

OPTIMIZING SEPARATION OF BONE MARKER QUADRANTS IN OSTEOPOROSIS PATIENTS TREATED WITH TERIPARATIDE

Xiaohai Wan, PhD, Lilly USA, LLC, Indianapolis, IN; John H. Krege, MD, Lilly USA, LLC, Indianapolis, IN; Xinming Hao, PhD, MedFocus, LLC, Chicago, IL

BACKGROUND: Osteoporosis is a metabolic bone disease characterized by reduced bone mineral density (BMD), deterioration in bone architecture, and increased risk of fracture. In postmenopausal women, this disease arises because of an imbalance between bone formation and resorption resulting in loss of BMD. Bone markers offer a means to assess bone metabolism and include both formation (F) and resorption (R) markers. While changes in bone markers have been correlated with changes in BMD, errors in the measurement of bone markers as well as BMD has limited the strength of the correlations. We propose a new way to use bone markers to assess later changes in BMD using a novel analytic approach called generalized boosted regression modeling (GBM).

METHODS: All 87 teriparatide-treated postmenopausal patients (aged 45 to 84 years) in the Forteo and Alendronate Comparator Trial were classified into four groups based on the maximum changes in one formation and one resorption bone marker (i.e. F+R+, F+R-, F-R- and F-R+) between 1 and 6 months from baseline. Formation markers include serum procollagen type I N-terminal propeptide (PINP), serum procollagen type I C-terminal propeptide (PICP), and serum bone specific alkaline phosphatase (BSAP); resorption marker includes urinary collagen type I cross-linked N-telopeptide/creatinine (NTX). Using maximum change of each marker as the predictor, four GBM models were built to predict 18-month changes in BMD. Cutoff levels for each marker are estimated from partial dependence plots between the markers and changes in BMD. Cutoff levels for the formation and resorption markers, which separate the quadrants of subgroups, were estimated using the GBM method based on their ability to best predict 18-month changes in BMD (Table).

RESULTS:

Pairs of Markers (Cutoff Level)		F+R+	F+R-	F-R-	F-R+	P-Value
PICP (85%) + NTX (10%)	Baseline BMD	0.74 ± 0.06	0.76 ± 0.13	0.73 ± 0.08	0.74 ± 0.07	0.95
	18-Month ΔBMD	0.09 ± 0.05	0.09 ± 0.02	0.06 ± 0.05	0.04 ± 0.04	0.0003
	Clinical Fracture	2/33 (6%)	1/5 (20%)	2/15 (13%)	4/34 (12%)	0.71
PINP (120%) + NTX (10%)	Baseline BMD	0.74 ± 0.07	0.73 ± 0.11	0.74 ± 0.09	0.74 ± 0.06	0.98
	18-Month ΔBMD	0.08 ± 0.04	0.09 ± 0.03	0.05 ± 0.05	0.02 ± 0.04	<0.0001
	Clinical Fracture	4/51 (8%)	2/9 (22%)	1/11 (9%)	2/16 (13%)	0.61
BSAP (15%) + NTX (10%)	Baseline BMD	0.74 ± 0.07	0.74 ± 0.09	0.73 ± 0.10	0.76 ± 0.06	0.85
	18-Month ΔBMD	0.06 ± 0.05	0.07 ± 0.04	0.06 ± 0.06	0.06 ± 0.06	0.91
	Clinical Fracture	6/60 (10%)	2/12 (17%)	1/8 (13%)	0/7 (0%)	0.71

Δ= change

CONCLUSIONS: This work should help to better identify optimum responders to teriparatide treatment based on changes in formation and resorption markers, and provide new information regarding the relationships between bone formation and resorption and how these predict changes in the skeleton.

HAND DOMINANCE AND BONE MICROARCHITECTURE AT THE DISTAL RADIUS BY HIGH-RESOLUTION MAGNETIC RESONANCE IMAGING - UPDATED DATA

Xiaohai Wan, PhD, Lilly USA, LLC, Indianapolis, IN; Pamela Seaman, PhD, MicroMRI, Langhorne, PA; Mayme Wong, PhD, Lilly USA, LLC, Indianapolis, IN; Kelly Krohn, MD, Lilly USA, LLC, Indianapolis, IN; Michael Kleerekoper, MD, Dept of Internal Medicine, St. Joseph Mercy Reichert Health Center, Ypsilanti, MI

BACKGROUND: Bone mineral density as measured using dual-energy X-ray absorptiometry has been found to be significantly higher in the hand, forearm, and calcaneus on the dominant side compared with the nondominant side. Whether hand dominance influences bone microarchitecture is unknown.

METHODS: Bone microarchitecture was measured bilaterally at the distal radius of 34 right-handed postmenopausal women with osteoporosis (aged 45 to 85 years) using noninvasive high resolution magnetic resonance imaging (μ MRI). In this post-hoc analysis, three-dimensional structural parameters of bone volume/tissue volume (BV/TV), trabecular thickness (Tb.Th), trabecular number (Tb.N), trabecular spacing (Tb.Sp), and cortical thickness (Ct.Th) were compared between the right (R) and left (L) radius in each woman. The Plate:Rod ratio was calculated from dividing the trabecular surface by the trabecular curve value. Arithmetic mean and standard deviation (SD) were calculated for the R and L radius parameters, and for the difference (R-L) and ratio (R/L).

RESULTS:

Structural Parameter	Mean \pm SD			
	Right Radius (R)	Left Radius (L)	Difference (R-L)	Ratio (R/L)
BV/TV (%)	10.40 \pm 1.26	10.12 \pm 1.35	0.26 \pm 1.12	1.03 \pm 0.11
Tb.Th (μ m)	83.41 \pm 8.87	81.71 \pm 7.62	1.43 \pm 7.76	1.02 \pm 0.10
Tb.N (per mm)	1.25 \pm 0.11	1.24 \pm 0.12	0.01 \pm 0.10	1.01 \pm 0.08
Tb.Sp (μ m)	723.21 \pm 69.92	732.11 \pm 75.66	-9.54 \pm 66.05	0.99 \pm 0.09
Ct.Th (mm)	1.61 \pm 0.25	1.57 \pm 0.23	0.03 \pm 0.15	1.02 \pm 0.09
Plate:Rod Ratio	6.31 \pm 2.00	6.12 \pm 1.85	0.16 \pm 1.65	1.05 \pm 0.27

CONCLUSIONS: BV/TV, Tb.Th, Tb.N, Ct.Th, and Plate:Rod ratio were not statistically significantly different between the R and L radius. Limitations of this analysis include the small number of subjects and resolution of the technology.

BONE TURNOVER MARKERS AND FRACTURE RISK IN AFRICAN AMERICAN KIDNEY TRANSPLANT RECIPIENTS WITH HYPOVITAMINOSIS D AND HYPERPARATHYROIDISM

Mariana Markell, MD, SUNY Downstate Medical Center, Brooklyn, NY; Sima Terebelo, RPA-C, MPH, SUNY Downstate Medical Center, Brooklyn, NY

The recommendation has been made that the majority of kidney transplant recipients would benefit from prophylactic bisphosphonate therapy, with the assumption that they are at increased risk for high turnover bone disease due to multiple factors, including corticosteroid therapy and hyperparathyroidism (hPTH). Few studies have looked at bone markers or actual fracture risk in this population, especially in African Americans, who make up an increasing number of pts due to their high prevalence of kidney disease. We studied bone markers and risk for osteoporosis through FRAX score in 26 African American and 2 Hispanic KTR's all of whom had preserved kidney function (creatinine <2.5 mg/dl) hyperparathyroidism and hypovitaminosis D. There were 14 men and 14 women in the cohort, and by t-test they did not differ for any parameters so the entire group was used for analysis. Mean age was 52.7+/-12.2 yrs, BMI 32.9+/-9.0, mean time since transplant 54.6+/-48.1 mos, months on dialysis 55.6+/-56.7, prednisone dose 7.5+/-2.3mg, creatinine 1.6+/- 0.4 mg/dl. Mean 25-OH Vit D was 15.9+/- 4.3 ng/dl, iPTH was 190.3+/-62.9. Bone markers were not elevated in the majority of pts, w mean osteocalcin 30.5+/-14.7, bone alkaline phosphatase (BAP)17.9+/-8.1 and c-telopeptide (C-tx) 459.6+/-247.2. C-tx was highly correlated with osteocalcin ($r=0.72$, $p<0.0001$) and BAP ($r=0.5$, $p<0.05$), and was directly correlated with time on dialysis ($r=0.5$, $p=0.011$), and cigarette smoking ($r=0.6$, $p=0.003$). Both BAP and C-tx were inversely correlated with 25-OH vitamin D levels ($r=-0.47$, $p=0.014$), but osteocalcin was not. There was no correlation of any bone marker with iPTH level, prednisone dose, age, gender, dose or level of tacrolimus, serum calcium, phosphorous or creatinine, or use of a diuretic. Of note, FRAX scores were low for the population as a whole (3.00+/-2.7). No pts reported a history of fracture, despite age, persistent hPTH and hypoD, dose of prednisone, length of time since transplant (on prednisone) and length of time on dialysis.

We conclude, in our population of African American KTR's with hypoD and hPTH: 1. Bone markers are only mildly elevated if at all; 2. Ctx and BAP are inversely related to degree of hypoD, and time on dialysis, 3. There was no correlation between bone markers and degree of hPTH, creatinine, time since transplant (time on prednisone) or dose of Prednisone, 4. Despite hPTH and hypoD, no pts experienced fracture, and FRAX score was low, 5. The assumptions that all KTR's are at high risk for fracture and high turnover bone disease & should be treated prophylactly with bisphosphonates should be re-evaluated, especially in the African American population.

ESTROGEN WITHDRAWAL

Bahaa Abu Bakr, MBBS, Ochsner Clinic Foundation, New Orleans, LA; Nathan Bolton, BS, Ochsner Clinic Foundation, New Orleans, LA; Lillian Yau, Ph. D, Ochsner Clinic Foundation, New Orleans, LA; Brandy Panunti, MD, Ochsner Clinic Foundation, New Orleans, LA; Alan Burshell, MD, Ochsner Clinic Foundation, New Orleans, LA

Background: Estrogen withdraw (EW) is associated with both increased fracture risk and decreased BMD. WHI published results in October 2002 suggested that the risks of hormonal therapy were greater than the benefits; hence many women discontinued hormonal therapy. The objective of this study was to follow BMD changes that occur after estrogen cessation, the period between the three scan varied, thus results were expressed as BMD % change/year.

Methods: This is a retrospective observational study in metropolitan New Orleans using a database of more than 30000 Hologic DEXA scans including basic demographics, fracture history, family history, current osteoporosis medications, glucocorticoids and tobacco use. EW group inclusion criteria included a DEXA scan on estrogen and 2 scans off vs. estrogen treatment (ET) taking estrogen during all 3 scans.

Results: There were 67 subjects in the ET group and 127 in the EW group.

There was significant decrease in the mean annual rate of BMD change at the lumbar spine (LS) in the EW group from scans 1-2 of -1.12% /year and between scans 2 - 3 of -0.42%/year. There was a small, statically significant increase in the mean annual rate of BMD change in the ET group across the three scans. At the total hip (TH), there was significant decrease in the mean annual rate of BMD change in the EW group from scan 1- 2 of -1.36%/yr, and between scans 2- 3 of -0.56%/year. TH BMD was unchanged in the ET group across the 3 scans. The variability of LS and TH BMD was greater between scans 2-3 than between 1-2.

Conclusions: EW was associated with an accelerated rate of bone loss between scans 1-2 and a reduced rate between scans 2-3 at the LS and TH, but lower than most previous studies. ET group maintained TH BMD and increased lumbar spine BMD, the latter is similar to alendronate reports. Although BMD declined less between scans 2-3, the variability of response increased in EW. This suggests that some subjects were gaining BMD after the accelerated bone loss phase in agreement with previous studies of both estrogen and denosumab. The variability of response needs further study.

Z - SCORE AN IMPORTANT CLUE TO DIAGNOSIS OF CO-MORBIDITIES AND FRACTURE RISK

John A. Goldman, MD, John A. Goldman, MD PC, Atlanta, GA

Background: Z - scores are related to age matched relationships of Bone Mineral Density and can be used to suggest possible secondary causes of low bone density. This study reviews the presence of low Z - scores and relevance to diagnosis, risk of fracture and therapeutic implications for evaluation of patients in a solo rheumatology practice.

Methods: Patients with DXA evaluations indicating low Z - scores $\leq - 1.0$ during the previous 24 months were identified. The Encore 700 was used to review the practice database of 2240 patients.

Results: 38 people (31 women and 7 men) were identified with low Z - scores with age range from 86 to 29 years (Average 66 years).

15 patients had lumbar spine Z < 1.0 and three < - 2. Twenty-two had lumbar T-score lower than - 1.0 and 6 of - 2.5. Three patients had Z - scores of minus 1 or less with normal T scores.

22 had low Femoral neck Z-Scores < -1.0 and 4 < -2.0. Thirty-two had low femoral neck T scores of minus 1.0, and 10 had T score of - 2.5. Two had Z scores of minus one with normal T- scores. Two had had hip surgery.

16 patients had total hip Z scores < -1 and 4 $\leq - 2$. Twenty-eight had total hip T scores of less than - 1.0 and 4 $\leq - 2.5$. Three had Z scores < - 1 with normal T-scores.

A total of six of these 38 people had Z scores ≤ 1 with normal T-scores.

18 had osteoporosis having T-Score $\leq - 2.5$ at one or more sites including: the AP Lumbar Spine (6), Lateral lumbar spine (1), total hip (4), femoral neck (9), trochanter (1), or radius 33% (4). Five had T scores of minus 2.5 at more than one site [2 at three sites, 3 at 2 sites]. Twelve people had a fracture and five had 2 or more fractures.

Seven patients had FRAX > 20 % and eighteen had a hip FRAX > 3 %.

People with low Z-scores had a variety co-morbidities:

Inflammatory polyarthritis - RA, PSA, Sarcoid 13

Connective Tissue Disease including SLE, Sjogren's, PM, MCTD, Scleroderma, Raynaud's - 8

Crystal Induced arthritis including gout, Apatite arthritis and pseudogout - 4

Monoclonal Gammopathy including multiple myeloma 3

Hyperparathyroidism 2

Guillian Barre - 2

Conclusion:

1. Patients with low Z - scores are patients at increased risk.
2. This study confirms that the presence of a low Z - score \leq minus 1.0 is an indicator of a risk for secondary co-morbidities and secondary causes of osteoporosis.
3. A Z - score of \leq minus 1.0 is an indicator of a higher risk of fracture.
4. A Z - score \leq minus 1.0 of the femoral neck is an indicator of a 3 % or greater risk for future hip fracture in the next 10 years.
5. Low Z - scores should be a regularly reported in DXA reports and their implications indicated.

Low Z - scores: site of changes in 38 patients and association with FRAX risk scores.

Site of Low Z score in 38 patients	Lumbar Spine	Femoral neck	Total Hip
Z score ≤ -1	16	22	16
Z score $\leq - 2$	3	4	3
Z score $\leq - 1$ and normal T score	3	2	3
Major FRAX $\geq 20\%$ and Z score ≤ -1	3	5	3
Hip FRAX $\geq 3\%$ and Z score $\leq - 1$	7	12	7

HIGH PREVALENCE OF NON-HIP NON-SPINE FRACTURES AMONG POST MENOPAUSAL WOMEN WITH RHEUMATOID ARTHRITIS

Maria Rell-Bakalarska, MD PhD, Rheuma Medicus Rheumatology and Osteoporosis Outpatient Clinic, Warsaw, Poland; Edward Franek, Prof, Department of Internal Diseases, Endocrinology and Diabetology CSK MSWiA, Warsaw, Poland; Krzysztof Rell, MD PhD, Emergency Ward, Infant Jesus Clinical Hospital - Injuries Treatment Center., Warsaw, Poland; Dariusz Gozdowski, bachelor, Department of Applied Statistics and Bioinformatics, Warsaw University of Life Science, Warsaw, Poland

Purpose: This study aimed to assess a prevalence of non-hip non-spine fractures in rheumatoid arthritis (RA) patients.

Methods: Into this cross-sectional study 534 consecutive rheumatoid arthritis patients from Outpatients Department of the Institute of Rheumatology in Warsaw were included. Mean age of the patients was 64.1 ± 9.4 years, BMI 26.5 ± 4.4 kg/m², RA duration 13.7 ± 9.9 years. In all patients prevalence of clinical low-energy fracture was assessed. Only fractures sustained after RA diagnosis were included. In case of clinical spine fractures a radiogram was required for diagnosis.

Results: A prevalent fracture was diagnosed in almost 42% of patients. Non-hip, non-spine fractures were most frequent (60.3% of all fractures), occurring in over 30% of patients, whereas spine fractures in 13.1 % and hip fracture only in 3,2% of patients. The most prevalent non-hip, non-spine fractures was Colles fracture (14% of patients). Patients with non-hip, non-spine fractures were younger (64.5 ± 9.4 vs. 69.1 ± 7.9 years, $p=0.003$) but time of RA duration and BMI was similar.

Conclusions: Non-hip non-spine fractures are most frequent type of fracture in RA patients.

SECONDARY CAUSES OF OSTEOPOROSIS IN 869 PATIENTS TREATED FOR OSTEOPOROSIS IN ROMANIA

Catalina Poiana, Associate Professor of Endocrinology, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; Carmen Barbu, Assistant Professor of Endocrinology, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; Alina Roman, MD, Elias University Hospital, Bucharest, Romania; Dariana Ionita, MD, Elias University Hospital, Bucharest, Romania; Aurelia Stefanopol, MD, Elias University Hospital, Bucharest, Romania; Cristina Stefan, MD, Elias University Hospital, Bucharest, Romania; Magda Gascan, MD, Elias University Hospital, Bucharest, Romania; Mara Carsote, MD, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; Simona Fica, Professor of Endocrinology, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

Aim of the study: To evaluate the prevalence of secondary causes of osteoporosis among patients treated for osteoporosis.

Materials and methods: 869 women with osteoporosis (age between 36 and 86, mean 64.7), treated through National Programme of Osteoporosis in 2008-2009 in two endocrine departments from Bucharest, Romania. They were diagnosed with osteoporosis according to WHO criteria and medical records contained also clinical and endocrine evaluation at the baseline. We retrospectively analyzed their medical records for secondary causes of osteoporosis and fractures.

Results: 221 patients (25%) were already diagnosed with a disease known to be cause of osteoporosis when they were referred. The most frequent situation was premature ovarian failure (40% from the cases) followed by hyperthyroidism with 19% of the cases, secondary hyperparathyroidism with 16% and primary hyperparathyroidism with 8%. All other causes (rheumatoid arthritis, systemic lupus, Cushing's disease, treatment with aromatase inhibitors or anticonvulsants), are under 5% level. After evaluation at baseline, the percent of patients with primary hyperparathyroidism increased to 24 %, and secondary hyperparathyroidism to 34%; hyperthyroidism increased also to around 21%, all secondary causes after careful evaluation being responsible for almost 64% of the cases.

22% from the study group patients had prevalent fracture at baseline, the highest percentage being among aromatase inhibitors users (34%), followed closely by premature ovarian failure, rheumatoid arthritis and hyperthyroidism (29-25%).

Conclusion: Secondary causes could be found on almost 64% from patients with osteoporosis. Our results suggest the importance of careful evaluation at baseline to improve the outcome of the treatment by treating associated diseases. On the other hand, this high prevalence of secondary causes of osteoporosis is raising a problem for proper evaluation of fracture risk in this specific population.