all compartments of vBMD. 3D-shaper offers a novel method for assessing changes in cortical and trabecular compartments using standard hip DXA images. Further research is needed to investigate impact of compartmental bone loss on bone fragility and fracture prediction.

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A case of Gnathodiaphyseal Dysplasia/"High Bone Mass Osteogenesis Imperfecta" due to novel COL1A1 mutation

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A 17-year-old year 11 student was reviewed in the Adult Endocrinology Outpatient Clinic for his recurrent fractures. Both the patient and his mother were previously diagnosed with Gnathodiaphyseal Dysplasia (GDD) and discovered to have a novel mutation in *COL1A1* (Ala1218Thr), previously published by McInerney-Leo et al. (1), where his mother's phenotype is described in detail. At that time the patient was 5 years of age and limited information was known about his phenotype. This case report provides further information regarding the clinical features of this patient.

The patient had right tibia fracture at age 9 weeks. At age four years he fractured several facial bones after falling off a tricycle, out of proportion to the mechanism of injury. A CT head at that time did not note any definitive sclerotic lesion in his jaw. At age 15 years he had a base of 5thmetatarsal fracture after an inversion injury, a weber A ankle fracture and acromion fracture after a fall from standing height. At age 16 years he had a metatarsal neck fracture. At the same age he also suffered a ligamentous injury to his ankle which required a period in a Controlled Ankle Motion Walker boot. At age 17 years he suffered 3 further metatarsal fractures. X-ray imaging has demonstrated abnormal bony texture with areas of diffuse sclerotic and osteopenic appearance on X-ray (see figures 1 to 3). Bone Mineral Densitometry at age 16 years revealed lumbar spine and whole body bone mineral density 5.4 and 5.6 standard deviations above the mean for age, respectively (figure 4). Blood tests show an elevated alkaline phosphatase (ALP) of 304 U/L (normal range 30-300 U/L). Samples have been sent for testing for bone turnover markers, the results of which are pending at time of writing.

As an infant he had a late-closing anterior fontanelle and continues to have a prominent forehead. He had otherwise normal growth and at most recent measurement is 172 cm tall. He had maxillary hypoplasia, prognathism and delayed primary dentition. CT Maxilla at age 13 years (figure 5) showed an area of idiopathic sclerosis in the left upper jaw. An Orthopantomogram (OPG) performed at age 12 did not show any focal bony abnormality, however repeat OPG at age 16 years showed a generalised sclerotic appearance of the bone (figure 6).

He had hypotonia and delay of gross motor milestones as an infant. He has been diagnosed with level 2 autism spectrum disorder (ASD) and dyslexia. He has features of hypermobility, with pes planus and genu valgum as well as mild scoliosis (figure 3). He

is obese with a BMI of 30 Kg/m2 at most recent measurement. He has no evidence of dentinogenesis imperfecta, cardiac valvular disease, hearing loss or blue sclerae.

Gnathodiaphyseal Dysplasia is a rare disorder characterized by bone fragility, fibro-osseous lesions in the skull and jaw, and abnormal modelling of long bones. The syndrome is associated with multiple fractures in childhood which tend to reduce in frequency with age. Mutations on in *ANO5* on chromosome 11p14.3 were identified to be responsible for most cases of GDD (2,3), as well as some forms of muscular dystrophy (4). The mechanism via which ANO5 mutations cause GDD is unknown.

Type I collagen is formed by the assembly of alpha-1(I) and alpha-2(I) chains which are initially synthesised as pre-molecules with amino (N-) and carboxyl (C-) propeptide ends attached. These propeptides must be removed proteinases, including bone morphogenic protein 1 (BMP1) which is responsible for removing the C-propeptide. The Ala1218Thr mutation noted in this patient and his mother appears to alter the BMP1 cleavage site of the alpha-1(I) chain and therefore preventing the removal of C-propeptide from type 1 collagen. It is speculated that retained C-propeptide could result in increased mineralisation of bone, and the characteristic osteosclerotic lesions of GDD in the jaw may be due to uneven retention (1,5). Osteogenesis imperfecta (OI) is frequently caused by mutations in the *COL1A1/COL1A2* type 1 procollagen genes (5) and variants in these genes have also been implicated in Ehlers-Danlos syndrome (6). Several case reports have described *COL1A1* C-propeptide cleavage site mutations associated with a "high bone mass OI-GDD" phenotype (5,7). Previous authors have noted that in these published cases, there was no evidence of jaw lesions, but postulated that as these reported cases were children, they may develop jaw lesion later in life (1). This patient was not found to have jaw lesions on CT scan at age 4 or OPG at age 12 years, but these lesions became evident on follow up scans more recently. There is no published evidence to guide the management of this condition.

There has been a link identified between hypermobility disorders and ASD (8). A question could be raised about the interrelatedness of this patient's ASD diagnosis and his bone and collagen disease.

Take Home Messages:

- This case report confirms a similar phenotype GDD as the patient's mother, previously described, with multiple fractures (especially small bones of the foot), sclerotic lesions of the jaw, maxillary hypoplasia, hypermobility and delayed primary dentition.
- This case demonstrates the gradual development of sclerotic bony lesions of the jaw in this phenotype of GDD.

- This patient also has a diagnosis of Autism, which may have an associated with hypermobility disorders.
- This case presents a difficult management problem and there is no evidence to guide treatment.

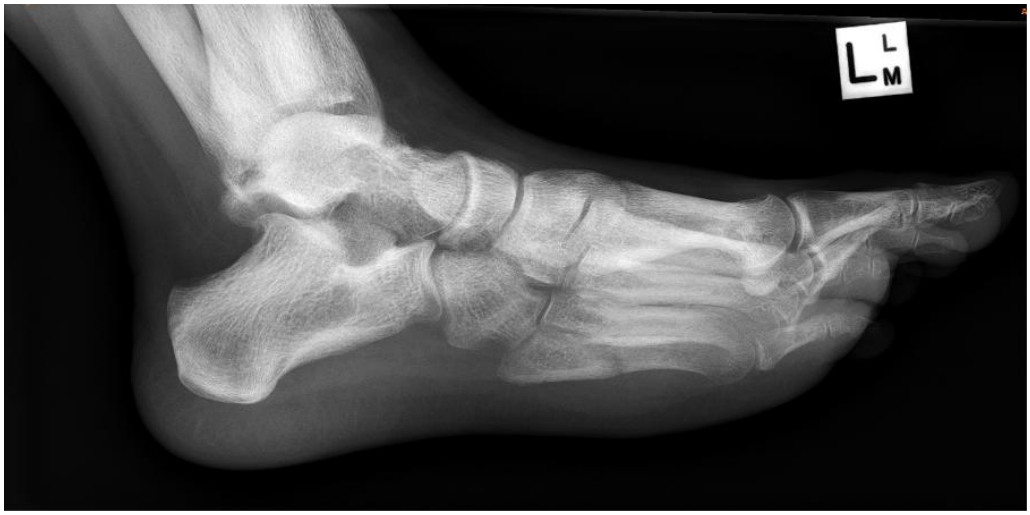

Figure 1: XR left foot demonstrating metatarsal fractures and a diffuse sclerotic appearance of the bones.

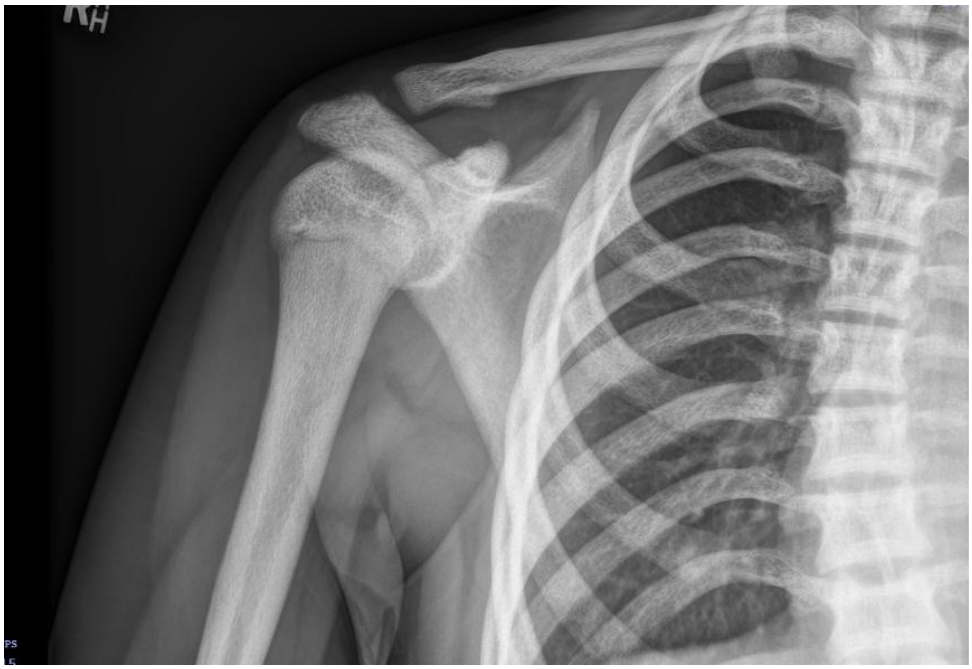

Figure 2: XR shoulder shows coarsening of bony trabecular pattern.

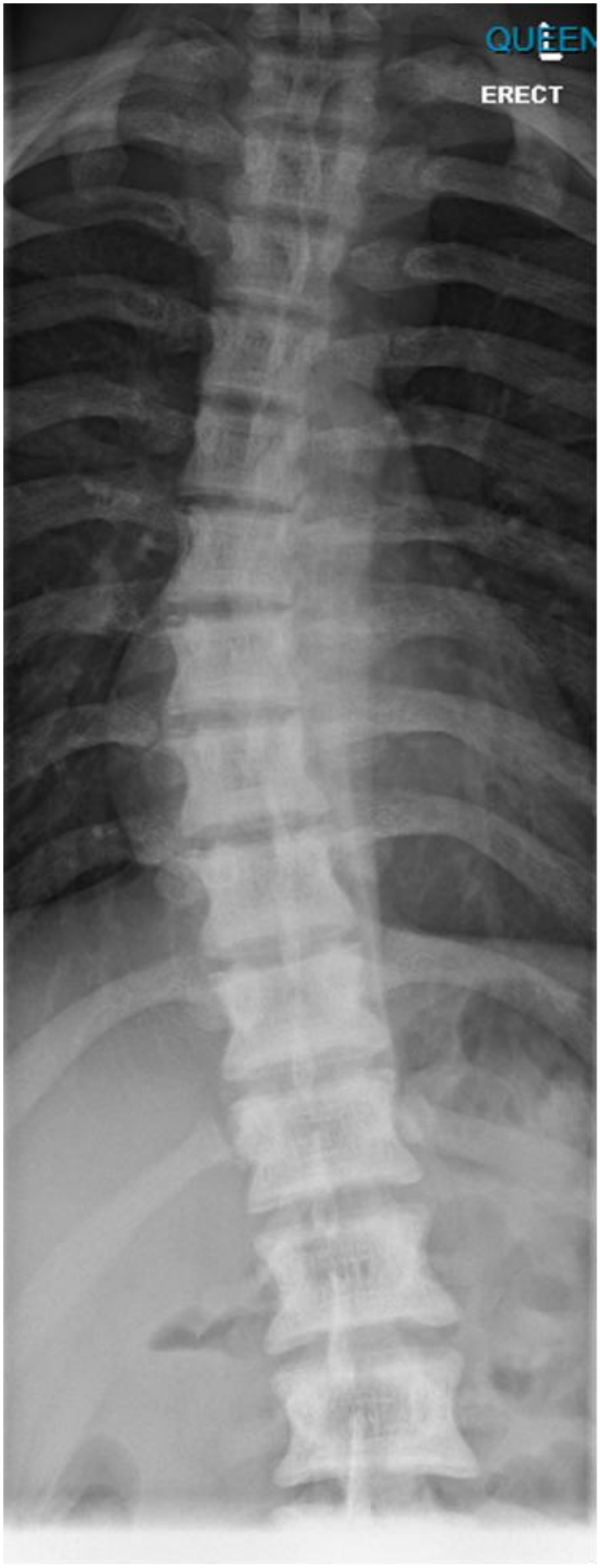
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Figure 3: XR thoracic spine demonstrates abnormal bony texture and mild scoliosis.

Region	Area [cm^2]	BMC [(g)]	BMD [g/cm^2]	Fat[(g)]	Lean [(g)]	Lean + BMC[(g)]	Total [(g)]	% Fat [(%)]	T-score	PR (Peak Reference)	Z-score	AM (Age Matched)
L Arm	210.88	301.67	1.431	2165.7	2610.8	2912.4	5078.2	42.6				
R Arm	228.45	295.48	1.293	2063.4	2558.2	2853.7	4917.0	42.0				
L Ribs	165.58	215.20	1.300									
R Ribs	178.46	220.34	1.235									
T Spine	146.05	223.21	1.528									
L Spine	55.84	117.10	2.097									
Pelvis	283.51	678.29	2.392									
Trunk		1454.14		17592.2	21255.6	22709.7	40302.0	43.7				
L Leg	383.87	926.72	2.414	6973.0	8697.4	9624.2	16597.1	42.0				
R Leg	371.38	922.56	2.484	7032.5	8853.0	9775.6	16808.1	41.8				
Subtotal	**2024.03**	**3900.57**	**1.927**	**35826.9**	**43975.1**	**47875.6**	**83702.5**	**42.8**			**5.6**	**184**
Head	256.57	838.04	3.266	1363.9	3219.6	4057.6	5421.5	25.2				
Total	2280.59	4738.61	2.078	37190.7	47194.7	51933.3	89124.0	41.7			6.0	183

Figure 4: Results of recent Bone Mineral Densitometry, performed at age 16, demonstrating bone mineral density measurements up to 6 standard deviations above the expected mean for the patient's age.

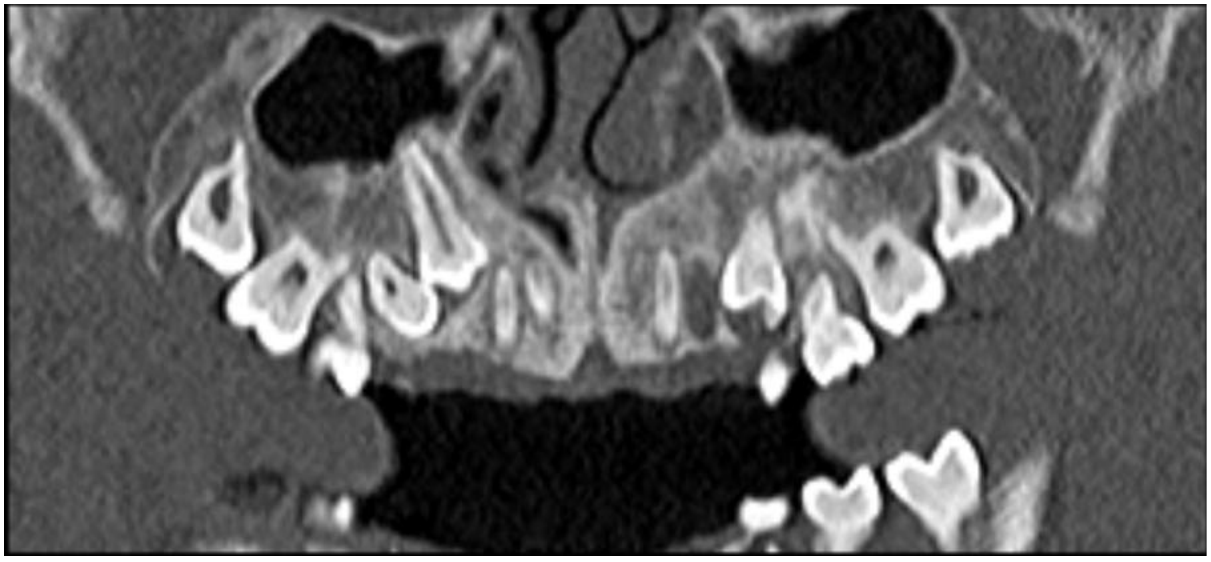

Figure 5: CT Maxilla at age 13 showing an area of idiopathic sclerosis lying between the roots of the 24, 25 and 65.

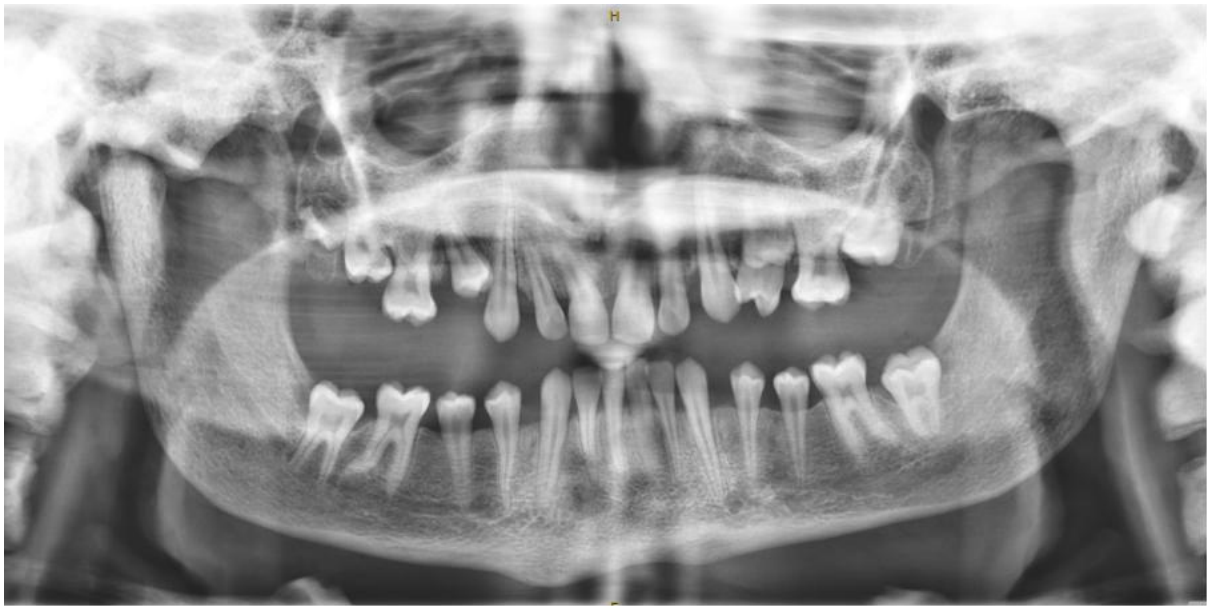

Figure 6: CR Orthopantomogram at age 16 demonstrating missing 14, 28, 38 and 48. 18 has delayed crown formation. Generalised sclerotic bone pattern observed.

1. 1. McInerney-Leo, A. M., Duncan, E. L., Leo, P. J., Gardiner, B., Bradbury, L. A., Harris, J. E., Clark, G. R., Brown, M. A., & Zankl, A. (2015). COL1A1 C-propeptide cleavage site mutation causes high bone mass, bone fragility and jaw lesions: a new cause of gnathodiaphyseal dysplasia?. Clinical genetics, 88(1), 49–55.
2. 2. Tsutsumi, S., Kamata, N., Maruoka, Y., Ando, M., Tezuka, O., Enomoto, S., Omura, K., Nagayama, M., Kudo, E., Moritani, M., Yamaoka, T., & Itakura, M. (2003). Autosomal dominant gnathodiaphyseal dysplasia maps to chromosome 11p14.3-15.1. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research, 18(3), 413–418.
3. 3. Tsutsumi, S., Kamata, N., Vokes, T. J., Maruoka, Y., Nakakuki, K., Enomoto, S., Omura, K., Amagasa, T., Nagayama, M., Saito-Ohara, F., Inazawa, J., Moritani, M., Yamaoka, T., Inoue, H., & Itakura, M. (2004). The novel gene encoding a putative transmembrane protein is mutated in gnathodiaphyseal dysplasia (GDD). American journal of human genetics, 74(6), 1255–1261.
4. 4. Bolduc, V., Marlow, G., Boycott, K. M., Saleki, K., Inoue, H., Kroon, J., Itakura, M., Robitaille, Y., Parent, L., Baas, F., Mizuta, K., Kamata, N., Richard, I., Linssen, W. H., Mahjneh, I., de Visser, M., Bashir, R., & Brais, B. (2010). Recessive mutations in the putative calcium-activated chloride channel Anoctamin 5 cause proximal LGMD2L and distal MMD3 muscular dystrophies. American journal of human genetics, 86(2), 213–221.

5. 5. Lindahl, K., Barnes, A. M., Fratzl-Zelman, N., Whyte, M. P., Hefferan, T. E., Makareeva, E., Brusel, M., Yaszemski, M. J., Rubin, C. J., Kindmark, A., Roschger, P., Klaushofer, K., McAlister, W. H., Mumm, S., Leikin, S., Kessler, E., Boskey, A. L., Ljunggren, O., & Marini, J. C. (2011). COL1 C-propeptide cleavage site mutations cause high bone mass osteogenesis imperfecta. Human mutation, 32(6), 598–609.

6. 6. Venable, E., Knight, D. R. T., Thoreson, E. K., & Baudhuin, L. M. (2023). COL1A1 and COL1A2 variants in Ehlers-Danlos syndrome phenotypes and COL1-related overlap disorder. American journal of medical genetics. Part C, Seminars in medical genetics, 193(2), 147–159.

7. 7. Pollitt, R., McMahon, R., Nunn, J., Bamford, R., Afifi, A., Bishop, N., & Dalton, A. (2006). Mutation analysis of COL1A1 and COL1A2 in patients diagnosed with osteogenesis imperfecta type I-IV. Human mutation, 27(7), 716.

8. 8. Baeza-Velasco, C., Vergne, J., Poli, M., Kalisch, L., & Calati, R. (2025). Autism in the context of joint hypermobility, hypermobility spectrum disorders, and Ehlers-Danlos syndromes: A systematic review and prevalence meta-analyses. Autism : the international journal of research and practice, 29(8), 1939–1958.

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Skeletons in the closet: Missed opportunities to institute osteoporosis therapy after minimal trauma fractures – a single-centre retrospective audit

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Background: Minimal trauma fractures (MTF) are associated with significant morbidity and mortality, with refracture risk peaking in the first few months following an index fracture[1]. Initiation of osteoporosis therapy is therefore both important and urgent. Our centre is yet to implement an osteoporotic refracture prevention (ORP) service.

Methods: We conducted a 6-month retrospective audit of patients aged ≥ 50 years who presented with radiologically confirmed MTFs to Bankstown-Lidcombe Hospital between January and June 2024 (data collection ongoing to include July-December 2024). Data were extracted from electronic medical records, including demographics,

history of prior MTF, and antiresorptive therapy. Fractures of the hand, foot, ankle, face and skull were excluded.

Results: We identified 351 MTF presentations, involving 348 unique patients (mean age 78.2 +/- 11.4 years; 71.0% female). Three patients presented twice within the audit period. Of all MTF presentations, 86/351 (24.8%) were refractures i.e. with a documented history of prior MTF; of these, only 44/86 (51.2%) had previously received antiresorptive therapy. Overall, 83/351 (23.6%) occurred despite prior antiresorptive therapy, including 64/351 (18.2%) on denosumab and 17/351 (4.9%) on bisphosphonates. The most common sites of fracture were the hip (90/351, 25.6%) and distal forearm (62/351, 17.4%). 224/351 (63.8%) required inpatient admission; the median length of stay was 13 days [IQR 6–28]. 67/351 (19.1%) had antiresorptive therapy initiated as an inpatient, 82/351 (23.4%) were provided with a discharge plan to initiate antiresorptive therapy as an outpatient, and 202/351 (57.5%) were discharged without a documented plan regarding osteoporosis management.

Conclusion: MTFs are a common hospital presentation and frequently represent refractures. Nearly half of refractures occurred in patients not receiving antiresorptive therapy. Most MTF presentations were discharged without a documented osteoporosis management plan. Our findings highlight an important gap in secondary fracture prevention and support the need for a local ORP service.

Table 1. Characteristics of minimal trauma fracture presentations (n = 351).

	n	(%)
Admitted as inpatient	224	(63.8)
Number of fractures		
1	261	(74.4)
2	49	(14.0)
3	19	(5.4)
4	11	(3.1)
≥ 5	11	(3.1)
Fracture site [a]		
Hip	90	(25.6)
Distal forearm	62	(17.4)
Rib	61	(17.4)
Spine	55	(15.7)
Humerus	42	(12.0)
Pelvis	28	(8.0)
Other	42	(12.0)
Refractures	86	(24.8)
Prior antiresorptive therapy		
PO bisphosphonate	14	(4.0)
IV bisphosphonate	3	(0.9)
Denosumab	64	(18.2)
Romosuzumab	1	(0.3)
Teriparatide	1	(0.3)
No prior antiresorptive therapy	268	(76.4)
Geriatrics, endocrinology or rheumatology involvement	139	(39.7)
Inpatient DEXA	19	(5.4)
Antiresorptive therapy		
Inpatient	67	(19.1)
Planned as outpatient	82	(23.4)
Not planned	202	(57.5)
Class of antiresorptive therapy [b]		
PO bisphosphonate	49	(32.9)
IV bisphosphonate	3	(2.0)
Denosumab	84	(56.4)
Not specified	13	(8.7)
Change in antiresorptive therapy [b]		
First time antiresorptive	79	(53.0)
Change in antiresorptive	4	(2.7)
Continued usual antiresorptive	66	(44.3)

[a] Percentages calculated out of 351 presentations. Some presentations involved more than one fracture site.

[b] Percentages calculated out of the 149 presentations where antiresorptive therapy was administered as inpatient or planned as outpatient.

1. Banefelt J, Åkesson KE, Spångéus A, etal. Risk of imminent fracture following a previous fracture in a Swedish database study. Osteoporos Int. 2019;30(3):601–609.

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A randomised controlled trial of vitamin D combined with exercise on arterial stiffness in vitamin D deficient, overweight/obese older adults

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Background: We report on the vascular outcomes of a vitamin D and exercise pilot trial in overweight/obese older adults with vitamin D deficiency.

Methods: Fifty individuals {19 (38%) men (median [95%CI] age: 58 [55 to 63] years; BMI 28. 5 [26.9 to 33.4] kg/m^2)} with 25-hydroxyvitamin D < 50 nmol/L were randomly allocated to receive either vitamin D3 (4,000 IU/day) or placebo for 24 weeks. Between weeks 12 - 24, all participants completed multimodal exercise while continuing with treatment. Mean changes in systolic (SBP), central SBP (cSBP), diastolic (DBP), central DBP (cDBP) and mean arterial (MAP) blood pressures (in mmHg)), heart rate (HR) as well as pulse wave velocity (PWV) and augmentation index (Aix) at weeks 12 and 24 were compared between groups. Analyses were conducted in the full cohort and in those with good adherence to the programme; and with outliers excluded.

Results: Vitamin D- and exercise-related changes in vascular outcomes did not differ between groups at 12 or 24 weeks. However, vitamin D supplementation alone appeared to (non-significantly) improve SBP [-7.03mmHg (-19.8 to 5.8)], cSBP [-7.38 mmHg (-17.2 to 2.4)], PP [-6.18 mmHg (-15 to 2.7)], HR [-3.84bpm (-12 to 4.3)] and Aix [-7.02% (-15.3 to 1.3)] but these changes were attenuated with the addition of exercise.

Interpretation: Vitamin D supplementation alone had potentially favourable but small effects on some vascular markers in overweight/obese older adults with vitamin D deficiency, but the addition of exercise appeared to add no further benefit.

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Relationship Between REMS-Derived Fragility Score, Age and Bone Mineral Density in Australian Patients

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Bone mineral density (BMD) and T-score remain the diagnostic standard for osteoporosis. However, fracture risk is multifactorial and not always well captured by BMD alone. REMS (Radiofrequency Echographic Multi-Spectrometry) reports the Fragility Score (FS), an index reflecting structural bone integrity independent of BMD. A 5-year prospective study (Pisani et al., 2023) found FS to be a superior fracture predictor vs BMD. FS was added to the Echolight/REMS ARTG Certificate by the TGA in March 2024.

REMS scans (femoral neck and lumbar spine) reporting BMD, T-score, and FS have been available in Australia since February 2023. This retrospective, real-world analysis explored the relationship between FS and age, and T-scores at both sites. We analysed REMS data from 924 female patients (mean age 60.6 years), collected between Feb 2023 and Jun 2025.

Age-FS Relationship: FS gradually increased with age, especially 65+, suggesting age-related microarchitectural deterioration independent of BMD.
T-score-FS Relationships: FS was also evaluated in relation to femoral neck and spine T-scores. FS correlated inversely with T-scores at both sites in a nonlinear manner. Four clinical quadrants were examined to compare BMD and fragility.

Table 1: Combined Left & right Femoral Neck T-score with Fragility Scores (n=2161 scans)

T-score Category	Low Risk (0–30)	Low-Moderate (30–39)	Moderate (40–59)	High Risk (60–100)	Total
Normal (≥ –1.0)	425 (87%)	36 (7%)	24 (5%)	4 (1%)	489 (100%)
Osteopenia (-1.1 to -2.4 inclusive)	779 (60%)	295 (23%)	167 (13%)	65 (5%)	1306 (100%)
Osteoporosis (≤ –2.5)	66 (18%)	86 (23%)	132 (36%)	82 (22%)	366 (100%)
Total	1270 (59%)	417 (19%)	323 (15%)	151 (7%)	2161 (100%)

Table 2: Lumbar Spine T-score with Fragility Scores (n=1861 scans)

T-score Category	Low Risk (0–30)	Moderate-Low (30–39)	Moderate (40–59)	Higher Risk (60–100)	Total
Normal (≥ –1.0)	151 (76%)	43 (22%)	5 (3%)	0	199 (100%)
Osteopenia (-1.1 to -2.4 inclusive)	614 (56%)	376 (34%)	73 (7%)	32 (3%)	1095 (100%)
Osteoporosis (≤ –2.5)	138 (26%)	189 (36%)	122 (23%)	79 (15%)	528 (100%)
Total	903 (50%)	608 (33%)	200 (11%)	111 (6%)	1822 (100%)

Key Clinical Findings: 14.5% of femoral neck scans and 8.5% of lumbar spine scans with normal/osteopenia T-scores had moderate-to-high FS (≥40), suggesting elevated fracture risk despite non-osteoporotic BMD. Conversely, some scans with osteoporosis also showed low-to-low-moderate FS (<40), (41% of femoral neck & 62% of lumbar spine scans), potentially suggesting better structural integrity than BMD alone might indicate.

These findings demonstrate that FS provides additional discriminative value to BMD measurement, particularly for identifying fracture risk in patients whose T-scores may not fully capture skeletal fragility. FS may serve as an important clinical tool to guide treatment decisions in osteoporosis or high fracture potential, enabling more personalized risk stratification beyond traditional BMD-based diagnosis.

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The Effect of Modern Pharmacotherapy on Bone Mineral Density in Rheumatoid Arthritis Patients

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Purpose:
RA is associated with increased fracture risk due to systemic bone loss. While new DMARD therapy over the past 30 years has improved disease control, its impact on BMD remains controversial. This meta-analysis investigates the effects of csDMARDs, bDMARDs, and tsDMARDs on BMD in RA patients, accounting for disease activity and glucocorticoid exposure.

Methodology:
MEDLINE, EMBASE, Cochrane, and Scopus were searched for studies published after 1980 that assessed longitudinal changes in BMD at the femoral neck and lumbar spine in RA patients on modern pharmacotherapy therapy. The analysis stratified data based on DMARD class, baseline disease activity score, glucocorticoid use, and anti-osteoporotic therapy. Random-effect modelling was employed to estimate pooled BMD changes and multivariable analysis to control for confounding effects of steroids and anti-osteoporotic therapy.

Results:
Among 46 studies (n = 11,578), the pooled BMD change was +0.18% (95% CI: -2.33% to 2.68%) at the lumbar spine and -0.46% (95% CI: -1.17% to 0.25%) at the femoral neck. No significant difference was observed between csDMARDs and b/tsDMARDs in preserving BMD. Higher baseline DAS correlated with greater BMD loss ($p = 0.009$), whereas ΔDAS had no effect. GCS use >5 mg/day negatively influenced LSBMD ($p = 0.006$) but had no impact on FNBMD. The presence of anti-osteoporotic therapy was associated with improved BMD.

Conclusion:
Short-term improvements in disease activity did not lead to improvements in BMD; however, long-term low disease activity did, emphasising the importance of long-term disease control in maintaining bone health in RA patients. Modern pharmacotherapy appears to stabilise BMD in RA patients, with neither csDMARD or later therapy proving superior. Strategies to improve bone health in RA patients should continue to emphasise long-term disease control, GCS minimisation, and use of anti-osteoporotic therapies, while further research evaluates the role of specific DMARD.

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Beware the rebound when breaking up with denosumab

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1. Case

A 66-year-old caucasian woman presented in February 2023 with three weeks of polyuria, polydipsia, abdominal pain, nausea, anorexia, brain fog and 4kg unintentional weight loss. On examination, she was clinically dehydrated. She had a background of postmenopausal osteoporosis managed with daily teriparatide 20mcg, calcium carbonate 600mg and 3–4 serves of dietary calcium. She had received subcutaneous denosumab 60mg biannually from 2012–2022. Teriparatide was commenced in August 2022 due to non-union of a painful and functionally limiting metatarsal fracture. Denosumab was ceased at the time of teriparatide commencement given limited safety data when denosumab use exceeds 10 years, and achievement of target bone mineral density (BMD). Teriparatide was commenced four months post last denosumab dose to initiate the anabolic window prior to commencement of the 'rebound effect' following denosumab discontinuation.

Outpatient investigations demonstrated hypercalcaemia (corrected calcium [CCa^{2+}] 3.18mmol/L [RR 2.15-2.55]) with acute kidney injury (creatinine 100µmol/L vs. baseline 60µmol/L). Repeat investigations on admission confirmed parathyroid hormone (PTH) independent hypercalcaemia, with CCa^{2+} 2.90mmol/L, PTH <0.8pmol/L (RR 2-9), 25-hydroxyvitamin D 87nmol/L (RR 50–150), and 1,25-dihydroxyvitamin D 34nmol/L (RR 60–200). Bone turnover markers (BTMs) were significantly elevated with C-terminal telopeptide (CTx) 2,422ng/L (RR 50–800) and procollagen type 1 N-terminal propeptide (P1NP) 511µg/L (RR 8–84). Urinary calcium excretion was elevated with calcium-to-creatinine clearance ratio 0.035, whilst serum protein electrophoresis, serum free light chains, cortisol, thyroid function tests, angiotensin-converting enzyme, lactate dehydrogenase and PTH-related peptide were within normal range. CT chest/abdomen/pelvis and ^{18}F-FDG PET/CT did not identify malignancy or bony lesions. ^{99m}Tc bone scintigraphy demonstrated diffuse cortical uptake in the bilateral long bones and skull consistent with a metabolic bone process, but no focal areas of

increased osteoblastic activity to suggest malignancy (Figure 1). Management involved cessation of teriparatide and calcium carbonate, and aggressive intravenous and oral fluid rehydration (4–5L/day). CCa2+ improved over several days to 2.59mmol/L and she was discharged.

Twice-weekly bloods for one-month post-discharge demonstrated stable CCa^{2+} 2.58mmol/L. BTMs remained elevated with CTx 2,710-3,220ng/L and P1NP 379-451µg/L. DEXA scan in April 2023 demonstrated a decline in BMD of 13.1% at the total mean hip and 2.8% at the lumbar spine in the six months post teriparatide commencement. This represented an 80% loss of the total mean hip BMD gained following 11 years of denosumab treatment (Figure 2). Denosumab 60mg was recommenced to prevent further bone loss and mitigate fracture risk. Six weeks post-denosumab reintroduction, she developed hypocalcaemia with secondary hyperparathyroidism (CCa^{2+} 2.11mmol/L, PTH 19.7pmol/L) and marked BTM suppression (CTx<70ng/L, P1NP 229µg/L) (Figure 3). Calcitriol 0.25µg twice daily was commenced to maintain normocalcaemia and ceased after five months. Six-monthly denosumab was continued, maintaining CTx<70ng/L and P1NP 30µg/L. Repeat DEXA in November 2024 demonstrated a BMD increase of 21.3% at the hip and 8.8% at L1-L4 since April 2023, indicating complete BMD recovery.

1. **Literature review**

Among Australians aged ≥50 years, 1 in 4 men and 1 in 5 women will experience a minimal trauma fracture.(1) Osteoporotic fractures are associated with significant morbidity and premature mortality.(2) Denosumab is the most commonly prescribed therapy for osteoporosis by general practitioners in Australia.(2, 3)

Denosumab is a potent antiresorptive that inhibits RANK ligand (RANKL), suppressing osteoclast activity and bone resorption.(4) The FREEDOM trial and its extension demonstrated 10 years of denosumab treatment was associated with sustained BMD increases and significantly reduced fracture risk.(5) However, long-term use carries rare but serious risks of atypical femoral fractures (0.8/10,000 person-years) and osteonecrosis of the jaw (5.2/10,000 person-years).(5, 6) Conversely, denosumab cessation leads to rebound RANKL expression and bone turnover (above baseline levels) with subsequent BMD loss and increased fracture risk.(7,8,9) Longer treatment duration is a risk factor for severity of BMD loss and rebound fractures on discontinuation.(9) For clinicians seeking to mitigate the risks of long-term denosumab, the optimal treatment approach remains unclear.

Teriparatide is a synthetic parathyroid hormone analogue approved for individuals at very high fracture risk.(2) Administered daily, this osteoanabolic agent stimulates osteoblast activity and reduces apoptosis.(2) Teriparatide increases BMD and reduces both vertebral and non-vertebral fracture risk in postmenopausal women.(10) However,

the DATA-Switch RCT demonstrated transitioning from denosumab to teriparatide results in transient BMD loss at the hip and spine, and progressive BMD loss at the radius.(11) This phenomenon may be due to teriparatide-induced stimulation of RANKL and osteoclastic resorptive activity.(11) This case illustrates how the transition from denosumab-to-teriparatide can amplify the RANKL-mediated 'rebound effect' with the significantly increased bone turnover evidenced by BTMs and the diffuse cortical uptake on ^{99m}Tc bone scintigraphy (Figure 1).

Evidence-based guidelines for long-term denosumab cessation are lacking. The 2020 European Calcified Tissue Society guidelines recommend bisphosphonates for 1-2 years after short-term denosumab (≤2.5 years).(12) This is supported by RCT evidence that a single zoledronate infusion can prevent rebound bone loss following short-term denosumab.(13, 14) For long-term use (>2.5 years), zoledronate is recommended 6 months after the final denosumab dose, with a repeat zoledronate infusion at 3-6 months if BTMs remain elevated.(12) However, a recent observational study demonstrated that among long-term denosumab users with CTx >280ng/L following denosumab cessation, two zoledronate infusions 6 months apart did not prevent BMD loss.(15)

Adding osteoanabolic agents in combination to ongoing denosumab is a potential alternative to sequential therapy.(16) Recent case series demonstrated overlapping denosumab with romosozumab or teriparatide increases lumbar spine BMD in established denosumab users.(16, 17) However, these approaches require ongoing denosumab use, and thus there remains no evidence-based approach to guide discontinuation of long-term denosumab.

Take Home Messages

- Discontinuing long-term denosumab results in a 'rebound effect' of increased bone turnover, BMD loss and increased fracture risk
- After short-term denosumab (≤2.5 years), a single zoledronate infusion can prevent rebound BMD loss
- There is limited evidence to prevent rebound BMD loss after stopping long-term denosumab (>2.5 years)
- Sequential denosumab-to-teriparatide should be avoided as this can amplify the RANKL-mediated 'rebound effect' resulting in increased bone resorption, BMD loss, and hypercalcaemia
- Initiating denosumab requires caution due to challenges in safely stopping long-term therapy

Figure 1

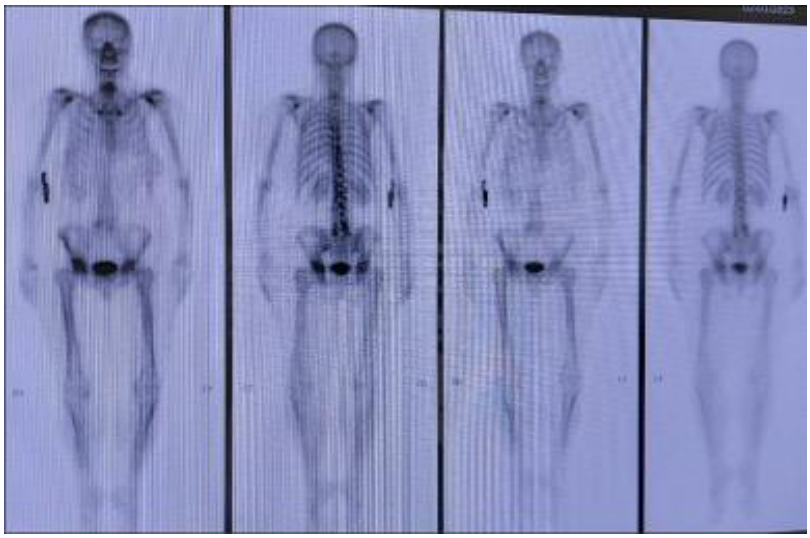
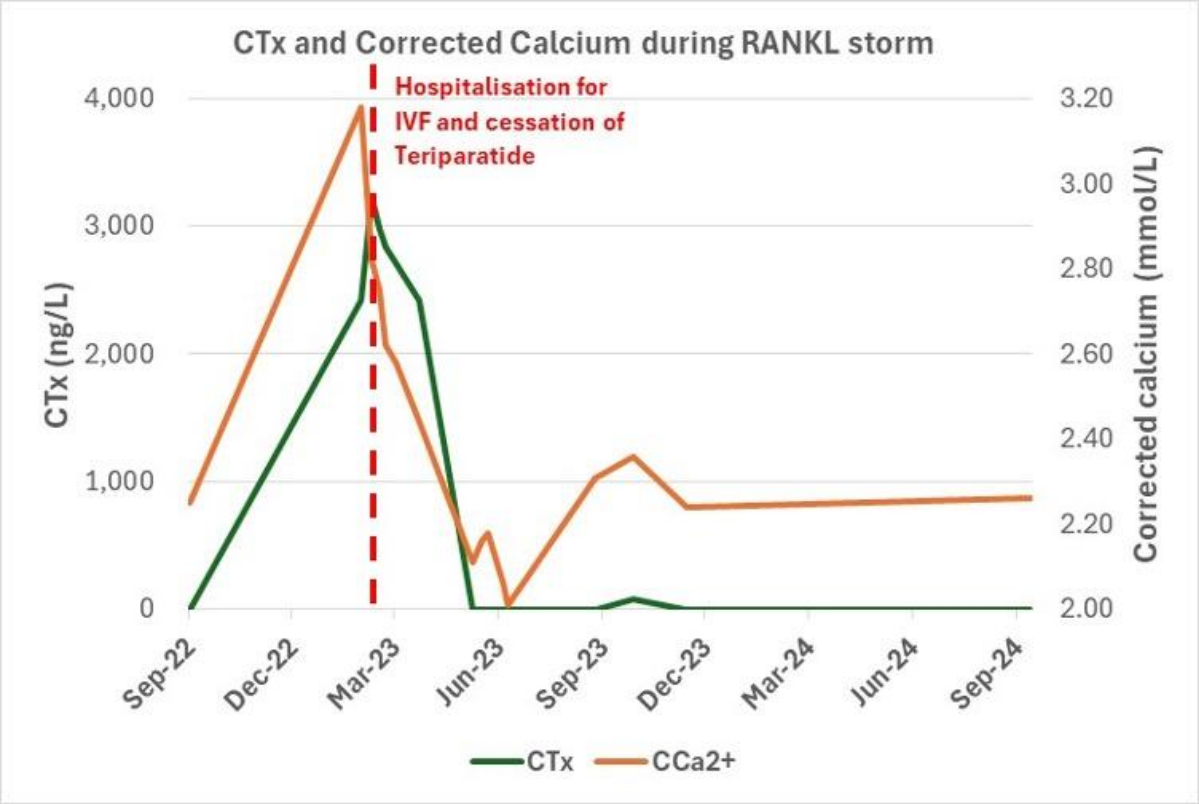


Figure 2

Figure 3



1. 1. Australian Institute of Health and Welfare. Estimating the prevalence of osteoporosis in Australia. Canberra: AIHW; 2014.
2. 2. Osteoporosis management and fracture prevention in postmenopausal women and men over 50 years of age. 3rd ed. Melbourne, Victoria: The Royal Australian College of General Practitioners; 2024.
3. 3. Naik-Panvelkar P, Norman S, Elgebaly Z, Elliott J, Pollack A, Thistlethwaite J, et al. Osteoporosis management in Australian general practice: an analysis of current osteoporosis treatment patterns and gaps in practice. BMC Fam Pract. 2020;21(1):32.
4. 4. Kim AS, Taylor VE, Castro-Martinez A, Dhakal S, Zamerli A, Mohanty S, et al. Temporal patterns of osteoclast formation and activity following withdrawal of RANKL inhibition. J Bone Miner Res. 2024;39(4):484-97.
5. 5. Bone HG, Wagman RB, Brandi ML, Brown JP, Chapurlat R, Cummings SR, et al. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. Lancet Diabetes Endocrinol. 2017;5(7):513-23.

6. 6. Ruggiero SL, Dodson TB, Aghaloo T, Carlson ER, Ward BB, Kademani D. American Association of Oral and Maxillofacial Surgeons' Position Paper on Medication-Related Osteonecrosis of the Jaws-2022 Update. J Oral Maxillofac Surg. 2022;80(5):920-43.

7. 7. Bone HG, Bolognese MA, Yuen CK, Kendler DL, Miller PD, Yang YC, et al. Effects of denosumab treatment and discontinuation on bone mineral density and bone turnover markers in postmenopausal women with low bone mass. J Clin Endocrinol Metab. 2011;96(4):972-80.

8. 8. Fassio A, Adami G, Benini C, Vantaggiato E, Saag KG, Giollo A, et al. Changes in Dkk-1, sclerostin, and RANKL serum levels following discontinuation of long-term denosumab treatment in postmenopausal women. Bone. 2019;123:191-5.

9. 9. Cummings SR, Ferrari S, Eastell R, Gilchrist N, Jensen JB, McClung M, et al. Vertebral Fractures After Discontinuation of Denosumab: A Post Hoc Analysis of the Randomized Placebo-Controlled FREEDOM Trial and Its Extension. J Bone Miner Res. 2018;33(2):190-8.

10. 10. Cranney A, Papaioannou A, Zytaruk N, Hanley D, Adachi J, Goltzman D, et al. Parathyroid hormone for the treatment of osteoporosis: a systematic review. CMAJ. 2006;175(1):52-9.

11. 11. Leder BZ, Tsai JN, Uihlein AV, Wallace PM, Lee H, Neer RM, et al. Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial. Lancet. 2015;386(9999):1147-55.

12. 12. Tsourdi E, Zillikens MC, Meier C, Body JJ, Gonzalez Rodriguez E, Anastasilakis AD, et al. Fracture risk and management of discontinuation of denosumab therapy: a systematic review and position statement by ECTS. J Clin Endocrinol Metab. 2020.

13. 13. Makras P, Papapoulos SE, Polyzos SA, Appelman-Dijkstra NM, Anastasilakis AD. The three-year effect of a single zoledronate infusion on bone mineral density and bone turnover markers following denosumab discontinuation in women with postmenopausal osteoporosis. Bone. 2020;138:115478.

14. 14. Anastasilakis AD, Makras P, Polyzos SA, Papapoulos SE. The Five-Year Effect of a Single Zoledronate Infusion on Bone Mineral Density Following Denosumab Discontinuation in Women with Postmenopausal Osteoporosis. Calcif Tissue Int. 2023;113(4):469-73.

15. 15. Grassi G, Ghielmetti A, Zampogna M, Chiodini I, Arosio M, Mantovani G, et al. Zoledronate After Denosumab Discontinuation: Is Repeated Administrations

More Effective Than Single Infusion? J Clin Endocrinol Metab. 2024;109(10):e1817-e26.

16. 16. Kumar S, Gild ML, McDonald MM, Kim AS, Clifton-Bligh RJ, Girgis CM. A novel sequential treatment approach between denosumab and romosozumab in patients with severe osteoporosis. Osteoporos Int. 2024;35(9):1669-75.

17. 17. Kumar S, Streeter C, McDonald MM, Clifton- Bligh RJ, Gild ML, Girgis CM. Combination or sequential teriparatide for osteoporosis treatment in denosumab-users: real-world bone mineral density outcomes. 2025;25:101847.

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Congenital Hypogonadotrophic Hypogonadism with FGFR1 mutation and progressive decline in bone mineral density.

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Case Summary - Congenital Hypogonadotrophic Hypogonadism with FGFR1 mutation and progressive decline in bone mineral density.

A 28-year-old woman was referred by her fertility specialist in 2015 for assessment of low bone mineral density (BMD) in the context of primary amenorrhoea, with no prior formal endocrinology review. Her menstrual history was notable for complete absence of menarche which had been attributed to hypogonadotrophic hypogonadism, and she had previously been treated with low-dose oestrogen for pubertal induction. At age 21, she was started on the combined oral contraceptive pill (COCP), which was ceased after 2 years due to irregular bleeding. She then recommenced Microgynon 30 until review.

Her medical history included craniosynostosis which was corrected surgically in infancy. Her sister had coeliac disease and there was no family history of osteoporosis. She had no history of smoking, alcohol, glucocorticoid use or gastrointestinal malabsorption. She reported minimal dairy intake and no regular exercise. Her only previous fracture was a right ankle avulsion fracture at age 23.

On examination, her BMI was 26.2kg/m^2. She had underdeveloped breasts of Tanner stage III–IV. There were no signs of hyperandrogenism or cushing's syndrome. Her visual fields were intact and she was normosmic.

Initial investigations confirmed hypogonadotropic hypogonadism: she had undetectable serum oestradiol (<70pmol/L) with inappropriately normal gonadotropins (FSH 6.1IU/L, LH 4.5IU/L), low AMH (2.9pmol/L), and a 46,XX karyotype. MRI of the brain showed a normal pituitary gland and normal olfactory bulbs. Pelvic ultrasound revealed a normal-sized uterus and small ovaries. Baseline BMD in December 2015 showed a

lumbar spine Z-score of –2.7 SD (0.896g/cm^2) and left hip Z-score of –3.0 SD (0.678g/cm^2). Her 24-hour urinary calcium was low (1.6mmol/24h), but serum calcium, phosphate, PTH, and vitamin D (76nmol/L) were within reference range. Her bone turnover markers were normal (P1NP51 µg/L and CTX 467ng/L). Coeliac serology was initially negative.

Given her plans for pregnancy, bisphosphonate therapy was avoided. She was commenced on oral calcium and advised to optimise dairy intake. The COCP was ceased at the time.

In 2016, she began IVF, achieving a successful pregnancy on the second cycle. She delivered a small-for-gestational-age male infant by caesarean in 2017. Postpartum, she remained amenorrhoeic and had no plans for further pregnancy. She was then recommenced on Microgynon 30.

Between 2015 and 2018, the patient's BMD progressively declined, particularly at the lumbar spine (0.832g/cm^2, Z score -2.9) and remained stable at the left total femur (0.670g/cm^2, Z score -2.7). She was commenced on vitamin D replacement in 2017 due to a slight reduction in her levels (64nmol/L). Due to side effects from the COCP (breakthrough bleeding and bloating), she transitioned to transdermal HRT (Estalis Sequi 50/250) in 2018. There was notable improvement in lumbar spine BMD by 2019 of roughly 7.9% (0.898g/cm^2, Z score -2.6) and ongoing stability at the left total femur (0.671g/cm^2, Z score -2.7).

In 2019, genetic testing confirmed a heterozygous pathogenic variant in the FGFR1 gene, consistent with Congenital Hypogonadotrophic Hypogonadism. FGFR1 mutations, which impair GnRH neuron development and migration are autosomal dominant with variable penetrance. In this case, the phenotype was normosmic CHH with craniosynostosis, a recognised associated feature.

In 2022, she ceased Estalis due to a skin rash as well as the calcium and vitamin d. Investigations revealed rising bone turnover markers (P1NP 86 µg/L, CTX 670ng/L) and declining BMD with reduction in lumbar spine of 6.1% (0.849g/cm^2, Z score -2.9) and a reduction of 6.3% in the L total femur (0.629g/cm^2, Z score -3.2). Coeliac serology was slightly positive (tTG-IgA 20U/mL), and HLA-DQ2.5 antigen was detected, though she denied any symptoms of coeliac disease. She was transitioned to transdermal Estrogel 1.5 mg daily and Prometrium 200 mg for 12 days/month, with gradual titration of Estrogel to 3 mg daily. Small bowel biopsy (2022) showed no evidence of coeliac disease. She then remained on a gluten-free diet.

Over 2023–2024, she reported stable weight and regular withdrawal bleeds. Her BMD was stable during this time with lumbar spine BMD 0.845g/cm^2 (Z-score –3.0) and total left femur BMD 0.656g/cm^2 (Z-score –3.0). However, by March 2025, her bone turnover markers rose (P1NP 97 µg/L, CTX 770 ng/L) and BMD again deteriorated with lumbar

spine BMD 0.813g/cm^2 (Z-score –3.4) and total left femur BMD 0.634g/cm^2 (Z-score –3.2).

She remained on adequate HRT with no plans for pregnancy. Antiresorptive therapy is being considered due to ongoing bone loss despite current treatment.

Literature Outline

Congenital hypogonadotrophic hypogonadism (CHH) is a rare disorder resulting from insufficient GnRH secretion or action. FGFR1 mutations account for 10–16% of CHH cases and exhibit variable expressivity and incomplete penetrance.[1] Female presentations are less common, with an estimated prevalence of 1 in 10,000 to 50,000.[2]

In women with CHH, untreated oestrogen deficiency impairs peak bone mass acquisition and increases long-term risk of osteoporosis. Even with HRT, full recovery of BMD may not be achieved, particularly if diagnosis is delayed. Studies show that delayed oestrogen replacement leads to a progressive decline in BMD.[3,4]

The literature supports physiological transdermal oestrogen replacement over COCPs for bone health in women with HH.[5] COCPs contain supraphysiological synthetic forms of oestrogen (ethinylestradiol) and have been shown to be inferior in improving BMD compared to transdermal or oral oestradiol.[6]

In cases of persistent low BMD despite optimal HRT and lifestyle modification, antiresorptive agents such as bisphosphonates or denosumab may be considered in women no longer planning pregnancy. However, the long skeletal retention and potential foetal toxicity must be discussed, and therapy individualised.[1]

Take-Home Messages

- FGFR1 mutations are an autosomal dominant genetic cause of CHH, with variable expression ranging from isolated amenorrhoea to craniofacial abnormalities such as cranial stenosis.
- Delayed diagnosis and treatment of CHH can significantly compromise peak bone mass, leading to an increased lifetime risk of osteoporosis and fracture.
- Physiological transdermal oestrogen replacement is superior to synthetic formulations (COCP), offering better outcomes for bone health and more closely mimicking natural puberty.
- In cases of declining bone mineral density despite optimal HRT and lifestyle interventions, antiresorptive therapy may be considered in women who have completed childbearing, with careful risk-benefit assessment.

1. 1. Jacques Young, Cheng Xu, Georgios E Papadakis, James S Acierno, Luigi Maione, Johanna Hietamäki, Taneli Raivio, Nelly Pitteloud, Clinical Management of Congenital Hypogonadotropic Hypogonadism, Endocrine Reviews, Volume 40, Issue 2, April 2019, Pages 669–710.

2. 2. Dzemaili S, Tiemensma J, Quinton R, et al. Beyond Hormone replacement: quality of life in women with congenital hypogonadotrophic hypogonadism. Endocrine Connections. 2017 Aug;6(6):404-412.

3. 3. Thierry Chevalley, Jean-Philippe Bonjour, Serge Ferrari, Rene Rizzoli, Influence of Age at Menarche on Forearm Bone Microstructure in Healthy Young Women, The Journal of Clinical Endocrinology & Metabolism, Volume 93, Issue 7, 1 July 2008, Pages 2594–2601.

4. 4. Mehmet Nuri Özbek, Hüseyin Demirbilek, Rıza Taner Baran, Ahmet Baran. Bone Mineral Density in Adolescent Girls with Hypogonadotropic and Hypergonadotropic Hypogonadism. J Clin Res Pediatr Endocrinol 2016;8(2):163-169.

5. 5. Dural, Ozlem et al. Effects of Hormone Replacement Therapy on Low Bone Mineral Density in Adolescents and Young Women with Hypogonadism: Comparison of Oral and Transdermal 17 Beta-Estradiol Administration. Journal of Pediatric and Adolescent Gynecology, Volume 35, Issue 6, 634 - 637.

6. 6. Beth Cartwright, Jillian Robinson, Paul T. Seed, Ignac Fogelman, Janice Rymer, Hormone Replacement Therapy Versus the Combined Oral Contraceptive Pill in Premature Ovarian Failure: A Randomized Controlled Trial of the Effects on Bone Mineral Density, The Journal of Clinical Endocrinology & Metabolism, Volume 101, Issue 9, 1 September 2016, Pages 3497–3505.

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Biannual Bone Bolstering Business - Insights from Following Up Continuation of Denosumab as Management of Clinical Osteoporosis at a Major Trauma Centre

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Background

Over the past fifteen years, the emergence of denosumab, a potent antiresorptive and RANKL inhibitor, has bridged an ongoing treatment gap in osteoporosis, especially clinical osteoporosis secondary to minimal trauma fractures (MTF). Its mechanism stipulates that denosumab must be administered every six months, and any delays in, or unplanned cessation to, treatment is dangerous, as it subjects recipients to rapid bone turnover and confers a higher risk of subsequent rebound vertebral fractures. To reinforce this practice, the MTF management guideline at a major trauma centre recommends that its use must be followed by clear instructions for continuation of therapy in each discharge summary. However, it remains unclear how well this has been implemented.

Aims

To determine:

1. proportion of individuals who received denosumab as antiresorptive therapy for minimal trauma fracture

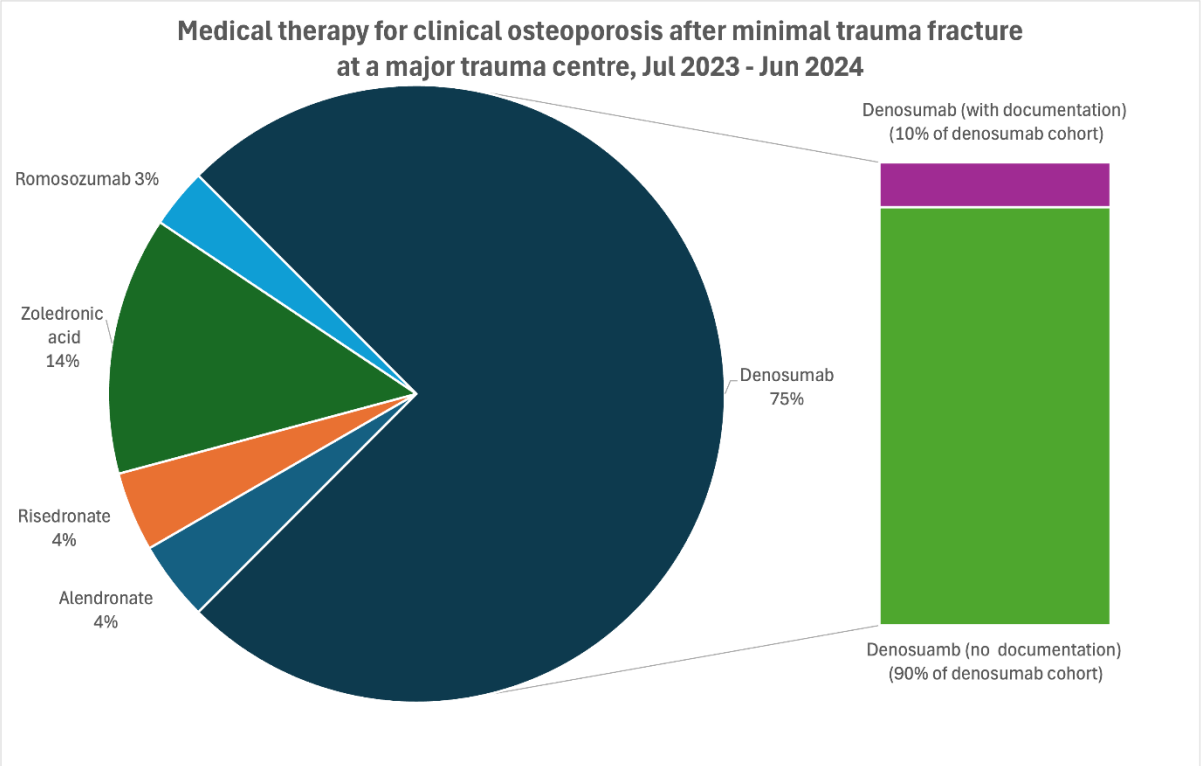
2. proportion of denosumab recipients who had appropriate instructions in discharge documentation

3. denosumab treatment continuation rates of eligible patients in the community after discharge.

Methods/Results

Initial screening was carried out with criteria as follows: age >50, inpatient admission >48 hours, and a primary diagnosis of minimal trauma fracture between a 12-month period between 1 July 2023 and 30 June 2024. An eligible cohort of 278 admissions was identified, of which 96 received antiresorptive therapy. Additionally, a targeted

questionnaire will be prospectively administered to the denosumab cohort, to determine treatment continuation rates.



Of 96 admissions receiving antiresorptive therapy, denosumab was the most frequently prescribed (n=72/75%). However, only 10% (n=7) had discharge summaries documenting importance of treatment continuation. Treatment continuation rates will be available upon completion of questionnaires by cohort.

Conclusion

Whilst denosumab is an efficacious drug for osteoporosis and constituted the majority of antiresorptive treatment prescribed in the cohort assessed, inadequate discharge documentation was found which raises concern that therapy may not have be continued as planned.

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Healthy Ageing Without Major Osteoporotic Fracture or Joint Replacement Surgery: A Time-Dependent Competing Risks Analysis Using Inverse Probability Weighting

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Background: Major osteoporotic fractures (MOFs) and joint replacement surgeries (JRS) are significant events in ageing populations. Identifying their determinants can improve prevention strategies. This study aimed to identify determinants of healthy ageing without MOFs and JRS.

Methods: Serial data from 1,443 women and 1,425 men (20–96y) participating in the Geelong Osteoporosis Study (GOS) were analysed. Anthropometry and clinical measures, including DXA (Lunar) were performed. Lifestyles, comorbidities and medications were self-reported and blood samples were collected. MOFs (hip, clinical spine, distal forearm, proximal humerus fracture, pelvic) were identified from radiological reports and JRS (hip, knee) were identified through self-report and data linkage with medical records and the Barwon Centre of Orthopaedic Research and Education (BCORE) Joint Registry (BJR). Time-dependent Cox proportional hazards models with age as the primary time scale were used to identify the determinants of MOF and JRS, accounting for death as a competing risk. Participants were followed from baseline until first MOF, JRS, death, migration or study end (31/05/2023). Inverse probability weighting adjusted for potential confounding and selection bias. Robust variance estimates accounted for clustering by individual. The model was adjusted for sex.

Results: Over a median 16.7y (IQR 9.7–23.2), 527(18.4%) MOFs, 221(7.7%) JRS and 1145(39.9%) deaths were identified. Protective factors for MOF and JRS were being a non-smoker (HR 0.88, 95%CI 0.78-0.99), lower serum high-density lipoprotein (HDL)

(0.84, 0.72-0.98), lower high-sensitivity C-reactive protein (hsCRP) (0.99, 0.98-1.00) and lower plasma glucose (0.75, 0.61-0,91). Additionally, those free of cancer (0.90, 0.79-1.02) and emphysema (0.78, 0.59-1.04) were also protected against MOFs and JRS.

Conclusions: Avoiding smoking, managing diseases such as emphysema and cancer are important for maintaining bone and joint health. Moreover, interventions targeting inflammatory, metabolic and endocrine factors such as hsCRP, HDL and plasma glucose may offer cross-cutting benefits for reducing the risk of MOFs or JRS during ageing.

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Trabecular bone score in lung transplant recipients

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Background
Lung transplant recipients are at an increased risk of osteoporosis due to prolonged steroid regimens, and risk factors including smoking, sarcopenia, and chronic inflammation. The poor correlation between fracture risk and bone mineral density (BMD) is particularly evident in steroid associated osteoporosis. Trabecular bone score (TBS) is a validated measure of bone microarchitecture that enhances fracture risk prediction when combined with BMD. TBS was introduced in June 2021 to Alfred Health, the state-wide lung transplant service in Victoria.

Aims
To evaluate the utility of TBS in lung transplant recipients by examining its correlation with BMD, its association with post-transplant fracture incidence, and its impact on fracture risk prediction through TBS-adjusted Fracture Risk Assessment (FRAX).

Methods
This was a retrospective study of patients aged >50 years who underwent lung transplantation from June 2021 to June 2024 at Alfred Health. Data collected from medical records included BMD, TBS, cumulative steroid use, lung function, and osteoporotic fractures.

Results
In our pilot study (n = 54), spine BMD and corresponding T-score improved following transplantation, with the T-score increasing from –1.2 ± 1.7 to –0.95 ± 1.5—shifting from

the osteopaenic to the normal bone density range. However, the TBS was unchanged post-transplant, varying only slightly from 1.27 ± 0.1 to 1.24 ± 0.1, remaining within the partially degraded bone category (TBS 1.2–1.35). We aim to further investigate this observed divergence between BMD and TBS in our ongoing expanded study of 104 participants (64 ± 6 years,
67% male). We will present these findings including correlation of baseline TBS and post lung transplant fractures, and correlation between FRAX, TBS-adjusted FRAX and post lung transplant fractures.

Conclusion
This study will provide insights into the utility of TBS and its clinical implications for managing osteoporosis in the lung transplant population

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Release of endogenous glutathione modulates CaSR sensitivity to extracellular Ca^{2+} and L-amino acids

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The calcium-sensing receptor (CaSR) plays important roles in (i) mineral metabolism by mediating Ca^{2+}-dependent feedback control of calcium homeostasis, and (ii) macronutrient metabolism by mediating L-amino acid (L-AA)-induced release of gastro-intestinal hormones including gastrin, CCK, and GLP-1.

Although Ca^{2+}_o reliably stimulates CaSR-mediated signaling via all known pathways in a widely-used model system, CaSR-expressing HEK-293 cells, AA effects are observed less reliably. Thus, AAs markedly stimulate CaSR-mediated Ca^{2+}_i mobilization in perifused HEK-293 cells but have more limited effects on inositol phosphate turnover or ERK phosphorylation (pERK) in static multi-well plate cultures. These observations led us to hypothesise that AA-activation of the CaSR is impaired by the local release of endogenous ligands of the CaSR's VFT binding site for AAs i.e., there is competition for AA-dependent activation of the receptor.

To investigate the hypothesis, we adapted assays for IP-1 accumulation and pERK to adherent HEK-CaSR cells, enabling us to more readily remove and replace the extracellular fluid than in suspension cultures. We found that washing cells was a necessary pre-condition for L-Phe stimulated Ca^{2+}_o-induced responses ($p < 0.05$) and that AA sensitivity was lost in the absence of washing. Furthermore, Ca^{2+}_o-stimulated pERK was enhanced when the interval between washing and activation was increased, suggesting the accumulation of an endogenous modulator in the extracellular milieu. Mass spectrometry analysis of samples of medium led us to identify reduced glutathione (GSH) as a candidate modulator. GSH accumulated to levels ≥ 1 μM in extracellular samples over 30-60 min. Furthermore, cells pre-treated with an inhibitor of GSH synthesis, buthionine sulfoximine (100 μM) maintained AA sensitivity while markedly suppressing the Ca^{2+}_o response.

Our findings indicate that in the medium of cell-types that release it, reduced glutathione competes with AAs for the CaSR's VFT domain canonical binding site, thereby reducing AA sensitivity and promoting Ca^{2+}_o sensitivity.

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A Case of Bilateral External Auditory Canal Osteonecrosis and Novel Treatment with Teriparatide

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Background

Medication-related osteonecrosis of the external auditory canal (MROEAC) is a rare but increasingly recognised complication of antiresorptive therapy.[1, 2] While fewer than 30 cases have been reported, none to date describe treatment with teriparatide, an anabolic agent shown to promote healing in medication-related osteonecrosis of the jaw (MRONJ).

We describe a case of bilateral MROEAC in an 81-year-old woman with long-standing osteoporosis treated with denosumab, complicated by previous systemic glucocorticoid therapy and active smoking. Management was with cessation of denosumab managed and initiation of teriparatide leading to clinical and biochemical improvement.

Case presentation

An 81-year-old woman with osteoporosis was hospitalized under Ear Nose and Throat (ENT) specialists with an initial diagnosis of bilateral otitis externa. She had received denosumab for ten years for the treatment of osteoporosis, had no previous fracture, and latest BMD showed T scores of -0.7, -2.5 and -2.5 at the lumbar spine, femoral neck

and total hip respectively. She was an active smoker, had past Giant Cell Arteritis treated with high dose prednisolone and previous hysterectomy.

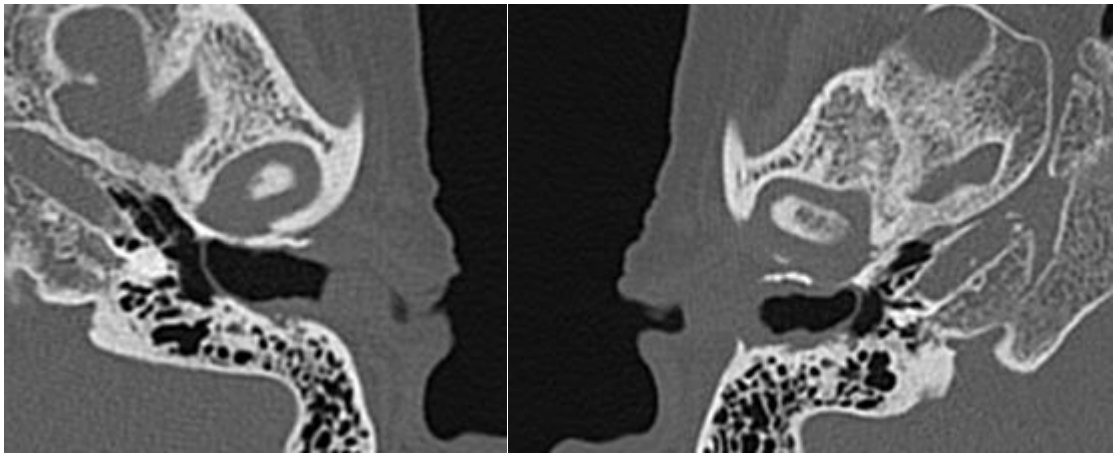
Symptoms began with a three-year history of pruritus on the right ear. Investigations 14 months earlier included bone gallium scan suggesting malignant otitis externa with early osteomyelitis (OM), and cultures growing abundant staphylococcus aureus and mixed bacteria. However CRP was 1-6 mg/L and ESR 1-2 mm/h throughout her treatment course. She completed twelve weeks empirical broad spectrum antibiotics for suspected OM of the right ear canal but symptoms progressed bilaterally, suggesting infection was not the main cause.

ENT revised the diagnosis to MROEAC following otoscopic findings of erosions in the right EAC with bone on view. MRI confirmed this diagnosis following a radiology MDT meetings discussion. C telopeptide (CTX) was low (73 ng/L) in keeping with suppressed bone turnover from longstanding denosumab treatment. Contributing factors included chronic otitis externa, previous high-dose glucocorticoids and smoking. Chronic suppurative otitis media, cholesteatoma, and neoplasia were excluded based on clinical findings, microbiology, and imaging.

Imaging

MRI features suggest bilateral medication related EAC osteonecrosis, more severe on the right, with probable superimposed bilateral mild otitis externa.

CT scan (baseline) shows:



Irregular bilateral osseous EAC irregular erosions with irregular soft tissue thickening, given clinical context – likely Denosumab related osteonecrosis with mild superimposed otitis externa

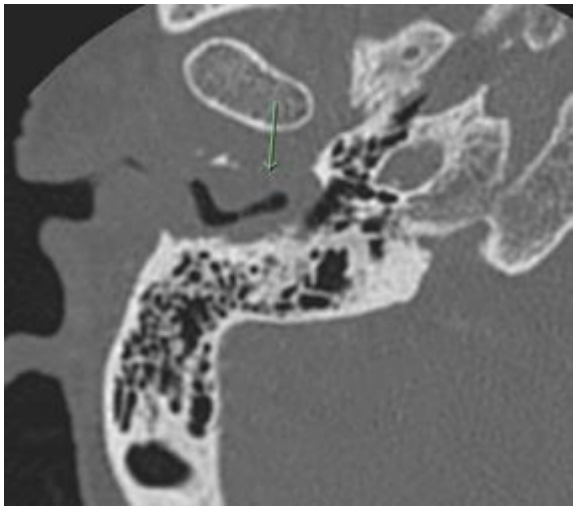
Treatment

A multidisciplinary team (Geriatric Medicine, ENT, Endocrinology and Radiology) managed the patient. Smoking cessation was advised but unsuccessful. Denosumab was discontinued (last dose 6th January 2025) and 20micrograms daily subcutaneous teriparatide commenced (on 18th July 2025, finish 11th September 2025), planning for an 8-week course on based on evidence in MRONJ studies.[3]

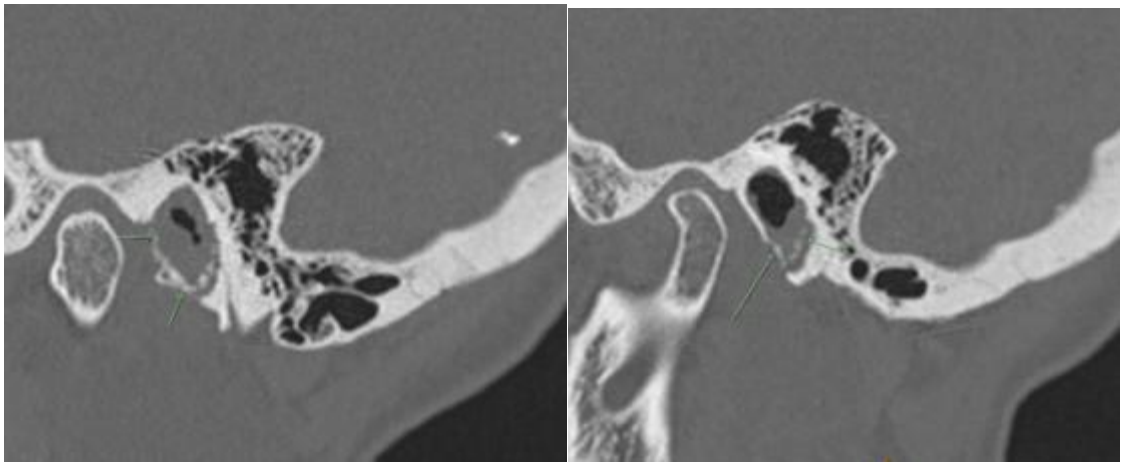
Right ear swab MC+S Grew Abundant non-albicans yeast, candida albicans and streptococcus anginosus. Initial treatment included aural toilet and topical therapies. She completed multiple courses of antibiotics including ciprofloxacin 500mg BD, and amoxicillin 500mg TDS for 21 days. Bilateral otitis externa improved. Inflamed polypoidal tissue and otitis externa bilateral ear canals was observed on otoscopy. Left otitis externa first reported to be improving on 3rd October 2025, 20 days after finishing her course of teriparatide. Right sided ear canal failing to improve, suspected synovial joint leaking into R EAC -> to be discussed at radiology MDT for blind sac closure surgery.

Interval CT scan 22/9/2025 showed

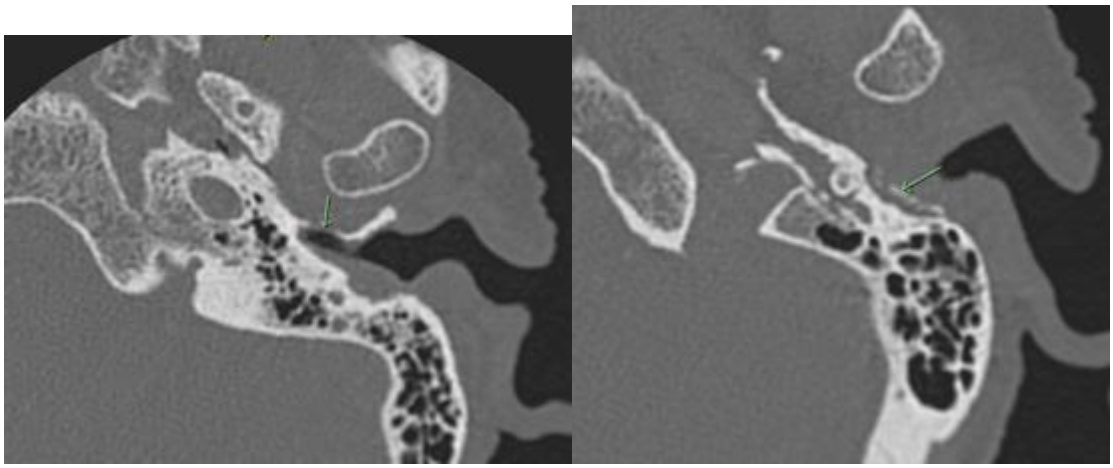
Extensive osseous scalloped erosions and bony sequestra in both external auditory canals, more extensive on the right, where there is wide deficiency of the anterior canal wall. In keeping with bilateral osteonecrosis of the EAC



R ear (thin)



MPR Auxillary



Left ear (CT thins)

The teriparatide treatment course was completed. There was symptomatic improvement of ear symptoms with less fluid and improvement of polypoidal inflammation. Post treatment CT scan showed:

Interval stability of the bilateral osseous EAC irregular erosion with irregular soft tissue thickening, given the clinical context, this may be a manifestation of Denosumab related osteonecrosis, likely with mild superimposed otitis externa.

MRI showed:

Bilateral medication related EAC osteonecrosis, more severe on the right, with probable superimposed bilateral mild otitis externa. No convincing features of malignant otitis externa. No skull base osteomyelitis identified.

Results

Monitoring of bone turnover markers and relevant biochemistry was performed to assess treatment response (Table 1). Before treatment, bone turnover was profoundly suppressed, with CTX 73 ng/L, remaining low at one and three months (CTX 61 and 112

ng/L, respectively). A marked rise to CTX 366 ng/L was observed at four months, indicating delayed recovery of bone resorption. Notably, CTX remained suppressed for nine months after denosumab cessation, considerably longer than typically reported (usually 3–6 months.[4] This suggests a more pronounced and sustained antiresorptive effect in this patient.

Serum calcium, phosphate, and vitamin D levels remained within reference ranges, and renal function was stable throughout. ALP values were modestly elevated but paralleled rises in GGT, consistent with hepatic rather than osseous origin.

P1NP, a marker of bone formation, was unavailable at baseline but rose to 63 µg/L during teriparatide therapy, subsequently declining to 27 µg/L one month post-cessation. This pattern supports a transient anabolic response followed by return to the patient's low baseline bone formation rate.

Table 1. Bone Turnover Markers and Biochemistry

	04/06/2025	08/08/2025	05/09/2025	08/10/2025
C Telopeptide of Collagen (ng/L) [50-800]				
Procollagen Type 1 N-Propeptide (U/L) [15-115]			63	27
Calcium (Ionised and measured) (mmol/L) [1.12-1.32]	1.12	1.25	1.29	1.19
Calcium (ionised and pH adjusted) (mmol/L) [1.12-1.32]	1.23	1.23	1.23	1.25
Phosphate (mmol/L) [0.75-1.50]	1.28	1.27	1.45	1.33
Creatinine (µmol/L) [45-90]	81	60	60	69
Parathyroid Hormone (pmol/L) [1.6-9.0]	7.1	3.2	3.5	4.1
Vitamin D (nmol/L) [>50]	170	130	130	140
Calcium creatinine ratio (mmol/mmol) [0.10-0.58]	0.25	0.59	0.36	0.23

Calcium excretion (µmol/L) [14-56]	20	36	21	16
TmP/GFR (mmol/L) [0.75-1.35]	1.22	1.22	1.44	1.36
ALP (U/L) [30-110]	149	133	145	117
GGT (U/L) [<40]	112	83	84	67

Overall, these results indicate markedly suppressed bone turnover in the context of denosumab exposure, partial biochemical recovery following teriparatide, and persistent low baseline activity consistent with prolonged skeletal suppression. Management is ongoing, with follow-up radiologic review pending at the multidisciplinary meeting.

Discussion

To our knowledge, this is the first case of MROEAC treated with teriparatide. Drawing on the existing literature supporting teriparatide for MRONJ, this case highlights the potential role of parathyroid-analogue therapy in managing extra-oral forms of antiresorptive-associated osteonecrosis.[3]

Current literature on MROEAC describe treatments by withdrawal of the offending medication, and trialling conservative management such as topical antibiotics and corticosteroids with or without systemic antibiotics[2,5]. Surgical options include debridement and removal of bony sequestrum, progressing to advanced resection and reconstruction in severe cases. However, prolonged withdrawal of denosumab carries the risk of rebound bone loss and a subsequent increased risk for osteoporotic vertebral fractures.[4,6]

Teriparatide has shown promise in the management of other complications of antiresorptive therapy such as MRONJ and surgically managed atypical femoral fractures.[7] Drawing on this literature, we felt it reasonable to trial teriparatide due to the likely similar underlying pathophysiology of over suppressed bone turnover with the aim of decreasing time to recovery. To minimize future risk of fractures, systemic topical oestrogen was our antiresorptive of choice following completion of teriparatide. Selective oestrogen receptor modulators were avoided in this case due to risk of DVT in the context of active smoking.[8]

Our patient had clinical improvement in her left ear following combined medical and ENT treatment.

The right ear is clinically taking longer to heal and has more bony destruction on CT, this may be related to her history of malignant otitis externa and possible osteomyelitis. The patient's CTX remained suppressed for nine months—longer than typical after

denosumab cessation—indicating profoundly reduced bone turnover. We propose that this excessive suppression predisposed her to EAC osteonecrosis and continues to impede recovery despite teriparatide therapy.

Whilst we did see an improvement of bone turnover throughout the clinical course of the case, it is difficult to tell how much this has improved her clinical recovery or what degree of improvement is due to the teriparatide.

Other factors which are associated with development of osteonecrosis include current smoker, previous high-dose steroids for treatment of GCA, and history of malignant otitis externa and osteomyelitis of the right ear.

Conclusion

Osteonecrosis of the external auditory canal, though rare, is a significant condition that requires awareness for timely diagnosis and management. Clinicians should consider this diagnosis in patients presenting with persistent otologic symptoms, especially those with a history of prolonged antiresorptive therapy. Early recognition and appropriate intervention can mitigate complications and improve patient outcomes. While teriparatide has shown promise in our case with clinical and biochemical improvement, further research is necessary to evaluate its safety and effectiveness for this rare condition. Lastly, strategies for reducing bone loss following denosumab discontinuation remains a challenging clinical scenario in those who develop complications related to long-term anti-resorptive therapy.

Learning points

Consider MROEAC in patients on antiresorptive therapy who present with chronic otologic symptoms.

Multidisciplinary assessment is critical to exclude infection or malignancy and guide management while ensuring underlying osteoporosis is appropriately managed.

Teriparatide was well tolerated and associated with clinical and biochemical improvement in this case. Further studies are needed to assess its efficacy and safety in management of EAC osteonecrosis

1. 1. Thorsteinsson AL, Lomholt AF, Eiken P. Bisphosphonate-induced osteonecrosis of the external auditory canal: a case report. J Clin Med Case Rep. 2015;2(1):3.
2. 2. Kumar V, Diamond T, Walton SF. Two cases of external auditory canal osteonecrosis in patients on antiresorptive therapy for osteoporosis. J Clin Endocrinol Metab Case Rep. 2023;1(2):luad021.

3. 3. Sim IW, Borromeo GL, Tsao CE, Hardiman R, Hofman MS, Ebeling PR. Teriparatide promotes bone healing in medication-related osteonecrosis of the jaw: a placebo-controlled, randomized trial. J Clin Oncol. 2020;38(26):2971–80.

4. 4. Bone HG, Bolognese MA, Yuen CK, et al. Effects of denosumab treatment and discontinuation on bone mineral density and bone turnover markers in postmenopausal women with low bone mass. J Clin Endocrinol Metab. 2011;96(4):972–80.

5. 5. Yamaguchi Y, Ueno T, Takahashi Y, et al. Bilateral osteonecrosis of the external auditory canal caused by bone-modifying agents for cancer. Jpn J Clin Oncol. 2025;55(2):77–81. doi:10.1007/s13691-025-00772-z

6. 6. Cosman F, Huang S, McDermott M, Cummings SR. Multiple Vertebral Fractures After Denosumab Discontinuation: FREEDOM and FREEDOM Extension Trials Additional Post Hoc Analyses. J Bone Miner Res. 2022 Nov;37(11):2112-2120. doi: 10.1002/jbmr.4705. Epub 2022 Oct 12. PMID: 36088628; PMCID: PMC10092421.

7. 7. van de Laarschot DM, McKenna MJ, Abrahamsen B, Langdahl B, Cohen-Solal M, Guañabens N, Eastell R, Ralston SH, Zillikens MC. Medical Management of Patients After Atypical Femur Fractures: a Systematic Review and Recommendations From the European Calcified Tissue Society. J Clin Endocrinol Metab. 2020 May 1;105(5):1682–99. doi: 10.1210/clinem/dgz295. PMID: 31867670; PMCID: PMC7121199.

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Radiofrequency Echographic Multi-Spectrometry (REMS) Diagnostic and Numerical T-score Concordance Rates in Over 1,000 Australian Patients

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Diagnostic concordance between skeletal sites is essential for accurate osteoporosis diagnosis and treatment decisions. The International Society for Clinical Densitometry (ISCD) defines **diagnostic discordance** as a discrepancy in osteoporosis diagnosis between anatomical sites. This can be classified as *minor* (e.g., normal / osteopenia, or osteopenia / osteoporosis) or *major* (e.g., normal / osteoporosis). **Numerical discordance** is defined as a T-score difference ≥1.0 between sites, suggesting further clinical evaluation is needed. Published rates of diagnostic discordance for dual-energy X-ray Absorptiometry (DXA) are from 30 to 67% for minor discordances, and from 2 to 17% for major discordances.

Radiofrequency Echographic Multi-Spectrometry (REMS) is a non-ionising imaging technology that measures BMD (g/cm^2), T-score, Z-score and a diagnostic category (WHO 1994) without radiation exposure. REMS was approved by the Therapeutic Goods Administration (TGA) in October 2021 and has been adopted at select Australian centres since mid-2023. Up to May 2025, more than 1,100 patients have undergone REMS scanning (88.3% female).

REMS-derived **Diagnostic** discordance:

Discordance	**Frequency (n=)**	**Percent**	**Cumulative Frequency**	**Cumulative (Percent)**
Major Discordance	3	0.27%	3	0.27%
Minor Discordance	314	27.84%	317	28.10%
No Discordance	811	71.90%	1128	100.00%

REMS derived **Numerical discordance** between femoral neck and lumbar spine T-scores was observed in 4.6% of left femoral neck scans (n=1087) and 4.7% of right femoral neck scans (n=1062). No numerical discordance between left and right femoral neck measurements

These findings demonstrate that REMS produces minor diagnostic concordance rates comparable to DXA (27.84% vs 30-67%), with notably lower major discordance rates (0.27% vs 2-17%). The low numerical discordance rate (<5%) indicates consistent T-score measurements between anatomical sites. REMS evaluations meet ISCD expectations and provide confidence in its clinical utility for reliable osteoporosis diagnosis across multiple skeletal sites, supporting its role as a radiation-free alternative to DXA

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A novel role of CXXC Finger Protein1 in calvarias development and osteoblast differentiation

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CXXC Finger Protein 1 (CFP1), an epigenetic regulator, is critical for skeletal stem/progenitor cell (SPC) function during development. Mice lacking CFP1 in Prx1+ cells (cKO^{Prx1}) fail to form forelimbs, have severely abnormal hindlimbs, and display defects in calvarial bone formation. To gain insight into CFP1 regulation of calvarial bone formation we examined the effect of CFP1 loss on both calvarial stem cells (CSCs) and pre-osteoblasts (Obs) obtained from calvarial digestion fractions. Interestingly, while isolated control CSCs (CD200^{+}CD105^{-}) grew in culture, mutant cells failed to survive, suggesting a role for CFP1 in stem cell maintenance. In contrast, Obs from cKO^{Prx1} mice grew normally in culture but failed to properly differentiate, compared to controls, as assessed by qRT-PCR analysis of osteogenic marker expression (*Runx2, Osx, Col1a1, Ocn*) and Alizarin red staining. Additionally, using mouse primary calvarial pre-osteoblasts with CFP1 Lox-P sites, we observed that in vitro transfection with an adenovirus expressing Cre recombinase (Ad-Cre) significantly reduces osteoblast differentiation capacity, as assessed by qRT-PCR. Consistent with this observation in primary cells, deletion of CFP1 in the calvarial-derived pre-osteoblastic murine cell line, MC3T3-E1, using CRISPR/Cas9, also resulted in a defect in osteoblast differentiation.

Mechanistically, CFP1 regulates osteoblast differentiation through the BMP/TGF-β signaling axis. Our findings indicate that the absence of CFP1 disrupts BMP signaling, and osteoblast differentiation can be restored with the addition of exogenous BMP, with or without TGF-β inhibition. Additionally, CFP1 plays an inhibitory role in the ERK MAPK pathway, as ERK inhibition restores pSmad 1/5/8 levels. In conclusion, CFP1 is essential during the early stages of calvarias skeletal cell differentiation and is required for proper BMP and TGF-β signaling. Future studies on CFP1 will provide valuable insights into the epigenetic regulation of the skeletal system.