Purpose: The aim of the present work is to assess the fracture risk associated with several GC requiring diseases.

Methods: We conducted a retrospective analysis of a nation-wide cohort. Many comorbidities were included (rheumatoid arthritis, psoriatic arthritis, UCTD, SLE, systemic sclerosis, COPD, multiple sclerosis, IBD, severe physical handicap, diabetes, Parkinson's and HIV). We generate groups of patients age and T-score matched via propensity score matching.

Results: 59950 women were included in the analysis. Among 13,546 women with comorbidity 3114 (23.0%) had diabetes; 3008 (22.2%) rheumatoid arthritis; 1910 (14.1%) UCTD; 1614 (11,9%) COPD; 942 (7,0%) IBD and 900 (6.8%) neurological diseases. Glucocorticoid intake ≥5 mg/day for ≥3 months (after 1:1 matching by age and T-scores) was significantly associated with vertebral fractures (aOR 1.5 95% CI 1.3-1.7) but not with non-femoral non-vertebral fractures (aOR 1.0 95% CI 0.9-1.2).

Figure 1 and **Figure 2** show the ORs for vertebral or hip fractures and non-vertebral or non-hip fractures. Diseases with increased risk of fracture, independently from glucocorticoid intake, were rheumatoid arthritis, COPD and neurological diseases for non-vertebral and non-hip fractures and COPD and neurological diseases for vertebral or hip fractures.

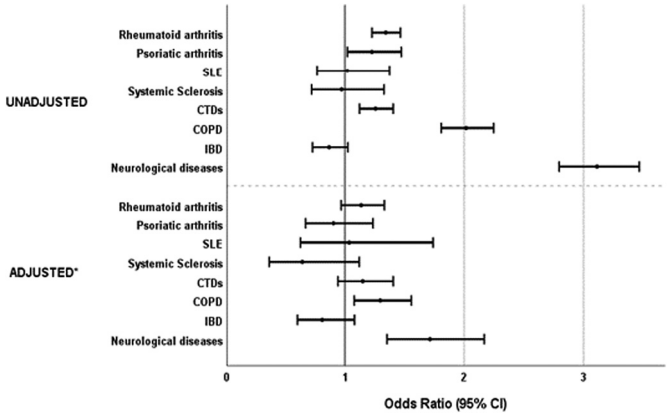

Figure 1. Forest plot showing the risk of vertebral or hip fractures in different diseases (adjusted for *age, bone mineral density, menopausal status, glucocorticoid intake and familiar history of fragility fractures)*

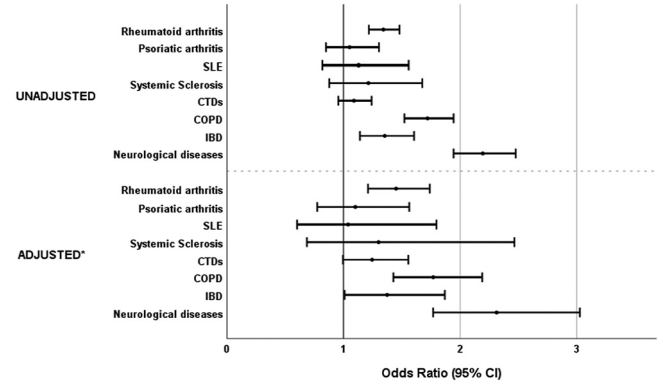

Figure 2. Forest plot showing the risk of non-vertebral and non-hip fractures in different diseases. (adjusted for *age, bone mineral density, menopausal status, glucocorticoid intake and familiar history of fragility fractures)*

Conclusion(s): Rheumatoid arthritis, COPD and neruological diseases were independently associated with an increased risk of non-vertebral and non-hip fractures whereas only COPD and neurological diseases were associated with vertebral or hip fractures.

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PLO09

Week 26 results from the PaTH Forward Open-Label Extension Trial Support TransCon PTH as a potential hormone replacement therapy for patients with hypoparathyroidism

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Background/Introduction: TransCon PTH is an investigational long-acting prodrug of PTH(1-34) for the treatment of hypoparathyroidism.

Purpose: Week 26 results are reported from the phase 2 PaTH Forward Open-Label Extension (OLE) Trial evaluating TransCon PTH in adults with hypoparathyroidism treated with standard of care (SoC; active vitamin D and calcium).

Methods: Subjects received fixed doses of TransCon PTH 15, 18, or 21 µg PTH(1-34)/day or placebo for 4 weeks, followed by an OLE period during which TransCon PTH dose was titrated (6–30 µg PTH[1-34]/day) with the goal to maintain normocalcemia. Efficacy end points evaluated at Week 26 included intake of active vitamin D and calcium supplements, 24-hour uCa, sCa, sP, and CaxP. Quality of life (QoL) was assessed by SF-36 and Hypoparathyroidism Patient Experience Scales (HPES).

Results: All 59 subjects completed the initial 4-week period and continued in the OLE. TransCon PTH enabled independence from SoC in most subjects by Week 26 (Table). Mean 24-hour uCa decreased from a baseline mean of 415 mg/24h to 178 mg/24h by Week 26 (n=44) while maintaining sCa and reducing sP and CaxP to fall within the normal range. SF-36 and HPES scores continued to improve through Week 26 for TransCon PTH subjects and placebo subjects switching to TransCon PTH. TransCon PTH continued to be well-tolerated with no treatment-related serious or severe adverse events.

End Points at Week 26	TransCon PTH(N=59)
Independence from SoC (no active vitamin D and Ca ≤500 mg/day)	91%
Independence from all supplements (no active vitamin D or Ca)	76%

Conclusion(s): Week 26 results from the PaTH Forward OLE demonstrated that TransCon PTH continued to enable independence from active vitamin D and calcium supplements for most subjects while maintaining normal sCa, sP, uCa, and demonstrating enhanced QoL. This supports TransCon PTH as a potential hormone replacement therapy for adults with hypoparathyroidism.

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PLO10

Adipose lipolysis is required for PTH-induced bone formation

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Background/Introduction: Lipolysis of triglycerides in adipose and release of fatty acids into the circulation provides an energy source for distant tissues. Previous work from our lab indicates mitochondrial oxidation of fatty acids increases during osteoblast differentiation and is necessary for normal bone formation.

Purpose: The goal of this study was to determine if the osteo-anabolic effect of intermittent parathyroid hormone (iPTH) treatment requires fatty acid oxidation by osteoblasts and to determine if adipocyte-derived fatty acids are essential for the anabolic effect.

Methods: Mice lacking the PTH receptor in adipocytes ($Pth1r^{flox/flox}$; AdipoQ-Cre), with impaired lipolysis due to the ablation of Atgl in adipocytes ($Atgl^{flox/flox}$; AdipoQ-Cre), or mice with impaired ß-oxidation in osteoblasts ($Cpt2^{flox/flox}$; Ocn-Cre) received saline or iPTH (100 ug/kg) for six weeks. Bone architecture and histomorphometry were assessed according to standard techniques. Animal procedures were approved by the local animal care and use committee.

Results: Acute PTH treatment induces a rapid increase in serum fatty acid levels in wild-type mice, but not those lacking Pth1r or Atgl in adipocytes. In turn, ablation of Pth1r and Atgl in adipocytes, but not osteoblasts, abolished the increase in bone volume after iPTH (Table I). Consistent with the notion that fatty acids are then used by osteoblasts to fuel bone formation, the ablation of Cpt2 in osteoblasts prevented iPTH-induced bone formation.

Table 1:

	% Δ in Serum FA		BV/TV in Distal Femur			
Mouse line	WT	KO	WT-Saline	WT-PTH	KO-Saline	KO-PTH
$Pth1r^{flox/flox}$; AdipoQ-Cre	+60.24	+12.35	12.38 ± 1.08	45.59 ± 4.57*	13.51 ± 1.92	16.55 ± 1.65#
$Atgl^{flox/flox}$; AdipoQ-Cre	+55.56	+11.85	12.10 ± 1.32	36.76 ± 4.38*	12.04 ± 2.31	17.00 ± 4.37 #
$Cpt2^{flox/flox}$; Ocn-Cre	N/A	N/A	12.83 ± 1.12	20.25 ± 2.97*	12.09 ± 1.61	10.99 ± 1.51#

Values are shown as mean ± SEM, * p <0.05 vs Saline-treated control, # p <0.05 vs PTH-treated control

Conclusion(s): Collectively, these data indicate that production and utilization of adipocyte-derived fatty acids are required for iPTH to increase bone mass.

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PLO11

Reactive oxygen species lead to age-related bone loss by accelerating senescence of osteoblasts in mice

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Background/Introduction: Reactive oxygen species (ROS) are mainly generated in mitochondria during cellular respiration and are eliminated by antioxidant defense mechanisms, including the mitochondrial enzyme superoxide dismutase (SOD)2. It has been shown that the activity of SOD2 in human osteoprogenitor cells decreased with donor age.

Purpose: In the present study, we established a mouse model of osteoblast-specific Sod2 deficiency to investigate the influence of increased ROS generation on bone mass in mice.

Methods: Female $Sod2^{fl/fl}$ and $Runx2CreSod2^{fl/fl}$ mice were sacrificed after 12 and 52 weeks, respectively. Their skeletal phenotype was analysed by µCT and histomorphometrically. Dihydroethidium was used to analyse ROS generation in bone cryosections and osteoblasts isolated from long bones. Proliferation rate and differentiation capacity of osteoblasts were assessed by BrdU assay and cytochemical stainings. Gene expression analysis was performed by qRT-PCR. Senescence-associated beta-galactosidase staining was used to detect senescent osteoblasts *in situ* and *in vitro*. Senescent-associated markers were assessed by immunohistochemical stainings in femur paraffin sections. n=6-8 per group.

Results: $Runx2CreSod2^{fl/fl}$ mice showed significantly decreased trabecular bone volume fraction, reduced trabecular number, increased trabecular separation and reduced cortical thickness in femurs compared with $Sod2^{fl/fl}$ mice. Moreover, the number and activity of osteoblasts was reduced while the number and activity of osteoclasts was increased in femurs from $Runx2CreSod2^{fl/fl}$ mice (12-weeks: NOb/BPm ($Sod2^{fl/fl}$) 19.87 ± 1.16 vs. ($Runx2CreSod2^{fl/fl}$) 11.69 ± 2.82 p<0.001; 1/mm). Increased ROS were detected in bones and osteoblasts from $Runx2CreSod2^{fl/fl}$ mice. Osteoblasts showed a decreased proliferation rate and an impaired differentiation capacity. Bones and osteoblast cultures revealed higher numbers of senescent cells. Expression levels of autophagy-associated markers Ulk1 and p62 were reduced, while expression levels of senescence-associated biomarkers p21 and $p16^{INK4a}$ were increased. Also, expression of FOXO1, IL6 and TNFα was increased in $Runx2CreSod2^{fl/fl}$ mice.

Conclusion(s): Our study suggests that osteoblast-specific Sod2 deficiency caused age-related bone loss by accelerating senescence of osteoblasts.

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PLO12

Inhibition of cyclin-dependent kinase 5 (Cdk5) increases osteoblast differentiation and bone mass through the MAPK pathway

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