with DXA. Fractures during follow-up were collected by self-report and, in some cohorts, confirmed by radiography. 10 year probability for fracture was calculated using FRAX version 3.2. An extension of Poisson regression was used to examine the relationship between the difference between LS and FN T-score (ΔLS-FN) and fracture risk adjusted for age and time since baseline within each cohort. Cohort-specific results were merged and weighted according to the variance. The women were divided in three categories according to their probabilities for fracture; low risk (<10%), moderate risk (10–20%) and high risk (>20%).

The women were aged 40–90 years (mean 63.3 years). The Δ LS-FN was greater than 2 SD for 2.4% and between 1 and 2 SD for 21% of the population. During an average follow-up of 7.5 years, 1934 osteoporotic fractures (339 hip fractures) occurred. Δ LS-FN was associated with a significant risk of fracture adjusted for baseline FRAX (HR per SD change=1.09; 95% CI=1.03–1.15). The gradient of risk was age dependent. 4.6% of the women moved to a higher or lower risk category when using FRAX with Δ LS-FN compared with FN-derived FRAX alone.

Our results are comparable to and, thus, validate those previously reported in a single cohort. Adjustment of FRAX scores on the basis Δ LS-FN is of value in the minority of women close to an intervention threshold.


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OPC04
High circulating serotonin in carcinoid syndrome is not associated with alterations in bone turnover or bone density
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cAbstract: Gut-derived serotonin has been proposed as a regulator of bone formation and inhibition of gut serotonin synthesis increases bone formation in rodents. Carcinoid neuroendocrine tumours can produce very high levels of circulating serotonin and so offer a model of serotonin excess in humans. There is very little information on the effects of carcinoid syndrome on bone.

We studied 26 patients with carcinoid syndrome and 26 healthy controls, individually matched to carcinoid patients by gender, age, height and BMI. We measured BMD of the lumbar spine and hip with DXA and bone geometry, density and microarchitecture of the distal radius and tibia with HR-pQCT. We measured 24 h urine 5HIAA (a serotonin metabolite) to assess circulating serotonin levels, and measured bone turnover with serum CTX, osteocalcin and PINP. We used paired samples t-tests to compare cases and controls.

Mean time since diagnosis of carcinoid disease was 5 years and 14 patients were currently treated with somatostatin analogues. Median 24 h urine 5HIAA was 105 μmol in carcinoid patients (range 27–1411) and 23 μmol in controls (range 11–49) (p=0.001). Twenty-four carcinoid patients and 2 controls had 5HIAA above the upper limit of the reference range (37 μmol). Lumbar spine and total hip BMD did not differ between cases and controls (0.982 vs 1.028 g/cm², 95% CI of the difference = 0.126 to 0.035, and 0.928 vs 0.981 g/cm², 95% CI of the difference = 0.119 to 0.014). There were no differences between cases and controls in any of the measures of bone density, geometry or microarchitecture at the radius or tibia. There were no differences between cases and controls in any of the three bone turnover markers (CTX 0.45 vs 0.41 ng/ml, 95% CI of the difference = 0.08 to 0.11; OC 25.4 ± 22.4 ng/ml, 95% CI of the difference = 2.3 to 8.5; PINP 48.8 vs 51.1 ng/ml, 95% CI of the difference = 13.5 to 9.1).

We conclude that high circulating serotonin in carcinoid syndrome is not associated with reduced bone formation or alterations in bone density or structure. This article is part of a Special Issue entitled ECTS 2012. Disclosure of interest: None declared.

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OPC06 (For more information visit the Amgen/GlaxoSmithKline scientific booth)
Denosumab treatment for 6 years in postmenopausal women with osteoporosis: The first 3 years of the freedom extension
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Abstract: Denosumab (DMAB) is approved for treatment of postmenopausal women with osteoporosis at increased risk of fracture. The 3-year FREEDOM trial demonstrated a favorable risk/benefit profile (Cummings NEJM 2009). The open-label, active-treatment Extension study, investigating efficacy and safety of DMAB (60 mg every 6 months) for up to 10 years, enrolled women who had received DMAB or placebo (Pbo) in FREEDOM. It allows evaluation of long-term efficacy and safety of continuous DMAB treatment (long-term group), and to replicate DMAB findings in FREEDOM (cross-over group). We report the results from the first 3 years, representing 6 continuous years of DMAB exposure (long-term group) and 3 years of DMAB exposure (cross-over group).
In the long-term group (N=2343), further significant mean increases in bone mineral density (BMD) resulted in cumulative 6-year gains (13.2% at lumbar spine and 7.5% at total hip). During the first 3 years of DMAb treatment during the Extension, the cross-over group (N=2207) had significant gains in BMD (9.4% at lumbar spine and 4.8% at total hip), similar to those observed in the FREEDOM group (10.1% and 5.7%, respectively). New vertebral, nonvertebral and major nonvertebral fracture rates remained low in the long-term group; fracture rates in the cross-over group were lower than those observed in the FREEDOM Pbo arm (Table). Serum CTX was rapidly and similarly reduced after the 1st (cross-over) or 7th (long-term) DMAb dose, with the characteristic attenuation observed at dosing period end. Adverse event (AE) and serious AE (SAE) incidences did not increase over time with DMAb treatment. 2 subjects in each group had AEs adjudicated as ONJ. Both cases in the cross-over group healed completely. 1 continues to receive DMAb. One case in the long-term group healed while the other case continues to follow. No atypical femur fractures have been observed.

DMAb treatment for 6 years (long-term group) continued to significantly increase BMD, maintained reduced bone turnover and remained well tolerated. Fracture incidence remained low. DMAb treatment for 3 years (cross-over group) reproduced FREEDOM observations.

**Disclosure of interest:** This article is part of a Special Issue entitled ECTS 2012.

**Abstract:** Denosumab (DMAb) is approved for treatment of osteoporosis in postmenopausal women at increased risk of fracture. It increases both the bone mineral density (BMD) and thickness of cortical bone and reduces cortical porosity, all contributing to improved bone strength. The FREEDOM study evaluated the effects of DMAb on cortical and trabecular bone at the radius using DXA and QCT scans, and on wrist fracture risk.

Women in FREEDOM received placebo (Pbo) or DMAb 60 mg every 6 months for 3 years. BMD, bone mineral content (BMC) and polar moment of inertia (PMI, a measure of bone strength) at the radius were assessed in a DXA (N=209 Pbo, N=232 DMAb) or QCT study (N=79 Pbo, N=103 DMAb). The incidence of wrist fractures was evaluated for all FREEDOM subjects (N=3906 Pbo, N=3902 DMAb) and in a subgroup at higher risk of nonvertebral fractures based on baseline femoral neck (FN) BMD (T-score ≤ −2.5; N=1406 Pbo, N=1384 DMAb) and a subgroup at lower risk (FN BMD T-score > −2.5; N=2484 Pbo, N=2465 DMAb).

DMAb significantly increased BMD at all radius regions of interest (1/3, ultradistal and total radius) by 2.3–5.7% vs Pbo and 2.2–3.4% vs baseline (all p<0.05). QCT BMD changes were consistent with DXA results. DMAb also significantly improved BMC and PMI at the proximal, distal and ultradistal radius vs Pbo (3.7–7.0% and 3.3–7.9%) and baseline (1.7–5.5% and 1.7–5.7%; all p<0.05). All measures decreased significantly from baseline in Pbo subjects (all p<0.05). The incidence of wrist fractures in the overall FREEDOM population was 2.9% and 2.5% for the Pbo and DMAb groups, respectively (hazard ratio 0.84; p=0.21). In the higher-risk subgroup, DMAb significantly reduced the absolute risk of wrist fracture from 4.0% to 2.4%, a relative risk reduction of 40% (p=0.03); and to an absolute risk level similar to that in Pbo-treated subjects in the lower-risk subgroup (Figure). Reductions in wrist fractures were not explained by fewer subjects reporting falls (7.4% Pbo, 7.2% DMAb; p=0.73).

DMAb significantly improved BMD, BMC and PMI compared with baseline and Pbo along the radius, at cortical as well as trabecular sites. It also significantly reduced wrist fracture risk in higher-risk women to a level similar to that observed in Pbo-treated women with lower fracture risk. The positive effects of DMAb on the cortical compartment help explain the beneficial wrist fracture outcomes in patients at higher risk of nonvertebral fractures.

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