Glucocorticoids prolong the reversal-resorption phase delaying bone formation in intracortical remodelling compared to postmenopausal and osteoporotic women

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disease activity visit. Flare was defined as an increase in DAS28-CRP of >1.2 points with current DAS28-CRP ≥3.2.

Results: 888 patients with RA with 3,396 follow-up visits were included in the study. 13,636 daily air pollution records were retrieved. We found an exposure-response relationship between the concentration of air pollutants and the risk of having abnormal CRP levels (**figure 1**). 440 patients (49.5%) had at least 2 follow-up visits with a difference in DAS28-CRP of more than 1.2 points (with current DAS28-CRP ≥3.2), serving as our sample for the case-crossover study. Concentrations of CO, NO, NO2, NOx, PM10, PM2.5 and O3 were higher in the 60-day period preceding a flare (**table 1**).

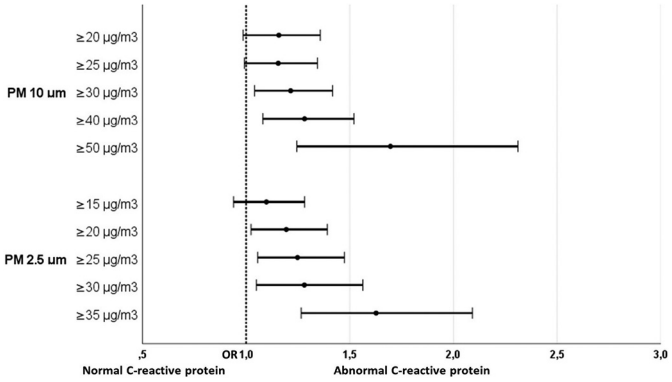

Figure 1. Odds of having abnormal CRP serum levels (≥5 mg/L)

Table 1
Area Under the Curve of air pollutants in the 60 days before low-disease activity visit and flare visit

Pollutant AUC ug/m3	Control period (n=440)	Flare period (n=440)	p value
CO	22.00	24.53	0.001
NO	1,120.53	1,403.88	0.002
NO2	1,800.96	1,892.05	0.040
NOx	3,515.77	4,041.06	0.004
PM10	1,789.22	1,942.52	0.005
O3	1,776.37	1,934.35	0.001
PM2.5	1,272.61	1,403.60	<0.001

Conclusion(s): We found a striking association between air pollution and RA disease severity and reactivations in a cohort of patients followed over a 5-year period. The exposure to high levels of air pollutants was associated with increased CRP levels and a higher risk of experiencing a flare of arthritis.

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COP15

In healthy men, early decline in trabecular bone mineral density is, in part, related to decreases in sex steroids

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Background/Introduction: Bone mass is known to decline in aging men and this decline is in part affected by sex steroid exposure. However, it is unclear how early after achieving peak bone mass bone loss begins and whether this decline is associated with sex steroid levels in young adulthood.

Purpose: Investigating longitudinal changes in trabecular and cortical vBMD in relation to sex steroid levels, body composition and lifestyle factors in young adult men.

Methods: Longitudinal observational study. 999 healthy men aged 24-46 years of whom 691 were re-evaluated after a mean period of 12 years. Serum sex hormone binding globulin (SHBG) levels were measured using immuno-assay. Testosterone (T), estradiol (E2), were measured using LC-MS/MS, free T calculated (cFT). Volumetric BMD was determined at the non-dominant arm (radius, at 4% and 66% of bone length from distal) using pQCT (Stratec XCT-2000, Stratec Medizintechnik, Germany, version 6.0). Linear mixed models were used for statistical analyses. All models comprised lifestyle factors and were adjusted for age and body mass index (BMI).

Results: Baseline age was 34±6 years. Mean BMI increased by 1.19kg/m². Trabecular vBMD decreased by 1.7% (228.9mg/mm³ vs 225.0 mg/mm³), no changes over time in cortical vBMD were observed. Mean T levels decreased by 14.2% (20.8nmol/l vs. 17.8nmol/l), cFT by 19.1% (392pmol/l vs. 317pmol/l). Mean E2 levels did not change over time. SHBG increased by 3.0% (39.8nmol/l vs. 41.0nmol/l). Larger decreases in T, cFT and E2 (all $p<0.03$) but not SHBG ($p>0.05$) were associated with more pronounced decreases of trabecular vBMD over time.

Conclusion(s): Shortly after achieving peak bone mass, a modest trabecular decline was appreciated. This decline was in part associated with declining sex steroid levels. Moreover this decline persisted after correction for changes in body composition and lifestyle factors.

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COP16

Glucocorticoids prolong the reversal-resorption phase delaying bone formation in intracortical remodelling compared to postmenopausal and osteoporotic women

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Background/Introduction: Studies in women have demonstrated an age-related increased cortical porosity attributable to accumulation of eroded type 2 pores (remodeling of existing pores) reflecting an extended reversal-resorption phase.

Purpose: This study addresses the histomorphometric changes in cortical bone remodeling in glucocorticoid-induced osteoporosis (GIO) versus postmenopausal osteoporosis (PMO) and postmenopausal controls.

Methods: We analysed 7-µm-thick Goldner-Masson trichrome stained sections from transiliac bone biopsies from i) postmenopausal women with GIO (n=19, age 71±5 years), ii) women with PMO, without prior glucocorticoid-treatment (n=17, age 71±6 years), and iii) postmenopausal healthy women (controls, n=21, age 71±7 years).

Results: We found statistically significantly thinner cortices (~40%) in both GIO and PMO relative to controls ($p<0.001$), but only in controls the change was correlating with age ($r_p=-0.49$, $p<0.05$). In the cortex remaining, PMO had a borderline significantly decreased porosity compared to controls ($p=0.054$) and GIO ($p=0.066$). The porosity correlated with mean pore diameter (GIO: $r_p=0.84$, $p<0.0001$, PMO: $r_p=0.93$, $p<0.0001$, controls: $r_p=0.54$, $p<0.05$), but not pore density. The percentage of porosity reflecting non-quiescent pores was high in all three groups, although highest in GIO (89.2%, $p<0.05$) and PMO (88.2%, $p=0.051$) compared to controls (79.5%). In GIO, a significant higher percentage of the porosity was represented by eroded pores compared to PMO ($p<0.05$) and controls ($p<0.01$). Furthermore, in GIO a significantly lower percentage of the porosity reflected mixed eroded-formative pores than in PMO ($p<0.05$). The pore diameter of quiescent osteons was lower in GIO ($p=0.053$) and PMO ($p<0.001$) compared to controls, suggesting an improved BMU balance. No significant correlation with dosage or treatment-time was found in GIO, possibly due to the late stage in glucocorticoid-treatment at biopsy collection (6.0 ± 5.1 years).

Conclusion(s): In conclusion, GIO and PMO reveal a pronounced cortical thinning. Especially in GIO, the cortical porosity reflects cortical remodelling with an extended reversal-resorption phase – not a negative BMU balance.

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COP17

A whole genome sequencing study to identify novel genetic variants associated with lean mass: Multi-ethnic meta-analysis

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Background/Introduction: Genome-wide association studies (GWAS) of whole-body (WB-) and appendicular (a-) LM are unlikely to identify rare variations that may have larger effect sizes than common variants.

Purpose: A whole-genome sequencing (WGS) study was performed to comprehensively discover sequence variants associated with variation in DXA-derived lean mass (LM), a proxy of muscular fitness.

Methods: We utilized deep-coverage WGS (average 30x) in ethnically diverse samples from the Trans-Omics for Precision Medicine (TOPMed) program (n=5744; 85% European-Ancestry, 7% African-Ancestry, 8% Hispanic /Latino); TOPMed participants had a mean age of 60.7 years (SD: 14.8) and >65% of participants were women. We then meta-analyzed results with the Louisiana Osteoporosis Study (LOS), n~5000, who included 58% European, 42% African ancestry, ~50% men, with a mean age of 39.2 years (SD: 11.2). Lean mass residuals were generated adjusting for age, age^2, sex, height, weight, total fat and study-specific variables. Genetic associations with inverse normal transformed residuals were evaluated using linear mixed-effects models. To meta-analyze variants with minor allele frequency (MAF) ≥ 0.1%, we used a fixed effects approach.

Results: In the single-variant analysis, several rare variants with MAF <1% were significantly ($p<5*10(-8)$) associated with WB LM: rs116652927, rs148735123, and rs77796060; while rs182466396 (MAF=1.5%) was associated with aLM. The latter is an intronic variant in *SSUH2*, a gene associated with rippling muscle disease 2, which is a form of limb-girdle muscular dystrophy. There were no known muscle GWAS signals within 1 Mb from these variants.

Conclusion(s): Additional analyses are underway, including sex- and ancestry-specific analyses. The discovery of novel genetic variants associated with lean mass may provide new insights into pathways influencing muscle metabolism and muscle mass regulation.

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COP18

HR-pQCT-based regional analysis reveals tibial spatial variability in cortical bone tissue quality in type 2 diabetic postmenopausal women with and without history of fragility fractures

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Background/Introduction: Type 2 diabetic (T2D) bone disease is characterized by an increased fracture risk which is partly ascribed to cortical deficits such as higher cortical porosity. While previous work identified midcortical and periosteal layers as potential high-porosity zones in T2D, the anatomical spatial variability of cortical porosity in T2D remains unknown.

Purpose: Using high-resolution peripheral quantitative computed tomography (HR-pQCT), we therefore aimed to characterize and compare the regional variability of cortical porosity and other cortical measures in T2D women with (DMFx) and without history of fragility fractures (DM).

Methods: 39 postmenopausal women (n=20 DMFx, n=19 DM) underwent HR-pQCT scanning of the distal tibia. Cortical parameters including cortical porosity measures were calculated for the overall tibial cortex and for the anterior, posterior, medial and lateral cortical quadrants which were defined based on anatomic axes.

Results: Using linear regression models we found that DMFx subjects exhibited significantly higher global macro-porosity (Ct.Po) than DM subjects (+128%, p=0.001), but also significantly higher regional macro-porosity in each of the four tibial quadrants (+94% to +134%, $0.033\leq p\leq 0.001$). In all but the anterior quadrant, significantly larger pores (Ct.Po.Dm: + 17% to +21%, $0.025\leq p\leq 0.003$), and larger pore heterogeneity (Ct.Po.Dm.SD, +24%