**Session Title**

*DXA in Pediatrics:*
- **Peak Bone Mass**
- **Evaluation of HIV-Related Bone Mineralization Problems in Infants and Children**

**Time**

4:50 - 5:50 PM

**Location**

Concourse 1

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**Babette Zemel PhD**

**Summary:** Peak bone mass is a concept based on a life cycle model of bone acquisition during childhood, stability of bone mass in young adulthood, and loss of bone mass later in life. Operationally it is thought of as the maximum amount of bone attained in young adulthood. However, studies reveal that the timing of peak bone mass is site specific. In addition, bone mass is only one factor determining bone strength and “peak bone strength” has not been characterized. It is widely held that maximizing bone acquisition during growth will result in optimal peak bone mass and prevent osteoporotic fractures later in life, although this supposition has a meager empirical basis. Limited longitudinal studies suggest that optimizing diet, physical activity and overall health during childhood to promote optimal peak bone mass can be successful, provided these strategies are maintained.

**CME Objectives:**

1. Define peak bone mass and when is it attained
2. Determine accrual of peak bone mass and its impact on adult fracture

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**Biographic Sketch**

Babette Zemel is an Associate Professor of Pediatrics at the University of Pennsylvania School of Medicine and Director of the Nutrition and Growth Laboratory at the Children’s Hospital of Philadelphia. She is also Associate Program Director of the Clinical and Translational Research Center at The Children’s Hospital of Philadelphia. Her global area of interest is growth and nutrition and she has been involved in pediatric bone density research for over fifteen years. She served on the ISCD Pediatric Task Force to develop the ISCD Pediatric Official Positions.

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**Speaker Disclosure of Commercial Interest**

Nothing to Disclose

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**George Siberry MD, MPH**

**Summary:** HIV infection and its treatment are linked to low bone mineral density (BMD) and increased fractures in adults. Assessing the impact of HIV infection and its treatment is more challenging in the context of growing and developing bones in fetuses, infants and children. The impact on future peak bone mass and fracture risk is unknown. Established pediatric normative BMD data permit use of DXA assessments to identify HIV-infected children with low BMD and track their response to interventions through years of expected rapid bone mineral accrual. HIV-uninfected fetuses and infants of HIV-infected women may also be at risk of poor bone outcomes related to exposures to HIV drugs during pregnancy and breastfeeding. Assessing potential bone effects in such exposed infants is hampered by lack of bone mineral reference standards for infants. Infant BMD assessments by standardized DXA techniques can be used to compare average BMD results of infants with and without specific maternal HIV drug use as evidence of potential infant BMD effects of maternal HIV drug use.

**CME Objectives:**

1. Understand the need to study HIV-related bone loss in children
2. Consider the unique challenges of using DXA with infants and young children
3. Recognize bone-related affects of HIV in children
Biographic Sketch

George Siberry is a Medical Officer at the Pediatric Adolescent Maternal AIDS (PAMA) Branch of the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health (NIH) in Bethesda, Maryland (USA). He develops research studies focused on prevention, treatment and complications of pediatric and adolescent HIV infection through several domestic and international HIV research networks. He is also the primary physician for children and youth with HIV infection at his weekly clinic in the Johns Hopkins University (JHU) Department of Pediatrics. He received his undergraduate degree from Brown University, his MD from the JHU School of Medicine, and his MPH in International Health from the JHU Bloomberg School of Public Health. He completed his residency training in pediatrics and fellowship in pediatric infectious disease at the JHU School of Medicine before joining the JHU faculty in 2003 as Director of the Harriet Lane Clinic and then the NIH in 2008. His current research interests are primarily focused on vaccine-preventable infections and bone health in HIV-infected and perinatally HIV-exposed infants and children.

Stock Ownership:

GE

Evaluation for Babette Zemel PhD

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<td>Presentation provided strategies to implement into your practice</td>
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Comments on the Session or Speaker:

What related topics and or speakers should be considered for next year’s Annual Meeting?
What is Peak Bone Mass (PBM)?

- Maximum bone mass attained in adulthood
- The amount of bone acquired when bone gain ceases or plateaus
  - Population: Based on cross-sectional studies or limited longitudinal studies
  - Individual
    - Full genetic potential is achieved
    - Maximal bone mass is acquired

Conceptual Model of PBM

- Bone accrual is rapid in childhood and adolescence, reaching a peak in young adulthood.
- Bone mass is stable in adulthood until it begins to decline after menopause in women and somewhat later in men.
- Failure to meet one’s full genetic potential for PBM leads to earlier onset of low bone mass in the “fracture risk zone” in late adulthood

What are the issues?

- How is PBM identified?
- What do we know about the age PBM?
- Is it site specific?
- Does PBM = maximum bone strength?
- What factors influence PBM?
- Does PBM affect lifelong fracture risk?
Bone Acquisition During Adolescence

- Bone accretion is fairly slow in childhood, but increases sharply in adolescence.
- Peak bone accretion follows peak height velocity (adolescent growth spurt).

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<tr>
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<th>Age at Peak Ht Velocity, y</th>
<th>Age at Peak Bone Accrual, y</th>
<th>Peak Bone Accrual g/y</th>
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<tr>
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<td>11.77</td>
<td>12.54</td>
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<tr>
<td>Boys</td>
<td>13.44</td>
<td>14.05</td>
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Summary of Age at Peak Bone Mass

- Most rapid period of bone acquisition is after the period of peak height growth.
- Changes continue into adulthood.
- Estimates of age at PBM have a wide range.
- Varies by site.

Does PBM = Bone Strength?

- Strength is determined by bone mass, density, geometry, micro-architecture, turnover, microfracture repair, and mineralization.
Summary of Development of Peak Bone Strength

- Dynamic changes in bone compartments through adolescence and young adulthood
- Trabecular and cortical bone strength have very different trajectories
- Little is known about how to define “peak strength”

What factors influence PBM?

- Non-modifiable
  - Body size
  - Timing of sexual maturation
  - Genetics
  - Disease related
    - Inflammation
    - Malabsorption
    - Immobility
    - Treatment effects

What Factors Influence PBM?

- Modifiable factors:
  - Diet
    - calcium, protein, vitamin D
  - Physical activity
    - weight-bearing
    - critical periods?
- Other lifestyle factors:
  - Smoking
  - Pregnancy, contraceptives
  - Obesity
TENOFOVIR

- Acyclic nucleotide analogue with activity against HIV-1, HIV-2, and hepatitis B virus
- Tenofovir (TFV): large, negatively charged (anionic) phosphonate that is not well absorbed
- Tenofovir disoproxil fumarate (TDF): chemically altered for oral administration
- TDF converted to TFV in the body (blood, breastmilk, urine)
- TFV converted intracellularly to active form: TFV-diphosphate
- First-line agent as part of combination ART for treatment of HIV infection in adults

Indirect Effect of Tenofovir on BMD

- Tenofovir-associated Proximal tubulopathy (PT) Mechanism
  - TFV eliminated by active tubular secretion + glomerular filtration
  - TFV accumulates in prox tubule via direct transport by human organic anion transporter 1 (hOAT1) on basolateral side of prox renal tubular cells
  - Secreted via the multidrug-resistance protein (MRP2) on apical side of proximal tubular cell. (Ritonavir inhibits MRP2.)
  - Mechanism of tubular toxicity unclear (direct effect? Mitochondrial depletion?)
- Effects of PT on bone and mineral homeostasis
  - Impairment of selective reabsorption (calcium, phos) of filtrate
  - ↑ urinary calcium and phos losses
  - ↑ (compensatory) bone resorption & impaired mineralization of forming bone
- May be exacerbated by PT-related impairment of 1’ hydroxylation of vitD

Pediatric HIV and Bone

- Prevalence of low BMD
  - Most studies compare to small “normal” control group
  - Pediatric HIV AIDS Cohort Study (PHACS): Among over 400 perinatally HIV-infected 7-16 year-olds, LS Z-score (Baylor norms)
    - < -1 in 20%, < -1.5 in 10%, < -2.0 in 5%
  - Cross-sectional studies with controls Vs Longitudinal
- No clear evidence of increase in fractures
  - Oldest perinatally infected only in 20s... what about in 40s?
- HIV-related cofactors
  - Growth impairment, Pubertal delay, Disrupted renal function, Poor nutrition – these cofactors likely ↓ with ART
  - ART in general and specific agents
- Sex and Puberty
  - Availability of longitudinal, sex-, race- and age-adjusted norms
  - Particular concern about Tenofovir
Infants of HIV infected women

- Maternal HIV infection and inflammatory state
- Direct exposure to maternal ARVs
  - Transplacental
  - Through breastmilk
- Indirect effect of maternal ARV
  - Maternal mineral homeostasis disrupted after ART initiation (HIV often diagnosed in pregnancy)
  - Mineral homeostasis disrupted specifically by tenofovir
  - ? Effect on breastmilk (international)
- Applies to HIV-infected and HIV-uninfected infants

Infant Bone Mineralization Status Norms

- Norms established for DXA-based bone density measurements in adults and children as young as 7 years old Kalkwarf J Clin Endocr Metab 2007
  - Hologic QDR4500A/W and Delphi A models
- Infant reference ranges established on older pencil-beam technology DXA scanners
- No infant reference standards or norms on fan-beam DXA scanners

Other Bone Mineralization Measurements in Infants

- Plain X-rays: insensitive
- Detects 20-40% mineral loss (osteopenia)
- Markers of bone turnover (BSA/PTH, DPA, Osteocalcin, CTX, D-pyr)
  - Wide range of normal in (growing) infants and children
- Peripheral CT (pCT)
  - No standards for infants. High radiation dose. Limb must be immobilized.
- Ultrasound Speed of Sound (SOS)
  - No radiation, easy to immobilize limb while scanning it.
  - Some normative data but no clear standards.
  - Limited to long bone assessment
  - May be harder to standardize data acquisition among users
- NONE (including DXA) well defined to predict fractures
Infant DXA Outcomes

- Outcome: Comparison of average BMC/BMD by Exposure
  - Not “normal” vs “abnormal”
  - Base sample size on detecting 0.5-1 SD difference
  - Adjust for relevant covariates in analysis (gestational age, birthweight, WAZ, LAZ, race, age)
- Standardize technique and equipment to reduce variability
  - Limit multicenter study to one scanner mfr
  - Infant-specific software - standardize acquisition
- Apex 3.1: infant spine
- Infant whole-body software
- Hologic QDR4500A/W, Discovery A/W, Delphi A/W
- Central DXA analysis
- Phantom

Newborn Bone Mineral Assessment By Ethnic Group


- LS BMC in 50 infants by ethnicity, matched for vitamin D status. 22 white vitD sufficient, 10 white vitD insufficient (<32.5 nmol/L), 10 First Nations, 8 Asian.
- Infant DXA for comparing infant bone mass among groups of infants with different “exposures” (ethnicity)
- Lower LS BMC for Asian infants than white or First Nations infants, even after adjustment for body size. Same pattern for LS BMD.
- No differences for Whole Body or Whole Femur BMC

Effect on Bone Mass of PreTerm vs. Term Formula at Discharge for PreTerm Infants

Picaud J Pediatr 2008

- PreTerm: <33wk, <1750g
- Randomized to Preterm (PF) vs Term Formula (TF) at discharge
  - Higher calcium, phos, protein and lipid in PF
  - N= 23 PF, 26 TF
- Hologic QDR4500 with infant whole-body software
  - WB BMC – 0, 2, 4 mos
- Baseline: No diff BMC, BMD
- Significantly greater BMC and BMD at 2 months and 4 months after discharge

BMC Effect of Earlier vs Standard Nutrition in PreTerm Infants <1200g

- WB, LS and Femur BMC
- At Term Age
- Factorial Design
  - Early Amino Acids
  - Early Min Enteral Feeds
  - Both
  - Std Timing
- Higher LS and Femur BMC with early MEF


Limitations to Infant DXA Approach

- Underestimation of BMD/BMC in undergrown infants
- Relative low mineralization (normal) of infant bones makes accurate/reliable bone border marking difficult
- Infant movement (sedation not feasible)
  - Feed and swaddle for whole-body; newborns only
  - Physically restrain for LS DXA; 0-18 months old
  - "Infants were clothed in gowns without snaps, zippers, or buttons and were swaddled in a thin cotton blanket to minimize movement. All infants were scanned with clean dry diapers and while sleeping." (Weiler 2006)
  - Hologic DXA scanner manuals indicate WB validation down to 6lbs, but Hologic confirms adequate data/experience at least down to 5lbs.
- Limiting allowed scanner excludes some sites
- Wide variation in acceptability in multisite study
  - IRB: no appreciable risk → unwarranted risk
  - Site experts: believers and non-believers
Didier Hans PhD, CCD

Summary: The WHO Collaborating Centre at Sheffield has developed FRAX which provides algorithms for the assessment of fracture probability using risk factors with or without the results of BMD testing (www.shef.ac.uk/FRAX/). Clinical risk factors included age, sex, previous fragility fractures, a family history of fracture, rheumatoid arthritis, smoking, alcohol and the use of oral glucocorticoids. The risk of fracture varies markedly around the world so that FRAX models need to be calibrated to the epidemiology of the country in which they are to be used. FRAX models are available for 31 different countries, including the US (www.shef.ac.uk/FRAX/)

Although FRAX has influenced guideline development, questions remain concerning the use of FRAX without BMD, the limited information on dose-response of exposure variables (e.g. dose of glucocorticoids), the exclusion of some clinical risk factors (e.g. falls risk) and the inability to take account of BMD results at sites other than the femoral neck. The presentation provides the rationale for the ISCD-IOF position statements on these matters.

CME Objectives:

1. Understand the ISCD official positions on use of the FRAX fracture prediction tool
2. Appreciate the strengths and limitations of the FRAX tool as it applies to treatment decision making
3. Implement use and applications of the FRAX tool into your clinical practice

Biographic Sketch

Didier Hans is currently Head of the Research and Development in Center of Bone diseases at the Bone and Joint Department, at the University of Lausanne, Switzerland. He is also the President of the International Society of Clinical Densitometry, member of the Scientific Advisory Committee of the International Osteoporosis Foundation and is a co-founder of Synarc (USA) and Ascendys (CH). He has 20 years of Clinical Research experience and is recognized as an expert on the cutting edge of Dual-Energy X-Ray Absorptiometry (DXA) and Quantitative Ultrasound Systems (QUS) technologies. He has particular expertise in validating and optimizing new technologies as well as developing DXA and ultrasound protocol, quality assurance and training of research assistants for large, multi-center clinical trials. Some of his latest developments are related to the ten year probability model for quantitative ultrasounds and the validation of a new bone micro-architectural score (TBS) extracted from 2D DXA image. Dr. Hans earned his PhD in human biology and medical physics from Claude Bernard University in Lyon, France.

John Kanis MD, FRCP

Biographic Sketch

John A. Kanis is Emeritus Professor in Human Metabolism, and Director, World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. He is the President of the International Osteoporosis Foundation. Prof. Kanis' research interests are largely related to disorders of skeletal metabolism including osteoporosis, Paget's disease of bone,

Speaker Disclosure of Commercial Interest

Consulting: Abiogen, Amgen, Bayer, Besins-Iscovesco, Biosintetica, Boehringer Ingelheim, Celtrix, D3A, EFPIA, Gador, GE, GSK, Hologic, Kaiser, Kissei, Leo Pharma, Lilly, Medtronic, Merck, Merlin Ventures, MRL, Novartis, Novo Nordisk, Nycomed, Stock and Ownership Interests: Synarc, Ascendys and TBS Patent from Medimaps
hyperparathyroidism, renal osteodystrophy and neoplasia affecting the skeleton. Contributions to research include cell biology, histomorphometry of bone, assessment and treatment of bone disorders, guideline development, health technology assessment, epidemiology and health economics. He is the Editor of Osteoporosis International and serves on the editorial board of several journals. He is the author of more than 800 papers, chapters and books on bone disease and metabolism. His current major interest is in the development of risk assessment algorithms and the formulation of practice guidelines in many regions of the world.


Research: Amgen, EFPIA, GSK, Kaiser, Eli Lilly, Novartis, Pfizer, Sanofi-Aventis, Servier, Springer, Warner Chilcott, Arthritis and Rheumatism Society, Medical Research Council, National Osteoporosis Society

Stock Ownership: D3A, ProStraken, Shire UK

Other: Officer in European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis, Research Agreement with Government of Manitoba, Board member of the International Bone & Mineral Society, Presient of IOF, Research Agreement with Singapore Ministry of Health, Member of National Osteoporosis Guideline Group (UK) and National Osteoporosis Society (UK) and Patron of Osteoporosis 2000

William D. Leslie MD, CCD, MSc, FRCPC

Biographic Sketch

William Leslie is Professor of Medicine and Radiology at the University of Manitoba. He obtained his specialty training from the University of Manitoba and McGill University, qualifying in Internal Medicine in 1989 and in Nuclear Medicine in 1990. He is clinically active in nuclear medicine and thyroid cancer, and has research interests in osteoporosis testing and other nuclear diagnostic techniques including PET scanning. Dr. Leslie joined the Scientific Advisory Council of Osteoporosis Canada in 1997. He was co-lead on the “2010 Clinical Practice Guidelines for the Diagnosis and

Speaker Disclosure of Commercial Interest

Advisory Board: Novartis, Amgen, Genzyme

Research: Merck Frosst, Genzyme, Amgen, sanofi-aventis, Proctor & Gamble

Speakers’ Bureaus: Merck Frosst, Amgen
Management of Osteoporosis in Canada”. He also contributed to the updated Osteoporosis Canada vitamin D recommendations and earlier reports “Recognizing and Reporting Vertebral Fractures” and “Recommendations for Bone Mineral Density Reporting in Canada”. He is currently Chair of the Scientific Advisory Council and Past Chair of the Guidelines Committee for Osteoporosis Canada, on the Board of the International Society for Clinical Densitometry, Director of the Manitoba Bone Density Program, and Co-Director of the Winnipeg PET Imaging Centre.

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**Comments on the Session or Speaker:**

**What related topics and or speakers should be considered for next year’s Annual Meeting?**
### Probability of Osteoporotic Fracture at Age 65

#### Men

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#### Women

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<td>30</td>
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### Ten Year Probability of Hip Fracture in Women

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<tr>
<td>Sweden</td>
<td>8</td>
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<tr>
<td>Taiwan</td>
<td>10</td>
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FRAX®: VAH Fracture Risk Assessment Tool

- **Calculation Tool**
  - **Questionnaire**
    - Age: 65 years
    - Prior fracture
    - Family history
    - Glucocorticoids
  - **Weight Conversion**
  - **Height Conversion**

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FRAX®: World Health Organization Framework

- **US Caucasian, no CRF, BMI=24**
  - Probability of osteoporotic fracture* at age 65
  - Probability of hip fracture in women

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FRAX®: International Society for Clinical Densitometry (ISCD)

- **Position Statements**
  - **FRAX®**
  - **USFRAX**
  - **ISCD**

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*Hip, spine, humerus, forearm*
"FRAX" without BMD selects women with low BMD

Less than 1% of women selected for treatment with FRAX but without BMD have a T-score >1.0 SD

Vertebral fracture increases the risk of subsequent vertebral fracture

Incidence (%) of vertebral fracture increases with the number of previous vertebral fractures at baseline.

Glucocorticoids and vertebral fracture

Incidence (%) of vertebral fracture increases with dose and age in both men and women.
### Adjustments (% of 10-year probabilities of major osteoporotic fracture by dose of glucocorticoids

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*No adjustment*

Kanis JA et al, 2011, Osteoporos Int, in press

### Falls should be included in FRAX

**For**
- A strong risk factor for fracture
- Included in other instruments (Garvan, QFracture)
- May characterise reversibility of risk (McCloskey)

**Against**
- May not identify reversibility of risk (McLung)
- Is already incorporated in FRAX, though not as an input variable
- No easily used international standardised question – meta-analysis
- FRAX does better than falls questionnaires (Toyabe and STRATIFY)
- A problem in integration of data

### BMI and fracture risk

- RR (20 v 25 kg/m²)


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### Kanis: FRAX and the New ISCD Position Statements
T-score discrepancies between
FN and LS BMD

Manitoba cohort: Referral population of 40,000 men and women
Followed for 10 years

Increase/decrease FRAX estimate for a major fracture by
one-tenth for each rounded T-score difference between LS and FN

Patients identified at moderate risk (10-20% FRAX probabilities)
Summary: The adult human skeleton is made up of 213 separate bones, each of which is sculpted by a process called modeling and each of which is constantly renewed by a process termed remodeling. Remodeling is accomplished by a group of different cell types collectively termed the bone remodeling unit (BRU). Remodeling occurs in four distinct phases: activation, resorption, reversal, and formation. As bone formation continues, osteoblasts are buried in the matrix becoming osteocytes. Although incarcerated in the matrix, the osteocytes maintain intimate contact with one another, as well as with the cells on the bone surface, by means of gap junctions between the cytoplasmic processes that extend through canaliculae. Each osteocyte becomes part of a large, three-dimensional, functional syncitium, which can “sense” a change in the mechanical properties of the surrounding bone and transmit this information to the cells on the surface to initiate or regulate bone remodeling when necessary. It has been suggested that bone cells behave like a neuronal network.

CME Objectives:
1. Understand mechanism and process of bone remodelling
2. Determine how bone remodeling effects fracture risk

Biographic Sketch
David W. Dempster is Professor of Clinical Pathology at Columbia University in New York. He obtained his PhD from the University of Glasgow in Scotland and completed postdoctoral studies in Switzerland and France. Dr. Dempster is a founding member of the International Society of Musculoskeletal and Neuronal Interactions. He is a Past President of the International Society of Bone Morphometry and a member of the Scientific Advisory Council of the National Osteoporosis Foundation. In addition, Dr. Dempster is a Fellow of the Royal Microscopical Society. Several of Dr. Dempster’s images of bone structure have been displayed at the Smithsonian Institution in Washington, DC. Dr. Dempster has published over 175 research papers on the pathophysiology and treatment of bone disease.

Speaker Disclosure of Commercial Interest
Consulting: Amgen, Eli Lilly, Merck
Speakers’ Bureau: Eli Lilly, Amgen, Genentech
Research: Eli Lilly

Evaluation for David W. Dempster PhD

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What strategies will you implement?

Comments on the Session or Speaker:

What related topics and or speakers should be considered for next year’s Annual Meeting?
Functions of Remodeling

• Calcium homeostasis (long-term)
• Repair of microdamage
• Acid/base balance
• Release growth factors
• Provide reservoir of labile mineral (short-term homeostasis)
• Replace osteocytes
• ???
Functions of the Osteocyte

- Mechanosensation and targeting microdamage repair
- Regulation of bone resorption and formation with RANKL and SOCS
- Short term mineral homeostasis with TRAP
- Phosphate metabolism with FGF23

Mechanisms of Cancellous Bone Loss


MICROARCHITECTURAL CHANGES IN OSTEOPOROSIS

© 2000, David W. Dempster, PhD.
**Session Title**: Bone and Fat: Paradoxes and Potentials  
**Time**: 11:00 - 12:00 PM  
**Location**: Chopin Ballroom  

**Cliff Rosen MD**

**Summary**: For the last three decades it's been recognized that fractures were a direct function of body mass index. However, a closer look at that correlation reveals that most of that curve is driven by low BMI related to fractures. At the upper end of the regression curve, there is a tick downward as BMI exceeds 30 and if you correct for BMD the correlation is much weaker. Studies from several laboratories have shown that children who are obese are at greater risk for radial fractures and that trabecular bone volume is lower in children and adults with the metabolic syndrome. The pathogenesis of these complex relationships will be discussed with an eye toward future directions for research in mice and man.

**CME Objectives:**  
1. Determine the relationship between brain, fat and bone physiology  
2. Understand the endocrine relationship  
3. Explore future potential influences within this complex inter-relationship

**Biographic Sketch**

Clifford J. Rosen is the Director of Clinical and Translational Research and a Senior Scientist at Maine Medical Center’s Research Institute. His other current positions include Adjunct Staff Scientist at the Jackson Laboratory, and Professor of Medicine at Tufts University School of Medicine. Dr. Rosen is the founder and Former Director of the Maine Center for Osteoporosis Research and Education. Dr. Rosen has overseen numerous phase II and III clinical trials, funded both privately and through the NIH. He is a member of the FDA Advisory Panel on Endocrinologic and Metabolic Drugs and a former chairperson of that committee. He was Permanent Chair of the NIH Review Panel for Skeletal Biology and Bone Diseases for 2002-2004, and is currently a member of the NIAMS Scientific Advisory Board. Dr. Rosen’s research interests include the genetic regulation of insulin-like growth factor relative to skeletal metabolism, PTH as an anabolic therapy, and the relationship between marrow adipogenesis and osteoblastogenesis.

**Evaluation for Cliff Rosen MD**

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**Comments on the Session or Speaker:**

What related topics and or speakers should be considered for next year’s Annual Meeting?
**Summary**

- Bone and Fat arise from the same stem cell
- Fat can have positive or negative effects on bone mass
- Brown fat may be very important for skeletal remodeling
- The sympathetic nervous system links fat with bone turnover

**Osteoblasts and Adipocytes arise from the same progenitor cell**

**Body weight may be related to fracture or BMD as a positive or negative determinant.**
**BMI vs BMD??**

- von Muhlen, OI, 2007: 18:1337 Rancho Bernardo Cohort: 1096 men and women: MS positive relationship to hip BMD, but greater fracture risk; adjusting for BMI, MS associated with lower BMD

- Tang J Clin Endocrinol Metab 2007-2751-7: 4500 Caucasian individuals: Several shared genomic regions for body fat mass and BMD

- Zhao L, J Clin Endocrinol Metab 2007:1640 4500 Caucasian individuals: Adjusting for body weight, fat mass inversely associated with BMD.

- Fragility Fracture Registry- England: 50% of women were obese or morbid obese Compston 2009 JBMR

**Summary**

- Obesity and Osteoporosis are growing epidemics
- Bone and fat cells arise from the same stem cell and interact with each other—Positive and negative regulation
- There is genetic linkage between obesity and osteoporosis
- PPARG is at the center of the interaction between bone and fat
- Therapies that alter OB adipocyte interactions may have promise
**Session Title**

Medical History for Technologists: How to Obtain Accurate Information for FRAX

**Time** 11:00 - 12:00 PM

**Location** Concourse 1

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**Summary:** History taking is a skill that takes time and training. It is important to prepare in advance so you have a good understanding of what information you need to gather before your start. Remember taking a history is a formal structured interview with the patient. In order to get the information you need in an efficient and professional manner, it is important to put the patient at ease, communicate slowly and clearly, and be non-judgemental. Make sure your patient understands the questions. Do not rely solely on the patient’s answers; verify some information from other sources if you can. There are 12 variables you can use to run the FRAX® tool. Age, gender, height and weight are essential, while others are optional. The importance of each variable will depend on the region of the globe you live in, what you are trying to predict, the patient demographics and what other characteristics you are entering. Remember an accurate history will give reliable results.

**CME Objectives:**

1. Take a medical history
2. Understand the FRAX variable definitions
3. Determine risk factors with greatest impact
4. Apply clinical integration methods

---

**Biographic Sketch**

John J. Carey is a Consultant Physician in Rheumatology and Medicine at Galway University Hospital and Clinical lecturer in Medicine, National University of Ireland, Galway. Dr. Carey is a graduate of University College Dublin Medical School (MBBChBAO), and Case Western Reserve University, Cleveland, Ohio (MS). He completed his clinical and research training in medicine and rheumatology at Boston University Medical Centre, Massachusetts and The Cleveland Clinic, Cleveland, Ohio. He has a subspecialty interest in osteoporosis and runs an osteoporosis service, fracture liaison programme and bone densitometry service with colleagues. His patient oriented clinical research focuses on studies of imaging and patient care pathways.

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**Speaker Disclosure of Commercial Interest**

**Consulting:** Eli Lilly, Wyeth, Merck Sharpe & Dhome, Novartis, Riche, Bristol Myers Squibb, Glaxo SmithKline, Amgen

**Speakers’ Bureaus:** Proctor & Gamble, Alliance for Better Bone Health, Merck Sharpe & Dhome, Novartis, Eli Lilly, A. Menarini Pharmaceuticals, Bristol Myers Squibb, Roche

**Research:** Proctor & Gamble, Abbott Laboratories, Wyeth, Centocor, Eli Lilly, Merck Sharpe & Dhome, Proctor & Gamble, Wyeth

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**Evaluation for John Carey MD, CCD**

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**Comments on the Session or Speaker:**

What related topics and or speakers should be considered for next year’s Annual Meeting?
Taking an Accurate History

- Definition: A structured patient interview
- History taking takes time, training and a level of skill
- Open communication
- Put patient at ease
- Non-judgemental
- Be professional

Get the basics right, everything else will follow

- Does your patient speak the same language?
- Is your patient hard of hearing or vision?
- Does your patient have any other form of cognitive impairment?
- Does your patient understand the question?

Clear Communication

Ideally your patient your questions should be:
1) Short
2) In simple easy to understand language
3) Relevant to the information you are trying to gather
4) Non-judgemental e.g. alcohol and tobacco use

Remember to speak slowly and repeat or rephrase if necessary
But you need to gather information

• Best to start with general questions
• Move to more specific questions once patient at ease
• Still have to explain DXA and what is happening
• Some things won’t necessarily be easy…
• Reliance on patient history alone is not sufficient but a good starting point

What is FRAX®?

◊ A prediction tool which can be used to estimate an individual’s fracture risk

◊ Gives a mean estimate of the 10 year risk of:
  1) “Any” Fracture: clinical spine, humerus, hip and forearm.
  2) Hip Fracture


FRAX® Variables

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<tr>
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<td>◊ Age</td>
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<td>◊ Weight</td>
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www.sheffield.ac.uk/FRAX/
FRAX® The impact of any given risk factor depends on:

1. Region from whence person you are trying to evaluate is residing...
2. What you are trying to predict: hip Vs other
3. Patient characteristics e.g. men Vs Women
4. Presence or absence of other risk factors, e.g. secondary osteoporosis and BMD.

Using the FRAX® Tool

- Remember to correctly select the region you live in....
- Remember you must enter patient age, gender, height and weight to run the tool, other information is optional.
- For the clinical risk factors a yes or no response is asked for. If the field is left blank, then a "no" response is assumed.
**Session Title**

**Poster / Abstract presentations**

- **Tristan Blackburn:** Utility of Spine Bone Mineral Density in Fracture Prediction, a Retrospective Analysis
- **Jessie Libber:** Technical Excellence is Required for Total Body DXA Acquisition and Analysis
- **Lorena Marquez:** Long-term clinical studies face common and challenging quality issues with device relocations and upgrades
- **Harry Genant MD:** Denosumab Significantly Improves Total, Trabecular, and Cortical Estimated Strength at the Hip and Spine Over the Duration of the FREEDOM Trial
- **Joseph Wilson:** Simplified four-compartment body composition model using dual-energy x-ray absorptiometry and total body water

**Time**

1:30 - 2:30 PM

**Location**

Grand Ballroom

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**CME only:** 1.0 Credit

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<td>Jessie Libber</td>
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<td>Lorena Marquez</td>
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<td>Harry Genant</td>
<td>Consulting Fees: GSK, Roche, Amgen, Merck, Eli Lilly, Pfizer, Novartis</td>
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**Evaluation for Tristan Blackburn**

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What strategies will you implement?

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**Evaluation for Jessie Libber**

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What strategies will you implement?
**Evaluation for Lorena Marquez**

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**Evaluation for Harry Genant MD**

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**Comments on the Session or Speaker:**

What related topics and or speakers should be considered for next year’s Annual Meeting?
Bess Dawson Hughes MD

Summary: This presentation will address the rationale for setting vitamin D intake recommendations, the importance of vitamin D for bone and muscle, the optimal serum 25-hydroxyvitamin D concentration, and a comparison of different guidelines for vitamin D adequacy.

CME Objectives:
1. Distinguish new guidelines from various organizations
2. Evaluate the evidence to determine what is likely related to vitamin D versus weaker observational associations
3. Clinically evaluate vitamin D status
4. Identify findings related to skeletal and extraskeletal effects of vitamin D
5. Evaluate current suggestions for vitamin D adequacy

Biographic Sketch
Bess Dawson-Hughes is an endocrinologist and Professor of Medicine and Director of the Bone Metabolism Laboratory at the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University. Dr. Dawson-Hughes is a member of the Board of Trustees and past-president of the National Osteoporosis Foundation. She currently is a trustee and the Secretariat General of the International Osteoporosis Foundation. Her research is directed at examining ways in which calcium, vitamin D, protein, and other nutrients influence bone, muscle, and risk of fracture.

Consulting:
Amgen, Cytochroma, Danone, Eli Lilly, Merck, Wright

What related topics and or speakers should be considered for next year’s Annual Meeting?
Objectives

- Potential functional indicators of adequacy
  - Falls
  - Fractures
  - Other potential indicators
- Target 25OHD level
- Guidelines to reach target
- Clinical evaluation and treatment

Organizations Recommending Vitamin D to Reduce Fall Risk

- AHRQ for US Preventive Services Task Force 2010
- IOF 2010
- NOF – 2008
- Endo Soc – ? (to be released spring, 2011)

Higher Dose Vitamin D Trials: RR of Non-vertebral Fractures

*(Range: 482 - 770 IU/d received dose; n = 33,265 from 9 trials)*

-29%  
-15%  
-20%

Variation of Hip Fracture Prevention by Received Dose and Achieved 25(OH)D

  - (Range: 340 - 760 IU/d; n = 40,886 from 8 trials)
  - (Range: 62 - 105 nmol/L; from 7 trials)

IOF Position Statement
Vitamin D Recommendations for Older Adults

- Average risk adults with little regular sun exposure should take 800 to 1000 IU/d of vitamin D3.
- This will bring their mean serum 25OHD to the desired level of 75 nmol/L (30 ng/ml).


IOF - Clinical Management

- Average risk adults
  800 to 1000 IU/d
  no need to measure 25OHD
- High risk adults
  measure 25OHD
  supplement to reach 75 nmol/L (30 ng/ml)
  re-measure 25OHD 3 mo later to confirm

High Risk Groups

- Osteoporosis
- Obese
- Little effective sun exposure (dark skin, little exposure, northern latitude, sunscreen use)
- Malabsorption
- Anti-epileptics (increase metabolism)
**Session Title**: Genome-wide Association Studies of Musculoskeletal Phenotypes  
**Time**: 2:40 - 3:40 PM  
**Location**: Chopin Ballroom

**Douglas Kiel MD, MPH**

**Summary**: This presentation will review and update the current status of genome-wide association studies of musculoskeletal phenotypes of interest to the field. Based on the availability of affordable dense arrays of single nucleotide polymorphisms, many of the large studies from around the world have been able to genotype thousands of individuals for relatively common variants across the entire genome. This has led to the discovery of known and novel associations between genes and musculoskeletal traits. This presentation will include some results from the large consortia of studies that have collaborated to produce results for bone density, hip geometry, vitamin D concentration and lean body mass. Ultimately these studies hope to identify novel pathways that are important for musculoskeletal health that will lead to new therapies. Also, there is an expectation that genetic risk factors identified through these efforts will be added to the current fracture risk assessment tools.

**CME Objectives:**

1. Use the genome to help make diagnosis and determine fracture risk
2. Determine prescription of potentially better pharmaceutical treatment in the future
3. Identify genes that influence bone density and bone strength
4. Anticipate how genetic profiling might influence treatment

**Biographic Sketch**

Douglas P. Kiel is currently a Professor of Medicine at Harvard Medical School and Director of Medical Research and of the Musculoskeletal Research Center at the Institute for Aging Research at Hebrew SeniorLife. His research focuses on the prevention of osteoporotic fractures and musculoskeletal decline. He is the Principal Investigator of the Framingham Osteoporosis Study, which has identified multiple risk factors for osteoporosis and related fractures. The Framingham Osteoporosis Study has been a major contributor to recent genome wide association studies of bone density and other musculoskeletal phenotypes. He is currently chair of the PhenX Skin, Bone, Muscle and Joint Working Group of the National Human Genome Research Institute “Consensus Measures for Phenotypes and Exposures” (PhenX).

**Speaker Disclosure of Commercial Interest**

Nothing to Disclose

**Evaluation for Douglas Kiel MD, MPH**

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**Comments on the Session or Speaker:**

What related topics and or speakers should be considered for next year’s Annual Meeting?
Kiel: Genome-wide Association Studies of Musculoskeletal Phenotypes

Why Genetics?

• Genetic tests - for high-risk individuals: Improve diagnosis of osteoporosis
• Modifiable environment - By identifying and characterizing interactions with environment, we have more opportunities to effectively “tailor” intervention strategies (examples: interaction of genes with age; other modifiable risk factors - diet, exercise)
• Genetic information will be used to plan appropriate intervention strategies (Response to medicines, pharmacogenomic research, clinical trials) – will ultimately translate into personalized medicine

Genetics of Osteoporosis

• Low BMD is strongly associated with fracture risk
• 50-80% of variability in normal BMD is genetically determined

Other traits that affect bone strength may be genetically determined
• bone size & shape
• trabecular bone density
• microarchitecture

A Catalog of Published Genome-Wide Association Studies

http://www.genome.gov/26525384

• As of March 13, 2011
  – 812 publications on genome wide association studies testing at least 100K SNPs had been published and 3,977 SNPs identified as having p-values < 1 X 10⁻⁵
  – 23 of the studies were related to skeletal phenotypes
GEFOS consortium
Genetic Factors for Osteoporosis

Aim: Identification of novel genetic determinants of fracture and osteoporosis traits using a hypothesis-free GWA approach

Number of subjects:
with GWAS: 34,000
With DNA: 50,000

www.gefos.org
www.genomos.eu

Genetic Architecture of BMD

Recent reports
GWA: Lancet, NEJM
LRP5: JAMA

New Challenges – Beyond Association Tests

- Identification of the causal variants
  - Fine-mapping, re-sequencing, functional studies
- Other source of variations
  - Copy Number Variations (CNVs), rare variants
- Better use of the phenotypes
  - Multi-variate analysis using multiple phenotypes, GxE interactions
- Integrating information
  - Genomics, Transcriptomics, Proteomics
  - miRNA
  - Diseases
### Influence of Structural Variants on Phenotype

- Structural variant can cause disease through a duplication or deletion event – a deletion can unmask a recessive mutation on the homologous chromosome.
- Genes that overlap structural variants can be disrupted directly by inversion, translocation or deletion, or copy-number variant breakpoints, which leads to the reduced expression of dosage-sensitive genes.
- Structural variants that are located at a distance from dosage-sensitive genes can affect expression through position effects.
- Structural variants can function as susceptibility alleles, where a combination of several genetic factors are required to produce the phenotype.

### Conclusions

- The study of the genetics of osteoporosis has progressed significantly from linkage studies to candidate gene association studies and now to the era of GWAS.
- It is not clear if genetic markers will be used for risk assessment.
- New biologic pathways may be identified in the search for new genes governing bone traits.
Michael McClung MD, CCD

**Summary:** This session is designed as a practical guide to precision assessments. The rational and mechanics of the assessment will be reviewed to justify the need. Additionally, barriers to completing this assessment in various clinical settings will be discussed, along with suggestions to overcome these barriers and the scientific validity of alternate methods.

**CME Objectives:**

1. Integrate precision into a variety of clinical settings and practice
2. Determine the scientific impact of various precision assessment methods
3. Obtain precision with multiple technologies, machines or sites
4. Perform precision assessment within local regulatory compliance

**Biographic Sketch**

Michael McClung is the Founding Director of the Oregon Osteoporosis Center in Portland. He received his medical degree from The University of Texas Southwestern Medical School in Dallas. After training in Internal Medicine at Parkland Hospital in Dallas, he completed a fellowship in Endocrinology at the National Institutes of Health in Bethesda, Maryland. He then joined the faculty at the Oregon Health and Science University in Portland, where he worked for many years. While there, he founded a clinic and research group devoted to the care and study of patients with disorders of bone and calcium metabolism, which is now known as the Oregon Osteoporosis Center. Dr. McClung has been involved in the planning, conduct and presentation of many of important clinical studies that resulted in the availability of the medications now used to treat osteoporosis. Dr. McClung is widely known as an educator, translating clinical research information into practical strategies of evaluation and treatment for other physicians. He serves on the Scientific Advisory Council of the National Osteoporosis Foundation, on the Committee of Scientific Advisors for the International Osteoporosis Foundation and was a member of the WHO Task Force on Fracture Risk Assessment that led to the development of the FRAX® Risk Assessment calculator.

**Speaker Disclosure of Commercial Interest**

**Consulting:** Amgen, Eli Lilly, Novartis, Merck

**Speakers’ Bureau:** Amgen, Eli Lilly, Novartis, Warner-Chilcott

**Research:** Amgen, Merck, Novartis, Warner-Chilcott
Sally Warner, PhD

Biographic Sketch

Sally (Sarah) Warner has been Medical Director of Musculoskeletal Imaging at Perceptive Informatics, an imaging core lab. She provides medical expertise in study design, protocol standardization and customization of analysis software tools for musculoskeletal clinical imaging trials. She supports the preparation of clinical protocols, journal articles and other documents. Dr. Warner has over 15 years experience in imaging for musculoskeletal research trials. Dr. Warner’s previous experience includes certification by the International Society for Clinical Densitometry as a Clinical Densitometrist and a DXA technologist as well as Radiology Practicing Technologist License in the state of Utah. She has held positions as senior research assistant at the University of Connecticut Health Center, research fellow at the University of Utah and senior research fellow in the department of Orthopaedics and Sports Medicine at the University of Washington. Dr Warner’s musculoskeletal research has been funded by NASA, the University of Utah, and other private organizations. Dr Warner’s musculoskeletal research has included the use of many different modalities for the assessment of bone metabolism including bone histomorphometry, 3-point bending, radiography, ultrasound, DXA, QCT, and high resolution CT imaging.

Speaker Disclosure of Commercial Interest

Salary: Perceptive Informatics

Evaluation for Michael McClung MD, CCD

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Comments on the Session or Speaker:

What related topics and or speakers should be considered for next year’s Annual Meeting?
Precision: Why it’s Important and Practical Suggestions to Incorporate into Complex Clinical Settings

Sally (Sarah) Warner, PhD, CCD
Michael McClung MD, CCD

Agenda

• What precision?
• Challenges to DXA precision
• Why is DXA precision important?
• When to assess precision
• How to assess precision
• Clinical Application
• Challenges

What is Precision?

• Precision = reproducibility
• The ability of a quantitative measurement technique to reproduce the same numerical result when repeatedly performed in an identical fashion
• In DXA, the ability of a DXA system to obtain consistent BMD values upon repeated measurements of the same patient over a short time
• In order to monitor bone loss or the efficacy of treatment good precision (i.e., small variations in serial measurements) is crucial
Why does DXA precision matter?

- Precision and the chosen confidence interval determine the LSC in BMD which can be recognized as a statistically real change in the patient’s BMD and not simply due to random errors in the measurement.
- Clinical DXA precision is influenced by a combination of short and long term variability of the scanner, patient motion, body habitus, and operator dependent factors such as patient positioning and scan analysis.
- Patient and operator related sources of variability are more important than the scanner variability itself with operator related factors having the most influence on the overall precision of DXA measurements.
- The calculated value for precision assessment is called the precision error.

When to do Precision assessments

- The precision error supplied by the manufacturer should not be used.
- Each DXA facility should determine its precision error and calculate the LSC.
- If a DXA facility has more than one technologist, an average precision error combining data from all technologists should be used to establish precision error and LSC for the facility, provided the precision error for each technologist is within a pre-established range of acceptable performance.
- Every technologist should perform an in vivo precision assessment using patients representative of the clinic’s patient population.

When to do Precision assessments

- Each technologist should do one complete precision assessment after basic scanning skills have been learned (e.g., manufacturer training) and after having performed approximately 100 patient-scans.
- A repeat precision assessment should be done if a new DXA system is installed.
- A repeat precision assessment should be done if a technologist’s skill level has changed.
Methods for DXA precision

- To perform a precision analysis:
  - Measure 15 patients 3 times, or 30 patients 2 times, repositioning the patient after each scan
  - Calculate the root mean square standard deviation (RMS-SD) for the group
  - Calculate LSC for the group at 95% confidence interval

Acceptable Precision

- The ISCD official position recommended minimum acceptable precision for an individual technologist is:
  - Lumbar Spine: 1.9% (LSC=5.3%)
  - Total Hip: 1.8% (LSC=5.0%)
  - Femoral Neck: 2.5% (LSC=6.9%)
  - Retraining is required if a technologist's precision is worse than these values

Clinical Application

- Precision assessment should be standard clinical practice. Precision assessment is not research and may potentially benefit patients.
- It should not require approval of an institutional review board. Adherence to local radiologic safety regulations is necessary.
- Performance of a precision assessment requires the consent of participating patients.
Challenges to Implementation

- Multiple technologists
- Multiple instruments
- Lack of volunteers
- Lack of time
- Justification

Scientific Impact of Precision

- Differentiates:
  - A significant response to treatment
  - A non-significant response to treatment
  - A significant decrease in BMD while on treatment

Summary

- Precision assessment required to determine whether a BMD difference is a genuine biological change or within the range of error.
- Precision assessment should be performed on patients typical of those tested at the center.
- Determination of the LSC by means of properly conducted precision assessment is essential to good densitometry practice.
- The value of precision measurements outweighs the small and entirely theoretical risk of cancer induction.
Session Title: Association of Calcium and Myocardia Infarctions  
Time: 3:45 - 4:45 PM  
Location: Grand Ballroom

Richard Prince MD

Summary:

CME Objectives:  
1. Investigate data on calcium supplementation and cardiovascular disease  
2. Explain relevance of these findings to clinical practice

Biographic Sketch
Richard Prince has been a Professor at University of Western Australia since 1993 and a consultant Endocrinologist at Sir Charles Gairdner Hospital since 1983. He continues in endocrinology practice at Sir Charles Gairdner Hospital and St John of God’s Hospital. He has been involved with the development and running of a bone density unit at Sir Charles Gairdner Hospital for 20 years. Current research interests are genetics, dietetics and endocrinology as they affect bone and cardiovascular structure and function. He has held a variety of Board positions on National and International Societies.

Speaker Disclosure of Commercial Interest
Research: Amgen, Servier, Wyeth

Evaluation for Richard Prince MD

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Prince: Calcium and Vitamin D are 1st Line Effective and Safe

Calcium and vitamin D are first line effective and safe osteoporotic fracture prevention interventions

Prof RL Prince
University of Western Australia and Sir Charles Gairdner Hospital

Outline

• Efficacy of calcium and D compared to placebo in fracture prevention in whole populations
• Comparison of calcium and D trials to pharmaceuticals as first line therapy
• Mechanism for the effects of calcium and D in the prevention of fractures in the elderly
• Adverse events
• Conclusions

Vitamin D3 and calcium to prevent hip fractures in the elderly women


3200 women aged 86 randomised to Calcium 1200mg and vitamin D 800IU or placebo
Why calcium and D trials cannot be compared to pharmaceutical trials

Pharmaceuticals
- Companies have tested their products in individuals at high risk of fracture ie low BMD and or spinal fracture
- The primary outcome variable is a reduction spinal fracture (deformity) compared to placebo as assessed by x-ray.
- The size of the treatment effect is much less in appendicular fractures than in spinal fractures
- When these agents have been studied in patient with normal T score the agents are not efficacious.

Calcium and D
- Tested in unselected individuals who have a lower risk of fracture
- The primary outcome variable is any clinical fracture compared to placebo - Usually excluding face, fingers and toes
- Most of these clinical fractures are appendicular not spinal
- Clinical investigators are not as well funded as pharmaceutical companies and run underpowered studies often due to lack of fracture events and poor compliance

ROLE OF CALCIUM IN THE PATHOPHYSIOLOGY OF AGE RELATED BONE LOSS IN MEN AND WOMEN

LOW GUT CALCIUM
  
LOW VITAMIN D
  
LOW BONE CALCIUM
  
ESTROGEN DECIENCY
  
OSTEOLYSIS REDUCED
  
MINERAL REDUCED
  
PTH INCREASED
  
EXTRA CELULAR CALCIUM BALANCE DECREASED

HIGH URINE SODIUM

HIGH URINE CALCIUM

Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials  BMJ 2009; 339:b3692
Prince: Calcium and Vitamin D are 1st Line Effective and Safe

Problems with hypothesis that calcium increases myocardial infarction risk

- Study design – “cherry picking” of adverse event to report
- Statistical approach
  - use of “trend” eg P >0.05
  - No data on time of event included in a proportional hazard model
  - Multiple testing with no adjustment of P value
- Use of self report for MI events – effect disappears after adjudication
- Calcium increases GI adverse events
- Other RCT data does report an effect

Example of inappropriate use of statistical tests

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<tr>
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<th>Placebo</th>
<th>Relative Risk (95%CI)</th>
<th>P value</th>
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<td>Self-reported myocardial infarction</td>
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<td>Prince</td>
<td>21/730 (2.9)</td>
<td>17/730 (2.3)</td>
<td>1.24 (0.66 to 2.32)</td>
<td>0.512</td>
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<td>Bolland</td>
<td>31/732 (4.2)</td>
<td>14/739 (1.9)</td>
<td>2.24 (1.20 to 4.17)</td>
<td>0.011</td>
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<td>Total</td>
<td>52/1462 (3.6)</td>
<td>31/1469 (2.1)</td>
<td>1.69 (1.09 to 2.61)</td>
<td>0.020</td>
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<tr>
<td>Prince</td>
<td>14/730 (1.9)</td>
<td>16/730 (1.9)</td>
<td>1.00 (0.48 to 2.32)</td>
<td>1.000</td>
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<td>21/732 (2.9)</td>
<td>18/739 (1.4)</td>
<td>2.12 (1.01 to 4.47)</td>
<td>0.068</td>
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<td>Total</td>
<td>35/1462 (2.4)</td>
<td>24/1469 (1.6)</td>
<td>1.45 (1.03 to 2.45)</td>
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<td>Prince</td>
<td>7/730 (1.0)</td>
<td>3/730 (0.4)</td>
<td>2.33 (0.61 to 8.99)</td>
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<td>Bolland</td>
<td>10/732 (1.4)</td>
<td>4/739 (0.5)</td>
<td>2.52 (0.80 to 8.01)</td>
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<td>Total</td>
<td>17/1462 (1.2)</td>
<td>7/1469 (0.5)</td>
<td>2.44 (1.02 to 5.87)</td>
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Results are number (%).

Adjudication of events shows excess of self report not adjudicated events in calcium group probably due to excess of GI complaints mistaken for MI
Calcium supplementation and the risks of atherosclerotic vascular disease in older women: results of a 5-year RCT and a 4.5-year follow-up


Calcium supplementation increases the risk for gastrointestinal complaints - data from RCTs

Random effects model Test for heterogeneity: I² = 0.0% P=0.62

Calcium and vitamin D had no effect on vascular disease

WHI RCT of calcium 1gm and vitamin D
36282 women 7 years
Myocardial infarction and coronary death

Calcium and vitamin D had no effect on vascular disease

Circulation, 2007;116;646-654
Session Title: Causes, Consequences and Management of Age-Related Hyperkyphosis for Fracture Prevention

Time: 3:45 - 4:45 PM
Location: Chopin Ballroom

Wendy Katzman DPTSc

Summary: This presentation will review the epidemiology, etiology and consequences of osteoporosis, kyphosis and fractures. We will define and describe the pathogenesis of the vertebral fracture cascade. We will review the scientific basis for exercise and physical activity in fracture prevention and present an evidence-based exercise program that was designed to promote bone health and prevent fractures for older community-dwelling adults.

CME Objectives:
1. Identify and quantify kyphosis in patients
2. Determine the utility of a kyphosis measurement to diagnose osteoporosis in patients

Biographic Sketch
Wendy Katzman is a physical therapist and board-certified Orthopedic Clinical Specialist. She received her BS in Physical Therapy from the University of Texas in Galveston. After years of clinical work, she recently completed a Doctorate in Physical Therapy Science (DPTSc) degree to study targeted effective therapies to reduce impairments associated with age-related functional decline. Her research focuses on the causal pathways of hyperkyphosis and functional limitations. She has conducted an uncontrolled clinical trial of the effects of exercise on hyperkyphosis in older community-dwelling women. Dr. Katzman is a current NIH-UCSF Building Interdisciplinary Research Careers in Women’s Health – BIRCWH K12 Scholar. She recently completed a year-long program in Advanced Training in Clinical Research.

Speaker Disclosure of Commercial Interest
Nothing to Disclose

Evaluation for Wendy Katzman DPTSc

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Epidemiology of Osteoporosis

- 1.5 million fractures in US annually
- 44 million in US at risk for fracture
  - 10 million Americans have osteoporosis
  - 34 million have low bone mass
- At age 50, lifetime risk
  - 1 in 3 women will have a fracture
  - 1 in 5 men will have a fracture

Surgeon General's Report on Bone Health and Osteoporosis, 2004

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Epidemiology of Fractures

- 300,000 hip fractures
- 250,000 wrist fractures
- 700,000 vertebral fractures

National Osteoporosis Foundation; Cooper CJ, Bone Min Res 1992

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Impact of Hip Fractures

- Disability
  - 30% permanent disability
  - 40% unable to walk independently
  - 50% unable to live independently
- Mortality
  - 24% mortality within 1-year

**Impact of Vertebral Fractures**

- Deformity
  - Hyperkyphosis /height loss (Ensrud, 1997)
- Poor health
  - Pulmonary dysfunction (Leech, 1990)
- Pain
  - Acute and chronic pain (Ettinger, 1994)
- Impaired function
  - Diminished quality of life (Martin, 2002)
- Mortality
  - 20% excess mortality in 5 yrs (Kado, 1999)

**Hyperkyphosis and Fractures**

- Hyperkyphosis increases risk of vertebral fractures regardless of underlying bone mineral density (Huang, 2006)
  - Wrist and hip fractures (Shipp, 2002; McGrother, 2002; Porter, 1990)
- Kyphosis increases mechanical load that in turn increases risk for fracture
- Hyperkyphosis increases risk for impaired balance
  - increased risk for falls (Katzman, 2011)

**Impact of Hyperkyphosis**

Mechanical effects of hyperkyphosis
- Higher spinal loads and greater trunk muscle forces required to maintain upright stance (Briggs, 2007)
- Zygoapophyseal joint capsule strain (Little, 2005)
- Limitation in rib cage expansion (Culham, 1994)
- Reduced vital capacity (Leech, 1990; Schlach, 1998; Di Bari, 2004)

Deformity
- Forward head posture (Lindsay, unpublished; Balbin, 2003; Schneider, 2004)
Bending and Lifting in Neutral Reduces Fracture Risk

- Compression loads imposed on the L3 motion segment (lower back) by 30° of trunk flexion
  - 1800 N with arms at chest
  - 2610 N with arms in front, holding 2 kg in each hand (Schultz et al. 1982)
- 300 to 1200 N enough to fracture an osteoporotic vertebra (Edmondston et al. 1997)
- Practical Application - bend and lift in everyday life with the trunk in relative neutral!

Lindsey and Bookstein, "Osteoporosis – what you should know" power point

Spinal Extension vs. Flexion Exercise Reduces Incidence of Vertebral Fractures

59 women with postmenopausal spinal osteoporosis and back pain were instructed in therapeutic exercises, 6 women no exercise.

Over 1-6 year follow-up, incident spinal fractures occurred in:
- ~16% extension group
- ~89% flexion group
- ~53% flexion and extension group
- ~67% no exercise group

Sinaki & Mikkelsen, 1984

Spinal Extensor Strengthening Reduces Incidence of Vertebral Fractures

- Randomized controlled trial
  - 50 postmenopausal women
- Back strengthening exercises 5x/wk for 2 years
- Kyphosis reduced
- Fewer fractures at 10-year follow-up

Interventions Reduce Kyphosis

- Mobilization, taping, postural exercise reduce kyphosis
  Bautmans, 2010

- Modified extension-biased yoga reduces kyphosis
  Greendale, 2009

- Spinal orthosis improves kyphosis, QoL, physical function
  Pfeifer, 2004

- Multidimensional group exercise improves kyphosis,
  musculoskeletal impairments and physical performance
  Katzman, 2007

Musculoskeletal Screening for Fracture Risk

- Kyphosis assessment
- Height loss
- Flexibility
  Shoulders, hips, spine
  Relative flexibility

- Strength
  Hip and spine extension, ankle
  Pelvic and scapular stabilization

- Body mechanics during ADLs, recreational activities

- Need for assistive devices

Measurement of Kypholordosis DVD, Lindsey
Session Title: Radiology of Osteoporosis – Mini Course
Time: 3:45 - 5:50 PM
Location: Concourse 1

CME Objectives (Overall):
1. Understand the importance of fracture recognition as a risk factor for further osteoporotic fracturing
2. Recognize the chief signs of fracturing
3. Know the role and limitations of advanced CT and MRI imaging in diagnosis and of vertebral supplementation techniques in management

Section 1 Title: Spinal Radiology
Summary: Vertebral fracture recognition is an important contribution to the evaluation of fracture risk. Vertebral fractures result in increased morbidity and mortality but are often overlooked by both radiologists and clinicians. Fractures can be recognized by loss of vertebral self-similarity resulting from signs such as loss of end-plate parallelism, end-plate breaks and cortical buckling. These signs and tools such as the Genant grading system will be presented as well as the principles of morphometry and automated morphometry for computer-aided diagnosis discussed. Vertebral fracture assessment (VFA) done with DXA machines can often be used in place of conventional radiography so that fractures may be more readily diagnosed in those at risk.

CME Objectives:
1. Understand the importance of fracture recognition as a risk factor for further osteopotic fracturing
2. Recognize the signs of vertebral fracturing
3. Recognize the major confounders in diagnosis

Section 2 Title: CT and MRI of Vertebral Fractures
Summary: CT scans and MRI examinations play an important role in the ancillary diagnosis of vertebral fractures. Both CT and MRI may be used if the plain film diagnosis of fracture is indeterminate. CT is used to evaluate the extent of the fracture, especially retropulsion of bone into the spinal canal. CT is also used for biopsy guidance if malignancy or infection is suspected. MRI is used to help determine the acuity of fracture and to help exclude malignancy as the cause of fracture. MRI is also used for excluding other sources of back pain especially arthritis, discitis, and disc herniation.

CME Objectives:
1. Comprehend how CT and MRI complement plain film diagnosis
2. Know contributions of CT and MRI in investigating spinal disease
3. Understand when supplementary investigation is indicated

Section 3 Title: Kyphoplasty and Vertebroplasty
Summary: Vertebral augmentation techniques using polymethylmethacrylate (PMMA) have been used for 3 decades. The indications and complications associated with the procedures are well established. Recently there are questions as to its efficacy, but the 2 studies that raised the question have been largely criticized. Kyphoplasty has been shown to increase vertebral high slightly more than vertebroplasty. Both techniques have been implicated in potentially resulting in fractures in adjacent vertebral bodies. The techniques will be described.
CME Objectives:
1. Determine the appropriateness of an individual to undergo Vertebral Augmentation
2. Define the possible benefits from Vertebral Augmentation
3. Discuss the difference between kyphoplasty and vertebroplasty procedures
4. Explain the potential complications associated with vertebral augmentation

Section 4 Title
Radiology of Non-Vertebral Fractures

Summary: Non-vertebral fractures are initially evaluated with plain films. If plain films are indeterminate and there is high clinical suspicion for fracture, CT, MRI, or scintigraphy may be used. The choice of these advanced imaging techniques is driven by the anatomic site suspected of fracture, the need to characterize the fracture, and the cost and availability of advanced techniques. In general, MRI is the most comprehensive but also the most expensive way to evaluate for fractures when plain films are normal or when plain films show a fracture but additional information is needed.

CME Objectives:
1. Understand the definition and distribution of osteoporotic fractures in the peripheral skeleton
2. Understand the signs of fracturing
3. Know the limitations of fracture diagnosis

Brian Lentle MB, MD, FRCPC, FRCR, FACR, CCD

Biographic Sketch
Brian Lentle is a Professor Emeritus of Radiology at the University of British Columbia and consultant radiologist to the Osteoporosis Clinic at the Women’s Health Centre in Vancouver. He has a long standing interest in the radiology of osteoporosis and directed a diagnostic reference centre in respect of the trials of risedronate in North America. He is radiologist to the Canadian Multicentre Osteoporosis Study (CaMos) and Chair of the CaMos Quality Assurance Committee, as well as Radiologist to the Steroid-Induced Osteoporosis in a Pediatric Population (STOPP) Study. At present, he is on the Board of the International Society for Clinical Densitometry, chair of their Vertebral Fracture Assessment Committee and an Emeritus Member of the Canadian Society of Nuclear Medicine, and past-president of the RSNA and the Canadian Association of Radiologists. Dr. Lentle is an Honorary Member of the American Association of Physicists in Medicine and the European Society of Radiology.

Leon Lenchik MD, CCD

Biographic Sketch
Leon Lenchik is Associate Professor, Section Head and Fellowship Director of Musculoskeletal Imaging in the Department of Radiological Sciences at Wake Forest University School of Medicine in Winston-Salem, North Carolina. He completed an undergraduate degree and received an MD from Northwestern University. After residency training in Diagnostic Imaging, he completed a fellowship in Musculoskeletal Imaging at the University of California, San Diego. His main research interest and academic focus is on body composition, bone densitometry, and osteoporosis. Dr. Lenchik is currently serving on the Board of Directors of the International Society for Clinical Densitometry.

Speaker Disclosure of Commercial Interest
Nothing to Disclose
Bradford Richmond MD, FCR, CCD

**Biographic Sketch**

Brad Richmond is a staff physician at the Cleveland Clinic Foundation. He is a native Clevelander and received a BS and MS in biology from Cleveland State University. Dr. Richmond graduated from Case Western Reserve University and completed residency in diagnostic radiology at the Cleveland Clinic Foundation. His fellowship in musculoskeletal radiology was at the University of California, San Francisco. He is Director of Bone Mineral Densitometry for the Metabolic Bone Disease Clinic. He has been involved in osteoporosis research with the Endocrinology and Rheumatology Departments since 1986. He has a joint appointment in the Department of Orthopaedic Surgery and in the Women’s Health Center.

**Speaker Disclosure of Commercial Interest**

Nothing to Disclose

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### Evaluation for Brian Lentle MB, MD, FRCPC, FRCR, FACR, CCD (Section 1)

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### Evaluation for Leon Lenchik MD, CCD (Section 2)

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### Evaluation for Bradford Richmond MD, FCR, CCD (Section 3)

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Comments on the Session or Speaker:

What related topics and or speakers should be considered for next year’s Annual Meeting?
Diagnostic tools:
- Visual inspection
- Six-point (+) morphometry
  Automated (G.E., Hologic, Optasia)
  (CAD, large scale research applications: FP,FN)
- Semi-quantitative method of Genant et al.
- Algorithm-based qualitative method (Jiang)

Radiological Signs of Fractures

Fracture signs with necrosis:
Genant tool: Normal (Gd. 0)

Normal

Grade 1: <25% deformity
Grade 2: 25 - 40% deformity
Grade 3: >40% deformity

? Wedge Biconcave Crush

Change in shape cf. change in integrity:
Lenchik: Radiology of Osteoporosis: CT and MRI of Vertebral Fractures

No Handout available
Kyphoplasty (KP) or Vertebroplasty (VP)

- Indications for the procedure:
  - Palliative procedure for pain secondary to vertebral compression fracture
  - Compression fracture less than 1 year old, decreased quality of life, level of analgesic required
  - Proposed but never substantiated – prevention of further collapse of a fractured vertebral body

Indications

- Pain related to vertebral compression fracture associated with:
  - Osteoporosis
  - Tumor infiltration

KP and VP

- Potential mechanism of action for pain relief:
  - PMMA heat resulting in denervation of nerves associated with the vertebral body
  - Kyphoplasty: because of restoration of vertebral body height – regain mechanical advantage and improve spinal alignment decreasing pain (facets)
  - Restoration of vertebral body height
  - Prevents further fracture of the involved vertebral body
KP or VP

- Contraindications for the procedure:
  - Anticoagulant therapy
  - Coagulopathy
  - Infection –spinal, systemic
  - PMMA allergy
  - Posterior wall interruption or retropulsion of vertebral body
  - Effective medical therapy
  - Stable, asymptomatic compression fracture
  - Severe height loss of more than 70% (?)
  - Tumor extending into the spinal canal

Contraindications:

- Moderate or severe retropulsion of the posterior vertebral body cortex into the spinal canal
- Height loss >70% (?)
No Handout available
**Bonehead Jeopardy**

Session Title: Bonehead Jeopardy  
Time: 4:50 - 5:50 PM  
Location: Theatre / Chopin Ballroom

Joseph Houston with Diane Schneider, Paul Miller & Neil Binkley

**Summary:** This interactive session will use a Jeopardy style format to test your bone knowledge. Three experts in the field have been invited as contestants, and the audience will be their team. Categories will be related to diagnosis, clinical care and treatment of osteoporosis and bone disease, sprinkled with some trivia from bone field and flash-backs to see what you remember from your training years.

**CME / CE:** Non-CME Event

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### Evaluation for Joseph Houston

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### Evaluation for Diane Schneider

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### Evaluation for Paul Miller

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### Evaluation for Neil Binkley

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**Comments on the Session or Speaker:**

What related topics and or speakers should be considered for next year’s Annual Meeting?
**Session Title**

**Plenary Session: Now and the Future - Osteoporosis Treatment**

- Current Treatment of Osteoporosis
- New and Emerging Therapies for Osteoporosis

**Time**

8:00 - 9:30 AM

**Location**

Grand Ballroom

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**Michael McClung MD, CCD**

**Summary:** Effective tools exist for the diagnosis of osteoporosis and the identification of patients at risk for fracture. Nonpharmacological management is important but not sufficient to treat patients at high risk of fracture. The recommendations about calcium and vitamin D intakes have changed — and will likely change again with new data. We have drug therapies that effectively prevent bone loss and significantly reduce fracture risk in patients with osteoporosis or at high risk of fracture. Major limitations in the effectiveness of current therapies include uncertainty about who should be treated, unfamiliarity with the effectiveness of our therapies, concerns about side effects and long-term safety and, most importantly, poor adherence to therapy.

**CME Objectives:**

1. Use currently available osteoporosis drugs
2. Explore controversies related to biphosphonate use
3. Compare evolving treatments for osteoporosis

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**Biographic Sketch**

Michael McClung is the Founding Director of the Oregon Osteoporosis Center in Portland. He received his medical degree from The University of Texas Southwestern Medical School in Dallas. After his training in Internal Medicine at Parkland Hospital in Dallas, he completed a fellowship in Endocrinology at the National Institutes of Health in Bethesda, Maryland. He then joined the faculty at the Oregon Health and Science University in Portland, where he worked for many years. While there, he founded a clinic and research group devoted to the care and study of patients with disorders of bone and calcium metabolism, which is now known as the Oregon Osteoporosis Center. Dr. McClung has been involved in the planning, conduct and presentation of many of the important clinical studies that resulted in the availability of the medications now used to treat osteoporosis. Dr. McClung is widely known as an educator, translating clinical research information into practical strategies of evaluation and treatment for other physicians. He is an active member of multiple international societies focusing on bone diseases and their treatment. He serves on the Scientific Advisory Council of the National Osteoporosis Foundation, on the Committee of Scientific Advisors for the International Osteoporosis Foundation and was a member of the WHO Task Force on Fracture Risk Assessment that led to the development of the FRAX® Risk Assessment calculator.

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**John Bilezikian MD, CCD**

**Summary:** Although safe and effective therapeutic agents are available for the prevention and treatment of osteoporosis, the quest continues for uses of approved drugs in combination and for even more effective drugs. This presentation will focus upon newer approaches to combination therapy and on agents whose mechanisms make them conceptually attractive as potential new approaches to the treatment of osteoporosis. Discussion topics will include: Combination Therapies, Antiresorptives, Osteoanabolics, and Serotonin Antagonism.
CME Objectives:
1. Use currently available osteoporosis drugs
2. Explore controversies related to biphosphonate use
3. Compare evolving treatments for osteoporosis

Biographic Sketch
John Bilezikian, the Dorothy L. and Daniel H. Silberberg Professor of Medicine and Professor of Pharmacology at the College of Physicians & Surgeons, Columbia University is Chief of the Division of Endocrinology and Director of the Metabolic Bone Diseases Program at Columbia University Medical Center. Dr. Bilezikian received his undergraduate training at Harvard College and his medical training at the College of Physicians and Surgeons. He completed four years of house staff training (internship, residency and Chief Residency) on the Medical Service at Columbia Presbyterian Medical Center. Dr. Bilezikian received his training in Metabolic Bone Diseases and in Endocrinology at the NIH in the Mineral Metabolism Branch under the tutelage of Dr. Gerald Aurbach. He is a major national and international spokesperson for the field of metabolic bone diseases. Dr. Bilezikian’s major research interests are related to the clinical investigation of metabolic bone diseases, particularly osteoporosis and primary hyperparathyroidism.

Speaker Disclosure of Commercial Interest
Consulting: GSK, NPS
Speakers’ Bureaus: Amgen, Eli Lilly, Novartis
Research: NPS

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What related topics and or speakers should be considered for next year’s Annual Meeting?
Vitamin D Supplements

- Prevalence of vitamin D deficiency (serum 25-OH vitamin D <20 ng/ml) is about 50%
- Clinical studies suggest that target serum level should be at least 30 ng/ml (physiology) or 20 ng/ml (clinical)
- Official recommendations:
  - Increased from 400-600 IU daily up to 800-2000 IU daily (IOM 600 IU daily – based on clinical evidence)
  - 1000 IU D3 daily increases serum 25-OH D by ~10 ng/ml


Calcium Intake and Supplements

- Recommended intake: 800-1200 mg daily
  - Previous higher intakes based on studies in vitamin D deficient subjects
  - In healthy, vitamin D-replete adults, no benefit of daily intake more than 800 mg
  - Dairy free diet provides ~300 mg
  - Maximal supplement required: 500 – 600 mg daily
  - Supplements of 1000 mg daily may increase risk of
    - renal stones
    - heart attacks in older women
      Ballard MJ et al. BMJ. 2006;332:262-66
Postmenopausal Osteoporosis: Approved Treatment Options 2011

No head-to-head trials comparing fracture outcomes

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Osteoporosis Treatment 2011: Benefits

- Many of these agents are very effective for treating osteoporosis
  - Vertebral fracture by 30-70%
  - Multiple vertebral fractures by 77-95%
  - Hip fracture by 40-50%
  - Non-vertebral fractures by 20-35%
- In general are well tolerated
- In clinical trials, have been very safe

Osteoporosis Treatment 2011: Limitations

- Real or perceived intolerance
- Awkward or inconvenient dosing regimens
- Poor compliance and persistence with therapy
- Concerns about long-term safety
- No “cure” yet available
- Cost

References:
Chesonb B et al. J Bone Miner Res. 2004;19:1241-6
Harris ST et al. JAMA 1999;282:1344-52
Ettinger B et al. JAMA 1998;280:637-45

OOO
Atypical Fractures of Femur In Patients Taking Bisphosphonates For Osteoporosis

- Atypical (tranverse) fractures of femoral shaft have been reported in patients taking oral bisphosphonates for osteoporosis
  - Minimal trauma
  - Often bilateral
  - Prodromal pain in 70%
  - Cortical thickening
  - Slow fracture healing
  - Often on other drugs (steroids, estrogen)
  - Incidence may be related to duration of therapy
  - 2/100,000 after 2 years; 78/100,000 at 8 years

Bisphosphonates: Drug Holiday?

- Some (but not all) bisphosphonates have lingering effect on reducing bone turnover after stopping treatment
- Discontinuing therapy results in increased risk of spine and other fractures
- Stopping alendronate after 2-5 years may be appropriate for low-moderate risk patients
- For patients at high risk of vertebral fracture, benefits of continuing treatment outweigh risks of treatment

Osteoporosis Therapy: GIO

- Pathogenesis of GIO quite different than of postmenopausal osteoporosis
  - Inhibition of osteoblast and osteocyte activity
  - Modest bone loss
  - Fracture risk not progressive with long-term therapy and returns to pre-treatment levels when GC therapy discontinued
  - Bisphosphonates effectively reduce vertebral fracture risk
  - Teriparatide reduces vertebral fracture risk by 90% compared to alendronate

References:
Summary

- We have effective tools for the diagnosis of osteoporosis and the identification of patients at risk for fracture.
- Recommendations about calcium and vitamin D intakes have changed – and will likely change again with new data.
- We have therapies that effectively prevent bone loss and significantly reduce fracture risk in patients with osteoporosis.
- Bisphosphonates are – and will continue to be – the mainstay of therapy.
- Concerns about long-term bisphosphonate therapy are real – but will become understood in next few years.

Opportunities for New Therapies

- Sustained anabolic effect – to “cure” osteoporosis – without adverse effects on non-skeletal tissues
- More robust efficacy – especially of non-vertebral fractures (is this possible?)
- Convenient dosing regimens – to improve compliance and persistence
- Combined antiresorptive and anabolic therapies to reduce concern about “over-suppression”
Besides non-pharmacological approaches, what do we have now in the USA?

- Estrogen
- Raloxifene
- Bisphosphonates
  - Alendronate
  - Risedronate
  - Ibandronate
  - Zoledronic acid
- Denosumab
- Calcitonin
- Teriparatide

Updated Summary of Effects of Osteoporosis Therapies on Vertebral and Nonvertebral Fractures

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Desired characteristics

- **Efficacy** (at vertebral and non-vertebral sites)
- **Convenience**
  - Different routes of administration (oral, intravenous, subcutaneous)
  - Different dosing schedules (daily, weekly, post-prandial (2011), monthly, quarterly, semi-annually, yearly)
- **Affordability**
- **Safety**
Outline of Presentation

• What we have now
• Advances upon what we have now
• New approaches based upon advances in bone cell biology

Antiresorptives
• Rank L inhibition
• Cathepsin K inhibition

Approaches to Combination or Sequential Therapy with Bisphosphonates and PTH

| Bisphosphonate | PTH | Bisphosphonate | PTH | PTH | Bisphosphonate |

3/20/2011
Odanocatib: summary of current data

- Greater inhibition of bone resorption than bone formation (greater difference than with other antiresorptive agents)
- Dose-dependent increases in bone mineral density
- No safety “signals” as with former Cathepsin K inhibitors
- Well tolerated
- Phase 3 trial being conducted

Outline of Presentation

• What we have now
• Advances upon what we have now
• New approaches based upon advances in bone cell biology

OSTEOANABOLIC THERAPY

New approaches to the therapeutic use of PTH

• PTHrP(1-36)
• Endogenous stimulation of PTH
  (Fitzpatrick, ASBMR, 2009; submitted, 2010)
• Transdermal route
  (Cosman et al., JCEM, 2010)
Conceptual Advances

- Perturbing the Wnt signaling pathway (sclerostin inhibition)
- New agents that influence bone formation (serotonin)

Challenges we face

- How are we going to "prove" efficacy?
- What instruments will be the best to demonstrate improved bone strength?
- On what bone qualities are we going to focus?
- Will these new approaches be safe?
- Will they be specific to bone?
- Will they be affordable?
Plenary Session:

Old Age is No Place for Sissies - Descriptions and Interventions of the Aging Musculoskeletal System

- The Role of Fat in the Age-Related Loss of Muscle Function
- "Sarcoporosis" What is it? Why Should We Care? What Can We Do?
- Frailty and Muscle Metabolism Dysregulation in the Elderly

9:30 - 11:00 AM
Grand Ballroom

CME / CE: 1.5 Credits

Bret Goodpaster PhD

Summary: Sarcopenia, or the age-related loss of muscle mass, has been hypothesized to be a major factor contributing to physical decline and disability in old age. The purpose of the presentation is to review recent research progress on the study of sarcopenia, including evolving definitions and progress with interventions. With the advent of lower cost and precise imaging methods, it is has become more feasible to characterize the prevalence, correlates and risk related to sarcopenia in older adults. Observational and intervention studies suggest that defining sarcopenia is challenging. Thinking about sarcopenia has evolved over time to incorporate aspects of overall body composition, including the interactions between fat and muscle mass. Recent findings, new conceptualizations and their implications for thinking about potential new directions in research will be discussed.

CME Objectives:
1. Describe differences between “young” and “old” muscle
2. Understand the clinical consequences of “old muscle”
3. Appreciate how clinical interventions for rehabilitation and repair need to be modified for older adults

Biographic Sketch
Bret H. Goodpaster is an Associate Professor and the Director of the Endocrinology and Metabolism Research Center at the University of Pittsburgh School of Medicine. Dr. Goodpaster has more than 100 publications in the areas of human metabolism and body composition. He currently has two NIH R01 grants and is a co-investigator on several other NIH grants. Goodpaster is known for his expertise in the effects of aging in skeletal muscle mitochondrial function, metabolism, insulin resistance, and obesity. His research has included how weight loss and exercise work together, especially in the presence of type II diabetes; whether exercise can prevent the seemingly inevitable losses of strength and muscle mass in older adults; and the use of positron emission tomography for insight into insulin resistance in skeletal muscle.

Consulting: GTX, Inc.

Neil Binkley MD, CCD

Summary: It is accepted that fracture risk increases dramatically due to "age" to a greater degree than bone mass declines. Some/much of this increased risk reflects concomitant sarcopenia; the age-related decline in muscle mass and function. It is likely that individuals with both sarcopenia and osteoporosis (sarcoporosis) are at greatest risk. Approaches to the diagnosis and treatment of the patient with sarcoporosis (both current and future) will be considered.

CME Objectives:
1. Appreciate the impact of the combination of low bone density and low muscle mass on fracture (either prevalence or risk)
2. Understand when to look for sarcopenia in your patient
3. Apply a multidisciplinary intervention to reduce fracture by improving both bone and muscle mass

### Biographic Sketch

Neil Binkley earned his medical degree from the University Of Wisconsin Medical School and, subsequently, received his training in internal medicine at the Marshfield Clinic. After several years in private practice, he returned to the University of Wisconsin in 1990 and completed a geriatric fellowship. He is Board Certified in internal medicine and geriatrics. In 1994, he was instrumental in establishing the UW Osteoporosis Clinical Center and the Osteoporosis Clinical Research Program. His research efforts focus on osteoporosis diagnosis, osteoporosis in men, vitamin D and the role of nutrition in bone loss. Dr. Binkley is a member of the American Geriatrics Society, American Society for Bone and Mineral Research, Gerontological Society of America, International Bone and Mineral Society, Wisconsin Bone Club, and the International Society for Clinical Densitometry.

### Speaker Disclosure of Commercial Interest

**Consulting:** Amgen, Eli Lilly, Merck, Tarsa  
**Research:** Amgen, Merck, Tarsa, Eli Lilly

### William J. Evans PhD

**Summary:** The frailty syndrome is recognized by geriatricians to identify elders who are at an extreme risk of adverse health outcomes. The physiological changes that result in frailty are complex and up to now have been extremely difficult to characterize due to the frequent coexistence of acute and chronic illness. Frailty is characterized by a decline in the functional reserve with several alterations in diverse physiological systems, including lower energy metabolism, decreased skeletal muscle mass and quality, altered hormonal and inflammatory functions. This altered network leads to an extreme vulnerability for disease, functional dependency, hospitalization and death. One of the most important core components of the frailty syndrome is a decreased reserve in skeletal muscle functioning which is clinically characterized by a loss in muscle mass and strength (sarcopenia), in walking performance and in endurance associated with a perception of exhaustion and fatigue. There are a number of physiological changes that occur in senescent muscle tissues that have a critical effect on body metabolism. The causes of sarcopenia are multi-factorial and can include disuse, changing hormonal function, chronic diseases, inflammation, insulin resistance, and nutritional deficiencies. This presentation will discuss the dysregulation of some biological mechanisms that may contribute to the pathophysiology of the frailty syndrome through age-related changes in skeletal muscle mass and function.

### CME Objectives:

1. Define sarcopenia and understand why it is an important clinical finding in your patients
2. Describe how to clinically diagnose sarcopenia
3. Implement interventions to improve muscle mass and function in patients
William J. Evans is a Vice President and Head of the Muscle Metabolism Discovery Performance Unit at GSK. He is also a Professor of Medicine in the Division of Geriatrics at the Duke University Medical Center. From 1997 – 2009 he was the Jane and Ed Warmack Chair of Nutritional Longevity and director of the Nutrition, Metabolism, and Exercise Laboratory in the Donald Reynolds Institute on Aging at the University of Arkansas for Medical Sciences. From 1993 to 1997 he was the director of the Noll Physiological Research Center and a Professor of Nutrition at the Pennsylvania State University and from 1982 to 1993 he served as the Chief of the Human Physiology Laboratory at the U.S.D.A. Human Nutrition Research Center on Aging at Tufts University. Much of his research has examined the functional and metabolic consequences of physical activity and diet in elderly people. His work has been featured on CBS evening news, 20/20, Good Morning America, the New York Times, PBS’s Infinite Voyage and NOVA and a variety of media outlets. In 2005, he was invited to testify before the Senate Special Committee on Aging on strategies to save Medicare through prevention of chronic diseases associated with aging.

Biographic Sketch

What related topics and or speakers should be considered for next year’s Annual Meeting?

Evaluation for Bret Goodpaster PhD

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<tr>
<th>Knowledge of Topic</th>
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Degree to which learning objectives were achieved

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What strategies will you implement?

Evaluation for Neil Binkley MD, CCD

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Degree to which learning objectives were achieved

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What strategies will you implement?

Evaluation for William J. Evans PhD

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Degree to which learning objectives were achieved

| Poor               | Poor                                     | Poor                | Poor                        |

What strategies will you implement?

Comments on the Session or Speaker:

Saturday, April 9 | 2011

What related topics and or speakers should be considered for next year’s Annual Meeting?
Consequences of sarcopenia

- Decreased muscle strength
- Reduced aerobic capacity
- Frailty
- Osteoporosis
- Falls & fractures
- Loss of physical function & independence
- Decreased activity levels
- Decreased basal metabolic rate (fat gain)
- Diabetes

Strength is lost more quickly than lean mass

- Men
- Women

* Significantly different from baseline
  P < 0.01

Delmonico et al. AJCN 2009.

Subcutaneous Adipose
Goodpaster: The Role of Fat in the Age-Related Loss of Muscle Function

Changes in Thigh Muscle Size and Adipose Tissue Content in All Men and Women

Effects of Physical Activity on Muscle Size

Effects of Physical Activity on Muscle Quality
Effects of Physical Activity on Intermuscular Adipose Tissue

![Graph showing IMAT Area change (cm²) for Control and Physical Activity groups.](image)

Limitations of the Current Paradigm About the Cause of Age-related Loss of Mobility

- Current common belief: decreased mobility with age is due to decreased muscle mass
- However, Health ABC has shown that:
  - Strength declines 3X faster than mass
  - Weakness and increased muscle fat are correlated with disability
  - After adjustment for strength and muscle fat, the association between muscle mass and risk of disability is weak and not significant
- Decreased quality of muscle is more important than decreased mass
- What ‘quality’ of muscle determines mobility?
- What are the mechanisms that may link muscle fat infiltration with muscle function?
Sarcopenia

Sarc for flesh (muscle), penia for deficiency

Defined as the age-related gradual loss of skeletal muscle mass, strength and function.

This condition is both a process and a diagnosis.

We Should Consider “Sarcoporosis” as a Diagnosis

Commonalities in the Pathogenesis of Osteoporosis and Sarcopenia

- Reduced physical activity
- Hormonal changes
  - Sex steroids, GH/IGF-1
- Nutritional deficiencies
  - Protein, vitamin D
- Increased inflammation
- Genetics
- Sarcopenia increases falls risk
- Falls lead to fractures
Hip Fracture Patients Often Have Sarcopenia and Osteoporosis by DXA

313 white women with low-trauma hip fracture
Sarcopenia; ALM/Ht2 < 5.45 kg/m²
Osteoporosis; Femur T-score ≤ -2.5

“We show... A significant association between sarcopenia and osteoporosis in a large sample of hip-fracture women. Data supports... preventive strategies and treatment options for sarcopenia and osteoporosis targeting both bone and muscle...”


REPORT
Sarcopenia: European consensus on definition and diagnosis

Report of the European Working Group on Sarcopenia in Older People

- Criteria for the diagnosis of sarcopenia
  - Diagnosis is based on documentation of criterion 1 plus (criterion 2 or criterion 3)
  1. Low muscle mass
  2. Low muscle strength
  3. Low physical performance

Cruz-Jentoft, et al, Age Ageing, 39;412-423, 2010

REPORT
Sarcopenia: European consensus on definition and diagnosis

Report of the European Working Group on Sarcopenia in Older People

Suggested algorithm for case finding

Cruz-Jentoft, et al, Age Ageing, 39;412-423, 2010
Caveats for ALM Measurement

- Technologist intervention is often necessary for correct measurement of appendicular lean mass
  - One or both shoulder lines: 37/40 (93%)
  - Lateral boundary around hip: 16/40 (40%)
  - Center line between feet/legs: 5/40 (13%)

“DXA Quality Matters”

Libber, et. al, ISCD Annual Meeting, 2011
Muscle Metabolism Discovery Unit: Mission

Increase skeletal muscle size and enhance muscle quality.

New Mechanisms Directed at Skeletal Muscle
- Safe and potent anabolic agents
- Improved mitochondrial function
- Enhanced contractile properties

Aspirational goal:
- Improve functional capacity in weak and frail people
- Enhance quality of life and independence
- Prevent loss of muscle mass due to atrophy and/or cachexia

Cachexia
Fat vs. Muscle
- Cachexia: increased muscle protein degradation
  - Often associated with weight loss
  - Aggressive TPN can maintain body weight but not muscle
  - Loss of fat is a result of increased energy expenditure and inadequate energy intake
  - Loss of muscle mass is ALWAYS associated with increased mortality
  - Loss of body fat is likely a surrogate of loss of muscle
- There is no compelling evidence that patient “run out” of fat. Amino acid availability limits essential components of protein synthesis in all tissues
  - No mechanism for fat as the most important factor for survival.
  - Catabolic cytokines are associated with increased body fatness

Sarcopenia
Loss of muscle by age
- 20 - 40: Decreased physical activity, decreased type II fiber size and amount. Maintenance of type I fibers
  - Maintenance of VO_{2max} with training
  - Decreased sprinting capacity
- 40 - 60: Loss of motor units accelerates. Decreased sprinting capacity and VO_{2max} even with training.
  - Concomitant increase in fat mass. Relative contribution of dietary fat to total energy intake increases. Visceral fat increases (decreased androgen levels), adipokine levels increase
  - Insulin resistance down regulates rate muscle protein synthesis (post prandial).
Sarcopenia

60 -70:
- Reduced physical activity
- Reduced androgen production and menopause
- Insulin resistance: Impaired glucose tolerance and type 2 diabetes.
- Inflammation (increased total body and visceral fat)
- Nutritional deficiencies (increased need for protein, micronutrients)
  - Impaired appetite regulation

70+:
- Further reduction in physical activity
  - Weakness and accelerated loss of VO₂max
  - Bouts of enforced inactivity due to illness, hospitalization, depression
  - Fear of falling, Mild cognitive impairment
  - Increased body, visceral, and intramuscular fat
    - Macronutrient intake (%) constant - 35 - 40% of energy from fat
- Reduce muscle protein synthesis
  - Decreased efficiency of synthesizing muscle protein
- Increased muscle protein breakdown?
  - Inflammation, chronic diseases, poor regulation of ubiquitin expression (and ATP dependent protein degradation).

Excessive Loss of Skeletal Muscle Mass in Older Adults with Type 2 Diabetes
Park, SW, et al, Diabetes Care, June 23 (epub) 2009
- Older adults with either diagnosed or undiagnosed type 2 diabetes showed excessive loss of appendicular lean mass compared with non-diabetic subjects
- Thigh muscle CSA declined two times faster in older women with diabetes than non-diabetic counterpart

These findings remained significant after adjusting for age, sex, race, clinic site, baseline body mass index, weight change intention, and actual weight changes over time.
Eight weeks of progressive resistance exercise training resulted in a 200% increase in strength and a 10% increase in muscle size in 90-year-old nursing home residents.

Results and Conclusions

• Significant Type II fiber atrophy and Z band and myofibril damage were present at baseline
• Combined weight lifting and nutritional supplementation increased strength by 257% and Type II fiber area by 10.1%
• Exercise was associated with a 2.5-fold increase in muscle neonatal myosin and a 491% increase in muscle IGF-1

Results and Conclusions

• Strength gains were greatest in the group that strength trained and received a protein-calorie supplement
• Muscle fiber and strength increases were significantly related to increased energy intake
Conclusions

• Regulatory agencies (FDA, EMEA) do not consider aging a disease, condition, or indication and are unlikely to approve an “anti-aging” medicine.
• Great opportunity in treating conditions that are common in elderly people and contribute to diminished functional capacity loss of independence
• Challenges are great due to the complex nature of treating elderly, frail patients with multiple chronic diseases and low functional reserve
**Session Title**

10 years of Studying Osteoporosis in Men: What have we learned, how are they different?

**Time**

11:00 - 12:10 PM

**Location**

Grand Ballroom

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**Eric Orwoll MD**

**Summary:** The MrOS study is a large, multicenter, observational study of musculoskeletal health and fracture in older men. 5994 men over 65, recruited in six communities in the US in 2000-2002. The mean age was 74 years and the ethnicity was 89% Caucasian. Men were extensively characterized at baseline with biospecimen collections, and followed regularly thereafter for approximately 8 years including several repeat clinic visits and additional phenotyping. Issues that have implications for understanding fracture risk and fracture prediction have been studied including Vit D deficiency, the pattern of bone loss, the association of BMI and fracture risk, particularly in light of the high prevalence of obesity in many western societies, assessments of physical performance in predicting fracture risk, sex steroid levels and testosterone therapy. In this presentation, the cumulative knowledge that has been learned on why men fracture will be presented and discussed.

**CME Objectives:**

1. Analyze findings of important studies on osteoporosis in men
2. Compare differences between women and men with respect to osteoporosis
3. Discuss treatment approaches to men with osteoporosis

---

**Biographic Sketch**

Dr. Orwoll is Professor of Medicine and Attending Physician in the Bone and Mineral Section of the Division of Endocrinology, Diabetes, and Clinical Nutrition. He is an internationally recognized expert in the area of bone biology and metabolic bone disease, and has considerable experience in basic, clinical, and epidemiological research. Major areas of research interest include the epidemiology, etiology and therapy of osteoporosis in men, the evaluation of new diagnostics and therapeutics, effects of sex steroids on skeletal biology, and skeletal genetics. He has been the principle investigator for many projects supported by the NIH, VA and foundations. He also is an experienced leader in academic medicine, with extensive responsibility for clinical and translational research planning and management. He is the Associate Vice-President for Research at OHSU, Associate Dean for Clinical Research in the School of Medicine, and the Director of the Oregon Clinical and Translational Research Institute.

**Speaker Disclosure of Commercial Interest**

Nothing to Disclose

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**Evaluation for Eric Orwoll MD**

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**Comments on the Session or Speaker:**

What related topics and or speakers should be considered for next year’s Annual Meeting?
10 years of studying osteoporosis in men: what have we learned, how are they different?

**Risk Factors for Non-Spine Fracture**

<table>
<thead>
<tr>
<th>Hazard ratio (± 95% CI)</th>
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<td>Fracture at or after age 50yrs</td>
</tr>
<tr>
<td>Age &gt; 80 yrs</td>
</tr>
<tr>
<td>Total hip BMD (per 1 SD)</td>
</tr>
<tr>
<td>Any fall in last year</td>
</tr>
<tr>
<td>Unable to complete narrow walk</td>
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</tbody>
</table>

- Compared with having none (48.0% of men), having three or more of the clinical risk factors (4.9% of men) increased fracture risk 5-fold, independent of BMD.
- Having three or more risk factors and being in the lowest tertile of BMD was associated with a 15-fold greater risk than having no risk factors and being in the highest BMD tertile.

Other risks: SSRI, smoking, alcohol, RA, BMI, more...

**Rate of bone loss by baseline BMD**

Men with the lowest BMD lose bone faster. Same pattern if analysis is by absolute change.
Summary: bone loss in older men

- Age is associated with increasingly rapid bone loss, especially in men with existing low BMD.
- The cause of the increase in bone loss with age is incompletely known, but is multifactorial.
- Higher rates of bone loss are associated with higher fracture risk.
- Should men with low normal BMD (not yet in the range requiring treatment) routinely have a repeat measure in ~3 yrs?
- Can risk factors for fracture be improved to identify men at risk?
- Should men with the greatest rate of bone loss be treated earlier?

BMI and fracture risk in older men

<table>
<thead>
<tr>
<th>Definitions (BMI)</th>
<th>Underweight</th>
<th>Normal</th>
<th>Overweight</th>
<th>Obese 1</th>
<th>Obese 2</th>
</tr>
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<tr>
<td></td>
<td>&lt;18.5</td>
<td>18.5-25</td>
<td>25-30</td>
<td>30-35</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Underweight</th>
<th>Normal</th>
<th>Overweight</th>
<th>Obese 1</th>
<th>Obese 2</th>
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<tr>
<td></td>
<td>6 (0.1%)</td>
<td>1628 (27%)</td>
<td>3049 (52%)</td>
<td>1034 (17%)</td>
<td>207 (4%)</td>
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<tr>
<td></td>
<td>0</td>
<td>202 (32%)</td>
<td>309 (49%)</td>
<td>97 (15%)</td>
<td>24 (4%)</td>
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<tr>
<td></td>
<td>0</td>
<td>48 (38%)</td>
<td>61 (48%)</td>
<td>68%</td>
<td>12% (10%)</td>
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<tr>
<td></td>
<td>0</td>
<td>5 (4%)</td>
<td>5 (4%)</td>
<td>62%</td>
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</table>

Summary: obesity and fracture risk

- Low weight is a risk factor for fracture, and that’s important for fracture prediction.
- But, underweight men are uncommon in most Western societies and most non-vertebral and hip fractures occur in overweight and obese men.
- At any BMD, increased weight is not protective, and very obese men are actually at increased risk.
- Clinical algorithms for assessing fracture risk in overweight men have not been developed. Is physical performance assessment a key factor?
- BMD measures should be considered in overweight/obese men and, if low, pharmacological treatment may be appropriate.
- Should we recommend weight loss to reduce the risk of fracture, at least in the most obese?
Annualized change in muscle mass and function by age


Summary: decreased physical performance fracture risk

- Frailty/disability increases markedly with age.
- Muscle mass/strength are associated with bone strength.
- Increased rate of falls is associated with increased fracture risk. Low muscle strength and physical performance are associated with increased fall risk.
- Low physical performance (using simple clinical tests) is associated with increased fracture risk. The use of a simple performance test could be a practical addition to fracture risk assessment.
- What test is best?
- Do anti-osteoporosis drugs work in men who are at risk because of falls?
- In frail elderly, exercise intervention is effective in increasing physical performance, and probably in reducing fall risk. Its usefulness in reducing fractures is less clear.
JoAnn Caudill RT, BD, CDT

**Summary:** A live software and case review of common, as well as uncommon, problems that might confuse analysis and interpretation of DXA using the GE Healthcare GE Lunar system. This will be a case by case presentation of common errors performed the software, positioning, acquisition and analysis of DXA scanning of the lumbar spine, femur and forearm. Uncommon errors by the software and the technologist with be demonstrated. These cases will be presented and scrutinized, encouraging attendee’s interaction and problem solving.

**CME Objectives:**

1. Demonstrate common and uncommon problems that might confuse analysis and interpretation of DXA

---

**Biographic Sketch**

JoAnn is a registered radiology technologist by training with over 21 years of experience in the field of bone densitometry. Obtained advanced registry and certification in bone densitometry with the American Registry of Radiologic Technologist (2001) and the International Society of Clinical Densitometry in 1996. JoAnn serves as a support group leader for the National Osteoporosis Foundation; and is currently on the editorial board. JoAnn developed and implemented the Bone Health Program for the Erickson Living Retirement Communities in December 2005. JoAnn serves as a consultant/educator for the University of Maryland, Baltimore Hip Studies. JoAnn promotes bone health and densitometry education through outreach to medical providers, technologists and the community at large.

**Speaker Disclosure of Commercial Interest**

Nothing to Disclose

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**Comments on the Session or Speaker:**

**What related topics and or speakers should be considered for next year’s Annual Meeting?**
Challenging and Interesting Clinical Cases for Technologists

JoAnn Caudill, R.T.,BD,CDT
Bone Health Program Manager
Erickson Living Retirement Communities

Objectives

• Understanding DXA equipment technology
• Applying and current software features
• Performing proper DXA acquisition and analysis
• Trouble shooting problem cases
• Decision making by the technologist is an establishment of confidence between the interpreting physician and the technologist.
• Understanding your population is very critical in your utilization of DXA equipment and software

• The skill and knowledge base of the technologist is essential.

Facility Protocol

• AP Lumbar Spine
• Dual Femurs
• Forearm with presence of primary hyperparathyroid
• Forearm scan when a discordance of more than 1 SD between scan sites
• VFA with a lifetime height loss of 1.5”
Questions

• When should reimbursement determine patient diagnosis?

• When is it safe to step out of the (protocol) box?

Example: Due to apparent T-score discordance between AP spine and dual femurs, a FA scan was performed with the finding of OP.

Following the facility protocol to only perform VFA according to ISCD guidelines and more recently not performing VFA due to lack of reimbursement does not always help in diagnosis.
Although there was only a 3/4” lifetime height loss noted, further scanning utilizing VFA was performed.

**Finding:** Multiple mild compression fractures in the thoracic spine and Osteoporosis in the radius 33%.

1. **Were the dual femur, AP lumbar spine scans acquired and analyzed correctly?**

   **ANSWER:** Yes, in accordance to manufacturer, ISCD guidelines and facility protocol.

2. **Why would you perform the additional VFA scan?**

   **ANSWER:** The technologist’s further inquiry divulged a new onset of back pain. No records in the EMR or by the patient for work up lead to the decision to acquire the VFA.
3. **Staying within the parameters of the facility protocol and ISCD guidelines, would these fractures have been missed?**

**Answer:** Yes, and may have effected the patient’s clinical management.

**Conclusion:**
Equipment, competency and communication are key elements to a successful comprehensive bone densitometry facility!

*Don’t be afraid to step out of our comfort zone with confidence!*
The ISCD recognizes and thanks our 2011 abstract reviewers:

- Anita Colquhoun, MRT(N), CDT
- Claus Glueer, PhD
- Fergus McKiernan, MD, CCD
- Harold Rosen, MD, CCD
- Joan Neuner, MD, MPH
- Latarsha Whittaker, CDT
- Michael Lewiecki, MD CCD
- Robert Adler, MD, CCD
- Robert Comello M.S., RT(R), CDT
- Satvinder Singh Dhaliwal, PhD, CCD
- Sylvia Hom RT(R)(D), CBDT
- Thomas Hangartner, PhD
- Bill Leslie, MD, FRCPC, MSc, CCD
- Ed Leib, MD, CCD
- Glen Blake, PhD
- Helmut Kaessman, MD
- Larry Jankowski, CBDT
- Mary Ellen Csuka, MD, CCD
- Nelson Watts, MD, CCD
- Robert Blank, MD CCD
- Robert Downs, MD CCD
- Susan Broy, MD, CCD
- Tamara Vokes, MD, CCD
001 - Utility of Spine Bone Mineral Density in Fracture Prediction, a Retrospective Analysis
Tristan Blackburn and Edward Leib; Fletcher Allen Health Care University of Vermont
Recipient of Best Clinician Abstract and Young Investigator Award; Invited Oral Presentation

Background: Predicting individuals at risk to experience a fracture and modifying that risk is important in preventative health. The WHO’s Fracture Risk Assessment Tool (FRAX) defines osteoporosis in terms of femoral neck T-score and allows use of total proximal femur, but the lumbar spine is frequently used in clinical practice and its use in diagnosis is supported by the ISCD and the NOF. Our aim is to determine the positive predictive value of fracture prediction using the lowest value at the femoral neck, total hip or spine and comparing this to femoral neck alone. Methods: We performed a retrospective analysis of 15,033 post-menopausal women over 9.2 years combining clinical risk factors (CRF) and bone density (BMD) results. Subjects were age and sex matched with controls in a 1:4 ratio. We performed a logistic regression to assess the contribution of age, BMI, number of CRFs, race, and T-score to the presence of fracture. T-scores were defined as femoral neck, total hip, and lumbar spine. We performed a logistic regression for the contribution of presence of osteoporosis or osteopenia at each site to presence of fracture. Results: In individuals with normal BMD at the femoral neck, few were osteoporotic at the lumbar spine (<1%) and more were osteopenic at the femoral neck and osteoporotic at the lumbar spine. These patients comprise 10% of our study population and are, generally, younger. In those who are osteoporotic at the lumbar spine but normal or osteopenic at the femoral neck, there is a 31% and 30% increased risk of fracture respectively. For patients less than 60 years old, the odds ratio of having a fracture based on lumbar spine osteoporosis was greater than the odds ratio based on femoral neck osteoporosis. This reversed for those = 65 compared with those <65 years old. For each age category, the presence of osteoporosis measured at the total hip correlated best with presence of hip fracture and was better than taking the lowest T-score at any site. Conclusions: It is most important to measure BMD at the lumbar spine in younger, post-menopausal women for fracture prediction. In our population total hip BMD is the best predictor of fracture. The spine BMD is a better predictor of fracture in women 60 years and younger. When using FRAX in post-menopausal women aged 60 or less, we recommend the 10-year fracture prediction be increased by 30% in those with osteoporosis at the spine and osteopenia or normal BMD at the femoral neck.

002 - Technical Excellence is Required for Total Body DXA Acquisition and Analysis
Jessie Libber1, Jesse Donnenwerth2, Neil Binkley1, Diane Krueger1; 1University of Wisconsin Osteoporosis Clinical Research Program, 2University of Wisconsin Department of Intercollegiate Athletics
Recipient of Best Technologist Abstract and Young Investigator Award; Invited Oral Presentation

Total body (TB) DXA is used in various situations, some of which require regional measurements. Such regional assessment may require more stringent patient positioning and analysis than needed for classical whole body assessment; thus greater attention to technical aspects may be required. The purpose of this report is to describe a uniform approach for TB DXA positioning and analysis, identify the frequency with which autoanalysis inaccuracies occur and evaluate their impact on regional body composition. In an effort to minimize variability, we implemented a rigorous protocol for TB DXA. Patients are positioned per GE recommendations. Bulky clothing is avoided; to facilitate region of interest (ROI) definition, fingers are bound together with hands placed as far from the body as possible. Additionally, sequential steps are followed for large individuals to facilitate containment within the scan field. Analysis ROIs are placed per GE recommendations: the chin line is placed directly under the mandible, the arm ROI’s are defined by placing a line between the glenoid and humeral head positioned to bisect the axilla, the iliac crest line defines the leg ROIs with a centerline dividing the legs. To evaluate the frequency with which changes to autoanalysis are needed and the impact on results, TB scans were obtained in 40 individuals (20F/20M) age range 18-93 years, mean BMI 24 kg/m2 (range 19-32). Analysis was performed using EnCore v13.4. Changes to the autoanalysis were often needed; the jaw line was altered in 39/40 (98%), one or both shoulder lines in 37/40 (93%) and the lateral boundary around the hip in 16/40 (40%). TB and regional BMD and body composition results were compared using linear regression and Bland-Altman analyses. Excellent correlation (r² 0.98-1.00) for bone, fat and lean mass was observed for the TB and all subregions; virtually no bias was present. However, mean bias of 43 and 203 grams respectively was observed for android fat and appendicular lean mass (ALM). In this cohort, a difference between auto and manual analysis greater than our LSC was observed in 5% for android fat and in 35% for ALM. In conclusion, manual correction of automated analysis in TB
DXA scans is commonly needed. These alterations do not affect TB measures, but do impact regional body composition results, notably ALM, in individuals. To avoid such preventable variation, technical excellence is required for optimal TB DXA assessment.

003 - Denosumab Significantly Improves Total, Trabecular, and Cortical Estimated Strength at the Hip and Spine Over the Duration of the FREEDOM Trial

Denosumab (DMAB), a fully human monoclonal antibody to RANKL, decreased bone resorption, increased bone mineral density (BMD), and significantly reduced the risk of new vertebral, nonvertebral, and hip fractures in the FREEDOM trial (Cummings et al, NEJM, 2009:361:756). FREEDOM was a phase 3 trial in women aged 60-90 years with postmenopausal osteoporosis randomized to 60mg DMAB or placebo (Pbo) every 6 months, plus daily calcium and vitamin D supplementation. In a FREEDOM substudy, hip and spine quantitative computed tomography scans were obtained at baseline, 12, 24 and 36 months. These scans were used to estimate patient-specific hip strength for a simulated sideways fall and L2 spine strength for a simulated compression overload, using non-linear 3D finite element analysis (51 DMAB; 48 Pbo). All analyses were exploratory. For women treated with DMAB, hip strength increased significantly compared with baseline by 5.4% (p<0.0001) at 12 months; this strength increased over time reaching 8.4% (p<0.0001) at 36 months (Fig. 1). In contrast, for women receiving Pbo, hip strength did not change at 12 months and decreased at 36 months compared with baseline (-5.4%, p<0.0001). The same temporal trends were observed at the spine but the changes were much larger than at the hip: at 36 months, spine strength increased by 18.1% (p<0.0001) for the DMAB group and decreased by -4.1% (p=0.004) for the Pbo group. For both the hip and spine, DMAB subjects displayed significant increases in cortical strength, estimated from the outer 3mm of bone at the hip and the outer 2mm at the spine, as well as in trabecular strength (Fig. 2). Pbo subjects exhibited a preferential loss of trabecular strength. Additionally, DMAB-related improvements in hip and spine strength were significantly correlated (r=0.38, p=0.02). At 36 months, all DMAB subjects had increased spine strength, and all but 2 had increased hip strength; while strength decreases were observed for the majority of Pbo subjects. From these findings, we conclude that DMAB treatment significantly increased both hip and spine estimated strength after 12 months compared with both baseline and Pbo, and positively influenced both the trabecular and cortical compartments. Hip and spine strength continued to improve over 36 months of treatment. These improvements in total strength, and in particular cortical strength, extend the understanding of the impact of DMAB in vertebral and nonvertebral fracture reductions.
004 - Simplified four-compartment body composition model using dual-energy x-ray absorptiometry and total body water

Joseph Wilson and John Shepherd; University of California San Francisco

Recipient of Young Investigator Award; Invited Oral Presentation

Two-compartment (fat and lean) body composition models from dual-energy x-ray absorptiometry (DXA) scans are not sufficient to measure changes in lean tissue mass during muscular degenerative disease progression. Although DXA is the de facto gold standard technique of measuring percent fat because of its high precision, extensive availability, good safety profile, and broad clinical range, DXA has significant errors in measuring total body functional lean soft tissue (protein) because water and protein both contribute to the estimated mass in the lean compartment. Therefore, variations in hydration status and water content in adipose tissues change the estimated protein content. The purpose of this study was to develop a method (4CDXA) to measure functional lean mass (protein) independently of water and lipid mass. Our approach was to solve for total body protein by combining DXA raw data with external measures of total body water.

An analytical solution is presented using the special case of dual-photon absorptiometry (DPA). We then show how this is empirically extended to DXA. The result is a four-compartment model that estimates each of the molecular body compartments (water, protein, bone mineral, and lipid) independently. A calibration phantom with 27 distinct regions of interest (ROI) of biologically-viable compositions was created and imaged on a Hologic Discovery DXA system. The accuracy and precision of the modeled protein and lipid masses will be presented. Preliminary data on several in vivo examples will be contrasted to the complete 4-compartment model including body density measures. We conclude that the 4CDXA method can provide quantitative information of the functional protein mass from a DXA and TBW measure and potentially be superior to DXA lean mass alone in monitoring functional tissue changes.

005 - Long-term clinical studies face common and challenging quality issues with device relocations and upgrades

Lorena Marquez, Bo Fan, Silva Arslanian, John Shepherd

1University of California San Francisco, 2Children’s Hospital of Pittsburgh

Recipient of Young Investigator Award; Invited Oral Presentation

BACKGROUND: In long term clinical studies, it is often necessary to upgrade or replace dual-energy X-ray Absorptiometry (DXA) systems. This is generally to be avoided since subtle shifts in the calibration of the bone mineral density (BMD) and body composition measures may obscure study findings. The purpose of this paper is to examine the validity of phantom methods used to calibrate the new DXA systems to the original. METHODS: During the course of the TODAY (Treatment Options for type 2 Diabetes in Adolescents & Youth) study, one site upgraded their system from a GE Lunar Prodigy to an iDXA. In addition, the iDXA system was relocated fourteen months later. In each case, the site performed both in vivo and phantom cross calibration procedures. For cross-calibration, the in vivo population consisted of 34 patients (age: 43.6 ± 12.0 years, weight: 67.1 ± 11.6 kg, height: 164.2 ± 7.2 cm) who received a whole body, spine, and hip scan. For the relocation, twenty-four patients (age: 40.0 ± 11.3 years, weight: 69.3 ± 15.0 kg, height: 168.4 ± 9.2 cm) received a whole body and spine scan. The Hologic whole body phantom and block phantom, and the European Spine Phantom were scanned in each case. Bland-Altman and liner regression analyses were used to represent differences in each comparison. RESULTS: Using the in-vivo data, the Prodigy and iDXA results were highly correlated, R² ranged from 0.95 (WB BMD) to 0.9997 (WB MASS). Systematic differences were observed for the whole body measures, ranging from 5.91% (BMC) to -0.96% (LEAN). The changes in whole body phantom measurements were substantially different from the in vivo population and did not fall within the best-fit 95% confidence range. For the relocation case, the whole body phantom again yielded statistically different results from the in-vivo cross-calibration study. Without the relocation in-vivo calibration dataset, correction factors would have been generated that ranged from -2.14% to 2.48% while the in-vivo cross calibration showed no significant differences (-0.59 to 0.54%). CONCLUSION: In this example, the Hologic Whole Body Phantom did not accurately represent the calibration differences in whole body scans incurred because of system upgrade and system relocation. Superior and practical whole body phantoms that better
010 - An evaluation of bone mineral density screening and technology frequency (2005-2008) among US women age 50 and older in a commercial medical claims database

Carrie McAdam-Marx, Sudhir Unni, Scott Nelson, Xiangyang Ye, Nancy Nickman
University of Utah Pharmacotherapy Outcomes Research Center

Recipient of Young Investigator Award

Background: Medicare reimbursement rates in the United States (US) for BMD testing were reduced in 2007 due to the US Deficit Reduction Act of 2005. This study evaluated annual BMD testing frequency and BMD imaging technique usage in US women age =50 over a time frame encompassing the reimbursement reduction. The study purpose was to determine if testing rates and technology used changed in concordance with reimbursement reductions. Methods: The MedStat MarketScan database captures medical and pharmacy claims data for patients with commercial insurance including those with employer sponsored Medicare supplemental coverage. Included women had continuous plan enrollment from 1/1/2004 – 12/31/2008, were age =50 years by 12/31/2004, and were not diagnosed or treated for osteoporosis during 2004. Descriptive statistics were used to characterize BMD testing frequency, time between tests, and technology type (dual energy x-ray absorptiometry [DXA] vs. other type) overall and for the subset of women age =65. Calendar year osteoporosis incidence rates were identified and stratified by diagnosis occurring after BMD test in the absence of fracture or diagnosis after fragility fracture. Results: The final study cohort included 1,365,859 women. Mean age on 1/1/2005 was 61.1 ±9.8 years; 29.7% were age =65. Overall, 42.5% received 1+ BMD test within the 4-year study period; 10.4% received 2 tests. Of those age =65, 37.9% received 1+ BMD test; 9.0% received 2 BMD tests. The average length of time between tests was 25.6 ± 8.1 months overall and 26.0 ± 7.8 months for women age =65. All BMD testing rates and distribution of tests by technology type stayed relatively constant over the 4-year study period (average 95.1% central DXA, 2.3% peripheral DXA). Of the 186,155 women age =50 with osteoporosis (13.6% of overall), 75% were diagnosed following BMD test, while 4% were diagnosed after fragility fracture. Of the subset of women age =65 with osteoporosis (74,179 or 18.3% of the subset) 71.5% were diagnosed following BMD test, and 6.7% were diagnosed after fragility fracture. Conclusion: Overall BMD testing rates and imaging techniques used remained relatively constant over the study period. Thus, osteoporosis screening by BMD in Medicare-eligible women with commercial supplemental health insurance did not appear to have declined due to Medicare reimbursement reductions for BMD testing.

011 - DXA Use in Athletes: Exploration of Regional Lean Mass Distribution and Correlation with Performance

Jesse Donnenwirth, Bryan Heiderschiet, Jessie Libber, Ellen Fidler, Diane Krueger, Neil Binkley, University of Wisconsin Department of Intercollegiate Athletics, University of Wisconsin Department of Orthopedics and Rehabilitation, University of Wisconsin Osteoporosis Clinical Research Program

Recipient of Young Investigator Award

DXA is commonly used for body composition assessment. However, the literature correlating distribution of lean mass as measured by DXA with performance variables such as force/power capabilities is quite limited. Moreover, regional mass distribution and its potential relationship with sports performance have not been evaluated. Therefore, the purpose of this report is to characterize DXA-measured lean mass regional distribution in Division 1 college student-athletes and to evaluate the correlation of lean mass with athletic performance as measured by jumping mechanography. In 159 (54F/105M) Division 1 student-athletes at the University of Wisconsin, total body DXA was performed using a GE Healthcare (Madison, WI) Lunar iDXA densitometer. All scans were obtained by ISCD-certified technologists and analysis was performed using EnCore software version 13.3. On the same day as DXA scanning, a subset (n = 25) performed counter-movement jumps while peak jumping force and power were measured using a force plate (Leonardo, Novotec, Pforzheim, Germany). Of the 159 student-athletes, asymmetries in lean mass distribution between the bilateral legs and sides of the trunk (p < 0.0001) were present in virtually all. Specifically, an average asymmetry of 1.8 ±1.4% (range 3-1,299 g) was observed between the right and left legs, with a 1.9 ± 1.3% (range 8 - 2,042 g) present between the right and left sides of the trunk. Of note, whichever lower extremity displayed greater lean mass, the opposite side trunk displayed greater lean mass, suggestive of a contralateral compensation in 70% of this cohort. In the subset of 25 athletes, asymmetries in lean mass were not apparent in the trunk. Therefore, the purpose of this report is to mimic in vivo calibration conditions are desperately needed. AcknowledgmentNIDDK: TODAY (Treatment Options for type 2 Diabetes in Adolescents & Youth).
male athletes, lean mass of the total body and body sub-regions (i.e., leg, trunk, right or left side) were highly correlated with force ($r^2 = 0.76$, $p < 0.01$) and power ($r^2 = 0.63$, $p < 0.01$) produced during counter-movement jumps. Despite differences in lean mass distribution, the force and power did not differ between right and left legs, further supportive of a functional performance link between the lower and upper body. In conclusion, lean mass as measured by DXA is highly correlated with vertical jumping force and power. Furthermore the greatest regional lean mass distribution between the legs and trunk is commonly contralateral in athletes. Subsequent investigation will explore other performance variables linked to mass distribution, symmetry and ground reaction forces.
AIMSTo describe the BMD results of two selected groups submitted to DXA examinations, analyzing all skeletal sites in the postmenopausal women classifying osteoporosis according to the OMS criteria, and the two major skeletal sites in the premenopausal women compared to respectively IMC. In postmenopausal women the results were also compared to evaluate if additional forearm study was of value, to osteoporosis diagnostic.

MATERIAL AND METHODS: We studied 343 postmenopausal women that came for routine DXA clinical investigation, November 2008 to October 2009, all submitted to forearm additional studies, with lumbar spine and hip sites qualified for diagnosis, and 159 premenopausal women with lumbar spine and hip sites analyzed only. The BMD was measured using GE Lunar DPX NT (pencil beam) at lumbar spine, hip and forearm for all the patients. A control phantom was scanned everyday and all DXA measurements were performed by the same experienced operator. All patients agreed with the complimentary DXA forearm study in the postmenopausal group. We excluded two patients because of surgical menopause and non valid lumbar spine site.

RESULTS: The mean age was 60 years (SD 13.2). We found significant statistically difference between means BMD values comparing pre and postmenopausal women in all skeletal sites. In the postmenopausal group the means T-score was -1.7 (lumbar spine); -1.5 (neck); -1.1 (total hip) and -1.7 (radius 33%). Comparing the skeletal sites T-score < or = -2.5 (osteoporosis) we observed that the radius 33% diagnosed more than the other sites, specially in elderly patients, probably because of the degenerative changes. The best osteoporosis diagnostic agreement was between radio 33% and neck (56%). When we considered the risk factors like family fractures, smoking and previous fractures, the last one was associated with the low BMD in both postmenopausal and premenopausal women, reaching statistically significance, mostly at neck site (P-value = 0.001). In the premenopausal group we did not find BMD below the values considered normal for the age. There was significant statistically difference according to IMC in pre e postmenopausal women.

CONCLUSIONS: The forearm seemed to be useful in postmenopausal elderly patients. As a risk factor, the previous fractures were more relevant. The importance of the relation IMC x BMD according to pre and postmenopausal women needs further studies with a larger sample.
are summarized in the Table. CONCLUSIONS In postmenopausal women with osteoporosis, denosumab significantly increased BMD across all measured skeletal sites over 36 mos. The increases in BMD occurred early and were robust and consistent at both primarily trabecular and primarily cortical bone sites, and were observed in nearly all subjects.

Table. Mean (95% CI) Changes in BMD at 36 Months

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Denosumab</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine</td>
<td>0.2 (-0.5, 1.0)</td>
<td>9.4 (8.6, 10.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total hip</td>
<td>-1.1 (-1.7, -0.6)</td>
<td>4.8 (4.3, 5.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>-0.9 (-1.6, -0.2)</td>
<td>3.9 (3.2, 4.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Trochanter</td>
<td>-0.8 (-1.5, -0.1)</td>
<td>7.1 (6.5, 7.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1/3 Radius</td>
<td>-1.2 (-1.8, -0.7)</td>
<td>2.2 (1.7, 2.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total body</td>
<td>-0.9 (-1.2, -0.5)</td>
<td>3.2 (2.9, 3.5)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

P value from baseline and from placebo

102 - PHYSICIAN TIME REQUIRED FOR PREPARATION OF BMD REPORTS USING BONESTATION, A SOFTWARE SYSTEM FOR REPORT PREPARATION AND DATA/WORKFLOW MANAGEMENT

Jessica Wong, LaTarsha Whittaker, Alan Malabanan, Harold Rosen; Beth Israel Deaconess Medical Center

BACKGROUND: Given the sharply curtailed reimbursement for densitometry, it is important to maximize efficiencies in densitometry practices. We recently started using BoneStation, a work-flow, data-storage and reporting system, which eliminates the “mechanical” chores in reporting, and we previously reported about savings in time, and improvements in image-clarity. We wondered whether BoneStation also helps reduce the amount of physician-time spent reviewing each BMD. CONCLUSIONS: Studies based in different centers once FRAX is incorporated into densitometry reporting are required before we have a truly representative estimate of physician time required for reporting. So far it seems that time-based reimbursement would give higher reimbursement for repeat than for initial BMDs. However certainly in our center reporting using BoneStation seems to have resulted in significant reductions in the amount of physician-time spent reviewing each BMD.

103 - SEVERE VITAMIN D DEFICIENCY AND LOW BONE MASS IN A TEENAGER ON A FAD DIET

Svekct Yigit, Priya Phulwani, Donna Steben, Elizabeth Estrada; Connecticut Children’s Medical Center

A 16 year old male presented with asymptomatic hypocalcemia diagnosed at a primary care visit for an unrelated complaint. He was previously a healthy teenager with normal growth and sexual maturation. His initial total calcium was 6.8 mg/dl (normal:8.4-10.2 mg/dl) with an ionized calcium level of 0.96 mmol/L (normal:1.2-1.35 mmol/L). His PTH was significantly elevated at 257 ng/L with 25 OH vitamin D level was 5.5 ng/ml. He was strictly on buckwheat diet with no nutritional supplements. He had severe low bone mass at lumbar spine (L1-4) and total body less head DXA measurement (Table). He was treated with high dose vitamin D and calcium replacement therapy. His calcium and vitamin D levels normalized in three months. His bone mineral density improved significantly in 6 months and normalized in a year (Table). In conclusion, fad diets may cause severe vitamin D deficiency and bone mineral density (BMD)
response to appropriate calcium and vitamin D replacement is dramatic.

### 104 - DO CHANGES IN THE FEMORAL NECK BOX SIZE MAKE SIGNIFICANT DIFFERENCES IN FEMORAL NECK BMD?

Sarah Morgan¹, Frederick Peace², Nancy Nunnally³, Leandria Burroughs³; ¹The University of Alabama at Birmingham, ²School of Public Health, ³The UAB Osteoporosis Prevention and Treatment Clinic

The default size of the femoral neck box on a Hologic scanner is 49 x 15 pixels. Occasionally when reviewing DXA scans the size of the analyzed femoral neck box differs from 49 x 15 pixels. We hypothesized that alterations in the size of the femoral neck box would significantly change the femoral neck bone mineral density (BMD). After obtaining institutional review board approval, we systematically evaluated the effect of altering the pixel size on femoral neck BMD in the same individual. One hundred scans were randomly selected and the DXA technologists systematically changed the length of the femoral neck box by adding or subtracting pixels (51 x 15 pixels and 47 x 15 pixels). In addition, the width of the femoral neck box was systematically changed by either adding or subtracting one pixel (49 x 16 and 49 x 14). The population randomly selected was 14% male, 86% female, 25% African American, 4% Asian, 1% Hispanic and 70% Caucasian. The mean age of the population was 60 ± 12.1 years. The BMD of differing femoral neck box size is displayed below. There was not a significant difference in the femoral neck bone mineral density, compared to the default pixel size for any other pixel box size. Clinicians should be alert to the size of the femoral neck box in pixels; however, small differences in femoral neck size have no significant effect on femoral neck BMD.

### 105 - Evaluation of An Automated Morphometry Software Program (SpineAnalyzer™) on VFA Images

Diane Krueger¹, Joes Staal², Peter Steiger², Bjoern Buehring³, Harry Genant⁴, Neil Binkley⁵; ¹University of Wisconsin Osteoporosis Clinical Research Program, ²Optasia Medical, Inc., ³Cleveland Clinic, ⁴University of California San Francisco/Synarc

Prior vertebral fracture increases future fracture risk. Thus, knowledge of fracture status is important in clinical practice. However, as many vertebral fractures are unappreciated, spine imaging is necessary for optimal clinical decision-making. Densitometric vertebral fracture assessment (VFA) to determine fracture status is a valuable addition to clinical densitometry. However, VFA identification of mild fractures is challenging. It is plausible that morphometry may facilitate VFA fracture identification. As such, this study evaluated the utility of SpineAnalyzer™, a proprietary software program using 95-point morphometry, on VFA images acquired with a GE Healthcare iDXA. VFA was performed in 103 subjects (79 F/24 M). Their mean (range) age, lowest T-score (spine/hip) and BMI was 72.6 (47.7 to 91.5) years, -1.5 (+3.7 to -3.4) and 26.5 kg/m² (17.1 to 36.5) respectively. Many individuals had spinal degenerative changes making fracture identification challenging. VFA interpretation was performed using printed images and applying the Genant visual semi-quantitative approach (VSQ) by a recognized expert whose reading was defined as the “gold standard” and by a non-radiologist clinician experienced in VFA interpretation. An ISCD-certified technologist used SpineAnalyzer to identify vertebral deformities in these same scans. Manual morphometry point adjustment was required on most images, primarily limited to some abnormal and/or upper thoracic vertebrae. The main outcome parameter was vertebral fracture number and grade from T4-L4 using SpineAnalyzer compared with gold standard and clinician. In this cohort, the gold standard analysis identified 53 vertebral fractures; SpineAnalyzer identified 43 and the clinician 41. For analysis as normal (VSQ 0) or fracture (VSQ 1, 2 or 3), moderate agreement was observed between the gold standard and both SpineAnalyzer and the clinician (kappa 0.54 and 0.50 respectively). When limiting evaluation to just grade 2 and 3 fractures (VSQ 0, 1 together vs. VSQ 2, 3 together) moderate agreement with the gold standard was again observed; kappa 0.57 for SpineAnalyzer and 0.56 for clinician. In conclusion, when evaluating VFAs in a cohort with substantial degenerative disease, SpineAnalyzer morphometry performed by a technologist is similar to an experienced clinician when comparing to a gold standard. Studies evaluating other populations are needed to better characterize the utility of SpineAnalyzer application to VFA image.

### 106 - Evaluation of Standardization Equations as a Substrate for Scanner Specific In Vivo Measurements

Kenneth Gaither, Thomas Fuert, Gillian Moyle, Elsa Griffith; CCBR-Synarc, San Francisco, CA
Background When switching from one scanner manufacturer to another, obtaining correction factors derived from volunteer subject measures on the two scanners is the current best practice method but these data can be logistically difficult to obtain, exposes volunteer subjects to additional radiation and is time consuming. Using published data of standardized BMD (sBMD) it is possible to create generic equations to convert from one scanner make to another which would have the advantage of being available when a scanner is no longer serviceable or volunteer subject measures are not practical. Methods Measures of AP Spine and Femur were obtained for two volunteer subject groups on both QDR-4500’s and Prodigy’s for the purpose of creating scanner specific cross calibration correction factors. Scans were analyzed at CCBR-Synarc using standardized procedures and result data were loaded into CCBR-Synarc’s data systems for analysis. The mean and standard deviation for AP Spine and Femur data were calculated for both subject groups (Table 1). Lunar data from both subject groups were converted to Hologic equivalent data using conversion equations derived from published sBMD equations. Means and standard deviations of the generically converted data were then compared against the original in vivo Hologic data and percent differences calculated (Table 1). Results For Group 1 and 2, mean Spine BMD for the QDR-4500, converted data and percent difference were 0.864g/cm², 0.874g/cm² and 1.2%; and 1.044g/cm², 1.071g/cm² and 2.7%. Similarly, Group 1 and 2’s mean Femur BMD for the QDR-4500, converted data and percent difference were 0.851g/cm², 0.834g/cm² and -2.0%; and 0.958g/cm², 0.988g/cm² and 3.1%. Conclusion Generic conversion equations were used to compare data acquired from two groups of volunteer subjects. While the generic conversion equations reduced much of the difference between the QDR-4500 and Prodigy data, there remained a significant difference between the two. This could be due to either a second order variation in the individual scanner calibrations or a systematic difference between the models used for these two subject groups and the models used for the standardization equations. This tends to suggest that using generic conversion equations may be a useful tool when no volunteer subject data is available but should not be considered an adequate or appropriate substitute for specific scanner to scanner conversion factors.

107 - Does DXA Precision Differ by Gender?

Nellie Vallarta-Ast, Jessie Libber, Mary Checovich, Diane Krueger, Neil Binkley; UW Osteoporosis Clinical Research Center

The ISCD recommends that precision assessment should be performed “using patients representative of the clinic’s patient population.” Given larger male bone size, it is possible that precision differs between men and women; however this has not been evaluated. The purpose of this study was to compare DXA precision in older men and women obtained by three ISCD-certified technologists. Thirty women and 30 men age 65+ were recruited and scanned using a GE Healthcare iDXA densitometer by each technologist (total n = 180). Data from the first technologist to complete this study are reported here. Two exams of the lumbar spine, bilateral hip, non-dominant forearm and total body were acquired on each subject with repositioning between exams. Least significant change (LSC) was determined using the ISCD precision calculating tool. The men and women were of similar age: 78.8 years ± 8.1 vs. 75 years ± 6.4 respectively (p = 0.3) but men were larger than the women: height: 174.5 cm ± 6.4 vs. 162.4 cm ± 5.1 (p<0.0001); weight 82.3 kg ± 13 vs. 70.5 kg ± 16.1 (p<0.0001) and BMI; 27.0 kg/cm² ± 2.3 vs. 26.7 kg/cm² ± 4.4 (p=0.002). As could be expected, male bone area (L1-L4, mean total femur and 1/3 radius) was larger (p < 0.00001) than females. The BMD LSC was virtually identical for both genders at the L1-L4 spine, mean total proximal femoral and 1/3 radius sites. Similarly, total body BMD and appendicular lean mass LSC was essentially identical in men and women (Table). This time scan acquisition is incomplete for the other two technologists; we will subsequently report these data and assess inter-technologist precision. In conclusion, this study suggests that the same LSC values can be applied to men and women.

108 - Identification of Atypical Subtrochanteric Femoral Fracture by DXA Exam

Michael McClung, Jenny Treiber, Edward Mossman; Oregon Osteoporosis Center

Atypical femoral fracture has been reported in patients on long-term bisphosphonate therapy. The diagnosis is usually made when the patient presents with a low-trauma fracture. Some patients have identified pre-fracture when they present with thigh pain and radiographic features including cortical thickening and...
focal cortical stress reaction, often seen bilaterally. We observed a patient on long-term bisphosphonate therapy with changes on proximal femur DXA that led to diagnosis of subtrochanteric stress fracture of the femur. A 72 year-old woman was found to have low bone mineral density in March 2000 (T-score values of lumbar spine (LS) and left total hip (TH) were -2.1 and -1.1, respectively. She began alendronate therapy which she took regularly without intolerance. She had not experienced a fracture and had no risk factors for bone loss other than her age and menopausal status. She took calcium and vitamin D supplements. Follow-up DXA testing was performed in June 2010. T-score values in the LS and left TH were -2.1 and -0.8, respectively. Focal thickening of the lateral aspect of the left femoral shaft was noted that was not present on her previous scan or her right femur. These findings were mentioned in the DXA report. Radiographs of the left femur demonstrated a stress fracture in the lateral cortex with callus formation. No generalized thickening of the femoral cortex had occurred between the two scans. She has no pain in her left thigh or groin. While DXA images are not used for diagnosis, interpreters of the scans should recognize abnormal radiographic features, including those of subtrochanteric femoral stress reactions, and mention them in the DXA report to the referring clinician so that appropriate evaluation and management can be effected.

109 - Short term versus long term precision. The Groote Schuur Hospital experience.

Masha Maharaj; Groote Schuur Hospital, University of Cape Town, South Africa

Introduction: According to the ISCD 2007 official positions of International Society for Clinical Densitometry, each DXA facility should determine its own precision error and least significant change (LSC). Previous authors have described short term and long term precision studies. AIM: To calculate and compare the precision and LSC in order to determine if there was any difference between the short term and long term precision studies in our unit. Methods and methodology: Two groups of 30 consecutive patients who had short term and long term follow-up studies. Short term was classified as two scans done on the same day. The long term was classified as a second scan done on day 2-21 after the baseline scan. The BMD precision study was done on the Hologic Discovery W QDR machine. All scans were done by the same experienced radiographer. The short term group comprised 23 females and 7 males with the minimum age being 22 and the maximum age being 79 years. The long term group comprised 27 females and 3 males with the minimum age being 34 and maximum age 69.5 years. Patient thickness and BMI was calculated for both groups. Results: In the short term the lumbar spine precision was better than that of the total hips. In the long term the total hip precision was better than that of the lumbar spine. The lumbar spine precision in the short term was better than the long term. The precision error in the total hips individually and in the two study groups was similar. Despite the precision values in the femoral neck being similar in both study groups, it had the highest precision error. Comment: At our centre the most reproducible site for follow-up appears to be the total hip.

110 - Lumbar spine or femur DXA scan? - densitometry profile in 740 patients with osteoporosis evaluated through central DXA

Carmen Barbu1, Dariana Ionita2, Catalina Poiana3, Simona Fica3, 1Carol Davila University, 2Elias Hospita, 3C.I. Parhon Institute

Aims: Aim of this study was to evaluate the densitometry profile of the patients with osteoporosis in terms of DXA scan sites and the differences between lumbar spine and femoral neck in terms of T score. Methods: 740 medical records of patients (718 postmenopausal women and 22 men, mean age 61.7 yrs) treated for osteoporosis through the National Program between 2008-2009 in two different endocrinology departments were evaluated. We compared the profile of the investigation (skeletal sites which were scanned) excluding that cases with fractures imposing specific sites to be measured; we calculated the difference between lumbar T score (in absolute value) and femoral neck T score (as negative value) and analyze the relation with the age of the patients. Results: We found that 74.3% of the patients had two standard regions scanned through DXA (lumbar spine and femoral neck), 25.2% had only lumbar spine scan, 0.01% only femoral neck and 0.49% had total body scan. In the 550 patients with 2 regions scanned we found 27.2% patients with no more than 1 SD difference between lumbar spine and femoral neck T score; we did not found any significant difference in terms of age between these patients and the rest of the study group. When segregate this group according to which T score is greater, only 10.3% had lower femoral T score and 89% had lower lumbar T score; mean age was not significantly different between these groups. However, the difference between lumbar T score and femoral T score analyzed by every five years of age, showed a slightly increase until 55-60 yrs age, with a significantly decrease in the next 15 years (where looks like a plateau), followed by significantly increase from the
age of 75 yrs. Conclusions: Our data suggests that even in conditions of good DXA evaluation reimbursement (available in the study period) there are still 25% patients without standard DXA evaluation at two skeletal sites. 72.8% had more than 1 SD difference between lumbar and femoral neck T score suggesting that evaluation of one site (femoral neck) could underestimate the fracture risk in spine. Overestimation of the lumbar spine due to artifacts seems to be maximum between 60 and 75 years.

111 - Cross calibration of Whole Body Scans between GE-Lunar and Hologic Systems: Bone and Body composition

John Shepherd, Bo Fan, XianPing Wu, David Ergun, Michael Levine; 1UCSF; 2The Second Affiliated Hospital, Hunan Medical University, 3GE-Lunar, 4The Children’s Hospital of Philadelphia

Objective: We investigated the relationship between GE-Lunar and Hologic systems for whole body DXA, as well as derived conversion equations between these two systems. This work extends previous work with more systems, representing both adult and pediatric results.

Methods: Two hundred participants (62 male) were recruited for this study from the US (40, aged from 6 to 16 years old) and China (160, aged from 5 to 81 years old) with mixed ethnicity. The mean age of the participants was 44.2 ± 20 yrs. Each participant was scanned on both GE-Lunar Prodigy and Hologic Delphi DXA systems on the same day using each manufacturer’s standard scan mode, positioning, as well as analysis protocols. The scans were analyzed using Hologic version 3.1 and GE-Lunar version 13.4 following the manufacturer’s guidelines. Paired t-tests were used to test the results differences between the systems. Multiple regressions were used to investigate the covariance (age, weight, and BMI). Deming regression was used to derive the cross calibration equations if covariance did not exist. Otherwise, multivariate regression was used to derive the cross calibration formulas. In addition, relationships for the sub-regional composition measures were also derived. Hologic systems use a variable bone threshold for individuals (children) below 40 kg total mass. Thus, cross-calibration equations were derived for above and below 40kg if statistically justified.

Results: The soft tissue and bone results were highly correlated between the Hologic and GE-Lunar systems, with r ranging from 0.96 (%Fat) to 0.98 (BMC). As expected, there were significant differences between the two systems for all variables (p<0.05 or less). The average absolute differences for %Fat, BMC and BMD were 2.5%, 216.2 g and 0.045 g/cm², respectively. Age and weight were only covariant for BMC. Conclusions: Our results suggested the need of whole-body standardization equations for both bone and soft tissue measures between GE-Lunar and Hologic systems. The equations we derived could reduce result differences between Hologic and GE-

112 - Correlations of Cross-Sectional BDM with BMI, Menopausal Status, Serum Estradiol, Smoking, and Exercise

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Introduction: Bone mineral density (BMD) was measured using a GE-Luna DXA Prodigy scanner in 200 postmenopausal women in a single-center study. The data were collected as part of the NOVEL clinical study that compared the efficacy of nitric-oxide–donor nitroglycerin with calcium and vitamin D. The authors present the baseline BMD of the study participants and its correlations with several variables, including body mass index (BMI), year since menopause, mean serum 17B-estradiol, smoking status, and level of exercise participants were engaged in at the time of enrollment. The study was approved by the Institutional Review Board and conducted under the supervision of a Data Safety Monitoring Board. Results: Correlations were obtained with the mean lumbar spine BMD and total hip data (sample size, between 221 and 325). BMD study data were validated by an external quality control unit from the University of California. Overall, the study revealed a normal distribution of BMD across the study population. Analysis of data revealed a weak positive relationship between BMD and BMI, year since menopause, mean serum 17B-estradiol, and smoking status, and level of exercise participants were engaged in at the time of enrollment. Exercise may have positive correlations with BMD levels, whereas smokers tended to have lower BMD levels. This postmenopausal group of subjects had very low serum estradiol levels, and this may influence the lack of correlations with the BMD.
Prevention and Treatment of Osteoporosis

113 - Open-label, Crossover Study Evaluating the Adherence, Preference, and Satisfaction of Denosumab and Alendronate Treatment in Postmenopausal Women: Results of the Second Year of the Study

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Background: Denosumab (DMab), a fully human monoclonal antibody to RANK ligand, is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture. The DAPS (Denosumab Adherence Preference Satisfaction) study compared treatment adherence, preference and satisfaction between subcutaneous (SC) injection of DMab (60mg, once every 6 months [Q6M]) and oral alendronate (ALN, 70mg, once weekly [QW]) in postmenopausal women in a 2-yr crossover design. First year results of this study indicated that greater treatment adherence was observed with Q6M SC DMab than for QW oral ALN. Final results for the study are presented here. Methods: DAPS was a 2-yr, multicenter, open-label, crossover study of postmenopausal women with no prior bisphosphonate treatment who had a BMD T-score of = 2.0 to = 4.0 at the lumbar spine, total hip, or femoral neck. Patients were randomized (1:1) to receive 60mg Q6M SC DMab in yr 1 followed by 70mg QW ALN in yr 2, or receive treatment in the reverse order. Patients were considered adherent to treatment if they received 2 DMab injections 6 months (±4 weeks) apart or they took =80% QW ALN and at least 2 ALN tablets in the last month, and if they returned for the final study visit. Results: A total of 250 patients were enrolled; 126 in the DMab/ALN group and 124 in the ALN/DMab group. Mean (SD) age for patients in DMab/ALN and ALN/DMab, respectively, was 65.1 (7.6) and 65.3 (7.7) yrs. A total of 95 (75%) and 103 (83%) patients, respectively, completed the 2-yr treatment period for the DMab/ALN and ALN/DMab groups. During yr 2, treatment with DMab compared with ALN was associated with significantly (p<0.0001) greater adherence (92.5% vs 63.5%), compliance (93.4% vs 67.8%), and persistence (97.2% vs 71.3%) with treatment. A total of 92.4% vs 7.6% preferred DMab injection over oral ALN (p<0.0001), and 91.2% vs 8.8% preferred DMab as a long-term treatment option over oral ALN (p<0.0001). During yr 2, significantly more patients were satisfied with DMab injection compared with ALN tablet (mean [SD] score of 4.5 [0.6] vs 3.2 [1.2], p<0.0001; score scale of 1 to 5, where higher score = higher satisfaction). Conclusions: The DAPS study shows substantially greater adherence, compliance, persistence, and satisfaction with DMab treatment than ALN. Patients preferred Q6M DMab injection over QW oral ALN. DMab presents an opportunity for treating osteoporosis with improved adherence, compliance, and persistence.

114 - Prevention of Bone Loss in Patients Taking Anti-Epileptic Drugs (AEDs)- Results of the Antiepileptic Drugs and Osteoporosis Prevention Trial (ADOPT).

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Patients with epilepsy have a nearly twofold increase risk of vertebral or non-vertebral fractures as compared to the general population. It is known that long term use of AEDs is associated with an increased rate of bone loss. The primary objective of this trial was to evaluate whether the use of an oral bisphosphonate can help in preventing bone loss and osteoporosis in an epileptic population treated with phenytoin, phenobarbital, sodium valproate or carbamazepine. This investigator initiated study design is a phase IV, prospective, randomized, placebo controlled, double-blind study involving 80 male veterans with epilepsy who were being treated with the above AEDs for at least 2 years. Patients who were found to be osteoporotic according to WHO criteria (BMD T-score < -2.5 at spine or hip) or were found to be vitamin D deficient were excluded from initial randomization. Patients who had a T score > -2.5 were randomized into one of two possible arms. A bisphosphonate group (B group) received 35 mgs of risedronate weekly and an other group received an identical placebo tablet weekly (P group); both groups received vitamin D and calcium supplementation. Enrolled patients bone densities of bilateral proximal femur, LVA, A-P lumbar spine, total body and forearm were evaluated utilizing a GE Lunar Bone Densitometer or an iDXA instrument and had measurements of 25-OH Vit D, NTX, serum calcium and blood chemistries. 80 patients were randomly enrolled in either the B or P groups. Baseline characteristics of both groups were similar. Average age was 60+/-13 years. Average bilateral total proximal femur mean BMD was 0.991+/-0.122 for the B group and 0.992+/-0.213 g/cm2 for the P group. Lumbar spine baseline BMD was 1.284+/-0.190 for the B group and 1.237+/-0.249 g/cm2 for the P group. In the B group 28 patients completed the study, there was 1 death and 11 withdrew for variable reasons. In the P group, 28 patients completed the study, there were 2 deaths and 10 withdrew for multiple reasons. At the end of the study all 28 patients from group B and 10 out 28 patients from group P had a significant increase of BMD as determined at the total proximal femur which was above the LSC for our site; further, 18 out of 28 of group B and 22 out of 28 on group P demonstrated a significant increase of BMD at the L-Spine. Improvement of BMD in more than 40% of
patients in the P or B groups may be related to calcium + vit.D supplementation.

115 - The C-3 epimer of 25-hydroxyvitamin D3 is Present in Older Adults
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Measurement of circulating 25-hydroxyvitamin D [25(OH)D] is accepted as the approach to determination of an individual’s vitamin D status. Improvements in 25(OH)D measurement methodology and standardization are ongoing. However, confounders to accurate vitamin D status assessment remain; one of these may be the presence of 3 epi-25(OH)D. Epimers have identical molecular structure but differ in stereochemical configuration. It is currently accepted that the C-3 epimer of 25-hydroxyvitamin D is found only in neonates. However, we have observed a peak consistent with 3 epi-25(OH)D3 in serum tested with a high-performance liquid chromatography (HPLC) method. Here we report serum 25(OH)D3 and 3 epi-25(OH)D3 concentrations in a cohort of adults age 65+ (n = 89) ranging in age from 65 to 92 years. HPLC with ultraviolet detection (HPLC/UV) and tandem mass spectrometry (LC/MS/MS) equipped with cyanopropyl analytical columns were used to baseline-separate and quantitate 25(OH)D3 and its C-3 epimer. Lower limit of detection for the C-3 epimer on LC/MS/MS was 0.1 ng/mL. The C-3 epimer was detected in all 89 of these samples. Concentrations ranged 0.1-4.3 ng/mL for 3 epi-25(OH)D3. The relative amounts of the epimer to 25(OH)D3 ranged from 1.5-11.0% (mean 4.4%). The absolute amount of epimer was higher in samples with greater amounts of 25(OH)D3. In sera with similar 25(OH)D3 concentration, the % epimer was variable. In this cohort, 13 individuals received vitamin D3 1,600 IU daily or 50,000 IU monthly for six months. In this small cohort, the mean 3 epi concentration increased (p < 0.05) from 1.3 to 1.7 ng/ml; the ratio of 3 epi to total 25(OH)D3 remained constant at 4.3%. In conclusion, 3 epi-25(OH)D3 is present in serum of older adults. While not a major component of total 25(OH)D, this epimer may confound assay standardization and contribute to uncertainty surrounding definition of an optimal 25(OH)D status. Though limited by small sample size, this preliminary study suggests that the 3-epimer is produced in vivo. Further work is needed to investigate the impact of 3 epi-25(OH)D3 on the various 25(OH)D assays and ultimately what role, if any, this epimer plays in vitamin D function.

116 - The Denosumab Adherence, Preference, Satisfaction (DAPS) Study: Bone Mineral Density Results at 24 Months
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Background: Denosumab (DMab) is a fully human monoclonal antibody to RANK ligand indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture. Previous studies show that women who initiated treatment with DMab had greater increases in bone mineral density (BMD) at the lumbar spine (LS), total hip (TH), and other sites compared with women who initiated treatment with oral alendronate (ALN). Additionally, women who transitioned from ALN to DMab treatment had further BMD gains and a greater reduction in bone turnover compared with women who continued ALN. The DAPS study compared treatment adherence, preference, and satisfaction between subcutaneous (SC) injection of DMab (60mg, once every 6 months [Q6M]) and oral ALN (70mg, once weekly [QW]) in postmenopausal women. BMD results for women who completed the study are presented here.Methods: DAPS was a 2-yr, multicenter, open-label, crossover study of postmenopausal women with no prior bisphosphonate treatment who had a BMD T-score of = -2.0 to = -4.0 at the LS, TH, or femoral neck. Patients were randomized (1:1) to receive 60mg Q6M SC DMab in yr 1 followed by 70mg QW ALN in yr 2 or receive ALN in yr 1 followed by DMab in yr 2. BMD changes were assessed as exploratory endpoints. All patients received calcium and vitamin D supplements.Results: 250 patients enrolled in the study; 126 and 124 in the DMab/ALN and ALN/DMab groups, respectively. Baseline age (mean [SD], 65.2 [7.6] yrs) and BMD values (mean [SD], LS: 1.96 [1.14], TH: 1.60 [0.75]) were similar between the two treatment groups. During yr 1, mean (95%CI) percent change from baseline in LS and TH BMD, respectively, were +5.4 (4.6, 6.2) and +3.1 (2.5, 3.8) in the DMab group and +4.9 (4.1, 5.7) and +2.4 (1.8, 3.0) in the ALN group. Switching from ALN to DMab lead to further BMD gains; mean (95%CI) percent change in BMD in yr 2 was +2.8 (2.1, 3.5) and +1.5 (1.0, 2.1) at the LS and TH, respectively. Patients who switched from DMab to ALN had mean (95%CI) percent change in BMD of +0.8 (0.0, 1.5) and +0.4 (0.2, 1.0) at the LS and TH, respectively, in yr 2. Serious adverse events were reported in 3.5% and 3.9% of patients receiving DMab and ALN, respectively.Conclusions: In this study, we confirmed that switching from ALN to DMab results in further BMD gains in the LS and TH. Additionally, we showed for the first time that switching from DMab to ALN maintains the significant gains in BMD initially achieved with DMab.
117 - Cell Viability Assessment With Alendronate And Pamidronate

Maria Carolina Virga¹, Alejandra Aguzzi¹, Adriana de Leonardi², Daniel Salicco², ¹School of Dentistry UNC Argentina, ²Healing Argentina, Institute of Internal Medicine, Osteology & MineralIM

Abstract: Before beginning an experiment in vivo, it is essential to carry out preliminary in vitro tests to detect and characterize the possible harmful effects of the active ingredients on the tissue level. We studied the in vitro cytotoxicity of Alendronate (AL), Pamidronate (PA) in a fibroblast-derived cell line to establish optimal concentrations. Materials and Methods: This study was conducted using the Neutral Red Uptake Method (NR Sigma). Cell viability was estimated by measuring enzymes present in cell vacuoles in living cells. The samples were observed by phase contrast microscopy. Also the material was analyzed by optical density at a wavelength of 546:1 nm, with the 404 nm reference. In experiment in vitro, each bisphosphonate with an increasing concentration above 40 µg / ml. was added to the MEM culture medium supplemented with serum. The culture was incubated at 37 °C. Results: At a concentration of 5µg/ml, AL presented a cell viability of 99.3% and PA presented a cell viability of 94.99%. At a concentration of 10µg / ml, AL presented a viability of 98.5% and PA presented a cell viability of 55.82%. At a concentration of 20µg / ml, AL and PA presented a cell viability of 87.5% and 32.37% respectively. Conclusions: At 10 µg / ml, PA is 28.78 times more toxic at the cellular level than AL and at 20µ g / ml, PA is 5.38 times more toxic than AL.

118 - The Effect of Subcutaneous Alendronate and Pamidronate on Bone Mineral Density

Maria Carolina Virga¹, Alejandra Aguzzi¹, Adriana de Leonardi², Daniel Salicco², ¹School of Dentistry UNC Argentina, ²Healing Argentina, Institute of Internal Medicine, Osteology & MineralIM

Abstract: Bisphosphonates are a class of drugs capable of modulating bone turnover and decreasing their repairs when there is reabsorption. The aim of this study was to investigate radiographic diagnosis of subcutaneous formulations based on Alendronate (AL) and Pamidronate (PA). Materials and methods: The pharmaceutical formulations were prepared at a dose of AL of 0.5 mg / kg weight, and PA of 0.6 mg / kg weight. They added special buffer with a pH of 5.5 in sterile media. The control (C) was saline. Radiographs were taken before and after surgery, analyzed with the software Image ProPlus version 4.1 of Media Cibernetics. We also evaluated alkaline phosphatase (ALP) in blood by colorimetric methods. Results: Radiographic studies showed that AL from day 0 begins to increase mean bone mineral density (BMD), finding the peak in 30 days with a value of 157.9, beginning to decline until day 60 where the values stabilize, reaching in day 90 a value of 156.1. PA behaves the same as at the beginning of treatment but has its peak in 45 days with a value of 161.8, declining in the following days and stabilized in 90 days with a value of 156.2. The values of the control group remain stable over time from 15 days down from 152.4. (P <0.001). ALP studies in 45 days revealed that PA has 1.13 times greater osteogenic activity than AL, while in 90 days this activity was 1.07 higher. Conclusion: In male rats to which an incision was made in their tibias, it was shown that the administration via subcutaneous route of AL or PA as local treatment had a local pharmacological effect with an increase in bone formation proved by the increase in ALP and BMD. This study suggests that subcutaneous application of bisphosphonates may be effective as an add-on therapy to reduce bone reabsorption after oral surgery.

119 - Malignant mesothelioma and hypophosphatemia: PTH dependent or independent mechanisms?

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Introduction Adult hypophosphatemia is a rare condition (in PTH independent situations). One of the most frequent mechanisms is the production of the FGF23 by rare conjunctive tissue tumors as those mesothelial. Aim We present a case of mesothelioma and hypophosphatemia in an adult female. Case report 61 yr old non-smoking female patient presented one year ago respiratory disturbances. The investigations lead to the conclusion of a pulmonary tumor for which a surgical procedure was performed. Right medio-inferior lobotomy was performed. During surgery, the diagnosis was appreciated as mediastinal sarcoma with pericardic and pleural infiltration. The pathological exam showed monophasic malign mesothelioma. She was treated for 12 months with chemotherapy. She presented high calcium levels so she was referred to an endocrinologist. The patient presented renal stones from almost a decade. The bone markers are presented in Table 1. Normal prolactine, TSH and metanephrines were found. Table 1: The lumbar spine DXA exam showed BMD=0.863g/cm², T-score: -2.5, Z-score: -2. The CT scan pointed out a left parathyroid adenoma of 0.33 by 0.22 cm. The Tc 99m parathyroid scintigram was negative. The FGG 23 is under evaluation. Antiresorbitive therapy (alendronate 70 mg/weekly) was started. Parathyroidectomy was recommended. The post operatory values of the phosphorus are mandatory related not only to the 25 OH vitamin D and PTH levels but also to the possible tumor production (in case of residual disease) of FGG23. Conclusion Oncogenic hypophosphatemia is a rare condition that may be overlapped to primary
Bone bars (BB) are struts of trabecular bone that cross the medullary portions of the metaphysis and diaphysis at right angles to the long axis of the shaft and have been described in the skeleton of osteopenic/elderly patients. BB at the femur intertrochanteric region have a high predictive association for low bone mineral density at the same region. This investigation determined whether the presence of BB on AP hip radiographs are more prevalent in patients with a hip fracture. The investigational group (+hip fracture) was identified and a control group (-hip fracture) was matched by age. Inclusion criteria included: a) postmenopausal Caucasian women aged 65 or older, and b) presence of an AP radiograph of the hip taken for reasons not associated with high-energy trauma. Exclusion criteria included: a) previous medical/surgical conditions known to be associated with osteopenia or fracture, b) individuals who had ever received medications known to affect bone mineral density and c) previous hip fracture of any kind. The hip radiographs were manipulated so that only one side of the hip was visible so that the reader was blinded to the contralateral hip, hiding the fractured hip if present. The control and investigational group radiographs were intermixed and randomly evaluated by two experienced musculoskeletal radiologists. The presence of BB at the intertrochanteric region of the proximal femur was scored as present or not present. There were 98 individuals in the control group and 92 in the investigational group. The mean age was 79.8±6.4 years and 79.9±6.6 years in the control and investigational groups, respectively. The prevalence of intertrochanteric BB in the control group was 38%-39% and 53%-75% in the investigational group. Regardless of the reader, BB are seen in a significantly higher percentage of women with a fracture (75% vs. 39%, p<0.001 or 53% vs. 38%, p=0.041) as compared to those without a fracture. BB are seen similarly in patients with femoral neck (intracapsular) and intertrochanteric (extracapsular) fractures. The kappa statistic was used to assess agreement on the presence of bone bars between readers. The kappa statistic was 0.41 and p-value was <0.001 which is considered moderate agreement. BB are significantly predicted in the presence of hip fracture. The presence of bone bars on a hip radiograph should be considered a potential radiographic predictor for hip fracture risk.

121 - A Helping of Hip and a Sprinkling of Spine: The Blended T-score is Equivalent to the Offset Enhancement for Fracture Prediction with FRAX

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Background: The FRAX® tool estimates 10-year probability of fracture based upon multiple clinical risk factors and an optional BMD measurement from the femoral neck (FN). Discordance between lumbar spine (LS) and FN T-scores is a source of confusion to some clinicians since the LS measurement is not an input variable for FRAX. A procedure for using the LS to enhance fracture risk assessment under the FRAX system adjusts FRAX probability based upon the T-score difference between the LS and FN (termed “offset”). We examined an alternative approach using a “blended” T-score input to FRAX calculated as the weighted mean of the FN and LS T-scores (reflecting the relative proportion of non-vertebral to vertebral fractures as 3:1). Methods: The Manitoba BMD database was used to identify men and women over age 50 with valid LS T-score (with exclusions), FN T-score, and FRAX probabilities (N=36,141). Major fracture probabilities were calculated as: FRAX (clinical), no BMD input; FRAX (hip): FN T-score; FRAX (blended): 0.75xFN T-score plus 0.25xLS T-score; FRAX (offset): FRAX (hip) with subsequent offset adjustment (10% per SD difference between LS and FN). Fracture outcomes were assessed from population-based administrative data (N=2,316 with a major osteoporotic fracture). Results: ROC area under the curve...
(AUC) analysis was performed for prediction of major osteoporotic fracture. The AUC for FRAX (clinical) was 0.666 (95% CI 0.654-0.677) and increased for FRAX (hip) 0.696 (0.685-0.707), FRAX (blended) 0.697 (0.686-0.708), and FRAX (offset) 0.698 (0.687-0.709). There was a statistically significant increase in the integrated discrimination improvement with FRAX (blended) versus FRAX (hip), p<.001 but no difference between FRAX (blended) and FRAX (offset), p=0.946. There was extremely close agreement (r=0.999) between probabilities obtained from FRAX (blended) and FRAX (offset) which closely approximated the line of identity: slope=0.99, Y-intercept=0.0 (Figure). Based upon 3 risk categories (<10%, 10-20%, >20%), the reclassification rates were: FRAX (femoral neck vs blended) 6.6%, FRAX (femoral neck vs offset) 6.9%, and FRAX (blended vs offset) 1.4%. FRAX (femoral neck) and FRAX (blended) showed equivalent calibration (grouped as risk quintiles). Conclusions: Major osteoporotic fracture probability from FRAX (blended) is quantitatively equivalent to FRAX (offset). Both approaches result in a small improvement in fracture prediction compared with FRAX (hip).

122 - Prevalence of Low BMD and Vitamin D Deficiency in Patients with Developmental Disabilities

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Introduction: The New Jersey Department of Health statistics indicate much lower hip fracture rates in the state for those older than 50 years than for patients with developmental disabilities (DD) who reside in the state’s seven DD centers. In comparison with ambulatory healthy people, residents of the DD centers had approximately 30-fold increased incidence of hip fractures. The age-adjusted prevalence of osteoporosis in New Jersey residents age 50 years and older is about 13% [confidence interval (CI), 12–14], in comparison with residents older than 85 years, which is 23% (CI, 19–26). http://nj.gov/health/senior/osteo/ (2005, BRFSS); For patients with DD in our center, the age-adjusted prevalence is approximately 66%. Thus, persons with DD have a much higher incidence of osteoporosis and fragility fractures. Results: Results from our study at the Hunterdon Developmental Center (HDC; Clinton, NJ), one of seven state-operated facilities for adults with DD, revealed only 110 of the 580 (19%) residents were receiving vitamin D supplements. The doses they were receiving were between 400 and 600 IU per day, and very few had undergone measurement of serum 25(OH)D levels, despite that low bone mineral density (BMD) and fractures are common in these residents. In our study, 80% of the 400 residents who had dual-energy X-ray absorptiometry (DXA) BMD evaluation were shown to have low BMD, with fragility fracture rates varying from 4.6% to 6.9% per annum. To alleviate these issues, we conducted a series of face-to-face and online continuing medical education (CME) programs in collaboration with UMDNJ-CCOE. Initially, a series of three online programs were offered to the staff physicians. Before the lecture series, 9 of 22 (41%) of the patients on one unit were receiving vitamin D supplements, and none (0%) had ever had serum 25(OH)D levels measured. After the CME series, serum 25(OH)D was determined in 100% (22/22). These educational activities at HDC led to additional vitamin D testing, initiation of vitamin D therapy, or increased dosages of vitamin D in 100% of this institutionalized patient population. Conclusion: Data suggest that vitamin D deficiency is very common in patients with developmental disabilities. The incidence of low bone mass is approximately 80%, and fracture rates are about 6% in this population. Direct teaching programs for physicians who care for this highly vulnerable population can be successful in changing their behavior.

123 - What is best to predict fracture risk, FRAX or T-score?

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Introduction: The introduction of FRAX in 2008 is a landmark in fracture risk assessment. But soon some limitations appeared, namely exclusion of spine T-scores and poor sensitivity in non Caucasian populations. Methods: We reviewed the data of 117
postmenopausal female patients with fragility fractures occurring less than 1 year before DXA and not in antiresorptive therapy. Using epidemiologic and densitometric data we simulated the 10 year probabilities given by FRAX, before fracture. All patients were examined in a LUNAR DPX-MD. Previous fractures were frequently confirmed by x-ray. FRAX was calculated with web version 3.1 in a Spanish population model. Results: The mean age of the population was 65.1 ± 9.8 years and BMI was 27.9 ± 4.8. Risk factors occurred in 39 patients, most of which were ‘parent fractured hip’ (12) or secondary osteoporosis (12). Thirty-nine patients had a diagnostic category of osteoporosis, which was attributed mainly by spine T-score (32/39). The category of “low bone mass” occurred in 41% of patients with fracture and in 48% of patients with no fracture. Based on the categories defined by NOF for treatment, “10 y risk of hip fracture = 3%” occurred only in 24 patients. There were no cases of “10 y risk of major osteoporotic fracture = 20%”. Conclusions: in our population, T-scores were more sensitive than FRAX for the identification of patients who suffered a fracture. The majority of osteoporosis diagnosis was conferred by spine values. This can reflect the lowest mean age of this population, when spine T-score regression is important.

124 - The DXA analyze in patients with fragility fracture risk appreciated by QUS

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Background: The fragility fracture risk is appreciated by the golden standard method DXA using the bone mineral density (BMD). There are alternative methods as quantitative ultrasound (QUS) that also may express the fragility fracture risk. The QUS is preferred because it is a non invasive, non ionizing method using mobile devices. In some countries, QUS is widely used because of the low cost involvements. Aim: We studied the DXA and QUS correlations in postmenopausal women. Subjects and method: 130 postmenopausal women were studied during 6 months in a prospective study. The patients were in menopause, regardless physiological or surgical (at least 6 months of secondary amenorrhea). We did not include the women treated for osteoporosis with anti-rezorbtive therapy. The informed patients’ consent was obtained. All the patients had QUS and DXA assessment. The bone strength was evaluated based on the propagation speed of ultrasonic waves using the heel GE Achilles Ultrasound Bone Densitometer. The statistical analyze used student t test. Results: 3 fracture risks groups were formed according to the known cut offs from literature. The BMD analysis was based on WHO criteria regarding the diagnosis of osteoporosis. Table 1 Discussion: The low correlation between DXA and QUS is frequent (r=0.4, p=0.01 from our data). The data interpretation must be performed according to the clinical risk factors profile and the age of the patient. Conclusion: The highest percent of patients with osteoporosis was found in the high risk group. Also, more than a half of the patients from the low risk group have normal DXA exam.
125 - Surgery should be performed as soon as possible in senile patients with hip fracture

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Objective: The aim of the clinical research is to investigate the relationship between timing of surgery and postoperative complications in senile patients with hip fractures, and try to find out other factors which are related to occurrence of these complications. Methods: Sixty-two patients, 28 males aged from 65 to 72 with a mean age of 76.3 years and 34 females aged from 65 to 95 with a mean age of 78.1 years, who had undergone orthopedic surgery because of hip fractures, were enrolled in a retrospective cohort study. The timing of surgery and surgical approach, the type of fracture, preoperative comorbidities, American Society of Anesthesiologists (ASA) score and volume of blood transfusion during operation were obtained from these patients who were followed up by telephone calls for the postoperative complications. All the patients were followed up at least for 1 year and were divided into subgroups according to their clinical characteristics and the results were analyzed by SAS software. Results: There was no significant differences in the morbidity of the postoperative complications with the gender, age, timing of surgery and surgical approach, or ASA score. There was significant difference in the morbidity of the postoperative complications relating to preoperative comorbidities and the volume of blood transfusion. There was a significant causality between preoperative comorbidities and postoperative complications. The morbidity of the postoperative complications was 1.651 times higher in patients with preoperative comorbidities than those without. Conclusion: There is no relationship between the timing of surgery and occurrence of postoperative complications in senile patients who received surgery for hip fracture in 1 year follow-up. No correlation is found between the postoperative complications and gender, age, type of fracture, surgical approach, ASA score and the volume of blood volume neither. Preoperative comorbidities is an independent predictor for postoperative complications. Hip surgery should be performed as soon as possible in senile patients in order to avoid the deterioration of preoperative comorbidities.

Tab. 1 Analysis of preoperative dependent and independent variables (X1-8)

<table>
<thead>
<tr>
<th>Variables</th>
<th>x² value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>X1</td>
<td>2.3852</td>
<td>0.1225</td>
</tr>
<tr>
<td>X2</td>
<td>0.0784</td>
<td>0.7794</td>
</tr>
</tbody>
</table>

126 - Case Series: Atypical Subtrochanteric Femoral Fractures After Potent Anti-Resorative Therapy

Sunil Wimalawansa1, Carlos Sagebiel2, Robert Masella1, David Redziani2, Jason Nitche3; 1UMDNJ-RWJMS, 2Orthopedic Surgery, 3RWJMS

For more than 2 decades bisphosphonates were used to treat bone diseases. The therapy maintains bone mineral density (BMD), reduces bone remodeling and fractures. However, there are no credible evidence indicates that bisphosphonate therapy beyond 5 to 6 years has added benefits for fracture reduction. Recent articles suggested an association of prolonged use of bisphosphonate and stress fractures or atypical subtrochanteric fractures. Characteristics of such fractures include classic thickened cortices, suppressed bone turnover, and cortical beaking. Prolonged use of bisphosphonate seems to increase the incidence of atypical subtrochanteric fractures in a few patients. Eight patients with antecedent thigh pain had subtrochanteric femoral fractures, including two with bilateral femoral fractures. All had been treated for osteoporosis with alendronate for at least 6 years; all sustained a low-energy subtrochanteric femur fracture through a clear region of chronic stress reaction in the bones and had choke stick-like horizontal fractures. There was no radiographic evidence of thin, osteoporotic cortices at any of the fracture sites; instead, all had bilateral thickened cortices around the fracture sites. The reported numbers of atypical subtrochanteric femoral fractures are insufficient to make conclusions about their etiology. Suggested reasons include genetic susceptibilities, preexisting conditions, inappropriate treatment with bisphosphonates, and long-term
bisphosphonate. The authors speculate that the incidence of such fractures and the correlation of long-term use of bisphosphonates may have been overlooked. This is important in that bisphosphonates such as alendronate have been on the market for about 15 years, and long-term complications may be beginning to surface with patients using bisphosphonates for long periods. If one of the key reasons for such fractures is marked suppression of bone turnover, then fractures may appear with time with the prolonged use of other potent anti-resorptive agents, such as denosumab. The authors suggest physicians have an index of suspicion for any patient taking bisphosphonate longer than 5 years who presents with thigh pain or dysfunction. Imaging with a 99Tc-bone scan or MRI may be helpful in identifying patients vulnerable for such fractures. Proactive identification and discontinuing bisphosphonate therapy, and treating with teriparatide would be helpful in preventing these fractures.

**Ultrasonometry**

127 - **Quantitative Calcaneal Ultrasonometry: Normative Data in the Taiwanese Population**

**Yi-Shi Hwuaw, Asphodel Yang, Li-Feng Lin; Central Taiwan University of Science and Technology**

The aim of this study was to define the normative data for bone mineral density in a large sample of Taiwanese population and to clarify sex differences as well as age-related changes. A total of 137 subjects (aged 20–87 yr) were screened with calcaneal ultrasound and were requested to complete a detailed questionnaire listing all important risk factors, diseases, and treatments affecting bone metabolism by National Osteoporosis Foundation. A total of 137 subjects (37 males and 100 females) were included in the study. Normative bone mineral density data was expressed using Z-score and T-score. According to the age, women were divided into three groups: group A included women between 20 and 39 years; group B women between 40 and 49 years and group C women between 50 and 77 years. Men were divided into two groups: group A included men between 20 and 49 years and group B men between 50 and 87 years. Each patient underwent a calcaneal ultrasound scan to determine the presence of osteoporosis, osteopenia and normal. QUS resulted in a greater number of women of group A (40/52) and of men of group A (12/12) at normal level of Z-score (more than -1.0), whereas more women of group C (5/24) and men of group B (3/25) were at increased osteoporotic risk (T-score is less than -2.5).

These results suggested that QUS scan may be suitable for screening of BMD but not applicable to diagnose osteoporosis.

128 - **The quantitative ultrasound assessment and the bone markers profile**

**Mara Carsoa, Valentin Radoi, Elena Neacsu, Catalina Poiana, Mihail Coculescu; 1Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, 2C.I.Parhon National Institute of Endocrinology**

Background The Quantitative Ultrasound (QUS) is widely used because of the facile access and manipulation. The QUS provides an evaluation of the fragility fracture risk based on different parameters as Stiffness Index (SI). Aim We studied the bone markers and QUS correlations in postmenopausal women.

**Subjects and method** We used the risk groups: high risk SI=59U, medium risk with SI between 59 and 83U, and low risk with SI=83, as shown in the literature. QUS and bone markers were evaluated. The informed patients’ consent was obtained. The bone strength was evaluated by the heel GE Achilles Ultrasound Bone Densitometer. The statistical analyze used student t test. Results 130 postmenopausal women were included in the study. The patients with anti-osteoporotic therapy were excluded. The group risk analyze is presented in the following table.

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of Patients</th>
<th>High Risk (SI=59U)</th>
<th>Medium Risk (59-83U)</th>
<th>Low Risk (SI=83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>40</td>
<td>20</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>24</td>
<td>12</td>
<td>12</td>
<td>0</td>
</tr>
</tbody>
</table>

Conclusions The high and medium risk groups as pointed by QUS are statistically different by serum calcium levels, as well as the high and low risk groups. The PTH levels analyze did not prove significant differences. The majority of the patients had suboptimal levels of 25 (OH) Vitamin D. These data suggest that a multifactorial correlation is necessary, probable a complex formula as FRAX provided starting from BMD as revealed by DXA.
Assessment of Bone Quality

129 - Image-based assessment of trabecular bone structure and cortical bone geometry using Multi-Detector Computed Tomography

Chu Wang1, Deena Lala2, Lora Giangregorio2, Angela Chung3; 1Duke University; 2University of Waterloo, 3University of Toronto; Christopher Gordon, Medical Physicist, Hospital for Sick Children, Toronto, ON

Purpose: Image based assessment of bone quality continues to be of interest for assessing bone strength and fracture risk. While dedicated high resolution peripheral Quantitative Computed Tomography (HRpQCT) is available more centers are likely to have access to Multi-Detector Computed Tomography (MDCT) units for detailed bone assessment. This work accesses how accurately MDCT measures trabecular architecture and cortical geometry at peripheral sites compared to HRpQCT.

Methods: Seven dried adult tibia bones were immersed in a saline solution and scanned on an Xtreme HRpQCT (Scanco Medical, Basserdorf, Switzerland) and a 64-slice MDCT scanner (General Electric Discovery 750HD, Wisconsin, USA). Each bone was housed in a 10 cm plastic cylinder and marked at the distal 4%, 14%, 38% and 66% of its length with aluminum beads which ensured that the same bone regions were compared between the two scanners. Scans done on the HRpQCT used the manufacturer’s protocol which acquired a set of 110 images over a 9 mm section with 82 µm isotropic voxels. The MDCT scans were done axial (10 cm field of view, 5122 matrix, 0.625 mm slice thickness) with an in-plane resolution of 195 µm. The MDCT images were reconstructed using two bone kernels to yield the sharpest images (HD Bone+ and HD Edge). The HRpQCT and MDCT images were analyzed for trabecular architecture (BV/TV, Tr. Th., Tr. Sp., Tr. N.) and cortical geometry parameters (Ct. Th., Izz) using the same analysis software (MicroView, GE, Wisconsin, USA). Automatic and global threshold methods were used for the analysis.

Results: Despite a lower resolution and larger slice thickness, MDCT accurately defined BV/TV compared to HRpQCT ($r^2 >0.95$, difference <10%). MDCT overestimated Tr. Sp and Tr. Th by a factor of 2 and 10, respectively but underestimated Tb. N by a factor of 5, despite strong correlation among the specimens ($r^2 > 0.8$). The distal to proximal changes in trabecular structure along each bone were accurately identified with MDCT: Tr. N and BV/TV decreased while Tr. Sp and Tr. Th increased. Cortical parameters were very accurately determined with MDCT ($r^2 >0.95$, difference <10%). The choice of bone kernels improved the agreement between the MDCT and HRpQCT measurements, with a sharper kernel providing more accuracy.

Conclusion: Although limited by slice thickness, MDCT can provide some reliable estimates of trabecular architecture and cortical geometry that are in line with the gold-standard HRpQCT system.

Epidemiology

130 - Trends in dual-energy x-ray absorptiometry (DXA) utilization, 2000-2009

Sarah Morgan1, Stephen Johnston2, Greg Lenhart3, Greg Cherkowski2, Lisa Palmer2; 1The University of Alabama at Birmingham, 2Thomson Reuters, 3Amgen

After a decade of policies encouraging DXA use, Medicare incrementally decreased reimbursement for non-facility based DXAs, effective 2007. This study quantifies trends in central DXA use before and after the change. Using 2000-2009 data from a large US administrative claims database, we selected subjects aged 50 or older with Medicare supplemental or commercial insurance. Data for study-eligible subjects were summarized into strata defined by calendar year and quarter, age, sex, geographic region, and payer. The central site DXA test (using CPT codes) rate was calculated within each stratum as the number of patients with a DXA test divided by the total number of patients. Quarterly and annual DXA test rates were directly standardized to the age, sex and regional distribution of the study population. Weighted piecewise linear regression, which allows for a change in slope of the fitted
regression line, was used to quantify change in DXA rates coincident with the 2007 reductions in Medicare reimbursement. The fitted rate from the model was compared to the projected rate based on the pre-2007 trend (see figure) and the difference between fitted and projected rates was calculated. In the 10-year period 2000-2009, slightly over 5 million central DXA scans were conducted within the study sample. Overall rates for females were similar for those with Medicare and commercial insurance (12.4%, 12.9%, respectively) but less so for males (1.8%, 0.6%, respectively). Among women with Medicare or commercial insurance, annual rates steadily increased until 2007 when they then leveled off. Regression modeling showed pre-2007 scan rates increased annually by 0.76% (0.72 – 0.80) and 0.76% (0.70 – 0.82) among those with Medicare and commercial insurance, respectively, and over 2007-2009, scan rates changed annually by +0.07% (-0.05% to +0.19%) and -0.12% (-0.29% to +0.04%), respectively. During 2007-2009 based on the pre-2007 trend, there were 3.1 (2.4-3.8) and 4.0 (3.1-4.9) fewer scans per 100 person years than expected for females with Medicare and commercial insurance, respectively. The post-2007 DXA scan rate was lower than what would have been expected had the observed trend of increasing annual DXA scan rates from 2000 to 2007 continued unabated beyond the Medicare reimbursement change in 2007. Continuing to provide access to DXA testing for those at increased risk of osteoporosis is important to providing high quality care for metabolic bone disease in the US.

**Monitoring Therapy**

131 - **Four-year Results of a Phase 2 Study of the Cathepsin K Inhibitor Odanacatib in Postmenopausal Women with Low Bone Mineral Density: Effects on Bone Mineral Density and Bone Turnover Markers**

Paul Miller1, Neil Binkley2, John Eisman3, Ian Reid4, Antonio Lombardi5; 1Colorado Center for Bone Research, 2Osteoporosis Clinical Center & Research Program & Institute on Aging, 3Garvan Institute of Medical Research, St Vincent’s Hospital, 4University of Auckland, 5Merck

Aim – Cathepsin K (CatK) is the primary collagenase in osteoclasts. In a 2-year phase 2 study and its 1-year extension, the selective cathepsin K inhibitor odanacatib (ODN) reduced bone resorption markers and progressively increased bone mineral density (BMD). The study was extended for 2 additional years to further assess ODN efficacy and long-term safety. Methods - Postmenopausal women with BMD T-scores between -2.0 and -3.5 at the lumbar spine, femoral neck, trochanter or total hip received placebo or ODN at 3, 10, 25 or 50 mg weekly during the 2-year study. In Year 3, participants were re-randomized to ODN 50 mg weekly or placebo. In Years 4/5, women who received placebo or 3 mg ODN in Years 1/2 and placebo in Year 3 were switched to 50 mg ODN for Years 4/5; all others continued with their Year 3 regimen. 141 women entered the extension, and 133 completed 4 years. Endpoints were BMD at the lumbar spine (primary), total hip and hip subregions, and 1/3 radius; levels of biochemical bone turnover markers; and assessments of safety. Results - During year 4, 100 women received 50 mg ODN and 41 received placebo. Continuous treatment with 50 mg ODN for 4 years induced significant BMD increases from baseline at the spine (10.7%), total hip (8.3%), femoral neck (8.9%), and trochanter (10.3%) and maintained BMD (-0.1%) at the 1/3 radius; BMD changes from Year 3 were 2.8% (spine), 2.5% (total hip), 3.9% (femoral neck), and 2.9% (trochanter). Serum CTx remained low at Year 4 (-41%), whereas BSAP was relatively unchanged (-2%) from baseline. Women who received active treatment for 2 years and switched to placebo for 2 years experienced bone loss, with BMD near baseline for most sites and decreased by 4.5% at the 1/3 radius at the end of Year 4. Levels of bone turnover markers in women who discontinued active treatment after 2 years rose in the first month off-treatment, but all levels returned to baseline by the end of Year 4. ODN was generally well tolerated. Conclusions - 4 years of ODN treatment increased lumbar spine and hip BMD and was generally well-tolerated in postmenopausal women with low bone mass. Bone formation markers remained relatively unaffected. Discontinuation of ODN after 2 years of treatment was promptly followed by resolution of effects on bone turnover and density such that BMD and bone biomarker levels at Year 4 were at or near baseline.
132 - DXA Body Scan Data from NHANES III: “Barrel” Body Fat Distribution Predicts Cardiovascular Mortality and Sarcopenia Predicts Non-cardiovascular Mortality

Jesse Krakauer; Middletown Medical; Nir Krakauer, The City College of New York

We previously defined DXA derived Barrel body fat distribution as Z-score % trunk fat/total fat (Z-%TF) > 0 and Z-score limb fat/height2 (Z-LF)<0 and found it to be predictive of 10-year cardiovascular mortality and that sarcopenia defined as Z-score limb lean/height2 (Z-LL)<0 predicted total mortality. (Preventive Cardiology, 2004;7:109-115) With the recent on-line availability of linked mortality data we examined these “Mesenchymal Risk” (MR) associations for the NHANES III DXA data. Methods: All data were downloaded from public access files (cdc.gov/nchs). Z-scores were computed from DXA scan data by gender, ethnicity (white, Mexican, black) and for age > 18 years, by decade. Cardiovascular (CV) and non-CV mortality were determined by cause of death ICD codes. Odds ratios for mortality were derived for MR with online statistics (faculty.vassar.edu/lowry). Cox proportional hazard modeling (www.r-project.org) for mortality was performed for age, gender, BMI, waist circumference (wc), sarcopenia (Z-LL) and barrel projection (BP = Z-%TF – Z-LF). Results: Mortality (as of 2006) for NHANES 1999-2000 (5161 subjects) was 10.6%, Odds ratios displayed in Table were significant, with the exception of sarcopenia in Blacks and Barrel in Mexicans. Cox modeling showed that CV mortality increased 24% per unit BP and non-CV mortality increased by 21 % per unit decrease in Z-LL. Conversely, CV mortality was not predicted by Z-LL, neither was non-CV mortality predicted by BP. As single variables CV-mortality was significantly associated only with BP (p=.013) but not with wc. Gender differences in mortality were entirely accounted for by MR in these models. Also we found notable that total mortality decreased by 10% for each unit increase in BMI, with a 3% higher risk for each centimeter increase in wc. In analysis of the full NHANES III cohort (14,479 subjects) for each unit decrease Z-LL, mortality increased 14%, but the increased CV mortality for BP was seen only for subjects followed for at least 4 years. Conclusions: The NHANES III data base confirms that DXA derived MR predicted mortality, with CV-mortality associated with BP and non-CV mortality with sarcopenia. Higher BMI was paradoxically associated with lower mortality while wc was a weaker predictor of CV-mortality than BP. Our results support further consideration of DXA derived MR for individual risk prediction, targeting interventions and design of clinical trials.

133 - Accuracy and Precision of the Hologic Reflection Technique for Obese Whole Body scan analysis

Mary Sherman¹, Bo Fan², Lori Borrud², Cassidy Powers³, John Shepherd³; ¹UCSF, San Francisco, CA ²Centers for Disease Control;

Background: Due to the increase in obesity and the associated health problems, the ability to scan patients 300 pounds and over has become a very useful capability for DXA systems. However, the size of the scanner tables is limited and in many cases not wide enough to include the full width of the patient. A technique called ‘Reflection’ is being used by Hologic to estimate whole body values even when an arm or leg falls outside the scan window. The subject is positioned off center so one side of the body is complete. Data from the complete side is “reflected” to the incomplete side. We asked what affect the use of this technique has on precision and accuracy. Methods: Four hundred and thirty four subjects from the NHANES study with repeat whole body scans were chosen, ranging in age from 16 to 69 years. Scans were acquired on Hologic QDR-4500A systems. To mimic “reflection” analysis, right arm measures were substituted for the left. Linear regression and Bland-Altman analysis was used to compare the reflected versus whole body scan versions. Precision was estimated as either RMSE and RMS-CV. Results: Right arm BMD was 3.4% higher than left arm BMD with no significant differences found in the total percent fat. A significant but small difference (250 g) was found for total mass. Small significant differences were observed for whole body bone but no differences on the soft tissue measures. In addition, there was no significant difference in the precision values for any of the variables. The highest RMSE being in the total fat (1.85) and the lowest in total mass (1.06). Conclusion: Reflected arm values on whole body scans have no impact on whole body precision. However, there may be an impact on the accuracy of bone measures.
Evaluation of whole body and subregional DXA precision

Cassidy Powers¹, Bo Fan¹, Lori Borrud², John Shepherd¹; ¹University of California, San Francisco, ²Center for Disease Control and Prevention

BACKGROUND: Short-term repeatability of whole body measurements using Dual-energy x-ray absorptiometry (DXA) has been shown to be very good with values less than 2% being typical. However, few studies have attempted to quantify long-term repeatability of whole body measurements as a more accurate description of precision. In addition, the impacts of BMI and age have not been well studied. The objective of this study was to investigate the repeatability of whole body and subregional measurements how the precision varies by weight, age and time between scans.

METHODS: Two whole-body DXA scans were acquired on 434 participants of the National Health and Nutrition Evaluation Survey (NHANES). Patients varied in ethnicity and gender, patient age ranged from 16 to 69 years old (mean, 38.3±17.4), and BMI ranged from 14.1 to 43.7 (mean, 26.7±5.0). Time between scans ranged from 3 to 51 days (mean, 18.6±8.4). Patients with scan artifacts were excluded. Precisions for whole body measures (BMD, BMC, lean mass, total mass, fat, pfat, android/gynoid pfat ratio) were calculated as root mean square coefficients of variation (RMS-CV) and standard deviation (RMS-SD). The population was divided into tertiles of BMI and time, and decades of age.

RESULTS: There were no significant trends evident for age, BMI, and time. The average precision values for most whole body variables were slightly worse than would be expected for short-term precision studies (RMS-CV and RMS-SD, 1.64 and 462.30, 1.17 and 27.42, 1.12 and 0.01, 1.41 and 717.27, 1.06 and 803.89, and 1.65 and 0.54 for fat, BMC, BMD, lean mass, total mass, and pfat, respectively). The android/gynoid pfat ratio also did not have any significant trends with respect to age, BMI, and time between scans and was 3.03 and 0.03 for RMS-CV and RMS-SD respectively.

CONCLUSION: Long-term precision is stable with respect to age, BMI, and time between scans, and similar to values typically found for short-term precision.

Body Composition and BMD after Total Hip Arthroplasty. A Randomised Clinical Trial of Two Different Postoperative Regimes with 5 years of follow-up.

Olof Wolf, Per Mattsson, Jan Milbrink, Sune Larsson, Hans Mallmin; Orthopedics, Surgical Sciences, Uppsala, Sweden

Introduction: There is now evidence to support full weight bearing (FWB) after uncemented total hip arthroplasty (THA) in terms of no adverse effects on stability of the femoral stem. The aim was to investigate the effect of FWB after unilateral uncemented THA on (1) the body composition (BC) of the legs, and on (2) the bone mineral density (BMD) of the heels and contralateral hip. We also followed the changes in BC and BMD for 5 years.

Methods: 38 patients (20 men), mean age 54 years, with strictly unilateral osteoarthritis of the hip (OAH) received an uncemented THA and were randomised to immediate FWB or partial weight-bearing for three months (PWB). The patients were investigated with a total body scanner (DPX-L⁰) and a heel-DXA (PIXI⁰) to assess BC and BMD preoperatively, and at 3, 12, 24, and 60 months postoperatively. We compared total, and regional fat mass (FM), lean mass (LM), and bone mineral content (BMC) for the lower extremities; the semi-manually created size of the regional ROI’s are to a certain extent operator-influenced, thus the absolute mass/content gram-values can be less reliable in a longitudinal study. In order to reduce such influences we therefore chose to also compare percentage FM%, LM% and BMC% for the lower extremities ROI’s for the THA-limb versus the non-operated limb. The BMD of the contralateral hip was assessed for the femoral neck, trochanter and total hip. BMD of the heels was followed for 24 months. Results: Preoperatively the OAH side contained more FM% and less LM% than the healthy side. There was no difference in change of BC or BMD at the contralateral hip or heels from baseline to 3 and 12 months between FWB and PWB. 5 years after THA.

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Miami, FL USA
there was a decrease in total body BMC% by 5%, in the operated leg’s BMC% of 9% and of the contralateral leg’s BMC% of 4%, but no changes in FM% or LM%. Also, the total body BMD decreased by 3%. The contralateral hip displayed a 2-3% decrease of BMD in all regions, but no changes at the heels. Conclusion: We found no effects of FWB on change in BC or BMD following the surgery. With this in mind we can recommend FWB after unilateral uncemented THA. Also, although we found a decrease of total body BMD and BMC% at 5 years, we could not find the expected age-related changes in FM% and LM%. Thus, THA seems to allow for physical activity counteracting the expected age-related changes seen in the population in BC but not in BMD.

136 - Lean and Fat Mass Relate Differently to Total Body Mass in Boys and Girls

Tom Sanchez, Jingmei Wang, Terry Schwalenberg, Kathy Dudzak; Norland—a CooperSurgical Company

Lean and fat mass have been implicated as major contributing factors in increasing bone mass. This study evaluates those relationships using Norland DXA based total body bone, lean and fat measurements in a population of children. A population of 150 children between 7 and 19 years old (75 boys and 75 girls) underwent whole body studies to assess bone, lean and fat mass using a Norland XR-36 fitted with Illuminatus software. A strong linear relationship was seen between lean mass and total body bone mass in the boys (y=0.05x + 408.2, r=0.9686, RMSE=185.0) and girls (y=0.0536x + 456.1, r=0.9290, RMSE=247.3). A weaker relationship was seen between fat mass and total body bone mass in boys (y=0.0107x + 1820.6, r=0.1609, RMSE=734.6) with a better relationship being seen in girls (y=0.0332x + 1319.4, r=0.5691, RMSE=549.4). In conclusion, total body bone mass is highly related to lean mass in boys with almost no relationship to total body fat mass. That contrasts with the strong relationship between total body bone mass and both total body lean mass and fat mass seen in girls.

137 - Regional Body Composition Least Significant Change is Different in Male and Female Division One Athletes

Diane Krueger1, Jessie Libber1, Irina Haller2, Neil Binkley1, Jesse Donnenwerth3; University of Wisconsin Osteoporosis Clinical Research Program, 2Essentia Institute of Rural Health 3University of Wisconsin Intercollegiate Athletics

Regional body composition measurement may be a useful training tool for elite athletes to enhance sports performance. Precision assessment as recommended by the ISCD Official Positions is necessary to calculate least significant change (LSC) thereby allowing determination of differences between measurements. As such, to allow monitoring of change over time associated with training or rehabilitation regimens, we performed precision assessments in male and female Division 1 athletes from the University of Wisconsin (UW). UW Male and female athletes (total n = 60) from hockey, basketball, golf and wrestling teams participated in this precision assessment. Only athletes that completely fit within the scan field were included. Two total body scans were obtained on a GE Healthcare Lunar iDXA densitometer with repositioning between scans. Total, lean and fat mass LSC was calculated for both men and women at the total body, arms, legs, upper body and trunk using the ISCD precision calculator. Right and left sides were also evaluated at these same regions. Precision was calculated separately for men and women. Mean ±SD age and BMI was 20.6 ± 1.3 and 19.9 ± 1.3 years and 25.6 ± 3.0 and 23.3 ± 2.3 kg/m2 in men and women respectively, with men having a greater BMI (p < 0.01). Consistent with this, the total and lean mass was higher (p < 0.01) at all sites in men than women. The LSC for total, lean and fat tissue at most regions of interest was numerically higher in the male athletes than women (Table). The difference in LSC for various body regions ranges from 47-219 g for total mass, 26-321 g for lean mass and 20-149 g for fat mass. In conclusion, LSC at the total body and most regions for total mass, lean mass and fat mass is numerically greater in male than female Division 1 athletes. Whether this greater LSC simply reflects larger body size remains to be determined. At this time, when performing serial body composition assessment in athletic individuals, especially if evaluating regional change, it is appropriate to perform precision assessments in both sexes.

<table>
<thead>
<tr>
<th>Site</th>
<th>Male LSC (g)</th>
<th>Male % CV</th>
<th>Female LSC (g)</th>
<th>Female % CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Body Mass</td>
<td>174</td>
<td>0.20</td>
<td>128</td>
<td>0.19</td>
</tr>
<tr>
<td>Total Body Lean</td>
<td>575</td>
<td>0.84</td>
<td>381</td>
<td>0.84</td>
</tr>
<tr>
<td>Total Body Fat</td>
<td>465</td>
<td>4.05</td>
<td>316</td>
<td>1.76</td>
</tr>
<tr>
<td>Trunk Total Mass</td>
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<td>1.27</td>
<td>394</td>
<td>1.29</td>
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<tr>
<td>Trunk Lean</td>
<td>734</td>
<td>2.23</td>
<td>472</td>
<td>2.14</td>
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<tr>
<td>Trunk Fat</td>
<td>413</td>
<td>7.73</td>
<td>305</td>
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<tr>
<td>Legs Total Mass</td>
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<td>1.65</td>
<td>408</td>
<td>1.81</td>
</tr>
<tr>
<td>Legs Lean</td>
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<tr>
<td>Legs Fat</td>
<td>232</td>
<td>5.91</td>
<td>184</td>
<td>2.82</td>
</tr>
</tbody>
</table>

138 - Correlation of Jumping Power with Commonly Used Muscle Function Tests and DXA Appendicular Lean Mass in Older Adults.

Bjoern Buehring1, Ellen Fidler2, Jessie Libber2, Mary Checovich2, Diane Krueger2, Neil Binkley2; Cleveland Clinic, 2University of Wisconsin Osteoporosis Clinical Research Program

Sarcopenia has gained attention due to its high prevalence and impact on quality of life, morbidity and mortality. However, how to best clinically define this disease is controversial; both measures of muscle mass and function
have been proposed. Jumping mechanography (JM), which measures jumping power and height, has potential to be a unifying method for sarcopenia assessment by evaluating the neuromusculoskeletal system. This study aimed to compare JM to commonly used function tests and correlate these measures with appendicular lean mass (ALM) as measured by dual energy x-ray absorptiometry (DXA). Independently living adults age = 70 participated. Total body DXA scans and vertebral fracture assessment were performed using a GE Healthcare (Madison, WI) iDXA, followed by JM, grip strength and the short physical performance battery (SPPB) which includes gait speed and chair rise time. Force was recorded and body weight corrected peak power and jump height were calculated using maximal countermovement jumps performed on a force plate (Leonardo, Novotec, Pforzheim, Germany). ALM was calculated from total body measurements and corrected for stadiometer-measured height (ALM/height² ratio). At this time, 79 volunteers (46 females, 33 males) have completed baseline testing. Their mean (SD) age, BMI and lowest BMD T-score (spine and hip) was 80.7 (5.9) years, 25.5 (4.0) kg/m² and -1.8 (1.2). Sixteen individuals had one or more vertebral fracture on VFA and 20 had T-scores = -2.5. Sarcopenia (ALM/height² <5.45 kg/m²) was present in 24% (19/79). Mean (SD) average jumping power and height was 19.4 (4.9) W/kg and 17 (5.6) cm. Regression analysis revealed significant relationships (p<0.001) between jumping power and other muscle function tests; R² for SPPB was 0.35, gait speed 0.21, chair rise time 0.33, and grip strength 0.43. Jumping power and ALM/height² were positively correlated (p<0.0001, R² = 0.2). Similarly, jump height correlated (p<0.0001) with ALM/height², grip strength, SPPB score, chair rise time and gait speed. Summarizing, in this group of older adults, jumping power and height correlated well with commonly used muscle function tests. Additionally, DXA-measured ALM correlates well with jumping force/height and commonly utilized functional tests. This study indicates that JM has potential to be a valuable tool in sarcopenia assessment. Future studies should investigate whether JM can predict adverse outcomes and can be used to monitor the effect of interventions.

139 - Total body DXA scanning in a study of sarcopenia, bone health and frailty in a cohort of Parkinson’s disease patients attending a Regional Geriatric Medicine Clinic in North-West Ireland

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Background: Parkinson’s disease (PD) is a recognised cause of disability in the elderly¹. Aims: We wished to ascertain the prevalence of non-motor symptoms, osteopenia and sarcopenia in these patients. Methods: PD patients attending our Geriatric Medicine Clinics were invited to partake in a disability, muscle and bone health study. Patients were assessed with the PDQ39 quality of life questionnaire and MDS UPDRS disease severity scale. Bone and soft tissue DXA was performed on a GE Lunar Prodigy. Vitamin D levels, upper limb grip strength, cognition and falls risk were assessed. Results: There were 51 respondents from 65 requests; 66.7% were male and mean age 73.47 years (CI 71.66 – 75.28). The mean Hoehn and Yahr Parkinson’s disease stage was 2.82 (CI 2.48 – 3.17) and mean MDS UPDRS score 87.09 (CI 77.04 – 97.13). Appendicular skeletal lean body mass (ASM) was calculated by soft tissue DXA and sarcopenia assessed by the formula (ASM)/Height². The mean was 7.37 kg/m², SD 1.25, range 5.15 – 10.42. Female ASM/h², mean 6.21, SD 0.709, range 5.15 – 7.41 Male ASM/h² 7.99, SD 1.03, range 6.16 – 10.42. Sarcopenia was present in 29% and Osteopenia or osteoporosis in 71% of cases scanned. 10-year fracture risk (FRAX method) was 11.23% (mean) for major osteoporotic fracture (CI: 8.271-14.18) and 4.41% (mean) for hip fracture (CI: 2.91-5.91). The mean VitaminD level was 51.07 nmol/L (CI 44.12 – 58.01). 60.8% reported falls and 23.5% fractures. On the PDQ-39 questionnaire, patients reported the following: 49% frightened or worried about falling over in public, 52.9% painful muscle spasms or cramps, 51% aches or pains. In the MDS-UPDRS(II-III) 37.3% reported feeling depressed, 45.1% anxiety, 58.8% pain and 32% apathy. Sarcopenic patients reported 45% higher scores cumulatively. Conclusions: Most patients had PD non-motor symptoms relevant to bone and muscle health; more disability was reported in the sarcopenic group. In PD patients sarcopenia assessment is feasible by DXA. Falls are common in PD; the hip fracture risk (FRAX method) suggests that all PD patients should be considered for DXA scanning. References: 1. Osteoporosis in Parkinson’s disease. M. Invernizzi, S. Carda, G. Viscontini, C. Cisari. Parkinsonism & Related Disorders, Volume 15, Issue 5, Pages 339-346 (June 2009). 2. Epidemiology of Sarcopenia among the Elderly in New Mexico. Baumgartner et al. AmEpidemiol,147:755-763.1988 Disclosure of Interest: None Declared

140 - The influence of body weight, body compartments and related hormones upon bone mass at pre- and postmenopausal women

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Background. Body weight is positively correlated to bone mass. Gravity represents a stimulative stress for bone turnover, but endocrine function of adipose tissue (androgen aromatisation and secretion of adipocytokines) might also influence bone especially during critical periods, such as after menopause. Aims: We wanted to investigate the relative influence of various factors (weight, body composition and level of estrogens, leptin, adiponectin...)

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and IGF1) upon bone mass in pre- and postmenopausal women. Methods: cross-sectional study including six groups of 8 to 16 healthy female volunteers of different ages (pre- and postmenopausal) and weights (lean - BMI<25 kg/sqm, overweight - BMI between 25-30 kg/sqm and obese - BMI>30 kg/sqm) not submitted to antosteoporotic therapy. Lumbar BMD and BC were evaluated by DXA (Hologic). Serum leptin, adiponectin, estradiol, estrone, SHBG and IGF1 were evaluated by ELISA. Results: lean and overweight postmenopausal women had lower BMD than premenopausal women. Bone mass of obese postmenopausal women did not differ from that of premenopausal women (fig. 1). Body weight and body compartments were all correlated to lumbar Z score. The best correlation was attained with lean mass, that was an independent predictor of bone mass irrespective of age (multivariate analysis, ANOVA) (fig. 2). Serum IGF1, estradiol and estrone were correlated to bone mass only in premenopausal, but not in postmenopausal women (fig. 3 and fig. 4). Estrone levels were not significantly different in obese postmenopausal volunteers when compared to the other weight groups. Leptin normalised to fat mass and adiponectin were negatively correlated to bone mass (fig. 5). Conclusions: increased body weight prevents bone loss in postmenopausal women. Lean mass predicts bone mass independently of body weight irrespective of age. Higher IGF1 at earlier age might contribute to increased lean and bone mass. Androgen aromatisation into estrone in adipose tissue seems not to play a protective role on bone mass in obese postmenopausal women. The beneficial role of fat mass and total body weight on bone mass through gravitational stress seems to be partially buffered by direct effects of adipokines on bone.

141 - Total Body Volume estimates from DXA whole body scans
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BACKGROUND: Body volume is used to calculate body density and percent fat using either hydrodensitometry or air displacement plethysmography. Is it possible to measure body volume using DXA? If so, a simplified 4-compartment measure may be obtained using DXA and total body water measures alone. The purpose of our preliminary investigation was to derive body volume using DXA attenuation values alone and compare to an independent measure. METHODS: Pixels containing bone were identified. The influence of the bone on the low and high energy attenuations was removed from these pixels using estimates from the neighboring pixels. The soft tissue attenuation values for all pixels were then used to generate pixel-specific volumes of lean and fat. The pixel volumes were used to create a total DXA body volume (DXA体积). As a proof of concept, we report the results of a comparison of the DXA and BodPod volumes as well as percent body fat for DXA, DXA体积 and BodPod. Eleven subjects were recruited to have both DXA and air displacement plethysmography measures. Air plethysmography was obtained using the BodPod Siri (Life Measurement, Concord, CA), and the DXA whole body scans using a Hologic QDR4500W (Hologic, Bedford, MA).CONCLUSION: We have derived a method that calculates whole body volume from a DXA whole body scan. This method may be useful in generating four-compartment body composition from DXA and total body water measures alone.

142 - Influences of Sickle Cell Disease on Whole Body Bone Density and Body Composition
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BACKGROUND: Sickle Cell Disease (SCD) has been previously shown to be associated with osteopenia and osteoporosis resulting from bone marrow hyperplasia. Jamaica has a high prevalence of SCD, but little information about bone density exists in this group. As part of a study of hypogonadism and testosterone levels, we also investigated the bone density between men with SCD and age matched controls.

DESIGN AND METHODS: Forty eight men, aged (20-50 years) with homozygous S SCD were age-matched to 48 controls (haemoglobin AA). Height, weight, serum markers, whole body dual-energy x-ray absorptiometry (DXA) scans were acquired. The DXA scans were acquired on a GE Lunar Prodigy. Correlations of bone/soft tissue DXA measures between the cases and controls were studied. RESULTS: SCDs had similar height but smaller BMIs (20.22.7kg/m2 vs. 26.24.3kg/m2), total body BMC (20.22.7kg vs 26.2 4.3kg), BMD (1.20), %total body fat (21.0 and android %fat (32.9. These differences were all highly statistically significant, p<0.001. After adjusting for weight, but not free testosterone, BMD differences became insignificant. Thirteen percent (n=6) and 8.7% (n=4) of SCDs had T-scores in the ranges of -1 <T< -2.5, and T=-2.5 and greater. All others including controls were within the normal range.

CONCLUSION: We found that the Jamaican SCD population has low BMC and BMD related to their low body weight that may increase their susceptibility to musculoskeletal disorders and fractures. Interventions to increase body weight may be appropriate to increase BMD and are justified for study in the future.

Bone Architecture/Microstructure

143 - Gender differences in bone size, shape and strength parameters in patients with end-stage renal disease

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Background: Female gender is an independent predictor of hip fracture in patients with end-stage renal disease (ESRD). Differences in bone size and shape parameters, which ultimately influence bone strength, might explain the association between fracture and gender; however, this association has not been examined.

Methods: To determine if men and women with ESRD exhibit differences in bone size, shape and strength parameters, we conducted a cross-sectional analysis in a cohort (n=44; 13 women) of adult patients (mean age=66 ± 8.68 years) with ESRD. Bone size, shape and strength parameters were assessed using peripheral quantitative computed tomography (pQCT) at the proximal tibia (66% site). Gender differences in these parameters were determined using general linear models adjusted for age, weight, tibia length and dialysis duration.

Results: Men had greater total area (841.29 vs. 621.76 mm2; p=0.014) and periosteal circumference (102.54 vs. 88.31 mm; p=0.007) compared to females, as well as greater bending (98259.91 vs. 48740.07 mm4; p=0.015) and torsional (157585.29 vs. 82367.36 mm4; p=0.046) strength indices. Muscle cross-sectional area was also greater in men (66.77 vs. 48.49 mm2; p=0.022).

Conclusions: Bone size, shape and strength differences may help to explain why men with ESRD have a lower relative risk of hip fracture than women, and could have implications for gender-specific treatment strategies in this population; however, these results need confirmation by larger studies.

144 - Trabecular Bone Score (TBS) the new parameter of 2D texture analysis for the evaluation of 3D bone microarchitecture status.

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X-Ray is a technology that is used for numerous applications in the medical field. The process of X-ray projection gives a 2-dimensions (2D) grey-level texture from a 3-dimensions (3D) object. Until now no clear demonstration or correlation has positioned the 2D texture analysis as a valid indirect evaluation of the 3D microarchitecture. TBS is a new texture parameter based on the measure of the experimental varioigram. TBS evaluates the variation between 2D image grey-levels. The aim of this study was to evaluate existing correlations between 3D bone microarchitecture parameters - evaluated from from µCT reconstructions – and the TBS value, calculated on 2D projected images. 30 dried human cadaveric vertebrae were acquired on a micro-scanner (eXplorer Locus, GE) at isotropic resolution of 93 µm. 3D vertebral body models were used. The following 3D microarchitecture parameters were used: Bone volume fraction (BV/TV), Trabecular thickness (TbTh), trabecular space (TbSp), trabecular number (TbN) and connectivity density (ConnD). 3D/2D projections has been done by taking into account the Beer-Lambert Law at X-ray energy of 50, 100, 150 KeV. TBS was assessed on 2D projected images. Correlations between TBS and the 3D microarchitecture parameters were evaluated using a linear regression analysis. Paired T-test is used to assess the X-ray energy effects on TBS. Multiple linear regressions (backward) were used to evaluate relationships between TBS and 3D microarchitecture parameters using a bootstrap process. BV/TV of the sample ranged from 18.5 to 37.6% with an average value at 28.8%. Correlations’ analysis showed that TBS were strongly correlated with
ConnD (0.856 = r = 0.862; p<0.001), with TbN (0.805 = r = 0.810; p<0.001) and negatively with TbSp (-0.714 = r = -0.726; p<0.001), regardless X-ray energy. Results show that lower TBS values are related to “degraded” microarchitecture, with low ConnD, low TbN and a high TbSp. The opposite is also true. X-ray energy has no effect on TBS neither on the correlations between TBS and the 3D microarchitecture parameters. In this study, we demonstrated that TBS was significantly correlated with 3D microarchitecture parameters ConnD and TbN, and negatively with TbSp, no matter what X-ray energy has been used.

**145 - Assessment of correlations between 3D µCT microarchitecture parameters and TBS: effects of resolution and correlation with TBS DXA measurements.**

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It was shown that TBS evaluated on 2D projected images of 3D µCT vertebra models (TBSµCT) at 93µm was strongly correlated with 3D microarchitecture parameters. Aims of this paper are: 1) to evaluate the image resolution degradation effects of these 2D projected images on the correlations between TBSµCT and 3D microarchitecture parameters and 2) to evaluate the relationship between TBS assessed from DXA (TBSDXA) and TBSµCT.30 human cadaveric vertebrae were acquired on a micro-scanner (xScouter Locus, GE) at an isotropic resolution of 93µm and on three bone densitometers (QDR4500A, Prodigy and iDXA). 3D vertebral body models and 3D microarchitecture parameters were obtained using MicroView (GE Healthcare). The 2D projections of these 3D models were generated by taking into account the Beer-Lambert law at a X-ray energy of 100keV. Different image resolution degradations were simulated (from 93 to 1488µm). Relationships between 3D microarchitecture parameters and TBSµCT at different resolutions were evaluated using linear regression analysis. Correlations between the different TBSµCT values (at different resolutions) were evaluated. Finally, relationship between TBSDXA and site matched TBSµCT were evaluated by linear regression. Bone volume fraction (BV/TV), connectivity density (ConnD), trabecular number (TbN) and trabecular space (TbSp) covered by studied samples ranged from 18.5 to 37.6%, from 1.33 to 6.6 mm-3, from 0.9 to 1.8 mm-1 and from 0.348-0.874 mm respectively. Significant correlations were obtained between TBSµCT and 3D microarchitecture parameters regardless of the resolution. Strong correlations were obtained with ConnD (0.843 = r = 0.867), TbN (0.764 = r = 0.805) and TbSp (-0.701 = r = -0.638) and those up to a resolution of 744µm. A 1488µm, the correlations are still significant but more moderate. For resolutions of up to 744µm TBSµCT values are highly correlated (r = 0.98) and strongly correlated with the values TBSµCT to 1488µm (0.85 = r = 0.88). Up to 744µm resolution very high correlations were obtained between TBSDXA and TBSµCT for iDXA and Prodigy densitometers (r = 0.9). Strong correlations were obtained with QDR4500A TBSDXA values (0.87 = r = 0.89). Correlations existing between TBSµCT at 93µm and 3D microarchitecture parameters are weakly impacted by the degradation of image resolution. Moreover, TBSDXA and TBSµCT measurements are highly correlated.

**146 - Assessment of osteopenic women microarchitecture with and without osteoporotic fracture by TBS on a new generation bone densitometer**

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BMD assessed by DXA does not take into account bone microarchitecture degradation. TBS (TBS iNsight®, Med-Imap, Pessac, FRANCE) is a grey-level texture measurement, which correlates with 3D bone microarchitecture parameters, regardless of BMD. Several cross-sectional studies have shown the ability of TBS to discriminate fractured from healthy subjects. The aim of our study was to assess the ability of spine TBS to diagnose vertebral fracture in a population of osteopenic subjects on a new generation bone densitometer. We present a prospective case-control study on osteopenic Caucasian women aged from 45 to 85. Fractured subjects were included if the presence of at least one vertebral fracture (low energy type, grade 2 or more) was confirmed by VFA-DXA. For each fractured subject, 3 control subjects were matched for age (± 3 years). BMD was measured at the lumbar spine (L1-L4) using an iDXA densitometer (GE-LUNAR). TBS was calculated at L1-L4 directly on the same image as the BMD. Descriptive statistics and tests of difference were used. Univariate and multivariate (backward logistic regressions) were used to investigate possible correlations between independent variables (weight, height, BMI, BMD and TBS) and the status of fracture. Odd ratio (OR) and area under the ROC curve (AUC) of discriminating parameters were calculated. After applying the selection criteria of subjects, a group of 116 patients was obtained. This group consists of 29 fractured subjects (age=70.0±8.4 years, BMI=25.1±3.9 kg / m²) and 87 control subjects (age=68.5±6.5 years, BMI=23.3±3.4 kg / m²) matched for age (p=0.240). A weak correlation was obtained between TBS and BMD and between TBS and BMI (r = 0.241 and r = 0.305, respectively, p<0.01). The average value of TBS and BMI between the control and fractured group were significantly different (p = 0.002; ΔTBS = 0.070 and p = 0.02; ΔBMI = 1.7 kg / m² respectively), whereas no difference between group N is obtained for BMD (p = 0.490; ΔDMO = 0.02 g / cm²). The OR per standard deviation and the AUC were OR = 1.98 [1.25-3.12] and 0.682 [0.589-0.765] for TBS, respectively. After adjusting for BMI, TBS remains significant OR = 1.77 [1.10-2.83]. This study showed the potential of TBS to discriminate healthy from fractured osteopenic subjects using new generation bone densitometer image (GE-iDXA).