Program and Abstracts

# Forum on Aging and Skeletal Health

March 21-22, 2011
Natcher Conference Center,
National Institutes of Health
Bethesda, Maryland, USA

*Supported by Grant U13AG037272 from the National Institute on Aging, the National Institute of Child Health and Human Development, and the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH*

**A Meeting Sponsored by**
American Society for Bone and Mineral Research

**Co- Sponsored by**
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American Geriatrics Society
Foundation for Osteoporosis Research and Education
Gerontological Society of America
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The Paget Foundation for Paget's Disease of Bone and Related Disorders
U.S. Bone and Joint Initiative

**CME Sponsored Event**

ASBMR®
The American Society for Bone and Mineral Research

# *Welcome!*

On behalf of the American Society for Bone and Mineral Research, we welcome and thank you for your participation.

Our goal is to bring together leaders in research on the biology of aging with those in the bone field to exchange cutting-edge concepts in aging research with ongoing and planned studies on the epidemiology, mechanisms, and prevention/treatment of age-related bone loss and fractures through formal and informal talks as well as poster presentations.

**CONTENTS**




The organizers wish to thank the following U.S. National Institutes of Health institutes for providing funding for this meeting through a U13 grant: the National Institute on Aging, the National Institute of Child Health and Human Development, and the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

We are grateful for the co-sponsorship of the following organizations:

- American Association of Orthopaedic Surgeons (AAOS)
- American College of Rheumatology (ACR)
- American Geriatrics Society (AGS)
- Foundation for Osteoporosis Research and Education (FORE)
- Gerontological Society of America (GSA)
- International Bone and Mineral Society (IBMS)
- International Society for Clinical Densitometry (ISCD)
- National Osteoporosis Foundation (NOF)
- Orthopedic Research Society (ORS)
- The Paget Foundation for Paget's Disease of Bone and Related Disorders
- U.S. Bone and Joint Initiative (USBJI)

We extend a special thanks to our many colleagues for ideas, recommendations and guidance along the way. We also want to thank the companies that have helped to support this meeting. Finally, we wish to thank the ASBMR staff who provided continuous organizational support.


Sincerely,

Sundeep Khosla, M.D.
*ASBMR President and Organizing Committee Chair*


*This meeting is supported by Grant U13AG037272 from the National Institute on Aging, the National Institute of Child Health and Human Development, and the National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute on Aging or the National Institutes of Health.*

# American Society for Bone and Mineral Research
# Forum on Aging and Skeletal Health

## Organizing Committee

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Mayo Clinic & Foundation, Rochester, Minnesota

**Teresita M. Bellido, Ph.D.**
Indiana University School of Medicine, Indianapolis, Indiana

**Catherine M. Gordon, M.D.**
Children's Hospital Boston and Harvard Medical School, Boston, Massachusetts

**Douglas P. Kiel, M.D., MPH**
Institute for Aging, Hebrew Senior Life, Boston, Massachusetts

**Barbara E. Kream, Ph.D.**
University of Connecticut Health Center, Farmington, Connecticut

**Meryl S. Leboff, M.D.**
Brigham and Women's Hospital, Boston, Massachusetts

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University of Massachusetts Medical School, Worcester, Massachusetts

**Charlotte A. Peterson, Ph.D.**
University of Kentucky, Lexington, Kentucky

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**Sherry S. Sherman, Ph.D.**
National Institute on Aging, NIH, Bethesda, Maryland

**Tamara B. Harris, M.D., M.S.**
National Institute on Aging, NIH, Bethesda, Maryland

**John P. Williams, Ph.D.**
National Institute on Aging, NIH, Bethesda, Maryland

**Karen Winer, M.D.**
National Institute of Child Health and Human Development, NIH, Bethesda, Maryland

## ASBMR Young Investigator Award Recipients

Supported by educational grants from Lilly USA, LLC and Pfizer, Inc.

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X. Sherry Liu, Ph.D.
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## Exhibitors

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# EXHIBITOR INFORMATION

### Amgen

*www.amgen.com*

Amgen is a leading human therapeutics company in the biotechnology industry. For more than 25 years, the company has tapped the power of scientific discovery and innovation to advance the practice of medicine. Amgen pioneered the development of novel products based on advances in recombinant DNA and molecular biology and launched the biotechnology industry's first blockbuster medicines. Today, as a Fortune 500 company serving millions of patients, Amgen continues to be an entrepreneurial, science-driven enterprise dedicated to helping people fight serious illness.

### Hologic, Inc

*www.hologic.com*

Hologic, a leading provider of women’s health products, showcases the Discovery™ series of bone densitometers. Discovery offers superb imaging for rapid assessment of bone density, vertebral fractures, aortic calcification visualization and detailed body composition. With the most comprehensive platform, Discovery provides a complete bone, cardiovascular and obesity assessment.

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*www.scanco.ch*

Scanco Medical is the leading global provider of μCT and HR-pQCT (XtremeCT) scanners. The scanners, together with standardized analysis and visualization software provide for a 3-dimensional comprehensive measurement and analyses of bone. Scanco Medical also provides contract based scanning and analyses services as well as custom software applications.

# General Information

## VENUE

This meeting will take place in the Kirschstein Auditorium of the Natcher Conference Center, National Institutes of Health located at 45 Center Drive, Bethesda, Maryland, USA.

## REGISTRATION

Registration will take place at the Hyatt Regency Bethesda on Sunday, March 20 on the lobby level and the Natcher Conference Center on Monday, March 21 and Tuesday, March 22 on the lobby level.

**Registration Hours**

| | | |
|---|---|---|
| Sunday, March 20, 2011 | 4:00 p.m. – 7:00 p.m. | Hyatt Regency Bethesda |
| Monday, March 21, 2011 | 7:00 a.m. – 3:00 p.m. | Natcher Conference Center, NIH |
| Tuesday, March 22, 2011 | 7:00 a.m. – 3:30 p.m. | Natcher Conference Center, NIH |

## SPEAKER READY ROOM

All speakers must check into the Speaker Ready Room, preferably 24 hours before presentation. At that time, you are encouraged to review your slides to ensure all Greek characters and graphs transferred successfully. The Speaker Ready Room is located in Conference Room B of the Natcher Conference Center.

**Speaker Ready Room Hours**

| | |
|---|---|
| Monday, March 21, 2011 | 7:00 a.m. – 5:00 p.m. |
| Tuesday, March 22, 2011 | 7:00 a.m. – 4:30 p.m. |

## POSTER INFORMATION

Posters will be displayed in the Atrium of the Natcher Conference Center. Poster presentation time is scheduled during the Poster Session on Monday, March 21 from 11:20 a.m. to 12:20 p.m. Presenters must be at their posters during this time and available to answer questions.

| | **Monday, March 21, 2011** | **Tuesday, March 22, 2011** |
|---|---|---|
| **Poster Set-Up** | 7:00 a.m. – 9:00 a.m. | |
| **Poster Dismantle** | | 3:30 p.m. – 4:30 p.m. |
| **Poster Viewing Opportunities** | | |
| Morning Break | 9:55 a.m. – 10:15 a.m. | 10:20 a.m. – 10:40 a.m. |
| **Presentation Time** | Poster Session<br>11:20 a.m. – 12:20 p.m. | |
| Lunch Break | 12:20 p.m. – 1:00 p.m. | 12:45 p.m. – 1:45 p.m. |
| Afternoon Break | 2:40 p.m. – 3:00 p.m. | 2:55 p.m. – 3:15 p.m. |
| Post-Meeting | 5:30 p.m. – 7:00 p.m. | |

## MEETING MEALS

Your registration for the meeting includes a continental breakfast and lunch on Monday, March 21 and Tuesday, March 22. Breakfast & lunch will be available in the Kirschstein Auditorium Foyer, at the Natcher Conference Center.

## MEETING OBJECTIVE

Age-related bone loss and osteoporosis are tremendous, and growing, public health problems. Approximately 10 million Americans over the age of 50 years already have osteoporosis by World Health Organization criteria, while 33 million more have “osteopenia” (analogous to “prediabetes”); the total with low bone mass could reach 61 million by the year 2020. Given the scope of this problem, it is critical to obtain a better

understanding of the factors determining the acquisition and loss of bone mass, from childhood to senescence. At a mechanistic level, there have been enormous advances in recent years in our understanding of the basic biology of aging; however, these concepts have not necessarily been tested for their relevance to skeletal aging. Thus, the goal of this meeting is to bring together current concepts in aging research with ongoing and planned studies on the epidemiology, mechanisms, and prevention/treatment of age-related bone loss and fractures.

The program objectives of this meeting include defining the pattern and mechanisms for the acquisition of bone mass during growth, identifying the genetic and modifiable risk factors for bone loss and fracture, discussing current concepts of the mechanisms of cellular and organismal aging, understanding mechanisms of bone loss based on animal and human studies, and identifying evolving and novel therapeutic approaches targeting bone and/or muscle. Based on the proceedings of listed objectives, identify a framework for future research in this field and the key questions that need to be addressed, both at a basic and clinical level.

## TARGET AUDIENCE

We anticipate that this meeting will bring together investigators currently working in the area of aging and bone metabolism with those within the bone community not currently focusing on aging research. We expect many attendees will be young investigators, NIH-funded investigators, industry scientists, intramural scientists and program staff at the various NIH Institutes, clinicians interested in osteoporosis, as well as geriatricians and gerontologists with an interest in aging and bone.

## CONTINUING MEDICAL EDUCATION

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of the Institute for the Advancement of Human Behavior (IAHB) and the American Society for Bone and Mineral Research. IAHB is accredited by the ACCME to provide continuing medical education for physicians.

IAHB designates this live activity for a maximum of 12.75 *AMA PRA Category 1 Credit(s)*$^{TM}$. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

You must submit your application for CME credits online at: www.CmeCertificateOnline.com.

- Scroll down to the ASBMR listing and click on the ASBMR Topical Meeting event.
- On the site, you will be asked to enter a password which is **11Topic**, and evaluate various aspects of the program.
- You may then print your certificate immediately (encouraged), anywhere you have internet access.
- A copy of the certificate will also be emailed to you in case you need to print additional copies. Your certificate will show the hours you entered.

**IMPORTANT!**

The online certificate site will be available the end of the day March 23, 2011 through May 6, 2011. After that date, the site will be removed and certificates no longer will be available. If you need a CME certificate, you must complete the evaluation and certificate process prior to that date; otherwise you will forfeit your credit for the course.

Questions regarding your continuing education credits should be directed to:

Attention: Jillian Davis
E-mail: Jillian@cmehelp.com
Tel: (651) 789-3722

## EXPECTATION OF PRESENTERS

Through ASBMR meetings, the Society promotes excellence in bone and mineral research. Toward that end, ASBMR expects that all authors and presenters affiliated with the ASBMR Forum on Aging and Skeletal Health will provide informative and fully accurate content that reflects the highest level of scientific rigor and integrity.

Furthermore, the ASBMR expects that authors and presenters will disclose any conflicts of interest, real or perceived; authors and presenters describing a study funded by an organization with a proprietary or financial interest must affirm that they had full access to all the data in the study. By so doing, they accept complete responsibility for the integrity of the data and the accuracy of the data analysis; the content of abstracts, presentations, slides, and reference materials must remain the ultimate responsibility of the authors and presenters; the planning, content, and execution of abstracts, speaker presentations, slides, abstracts, and reference materials should be free from corporate influence, bias, or control; and all authors and presenters (invited and abstracts-based oral and poster presenters) should give a balanced view of therapeutic options by providing several treatment options, whenever possible, and by citing the best available evidence.

## DISCLOSURE/CONFLICT OF INTEREST

ASBMR is committed to ensuring balance, independence, objectivity, and scientific rigor in all education activities. ASBMR requires that presenters inform the audience of the presenters' (speakers', faculties', authors', and contributors') academic and professional affiliations and disclose the existence of any financial interest or other relationships a presenter has with the manufacturer(s) discussed in an educational presentation. For full-time employees of industry or government, the affiliation listed in the program will constitute full disclosure.

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## AUDIO AND VIDEO RECORDING

ASBMR expects that attendees will respect a presenter's willingness to provide free exchange of scientific information without the abridgment of his or her rights or privacy and without the unauthorized copying and use of the scientific data shared during his or her presentation. The use of cameras, audio recording devices, and video recording equipment is strictly prohibited within all Oral Scientific Sessions and the Poster Sessions without the express written permission of the ASBMR. Unauthorized use of recording equipment may result in the confiscation of the equipment or the individual being asked to leave the Scientific Session. These rules will be strictly enforced.

## ASBMR MEMBERSHIP

The ASBMR Membership Booth will be located in the Kirschstein Auditorium Foyer of the Natcher Conference Center, National Institutes of Health. Stop by and meet the ASBMR staff, make a donation to support Young Investigators and pick up information about the Society, the high-ranking *Journal of Bone and Mineral Research* (*JBMR*), and the upcoming ASBMR 2011 Annual Meeting in San Diego, California, USA, September 16-20, 2011.

## MEETING EVALUATION

An online evaluation form for the ASBMR Forum on Aging and Skeletal Health will be available on the ASBMR Website at www.asbmr.org after the meeting. You will also receive an email reminder from ASBMR. Your participation in this evaluation is extremely important to us. Please take a moment to complete the evaluation of this meeting to aid in planning future meetings. Thank you in advance for your feedback.

## USE OF ASBMR NAME AND LOGO

ASBMR reserves the right to approve use of its name in all material disseminated to the media, public, and professionals. ASBMR's name, meeting name, logo, and meeting logo may not be used without permission. Use of the ASBMR logo is prohibited without the express written permission of the ASBMR Executive Director. All corporate supporters should share their media outreach plans with the ASBMR Executive Director before any release.

No abstract presented at the ASBMR Forum on Aging and Skeletal Health may be released to the press before its official presentation date and time. Press releases must be embargoed until 1 hour after the presentation.

## FUTURE ASBMR MEETING DATES

**ASBMR 2011 Annual Meeting**
September 16 - 20, 2011
San Diego Convention Center
San Diego, California, USA

**ASBMR 2012 Annual Meeting**
October 12-16, 2012
Minneapolis Convention Center
Minneapolis, Minnesota, USA

# American Society for Bone and Mineral Research
# Forum on Aging and Skeletal Health

## Schedule-at-a-Glance

***Monday, March 21, 2011***

| Time | Session | Location |
|---|---|---|
| 7:00 a.m. – 8:00 a.m. | Breakfast | Kirschstein Auditorium Foyer |
| 8:00 a.m. – 8:15 a.m. | Welcome & Opening Remarks | Kirschstein Auditorium |
| 8:15 a.m. – 9:55 a.m. | Session 1: Bone Accretion and Loss: Influence of Nutrition and Physical Activity | Kirschstein Auditorium |
| 9:55 a.m. – 10:15 a.m. | Break/Exhibits Open/Poster Viewing | Kirschstein Auditorium Foyer |
| 10:15 a.m. – 11:20 a.m. | Session 1 (Continued) | Kirschstein Auditorium |
| 11:20 a.m. – 12:20 p.m. | Poster Session | Atrium |
| 12:20 p.m. – 1:00 p.m. | Lunch and Poster Viewing/Exhibits Open | Atrium & Kirschstein Auditorium Foyer |
| 1:00 p.m. – 2:40 p.m. | Session 2: Genetic and Other Risk Factors for Bone Loss and Fracture | Kirschstein Auditorium |
| 2:40 p.m. – 3:00 p.m. | Break/Exhibits Open/Power Viewing | Kirschstein Auditorium Foyer |
| 3:00 p.m. – 4:05 p.m. | Session 2 (Continued) | Kirschstein Auditorium |
| 4:05 p.m. – 5:30 p.m. | Plenary Session: Treatment Approaches for Aging and Bone | Kirschstein Auditorium |
| 5:30 p.m. – 5:50 p.m. | Young Investigator Awards Presentation | Kirschstein Auditorium |
| 5:50 p.m. – 7:00 p.m. | Welcome and Networking Reception/ Poster Viewing | Atrium |

***Tuesday, March 22, 2011***

| Time | Session | Location |
|---|---|---|
| 7:00 a.m. – 8:00 a.m. | Breakfast/Exhibits Open | Kirschstein Auditorium Foyer |
| 8:00 a.m. – 10:20 a.m. | Session 3: Aging Related Changes in Bone Structure and Cellular Activity | Kirschstein Auditorium |
| 10:20 a.m. – 10:40 a.m. | Break/Exhibits Open/Poster Viewing | Kirschstein Auditorium Foyer |
| 10:40 a.m. – 12:45 p.m. | Session 4: Mechanisms of Cellular Aging | Kirschstein Auditorium |
| 12:45 p.m. – 1:45 p.m. | Lunch and Poster Viewing/Exhibits Open | Atrium & Kirschstein Auditorium Foyer |
| 1:45 p.m. – 2:55 p.m. | Session 5: Understanding Physiological Signals Contributing to Age-Related Bone Loss | Kirschstein Auditorium |
| 2:55 p.m. – 3:15 p.m. | Break/Exhibits Open/Poster Viewing | Kirschstein Auditorium Foyer |
| 3:15 p.m. – 4:20 p.m. | Session 5 (Continued) | Kirschstein Auditorium |
| 4:20 p.m. – 5:15 p.m. | Session 6: Meeting Wrap Up | Kirschstein Auditorium |
| 5:15 p.m. | Meeting Adjourns | |

***EXHIBIT HOURS***

| Monday, March 21, 2011 | Tuesday, March 22, 2011 |
|---|---|
| 9:55 a.m. – 10:15 a.m. | 7:00a.m. – 8:00 a.m. |
| 12:20 p.m. – 1:00 p.m. | 10:20 a.m. – 10:40 a.m. |
| 2:40 p.m. – 3:00 p.m. | 12:45 p.m. – 1:45 p.m. |
| | 2:55 p.m. – 3:15 p.m. |

# American Society for Bone and Mineral Research
## *Forum on Aging and Skeletal Health*

***Monday, March 21, 2011***

**BREAKFAST**
**7:00 a.m. – 8:00 a.m.**
**Kirschstein Auditorium Foyer**

**INTRODUCTION**
**8:00 a.m. – 8:15 a.m.**
**Kirschstein Auditorium**

**8:00 a.m. Welcome and Opening Remarks**
Sundeep Khosla, M.D., ASBMR President, Mayo Clinic, Rochester, Minnesota, USA

Jane B. Lian, Ph.D., ASBMR Immediate Past President, University of Massachusetts, Worcester, Massachusetts, USA

Richard J. Hodes, M.D., National Institute on Aging, NIH, Bethesda, Maryland, USA

Yvonne Maddox, Ph.D., Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH, Bethesda, Maryland, USA

Stephen I. Katz, M.D., Ph.D., National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, Bethesda, Maryland, USA

**SESSION 1:**
**8:15 a.m. – 9:55 a.m.**
**Kirschstein Auditorium**

**Bone Accretion and Loss: Influence of Nutrition and Physical Activity**
Chairs: Catherine M. Gordon, M.D., Children's Hospital Boston and Harvard Medical School, Boston, Massachusetts, USA
Karen K. Winer, M.D., National Institute of Child Health and Human Development, NIH, Bethesda, Maryland, USA

**Presentation Number**

**8:15 a.m. Effects of Puberty on Bone Structure and Strength** **1**
Frank Rauch, M.D., Shriners Hospital for Children, Montreal, Canada

**8:40 a.m. Effect of Physical Activity on Growing Bone** **2**
Heather A. McKay, Ph.D., University of British Columbia, Vancouver, Canada

**9:05 a.m. Evaluation of Bone in Children with Chronic Illness** **3**
Mary B. Leonard, M.D., Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

**9:30 a.m. Effects of Vitamin D on Bone in Children and Mouse Models** **4**
Marie Demay, M.D., Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA

**BREAK/EXHIBITS OPEN/POSTER VIEWING**
**9:55 a.m. – 10:15 a.m.**
**Kirschstein Auditorium Foyer**

**SESSION 1 (Continued)**
**10:15 a.m. – 11:20 a.m.**
**Kirschstein Auditorium**

**Presentation Number**

**10:15 a.m.** **Effect of Nutritional Deprivation on Bone (Pediatrics and Anorexia Nervosa)** **5**
Catherine M. Gordon, M.D., Children's Hospital Boston and Harvard Medical School, Boston, Massachusetts, USA

**10:40 a.m.** **YOUNG INVESTIGATOR AWARD PRESENTATION**
**Geometric Bone Adaptations from Childhood to Early Adulthood in Males and Females: A Longitudinal Assessment** **6**
Stefan Jackowski, M.Sc., University of Saskatchewan, Saskatoon, Saskatchewan, Canada

**10:55 a.m.** **Session 1 Panel Discussion**
Moderators: Arline Bohannon, M.D., Virginia Commonwealth University, Richmond, Virginia, USA
Lynda F. Bonewald, Ph.D., University of Missouri, Kansas City, Missouri, USA
All Session 1 speakers and chairs

**POSTER SESSION**
**11:20 a.m. – 12:20 p.m.**
**Atrium**

**LUNCH/EXHIBITS OPEN/POSTER VIEWING**
**12:20 p.m. – 1:00 p.m.**
**Kirschstein Auditorium Foyer and Atrium**

**SESSION 2:**
**1:00 p.m. – 2:40 p.m.**
**Kirschstein Auditorium**

**Genetic and Other Risk Factors for Bone Loss and Fracture**
Chairs: Douglas P. Kiel, M.D., M.P.H., Institute for Aging Research, Hebrew Senior Life, Boston, Massachusetts, USA
Sherry S. Sherman, Ph.D., National Institute on Aging, NIH, Bethesda, Maryland, USA

**Presentation Number**

**1:00 p.m.** **Advances in Bone Genetics: BMD and Fracture** **7**
Andre G. Uitterlinden, Ph.D., Erasmus University, Rotterdam, Netherlands

**1:25 p.m.** **Relation of Race and Ethnicity to Fracture Risk** **8**
Anne Looker, Ph.D., National Center for Health Statistics, Hyattsville, Maryland, USA

**1:50 p.m.** **Impact of Changes in Renal Function on Bone Metabolism, Contrast of Aging and Kidney Disease** **9**
Keith A. Hruska, M.D., Washington University at St. Louis, St. Louis, Missouri, USA

**2:15 p.m.** **Relation of Vitamin D to Falls in the Elderly** **10**
Paul T. Lips, M.D., Ph.D., VU University Medical Center, Amsterdam, Netherlands

**BREAK/EXHIBITS OPEN/POSTER VIEWING**
**2:40 p.m. – 3:00 p.m.**
**Kirschstein Auditorium Foyer**

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**SESSION 2 (Continued)**
**3:00 p.m. – 4:05 p.m.**
**Kirschstein Auditorium**

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**Presentation Number**

**3:00 p.m.** **Frailty and Falls as Contributors to Fracture** **11**
Laurence Z. Rubenstein, M.D., M.P.H., F.A.C.P., Oklahoma University Health Science Center, Oklahoma City, Oklahoma, USA

**3:25 p.m.** **YOUNG INVESTIGATOR AWARD PRESENTATION** **12**
**Age-Related Differences in Skeletal Microstructure and Mechanical Competence in Chinese-American and Caucasian Women**
X. Sherry Liu, Ph.D., Columbia University, New York, New York, USA

**3:40 p.m.** **Session 2 Panel Discussion**
Moderators: Robert Pignolo, M.D., Ph.D., University of Pennsylvania, Philadelphia, Pennsylvania, USA
Charlotte A. Peterson, Ph.D., University of Kentucky, Lexington, Kentucky, USA
All Session 2 speakers and chairs

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**PLENARY SESSION:**
**4:05 p.m. – 5:30 p.m.**
**Kirschstein Auditorium**

**Treatment Approaches for Aging and Bone**
Chairs: Jay S. Magaziner, Ph.D., MSHyg, University of Maryland, Baltimore, Maryland, USA
Clifford J. Rosen, M.D., Maine Medical Center Research Institute, Scarborough, Maine, USA

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**Presentation Number**

**4:05 p.m.** **Mid-life Changes in Femur Shape as a Predictor of Longevity in Mice: New Marker for Intervention Studies?** **13**
Richard A. Miller, M.D., Ph.D., University of Michigan, Ann Arbor, Michigan, USA

**4:35 p.m.** **Special Considerations in Treating Osteoporosis in the Elderly** **14**
Susan L. Greenspan, M.D., University of Pittsburgh, Pittsburgh, Pennsylvania, USA

**5:05 p.m.** **Discussion**

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**YOUNG INVESTIGATOR AWARDS PRESENTATION**
**5:30 p.m. – 5:50 p.m.**
**Kirschstein Auditorium**

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**WELCOME AND NETWORKING RECEPTION/POSTER VIEWING**
**5:50 p.m. - 7:00 p.m.**
**Atrium**

***Tuesday, March 22, 2011***

**BREAKFAST/EXHIBITS OPEN**
**7:00 a.m. – 8:00 a.m.**
**Kirschstein Auditorium Foyer**

**SESSION 3:**
**8:00 a.m. – 10:20 a.m.**
**Kirschstein Auditorium**

**Aging-Related Changes in Bone Structure and Cellular Activity**
Chairs: Meryl S. LeBoff, M.D., Brigham and Women's Hospital, Boston, Massachusetts, USA
Orhan K. Oz, M.D., Ph.D., University of Texas Southwestern Medical Center, Dallas, Texas, USA

**Presentation Number**

**8:00 a.m.** **Effects of Body Composition on Bone and the "Muscle Bone Unit" in Healthy Youth** **15**
Nicola Crabtree, Ph.D., Queen Elizabeth Hospital, Birmingham, United Kingdom

**8:25 a.m.** **Changes in Bone Strength and Skeletal Loading with Age** **16**
Mary L. Bouxsein, Ph.D., Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA

**8:50 a.m.** **Role of the Osteocyte in Mechanotransduction and in Age-Related Bone Loss** **17**
Lynda F. Bonewald, Ph.D., University of Missouri, Kansas City, Missouri, USA

**9:15 a.m.** **Exercise and the Preservation of Bone Health with Aging** **18**
Wendy M. Kohrt, Ph.D., University of Colorado, Denver, Colorado, USA

**9:40 a.m.** **YOUNG INVESTIGATOR AWARD PRESENTATION** **19**
**Age-Related Increases in Constitutive Expression of RANK, c-fms, and PPARγ and in Osteoclast Potential in Human Marrow Stem Cells**
Regina O'Sullivan, Ph.D., Brigham and Women's Hospital, Boston, Massachusetts, USA

**9:55 a.m.** **Session 3 Panel Discussion**
Moderators: Elizabeth Shane, M.D., Columbia University, New York, New York, USA
Roberto Pacifici, M.D., Emory University School of Medicine, Atlanta, Georgia, USA
All Session 3 speakers and chairs

**BREAK/EXHIBITS OPEN/POSTER VIEWING**
**10:20 a.m. – 10:40 a.m.**
**Kirschstein Auditorium Foyer**

**SESSION 4:**
**10:40 a.m. – 12:45 p.m.**
**Kirschstein Auditorium**

**Mechanisms of Cellular Aging**
Chairs: Teresita M. Bellido, Ph.D., Indiana University, Indianapolis, Indiana, USA
John P. Williams, Ph.D., National Institute on Aging, NIH, Bethesda, Maryland, USA

**Presentation Number**

**10:40 a.m.** **The Aging Cell** **20**
Judith Campisi, Ph.D., Lawrence Berkeley Laboratory, Berkeley, California, USA

**11:05 a.m. Autophagy and Aging Cartilage** **21**
Martin Lotz, M.D., The Scripps Research Institute, La Jolla, California, USA

**11:30 a.m. Regulation of Life Span and Age-Related Diseases by Caloric Restriction** **22**
Holly Van Remmen, Ph.D., University of Texas Health Science Center, San Antonio, Texas, USA

**11:55 a.m. Muscle Stem Cell Function in Aging** **23**
Zipora Yablonka-Reuveni, Ph.D., University of Washington School of Medicine, Seattle, Washington, USA

**12:20 p.m. Session 4 Panel Discussion**
Moderators: James Kirkland, M.D., Ph.D., Mayo Clinic, Rochester, Minnesota, USA
Tamara B. Harris, M.D., National Institute on Aging, NIH, Bethesda, Maryland, USA
All Session 4 speakers and chairs

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**LUNCH and POSTER VIEWING**
**12:45 p.m. – 1:45 p.m.**
**Kirschstein Auditorium Foyer and Atrium**

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**SESSION 5:**
**1:45 p.m. – 2:55 p.m.**
**Kirschstein Auditorium**

**Understanding Physiological Signals Contributing to Age-Related Bone Loss**
Chairs: Marja Marie Hurley, M.D., University of Connecticut, Farmington, Connecticut, USA
Sundeep Khosla, M.D., Mayo Clinic, Rochester, Minnesota, USA

**Presentation Number**

**1:45 p.m. Overview from Clinical Studies in Humans on Bone Loss Through the Menopausal Transition** **24**
Jane A. Cauley, Ph.D., University of Pittsburgh, Pittsburgh, Pennsylvania, USA

**2:10 p.m. Role of Oxidative Stress in Age-Related Bone Loss** **25**
Stavros C. Manolagas, M.D., Ph.D., University of Arkansas, Little Rock, Arkansas, USA

**2:35 p.m. Potential Role of T- and Other Immune Cells in Estrogen Deficiency Mediated Bone Loss** **26**
Roberto Pacifici, M.D., Emory University School of Medicine, Atlanta, Georgia, USA

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**BREAK/EXHIBITS OPEN/POSTER VIEWING**
**2:55 p.m. – 3:15 p.m.**
**Kirschstein Auditorium Foyer**

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**SESSION 5 (Continued)**
**3:15 p.m. – 4:20 p.m.**
**Kirschstein Auditorium**

**Presentation Number**

**3:15 p.m. Role of the CNS in Mediating Age-Related Bone Loss** **27**
Edith M. Gardiner, Ph.D., University of Washington, Seattle, Washington, USA

**3:40 p.m. YOUNG INVESTIGATOR AWARD PRESENTATION** **28**
**The Misty Mouse Is a Model for Age-Related Bone Loss Due to Sympathetic Nervous System Hyperactivity**
Katherine Motyl, Ph.D., Maine Medical Center Research Institute, Scarborough, Maine, USA

**3:55 p.m. Session 5 Panel Discussion**
Moderators: Thomas L. Clemens, Ph.D., Johns Hopkins University, Baltimore, Maryland, USA
Jane B. Lian, Ph.D., University of Massachusetts Medical School, Worcester, Massachusetts, USA
All Session 5 speakers and chairs

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**SESSION 6:**
**4:20 p.m. – 5:15 p.m.**
**Kirschstein Auditorium**

**Meeting Wrap Up**
Chair: Sundeep Khosla, M.D., Mayo Clinic, Rochester, Minnesota, USA

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**4:20 p.m. Session Chairs Highlight Key Aspects of Their Sessions**
All Session Chairs

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**Meeting Adjourns**
**5:15 p.m.**

***Note:*** *"*" in author block refers to presenting author.*

## Session 1: Bone Accretion and Loss: Influence of Nutrition and Physical Activity

### 1

**Effects of Puberty on Bone Structure and Strength**

F. Rauch*, Shriners Hospital for Children, Montreal, Canada

During puberty, the growing bone faces the difficult task of remaining stable despite rapid increases in bone length and mechanical loads. Bone can only withstand these loads if its axis is aligned with the direction of the largest forces to which it is exposed. To this end, a feedback mechanism must exist in the growth plates which ensures that bone growth proceeds in the direction of the predominant mechanical forces. Although the actions of this mechanism are obvious in everyday clinical practice, mechanistic data are scarce. Bone strength increases during puberty mostly by growth in width. This occurs through perichondral and periosteal apposition. There is presently little information on how growth in width is linked to growth in length but it is clear that mechanical loads are important determinants of this process. The high fracture rates at the distal radius during early puberty are an example of imperfect structural adaptation of the bone to increasing mechanical demands during rapid growth. Bone structure can be determined with clinically applicable methodologies, but it remains difficult to determine mechanical loads on the skeleton in the clinical setting. This methodological gap hampers our understanding of how hormonal and mechanical factors interact to increase bone strength during puberty.

***Disclosures: F .Rauch***, None.

### 2

**Effect of Physical Activity on Growing Bone**

H. A. McKayV, University of British Columbia, Vancouver, Canada

Well-designed dual energy x-ray absorptiometry (DXA)-based intervention studies provide level 1 evidence (Oxford classification) that physical activity augments bone mass and density during childhood [1.] Although DXA technology was instrumental in setting the course for pediatric bone science, it has a number of limitations that are well-appreciated by forum attendees. Importantly, the limitations of DXA mean that the older studies are likely to have underestimated the benefits of exercise for enhancing bone strength. There remains a dearth of evidence from well-designed RCTs to support the role of physical activity on children's bone *strength*. A recent systematic review and meta-analysis examined RCTs with interventions of > 6 months duration that reported bone strength [2]. There was a small positive effect of weight-bearing exercise on various estimates of bone strength in especially among prepubertal boys, but not among girls. Not surprisingly – beneficial effects in adolescent boys and girls were linked with exercise compliance. Different types of weight-bearing activities that imposed loads of from three to nine times body weight, performed three to five times per week for 10-45 minutes per session – were most effective.

***Disclosures: H.A. McKay***, None.

### 3

**Evaluation of Bone in Children with Chronic Illness**

M. B. Leonard*, Children's Hospital of Philadelphia, Philadelphia, PA

Chronic diseases during childhood pose numerous threats to bone health. The impact may be immediate, resulting in fragility fractures, or delayed, caused by suboptimal peak bone mass with subsequent fractures in adulthood. Risk factors for impaired bone accrual include poor growth, delayed maturation, malnutrition, muscle deficits, decreased physical activity, chronic inflammation, and medications such as glucocorticoids.

Skeletal development is characterized by sex- and maturation-specific increases in trabecular and cortical volumetric bone mineral density (BMD) and cortical dimensions. Studies in varied chronic childhood diseases demonstrate that disease and treatment effects are site-specific. For example, Crohn's disease and juvenile idiopathic arthritis are characterized by decreased trabecular BMD, significant muscle deficits, and cortical thinning with decreases in periosteal circumference and expansion of the endosteal circumference. Preliminary data suggest that treatment of Crohn disease with anti-TNF- therapy (infliximab) is associated with gains in trabecular BMD and endocortical bone with consequent reductions in cortical BMD. In contrast, high-dose chronic glucocorticoid therapy in childhood steroid dependent nephrotic syndrome is associated with obesity, increased muscle mass, modest reductions in trabecular BMD, and increased cortical BMD and cortical area. Advanced chronic kidney disease and secondary hyperparathyroidism are associated with decreased cortical BMD and cortical area; the cortical thinning does not improve following transplantation despite gains in muscle mass. Additional studies in childhood leukemia, bone marrow transplantation, and neuromuscular disease also demonstrate distinct patterns of musculoskeletal deficits.

Dual energy x-ray absorptiometry (DXA) is the most widely available tool for the non-invasive assessment of bone mass. However, DXA is a 2D projection technique that is confounded by poor growth. There is little consensus regarding strategies to adjust DXA results for bone size, body composition, and maturation. Furthermore, DXA does not distinguish between cortical and trabecular bone. Quantitative computed tomography (QCT) has the advantage that is provides 3D measures of trabecular and cortical BMD and cortical geometry. However, QCT is not widely available and reference data are limited. Future studies are needed to establish strategies to diagnosis and monitor bone deficits, and to guide therapy in childhood chronic disease.

***Disclosures: M.B. Leonard***, None.

### 4

**Effects of Vitamin D on Bone in Children and Mouse Models**

M. Demay*, Massachusetts General Hospital and Harvard Medical School, Boston, MA

Humans and mice with impaired vitamin D action exhibit hypocalcemia and secondary hyperparathyroidism, the latter of which results in hypophosphatemia due to impaired tubular reabsorption of phosphate. In association with these biochemical abnormalities, they have impaired skeletal mineralization

(osteomalacia) and, in growing animals, the cartilaginous growth plate is expanded (rickets). Investigations in children with vitamin D receptor (VDR) mutations demonstrated that bypassing the defect in intestinal calcium absorption, by intravenous administration, normalizes mineral ion levels and leads to resolution of rickets and osteomalacia. This prompted investigations in mouse models of VDR ablation, to determine what actions of the VDR on the skeleton were direct, and which were a result of impaired mineral ion homeostasis.

Studies in VDR null mice revealed that rickets is due to expansion of the late hypertrophic chondrocyte region, associated with impaired apoptosis of these cells. Prevention of abnormal mineral ion levels led to a histologically, histomorphometrically and biomechanically normal skeleton. Complementary studies in the murine model of X-linked hypophosphatemia and in mice with diet induced hypercalcemia/hypophosphatemia established that low levels of circulating phosphate were responsible for impaired hypertrophic chondrocyte apoptosis. Investigations in cellular models demonstrated that phosphate induces hypertrophic, but not proliferative, chondrocyte apoptosis by activating the caspase-9 dependent mitochondrial apoptotic pathway. This differential susceptibility to apoptosis was associated with a decrease in mitochondrial membrane potential during chondrocyte maturation. Phosphate treatment of hypertrophic, but not proliferative, chondrocytes resulted in a further decrease in mitochondrial membrane potential and induction of Erk1/2. Prevention of Erk1/2 phosphoryation inhibited hypertrophic chondrocyte apoptosis *in vivo* and *in vitro*.

Studies in mice lacking Npt2a also develop hypophosphatemia, but their growth plate phenotype resolves in association with an increase in endogeous 1,25-dihydroxyvitamin D production. However, VDR/Npt2a double knockout mice exhibit severe rickets. Thus, the receptor–dependent actions of 1,25-dihydroxyvitamin D can compensate for hypophosphatemia and lead to normal growth plate maturation.

***Disclosures: M .Demay***, None.

## 5

**Effect of Nutritional Deprivation on Bone (Pediatrics and Anorexia Nervosa)**

C. M. Gordon*, Children's Hospital Boston and Harvard Medical School, Boston, MA

The childhood and adolescent years are critical ones for bone accrual and the achievement of peak bone mass. Growth, pubertal development and bone accretion occur simultaneously in a healthy young child or adolescent, and are nutrition-dependent physiological processes. Many common pediatric chronic diseases afflict children during these formative years, several which are associated with malnutrition. The malnourished state can stem from poor appetite, malabsorption of vitamin D and other key nutrients, as well as underlying disease-related factors that alter the patient's hormonal milieu, and ultimately, bone turnover.

An overview of longterm skeletal effects of malnutrition will be provided in the context of specific pediatric chronic diseases. Inflammatory bowel disease, cystic fibrosis, and anorexia nervosa will be discussed as models that illustrate how malnutrition mediates bone loss in a young skeleton. The role of body weight and lean body mass, proresorptive cytokine secretion, growth factors, and alterations of bone turnover will be explored in each model. In anorexia nervosa, hormonal abnormalities and changes in bone marrow composition will be reviewed that appear to be secondary to chronic severe malnutrition. An overview will then be presented of current therapeutic strategies to counter bone loss in adolescents with this disease. Lastly, new data from a pediatric model of aging, Hutchinson-Gilford Progeria Syndrome ("Progeria", or "HGPS") will be presented. Children with this rare, fatal genetic condition have a strikingly similar phenotype and appear emaciated. Interestingly, their caloric intake meets the established requirements for age, but these children exhibit extreme short stature and unique skeletal abnormalities.

***Disclosures: C.M. Gordon***, None.

## 6

**YOUNG INVESTIGATOR AWARD PRESENTATION**
**Geometric Bone Adaptations from Childhood to Early Adulthood in Males and Females: A Longitudinal Assessment**

S. A. Jackowski*, S. A. Kontulainen, D.M. Lane Cooper, J.Lanovaz, A. D.G. Baxter-Jones, University of Saskatchewan, Canada

The purpose of this study was to describe the development of bone density, size and estimate bone strength at the proximal femur in a healthy population of males and females followed longitudinally and identify the ages at which peak values of areal bone mineral density (aBMD), cross sectional area (CSA) and section modulus (Z) occur. Methods: Participants consisted of 165 (73 males, 92 females) individuals from the Saskatchewan Pediatric Bone Mineral Accrual Study (PBMAS). Areal BMD, CSA and Z were serially assessed at the narrow neck (NN), intertrochanter (IT) and femoral shaft (S) sites using hip structural analysis (HSA) covering the age span of 8-30 years. Peak values for aBMD (aBMDp), CSA (CSAp) and Z (Zp) were determined and the chronological ages of aBMDp, CSAp and Zp ascertained. Chronological ages were converted to biological age using years away from peak height velocity. A 2x3 (sex by site) factorial MANOVA with repeated measures was used to test for differences between the biological ages at aBMDp, CSAp and Zp between sexes. Results: Significant sex difference in the development of peak bone outcomes were observed ($p>0.05$). Intertrochanter aBMDp ($6.6 \pm 3.4$y) occurred significantly earlier than IT CSAp ($7.7 \pm 3.4$y) and IT Zp ($7.9 \pm 3.4$y) in males ($p>0.05$). In females, both IT aBMDp ($6.8 \pm 3.5$y) and IT Zp ($6.6 \pm 4.0$y) occurred significantly earlier than IT CSAp ($7.5 \pm 3.4$y; $p<0.05$). At the S, the opposite relationship was observed. At all sites, aBMDp occurred approximately 1 year earlier than CSAp for both sexes. Conclusions: There are significant sex differences in the developmental timing of bone density, size and estimated strength at the proximal femur, but despite these sex differences, aBMDp occurred significantly earlier than CSAp at all sites. These findings suggest that the changes in aBMD precede geometric adaptations.

***Disclosures: S.A. Jackowski***, None.

# Session 2: Genetic and Other Risk Factors for Bone Loss and Fracture

## 7

**Advances in Bone Genetics: BMD and Fracture**

A. G. Uitterlinden*, Erasmus University, Rotterdam, Netherlands

Many common traits and diseases, including height, osteoporosis and osteoarthritis, have moderate to strong genetic influences.

Intense efforts are ongoing to identify the underlying genetic variants, while knowledge of these variants can help in understanding the disease process and might benefit development of interventions and diagnostics. Genome-Wide Association studies (GWAS) have now become the standard approach and builds upon (1) availability of extensive data on human genetic variation, (2) novel genotyping technology, e.g., very high-density single nucleotide polymorphism (SNP) arrays, (3) bio-banks of large population cohorts and case-control series with DNA and phenotype information, and (4) a collaborative spirit among researchers. GWAS usually happens within the context of consortia with very large collections of DNA samples with a certain phenotype. For height this would be the GIANT consortium, for osteoporosis this is the GEFOS/GENOMOS consortium, and for osteoarthritis this is the TREAT-OA consortium.

In the past few years GWAS has proven to be widely successful for almost all complex traits and diseases in discovering novel and common risk genes, although mainly in Caucasian populations and mostly with modest effect size. For example, for height, osteoporosis, and osteoarthritis several large GWAS have been published, while also for other bone phenotypes such as seen in Paget's disease. For example, 80 loci have been identified for bone mineral density (BMD), ~200 loci for height, and several loci for Paget's and OA. Interestingly, experience so far has shown that a) GWAS identifies DNA variants rather then genes, and b) the effects per variant are generally modest, e.g., with Odds Ratios ranging from 1.1 –1.7, and explained variance of combined common variants, e.g., for height being 10-15% and for BMD being 3-7 %. For fracture or bone loss no individual GWAS have been performed. Pharmaco-genetic studies of osteoporosis are still scarce, but for some other disease-treatments they have resulted in identification of sometimes substantial genetic influences on the response-to-treatment.

Together with genetic studies on more rare genetic syndromes, the GWAS approach is clarifying part of the genetic architecture of complex traits and diseases, including aspects of the skeleton. GWAS techniques using SNP arrays are assessing only a small part, 0.1-0.2%, of the base pairs constituting the human genome. Newly developed high throughout sequencing technology allows to asses all coding parts of the genome (~1% of bp) and even the majority of bp by full-genome sequencing (~95% of bp). These approaches are now underway and will again also be based on association approaches in large consortia, and will likely contribute to a further understanding of the genetics of bone.

***Disclosures: A.G. Uitterlinden,***

## 8

**Relation of Race and Ethnicity to Fracture Risk**

A. Looker*, National Center for Health Statistics, Hyattsville, MD

Understanding how fracture risk differs between racial and ethnic groups may provide important insights about the pathogenesis of this condition. This presentation will summarize available data on fracture incidence, bone mineral density (BMD) and bone loss in different race/ethnic groups in the U.S. Most data on fracture incidence in nonwhites focuses on blacks, who have lower fracture rates at many skeletal sites, including hip, clinical vertebral, upper and lower appendages. Smaller amounts of data suggest lower hip fracture rates in Hispanics and Asian Americans than whites; limited data suggests this may also be true at some other skeletal sites. Fracture data for other race/ethnic groups are very sparse. A somewhat different pattern by race/ethnicity emerges for BMD: blacks have higher BMD than whites, Asian Americans have lower BMD and the difference for Hispanics may depend on skeletal site. These BMD differences tend to be reduced in magnitude or removed if adjusted for body size differences. Limited prospective data on bone loss with aging in blacks and in Asians have reported slower or similar rates of loss as whites, depending on sex. Overall, there are many gaps in fracture risk data by race/ethnicity. The meaning of race/ethnicity and its measurement are additional issues. An expert panel of the Institute of Medicine recommended that race be considered a "construct of human variability based on perceived differences in biology, physical appearance and behavior". The US Census Bureau reports data for 5 broad race/ethnic groups, but these can be further subdivided into numerous sub groups. Limited data suggest skeletal status might differ within different race/ethnic subgroups, but it is unlikely to be feasible to obtain data for all possible subgroups. Studies may differ in how they measure race/ethnicity, which hampers inter-study comparisons.

***Disclosures: A. Looker***, None.

## 9

**Impact of Changes in Renal Function on Bone Metabolism, Contrast of Aging and Kidney Disease**

K. A. Hruska*, Washington University at St. Louis, St. Louis, MO

***Disclosures: K.A. Hruska***, Shire 5, 8.

## 10

**Relation of Vitamin D to Falls in the Elderly**

P. T. Lip*s, VU University Medical Center, Amsterdam, Netherlands

Vitamin D and calcium were shown to prevent fractures compared to placebo in French nursing home residents in the Decalyos Study in Lyon. This treatment effectively decreased the number of non-vertebral fractures already after 6 months suggesting an effect on fall incidence. Epidemiological studies, such as the Longitudinal Aging Study Amsterdam (LASA) showed associations between vitamin D deficiency and falls and fractures. The fall risk was increased when serum 25-hydroxyvitamin D (25(OH)D) was lower than 25 nmol/l. In later intervention studies, the effect of vitamin D with calcium on fractures and falls was ambiguous. Several meta-analyses of these studies on the effect of vitamin D on falls showed a significant decrease of fall incidence of 5 to 20 %. The vitamin D dose for this effect should be higher than 400 IU/d, and studies in the very old and in the institutionalized were more often significant. However, a recent Australian study using a vitamin D dose of 500,000 IU once per year showed a significant increase in fall incidence in the 3 months after the dose. This was associated with a very high mean serum 25(OH)D level of 120 nmol/l.

The mechanism why vitamin D prevents falls is not completely clear. Vitamin D status is related to physical performance tests as has been shown in the NHANES and LASA studies.

These physical performance tests assess muscle strength and balance. Improvement of these tests in vitamin D intervention studies has not been clearly demonstrated. One study in older persons showed a decrease of sway after treatment with 1200 IU/d in comparison with placebo, but this was a posthoc analysis in persons with high baseline sway. In conclusion, vitamin D has a small to moderate effect on fall incidence in older persons, especially in the institutionalized. It is uncertain whether a dose

response effect exists, and whether it works in most older persons or only in the frail or those with increased sway. The mechanism should be clarified. The relationship between vitamin D status and falls may be U-shaped, with an increased fall risk with very low and very high serum 25(OH)D levels.

***Disclosures: P.T. Lips***, None.

## 11

**Frailty and Falls as Contributors to Fracture**

L. Rubenstein*, Oklahoma University Health Science Center, Oklahoma City, OK

Falls are common in older adults and are associated with high morbidity, mortality, and cost—the most serious of which involve fractures. Falls have many underlying risk factors that can be identified and used in planning prevention measures and interventions. The most important include: muscle weakness, gait & balance disorders, prior falls, impaired vision, memory loss, functional impairment, psychoactive medications, and environmental hazards. These factors interact with osteopenia to increase risk for injurious falls and fractures. The field of fall prevention has grown considerably in the past 15 years, with several intervention strategies proven to reduce risk of falls in multiple controlled trials and meta-analyses. The most powerful interventions include multi-factorial fall risk assessments with appropriate follow-up, targeted exercise programs, environmental inspection and modification programs. In addition, a number of single interventions (e.g., Vitamin D, hip protectors, cataract surgery, and anti-skid footwear) have been shown to be helpful. Clinical guidelines have been developed to assist healthcare professionals. Remaining research questions exist in all major areas of epidemiology, risk factor identification, and efficacy and effectiveness of interventions.

***Disclosures: L. Rubenstein***, None.

## 12

**YOUNG INVESTIGATOR AWARD PRESENTATION**
**Age-Related Differences in Skeletal Microstructure and Mechanical Competence in Chinese-American and Caucasian Women**

X. S. Liu*[1], M. D. Walker[1], E. M. Stein[2], B. Zhou[1], J. Udesky[1], G. Liu[3], E. Shane[2], J. Bilezikian[2], X. E. Guo[1], [1]Columbia University, New York, NY, [2]Columbia University College of Physicians and Surgeons, New York, NY, [3]New York Downtown Hospital, New York, NY

Despite lower areal BMD (aBMD) by DXA, Chinese-American (CH) women have fewer fractures than Caucasian (CA) women. To address this, we applied individual trabeculae segmentation (ITS), a novel image analysis technique, and finite element analysis, to high-resolution peripheral QCT (HR-pQCT, Scanco Medical) images of pre- (PreM; n=95) and post-menopausal (PostM; n=97) CH and CA women at the distal radius (DR) and tibia (DT) to quantify trabecular (Tb) plate- and rod-microarchitecture and bone stiffness. Age did not differ among PreM groups (CH 36±7 vs. CA 35±7 yrs) but was lower in PostM CH women (CH 61±2 vs. CA 64±3 yrs). Height and weight were lower in the CH vs.CA groups (PreM: CH 162cm 57Kg vs. CA 165cm 63Kg; PostM: CH 157cm 58Kg vs. CA 163 cm 66Kg, $p<0.05$). aBMD did not differ at the spine, hip or 1/3 radius in either age group. Remarkably, PreM CH had 94% (DR) and 80% (DT) higher plate bone volume fraction (pBV/TV) and 20% (DR) and 18% (DT) higher plate number density (pTb.N) compared to PreM CA women ($p<0.001$). The amount and number of trabecular rods (rBV/TV and rTb.N) were similar. Despite smaller bone size (-9% & -6%, $p=0.03$ & 0.08 at DR & DT), thicker cortical (Ct) bone (18% and 10%, $p<0.05$) and more Tb plates led to 14% (DR) and 8% (DT) greater whole bone stiffness ($p<0.05$) in PreM CH vs. CA women. At DR, the deterioration in Tb microstructure and stiffness with age (PostM vs. PreM) was greater in CH than CA but loss in Ct bone was similar, resulting in a shifted load distribution toward Ct bone in CH but not in CA women. At DT, a reduction in Tb microstructure and stiffness occurred only in CH, with loss in Ct bone in both CH and CA, resulting in a shifted load distribution toward Tb bone in CA but not in CH women. Furthermore, PostM CH had 25% (DR, $p=0.06$) and 23% (DT, $p=0.005$) higher pBV/TV but similar pTb.N compared to CA women. In contrast, rBV/TV and rTb.N were 26% and 12% lower at DR and 12% and 6% lower at DT in PostM CH vs. CA ($p<0.05$) women. Despite smaller bone size (-13% & -11%, $p<0.001$ at DR & DT), PostM CH had thicker cortices (13% and 16%, $p<0.05$) and relatively intact Tb plates, leading to similar whole bone stiffness compared to CA women. There are greater microstructural advantages in both Ct and Tb bone in PreM CH women. However, there is greater Tb bone loss with age in CH women, especially at DT. Nevertheless, advantages such as thicker cortices and more plate-like Tb bone remain in PostM CH vs. CA women.

***Disclosures: X.S. Liu***, None.

# Plenary Session: Treatment Approaches for Aging and Bone

## 13

**Mid-life Changes in Femur Shape as a Predictor of Longevity in Mice: New Marker for Intervention Studies?**

R. A. Miller*, University of Michigan, Ann Arbor, MI

If aging affects multiple tissues, and if individuals differ in their rate of aging, then it may be possible to find early and mid-life markers that discriminate between individuals that are aging at different rates. In a study of the femurs of genetically heterogeneous mice, we have found evidence for two such predictive factors. Young adult mice that have smaller bones (shorter length, thinner cortex, lower cross-section) live longer than mice with larger femurs, perhaps reflecting alterations in growth hormone and/or IGF-1 levels that affect both early bone growth and late-life disease risks. In addition, mice whose endosteal cavity expands in mid-life have higher mortality risks than sibs with smaller rates of change in endosteal diameter. Combining both indices provides a better predictor of lifespan than either taken alone. Most of these mice die of cancer, and none die of bone diseases: the femoral changes are therefore surrogate indices of systemic changes that influence the pace of aging, or cancer, or both. The NIA-sponsored "Intervention Testing Program" has begun to survey a wide range of possible anti-aging drugs, and found replicable longevity benefits from rapamycin, an inhibitor of the "TOR" protein kinase. Evaluation of age-sensitive endpoints, and of developmental changes that predict lifespan, may provide important clues to the mechanisms linking cellular pathways to aging and late-life diseases. Studies of bone-related predictors of lifespan in mice justify a search for similar associations in humans.

***Disclosures: R.A .Miller***, None.

## 14

**Special Considerations in Treating Osteoporosis in the Elderly**

S. L. Greenspan*, University of Pittsburgh, Pittsburgh, PA

Although osteoporosis is common and costly in older individuals, residents in long term care have both the greatest risk and neglect. 85% of nursing home women over age 80 have osteoporosis. Hip and nonvertebral fractures are 2.5 to 3.5 times more common than in the community. For the elderly in long term care there are gaps in our understanding of 1) treatment thresholds, 2) treatment efficacy 3) barriers to treatment and 4) barriers to perform clinical research. The National Osteoporosis Foundation treatment guidelines utilizing bone mineral density, clinical fractures or FRAX, may be less relevant and misleading for the frail older population. A study in long term care residents using bone mineral density, vertebral fractures, FRAX or combinations of these tools reported treatment threshold ranged from 44 to 99% of participants depending on the criteria used. Furthermore, FRAX omits important risk factors for the elderly including falls assessment, cognitive impairment, poor balance, poor eyesight, malnutrition, multiple morbidity and multiple medications. For treatment efficacy there are post-hoc, subanalyses of pivotal trials that examine patients age 75 and older. Most demonstrate fracture reduction in healthy, older community dwelling women. Nursing home residents are routinely excluded from the pivotal trials due to impaired mobility, poor cognition, psychotropic medicines, and high fall risk. Hip protectors have questionable efficacy and poor compliance. There are barriers to treatment in long term care facilities. Only 36% of long term care residents receive any bone protection. Patients are less likely to receive treatment if they are cognitively impaired, immobilized, or have significant comorbidities or GI diseases. Barriers to implementation in this cohort include lack of evidence, safety issues, poor compliance and expense. There are concerns about gastrointestinal side effects from oral bisphosphonates. Renal impairment and infusion logistics limit intravenous medication. In the community, post fracture interventions such as physician education, electronic medical records, patient reminders, and alternatives for service delivery have increased bone density screening by 36% and osteoporosis treatment by 20%. Similar studies are needed in long term care. Finally there are barriers to research in long term care. There is skepticism from the staff, administration, families and patients. Patients will not leave the facility for research. The staff is overcommitted. There is the perception that the patients are too sick, too old or on too many medications to participate. In summary we have made great strides in osteoporosis assessment and treatment for our younger counterparts. Now we need to refocus these achievements for our older frail patients who have the greatest risk for fracture and suffer the considerable consequences.

***Disclosures: S.L. Greenspan***, Merck 5; Amgen 5; Lilly 2; Warner Chilcott 2.

# Session 3: Aging-Related Changes in Bone Structure and Cellular Activity

## 15

**Effects of Body Composition on Bone and the "Muscle Bone Unit" in Healthy Youth**

N. Crabtree*, Queen Elizabeth Hospital, Birmingham, UK

The skeletal system adapts to the energetic constraints imposed by the somatic growth and functional demands of the child through successive stages of development. As such, the acquisition of optimal bone mass is largely a reflection of increases in body size. However, it is not solely these factors which control growth, but the effect that increasing growth has on the mechanical system by increasing muscle force and bone lever arms, which has caused increasing interest in recent years.

It is well established that the skeleton is a mechanically optimized organ where its strength is regulated by loads routinely applied to it. According to the muscle-bone mechanostat theory, skeletal loads mainly arise from muscle forces actuating bony levers such that limb muscle mass should be a reasonable measure of skeletal load. As children grow they gain both body weight and muscle mass, with increasing muscle strength. This increasing load will lead to increased strain which can be sensed within the bone. The bone cells will in turn respond by increasing bone modeling and remodeling to increase the whole bone strength and mass. As body weight and muscle mass reach a plateau in early adulthood there should be a catch up in bone growth which should slow down and eventually switch off bone modeling as the strain within the bone is reduced.

However, the muscle-bone mechanostat may be influenced other factors such as adiposity and physical activity and non-mechanical factors such as puberty, nutrition, and genetics. Variations in body fat and regional adiposity have produced conflicting results. Some researchers have shown beneficial effects of increased fat mass whist others have shown adverse affects of both too little and too much body fat. The timing of changes in body composition may also play a significant role. Unfavorable body composition during sexual maturation may result in sub optimal bone strength in both early adulthood and later life.

As such, understanding and being able to assess the important factors of bone health during childhood is essential when monitoring the acquisition of bone strength, given that, by the time growth has ceased, the skeleton is believed to be as strong as it is ever going to be. Consequently, optimizing bone strength during this time will have an impact on both current and future risk of fracture.

***Disclosures: N. Crabtree***, None.

## 16

**Changes in Bone Strength and Skeletal Loading with Age**

M. L. Bouxsein*, Beth Israel Deaconess Medical Center, Boston, MA

The marked increase in fracture risk with age is likely due to decreased bone strength combined with increased forces applied to the skeleton. With regard to age-related declines in bone strength, studies used human cadaveric specimens have demonstrated significant declines in whole bone strength, with younger specimens

being 3 to 10 fold stronger than older specimens. Further, population based studies have used 3D-QCT imaging and demonstrated greater declines in vertebral compressive strength over life in women than men (-43% vs -31%, p <0.01)(Bouxsein et al, JBMR 2006). In the femur, declines in femoral strength in a sideways fall configuration are greater in women than men (-55% vs -39%, p < 0.01), and exceed the declines in femoral BMD (-26% for women, -21% for men)(Keaveny et al, JBMR 2010). Moreover, age-related declines in femoral strength are greater for fall-loading condition than for stance phase loading (Keyak et al, ASBMR 2010). Changes in bone morphology and microarchitecture contributing to these declines in whole bone strength will be reviewed.

In contrast to the knowledge on age-related changes in bone strength, there are relatively few studies that have explored age-related changes in skeletal loading. A number of factors contribute to increased fall risk among elder individuals. Once a fall does occur, age-related changes in height, weight, and for the hip, trochanteric soft tissue thickness, will influence the forces applied to the skeleton. Whereas cross-sectional studies show minimal effects of cross-sectional changes in ht and wt (Riggs et al, JBMR 2006), little is known about possible age-related changes in soft tissue about the hip. Another poorly explored area is the impact of age-related declines in muscular strength on skeletal loading. Muscle strength and power decline 10 – 20% per decade after age 50. These declines will obviously impact the risk of falls, and perhaps the severity of falls, but may also influence loads applied to vertebral bodies during daily activities. Our data using a biomechanical model of the spine indicates that the influence of muscle strength on vertebral body compressive forces depends on the activity being performed. Vertebral compressive forces may remain unchanged, decrease, or greatly increase with reduced muscle strength. Greater understanding of how age-related changes in muscle function alter skeletal loading is needed.

***Disclosures: M.L. Bouxsein***, None.

## 17

**Role of the Osteocyte in Mechanotransduction and in Age-Related Bone Loss**

L. F. Bonewald*, University of Missouri, Kansas City, MO

Osteocytes, found to be multifunctional cells working as orchestrators of bone remodeling and regulators of mineral homeostasis are best known as mechanosensory cells. Osteocyte morphology is highly dendritic and intricately connected within the bone matrix, not only with each other, but with the bone surface cells and the vasculature making them ideal mechanosensors and mechanotransducers of loading or unloading. Osteocytes are exquisitely sensitive to load, especially in the form of shear stress. In vivo, the earliest cells that appear to respond to load are osteocytes within the bone followed by cells on the bone surface. Small early signaling molecules include Ca+, ATP, nitric oxide, and prostaglandins and an early, major signaling pathway is the Wnt/b-catenin pathway. The cell is bathed in bone fluid that passes along its cell body and dendritic processes tethered to their lacunar and canalicular walls by integrins that may act to mediate the effects of bone fluid flow on the cell membranes. This bone fluid is also thought to perturb cilia which contribute to the mechanical stimulation received by the cell body and dendritic processes. Clearly perturbing any one or a combination will lead to different or a combination of signaling events and outcomes.

The skeleton becomes less responsive to anabolic loading with age which may be due to either the osteocyte or the surrounding matrix becoming compromised. OSteocytes are the longest lived bone cell, up to decades within the bone matrix. With age, a greater number of dying osteocytes are observed. Osteocytes can undergo different forms of 'dying' from necrosis to apoptosis. A number of factors have been shown to induce osteocyte death such as cytokines, oxidative stress, hypoxia, glucocorticoids, lack of estrogen, and others. Osteocytes under stress can also undergo states of self-preservation called autophagy and if the stress is not removed in a timely fashion, the cell dies. Aging osteocytes die and either leave behind empty lacunae or can undergo micropetrosis filling the lacunae with mineralized material. Increases in number of empty lacunae or increases in 'filled-in' lacunae or a combination can result in dramatic changes in porosity and fluid flow within the osteocyte networks, thereby altering how remaining osteocytes are exposed to shear stress. Also, greater accumulation of microcracks occurs with age which may contribute to osteocyte cell death. However, unlike cell death in young osteocytes that leads to recruitment of osteoclasts followed by new bone formation, this remodeling is uncoupled with age. This results in increased osteoclast activity and greater bone loss. Another factor to be considered with aging are changes in the osteocyte perilacunar matrix. The tissue modulus (hardness or softness) of this matrix would have a dramatic effect on mechanosensation by osteocytes. Therefore, a number of factors appear to converge on the osteocyte with aging.

***Disclosures: L.F. Bonewald***, None.

## 18

**Exercise and the Preservation of Bone Health with Aging**

W. M. Kohrt*, University of Colorado, Denver, CO

Prospective cohort studies indicate that relatively high levels of physical activity are associated with a reduction in hip fracture risk of 30% to 40%. The few studies that evaluated physical activity exposure in a quantitative manner suggest that the dose to achieve this protection is roughly equivalent to 3 to 4 hours of walking per week. Evidence as to whether risk reduction is related to specific characteristics of the activity (i.e., frequency, duration, intensity, mode) is sparse, but suggests that both total volume (frequency x duration) and intensity may be important factors. It is not clear whether the apparent benefit of physical activity to reduce hip fracture risk is mediated through effects on bone mass, bone strength, and/or falling risk. Numerous clinical intervention trials have demonstrated that exercise training can generate increases in BMD of 1% to 3% in skeletal regions susceptible to osteoporotic fracture, even in older adults. The stronger association of bone mass with lean body mass than with fat mass suggests that resistance exercise may be a more effective means of increasing or maintaining BMD than endurance exercise, because the latter does not build (or preserve) muscle mass. However, both resistance and endurance exercise training have been found to generate increases in BMD. Although no clinical studies have determined whether small exercise-induced changes in BMD confer fracture prevention, pre-clinical studies demonstrate that improvements in bone strength are several-fold larger in response to mechanical loading than in response to pharmacologic intervention. This suggests that exercise may be more effective than pharmacotherapy in preserving bone strength, but clinical evidence for this is lacking. Current exercise recommendations for the prevention and treatment of osteoporosis derive from general exercise guidelines for maintaining good health, with emphasis on factors specific to skeletal adaptation (e.g., high strain magnitudes and rates). Improving these recommendations will require better translation of preclinical discoveries to mechanistically-driven clinical research.

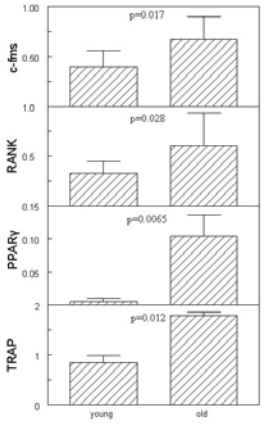
***Disclosures: W.M. Kohrt***, None.

## 19

**YOUNG INVESTIGATOR AWARD PRESENTATION**
**Age-related Increases in Constitutive Expression of RANK, c-fms, and PPARγ and in Osteoclast Potential in Human Marrow Stem Cells**

R. O'Sullivan*, P. Chung, S. Zhou, M. S. Leboff, J. Glowacki,
Brigham and Women's Hospital, Boston, MA

The loss of bone mass with age is due to more osteoclastic bone resorption relative to osteoblastic bone formation. Wan et al., suggest that PPARγ is an essential mediator of osteoclastogenesis in mice (Nat. Med. 2007; 13: 1496), but there is no information whether this occurs in human cells or whether it changes with age. We tested the hypothesis that expression of osteoclast receptors c-fms and RANK and of PPARγ change with age. Methods. We obtained discarded bone marrow from 19 patients (27 to 82 years) who underwent total hip replacement, with IRB approval. Mesenchymal and hematopoietic progenitors were enriched by density centrifugation with Ficoll/Histopaque 1077. Total RNA from low-density progenitor cells was extracted with Trizol reagent and PCR products were separated by agarose gel electrophoresis and were quantified by densitometry Image J software. Data were expressed by normalizing to GAPDH (internal control). Some samples were cultured for 14 days (without added osteoclastogenic factors) in order to measure basal osteoclast differentiation by tartrate-resistant acid phosphatase (TRAP) expression.
Results. Expression of c-fms was correlated with age (r=0.61, p=0.006), and was 1.7-fold higher (p=0.017) in progenitors from the older subjects (n=9) than the younger subjects (n=10) (Fig). RANK expression was correlated with age (r=0.59, p=0.008), and RANK mRNA was 1.9-fold higher (p=0.028) in marrow from the older subjects (n=9) than the younger subjects (n=10) (Fig). There was a correlation between c-fms and RANK gene expressions (r=0.85, p=0.0001). Constitutive PPARγ expression was 20.1-fold higher (p=0.0065) in marrow from older subjects (n=13) than from the younger subjects (n=6) (Fig). After culture, the expression of TRAP was measured as an index of osteoclast differentiation, in 16 samples (36-84 years) and showed an age-dependent increase (r=0.75, p=0.037); TRAP was 1.4-fold higher (p=0.012) in cultures from older subjects (n=9) than younger subjects (n=7) (Fig). Conclusions. This study shows age-related increases in constitutive expression of PPARγ, and of c-fms and RANK, receptors known to mediate osteoclast differentiation. There is an age-related increase in osteoclastogenic potential in human marrow progenitor cells that may be due to PPARγ regulation of c-fms and RANK. The data suggest that PPARγ may be an important factor in human skeletal aging, as has been reported in mice.




***Disclosures: R. O'Sullivan,*** None.

# Session 4: Mechanisms of Cellular Aging

## 20

**The Aging Cell**

J. Campisi*, Lawrence Berkeley Laboratory, Berkeley, CA

Age is the largest single risk factor for developing a panoply of diseases, including those of the bone and joints. Most age-related diseases are degenerative in nature – that is, cells and tissues lose integrity and/or function. This is certainly true of the skeleton, which is marked by an age-related loss of mass and function. An exception to age-related degeneration is cancer, a hyperproliferative disease that entails the acquisition of new, albeit aberrant, cellular phenotypes and tissue structure. Is there, then, a common biology that links aging, degenerative disease and cancer? If so, understanding this biology holds promise for ameliorating age-related skeletal changes in a concerted manner that may treat or postpone multiple age-related pathologies.
We propose that one common link between aging and most age-related diseases is the accumulation of senescent cells. Cellular senescence, also known as cellular aging, is a potent tumor suppressive response by which cells irreversibly arrest proliferation and acquire a robust secretory phenotype which we term the senescence-associated secretory phenotype or SASP). Cells undergo senescence in response to a wide range of stimuli. Moreover, senescent cells accumulate in aged tissues and at sites of age-related pathology, both degenerative and hyperproliferative, including arthritic joints. We and others have shown that senescent cells, and particularly the SASP, can disrupt normal tissue structure and function, and, ironically, can fuel cancer progression. Many of these SASP activities may be due to the pro-inflammatory nature of the SASP.
The SASP is conserved between human and mouse cells, indicating that the mouse can be used to model this process in humans. It is also largely conserved among cell types to the extent it has been examined. We have examined the SASP in mesenchymal and epithelial cells, and find substantial overlap, although there are also cell type-specific differences.
We have identified three major pathways that regulate the SASP in human fibroblasts; when dampened, these pathways suppress a portion of the SASP, particularly the pro-inflammatory arm of the SASP. These pathways include the DNA damage response pathway, the p38MAPK-NF-kB pathway, and the evolutionarily

conserved mTOR pathway. Suppressing the SASP may be key to ameliorating many diseases of aging, both degenerative and proliferative.

***Disclosures: J. Campisi***, None.

## 21

**Autophagy and Aging Cartilage**

M. Lotz*, The Scripps Research Institute, La Jolla, CA

Osteoarthritis (OA) is the most prevalent musculoskeletal disorder and aging is one of its most important risk factors. The disease process affects all joint tissues but articular cartilage, and the superficial zone (SZ) in particular, is most susceptible to damage. Understanding mechanisms of joint homeostasis and causes of aging-related decompensation may provide opportunities for OA prevention. Cartilage is a postmitotic tissue with very low rates of cell replication. Cells in such tissues depend on autophagy as a principal mechanism that removes damaged and dysfunctional organelles and macromolecules and supports cell survival, and normal biosynthetic function.
In articular cartilage autophagy is a constitutively active and apparently protective process for the maintenance of tissue homeostasis. The cartilage SZ shows the strongest expression of the autophagy regulators ULK1, Beclin1, and LC3. Human OA and aging-related and surgically-induced OA in mice are associated with a reduction and loss of ULK1, Beclin1 and LC3 expression in articular cartilage and this is accompanied by increased apoptosis. Mechanical injury, a cause of cartilage damage also significantly decreased ULK1, Beclin1 and LC3 expression in the cartilage SZ. Rapamycin, which activates autophagy and was recently shown to extend lifespan in mice, prevented cell death and loss of extracellular matrix caused by mechanical injury. These early observations indicate that autophagy is an important homeostasis mechanism in cartilage. Reduced expression of key autophagy regulators in aging and following mechanical injury is associated with cell death and extracellular matrix degradation. Protective effects of rapamycin support the hypothesis that pharmacological interventions that enhance autophagy may have chondroprotective activity after mechanical injury to articular cartilage and possibly also in aging-related SZ cell death and dysfunction.

***Disclosures: M. Lotz***, None.

## 22

**Regulation of Life Span and Age-Related Diseases by Caloric Restriction**

H. Van Remmen*, University of Texas Health Science Center, San Antonio, TX

Dietary restriction (DR) is a powerful intervention that delays aging and extends lifespan in diverse species ranging from worms to mammals. The proposed mechanisms by which DR increases both lifespan and health span include, but are not limited to, an increase in resistance to oxidative stress and the attenuation of the onset of age-related diseases. We have utilized mice lacking CuZnSOD (*Sod1*$^{-/-}$), a major antioxidant enzyme, as a model to test the effects of increased oxidative stress on aging and age-related pathology and the effect of DR on these processes. *Sod1*$^{-/-}$ mice have very high levels of oxidative stress and damage and show a significant reduction in lifespan, an acceleration of age-related loss of skeletal muscle mass, and a high incidence of liver cancer. We were interested in determining whether DR (60% of *ad libitum*-fed mice) over the lifespan of the mice would have a positive impact on the lifespan of the *Sod1*$^{-/-}$ mice. *Sod1*$^{-/-}$ mice on DR have a lifespan that is similar to, but not longer than, the lifespan of wild type mice fed *ad libitum*. DR reduced death from both neoplastic and non-neoplastic disease *Sod1*$^{-/-}$ mice, and the incidence of hepatocellular carcinoma decreased significantly in dietary restricted *Sod1*$^{-/-}$ mice. The effect of DR may be due in part to a reduction in oxidative damage ($F_2$-isoprostanes) in *Sod1*$^{-/-}$ mice on DR. We have also shown that DR protects against age-related loss of muscle mass and function by maintaining mitochondrial integrity, reducing mitochondrial reactive oxygen species generation, and lowering the high levels of oxidative damage in muscle from *Sod1*$^{-/-}$ mice. Skeletal muscle mitochondria from *Sod1*$^{-/-}$ mice on DR generate less mitochondrial $H_2O_2$ and deficits in mitochondrial respiration, and ATP production found in *Sod1*$^{-/-}$ mice is restored in *Sod1*$^{-/-}$ on DR. Muscle atrophy, fiber cross-sectional area, and fiber morphology are significantly improved in *Sod1*$^{-/-}$ DR mice compared to *Sod1*$^{-/-}$ mice fed *ad libitum*. At 18 months of age, gastrocnemius muscle mass is reduced ~45% compared to age-matched wild type; however, in *Sod1*$^{-/-}$ mice on DR, gastrocnemius mass was decreased by only ~20%, suggesting a protective effect of DR on sarcopenia. The age-associated loss of innervation is also partially protected in *Sod1*$^{-/-}$ mice on DR mice. While 63% of the neuromuscular junctions are denervated in *Sod1*$^{-/-}$ mice, only 38% are denervated in *Sod1*$^{-/-}$ mice on DR. Thus, the reduction in sarcopenia by DR could be due to maintenance of neuromuscular junction integrity. *Sod1*$^{-/-}$ mice on DR also show a significant improvement in neurological motor function as measured by rotarod performance and an increase in endurance exercise capacity compared to *Sod1*$^{-/-}$ mice fed *ad libitum*. Overall, our results demonstrate that DR is a powerful anti-aging intervention that attenuates oxidative stress-induced age-related muscle loss, reduces pathology, and extends the lifespan of *Sod1*$^{-/-}$ mice. ** Supported by NIH P01 AG20591 and a Julie Martin Mid-Career Award (AFAR)

***Disclosures: H. Van Remmen***, None.

## 23

**Muscle Stem Cell Function in Aging**

Z. Yablonka-Reuveni*, University of Washington School of Medicine, Seattle, WA

Sarcopenia, the age-related decline in mass and strength of skeletal muscles, is associated with myofiber atrophy, motor unit loss, fibrosis and intermuscular fat accumulation. We study the effects of age on satellite cells, myogenic stem cells that reside under the myofiber basal lamina. Reduction in numbers and/or myogenic aptitude of satellite cells may impede proper myofiber maintenance and contribute to the age-associated decline in muscle mass and repair capacity. Satellite cell populations isolated from old rodents were shown to contribute myogenic progeny and self-renew when cultured in a growth-promoting environment or when transplanted into young host muscles. These findings support the hypothesis that at least some satellite cells within aging muscle maintain myogenic stem cell properties. However, in such studies satellite cells are recruited “en masse” with the better performing progenitors becoming dominant. Differently, routine muscle activity results in subtle injuries and requires activation of single satellite cells for focal myofiber repair. Therefore, it is important to define possible changes in satellite cells at the single myofiber/cell level. Indeed, we demonstrated an age-associated decline in satellite cell numbers, concomitant with a vast increase in myofibers that lack satellite cells, when analyzing myofibers from limb muscles of mice and

rats. This satellite cell diminution appeared more prominent in females compared to males. Moderate-intensity endurance exercise led to an increase in myofibers that contain higher numbers of satellite cells. Myogenic performance of individual cells associated with myofibers of old animals was also enhanced while the frequency of nonmyogenic cells was reduced. The origin of at least some of these fibroblast-like cells has been attributed to satellite cells undergoing mesenchymal transition in the aging niche, but this notion remains a subject of debate. To further decipher the interplay between the aging muscle niche and satellite cell performance we use Cre-LoxP mice for tracing the fate of the myogenic progenitors in models of muscle wasting and enhanced fibrosis. This approach will also allow determining the origin of intramuscular adipogenic progenitors and the cues that encourage fat/fibrotic accumulation in aging muscle. Uncovering how aging affects the intrinsic properties of resident stem cells is a prerequisite for developing new therapies for combating sarcopenia. Supported by NIA.

***Disclosures: Z. Yablonka-Reuveni***, None.

## 24

**Overview from Clinical Studies in Humans on Bone Loss through the Menopausal Transition**

J. A. Cauley*, University of Pittsburgh, Pittsburgh, PA

Seventy years ago, Dr. Fuller Albright made the seminal observation that 40 of 42 patients with osteoporosis before age 65 were past menopause or post-oophorectomy. Since then, a substantial body of evidence supports the observation that bone loss starts before menopause. Rates of bone loss are highest during the late perimenopausal period and within 2 years of the final menstrual period, especially at trabecular sites. The rate of change in bone mineral density (BMD) appears similar across ethnic groups after adjusting for body weight despite ethnic differences in absolute BMD levels prior to menopause. The annual rates of loss during the late perimenopausal period and early postmenopausal period are approximately 1.8-2.3% at the spine and 1-1.4% at the total hip. Bone resorption markers appear to rise before the onset of irregular menstrual cycles. These early changes in BMD and bone turnover occur in the presence of normal estradiol levels. Increased levels of follicle stimulating hormone (FSH) have been correlated with changes in BMD across menopause. Decreases in gonadal inhibins, specifically, inhibin B contributes to the rise in FSH. The rate of bone loss across 6-8 years after menopause ranges from no loss to up to 50% loss. The reasons why some women lose bone more rapidly than others is not known. Rates of BMD loss differ significantly by level of obesity with slower rates of bone loss among obese compared to non-obese women. Other factors likely contribute including changes in muscle mass and strength. Concomitant with the increase in BMD loss in late perimenopause and early postmenopausal periods, results of bone biopsy studies showed evidence of trabecular perforation and loss. This perforation weakens bone to a greater degree than trabecular thinning. Studies also suggest that through the menopausal transition women also experience increases in skeletal size as a result of periosteal apposition. This change is likely a compensatory mechanism to account for the loss in bone mineral. Of importance, these processes of loss of BMD and trabecular perforation are irreversible. Thus, prevention is key. Efforts to better identify women who are more likely to experience more rapid bone loss across menopause are needed to target preventive efforts for these women.

***Disclosures: J.A. Cauley***, None.

## 25

**Role of Oxidative Stress in Age-Related Bone Loss**

S. C. Manolagas*, University of Arkansas, Little Rock, AR

The doubling of life expectancy in the last 200 years has made it imperative to elucidate whether skeletal involution is an inexorable accompaniment of longevity; and if so, whether it can be combated by targeting molecular pathways and mechanisms of aging. Reactive oxygen species (ROS) attenuate osteoblastogenesis and shorten the lifespan of osteoblasts and osteocytes. ROS, on the other hand, are required for osteoclast generation, function, and survival. Increased ROS generation leads to the activation of FoxOs – transcription factors that are an important defense mechanism against oxidative stress (OS) – and global somatic deletion of FoxOs in young mice increases OS and recapitulates the adverse effects of aging on bone. Conversely, FoxO3 overexpression in mature osteoblasts decreases OS and increases bone mass; while FoxO3 overexpression in the osteoclast lineage decreases osteoclastogenesis, increases osteoclast apoptosis, and increases bone mass. Albeit, in keeping with evidence that FoxOs divert β-catenin away from Tcf transcription, selective inactivation of FoxOs in committed osteoblast precursors expressing osterix increases Wnt signaling, causes bone anabolism, and postpones the adverse effects of aging on the skeleton, suggesting that removal of the restraining effects of FoxOs on Wnt signaling increases the number of osteoblasts to an extent that overcompensates for the adverse effects of ROS on cell survival. Both, aging and estrogen deficiency increase the generation of ROS and the activity of $p66^{Shc}$ - a redox enzyme that amplifies ROS- in the murine skeleton; and the adverse effects of estrogen loss on bone are prevented by anti-oxidants. Conversely, estrogens decrease oxidative stress and $p66^{Shc}$ and antagonize ROS-induced osteoblast apoptosis and NF-kB activation as well as the pro-survival effects of RANKL on osteoclasts via cell autonomous DNA-binding independent actions of the ERα. Attenuation of Wnt signaling by the activation of PPARγ by ligands generated from free fatty oxidation also contributes to the age-dependent decrease in bone formation. Additionally, increased glucocorticoid production and sensitivity with advancing age decrease skeletal hydration and thereby increase skeletal fragility, secondary to attenuating VEGF production by osteoblasts/osteocytes, the volume of the bone vasculature, and skeletal fluid flow. Elucidation of these mechanisms provides a paradigm shift from the "estrogen-centric" account of the pathogenesis of involutional osteoporosis to one in which age-related mechanisms intrinsic to bone are protagonists, and age-related changes in other organs and tissues, such as ovaries and the adrenals, are contributory.

***Disclosures: S.C. Manolagas***, None.

## 26

**Potential Role of T- and Other Immune Cells in Estrogen Deficiency Mediated Bone Loss**

R. Pacifici*, Emory University School of Medicine, Atlanta, GA

T cells are known to secrete osteoclastogenic cytokines and have been implicated in the bone loss induced by infection and inflammation. T cells express estrogen receptors and estrogen deprivation leads to T cell activation. T cells represent 5-8 % of the bone marrow (BM) cells and aging leads to the accumulation in the BM of highly reactive CD8+ memory T cells, a population which

secrete large amounts of TNF. Studies in T cell deficient nude mice and WT mice depleted of T cells by treatment with anti T cell Abs have disclosed that ovariectomy (ovx) does not induce cortical and trabecular bone loss in mice lacking T cells. Ovx induced bone loss is restored by reconstitution of a normal T cell population. Confirmation of the pivotal role of T cells in inducing bone loss after ovx has been provided by the finding that ovx-induced bone loss is prevented by treatment with CTLA4-Ig, an immunosuppressant that causes T cell anergy and apoptosis, and by the silencing of CD40L, a surface molecule of T cells required for T cell activation. An independent confirmation of the role of T cells was provided by Yamaza et al who reported that ovx fails to induce bone loss in nude mice and in WT mice in which T cell activation was blocked by aspirin. Ovx increases T cell production of TNF, a cytokine which stimulates osteoclast (OC) formation by potentiating the activity of RANKL and by promoting the production of RANKL by osteoblastic cells. Ovx also upregulates the T cell expression of CD40L, a costimulatory molecule that induces CD40 signaling in osteoblastic cells. CD40 signaling expands BM stromal cells, favors their entrance into the osteoblastic pool, promote osteoblast differentiation, and regulate their production of M-CSF, RANKL and OPG. Thus, ovx disregulates both osteoblast and OC formation through CD40L. Increased TNF production and CD40L expression result primarily by an increase in the number of BM T cells which home preferentially near the endosteal surfaces to support the nearby formation of OCs. The expansion in the BM of activated T cells which produce TNF results from enhanced thymic-dependent differentiation of BM-derived progenitors and peripheral expansion of mature T cells. Ovx causes the peripheral expansion of CD4+ and CD8+ T cells by increasing the presentation to T cells of antigen (Ag) fragments bound to MHC molecules expressed on Ag presenting cells (macrophages and dendritic cells). This phenomenon is due to increased expression of MHC molecules which, in turn is driven by increased production of IFNγ and IL-7, blunted generation of TGFβ in the BM, and upregulation of the dendritic cell costimulatory molecule CD80 secondary to increased oxidative stress. Accumulation in the BM of reactive oxygen species (ROS) is the most upstream event induced by ovx. Accordingly the activation of APCs and T cells and the resulting bone loss are blocked by antioxidants. In summary multiple line of evidence support the hypothesis that T cells play a pivotal role in the mechanism of ovx induced bone loss in the mouse.

***Disclosures: R. Pacifici***, None.

## 27

**Role of the CNS in Mediating Age-Related Bone Loss**

E. M. Gardiner*, University of Washington, Seattle, WA

The central nervous system (CNS) coordinately regulates bone and adipose tissue homeostasis by neuroendocrine and neuronal mechanisms. Hypothalamo-pituitary (HP) axes regulate sex steroids, cortisol and IGF-1 to conserve adiposity at the expense of bone mass[1]. The hypothalamus also maintains bone and adipose masses through direct signals. Leptin, an adipocyte-derived satiety hormone, attenuates bone mass via a central sympathetic (SNS) circuit, stimulating osteoblastic 2-adrenergic receptor to activate the molecular clock and control timing of osteoblast proliferation[2]. Other hypothalamic neuropeptides involved in SNS regulation of bone mass include neuromedin U (NMU), the cocaine and amphetamine-regulated transcript (CART), the cannabinoid type 1 (CB1) receptor and neuropeptide Y (NPY), although hypothalamic NPY regulation of bone mass is primarily through neuronal activation of osteoblastic Y1 receptor. Moreover, NPY is produced by mature osteoblasts and osteocytes, suggesting NPY paracrine regulation of bone[1]. Finally, sensory innervation, which degrades with age, holds potential to modulate bone cell function[3]. Interactions between the NPY and SNS circuits, between NPY and sex steroids, and between CNS modulation and more focal stimuli such as mechanical loading underscore the complexity of integrated physiological responses underlying CNS regulation of bone mass. Despite the many indications that neuronal pathways regulate normal bone homeostasis, the evidence for CNS involvement in age-related bone loss is inconclusive. Reports of increased bone mass and reduced fracture incidence in post-menopausal -blocker users are inconsistent[4] and rodent studies investigating SNS-bone mass association have led to differing conclusions[5,6]. Hypothalamic aging effects leading to reduced food intake are seen in humans and rodents, with response to the appetite stimulating factor NPY suppressed while leptin is increased; however, the relationship of these age-associated changes to skeletal homeostasis is not yet known. Integration of age-related changes in hypothalamic neuronal circuits and HP or sensory nerve signaling that contribute to bone loss may also be important aspects of the regulation of bone mass in the elderly.

***Disclosures: E.M.Gardiner***, None.

## 28

**YOUNG INVESTIGATOR AWARD PRESENTATION**
**The Misty Mouse is a Model for Age-Related Bone Loss due to Sympathetic Nervous System Hyperactivity**

K. Motyl*, M. Kawai[1], S. A. Bornstein[1], V. E. Demambro1, S. Lotinun[2], M. J. Devlin[3] M.L. Bouxsein3, M. C. Horowitz[4], R. Baron[2] , C. J. Rosen[1], [1]Maine Medical Center Research Institute, Scarborough, ME, [2]Harvard School of Dental Medicine, Boston, MA, USA [3]Beth Israel Deaconess Medical Center, Boston, MA, [4]Yale University School of Medicine, New Haven, CT

Physiologic changes with advancing age include brown adipose tissue (BAT) atrophy, increased sympathetic nervous system (SNS) activity and bone loss. Interestingly, heart rate is one of the best predictors of fracture risk, but the role of the sympathetic nervous system in age-related bone loss has not been described. Misty mice have accelerated atrophy of brown adipose tissue, are lean and have more bone loss with age compared to wild type mice. Interestingly, Misty mice are significantly hypothermic compared to wild type, have increased energy expenditure and have impaired BAT gene expression (UCP1, PGC1a) in response to the beta 3 adrenergic receptor agonist BRL. Despite reduced trabecular and cortical BV/TV in Misty due to increased osteoclast and reduced osteoblast activity, ex vivo bone marrow osteoblast and osteoclast cultures from Misty mice did not demonstrate impaired differentiation compared to wild type. We believe that the mutation in Misty mice (a premature stop codon in translation of the guanidine nucleotide exchange factor DOCK7) results in cell autonomous impairment of brown adipose tissue function, which leads to SNS over-activity for thermogenesis (as demonstrated by increased energy expenditure and reduced white adipose tissue). We therefore hypothesized that the increase in SNS activity leads to bone loss in Misty mice. To test this, we treated 12-week old Misty and wild type mice with the beta-blocker propranolol or vehicle in drinking water for 8 weeks and analyzed areal bone mineral density and trabecular micro-architecture. We found that propranolol increased areal femur bone mineral density and whole body bone mineral content in Misty mice while it had little effect in wild type controls. Additionally, Misty trabecular BV/TV was elevated by propranolol indicating that bone loss in Misty is at least in part due to SNS activity. Thus, the Misty

mouse provides evidence for a mechanism of age-related bone loss due to increased sympathetic nervous system activity.

***Disclosures: K. Motyl,*** None.

*Note: "*" in the author block refers to presenting author*

# POSTERS

## Aging Related Changes in Bone Structure and Cellular Activity

### P1

**Adult Bone Geometry is a Major Determinant of the Biology of Aging.**

Karl Jepsen*, Nelly Andarawis-Puri. Mount Sinai School of Medicine, USA

Because variation in periosteal expansion with aging may be a major contributor to fracture risk [1], having a better understanding of the factors contributing to the variation in this biological process will benefit efforts to reduce fracture incidence. Many factors contributing to the variation in periosteal expansion have been identified, but a critical, largely neglected factor is adult bone geometry. Prior theoretical work [2] did not incorporate the variation in acquired trait sets exhibited by human long bones [3], and thus it is curently unclear how the amount of periosteal apposition varies among individuals to maintain strength with aging. Given that long bones show a pattern of acquired trait sets [3], we hypothesize the amount of periosteal expansion required to maintain strength during aging will depend on external bone size. To test our hypothesis, we developed a new model that predicts the periosteal expansion rate required to maintain strength based on adult bone morphology and tissue-quality. We used this model to predict how the rate of periosteal expansion (dR/dt) should change to maintain a constant stiffness over time (dEI/dt = 0) for a population with diaphyseal cross-sectional morphologies that varied in width similar to human tibiae [3]. The model predicted that periosteal expansion rate is linearly related to the rate of marrow expansion (dr/dt), the rate of change in bone stiffness (dEI/dt), and the rate of change in tissue-modulus (dE/dt). Importantly, periosteal expansion rate was inversely related to adult tissue-modulus and highly nonlinearly related to adult bone morphology ($1/R^3$ and $(r/R)^3$), where R=outer radius and r=inner radius. Periosteal apposition rate was approximately 3-times greater for robust bones compared to slender bones. Importantly, periosteal apposition rate (dR/dt) increased over time to maintain bone stiffness, and this varied significantly with bone size. Although slender bones required significantly less periosteal expansion to compensate for endocortical bone loss compared to robust bones, the amount of apposition required to maintain strength over time increased to a much greater extent for slender bones compared to robust bones. Our model showed for the first time that the biological processess underlying periosteal expansion, which is required to maintain strength with aging, are highly dependent on adult bone morphology.

[1] Szulc, Bone 2006. [2] Lazenby, Am J Phys Anthropol 1990. [3] Tommasini, JBMR 2005.

***Disclosures: Karl Jepsen**, None.*

### P2

**Age and Gender Related Differences in Post-Fracture Osteoporosis Care.**

Bjoern Buehring*[1], Abby Abelson[2], Chad Deal[2], Andrea Sikon[1]. [1]Cleveland Clinic, USA, [2]Cleveland Clinic Foundation, USA

Osteoporosis (OP) related fractures lead to increased morbidity and mortality as well as decreased quality of live and physical functioning. Additionally, prevalent fractures increase the risk for future fracture. Despite the wide acceptance of guidelines for the management of post-fracture OP care, a large gap exists between these recommendations and the care patients actually receive. This study aims to examine whether there are age and gender related differences in the post-fracture OP care.

We identified individuals age 50 or above with a fragility fracture in the Cleveland Clinic electronic medical records who had visits in Primary Care, Women's Health, Orthopedics, or Rheumatology from 07/2007 to 06/2008. Fragility fractures included vertebral, humeral and forearm, femur and ankle fractures. Individuals were separated by gender and by age (50-64, 65-84, 85+). OP care was defined as whether individuals received OP pharmacotherapy and whether they had a dual x-ray absorptiometry (DXA) assessment documented in the chart. In addition to the 2007/2008 dataset we started analyzing an additional 12 month data sample from 2009 to look for changes over time.

There were 1970 (67% females) with fragility fractures in the 2007/2008 data set. Females received treatment and DXA scans more often than males (treatment: 67% vs. 31%; DXA: 67% vs. 24%). When separated by age, the 65-84 age group had the highest percentages in treatment (64% overall, 74% females, 32% males) and DXA assessment (67% overall, 76% females, 39% males). Percentages were less in the younger cohort (treatment: 44% overall, 57% females, 11% males; DXA: 51% overall, 63% females, 18% males). In the 85+ cohort treatment percentages were higher (72% overall, 76% females, 56% males). Interestingly DXA assessment overall was slightly lower (60%) but females has significantly lower percentages (60%) and males significantly higher (59%). In the more recent 2009 cohort 2492 persons (76% females) had fractures. Again females had higher percentages in OP pharmacotherapy (67 vs. 28%) and DXA assessment (70 vs. 30%).

This retrospective analysis of fragility fractures shows that the osteoporosis care gap continues to exist and did not improve over time. Males and younger individuals are at a particular high risk of not getting recommended DXA assessment and OP pharmacotherapy after fragility fractures. Interventions to reduce the gap in post-fracture care need to include these populations.

***Disclosures: Bjoern Buehring**, None.*

### P3

**Does "Sarco-Osteoporosis" Explain the Increase in Fracture Risk With Advancing Age?**

Bjoern Buehring*[1], Diane Krueger[2], Neil Binkley[3]. [1]Cleveland Clinic, USA, [2]University of Wisconsin, Madison, USA, [3]University of Wisconsin, USA

Chronologic age is a poor predictor of functional status. Nonetheless, age is currently included in the FRAX® fracture risk calculator but functional status is not. Sarcopenia (SP, the age-related loss of muscle mass/function) is clinically quantifiable and potentially an independent contributor to fracture risk. Individuals with both osteoporosis (OP) and SP, so called "sarco-osteoporosis" (SOP), may be at higher fracture risk than those with OP or SP alone. This study examined prevalence and overlap of OP and SP in older adults. Additionally, approaches to facilitate SOP identification, i.e., radius bone mineral density (BMD) measurement, and use of tallest, rather than current, height for SP diagnosis were explored.

BMD and total body composition data were acquired in community dwelling adults age 60+ by DXA using a GE Lunar iDXA. OP and SP were defined using standard criteria: T-score ≤

-2.5 at the spine or hip and appendicular lean mass (ALM)/current height$^2$ <5.45 kg/m$^2$ (F) and 7.26 kg/m$^2$ (M). "Sensitive" OP criteria added the 1/3$^{rd}$ radius T-score, while "sensitive" SP criteria used historical tallest height instead of current height. The primary outcome was SOP prevalence by decade (60-69, 70-79, 80+).

235 individuals (132 F/103 M) were included in this analysis. OP, SP and SOP prevalence was higher ($p < 0.05$) with the "sensitive" criteria and increased with advancing age (Table).

In conclusion, sarco-osteoporosis becomes more common with advancing age and affects over 25% of those age 80+. The easily clinically quantifiable concept of sarco-osteoporosis may more accurately predict fracture risk than simple use of age. Similarly, use of the 1/3$^{rd}$ radius might improve fracture risk prediction in older adults. Finally, for SP diagnosis, using historical tallest height is reasonable given use of young adults to define the normal ALM/height$^2$ ratio. Use of historical tallest height and 1/3$^{rd}$ radius BMD may more appropriately identify those with sarco-osteoporosis. Future studies need to define the utility of 1/3$^{rd}$ radius BMD measurement and use of tallest height and examine if or how sarco-osteoporoisis might be integrated in fracture risk prediction models.

**Table 1**

Table: Osteoporosis, Sarcopenia and Sarco-osteoporosis Prevalence by Age

| Age [years] | OP (spine & hip) [%] | OP (including radius) [%] | SP (standard criteria) [%] | SP (sensitive criteria) [%] | SOP (standard criteria) [%] | SOP (sensitive criteria) [%] |
|---|---|---|---|---|---|---|
| 60-69 | 2.9 | 11.6 | 5.8 | 9.0 | 1.4 | 3.0 |
| 70-79 | 19.5 | 33.3 | 16.1 | 21.4 | 3.4 | 7.1 |
| 80+ | 27.9 | 46.8 | 26.6 | 48.7 | 10.1 | 25.6 |

***Disclosures: Bjoern Buehring**, None.*
*This study received funding from: Merck*

## P4

**Aging C57BL/6J Mice Deposit Inferior Lamellar Bone Matrix.**

Wynee Lee[1], Edward Mertz*[2]. [1]NICHD / NIH, USA, [2]National Institutes of Health, USA

About 30% of aging humans with increased bone fracture risk have nearly normal bone mass, suggesting that weakening of bone material with age may contribute to the fractures. To understand if such weakening can be due to changes in newly formed extracellular matrix, we studied age evolution of matrix across the femoral mid-diaphysis cortexes of 1-10 month old C57BL/6J mice widely used in bone research. These mice lack cortical bone remodeling, allowing us to track material aging and compare material deposited at different ages. We measured mineral and organic matrix composition of the extracellular matrix in cortical cryosections using Raman microspectroscopy in high-definition mode, reducing instrumental errors. We used bright-field and dark-field polarized visible microscopy of these sections to distinguish lamellar and woven bone types, which have different collagen organization and material strength. We found that mineral/organic matrix ratio of lamellar bone increased from endosteal toward periosteal surface at all ages between 4 and 10 months, with the increment rising with age and reaching 40%. Because femoral mid-diaphysis grows in diameter by adding bone material at the periosteal side and resorbing bone at the endosteal side, such an increase suggests that mature bone matrix deposited at older age has higher mineralization than that deposited at younger age. Brittleness of these diaphyses is known to increase rapidly starting from 4 months despite replacement of poor woven bone and older lamellar bone by newer lamellar bone, suggesting that the increasing brittleness may be due to hypermineralization of matrix deposited at older age. Preliminary data indicate that the mineralization increase may be due to decreased collagen content of the organic matrix. If human lamellar bone deposited at older ages becomes similarly weaker, remodeling of cortical and trabecular bone can make bones more brittle than they were at younger age. If so, mice may help in finding genetic and structural origins of bone matrix weakening, and our results may guide where and when to search.

***Disclosures: Edward Mertz**, None.*

## P5

**Associations between Femur Neck BMD and Antihypertensive Medications Affecting Rennin-angiotensin System in Elderly Men and Women of the Health ABC study.**

Nahid Rianon*[1], Melissa Garcia[2], Angela Stotts[3], Weiwei Wang[3], Ann Schwartz[4], Frances Tylavsky[5], Jane Cauley[6], Brendan Lee[7], Tamara Harris[2]. [1]UTHealth The University of Texas Medical School at Houston, USA, [2]National Institute on Aging, USA, [3]University of Texas Health Science Center Houston, USA, [4]University of California, San Francisco, USA, [5]University of Tennessee Health Science Center, USA, [6]University of Pittsburgh Graduate School of Public Health, USA, [7]Baylor College of Medicine, USA

Purpose: Osteoporosis and hypertension (HTN) are two major age-related chronic health problems which are managed separately by medications indicated for their treatments. Evidence from previous animal studies indicate a potential to prevent age related bone loss with FDA-approved antihypertensive medications affecting renin-angiotensin system (RASMed), e.g., angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB). Increases in bone volume and bone mineral density (BMD) were reported in mice exposed to RASMed and presumed to reflect improved balance of bone turnover with decreased resorption and increased formation. We investigated if RASMed use for treating HTN was associated with higher femur neck BMD in older men and women in the Health Aging and Body Composition (Health ABC) study than those without RASMed use.

Methods: This cross-sectional study included 1076 men and 1195 women (age 70-79 at baseline; 58% white and 42% Black) using year 5 data from the Health ABC study. We defined RASMed as use of ACEI and/or ARB. Gender-stratified multiple regression models were used to test for associations between femur neck BMD and RASMed (ascertained from medications brought to clinic) at year 5 follow up of the study. In addition, we controlled for age, weight, height, race, self reported HTN and diabetes mellitus, bone promoting medication use, use of thiazide, steroid, calcium and vitamin D supplements and oral estrogen use in women.

Results: Mean ($\pm$standard deviation) age for men and women was 78 ($\pm$30) years. About 32% men and 31% women reported RASMed use. Multiple linear regression analyses showed no statistically significant association between femur neck BMD and RASMed use in women. The femur neck BMD among men with RASMed use was 0.018 gm/cm$^2$ higher [95% confidence interval (CI): 0.001 to 0.034] (calculated odds ratio, 95% CI = 1.02, 1.00 to 1.04) than in men not using RASMed.

Conclusions: RASMed use seems to have a positive effect on femur neck BMD of elderly men in the Health ABC study. The results need confirmation by analysis of longitudinal effects of RASMed on bone and by effects of bone markers.

***Disclosures: Nahid Rianon**, None.*

## P6

**Autophagy in Aged-related Losses in Bone Formation and Osteogenic Potential.**

Min Guan*, Nancy Lane, Junjing Jia, Wei Yao. University of California, Davis Medical Center, USA

Introduction. Bone loss is a normal consequence of aging and occurs in both genders starting from the middle of the third decade. The accelerated bone loss during post-menopausal period is associated with increased osteoclast activity due to the decline of the estrogen. The more gradual bone loss with aging results from reduced osteoblast recruitment and activity. In addition to reduced osteoblast activity, the osteogenic potential of bone marrow cells may also decline with aging. We hypothesize that aging reduces both the ability to maintain mesenchymal osteogenic potential and progenitor functionality due to the accumulation of oxidative damage and an increase in autophagy, a cell survival mechanism during stress.

Methods. In order to test this hypothesis, we performed three studies: First, we evaluated osteoblastogenesis and activation of the autophagy pathway using primary bone marrow cell cultures from 3, 12 and 24 weeks old C57BL/6 mice. Second, we evaluated the association of oxidative stress gene expression from the cortical bone of rats during aging (6, 12, 18 and 24 months) and autophagy level and bone formation. Third, we evaluated the association of oxidative stress, autophagy and bone formation in the model of accelerated aging – glucococrticoid excess (GC, 1.4mg/kg/d x 28 days). Study outcomes measures included focused RT-PCR gene arrays, western blots and bone histomorphometry.

Results. There was an age-related decrease in the activation of autophagy and osteogenic gene expression in the bone marrow of mice (average of 3-fold lower in 24 week-old vs. 3-week-old). Aging decreased oxidative stress responsive gene expressions, autophagy level and bone formation in vivo by an average of 3-fold in rats from 18 months of age as compared to the 6 months old rats. Short term GC exposure increased anti-oxidative responsive as well as autophagy pathways by an average of 50-fold.

In summary, aging-related decreases in bone formation was associated with reduced activation of anti-oxidative responsive gene expression, decreased bone marrow osteogenic potential, reduced autophagy and bone formation. Modulation of the oxidative and autophagic pathways provide promising new targets via sustaining autophagy and maintaining bone formation, which over time may preserve bone mass. Autophagy helps the cells to survive, which will keep pool of osteoprogenitor pool large and maintain osteogenic potential high, and could prevent reduction in bone formation with aging.

***Disclosures: Min Guan**, None.*

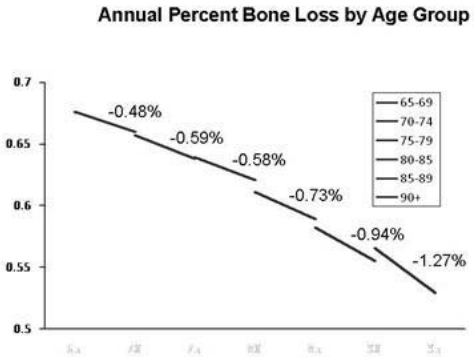
## P7

**Bone Loss Accelerates with Advanced Aging.**

Steven Cummings*[1], Lily Lui[1], Jane Cauley[2], Kristine Ensrud[3], Teresa Hillier[4], Marc Hochberg[5]. [1]San Francisco Coordinating Center, USA, [2]University of Pittsburgh Graduate School of Public Health, USA, [3]Minneapolis VA Medical Center / University of Minnesota, USA, [4]Center for Health Research, Kaiser Permanente Northwest, USA, [5]University of Maryland School of Medicine, USA

Background: Loss of BMD begins in midlife, increases around menopause then continues at a slower pace. Women who have slower bone loss also have a lower mortality rate. Cross-sectional studies suggest that bone is lost at a steady rate after age 60 years. However, the course of bone loss with very advanced age – over age 90 – is not known. Methods: In a prospective cohort study, we measured femoral neck BMD periodically during 20 years of follow-up of a cohort of women age 65 or older at baseline. Bone mineral density (BMD, g/cm$^2$) for the total hip and its femoral neck sub region was measured using dual X-ray absorptiometry with Hologic QDR-1000 (Hologic Inc., Waltham, MA). We analyzed rates of change in BMD in 3741 women who attended at least 2 scheduled exams with BMD measurements and excluded women who took treatments that may affect bone. The change in bone mass was expressed in terms of change in absolute values of BMD in mg/cm$^2$ per year. We also expressed the change in bone mass as a percentage of the initial value. The difference of BMD change for each of six age groups (65-69, 70-74, 75-79, 80-84, 85-89, 90+) was examined by comparing the mean change (absolute and percentage) in BMD per year at the femoral neck using pair-wise t-test. We also examined the difference of baseline weight adjusted change in BMD among six age groups. Results: Femoral neck BMD decreased at approximately 0.5% per year from age 67 through age 79 years. Bone loss began to accelerate after age 80 reaching a rate of 1.3% per year after age 90 years (figure). The results were similar when analyzed as absolute change in mineral or by percentage loss and were also unchanged by adjustment for weight. Conclusion: In women, the loss of BMD in the femoral neck remains constant through the 7th and 8th decade of life, but begins to accelerate after age 80 reaching 6% per 5 years after age 90. This acceleration is not due to the loss of weight with aging. This also suggests that the benefit of therapy might increase with very advanced aging.

**Figure - ASBMR Abstract**




***Disclosures: Steven Cummings**, None.*

## P8

**Bone Marrow Mesenchymal Stem Cell and Bone Loss with Aging.**

Weixi Zhang[1], Mark Hamrick[2], Kehong Ding[2], Karl Wenger[2], William Hill[2], Carlos Isales[2], Xing-Ming Shi*[2]. [1]Sun Yat-sen University, China, [2]Medical College of Georgia, USA

Osteoporosis is multifactorial ranging from genetic to life style. Since the bone marrow mesenchymal stem cell (MSC) is the origin of bone forming osteoblasts, we asked whether the number, or the osteogenic differentiation potential (or both) of MSCs is reduced with advancing age. To address these questions, we first prepared bone marrow aspirates from different age groups of C57BL/6 mice (3, 6, 12, 18, and 24-month-old) and performed colony-forming unit (CFU) assays. Results show that the colony numbers of the CFU-fibroblasts (CFU-f), CFU-osteoblasts (CFU-ob), and CFU-adipocytes (CFU-ad) increased between 3 and 18-months of age, but declined sharply at 24-months of age. Consistent with these results, alkaline phosphatase activity and mineralized bone nodule (von Kossa) formation also increased between 3 and 18 months. These data indicate that the number of multipotential MSCs increases as the mice age between youth (3-month) to middle-age

(12 – 18-month) but decline thereafter as they become elderly (after 18 months). Since the whole bone marrow cells are heterogeneous and contain preosteoblasts and preadipocytes, the results of CFU assays or the numbers of colonies do not reflect their differentiation potential, we next purified MSCs from these different age groups of mice using a negative immune-depletion followed by a positive immune-selection approach. Our results show that the purified MSCs, which are CD11b, CD11c and CD45-negative, and Sca-1-positive, exhibited a similar osteogenic differentiate pattern as the CFU assays. Taken together, our studies demonstrated that with advancing age both the numbers of MSCs and their osteogenic differentiation potential increases continuously as the animals mature but declines rapidly as the animals become old.

***Disclosures: Xing-Ming Shi**, None.*

## P9

**Caspase-2 Plays An Important Role In Male Age-Related Osteoporosis.**

Sherry Abboud-Werner, Roberto Fajardo, Maria Luisa Lopez-Cruzan, Danielle Victor, Difernando Vanegas*, Stephen Harris, Brian Herman, Ramaswamy Sharma, Kathleen Woodruf. University of Texas Health Science Center at San Antonio, USA

Caspase-2 is a cysteine protease that plays a key role in mitochondrial oxidative stress-induced apoptosis. For the past several years, characterization of Caspase-2-/- mice did not reveal any overt phenotype except for an increase in the number of oocytes. Recently, we have shown that loss of caspase-2 results in premature aging, including a shortened maximum lifespan, impaired hair growth, reduced body fat content and, importantly, age-related osteoporosis. Herein, we show by immunohistochemistry that caspase-2 is constitutively expressed in bone marrow cells, osteoblasts, and the lining cells in femur and tibia of wild type mice, at all ages tested. Dual energy X-ray absorptiometry (DXA) on femurs of aged (27 months, n=5) male Caspase-2-/- mice showed decreased bone mineral density as compared to wild type mice. In addition, 3-dimensional micro-computed tomography (μCT) analysis on the same animals indicated significant decreases in metaphyseal bone volume fraction and trabecular number, indicating trabecular bone loss. However, there was no significant change in diaphyseal cortical bone thickness. Bone histomorphometry showed a significant decrease in the growth plate, as well as an increase in the number of osteoclasts. These results are suggestive of increased osteoclastic activity that results in the reduction of trabeculae. ELISA analysis of bone lysates indicated >2-fold increase in CSF-1, which enhances differentiation of hematopoietic stem cells into osteoclasts. In contrast, BMP-2 protein, which is required for osteoblast differentiation, is decreased in Caspase-2-/- mice. Taken together, these data highlight a critical functional role for caspase-2 in male age-dependent osteoporosis. Because mortality following fracture is higher in older men as compared to women, our study suggests the use of caspase-2 as a diagnostic marker for osteoporosis as well as a putative target for treating osteoporotic disorders.

***Disclosures: Difernando Vanegas**, None.*

## P10

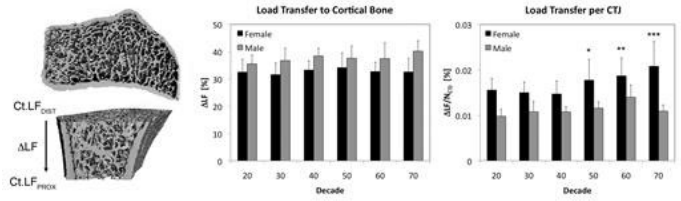
**Age-related Differences in Cortico-trabecular Connectivity and Load Transfer in the Distal Radius Measured In Vivo by HR-pQCT.**

Andrew Burghardt*, Galateia Kazakia, Thomas Link, Sharmila Majumdar. University of California, San Francisco, USA

Introduction: Trabecular bone reinforces broad articular contact areas in the epiphysis of long bones, and must efficiently transfer load to the compact cortical bone of the diaphysis. Age-related loss of metaphyseal trabecular bone and cortical thinning increases the risk of osteoporotic fracture at the ultra-distal extent of the radius[1]. We hypothesize that cortico-trabecular connectivity declines with age, thereby increasing the load burden of individual cortico-trabecular junctions (CTJ). Combining novel morphological measures of cortico-trabecular connectivity and micro-finite element analysis (μFEA) to determine cortico-trabecular load distribution, this study evaluated age-related changes in load transfer patterns in the distal radius for a normal population of men and women using *in vivo* high-resolution peripheral computed tomography (HR-pQCT). Methods: The distal radii of 154 subjects (58 male, 96 female; $47 \pm 16$ yrs; range: 20-80 yrs) were imaged using HR-pQCT (XtremeCT, Scanco Medical). The endocortical boundary was identified using an automated contouring segmentation procedure[2] and the cortico-trabecular envelope was defined as a 164μm margin mesial to this boundary. Cortico-trabecular junctions were counted ($N_{CTJ}$) as the set of contiguous objects in this region. μFEA was used to simulate 1% uniaxial compression. The fraction of load transferred from trabecular to cortical bone (ΔLF [%]) was calculated over the distal to proximal range of the 9mm scan. The mean load transfer per CTJ was calculated as the ratio ΔLF / $N_{CTJ}$. Results: Compared to men, women had significantly more load transferred to the cortex (ΔLF) across the scan range ($p<0.05$) and greater load per cortico-trabecular junction (ΔLF / $N_{CTJ}$, $p<0.01$). ΔLF did not exhibit significant age-related changes for men or women, however both men and women did show significant increases in ΔLF / $N_{CTJ}$ with age. In particular the change in women was increasingly significant following the onset of menopause ($p<0.05$ for >50yrs, $p<0.01$ for >60yrs, $p<0.001$ for >70yrs). Conclusion: The results of this study indicate that, while the load distribution between trabecular and cortical bone is maintained during aging, the load burden on individual cortico-trabecular junctions is significantly higher in elderly individuals. The increase in load through individual junctions may be associated with an increase risk of fracture, particularly for women after menopause.

References:
1. Melton LJ, 3rd, *et al.* 2007. J Bone Miner Res 22:1442-1448
2. Burghardt AJ, *et al.* 2010. Bone 47:519-528

**Figure**




***Disclosures: Andrew Burghardt**, None.*

## P11

**Effects of Age and Body Mass Index on Bone Mineral Density in Women and Men with Hip Osteoarthritis.**

Julie Glowacki*, Meryl Leboff. Brigham & Women's Hospital, USA

Osteoarthritis (OA) and osteoporosis (OP) are two age-related degenerative diseases previously believed to be mutually exclusive. Recent evidence, however, shows that patients can have both OA and OP. With a previous cohort of 68 post-menopausal women with advanced hip OA requiring arthroplasty, we measured bone mineral density (BMD) by DXA of the spine, femoral neck (FN), and greater trochanter, and determined that 25% had occult OP on the basis of T-score at any site of less than -2.5 [J Bone Joint Surg.

2003;85A:2371]. In a Finish study with cohorts and methods similar to ours, a series of 61 OA women included 28% with OP and 45% with osteopenia [Bone. 2007;40:1041].

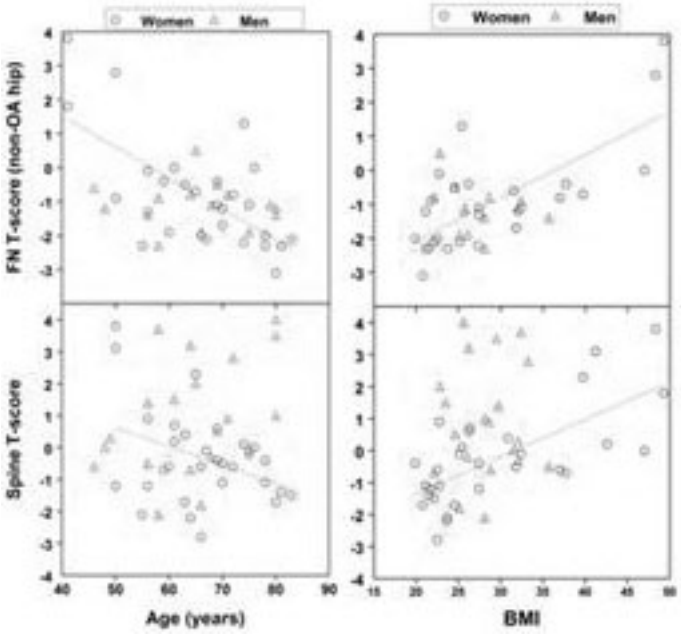
In this study, we evaluated the effects of age, BMI, and gender on BMD (in Spine and in both the OA and contralateral, non-OA hip) in 32 women and 22 men with unilateral hip OA. The study was approved by the Institutional Review Board for Human Research. It was important to assess both hips because we recently showed that there was discordance in hip T-scores, with significantly lower scores for the non-OA hip [J Clin Densitom. 2010;13:24]. Further, we found that fracture risk was underestimated with the FRAX® calculator on the basis of T-scores for the OA hips, compared with the non-OA hips [J Bone Mineral Res. 2010;25:S115].

Of the women with unilateral hip OA, 37% had T-score below -1 in the Spine, 37% in the OA FN, and 60% in the non-OA FN. For the women, Spine T-scores were correlated with BMI ($r=0.69$, $p<0.0001$) and inversely associated with age ($r=-0.44$, $p=0.014$). For the women, FN T-scores for the non-OA hip were correlated with BMI (0.73, $p<0.0001$) and inversely correlated with age ($r=-0.60$, $p=0.0009$). Co-variance analysis for Spine in the women showed that 50.5% of variance in T-score was explained by BMI ($p<0.0001$). Co-variance analysis for non-OA hips in the women showed that 36.2% of variance in T-score was explained by age ($p=0.0009$) and 19.9% was explained by BMI ($p=0.023$).

Of the men with unilateral hip OA, 10% had T-score below -1 in the Spine, 33% in the OA FN, and 60% in the non-OA FN. For the men, there were no significant correlations with BMI or age.

The occurrence of low bone mineral density in patients with osteoarthritis is underappreciated [Minerva Ortoped Traum 2010;61:115]. This study shows that advanced age and low BMI are associated with low BMD in women with advanced unilateral hip OA.

**Figure**




***Disclosures: Julie Glowacki**, None.*

## P12

**Establishment of Interactions Among Porosity, Mineralization and Morphology in the Human Tibial Cortex.**

Naomi Hampson*[1], G. Felipe Duarte[2], N. Remi Gendron[2], Karl Jepsen[2], Haviva Goldman[3]. [1]Drexel University, USA, [2]Mount Sinai School of Medicine, USA, [3]Drexel University College of Medicine, USA

Purpose: Previous studies of the human tibia have demonstrated a higher ash content amongst individuals with more slender bone phenotypes possibly as a compensatory mechanism to increase whole bone stiffness. We aimed to investigate the relationship between variation in volumetric porosity, ash content and robusticity in order to better understand the tissue level adaptations that may occur in the establishment of cross-sectional properties. Methods: 2.5mm cross-sections of 10 tibiae (6 male, 4 female, age 37 +/- 8 yrs) were obtained from sites located 38% and 66% from the distal articular surface, radially sectioned into 6 wedges, and imaged using a Skyscan 1172 μCT at a 5μm resolution. The total tissue volume (TV) and total canal volume (CV) of the cortical bone were determined using Skyscan's CT Analyzer for each location and analyzed by wedge and then combined to obtain a %CV of the entire tibial cortex for each location. Tissue Mineral Density (TMD) for the entire cross section was obtained from pQCT of the adjacent block of tissue, which was then ashed to produce a measure of mineralization density. Results: At both 38% and 66% locations, the anterior segment was significantly ($p < 0.05$) more porous than all medial and some lateral segments. At the 66% location, the posterior segment was significantly more porous than the antero-medial and postero-lateral segments. The higher porosity values noted anteriorly (and to a lesser degree, posteriorly) may reflect higher remodeling rates in these cortices, and relate to the A-P orientation of the axis of greatest bending rigidity. Porosity explained 62.5% (adjusted R2) of the variation in TMD determined by pQCT, and together with ash content explained 67.3% (adjusted R2) of the variation. Both porosity and ash content were correlated with robustness, such that more slender phenotypes not only had more mineralized cortices but also contained less porous bone. Conclusions: We found that there were significant differences around the cortex with respect to porosity. Variation in porosity explained a large part of the variation in TMD among individuals. Our results suggest that aspects of tissue level organization and composition play a compensatory role in the establishment of adult bone mass during growth and development, and may contribute to differences in bone aging between robust versus slender bone phenotypes.

***Disclosures: Naomi Hampson**, None.*
*This study received funding from: Department of Defense*

## P13

**Estrogen Deficiency and Mechanical Loading Alter Cancellous Architecture Through Different Mechanisms in Aging Mice.**

Maureen Lynch[1], Russell Main[2], Mitchell Schaffler[3], Timothy Wright[4], Marjolein Van Der Meulen*[1]. [1]Cornell University, USA, [2]Purdue University, USA, [3]City College of New York, USA, [4]Hospital for Special Surgery, USA

Mechanical stimuli are a potential therapy for bone loss following sex hormone deficiency. Bone mass is regulated by estrogen in males and females. In growing male mice we find mechanical loading can rescue bone mass loss at cancellous sites following orchidectomy. However, cancellous bone adaptation to mechanical loading is poorly understood in the context of estrogen deficiency and aging. In this study we examined the effects of

estrogen withdrawal on the adaptive response of bone to in vivo loading in adult female mice.

26 week-old C57Bl/6 mice underwent ovariectomy (OVX) or sham surgery and were further divided into 1, 2 and 6 wk loading groups (n=12/gp for OVX and Sham). Cyclic compression was applied to the left tibia, starting immediately postoperatively. A 9N peak compressive load was applied for 1200 cycles, 5d/wk at 4 Hz. The right tibia served as the unloaded control. Following euthanasia, all tibiae were scanned using quantitative microcomputed tomography at 15 μm voxel resolution. Cancellous bone from the proximal metaphysis was analyzed for bone volume fraction, tissue mineral density, and trabecular thickness and separation. Cortical bone at the mid-diaphysis was characterized by cortical area and principal moments of inertia.

Estrogen deficiency did not inhibit the adaptive response to load of cancellous bone in adult female mice. After 6 wks of loading, cancellous bone mass increased similarly in OVX and sham mice. Loading primarily increased trabecular thickness while estrogen deficiency primarily increased trabecular separation, each at a different rate (Fig 1, groups with different letters are different, $p<0.05$). As a result, cancellous bone mass increased bimodally. No differences in the control limbs between Sham and OVX groups were observed within the 6-wk time period. The cortical compartment showed no effects of OVX and increased bone mass with loading in a dose-dependent fashion with longer experimental duration (Fig 2).

In summary, in vivo tibial compression increased both cancellous and cortical bone mass in adult osteoporotic female mice after 6 weeks of loading. In cancellous bone, loading and OVX altered bone architecture through different mechanisms and at different rates producing a bimodal effect over time. In cortical bone, loading had a dose-dependent positive effect. Overall loading effectively enhances bone mass independent of estrogen status in adult female mice.

**Figure 1: Cancellous bone volume fraction at the proximal tibial metaphysis (mean, SD)**

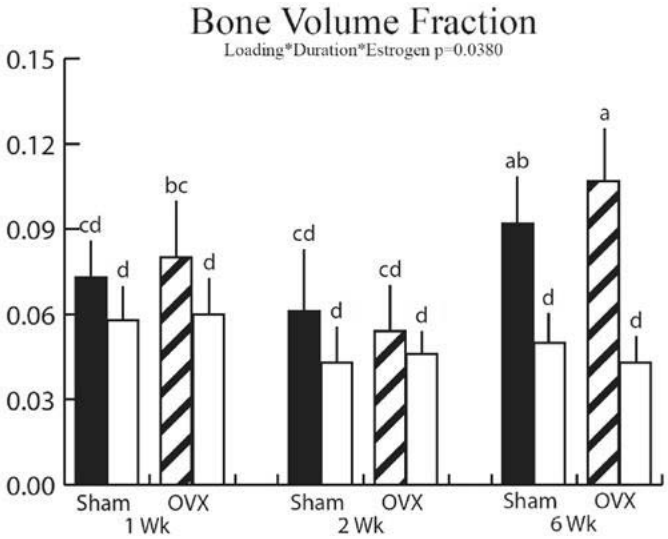
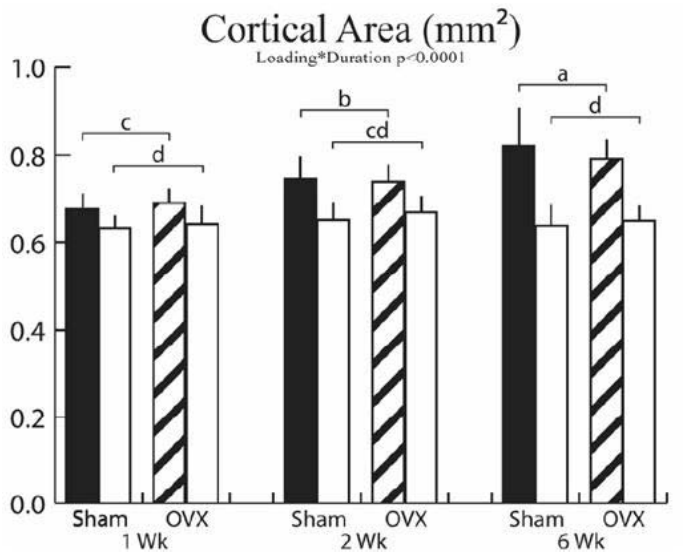



**Figure 2: Cortical area at the tibial mid-diaphysis (mean, SD)**




***Disclosures: Marjolein Van Der Meulen**, None.*
*This study received funding from: NIH R01-AG028664*

## P14

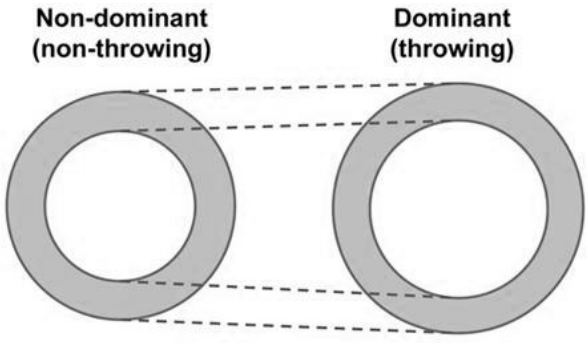
**Exercise During Growth Provides Lifelong Benefit to Bone Structure and Strength: A Case Study.**

Sara Mantila Roosa*[1], Stuart Warden[2]. [1]Indiana University-Purdue University Indianapolis (IUPUI), USA, [2]Indiana University, USA

Exercise induces greatest gains in bone health during skeletal development, yet reduced bone strength is predominantly an age-related phenomenon. This dichotomy has raised the question of whether exercise-induced changes in bone health when young persist into late adulthood where they may have benefits on bone health and fracture risk. Previous work has suggested exercise-induced gains in bone mass are lost with aging; however, 1) exercise during growth predominantly influences bone structure rather than mass to increase bone strength and 2) mechanisms exist for the long-term maintenance of exercise effects on bone structure. The aim of the current case was to explore whether exercise-induced gains in bone structure and strength accrued when young persist lifelong. The subject was an 81-year-old former Major League Baseball (MLB) pitcher who played competitively for 21 years before ceasing play in 1965. Throwing athletes are a unique model to investigate the skeletal effects of exercise as: 1) the unilateral upper extremity loading associated with throwing enables the contralateral side to serve as an internal control site and 2) throwing athletes have large dominant-to-nondominant (D-to-ND) differences in midshaft humeral bone properties. Peripheral quantitative computed tomography slices of the subject's dominant and nondominant humerii were taken at 50% humeral length, and D-to-ND percent differences in bone properties were calculated and compared to those observed previously in non-throwing controls. Data are shown in Figure 1. Exercise when young had no lasting effects on D-to-ND difference in cortical bone mass or area; however, D-to-ND difference in total area was nearly 4-times that observed in controls. The maintenance of exercise effects on total area resulted from persistence of benefits on periosteal perimeter, with the loss of cortical bone mass and area benefits being due to greater endosteal expansion (perimeter). As a result of the maintenance of exercise-induced benefits on bone structure, D-to-ND difference in ability to resist torsional forces (polar moment of inertia) was more than double that observed due to habitual loading associated with arm dominance in controls.

The maintenance of exercise-induced benefits on bone structure in the current case, despite exercise ceasing 45 years ago, supports the hypothesis that exercise when young can have lasting benefits on bone strength independent of maintenance of bone mass effects.

**Figure 1. D-to-ND percent differences in humeral bone properties in the case study and controls**




| Midshaft humerus property | Case study D-to-ND diff. | Control D-to-ND diff. |
|---|---|---|
| Bone mineral content | 1.4% | 4.3% |
| Periosteal perimeter | 9.6% | 3.6% |
| Endosteal perimeter | 18.1% | 3.9% |
| Cortical area | 1.5% | 5.0% |
| Total area | 20.0% | 5.2% |
| Polar moment of inertia | 26.7% | 11.5% |

***Disclosures: Sara Mantila Roosa**, None.*

## P15

**Increased Bone Turnover (N-telopeptides) Across the Menopause Transition: Study of Women's Health Across the Nation (SWAN).**

Mary Fran Sowers*[1], Huiyong Zheng[1], Jane Cauley[2], Gail Greendale[3], Joan Lo[4], Joel Finkelstein[5]. [1]University of Michigan, USA, [2]University of Pittsburgh Graduate School of Public Health, USA, [3]University of California, Los Angeles, USA, [4]Kaiser Permanente, USA, [5]Massachusetts General Hospital, USA

While bone turnover is thought to increase with ovarian aging and the menopause, no study has quantified the amount of bone turnover [N-telopeptides of type I collagen (NTX).] during the menopause transition and there is little information regarding the extent to which increase in bone turnover is directly related to the fall in estradiol (E2) and/or rise in follicle stimulating hormone (FSH) levels during the transition. We assayed urinary NTX/Cr (nM BCE) and serum E2 (pg/ml) and FSH (mlU) in samples collected annually over an 8-year observation period in 918 SWAN enrollees with an observed natural final menstrual period (FMP). Using semiparametric stochastic modeling, the mean NTx/Cr increased from 35 to 47 nM BCE in the 4-year period around the FMP. Beginning 2 years before the Final Menstrual Period (FMP), the NTX/Cr trajectory accelerated at a rate of 4.13 nM BCE per year ($p<0.0001$). This accelerated rate of change in NTX lasted 4 years until 2 years following the FMP at which time the NTX/Cr levels achieved a plateau. On average, the values 2 years after the FMP were 40% greater than the values from the initial point of change 2 years before the FMP. These changes occurred in conjunction with the fall in E2 and accelerating rise in FSH levels ($p < 0.0001$ and $p < 0.0001$, respectively). Notably, the mean 4-year increase in NTX/Cr was only 7.35 nM BCE in obese women (BMI>30 kg/m$^2$) whereas the 4-year NTX/Cr increase was 16.7 nM BCE around the FMP in women whose BMI < 25 kg/m$^2$ (see Figure). Overweight women (25 <BMI < 29.99 kg/m$^2$) had an intermediate increase in NTX/Cr. The greater bone turnover observed in the body size groups was accompanied by comparable differences in E2 and FSH changes, as seen in the following Figure.

Supported by: NIH Grants NR004061; AG012505, AG012535, AG012531, AG012539, AG012546, AG012553, AG012554, AG012495 and AG017719.

**Patterns of Change**

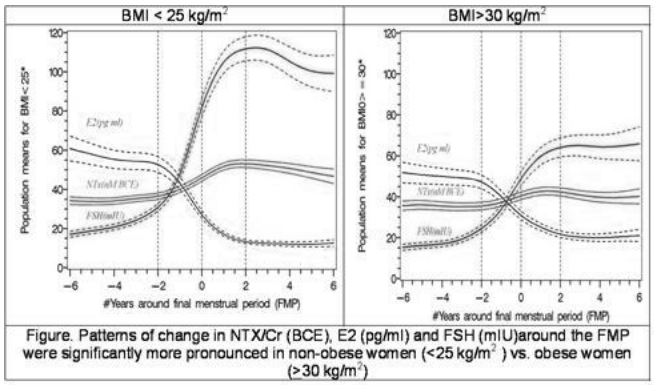



Figure. Patterns of change in NTX/Cr (BCE), E2 (pg/ml) and FSH (mIU)around the FMP were significantly more pronounced in non-obese women (<25 kg/m$^2$ ) vs. obese women (>30 kg/m$^2$)

***Disclosures: Mary Fran Sowers**, None.*

## P16

**Patterns of Skeletal Trait Interactions that may Prove Useful in Prognosticating Bone Health.**

Yan Epelboym*, Richard Ghillani, Damian Laudier, Karl Jepsen. Mount Sinai School of Medicine, USA

Prior work has shown that bone traits in the human tibia and human metacarpal co-vary in a predictable way when viewed across a population of genetically distinct individuals with diverse life histories [1]. Slender bones (narrow cross sectional area relative to length) maintain stiffness and strength by an increase in relative cortical area and tissue-mineralization, whereas robust bones (wide cross sectional area relative to length) maintain similar levels of stiffness and strength by having a reduced relative cortical area and reduced mineralization. Prior work has shown that compensatory changes in composition (mineralization) required for making a slender bone stiff and strong also make the bone more brittle and prone to fracturing. To determine whether similar patterns exist in the femoral neck, we used peripheral Quantitative Computed Tomography (pQCT) to quantify these traits. We analyzed the narrowest cross sectional area of 58 intact cadaveric femoral necks in 40 females and 18 males, mean age 68, range 37-93 years. The following traits were quantified using image analysis software: robustness (neck cross sectional area(TtAr))/(femoral neck axis length (NAL)), cortical tissue mineral density (CtTMD), relative cortical area (RCA = cortical area/TtAr), and trabecular tissue mineral density (TbTMD). As expected, males showed significantly more robust femoral necks compared to women ($p<0.0001$, t-test), and this was due to longer NAL and larger TtAr in males. In concert with work by others [2], a linear regression analysis displayed a significant, negative relationship between robustness and relative cortical area for males and females ($p<0.01$), with slender necks having proportionally thicker cortices. Females displayed a significant relationship between RCA and CtTMD ($p<.05$), as well as RCA and TbTMD ($p<0.05$), showing that bone with thicker cortices mineralized the cortical and trabecular matrix to a greater degree than bones with thinner cortices. Males displayed a similar but weaker trend. ANCOVA analysis showed that men had a greater RCA than women for any given robustness value ($p<0.01$). These preliminary findings suggest that both morphological and tissue-quality traits co-vary in a coordinated pattern relative to the natural variation in

robustness of the femoral neck. These patterns may prove useful as a way of prognosticating fracture risk.

[1] Tommasini et al, JBMR 2005; [2] Zebaze et al, JBMR 2007

***Disclosures: Yan Epelboym**, None.*

## P17

**The Impact of Dietary Protein on Bone Mass and Strength in the Aging Animal.**

Carlos Isales*[1], Mark Hamrick[1], Kehong Ding[1], Qing Zhong[1], Wendy Bollag[1], Xing-Ming Shi[1], William Hill[1], Jarrad Rowse[1], Mohammed Elsalanty[1], Norman Chutkan[1], Karl Insogna[2]. [1]Medical College of Georgia, USA, [2]Yale University School of Medicine, USA

It is estimated that up to 50% of elderly subjects (60-94 years of age) have inadequate dietary protein intake. There is also a high prevalence of malnutrition in the elderly. According to the Health And Nutrition Examination Survey (HANES) study as much as sixteen percent of the US population over the age of sixty-five consume less than 1,000 calories. In studies where other dietary factors are controlled, low dietary protein intake has been consistently linked to reduced bone mineral density and increased rates of bone loss. Our previous in vitro data had demonstrated that individual amino-acids (AA, particularly members of the aromatic group) act directly on mesenchymal stem cells to promote osteoblastic differentiation. To better define the impact of dietary protein on aging bone in vivo we utilized an aging animal model, C57Bl6 mice, which we have previously characterized. Mature (12 month) or aged (24 month) mice were divided into three dietary groups (n=10 mice/group), a balanced standard protein diet (18%) or a low protein (8%) diet as well as a diet in which the low protein diet was supplemented solely with the aromatic AAs (tyr, trp and phe) to attain the 18% level. At the end of an eight-week period animals were sacrificed and femoral bones removed for micro CT, histomorphometry and biomechanical testing. We found that reduced dietary protein resulted in significant bone loss in aged mice (24 months old), but did not significantly affect bone volume parameters in mature mice (12 months old). Most significantly, supplementation of the low protein diet with aromatic AAs alone was able to suppress bone loss. Bone histomorphometry revealed that aged mice receiving the aromatic AA supplement had increased osteoblastic number and decreased osteoclastic number. In young and aged mice similarly maintained on low, low +AA supplemented or normal protein diets, the low protein diet had no impact on bone strength in young mice, but significantly reduced bone strength in the aged mice. This drop of bone strength on the low protein diet was prevented by selective AA supplementation. Biochemical measurements revealed that IGF-1 was also significantly decreased by the low protein diet, and this drop in IGF-1 levels was prevented by aromatic AA supplementation. In summary our data demonstrates that dietary protein, and in particular some selected AAs, can modulate bone mass in the aging mouse and emphasizes the importance of diet composition in the elderly.

***Disclosures: Carlos Isales**, None.*

## P18

**Tibia Morphology and Hip Bone Density in Premenopausal and Postmenopausal Women Not Taking Exogenous Hormones.**

Vanessa Sherk*, Sojung Kim, Debra Bemben. University of Oklahoma, USA

Age- and menopause-related bone loss is site specific, and is partly explained by body composition changes. Tibia bone mass and distribution ratios measured by pQCT have recently been proposed for detecting trabecular- or cortical-specific bone loss, but it is unclear whether these ratios differ with age or menopause. The purpose of this study was to compare tibia characteristics assessed by pQCT between healthy premenopausal (PreM) and postmenopausal (PostM) women. We also examined relationships between tibia bone mass and distribution ratios and hip areal bone mineral density (aBMD). Methods: Late premenopausal (n=34, age: $44.4 \pm 0.7$ yrs) and postmenopausal women (n=30, age: $57.9 \pm 0.9$ yrs) not taking exogenous hormones had their total body and proximal femur aBMD assessed with DXA (GE Lunar Prodigy). Non-dominant tibias were scanned at 4%, 38%, and 66% of the limb length with pQCT (Stratec XCT 3000) to assess volumetric BMD (vBMD), bone content (BMC), and area of total, trabecular, and cortical bone. Periosteal and endosteal circumferences, bone strength index (BSI), strength strain index (SSI), and circularity index were determined. Results: PostM were ($p<0.01$) older than PreM. Height, weight, and body composition variables were not significantly different between groups. Femoral neck and total hip aBMD were 8.0% and 6.9% lower in PostM. Tibia 4% trabecular area was significantly greater in PostM ($745.19 \pm 29.59$ vs. $825.35 \pm 21.17$, $p<0.05$). At the tibia shaft sites, total BMC was 6.3-7.4% lower in PostM, resulting from 7.4-7.9% lower cortical BMC. Total and cortical vBMD were significantly lower in PostM at tibia 38% (PreM: $928.16 \pm 9.84$ and $1185.90 \pm 4.59$ vs. PostM: $880.62 \pm 12.68$ and $1152.62 \pm 6.57$, $p<0.01$), but only cortical vBMD was lower at tibia 66% ($1136.44 \pm 4.95$ vs. $1107.44 \pm 6.47$, $p<0.01$). SSI was 9% lower in PostM. The ratio of total BMC between the 4% and 38% sites was significantly lower in PreM ($0.816 \pm 0.013$ vs. $0.864 \pm 0.019$, $p<0.05$). There were no significant differences in periosteal or endosteal circumferences, SSI/Total BMC ratios, or Imax/Imin ratios at the shaft sites. Tibia 4% total BMC, total vBMD, and BSI were the strongest correlates of hip aBMD variables ($r = 0.54\text{-}0.78$, $p<0.001$). Conclusion: Tibia shaft sites were more sensitive for detecting group differences not attributable to body size differences, but distal tibia variables were better predictors of hip aBMD. The clinical implications of using bone mass ratios are unclear.

***Disclosures: Vanessa Sherk**, None.*

## P19

**Ultra High Field MRI of the Distal Femur and Proximal Tibia: Insight into the Structural and Mechanical Properties of Bone in Healthy Subjects.**

Gregory Chang*, Malika Rajapakse, James Babb, Ravinder Regatte. NYU Langone Medical Center, USA

Introduction. Our goal was to test the feasibility of using ultra high field (UHF, 7 Tesla) magnetic resonance imaging (MRI) to non-invasively evaluate mechanical and structural properties of whole bone (Wb), cortical bone (Cb), and trabecular bone (Tb) in healthy subjects. Methods. 14 healthy subjects without history of bone disorder or bone-altering medication use were recruited (10 females, median age=46.5 years, range 21-68; 4 males, median age=27 years, range 25-30). The right knee was scanned on a 7 T MR scanner using a 3D fast low-angle shot sequence (0.242 mm x 0.242 mm x 1 mm voxel size, 7 minutes 2 seconds imaging time). Bone was analyzed at the distal femoral metaphysis (DFM), distal femoral epiphysis (DFE), and proximal tibia (PT). Bone volume fraction (BVF), Wb, Cb, and Tb area, and Cb thickness were measured. Micro-finite-element analysis (FEA) was performed to compute stiffness of Wb, Cb, and Tb under simulated axial loading conditions. ANOVA was utilized to compare bone parameters at the three locations. Spearman rank correlation coefficients were utilized to characterize correlations between 1) bone stiffness with structural parameters and 2) all bone parameters with age and body mass index (BMI). Results. *Inter-Site Comparison of Bone Parameters.* Mean values for Wb, Cb, and Tb stiffness at the three

locations are shown in Figure 1. Tb bone accounted for the majority of bone stiffness in all three locations ($68 \pm 7.4\%$, $p<0.05$). There was no difference in bone stiffness (Wb, Cb, or Tb) across the three locations. *Bone Stiffness vs. Bone Structure.* Wb, Cb, and Tb stiffness positively correlated with BVF (R=0.75, 0.73, 0.69, $p<0.05$ for all) and inversely correlated with corresponding Wb (R=-0.54), Cb (R=-0.6), and Tb areas (R=-0.56) ($p<0.05$ for all). Stiffness showed no correlation with Cb thickness. *Bone Stiffness vs. Age and BMI.* Wb, Cb, and Tb stiffness positively correlated with age (R=0.75, 0.69, 0.73, $p<0.05$ for all) and BMI (R=0.62, 0.66, 0.68, $p<0.05$ for all). Age and BMI also positively correlated (R=0.81, $p<0.05$). Conclusion. MRI combined with FEA can provide insight into mechanical and structural properties of bone. The imaging method, which takes 7 minutes, can be added to routine MRI protocols and could be used:1) to investigate how structural derangements in cortical or trabecular bone differentially affect bone mechanical competence and 2) to identify novel imaging biomarkers for bone disorders.

**Figure 1**

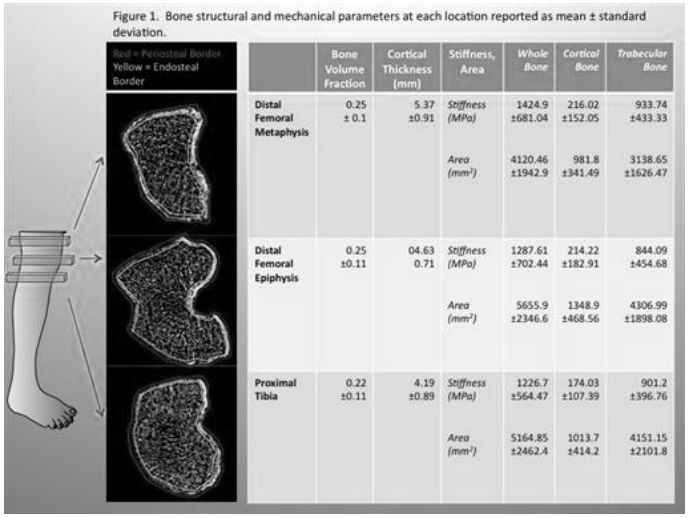


Figure 1. Bone structural and mechanical parameters at each location reported as mean ± standard deviation.

Red = Periosteal Border
Yellow = Endosteal Border

| | Bone Volume Fraction | Cortical Thickness (mm) | Stiffness, Area | Whole Bone | Cortical Bone | Trabecular Bone |
|---|---|---|---|---|---|---|
| Distal Femoral Metaphysis | 0.25 ± 0.1 | 5.37 ±0.91 | Stiffness (MPa) | 1424.9 ±681.04 | 216.02 ±152.05 | 933.74 ±433.33 |
| | | | Area ($mm^2$) | 4120.46 ±1942.9 | 981.8 ±341.49 | 3138.65 ±1626.47 |
| Distal Femoral Epiphysis | 0.25 ±0.11 | 04.63 0.71 | Stiffness (MPa) | 1287.61 ±702.44 | 214.22 ±182.91 | 844.09 ±454.68 |
| | | | Area ($mm^2$) | 5655.9 ±2346.6 | 1348.9 ±468.56 | 4306.99 ±1898.08 |
| Proximal Tibia | 0.22 ±0.11 | 4.19 ±0.89 | Stiffness (MPa) | 1226.7 ±564.47 | 174.03 ±107.39 | 901.2 ±396.76 |
| | | | Area ($mm^2$) | 5164.85 ±2462.4 | 1013.7 ±414.2 | 4151.15 ±2101.8 |

***Disclosures: Gregory Chang**, None.*

## Bone Accretion During Growth

## P20

**Absence of BMP2 Impairs PTH Effects on the Periosteum.**

Luciane Capelo*, Vicki Rosen. Harvard School of Dental Medicine, USA

Bone morphogenetic proteins (BMPs) have fundamental roles in bone formation and repair. Removal of Bmp2 from cells that originate from a Prx1 positive lineage in the early limb ($Bmp2^{fl/fl}$; Prx1:Cre, here noted as Bmp2cKo) does not affect BMD, but has disastrous effects on bone geometry as impaired Bmp2 signaling in the periosteum arrests appositional but not longitudinal growth, making the bones unstable and susceptible to fractures (100% at 23 weeks). From these results, we believe BMP2 is a local factor regulating periosteal growth. Since Parathyroid hormone (PTH) is one endocrine factor that regulates periosteal function, we hypothesize that PTH effects on periosteal growth are BMP2 dependent. To test our hypothesis, 2 week-old WT and Bmp2cKo mice were administered intermittent PTH (1-34) (iPTH) (Bachem, Inc.; 100ng/g/day) or saline for 2 weeks (n=4-5). Mice were then euthanized and serum and bones (femurs, tibiae, humerus, radius and ulna) collected for examination. PTH treatment significantly increased calcium and decreased serum phosphorus levels in WT and Bmp2cKo mice and morphological analysis of the femurs indicates that PTH treatment has anabolic effects on cortical and trabecular bone formation in both WT and Bmp2cKo mice. Cortical thickness, total cross-sectional area, trabecular number, thickness, connectivity and bone volume fraction (BV/TV) were equally increasd in the WT and Bmp2cKo groups. However, the impaired periosteal growth observed in Bmp2cKo mice is not rescued by PTH administration (Fig. 1A). While WT radial bones increased 40% in width after iPTH treatment, no increase is observed in the absence of Bmp2 (Fig.1B). Intermittent PTH treatment also enhanced bone mechanical properties (bone strength, rigity and modulus) in WT mice but had no effect on these parameters in the absence of Bmp2. Our data suggest that in the absence of BMP2, iPTH treatment does not stimulate periosteal growth, and that the anabolic effects of iPTH on appositional bone growth are dependent on intact BMP signaling in periosteal cells.

**Figure 1 Capelo LP**

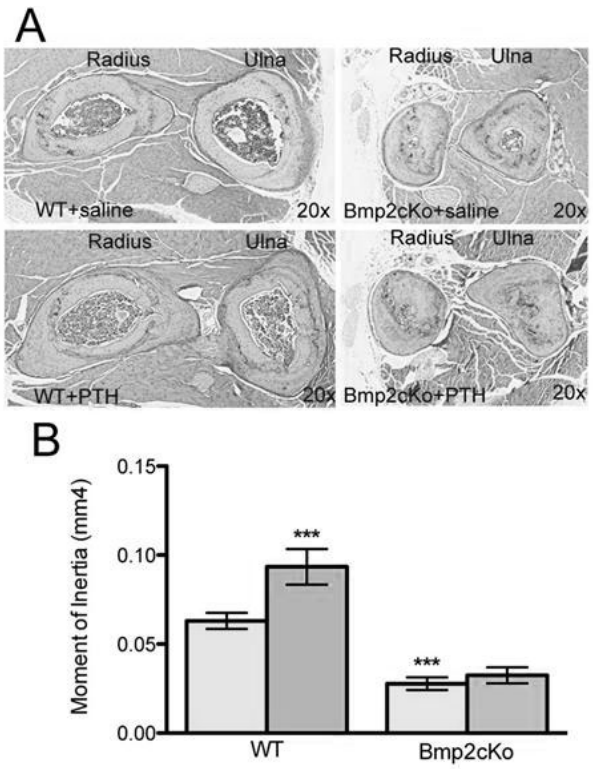



Figure 1: Intermittent PTH treatment does not stimulate periosteal growth in Bmp2cKo mice. (A) Cross-sections of radius and ulna mid-diaphysis stained with Toluidine Blue. (B) Moment of inertia evaluated by μCt analysis. ***p<0.05 vs. WT-Vehicle.

***Disclosures: Luciane Capelo**, None.*

## P21

**Anabolic Response of Mice to Mechanical Loading during Growth and Maturation.**

Matthew Silva*[1], Michael Brodt[2], Roberto Civitelli[1]. [1]Washington University in St. Louis School of Medicine, USA, [2]Washington University, USA

Physical loading is important to bone health. Direct skeletal loading is a well established method to stimulate bone formation in mice under controlled conditions. However there are few studies comparing the anabolic effects of skeletal loading at different ages. We recently reported that mature (7-month) and aged (22-month)

mice increase cortical bone formation by similar amounts following 1 week of daily tibial compression (Brodt, 2010). This finding contradicts the conventional paradigm that the skeleton loses its ability to respond to loading with age. Because we observed no age effect between 7 and 22 months, we asked: Does an age effect occur earlier in life? In the current study, we examined the response to axial tibial compression in mice at 2 months (''rapidly growing"), 4 months (''maturing'') and 7 months (''mature''). We hypothesized that younger mice are more responsive to tibial compression than their older counterparts. Prior to in vivo loading, we determined tibial force-strain relationships and selected forces that produce an estimated peak periosteal strain of -2200 ?? at the mid-diaphysis. Under anesthesia, right legs were loaded 60 cycles/day, for 5 days (days 1-5); left legs were not loaded (control). Bone morphology was assessed by in vivo microCT at baseline (day 0) and terminal (day 11) timepoints. Mid-diaphyseal cortical bone volume increased significantly in the loaded tibias from the 2- and 4-month groups ($p<0.02$), but not the 7-month group. Based on dynamic histomorphometry, there were double-fluorochrome labels on the periosteal mid-diaphysis of each loaded tibia (absent in most controls). Periosteal mineralizing surface (MS/BS) was significantly greater in loaded tibias vs. controls at each age, although there was no clear age dependence. In slight contrast, there was a trend ($p=0.09$) for decreasing periosteal MAR on the loaded tibias with age. In agreement with our hypothesis, younger mice seemed more responsive to loading than the older mice. The growing (2-mo) and maturing (4-mo) mice had significant increases in bone volume and a trend of higher MAR in loaded tibias. Together with our previous study, we have demonstrated that bones of mice across the lifespan (2-22 months) are responsive to tibial loading. However, the short-term response may be more effective in younger mice as observed by the rapid accrual of bone volume in the youngest age group.

***Disclosures: Matthew Silva**, None.*
*This study received funding from: NIH*

## P22

**Biologically Inspired Nanobiomaterials for Bone Tissue Engineering and Regenerative Medicine.**

Lijie Zhang*. George Washington University, USA

Bone defects, which are caused by a variety of reasons such as fractures originating from trauma, osteoarthritis, osteoporosis or bone cancers, represent a common and significant clinical problem all over the world. Traditional autografts and allografts of treating bone defects have many shortcomings including donor site morbidity, donor tissue shortage, infection, extensive inflammation and transmission of diseases, etc., leading to implant failures. Thus, it is urgent to develop a new generation of biocompatible bone substitutes that can quickly restore, maintain, and improve injured or diseased bone functions. Because natural bone is nanometer in dimension, nanomaterials with the required biomimetic features and excellent physiochemical properties become promising for guiding and stimulating bone regeneration. Therefore, the objective of our study is to design and evaluate biologically inspired tissue-engineered bone substitutes via state-of-the-art nanotechnology and biotechnology for replacing damaged or diseased bone and recovering their functionality.

A series of nanostructured 3D scaffolds with excellent cytocompatibility and mechanical properties based on biomimetic nanoceramic particles (nano hydroxyapatites), rosette nanotubes (a novel biologically inspired nanotube obtained through the self-assembly of DNA base pairs in water), collagen and hydrogels were fabricated. Osteoblasts (bone forming cells) and bone marrow-derived mesenchymal stem cells were used to investigate the cytocompatibility properties of these nanostructured scaffolds. Our long term in vitro results demonstrated that these biomimetic nanocomposites with controllable surface chemistry can greatly enhance osteoblast functions and osteogenic differentiation of mesenchymal stem cells, thus making them promising for further study in bone tissue engineering and regenerative medicine. In addition, cartilage regeneration was studied as well. Specifically, through a tissue engineered method, a cartilage construct was grown from chondrocytes and the mechanical, optical properties and extracellular matrix distribution of these constructs were measured and correlated under novel non-destructive imaging technologies over times. In summary, our study showed the potentials of the novel biologically inspired nanomaterials for next generation of bone and cartilage regeneration.

***Disclosures: Lijie Zhang**, None.*

## P23

**Characteristics of Bone Structure during Growth: Differential Patterns of Change in Cortical Bone Geometry and Trabecular Bone Microarchitecture in the Human Tibia.**

Zachariah Hubbell*[1], James Gosman[1], Timothy Ryan[2], Colin Shaw[2], Richard Ketcham[3]. [1]The Ohio State University, USA, [2]Pennsylvania State University, USA, [3]University of Texas at Austin, USA

Trabecular microarchitecture has been demonstrated to reach adult configuration in late childhood, whereas the geometric properties of cortical bone continue to change past adolescence. The objective of this research is to examine the developmental trajectories of the trabecular, periosteal, and endocortical bone surfaces with regard to shape differentiation. We test the hypothesis that the cross-sectional shape of the tibia transforms from rounded to triangular in association with the acquisition and maturation of gait kinetics and kinematics and continues to differentiate in shape well into skeletal maturity, in contrast to trabecular bone developmental patterns. MicroCT slices of the tibial midshaft were taken from 30 individuals ranging developmentally from neonate to skeletally mature from the SunWatch Village skeletal collection, an Ohio Valley agricultural village (AD 1200-1300). Cortical geometric properties (Imax, Imin, and J) were calculated using a custom code written in IDL and polar plots of multiple centroid radii were measured using ImageJ. Results demonstrate a dramatic differentiation in tibial midshaft shape from birth to late adolescence. Increasing Imax/Imin ratios correlate with increasing age (Pearson correlation of 0.847, p-value=0), showing that tibial cross-sectional shape becomes progressively less rounded throughout ontogeny. The differential distances to the periosteal and endosteal bone surfaces reveal age-associated patterns of bone formation and resorption corresponding to the observed shape changes. At birth, cortical bone shape and thickness are related to periosteal bone formation. At 4 months of age, early endosteal resorption is evident and periosteal formation continues. Between 2 and 5 years of age, endosteal shape begins to more closely mirror periosteal shape, combined with endosteal formation by age 7. In late adolescence, endosteal and periosteal shape reciprocally match one another. These data analyze the pattern of age- and locomotor-associated shape and bone surface changes in the tibia. They demonstrate that trabecular and cortical geometries arrive at their adult patterns by differing developmental trajectories, and thus advance the understanding of bone accretion during growth.

***Disclosures: Zachariah Hubbell**, None.*

## P24

**Correlation of Strain Magnitudes using Digital Image Correlation with ß-catenin Transcriptional Activation and Down-Regulation in Expression of Sclerostin upon *In Vivo* Loading.**

Peter Maye[1], Mark Johnson[2], David Rowe[1], Shiva Kotha*[3]. [1]University of Connecticut Health Center, USA, [2]University of Missouri, Kansas City Dental School, USA, [3]Rensselaer Polytechnic Institute, USA

*In Vivo* mechanical loading is an important factor determining the sites at which bone mass is added or removed. The site of bone accretion in response to mechanical load is thought to be regulated by local activation of Wnt signaling, especially in cells that are ideally situated to sense mechanical stress, namely, the osteocytes. In this study, we test the hypothesis that local strain magnitudes after *in vivo* mechanical loading are correlated with transcriptional activation of beta-catenin, a molecule that is involved in transcription of genes involved in bone formation, using a reporter mouse model. In this reporter mouse model, transcriptional activation of beta-catenin results in beta-galactosidase expression. We also test the hypothesis that local strain magnitudes correlate with downregulation of sclerostin, an inhibitor of Wnt signaling. To test these hypothesis, *in vivo loading* was performed using the mouse forearm compression loading model using loads that have previously been demonstrated to generate a highly localized anabolic bone formation response. At 24 hours after loading, ulnae were excised and stained for beta-galactosidase. Subsequently, strain magnitudes were obtained by digital image correlation of excised mouse ulnae that were subjected to loading under an synchrotron micro-computed tomography beamline. Bone sections were obtained and immunostained for sclerostin. Image processing was conducted on select sections to evaluate the extent of beta-galactosidase and sclerostin expression. Subsequently, strains in close proximity to individual osteocyte lacunae were correlated to osteocyte expression of beta-galactosidase and sclerostin. Results demonstrate that local strain magnitudes were highly heterogenous within the bone cross-section. Also, local strain magnitudes were correlated to expression of beta-galactosidase and to sclerostin within the cross-section. In conclusion, we have developed a novel technique to determine strains in close proximity to individual osteocytes using digital image correlation. This was then used to correlate to activity of individual osteocytes in response to *in vivo* mechanical loading.

***Disclosures: Shiva Kotha**, None.*

## P25

**Effect of High Fat Diet on Bone and Fat in Sprouty Mice.**

Lucy Liaw[1], Terry Henderson[1], Clifford Rosen[2], Sumithra Urs*[3]. [1]MMCRI, USA, [2]Maine Medical Center, USA, [3]Maine Medical Center Research Institute, USA

Purpose: We recently showed Sprouty1 as a regulator of osteogenesis while suppressing adipogenesis during MSC lineage specification (FASEB Journal, 2010; 24:3264-3273). Given the role of Sprouty in differentiation and lineage commitment of MSCs, we test the hypothesis that Sprouty1 expression can prevent bone loss associated with high fat diet induced obesity in aP2-Spry1 mice while loss of Spry1 can lead to increased bone loss and body fat resulting in obesity associated co-morbid disease. Here, we ask if sprouty1 has long term protective effects on body mass and bone density in mice exposed to high dietary fat. Methods: Using conditional expression and knockout genetic mouse models of Spry1 in adipocytes under the fatty acid binding promoter (aP2) we demonstrate the influence of high fat diet on bone and body fat. Mice were divided into groups based on gender and diet (standard chow Vs high fat diet) and given the assigned diet for 20 weeks starting for 5 weeks after birth. Appropriate control groups were maintained for each group. Evaluation was based on DXA, microCT, histology and blood sera analysis. Results: Loss-of function of Spry1 on a HFD had a dramatic negative influence on body composition and metabolism with impaired glucose tolerance and increased body fat accumulation with lowered bone mass and BV/TV. Additionally, mice develop liver steatosis along with lowered circulating insulin and increased leptin and there is increased bone marrow adiposity associated with HFD feeding. Gain-of function of Spry1 mice were responsive to HFD with increased body weight and body fat. However, the weight and percent body fat were significantly lower than the controls. Additionally, there was less bone loss in the Spry1 expressing mice exposed to HFD. These mice show normal glucose tolerance and liver morphology. Conclusion: Our results show Sprouty1 over-expressing mice do not develop symptoms associated with high fat feeding including obesity, bone loss, metabolic syndrome and osteoporosis. Therefore Sprouty provides protection from diet induced obesity and confirms its potential as therapeutic drug targeting obesity and osteoporosis. Keywords: Sprouty, diet, bone mass, body fat

***Disclosures: Sumithra Urs**, None.*

## P26

**Lumbar Spine BMAD Fails to Characterize Skeletal Strength and Adaptation to Mechanical Loading.**

Jodi Dowthwaite*[1], Paula F. Rosenbaum[2], Tamara A. Scerpella[3]. [1]State University of New York, Upstate Medical University, USA, [2]Public Health & Preventative Medicine, SUNY Upstate Medical University, USA, [3]Department of Orthopedics & Rehabilitation, USA

Purpose: We evaluated theoretical skeletal strength and fracture risk at the lumbar spine in late childhood and early adulthood using gymnastics as a model of mechanical loading.

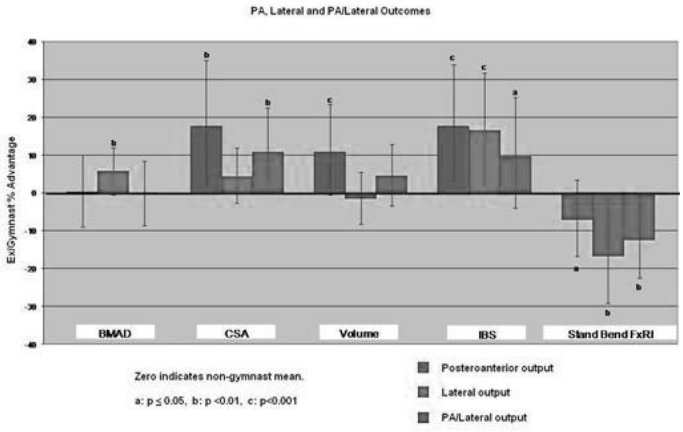
Methods: Posteroanterior (PA), lateral (LAT) and paired (PALAT) DXA scans of the lumbar spine were performed for dual mode assessment of BMC, geometry, density and biomechanical indices. Scans from 114 subjects (60 ex/gymnasts, 54 non-gymnasts) were analyzed to evaluate associations of gymnastic exposure during growth with BMC, areal BMD, vertebral body dimensions, bone mineral apparent density (BMAD), axial compressive strength (IBS), theoretical skeletal stresses and a fracture risk index. Vertebral body geometry was modeled as an ellipsoid cylinder. Two-factor ANCOVA tested for effects of gymnastic exposure, menarche status and their interaction, adjusting for age and height as appropriate.

Results: Compared to non-gymnasts, ex/gymnasts exhibited greater PABMD, PABMC, PAWIDTH, PACROSS-SECTIONAL AREA, PAVOLUME, LATBMD, LATBMAD, PALATCSA and PALATIBS ($p<0.05$). Non-gymnasts exhibited greater LATDepth/PAWidth, LATBMC/PABMC, LATHeight, LAT projected area, PALAT standing stress, PALAT bending stress and PALAT Fracture Risk. Using ellipsoid models, no significant differences were detected for PA or PALAT BMAD. Using cuboid models of vertebral geometry (Carter 1992), the results indicated spurious advantages for ex/gymnast PABMAD ($p<0.05$).

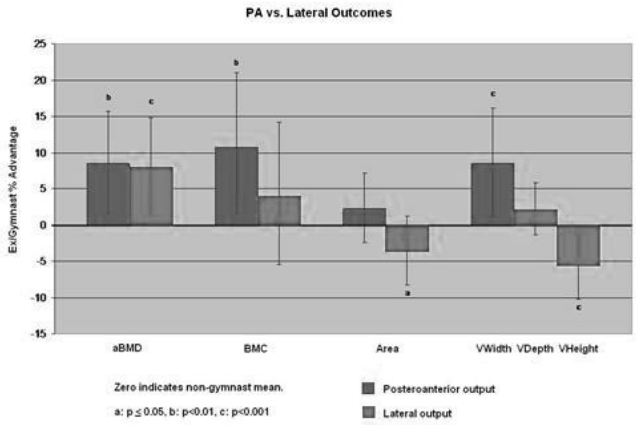
Conclusions: The primary characteristics associated with exposure to gymnastic loading during growth were shorter vertebrae, wider vertebral body PA width and cross-sectional area, wider PA width relative to LAT depth and greater BMC in the posterior elements. These properties were associated with theoretical biomechanical differences including greater axial compressive strength, lower vertebral stresses and lower fracture risk, but no difference in BMAD. Furthermore, assumptions of proportional variation in linear skeletal dimensions required for cuboid BMAD calculations were shown to be invalid, leading to

erroneous findings. Our results corroborate those of other studies, indicating that bone geometry plays at least as great a role in fracture risk as apparent density. Thus, pediatric and adult assessments of skeletal strength should not "remove" the effects of bone geometry, as this procedure neglects a major source of skeletal robusticity and may compound the effects of bone geometric differences in single plane data.

**PA, Lateral and PA/Lateral Output**




**PA and Lateral Output**




***Disclosures: Jodi Dowthwaite**, None.*

## P27

**Metabolic Response to High Fat Diet, and Not Macronutrient Intake, Underlies Fat-Induced Impairments in Skeletal Acquisition and Maintenance.**

Maureen Devlin*, Alison Cloutier, Sarah Sprague, Leeann Louis, Christine Conlon, Mary Bouxsein. Beth Israel Deaconess Medical Center, USA

There is increasing evidence that obesity impairs skeletal acquisition, but it is difficult to distinguish between the effects of high fat mass and high fat intake on bone. We hypothesize that inadequate metabolic response to high fat diet is more deleterious to the skeleton than fat intake per se, given evidence for adipokine suppression of osteoblast differentiation. To test this hypothesis, we compared the effect of high fat diet on bone mass and microarchitecture during rapid skeletal growth and aging in two inbred mouse strains: FVB/J, which resist diet-induced obesity (DIO), and C57Bl/6J (B6), which are DIO-susceptible. Methods: At 3 wks of age we weaned female FVB and B6 mice (N=7-10/grp) onto normal (N, 10% Kcal/fat) or high fat diet (HF, 45% Kcal/fat). Outcomes at 6, 12, and 20 wks of age included body mass and length; % fat and whole body bone mineral density (WBBMD, g/cm$^2$) via pDXA; and cortical (Ct) and trabecular (Tb) bone architecture at the midshaft and distal femur via μCT. Results: In FVB, body mass, length, % body fat, and WBBMD did not differ significantly in HF vs. N at any age. However, Tb bone volume fraction (BV/TV, %), number (Tb.N), and thickness (Tb.Th), and body mass-adjusted Ct bone area, were lower in HF vs. N at 6 wks ($p<0.05$), but not at 12 or 20 wks of age. In contrast, in B6, HF were heavier and longer at 12 and 20 wks of age, with 23% and 45% higher body fat vs. N, respectively ($p<0.05$). Consistent with their higher body mass, WBBMD was higher in HF vs. N ($p<0.05$) at 9 and 12 wks of age. However, Tb.BV/TV and Tb.N at 12 and 20 wks of age, and body mass-adjusted Ct bone area at 20 wks of age, were lower in HF vs. N ($p<0.05$). Conclusion: In FVB, HF diet does not increase body mass and appears to impair skeletal acquisition only at a young age, with little effect during skeletal maintenance or aging. In comparison, HF diet in B6 leads to higher WBBMD, coinciding with increased body mass and fat, during middle age. However, Tb and Ct microarchitecture are significantly lower than predicted for this increased body weight. These results suggest that the metabolic response to HF diet, rather than macronutrient intake per se, underlies fat-induced impairments in acquisition and maintenance of bone mass and microarchitecture.

***Disclosures: Maureen Devlin**, None.*

## P28

**Volumetric Bone Density, Cortical Morphometry and Trabecular Bone Micro-architecture Profiles in Normal Adolescent Girls - A Cross-sectional Study with High Resolution pQCT.**

Tsz Ping Lam*, Vivian Wing Yin Hung, Ka Yan Chan , Fiona Wai Ping Yu, Hiu Yan Yeung, Bobby Kin Wah Ng, Kwong Man Lee, Wing Sze Yu, Ling Qin, Jack Chun Yiu Cheng. The Chinese University of Hong Kong, China

Purpose of the study: Bone density and quality in terms of cortical morphometry, trabecular porosity and connectivity are key components for assessing bone health. Elucidation of these important bone parameters with ages can help define morphological changes that occur with modeling during skeletal growth. With availability of high resolution pQCT, in-vivo micro-imaging and derivation of these key parameters can be obtained. Our objective is to formulate their profiles as a function of ages in normal adolescent girls. Methods: 102 normal girls were recruited. Non-dominant distal radius was assessed with XtremeCT utilizing a standardized protocol. Bone parameters including volumetric bone mineral densities, cortical morphometry and trabecular bone micro-architectures were obtained and compared between three age groups, namely Group-1(< 12.5 yr), Group-2(12.5 to 14.99) and Group-3(>=15). ANOVA was used for statistical analysis. Results: The age ranged from 11.5-19.5 with a mean of 14.0. Average Bone Density, Compact Bone Density, Cortical Area, Cortical Thickness and Trabecular Thickness were statistically different between the three age groups. These parameters and others including Trabecular Bone Density, Inner Trabecular Bone Density, Cortical Periosteal Perimeter, Trabecular Separation and Trabecular BV/TV showed increasing trends with ages whereas Trabecular Area and Trabecular Number showed decreasing trends with ages. Conclusions: The results indicated age-dependent variation in bone parameters reflecting the morphological changes that occurred with modeling during skeletal growth. It follows that

interpretation of these parameters should be made with adjustment of ages. With larger sample sizes for both genders spanning a wider age range, a normogram can be established and will be indispensable for future clinical assessment and musculoskeletal researches.

***Disclosures: Tsz Ping Lam**, None.*
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## Genetic and Modifiable Risk Factors for Bone Loss and Fracture

## P29

**25-hydroxyvitamin D Delayed Response to Seasonal Ultraviolet Radiation Type B Variation: The São Paulo Vitamin D Evaluation Study (SPADES).**

Sergio Maeda[1], Gabriela Saraiva[1], Marcelo Correa[2], Carlos Henrique Mesquita[3], Marise Lazaretti Castro*[4]. [1]Federal University of Sao Paulo, Brazil, [2]Universidade de Sao Paulo, Brazil, [3]Universidade Sao Paulo, Brazil, [4]Federal University of Sao Paulo, Brazil

Evaluation of 25-hydroxyvitamin D (25OHD) concentrations and its determining factors, in individuals in the city of São Paulo (23˚S)belonging to different age groups and presenting different behavioral characteristics, and correlate it with ultraviolet radiation (UVR). Casuistic and Methods: 591 people were included and distributed as follows: 177 were living in institutions (NURSING, $76.2 \pm 9.0$ years), 243 were elderly individuals from the community (COMMUNITY, $79.6 \pm 5.3$ years), 99 were enrolled in a outdoor physical activity program destined to the elderly (ACTIVE, $67.6 \pm 5.4$ years) and 72 were healthy young (YOUNG, $23.9 \pm 2.8$ years). Blood samples from all individuals were collected along the year to measure Ionized calcium, PTH, 25OHD and creatinine. UVR measurements were informed by an official meteorology institution. Results: 25OHD mean values during winter for the different groups were $36.1 \pm 21.2$ nmol/L (NURSING), $44.1 \pm 24.0$ nmol/L (COMMUNITY), $78.9 \pm 30.9$ nmol/L (ACTIVE) and $69.6 \pm 26.2$ nmol/L (YOUNG) ($p<0.001$) while during summer they were $42.1 \pm 25.9$ nmol/L, $59.1 \pm 29.6$ nmol/L, $91.6 \pm 31.7$ nmol/L and $103.6 \pm 29.3$ nmol/L, respectively ($p<0.001$). The equation which predicts PTH values based on 25OHD concentration is PTH=10+104.24.e-(vitD-12.5)/62.36 and the 25OHD value above which correlation with PTH is lost is 75.0 nmol/L. In a multiple regression analysis having 25OHD concentration as the depending variable, the determining factors were PTH, ionized calcium and month of the year ($p<0.05$). UVR and 25OHD values vary along the year, following a sinusoidal-like pattern and general formula to represent this phenomenon was defined. 25OHD mean concentrations and amplitude were significantly higher for the groups YOUNG and ACTIVE, when compared to COMMUNITY and NURSING groups. The nadir for UVR was in June, while the one for 25OHD was in October, showing a 3-month delay. Conclusions: Much lower 25OHD values were found for the elderly both from nursing homes and the community. However, when exposed to sun light, active elderly people were able to produce 25OHD as much as young healthy people. Based on PTH levels, the desirable 25OHD concentrations should be above 75.0 nmol/L. A seasonal variation of 25OHD was found for all the studied groups; however, the amplitude of variation was higher for the young and physically active people, possibly due to the more significant sunlight exposure. At this latitude (23˚S), the lowest 25OHD concentrations occurred in October.

***Disclosures: Marise Lazaretti Castro**, None.*
*This study received funding from: FAPESP*

## P30

**Age-related Bone Loss Is Associated with Younger Maternal Age at Death.**

Laura Yerges-Armstrong*[1], Kathleen Ryan[1], Elizabeth Streeten[2], Woei-Jyh Lee[3], Alan Shuldiner[1], Alejandro Schaffer[3], Braxton Mitchell[4]. [1]University of Maryland, USA, [2]University of Maryland School of Medicine, USA, [3]National Institutes of Health, USA, [4]University of Maryland, Baltimore, USA

Higher rates of bone loss at older ages are associated with increased risk of fracture, overall disability, and mortality. There is some evidence that rate of bone loss may be heritable. Hypothesizing that age-related bone loss could represent a biomarker of generalized aging and since such an aging phenotype could be heritable, we examined whether bone loss was associated with parental age at death. We carried out this study in an Old Order Amish population characterized by a very homogeneous lifestyle to minimize confounding by soci-economic status. Included for study were 310 Amish men and women whom had undergone repeat bone mineral density (BMD) measurements (2-8 yrs apart) of the femoral neck after age 45 and in whom at least one parent had a known age of death (AOD). The percent change in BMD was calculated as the difference between follow-up and baseline BMD divided by the product of baseline BMD and years between BMD measurements. We used general linear models to determine if percent change in BMD was correlated with maternal (or paternal) age at death, while adjusting for gender and age at baseline BMD. On average, maternal AOD in this sample was 79.7 years (range 35-99) and paternal AOD was 76.4 years (range 22-101). There was a strong and consistent correlation between greater bone loss and earlier maternal AOD. Specifically, older maternal AOD was associated with less loss of femoral neck BMD ($p=0.005$) and a higher baseline femoral neck BMD ($p=0.04$). Compared to subjects whose mother died between ages 60-80, those whose mothers died before age 60 had a 0.63 standard deviation greater BMD loss ($p=0.01$) and those whose mothers died after age 80 had no statistically significant differences in rate of bone loss. In contrast, there was no association between paternal AOD and rate of bone loss. While refinement and replication of this relationship are needed, this observation may indicate the presence of common genetic factors between increased longevity and successful skeletal aging.

***Disclosures: Laura Yerges-Armstrong**, None.*

## P31

**Decreased Muscle Strength may Increase Vertebral Compression Forces in Certain Activities.**

Dennis Anderson*[1], John D'Agostino[1], Alexander Bruno[1], Sravisht Iyer[2], Mary Bouxsein[1]. [1]Beth Israel Deaconess Medical Center, USA, [2]Harvard-MIT Health Sciences & Technology Program, USA

The purpose of this study was to examine how muscle strength affects compressive loads applied to the vertebral body. Aging is accompanied by a loss in muscular strength of about 12-15% per decade after the age of 50. This strength decline may alter the loads applied to vertebral bodies when performing activities of daily living with implications for the risk of vertebral fractures.

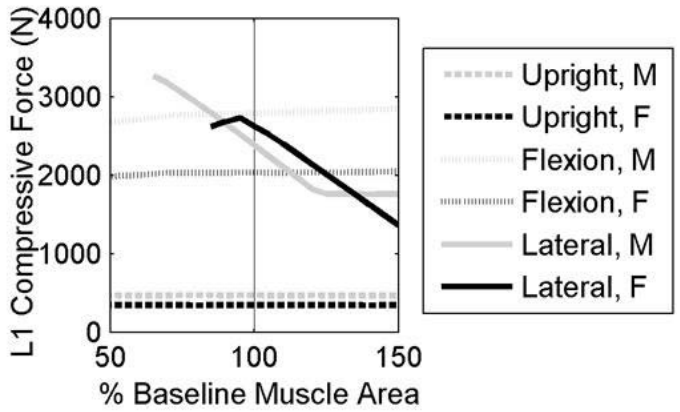
A musculoskeletal model of the spine was used to estimate the compressive loads on the L1 vertebral body, a common site for vertebral fractures, during three activities: 1) upright standing, 2) forward flexion to 90˚ while lifting 20 kg, and 3) a 20˚ lateral bend to the right while lifting 20 kg in the right hand. Muscle forces to balance the external moments about the vertebral body were estimated using a static optimization approach. To model changes

in muscle strength, muscle cross-sectional areas were varied from 50% to 150% of baseline, where baseline muscle areas were chosen to represent a 50 year old male and female of median height and weight (male: 1.77 m, 87.1 kg; Female: 1.63 m, 68.9 kg).

Vertebral compressive forces during upright standing and forward flexion with lifting were largely unaltered by changes in muscle area, and were about 27% lower in the female model than the male. However, for lateral bending, vertebral compressive forces increased by about 24 N per 1% reduction in muscle area at baseline strength, and were about 10% higher in the female model. In addition, when muscle area was reduced by 40% in males and 20% in females, the model had insufficient strength to solve for this condition.

The effect of muscle strength on vertebral body compressive forces appears to be dependent on the activity being performed. Vertebral compressive force may remain unchanged, decrease, or greatly increase with reduced muscle strength. If muscle strength is insufficient to balance the moments about the vertebral body in the most optimal manner, a less optimal solution may be used in order to perform the task. These effects appear to be highly dependent on the activity being performed. While only three activities were examined here, this study indicates that performing some activities may cause large loads to be placed on vertebral bodies. This may have implications for the risk of vertebral fractures in older adults with reduced bone and muscle strength performing certain activities of daily living.

**Figure 1: Variation in L1 Compressive Force with Muscle Area for Three Activities**




***Disclosures: Dennis Anderson**, None.*

## P32

**Depressive Symptoms, Antidepressants, and Bone Mineral Density in Older Puerto Ricans: The Boston Puerto Rican Health Study.**

Shilpa Bhupathiraju*[1], Anastasia Sofianou[2], Marian Hannan[3], Katherine Tucker[4]. [1]Tufts University, USA, [2]Department of Health Sciences, Northeastern University, USA, [3]HSL Institute for Aging Research & Harvard Medical School, USA, [4]Northeastern University, USA

Previous studies suggest an association between depression and bone loss. Few analyses examine how this association may differ by antidepressant use. We compared bone mineral density (BMD) of the femoral neck (FN), total hip (TH), trochanter, and lumbar spine (L2-L4) by depressive symptoms and antidepressant use in 711 Puerto Ricans, aged 47-76 years, who participated in the Boston Puerto Rican Bone Study, an ancillary study to the Boston Puerto Rican Health Study. BMD was measured using dual energy X-ray absorptiometry (Lunar Corp, WI). Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression (CESD) scale (0-60). Participants were considered to have high depressive symptoms if their CESD scores were $\geq$16, and low depressive symptoms if their CESD scores were $<$16. The sample was further classified by antidepressant use, creating four exposure levels: high depressive symptoms and taking antidepressants (n= 241); high depressive symptoms and not taking antidepressants (n= 61); low depressive symptoms and taking antidepressants (n=190); and low depressive symptoms and not taking antidepressants (n=205). The association was also considered using CESD score (continuous), controlling for antidepressant use. Models were sequentially adjusted for age (y), sex (men, premenopausal women, postmenopausal women), waist circumference (cm), height (m), smoking (y/n), alcohol (y/n), physical activity score, osteoporosis medication (y/n), season of BMD measurement (spring/summer/fall/winter), plasma vitamin D (ng/mL), total calcium (mg/d), total energy (kcal), and perceived stress. CESD score was not associated with BMD at any of the four bone sites in our fully controlled model ($\beta$=-0.001 - 0.003, P$>$0.10). Power calculations indicate that our sample is sufficiently large to accurately test our observed effect sizes. Multiple pairwise comparisons showed no significant differences in adjusted mean BMD by depressive symptomology (P$>$0.010). When we compared depression categories, irrespective of antidepressant use, differences remained non-significant. Our results suggest that for older Puerto Rican adults of ages 47-76y, there are no significant associations between depressive symptoms, antidepressant use, and BMD. However, our results may need to be confirmed for longitudinal bone loss.

**Table 1**

Table 1: Adjusted least square mean (SE) bone mineral density (g/cm$^2$) across depressive symptoms stratified by antidepressant use in the Boston Puerto Rican Health Study[1]

| | Low depressive symptoms | | High depressive symptoms | |
|---|---|---|---|---|
| | No antidepressants (n=228) | Antidepressants (n=58) | No antidepressants (n=180) | Antidepressants (n=190) |
| **Femoral Neck** | | | | |
| *Model 1* | 0.94(0.023)[a] | 0.95(0.027)[a] | 0.94(0.023)[a] | 0.931(0.024)[a] |
| *Model 2* | 0.896(0.027)[a] | 0.902(0.032)[a] | 0.912(0.027)[a] | 0.902(0.027)[a] |
| *Model 3* | 0.892(0.027)[a] | 0.900(0.032)[a] | 0.916(0.027)[a] | 0.908(0.028)[a] |
| **Total Hip** | | | | |
| *Model 1* | 1.03(0.025)[a] | 1.04(0.030)[a] | 1.027(0.025)[a] | 1.022(0.025)[a] |
| *Model 2* | .994(0.030)[a] | 0.990(0.035)[a] | 0.994(0.030)[a] | 0.991(0.030)[a] |
| *Model 3* | 0.988(0.030)[a] | 0.988(0.035)[a] | 1(0.030) | 1(0.031)[a] |
| **Tochanter** | | | | |
| *Model 1* | 0.820(0.022)[a] | 0.824(0.027)[a] | 0.811(0.023)[a] | 0.812(0.023)[a] |
| *Model 2* | 0.789(0.027)[a] | 0.785(0.032)[a] | 0.782(0.027)[a] | 0.789(0.027)[a] |
| *Model 3* | 0.783(0.027)[a] | 0.782(0.032)[a] | 0.788(0.027)[a] | 0.797(0.028)[a] |
| **Lumbar spine** | | | | |
| *Model 1* | 1.172(0.031)[a] | 1.208(0.037)[a] | 1.182(0.031)[a] | 1.171(0.032)[a] |
| *Model 2* | 1.121(0.036)[a] | 1.157(0.043)[a] | 1.142(0.036)[a] | 1.147(0.037)[a] |
| *Model 3* | 1.122(0.037)[a] | 1.157(0.043)[a] | 1.142(0.037)[a] | 1.146(0.038)[a] |

Model 1: Adjusted for age (years), sex, menopause, waist (cm), height (m), current smoking (y/n), alcohol (y/n), physical activity score, osteoporosis medication (y/n), season of BMD measurement (summer, spring, fall, winter).
Model 2: Model 1 + plasma vitamin D status (ng/mL), intakes of total energy (kcal/d) and calcium (mg/d)
Model 3: Model 2 + perceived stress score

[1] Least square means with different superscripts in the same model and bone category are significantly different.

***Disclosures: Shilpa Bhupathiraju**, None.*

## P33

**Gender Dimorphism in the Relationship of 25(OH)D and Hip Structure in a Cohort of Adolescent Twins in Rural China.**

Lester Arguelles*[1], Xiumei Hong[1], Xin Liu[2], Craig Langman[1], Xiaobin Wang[2]. [1]Children's Memorial Hospital, USA, [2]Mary Ann & J. Milburn Smith Child Health Research Program, Department of Pediatrics, Northwestern University Feinberg School of Medicine & Children's Memorial Hospital & Children's Memorial Research Center, USA

Purpose: To examine the relationship between, and estimate the co-heritability of, vitamin D and measures of hip structure at the femoral neck including cross-sectional area (CSA), section modulus (SM), and cross-sectional moment of inertia (CSMI).

Methods: This report included 465 adolescent twins, age 13 to 18 years, from the Anqing region of China. Dual-energy X-ray absorptiometry (DEXA) measures included: percent body fat (%BF), CSA, SM, and CSMI. Serum 25(OH)D was measured using HPLC tandem mass spectrometry. Linear mixed models were used to estimate the strength the association, and structural equation modeling was used to estimate heritability.

Results: Significant linear associations between 25(OH)D and CSMI, SM, and CSA, adjusting for gender, age, season, physical activity, occupation, Tanner stage, height, and weight: βCSMI(se)= 27.2(14.3), p=0.05; βSM(se)=1.6(0.7), p=0.02; βCSA(se)=0.4(0.1), p=0.005. %BF did not mediate these associations. Although tests for interaction were not significant, stratification by gender showed that these positive associations were largely driven by the association in males: βCSMI(se)=40.6(21.9), p=0.05; βSM(se)=2.3(1.0), p=0.02; βCSA(se)=0.5(0.2), p=0.008. Consistent with our previous findings, the heritability of 25(OH)D was only significant in males 0.66(95%CI 0.23-0.86), but not in females, 0.17(0-0.63). The bivariate Cholesky decomposition analysis indicated that the phenotypic correlations between 25(OH)D and hip structure measures in males were largely driven by common environmental factors.

Conclusion: This analysis demonstrated in males that measures of hip structure increase significantly with increasing 25(OH)D levels and that the phenotypic correlations between 25(OH)D and hip structure are largely driven by shared, or familial, environmental factors.

***Disclosures: Lester Arguelles**, None.*

## P34

**Genome-wide Association Study (GWAS) of an Integrated Musculoskeletal Phenotype: The Framingham Study.**

David Karasik*[1], YanHua Zhou[2], L. Adrienne Cupples[2], Douglas Kiel[1], Serkalem Demissie[2]. [1]Hebrew SeniorLife, USA, [2]Department of Biostatistics, Boston University School of Public Health, USA

Osteoporotic fracture is a product of both bone strength and applied forces. Previous genetic studies of the factors contributing to the risk of osteoporotic fractures have largely focused on single factors. Therefore the purpose of this study was to use a genome wide association approach to identify new genetic pathways for osteoporosis risk factors by simultaneously examining multiple phenotypes. Principal component analyses (PCA) were conducted in participants of the Framingham Osteoporosis Study on 17 measures including BMD (hip and spine), heel ultrasound, hip geometric indices, and leg lean mass (LLM), adjusted for covariates (age, height, BMI). The sex-specific analysis was performed in 1180 men and 1758 women, separately. The PCA revealed 5 principal components (PCs) that were above the 1.0-eigenvalue threshold in men, which jointly explained 76.9% of the total variability of musculoskeletal traits, and 4 PCs (69.3% variance) in women. Here we focus on PC4, since we have previously found that there is a substantial genetic correlation between LLM and hip geometry. In men, PC4 mostly correlated with LLM and shaft cross-section area (explaining 6.2% of the total variance), and in women, with LLM, femoral neck-shaft angle, and femoral neck buckling ratio (6.8% of the total variance). We then evaluated ~2.5 mil SNPs genome-wide for association with PC4s using linear mixed effects models, performed separately in men and women. At a suggestively-significant threshold (defined as $p < 5*10^{-5}$), there were 149 SNPs associated with PC4 in men and 178 SNPs in women. A SNP in the *COL4A1*/*COL4A2* locus was associated with PC4 in women at a genome-wide significant level ($p=1.0*10^{-8}$). The *COL4A1* and *COL4A2* genes code for collagen type IV, which has been shown to be involved in bone formation and angiogenesis. In conclusion, genome-wide associations of the linear combinations of lower extremity lean mass and proximal femoral geometry suggests that there are genetic variants with potentially pleiotropic effects. Genome-wide significant association in women might be attributed to a larger sample size in women than in men. If confirmed with functional evidence, these results will illuminate biological pathways jointly affecting osteoporosis- and sarcopenia-related phenotypes.

***Disclosures: David Karasik**, None.*

## P35

**High Prevalence of Vertebral Fractures in Geriatric Outpatients.**

Hanna Van Der Jagt-Willems*[1], Marijn Vis[2], Linda Tulner[3], Jos van Campen[3], Willem Lems[2]. [1]Slotervaart Ziekenhuis, The Netherlands, [2]VUMC, Netherlands, [3]Slotervaart Ziekenhuis, Netherlands

Purpose of the study: In a retrospective study, we found a prevalence of 50% of vertebral fractures, based on lateral X-rays of the chest, among geriatric out clinic patients (mean age 80 years, 64% female), visiting our diagnostic day hospital in the Slotervaart Hospital, a teaching hospital, in Amsterdam, the Netherlands (van Hengel et al, submitted). However, data on vertebral fractures at the lumbar spine were not available; therefore we started a prospective study, in which X-rays of the thoracic and lumbar spine were performed. The aim is to investigate the prevalence of vertebral fractures in the total spine, and to evaluate whether the x-ray of the lumbar spine has additional value. Finally to identify any additional risk factors in this population.

Patients and Methods: We performed X-rays of thoracic and lumbar spine in all 303 patients who visited our geriatric diagnostic day hospital from April until July 2007. The X-rays were scored separately by two observers, according to the semi-quantative method of Genant (J.Bone Miner Res.1993;8(9):1137-48). Their conclusions were compared, and if the conclusion didn't match, consensus was reached. This was considered as gold standard. Cognitive function was assessed, and mobility was tested through the Timed up and go test (Podsiadlo D, J Am Geriatr Soc.1991;39(2):142-148) and reported falls of the last year were noted. The official reports of the radiologist were compared to the gold standard. Results: We found a prevalence of vertebral fractures of 51% (156/303) in geriatric patients with mean age of 82 years and 63% female. Almost 70% of the patients with a fracture had a moderate to severe fracture. In 33 patients we found a new diagnosis of vertebral fracture diagnosed on the lumbar spine x-ray alone. Reported falls in the last year was identified as a risk factor for vertebral fracture in this population. Radiologists identified in 82 out of 156 cases (53%) a fracture of any kind. Conclusions:

We confirmed the data from our retrospective study, in which we found a high prevalence of vertebral fractures of 51% among geriatric patients. The additional value of a lumbar spine X-ray seems to be small, since in only 11% of the patients a vertebral fracture was only recognized on the lumbar spine X-ray. Under-reporting by radiologists is very high. Reported falls in the last year is identified as a risk factor.

***Disclosures: Hanna Van Der Jagt-Willems**, None.*

## P36

**Microstructural and Mechanical Differences among Postmenopausal Caucasian, African, and Hispanic American Women.**

X Guo*[1], Xiaowei Liu[1], Bin Zhou[1], Emily Stein[2], Marcella Walker[1], Thomas Nickolas[3], Michael Yin[1], Donald McMahon[2], Elizabeth Shane[2]. [1]Columbia University, USA, [2]Columbia University College of Physicians & Surgeons, USA, [3]Columbia University Medical Center, USA

Many studies suggest that BMD is higher and fracture risk lower in African American (AA) than Caucasian (CA) women. However, few data are available on trabecular bone morphology, which may underlie these differences in BMD and fracture risk. Moreover, data on Hispanic (HISP) women of Caribbean origin, who manifest significant racial admixture and comprise a large proportion of the Latina population of the eastern US, are lacking. To explore racial/ethnic differences in trabecular bone microstructure in these underrepresented populations, we applied novel individual trabeculae segmentation (ITS) and micro finite element (μFE) analyses to high resolution peripheral QCT (HR-pQCT; Xtreme CT) scans of postmenopausal women (27 CA age $62 \pm 3$; 18 AA age $58 \pm 6$; and 30 HISP age $59 \pm 7$). At the distal radius (DR), total bone area for CA and HISP women was 15% and 12% lower respectively than AA women (both $p<0.05$). As a result, whole bone stiffness of CA and HISP women was 17% and 24% lower respectively than African-American women (both $p<0.05$). At the distal tibia (DT), total bone area for HISP women was 10% and 11% lower respectively than CA and AA women (both $p<0.05$); cortical thickness of CA and HISP women was 25% and 6% lower respectively than AA women (both $p<0.001$), resulting in 16% and 21% lower whole bone stiffness than AA women (both $p<0.01$). These data suggest that HISP women more closely resemble CA than AA women in terms of whole bone size and strength. Trabecular microstructure was similar in three racial groups at DR. However, DT rod bone volume fraction (rBV/TV) of CA women was 24% and 26% higher, and rod trabecular number (rTb.N) 10% and 11% higher than AA and HISP women, respectively ($p<0.05$). Furthermore, rod-rod junction density of CA women was 43% and 41% higher than AA and HISP women ($p<0.005$). These data suggest that trabecular bone microstructure of HISP women more closely resembles that of AA than CA women, in that both HISP and AA women have less "rod-like" microstructure than CA women. Consistent with this, DT trabecular stiffness of CA women was 21% lower than AA women. However, the trabecular stiffness of HISP women was 16% lower than AA women ($p<0.005$), likely because trabecular bone area of HISP women was 11% smaller than AA women. These results illustrate the importance of more complete characterization of bone microstructure and strength in premenopausal and postmenopausal CA, AA and HISP women of Caribbean descent.

***Disclosures: X Guo**, None.*

## P37

**p62 and Dysregulated Osteoclastogenesis in Paget's Disease of Bone.**

Tamer Hadi*, Mark Subler, Greg Campbell, Jillian Stafflinger, Jolene Windle. Virginia Commonwealth University, USA

Purpose: Although Paget's disease of bone (PDB) afflicts millions worldwide, its etiology remains poorly understood. *p62*, the gene most frequently linked to PDB, encodes an adaptor protein in the RANK-NFκB signaling pathway that is critical for osteoclast (OCL) differentiation. Although its specific role is not well-understood, p62 positively regulates ubiquitination and downstream signaling of TRAF6, the key transducer of RANK signaling. Furthermore, the deubiquitinase CYLD, a key negative regulator of TRAF6 and osteoclast signaling, exerts its effect only in the presence of p62 with an intact ubiquitin binding (UBA) domain. We hypothesize that (a) p62 regulates RANK signaling biphasically, mediating the orderly ubiquitination and de-ubiquitination of TRAF6, and that (b) PDB-associated mutations in the p62 UBA domain may impair CYLD binding or activity, predisposing affected cells to diminished negative feedback regulation of TRAF6, thereby enhancing the osteoclastogenic potential of pagetic pre-OCLs. The purpose of the present study was to elucidate the temporal regulation of RANK signaling in pre-OCLs. In particular, we asked: how does p62 regulate RANK signaling in wildtype pre-OCLs and how does the PDB-associated p62 P394L mutation alter this signaling? Methods: Previously, we generated knock-in (KI) mice with a P394L mutation in *p62*, the murine equivalent of the most common human PDB-associated mutation, demonstrating that KI mice are osteopenic and that pre-OCLs from these mice exhibit enhanced cytokine-mediated osteoclastogenesis. Here, we isolated bone marrow from p62 KI, p62 KO, and WT mice, and induced OCL differentiation by the addition of RANKL + M-CSF. At various timepoints following RANKL addition, we performed co-immunoprecipitation and Western blot analysis to examine expression levels and interactions between CYLD, RANK, TRAF6, and p62. Results: Preliminary data indicate that (a) p62 expression peaks between 6 hours and 24 hours post-RANKL stimulation, then falls by 48 hours in WT and KI pre-OCLs, (b) p62 is not required to mediate TRAF6-CYLD interaction, and (c) mutation in p62 is associated with decreased TRAF6-p62 interaction TRAF6-CYLD interactions. Conclusions: These data suggest that the Paget's associated p394L mutation in p62 may exert its pro-osteoclastogenic effect not by abrogating normal protein-protein interactions, but by altering the temporal regulation of critical intermediaries in the RANK signaling pathway.

**Fig 1. Expression levels of critical endogenous intermediaries in the RANK signaling pathway.**

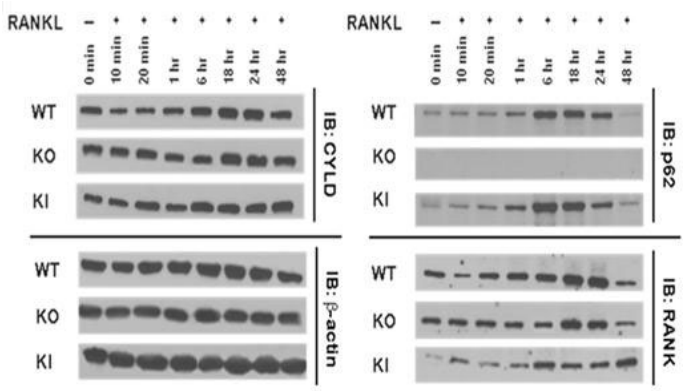
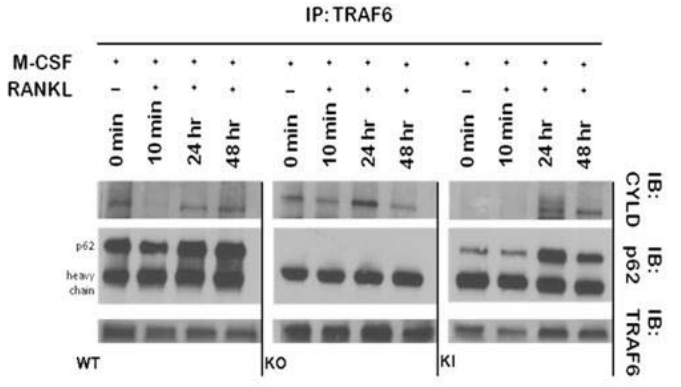



**Fig 2. Co-Immunoprecipitation to detect TRAF6, p62 and CYLD interactions after RANKL treatment.**




***Disclosures: Tamer Hadi**, None.*

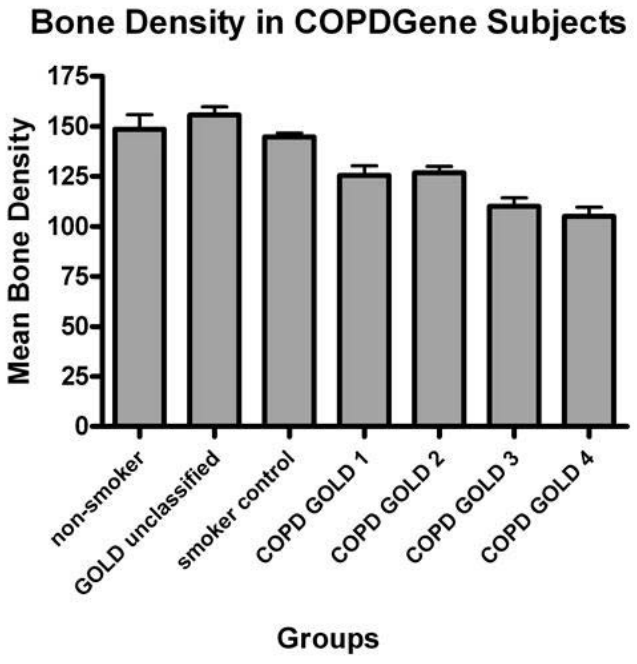
## P38

**Severe Bone Loss in COPD Predicts Worse Lung Disease.**

Elizabeth Regan*[1], John Hokanson[2], James Murphy[3], Francine Jacobson[4], James Crapo[3]. [1]National Jewish Health, USA, [2]University of Colorado, USA, [3]National Jewish, USA, [4]Brigham & Women's Hospital, USA

Accelerated bone loss occurs in association with chronic obstructive pulmonary disease but is often ascribed to steroid use. We studied a large cohort of smokers with and without COPD to determine the relationship of bone loss to severity of lung disease by spirometry and to emphysema and airway subtypes on CT scan. We hypothesized that bone loss would be greater in subjects with more emphysema. Methods: COPDGene is a multicenter cohort of 10,000 smokers with and without COPD recruited for genetic association studies. Each subject had pre and post bronchodilator spirometry done with a high resolution CT of the chest and provided extensive in formation regarding symptoms, quality of life, medical conditions and medication use. We measured bone density in the thoracic vertebrae using quantitative CT on 1200 subjects. Results: In subjects whose chest CT scan was performed with a calcium calibration phantom we were able to measure quantitative bone density in the thoracic vertebrae. Bone density is reduced signficantly in COPD subjects compared to smokers without disease (Figure 1). The relationship between severity of COPD and reduced bone mass persists after adjustment for age, gender, BMI and steroid use. Bone density is strongly associated with severity of emphysema (as measured as percent of lung volume at -950 HU) but does not associate with measures of airway disease (airway wall thickness or Pi10). Conclusions: Reduced bone density is common in a cohort of smokers and strongly associated with severity of disease in COPD as measured by spriometry. Up to 50% of the population is a current or former smoker and therefore at risk of occult COPD. Current and former smokers should be targeted for screening for bone density. In COPD patients measurements of bone density can be made using quantitative CT on the thoracic vertebrae and percent emphysema

**Figure 1 Bone Density in COPDGene by GOLD Stage**




***Disclosures: Elizabeth Regan**, None.*

## P39

**Socioeconomic and Racial Differences in Bone Turnover Markers in the MIDUS Study.**

Carolyn Crandall*[1], Dana Miller-Martinez[2], Gail Greendale[1], Neil Binkley[3], Teresa Seeman[2], Arun Karlamangla[2]. [1]University of California, Los Angeles, USA, [2]David Geffen School of Medicine at University of California, Los Angeles, USA, [3]University of Wisconsin, USA

Purpose : To examine associations of economic status and race with serum levels of bone turnover marker in participants of MIDUS II, a subsample of 1255 participants of the Mid-Life in the U.S. Study of adults aged 25 to 74 years at baseline. Methods: Based on self-assessment questionnaire and bone turnover assay data, we used multivariable linear regression to examine cross-sectional associations of race, education, and family-adjusted poverty-to-income ratio (PIR) with levels of N-telopeptide (Ntx), bone-specific alkaline-phosphatase (BSAP), and procollagen type I N-terminal propeptide (PINP) in gender-stratified models, adjusting for body weight, clinical site, and age (men) or menopausal transition stage (women). Results: Complete information regarding bone turnover marker levels, PIR, and covariates was available for 954 participants. Among women, but not among men, body weight was statistically significantly inversely correlated with higher levels of Ntx and PINP (please see Table). Among women, but not men, and after controlling for body weight, Ntx, BSAP, and PINP levels were statistically significantly higher among Black than among non-Black participants. Among men, but not among women, compared to a PIR of $\geqslant$ 600 %, a PIR of $<$300% was associated with statistically significantly higher levels of each bone turnover marker. Maximum level of education attained was not statistically significantly associated with level of any bone turnover marker (data not shown). Conclusions: We found sex-specific associations of poverty-to-income levels, Black race, and body weight with levels of bone turnover markers. This research was supported by National Institutes of Health grant numbers 1R01AG033067, R01-AG-032271, and P01-AG-020166.

**Associations between family poverty-to-income ratio and bone turnover markers**

| Table 1. Associations between family poverty-to-income ratio and bone turnover markers in women (N = 449)[1] | | | |
|---|---|---|---|
| Ntx | nM BCE difference | SE | P |
| Family PIR <300% [2] | -0.666 | 0.863 | 0.44 |
| Family PIR 300%-599% | 0.677 | 0.888 | 0.45 |
| Early peri (N = 55) [3] | -0.627 | 1.396 | 0.65 |
| Late peri/post no hormone (N = 277) [4] | 2.384 | 0.976 | **0.02** |
| Post hormone user (N = 50) [5] | -1.573 | 1.211 | 0.20 |
| Black | 3.688 | 1.100 | **0.001** |
| Bodyweight | -0.056 | 0.016 | **0.001** |
| **BSAP** | **U/L Difference** | **SE** | **P** |
| Family PIR <300% | -0.063 | 1.180 | 0.96 |
| Family PIR 300%-599% | 2.311 | 1.335 | 0.08 |
| Early peri | 0.134 | 1.788 | 0.94 |
| Late peri/post no hormone | 4.620 | 1.324 | **0.001** |
| Post hormone user | -1.012 | 1.819 | 0.58 |
| Black | 5.267 | 1.852 | **0.005** |
| Bodyweight | -0.042 | 0.028 | 0.14 |
| **PINP** | **M g/L difference** | **SE** | **P** |
| Family PIR <300% | -3.448 | 3.655 | 0.35 |
| Family PIR 300%-599% | -1.098 | 3.583 | 0.76 |
| Early peri | -1.273 | 5.175 | 0.81 |
| Late peri/post no hormone | 16.107 | 3.802 | **<0.001** |
| Post hormone user | -4.553 | 5.863 | 0.44 |
| Black | 11.506 | 4.450 | **0.008** |
| Bodyweight | -0.265 | 0.068 | **<0.001** |
| **Table 2. Associations between family poverty-to-income ratio and bone turnover markers in men (N = 505)** | | | |
| **Ntx** | **nM BCE difference** | **SE** | **P** |
| Family PIR <300% [6] | 1.713 | 0.882 | **0.05** |
| Family PIR 300%-599% | 0.335 | 0.583 | 0.57 |
| Men 50-64 (N = 217) (ref. <50 years) | -0.550 | 0.639 | 0.39 |
| Men 65+ (N = 133) | 0.324 | 0.002 | 0.69 |
| Black | 0.175 | 1.041 | 0.87 |
| Bodyweight | -0.021 | 0.019 | 0.27 |
| **BSAP** | **U/L Difference** | **SE** | **P** |
| Family PIR <300% | 3.222 | 1.391 | **0.02** |
| Family PIR 300%-599% | -0.938 | 0.893 | 0.28 |
| Men 50-64 | -0.784 | 1.087 | 0.47 |
| Men 65+ | 0.791 | 1.364 | 0.56 |
| Black | 1.781 | 1.778 | 0.32 |
| Bodyweight | 0.027 | 0.030 | 0.38 |
| **PINP** | **µg/L difference** | **SE** | **P** |
| Family PIR <300% | 7.399 | 3.165 | **0.02** |
| Family PIR 300%-599% | -3.737 | 2.294 | 0.10 |
| Men 50-64 | -6.365 | 2.636 | **0.02** |
| Men 65+ | -6.228 | 3.047 | **0.04** |
| Black | 3.458 | 4.045 | 0.39 |
| Bodyweight | -0.063 | 0.064 | 0.36 |

[1] Multivariable linear regression includes menopausal transition stage (for women) or age category (for men), race (Black vs. non-Black), body weight (kilograms), and clinical study site. BSAP = bone-specific alkaline phosphatase. PINP = procollagen type I N-terminal propeptide. Ntx = N-telopeptide. Reference group: premenopausal.
[2] Family poverty-to-income ratio, where reference is ?600%.
[3] early peri: early perimenopausal
[4] late peri/post no hormone: late peri- or postmenopausal not currently taking exogenous hormone therapy
[5] Post hormone user: postmenopausal taking exogenous hormone therapy
[6] Family poverty-to-income ratio, where reference is ?600%.

***Disclosures: Carolyn Crandall**, None.*

## P40

### Vitamin D Intake and Status in Veterans Living in Long-Term Care Facility.

Isabelle Germain*, Hope A. Weiler. McGill University, Canada

Purpose: To provide a comprehensive evaluation of vitamin D intake, and serum 25(OH)D plus related biomarkers of bone metabolism in association with health outcomes in elderly veterans living in a long-term care facility (LTCF). Methods: In Phase I of this prospective cohort study (n=40 males), participants were enrolled (April 2008) to assess vitamin D consumption using 5 day menu selection every 8 weeks and bone biomarkers over a spring-summer period of 16 weeks (Week 1, Week 8 and Week 16). Followed in October 2008 as Phase II, the same participants (n=30) continued for a more detailed analysis of food intake using 3 x 3-d weighed food audits and bone biomarkers over the fall-winter period (Week 1, Week 8 and Week 16). Anthropometric data, Mini-Mental State Evaluation (MMSE) scores and sun exposure were documented. Functional capacity was assessed using the Frail Elderly Functional Assessment Tool (FEFA). Serum 25(OH)D, PTH, osteocalcin (Liaison, DiaSorin) and Ctx (sandwich ELISA, IDS) were measured in both phases. In phase II, handgrip strength was measured. Pearson correlations and mixed model ANOVA analyses using the Tukey-Kramer adjustment were done, using SAS v.9.2 (2010). Results: Participants were similar in Phase I and II for mean age 85 ± 3 y (Mean ± SD), BMI 26.1 ± 4.3 kg/m$^2$, MMSE 25 ± 5, FEFA 13 ± 8 and handgrip 22 ± 8 lbs. Sun exposure was minimal (<0.25 h/d). Serum values of bone biomarkers are presented in Table 1. No vitamin D deficiency (< 37.4 nmol/L) was seen in August Daily vitamin D intake values are presented on Graph 1. Menus offered 52% of vitamin D from fortified milk and margarine, desserts and meal supplements. Weighed vitamin D intake was correlated to weighed energy intake (Pearson r = 0.4816 p<0.03). No correlation was seen between 25(OH)D serum concentration and handgrip strength, MMSE nor FEFA scores. Conclusions: This study captured vitamin D status of aging males across all seasons. The very old population living in LTCF, seems highly dependable on foods and meal supplements for vitamin D supply. However, tablet supplements are needed to reach the new RDA of 20 µg for the 70 y+ group. Future studies should also assess bone mineral density and document muscle mass in association with the various bone biomarkers to help determine benefits of adequate bone health on mobility and overall health in this aged population. RCTs would better detect the causal effects of various vitamin D intake levels on these outcomes.

**Graph 1: Vitamin D Intake**

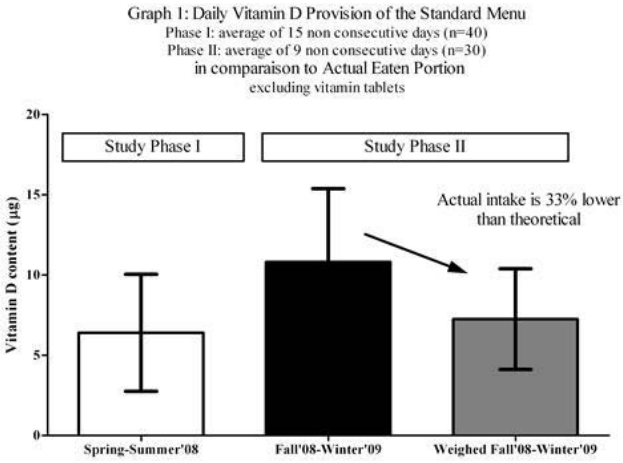



**Table 1: Biomarkers of Bone Metabolism in Elderly Men**

Table 1: Biomarkers of bone metabolism in elderly men living in LTC facility (Mean±SD)

| | 25(OH)D nmol/L | PTH pmol/L | Osteocalcin nmol/L | Ctx ng/L |
|---|---|---|---|---|
| April'08 (n=40) | 60.9 ± 24.4$^{ac}$ | 6.41 ± 3.33$^{a}$ | 5.07 ± 2.84 | 941 ± 533$^{a}$ |
| June'08 (n=40) | 68.2 ± 24.6$^{a}$ | 7.36 ± 6.61$^{ab}$ | 4.63 ± 2.19 | 915 ± 529$^{ab}$ |
| Aug.'08 (n=36) | 76.1 ± 22.4$^{b}$ | 7.51 ± 3.18$^{ab}$ | 5.23 ± 3.15 | 828 ± 419$^{ab}$ |
| Oct.'08 (n=30) | 57.7 ± 24.1$^{c}$ | 7.85 ± 3.22$^{ab}$ | 5.01 ± 2.76 | 834 ± 379$^{b}$ |
| Dec.'08 (n=29) | 62.9 ± 30.7$^{ac}$ | 10.38 ± 4.60$^{d}$ | 4.80 ± 3.26 | 899 ± 458$^{ab}$ |
| Feb.'09 (n=28) | 61.3 ± 29.2$^{ac}$ | 8.40 ± 3.65$^{abc}$ | 5.19 ± 3.04 | 920 ± 593$^{ab}$ |

For subjects participating in Phase I and II, mixed model ANOVA using Tukey-Kramer adjustment for multiple comparisons was used;
Means followed by different superscript lowercase letters, within columns, differ (P<.05)
Values were log transformed for statistical analyses but are presented in their original units

***Disclosures: Isabelle Germain**, None.*

## P41

**Vitamin D Supplementation and Caloric Restriction Influence Serum Osteocalcin and Insulin in Postmenopausal Women.**

Deeptha Sukumar*[1], Stephen Schneider[2], Hasina Ambia-Sobhan[1], Sue Shapses[1]. [1]Rutgers University, USA, [2]Department of Endocrinology, Metabolism & Nutrition, UMDNJ-RWJ Medical School, USA

Osteocalcin (OC) is a bone matrix gla protein and a marker of bone formation and may be influenced by vitamin D or weight loss. Recent reports suggest that OC may also be responsible for regulation of energy metabolism and influences glucose homeostasis. Vitamin D and calcium supplementation suppress parathyroid hormone (PTH) levels, which may attenuate the increased bone turnover (BT) associated with caloric restriction. In addition, vitamin D may also improve insulin sensitivity in glucose intolerant individuals. In this randomized double blind trial, we examined whether vitamin D supplementation has differential effects on OC compared to other BT markers in overweight/obese postmenopausal women without evidence of type 2 diabetes, during 6 weeks of caloric restriction. Beginning at 1 month prior to baseline measurements, both groups received 1.2 g Ca /day and a multivitamin with 400 IU/d vitamin D. Women were supplemented with vitamin D3 (vitD) or placebo so total supplementation was 2500 IU/d or 400 IU/d in the groups, respectively. Forty-two women (58 $\pm$ 6 yrs, 31 $\pm$ 4 kg/m$^2$) lost 4 $\pm$ 1% of body weight with no differences between groups. Serum 25-hydroxyvitamin D (25OHD) increased (7.5 $\pm$ 5.8 ng/ml) in vitD group, but not the placebo group (0.5 $\pm$ 4.7 ng/ml) ($p < 0.01$). PTH, propeptide of type 1 collagen, N-telopeptide of type 1 collagen and pyridinium cross links did not differ between groups, whereas the decline in OC was attenuated in the vitD group compared to the placebo group ($p<0.01$). Serum insulin was measured in a subset of 36 women, and showed a decrease in the vitD group ($p < 0.05$), but not in the placebo group. In addition, there was a trend for an inverse correlation between the change in osteocalcin and insulin ($r = 0.30$; $p < 0.07$). These results suggest that vitamin D supplementation attenuates the decline in OC during caloric restriction, and the decrease in serum insulin raises the possibility that it affects insulin sensitivity.

***Disclosures: Deeptha Sukumar**, None.*

# Mechanisms of Cellular Aging

## P42

**A Tissue Stem Cell Niche Regulates Oxidative-Mechanical Lrp5 Aortic Valve Osteoblastogenesis.**

Nalini Rajamannan*. Northwestern University Medical School, USA

Introduction: Calcific aortic valve disease(CAVD) is the most common indication for valve surgery in the USA. Cellular mechanisms are under investigation. This study hypothesizes that CAVD develops secondary to Wnt3a/Lrp5 activation via oxidative- mechanical stress a tissue stem cell niche resident in the aortic valve. Methods: eNOS-/-, Lrp5-/-, and ApoE-/- mice were tested with experimental diets including a control (n=20), cholesterol (n=20), cholesterol + Atorvastatin (n=20). Different genotypes were utilized for examining oxidative stress and mechanical force mechanisms in valve disease. After 23 weeks the mice were tested for the development of aortic stenosis by Echo, Histology, MicroCT and RTPCR for bone markers. In vitro studies were performed to measure Wnt3a secretion from aortic valve endothelial cells and to determine oxidative stress by measuring eNOS activity in these cells. Anion exchange chromatography was performed to isolate the mitogenic protein. Myofibroblast cells were tested to induce bone formation. Results: Cholesterol treated bicuspid eNOS-/- mice develop severe stenosis with an, increase in Lrp5, Cbfa1, (3-fold increase($p<0.0001$) in the aortic valves as compared to the tricuspid aortic valves. Tricuspid Lrp5-/- mice developed no CAVD. Tricuspid ApoE-/- developed mild stenosis by echo associated with calcification. Secretion of Wnt3a from aortic valve endothelium in the presence of abnormal oxidative stress was confirmed by diminished eNOS enzymatic activity and tissue nitrite levels. Isolation of an anionic mitogenic factor confirms the cell-cell communication in the tissue stem cell niche. Dikkopf1 was increased in the atorvastatin treated conditioned media. Osteogenic media induced calcification in the valve interstitial cells. Conclusion: Targeting the Wnt3a/Lrp5 pathway in valve calcification and activation of osteogenesis is via oxidative-mechanical stress in CAVD. These findings provide a foundation for targeting the cross talk mechanism in the aortic valve.

***Disclosures: Nalini Rajamannan**, None.*

## P43

**CITED2 is Required for Maintenance of Tendon Stem Cells.**

Lili Xu[1], Zuping Zhou[1], Takintope Akinbiyi[1], Alicia Harrison[1], Andrew Neviaser[1], Daniel Leong[1], Robert Majeska[2], Evan Flatow[1], Herb Sun*[1]. [1]Mount Sinai School of Medicine, USA, [2]City College of New York, USA

Aging tendons become increasingly susceptible to injury. Our recent work shows that the pool of tendon stem cells (or tendon-derived stem/progenitor cells, TSPCs) declines substantially with age, suggesting that a shortage of tissue-resident stem cells may underlie the compromised replenishment of tenocytes observed in aging tendons and ultimately lead to tendon failure. However, the molecular mechanisms responsible for maintaining the TSPC pool remain unclear. CBP/p300-interacting transactivator with ED-rich tail 2 (CITED2) is a transcriptional factor critically involved in embryonic fibroblast cell survival. Our pilot studies suggested that CITED2 might play a similar role in TSPCs. We found that CITED2 expression significantly declined with age in rat TSPCs, and that diminished CITED2 expression correlated with a higher percentage of TSPCs in G2/M cell cycle arrest. In the present study we sought to relate changes in human TSPC function and number with age to CITED2 expression, and to identify mechanisms by which CITED2 could regulate TSPC survival and proliferation. Utilizing biceps tendon tissues from patients of different ages undergoing shoulder replacement, we found that CITED2 expression in human tendons declined with age. This decline correlated with reduced TSPC colony forming ability and increases in senescence, apoptosis, and G2/M phase arrest, both under basal culture condition and in response to experimental oxidative stress ($H_2O_2$). CITED2 knockdown increased senescence and apoptosis in both young and aged TSPCs, while CITED2 overexpression opposed those effects. Furthermore, a targeted gene expression and protein interaction analysis reveal that reduction of CITED2 is correlated with downregulation of Bmi1 and cdc2, and upregulation of $p19^{Arf}$, p53 and p21 in aged TSPCs. Intriguingly, overexpression of CITED2 can rescue those aging-associated alternations in gene expression. These findings suggest that CITED2 may help control expression and activities of cell cycle/death-related signaling molecules, particularly interactions between cdc2 and Cyclin $B_2$ that are crucial to determining whether cells continue to cycle, arrest at G2/M, senesce or die by apoptosis. Our study provides evidence that CITED2 is critical for both proliferation and survival of human TSPCs. The identification of CITED2 as a key transcriptional factor governing TSPC main-

tenance may offer an appealing therapeutic target for treatment of age-related tendon pathologies.

***Disclosures: Herb Sun**, None.*

## P44

**Differential Impact of Resveratrol and Resveratrol Mimetics on Actin Ring Formation and Osteoclastogenesis.**

Manhui Pang*[1], Maria Rodriguez-Gonzalez[1], Mireya Hernandez[1], Bruce Troen[2]. [1]VAMC, USA, [2]Miami VA GRECC, University of Miami Miller School of Medicine, USA

Osteoporosis is a widely prevalent contributor to frailty and results from an imbalance between bone resorption and bone formation leading to progressive bone loss, fractures, and increased morbidity and mortality. Actin ring formation plays a critical role in the formation of osteoclasts and bone resorption. Sirtuin activating compounds such as resveratrol (RSV) are pro-longevity agents that can extend health span in vertebrates. RSV enhances bone mineral density in mice, and sirtuin knockout mice exhibit increased osteoclastogenesis. Sirt1 expression decreases with ovariectomy and is increased by estrogen treatment in vivo. We are therefore investigating the impact of RSV and novel resveratrol mimetics (SRT2183 and SRT1720) on bone. We have found that SRT2183 and SRT1720 inhibit osteoclast formation in a dose-dependent manner in both RAW264.7 cells and bone marrow cells during osteoclastogenesis, whereas RSV does not. In addition, SRT2183 and SRT1720 dose-dependently inhibit actin ring formation, whereas RSV does not. To assess whether these impacts are due the inhibition of osteoclast formation, we have treated mature osteoclasts and found that SRT2183 and SRT1720 markedly disrupted actin rings, whereas RSV does not. Furthermore, SRT2183 and SRT1720 both inhibit resorption by mature osteoclasts, and again RSV does not. To assess the role of Sirt1, we assessed the in vitro impact on osteoclastogenesis in bone marrow cells from osteoclast specific Sirt1 knockout mice. Both SRT2183 and SRT1720 markedly inhibited osteoclast formation, despite the absence of Sirt1 expression, whereas RSV did not. Interestingly, although RSV was ineffective in vitro, RSV treatment in vivo of young mice decreased ex vivo osteoclastogenesis and increased ex vivo osteoblastogenesis. RSV treatment for 6 weeks in 26-month-old mice markedly increased bone volume and indices as indicated by micro CT. Therefore SRT2183 and SRT1720 are effective inhibitors of osteoclast formation and function in vitro, and this does not depend upon Sirt1 expression. Conversely, RSV appears to exert potent in vivo effects upon bone in both young and very old mice. This anabolic impact of RSV may be mediated by direct effects upon osteoblasts, rather than osteoclasts. These compounds may hold promise for combined anabolic and anti resorptive treatment of osteoporosis. But further studies are needed to determine the in vivo cellular impacts of both RSV and the RSV mimetics.

***Disclosures: Manhui Pang**, None.*

## P45

**Effects of Age on Parathyroid Hormone Signaling in Human Marrow Stromal Cells: Roles of CREB and Wnt Signaling.**

Shuanhu Zhou*, Ericka Bueno, Sung Won Kim, Ilaria Amato, Longxiang Shen, Jochen Hahne, Julie Glowacki. Brigham & Women's Hospital, USA

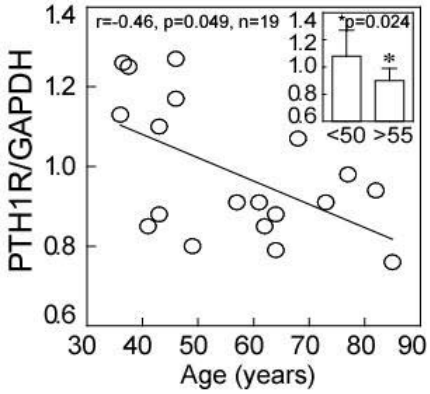
There are age-related decreases in proliferation and osteoblast differentiation in human marrow stromal cells (hMSCs). Parathyroid hormone (PTH) has osteoanabolic effects in a variety of systems. We tested the hypothesis that age influences hMSC responses to PTH1-34.

*Methods.* Human MSCs were obtained from discarded femoral heads with IRB approval. The effects of PTH on cell counts were enumerated; p-CREB and ß-catenin were measured by Western immunoblot; and osteoblast differentiation was measured by RT-PCR and biochemical assays for alkaline phosphatase activity.

*Results.* PTH significantly stimulated proliferation of hMSCs. The PKC inhibitor (chelerythrine chloride), but not the PKA inhibitor (H-89), significantly diminished the stimulation by PTH; this indicates that PKC signaling is necessary for PTH stimulation of proliferation. PTH1-34 upregulated expression of *Wnt2* and *Wnt10B* genes in hMSCs; this suggests a possible autocrine mechanism for PTH activation of the Wnt/ß-catenin signaling pathway. PTH1-34 increased ß-catenin and p-CREB signaling in hMSCs, but there was an age-related decline in the magnitude of activation of p-CREB (Spearman r=-0.93, p=0.0067, n=7) and stabilization of ß-catenin (r=-0.96, p=0.0028, n=7). Osteoblast differentiation was stimulated by PTH1-34 with a 67% increase in hMSCs from younger subjects (<50-year-old, n=5) and 18% increase in the cells obtained from older subjects(>55-year-old, n=7; p=0.042 for the different age groups). There was an age-related decline in the constitutive levels of expression of PTH/PTHrP type I receptor (*PTH1R*) gene in hMSCs (Figure). The expression of *PTH1R* in hMSCs obtained from older subjects (n=10) was significantly lower than in hMSCs from young subjects (n=9) (Insert). Osteoblast differentiation was reduced by knockdown of CREB with siRNA ($p<0.05$) or by inhibition of PKA signaling with H-89 ($p<0.001$). Knockdown of CREB also blocked the stimulation of osteoblast differentiation by PTH.

*Conclusions.* These studies demonstrate that there is an age-related decrease in *PTH1R* expression and in PTH signaling in hMSCs. The effects of age on hMSCs were reproduced by blocking PKA, PKC, or CREB signaling by pharmacologic or genetic approaches. The age-related intrinsic alterations in signaling responses to osteoanabolic agents like PTH may contribute to cellular and tissue aging of the human skeleton.

**Figure**




***Disclosures: Shuanhu Zhou**, None.*

## P46

**FGF2 Positive Regulation of Osteoblasts Differentiation and Bone Formation is Partially Mediated by Modulation of the Wnt Pathway.**

Yurong Fei*[1], Liping Xiao[1], Thomas Doetschman[2], J.Douglas Coffin[3], Marja Marie Hurley[4]. [1]University of Connecticut Health Center, USA, [2]University of Arizona, USA, [3]The University of Montana, USA, [4]University of Connecticut Health Center School of Medicine, USA

Purpose of the study: We previously reported that disruption of Fgf2 gene resulted in age-dependent bone loss and bone marrow fat accumulation, suggesting that Fgf2-/- mice represent a model to study the mechanisms of age-related bone loss. Wnt signaling is important for bone homeostasis. The Fgf2 gene encodes for multiple protein isoforms. We recently reported that mice deficient in 18kDa FGF2 isoform displayed reduced bone mineral density (BMD) and increased expression of Wnt antagonist secreted frizzled receptor 1 in bones and bone marrow stromal cells (BMSCs). Here, we further explore modulation of Wnt signaling pathway in Fgf2-/- mice (FGF2 all isoforms null).

Methods: Adult mice (from 3ms to 12ms) on a black/swiss/129Sv/FVBN background were used. BMD was measured by dual energy Xray absorptiometry. BMSCs for osteoblast differentiation were cultured in αMEM with 10% FBS, 8mM β-glycerophosphate, and 50μg/ml ascorbic acid. We performed staining for alkaline phosphatase (ALP) and mineralized nodules by von Kossa. We analyzed mRNA expression using quantitative real-time PCR and protein expression using Western blots and immunofluorescence staining.

Results: The Fgf2-/- mice displayed decreased BMD, consistent with a previous report of Fgf2-/- mice on a black/swiss/129Sv background. In vitro osteoblast differentiation was also decreased in Fgf2-/- BMSCs, characterized by reduced ALP-positive mineralized nodules. The data also showed reduced expression of the osteoblast differentiation related genes runt-related transcription factor 2, activating transcription factor 4 and mature osteoblast marker osteocalcin. Interestingly, canonical Wnt gene Wnt10b and ß-catenin mRNA expression were significantly reduced from early to late stages of osteoblast differentiation in Fgf2-/- BMSCs. In addition, we observed marked reduction of ß-catenin protein expression in Fgf2-/- mice both in vitro and in vivo. However, exogenous FGF2 was able to rescue the reduced ß-catenin mRNA and protein expression as well as the decreased mineralization in Fgf2-/- BMSCs. These results collectively demonstrated the modulation of the Wnt signaling pathway by FGF2.

Conclusion: Our findings suggest that FGF2 positive regulation of osteoblast differentiation and bone formation is partially mediated by modulating the Wnt signaling pathway.

***Disclosures: Yurong Fei**, None.*

## P47

**Identification of MuRF1 Inhibitors Using a Novel E3 Ligase Assay.**

Jeffrey Marblestone*, Michael Eddins, Suresh Kumar, Craig Leach, Benjamin Nicholson, Michael Mattern. Progenra Inc, USA

Muscle atrophy (wasting), also known as myopathy, is a pathological condition of many diseases, including cancer, AIDS, and diabetes. Myopathy has also been shown to be a dose-limiting side effect of synthetic glucocorticoid treatment, and is a natural consequence of inactivity and aging. Muscle atrophy follows a disturbance in protein homeostasis in muscle, reflected by increased rates of protein catabolism and decreased anabolic activity. The expression of a group of novel genes called atrogins (atrophy-specific genes) has been implicated in the degradation of key muscle proteins. One of these, MuRF1 (Muscle-specific RING Finger), is a RING finger domain E3 ubiquitin ligase and is upregulated in at least 13 different models of atrophy. MuRF1 is associated with a number of myofibrillar proteins and is a very attractive target for preventing or reversing muscle wasting associated with various pathologies. Importantly, MuRF1 knock-out mice have been shown to be resistant to skeletal muscle atrophy under starvation conditions and also post-denervation.

To identify novel small molecule modulators of MuRF1 activity, we developed a novel HTS-assay to screen for inhibitors of E3 ligases. This assay format has been validated for use with a number of E3s, including MuRF1. The assay is based on the ability of an ubiquitin binding domain (UBA) to preferentially bind polyubiquitin relative to monoubiquitin. The benefit of the assay is that the reaction components can be native, non-tagged, and free in solution. UBA is the only component immobilized, which then binds polyubiquitylated substrates or autoubiquitylated E3s. The assay format is versatile, being able to detect K48-linked or K63-linked polyubiquitin chains. Furthermore, in addition to simple RING domain E3s, the assay works with SCF RING E3s and HECT domain E3s. Utilizing this assay platform, we identified P013222 as an inhibitor of MuRF1. Initial follow-up experiments confirmed the ability of P013222 to inhibit ubiquitylation of the MuRF1 substrate MyHC in a dose dependent manner and it is now being investigated in cell based models of muscle catabolism. The assay along with our recent progress on the P013222 compound series will be presented.

***Disclosures: Jeffrey Marblestone**, None.*

## P48

**Rejuvenation of Age-related Dysregulation of Osteoblast Differentiation and Vitamin D Metabolism in Human Mesenchymal Stem Cells.**

Shuo Geng*, Shuanhu Zhou, Julie Glowacki. Brigham & Women's Hospital, USA

With aging, there is a decline in bone mass and in osteoblast differentiation of human mesenchymal stem cells (hMSCs) in vitro. Osteoblastogenesis can be stimulated with 1,25-dihydroxyvitamin $D_3$ [$1,25(OH)_2D_3$] and, in some hMSCs, by 25-hydroxyvitamin $D_3$ ($25OHD_3$). CYP27B1/1α-hydroxylase activates $25OHD_3$; we reported that, to a variable degree, hMSCs express CYP27B1. In this study, we tested the hypothesis that age affects responsiveness to $25OHD_3$ and expression/activity of CYP27B1.

*Methods* We evaluated hMSCs from 27 subjects (41 to 87 years) by RT-PCR, Western immunoblot, alkaline phosphatase activity, synthesis of $1,25(OH)_2D_3$, targeted silencing of CYP27B1 and CREB, and for rejuvenation with PTH1-34 treatment.

*Effect of Age* The level of CYP27B1 in hMSCs from older subjects (>55, n=15, p=0.007) was 56% compared with the younger group (<50, n=12). There was an inverse correlation between CYP27B1 expression and age (r=-0.498; p=0.008).

*Effect of 25OHD₃* For further analysis, we chose young ($hMSCs^{YOUNG}$) and old ($hMSCs^{OLD}$) representing high and low CYP27B1, respectively. Osteoblast differentiation of $hMSCs^{YOUNG}$ was stimulated by both $1,25(OH)_2D_3$ and $25OHD_3$, but $hMSCs^{OLD}$ was resistant to stimulation by $25OHD_3$. Synthesis of $1,25(OH)_2D_3$ by $hMSCs^{OLD}$ was 37% of $hMSCs^{YOUNG}$.

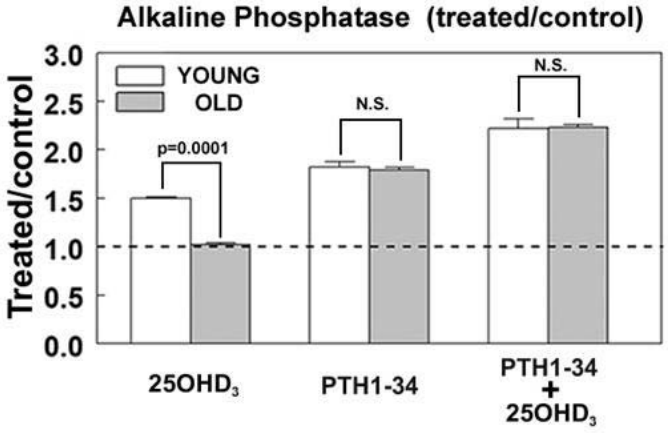
*Role of CYP27B1* CYP27B1 in $hMSCs^{YOUNG}$ was experimentally reduced with ketoconazole or with CYP27B1-siRNA. With either manipulation, $hMSCs^{YOUNG}$ lost osteoblastogenic response to $25OHD_3$.

*Rejuvenation with PTH* Pre-treating $hMSCs^{OLD}$ with PTH1-34 resulted in stimulation of osteoblastogenesis by $25OHD_3$ (Figure), and in upregulation of CYP27B1 gene and protein expression and

$1,25(OH)_2D_3$ synthesis. Experiments with CREB-siRNA, KG-501(which disrupts the downstream interaction between p-CREB and CBP/p300), or AG1024 (an inhibitor of IGF-IR) showed that PTH1-34 "rejuvenation" of age-related dysregulation of osteoblastogenesis was mediated by upregulation of CYP27B1 through CREB and IGF-I pathways.

*Conclusions* In hMSCs, there is an age-related decline of CYP27B1 expression and activity, and in responsiveness of osteoblastogenesis to $25OHD_3$. PTH1-34 "rejuvenated" hMSCs by upregulation of CYP27B1 through CREB and IGF-I mediated pathways. These findings provide new targets to revive the aged bone microenvironment. Osteoanabolic PTH and vitamin D may have synergistic effects to potentiate osteoblast differentiation in elders.

**Figure**




***Disclosures: Shuo Geng**, None.*

## Physiological Signals Contributing to Age-Related Bone Loss

## P49

***Igfbp-2* Null Mice Exhibit Protection From Age Related Loss of Bone With Increased Susceptibility to Obesity and Insulin Resistance.**

Victoria Demambro*[1], Katherine Shultz[2], Jane Maynard[2], Harold Coombs[2], David Clemmons[3], Wesley Beamer[2], Clifford Rosen[4]. [1]Maine Medical Research Institute, USA, [2]The Jackson Laboratory, USA, [3]University of North Carolina Chapel Hill, USA, [4]Maine Medical Center, USA

As humans age IGFBP-2 serum levels increase and this has been associated with reduced BMD in population based studies. Transgenic IGFBP-2 mice exhibit resistance to age related obesity and insulin resistance. We have previously reported on an IGFBP-2 global knockout, which exhibits decreased bone volume and turnover with increased adiposity. To test the effect of IGFBP-2 absence over time, we aged *Igfbp2* null (-/-) and control (+/+) males to 24 months of age. Body composition was examined by DEXA at 2, 4, 6, 12, 18 and 24 months. Femurs were analyzed by pQCT at 4, 12 and 24 months for vBMD and MicroCT for structural changes at 4 and 12 months. Metabolic status was evaluated by ITT, GTT and euglycemic clamp studies at 12 months of age. Serum levels of insulin, leptin, osteocalcin and adiponectin were also measured. The -/- males were heavier with increased fat mass at all time points. Whole body BMC was significantly reduced in -/- mice compared to +/+ control mice through 18 months. At 12 months of age -/- mice had a 41% increase in fat mass compared to controls. Analysis of the femur revealed increases in vBMD and cortical thickness compared to +/+ controls in contrast to what was observed at 16 weeks of age. At 12 months of age, serum insulin was increased in -/- mice compared to +/+ mice. When glucose challenged, -/- mice exhibited higher glucose values and ITT results showed a decrease in the hypoglycemic response. Decreased glucose infusion rates coupled with significantly increased insulin levels during the euglycemic clamp studies confirmed the insulin resistance and hyperinsulinemic state in the -/- mice. Serum analysis revealed a 45% increase in fasted leptin levels compare to +/+ controls. Interestingly, uncarboxylated osteocalcin levels were slightly (6%) but significantly increased in the -/- despite the mild insulin resistance noted. Remarkably, between 12 to 24 months, +/+ males had a dramatic loss in weight (-19%), whole body BMC (-13%), and fat mass (-27%), while -/- mice appeared protected from these age related decreases by showing a significant increase in BMC (+7%) and a trend towards increased fat mass (+5%) during this same time period. In summary, *Igfbp-2* null males appear to be protected from age related loss of bone with minor reductions in cortical mass and increased trabecular thickness. On the other hand, they seem to be more susceptible to age related increases in obesity and insulin resistance.

***Disclosures: Victoria Demambro**, None.*

## P50

**A Single Intravenous Bisphosphonate Treatment Prolonged the Suppression of TGF-β1 Secretion and Bone Formation.**

Sarah Mugongo*[1], Wei Yao[2], Zhiqiang Cheng[3], Nancy Lane[2]. [1]UC Davis Medical Center, USA, [2]University of California, Davis Medical Center, USA, [3]University of California, San Francisco, USA

Anti-resorptive agents are frequently used for the treatment of osteoporosis. While a number of studies have reported that osteoclast apoptosis is responsible for the anti-resorptive action of bisphosphonates, others have reported that bisphosphonates may also regulate osteoblast function via altering the release of TGF-β1 from bone matirx. We evaluated the role of bisphosphonates and raloxifene in the regulation of the TGF-β1/Smad signaling and bone turnover.

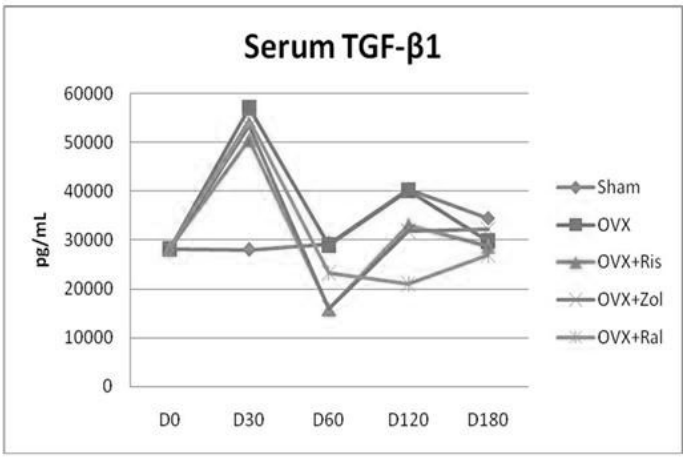
Methods. Eighteen-month-old female Fischer 344 rats were randomized into Sham, ovariectomized (OVX), OVX+ Risedronate (Ris, 500μg/kg, single iv) or OVX + Zoledronate (Zol, 100μg/kg, iv.) or Raloxifene (Ral,2mg/kg/d, po 3x/week) and treated one day post-OVX. Rats were sacrificed at days 30, 60, 120 and 180 post- OVX. Whole bone TGF-ß1 and Smads mRNA expression was monitored with real-time PCR. Serum TGF-β1 and TRAP5b levels were monitored with ELISA. Immunohistochemistry was used to confirm the in situ expression of TGF-ß1 and Smads, and histomorphometry for surface-based bone turnover.

Results. OVX increased serum TGF-ß1 levels (100%) from day 0 until day 30 post-OVX, and then the levels returned to the sham-control level from days 30 - 180 post-OVX. The maximum suppression of TGF-ß1 following a single I.V. Ris or Zol treatment was observed 60 days (-50%) and returned to the sham-control level by day 180. Both bisphosphonates had prolonged suppression of whole bone gene expression of TGF-β1 (3 fold from sham) and Smad 3 (10 fold from sham) at day 180; raloxifene was not different from sham. Changes in serum Trap5b were similar to TGF-ß1 in both bisphosphonates and Raloxifene. In both bisphosphonate treated groups, BFR/BS from 5th vertebral body was more than 70% lower than the sham or OVX levels from days

30 -180. Raloxifene treated animals were not different from sham levels for BRF/BS at day 180.

Conclusion. A single intravenous injection of either risedronate or zoledronate suppressed TGF-ß1 serum levels up to 120 days post-OVX and this suppression was associated with a reduction in bone formation. These data support serum TGF-β1 as a potential biomarker for suppression of bone formation after anti-resorptive therapy. Serial measurements of TGF-β1 serum levels may help to guide clinicians on the appropriate drug treatment intervals for osteoporosis treatment interventions.

**Serum TGF-beta1-Bis**




***Disclosures: Sarah Mugongo**, None.*

## P51

**Biological Aging Alters Circadian Mechanisms In Murine Adipose Tissues: Implications For Bone Biology.**

Susan Newman[1], Michael Freitas[2], Indu Kheterpal[1], Andrey Ptitsyn[3], Bruce Bunnell[4], Xiying Wu[1], Claudia Leonardi[1], Kenneth Eilertsen[1], Elizabeth Floyd[1], Katie Hamel[1], Jeffrey Gimble*[1], Armand Centanni[1], Gregory Sutton[1], Gang Yu[1]. [1]Pennington Biomedical Research Center, USA, [2]Ohio State University, USA, [3]Colorado State University, USA, [4]Tulane University, USA

Biological aging alters the volume of adipose tissue depots in bone marrow and in peripheral adipose depots. The bone marrow mesenchymal stromal/stem cell's inverse relationship between adipogenic and osteogenic commitment is postulated to account for the central mechanism underlying the etiology of osteoporosis associated with aging. Recent evidence suggests that circadian mechanisms play a role in regulating adipogenesis and osteogenesis as well as metabolism in bone and fat. The current study compared cohorts of young (5-8 mo) and old (24-28 mo) C57BL/6 mice as a function of both biological age and circadian time with respect to peripheral adipose tissue function. Increased age significantly reduced the weight of peripheral adipose depots. Older mice reduced their physical activity by >50% and delayed their activity initiation after light offset. The expressed transcriptome in brown and white adipose depots of young and older cohorts displayed evidence of circadian rhythmicity; however, the oscillating mRNAs differed significantly between age groups and across tissues. The amplitude of *Cry1*, a component of the negative arm of the circadian apparatus, and downstream regulators such as *Rev-erbα* were elevated in the old relative to the young cohorts as a function of circadian time. Overall, the microarray expression levels differed significantly for 557 (inguinal adipose), 1016 (liver), and 1021 (brown adipose) expressed sequences between the young and old cohorts based on phase and synchronization. These included multiple mRNAs within the canonical and non-canonical Wnt pathways. Since the Wnt pathway regulates mesenchymal stem cell lineage commitment between the adipocyte and osteoblast pathways and shares a critical enzyme, glycogen synthase kinase 3β, with the circadian mechanism, the intersection between these two fundamental regulatory mechanisms merits further investigation in the context of osteoporosis, lipodystrophy, and the etiology of frailty in the geriatric population. Similar studies on circadian mechanisms and loss of synchronization of gene expression in aging bone depots of young vs. older mice will be an active area for exploration.

***Disclosures: Jeffrey Gimble**, None.*

## P52

**Bone Density Loss Across the Menopause Transition: The Study of Women's Health Across the Nation (SWAN).**

Gail Greendale*[1], Weijuan Han[2], MaryFran Sowers[3], Joel Finkelstein[4], Mei-Hua Huang[2], Carolyn Crandall[1], Jennifer Lee[5], Arun Karlamangla[2]. [1]University of California, Los Angeles, USA, [2]UCLA School of Medicine, USA, [3]University of Michigan, USA, [4]Massachusetts General Hospital, USA, [5]University of California, Davis, USA

Accelerated bone loss during the menopause transition (MT) has been described, but no study has examined this phenomenon longitudinally in a multiethnic cohort during a 10 year period bracketing the final menstrual period (FMP). We evaluated: the timing of the onset and offset of MT-related bone mineral density (BMD) loss; the rate and amount of BMD decline during the MT; and whether age at final menstrual period (FMP), body mass index (BMI) or race influenced the rate of BMD loss during the MT. The sample included 277 African-American, 417 Caucasian, 125 Chinese and 127 Japanese women, pre- or early peri-menopausal at baseline, who had experienced their FMP. BMD of the lumbar spine (LS) and femoral neck (FN) was measured with cross-calibrated dual energy X-ray aborptimeters. Loess-smoothed curves of baseline-normalized BMD as a function of time prior to or after the FMP showed that: a) the rate of BMD loss accelerated 1 year before the FMP at the LS and FN; b) BMD loss decelerated at 2 years after the FMP at the LS and 2.33 years post FMP at the FN; and c) BMD declines were linear within the 3 segments defined by these acceleration and deceleration points. To examine the influences of age at FMP, BMI and race/ethnicity on rates of loss during each segment, we used linear, mixed effects regression to fit piece-wise models with fixed knots at the acceleration and deceleration points. Greater BMI and African-American heritage were associated with slower rates of BMD loss, while Japanese and Chinese ancestry were related to higher BMD loss rates (Table). Supported by: the National Institutes of Health (NIH), DHHS, through the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR) and the NIH Office of Research on Women's Health (ORWH) (Grants NR004061; AG012505, AG012535, AG012531, AG012539, AG012546, AG012553, AG012554, AG012495). This content is solely the responsibility of the authors and does not necessarily represent the official views of the NIA, NINR, ORWH or the NIH.

**Effects of Selected Characteristics on Rates of BMD loss at the LS and FN During the MT**

| Effects of Selected Characteristics on Rates of BMD loss at the LS and FN During the MT* | | | | |
|---|---|---|---|---|
| | Annualized slopes in each segment prior to and after the FMP | | | 10-yr change -5 to +5 yr |
| **Lumbar Spine** | -5 to – 1 yr prior to FMP | -1 yr prior to +2 yr after FMP | + 2 yr to +5 yr after FMP | |
| Reference values** | ***- 0.14%*** | ***-2.37%*** | ***-1.15%*** | ***-13.1%*** |
| Age at FMP (per year) | ***-0.052%*** | -0.005% | +0.053% | -0.06% |
| Baseline BMI (per kg/m$^2$) | ***+0.015%*** | ***+0.059%*** | +0.023% | ***+0.31%*** |
| Japanese | +0.12% | +0.10% | -0.02% | +0.7% |
| Chinese | ***-0.28%*** | -0.12% | -0.23% | ***-2.2%*** |
| African American | -0.20% | ***+0.34%*** | +0.19% | +0.8% |
| **Femoral Neck** | 5 to – 1 yr prior to FMP | -1 yr prior to +2.33 yr after FMP | + 2.33 yr to +5 yr after FMP | 10-year change |
| Reference values** | ***- 0.18%*** | ***-1.60%*** | ***-1.29%*** | ***-9.49%*** |
| Age at FMP (per year) | ***-0.041%*** | -0.002% | -0.007% | -0.19% |
| Baseline BMI (per kg/m$^2$) | +0.005% | ***+0.022%*** | +0.004% | ***+0.10%*** |
| Japanese | +0.10% | ***-0.55%*** | +0.18% | -0.9% |
| Chinese | -0.09% | ***-0.41%*** | +0.37% | -0.8% |
| African American | +0.02% | +0.18% | +0.04% | +0.8% |

*Statistically significant associations ($p < 0.05$) are in ***bold italic font.***
**The reference values for bone loss in each segment are for Caucasian women of average age at FMP (51.9 years), average BMD at baseline (1.07 gms/cms$^2$,spinel 0.83 gms/cm2, femoral neck) and BMI at baseline (28 kg/m$^2$). Models adjusted for clinical site and baseline BMD.

***Disclosures: Gail Greendale**, None.*

## P53

**Improving Musculoskeletal Outcomes for Individuals with Osteogenesis Imperfecta.**

Adele Boskey[1], Mathias Bostrom[1], Susan Bukata[2], Paul Esposito[3], Annie Kennelly[4], Frank Rauch[5], Peter Smith[6], Laura Tosi*[4]. [1]Hospital for Special Surgery, USA, [2]University of Rochester, USA, [3]Children's Hospital Omaha, USA, [4]Children's National Medical Center, USA, [5]Shriners Hospital for Children, Canada, [6]Shriners Hospital for Children, USA

Purpose: The 10th Scientific Meeting of the Osteogenesis Imperfecta Foundation held in April 2010 met to 1) summarize the state of knowledge regarding the musculoskeletal aspects of aging with OI; 2) explore the potential for new diagnostic and therapeutic techniques for the treatment of OI; and 3) consider better quantitative measurement tools with which to analyze the outcome of these interventions. Methods: Workshop sessions focused on a broad array of topics. First, the paucity of studies on aging with OI was discussed and the risks of aging poorly were underscored. Drawing from bedrest studies and space research, the importance of exercise to maintain both muscle function as well as bone health was reviewed, and exciting new therapies to improve muscle function and bone health were highlighted. The potential for non-invasive technologies designed to measure bone quality in individuals with osteoporosis were discussed as they may serve to better inform researchers and clinicians about the status of bone in individuals with OI. The workshop paid particular attention to the broad range of orthopaedic problems found in OI including spondylolysis/spondylolithesis, scoliosis, long bone fractures and joint replacement: issues that affect a person's ability to function across the life span. Results: As a result of the conference, attendees formed collaborations to expand data on spondylolysis/spondylolithesis prevalence and management. They also initiated the development of a protocol to establish the prevalence of tendon injuries in adults with OI and investigate the steps needed to create a set of reference data for bone turnover markers. Most important, the first steps were taken to develop a tool for evaluating the health status of adults with OI. This included organization of focus group sessions to be held at the OIF Family Conference in July 2010 in order to begin assessing the unmet needs of the adult OI population.

Conclusion: The workshop closed with a commitment to develop a better understanding of the unmet healthcare needs of adults OI and to improve tools for assessing musculoskeletal health as well as other health and quality of life concerns. The meeting also articulated the need to improve the quality, safety, efficiency and effectiveness of all treatment options. Finally workshop members spoke to the need for additional opportunities for health care providers to connect and share questions/expertise about care for adults with OI.

***Disclosures: Laura Tosi**, None.*

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**mTOR Stimulates Osteogenesis and Lipogenesis in Osteoblastic Cells: Possible Implications for the Pathogenesis of Age-Related Osteoporosis.**

Lee-Chuan C. Yeh, Xiuye Ma, Martin L. Adamo*, John Lee. University of Texas Health Science Center at San Antonio, USA

Aging is associated with accretion of lipid in several soft tissues, which appears to impede tissue function and induces metabolic syndrome. Recently bone has also been shown to accumulate lipid with aging and skeletal lipotoxicity has been proposed to be a component in the pathogenesis of osteoporosis. In soft tissues the mTOR pathway has been shown to mediate several anabolic processes in response to growth factor stimulation; however, dysregulated activation of mTOR has been proposed to be a pathogenic mechanism in toxic lipid accretion. We have now made the novel observations that Bone Morphogenetic Protein-7 (BMP-7) potently stimulates mTOR and p70S6K phosphorylation and increases mRNA and protein expression of several lipogenic enzymes in calvarial cells. The induction of both the osteogenic and the lipogenic phenotypes by BMP-7 in osteoblast cells is attenuated by rapamycin suggesting that BMP-7 acts on these anabolic processes *via* mTOR. We have also found that in aging mice BMP-7-induced ectopic bone formation is attenuated in association with increased fat content and lipogenic enzyme expression. A similar effect is also observed in young *Igf1r*+/- mice that are resistant to the bone inductive effect of BMP-7 and IGF-1. Collectively, our results suggest that growth factors activate both osteogenic and lipogenic pathways *via* mTOR. We hypothesize that, analogous to what occurs in insulin resistant states in metabolic tissues, the aging skeleton remains sensitive to the lipogenic effects of mTOR activation. We are currently determining whether this mechanism contributes to a furtherance of lipotoxicity and resistance to growth factor simulated osteogenesis.

***Disclosures: Martin L. Adamo**, None.*

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