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GENERAL MEETING INFORMATION

Registration

Registration desks will be open for new registrants in the Orange County Convention Center in the Registration Hall located in the Valencia Lobby on **Thursday, September 19 from 7:00 am – 6:00 pm.**

Organizing Committee

Peggy Cawthon, M.D., M.P.H.
Karyn Esser, Ph.D.
Gustavo Duque, M.D., Ph.D.

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This activity has been planned and implemented by Creighton University Health Sciences Continuing Education (HSCE) and The American Society for Bone and Mineral Research (ASBMR) for the advancement of patient care. Creighton University Health Sciences Continuing Education is accredited by the American Nurses Credentialing Center (ANCC), the Accreditation Council for Pharmacy Education (ACPE), and the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing education for the healthcare team.

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Online Evaluation to Receive CME

The online evaluation to receive CME will be available beginning Friday, September 20. You will receive an email from ASBMR with instructions on how to claim credit.

Target Audience

This meeting will bring together national and international investigators currently working in the field of muscle and bone, as well as young and established investigators, industry scientists, NIH intramural scientists and program staff, clinicians, endocrinologists and basic and translational researchers.

Learning Objectives

Upon returning home from the meeting, participants should be able to:

1. Provide an understanding of the quickly changing research landscapes that aim to understand the biological pathways involved in age-related muscle loss and declines in muscle quality is rapidly evolving, leading to revision of popular hypotheses and spurring new scientific directions.
2. Clarify the use of several competing definitions of sarcopenia has important clinical implications, as there is now an ICD-10 code for this condition. Novel ways to assess muscle mass in clinical settings may present opportunities to move this field forward.
3. Share sarcopenia and muscle knowledge across a broader range of sciences to encourage collaboration and will forge a path forward in this research area.

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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 Symposium on Muscle: The Path Forward to New Therapeutic Targets will provide informative and fully accurate content that reflects the highest level of scientific rigor and integrity.

ASBMR depends upon the honesty of the authors and presenters and relies on their assertions that they have had sufficient full access to the data and are convinced of its reliability.

Furthermore, ASBMR expects that:

- Authors and presenters will disclose any conflicts of interest, real or perceived.
- Authors of an abstract 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 author(s) or faculty.
- The planning, content and execution of abstracts, speaker presentations, slides, abstracts and reference materials should be free from corporate influence, bias or control.
- 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 always citing the best available evidence.

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The ASBMR is committed to ensuring the balance, independence, objectivity and scientific rigor of all its individually sponsored or industry-supported educational activities. Accordingly, the ASBMR adheres to the requirement set by ACCME that audiences at jointly-sponsored educational programs be informed of a presenter's (speaker, faculty, author, or planner) academic and professional affiliations, and the disclosure of the existence of any significant financial interest or other relationship a presenter or their spouse has with any proprietary entity over the past 12 months producing, marketing, re-selling or distributing health care goods or services, consumed by, or used on patients, with the exemption of non-profit or government organizations and non-health care related companies. When an unlabeled use of a commercial product, or an investigational use not yet approved for any purpose, is discussed during the presentation, it is required that presenters disclose that the product is not labeled for the use under discussion or that the product is still investigational. This policy allows the listener/attendee to be fully knowledgeable in evaluating the information being presented. The On-Site Program book will note those speakers who have disclosed relationships, including the nature of the relationship and the associated commercial entity.

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Meeting Evaluation

An online evaluation form for the ASBMR Symposium on Muscle: The Path Forward to New Therapeutic Targets will be available on the ASBMR Website at www.asbmr2019.org after the meeting and sent to you via email. 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.

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Future ASBMR Annual Meeting Dates

ASBMR 2020 Annual Meeting
Washington State Convention Center, Seattle, WA, United States
September 11 – 14, 2020

ASBMR 2021 Annual Meeting
Metro Toronto Convention Centre, Toronto, Ontario, Canada
October 1-4, 2021

THURSDAY, SEPTEMBER 19, 2019

CONTINENTAL BREAKFAST

8:00 am – 9:00 am **Room 304GH**

EMERGING BASIC SCIENCE IN MUSCLE

9:00 am – 10:30 am **Room 304EF**

Co-Chairs:
Karyn Esser, Ph.D., University of Florida, United States
Mark Hamrick, Ph.D., Georgia Health Sciences University, United States

9:00 am **Autophagy in Muscle**
Fabio Demontis, Ph.D., St. Jude Children's Research Hospital, United States
Disclosures: None

9:30 am **Mitochondrial Reticulum**
Russell T. Hepple, Ph.D., University of Florida, United States
Disclosures: None

10:00 am **Glucose Metabolism/Oxidative Stress**
Gordon Lynch, Ph.D., University of Melbourne, Australia
Disclosures: None

BREAK AND POSTER VIEWING

10:30 am – 11:15 am **Room 304GH**

EMERGING BASIC SCIENCE

11:15 am – 12:45 pm **Room 304EF**

Co-Chairs:
Robert Pignolo, M.D., Ph.D., Mayo Clinic, United States
Meghan McGee-Lawrence, Ph.D., Augusta University, United States

11:15 am **Evolving Roles for Satellite Cells in Skeletal Muscle Adaptation and Aging**
Charlotte Peterson, Ph.D., University of Kentucky, United States
Disclosures: None

11:45 am **Oxidative Stress on Muscles and Aging**
Holly van Remmen, Ph.D., Oklahoma Medical Research Foundation, United States
Disclosures: None

12:15 pm **Biomarkers from DMD Applying to Clinic**
Glenn Walter, Ph.D., University of Florida, United States
Disclosures: None

LUNCH AND POSTER VIEWING

12:45 pm – 2:00 pm **Room 304GH**

EMERGING TRANSLATIONAL RESEARCH

2:00 pm – 3:30 pm **Room 304EF**

Co-Chairs:
Gustavo Duque, M.D., Ph.D., University of Melbourne, Australia
Susanna Del Signore, United Kingdom

2:00 pm **Combined Anti-myostatin/Sclerostin**
Gary Krishnan, Ph.D., MSc, Eli Lilly, United States
Disclosures: Eli Lilly and Company, Employee, Stock Owner

2:30 pm **Effects of Exercise and Nutrition on Muscle**
Belinda Beck, Ph.D., Griffith University, Australia
Disclosures: None

3:00 pm **Targeting the Sarcomere in Neuromuscular Disease**
Fady Malik, M.D., Ph.D., FACC, Cytokinetics, Inc., South San Francisco, United States
Disclosures: None

BREAK

3:30 pm – 3:45pm **Room 304GH**

EMERGING CLINICAL RESEARCH

3:45 pm – 5:15 pm **Room 304EF**

Co-Chairs:
Peggy Cawthon, MPH, Ph.D., San Francisco Coordinating Center, United States
Bruce Troen, M.D., University of Buffalo, United States

3:45 pm **Competing Sarcopenia Definitions**
Cyrus Cooper, M.D., University of Southampton, United Kingdom
Disclosures: None

4:15 pm **Muscle Imaging: Structure and Function**
Bruce Damon, Ph.D., Vanderbilt University, United States
Disclosures: None

4:45 pm **The Roles of Myosteatosis in Aging and Disease**
Iva Miljkovic, M.D., Ph.D., FAHA, University of Pittsburgh, United States
Disclosures: None

CLOSING REMARKS

5:15 – 5:20 pm **Room 304EF**

RECEPTION AND POSTER VIEWING

5:20 pm – 6:00 pm **Room 304GH**

POSTERS

All posters presented at the ASBMR Symposium on Muscle: The Path Forward to New Therapeutic Targets will also be presented at the ASBMR 2019 Annual Meeting, September 20-23, in the Orange County Convention Center.
**Denotes Presenting Author*

P-01

Obesity History Influences Bone Health Independently from Diet Composition, but Bone can be Improved with Moderate Intensity Aerobic Exercise Training *Beatriz Bermudez[1],R Dana Carpenter[1],Rebecca M Foright[2],David M Presby[2],Ginger C Johnson[2],Janine A Higgins[2],Matthew R Jackman[2],Julie A Houck[2],Paul S MacLean[2],Vanessa D Sherk[2]. 1University of Colorado Denver, United States,[2]University of Colorado Anschutz Medical Campus, United States

Obesity is a result of physical inactivity and overconsumption of food; each can reduce bone formation rate. Yet, the effect of weight loss on bone health and the exercise mode and intensity needed to promote bone health during weight loss are controversial. Both outcomes may depend on the presence of metabolic dysfunction in bone and the habitual loading en- vironment at baseline. The purpose of this study was to test whether skeletal adaptations to aerobic exercise are influenced by obesity in sedentary rats raised on a high fat diet (HFD). Female Wistar rats (n=32, 8/grp) were fed ad libitum HFD to reveal Obesity Prone (OP) and Obesity Resistant (OR) groups. Rats were then calorically restricted to induce and maintain a 15-18% weight loss with medium fat diet (MFD) plus treadmill exercise (EX: 8-10w, 1h/d, 6d/w, 15m/min) or sedentary control (SED). Body composition was measured using quantitative magnetic resonance. BMD and BMC were measured by DXA. Hindlimb bone characteristics were quantified with microCT and mechanical testing. BMC increased in all groups after weight loss and switching to MFD (12.0±4.6% to 19.9±5.1%). Change in lean mass with MFD was different between OP (SED: -3.9±2.6g v EX: -6.2±2.6g) but not OR. OP lost more fat mass (OP:-57.9±4.1 v OR:-39.3±2.6 g). After weight loss, OP still had more fat mass (57.1±5.2 vs 27.1±4.4g) and tended (p=0.064) to have more lean mass than OR. Lean mass, but not fat mass, was positively associated (r=0.36-0.72) with most skeletal outcomes. Compared to SED, EX increased tibial cross-sectional area (CSA; 4.71±0.08 v 4.40±0.08 mm2), thickness (C.Th; 0.85±0.01 v 0.80±0.01 mm), and minimum bending resistance (Imin; 2.10±0.08 vs 1.84±0.09 mm4) and modulus, Zmin. Changes in bone outcomes were not different between OR and OP. However, when adjusting for lean mass, OR had higher tibias Imin (2.10±0.08 vs 1.84±0.09), and Zmin. Bones of OP rats were not as strong or tough as would be expected for their increased lean mass and body weight, indicating an effect of energy overconsumption that is independent from dietary composition. Moderate intensity exercise can improve bone health in OR and OP rats. Future work is needed to understand the loading-independent effects of obesity on bone accrual.
***Disclosures: Beatriz Bermudez**, None*

P-02

Collagen Fibril Plasticity is altered in Individuals with Type 2 Diabetes Mellitus and non-osteoporotic Bone Mineral Density *Eva Maria Wölfel[1],Anna Kornelia Siebels[1],Liang-Yu Ma[1],Annika vom Scheidt[1],Felix Nikolai Schmidt[1],Michael Amling[1],Katharina Jähn[1],Björn Busse[1],Elizabeth Zimmermann[2],Birgit Wulf[3],Herbert Mushumba[3],Klaus Püschel[3],Eric Schaible[4]. [1]University Medical Center Eppendorf, Dept. of Osteology and Biomechanics, Germany,[2]University Medical Center Hamburg-Eppendorf,Department of Osteology and Biomechanics; Shriners Hospitals for Children Canada, Montreal, Canada, Germany,[3]University Medical Center Eppendorf, Dept. of Forensic Medicine, Germany,[4]Advanced Light Source, Lawrence Berkeley National Laboratory, United States

Diabetes mellitus is associated with an increased fracture risk, yet the underlying mech- anisms are not identified. Patients with Type 2 Diabetes Mellitus (T2DM) usually present a normal to high BMD aggravating the identification of patients at risk. This points to an impaired bone quality which is likely to affect the plasticity and brittleness of diabetic bone. Here we utilize clinical imaging methods (CT, DXA) ex vivo in combination with analyses of multi-scale bone deformation to combine standard imaging techniques with data on the fibril- and tissue-scale mechanical resistance of diabetic bone. We hypothesize that the in- trinsic bone properties at fibrillar length scale are impaired in diabetic bone while presenting with normal BMD.From 21 T2DM-diagnosed cases (74.96±7.34 yrs) and 23 age-matched controls (73.71±7.6 yrs), the mid-diaphyseal femoral cortex and 12th thoracic vertebra were collected during autopsy with IRB approval. DXA measured vertebral osteoporotic fracture risk based on areal BMD (aBMD) in anterior-posterior (AP) and lateral (LAT) scan orienta- tions. High-resolution peripheral quantitative CT (HR-pQCT) measured cortical volumetric BMD (Ct.vBMD) and microstructure in femoral samples. Synchrotron small angle x-ray scattering (SAXS) of small cortical bone beams during simultaneous tensile testing (n=12 controls, n=9 T2DM) was used to investigate the mechanical deformation at multiple length-scales. T-tests were tested for significance between the groups (α=0.05).DXA data revealed no significant differences in aBMD between control and T2DM groups in AP (0.855±0.254g/ cm² vs. 0.867±0.177g/cm²) and LAT (0.678±0.186g/cm² vs. 0.598±0.134g/cm²). HR-pQCT data showed a tendency for lower Ct.vBMD in the T2DM group with 1032.13±42.28mgHA/ cm³ vs. 1061.86±30.2mgHA/cm³ in controls (p=0.061). Finally, tensile tests during SAXS measurements showed that T2DM cases present with a lower fibril strain compared to age- matched controls, where increasing tissue strain and lower stress at higher strain rates in the T2DM group were evident when compared to age-matched control groups.Taken together, our results not only point to current challenges to identify diabetic patients at fracture risk, but they also highlight changes in plasticity in diabetic bone leading to lower fibril strain compared to controls. These changes at the fibrillar length scale provide possible mecha- nisms leading to the increased fracture risk observed in T2DM individuals independent of BMD.
***Disclosures: Eva Maria Wölfel**, None*

P-03

Lumbar Spine Quantitative Computed Tomography (QCT) Is A Better Predictor of Vertebral Fracture in Boys with Duchenne Muscular Dystrophy (DMD) Than either DXA or Peripheral QCT *Nicola Crabtree[1],Michael Machin[2],Eleni Kariki[2],Raja Padidela[3],Imelda Hughes[3],Zulf Mughal[3],Michael Machin[4],Eleni Kariki[4],Nicholas Shaw[5]. 1Birmingham Women's and Children's Hospital NHS Foundation Trust, United Kingdom,[2]Central Manchester University Hospitals NHS Foundation Trust, United Kingdom,[3]Royal Manchester Children's Hospital, United Kingdom,[4]Central Manchester University Hospitals NHS Foundation Trust, United Arab Emirates,[5]Birmingham Women's and Children's NHS Foundation Trust, United Kingdom

Vertebral fractures are common in boys with DMD taking daily corticosteroids. Treat- ment is usually initiated when vertebral fractures have been identified. However, prophy- lactic treatment may be possible if reliable risk factors for vertebral fracture can be identi- fied. The aim of this work was to compare the diagnostic accuracy of three different bone strength assessment techniques in a cohort of DMD boys.Thirty-three boys with DMD (mean age=8.3(SD2.3) years) were followed over 3.4(SD1.8) years. All boys had size ad- justed lumbar spine DXA (BMAD), distal radius peripheral QCT (pQCT) and axial QCT at baseline and DXA and pQCT at follow-up. Lateral spine imaging was performed to identify incident vertebral fractures. Mobility status and cumulative corticosteroid (CS) exposure were also recorded. Logistic regression analysis was used to identify significant predictors of vertebral fracture and diagnostic testing using a threshold of Z 8 years was performed with all baseline values. At baseline 31/33 boys were mobile. During follow-up 20 boys sustained 48 mild and 7 moderate vertebral fractures and 13 boys remained fracture free(FF). There were no differences in cumulative CS exposure, height, weight or body mass index SDSs but boys who remained fracture free at follow up were on average 2.1(0.7) years younger than those who suffered a vertebral fracture (VF), p=0.02. There were no significant differences in baseline or follow up LS BMAD or distal radius pQCT bone densities. In contrast, VF boys had a 1.1(0.4)SD lower QCT Z-score than FF boys at baseline, p=0.005. Logistic re- gression demonstrated that QCT Z-score was the only significant bone predictor of fracture (Exp(B) = 0.4, p=0.01). However, age alone, regardless of bone density, was the strongest overall predictor of future fracture (Exp(B) = 1.9, p=0.02). In conclusion, axial QCT is the best predictor of vertebral fracture in boys with DMD taking daily corticosteroids. Given, the progressive nature of the disease and prolonged exposure to corticosteroids, it is not surprising that age was the strongest overall predictor of fracture. However, using QCT in combination with age may be a more robust approach when considering prophylactic treat- ment of vertebral fractures in this population.
***Disclosures: Nicola Crabtree**, None*

P-04

Molecular Mechanisms for Pamidronate Rescue of Post-burn Muscle Loss in Children *Fabrizio Pin[1],Lynda Bonewald[1],Andrea Bonetto[2],Gordon Klein[3]. 1Department of Anatomy and Cell Biology, Indiana University School of Medicine, United States,[2]Department of Surgery, Indiana University School of Medicine, United States,[3]Department of Orthopaedic Surgery, University of Texas Medical Branch, United States

Pamidronate has been shown to prevent inflammation-associated bone resorption fol- lowing burn injury. We previously reported that burned children who received pamidronate also had reduced muscle protein breakdown and positive muscle protein balance (Borsheim et al JBMR 2014). The aim of this study was to identify molecular mechanisms responsible for the beneficial effect of serum from pamidronate vs placebo/standard of care-treated burn patients on muscle. Mature myotubes, generated by differentiating murine C2C12 myoblasts for 5d, were exposed for 48h to 1% or 5% serum obtained from 3 groups of children: Normal unburned (N), burned receiving placebo/standard of care after 30d (B), and burned receiving standard of care and single-dose pamidronate after 30d (B+P) , n=5. Exposure to B and B+P serum caused dose-dependent myotube atrophy compared to N serum, reproducing the muscle wasting induced by burn injury in humans and animals (Quintana et al Inflamm Res 2015, Song et al Shock 2015). When C2C12 myotubes were treated with B+P serum, their size was partially rescued compared to myofibers exposed to B serum. At the molecular level, myotube atrophy induced by B serum was associated with reduced phosphorylaton of AKT and its downstream target mTOR, suggesting muscle anabolism was significantly downregulated. In addition, muscle protein catabolism appeared to be greater in the myo- tubes exposed to B serum. as shown by increased STAT3 activation, reduced phosphoryla- tion of FOXO3a, and overall elevated protein ubiquitination. In accordance with the effects on fiber size, B+P serum was able to partially restore the phosphorylaton of AKT and mTOR as well as reduce protein ubiquitination, but no differences were observed between B and B+P serum relative to STAT3 and FOXO3a activation. Anti-TGF beta (TGFb) added to B serum increased myotube size to that of B+P serum, while anti TGFb added to B+P se- rum did not further increase myotube size. These data show that the rescue effect of serum from pamidronate-treated burn patients appears related to the reactivation of the anabolic AKT-mTOR pathway. The reduction in protein ubiquitination associated with B+P serum is consistent with previously reported retrospective findings of stable isotope studies showing less muscle protein breakdown in the pamidronate-treated patients. The data suggest that bi- sphosphonate prevention of bone resorption prevents the release of muscle catabolic factors, such as TGFb into the circulation
***Disclosures: Fabrizio Pin**, None*

P-05

Muscle Trauma Activates Satellite Cells to Contribute to Ectopic Bone *Beth Bragdon[1],William Moore[1],Yu Liu[1],Amanda Molinelli[1],Louis Gerstenfeld[1]. [1]Boston University School of Medicine Dept of Orthopaedic Surgery , United States

Trauma to the musculoskeletal system can result in heterotopic ossification, a condi- tion where bone tissue develops in soft tissue. Satellite cells expressing Pax7 are the pre- dominant stem cell population within adult skeletal muscle and are implicated in skeletal muscle regeneration. Our previous research has shown no Pax7 derived cells in the fracture callus or ectopic bone induced by demineralized bone matrix (DBM). Questions however persist whether trauma can activate Pax7 cells to contribute to ectopic bone formation and whether muscle trauma will enhance the ability to induce ectopic bone. To answer these questions the DBM-induced ectopic bone model was used in conjunction with a muscle trauma model to characterize the contribution of Pax7 cells using in vivo linage tacking and quantify the DBM-induced ectopic bone volume. The tamoxifen inducible Pax7tm1(cre/ ER2)Gaka/J transgenic mice were crossed with B6.Cg-Gt(ROSA)26sor/J to create Pax7/ Ai14 reporter. These mice were subsequently crossed with B6,129S7-Rag1tm1Mom/J mice creating a transgenic reporter mouse allowing for the implantation of human DBM. Male and female mice received tamoxifen followed by a month washout period. Ectopic bone was induced by surgically implanting DBM (50 mg) with 0.1 µg of bone morphogenetic protein 2 (BMP2) on the femoral periosteum or within the skeletal muscle tissue of the upper hind limb. Following implantation, mice received a blunt force trauma at the surgical site. Ectopic bone was evaluated radiologically (plain film and micro-computed tomography) and histo- logically. These results were compared to previous studies of DBM-induced ectopic bone in the absence of muscle trauma. Between studies, no changes in bone volume observed at the periosteum site. Muscle trauma however did effect DBM/BMP2 induced ectopic bone for- mation in the muscle with 0.16 mm3 of ectopic bone being formed while none was observed in absence of muscle trauma. Intriguingly, muscle trauma resulted in the recruitment of Pax7 positive cells to the DBM-induced ectopic bone at both periosteal and skeletal muscle im- plant sites. These results suggest that trauma may sensitize the stem cell populations that contribute to ectopic bone to BMP induction and affect the plasticity of Pax7 satellite cells enabling them to contribute to ectopic bone formation**.** These studies provide basis for the identification of novel therapeutic targets to treat heterotopic ossification.

Disclosures: Beth Bragdon*, None*

P-06

Lack of osteocytic-miR2[2] promotes skeletal muscle mass growth in a sex- specific manner *Alyson Essex[2],Hannah Davis2,Padmini Desolthate 2,Andrea Bonetto[3],Lilian Plotkin[4]. [2]Indiana University School of Medicine Department of Anatomy and Cell Biology, Indiana Center for Musculoskeletal Health, United States,2Indiana University School of Medicine Department of Anatomy and Cell Biology, United States,[3]Indiana University School of Medicine Department of Surgery, Indiana Center for Musculoskeletal Health, United States,[4]Indiana University School of Medicine Department of Anatomy and Cell Biology, Indiana Center for Musculoskeletal Health, Roudebush Veterans Administration Medical Center, United States

Osteocytic microRNA21 (miR21) removal not only differentially alters cytokine pro- duction and bone mass, as well as osteoclast and osteoblast differentiation and activity in a sex-dependent manner in mice, but also produces sex-independent increases in mechani- cal bone strength. Because changes in bone remodeling and strength affect skeletal muscle through bone-muscle crosstalk, we aimed to investigate whether osteocytic miR21 deletion influences skeletal muscle. For this, we crossed miR21fl/fl mice with 8kbDMP1-Cre mice to obtain OtmiR21Δ and miR21fl/fl control mice. Long bones (femora and tibiae without bone marrow) were obtained from female and male OtmiR21Δ and miR21fl/fl littermate control mice, and cultured for 48h in the presence of 10%FBS/αMEM. Conditioned media (CM) was then collected to test the effects of factors released by bone cells on skeletal mus- cle cells. C2C12 cell differentiation was induced with 2% horse serum-containing medium and the differentiated myotubes were exposed to media containing 5% bone CM for 48h. Exposure to CM from female OtmiR21Δ bones led to a 12% increase in average fiber size compared to CM from miR21fl/fl mice. Interestingly, CM generated from male bones did not change myotube diameter. Further, mRNA levels of IL6, a cytokine known to induce skeletal muscle atrophy, were 40% lower in bones from female OtmiR21Δ compared to control mice; whereas a Multiplex array showed that the levels of active phosphorylated-Stat3 (p-Stat3), a transcription factor activated by IL6-type cytokines, were 26% lower in the miR21-deficient bones. On the other hand, no changes in IL6 or p-Stat3 levels were seen in male bones. Fur- ther, we found an 6% increase in lean body mass (Dxa/Piximus) only in female OtmiR21Δ mice, even though gastrocnemius muscle miR21 levels (qPCR) were similar in miR21fl/fl (0.05±0.02) and OtmiR21Δ (0.09±0.04) mice. To further study the role of osteocytic miR21 on skeletal muscle, we generated a new cohort of OtmiR21Δ mice. These mice exhibited increased soleus (42%) and gastrocnemius (21%) muscle weight only in females, while no changes were found in males. These data present a novel aspect of bone-muscle crosstalk in which osteocyte-derived miR21 negatively influences skeletal muscle size in female but not male mice. Further studies are underway to elucidate the potential role of IL6 and the novel mechanism(s) responsible for miR21 effects on the bone-muscle crosstalk.

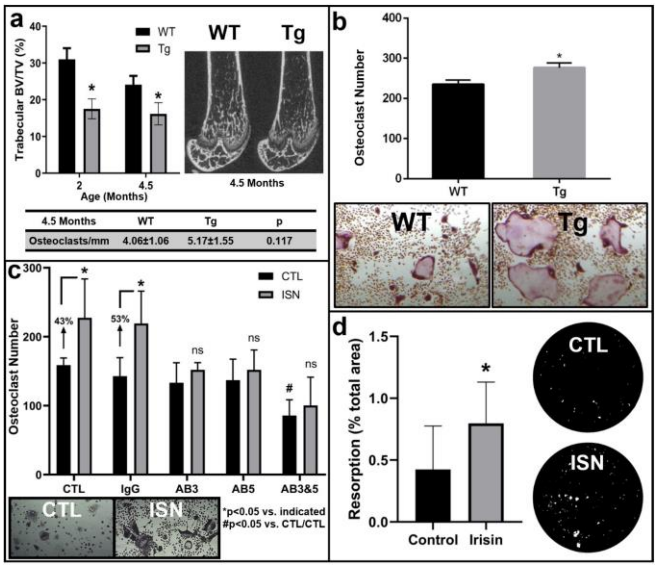
Disclosures: Alyson Essex*, None*

P-07

Irisin Directly Regulates Osteoclastogenesis via αV Integrin Receptors In Vitro and In Vivo *Eben Estell[1],Phuong Le[1],Yosta Vegting[1],Clifford Rosen[1],Hyeonwoo Kim2,Bruce Spiegelman2. [1]Maine Medical Center Research Institute, United States,2Harvard Medical School, Dana-Farber Cancer Institute, United States

Irisin, a myokine produced from proteolysis of FNDC5 on skeletal muscle during exer- cise, has been shown to increase cortical bone formation and prevent disuse-associated bone loss. In a genetic loss of Fndc5 model, we reported protection against ovariectomy-induced bone loss by blocking bone resorption and osteocytic osteolysis via αV integrin receptors. However, irisin has also been reported to exogenously suppress osteoclastogenesis. The present work addresses these contradictory studies by examining a genetic model of Fndc5 expression in muscle and irisin's effect on osteoclastogenesis in vitro.Forced over-expres- sion of Fndc5 using the McK promoter resulted in mice with significantly lower trabecular and cortical bone mass at 2 and 4.5 months of age. By histomorphometry at 4.5 months, bone volume was reduced and there was a trend toward greater number of osteoclasts per bone perimeter (Fig. 1a). Primary bone marrow stromal cells (BMSCs) from these mice cultured with mCSF and RANKL showed greater osteoclastogenesis versus wild type (Fig. 1b). To further characterize the effects of physiologic concentrations of irisin on osteoclast differentiation, we cultured primary BMSCs from C57BL/6J (B6) female mice with mCSF, RANKL, and 10 ng/mL irisin (ISN). Continuous irisin treatment for 7 days significantly increased osteoclast numbers compared to untreated controls. Treatment with antibodies for integrins αVβ3 (AB3) and αVβ5 (AB5) demonstrated that blocking either receptor complete- ly suppressed the effect of irisin, while blocking both receptors also significantly decreased baseline differentiation (Fig. 1c). Irisin treatment also showed increased total resorption for osteoclasts on Corning Osteo Assay Surface plates (Fig. 1d).The present work demonstrates that irisin acts via αV integrin receptors to drive increased osteoclastogenesis and reduced bone formation, supporting the protection from bone loss and inhibition of resorption ob- served in the genetic loss-of-function model. Further studies will determine the specific role of these integrin receptors in the irisin signaling pathway, and explore other mechanisms of irisin's effect on bone formation such as stimulation of clastokine release. Future work will seek to characterize the effect of irisin on each cell type in the remodeling unit, to more fully elucidate the role of this myokine in bone homeostatis and response to physical activity.

Disclosures: Eben Estell*, None*



P-08

Skeletal muscle mitochondrial dysfunction and whole body metabolic alterations in the osteogenesis imperfecta murine (oim) model of Osteogenesis imperfecta (OI) *Victoria L Gremminger[1],Elijah Miranda[1],Laura C Schulz2,R. Scott Rector [3],Charlotte L Phillips[4]. [1]Department of Biochemistry, University of Missouri, Columbia, MO [65]2[11], United States,2Department of Obstertrics, Gynecology, and Women's Health, University of Missouri, United States,[3]Departments of Nutrition and Exercise Physiology and Medicine- GI, University of Missouri; Harry S Truman Memorial VA Hospital , United States,[4]Departments of Biochemistry and Child Health, University of Missouri, Columbia, MO, United States

OI is a heritable connective tissue disorder with an incidence rate of approximately 1:15,000 births. Roughly 85% of the mutations leading to OI are found in the type I collagen genes: Col1a1 and Col1a2. OI can be characterized into four classical types (I-IV) with clin- ical severity of the disease varying greatly among the different types. Although bone fragility is the most common manifestation of the disease, innate muscle weakness is a major concern for OI, affecting roughly 80% of OI patients. Recently, severe mitochondrial dysfunction has been described in the homozygous osteogenesis imperfecta murine (oim/oim) mouse modeling moderately severe human OI type III. This mitochondrial dysfunction was evi- denced by significant reductions in gastrocnemius mitochondrial respiration rates (35-48% of wildtype [WT] mitochondrial respiration rates) and decreased citrate synthase activity. Previously, studies involving another mouse model of OI, the Col1a1Jrt/+ mouse, demon- strated a metabolic phenotype relative to

WT mice, including increased energy expenditure. While mitochondrial dysfunction has not been studied in patients, metabolic alterations have been described, especially cases of hypermetabolism. Because mitochondria play essential roles in the metabolism and bioenergetics of the cell, we have begun investigating several parameters associated with metabolic health including glucose tolerance, energy expendi- ture, VO2 consumption, VCO2 production, and respiratory quotient (RQ) in oim/oim mice. RQ is defined as the ratio of CO2 expelled to O2 consumed, and can predict the primary fuel sources being utilized. Preliminary data in male oim/oim mice suggests that while glucose tolerance is not altered, energy expenditure and VO2 consumption are increased whereas the RQ is reduced compared to WT mice; this indicates a change in metabolic fuel preference has occurred. In addition male oim/oim mice exhibit increased percentages of lean mass and reduced percentages of fat mass as well as reduced inguinal and gonadal fat pad weights. Furthermore, oim/oim mice do not display changes in food or water uptake during either day or night cycles. While further evaluation of these parameters is still required, preliminary data suggests that oim/oim mice may exhibit a metabolic phenotype with potential changes in metabolic fuel utilization in addition to the previously observed mitochondrial dysfunc- tion and compromised skeletal muscle force.

***Disclosures: Victoria L Gremminger**, None*

P-09

Zoledronic acid improves muscle function in mice treated with chemotherapy *Brian Hain[1],Baptiste Jude[1],Haifang Xu[1],Dallas Smuin[1],Edward Fox[1],John Elfar[1],David Waning[1]. [1]Penn State College of Medicine, United States

Carboplatin, a platinum-based chemotherapy, causes an array of side-effects including loss of bone mass, muscle atrophy, and muscle weakness. The goal of this study was to determine if bone-muscle crosstalk was mediating muscle weakness in mice treated with carboplatin. In order to determine the role that bone plays in carboplatin-induced muscle weakness, female Balb/C mice were treated with carboplatin and the anti-resorptive bisphos- phonate, zoledronic acid (ZA). 7 days later mice were euthanized and whole muscle contrac- tility was measured using the extensor digitorum longus (EDL) muscle. Specific force was significantly lower in carboplatin treated mice which was prevented by the addition of ZA. However, ZA did not rescue the loss of muscle mass or reduction in myofiber cross-sectional area (CSA) in mice treated with carboplatin. Carboplatin had severe effects on bone with reduced bone volume fraction (BV/TV), trabecular thickness (Tb.Th), and number (Tb.N), and increased trabecular separation (Tb.Sp) in the tibia and femur. ZA prevented the car- boplatin-induced loss of bone. TGFβ is stored in the mineralized bone matrix and released during bone resorption and results in muscle weakness. Therefore, carboplatin treated mice were also administered the anti-TGFβ antibody, 1D11. We found that 1D11 treatment pre- vented carboplatin-induced muscle weakness but did not prevent muscle atrophy. Finally, to establish the direct role of carboplatin on skeletal muscle function in the absence of bone resorption, mice were treated with carboplatin for 1 or 3 days. No changes in EDL mus- cle function, muscle mass, myofiber CSA, or bone microCT were observed compared to control mice. We confirmed carboplatin presence in the EDL muscle by platinum analysis using inductively coupled plasma mass spectrometry (ICP-MS). Platinum concentration was at a clinically relevant level of 1.0 ng/mg in muscle tissue 24 hours after injection with a steady decline to 0.6 ng/mg by 10 days, compared to 0.08 ng/mg in untreated mice. Our data suggests that carboplatin-induced muscle weakness is caused by bone resorption, while muscle atrophy is caused by direct effects on muscle. These findings are clinically relevant to prevent muscle weakness in cancer patients, and can be readily addressed using clinically available drugs (ZA).

***Disclosures: Brian Hain**, None*

P-10

Increased Expression of FGF2[1] from Dystrophic Skeletal Muscle Negatively Affects Bone Homeostasis in Dystrophic Mice *hongshuai Li[1],Baoli qian[1],ling wang[1],MaCalus Hogan[1]. [1]University of Pittsburgh, United States

Duchenne muscular dystrophy (DMD) is the most common muscular dystrophy seen in children. In addition to skeletal muscle, DMD also has a significant impact on bone. The pathophysiology responsible for bone deficiencies in DMD patients is still unclear. Recently, we have identified a novel bone-regulating cytokine, fibroblast growth factor 21 (FGF21), which is dramatically upregulated in skeletal muscle tissues from DMD animal models. In this study, we further investigated the expression and pathological function(s) of muscle derived FGF21 on bone homeostasis in DMD. Male Dystrophin/utrophin double-knockout (dKO) were used in this study. The levels of serum FGF21 were significantly higher in dKO mice compared to WT control mice (234 ± 57.56 pg/ml vs 51.57 ± 6.228 pg/ml). Further tests on FGF21 expressing tissues revealed that both FGF21 mRNA and protein expression were dramatically upregulated in dystrophic skeletal muscle (over 200-fold higher in pro- tein, and 20-fold increase in mRNA), while FGF21 mRNA expression was downregulated in liver and white adipose tissue (WAT) compared to WT controls. These data indicate that the increased circulating FGF21 in dystrophic mice mainly originated from dystrophic muscle. FGF21's action was blocked by IP injected neutralizing Abs. μCT analysis on weight-bear- ing bones (lumber spine, femur, and tibia) and on non-weight-bearing bones (parietal bone) demonstrated significantly increased bone mass and improved bone quality in dKO mice after FGF21 neutralization. Histomorphometric analysis showed decreased number and area of osteoclasts after FGF21 neutralization. These data suggest that muscle derived FGF21 negatively regulates bone homeostasis in dKO mice. To investigate the mechanism(s), we verified that FGFRs (1 to 4) and β-klotho (KLB)were expressed at detectable levels in bone tissue; and higher KLB levels were found in bone of dystrophic mice when compare to WT. Mechanistically, FGF21 directly promoted RANKL induced osteoclastogenesis from primary bone marrow macrophages as well as promoted adipogenesis while concomitantly inhibiting osteogenesis of bone marrow mesenchymal stem cells.This study demonstrates that dystrophic skeletal muscle expresses and secretes significant level of FGF21,

which negatively regulates bone homeostasis and represents an important pathological factor for bone abnormalities in DMD. The current study highlights the importance of myokine(s) in the pathogenesis of DMD.
***Disclosures: hongshuai Li**, None*

P-11

Lipocalin 2: a possible target in DMD-induced bone loss. *Marco Ponzetti[1],Argia Ucci[1],Antonio Maurizi[1],Annamaria Teti[1],Nadia Rucci[1]. [1]University of L'Aquila, Department of biotechnological and applied clinical sciences, Italy

Lipocalin 2 (Lcn2) is an adipokine linked to bone and energy metabolism. Its se- rum levels directly correlate to mechanical unloading and inflammation, both hallmarks of Duchenne Muscular Dystrophy (DMD). We therefore investigated the role of Lcn2 in muscle failure-induced bone loss, using the MDX mouse model of DMD. We found in- creased Lcn2 serum levels in MDX mice at 1(1.72-fold,p=0.006), 3 (1.98-fold,p=0.0049), 6 (1.42-fold,p=0.002) and 12 (2.06-fold,p=0.01) months of age. Consistently, Lcn2 mRNA was higher in MDX versus WT diaphragm (2.93-fold,p=0.014), quadriceps (2.8-fold,p=0.024), soleus (2.38-fold,p=0.042) and extensor digitorum longus (5.7-fold,p=0.005) muscles. Immunohistochemistry confirmed this and also showed that Lcn2 is mainly expressed by mononuclear cells in diaphragm and quadriceps, although positive muscle fibers were also observed. Based on these results, we ablated Lcn2 in MDX mice by cross-breeding them with Lcn2KO mice (MDXxLcn2KO, dMUT) and analysed their bone and mus- cle phenotype. MicroCT analyses showed higher trabecular Bone volume/Tissue volume (BV/TV) % (1.72-fold,p=0.0034) and number (1.61-fold,p=0.0056) in dMUT mice com- pared to MDX, likely due to reduced bone resorption, evaluated by serum CTx (0.37-fold, p=0.0026). Similar results were found at 6-month-old-mice, although also osteoblast num- ber (Ob.N) was increased in dMUT, compared to MDX (1.3-fold, p=0.032). Intriguingly, 3-month-old dMUT mice had higher muscle strength, evaluated by grip strength meter, (1.4-fold,p<0.0001). This was consistent with the fact that dMUT had increased intact mus- cle fibres (1.6-fold,p=0.0019) and strongly reduced serum creatine kinase levels, which indi- cates reduced muscle damage (0.097-fold,p<0.0001). Similar results were found in 6-month- old mice, where also quadriceps fibrosis was reduced (0.61-fold, p=0.0078). To strengthen these results, we inhibited Lcn2 by treating 2-month-old MDX mice with a Lcn2-blocking monoclonal antibody, which increased Tb.BV/TV (+22%,p=0.01), and reduced osteoclast surface/bone surface (0.58-fold, p=0.02) compared to MDX treated with irrelevant IgGs. On the muscle side, grip force was increased (1.2-fold,p=0.006) and diaphragm fibrosis was reduced (0.62-fold,p=0.0378) by the Lcn2-mAb. Increased BV/TV was also observed when treating 2-week-old MDX (+15%,p=0.0095) to simulate a preventive treatment. These re- sults point at Lcn2 as a possi muscle wasting in the
MDX mouse model of DMD.
***Disclosures: Marco Ponzetti**, None*

P-12

Distinctive role of muscle-specific ubiquitin ligases in bone microarchitecture *Vidyani Suryadevara[1],Monte Willis[1]. [1]IUPUI, United States

Introduction: People with osteoporosis have increased risk of fractures and abnormal bone quality due to reduced bone strength. Over the age of 50, one in two women and one in four men are prone to this bone loss. Ubiquitin proteasome system was found to regulate bone loss by modulating osteoblast differentiation and bone formation as well as formation of osteoclasts that contribute to bone resorption. Ubiquitin ligases (E3s) have been shown to play an important role in bone turnover and metabolism. Our group has identified multiple roles for the "muscle-specific" E3s MuRF1, MuRF2, MuRF3, and Atrogin-1, including the regulation of muscle mass in pathological and physiological cardiac hypertrophy and the regulation of metabolism via nuclear receptors in cardiomyocytes. Recent studies have re- ported MuRF1 mRNA expression in bone cells while evidence for muscle-bone interactions in sarcopenia and osteoporosis continues to be discovered. This led to the current investiga- tion of how MuRF1, MuRF2, MuRF3, and Atrogin-1 might play a role in bone homeostasis in vivo. Methods: The role of MuRF1, MuRF2, and MuRF3 was studied using MuRF1+/+, MuRF1+/- & MuRF1-/-; MuRF2+/+, MuRF2+/- & MuRF2-/-; and MuRF3+/+, MuRF3+/-& MuRF3-/- mice. The femoras were dissected, cleaned of soft tissue and wrapped in saline soaked gauze and frozen at -20°C. The femoras were assessed with microCT using the Sky- Scan system to look at the bone microarchitecture in the distal femur metaphysis (1mm) and mid-diaphysis region. Further three-point bending test was performed to assess the material and structural properties of the bone. Results: The cortical area at the femoral mid-diaphysis region was higher in MuRF1+/- mice compared to WT mice, which was further higher in MuRF1-/- mice. Also, the cortical thickness was higher in MuRF1+/- mice compared to WT mice. However, depletion of MuRF2 and MuRF3 in mice did not have any effect on the cortical parameters, thus highlighting the distinct role on MuRF1. Interestingly, the MuRF2 deficiency seems to alter the structural properties of the bone as seen in increase in toughness in MuRF2+/- mice compared to MuRF2+/+ mice. Conclusion: Muscle atrophy related E3s distinctly regulate bone microarchitecture and should be considered as a therapeutic target. Inhibiting MuRF1 and MuRF2 may protect against bone loss and should be considered in age-related bone loss, osteoporosis, and in other diseases that involve both muscle and bone loss.
***Disclosures: Vidyani Suryadevara**, None*

P-13

Changes in spinal bone density, back muscle size and visceral fat and their interaction following an ^{18}-month multi-component exercise program in older men *Anne-Frédérique Turcotte[1],Sonja Kukuljan2,Claudia Gagnon[3],Caryl Nowson[4],Robin M Daly[4]. [1]CHU de Québec-Université Laval, Canada,2Institute for Physical Activity and Nutrition, Deakin University , Australia,[3]CHU de Québec - Université Laval, Canada,[4]Institute for Physical Activity and Nutrition, Deakin University, Australia

Exercise is promoted as an effective approach to simultaneously improve BMD and muscle mass and reduce fat mass in older adults. Given that muscle and bone are biome- chanically linked, it is often assumed that any changes in muscle will lead to correspond- ing changes in bone. However, few interventions have evaluated whether exercise-induced gains in muscle mass or cross-sectional area (CSA) in older adults are positively associated with changes in bone. It is also unknown whether exercise-induced losses in fat, particularly excess visceral adipose tissue (VAT) which is reportedly detrimental to bone, also has beneficial effects on bone. In an 18-month RCT in older men, we previously found that a multi-component exercise program including progressive resistance training (PRT) was effective for improving lumbar spine (LS) trabecular volumetric BMD (net 2.2% gain). Therefore, in a secondary analysis, this study aimed to: 1) investigate whether the multi-component exercise program improved back muscle (psoas and erector spinae) CSA and reduced VAT, and 2) if any exercise-related changes in back muscle CSA and/or VAT were associated with changes in LS trabecular vBMD. Men (n=180) aged 61+/-7 years were randomized to exercise or no-exercise. The exercise consisted of high-intensity PRT (60- 85% max) with weight-bearing impact exercise performed 3 d/wk for 18 months. QCT was used to assess L1-L3 vBMD, back muscle and VAT CSA. Relative to no-exercise, exercise resulted in a 2.6% ($P<0.01$) net gain in back muscle CSA, with a trend towards a reduction in VAT (-1.9%, $P=0.09$). However, in both groups the changes in LS trabecular vBMD were positively associated with changes in back muscle CSA ($r=0.33$ to 0.46, $P<0.01$) and nega- tively with changes in VAT ($r=-0.24$ to -0.27, $P<0.05$). Further analysis revealed that there were no group differences in the slopes for the muscle-bone or VAT-bone changes. Pooling the data for both groups, multiple regression analysis revealed that both back muscle CSA and VAT were significant independent predictors ($P<0.01$) of the change in LS trabecular vBMD, explaining 21% of the variance. In conclusion, this study indicates that an 18-month multi-component exercise program in older men has beneficial effects on spinal trabecular BMD, back muscle size and to a lesser extent visceral fat, and that any improvements in muscle and visceral fat were associated with the changes in spinal BMD, but this was inde- pendent of the exercise intervention.

***Disclosures: Anne-Frédérique Turcotte**, None*

P-14

Effects of RANKL producing compared to non-RANKL producing tumors on muscle and bone. *Fabrizio Pin[1],Lynda F. Bonewald2,Andrea Bonetto[3]. [1]Department of Anatomy and Cell Biology, Indiana University School of Medicine, United States,2Department of Anatomy and Cell Biology, Indiana Center for Musculoskeletal Health, Indiana University School of Medicine, Indianapolis, IN, United States,[3]Department of Anatomy and Cell Biology; Department of Surgery; Indiana Center for Musculoskeletal Health; Simon Cancer Center, Indiana University School of Medicine, Indianapolis, IN, United States

Non-bone tumors can have dramatic effects on bone mass even in the absence of metas- tases. Many of these tumors induce skeletal muscle loss resulting in cachexia. To determine if cachexia and bone loss could be linked, two cancer models were examined, the ES-2 high-grade serous ovarian cancer and the C26 adenocarcinoma. As previously shown, ES-2 tumor growth was associated with body wasting, muscle atrophy and bone loss (Pin et al, JCSM 2018). The C26 model was also characterized by body and muscle wasting (Bonetto et al, JVE 2016), but here we show only a modest effect on bone mass (Tb.Th. -10% vs. C, $p<0.05$). In accordance, bone histomorphometry showed a dramatic increase in osteoclasts in the femurs from ES-2 hosts (OcS/Bs +149%, $p<0.01$; N.Oc/B.Pm +37%, $p<0.05$) and, though a trend, no significant effects were observed in the C26-bearing mice. Both models showed a dramatic increase in osteocyte apoptosis (+2800%, $p<0.001$ for ES2; +2500% $p<0.001$ for C26) and empty lacunae (+93%, $p<0.05$ for ES2; +100%, $p<0.05$ for C26). On the other hand, expression of sclerostin was downregulated in the bone from C26 tumor bearing mice (-90% vs. C, $p<0.001$), but no change was detected in osteocyte sclerostin in the ES-2 hosts. To identify the cause of the dramatic bone resorption, RANKL was found increased in the plasma of ES-2 mice (+420% vs. C, $p<0.05$), but decreased in the C26 hosts (-70% vs. C, $p<0.05$). Interestingly, the ES-2 cells were found to be a source of RANKL, as shown by high levels in the ascites of the ES-2 mice (140 ρg/ml) and highly elevated secre- tion by cultured ES-2 cells (+246%, $p<0.001$) compared to the C26. In order to investigate whether elevated RANKL could play a role not only in bone loss, but also in muscle wasting, we exposed mature C2C12 myotubes to 200 ng/ml recombinant RANKL. After 72 hours of treatment the myotubes exhibited marked fiber atrophy (-20% vs. C, $p<0.01$), also consistent with elevated TRAF6 and reduced activation of the anabolic AKT/mTOR pathway, thus suggesting that RANKL might be responsible for muscle wasting in the ES2 mice by directly impairing muscle protein anabolism. Overall, these studies emphasize that non-metastatic tumors can have differential effects on bone and suggest that treatment should be adjusted to target tumor type. Studies are underway to determine if anti-RANKL therapies may serve as strategies to reduce the negative effects associated with growth of the ES-2 tumor not only on bone, but also on muscle.

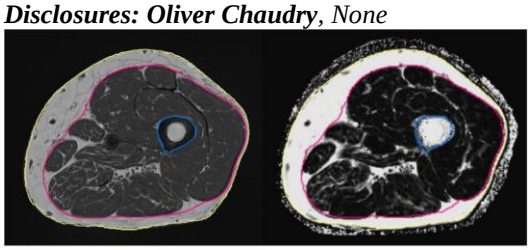
***Disclosures: Fabrizio Pin**, None*

P-15

Reproducible Segmentation of the Fascia and Quantification of Muscle Fat Fraction in the Thigh *Oliver Chaudry[1],Andreas Friedberger[1],Alexandra Grimm[1],Wolfgang Kemmler[1],Klaus Engelke[1]. [1]Institute of Medical Physics, University Erlangen-Nuremberg, Germany

BackgroundSarcopenia is characterized by a progressive loss of skeletal muscle mass, which is substituted by adipose tissue. Dual energy x-ray absorptiometry can only differen- tiate overall lean and fat mass. However, a local muscle analysis requires 3D imaging like magnetic resonance imaging (MRI). For analysis, appropriate 3D segmentation techniques are required. Our aim was to develop a segmentation method in oder to measure the fat con- tent of the thigh muscles in a combination of T1 weighted turbo spin echo (T1wTSE) and corresponding 6pt Turbo Spin Echo (TSE) Dixon Fat Fraction (FF) images.MethodsMRI acquisition was performed using a 3T scanner (MAGNETOM Skyrafit Siemens; 18-channel body surface coil). T1wTSE and 6pt TSE Dixon sequences were acquired at the mid-thigh (length 10 cm, 34 slices, voxel size 0.5x0.5x3.0 mm^3 and 0.8x0.8x3.0 mm^3, respectively). Since the fascia is difficult to detect in the FF images, the T1wTSE images were used for segmentation. This process was started using fuzzy c-mean clustering to differentiate mus- cle, adipose tissue, bone, background and fibrotic tissue located at interfaces or inside the subcutaneous fat. The resulting initial fascia surface was refined by enhancing 3D surface like structures representing fascia tissue. For this purpose a level set algorithm was applied to obtain a closed, accurately fitting 3D surface around the muscle tissue. If necessary, re- sults were manually improved slice by slice, guided by the prefiltered structures. Segmented masks were transferred to the FF images by 3D rigid registration (see figure). 15 sarcopenic (80±5 yrs) and 5 healthy (28±4 yrs) males were analyzed by three operators once, in addition one operator analyzed each dataset three times.ResultsInter- and intra-operator variability results are shown in the table as mean / root mean square of the standard deviation (RMS- SD) in units of the measured variable / coefficient of variation (RMS-CV) in %. Precision was excellent with errors below 0.5 %.ConclusionA highly automated segmentation for the fascia of the thigh was developed. The very low precision error showed that the impact of the user interaction on the segmentation was almost negligible. By transferring the segmenation of T1wTSE to the Dixon FF images, FF analysis with excellent precision can be achieved.

***Disclosures: Oliver Chaudry**, None*



	FF [%]	Volume FF [cm^3]	Volume T1 [cm^3]
Inter-	12.6 / 0.11 / 0.13	1183 / 10.9 / 0.14	1160 / 2.4 / 0.03
Intra-	12.6 / 0.06 / 0.08	1190 / 9.6 / 0.12	1160 / 0.87 / 0.01

P-16

KLF10 is a novel regulator of TCA cycle metabolism and mediates skeletal muscle cell differentiation and function.
*Malayannan Subramaniam[1],Michael Emch[1],Elizabeth Bruinsma[1],Molly Nelson Holte[1],John Hawse[1],Malek Kammoun[2],Sabine Bensamoun[2]. [1]Mayo Clinic, United States,[2]Université de Technologie de Compiègne, France

KLF10 is a member of the Krüppel-like family of transcription factors that is known to play important roles in homeostasis of the musculoskeletal system. KLF10 is highly ex-pressed in skeletal muscle, yet little is known regarding its functions in this tissue. siR- NA-mediated suppression of KLF10 in C2C12 myocyte precursor cells resulted in inhibition of myocyte differentiation and fusion as well as decreased mitochondrial numbers and ATP levels. RNAseq analysis identified altered expression of 504 and 612 genes following knock- down of KLF10 in undifferentiated and differentiated C2C12 cells respectively. Differential- ly expressed genes were associated with impaired MyoD signaling, calcium signaling, skel- etal muscle contraction and skeletal muscle function pathways. Mass-spectrometry based metabolomics analyses revealed alterations in a number of critical metabolites involved in the TCA cycle including lactate, succinate, aspartate and isocitrate following suppression of KLF10, potentially explaining some of the defects observed with regard to ATP production in KFL10 depleted cells. To translate these findings in vivo, the impact of KLF10 knockout on slow and fast twitch muscles of mice was assessed. Electron microscopic analyses re- vealed striking defects in skeletal muscle architecture including lack of I-bands, decreased mitochondrial numbers and changes in mitochondrial organization, size and shape. Interest- ingly, these phenotypes were only observed in female animals. We also assessed the activity of specific respiratory chain complexes in situ using skeletal muscle fibers isolated from WT and KLF10 KO mice. These studies revealed a significant decrease in respiration rates for complexes I, II and IV in KLF10 KO mice compared to WT littermates. Histochemical analysis of critical muscle related enzymes revealed a nearly complete lack of succinate dehydrogenase activity in KLF10 KO muscle. This enzyme is responsible for conversion of succinate to fumarate and its decreased activity in KLF10 KO muscle correlates well with the accumulation of succinate observed following knockdown of KLF10 in C2C12 cells. Phenotypically, treadmill studies revealed that female KLF10 KO mice, but not male mice, exhibit an early onset of exercise fatigue compared to WT controls. Taken together, these data implicate novel roles for KLF10 in regulating mitochondrial complex activity and function as well as skeletal muscle differentiation and metabolism.

***Disclosures: Malayannan Subramaniam**, None*

P-17

Bone-derived TGF-ß Impairs Glucose Metabolism and Insulin Release by Oxidation of RyR2 Ca2+Release Channel in Pancreatic ß-cells in the Setting of High Bone Turnover, Aging and High Fat Diet *Trupti Trivedi[1],Jenna Regan[2],Asma Bahrami[2],Jennymar Rojas[3],Steven Reiken[4],Sutha John[5],Sukanaya Suresh[5],Sreemala Murthy[5],Yun She[5],Gabriel Pagnotti[5],Sarah Tersey[6],Xu Cao7,Andrew Marks8,Carmella Evans-Molina9,Khalid Mohammad[1]0,Theresa Guise[11]. [11]Division of Endocrinology, Department of Medicine; Indiana University School of Medicine,Indianapolis,Indiana, United States,[2]Division of Endocrinology, Department of Medicine; Indiana University School of Medicine,Indianapolis,Indiana, United States,[3]Division of Endocrinology, Department of Medicine; Indiana University School of Medicine, Indianapolis, Indiana, United States,[4]Department of Physiology and Cellular Biophysics, Helen and Clyde Wu Center for Molecular Cardiology, College of Physicians and Surgeons, Columbia University, New York, United States,[5]Division of Endocrinology, Department of Medicine; Indiana University School of Medicine; Indianapolis, Indiana, United States,[6]Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN, United States,7Department of Orthopedic Surgery, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States,8Department of Physiology and Cellular Biophysics, Helen and Clyde Wu Center for Molecular Cardiology, College ofPhysicians and Surgeons, Columbia University, New York, United States,9Division of Endocrinology, Department of Medicine; Indiana University School of Medicine;Indianapolis, Indiana;Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN, United States,[1]0Division of Endocrinology, Department of Medicine; Indiana University School of Medicine; Indianapolis, Indiana, United States,[11]Division of Endocrinology, Department of Medicine; Indiana University School of Medicine; Indianapolis, Indiana, United States

Bone destruction in cancer or other pathology causes fractures, pain and muscle weak- ness.TGF-ß released from bone via osteoclastic bone resorption, acts systemically to cause skeletal muscle weakness through oxidation of sarcoplasmic reticulum Ca+2channel, ryan- odine receptor (RyR). Since oxidation of pancreatic-ß-cell RyR2 can impair insulin secre- tion and bone destruction results in systemic TGF-ß effects, we hypothesized that states of increased bone resorption with release of TGF-ß causes oxidation of pancreatic-ß-cell RyR2 to impair insulin secretion and glucose homeostasis.We studied the effects of bone-derived TGF-ß on the pancreas using a model of Camurati-Engelmann disease (CED), a bone dys- plasia with increased bone turnover. CED mice had increased circulating TGF-ß, reduced serum insulin, and increased pSmad2/3 in pancreatic-ß-cells. Forty-five-week-old CED mice fed high-fat diet (HFD) for 15 weeks developed glucose intolerance ($p<0.01$), and impaired insulin ($p<0.01$) secretion (glucose-stimulated insulin secretion in isolated islets) vs HFD- WT mice. Both HFD-CED and HFD-WT had insulin resistance (via ITT) compared with CED and WT fed low-fat diet (LFD). HFD-CED mice had higher fat mass ($p<0.001$), skel- etal muscle weakness ($p<0.001$), and reduced muscle-fiber diameter ($p<0.001$) compared to HFD-WT.HFD-CED mice had reduced bone mineral density ($p<0.001$)and increased cortical porosity ($p<0.01$) compared to HFD-WT mice. Impaired insulin secretion and skel- etal muscle weakness in HFD-CED mice were associated with Nox4-mediated oxidation of pancreatic-ß-cell RyR2 and skeletal muscle RyR1 respectively. TGF-ß had direct effects on insulin secretion as isolated pancreatic islets from WT mice treated with TGF-ß showed increased phosphoSmad3 and Nox4-mediated oxidation of RyR2. Further,TGF-ß decreased expression of pro-insulin (ins-1 and ins-2) mRNA.Collectively, these data suggest that states of increased bone destruction can disrupt glucose metabolism, pancreatic-ß-cell insulin se- cretion and causes muscle weakness, via systemic effects of bone-derived TGF-ß to oxidize RyR. These effects, exacerbated by HFD and aging, have implications for bone health as im- paired glucose metabolism and muscle weakness can further increase fracture risk. Blocking bone destruction, the release of TGF-ß and preventing RyR Ca2+leak in pathologic bone destruction should reduce fracture risk by improving hyperglycemia, muscle weakness and subsequent bone quality.

***Disclosures: Trupti Trivedi**, None*

P-18

Vitamin D receptor signaling prevents the adverse actions of glucocorticoid excess in bone, skeletal muscle, and the heart, by interfering with the atrogene pathway. *Amy Y Sato[1],Meloney Cregor[1],David L Halladay[1],Karyn A Esser[2],Munro Peacock[3],Monte S Willis[4],Teresita M Bellido[5]. [1]Department of Anatomy and Cell Biology, Indiana University School of Medicine, United States,[2]Department of Physiology and Functional Genomics, University of Florida College of Medicine, United States,[3]Department of Medicine, Division of Endocrinology, Indiana University School of Medicine, United States,[4]Indiana Center for Musculoskeletal Health, University of Indiana School of Medicine, United States,[5]Department of Anatomy and Cell Biology; Department of Medicine, Division of Endocrinology, Indiana University School of Medicine; Roudebush Veterans Administration Medical Center , United States

Glucocorticoid (GC) excess has adverse effects in bone and skeletal muscle that lead to increase in fracture risk. GCs upregulate in both tissues the expression of the proteasomal degradation inducers MuRF1, atrogin1, and MUSA1 (atrogenes), thus providing a targetable pathway to prevent GC musculoskeletal actions. We investigated here whether Vitamin D receptor (VDR) activation, which has beneficial effects in bone and may prevent muscle weakness and falls, blocks GC-induced activation of the atrogene pathway and prevents bone and muscle loss. 1,25D3 (calcitriol) prevented dexamethasone (dex)-induced atrogene expression ex vivo in murine bone and muscle organ cultures. In vivo, 1,25D3 or the less hypercalcemic VDR ligand eldecalcitol-71 (ED) at 50ng/kg/d 5x/wk prevented the decrease in BMD induced by GC (2.1 mg/kg/d prednisolone pellets, 8 wks, N=10-12) in 4mo C57Bl6 female mice and simultaneously prevented the increase in atrogene expression in bone. Fur- ther, 1,25D3 and ED prevented GC-mediated increase in the bone resorption marker CTX and the decrease in the bone formation markers P1NP and OCN. Both VDR ligands also pre- vented GC-induced loss of lean body mass, a muscle mass index measured by DEXA, and the decrease in muscle strength, assessed in vivo

by plantarflexion torque function testing. Further, consistent with clinical evidence, in vivo echocardiography demonstrated that GC induced cardiac dysfunction in our mouse model of GC excess. GC-treated mice exhibited decreased left ventricular (LV) anterior and posterior wall thickness at diastole (relaxed) and systole (contracted). In addition, GC increased LV volume at systole, reduced ejection frac- tion, and decreased fractional shortening, all indexes of inefficient heart contraction. Both VDR ligands prevented LV wall thinning and the dysfunctional heart contraction induced by GC. GC or the VDR ligands did not alter total heart mass, LV mass, or heart rate. Further, GC increased atrogene expression also in the heart in vivo and ex vivo in murine LV organ cultures. 1,25D3 prevented GC-induced atrogene expression ex vivo, and both 1,25D3 and ED prevented the increase in MuRF1 induced by GC in vivo. These findings demonstrate that atrogene upregulation is a common mechanism underlying the damaging effects of GC excess in bone, skeletal muscle, and heart; and that activation of VDR signaling preserves tissue mass and function by interfering with GC actions on the atrogene pathway in each of these organs.
***Disclosures: Amy Y Sato**, None*

P-19

PAI-1 accelerates sarcopenia and ageing-related osteoporosis. Aihemaiti[1],Naoki Yamamoto[1],Alkebaier Aobulikasimu[1],Hiroki Ochi[1],Shingo Sato[1],Atsushi Okawa[1],Yoshinori Asou[1],Takuya Oyaizu[2],Kunikazu Tsuji[3],Toshio Miyata[4]. [1]Department of Orthopedics Surgery, Tokyo Medical and Dental University, Japan,[2]Department of Orthopedics Surgery, Tokyo Medical and Dental University,, Japan,[3]Department of Cartilage Regeneration, Tokyo Medical and Dental University, Japan,[4]Department of Molecular Medicine and Therapy, United Centers for Advanced Research and Translational Medicine, Tohoku University Graduate School of Medicine , Japan

Ageing is a risk factor for osteoporosis and sarcopenia. In recent years, there is mount- ing evidence that senescent cells contribute to ageing and age-related disease by generating a low-grade inflammation state (senescence-associated secretory phenotype-SASP). Plas- minogen activator inhibitor-1(PAI-1), a serpin (serine protease inhibitor), is a 50-kDa single chain glycoprotein that inhibits urokinase/tissue plasminogen activator. PAI-1 is not only a marker but also a mediator of cell senescence. We previously reported a small molecule PAI- 1 inhibitor prevents ovariectomy-induced bone loss, however, the effects of PAI-1 inhibitor on musculoskeletal ageing is unknown. In this study, we examined the effects of small mol- ecule PAI-1 inhibitor, TM5484, on ageing-related osteoporosis and sarcopenia using aged mouse model. C57BL/6J male mice in six months old were divided into two groups, such as ΔP-group in which mice were administered TM5484 in diet (0.01%, 100mg/kg d-1 in MR stock) for six months, and control group fed MR stock. At twelve months of age, we evaluated grip strength by using a specific grip meter. In control group, the grip strength was decreased compared with young mice, however, ΔP-group showed significantly higher grip compared with the control group. Next, we evaluated maximum twitch and tetanic isometric tensile strengths of gastrocnemius under anesthesia by stimulating the common tibial nerve at 1Hz (twitch) or 50 Hz (tetanus) using a surface electrode. Both maximum twitch and tetanic isometric tensile strengths were higher in ΔP-group compared to control as well. The mice were sacrificed after muscle strength evaluation. The body weight and the weights of quadriceps muscles and gastrocnemius muscles were similar between the control group and Δ P-group. Micro-CT analysis indicated BV/TV ratio of cancellous bone in both distal fem- ora and lumbar spine was significantly higher in ΔP-group compared to control. BMD in the mid-shaft of femora was also higher in ΔP-group. In conclusion, PAI-1 inhibitor TM-5484 prevented ageing -related bone loss and muscle power weakness in mouse model of ageing. We are currently analyzing the molecular mechanisms of the effect of TM-5484 on bone and muscle metabolism. Our results suggest that PAI-1 blockade via a small molecule inhibitor is a new therapeutic approach to prevent sarcopenia and osteoporosis during aging progress.
***Disclosures: Aidehamu Aihemaiti**, None*

P-20

D3Cr muscle mass, DXA appendicular lean mass (ALM), and their relationships with "bone quality" and "muscle quality" in older men *Peggy Cawthon[1],Sheena Patel[1],Steven Cummings[1],Eric Orwoll[2],Andrew Burghardt[3],Kate Duchowny[3],Lisa Langsetmo[4],Kristine Ensrud[4],Elsa Strotmeyer[5],Joe Zmuda[5],Jane Cauley[5],Miljkovic Iva[5],Nancy Lane[6],William Evans7. [1]California Pacific Medical Center, Research Institute, United States,[2]Oregon Health and Sciences University, United States,[3]University of California, San Francisco, United States,[4]University of Minnesota, United States,[5]University of Pittsburgh, United States,[6]University of California, Davis, United States,7University of California, Berkeley, United States

Low muscle mass by D3-creatine dilution (D3Cr muscle mass) is associated with an increased risk of fractures in older men, while there is no association between low appen- dicular lean mass (ALM) by dual x-ray absorptiometry (DXA) and risk of fracture. DXA measures lean mass (including water, muscle, and non-bone non-fat tissue), not muscle mass per se. We posit that the measurement error inherent in DXA's inaccurate approximation of muscle mass explains these discrepant results. Herein we describe how D3Cr muscle mass vs. DXA lean mass differentially relate to measures of "bone quality" [bone mineral density (BMD) and strength by DXA and high resolution peripheral computed tomography (HRpQCT)] and "muscle quality" [calf muscle cross-sectional area (CSA), density and fat by peripheral computed tomography (pQCT)]. In a subset of MrOS men with complete data for pQCT, HRpQCT, DXA and D3Cr muscle mass at Year 14 visit (N=177), we calculated partial correlations (weight, height adjusted) between D3Cr muscle mass or DXA ALM with bone density (DXA femoral neck and total hip aBMD; HRpQCT distal radius and tibia integral BMD) and strength (HRpQCT distal radius and tibia failure load). We also calcu- lated partial correlations between D3Cr muscle mass or DXA ALM with pQCT calf muscle measures (density, intermuscular fat, total calf fat, and muscle CSA) and DXA total body % fat. D3Cr muscle mass was positively correlated with bone strength and BMD at the distal tibia and radius (but not the total hip or femoral neck, Table), whereas DXA ALM was only significantly correlated with bone strength at distal sites. In addition, D3Cr

muscle mass and DXA ALM were positively correlated with calf muscle CSA and negatively correlated with calf and percent total body fat. The correlation between D3Cr muscle mass and calf mus- cle density was stronger than the correlation between DXA ALM and calf muscle density. Only D3Cr muscle mass was negatively correlated with calf visible intermuscular fat. In summary, D3Cr muscle mass is positively correlated with muscle size and density, as well as measures of bone strength and density at distal skeletal sites. Associations between DXA ALM with muscle density, bone density and bone strength were weaker in magnitude; DXA ALM was unrelated to bone density. These data suggest that the relation of D3Cr muscle mass with "muscle quality" and "bone quality" is more robust than is the relation of DXA ALM with these measures.

***Disclosures: Peggy Cawthon**, None*

Table. Pearson (or Spearman) correlations between D_3Cr muscle mass or DXA ALM with calf muscle; fat; and bone density and strength measures

Calf muscle & fat measures	D_3Cr muscle	DXA ALM	Bone density & strength measures	D_3Cr muscle	DXA ALM
pQCT calf muscle cross-sectional area	**0.55**	**0.65**	HRpQCT distal tibia integral vBMD	**0.17**	-0.04
pQCT calf muscle density (total)	**0.49**†	**0.29**†	HRpQCT distal tibia failure load	**0.25**	**0.15**
pQCT visible calf intermuscular fat	**-0.31**†	-0.13†	HRpQCT distal radius integral BMD	**0.19**	0.05
pQCT calf muscle density (w/o visible fat)	**0.36**	**0.22**	HRpQCT distal radius failure load	**0.23**	**0.16**
pQCT total fat (calf)	**-0.48**†	**-0.43**†	DXA femoral neck aBMD	0.08	-0.05
DXA whole body percent body fat	**-0.48**	**-0.77**	DXA Total hip aBMD	0.15	0.01

Bold text indicates p<.05; Partial Pearson correlations reported except for skewed variables where partial Spearman correlations reported (indicated by †); adjusted for height and weight

P-21

Effects of Cocoa Supplementation on Muscle Function in Older Persons: Preliminary Results from a 3-month Pilot Randomized Controlled Trial *Deborah Kado[1],Jian Shen[1],David Wing[1],Sandra Rabat[1],Jeanne Nichols- Forward[1],Francisco Villarreal[1]. [1]University of California San Diego, United States

Skeletal muscle mass and function tends to decline with age, leading to a propensity for developing adverse outcomes including falls and fractures. Other than exercise, there are no pharmacologic strategies available to combat age-related muscle functional decline, but ani- mal studies demonstrate that (-)-epicatechin, the primary flavonoid in cacao, enhances skele- tal muscle and function to levels comparable to the positive effects triggered by exercise. The primary aim of this exploratory 3-month pilot double blinded randomized controlled trial was to test whether older persons, aged 65-80, treated with a cocoa supplement (Cocoavia®) versus placebo, would demonstrate improved muscle function measured by grip strength, timed up and go (TUG) testing, and quadriceps power, torque and fatigue, assessed by the Biodex System 4 Pro (Multi-Joint System Dynamometer). Twenty-one women and 13 men of mean age 72 (SD = 4.6) completed the study. There were no significant group differences in any of the baseline characteristics including age, sex, BMI (27 kg/m2, SD 4.7), race (89% white), self-reported physical activity, alcohol, tea or chocolate consumption, and no differences in any of the muscle function measures. The study participants were generally healthy, with 91% reporting good, very good, or excellent health. There were no smokers, 68% reported no alcohol intake, 46% consumed no dark chocolate, and 41% never drank tea. 70% of the participants reported engaging in at least moderate or vigorous activities in the past week. After 3 months of treatment with either Cocoavia® or placebo, there were no significant differences between groups in functional measures of grip strength and TUG, nor changes in measures of muscle power or fatigue. Notably with the clinical measures of grip strength and TUG, there was a mean decline noted in both groups, with a trend towards less decline in grip strength in those who took the Cocoavia®(see Table). Maximum peak torque extensor and flexion power improved in the treatment group, but there was only a slight trend towards significance compared to the placebo group. These preliminary study results suggest that functional decline does occur over even only a 3 month period in older persons, and that there may be some benefit of the epicatechin in mitigating that loss, though larger and perhaps longer studies are warranted to co e over 3 months of muscle function parameters (Mean ± SD).

***Disclosures: Deborah Kado**, None*

Change in Muscle Parameter	Cocoa Group	Placebo Group	P-value
Maximum Grip Strength (kg)	-0.28 ± 2.4	-1.6 ± 2.6	0.14
Timed Up and Go (TUG), seconds	-0.16 ± 0.7	-0.10 ± 0.89	0.83
Maximum Peak Torque Extensor (Ft-Lbs)	0.74 ± 3.8	-1.9± 5.0	0.13
Maximum Peak Torque Flexion (Ft-Lbs)	0.9 ± 2.5	0.01 ± 4.0	0.49
Quadriceps Muscle Fatigue (Extension)*	-8.1 ± 21.7	-7.6 ± 15.7	0.95
Quadriceps Muscle Fatigue (Flexion)*	-5.8 ± 8.3	-1.9 ± 16.5	0.44

*Percent decline in work during final third of exercise

P-22

Is low impact physical activity associated with lower limb bone and muscle outcomes? Results from the Hertfordshire Cohort Study *Camille Parsons[1],Elaine Dennison[1],Cyrus Cooper[1],Kate Ward[1],Jon Tobias[2]. [1]MRC Lifecourse Epidemiology Unit, University of Southampton, United Kingdom,[2]University of Bristol, United Kingdom

Numerous studies have shown the positive benefits of physical activity (PA), in particu- lar medium and high impact PA has been shown to increase bone mineral density and muscle strength. In this study we examined relationships between low impact PA, lower limb bone and muscle outcomes in community dwelling older adults.The Hertfordshire Cohort Study, consists of men and women

born in 1931-9 in the UK county of Hertfordshire. In 2011-12, participants underwent a pQCT scan of the tibia (4%, 38%, 66% sites) for measures of BMD, bone and muscle size, muscle density (Stratec 2000); jump power, velocity and force were assessed from a two-footed countermovement jump on a Leonardo Mechanography Ground Reaction Force Platform (Novotec Medical GmbH). Participants wore triaxial ac- celerometers for 7-days and counts of low (0.5-1.0g), medium (1.0-1.5g) and high (>1.5g) impact activity were calculated. Linear regression was used to quantify associations between bone and muscle parameters, and low impact PA. To avoid multi-collinearity problems, a standardised residual of medium- and high- impact PA adjusted for low impact PA was de- rived. Results are presented B (95% confidence interval).105 participants, mean(SD) age 76.1(2.7) years, wore accelerometers; jumping mechanography (JM) was available for 78 participants(65.4% male). Low impact PA was positively associated with maximum power (w/kg) (1.82(0.92, 2.72), and maximum relative velocity (m/s) (0.09 (0.04, 0.13)), with rela- tionships remaining after adjustment for age, sex and medium and high impact PA. Signifi- cant positive associations were found between total area (mm2) at 4% slice and low impact activity counts (38.7(11.8, 65.7)). Cortical thickness (mm), cortical area (mm2) and polar strength strain index (mm3) were also positively associated with PA at 38% slice ((0.2 (0.6, 0.3) (10.5 (2.4, 18.6)) (60.4 (1.4, 119.5))). Increased low impact PA was significantly associ- ated with increased muscle density (0.48 (0.04, 0.92)) but not calf muscle area. Relationships with cortical area, cortical thickness and calf muscle density were robust to adjustment age, sex, BMI and medium and high impact PA.Low impact physical activity was associated with improved parameters of tibial bone and calf muscle strength assessed by pQCT. In addition, those with higher counts of low impact activity had better muscle power and velocity. These data suggest that maintaining any low impact activity is beneficial to bone and muscle in an elderly population.
***Disclosures: Camille Parsons**, None*

P-23

1,25-Dihydroxyvitamin D Induces Intracellular Calcium Rise in Normal Human Skeletal Muscle Myotubes via Phospholipase C-γ1 *Dexing Dai[1],Zhongjian Xie[1]. [1]Department of Endocrinology and Metabolism, Hunan Provincial Key Laboratory of Metabolic Bone Diseases, National Clinical Research Center for Metabolic Disease, the Second Xiangya Hospital, Central South University, China

1,25-Dihydroxyvitamin D [1,25(OH)2D] has been shown to induce intracellular calci- um rise in skeletal muscle myotubes. However, the underlying mechanism is unclear. The goal of the present study was to investigate the mechanism by which 1,25(OH)2D induces intracellular calcium rise in primary human skeletal muscle myotubes. To reach this goal, we isolated myoblasts from human skeletal muscle and induced myoblast differentiation into myotubes under low serum conditions. Then, we examined the effect of 1,25(OH)2D on the levels of intracellular calcium in myotubes. The results showed that 1,25(OH)2D induced a sustained intracellular calcium rise in myotubes. However, these effects were abolished when the internal Ca2+ store was depleted by thapsigargin, a Ca2+-ATPase in- hibitor. These data suggest that 1,25(OH)2D induced intracellular calcium rise is calcium store dependent. Since phospholipase C-γ1 (PLC-γ1) is one of the most abundant isoforms of phospholipase C in human skeletal muscle myotubes, we examined whether PLC-γ1 me- diates 1,25(OH)2D-induced intracellular calcium rise in myotubes. The results showed that knockdown of PLC-γ1 blocked 1,25(OH)2D-induced intracellular calcium rise in myotubes, suggesting that 1,25(OH)2D induces intracellular calcium rise via PLC-γ1 in myotubes. In conclusion, 1,25(OH)2D induces intracellular calcium rise via PLC-γ1 in human skeletal muscle myotubes.
***Disclosures: Dexing Dai**, None*

P-24

Aberrant muscle tissue repair by mutant ACVR1 FOP progenitor cells *Alexandra Stanley[1],Elisia Tichy[1],Foteini Mourkioti[1],Eileen Shore[1]. [1]University of Pennsylvania, United States

In the rare genetic disease fibrodysplasia ossificans progressiva (FOP), progenitor cells are mis-regulated to differentiate to heterotopic extra-skeletal bone in connective tissues. Mutations in the BMP type I receptor ACVR1/ALK2 cause FOP, with the R206H muta- tion as the most prevalent. This increases BMP signaling to promote increased downstream chondro-/osteogenic gene expression and heterotopic ossification (HO) formation in FOP patients. HO formation is often initiated by injury to skeletal muscle. In the conditional knock-in mouse model for ACVR1R206H, HO develops within skeletal muscle following cardiotoxin (CTX) injury. Injured Acvr1R206H/+ muscle tissue becomes more fibrotic and does not repair as efficiently as Acvr1+/+ muscle tissue, indicating that skeletal muscle repair is impeded by the ACVR1R206H mutation. The regenerative potential of skeletal muscle is dependent on the function of muscle stem cells (MuSCs). Non-myogenic mes- enchymal stem cells (or fibro/adipogenic progenitors, FAPs) are in close association with regenerating muscle fibers and are a source of pro-myogenic signals that support muscle re- generation. To examine the effect of the ACVR1R206H mutation on proliferation of MuSCs and FAPs, we isolated the two populations from uninjured and CTX injured muscle using fluorescent activated cell sorting (FACS) and determined that Acvr1+/+ and Acvr1R206H/+ MuSCs and FAPs proliferated similarly. In vitro MuSC differentiation assays showed that Acvr1+/+ MuSCs cultured in myogenic media differentiate normally, forming branching myofibers (high fusion index) by day 7 of culture, but Acvr1R206H/+ MuSCs form underde- veloped fibers that fail to fuse (low fusion index). However, Acvr1+/+ FAPs co-cultured with Acvr1R206H/+ MuSCs induce proper myofiber formation and fusion, rescuing the mutant MuSCs. In contrast, Acvr1R206H/+ FAPs cultured with Acvr1+/+ MuSCs form undevel- oped fibers with a low fusion index suggesting that the FAP population under the influence of the ACVR1R206H mutation contributes largely to the poor muscle regeneration in FOP le- sions. Demonstrating the influence of the mutant ACVR1R206H tissue environment in vivo, Acvr1+/+ MuSCs transplanted into injured Acvr1R206H/+ skeletal muscle tissue showed

decreased engraftment. Taken together, our data support the impact of the ACVR1R206H FOP mutation on the differentiation capacity of MuSCs to regenerate skeletal muscle and the impact of FAPs on the function of MuSCs.
***Disclosures: Alexandra Stanley**, None*

P-25

Is LBX[1] Playing a Role in the Differentiated Paraspinal Muscle Phenotypes and Muscle-bone Interaction in Adolescent Idiopathic Scoliosis (AIS) *Yujia Wang[1],Ka-Lo Cheng[1],Jiajun Zhang[1],Tsz-ping Lam[1],Alec LH Hung[1],Jack CY Cheng[1],Wayne YW Lee[1],Zhenhua Feng[2],Leilei Xu[2],Yong Qiu[2]. [1]Department of Orthopaedics and Traumatology, SH Ho Scoliosis Research Laboratory, The Chinese University of Hong Kong, Hong Kong,[2]Spine Surgery, Nanjing Drum Tower Hospital, Nanjing University, China

Purpose: AIS is a three-dimensional spinal deformity with unclear etiopathogene- sis. LBX1 is so far the only multi-centers validated AIS predisposing gene. The posterior paraspinal muscles provide dynamic stability to the spinal column and their imbalance has been speculated as an important factor in AIS etiopathogenesis. It is poorly understood how LBX1 contribute to the abnormal paraspinal muscle phenotypes and onset/progression of AIS. We hypothesized that there is differentiated expression of LBX1 between paraspinal muscles at the concave and convex side of the apex of major curve in AIS, and such dis- crepancy could lead to imbalance myoblasts activities resulting in differentiated muscle phenotypes, and potentially influence muscle-bone interaction via differentiated myokines expression.Method: Paraspinal muscles from AIS and age- and curvature-matched CS (con- genital scoliosis) patients were collected for fiber types analysis and staining of satellite cell marker. Biopsies were also subjected to RT-qPCR and western blot to validate muscle related markers. Non-scoliosis control biopsies were included in this study as well to serve as normal reference. HSMM (human skeletal muscle myoblast) cells were used as cellular model for LBX1 gain- and loss-of-function study in vitro.Result: Muscle fiber types analysis showed cross-sectional area of type I and type IIX/IIAX fibers were significantly different between AIS concave and convex but not in the two sides of CS. mRNA expression levels of myogenic markers were significantly different between the convex and concave sides in AIS but not in CS (Fig 1). Gain- and loss-of-function study in HSMM showed that LBX1 could negatively regulate myoblast fusion (Fig 2) and impair myokines expression.Conclusion: Our results demonstrated for the first time, asymmetric muscle profiles and different expres- sion levels of LBX1 between the concave and convex sides paraspinal muscles in AIS. In vitro study supported the hypothesis that abnormal LBX1 expression could modulate myo- blast activities and myokines expression, which may contribute to the observed imbalance of paraspinal muscles as well as structural abnormalities of osteocyte lacuno-canalicular network in two sides of facet joints. Further investigation with appropriate animal models is warranted to explore if abnormal activity of LBX1 could result in distinct muscle pheno- types and asymmetric bone qualities thus affect the progression of spine curvature in AIS.
***Disclosures: Yujia Wang**, None*

Fig. 1. Myogenic markers in paraspinal muscle biopsies

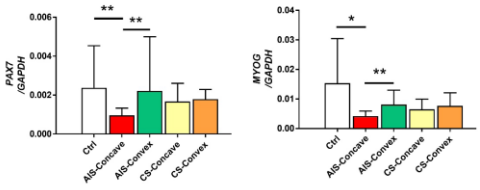
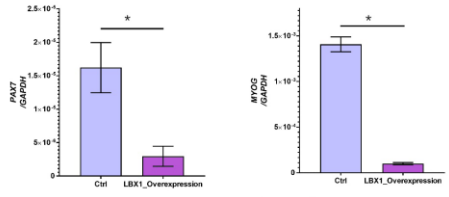


Fig. 2. Myogenic markers in gain-of-function cell model



Results are shown with mean±SD
Mann-Whitney *U*, *p-values≤0.05, **p-values≤0.01

P-26

Gli1 labels a subpopulation of FAP cells that respond to muscle injury *Lutian Yao[1],Elisia Tichy[1],Leilei Zhong[1],Luqian Wang[1],Foteini Mourkioti[1],Ling Qin[1],*Lutian Yao[2],Elisia Tichy[2],Leilei Zhong[2],Luqian Wang[2],Foteini Mourkioti[2],Ling Qin[2]. [1]University of Pennsylvania, United States,[2]University of Pennsylvania, United States Minor Outlying Islands

Skeletal muscle has a remarkable capacity for regeneration after injury. Recently, a new type of muscle-resident progenitor cell, referred to as fibro-adipogenic progenitors (FAPs), was identified to be critical in supporting the process of injured muscle regeneration. To date FAPs remains a poorly defined, heterogeneous population. Here, using lineage tracing of Gli1-CreER Rosa-tdTomato (Gli1/Td) mice,we found that Td+ cells are located in the inter- stitial area of myofibers and express markers previously associated with FAPs, such as PDG- FRα and Sca1. Flow cytometry analyses found that Gli1 labels 3.17+/-0.09% of all digested muscle cells collected at P66 (Tamoxifen, Tam, at P61-65). These cells are CD45/CD31/ CD11b- (Lin-) and contain 78.45+/-4.23% Sca1+ cells, thus constituting 10.93+/-0.67% of FAPs (Lin-/Sca1+/CD34+/Integrin α7-). At P72, Td+ cells increase to 7.59+/-0.47% of all muscle cells, and constitute 17.3+/-0.25% of FAPs. Histologic analyses showed that Td+ cells are 147.09+/-14.98 cells/mm2 in

adult mice (Tam at P61-P65, harvest at P66), but decrease to 95.15+/-4.45 cells/mm2 (P<0.05) in old mice (Tam at P366-P370, harvest at P371). When all digested muscle cells were seeded in dishes, 40% of the growing cells were Td+ when confluent. We next sorted out Td+ cells for culture. Interestingly those cells had fibroblastic and adipogenic differentiation abilities, but not osteogenic differentiation ability. To investigate the in vivo function of these cells, we intramuscularly injected P72 mice (Tam at P61-65) with Notexin to create acute muscle injury. Td+ cells peaked at day 3 post injury (711.70+/-78.69 cells/mm2), then gradually decreased at day 6 (481.19+/-70.33 cells/mm2) and almost receded to normal levels by day 9. This cell number kinetics mimics the reported cellular dynamics of FAPs under muscle injury. To further validate the role of Gli1 labeled cells in chronic injury, we crossed Gli1/Td mice with dystrophic mdx mice. Our experiments unveiled that Td+ cells significantly increase in Gli1/Td/mdx muscle (Tam at P61-65, Har- vest at P72) in the interstitial area of myofibers compared to Gli1/Td control muscle (control: 198.81+/-22.66 cells/mm2, mdx: 360.33+/-53.70 cells/mm2, P<0.05). Taken together, our data indicate that Gli1 labels a subpopulation of FAP cells that have important roles in the regeneration process of injured skeletal muscles.
***Disclosures: Lutian Yao**, None*

P-27

Osteocyte-specific deletion of the auxiliary α2δ1 voltage sensitive calcium channel subunit impairs skeletal strength and decreases both lean and fat masses. *Christian S. Wright[1],Xin Yi[1],William R. Thompson[1],Artur Schneider[2],Molly Pederson[3],Mary C. Farach-Carson[4],Alexander G. Robling[5]. [1]Department of Physical Therapy, School of Health and Rehabilitation Sciences, Indiana University, United States,[2]Department of Physiology, College of Osteopathic Medicine, Marian University, United States,[3]School of Science, Indiana University-Purdue University, United States,[4]Department of Diagnostic and Biomedical Sciences, School of Dentistry, University of Texas, Health Science Center, United States,[5]Department of Anatomy & Cell Biology, School of Medicine, Indiana University, United States

Osteocytes are the most abundant and mechanosensitive cells in the skeleton. They are essential for sensing and responding to mechanical forces by controlling the activity of other cells. However, the mechanisms by which osteocytes sense force input and transmit signals to other cells remains unclear. Voltage sensitive calcium channels (VSCCs) regulate anabolic responses to mechanical loading, and inhibition or deletion of these channels im- pairs bone accrual, mechanosensation, and skeletal integrity. Activity of VSCCs is regulated by auxiliary subunits, which bind the pore-forming α1 subunit to influence calcium influx. Through its transmembrane domain and large extracellular region, the α2δ1 auxiliary sub- unit controls the calcium-gating kinetics of the α1 channel pore, the interaction with and subsequent response to extracellular ligands, and the forward-trafficking of the α1 channel pore to the cell membrane. Knockdown of α2δ1 in MLO-Y4 osteocytes decreases the cell's ability to respond to membrane stretch, and global deletion of α2δ1 in mice results in os- teopenia. Therefore, we hypothesized that osteocyte-specific deletion of α2δ1 would impair skeletal development. Mice (C57BL/6) with LoxP sequences flanking crucial exons of Cac- na2d1, the gene encoding α2δ1, were crossed with mice expressing Cre under the control of the Dmp1 promoter (10 Kb). To assess skeletal phenotype, longitudinal whole body and site-specific DXA and in vivo μCT (10 wk old) were assessed. Three-point bending and ex vivo μCT were also conducted following sacrifice (20 wk old). Osteocyte-specific deletion of α2δ1 in male mice decreased femoral BMC (p=0.0213) by DXA and impaired cancellous bone at the proximal tibia by μCT, showing decreased trabecular thickness (p=0.0097) and a trend for lower BV/TV (p=0.057) at 10wks. Cacna2d1f/f, Cre+ male mice also displayed reduced ultimate force (p=0.0009) and energy to failure (p=0.0151) with femora 3-point bending, compared to Cacna2d1f/f, Cre- controls. In addition to these skeletal outcomes, osteocyte-specific deletion of α2δ1 decreased total body lean (p=0.0362) and fat (p=0.009) masses by DXA. Collectively, the α2δ1 auxiliary subunit is essential for osteocyte's regula- tion of trabecular structure and femur strength. Furthermore, these data suggest that the α2δ1 auxiliary VSCC subunit controls release of extracellular signals from osteocytes to regulate body composition.
***Disclosures: Christian S. Wright**, None*

P-28

Musculoskeletal Failure: A Proposal *Robert Blank[1]. [1]Garvan Institute and Medical College of Wisconsin, Australia

Mobility disorders cause enormous human suffering and societal expense, yet their sig- nificance is widely underappreciated. For example, fractures are perceived as unfortunate accidents rather than as the consequence of underlying osteoporosis. Similarly, the impact of fracture on survival, functional capacity, and quality of life is not recognized. Ignorance of the disease burden contributes to the osteoporosis treatment gap. Osteoporosis-related frac- tures, arthritides, sarcopenia, neuromuscular disorders, and spinal cord injury all converge on a final common pathway of impaired mobility, with consequent decline in performance status. Approximately 90 years ago, the New York Heart Association (NYHA) developed a functional classification of heart failure, based on a quick and easy assessment of the patient's exercise tolerance. This scheme is widely used today in multiple settings and could easily be adapted to bone, joint, and muscle disorders. The following is a proposed scheme for musculoskeletal failure (MSKF): Class 0 is normal ambulation and function as would be present in a sedentary individual, or better. Class 1 MSKF is characterized by ability to undertake a full range of activity, but with symptoms. Class 2 MSKF requires assistive de- vices or human assistance for activities outside the home, such as grocery shopping. Class 3 MSKF requires assistive devices or human assistance for activities inside the home. Class 4 MSKF is inability to ambulate. Implementation of this scheme could provide many benefits, as the NYHA scheme has. It can serve as a means of quantifying disability due to mobility impairment. It can serve as both an entry criterion and an endpoint in clinical trials. In the former case, it helps to ensure balance among groups. In the latter case, it provides a standard for judging the effectiveness of interventions. It can provide a basis for expanding epidemiological and natural history studies to stratify risks of hard

endpoints such as death and nursing home admission. There are potential problems with this scheme as well. There may be problems regarding calibration and agreement among observers. MSKF class may prove not to be useful. These issues could be addressed by straightforward investigations.

***Disclosures: Robert Blank**, Amgen, Other Financial or Material Support, Novo-Nordisk, Consultant*

P-29

Lower-extremity muscle power and grip strength are related to HR-pQCT radius and tibia bone parameters *Elsa Strotmeyer[1],Robert Boudreau[1],Mary Winger[1],Jane Cauley[1],Sheena Patel[2],Peggy Cawthon[2],Paolo Caserotti[3],Andrew Burghardt[4]. [1]Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, United States,[2]California Pacific Medical Center Research Institute, United States,[3]Department of Sports Science and Clinical Biomechanics and the Center for Active and Healthy Ageing, University of Southern Denmark, Denmark,[4]Department of Radiology & Biomedical Imaging, University of California, United States

The "mechanostat theory" proposes that loading exerted by muscle contraction impacts bone morphology and strength, though bidirectional muscle-bone signaling is also recog- nized. To examine muscle-bone associations in the Osteoporotic Fractures in Men Study (MrOS; N=1097; age 83.7+/-3.7 years; 11% minorities), we examined relationships of peak muscle power (W/kg body weight) from jump testing on a force plate and maximum grip strength (kg/kg body weight) from dynamometer testing with high-resolution peripheral quantitative computed tomography (HR-pQCT) bone parameters at the tibia and radius and total hip areal BMD (aBMD) from DXA. Weight-standardized peak jump power was 21.0+/-5.3 W/kg (range: 5.0-37.5 W/kg) and maximum grip strength was 0.47+/-0.10 kg/ kg (range: 0.16-0.89 kg/kg). Higher power/kg had significant positive though weak partial correlations (adjusted for age, race, site, height) with HR-pQCT tibial and radial failure load (r=0.13 and 0.06, respectively), cortical BMD (Ct. BMD; r=0.18 and r=0.14, respectively) and cortical thickness (Ct. Th.; r=0.12 and r=0.10, respectively), and total BMD (Tt. BMD; r=0.11 and 0.08, respectively) (Table 1, all $p<0.05$); but not with tibial or radial trabecular BMD (Tb. BMD) and thickness (Tb. Th.), or total hip aBMD. Higher grip strength per kg body weight (kg/kg) was associated with higher tibial and radial cortical BMD, radial failure load and radial cortical thickness, but lower hip aBMD and lower tibial trabecular BMD, thickness, and total BMD. All associations were maintained with multivariate adjustment in linear regression models. Findings indicate that higher peak muscle power, and maximal grip strength though less consistently, may be more related to cortical and total bone param- eters of HR-pQCT vs. trabecular bone or areal hip BMD, suggesting potential targets for bone-muscle interventions.

***Disclosures: Elsa Strotmeyer**, None*

Table 1. Power (W/kg) and grip strength (kg/kg) associations with total hip BMD from DXA and HRpQCT radial and tibial bone parameters.*

	Hip	Distal tibia						Distal radius					
Muscle function per kg body wt	aBMD, g/cm^2	Est. failure load, N	Tb. BMD, mg/cm^3	Tb. Th., mm	Ct. BMD, mg/cm^3	Ct. Th., mm	Tt. BMD, mg/cm^3	Est. failure load, N	Tb. BMD, mg/cm^3	Tb. Th., mm	Ct. BMD, mg/cm^3	Ct. Th., mm	Tt. BMD, mg/cm^3
Power (W/kg)	0. 01	***0.13***	0.02	-0.003	***0.18***	***0.12***	**0.11**	**0.06**	0.02	0.004	***0.14***	**0.10**	**0.08**
Grip strength (kg/kg)	***-0.16***	-0.05	***-0.10***	**-0.08**	**0.07**	-0.05	**-0.06**	**0.08**	-0.007	0.02	***0.12***	**0.08**	0.04

P<0.05**, ***P≤0.001; Partial correlations adjusted for age, race, height and clinic site.

P-30

How Exercise Professionals support Individuals with Acute Vertebral Fractures *Isabel Rodrigues[1],Maureen Ashe[2],Joan Bartley[3],Debra Butt[4],Phil Chilibeck[5],John Wark[6],Lora Giangregorio7. [1]University of Waterloo, Canada,[2]University of British Columbia, Canada,[3]Osteoporosis Canada, Canada,[4]University of Toronto, Canada,[5]University of Saskatchewan, Canada,[6]University of Melbourne, Australia,7University of Waterloo, Schlegel UW Research Institute for Aging, Canada

Purpose: Little is known about the efficacy and safety of non-surgical treatment options such as bed rest, braces, or exercise to support fracture symptoms in people with acute osteo- porotic vertebral fractures. Understanding exercise professionals' (e.g., kinesiologists, phys- ical therapists, exercise instructors, etc.,) current practices may provide insight into what works or identify knowledge gaps. The objectives are to explore exercise professionals' practices in supporting people with acute osteoporotic vertebral fractures and identify gaps for future research.Methods: We used an open-ended survey asking exercise professionals what they recommend for people with acute vertebral fractures. We distributed the survey to 8 national and international organizations representing exercise professionals, researchers, and clinicians in the field and via Twitter and Facebook. We used conventional content anal- ysis to analyze the data. All answers were read to gain an overarching understanding of the responses and then codes describing support of acute vertebral fractures were derived from the text. When data did not fit into an existing code a new code was created. Codes were then sorted into categories and subcategories. Categorical data are reported as a count (%). Results: We gathered data from 152 respondents, 84% from North America, 7% Europe, 2% Asia, and 7% did not reply. Most identified as women (82%); 64% were physiotherapists and 15% kinesiologists. About 94% were very comfortable prescribing an exercise program to individuals at low risk of fractures while only 54% were very comfortable prescribing exercise to people at high risk. One-third suggested future osteoporosis exercise guidelines should provide specific recommendations to people with vertebral fractures. Of the 152 re- spondents, 45 provided rehabilitation to people with acute vertebral fractures. We identified 4 categories: 1) remain active as much as possible; 2) avoid immobility (e.g., prolonged sitting or bed rest); 3) encourage safe movement education (e.g., avoid forward flexing, lateral bending, rotating, and

reaching overhead); and 4) interventions to alleviate back pain (e.g., analgesics, exercise, heat/ice, etc.,).Conclusion: Some exercise professionals may not be comfortable prescribing exercise to individuals at high risk of fractures. Strategies for managing symptoms include remaining active, avoiding immobility, encouraging safe movement, and interventions to alleviate back pain.
***Disclosures: Isabel Rodrigues**, None*

P-31

Anti-myostatin and anti-activin A antibody treatment improves bone strength and microarchitecture in C57BL6J mice.
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Osteoporosis is a serious public health issue with a high burden of morbidity and fi- nancial costs that arises from a quantitative loss in bone mineral density (BMD) as well as disruption of bone microarchitecture; predisposing affected individuals to skeletal fractures. Peak bone mass, a critical determinant of one's bone health in later life, is generally reached by the mid-twenties in humans and is influenced by genetic and environmental factors.Re- search into improving musculoskeletal health by exploring the synergy between bone and muscle has revealed that inhibition of myokines like myostatin increases muscle mass and strength. In this study, we explored the possibility of increasing peak bone mass via phar- macological inhibition of myostatin and activin A, ligands of the TGF-β superfamily whose inhibition by the soluble activin receptor IIB decoy molecule (sActRIIB-mFc) improved bone and muscle properties in mouse models of compromised bone including osteogenesis imperfecta (OI). However, the lack of specificity of sActRIIB-mFc for only myostatin or ac- tivin A led to unexpected adverse side-effects in human clinical trials.To explore the discrete effects of myostatin or activin A inhibition on bone, 5-week-old male and female wild type C57BL6 mice were treated with 10 mg/kg per body weight of monoclonal anti-myostatin, anti-activin A or a control antibody (Regeneron Pharmaceuticals) for either 7 weeks fol- lowed by a treatment hiatus or for 11 weeks. A treatment hiatus at 12 weeks of age allowed investigation of a drug holiday. All mice were sacrificed at 16 weeks of age.Myostatin and activin A inhibition resulted in significantly increased cortical and trabecular bone mass in male mice. Bone strength as determined by 3-point bend, also showed significant increases in ultimate load and yield load regardless of treatment duration. However, male mice only reached significance for increases in muscle weights with the anti-myostatin antibody treat- ment.Female mice showed significant increases in muscle weight regardless of treatment type or duration but had less robust changes in bone strength or microarchitecture with treat- ment. Importantly, a treatment holiday did not affect treatment efficacy in bone or muscle for males and females respectively.This newly identified benefit of activin A and myostatin inhibition treatment may provide therapies for sarcopenic, osteopenic and osteoporotic dis- ease by improving peak bone mass and reducing fracture rates.
***Disclosures: Catherine Omosule**, None*

P-32

A Protective Role of an FDA-Approved Generic Drug for Demyelination Against Neurogenic Muscle Atrophy *M A Hassan Talukder[1],Jung Lee[1],Anagha Gurjar[1],Mary O'Brien[1],John Elfar[1],Li Yue[2]. [1]Penn State College of Medicine, United States,[2]The Warren Alpert Medical School of Brown University , United States

Background: Traumatic peripheral nerve injury (TPNI) represents a major health prob- lem that often leads to significant functional impairment and permanent disability from the loss in axonal continuity, neuronal cell death, nerve demyelination, conduction defects, mus- cle denervation and muscle atrophy. 4-Aminopyridine (4AP), a broad-spectrum potassium channel blocker and FDA-approved drug, improves neuromuscular function in patients with diverse demyelinating disorders. The neurological benefits of 4AP are believed to result from increases in action potential duration, calcium influx, neurotransmitter release and syn- aptic transmission. We have recently repurposed the use of 4AP and demonstrated that both systemic and local 4AP administration enhances global functional recovery of the affected limb, promotes remyelination of the nerve and improves the nerve conduction velocity in a mouse model of TPNI. While muscle atrophy occurs very rapidly following nerve injury, the effect 4AP on muscle atrophy and muscle contractile function is largely unknown. Methods: This study was designed to explore the possible beneficial effects of 4AP treatment in muscle atrophy, intrinsic muscle function, and muscle regeneration following acute sciatic nerve crush injury. Mice with or without moderate sciatic nerve crush injury were followed for 3, 7 and 14 days with or without 4AP (10 microgram/daily, ip) versus saline treatment. Morpho- logical, functional and transcriptional properties of skeletal muscle were assessed. Results: In addition to improving in vivo global motor function as early as post-operative day 3, 4AP treatment significantly attenuated muscle atrophy in the injured limb with increased muscle mass and muscle fiber area. 4AP also improved ex vivo intrinsic muscle contractile force 7 days post-injury. Most importantly, the reduced muscle atrophy with 4AP treatment was concurrent with significantly reduced expression of atrophy-related genes (myogenin, MuRF-1, FoxO1, FoxO3) and increased expression of Pax7+ satellite cells and proliferating Ki67+ cells. Conclusions: These findings provide new insights into the beneficial effects of 4AP in nerve injury-induced muscle atrophy and dysfunction and open a new window for further investigation in neuromuscular injury-induced muscle loss.
***Disclosures: M A Hassan Talukder**, None*

P-33

Targeted Deletion of Erythropoietin Receptor (EPOR) in Schwann Cells Abolishes the Neuroprotective Effect of EPO on Peripheral Nerve Injury Recovery and Exacerbates Muscle Atrophy *M A Hassan Talukder[1],Jung Lee[1],Mary O'Brien[1],Zara Karuman[1],John Elfar[1]. [1]Penn State College of Medicine, United States

Background: Erythropoietin (EPO) is a pleiotropic hormone with neuroprotective and neurotrophic properties. Both EPO and EPO receptor (EPOR) are present in the peripheral nervous system, and Schwann cells express EPOR. While muscle atrophy occurs very rap- idly following nerve injury, the role EPO and EPOR on muscle atrophy is largely unknown. This study was designed to explore the role EPOR on EPO-induced functional recovery (sciatic function index, SFI) following acute nerve injury, and the loss of muscle mass in tibialis anterior (TA) muscle was also evaluated. Methods: We developed a myelin pro- tein zero (MPZ) promoter-driven deletion model targeting EPOR in Schwann cells of mice (MPZ-Cre EPOR f/f). Female MPZ-Cre EPOR f/f (EPOR knockout) and wild-type (WT) mice were assigned to sciatic nerve crush injury and followed for 21 days with EPO (5000 units/kg, ip, immediately after the nerve injury) or saline treatment (n = 7/group). Results: In saline-treated groups, post-injury SFI recovery was comparable between EPOR knockout and WT mice. Interestingly, while EPO treatment markedly accelerated functional recovery in WT mice at post-injury day 3 (SFI, -17.2), SFI in EPO-treated EPOR knockout mice was markedly impaired (SFI, -48.1, $P < 0.001$) by day 3. At post-injury day 7, SFI recovery was complete in EPO-treated WT mice (-3.3), whereas it was -40.7 ($P < 0.001$) in EPO-treated EPOR knockout mice. Importantly, compared to saline-treated EPOR knockout mice, SFI recovery in EPO-treated EPOR knockout mice was significantly low at day 7 (-18.8 vs -40.7, $P < 0.01$) and day 14 (-1.3 vs -13.7, $P < 0.05$). In saline-treated groups, loss of TA muscle mass (as a percentage of healthy TA muscle) was comparable (~12%) between WT and EPOR knockout mice. In EPO-treated WT mice, there is no significant loss of muscle mass in the injured limb (<4%). However, muscle mass in the injured limb of EPO-treated EPOR knockout mice was significantly lost (19%, $P < 0.001$) and it was also significantly different from EPO-treated WT mice (12%, $P < 0.05$). Compared to saline group, EPO treatment sig- nificantly prevented muscle loss in WT mice (4% vs 12%, $P < 0.05$), but the muscle loss was exacerbated by EPO treatment in EPOR knockout mice (19% vs. 12%, $P < 0.05$). Conclu- sions: These findings provide direct evidence for an obligatory role of Schwann-cell specific EPOR in EPO-induced functional recovery and muscle atrophy following nerve injury, and open a new window for further investigations.

***Disclosures: M A Hassan Talukder**, None*

P-34

Body Weight Loss Improves Bone Quality in High Fat Diet fed Female Rats following Short-term Treatment with a GLP1/glucagon Co-agonist and Food Restriction *Jennifer Rojas[1],Inger Thorup[1],Florian Bolze[1],Johannes Fels[1],Majken Dalgaard[1],Martin Guillot[2],Aurore Varela[2],Gabrielle Boyd[2],Yulia Tingle[3]. [1]Novo Nordisk A/S, Denmark,[2]Charles River, Canada,[3]Envigo, United Kingdom

Background and study aim: Previous animal and human data show that excessive fat accumulation, food restriction and body weight loss can affect bone quality. In this explor- ative rat study, we investigated the effect of body weight loss on bone quality in normal weight and obese rats using food restriction and an anti-obesity drug, a GLP1/glucagon co-agonist. Method: Six-week old Sprague Dawley rats, n=10-16/sex/group, were fed either a chow or a high fat diet (HFD) for 23 weeks. Subsequently, rats were subjected to daily subcutaneous treatments with either vehicle or the co-agonist for 4 weeks. To discriminate drug-related from weight loss-related effects, we additionally included food restricted (FR) rats and aimed at a body weight lowering effect of maximum 20%. Ex vivo bone densi- tometry, biomechanical testing, histology and bone-related hormones (leptin, FGF23, PTH, osteocalcin, adiponectin, ACTH, TSH, T4, estradiol, testosterone) were applied to charac- terize the impact of drug-dosing and FR on bone quality.Results: HFD feeding in females resulted in slight increases in bone size at the distal femur metaphysis and diaphysis and in L4 vertebra, associated with marginal decreases in trabecular bone (Tb) density when com- pared to chow fed vehicle-treated rats. This was substantiated by decreases in Tb number, Tb thickness and increased Tb separation at the distal femur metaphysis. Additionally, most of the intrinsic strength parameters were decreased in L4 following compression consistent with the decreases in Tb bone density, suggesting that bone quality was marginally decreased in HFD fed females. Similar changes in bone densitometry were observed in males but without meaningful impact on bone strength. Co-agonist treatment as well as FR normalized the negative effects on bone quality in HFD fed females, suggesting that the improved bone quality was weight loss-related, independent from the type of intervention. No changes were detected by histopathology in femur/tibia and sternum. Normalization of the bone quality was not reflected in any of the measured hormones.Conclusion: Body weight loss induced by either FR or a GLP-1/glucagon co-agonist is beneficial for bone quality in HFD fed female rats and can be identified even in a short-term study of just four weeks duration.

***Disclosures: Jennifer Rojas**, Novo Nordisk A/S, Grant/Research Support*

P-35

Differential muscle fiber typing and energetics defines a muscle weakness phenotype in HPP sheep *Joshua Bertels[1],Kirby Sherman[1],Alyssa Falck[2],Shannon Huggins[3],Cassandra Skenandore[3],Charles Long[3],JonPaul Elizondo[4],Harry Hogan[4],Jordan Ankerson[4],Michael Moreno[4],Sarah White[5],Larry Suva[6],Dana Gaddy7. [1]Veterinary Integrative Biosciences, Texas A&M University, United States,[2]Veterinary Integrative Biosciences, United States,[3]Veterinary Physiology and Pharmacology, Texas A&M University, United States,[4]Department of Mechanical Engineering, Texas A&M University, United States,[5]Department of Animal Sciences, Texas A&M University, United States,[6]Department of Veterinary Physiology and Pharmacology, Texas A&M University, United States,7Department of Veterinary Integrative Biosciences, Texas A&M University, United States

Hypophosphatasia (HPP) is a rare inherited disorder of mineral metabolism, the result of inactivation of the tissue-nonspecific alkaline phosphatase (TNSALP) gene (ALPL) that primarily affects the development of bones and teeth. However, the highly variable clinical presentation frequently also includes profound muscle weakness. Using CRISPR/Cas9, a common ALPLgene mutation in exon 10 (Isoleucine -> Methionine (c.1077 C>G)) was introduced into the Rambouillet sheep genome. Compared to wild-type (WT) controls mu- tant HPP sheep have significantly reduced serum alkaline phosphatase activity. As expected, these animals at birth and throughout life experience myasthenia, in addition to a hypomin- eralized skeleton, decreased vertebral bone size, associated with diminished stiffness and elastic modulus, as well as pronounced metaphyseal flaring and premature tooth loss. HPP sheep have altered gait biomechanics (2 months and 12 months of age) with marked spinal sway and altered peak vertical force in the front limbs, likely the biomechanical conse- quence of a more the lateral displacement of loads experienced during altered gait. Initial characterization of gluteal muscle biopsies included measurement of mitochondrial protein enzyme activities, oxygen consumption rate using freshly isolated muscle fibers (Oxygraph) and immunohistochemistry of fiber type composition in WT and HPP sheep. Levels of mitochondrial complex I are upregulated in HPP sheep whereas no differences were apparent in cytochrome oxidase. Specific muscle fiber type staining of WT and HPP mutants revealed differential staining of type 1 and 2x fibers. These data provide the first direct insights into the mechanism of the well-known but poorly characterized muscle weakness phenotype of HPP patients. Perhaps more provocatively, the data suggest a novel role for TNSALP in the context of normal muscle function that will require longitudinal assessment of the muscle energetics phenotype in HPP sheep.
***Disclosures: Joshua Bertels**, None*

P-36

Sarcopenia Is Widespread In Females With Anorexia Nervosa But Exercise Is Not Protective *Anne Drabkin[1],Brianne Sutton[1],Philip Mehler[1],Micol Rothman [2],Christine Swanson[2]. [1]Denver Health Medical Center, United States,[2]University of Colorado School of Medicine, United States

Introduction: Sarcopenia, a condition describing the loss of muscle mass, strength and function, has been linked to low bone mineral density (BMD), disability, falls and increased health care costs in the elderly. Physical activity and exercise are accepted countermeasures to this condition. We hypothesized that exercise may also have similar benefits in a popula- tion of patients with anorexia nervosa. Methods: Females with anorexia nervosa binge-purge and restricting subtypes (AN-BP and AN-R, respectively) were admitted to an inpatient eat- ing disorder stabilization unit where grip strength, gait speed, body composition and BMD were evaluated. A detailed exercise history was obtained by the admitting physician. Per the European Working Group on Sarcopenia in Older People (EWGSOP), the conditions of pre-sarcopenia (PS), sarcopenia (SA) and severe sarcopenia (SS) were defined as the presence of low muscle mass (PS), low muscle mass plus lower than expected grip strength (SA) and low muscle mass plus low grip strength plus lower than expected gait speed (SS). Results: 40 females with anorexia (24 with AN-R and 16 with AN-BP) were, on average, 30.8 years old, had a BMI of 13.0 kg/m2 and exercised 15.3 hours/week. Types of exercise included running, strength training and swimming. 84% of participants demonstrated some degree of sarcopenia. 51% had SS, 34% had SA, 0% had PS and 15% had no sarcopenia. Average appendicular lean mass (ALM) was 4.87kg/m2 (expected 5.67), average gait speed was 0.92m/s (expected 1.0) and grip strength was 13.6kg less than expected for age. Hours of weekly exercise did not correlate with the degree of sarcopenia (p=0.69, r=-0.1) or BMD Z-scores (spine: p=0.40, r=0.14; femoral neck: p=0.17, r=0.22; total hip: p=0.15, r=0.23) but did correlate to ALM in AN-R only (r=0.51, p-0.013). Conclusion: Countless studies demosntrate the benefits of exercise on muscle health to attenuate the risk of sarcopenia but this is not supported in young females with AN. Although exercise improved ALM in patients with AN-R, it did not improve sarcopenia severity in patients with anorexia ner- vosa. Whether the type of exercise (e.g. weight bearing) affects sarcopenia requires futher evaluation. Exercise may further hasten weight loss in patients with AN and is, therefore, generally not recommended.
***Disclosures: Anne Drabkin**, None*

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Which diagnosis of sarcopenia presents greater association with clinical vulnerability? *Alberto Frisoli[1],Jairo Borges[2],Angela Paes[2],Antonio Carvalho[2],Julia Menezes[3]. [1]Cardio Geriatric Division- Federal University of Sao Paulo, Brazil,[2]Cardio Geriatric Division, Brazil,[3]Albert Einstein School of medicine, Brazil

Currently, there are many criteria to diagnose sarcopenia. The differences between them are in the methods and cutoff points used to define low muscle mass and low physical per- formance (grip strength, walking speed, chair test, SPPB). This variability can determine a significant variation in the association of sarcopenia with bad physical phenotypes.Aim: To evaluate the association of sarcopenia by FNIH and EWGSOP 2 with loss of mobility, disability and frailtyMethod: Cross sectional analyzes of 301 patients from SARCOS study, an observational study of the epidemiology of Sarcopenia and Osteoporosis in older out- patients from Sao Paulo-Brazil. All patients were underwent DXA of total body and bone sites. Sarcopenia was diagnosed as recommended by FNIH (SFNIH) and by the new EWG- SOP (SEWGSOP-II) recommendation. Clinical vulnerability was composed by: Frailty by Fried's criterion; Loss of mobility: chair stand test positive or walking speed < 25% of the sample velocity; Disability: loss of 2 tasks of IADL (Lawthon) and/or 1 task in ADL (Katz). Results: We found four phenotypes according to the presence of the criteria of sarcopenia: Robust with 52.5% (n=158); SEWGSOP-II only: 20.9% (n=63); SFNIH only:12.9% (n=39); and SarcoBoth (SEWGSOP-II and SFNIH): 13.6% (n=41) (p<0.001). The mean age of the groups were: 78.2 (6.7)yo. of robust; 79.0(7.2) yo. in SEWGSOP-II only;

80.4(7.2) in SF- NIH only and 81.4(5.8) in SarcoBoth (p=0.029). SEWGSOP-II only was more prevalent in women (61.9%) while SFNIH only occurred more in men (61.5%). The prevalence of loss of mobility was 46.7%, disability 47 %, and frailty 17.9%. Prevalence of the sarcopenia phenotypes in older adults with clinical vulnerability were described in table 1. Regression analyses adjusted for female and age, SFNIH only presented higher association with loss of mobility and frailty, than SEWGSOP-II only, while Sarcoboth presented higher intensity in the association with frailty and disability, compared to others phenotypes (table 2). Conclusion: There is significant heterogeneity in the association between sarcopenia diagnosed by FNIH and by EWGSOP II criteria with loss of mobility, disability and frailty. In the isolated way, the sarcopenia by FNIH seems to be more representative of clinical vulnerability than EWGSOP II, while the presence of both increases the strength of this association.

***Disclosures: Alberto Frisoli**, None*

Table 1- Prevalence of the sarcopenia phenotypes in older adults with clinical vulnerability

	Loss of mobility (%)	Disability (%)	Frailty (%)
Robust	33.7	41.3	5.9
SEWGSOP-II only	39.3	40.7	25
SFNIH only	60	59.4	30
Sarcoboth	52.4	73.7	42.9
p	0.110	*0.001*	*<0.001*

Table 2- Regression analyses for clinical vulnerability, from sarcopenia phenotypes

	Loss of mobility (%)	Disability (%)	Frailty (%)
SEWGSOP-II only	0.97 (CI:0.37-2.51; p=0.960)	0.914 (CI:0.48-1.73; p=0.783)	4.50 (CI:1.25-16.21; *p=0.021*)
SFNIH only	3.99 (CI:1.35-11.77; *p=0.012*)	1.85 (CI:0.82-4.15; p=0.135)	9.63 (CI:2.35-39.50;*p=0.002*)
Sarcoboth	2.58 (CI:0.90-7.37;*p=0.075*)	3.47 (CI:1.51-7.69; *p=0.003*)	17.49 (CI:4.42-69.19;*p<0.001*)

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Effect of High-Intensity Interval Training on Peripheral Quantitative Computed Tomography Measures of Quadriceps Muscle and Adipose Tissue Properties in Obese, Osteopenic Older Women *Jenna C Gibbs[1],Livia P Carvalho[2],Vincent Marcangeli[2],Guy El Hajj Boutros[2],Maude C Dulac[2],Mylène Aubertin-Leheudre[2]. [1]McGill University, Canada,[2]Université du Québec à Montréal, Canada

Age-related muscle and bone loss alongside an increase in adiposity can lead to func- tional decline, an increased risk of falls and fractures, and even mortality. High-intensity interval training (HIIT) is a promising and time-efficient intervention strategy for maintaining muscle function and body composition with aging. However, the efficacy of HIIT to improve lean muscle and adipose tissue distribution in obese, osteopenic older adults is unclear. Purpose: To evaluate the effect of HIIT compared to moderate-intensity continuous exercise training (CONT) on peripheral quantitative computed tomography (pQCT) mea- sures of quadriceps muscle and adipose tissue properties in obese, osteopenic older women. Methods: Nineteen obese and osteopenic older women (mean+/-SD age 67.5+/-2.7 years; body fat 43.0+/-1.3%; number of steps/day 6463+/-2619; areal bone mineral density T-score <-1 SD) were randomly allocated to a 12-week HIIT group (n=9; elliptical for 30 seconds at 85% age-predicted maximal heart rate [MHR] and 90 seconds at 65% MHR, 3 times/ week for 30 minutes) or a 12-week CONT group (n=10; treadmill at 65-75% MHR, 3 times/ week for 60 minutes). Quadriceps muscle cross-sectional area (cm2) and density (mg/cm3; density of tissue within the muscle compartment excluding intramuscular fat and bone areas) and intramuscular and subcutaneous fat areas (cm2) were measured by pQCT at baseline and after 12 weeks using the ImageJ software. Independent t-test analyses compared the mean changes in pQCT outcomes between the HIIT and CONT groups. Results: Quadriceps muscle area improved in the HIIT group (1.93+/-5.89 cm2) relative to the CONT group (-12.06+/-14.20 cm2, p=0.020). However, subcutaneous fat area decreased to a greater ex- tent in the CONT group (-26.63+/-15.08 cm2) than the HIIT group (-4.57+/-10.30 cm2, p=0.002). There were no between-group differences in change in quadriceps muscle density (HIIT=1.31+/-3.92 mg/cm3 vs CONT=-1.69+/-2.45 mg/cm3, p=0.069) and intramuscular fat area (HIIT=0.51+/-2.66 cm2 vs CONT=-0.80+/-2.34 cm2, p=0.283). Adherence was 86% and 97% in the HIIT and CONT groups, respectively. Conclusions: HIIT may represent a promising intervention strategy for improving lean muscle and adipose tissue properties in obese, osteopenic older adults compared to traditional exercise training approaches. Further investigation in a larger sample size over a longer duration is needed to confirm the clinical relevance of our pilot trial results for fall and fracture prevention.

***Disclosures: Jenna C Gibbs**, None*

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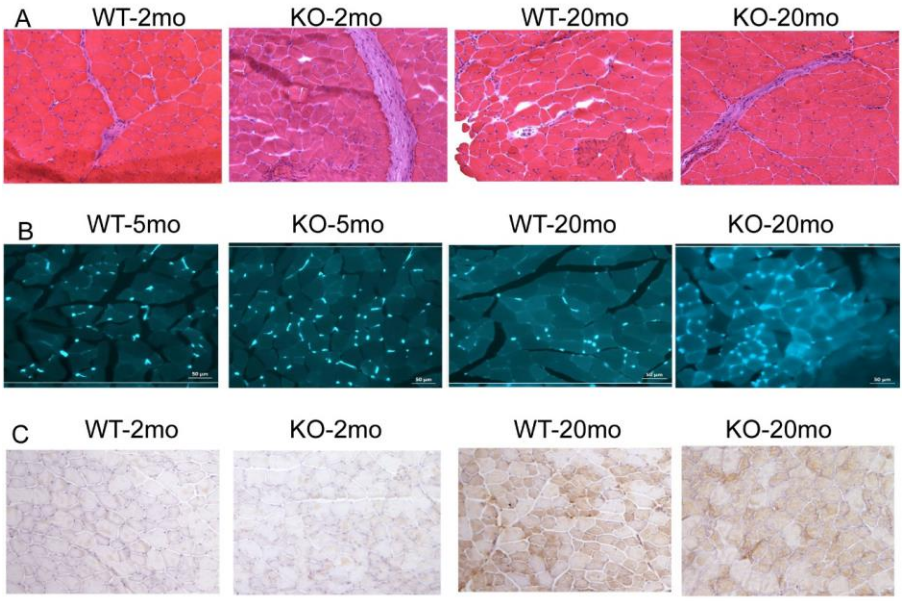
Muscle dysfunction in Female Fibroblast Growth Factor 2 Knockout Mice *Marja Hurley[1],Liping Xiao[1]. [1]UConn Health, United States

Fibroblast growth factor 2 (FGF2) is important in bone and skeletal muscle homeo- stasis. However, the impact of Fgf2 knockout (Fgf2KO) on skeletal muscle phenotype and function has not been reported. Since Fgf2KO mice develop osteoporosis associated with

increased bone marrow adipocytes with age we assessed skeletal muscle function as well as whether there were changes in adipogenic marker adipocyte fatty acid binding protein (AP2) in skeletal muscle of Fgf2KO mice, utilizing mice that are homozygous for the reporter construct aP2Cyan (Ap2WT) and mice that harbor the AP2 reporter and are Fgf2 null (Ap2Fgf2KO). Gait analysis of 2, 12, and 19-months old female Ap2WT and Ap2Fgf2KO littermates revealed similar hind limb propulsion duration in 2 and 12-month Ap2WT and Ap2Fgf2KO, but significantly shorter in 19-month Ap2Fgf2KO mice. Hind paw eversion was significantly greater in 19-month Ap2Fgf2KO mice compared with Ap2WT. Assess- ment of FGF2 in skeletal muscle of 2 and 19-month mice revealed no expression of Fgf2 mRNA in Ap2Fgf2KO. Interestingly Fgf2 mRNA and protein was markedly decreased in 19-month Ap2WT compared with 2-months-old Ap2WT. Phenotypic assessment revealed increased fibrosis and inflammatory cells in old Ap2WT and young and old Ap2Fgf2KO (Fig. 1A). Gastrocnemius muscle fiber cross-sectional area was significantly reduced in 20-months-old Ap2WT and Ap2Fgf2KO compared with 5-months-old of both genotypes. Assessment of lipid related genes revealed significantly increased Perillipin 1 and Fgf21 mRNAs in 20-month Ap2WT and Ap2Fgf2KO compared with 5-month-old Ap2WT and Ap2Fgf2KO. There was marked accumulation of fibro-adipocytes in muscle of young and old Ap2Fgf2KO (Fig.1B) and FGF21 protein was also increased in 20-month-old Ap2WT and Ap2Fgf2KO. (Fig. 1C). We conclude that knockout of Fgf2, and decreased FGF2 ex- pression in old Ap2WT mice, associated with evidence of sarcopenia as well as altered ex- pression of FGF21 in the setting of impaire ribute to impaired skeletal muscle function with age in mice.

***Disclosures: Marja Hurley**, None*



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Higher pulsatility index is associated with loss of grip strength and gait speed over time: the Framingham Heart Study

*Shivani Sahni[1],Alyssa B. Dufour[1],Douglas P. Kiel[1],Marian T. Hannan[1],Paul F. Jacques[2],Roger A. Fielding[2],Emelia J. Benjamin[3],Ramachandran S. Vasan[3],Joanne M. Murabito[3],Gary F. Mitchell[4],Naomi M. Hamburg[5]. [1]Marcus Institute, Hebrew SeniorLife and Harvard Medical School, United States,[2]Jean Mayer USDA HNRCA, Tufts University School of Nutrition, United States,[3]BU School of Medicine and Framingham Heart Study, United States,[4]Cardiovascular Engineering, Inc., United States,[5]BU School of Medicine, United States

Impaired vascular function and increased aortic stiffness with aging is associated with decreased physical function. Yet, longitudinal studies relating vascular function with muscle strength and physical function are lacking. We sought to evaluate whether alterations in aortic stiffness and microvascular function relate to muscle dysfunction and loss of physical function in a large community-based prospective cohort. We examined the longitudinal association of measures of brachial artery function [resting flow velocity, baseline diameter, hyperemic flow response, flow mediated dilation percent (FMD%), and pulsatility index] and aortic stiffness [carotid-femoral pulse wave velocity (CFPWV) and brachial pulse pres- sure] with annualized percent change in grip strength (Δgrip%) and gait speed (Δgait%) over ~11.5 years in 2,369 older adults from the Framingham Offspring Study. Vascular measures were collected using high-resolution ultrasound, Doppler and arterial tonometry (1998-2001, baseline). CFPWV was inverse transformed prior to analysis. Pulsatility index, which reflects the dynamic pulsatile load in the arterial system and is related to central aortic stiffness was calculated as [(maximum ? minimum blood flow velocity)/average velocity]. In 1999-2005 and at two follow-up examinations (2005-2008 and 2011-2014), grip strength from isometric hand dynamometer (maximum of 3 readings per hand, kg) and gait speed on a 4-m walk (faster of two trials, m/s) were measured. Multivariable linear regression estimat- ed the association of vascular measures with Δgrip% and Δgait% [calculated as (follow-up measure ? baseline measure)/baseline measure x100, divided by longest available follow-up time (y)] in models adjusting for standard cardiovascular disease risk factors (Table). Mean age was 61±9y (range 33-88) and mean Δgrip% and Δgait% were -0.73± 2.97% and -0.93 ± 2.19%, respectively, over a 11.5y follow-up. Associations were similar in men and women. In sex-combined analysis, higher pulsatility index at baseline was related with greater loss of grip strength over

time. Higher hyperemic flow at baseline was related with less of a loss in gait speed whereas higher brachial pulse pressure and pulsatility index were related with greater loss of gait speed over time. Higher brachial artery pulsatility index and pulse pres- sure at baseline were related with greater muscle dysfunction and loss of physical function, whereas higher microvascular reactivity was related with preservation of function over time. This could be partly due to negative impacts on nutrient delivery and consequent effects on skeletal muscle anabolic capacity. Our findings are consistent with the possibility that altered vascular flow induces microvascular damage in muscle tissue that adversely affects muscle function in older adults.

***Disclosures: Shivani Sahni**, None*

Table. Association of vascular measures with annualized percent change in grip strength and gait speed in men and women (n=2,369) from the Framingham Offspring Cohort.

Vascular measures	Annualized percent change in grip strength (%)		Annualized percent change in gait speed (%)	
	β± SE	p value	β± SE	p value
Baseline Flow	0.056±0.08	0.49	0.095±0.05	0.07
Baseline diameter	-0.052±0.11	0.63	0.006±0.07	0.93
FMD%	0.087±0.08	0.26	0.096±0.05	0.06
Hyperemic flow	0.061±0.09	0.48	0.151±0.06	0.010*
Mean aortic pressure	0.051±0.08	0.50	0.095±0.05	0.07
Baseline pulsatility index	-0.309±0.15	0.044*	-0.308±0.10	0.003*
Brachial PP	0.022±0.09	0.80	-0.142±0.06	0.017*
-1000/CFPWV	-0.091±0.12	0.44	-0.094±0.08	0.22

Models were adjusted for age, sex, height, weight, heart rate, mean aortic pressure, total/HDL ratio, triglycerides, glucose, anti-hypertensive treatment, lipid-lowering treatment, current smoking, baseline grip strength or gait speed and diabetes status.

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Markers of Sarcopenia and Incident Mobility Limitation: The Tobago Longitudinal Study of Aging *Adam Santanasto[1],Iva Miljkovic[1],Ryan Cvejkus[1],Joseph Zmuda[1],Victor Wheeler[2]. [1]University of Pittsburgh, United States,[2]Tobago Health Studies Office, Trinidad and Tobago

“Sarcopenia”, the age-related loss of muscle mass and muscle function, varies by eth- nicity and has a major impact on health status. However, little is known about sarcopenia and its consequences in African-ancestry populations, particularly outside the U.S. Com- pounding the problem, African-ancestry populations are expected to age rapidly and are at high risk of sarcopenia and mobility limitations. Purpose: We quantified changes in markers of sarcopenia and their association with incident mobility limitations in a large cohort of African-ancestry men on the Caribbean island of Tobago who were initially free of mobility limitations (n=1455, age: 56.4±8.8 years, range: 41-86 years, BMI 27.5±4.3). Methods: Grip strength was measured with a Jamar dynamometer and appendicular lean mass (ALM) was measured with DXA (Hologic QDR 4500) at baseline and after 6.1±0.5 years. Mobility limitations were defined as being unable to climb 1-flight of stairs or walk 2-3 blocks. Annu- alized percent change in Foundation for the National Institutes of Health sarcopenia markers of “weakness” [grip strength/BMI (gripBMI)] and “low ALM” [ALM/BMI (almBMI)] were examined per 10-year age group. For interpretability, the odds of mobility limitation were calculated per standard deviation of absolute changes in almBMI and gripBMI using logistic regression. Analyses were adjusted for baseline age, smoking, congestive heart failure, ar- thritis, diabetes, follow-up time and physical activity (walking for leisure). Results: In men in the collapsed age range of 40-74 (n=1405), almBMI declined by -0.86%/yr vs. gripBMI, which decline by -1.59%/yr. Among men aged 75+ (n=50), almBMI declined by -0.87%/yr vs. gripBMI, which declined by -2.54%/yr. Higher baseline gripBMI was strongly associated with lower risk of mobility limitation (OR:0.49; 95%CI: 0.38-0.65) but not change in gripB- MI (0.81; 0.63-1.05). Higher baseline almBMI (0.61; 0.48-0.78) and less loss of almBMI (0.66; 0.52-0.83) were each associated with lower risk of mobility limitation. Conclusions: Men of African-ancestry in Tobago have an accelerated loss of grip strength relative to ALM, especially after age 75. GripBMI measured at one time was a particularly powerful predictor of future mobility limitations in this cohort. Additional research is needed to better define the clinical and ph itations among older African ancestry men.

***Disclosures: Adam Santanasto**, None*

P-42

Higher Concentrations of Parathyroid Hormone (PTH) are Associated with Reduced Gait Velocity in Adults: A Systematic Review *Lavanya Srinivasa Murthy[1],Gustavo Duque[1],Natasha A Grande de França[2],Guillaume T Duval[3],Sara Vogrin[4],Cedric Annweiler[5]. [11]. Australian Institute for Musculoskeletal Science (AIMSS), The University of Melbourne and Western Health, St. Albans, Victoria, Australia. , Australia,[23]. Department of Nutrition, School of Public Health, University of São Paulo, São Paulo, Brazil., Brazil,[3]Department of Neuroscience and Aging, Division of Geriatric Medicine and Memory Clinic; Research Centre on Autonomy and Longevity; Angers University Hospital; University of Angers, Angers, France., France,[4]. Australian Institute for Musculoskeletal Science (AIMSS), The University of Melbourne and Western Health, St. Albans, Victoria, Australia. , Australia,[5]. Department of Neuroscience and Aging, Division of Geriatric Medicine and Memory Clinic; Research Centre on Autonomy and Longevity; Angers University Hospital; University of Angers, Angers, France., France

Introduction/Objectives: High serum concentrations of parathyroid hormone (PTH) have been associated with osteosarcopenia. Gait velocity is a predictor of adverse outcomes in osteosarcopenic subjects. This systematic review aimed to assess evidence for the effect of high PTH levels on gait velocity in adults.Methods: We searched PubMed, Embase (Ovid interface) and Cochrane (CENTRAL) for published studies evaluating circulating PTH in human adults aged >20years, without date or language restriction. We excluded studies with patients on dialysis and if PTH was measured following any intervention having potential effect on its concentrations.

Primary outcome was gait velocity defined as the time needed to walk a predetermined distance, or distance walked during a fixed period at usual pace or fast pace. Two independent researchers conducted data extraction and evaluated the risk of bias. Disagreements were resolved by a third reviewer. Risk of bias assessment was done using the National Heart, Lung and Blood Institute quality assessment tool.Results: A total of 681 articles were retrieved from the systematic search. Following full text review and risk of bias assessment, 8 studies were included for final analysis. Of the included studies, half (n=4) demonstrated a significant inverse association between high PTH concentrations and gait velocity, one study showed a nonsignificant association of increasing PTH levels with declining gait speed, and the remainder showed no relation. In addition, three studies also highlighted a negative correlation between PTH levels and muscle strength.Conclusion: Our review of published studies suggests higher concentrations of PTH are associated with reduced gait velocity in adults. This relationship deserves further exploration with RCTs designed to assess the effects of correcting abnormal circulating PTH levels on physical performance in adults.
Disclosures: Lavanya Srinivasa Murthy*, None*

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Prevalence of Sarcopenia in Patients with a Recent Fracture According to the revised EWGSOP definition *Caroline E. Wyers[1],Lisanne Vranken[1],Irma J.A. de Bruin[1],Robert Y. van der Velde[1],Heinrich M.J. Janzing[2],Sjoerd Kaarsemaker[3],Piet P.M. Geusens[4],Joop P.W. van den Bergh[5]. [1]Department of Internal Medicine, VieCuri Medical Center; NUTRIM School for Nutrition and Translational Research in Metabolism, Maastricht University; Department of Internal Medicine, Maastricht University, Netherlands,[2]Department of Surgery, VieCuri Medical Center, Netherlands,[3]Department of Orthopedic Surgery, VieCuri Medical Center, Netherlands,[4]Department of Internal Medicine, Subdivision of Rheumatology, Maastricht UMC+; Hasselt University, Netherlands,[5]Department of Internal Medicine, VieCuri Medical Center; NUTRIM School for Nutrition and Translational Research in Metabolism, Maastricht University; Department of Internal Medicine, Maastricht University; Hasselt University, Netherlands

Introduction: Fractures are often the consequence of a fall which can be caused by multiple factors including low muscle strength, quality or performance. Although sever- al assessments to diagnose sarcopenia are performed at a Fracture Liaison Service (FLS), the diagnosis of sarcopenia is often not included in the evaluation. Recently, the European Working Group on Sarcopenia in Older People (EWGSOP) has revised their definition of sarcopenia. The aim of this study was to identify the prevalence of sarcopenia according to the new EWSGOP definition in patients with a recent clinical fracture.Methods: All con- secutive patients aged 50-90 with a recent radiographically confirmed fracture who under- went evaluation of fracture risk, osteoporosis and underlying metabolic bone diseases at the FLS were included. According to EWGSOP, probable sarcopenia is defined as low muscle strength (criterion 1), assessed by measurement of grip strength and chair stand test. Diag- nosis of sarcopenia is confirmed if in addition to low muscle strength, low muscle quantity or quality (criterion 2) is present. Muscle quantity is assessed by measuring appendicular skeletal muscle mass with DXA. If in addition to low muscle strength and low muscle quan- tity, low muscle performance (criterion 3; assessed by gait speed or time up and go test) is present, sarcopenia is considered as severe.Results: In total, 1535 patients (71% women; mean age 66.7 ± 9.5 years) were evaluated at the FLS of whom 714 sustained a major os- teoporotic fracture (MOF). At the time of the FLS visit, 176 (14%) patients presented with probable sarcopenia defined as only low muscle strength (criterion 1); 24 patients presented with sarcopenia (criteria 1 &2), and 24 with severe sarcopenia (criteria 1, 2 & 3). In patients who presented with probable sarcopenia, sarcopenia and severe sarcopenia, osteoporosis was diagnosed in 32%, 58% and 62% of patients respectively (p=.000). In multivariate logis- tic regression analyses adjusted for age, sex, MOF, BMD (normal vs. osteopenia vs. osteopo- rosis), only age was significantly associated with sarcopenia (OR=1.06; 95% CI 1.04-1.07). Conclusion: In patients with a recent fracture attending the FLS for fracture risk evaluation, one out of seven patients can be identified with probable sarcopenia, while only 3.1% were diagnosed with sarcopenia and 1.5% with severe sarcopenia according to the recently updat- ed EWGSOP definition of sarcopenia.
Disclosures: Caroline E. Wyers*, None*

P-44

TRAF6 mediates impaired muscle regeneration induced by TNFα *Xiangjiao Yi[1],Jinbo Li[1],Lianping Xing[1],Zhenqiang Yao[2],Brendan Boyce[2]. [1]Pathology , United States,[2]Pathology, United States

TNFα induces muscle loss and inhibits myogenesis and muscle regeneration. Signal- ing through TNF receptors (TNFRs) requires TNF receptor-associated factors (TRAFs), in particular, TRAF6, which mediates denervation-induced muscle atrophy by increas- ing expression of the muscle-specific E3 ubiquitin ligase, muscle atrophy F-box (MAF- bx), and promotes myosin heavy chain (MyHC) ubiquitination and degradation. Unlike MyHC, TRAF6 ubiquitination leads to its activation. However, if and how TRAF6 mediates TNF-induced impairment of muscle regeneration is unclear. We generated TNF transgenic (TNF-Tg)/TRAF6+/- double mutant (DM) mice to study the effect of TRAF6 reduction on TNF-induced muscle damage and regeneration following injury. Without injury, TNF-Tg mice have significant muscle atrophy (tibialis anterior (TA) muscle fiber area: 1589+/-353 vs 3306+/-65μm2 in WT; $p<0.001$) associated with a 2-3 fold increase in TRAF6 protein and mRNA levels. These parameters were restored to normal WT levels in DM mice. 5 days post BaCl2 injury, the muscle damage area was significantly higher in TNF-Tg mice (47+/-2% total muscle area) than in WT mice (29+/-5) and it was reduced to WT levels in DM mice (29+/-10, $p<0.05$ vs TNF-Tg), evaluated by TA H&E staining. Interestingly, mean cross-sectional area of MyHC-positive myofibers, which reflects muscle regeneration, was significantly lower in TNF-Tg mice (296+/-29μm2) than WT (482+/-55; $p<0.001$) and it was significantly increased in DM mice (372+/-35, $p<0.05$ vs TNF-Tg). Mechanistical- ly, TNF increased TRAF6 mRNA expression and protein levels in C2C12 cells as well as binding of TRAF6 to TNFR2, but not 1 (by IP and WB), associated with increased TRAF6 ubiquitination, which

positively correlates with TRAF6 activity. The ubiquitinated TRAF6 level was higher in the gastrocnemius (GN) of TNF-Tg than WT mice. Of note, TNFα in- creased the mRNA level of MAFbx 3.4-fold in C2C12 cells. Consistent with this, MAFbx mRNA levels were 2.2-fold higher in the GN of TNF-Tg than WT mice, associated with an increase in ubiquitinated MyHC protein and reduced total MyHC protein levels, while levels of these parameters in the GN of DM mice were effectively rescued to levels similar to WT mice. Our findings indicate that TNFα promotes TRAF6 transcription, activation and bind- ing to TNFR2, leading to increased levels of MAFbx and ubiquitin-mediated degradation of MyHC. Thus, pharmacologic inhibition of the destructive TNF-TRAF6 signaling axis could enhance muscle regeneration.

***Disclosures: Xiangjiao Yi**, None*

P-45

Toward a novel muscle anabolic strategy for sarcopenia: targeting the interaction between long noncoding RNA lncRNA-3 and MyoD1 promoter to promote myogenesis *Zong-Kang Zhang[1],Zhenjian Zhuo[1],Bao-Ting Zhang[1],Daogang Guan[2],Aiping Lu[2],Ge Zhang[3]. [1]School of Chinese Medicine, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong,[2]Institute of Integrated Bioinformedicine and Translational Science, School of Chinese Medicine, Hong Kong Baptist University, Hong Kong,[3]Institute for Advancing Translational Medicine in Bone & Joint Diseases, School of Chinese Medicine, Hong Kong Baptist University, Hong Kong

Sarcopenia, age-related loss of skeletal muscle mass and strength, is associated with serious health consequences, but there is no clinically established therapy for sarcopenia to date. Here, we identified a sarcopenia-related lncRNA (lncRNA-3), which was significantly up-regulated in gastrocnemius muscle of aged sarcopenic mice (Figure 1). LncRNA-3 neg- atively regulated muscle mass and MyoD protein level in skeletal muscles of mice (Figure 2). Mechanistically, lncRNA-3 could interact with RbAp46/48, a subunit of Polycomb re- pressive complex 2 (PRC2), guide PRC2 to MyoD1 promoter, in turns catalyze the methyl- ation of histone H3 at lysine 27 (H3K27) at MyoD1 promoter region and mediate MyoD1 gene silencing (Figure 3). Skeletal muscle-specific knockdown of lncRNA-3 promoted MyoD1 mRNA level and muscle mass in muscle-specific lncRNA-3 knockin mice (Figure 4). Low conservation in sequence limits the translation of lncRNA research. LncRNA-3 was functionally conserved in human (lncRNA-3H), which was also interacted with PRC2 and MyoD1 promoter. LncRNA-3H knockdown promoted MyoD1 mRNA level and ln- cRNA-3H overexpression inhibited MyoD1 mRNA level in human skeletal muscle cells (Figure 5). To interfere with the interaction between lncRNA-3 and MyoD1, the MyoD1 promoter sequence was overexpressed in C2C12 cells and the skeletal muscle of aged mice. The cell differentiation of C2C12 cells was enhanced after MyoD1 promoter overexpres- sion (Figure 6). Enhanced MyoD1 promoter expression in skeletal muscle suppressed the function of lncRNA-3 and counteract sarcopenia development in aged mice (Figure 7). The study uncovered the functional role of lncRNA-3 as an epigenetic regulator (Figure 8) and suggested the interaction between lncRNA-3 and MyoD1 promoter could be a potential therapeutic target to counteract sarcopenia development. It also provided a novel therapeutic strategy which to target the interaction between lncRNA and its conserved target protein or gene to overcome the limitation of low conservation of lncRNAs. Acknowledgments: This study was supported by the Hong Kong General Research Fund (14112915 and 14100218) and Direct Grant of The Chinese University of Hong Kong (2017.077).

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