

Abstracts Selected for Oral Presentation

Oral Number 001

DENOSUMAB INCREASED BMD OF THE LUMBAR SPINE, TOTAL HIP, FEMORAL NECK, AND TROCHANTER AS MEASURED BY QCT IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS

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Background: Denosumab (DMAb), a fully human monoclonal antibody to RANKL, decreases bone turnover, increases DXA areal bone mineral density (aBMD), and reduces fracture risk in postmenopausal women with osteoporosis that participated in the FREEDOM trial (Cummings et al., NEJM 2009;361:756). Here we describe the effect of DMAb on lumbar spine and hip (total hip, femoral neck, and trochanter) BMD as measured by quantitative computed tomography (QCT) in a subset of women that participated in the FREEDOM trial.

Methods: FREEDOM was a 3-year, multinational, randomized, double-blinded trial that enrolled women aged 60-90 years with a lumbar spine and/or total hip DXA T-score < -2.5, and not < -4.0 at both sites. Participants received placebo or 60 mg DMAb every 6 months with daily calcium and vitamin D. Lumbar spine, total hip, femoral neck, and trochanter BMD were measured by QCT at baseline and at months 12, 24, and 36, in a subset of women.

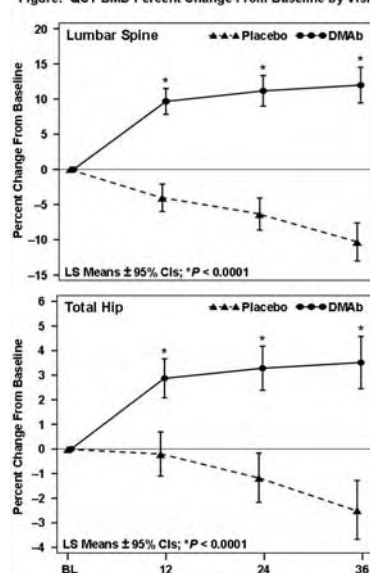
Results: Subjects with values at baseline and at ≥ 1 post-baseline visit at or prior to the time point of interest were included in the analyses (month 36 - lumbar spine: n=84 placebo, n=95 DMAb; hip: n=42 placebo; n=53 DMAb). Baseline characteristics were balanced between the placebo and DMAb groups. BMD increased from baseline in the DMAb group and decreased from baseline in the placebo group at the lumbar spine, total hip, femoral neck, and trochanter over the study period (Figure and Table). Significant BMD differences from placebo were demonstrated for all sites at all time points, reaching 22.3%, 6.0%, 4.7%, and 9.4%, respectively for the lumbar spine, total hip, femoral neck, and trochanter at 36 months (Table; all $P < 0.0001$).

Conclusion: DMAb significantly increased BMD at the lumbar spine and hip at all measured time points as assessed by QCT in a subset of women who participated in the FREEDOM trial.

Table: Lumbar Spine and Hip QCT BMD Percent Change From Baseline at Month 36

		% Change From Baseline		Difference From Placebo	
		n	LS Mean (95% CI)	LS Mean (95% CI)	P-value
Lumbar Spine	Placebo	84	-10.3 (-13.0, -7.6)	22.3 (18.6, 26.0)	< 0.0001
	DMAb	95	12.0 (9.4, 14.5)		
Total Hip	Placebo	42	-2.5 (-3.7, -1.3)	6.0 (4.4, 7.6)	< 0.0001
	DMAb	53	3.5 (2.5, 4.6)		
Femoral Neck	Placebo	42	-2.9 (-4.3, -1.4)	4.7 (2.8, 6.6)	< 0.0001
	DMAb	53	1.9 (0.6, 3.1)		
Trochanter	Placebo	42	-2.8 (-4.2, -1.4)	9.4 (7.6, 11.3)	< 0.0001
	DMAb	53	6.6 (5.3, 7.8)		

Figure: QCT BMD Percent Change From Baseline by Visit



Abstracts Selected for Oral Presentation

Oral Number 002

IMPROVING POST HIP FRACTURE CARE IN VETERANS

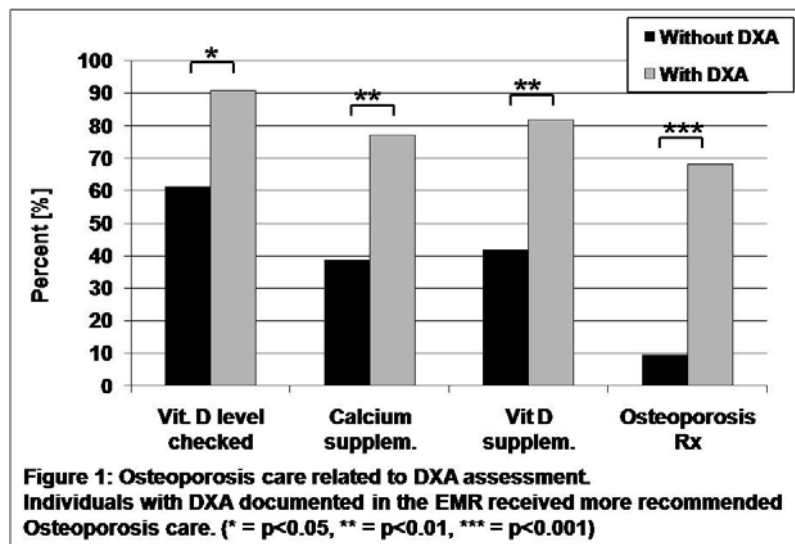
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Purpose: Despite documented treatment efficacy and comprehensive guidelines, osteoporosis (OP) is inadequately managed following fragility fracture. This retrospective chart review and quality improvement project evaluated care following hip fracture and developed interventions based on these findings.

Methods: Patients hospitalized with hip fracture from July 2007-April 2009 were identified through ICD-9 codes. Electronic medical records (EMR) were reviewed to assess the following: Diagnosis of OP, performance of DXA assessment, 25(OH)D measurement, calcium/vitamin D supplementation, and prescription of OP medications. These results were used to explore barriers limiting adequate post hip fracture care. Following this, possible interventions were developed.

Results: The EMR search revealed 63 cases. After excluding patients due to death within 3 months of hip fracture (7) or other causes (3), 53 patients were analyzed. Mean age was 73 years and 51 were male. Only 34% had OP documented in the EMR. DXA was obtained in 42% and 25(OH)D level checked in 74%. Calcium and vitamin D supplements were recommended for 55% and 59% respectively. OP medications were prescribed for 34%. Of those in whom DXA was obtained a significantly greater proportion received recommended OP care compared to those that did not have a DXA scan in the EMR (Figure 1). Based on an analysis of potential barriers, two interventions were selected; 1. A reminder will be added to the EMR including current diagnostic and treatment guidelines and an order set for OP management. This reminder will automatically be activated if fragility fractures, OP or an abnormal DXA (as coded by the reading physician) are recorded in the EMR. Secondly the local OP clinic will review new hip fracture cases monthly to enhance communication regarding necessary OP care (DXA imaging and treatment) with the primary care team and patients through the EMR and mail.

Conclusion: The gap between recommended osteoporosis management and actual care in post-hip fracture patients is evident in our chart review. DXA measurement is associated with a greater likelihood that a hip fracture patient will receive recommended therapy. Interventions designed to improve communication between the inpatient and outpatient setting, enhance knowledge of current guidelines, encourage DXA testing, and use of pharmacologic therapy were evaluated and established. The next steps include re-analyzing the chosen process measures to assess whether our interventions were successful and to further refine them.



Abstracts Selected for Oral Presentation

Oral Number 003

OLDER MEN WITH EXTENDED AORTIC CALCIFICATIONS HAVE MORE VERTEBRAL FRACTURES - A CROSS-SECTIONAL STUDY IN THE STRAMBO COHORT USING THE HOLOGIC VFA SOFTWARE

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Older men with the extended aortic calcifications assessed on lateral spine radiographs with a 24-point score (aortic calcification score, ACS>6) had an increased risk of fracture (Szulc & al., *JBMR*, 2008). In this study carried out in 912 men aged 50 and over, we assess the association between prevalent vertebral fractures and ACS identified on the lateral spine scans obtained using the Vertebral Fracture Assessment software on the HOLOGIC Discovery A device. Vertebral fractures were diagnosed in 166 men with the semiquantitative method: Grade 1 (mild, n=87 including 18 probably osteoporotic fractures), Grade 2 (moderate, n=59), Grade 3 (severe, n=21). ACS was assessed using the same 24-point score. Bone mineral density (BMD) at lumbar spine, hip, whole body and radius was measured on the same HOLOGIC device.

ACS increased with age ($r=0.35$, $p<0.001$). Current and former smokers had higher ACS than never smokers ($p<0.005$). Men who had smoked >17.5 packet-years (median) had higher ACS than those who had smoked less ($p<0.05$) and those who never smoked ($p<0.001$). Self-reported high blood pressure, diabetes, ischemic heart disease and peripheral arterial disease were each associated with higher ACS ($p<0.05$ - 0.001). Vertebral fracture prevalence was assessed in groups classified according to ACS: 0 (n=403), 1-2 (n=245), 3-6 (n=151), >6 (n=113). It varied across the groups (18.1 %, 15.5 %, 12.3 %, 30.6 %, $p<0.001$). After adjustment for age, weight, smoking status, cardiovascular diseases and BMD; elevated ACS (>6) was associated with a two-fold higher prevalence of vertebral fractures (OR= 1.99, 95%CI: 1.22-3.27, $p<0.01$). This association was significant for the moderate and severe fractures (OR= 2.56, 95%CI: 1.36-4.82, $p<0.005$), but not for the mild fractures (OR= 1.43, 95%CI: 0.71-2.88). In the 98 men with presumably osteoporotic fractures, elevated ACS was associated both with the presence of one fracture (OR= 2.00, 95%CI: 1.01-3.97, $p<0.05$) and of multiple fractures (OR= 2.71, 95%CI: 1.12-6.53, $p<0.05$). This analysis confirms the association between severe osteoporosis and advanced cardiovascular diseases. The HOLOGIC VFA software can be used both for assessment of vertebral fracture and of aortic calcifications.

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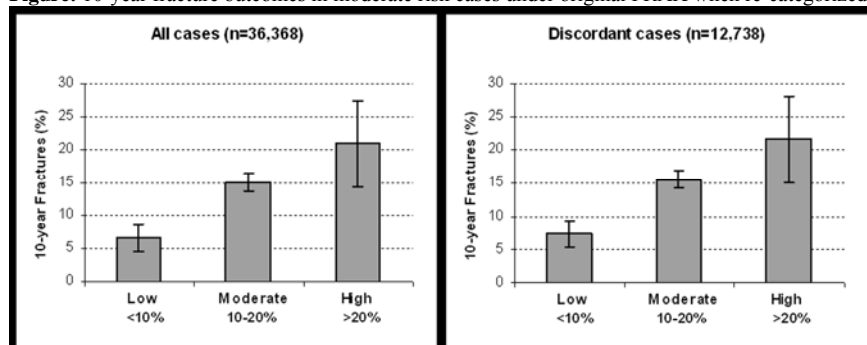
Oral Number 004

SPINE-HIP DISCORDANCE AND FRACTURE RISK ASSESSMENT: A PHYSICIAN-FRIENDLY FRAX ENHANCEMENT

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Background: The WHO fracture risk assessment (FRAX) tool estimates ten-year probability of fracture based upon multiple clinical risk factors and an optional BMD measurement obtained from the femoral neck. Discordance between lumbar spine (LS) and femoral neck (FN) T-scores is common and a source of clinical confusion since the LS measurement is currently ignored under the FRAX formulation. **Objective:** To develop and test a procedure for adjusting fracture risk based upon the T-score discordance between the LS and FN. **Methods:** The Manitoba BMD database was used to identify baseline LS and FN DXA examinations (33,850 women and 2,518 men) in individuals age 50 years and older with ten-year osteoporotic FRAX estimates (US white tool) categorized as low (<10%), moderate (10-20%) and high (>20%). Fracture outcomes were assessed from validated population-based administrative data linked to BMD data. Analyses were conducted using Cox regression. **Results:** The T-score difference (LS minus FN) was found to significantly affect fracture risk independent of FRAX score (HR 1.10 [95% CI 1.06-1.14] per unit LS T-score lower than FN) without significant interactions with baseline FRAX risk, age, or sex. The following rule was formulated to enhance the FRAX prediction: "Increase/decrease osteoporotic FRAX estimate by one-tenth for each rounded T-score difference between LS and FN". There was a small improvement in ROC area under the curve with this LS-enhanced FRAX estimate for vertebral fractures (0.752 [95% CI 0.734-0.770]) versus original FRAX estimate (0.742 [95% CI 0.724-0.761]) and for discordant cases with T-score difference >1 SD (0.695 [95% CI 0.676-0.714] versus 0.691 [95% CI 0.672-0.711]). Risk stratification was also improved using the LS-enhanced FRAX system. For those at moderate risk with original FRAX, 12.3% showed recategorization with LS-enhanced FRAX to a risk level that more accurately reflected their actual risk (Figure). For moderate risk discordant cases with T-score difference >1 SD, there was 24.9% recategorization and a similar improvement in fracture prediction. In contrast, for those at moderate risk with LS-enhanced FRAX, the original FRAX estimate provided no appreciable change in risk stratification. **Conclusion:** A simple procedure based upon the difference between LS and FN T-scores enhances fracture risk prediction under the FRAX system.

Figure: 10-year fracture outcomes in moderate risk cases under original FRAX when re-categorized with the LS-enhanced FRAX.



Abstracts Selected for Oral Presentation

Oral Number 005

BEST CLINICIAN ABSTRACT

GENISTEIN AGLYCONE IS EFFECTIVE IN REDUCING BONE LOSS AND SOME PREDICTORS OF CARDIOVASCULAR RISK IN POSTMENOPAUSAL WOMEN: A 3-YEARS STUDY

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Genistein aglycone improves bone metabolism and has received wide attention over the last few years because of its potential preventive role for cardiovascular disease. However, questions about the long-term safety of genistein on reproductive tissues as well as its continued efficacy still remain. We assessed the continued safety profile of genistein aglycone on breast and endometrium, and its effects on bone metabolism and some predictors of cardiovascular risk after 3 years of therapy.

The parent study was a randomized, double-blind, placebo-controlled trial involving 389 osteopenic, postmenopausal women for 24-months. Subsequently, a subcohort (138 patients) continued therapy for an additional year.

Participants received 54 mg of genistein aglycone daily (n=71) or placebo (n=67). Both arms received calcium and vitamin D3 in therapeutic doses. Moreover, 4 weeks before randomization procedures and during our study, all patients received dietary instructions in an isocaloric fat-restricted diet.

FRAX index and lumbar spine and femoral neck BMD were assessed. Mammographic density was assessed at baseline, 24 and 36 months by visual classification scale and digitized quantification. BRCA1 and BRCA2, sister chromatid exchanges and endometrial thickness were also evaluated. Secondary outcomes were biochemical levels of bone markers, fasting glucose and insulin, HOMA-IR, fibrinogen, and homocysteine. Standard clinical evaluations and laboratory analyses, including hematologic, kidney, and liver function tests, were done every 6 months.

FRAX-index calculated at the beginning and at the end of the treatment period showed a significant decrease in the genistein group compared with placebo after 3yrs.

After 36 months, genistein did not significantly change mammographic breast density or endometrial thickness, BRCA1 and BRCA2 expression was preserved while sister chromatid exchanges were reduced compared with placebo. BMD increases were greater with genistein for both femoral neck and lumbar spine compared to placebo. Genistein significantly reduced PYR, as well as serum CTX and sRANKL while increasing B-ALP, and OPG levels. Moreover, genistein significantly decreased fasting glucose and insulin, HOMA-IR, fibrinogen and homocysteine. Results on routine testing did not change over time in placebo or genistein recipients.

After 3-years of treatment, genistein exhibited a promising safety profile with positive effects on bone in a cohort of osteopenic, postmenopausal women.