IBDW/ESUCB

21st International Bone Densitometry Workshop

7th European Symposium on Ultrasonic Characterization of Bone

June 26-30, 2017
Monastery Banz | Germany

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Dear colleagues and friends,

with great pleasure we welcome you to the 21st International Bone Densitometry Workshop (IBDW) and the 7th European Symposium on Ultrasonic Characterization of Bone (ESUCB). We are proud to continue the tradition of these conference series, which started in 1979 in San Francisco and 2005 in Paris. One of the main intention of these meetings is the introduction and critical discussion of novel technologies and applications for the quantitative assessment of the skeleton. Today, this topic is as relevant as it has been several decades ago but the scope of this meeting has broadened significantly covering now the range from bone material characterization at multiple length scales to quantitative bone, and for the first time, muscle imaging to clinical applications in osteoporosis, rheumatoid, and osteoarthritis.

The combination of the IBDW and ESUCB meetings is an important milestone to achieve synergistic effects. Today, quantitative bone ultrasound is an exciting research field. Several ultrasound sessions of general interest have been integrated in the main program to share this information with all participants while the parallel sessions are dedicated to more in-depth technical information.

We really appreciate the support of many sponsors that allowed us to invite more than 30 young researchers to the workshop to demonstrate the full extent of our field, to give them the audience for presentation and discussion of their results and to let them benefit from the advice of experienced researchers, many of them who have organized prior workshops of this series, including their founders Harry Genant and Pascal Laugier.

The large participation of researchers not only from Europe but also from Asia, North, Central and South America, and Australia again demonstrates the international character of our field. Many participants have been or are collaborating on joint projects and it is an important aim of our workshop to strengthen the existing ties between academic and industrial partners. We encourage all attendees to join the discussions and to develop new innovative ideas and future programs.

We hope that the setting of the conference in the former monastery of Banz will stimulate these goals. Last but not least Franconia and in particular the area around Banz and Bamberg has the highest density of beer breweries in Germany. The local ‘beer gardens’ provide good beer and food under shady trees, which hopefully offers the perfect occasion for contemplation, discussion, scholarship, research and education.

Kay Raum   Tobias Bäuerle   Klaus Engelke

For further information visit us at the ASBMR 2017 or contact meanwhile trip@medimapsgroup.com
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**Legend**
- **IBDW**
- **ESUCB**
- **Keynote**
- **Poster**
- **Workshop**
Monday, June 26th

09:00 – 10:30

**DXA & QCT – New Developments**

Chairs: Harry Genant & Andrew Burghardt

- Feasibility study of quality control methodology for TBS
  - Franck Michelet, Diane Krueger, Neil Binkley

- Volumetric bone segmentation method for comparative bone structural analysis
  - Jérôme Thevenot, Jukka Hirvasniemi, Simo Saarakkala

- Cortical measurements in QCT: still challenging despite progress
  - Olea Museyko, Andreas Friedberger, Klaus Engelke

  > Automatic segmentation of the spine in CT Images using a highly generalisable deep-learning based framework.
  > Anjany Sekuboyina, Jan Kukačka, Jan S. Kruchke, Bjorn H. Menze, Alexander Valentinitsch

- Innovative QCT to differentiate newly formed bone from resorbable calcium sulfate/phosphate implant material injected locally into osteoporotic proximal femurs
  - Olea Museyko, Oleg Museyko, James Howe, Dominique Favell, Ronald Hill, Harry Genant

11:00 – 12:30

**QUS – New Developments**

Chairs: Marie Müller & Guillaume Renaud

- Cortical thickness and porosity assessment on ex vivo radius with axial transmission
  - Quentin Vallet, Jean-Gabriel Minonzio, Nicolas Bochud, Johann Bala, Hélène Fallet, Pascal Laugier

- Ex-vivo validation of the osteoporosis score for estimating bone mineral density through comparison with micro-CT measurements
  - Marco Pecoraro, Tommaso De Marco, Francesco Conversano, Paola Pisani, Ernesto Casciaro, Antonio Greco, Roberto Franchini, Sergio Casciaro

- Ex-vivo multiscale assessment of bone properties by ultrasound
  - Quentin Grimat, Kay Raum

- Fracture discrimination using ultrasound biomarkers of cortical bone
  - Jean-Gabriel Minonzio, Nicolas Bochud, Quentin Vallet, Adrien Etcheto, Karine Briot, Sami Kolta, Christian Roux, Pascal Laugier

- High-frequency backscatter from cortical bone
  - Vantte Kilappa, Jonas Hakenbeck, Gianluca Iori, Kay Raum

13:30 – 15:00

**Poster Session I**

Chairs: Ralph Müller & Juan Du

- 3D characterization of the morphology changes in the intervertebral disc and endplate during aging: A synchrotron CT study
  - Yong Cao, Nishuangfei Fei, Jianzhong Hu, Hongbin Lu

- A research of the correlation of nerve growth factor serum levels and osteoporotic fractures
  - Yupeng Liu, Dewei Zhao

- Assessing volumetric bone mineral density in adolescent idiopathic scoliosis: Quantitative computed tomography vs high-resolution peripheral quantitative computed tomography
  - Elisa Man-Shan Tam, Fiano WP Yu, Wai Ho Hung, Lin Shi, Ling Qin, Bobby KW Ng, Winnie CW Chu, James Griffith, Jack CT Cheng, Tsz Ping Lam

- Assessment of cortical bone in hemodialysis patients using ultrasound-evaluation of the usefulness of cortical QUS
  - Ayachi Suresh, Takayuki Harano, Isao Matsui, Satoshi Mikami, Yasue Obi

- Dependence of cortical bone anisotropic elasticity on anatomical location
  - Laura Peralta, Arien Cai, Pascal Laugier, Kay Raum, Quentin Grimat

- Femoral neck cortical bone stiffness measured by resonant ultrasound spectroscopy correlates strongly with its density
  - Oliver R Boughton, Xiran Cai, Laura Peralta, Shaocheng Ma, Ulrich Hansen, Richard Abel, Pascal Laugier, Justin P Cobb, Quentin Grimat

- Long bone fatigue evaluation using coded nonlinear ultrasonic guided wave
  - Fiao Xu, Dan Liu, Chengcheng Liu, Lawrence H. Le, Dean Ta

- Non-ionized microwave radiation on decalcified bone samples: instigating correlative bone analysis
  - Thadh El Khassawna, Diao Eldin S. Daghma, Deeksha Malhan, Christian Heiss

- Protocols for serial block-face scanning electronic microscopy of bone tissue
  - Patricia Goggin, Elaine Ho, Richard O C Oreffo, Philipp Schneider

- Toward measuring elastic properties of small animal cortical bone using resonant ultrasound spectroscopy: An aluminium phantom study
  - Kailiang Xu, Pascal Dargent, Pascal Laugier, Quentin Grimat

15:00 – 15:30

**K1 – Past, presence and future of quantitative bone ultrasound**

Speaker: Pascal Laugier

15:30 – 17:00

**High-Resolution In-Vivo Imaging I**

Chairs: Georg Schett & Gianluca Iori
Scientific Program – Monday, June 26th

Differing patterns of age-related bone loss between Chinese men and women: A population-based HR-pQCT study
Tracy Y. Zhu, Vivian WY Hung, Carol WY Choy, Carol KL Cheng, Jack CY Cheng, Ling Qin

Constructing age-specific reference curves for volumetric BMD and bone microarchitecture from HR-pQCT: The normal reference study
Tracy Y. Zhu, Vivian WY Hung, Carol WY Choy, Carol KL Cheng, Jack CY Cheng, Ling Qin

Lower trabecular density determines estimated bone strength in radial HR-pQCT measurements in rheumatoid arthritis patients – preliminary results
Fabian Stemmer, Anna-Maria Liphardt, David Simon, Juergen Rech, Axel Hueber, Georg Schett, Klaus Engelke, Arnd Klauser

Microarchitectural deterioration in patients with chronic kidney disease
Ali Ghasem-Zadeh, Rizwan Jaipurwala, Peter Mount, Xiaofang Wang, Leniod Churilov, Sandra Iuliano, Roger Zebaze, Cherie Chiang, Ego Seeman

The common region of interest between fixed offset and relative offset protocols in high-resolution peripheral quantitative computer tomography

17:30 – 19:00

FEA & Bone Strength
Chairs: Philippe Zysset & Graeme Campbell

A fast homogenized finite element approach for distal radius strength calculations from HRpQCT images
Andrés Julián Arias-Moreno, Hadi S. Hosseini, Kerta Ito, Philippe K. Zysset, Bert van Rietbergen

Cortical bone histomorphometry of the human femoral shaft: Relations with hip strength
Gandrafa Bay, Andreas Reisinger, Laura Peralta, Melanie Graisel, Reinhard Barkmann, Dieter Pahr, Kay Raum

QCT-based finite element estimation of hip strength: Role of anisotropy
Janurani Panyasaitiurai, Ghislain Maquier, Enrico Dall’Ara, Dieter Pahr, Philippe Zysset

The relationship between advanced glycation endproducts and local bone mechanics using fluorescence microscopy and reference point indentation
Graeme M. Campbell, Felix N. Schmidt, Michael M. Morlock, Bjorn Busse

Effects of subject-specific geometry, bone density and loading conditions on the strains at the femur neck
Pim Pelletizen, Zohra Asahampour, Ise Jonkers, G. Harry van Lenthe, Jos Vander Sloten

20:30 – 21:30

W1 DXA – Basic Concepts, Assumptions and Error Sources
Speaker: Kevin Wilson

20:30 – 21:30

W2 Creating FE Models from CT Data
Speaker: Dieter Pahr

Scientific Program – Tuesday, June 27th

Tuesday, June 27th

09:00 – 10:30

Opportunistic Screening
Chairs: John Shepherd & Klaus Engelke

Automatic re-dose analysis of bone mineral density in an incidental screening scenario
Wolfram Timm, J. Keenan Brown, Claus C. Gluer, Reimer Andriesen

Discrepancies between synchronous and asynchronous phantom based BMD calibration in QCT
Olga Muschev, S. Holz, P. Dankerl, M. Uder, Klaus Engelke

Opportunistic fracture risk estimation based on multi-detector CT images of the spine via local classification of textures
Alexander Valentinitsch, Stefano Trebeschi, Johannes Kaesmacher, Thomas Baum, Jan S. Kirschke

Opportunistic identification of osteoporotic vertebral fractures with computed tomography: clinical practice compared to a semi-automatic computer-assisted diagnosis system
Eleni P. Kariki, Paul A. Bromiley, Timothy F. Cootes, Judith E. Adams

Validation of asynchronous quantitative bone densitometry of spine: Accuracy, short-term reproducibility, and a comparison with conventional quantitative computed tomography
Ling Wang, Xiaoguang Cheng, Yongbin Su, Qiangian Wang

09:00 – 10:30

US – Guided Waves
Chairs: Mami Matsukawa & Xiran Cai

Application of dispersive Radon transform to process ultrasonic guided waves signals in long cortical bone
Kailiang Xu, Pascal Laugier, Jean-Gabriel Minonzio

Assessment of cortical thickness and elasticity using ultrasonic axial transmission
Nicolas Bouchud, Quentin Vallet, Xiran Cai, Quentin Grimard, Jean-Gabriel Minonzio, Pascal Laugier

Cortical thickness and porosity assessment on ex-vivo tibia with axial transmission
Johannes Schneider, Donatien Ramiandriosa, Gianluca Iori, Melanie Graisel, Reinhard Barkmann, Kay Raum, Pascal Laugier, Jean-Gabriel Minonzio

Low-cost Lamb wave characterization technique using one transmitter and two receivers: An experimental study
Shintoshi Okumura, Yu-Heu Nguyen, Hirofumi Taki, Toru Sato

Suitability of low-frequency axial transmission acoustics as a screening method for bone mass density-defined osteoporosis
Florian Voel, Bernd Friesebichler, Hans Gerber, William R. Taylor, Ines Anne Kramers-de Quervain
11:00 – 12:30

**Future US Cortical Bone Biomarkers**

Chairs: Reinhard Barkmann & Florian Vogl

A new QUS approach for measuring cortical porosity and other bone properties relevant for discriminating patients with different mineralization statuses
Melanie Grasel, Claus C. Gluer, Reinhard Barkmann

Characterization of cortical bone using multiple scattering of ultrasound
Yasamin Karbalaeisadegh, Omid Yousefi, Gianluca Iori, Kay Raum, Mike Muller

Estimation of cortical bone porosity by applying traditional and multivariate analysis on ultrasound pulse-echo signals – a FDTD study
Satu Inkinen, Juha Toyras, Jukka Jurvelin, Markus Malo

Imaging of cortical pores using ultrasound contrast agents: A phantom study
Jian Yu, Melanie Grasel, Reinhard Barkmann, Kay Raum

Ultrasound imaging of cortical bone at the distal radius
Guillaume Renaud, Peter Kruizinga, Pascal Laugier

11:00 – 12:30

**Fractures & Implants**

Chairs: Bert v. Rietbergen & Timo Damm

Effect of preparation method and bone mineral density on bone-interface densification in hip arthroplasty
Johanna Bots, Philipp Messer, Frank Lampe, Klaus Pauschel, Anke Klein, Michael M. Morlock, Graeme M. Campbell

Effect of semi-automatic contouring on short-term reproducibility of bone parameters obtained from HRpQCT measurements of distal radius fractures
Fanni Heuer, Jacobus de Jong, Martin Poeze, Paul Willems, Bert van Rietbergen, Joop van den Bergh

Fabrication of oriented hydroxyapatite film by RF magnetron sputtering
Takahumi Kubota, Keshiro Hirata, Kazuma Mori, Shohei Tokuda, Daisuke Koyama, Mami Matsukawa

Quantitative assessment of radial bone structural distribution in the proximity of degradable implants by micro-computed tomography
Tomo Dominy, H. Naujokat, J. Willfang, Claus C. Gluer

Spatial assessment of bone microarchitecture in postmenopausal women with a recent Colles’ fracture
Andrew J. Burghardt, James M Peterson, Sundeep Khosla, Julio Carballido-Gamio

13:30 – 15:00

**Poster Session II**

Chairs: Philip Schneider & Marco Peccarisi

Bone densitometry in patients with acromegaly may be misleadingly normal while vertebral fractures are prevalent yet often remain occult
Marko Stojanovic, Dragana Miljic, Sandra Pekic, Mirjana Dokmic, Marina Nikolic Djurovic, Zvezdana Jemudovic, Vera Popovic, Milan Petakov

Estimation of piezoelectric sensitivity at an ultrasound frequency in bovine cancellous bone
Atsushi Hosokawa

Exploratory study of rats femorale bone with experimentally induced diabetes by resonant ultrasound spectroscopy
Paulina Alicia Irais Hernández-Becerra, Miguel Vargas-Luna, María Raquel Huerta-Franco, Isabel Delgadillo-Holtfort, Gabriel Herrera-Pérez, Rafael Vargas-Bernal, Xóchitl Sofia Ramírez-Gómez, Esmeralda Rodríguez-Miranda

Fabrication of a self-assembling poly γ-glutamic acid based nanoparticle loaded triptolide for the treatment of rheumatoid arthritis
Zhang Li, Junli Chang, Yongjian Zhao, Hao Xu, Tengteng Wang, Qiang Li, Yongjun Wang, Qianqian Liang

Microstructural decay in spinal cord injury
Ali Ghasem-Zadeh, Roger Zebaz, Andrew Kunn, Maya Panissit, Xiao-Fang Lian, Mary P Gales, Ego Seeman

Prevalence of sarcopenia in community dwelling German males and females 70+ using different recognized definitions. A BIA based approach
Wolfgang Kemmler, Simon von Stengel, Klaus Engelke

Sexual dimorphism in cortical bone morphology during pubertal growth in Chinese adolescents
Ka-Yee Cheuk, Xiaofang Wang, Fiona Wong, Yu, Elisa Man-Shan Tam, Bobby Kin-Wah Ng, Ti Ping Lui, Ali Ghasem-Zadeh, Roger Zebaz, Ego Seeman, Jack Chun-Yiu Cheng

Skeletal site and location dependent elastic properties of human cortical bone measured by resonant ultrasound spectroscopy
Xiran Cai, Laura Perrella, Quentin Vallet, Nicolas Rochod, Oliver Boughton, Richard Abell, Justin Cobb, Kay Raum, Jean-Gabriel Minonzio, Pascal Laugier, Quentin Grimal

Ultrasound computed tomography based on full-waveform inversion for bone quantitative imaging
Simon Renaud, Vladimir Monteleone, Dimitri Komatitsch, Philippe Lasaygues

Ultrasonically induced electrical potentials in bovine cortical bone
Taiki Muroka, Koki Takano, Takafumi Kubota, Sayaka Matsukawa, Shinji Takayanagi, Takahiko Yanagitani, Mami Matsukawa
Scientific Program – Tuesday, June 27th

15:00 – 15:30
K2 – Impact of deep learning and big data analysis in MSK radiology
Speaker: John Shepherd

15:30 – 17:00
Clinical Applications I
Chairs: Jean-Denis Laredo

Estimation of fracture risk based on the concept of the muscle bone unit
Rainer Rawer, Johannes Willnecker

Optical body shape phenotypes using statistical shape modeling for predicting osteopenia, sarcopenia, and obesity status in women
John Shepherd, M. Sommer, Ey. Liu, B. Fan, B. Ng, J. Mastick, C. Miaskowski

Personalised bone health prognosis through integrated patient big data analysis of medical images, molecular profiles and physical activity levels
Nicholas Ohs, Jan Kleffmann, Yuk-Wai Wayne Lee, Chun-Yiu Jack Cheng, Peter Arbenz, Ralph Müller, Patrik Christen

Unique correlation pattern between cortical and trabecular bone qualities and standard dynamometer grip strength in girls with adolescent idiopathic scoliosis
Duncan C. Betts, Elliott Goff, Michele Casanova, Zihui Li, Patrik Christen, Ralph Müller

Prevalence of trabecular microcalli in human vertebrae increases with alendronate treatment
Annika vom Scheidt, Michael Amling, Klaus Püschel, Björn Busse

Three-dimensional imaging of crack path and osteonal microstructure in human cortical bone on three paired anatomical locations
Rémy Gauthier, Max Langer, Hélène Fallet, Cécile Olivier, Frédéric Rongiéras, David Motton, Françoise Peyrin

Extending Synchrotron X-ray Microscopy to the Laboratory_X-Ray Microscopy as a correlative imaging technique
Mohsen Samadi

Whole body vibration therapy reduces local peak loading in the distal tibia of girls with adolescent idiopathic scoliosis
Gianna Marano, Yuk-Wai Wayne Lee, Tsz-Ping Lam, Ralph Müller, Patrik Christen

17:30 – 19:00
Advanced Microscopy & Tomography
Chairs: Ling Qin & Duncan Betts

Assessment of the lacuno-canicular network in human bone from magnified phase nano-CT images
Boliang Yu, Max Langer, Alexandra Pascuenska, Cécile Olivier, Pierre-Jean Gouttenoire, Peter Cloetens, Françoise Peyrin

Nano-imaging of bone mineral using qSAXSI: a contribution to specifying bone quality
Aurélien Gouzet, Manana Verezhak, Hélène Fallet, Delphine Farlay

Osteocyte lacuna segmentation from ultra-high resolution desktop micro-CT images: Low precision reveals limitation of state of the art
Duncan C. Betts, Elliott Goff, Michele Casanova, Zhi Li, Patrik Christen, Ralph Müller

20:30 – 21:30
W3 DXA: Advanced Applications
Speaker: John Shepherd

W4 Small Animal Imaging Techniques
Speaker: Claus Glüer & Tobias Bäuerle
Scientific Program – Wednesday, June 28th

Wednesday, June 28th

09:00 – 10:30

Small Animal Imaging
Chairs: Sharmila Majumdar & Christine Chappard

3D digital anatomic angiarchitecture of the mouse spinal cord: A synchrotron radiation micro-CT study
Hongbin Lu, Yong Cao, Nishuangfei Fei, Jianzhong Hu

In-vivo tracking of individual cortical bone remodeling events in a rabbit model
Arash Panahifar, Kimberly Harrison, David M. L. Cooper

Therapeutic effects of low-intensity pulsed ultrasound with different intensities on osteoporosis in OVX rats
Shuoin Sun, Lijun Sun, Liang Tang, Ying Kang, Tingting Zhao, Tao Zhou, Dean Ta

Using active shape models to quantify impeded skeletal development in an early-onset rat model of type 2 diabetes mellitus
Graeme M. Campbell, Ann-Kristin Picke, Christine Hofbauer, Bjørn Busse, Lorenz C. Hofbauer, Michael M. Morlock

Visualization and pathological characteristics of cartilage and subchondral bone change in lumbar facet joint OVX mouse model using PPCT imaging
Jian-Zhong Hu, Yong Cao, Hongbin Lu

11:00 – 12:30

Cell & Molecular Imaging
Chairs: Claus Glüer & Tobias Bäuerle

Assessment of bone marrow metabolism by FDG PET allows early detection of experimental osteolytic bone metastasis
Stephan Eimann, Lisa Seyler, Jochen Evers, Henrik Heinen, Michael Uder, Tobias Bäuerle

Dual energy synchrotron X-ray imaging of bone-seeking tracer elements
Arash Panahifar, Nazanin Samadi, L. Dean Chapman, David M. L. Cooper

IL-20R1, IL-22R1 and bone quality: new therapeutical targets against bone fragility and osteoporosis
Julia Triebus, Gianluca Iori, Johannes Schneider, Kay Raum, Robert Sabat

Material science meets biology: Study of the 3D structural and mechanical environment of cells regulating modeling in bones without osteocytes
Lee Ciley, Elazar Zelzer, Paul Zaslansky, Ron Shahar

Receptor-specific imaging in experimental breast cancer bone metastasis by MRI and PET using a signal amplification strategy
Aleksei Bogdanov, Suresh Gupta, Aurora Rodríguez-Rodríguez, Peter Caravan, Zheng Shaokuan, Tobias Bäuerle

13:30 – 15:00

High-Resolution In-Vivo Imaging II
Chairs: Steven Boyd & Frans Heyer

Bone structural analysis of CT-images of OA knees comparing subchondral bone under meniscus and not under meniscus
Frederike Sannmann, Christine Chappard, Jean-Denis Laredo, Klaus Engelke

BMD-calibrated measurements of local porosity in human femoral cortical bone
Gianluca Iori, Vantte Kilappa, Frans Heyer, Caroline Wyers, Peter Varga, Johannes Schneider, Joop van den Bergh, Kay Raum

Human knee bone microarchitecture six years post anterior cruciate ligament reconstructive surgery as assessed by HR-pQCT
Andres Kroker, Sarah Manske, Ying Zhu, Rhamona Barber, Nicholas Mohtadi, Steven Boyd

Optimising the quantification of bone microstructure in the human calcaneus using HR-pQCT
Louis M. Metcalf, Jenna A. Fogden, Rhea H. Patel, Margaret A. Paggio, Graham J. Kemp, Eugene V. McCloskey

Three-dimensional mapping of the joint space for knee osteoarthritis based on high-resolution computed tomography: A multiscale analysis
Houda Mezlini-Gharallilat, Rabaa Youssef, Jean Denis Laredo, Christine Chappard
Thursday, June 29th

09:00 – 10:30

**Numerical US Simulation Models**
Chairs: Dean Ta & Melanie Gräsel

- A real-size FDTD simulation of ultrasound propagation inside human radius
  Yoshiki Nagatani, Isao Mano, Mami Matsukawa, Koki Takara, Ko Chiba

- Bone repair and ultrasound stimulation: a multiscale computational study
  Cécile Baro, Carne Guivier-Curien, Yu-Heu Nguyen, Salah Nall

- Influence of trabecular microstructure on the simulation of ultrasound through the skull
  James L. B. Robertson, Jillian E. Urban, Joel D. Stitzel, Ben T. Cox, Bradley E. Treeby

- Physical and mathematical modeling of guided waves propagation in cortical bone in presence of soft tissues
  Alexey Tatarinov, Arcady Soloviev, Vladimir Panov

Simulation study on axial ultrasound propagation in cortical bone model – effects of shape and heterogeneity
Koki Takara, Yoshiki Nagatani, Mami Matsukawa

09:00 – 10:30

**Bone & Soft Tissue**
Chairs: James Griffith & Andreas Friedberger

- Integrating dual energy X-Ray and 3D surface imaging for enhanced multicompartment tissue composition assessment: The Ultra DXA project
  Bennett K. Ng, Wei Wang, Chao Huang, Howard Weiss, Thomas L. Kelly, Kevin E. Wilson, John A. Shepherd

- Magnetic Resonance Imaging (MRI) and Spectroscopy (MRS) methods for quantitative evaluation of intramuscular adipose tissue (IMAT)
  Alexandra Grimm, Heiko Meyer, Matthias Nittka, Esther Raithel, Oliver Chaudry, Andreas Friedberger, Michael Uder, Wolfgang Kemmler, Harald R. Quick, Klaus Engelke

- Predicting body composition from forearm and lateral distal femur hologic bone densitometry scans
  Bo Fan, Bennett K. Ng, Natasha Din, Leila Kazemi, Babette Zemel, Heidi Kalkwarf, Andrea Kelly, James Heubi, Kimberly Tolman, Amir Pasha Mahmoudzadeh, John Shepherd

- Quantification of muscle fat fraction from a combined analysis of T1 weighted and dixon MRI images of the thigh
  Oliver Chaudry, Andreas Friedberger, Alexandra Grimm, Marc Teschler, Oleg Museyko, Wolfgang Kemmler, Klaus Engelke

- Random forest based segmentation of hand muscle in MRI
  Andreas Friedberger, Camille Figueiredo, Oleg Museyko, Alexandra Grimm, Isabelle d’Oliveira, Tobias Bäuerle, Jürgen Reich, Oliver Chaudry, Michael Uder, Georg Schett, Klaus Engelke

11:00 – 12:30

**US – Propagation Models**
Chairs: Quentin Grimal & Yoshiki Nagatani

- The relationship between ultrasonic backscatter propagation properties and cancellous bone microstructural variations
  Xiaoming Chou, Feng Xu, Ying Li, Chengcheng Liu, Dean Ta

- Contrast resolution enhancement in ultrasonic computed tomography of bones by way of a wavelet-based coded excitation method
  Philippe Lozyraou, Khaid Metwally, Cecile Baron, Samantha Fernandez, Laura Balosse

- Studying the effect of porosity and pore size in cortical bone on ultrasonic parameters
  Omid Yousefiyan, Yasamin Karbalaeisadegh, Gianluca Ion, Kay Raum, Marie Muller

- Ultrasonic backscatter characterization of cancellous bone using Nakagami model
  Chengcheng Liu, Boyi Li, Ying Li, Feng Xu, Dean Ta, Weiqi Wang

11:00 – 12:30

**Bone Structure & Texture**
Chairs: Françoise Peyrin & Tracy Y. Zhu

- A multiscale analysis of tibial subchondral bone micro-architecture based on cone beam computed tomography
  Gaëlle Mitton, Hamid Bouhadou, Elza Budyn, Klaus Engelke, Jean Denis Laredo, Christine Chapard

- Fractal texture phantom for TBS calibration
  Franck Michelet, Christophe LeLon

- Quantification of bone microstructure using cone-beam computed tomography
  Karen My, Filip Stockmans, Eve Vereecke, G. Harry van Lenthe

- Quantitative comparison of different micro CT based trabecular bone image analysis software tools
  Pierre Paly, Lukas Steiner

- Relationships between cortical bone microstructure and the effective mesoscopic elasticity
  Yuan Cao, Renald Brenner, Laura Peralta, Cécile Olivier, Pierre-Jean Gouttenoire, Françoise Peyrin, Pascal Laugier, Quentin Grimal

15:00 – 15:30

**K3 – Fancy ways of looking at muscle**
Speaker: James F. Griffith

15:30 – 17:00

**Clinical Applications II**
Chairs: Valerie Bousson & Alexander Valentinitisch
Scientific Program – Thursday, June 29th

Calcium plus Vt D for adolescent idiopathic scoliosis: A randomized double-blinded placebo-controlled trial using HR-pQCT and FEA
Tsz Ping Lam, Benjamin Hon-kei Yip, Xi-ye Cheuk, Elisa Man-shan Tam, Wayne Yuk-wai Lee, Kwong-man Lee, Fiona Wai-ping Yu, Alec Lik-hang Hung, Bobby Kin-wah Ng, Jack Chun-yiu Cheng, Vivian Hung

Osteoporotic fracture in elderly Chinese men and women: A comparison of vertebral-cortex-fracture based and vertebral-deformity based methods
Min Deng, James F. Griffith, Jason Leung, Anthony Kwek, Timothy Kwek, Ping Chung Leung

Persistent Low Bone Mass (LBM) at Maturity in Adolescent Idiopathic Scoliosis(AIS) Patients – A 4-year Longitudinal Follow-up Study
Wai Ping Fiona Yu, Vivian Woon Yu Hung, Benjamin Hon Kei Yip, Ling Qin, Tsz Ping Lam, Jack Chun Yu Cheng

Short-term monitoring of Denosumab treatment effectiveness on BMD recovery in breast cancer patients assessed through the echosound approach
Pamela Pino, Maurizio Muratore, Francesco Conversano, Marco Di Paola, Rosalia Forcignano, Manuela Ciccarese, Giarmamco Corsa, Laura Quarta, Eugenio Quarta, Richard Taparelli, Sergio Caccia

Thoracolumbar intervertebral disc area morphometry in elderly Chinese: radiographic quantifications at baseline and year-4 follow-up
Jun-Qing Wang, Zoltan Kapištor, Jason Leung, James F. Griffith, Ping Chung Leung, Yi-Xiang Wang

17:30 – 19:00
Measurement & Interpretation of Material Properties
Chairs: Mary Bouxsein & Aurelien Gourrier

Determination of anisotropic elastic properties of cortical bone matrix using FFT-based inverse homogenization
Seán Cao, Laura Peralta, Renald Brenner, Pascal Laugier, Quentin Grimal

CT calibration for micro structural parameters on multi-site studies
Felix Sebastian Leo Thomsen, Claus C. Glüer, Claudio Augusto Delrieux

Evaluation of trabecular tissue stiffness in patients with atrophic vertebral fractures
Johannes Schneider, Matthias Pumberger, Michael Putzier, Kay Raum

On the cortical bone elasticity, toughness and bone quality
Seán Cao, Remy Gauthier, Laura Peralta, Yelène Follet, Evelyne Gireyts, Max Langer, BoXIang Yu, Cécile Olivier, Françoise Peyrin, Pascal Laugier, David Minton, Quentin Grimal

Trabecular tissue Young’s modulus assessed from resonant ultrasound spectroscopy
Hassiba Daoui, Xian Cai, Fouad Bouhinder, Pascal Laugier, Quentin Grimal

Scientific Program – Friday, June 30th

Friday, June 30th

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W5 US Hands On Workshop: High-Frequency Ultrasound Backscatter I
Speaker: Marie Mueller

09:00 – 10:30
W6 US Hands On Workshop: Guided Wave Signal Processing
Speaker: Jean-Gabriel Minonzio

11:00 – 12:30
W7 US Hands On Workshop: High-Frequency Ultrasound Backscatter II
Speaker: Kay Raum & Juan Du

11:00 – 12:30
W8 QCT – How Does It Really Work?
Speaker: Klaus Engelke

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<td>James Robertson</td>
<td>University College London, London, United Kingdom</td>
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<td>Frederike Sannmann</td>
<td>University of Erlangen, Erlangen, Germany</td>
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<td>Anjany Sekuboyina</td>
<td>Technische Universität München, Munich, Germany</td>
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<td>John Shepherd</td>
<td>University of California San Francisco, San Francisco, USA</td>
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<tr>
<td>Marko Stojanovic</td>
<td>Clinic for Endocrinology, Clinical Centre of Serbia, University of Belgrade, School of Medicine, Belgrade, Serbia</td>
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<td>Alexander Valentiniitsch</td>
<td>Technische Universität München, Munich, Germany</td>
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<td>Bert van Rietbergen</td>
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<td>Florian Vogl</td>
<td>Institute of Biomechanics, ETH Zurich, Zurich, Switzerland</td>
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<tr>
<td>Annika vom Scheidt</td>
<td>University Medical Center Hamburg-Eppendorf, Hamburg, Germany</td>
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<tr>
<td>Ling Wang</td>
<td>Beijing Jishuitan Hospital, Peking University, Beijing, China</td>
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<td>Vivian Wing Yin Hung</td>
<td>The Chinese University of Hong Kong, Shatin, N.T., China</td>
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<td>Boliang Yu</td>
<td>Villeurbanne, France</td>
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<tr>
<td>Tracy Y. Zhu</td>
<td>Dept. of Orthopaedics &amp; Traumatology, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong SAR, China</td>
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<td>Philippe Zysset</td>
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Effects of subject-specific geometry, bone density and loading conditions on the strains at the femur neck

Pim Pellikaan¹, Zahra Asgharpour², Ilse Jonkers³, G. Harry van Lenthe¹, Jos Vander Sloten¹

Zahra.Asgharpour@materialise.be

¹ Biomechanics Section KU Leuven, Belgium
² Materialise NV, Leuven, Belgium
³ Human Movement Biomechanics Research Group KU Leuven, Belgium

Introduction
In order to quantify bone fragility at the hip and to predict bone adaptation processes as a result of mechanical loading, an accurate strain quantification is necessary. Several finite element models, which can provide detailed information on the strain levels in the bone, have been presented. Yet, these models differ in several aspects such as geometry, relationships between bone density and material properties [1] and loading conditions. A full understanding on how these model parameters affect the calculated strains is lacking. Therefore, the aim of this study was to quantify the effects of subject-specific geometry, density, and loading conditions on the strains at the femur neck.

Methods
CT scans of the femur and gait data at several speeds of walking and running were collected from 9 elderly women, 70.1 ± 3.6 years old. Full-body generic and subject-specific musculoskeletal models were used to calculate hip contact and muscle forces for each gait speed [2]. CT-based FE models were generated; material properties were estimated from a template or subject’s CT using the Mimics Innovation Suite (Materialise NV, Leuven, Belgium) by relating Hounsfield units to bone density [3] and bone density to Young’s modulus [4]. Peak minimal and maximal principle strains were calculated at the inferior and superior part of the femur neck.

Results
Principle strains for the generic models were around twice as high compared to the subject-specific models (Fig. 1). Furthermore, the geometry and bone density from the subject’s CT had a greater influence on the calculated strains than the loading conditions.

Discussion
Results showed a clear need for subject-specific models to obtain reliable results for each individual. However, creating subject-specific models is highly time consuming and therefore generic models are often used to speed up the process regardless of their potential inaccuracies. Scripting appears very attractive to create patient-specific models in a fast and accurate manner.

References
Feasibility study of quality control methodology for TBS
Franck Michelet1, Diane Krueger2, Neil Binkley2
fmichelet@medimapsgroup.com
1 Medimaps SASU, Merignac, France
2 Osteoporosis Clinical Research Program, University of Wisconsin, Madison, United States

Objective
The aim of this study is to develop a TBS Quality Control (QC) methodology using the new TBS phantom.

Material & Method
TBS phantom data has been acquired on two GE-Lunar devices (iDXA and Prodigy) during 146 non-consecutive days over 11 months. The phantom is composed of a soft tissue part and a fractal metallic part which generates 4 different TBS values. During the first 45 days, two sets of 5 acquisitions were done each day, with complete repositioning between the two sets. Over the following 9 months, a single scan was performed each day. We used data from the 10 first days to create reference values for this QC. Phantom precision for TBS was computed for both devices. We followed the methodology proposed by Lu et al. (JBMR, 1996) using Shewart2 and Tabular CUSUM techniques. TBS precision threshold for the QC was established to be similar to the BMD QC sensitivity. TBS phantom precision was compared to our QC precision threshold.

Results
Phantom precision error is lower than the precision target for both devices (0.007 and 0.003 for Prodigy and iDXA respectively, target was 0.008). No confirmed alarms were risen for either DXA device over the course of this study. Shewart and CUSUM graphs for Prodigy are presented in Fig.1.

Conclusion
This study demonstrates the feasibility of developing a QC approach for TBS. These two devices provided stable measurements during the 11 months of follow-up. The phantom TBS precision is sufficient to perform a daily QC. The number of days required to create a stable reference value, and the minimum number scans each day have to be optimized. Further studies are needed to make sure this method can detect drifts or changes of the TBS values produced by DXA devices.

Bone structural analysis is at utmost interest for bone disorder diagnostics since the architectural adaption of the bone to medical conditions can help practitioners in their daily work. Open cone-beam computed tomography (CBCT) devices offer a new volumetric (3D) imaging solution with low radiation doses but with limited resolution. Here we propose a fully automatic method to segment the bone from CBCT data, using multi-scale 3D local binary patterns (LBPs) -based method to select solely bone structures and their edges from an analysis of bone continuity. Briefly, the method fits multiple spheres at different radius for each studied voxels to assess the surroundings volumetrically and to evaluate the real local bone content from an adaptive Otsu –based approach to estimate voxels weight. To validate the method, both micro-CT (voxel size: 17.4 μm) and cone beam CT (voxel size 200 μm) scans were acquired for a total of 22 human cadaveric tibias. Volumes of interest (subchondral plate and trabecular bone separated) were then selected and co-registered between the two modalities. The automatic segmentation was then applied to the CBCT data and the percentage of bone volume was then calculated for each volume of interest using the developed method to evaluate its accuracy while compared to the micro-CT data. The percentage of bone volume was highly correlated between the modalities (R²=0.88), with a equation close to Y=X for both the trabecular bone and subchondral plate compartments. The results obtained here suggest that the method is insensitive to bone density as the information from both compartments behaved similarly. Here we propose a novel method which gives similar bone information for modalities with high difference in resolution. In the future, this approach can provide new leads for comparative studies between experimental and clinical data.

Volumetric bone segmentation method for comparative bone structural analysis
Jérôme Thevenot1, Jukka Hirvasniemi1, Simo Saarakkala2
jerome.thevenot@oulu.fi
1 Medical Imaging, Physics and Technology Research unit, University of Oulu, Oulu, Finland
2 Department of Diagnostic Radiology, Oulu University Hospital, Oulu, Finland

Objective
The aim of this study is to develop a TBS Quality Control (QC) methodology using the new TBS phantom.
Automatic segmentation of the spine in CT Images using a highly generalisable deep-learning based framework

Anjany Sekuboyina1, Jan Rukačka1, Jan S. Kirschke1, Alexander Valentinitsch2

1 Klinikum rechts der Isar der TUM & Technische Universität München
2 Abteilung für Neuroradiologie, Klinikum rechts der Isar der TUM

Abstracts IBDW/ESUCB 2017

Anjany Sekuboyina, Andreas Friedberger, Klaus Engelke
Institute of Medical Physics, University of Erlangen-Nürnberg, Germany

Introduction
Cortical bone is an important contributor of bone strength but due to the limited spatial resolution of clinical whole body CT scanners its assessment remains difficult. Different segmentation techniques introduced over the recent years will be reviewed and strength and weaknesses compared.

Materials
Main approaches in use for cortical segmentation are (1) global (GT), (2), local adaptive thresholds (LAT), and (3) deconvolution techniques (DT). Threshold based methods do not assume any particular structure of the cortex, whereas DT typically model the cortex as a simple step. For GT the correct threshold shall be used, but there cannot be a single threshold value for all cortical thicknesses. LAT does not depend on predefined values and is quite robust but overestimates the thickness of thin cortex. DT significantly improves the accuracy of thickness but requires true cortical density (BMDref) as input. GT methods can achieve subvoxel accuracy but current model assumptions oversimplify the real cortex (see Figure) and the local determination of BMDref is questionable in the presence of unknown porosity. Also DT is affected by the general complexity of the corresponding inverse problem.

Results
Cortical parameters measured in the total femur by threshold and DT methods were compared using two different reconstruction kernels (low and high resolution) and various BMDref levels. Longitudinal changes were simulated. Dependency of accuracy on model parameters and on resolution was significant. Cortical BMC by LAT was least affected by spatial resolution. One major difficulty of cortical thickness estimation is the absence of a true gold standard with known variations of porosity, pore size and distribution and degree of bone matrix mineralization.

References

Cortical measurements in QCT: still challenging despite progress

Oleg Museyko, Andreas Friedberger, Klaus Engelke
Institute of Medical Physics, University of Erlangen-Nürnberg, Germany

Introduction
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Results
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References

Figure: Compares our approach (red) with Klinder et al. [1] (blue) with the ground truth (yellow contour) as the reference. Top row: Healthy cases. Our method does not suffer from over-segmentations, exactly matching the shape to the vertebral structure. Bottom row: Fractured cases. Our model-free approach captures the unique deformation of the fractured vertebra, as opposed to the model-based method.
Innovative QCT to differentiate newly formed bone from resorbable calcium sulfate/phosphate implant material injected locally into osteoporotic proximal femurs

Klaus Engelke1, Oleg Masyuk2, James Howe1, Dominique Favell3, Ronald Hill1, Hany Geman4
1 Bioclinica Inc, Hamburg Branch, Germany
2 Institute of Medical Physics, University of Erlangen-Nürnberg, Germany
3 AgNovos Healthcare, Rockville, MD 20855, USA
4 Dep. of Radiology, UCSF, San Francisco, USA

Material and Methods

A unique triphasic calcium sulfate/calcium phosphate implant (CI) to treat osteoporosis was injected into the left proximal femur of 12 post-menopausal women (average age 72, range 56-89) with osteoporosis of the hip. QCT images were obtained before and 12, 24 and 315 weeks after the injection. 3D periosteal and endosteal surfaces of the total hip were segmented using standard MIAF procedures. The CI VOIs in the follow-up scans were determined from the difference between post and pre-injection images. In the difference image a threshold T1 was determined from a histogram analysis of the trabecular VOI. All voxels with HU values > T1 defined a preliminary CI VOI, which was refined by removing isolated voxels and improving connectivity. In addition, a second threshold T2 > T1 was used to define a core CI VOI that consisted of presumably non-absorbed CI in the center of the CI VOI. For the preinjection visit a virtual CI VOI was determined by 3D registration, assuming the same size and location as in the 12W visit. Further it was assumed that the core CI at preinjection had the same size as at the CI VOI.

Results

The figure shows multiplanar reformation of one CT dataset from 12W. In all 10 study completers CI had been completely absorbed at 315W (Table). Average volume of the CI VOI almost halved between the 12W and 315W visits two visits while BMD was stable.

Conclusions

Proximal femurs of post-menopausal osteoporotic patients treated with a new local osteo-enhancement procedure (LOEP) and a unique triphasic implant material demonstrated substantial and sustained BMD increase up to 72 months post-treatment which correlated with integrated bone replacing the implant material. These results support the safety and efficacy of this local osteo-enhancement procedure and implant material to treat the effects of osteoporosis in the proximal femur of post-menopausal women.

Cortical thickness and porosity assessment on ex vivo radius with axial transmission

Quentin Vallet1, Jean-Gabriel Minonzio1, Nicolas Bochud1, Yoann Bala2, Hélène Follet1, Pascal Laugier1
1 Sorbonne Universités, UPMC Univ Paris 06, CNRS UMR 7371, INSERM UMR S1146, Latoanatoire d’Imagerie Biomédicale, Paris, France.
2 Univ Lyon, Université Claude Bernard Lyon 1, INSERM UMR 1033, Lyon, France,

Key factors of fracture risk, such as cortical bone thinning and porosity increase, are imperfectly captured with currently available X-ray densitometry techniques. Several studies showed that long bones such as the radius or the tibia behave as waveguide for ultrasound. The axial transmission (AT) technique has been developed to measure the propagation of guided waves (GWs) in the cortical shell along the main axis of bone and to infer from measurements of GWs dispersion curves bone properties, such as cortical thickness and material properties.

Thirty human radii harvested from donors (56 to 96 years) underwent AT measurements using a custom made axial transmission device (Azalée, Paris, France). A singular value decomposition combined with a 2-D spatio-temporal Fourier transform was applied to extract the dispersion curves. A model-based inverse problem solving, along with a genetic algorithms optimization, were used to estimate cortical thickness (CT.Th) and cortical porosity (CT.Por) by fitting a 2-D free transverse isotropic plate waveguide model to the experimental dispersion curves. Independent site-matched reference CT.Th and CT.Por values were obtained using X-ray microcomputed tomography (μCT) with a voxel size of 9 μm. Estimates of CT.Th and CT.Por were successfully obtained on 23 radii out of 30. The poor response of 7 specimens did not allow finding a reliable solution to the inverse problem. Highly significant correlations (p < 0.04) were found between CT.Th and CT.Por estimates and reference values (CT.Th: R2 = 0.84, RMSE = 0.3 mm; CT.Por: R2 = 0.55, RMSE = 2.7 %). No significant bias was observed. The study shows feasibility for characterizing cortical bone using GWs and demonstrates a promising approach for in vivo applications.

JGM: consultant to Azalée, royalties
JGM and PL: cofounders of Azalée, stock options
Research Grant: Azalée

The remaining authors state that they have no conflicts of interest.
Fracture discrimination using ultrasound biomarkers of cortical bone
Jean-Gabriel Minonzio1, Nicolas Bochud1, Quentin Vallet1, Adrien Etcheto2, Katrine Bredt3, Sami Kallol4, Christian Roux5, Pascal Laugier3
1 Sorbonne Universités, UPMC Univ Paris 06, CNRS, INSERM, Laboratoire d’Imagerie Biomédicale, F-75006, Paris, France
2 INSERM, U153, Rheumatology Department, Cochin Hospital, Paris Descartes University, Paris, France

Structural decay of bone is not fully assessed by current X-ray methods, and there is an unmet need in identifying women at risk of fracture who should receive a treatment. Recent axial transmission (AT) techniques exploit the multimode waveguide response of long bones such as the radius. The objective of this cross sectional study was to evaluate if the AT device can discriminate between fractured and non-fractured postmenopausal women.

Two hundred and thirty two postmenopausal women were included, among whom 119 were non fractured (subgroup NF 63±10 years), 103 with one or more non-traumatic fractures (subgroup F 69±10 years), 20 with hip fractures (subgroup HF 65±11 years) and 28 with vertebral fractures only (subgroup VF 70±9 years). The fundamental wave velocity (vA0), the cortical thickness (C.Th) and a cortical porosity index (C.Pi) were estimated using a prototype device (Azalée, Paris, France). The bone mineral density (BMD) was obtained using DXA at the femur and the spine. A weak but significant correlation was found between femoral BMD and vA0 (R=0.31, p<0.003), C.Th (R=0.20, p<0.05), C.Pi (R=−0.19, p<0.05).

The measured characteristics, except the spinal BMD, could discriminate between the sub-group F from the control group (t-test, p<0.05). Fracture prediction was significant for the subgroup F with vA0, C.Pi and femoral BMD with odds ratios (ORs): US 1.35–1.43, BMD 1.53–1.62 and areas under the ROC curve (AUCs): US 0.70, BMD 0.71–0.72, for the subgroup F with C.Th (OR 1.97 and AUC 0.69) and for the subgroup VF with vA0 and C.Pi (ORs 1.49–1.69, and AUCs 0.77–0.78). All variables were age- and BMI-adjusted. These results suggest that the multimode AT has the potential to yield cortical bone biomarkers to predict fracture risk in postmenopausal women. The study has to be confirmed by other clinical studies.

This work received research grants from the Fondation pour la Recherche Médicale (FRM DBS201311228444), MSD and Azalée. CR, KB, SK: occasional interventions: honoraria as an expert or speaker for Alexion, Amgen, Lilly (France), MSD, and UCB. JGM and PL: cofounders of Azalée, stock options. The remaining authors state that they have no conflicts of interest.

Table 1: Descriptive characteristics, Odds ratios (OR) and areas under the ROC curve (ORs) for the control group (NF) vs the fractured group (F)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NF (N=119)</th>
<th>F (N=103)</th>
<th>OR (95% CI)</th>
<th>AUC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>vA0</td>
<td>67.0±14.5</td>
<td>67.6±15.7</td>
<td>1.49 (1.20–2.03)</td>
<td>0.70 (0.65–0.75)</td>
</tr>
<tr>
<td>C.Th</td>
<td>0.71±0.17</td>
<td>0.70±0.18</td>
<td>1.02 (0.96–1.07)</td>
<td>0.72 (0.64–0.82)</td>
</tr>
<tr>
<td>C.Pi</td>
<td>0.49±0.21</td>
<td>0.52±0.20</td>
<td>1.05 (0.98–1.13)</td>
<td>0.76 (0.68–0.84)</td>
</tr>
<tr>
<td>BMD</td>
<td>0.74±0.19</td>
<td>0.72±0.18</td>
<td>1.01 (0.96–1.07)</td>
<td>0.70 (0.64–0.77)</td>
</tr>
</tbody>
</table>

Conclusions
The echographic parameter OS is highly correlated with bone quantity (i.e. bone density) as measured through micro-CT, confirming its usefulness for osteoporosis diagnosis.

References
Conversano UMB, 41(1): 281-300.

Casciaro S, Casciaro E and Conversano F are shareholders of Echolight Spa, a National Research Council spin-off that may or may not benefit from results of this study.

NOTES
Each bone sample was insinified employing the EchoS device equipped with a 3.5-MHz convex probe along 30 different transversal sections through its neck-head axis. Echographic images and the corresponding “raw” radiofrequency signals were analyzed offline. In order to reproduce the in vivo calculation of the OS [1], signals acquired from the first sample were used to derive the reference spectral models of “osteporic” and “healthy” bone regions, based on the bone density level measured through micro-CT. These models were then used to calculate the OS for the second sample regions. Pearson correlation coefficient (r) and linear regression analysis were used to quantify the correlation between OS and micro-CT parameters.

Materials and Methods
Two excised femoral head samples underwent a micro-CT scan and the following echographic acquisi-

Objective
To provide a direct experimental validation of the Osteoporosis Score (OS), a recently introduced echographic parameter for osteoporosis diagnosis, through a comparison with local structural properties of human femoral head samples as quantified by high-resolution micro-computed tomography (micro-CT). The rationale for using just femoral heads relies on their relatively easy availability as excised samples and on the advantageously high volume of analyzable bone per sample.

Ex-vivo validation of the osteoporosis score for estimating bone mineral density through comparison with micro-CT measurements
Marco Peccanì1, Tommaso De Marco1, Francesca Conversano1, Paola Pisani1, Ernesto Casciaro2, Antonio Greco1, Roberto Franchini1, Sergio Casciaro1
1 Echolight Spa, Lecce, Italy
2 National Research Council, Institute of Clinical Physiology, Lecce, Italy

Results
The calculated OS values showed an appreciable correlation with the corresponding bone volume fractions computed through micro-CT (r=0.80). The correlation became slightly stronger (r=0.83) when a regression analysis was employed to correlate the OS values with a linear combination of micro-CT parameters indicative of bone quality (bone surface area, number of trabeculae per unit volume, structure model index).

CONCLUSIONS
The echographic parameter OS is highly correlated with bone quantity (i.e. bone density) as measured through micro-CT, confirming its usefulness for osteoporosis diagnosis.
Clinical studies using HRpQCT have revealed that cortical bone porosity is a major risk factor for fracture. Not only average porosity but also pore size and local accumulation of large basic multicellular units (BMUs) have been associated with a reduction of the hip strength. However, an increase of cortical pore dimensions is poorly captured by X-ray based techniques. A previous in-silico study provided evidence of the dependency of the high-frequency backscatter bandwidth (1-5 MHz) on pore size [1]. In this study, a conventional 3D medical ultrasound scanner (Ultrasonic Touch Research) was used in combination with a 3D linear transducer array (4DL14-5/38) and a 128-channel data acquisition box. Special beam-steering sequences were developed to send focused beams at multiple inclination angles to the cortical bone surface. The sweep motor of the probe allows to scan a 3D volume (Fig 1b). For each transmitted beam, the full aperture is used to obtain a wide-angle phase-sensitive detection of backscattered signals. The data analysis consists of i) detecting the outer bone surface from the receive-beamformed 3D volume, ii) determining a reference spectrum from surface reflections measured at normal incidence, iii) calculating a depth-dependent normalized backscatter spectrum for each scan position, iv) creating representative parameter maps, e.g. of apparent integrated backscatter amplitude (AIB) and spectral slope (AFB). The method was applied ex-vivo to 18 human proximal femur shaft bones. Site-matched pore morphology was obtained from 100-MHz acoustic microscopy images (Fig 1b). An excellent correlation (adj. R² = 0.85) of the pore diameter was obtained with the slope of the inclination controlled apparent backscatter (AIBs-lope) (Fig 1c). The method allows a spatially resolved assessment of pore size, which is an early indicator of osteoporosis and treatment related changes in bone remodeling.

References

Fig. 1: (a) 3D multi-angle pulse sequence for the cortical backscatter measurement (red: multi-angle beam inclination with respect to the array normal direction; blue: multi-angle sweep of the array along the bone longitudinal direction; green: beam scan along the array direction). (b) Segmented acoustic microscopy images shows two samples with extreme differences in the median pore diameter (only a 2-mm stripe below the outer bone surface was evaluated). (c) Correlation between pore diameter and the depth-dependent slope of AIB.
Assessing volumetric bone mineral density in adolescent idiopathic scoliosis: Quantitative computed tomography vs high-resolution peripheral quantitative computed tomography

Elisa MS Tam\textsuperscript{1}, Fiona WP Yu\textsuperscript{2}, Vivian WY Hung\textsuperscript{2}, Lin Shi\textsuperscript{3}, Ling Qin\textsuperscript{2}, Bobby KW Ng\textsuperscript{1}, Winnie CW Chu\textsuperscript{4}, James Griffith\textsuperscript{4}, Jack CY Cheng\textsuperscript{2}, Tsz Ping Lam\textsuperscript{2}
\textsuperscript{1}vivi@ort.cuhk.edu.hk
\textsuperscript{1}Department of Orthopaedics & Traumatology, The Chinese University of Hong Kong, Hong Kong
\textsuperscript{2}Department of Orthopaedics & Traumatology, The Chinese University of Hong Kong, Hong Kong; Bone Quality and Health Centre, Department of Orthopaedics & Traumatology, The Chinese University of Hong Kong, Hong Kong
\textsuperscript{3}Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong
\textsuperscript{4}Department of Imaging & Interventional Radiology, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong

\textsuperscript{1} A case-control study was carried out with 102 postmenopausal women with osteoporosis fractures, 102 postmenopausal women with osteoporosis and 102 healthy women of similar age. After fasting, 5 ml
Assessment of cortical bone in hemodialysis patients using ultrasound – evaluation of the usefulness of cortical QUS

Ryoichi Suetoshi1, Takayuki Hamano1, Iiao Matsui1, Satoshi Mikiyama1, Yasue Obi2
1 Technology Development & Researching Laboratory, Furuno Electric Co., Ltd
2 Department of Comprehensive Kidney Disease Research, Osaka University Graduate School of Medicine

Introduction

The speed of propagation through the cortical bone is influenced by material properties like mineral microstructure. In our previous clinical study using HR-pQCT, we obtained a strong correlation between cSOS (cortical Speed of Sound) and the Ct.v/TMD (Cortical volumetric Tissue Mineral Density, depending on mineralization and cortical porosity). In this study, we evaluated cortical bone using DEXA and ultrasounds in hemodialysis patients, who are often complicated with cortical bone impairment, to show the clinical usefulness of cortical QUS (Quantitative Ultrasound).

Methods

In 165 hemodialysis patients (106 males), cSOS at the mid-tibia was measured non-invasively using an ultrasonic device in development. This device is comprised of a high frequency (3MHz) array probe allowing the measurement of cSOS without being influenced by the cortical thickness. Femoral neck BMD was measured by DEXA. Finally, Pearson correlation coefficients between these measurements and bone turnover markers (BAP, TRACP-5b and intact-PTH) and dialysis vintage were calculated, in order to compare cortical QUS and DEXA.

Results

There was no correlation between tibial cSOS and femoral neck BMD, suggesting that cSOS is not a proxy of BMD (Table 1). In male, cSOS and BMD weakly correlated with BAP and TRACP-5b. In female, cSOS correlated with BAP and intact-PTH, but BMD did not correlate with any of the bone turnover markers. Additionally, intermediate negative correlations between cSOS and dialysis vintage were observed for both males and females. However, no decrease of BMD with dialysis vintage was found.

Discussion

These results suggest that our ultrasonic device may have a better sensitivity than DEXA in detecting bone turnover and bone drange- ment specific for hemodialysis patients with long dialysis vintage, such as cortical porosity. The assumption that this novel method reflects bone quality needs to be confirmed in further studies.

Dependence of cortical bone anisotropic elasticity on anatomical location

Laura Peralta1, Xinran Cai1, Pascal Laugier1, Kay Raum2, Quentin Grimal1
1 Sorbonne Universités, UPMC, INSERM UMR-S 1146, CNRS UMR 7371, Laboratoire d’Imagerie Biomédicale, 75006 Paris, France
2 Julius-wolff-Institute & Berlin Brandenburg School of Regenerative Therapies, Charité-Universitätsmedizin Berlin, Germany

Cortical bone is an anisotropic material that can be characterized by five or nine independent elastic constants. Previous studies suggest that its effective stiffness coefficients and anisotropy ratios may all be related to mass density. However, these relationships have not been investigated so far and little is known about their dependence on anatomical locations. This study aims at further investigating the anisotropic elastic properties of cortical bone, their relationships with density and their dependency on anatomical locations. Bone specimens were harvested from the femora and tibiae of 20 cadavers. At the upper shaft of the femur, 67 cuboid samples were prepared (3x4x5 mm3 in radial, transverse and axial directions). Another set of 53 cuboid samples (2x3x4 mm3) was prepared from the medial tibia face at the mid-diaphysis. Their anisotropy could be related to minute adaptations of elasticity to site-specific mechanical loading.

Table 1

<table>
<thead>
<tr>
<th>Male</th>
<th>Femoral neck (DEXA)</th>
<th>Tibial cSOS (coronal QUS)</th>
<th>Femoral BMD (DEXA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>0.096</td>
<td>0.196</td>
<td>0.196</td>
</tr>
<tr>
<td>log (BAP)</td>
<td>0.056</td>
<td>0.069</td>
<td>0.069</td>
</tr>
<tr>
<td>log (TRACP)</td>
<td>0.172</td>
<td>0.233</td>
<td>0.233</td>
</tr>
<tr>
<td>log (PTH)</td>
<td>0.123</td>
<td>0.191</td>
<td>0.191</td>
</tr>
<tr>
<td>dialysis vintage</td>
<td>0.017</td>
<td>0.017</td>
<td>0.017</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Female</th>
<th>Tibial cSOS (coronal QUS)</th>
<th>Femoral BMD (DEXA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>0.096</td>
<td>0.196</td>
</tr>
<tr>
<td>log (BAP)</td>
<td>0.056</td>
<td>0.069</td>
</tr>
<tr>
<td>log (TRACP)</td>
<td>0.172</td>
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<tr>
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<td>0.123</td>
<td>0.191</td>
</tr>
<tr>
<td>dialysis vintage</td>
<td>0.017</td>
<td>0.017</td>
</tr>
</tbody>
</table>

Results show that, for the two anatomical locations, all stiffness coefficients significantly correlated with density (r>0.52, p<0.001). Significant differences were found between femur and tibia in stiffness coefficients C11, C13 and C44, while there were no significant differences in C33 and C66. Overall, coefficients C11 and C13 were lower in tibia than femur (p<0.001). Anisotropy ratios showed different trends (Figure 1). For the ratio C33/C11 there was no clear dependency on density in femur, while in the case of tibia, it significant-ly decreased with density (r=0.53, p<0.001). Significant negative correlations were found between the ratio C44/C66 and density of both femur and tibia. These anatomical differences may be related to minute adap-tations of elasticity to site-specific mechanical loading.

Figure 1: Longitudinal stiffness coefficients and anisotropy ratio C33/C11 of cortical bone at different anatomical locations. F: femur; T: tibia.

NOTES
Nonlinear ultrasonic guided wave has good sensitivity for micro crack detection. This study introduces coding methods into long bone fatigue evaluation using nonlinear ultrasonic guided wave. Thousand times of fatigue test are taken, to study the possibility for the evaluation of long bone fatigue degree using nonlinear parameters.

Methods
Fatigue loading instrument is used to make tensile fatigue load on in vitro bovine tibia samples. The fatigue test is repeated thousands of times.

Discussion
Femoral neck cortical bone stiffness strongly correlated to its density in this study and had an anisotropy ratio of 1.5 between its compressive and radial axes. These results can be used to inform finite element models of the proximal femur and may aid in the development of hip surgery devices.

Results and Discussion
The relationship of normalized A2f0/ distance z is shown in Figure 1. The result is processed using linear fitting method. Before fatigue test, the linear fitting coefficient is $r = 12.9$. After 5000 times of fatigue test, the coefficient is $r = 13.6$, 5.43% larger than that before test. After 10000 times, the coefficient is $r = 14.2$, 10.08% larger than that before test. When more tests are taken, the fatigue damage becomes more heavy, and the accumulation effect of the second harmonic with distance becomes more remarkable.

Conclusions
In this paper, coding method is introduced in the nonlinear ultrasonic guided wave method. Fatigue tests are taken on the long bone. The experiment results show that the coefficient is positively related to the fatigue test times. It could be a good parameter for long bone fatigue evaluation.
Protocols for serial block-face scanning electron microscopy of bone tissue

Patricia Goggin¹, Elaine Ho¹, Richard O C Cheff³, Philipp Schneider¹

¹ Bioengineering Science Research Group, Faculty of Engineering and the environment, University of Southampton, UK
² Bone and Joint Research Group, Centre for Human Development, Stem Cells and Regeneration, Faculty of Medicine, University of Southampton, UK

Abstract: Osteocyte mechanosensation and mechanotransduction are crucial processes in growth, repair and aging of bone. To better understand these processes, high-resolution 3D imaging techniques are needed. Electron microscopy (EM) is a high-resolution, but inherently 2D method. Micro-computed tomography (μCT) is a non-destructive, 3D technique, but does not achieve sufficient spatial resolution to visualise fine osteocyte details. Serial block-face scanning EM (SBF SEM) is becoming established as a reliable technique for high-resolution 3D images of both biological and non-biological samples. It has had considerable exploitation in the neuroscience field, but has not been introduced for bone.

An ultramicrotome mounted within the chamber of an SEM automatically sections a resin-embedded tissue block and repeated scans of the surface produce a stack of 2D images, which provides a 3D representation of the specimen. SBF SEM offers higher spatial resolution (typically 5-20 nm) than light microscopy (>200 nm) and μCT (typically 1-10 μm) (Table 1). SBF SEM also covers volumes containing multiple osteocytes, while the accessible volumes of established 3D EM methods such as serial section TEM and novel approaches, such as serial focussed ion beam SEM or ultra-high voltage TEM, are more limited. Finally, SBF SEM provides sufficient image contrast to segment both the soft cellular osteocyte network and the hard matrix surrounding the lacuno-canalicular network simultaneously.

Figure 1: SBF SEM imaging of an osteocyte from mouse tibia. A. An individual image from the dataset showing cellular details: nucleus (N), mitochondria (M), cell processes (P), pericellular space (PC) and the collagenous extracellular matrix (ECM). B. A reconstruction of 150 sections. Schneiden et al.

Notes:

Bone histology remains the main investigation methodology of cellular imbalance in diseased bone. On the other hand, bone densitometry is the standard in clinical diagnosis. Correlating bone densitometry and microstructure structure of bone with histological analysis and ultrastructural investigation is a huge challenge. The essence of accomplishing such a goal is the sample preparation whether preclinical sample or patient biopsy. The experimental design in bone investigation relies on versatile sample embedding or processing which can lead to misinterpretations. Therefore, we have developed a reproducible, shorter technique (72% less sample preparation time) of sample fixation and embedding using non-ionized microwave radiation on decalcified bone samples.

The method enhanced histological and ultrastructural preservation of bone samples and provided better micro-CT analysis. A further advantage of the method beside the single sample utilization for correlative radiology, histology and electron microscopy is the reduction of the number of experimental animals needed and maximize the use of clinical samples. We could show that conventional fixation and Epon 812 embedding of bone samples limit information deduction. In most cases sectioning of whole samples to acquire overview resulted in partial breakage. Electron micrographs showed that subcellular structure was undistinguishable in osteocytes, and cellular network was less defined. No further immunostaining was possible. Whereas microwave assisted fixation and Spurr’s resin embedding maximized sample utilization and enhanced visualisation quality. Electron micrographs showed enhanced subcellular structure matrix arrangement. Osteocyte submersed in bone matrix with defined nucleus and mitochondria and displaying a communication channel with an adjacent cell. Further investigative stains, immunostaining and immunofluorescent stains were successful. High quality imaging was possible and reproducible even in large bone samples. The rapid fixation and infiltration with today’s technology can transform the routine testing of patient’s biopsies and provide researchers with same sample analysis to enrich our understanding of diseases.
Toward measuring elastic properties of small animal cortical bone using resonant ultrasound spectroscopy: An aluminium phantom study
Kailiang Xu, Pascal Dargent, Pascal Laugier, Quentin Grimal
xukl.fdu@gmail.com
Sorbonne Université, UPMC Univ Paris 06, INSERM UMR S 1146, CNRS UMR 7371, Laboratoire d’Imagerie Biomédicale, F-75006, Paris, France

The elasticity of the cortical bone material of small animals is usually measured with 3- or 4-point bending tests. However, their accuracy is often questioned. More precisely, Young’s modulus E is deduced from a formula valid only for a bending beam whose slenderness is somewhat larger than that of a typical bone diaphysis. There is a clear call for an alternative measurement approach that (1) applies to small size specimens (e.g., from small animal) (2) provides not only Young’s modulus but also shear modulus and possibly information of elastic anisotropy. Resonant ultrasound spectroscopy (RUS) has been recently developed to determine the elastic properties of highly-attenuating anisotropic materials, such as cortical bone. The basic strategy of RUS is to retrieve the stiffness coefficients which optimize the eigen-frequencies of the forward model to be as close as the measured resonant frequencies in the experimental spectrum. In practice, RUS has been exclusively used to measure cubic bone specimens for which the forward problem can be analytically solved. Such specimens of regular shape can hardly be obtained from small animal bone.

In this study, we investigated the feasibility of applying RUS to characterize the elastic coefficients of small bone specimens with complex shapes which can be readily prepared from a long bone diaphysis. A phantom made of aluminum was prepared by CNC milling. The geometry was fabricated corresponding to the mid-diaphysis of a mature rabbit femur. The dimension of the phantom is around 5.6×407.9 mm3. The 3-D geometry was meshed and the eigen-frequencies were computed using the finite element (FE) method (code_aster, www.code-aster.org/). A Monte Carlo Markov Chain sampling strategy is used to solve the inverse problem of elasticity coefficients determination in a Bayesian framework. The results illustrate the possibility of applying FE-RUS method to evaluate the elasticity of the irregular-shaped small animal cortical bone.

Fig. 1 (a) CT scan of the aluminum specimen, (b) comparison between the measured RUS spectrum (lines) and the FE frequencies (+) of the aluminum specimen

Ex-vivo multiscale assessment of bone properties by ultrasound
Quentin Grimal, Kay Raum
quentin.grimal@upmc.fr
Julius-wolff-Institute & Berlin Brandenburg School of Regenerative Therapies, Charité-Universitätsmedizin Berlin, Germany

Scanning acoustic microscopy (SAM) has been invented 3 decades ago and has emerged from a qualitative imaging modality to a quantitative measurement tool that provides fast and nondestructively maps of bone structure and anisotropic elastic properties with microscale resolution. In particular, the spatial registration with complementary modalities provides unprecedented inside into structure-composition-function relations, tissue changes with respect to adaptation, ageing, pathologies, and healing. Elastic maps generated by acoustic microscopy can serve as direct input for numerical simulations. Resonance ultrasound spectroscopy (RUS) was developed in the 1990’s to measure small (a few millimeters) specimens of anisotropic metallic materials. The technique was recently adapted to measure cortical bone which, as opposed to metal, strongly attenuates ultrasonic waves. RUS now appears as a faster and more precise alternative to the measurement of speed of sound to determine ex-vivo all shear and longitudinal elastic constants of a bone specimen. In recent years, RUS has been used extensively to validate in vivo QUS methods and to investigate the determinants of bone elasticity at various skeletal sites. This talk will review the key theoretical principles and experimental clues of these methods and will present recent findings obtained by correlative SAM imaging and RUS-based assessment of mesoscale elastic bone properties.
Differing patterns of age-related bone loss between Chinese men and women: A population-based HR-pQCT study

Tracy Y Zhu, Vivian WY Hung, Carol WY Choy, Carol KL Cheng, Jack CY Cheng, Ling Qin
tracyzhu@cuhk.edu.hk
Bone Quality and Health Center, Dept. of Orthopaedics and Traumatology, The Chinese University of Hong Kong

Aims
A population-based study was conducted to describe gender differences in age-related changes in bone density and microarchitecture in a large cohort of Chinese men and women.

Methods
One thousand and fourteen Chinese (487 men and 527 women) aged between 20 to 79 years were recruited from local community of Hong Kong. All subjects were carefully screened to rule out disorders and/or medications that affected bone metabolism. Bone geometry, volumetric bone mineral density (vBMD) and bone microarchitecture were assessed using high resolution peripheral quantitative computed tomography (HR-pQCT) at distal radius and tibia. Linear or quadratic regression analyses were performed to estimate predictive age-related changes and compare between genders.

Results
In both gender, during ageing, trabecular bone loss exhibited as a linear pattern, and except for cortical porosity (Ct.Po), which showed a linear increase in men, cortical bone loss exhibited as a quadratic pattern. In women, cortical bone loss, manifested as decreased cortical vBMD and Ct.Th and increased Ct.Po, became more evident after mid-life. From the second to the seventh decade of life, at distal radius, men lost significantly fewer cortical bone (vBMD decreased by -5.0%, Ct.Th by -4.0%, and Ct.Po increased by 3.2 folds) than women (-11.8%, -23.5%, 7.5 folds, respectively, all p<0.0005). Similar amount of trabecular bone was lost in both genders. But men experienced mostly thinning of trabeculae (thickness by -4.8%), whilst women lost trabecular bone (number by 2.8%), leaving a significantly better connected trabecular network in men than in women. Similar differences were found at distal tibia.

Conclusions
Our findings highlight the important gender differences in patterns of age-related bone loss. The significantly greater loss of cortical bone and trabecular network integrity during ageing in women may underpin gender differences in fracture risk.

Parameters of volumetric BMD (vBMD) and microarchitecture obtained HR-pQCT have been increasingly used in research. Before these parameters can be interpreted in clinical practice, age-specific reference intervals need to be constructed to identify subjects who are unusual. The Normal Reference Study (NRS) is a population-based study in Hong Kong with the primary aim to construct reference centile curves for these parameters. Healthy ambulatory Chinese men and women aged between 20-79 were recruited from community. Participants received standard HR-pQCT imaging at distal radius and tibia. Recruitment was to achieve at least 80 radii and 80 tibiae at each age decade and each gender. The abstract presents analyses of parameters at distal radius (450 radii in men and 487 radii in women) in 1,014 participants who completed the study. Generalized Additive Models for Location, Scale and Shape (GAAMLLS) in R environment was used to construct centile curves. GAAMLLS models location, scale, skewness and kurtosis parameters for distribution of response variable as a function of explanatory variable (age). We tested three distributions (normal, BCT, and BCPE). Smoothing parameters were estimated automatically within GAAMLLS. Figure 1 shows the fitted centile curves for trabecular vBMD (Tb.vBMD) and number (Tb.N), cortical vBMD (Ct.vBMD) and porosity (Ct.Po) in men and women. These curves showed noticeable gender differences, particularly, the dramatic loss of cortices in women after midlife. We can also construct value-for-age. For example, a 25-year-old woman at 97th percentile has Tb.vBMD of 223.7mgHA/cm³ and a man of 296.9mgHA/cm³. A cortical thickness of 1mm places a 45-year-old woman at 26th percentile or a 75-year-old woman at 89th percentile. For a man, it places him at 21st and 42nd percentile, respectively.

The Normal Reference Study is supported fully by a research grant from Health and Medical Research Fund of Food and Health Bureau, Hong Kong SAR (Ref: 12130841).
Lower trabecular density determines estimated bone strength in radial HR-pQCT measurements in rheumatoid arthritis patients – preliminary results
Fabian Stemmer1, Anna-Maria Liphardt1, David Simon2, Axel Hueber2, Georg Schett2, Klaus Engelke1, Arnd Kleyer1
1 Friedrich-Alexander-University Erlangen-Nürnberg (FAU), Department of Internal Medicine 3 – Rheumatology and Immunology, Universitätsklinikum Erlangen, Erlangen, Germany
2 Institute of Medical Physics (IMP), University of Erlangen, Erlangen, Germany

Introduction
Bone density measurements using DXA lacks sensitivity in identifying persons sustaining fractures because most fractures occur in persons without osteoporosis. Identifying these at-risk individuals is an unmet need. High porosity is a consistent observation in animal models of renal disease.

Material and Methods
One hundred and one (52 male) subjects with CKD (79 transplants, 22 dialysis) and 188 (76 males) healthy age-sex matched were recruited for measurements bone microarchitecture by HR-pQCT. Distal radius image of 31 CKD cases women (59 yrs, 22-81) were analysed by StrXh.1.0 software for cortical porosity and matrix mineral density and compared with 112 sex and age-matched controls (57 yrs, 26-79).

Results
Compared to controls, women with CKD had 1.2, 1.34 SD higher total cortex and compact cortex porosity on distal radius in addition 1.17, 1.38 SD higher inner and outer transitional zones, respectively, and 0.95 SD lower trabecular number, respectively and 1.2 SD higher trabecular separation (all p<0.001).

Conclusions
Negative remodelling balance and increased remodelling rate impair bone microstructure in CKD patients and antiresorptive therapy may compromise bone’s ‘toughness’ – its ability to absorb energy – predisposing to fractures.

NOTES

Microarchitectural deterioration in patients with chronic kidney disease
Ali Ghasem-Zadeh, Rizwan Jaipurwala, Peter Mount, Vuolfgang Wang, Leniad Chunilo, Sandra Iuliano, Roger Zebaze, Cherie Chiang, Ego Seeman
alig@unimelb.edu.au
Department of Endocrinology and Medicine, Austin Health, University of Melbourne

Introduction
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NOTES
The common region of interest between fixed offset and relative offset protocols in high-resolution peripheral quantitative computed tomography

Kai-Yee Cheuk1, Elisa Man-Shan Tam1, Fiona Wai-Ping Yu1, Xiaofang Wang2, Vivian Wing-Yin Hung3, Wayne Yuk-Wai Lee1, Ali Ghassem-Zadeh1, Roger Zebaze1, Ego Seeman1, Jack Chun-Yiu Cheng1, Tsz Ping Lam2
1 Department of Orthopaedics and Traumatology, The Chinese University of Hong Kong, Hong Kong
2 Bone Quality and Health Centre, Department of Orthopaedics and Traumatology, The Chinese University of Hong Kong, Hong Kong
3 Departments of Endocrinology and Medicine, Austin Health, University of Melbourne, Australia

Objective
Currently there is no consensus on the scanning protocol for young subjects with open growth plates which are radiation sensitive regions and should be avoided during scanning. Due to the diversity of existing protocols, it is difficult to perform meaningful cross-study comparisons and to merge datasets from different centers for analysis. This study aimed to investigate whether common region of interest (common ROI) exists between two different scanning protocols.

Material and methods
Twenty-six boys and 26 girls aged between 13 and 16 years old were recruited. Non-dominant distal radius was scanned by two high-resolution peripheral quantitative computed tomography (HR-pQCT) protocols, namely, the “5-mm protocol,” where the distal end of ROI started at 5 mm proximal to a reference line, and the “4-mm protocol,” where the ROI started at 4 mm of the ulnar length proximal to another reference line. The value of HR-pQCT parameters from slice by slice was extracted.

Results
Discrepancies between the 2 protocols were found in both genders when the complete sets of 110 slices were analyzed. The number of slices in common ROI was 66 (60.0% of 110 slices) in boys and 57 (51.8% of 110 slices) in girls. No significant difference was noted between the protocols for both genders when using the common ROI.

Conclusion
This study compared the differences on parameters obtained from HR-pQCT in young adolescents between two scanning protocols at the distal radius. The results showed that systematic discrepancies exist when using 2 different scanning protocols. However, it is possible to use with the common ROIs that overlapped between the two protocols for minimizing this difference.

Acknowledgement
RGC of HKSA (468411).

A fast homogenized finite element approach for distal radius strength calculations from HRpQCT images

Andrés Julián Arias-Moreno1, Hadi S. Hosseini2, Keita Ito3, Philippe K. Zysset2, Bert van Rietbergen1
1 Orthopaedic Biomechanics, Department of Biomedical Engineering, Eindhoven University of Technology, Eindhoven, the Netherlands
2 Institute for Surgical Technology and Biomechanics, University of Bern, Bern, Switzerland
3 Department of Mechanical Engineering and Production, Autonomous University of Manizales, Manizales, Colombia

Micro-finite element (mFE) analysis is commonly used to estimate bone strength based on in-vivo high-resolution peripheral quantitative computer tomography (HR-pQCT) images. With the increased resolution of the second generation of HRpQCT devices, however, computation times for mFE analysis have increased to 6-24 hours. Recently, we introduced a fast non-linear homogenized-FE (hFE) approach using continuum models generated from HRpQCT images with material properties accounting for density and fabric, and demonstrated that these can accurately predict stiffness and strength of 20mm distal radius segments as measured in compression experiments.1 In clinical practice, however, only a 10mm region is scanned. The purpose of the present study therefore was to investigate the accuracy of hFE strength predictions when limited to the clinical scan region. HRpQCT images (61 microns resolution) and experimental test results were obtained from the previous study for 22 distal radius segments of 20 mm in size. hFE analyses using hexahedral elements of 1.7 mm were performed first to simulate compression tests on the full segments. Following, hFE and mFE analyses were performed for the clinical scan region only. The experimentally measured failure load was well predicted by hFE for the 20mm sections (R2=0.96), although linear regression revealed a slight overestimation by 7.6%. For the clinical region hFE the correlation was the same, but the failure load overestimation was considerably higher at 46%, indicating that failure initiates outside the clinical regions. For the mFE analyses, the correlation was similar (R2=0.94) but failure load values underestimated by 30% due to the use of material parameters optimized for the previous HRpQCT generation. Average computation time for full non-linear hFE analyses was 13 minutes, while for mFE analysis this was around 7 hours.

Considering the good correlation and the greatly reduced computation time it is concluded that the hFE analyses can provide a fast alternative for the mFE analyses.

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RGC of HKSAR (468411).
Cortical bone histomorphometry of the human femoral shaft: relations with hip strength
Gianluca Iori1, Andreas Reisinger2, Laura Peralta3, Melanie Doughes4, Reinhard Barkman1, Dieter Pahr1, Kay Raum1
1 Berlin-Brandenburg Center for Regenerative Therapies, Charité - Universitätsmedizin Berlin, Germany
2 Institute for Lightweight Design and Structural Biomechanics, TU Wien, Austria
3 Sorbonne Universités, UPMC, INSERM UMR-S 1146, CNRS UMR 7371, Laboratoire d’Imagerie Biomédicale, Paris, France
4 Klinik für Diagnostische Radiologie, Universitätsklinikum Schleswig-Holstein Kiel, Kiel, Germany

In clinical practice, hip strength is estimated by Bone Mineral Density (BMD) as measured by dual-energy X-ray absorptiometry (DXA), thus accounting for 60 up to 70% of its variation (1). Structural changes of cortical bone not accounted by DXA may additionally contribute to the impairment of the hip fracture resistance. In this study, 10 pairs of proximal femur samples were obtained from human donors (6 M, 6 F; age: 69–94 yrs, mean: 83.4±9.0 yrs). DXA measurements were performed before testing the bones until mechanical failure. One sample from each pair was randomly selected for testing in side-fall configuration, whereas counter legs were tested in one-legged stance, simulating the spontaneous fracture of the hip. Tests were performed following an established protocol (2). Hip strength was calculated as the maximum force reached by the load-displacement curve. Cross-sectional slices of the proximal shaft were extracted 18 mm below the midpoint of the lesser trochanter for Scanning Acoustic Microscopy (SAM) measurements. Surfaces were polished and measured using a custom microscope (3) equipped with a 100-MHz transducer providing a spatial resolution of 12 μm. Histomorphometric analysis of the cortical bone compartment was performed segmenting the SAM images using an adaptive threshold (4) and excluding trabecular areas from the calculation (5). Cortical Porosity (Ct.Po) and the median of the pore diameter distribution (Pd.Dm) were characterized for each cross section. Adj-R² of the correlation between hip strength and DXA areal BMD (aBMD) were 0.73 and 0.81, for stance and fall test configuration, respectively. For stance samples, both Ct.Po and Pd.Dm were independently correlated to hip strength (p<0.05). When added to the correlation (by means of stepwise regression), the adj-R² increased to 0.91. The same behavior was not observed for fall cases. Our results underline the important role of parameters describing properties of cortical bone pores as predictors of the hip strength.

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QCT-based finite element estimation of hip strength: Role of anisotropy
Jarunun Panayasantisuk1, Ghislain Maquer1, Enrico Dall’Ara2, Dieter Pahr3, Philippe Zysset1
1 Institute for Surgical Technology and Biomechanics, University of Bern, Switzerland
2 INSIGNEO Institute for in silico Medicine, University of Sheffield, United Kingdom
3 Institute of Lightweight Design and Structural Biomechanics, Vienna University of Technology, Austria

Finite element analysis (FEA) is receiving increasing attention for estimation of hip strength when CT scans are available. FEA involves a sequence of operations from calibration, segmentation, statistical modeling, meshing and application of boundary conditions to the selection of a material model. No standard is currently emerging from the literature and the aim of this work was to explore the role of anisotropy in FEA of the proximal femur loaded in both stance and side-fall configurations.

Sixty-nine human proximal femora were scanned with HR-pQCT, clinical QCT and tested to failure in either stance or side-fall configuration. One sample from each pair was randomly selected for testing in side-fall configuration, whereas counter legs were tested in one-legged stance, simulating the spontaneous fracture of the hip. Tests were performed following an established protocol (2). Hip strength was calculated as the maximum force reached by the load-displacement curve. Cross-sectional slices of the proximal shaft were extracted 18 mm below the midpoint of the lesser trochanter for Scanning Acoustic Microscopy (SAM) measurements. Surfaces were polished and measured using a custom microscope (3) equipped with a 100-MHz transducer providing a spatial resolution of 12 μm. Histomorphometric analysis of the cortical bone compartment was performed segmenting the SAM images using an adaptive threshold (4) and excluding trabecular areas from the calculation (5). Cortical Porosity (Ct.Po) and the median of the pore diameter distribution (Pd.Dm) were characterized for each cross section. Adj-R² of the correlation between hip strength and DXA areal BMD (aBMD) were 0.73 and 0.81, for stance and fall test configuration, respectively. For stance samples, both Ct.Po and Pd.Dm were independently correlated to hip strength (p<0.05). When added to the correlation (by means of stepwise regression), the adj-R² increased to 0.91. The same behavior was not observed for fall cases. Our results underline the important role of parameters describing properties of cortical bone pores as predictors of the hip strength.

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Accumulation of non-enzymatic cross-links, or advanced glycation endproducts (AGEs) may contribute to bone fragility in type 2 diabetes, where fractures increase despite normal bone mineral density. Direct assessment of AGES and bone tissue mechanics using fluorescence microscopy and reference point indentation (RPI), respectively, could provide novel diagnostic tools to study disease progression and therapy. Therefore, the purpose of this study was to determine the mechanical parameters obtained from RPI that are associated with AGE content.

Bone cortical samples were incubated in ribose or control solutions (N=3/group) for 38 days to induce AGE accumulation. RPI was performed at five locations on each sample to give 15 measurements per group (FRI, 6N, 10 indentations per measurement). The first cycle indentation distance (IDI), total indentation distance (TID), indentation distance increase (EDI) and energy dissipation (ED) were determined. Fluorescence microscopy images were obtained from neighbouring demineralised sections (excitation: 370nm, emission: 440nm). Photographs of the indentation cross-sections were aligned to the microscopy images, and fluorescence intensity (FI) quantified within each RPI area (Figure 1). One-way ANOVAs assessed group differences and the relationships between AGES and mechanics studied with linear regression. Significance was considered at p<0.05.

Ribose incubation increased FI (+3.36%), and reduced ID1 (-5.6%), with trends towards reduced TID (-4.4%, p=0.09). In the ribose specimens, FI correlated negatively with IDI (R2 = 0.30), TID (R2 = 0.29) and ED (R2 = 0.29). In the controls, FI correlated negatively with IDI (R2 = 0.26), but positively with ED (R2 = 0.39). AGE accumulation was associated with reduced bone mechanics. Up to 40% of the variation in the indentation properties was explained by FI, suggesting that RPI is able to capture pre- and post-yield changes to the bone tissue resulting from non-enzymatic cross-linking.

Automatic spine and femur analysis from existing CT scans, without the application of dose or manual work, have the potential to identify patients which should be forwarded to a standard procedure for the determination of the bone status. A workflow can be established either from a site’s CT or PACS.

A new screening module within the Mindways QCT Pro framework (Mindways Software, Inc., Austin, TX, USA) was applied to a set of native CT scans obtained from clinical investigations other than bone densitometry. Within the CT scans of 30 patients, the screening module automatically identified slices containing vertebrae, placed cylindrical ROIs inside them, filtered out endplates and intervertebral discs based on the higher dispersion of density compared to slices from within vertebrae, and computed a calibrated mean volumetric bone mineral density. Within the CT scans of 14 patients an automatic detection of the hip identified left and right total hip areal bone mineral density. Results were compared to a standard analysis by Mindways QCT Pro 3D Spine and CTXa Hip modules. Five patients with vertebral ROIs misplaced by the impact of non-i.V. contrast agent in the gastrointestinal passage were identified by comparison to a threshold of 160mg/cm3. Hip-protrometinns were identified by densities above 2g/cm3. The densities obtained by the automatic screening module predicted the results of the standard analysis well (spine: R2=87.1%, Residual Std. Error: 11.66 mg/cm3; (44.8% of a population standard deviation), vBMD/standard deviation = 9.95 + 1.03 x vBMDscreening; hip: R2=86.4%, Residual Std. Error: 0.06 g/cm2; (51.7% of a population standard deviation), aBMD/standard deviation = 0.22 + 0.34 x aBMDscreening).

The new QCT Pro automatic screening module allowed to predict bone mineral density without any further dose and manual work. Prediction is suitable to identify patients at risk of osteoporosis which may benefit from clinical standard procedures.

J. Keenan Brown and Wolfram Timm are employees of Mindways Software, Inc.
Discrepancies between synchronous and asynchronous phantom based BMD calibration in QCT

O. Museyko¹, S. Holz², P. Dankerl², M. Uder¹, K. Engelke¹
¹ University of Erlangen-Nuremberg, Institute of Medical Physics, Erlangen
² University of Erlangen-Nuremberg, Institute of Radiology, Erlangen

Objectives
Opportunistic screening subsumes techniques to use routine clinical CT scans obtained without a phantom (CP) to calibrate for BMD, for osteoporotic fracture risk prediction. One solution is asynchronous calibration (AC) where CP is measured separately from the patient. We evaluated accuracy errors of AC.

Methods
Thorax CT acquisitions of 55 patients scanned on top of a Siemens Osteo CP on Siemens Definition AS and AS+ scanners at 100 or 120 kV were used. BMD values calibrated with the in scan Osteo phantom (SC) were compared to those by AC, derived from an ESP phantom. The same table height was used for all ESP scans but differed widely for the clinical CT scans.

Results
The table shows mean differences ± standard deviation between SC and AC, exemplified for 0, 100, 200, and 300 mg/cm³. Differences from the whole sample and cofactor kV were significant (p<0.001). Table height correlated with the BMD difference (p=0.001, 0.79).

Discussion
Calibration differences can be explained by: scanner instabilities (ESP and patients were not measured same day), material differences between the Osteo phantom and ESP, variation in table height and in body size causing beam hardening differences.

Scanners were stable (data not shown): A variation of table height by 3 cm caused a BMD change of about 5% but table height variation among patients was >10 cm. If uncorrected, calibration differences of up to 23 mg/cm³ on average (table) must be compared to about 40 mg/cm³ difference in vertebral BMD between normal (>120 mg/cm³) and osteoporotic (<80 mg/cm³) subjects. These data suggest that a classification of subjects into high/low fracture risk group will be possible even in the presence of calibration errors which may be reduced when adjusting for differences in table height and body size.

Opportunistic fracture risk estimation based on multi-detector CT images of the spine via local classification of textures

Alexander Valentinitsch¹, Stefano Trebeschi², Johannes Kaesmacher¹, Thomas Baum¹, Jan S. Kirschke¹
¹ Department of Diagnostic and Interventional Neuroradiology, Klinikum rechts der Isar, Technische Universität München, München, Germany
² Netherlands Cancer Institute, Department of Radiology, Amsterdam, Netherlands

Predicting vertebral fractures is highly relevant to optimize prevention strategies in osteoporosis. There are many CT scans available of patients at risk, which can be used for ‘opportunistic screening’ (using CT without additional radiation).

In this cross-sectional study, we aimed to develop a quantitative method for the identification of patients with prevalent or incidental osteoporotic vertebral fractures in existing CT images using a random forest classifier that uses 3D texture features in combination with volumetric BMD. In total, we included 181 patients. 101 had no signs of osteoporotic fractures at baseline and during a 12-month follow-up (noFx) and 80 had prevalent and/or incidental fractures during follow-up (Fx). For 3D texture analysis we extracted gray-level co-occurrence matrix Haralick features (3DGLCM), histogram of gradients (3DGdG), local binary patterns (3DLBP), and 3D wavelets. The performance was computed in a 4-fold cross validation.

The results showed a high discriminatory power (AUC = 0.84, p < 0.05) between Fx and noFx patients. Importantly, the AUC of such a combination of BMD and 3D texture analysis was much higher than that of volumetric BMD alone (AUC = 0.68, p < 0.05).

In conclusion, the presented predictive model based on a random forest classifier using 3D texture features showed high potential for identifying patients with vertebrae susceptible to fracture.

Figure 1. Texture analysis using 3D local binary pattern (3D LBPI). Representatives in visualizing the differences in local binary patterns of L1 between a healthy 71 years old female (noFx) and 72 years old female from the fracture cohort (Fx).

Notes
Opportunistic identification of osteoporotic vertebral fractures with computed tomography: clinical practice compared to a semi-automatic computer-aided diagnosis system

Eleni P. Kariki1,2, Paul A. Bromiley1, Timothy F. Cootes1, Judith E. Adams1,2

1 Manchester Royal Infirmary, Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK
2 Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK

Osteoporosis is often clinically silent until a low trauma fracture occurs. Osteoporotic vertebral fractures (VFs) generally occur earlier than wrist and hip fractures, are powerful predictors of future fractures (x3 VF, x2 hip), and significantly increase morbidity and mortality. VFs are identified in images performed specifically for the spine, but can also be evident incidentally (opportunistically) in examinations performed for other clinical reasons, the most widely utilised and sensitive are midline sagittal CT reformats (SRCT).

Under-reporting of VFs is well documented. We implemented routine CT sagittal reformations at the time of image acquisition to improve VF diagnosis. We have also developed a semi-automatic computer-aided diagnostic (CAD) tool, which uses Random Forest Regression Voting Cons-trained Local Models (RFV-CLMs) to identify and classify VFs.

We retrospectively reviewed 1000 SRCT (468 women) of patients over 50 (median 74, m69) years, in which the thoracic and/or lumbar spine was included. Vertebrae were described using the terms normal, non-osteo-porotic deformity, or fractured (grade 1 mild, grade 2 moderate, grade 3 severe). The original reports were reviewed for whether a VF was re-port-ed and the terminology used. At least one VF was present in 260 (26%) scans. Only in 94 (36%) was a VF re-port-ed; in 166 (64%) they were not. In only 30 (32%) of those was the term “fracture” used.

We applied our CAD tool on the SRCT images, with manual initialisation of vertebral localisation. We achieved 7.2% sensitivity at a precision of 90%. The routine sagittal CT image reformation improved VF reporting rates 3-fold, but still 64% of the exams with a VF remained unreported. The tool further doubled our VF reporting performance, with a low false-positive rate (10%), and has the potential to remedy some of the under-reporting of VFs by radiologists.

Acknowledgements
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Materials and methods
We provide a validation of asynchronous QCT using the European spine phantom (ESP), which is a recognized standard evaluation tool for bone densitometry, and data from 30 retrospectively enrolled patients with low-to-normal bone mass. We used the ESP with repositioning during scanning and assessed the accuracy and short-term reproducibility of asynchronous QCT. Intra-scanner and intra-observer precision were each calculated as the root mean square of the standard deviation (RMSD) and the coefficient of variation (CV-RMSSD). We also compared asynchronous and conventional QCT results in 30 clinical subjects.

Results
The accuracy of asynchronous QCT for three ESP vertebrae ranged from 1.4–6.7%, whereas intra-scanner precision for these vertebrae ranged from 0.53–0.91 mg/cc. For intra-observer variability, overall precision error was smaller than 3%. In clinical subjects there was excellent agreement between the two calibration methods with correlation coefficients ranging from 0.98–0.99. A Bland–Altman analysis demonstrated that methodological differences might depended on the magnitude of the BMD variables.

Conclusion
Our findings indicate that the asynchronous QCT has good accuracy and precision for assessing trabecular BMD in the spine.
Assessment of cortical thickness and elasticity using ultrasonic axial transmission
Nicolas Bochud, Quentin Vallet, Xiran Cai, Quentin Grimal, Jean-Gabriel Minonzio, Pascal Laugier
jean-gabriel.minonzio@upmc.fr
Sorbonne Universités, UPMC Univ Paris 06, INSERM UMR-S 1146, CNRS UMR 7371, Laboratoire d’Imagerie Biomédicale, Paris, France

This study reports assessment of cortical bone properties using a custom-made axial transmission device (Azalée, Paris, France). Our approach is based on the assumption that the cortical shell of long bones behaves as an ultrasonic waveguide. Like so, bone properties are retrieved from the comparison between the dispersion characteristics of a waveguide model and the measured dispersion curves, using an inverse problem approach.

A multi-parametric inversion in terms of thickness (h) and stiffness (c33/c11, c13/c11, bulk longitudinal wave velocity in the transverse direction VLP per and bulk shear wave VT), using a genetic algorithm-based optimization, was applied with a 2-D inverse isotropic free plate model on twelve ex vivo human radius specimens. Reference thickness and stiffness values were obtained using microcomputed tomography (voxel size 90 μm) and resonant ultrasound spectroscopy (RUS). Significant correlations were found between measured and reference values for h (r = 0.82), c33/c11 (r = 0.7) and VLP er (r = 0.68). No significant correlation was found for VT.

The discrepancy on the inferred estimates of VT may be explained by the poor A0 mode in the experimental data. The A0 mode is expected to be mostly sensitive to the transverse bulk wave velocity component. The results associated with c33/c11 are not reported, as both RUS and axial transmission methods are poorly sensitive to c13. For three specimens, the inverse procedure failed. Rather than a misidentification of the inverse procedure, the three failures cases were due to a lack of information in the experimental dispersion curves. A five parameters inversion is challenging. Despite these limitations, these findings reflect the feasibility of guided waves measurements to provide estimates of cortical thickness and stiffness on ex vivo radius specimens. The next step will be to achieve measurements in vivo.

JGM: consultant to Azalée, royalties
JGM and PL: cofounders of Azalée
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NOTES
Cortical thickness and porosity assessment on ex-vivo tibia with axial transmission

Johannes Schneider 1, 2, Donatien Ramiandriosa 3, Gianluca Iori 4, Melanie Giessler 5, Reinhard Barkmann 1, Kay Raum 2, Pascal Laugier 6, Jean-Gabriel Minonzio 2
sokumura@sato-lab.ot0.jp
1 Graduate School of Informatics, Kyoto University.
2 Université Paris-Est, Laboratoire Modélisation et Simulation Multi Echelle, MSME UMR 8208 CNRS.
3 Graduate School of Biomedical Engineering, Tohoku University.

Osteoporosis is an underdiagnosed and undertreated metabolic bone disease. Currently, clinical fracture risk prediction is mainly based on a single parameter, i.e., bone mineral density (BMD). However, fracture resistance of bone is determined by a complex combination of micro-architectural, material and geometrical properties. Ultrasonic axial transmission (AT) measures the dispersion curves of guided waves (GWs) that propagate along the cortical layer of long bones, such as tibia and radius. Dispersion characteristics of GWs are determined by cortical thickness (C.Th) and mesoscopic stiffness, this latter material property depending strongly on cortical porosity. The goal of this study was to validate the cortical biomarkers at the tibia measured using AT. Twenty tibiae from human cadavers were measured ex vivo using a custom-made AT device (Azalée, Paris, France). Singular-value decompositions combined with 2D spatio-temporal Fourier transform were applied to extract the guided wave dispersion curves (Minonzio et al. JASA 2010). C.Th and an index of cortical porosity (C.PI) were estimated after solving an inverse problem by fitting a 2D free transverse isotropic plate waveguide model to the experimental curves. Independent site-matched reference C.Th values were obtained from 39 μm voxel size high-resolution x-ray tomography (microCT). Reference C.PI was estimated from local bone mineral density (BMD) using a relation established in another study [Iori et al. BMD-calibrated... IBDW/ESUCB 2017].

C.Th and C.PI were successfully obtained for 16 tibiae. The inverse problem could not be solved for 4 specimens due to poor ultrasonic response. Significant correlations (p < 0.001) were found between AT and the reference method (C.Th: R2 = 0.84, RMSE = 0.4 mm; C.PI: R2 = 0.63, RMSE = 3.1%). For C.Th and C.PI biases of -0.12 mm and 0.52% were observed, respectively. The cortical bone at the tibia was successfully characterized using AT ex vivo. Further effort is now required to assess whether measurement of these bone strength related parameters enhance the prediction of atraumatic bone fractures.

Low-cost Lamb wave characterization technique using one transmitter and two receivers: An experimental study

Shiopaki Okumura 1, Vu-Hieu Nguyen 2, Hirofumi Takei 3, Toru Sato 1
sookumura@sato-lab.ot0.jp
1 Graduate School of Informatics, Kyoto University.
2 Université Paris-Est, Laboratoire Modélisation et Simulation Multi Echelle, MSME UMR 8208 CNRS.
3 Graduate School of Biomedical Engineering, Tohoku University.

The axial transmission (AT) technique that characterizes Lamb waves is promising for cortical bone quality assessment. Most conventional AT techniques employ multiple receivers. In this study, we propose a Lamb wave characterization technique that estimates thickness, and shear and longitudinal wave velocities, using one transmitter and two receivers. The phase velocity and waveform of the Lamb wave depend on the thickness, and shear and longitudinal wave velocities. By using the two receivers, the phase velocity of a single mode may be estimated depending on the phase difference between these two receivers. Since the zero-th order anti-symmetric (A0) mode is dominant in the lower frequency range, we first partially estimate the A0 mode phase velocity at low frequencies. Using the estimated phase velocity, we next roughly estimate the thickness, and the shear and longitudinal wave velocities by inversely solving the Rayleigh-Lamb equation. Finally, we employ a linear least fitting procedure that minimizes the difference between the received signal and the theoretically predicted wave for conclusive estimation with higher-order propagation modes. The proposed technique has been applied to experimental data obtained by testing a 2.0-mm-thick copper plate. The center frequency was 1.0 MHz, and the distance from the transmitter to the first and second receivers were 20 mm and 40 mm, respectively. The figure shows the experimental results of the fitting procedure. The estimation errors in the thickness, and the shear and longitudinal wave velocities, were 0.05 mm, 5 m/s, and 35 m/s, respectively. The fitting residue was ~7.0 dB, and the calculation time was 8.6 s using a desk top PC. The proposed method succeeded in estimating the thickness and two wave velocities accurately. We believe that the proposed method is suitable for low-cost bone-quality assessment.

NOTES

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Suitability of low-frequency axial transmission acoustics as a screening method for bone mass density-defined osteoporosis

Florian Vogl1, Bernd Friesenbichler, Hans Gerber, William R. Taylor2, Inés Anne Kramers-de Quervain
1 Institute for Biomechanics, ETH Zürich, Switzerland
2 Department for Rheumatology and Rehabilitation, Schuchthaus Clinics, Switzerland

Purpose
Osteoporosis is a ubiquitous challenge for society, health care providers and the economy in general, affecting 200 million women worldwide. The gold-standard for diagnosing osteoporosis is dual x-ray absorptiometry (DXA), which due to the involved radiation exposure is unsuitable for routine check-ups. This, together with DXA’s limited availability caused by expensive equipment, low portability, and the need for highly trained personnel, leads to under-detection of osteoporosis, especially in non-developed countries and for people younger than 65 years. Quantitative acoustic (QA) methods have recently received renewed attention as a promising non-radiative, non-invasive, inexpensive, and portable assessment technique of bone health. While most research focuses on using QA to gather bone information inaccessible by DXA, the presented work investigates the suitability of axial transmission QA as a screening approach for DXA-defined osteoporosis, thereby improving resource allocation in the clinics as well as bringing osteoporosis early detection to a general health practitioner level and to non-developed countries.

Materials and Methods
40 female subjects above the age of 65 years were measured using axial-QA at the mibia (center frequency: 3MHz) and using dual-energy x-ray absorptiometry (DXA) at the hip, distal radius, and spine. The performance of classifying the DXA-based osteoporotic state at each location was quantified for following axial-QA classifiers: a) a threshold classifier based on the extracted phase velocity and b) a support vector machine (SVM) classifier based on the raw acoustic signals.

Results and Discussion
The Receiver-Operating Characteristic for the threshold classifier resulted in an area-under-curve value of 0.78 (see Fig. 1). The median and inter-quartile range of the SVM’s classification accuracy determined by subject-grouped 8-fold cross-validation was 0.63 and 0.19. While the SVM’s performance lags behind expectations, indicating that further development of this approach is required, the performance of the threshold classifier appears promising for screening applications.

Notes
A new QUS approach for measuring cortical porosity and other bone properties relevant for discriminating patients with different mineralization statuses

Melanie Gräsel1, Claus-Christian Güler1, Reinhard Barkmann1
1 Section Biomedical Imaging, University Hospital Schleswig-Holstein, Kiel
m.daugschies@rad.uni-kiel.de

Cortical porosity is associated with bone fragility and disease. Furthermore, the anisotropy of the cortex, i.e. the ratio of the elasticity coefficients along and perpendicular to the axis of long bones, is altered with its porosity and so are the ultrasound velocities in the above-mentioned directions. Due to the limited width of the human tibia, measurement of ultrasound velocity 90° to the bone axis is not feasible. Because cortical bone is transverse isotropic, the velocity follows a cosine curve when measured under different angles to the bone axis and so a measurement in 90° direction could be replaced by any another angle unequal to 0 to gain a measure for cortical anisotropy. Therefore, we developed a quantitative ultrasound (QUS) probe to measure velocities parallel and tilted (38° angle) to the axis of the human tibia shaft using bidirectional axial transmission. A phantom study had shown that both velocities were differently influenced by porosity and that porosity was positively correlated with the anisotropy index AI, calculated as squared ratio of these velocities. We verified these findings by in vivo measurements in intact human tibiae and tested whether the new method can be used to discriminate groups of different mineralization status. 32 female tibiae (age 81±7 years) classified in three groups were used: (1) vitamin-D deficient (n=10), (2) osteoporotic (n=12), (3) bisphosphonate (BP) therapy >2 years (n=10). These were measured using µCT (isotropic voxelsize 14µm) and QUS at five different regions at the shaft. Cortical porosity obtained from µCT, ultrasonic velocities in both directions, and AI were evaluated. Porosity was 0.106±0.05 (mean±SD), axial velocity 3753±110m/s, tilted velocity 3355±134m/s and AI 1.25±0.05. Axial and tilted velocities correlated significantly (p<0.0001) with cortical porosity, with r²=0.49 (RMSE=0.036). AI showed no correlation, but contributed significantly in combination with tilted velocity in the best multivariate model (r²=0.70, p<0.0001, RMSE=0.028; see figure). The tilted velocity could distinguish the vitamin-D deficient and the BP treated group (t-test, p=0.050) and performed therewith numerically better than porosity (p=0.29) or the other QUS parameters (p>0.12) alone. Our results indicate that the velocity measured in 38° direction yields information about bone status beyond porosity independently of the axial velocity.
Abstracts IBDW/ESUCB 2017

Characterization of cortical bone using multiple scattering of ultrasound
Yasamin Karbalaeisadegh1, Omid Yousefi1, Gianluca Iori2, Kay Raum2, Marie Muller1
1West Virginia University School of Medicine, Morgantown, WV, USA; 2Charité - Universitätsmedizin Berlin, Germany

While characterization of trabecular bone has long been used to assess different stages of osteoporosis [1, 2], the cortical bone micro-structure also provides relevant information on bone strength. Osteoporosis leads to changes in thickness, pore size and density. This simulation study aims at characterizing the microarchitecture of cortical bone segments using ultrasound multiple scattering. We present measurements of the diffusion constant and transport mean free path in bone using finite differences simulations.

2D cross-sectional image of the human proximal femur shaft, obtained by time-resolved 100 MHz Scanning Acoustic Microscopy (SAM). In order to investigate the effect of porosity changes on the transport parameters, various porous geometries are generated from the original scanned image. Because osteoporosis mainly impacts the endosteal region, a pore size gradient was artificially created (fig. 1). With an increase in porosity, the diffusion constant and transport mean free path were found to decrease consistently (fig 1). These results suggest that measuring the transport mean free path could be used to assess cortical porosity.

References
2) Hans et al., The Lancet, 1996.

Estimation of cortical bone porosity by applying traditional and multivariate analysis on ultrasound pulse-echo signals – a FDTD study
Satu Inkinen*, Juha Toyni*, Jukka Jurvelin*, Markus Malo*
*Departments of Applied Physics, University of Eastern Finland, P.O. Box 1637, Kuopio FI-70111, Finland; 2Finland and Diagnostic Imaging Center, Kuopio University Hospital, P.O. Box 100, Kuopio FI-70729, Finland

Purpose
Porosity of cortical bone increases with age and together with cortical thinning elevates fracture risk. Porosity affects propagation and scatter of ultrasound (US) wave. As US is attenuated and higher frequencies are removed from the US spectrum in overlying soft tissue, potential information on cortical porosity may not be captured by traditional backscatter parameters. In the present modeling study, using multivariate analysis of backscattered and reflected signals, effects of bone porosity on pulse-echo (PE) US signal are evaluated.

Methods
Porous structure of cortical samples (n=40, thickness=2mm, 17 human femoral diaphysis, anterior direction) were derived in 3D using Semiautomatic Bone Segmentation and Computer-Aided Detection of Cortical Porosity (SABS) [3]. Ultrasound parameters were calculated in frequency (IRC, AIB, FSAB, TSAB) and time domain [peak-to-peak attenuation (P2Patt)]. Using two sample sets, i.e., a model set (n=96) and a separate test set (n=24) partial least squares (PLS) multivariate regression analysis was applied for the PE-signal and results were related to known porosity of the test samples.

Results
Traditional US parameters showed weak to moderate correlations with cortical porosities (0.042<0.74, Table 1). PLS regression analysis was applied successfully for both, the model (n=96) and test set (n=24), allowing us to establish a new method for estimating cortical bone porosity.[4] There was no bias between the PLS predicted and known (µCT) porosities (Figure 1).

Conclusion
In this FDTD study, as compared to traditional ultrasound parameters, PLS analysis of the backscatter signal could be used to predict cortical bone more accurately.

Table 1: Pearson correlation coefficients (R²) between cortical porosities and traditional frequency and time domain US parameters (n=120).

<table>
<thead>
<tr>
<th>Frequency domain</th>
<th>Porosity</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRC</td>
<td>0.04</td>
</tr>
<tr>
<td>AIB</td>
<td>0.06</td>
</tr>
<tr>
<td>FSAB</td>
<td>0.16</td>
</tr>
<tr>
<td>TSAB</td>
<td>0.04</td>
</tr>
<tr>
<td>tAIB</td>
<td>0.10</td>
</tr>
<tr>
<td>IRC back</td>
<td>0.74</td>
</tr>
<tr>
<td>Time domain</td>
<td>P2Patt</td>
</tr>
</tbody>
</table>

FIGURE 1. US predicted-µCT porosity differences versus mean with 95% limits of agreement (Bland–Altman plot).

NOTES

Conflicts of Interest
This research was supported by grants from the University of Eastern Finland and from the Academy of Finland (project 315653).


*Address for correspondence: markus.malo@uef.fi

Department of Applied Physics, University of Eastern Finland, P.O. Box 1637, Kuopio FI-70111, Finland. 2) Finland and Diagnostic Imaging Center, Kuopio University Hospital, P.O. Box 100, Kuopio FI-70729, Finland.

A 64-elements linear array transducer is simulated at one end of a 2D slab of cortical bone. One by one, all of the elements of the array transmit an 8-MHz Gaussian pulse. For each transmit, the backscattered signals are recorded on the whole array. The backscattered intensity is calculated as a function of time. The incoherent contribution is extracted, which exhibits the spatial spread of the diffusive halo over time, enabling the calculation of the diffusion constant and transport mean free path. Simulations are performed on binarized cross-sectional image of the human proximal femur shaft, obtained by time-resolved 100 MHz Scanning Acoustic Microscopy (SAM). In order to investigate the effect of porosity changes on the transport parameters, various porous geometries are generated from the original scanned image. Because osteoporosis mainly impacts the endosteal region, a pore size gradient was artificially created (fig. 1). With an increase in porosity, the diffusion constant and transport mean free path were found to decrease consistently (fig 1). These results suggest that measuring the transport mean free path could be used to assess cortical porosity.

References
2) Hans et al., The Lancet, 1996.
Imaging of cortical pores using ultrasound contrast agents: A phantom study

Juan Du1, Melanie Gräsel2, Reinhard Barkmann1, Kay Raum1
1 Berlin-Brandenburg Center for Regenerative Therapies, Charité - Universitätsmedizin Berlin, Germany
2 Klinik für Radiologie und Neuroradiologie, Universitätsklinikum Schleswig-Holstein, Kiel, Germany

Cortical bone porosity and pore size play important roles in the fracture toughness and strength of bone [1-2]. The current standard diagnosis (DXA; X-ray absorptiometry) measures bone mineral density, which is rather insensitive to cortical porosity and pore size. Conventional ultrasound imaging is limited by the strong specular reflection from bone surface and high attenuation in cortical bone tissue. However, ultrasound contrast agent (UCA) enhanced ultrasound imaging could be a potential way of imaging cortical pores due to their acoustic impedance mismatch and the generation of harmonic response. In this study, a 3D porous phantom was scanned with different transducers (center frequency 2.5 MHz). The ultrasonic data were acquired using the beam-steering sequences with an angle of -10° (a), 10° (b) and 0° (c). The microCT image of the porous phantom was used as a ground truth. As illustrated in Figure 1, more than 50% of the pores were detected. The quantification of porosity and pore area is underway.

Fig. 1: The maximum intensity projection (a-d) and a microscope image of the porous phantom (d). The ultrasonic data were acquired using beam-steering sequences with an angle of -10° (a), 10° (b) and 0° (c).

Ultrasound imaging of cortical bone at the distal radius

Guillaume Renaud1, Pieter Kruizinga2, Pascal Laugier1
1 Sorbonne Universités, UPMC Univ Paris 06, CNRS UMR 7371, INSERM UMR S1146, Laboratoire d’Imagerie Biomédicale, Paris, France
2 Department of Biomedical Engineering, ThoraxCenter, Erasmus MC, Rotterdam, The Netherlands

Cortical bone thickness and ultrasound wavespeed were proposed as biomarkers of bone quality. However, they cannot be assessed with conventional ultrasonography. Current clinical ultrasound scanners do not take into account refraction of ultrasound at interfaces between soft tissues and bone in their image reconstruction. Therefore, a region containing bone cannot be properly imaged. In this work, we show that ultrasonography of cortical bone is possible if one takes into account refraction and the elastic anisotropy of cortical bone. We also describe how the process of image reconstruction leads to an estimation of wavespeed in bone. Ultrasound images of the radius of two healthy volunteers (34y/o and 32y/o) are reconstructed and compared to images obtained with high-resolution X-ray Computed Tomography. A research ultrasound system and a clinical probe (frequency 2.5 MHz) were used to acquire raw ultrasound signals. Optimal wavespeeds in soft tissue and in cortical bone are found by searching optimal focus quality (maximum intensity and sharpness of the image) of the specular reflection produced by the periosteum and the endosteum, respectively. The measurements were repeated 5 times with systematic repositioning of the ultrasound probe. As illustrated in the figure, the cortical thickness and wavespeed of volunteer 2) in the direction that is parallel to osteons. These values are in agreement with literature.
Effect of preparation method and bone mineral density on bone-interface densification in hip arthroplasty

Johanna Bätz1, Philipp Messer1, Frank Lampe2, Klaus Puschel3, Anke Klein1
1TUHH Hamburg University of Technology, Hamburg, Germany
2Department of Life Sciences, Hamburg University of Applied Sciences, Germany
3Department of Legal Medicine, University Medical Center Hamburg-Eppendorf, Germany

Loosening is a major cause for revision in uncemented hip prostheses due to insufficient primary stability, and may be affected by the cavity preparation technique. Preparation is achieved through extraction (removes bone or compaction (crushes bone) broaching. The latter increases bone densification at the cavity interface, the amount of densification, and therefore increase in stability, may be limited by the patient's bone quality. The aim of this study was to determine the degree to which the broaching method and initial bone mineral density (BMD) affect densification at the bone-cavity-interface.

Paired human femora (n=25, age=57±19y) were prepared with compaction and extraction broaches. QCT scans were conducted with a calibration phantom before and after broaching and the images resampled (voxel size: 0.5x0.5x1 mm). The mean trabecular BMD of the intact proximal femur was determined. The cavity volume was segmented (threshold -250 mg HA/cm^3). Ring volumes of interest (ROIs) of one-voxel thickness were added around the cavity. The ring 1.5 mm from cavity was divided into anatomical quadrants (pQOIs, Figure 1). The VOIs were transferred to the pre-broach image and bone densification was calculated within each VOI. Broaches were weighed before and after broaching. Trabecular BMD ranged from 84 to 221 mg HA/cm^3. Densification was higher with compaction compared to extraction broaching within 2 mm from the cavity (p=0.028, ANCOVA), but was not affected by BMD and occurred homogenously in all anatomical quadrants (Table 1). Preparation method and BMD both affected removed mass (p=0.001, p=0.038, ANCOVA). More tissue mass was removed with extraction broaches than with tissue mass (p=0.012, related-samples Wilcoxon signed rank test).

The study suggests that within the BMD range measured, densification is increased using compaction broaching irrespective of patient's BMD, which could improve primary stability of hip replacements in osteoporotic patients.

Conflict: The study has been financially supported by DePuy Synthes, Leeds, UK.

Effect of semi-automatic contouring on short-term reproducibility of bone parameters obtained from HR-pQCT measurements of distal radius fractures

Franz Heyer1,2, Joost de Jong1, Jacobus Arts5, Martijn Poelse3, Paul Willems4,6, Piet Geusens4,7, Bert van Rietbergen4,1,4,8
1Research School NUTRIM, Maastricht University, The Netherlands
2Department of Surgery, Maastricht University Medical Center, The Netherlands
3Department of Internal Medicine, VieCuri Medical Center Venlo, The Netherlands
4Department of Rheumatology, Maastricht University Medical Center, The Netherlands
5Research school CAPHRI, Maastricht University, The Netherlands
6Department of Orthopedic Surgery, Maastricht University Medical Center, The Netherlands
7Faculty of Medicine and Life Sciences, Hasselt University, Belgium
8Faculty of Biomedical Engineering, Eindhoven University of Technology, The Netherlands

It has been shown that high-resolution peripheral quantitative computed tomography (HR-pQCT) can detect and quantify changes in bone microarchitecture and bone stiffness during the healing of distal radius fractures.1 Although the short-term reproducibility of HR-pQCT-based analyses has been validated extensively for measurements of unfractioned bone,2 the effect of manually defining the region of interest (ROI), i.e. contouring the fractured bone fragments, on short-term reproducibility has not been investigated before. In the current study, we analyzed the effect of different operators defining the ROI on scans of fractured distal radii at two timepoints. HR-pQCT scans (XtremeCT-1, Scanco Medical) of the fractured distal radius of 9 postmenopausal women were performed at 2 and 12 weeks post-fracture. The ROI on each scan was defined by two operators separately. In addition, an octagonal ROI was drawn around each fractured radius. Standard HR-pQCT and finite element analyses (FEA) using software provided by the manufacturer were performed as described earlier.1 Intraclass correlation coefficients (ICC) and root-mean-square error of percentage difference (RMSE%) were calculated between all operators.

It has been shown that cavitation of the interface in hip arthroplasty is a major cause for revision due to insufficient primary stability, and may be affected by the preparation technique. Preparation is achieved through extraction (removes bone or compaction (crushes bone) broaching. The latter increases densification at the cavity interface, the amount of densification, and therefore increase in stability, may be limited by the patient’s bone quality. The aim of this study was to determine the degree to which the broaching method and initial bone mineral density (BMD) affect densification at the bone-cavity-interface.

Paired human femora (n=25, age=57±19y) were prepared with compaction and extraction broaches. QCT scans were conducted with a calibration phantom before and after broaching and the images resampled (voxel size: 0.5x0.5x1 mm). The mean trabecular BMD of the intact proximal femur was determined. The cavity volume was segmented (threshold -250 mg HA/cm^3). Ring volumes of interest (ROIs) of one-voxel thickness were added around the cavity. The ring 1.5 mm from cavity was divided into anatomical quadrants (pQOIs, Figure 1). The VOIs were transferred to the pre-broach image and bone densification was calculated within each VOI. Broaches were weighed before and after broaching. Trabecular BMD ranged from 84 to 221 mg HA/cm^3. Densification was higher with compaction compared to extraction broaching within 2 mm from the cavity (p=0.028, ANCOVA), but was not affected by BMD and occurred homogenously in all anatomical quadrants (Table 1). Preparation method and BMD both affected removed mass (p=0.001, p=0.038, ANCOVA). More tissue mass was removed with extraction broaches than with tissue mass (p=0.012, related-samples Wilcoxon signed rank test).

The study suggests that within the BMD range measured, densification is increased using compaction broaching irrespective of patient’s BMD, which could improve primary stability of hip replacements in osteoporotic patients.

Conflict: The study has been financially supported by DePuy Synthes, Leeds, UK.
Fabrication of oriented hydroxyapatite film by RF magnetron sputtering
Takafumi Kubota, Keshiro Hirata, Kazuma Mori, Shohei Tokuda, Daiki Koyama, Mami Matsuokawa
Doshisha University

Hydroxyapatite (HAp) is compatible with bone tissue and used as a bone prosthetic material, especially for the coating of implants. The c-axis of biological apatite (BAp) in bone is usually oriented in the bone axis direction due to the mechanical stress. In addition, in new bone on the artificial bone surface, BAp orientation is influenced by HAp orientation of artificial bone [1]. The implant coating with the oriented HAp film is then expected to improve the healing speed. In this study, we tried to fabricate the C-2015 uniaxially oriented HAp film by RF magnetron sputtering. The control of orientation was achieved by changing the amount of infusing oxygen, following our former study on the fabrication of oriented ZnO film [2]. HAp film samples were fabricated on a glass plate by changing the gas pressure (0.1, 0.2, and 0.4 Pa) and the gas type (Ar only, or Ar : O2 = 1 : 3) during sputtering. The applied voltage of RF power was 100 V and the discharge time was 24 hours. The X-ray diffraction patterns of the samples changed due to the gas type. The sample fabricated with only Ar showed strong (002) peak, which means the alignment of HAp perpendicular to the film surface. The sample fabricated with mixture gas showed (002) and (211) peaks (Fig. 1), telling the partly in-plane alignment of HAp. The (211) peak increased and (002) peak decreased due to the decrease of gas pressure. In addition, from X-ray pole figure analysis, a small tilt of HAp orientation was found in the sample fabricated with mixture gas. These data indicate the possibility of HAp orientation control in the coating film.

References

Quantitative assessment of radial bone structural distribution in the proximity of degradable implants by micro-computed tomography
T. Damm, H. Naugakot, J. Wiltfang, C.-C. Gluer

Degradable bone implants may promote fracture healing and improve quality of life by stimulating bone formation and obliterating the need for second surgery to remove the implant. In order to optimize alloy composition and degradation properties, in vivo monitoring of the degradation process and its impact on bone formation is essential. The methods presented have been developed for use in several implant studies including the BMBF project “MgBone”. A newly developed method for quantitative assessment of changes in bone volume close to the implant surface, a region key to stable fixation within the bone, is presented. Degradable magnesium-alloy plates (MgYREZr-system, >90 wt%Mg) placed above the frontal sinus of miniature pigs were fixed with screws of identical material. Titanium implants served as control. Animals were sacrificed at three time points (10, 20, 30 weeks post implantation). 3 samples per group were harvested. µCT scans were performed (Scanco VivaCT 80, 70 kVp, 114mAs, 1000 projections/180°, 20.4µm isotropic voxel-size). Two image analysis approaches were employed (Fig. 1): (I) Evaluation within a narrow “proximity-shell” of 120µm width, center-position 180µm away from implant-surface and (II) radial density-distribution calculation averaged within equidistant “onion-like” shells. Analyzing the proximity shell, for the magnesium alloy implant we observed an increase in bone volume fraction (BV/TV) of 3.4% per month (r=0.52, p<0.029) reaching a BV/TV of 30% after 30 weeks. For the Ti-implant BV/TV stayed relatively constant at levels of ~60%.

Bone (re-)modeling as a function of distance from the implant surface can be investigated. The cross-sectional study design and small sample size does not permit to draw generalizable conclusions about the implant materials and solely serves to document the method’s functionality, which is suited for use in time-lapse µCT protocols to quantify implant corrosion and bone in-growth over time.

Fig. 1) 3D visualization (top left) and BV/TV assessed a proximal shell (top right), radial BV/TV-distribution, implant surface at d=0mm (bottom left) and “onion-like” shell segmentation (bottom right).
Spatial assessment of bone microarchitecture in postmenopausal women with a recent Colles’ fracture
Andrew J. Burghardt1, James M. Peterson2, Sundeep Khosla2, Julio Carballido-Gamio1
1University of California, San Francisco
2Mayo Clinic
3University of Colorado, Denver

The spatial assessment of bone with data-driven image analysis techniques, including statistical parametric mapping (SPM), could identify biologically-relevant regions and bone features that distinguish clinical populations. We applied SPM to a case-control study of Colles’ fracture. The forearms of postmenopausal women with (N=84) and without (N=98) a recent fracture were imaged using HR-pQCT. The distal radius was segmented and spatially normalized to a template effectively aligning corresponding anatomical regions across the study population. These transformations were applied to voxel-based maps of local bone volume fraction (BV/TV), homogenized volumetric bone mineral density (vBMD), strain energy density (SED) from µFEA, and inter-trabecular distances (Tb(1/N)). Surface-based maps of cortical thickness (CTh), CtvBMD, and CtSED were used to study the cortex. Voxel/ver-text-wise comparisons between cases and controls were performed in the space of the template using general linear models with the bone features as dependent variables, group membership (cases-controls) as the independent variable, and age, height, weight and the first 5 principal scores of shape as covariates. These comparisons yielded Student’s t-test statistical maps (T-Maps), which were corrected for multiple comparisons using the false-discovery rate approach (q<0.05). Voxel comparisons indicated that the central medullary space, medial cortex, and more proximal slices were different between populations (Figure 1). The fracture group had reduced SED in the central medullary region near the proximal boundary, but high SED in the palmar cortex near the distal boundary, suggesting impaired load distribution. Although global CTh and CtvBMD were significantly different (p<0.05), vertex comparisons yielded only nonsignificant differences after correction for shape. Our results indicate a nonuniform spatial association between fracture and bone features, highlighting the value spatial assessments bring to understanding the structural basis of fracture risk.

NOTES

Bone densitometry in patients with acromegaly may be misleadingly normal while vertebral fractures are prevalent yet often remain occult
Marko Stojanovic1, Dragana Miljic2, Sandra Pekic1, Mirjana Doknic1, Marina Nikolic Djurovic2, Zvezdana Jemuovic2, Vera Popovic1, Milan Petakov1
1Clinic for Endocrinology, Diabetes, and Metabolic Diseases, Clinical Centre of Serbia, University of Belgrade, School of Medicine
2Clinic for Endocrinology, Diabetes, and Metabolic Diseases, Clinical Centre of Serbia
3University of Belgrade, School of Medicine

Introduction
Skeletal complications of acromegaly are persistent and invalidating. Dual-X-ray absorptiometry (DXA) alone might be insufficient or even misleading for bone health assessment in acromegaly. Vertebral Fracture Assessment (VFA) is a DXA-based semi-quantitative method. It is a quick, low radiation and cost-effective way of screening TH4 to L4 to identify clinically silent vertebral fractures (VF). Patients and methods: Patients with acromegaly (N=170) were classified as active (N=104), operatively cured (N=34) or medically controlled (N=32). 57 males and 113 females were included, 52.8 (22.0-78.5) years old. Bone mineral density (BMD) was assessed at L1-L4 and Femoral neck using DXA Hologic Discovery-W-QDR. BMD results were expressed as Z score, accounting for age and gender. VFA on Th4-L4 was performed in 71 patients (24 male, 47 female) identifying their location, type and severity.

Results
L1-L4 BMD was normal in all patients and not significantly different in active (Zsc: 0.61±0.13) cured (Zsc: 0.32±0.25) or controlled acromegaly (Zsc: 0.17±0.32). FN BMD was normal in all and not significantly different in active (Zsc: 0.61±0.11) cured (Zsc: 0.59±0.19) or controlled acromegaly (Zsc: 0.49±0.22). VFs were identified in 23.9% patients (17/71). Prevalence in males was significantly higher than females (33.3% vs. 19.2% p<0.01).

Patients with and without VF did not differ in BMD L1-L4 Zsc (0.98±0.06 vs. 1.04±0.02) or FN Zsc (0.83±0.05 vs. 0.86±0.02) but were significantly different in active vs. controlled acromegaly (0.62±0.13 vs. 0.32±0.25, p<0.01). VFs were identified most often in males (24.0%) when compared to females (20.1%) acromegaly (p<0.01). VFs have most often involved a single vertebra, were mild in severity and wedge shaped.

Conclusion
Considerable prevalence of vertebral fractures (24%) was identified in a large cohort of patients with acromegaly, supporting previous reports. VFs are important, persistent and invalidating yet often under-recognized complication of acromegaly.
Bone formation driven by mechanical loads can be accompanied with the piezoelectric effect. To realize effective healing of bone fracture using low-intensity pulsed ultrasound (ULPUS), the piezoelectric effect under ultrasound irradiation should be elucidated. However, the piezoelectric properties at ultrasound frequencies in bone, particularly in cancellous bone, are not sufficiently clarified yet. In this study, using a piezoelectric cell (PE-cell), in which the parallelepiped cancellous bone specimen was electrically shielded to prevent electromagnetic noise, the piezoelectric signal generated in the bone by ultrasound radiation was experimentally observed in water. The cancellous bone specimen of approximately 25 × 25 mm2 area and 8.5 mm thickness was cut from the distal epiphysis of a bovine femur, and the pore spaces were saturated with air after the removal of bone marrow. The trabecular structure was analyzed from the three-dimensional X-ray microminimal computerized tomographic (MD-μCT) image. The orientation of the trabecular network tended to be parallel to the thickness direction, and the porosity was varied from 0.63 to 0.72 (63–72%) with the local position. A Pb(Zr,Ti)O3 (PZT) ultrasound transmitter was used to radiate a burst ultrasound wave at 1 MHz toward the PE-cell in the thickness direction of the cancellous bone specimen. The ultrasound wave received at various positions in the PE-cell. The piezoelectric sensitivity of the PE-cell was estimated by comparison calibration with a poly(vinylidene fluoride) (PVDF) ultrasound receiver. As shown in the figure, the piezoelectric sensitivity tended to decrease with the cancellous bone porosity at the receiving position, but the correlation was low (R2 = 0.33 (P = 0.11)). This was considered to be because the effect of the trabecular structure was relatively large.
Fabrication of a self-assembling poly γ-glutamic acid based nanoparticle loaded triptolide for the treatment of rheumatoid arthritis

Ali Ghasem-Zadeh1, Roger Zebaze1, Andrew Nunn2, Maya Panisset2, Xiao-Fang Wang1, Mary P Galea3, Ego Seeman1, 4
alig@unimelb.edu.au

1Departments of Medicine and Endocrinology, Austin Health, University of Melbourne, Melbourne, Australia
2Victorian Spinal Cord Service, Austin Health, University of Melbourne, Melbourne, Australia
3Department of Medicine, Royal Melbourne Hospital, University of Melbourne, Australia
4Institute for Health and Aging, Australian Catholic University, Melbourne, Australia

Triptolide (TP) exhibits immunosuppressive, cartilage protective and anti-inflammatory on both humans and animals for RA. However, the use of TP increases the risk for the occurrence of side effects, including nephrotoxicity and hepatitis. To decrease the toxic and side effects of TP, we developed a novel drug carrier system (PAT) containing TP using γ-PGA-grafted-L-Asp-OtBu. The average diameter of PAT was 78±12nm, the polydispersity index was 0.18, the zeta potential was -32 mV and the encapsulation efficiency was 46.3%, and TP was released from PAT in controlled manner. Intravenous injection of PAT, which accumulated in inflammatory joints, improved the survival rate, and had fewer side effects on tumor necrosis factor a transgenic (TNF-Tg) mice, compared to TP. In addition, PAT reduced inflammatory synovial tissue area, bone erosion, cartilage loss, and TRAP+ osteoclast area in both knee and ankle joints of TNF-Tg mice, which show similar beneficial effect of TP. Therefore, PAT represents a very effective drug candidate for inflammatory arthritis with low adverse side effect.

Key words
Triptolide, Rheumatoid arthritis, γ-PGA, Tumor necrosis factor a transgenic mice

Microstructural decay in spinal cord injury

Ali Ghasem-Zadeh1, Roger Zebaze1, Andrew Nunn2, Maya Panisset2, Xiao-Fang Wang1, Mary P Galea3, Ego Seeman1, 4
alig@unimelb.edu.au

1Departments of Medicine and Endocrinology, Austin Health, University of Melbourne, Melbourne, Australia
2Victorian Spinal Cord Service, Austin Health, University of Melbourne, Melbourne, Australia
3Department of Medicine, Royal Melbourne Hospital, University of Melbourne, Australia
4Institute for Health and Aging, Australian Catholic University, Melbourne, Australia

Background
Spinal cord injury (SCI) causes rapid bone loss due to a reduction in bone formation at the basic cellular unit (BMU) level and increased rate of bone remodelling at the surface level, changes that result in microstructural deterioration and increased fracture risk. There is lack of information concerning the effects of paralysis on bone microstructure. We hypothesised that SCI individuals have i) a severe trabecular bone microstructural deterioration ii) higher cortical porosity in comparison to controls.

Methods
We studied 31 men with chronic complete SCI (age 43.5±14.2 yrs, duration of paralysis of 1.7-22 yrs), and 90 age and sex-matched healthy ambulatory controls, recruited at Austin Health, University of Melbourne. Images of the non-dominant distal tibia were obtained using high-resolution quantitative computed tomography (HR-pQCT, Scanco, 82 micron isotropic voxel size). Manufacturer’s and StrAx algorithm (StraxCorp, Melbourne, Australia) were used to quantify trabecular and cortical compartments indices.

Results
Compared with controls, SCI cases had 2.295% CI 1.8 to 2.6), 1.75D (1.31 to 2.13), 2.35D (1.95 to 2.78) and 1.74 SD (1.32 to 2.15) higher porosity in the total cortex, compact cortex, inner and outer transitional zones and 1.75D (-2.15 to -1.3) lower matrix mineralisation density. Total and cortical vBMId were reduced by 2.22 SD and 2.25 SD, respectively, all (p<0.01). Trabecular bone volume fraction was 1.8 SD (-2.21 to -1.38) lower in cases due to 1.74 SD (-2.17 to -1.34) lower number of trabeculae and 2.35D (1.81 to 2.78) higher separation. Trabecular bone surface and connectivity density were decreased by 0.905 to 1.3) and 1.4 SD (1.1 to 2.2), respectively (all p<0.01).

Conclusion
We infer that spinal paralysis produces profound and rapid loss of cortical and trabecular bone suggesting antiresorptive therapy should be commenced at the time of presentation.
Prevalence of sarcopenia in community dwelling German males and females 70+ using different recognized definitions. A BIA based approach

Wolfgang Kemmler, Simon von Stengel, Klaus Engelke
Institute of Medical Physics, Friedrich Alexander University Erlangen-Nürnberg, Germany

Sarcopenia is becoming increasingly important for our fast aging societies. However, with respect to varying definitions, components and cut-off points it is difficult to determine the prevalence of this “geriatric syndrome” in a given population. The aim of the study was to determine the prevalence of sarcopenia in community-dwelling (cwd) Caucasian German men and women 70+ using the definitions of the European Working Group on Sarcopenia in Older People (EWGOP), the International Working Group on Sarcopenia in Older People and the Foundation for the National Institutes of Health.

Altogether, 2290 cwd females and males 70+ living in Northern Bavaria were screened for sarcopenia parameter according to recent recognized definitions including appendicular muscle mass, handgrip strength and/or gait velocity. Muscle mass (i.e. skeletal muscle mass index, SMI) was determined via multi-segmental, multi-frequency Bio-Impedance Analysis (Inbody 770, Korea). The data of anthropometry, family-, educational-, social status, lifestyle, number/distribution of diseases and medication of our participants were comparable with those of German men and women 70+. Thus, we assume that our results are highly representative for the corresponding German population. In summary, the prevalence of sarcopenia in the cwd German population 70+ averaged between 3.3% (EWGS) and 4.9% (FNIH) and did not relatively vary between women and men (e.g. EWGS: 4.5% vs. 4.9%). However, with respect to morphometric and functional sarcopenia parameters, men and women considerably differ. E.g. applying the FNIH cut-point for SMI of 0.512 and 0.789 (ASM/BMI) respectively, 9.7% of the women versus 21.6% of the men fell within the sarcopenia criteria. Vice versa, a significantly lower amount of men showed a low grip strength (20 or 30 kg).

In summary, the prevalence of sarcopenia is rather low (<5%) in cwd German men and women 70+. Although the prevalence of sarcopenia was consistently given, the diagnostic overlap between the applied definitions was rare.

Acknowledgement
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Sexual dimorphism in cortical bone morphology during pubertal growth in Chinese adolescents

Ka-Yee Cheuk1, Xiaofang Wang2, Fiona Wai-Ping Yu3, Elisa Man-Shan Tam1, Bobby Kin-Wah Ng4, Tsz Ping Lam5, Ali Ghasem-Zadeh6, Roger Zebaze6, Ego Seeman7, Jack Chun-Yiu Cheng1,3
1Department of Orthopaedics and Traumatology, The Chinese University of Hong Kong, Hong Kong
2Departments of Endocrinology and Medicine, Austin Health, University of Melbourne, Australia
3Bone Quality and Health Centre, Department of Orthopaedics and Traumatology, The Chinese University of Hong Kong, Hong Kong

During puberty, children had higher risk of limb fracture due to rapid bone expansion with insufficient bone mineral accretion. Previous studies in Hong Kong reported boy-to-girl ratio of limb fracture was 5.5:1 in adolescent group. This study aimed to investigate sex difference on cortical growth in Chinese adolescents during puberty. 214 boys and 219 girls aged between 7 and 17 years old were recruited. Maturity was assessed by Tanner staging. Images of non-dominant distal radius were obtained using high-resolution peripheral quantitative computed tomography. Proximal 40 slices of 110 slices were analysed by StrAxt 0. Cortical cross-sectional area (CSA), cortical porosity, volumetric bone mineral density (vBMD), and matrix mineral density were measured. ANCOVA was used to identify sex difference on bone parameters after adjustment for age, height, weight, dietary calcium intake (Ca) and physical activity (PA).

After adjusting for confounders, boys had 11.1–12.8% larger total CSA than girls across puberty, but boys had 1–4% lower cortical CSA/total CSA in Tanner 2-5. In Tanner 1, cortical thickness was 6.1% greater in boys. From Tanner 2, boys had 8.4–12.6% higher cortical porosity. Boys had 0.7–1.6% lower matrix mineral density in Tanner 3-5 after adjusting for age, Ca and PA. In boys, 15.1–21.3% lower total vBMD and 14.3–23.8% lower cortical vBMD were found in Tanner 2-5 compared to girls. Boys had 13.8–15.2% greater trabecular vBMD after adjusting for age, Ca and PA. Transient physiologically changes of the cortical morphology, reduced bone density and higher cortical porosity in Tanner 2 boys might partly decrease bone mechanical strength and contribute to the increased risk of distal forearm fracture.

Acknowledgement
RGC of HKSAR (468809 & 468411).
Skeletal site and location dependent elastic properties of human cortical bone measured by resonant ultrasound spectroscopy

Xiran Cai, Laura Peralta, Quentin Vallet, Nicolas Bochud, Oliver Boughton, Richard Abel, Justin Cobb, Kay Raum, Jean-Gabriel Minonzio, Pascal Laugier, Quentin Grimail

Sorbonne Universités, UPMC Univ Paris 06, INSERM UMR-S 1146, CNRS UMR 7371, Laboratoire d’Imagerie Biomédicale, 75006 Paris, France

The MSk Lab, Imperial College London, U.K

Julius-wolf-Institute & Berlin Brandenburg School of Regenerative Therapies, Charité-Universitätsmedizin Berlin, Germany

Although human cortical bone is an anisotropic material, isotropic stiffness is assumed in most finite element analysis for studying bone macroscopic mechanical behavior, e.g., for prediction of bone strength.

To better simulate bone macroscopic mechanical behavior, precise knowledge of the mesoscopic (mm-scale) anisotropic stiffness of bone is important. In this work, we report the value of anisotropic stiffness and anisotropy of human cortical bone from various skeletal sites (femur, radius and tibia).

From a cohort of femora, 19, 55 and 73 specimens were harvested at different locations: neck, upper-shaft and mid-diaphysis site, respectively. From one-third proximal radius of 20 donors, 42 specimens were prepared and 35 specimens were obtained at the mid-diaphysis of the tibia from another cohort of 20 donors. All specimens were prepared into cuboid shape, sized 1–5mm. Specimen orientation was defined by bone anatomic shape radial (axis 1), circumferential (axis 2) and axial direction (axis 3). The stiffness coefficients $C_{ij}$ of the specimens were measured by a custom-made setup of resonant ultrasound spectroscopy.

Overall, the radius showed the highest compressional and shear stiffness coefficients (Figure 1). The mean $C_{11}$, $C_{22}$ and $C_{66}$ of the femur-tibia, while there was a good overlap between them for $C_{33}$, $C_{44}$ and $C_{55}$. The mean $C_{11}$ of femoral cortical bone at the mid-diaphysis-upper-shaft–neck (Table 1) which may be due to lower mass density at the proximal location of femur, because they follow a similar empirical law. Negative relationship between anisotropy ratio $C_{33}/C_{11}$ and mass density was observed for the tibia, while $C_{33}/C_{11}$ of the femur and radius remained constant. The mean $C_{33}/C_{11}$ of the tibia-radius-femur and the mean $C_{44}/C_{66}$ of tibia-radius-femur. This study demonstrates possible skeletal site and location dependency of anisotropic elastic properties of human cortical bone.

Table 1: The anisotropic stiffness coefficients, anisotropy ratio and mass density of the bone specimens from human mid-diaphysis (femur shaft), neck (femur neck), upper-shaft (femur upper), radius and tibia. All values are in normalized.

<table>
<thead>
<tr>
<th>$C_{ij}$ (GPa)</th>
<th>femur shaft</th>
<th>femur neck</th>
<th>femur upper</th>
<th>radius</th>
<th>tibia</th>
</tr>
</thead>
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<tr>
<td>$C_{11}$</td>
<td>10.76±1.85</td>
<td>17.62±3.20</td>
<td>17.96±2.82</td>
<td>16.70±3.12</td>
<td>14.75±1.28</td>
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<tr>
<td>$C_{22}$</td>
<td>9.94±1.41</td>
<td>16.84±2.86</td>
<td>16.37±3.75</td>
<td>15.63±2.69</td>
<td>14.56±2.18</td>
</tr>
<tr>
<td>$C_{33}$</td>
<td>5.08±0.50</td>
<td>5.39±0.72</td>
<td>5.28±0.80</td>
<td>5.01±0.27</td>
<td>5.21±0.85</td>
</tr>
<tr>
<td>$C_{44}$</td>
<td>5.08±0.50</td>
<td>4.92±0.48</td>
<td>5.09±1.09</td>
<td>5.01±0.27</td>
<td>5.21±1.65</td>
</tr>
<tr>
<td>$C_{55}$</td>
<td>5.08±0.50</td>
<td>4.92±0.48</td>
<td>5.09±1.09</td>
<td>5.01±0.27</td>
<td>5.21±1.65</td>
</tr>
<tr>
<td>$C_{66}$</td>
<td>5.08±0.50</td>
<td>4.92±0.48</td>
<td>5.09±1.09</td>
<td>5.01±0.27</td>
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</tbody>
</table>

Ultrasonic computed tomography based on full-waveform inversion for bone quantitative imaging

Simon Bernard, Vladim Montelle, Dmitri Komatitsch, Philippe Lasaygues

s.bernard.simon@gmail.com

Aix Marseille Univ, CNRS, Centrale Marseille, LMA, Marseille, France

Full waveform inversion (FWI) is an imaging method based on the numerical modeling of wave propagation in heterogeneous media and on the minimization of the mismatch between experimental and computed waveforms. So far, FWI has been developed mostly in the geophysical community, where it offers improved resolution and accuracy compared to methods based on approximations of the wave propagation (e.g., ray tracing), at a higher computational cost.

In this work, we investigate its application for quantitative wave-speed imaging in the cross-section of long bones. Minimizing the misfit function requires computing its partial derivatives with respect to each model parameter (discretized velocity and density maps). This gradient is obtained from the adjoint-state method, which consists in time-correlating the forward field with an adjoint field resulting from the back-propagation of the time-reversed residuals in the medium. The gradient is thus computed based on only two wave propagation simulations (20 finite differences per source). We then use in an efficient quasi-Newton minimization method called HFGS, which avoids explicit storage and inversion of the Hessian matrix of the problem. In our numerical example (Fig. 1), synthetic data are generated for a circular array surrounding a tibia/fibula bone pair with realistic velocity and density values. The inversion is started from a homogeneous water medium. To avoid trapping into local minima of the non-linear cost function, which occurs in the case of travel-time differences larger than half-a-period between the intial and true media, we start the inversion with low-pass filtered data. We then gradually increase the upper frequency, using the solution of the previous inversion as a new initial guess. Our results demonstrate the potential of FWI-based ultrasonic computed tomodiography for the evaluation of bone geometry and elastic properties. In particular, cortical bone thickness can be estimated. Future work will focus on the inversion of experimental data.

Figure 1: The relationships between anisotropic stiffness coefficients, anisotropy ratio and mass density of the bone specimens from human mid-diaphysis (femur shaft), neck (femur neck), upper-shaft (femur upper), radius and tibia.
Ultrasonically induced electrical potentials in bovine cortical bone
Takji Makino, Koki Takano, Takashi Funato, Sayaka Matsukawa, Shinji Takayanagi, Takahiko Yanagitani, Mami Matsukawa

Background, Motivation and Objective
Piezoelectricity in bone is well known after Fukada and Yasuda’s studies in the low frequency range. However, the piezoelectricity of bone in the MHz range has not been investigated in detail. To evaluate the induced electrical potentials, we have fabricated ultrasound transducers using bone as piezoelectric devices and could observe ultrasound waves as the output of the electrical potentials. The purpose of this study is to investigate the characteristics of piezoelectricity in the bovine cortical bone by longitudinal and shear ultrasound irradiation.

Statement of Contribution/Methods
Three kinds of circular plate cortical bone samples (diameter; 10 mm, thickness; 3.00±0.01 mm, normal direction; radial, tangential and bone axis) were prepared from a bovine femur. Using these plates as piezoelectric materials, we fabricated bone transducers as receivers. For longitudinal wave irradiation, a PVDF focus transducer (diameter: 20 mm, focal length: 40 mm, Toray Engineering) was used as a transmitter. For shear wave irradiation, a shear wave transducer (22±10x10 SN, Japan Probe) was used as a transmitter with a coupling material and a delay line (acrylic resin). A short ultrasound pulse of 70 Vpeak-peak was applied to the transmitters, and the transmitted ultrasound was received by bone transducers.

Results/Discussion
Figures 1 (a) and (b) show relationships between the amplitudes of induced electrical potentials and ultrasound propagation directions. The amplitudes were minimum when longitudinal wave propagated in the tangential and axial directions, whereas they showed maximum for the propagation in the off axis directions. In the case of shear waves, the amplitudes were maximum in the axial direction and minimum in the tangential direction. The propagation direction dependence of potentials reflects the characteristic anisotropic behavior of bone piezoelectricity in the MHz range. These results also indicate that there are appropriate irradiation directions of ultrasound to generate electrical potentials.

Estimation of fracture risk based on the concept of the muscle bone unit
Rainer Rawer, Johannes Willnecker
rrawer@gmx.de
Stratec Medizintechnik GmbH

Harold Frost developed the concept of the mechanostat that explains how bone adapts geometry and strength to muscle forces. Besides this direct influence of muscle on bones, muscle function is a critical determinant of fall risk. Most peripheral fractures are caused by falls hence fracture risk depends on fall risk. Measurement of bone density alone is not sufficient for fracture prediction. Any concept for the estimation of fracture risk and the prevention of fractures must therefore include muscle. Our concept of the diagnosis of Sarcopenia or Osteoporosis includes the measurement of bone strength, bone density along with muscle geometry and density with pQCT and muscle function using Mechanography. pQCT is a well-proven technology to measure bone density and geometry as well as bone strength. Lately muscle parameters like area and density were added. Studies show that the muscle and bone cross sectional area is closely connected. The ratio of bone and muscle area might serve as new parameter to distinguish a disuse Osteopenia from a true Osteoporosis. In several recent studies muscle density was used to determine age-related fatty infiltration in the muscle and could support the diagnosis of Sarcopenia. Muscle density is an independent risk factor for frailty, hospitalization, falls and fractures. But bone strength does not adapt to muscle size but to muscle function. So it is essential also to determine muscle forces preferably reflecting natural movements. This can be assessed by Mechanography. Muscle force per unit muscle area can be used as a muscle quality parameter. In addition low muscle power is a major risk factor for falls. Mechanography can also reveal important information about balance and coordination that also predict fall risk. Inclusion of muscle parameter may improve the estimation of fracture risk and offers new strategies also for the prevention of fractures.

Rainer Rawer and Johannes Willnecker are employees of Stratec Medizintechnik GmbH

NOTES
Optical body shape phenotypes using statistical shape modeling for predicting osteopenia, sarcopenia, and obesity status in women

J.A. Shepherd1, M. Sommer2, E.Y. Liu EY3, B. Fan4, B. Ng B5, J. Mastick2, M. Miaskowski1, Chris.miaskowski@ucsf.edu

1 Department of Radiology and Biomedical Imaging, UCSF
2 Bioengineering Department, UC Berkeley
3 School of Nursing, UCSD

Background
Sarcopenic obesity (OB-S) is defined as excess adiposity with reduced muscle mass. OB-S increases the risk of fractures and falls in older individuals. Whole body, three-dimensional optical (3DO) scanning is an automated, highly accessible technology shown to accurately predict fat and lean mass status. In this study, we investigate the ability of 3DO to predict the status of Osteopenia (OP), Obesity (OB), and Sarcopenia (S) in women.

Methods
The RFBCL is a study of 815 women that have had breast cancer. Each woman received spine, hip, and whole body DXA scans using a Hologic Horizon scanner and one 3DO scan using a Fit3D Proscanner. Subjects were classified as sarcopenic if their appendicular skeletal mass index was lower than 5.45 kg/m2, obese if their body percent fat was greater than 40% body fat (BF), and osteopenic if their hip or spine T-score was < -1.0. We noted the combinations of categories.

Results
We have evaluated 85 women to date. Nine PCA components described 99% of the shape variance. Models for predicting OP, OB, and S were derived using logistic regression analysis. Probabilities of OP, OB, and S were quantified using principal component analysis. Visual PCA shape models were created for each category.

Conclusion
3DO whole body imaging shows promise as a fast, inexpensive and automated screening technology for identifying women with OB, S, and OB-S.

Personalised bone health prognosis through integrated patient big data analysis of medical images, molecular profiles and physical activity levels

Nicholas Ohs1, Jan Kleffmann1, Yuk-Wai Wayne Lee3, Chun-Yiu Jack Cheng2, Peter Airen2, Ralph Müller1, Patrik Christen1

1 ETH Zurich, Institute for Biomechanics, Zurich, Switzerland
2 The Chinese University of Hong Kong, Department of Orthopaedics & Traumatology, Prince of Wales Hospital, Shatin, NT, Hong Kong SAR, China

The advancement in clinically relevant big data acquisition and analysis offers a solution to the clinical challenge of accurate prognostication of complex trait diseases to allow timely treatments. Adolescent idiopathic scoliosis (AIS) is the most common three-dimensional spinal deformity during pubertal growth period without clear etiology and pathogenesis. Low bone mass is a significant prognostic factor for curve progression which could be due to genetic and epigenetic anomalies, reduced physical activity, and vitamin D insufficiency. To deepen disease understanding, we here propose a simulation based medical data science framework to prognosticate personalised bone health in a first AIS prototype.

A cellular automaton (CA) was used to integrate medical image data, micro-finite element analysis to integrate physical activity levels, and a Boolean network to integrate molecular and hormone profiles into a simulation based big data analysis. All the inputs were linked with the update rule of the cellular automaton. The Boolean networks model molecular interaction on a per image voxel basis either with available molecular images or in our prototype via statistical distributions of global measurements.

In the AIS prototype, high-resolution peripheral quantitative computed tomography (HR-pQCT) medical images of the distal tibia, physical activity levels, and circulating vitamin D and parathyroid hormone (PTH) levels were integrated. Personalised bone health prognosis of an AIS patient with normal physical activity and patient-specific vitamin D and PTH levels showed minor changes in bone mass whereas the prognosis with reduced physical activity of the same patient led to reduced bone mass. We conclude that our integrated data analysis allows accounting for a variety of patient big data, especially imaging, molecular, hormonal, and physical activity data to study complex trait diseases and perform personalised bone health prognosis.
Unique correlation pattern between cortical and trabecular bone qualities and standard dynamometer handgrip strength in girls with adolescent idiopathic scoliosis

Elisa MS Tam, Ko Yee Cheuk, Vivian WY Hung, Fiona WP Yu, Bobby RW Ng, Edward XQ Guo, Jack CY Cheng, Tsz Ping Lam
1Department of Orthopaedics & Traumatology, The Chinese University of Hong Kong, Hong Kong
2Bone Quality and Health Centre, Department of Orthopaedics & Traumatology, The Chinese University of Hong Kong, Hong Kong
3Department of Biomedical Engineering, Columbia University, USA

Introduction
Grip strength is a marker of muscle mass which can optimize bone strength. While previous studies have shown girls with adolescent idiopathic scoliosis (AIS) had poor bone quality and mechanical properties, the correlation between bone qualities and handgrip strength in AIS remains undefined. This study aimed to investigate the correlation between handgrip strength and bone qualities including volumetric BMD (vBMD), bone geometry, trabecular micro-architecture and bone mechanical properties in AIS girls versus age- and gender-matched controls.

Results
After adjusted for confounders, positive correlation between handgrip strength and bone geometry (cortical area, trabecular area and cortical thickness) was detected in both AIS and controls (all p<0.05). Stiffness and failure load by FEA were also positively correlated with handgrip strength in both AIS and controls. In contrast, positive correlations between handgrip strength and cortical and trabecular vBMD, trabecular plate structure by ITS (pBV/TV, pTb.N, P-P Junc. D. and P-R Junc. D) were only seen in AIS (p=0.003 to 0.015) but not in controls.

Conclusions
Handgrip assessment can be useful for predicting bone qualities in AIS. Unique correlation patterns between bone qualities and handgrip strength were seen in AIS, including the characteristic microstructural trabecular pattern and connectivity as shown by the ITS analysis. Further longitudinal studies are warranted to investigate the relationship between muscle strength, bone qualities and curve severity and the therapeutic implications.

Whole body vibration therapy reduces local peak loading in the distal tibia of girls with adolescent idiopathic scoliosis

Gianna Marano, Yuk-Wai Wayne Lee, Tsz-Ping Lam, Ralph Müller, Patrik Christen
1ETH Zurich, Institute for Biomechanics, Zurich, Switzerland
2The Chinese University of Hong Kong, Department of Orthopaedics & Traumatology, Hong Kong, China

Adolescent idiopathic scoliosis (AIS) is a three-dimensional spinal deformity that can lead to severe morbidity and mainly affects peripuberal girls. AIS is associated with osteopenia, inferior mechanical and abnormal bone structural properties. Whole body vibration (WBV) has been shown to improve DXA parameters at the femoral neck and lumbar spine in AIS girls, however, it remains elusive whether WBV is mechanically advantageous. We hypothesize that WBV increases bone strength and reduces local peak loading due to load-driven bone formation.

Longitudinal high-resolution peripheral quantitative computed tomography images of the distal tibia in AIS girls from a previous study were used in the current study. The treatment group (n=30) was standing on a low-magnitude high-frequency WBV plate for 20 min/day, 3 days/week for 12 months, whereas the AIS control group (n=24) was only observed. Imaging was performed at baseline and after 12 month. Bone tissue loading and strength were estimated using micro-finite element analysis. There were little changes in bone strength between groups. However, the treatment group showed higher bone strength increases and larger variation between subjects, implying that WBV influenced bone mechanics in some subjects. Treated patients showing a considerable increase in bone strength (upper third group, n=10) revealed a significant (p<0.01) decrease of local peak loading (98th percentile) after 12-month WBV. In contrast, treated patients showing a considerable decrease in bone strength (lower third group, n=9) revealed a significant (p<0.01) difference of local peak loading (98th percentile). Unlike treated subjects, control subjects with a considerable increase in bone strength (upper third group, n=18) did not show a reduction in local peak loading but a significant increase in cortical thickness (p<0.05) and bone volume (p<0.01).

These results suggest that WBV therapy improves bone strength in individual AIS patients through load-driven bone formation reducing local peak loading in the bone.
Assessment of the lacuno-canalicular network in human bone from magnified phase nano-CT images
Bolian Yu1, Max Langner2, Alexandra Pacoureas1, Cécile Olivier1,2, Pierre-Jean Gouttenoire1,2, Peter Cloetens3, François Peyrin1,2
1 Univ Lyon, IRIS Lyon, Université Claude Bernard Lyon 1, CNRS UMR 5220, Inserm U1208, Creatis, 69627 Lyon, France
2 ESRF, 38043 Grenoble Cedex, France

The osteocyte system, which plays a major role in the triggering of bone remodeling, has recently attracted increasing attention but its properties in association to bone fragility are still unclear. It is residing the lacuno-canalicular network (LCN) which appears as a complex mesh where lacunae serve as nodes connected with each other by many small channels (canaliculi). Since it is deeply embedded inside bone tissue, the 3D analysis of the LCN at high spatial resolution is still challenging, although a number of 3D imaging techniques have recently been proposed. Here, we propose to use X-ray magnified phase nano-CT (nCT) to extract quantitative information about the LCN in human bone. Small samples were cut from cross sections of the mid-diaphysis of the left femur of 4 women cadavers (ages 56 - 95 years old). Imaging experiments were performed at the beamline ID16A of the European Synchrotron Radiation Facility (ESRF), Grenoble. For each samples, phase contrast CT scans were acquired at four different propagation distances, at voxel sizes of 1.20 and 30 nm. After phase retrieval and tomographic reconstruction, the lacunae and canaliculi were segmented from the volumes at 120 nm, by the hysteresis thresholding algorithm and a dedicated 3D minimal path method respectively. Due to the large nCT data sets (32 GB/ (2048)3 image), the computations for the canaliculi segmentation were parallelized on a cluster of computers. Quantitative parameters could then be calculated from the binary images. Table 1 presents lacunae parameters including the lacuna porosity, density as well as morphological parameters. The development of image analysis methods for the images at 30 nm is in progress. This work is expected to bring new characteristics of the LCN in three dimensions at the nano scale which will be correlated to biomechanical parameters measured on the same subjects.

Assessment of the lacuno-canalicular network in human bone from magnified phase nano-CT images
Bolian Yu1, Max Langner2, Alexandra Pacoureas1, Cécile Olivier1,2, Pierre-Jean Gouttenoire1,2, Peter Cloetens3, François Peyrin1,2
1 Univ Lyon, IRIS Lyon, Université Claude Bernard Lyon 1, CNRS UMR 5220, Inserm U1208, Creatis, 69627 Lyon, France
2 ESRF, 38043 Grenoble Cedex, France

Figure 1: X-ray phase nano-CT images. (a) Minimum Intensity Projections (MinIPs) of 100 slices in the middle of the reconstructed volume at 120 nm; (b) MinIPs of the reconstructed volume at 30 nm; (c) Segmentation of LCN at 120 nm

NANO-imaging of bone mineral using qsSAXS: a contribution to specifying bone quality
Aurelien Gourrier1, Mariana Verezhak1, Helene Follet1, Delphine Farlay1
1 LIPHY, CNRS - Univ. Grenoble Alpes, France
2 LYOS, INSMR U1033, Lyon, France

Bone mineral is, in principle, a simple calcium phosphate with carbonated hydroxyapatite crystal structure that plays a role on the biomechanical properties and calcium homeostasis, two of the main functions of bone. Hence, any alteration of the structure and composition of the mineral could affect either or both those functions. It is, now, well known that the mineral nanocrystals in bone have unusually small dimensions (platelet shaped with ~ 5 nm in thickness) with respect to geological crystals of similar structure and composition. Furthermore, it has also been shown that such nanocrystal morphology is associated with a high degree of crystalline disorder due to size-scale effects, chemical substitutions, hydration and interactions with the organic matrix. Therefore, the identification of structural markers of such disorder should allow to better identify the origin and mechanisms of pathological structural disorders as well as the effect of specific drugs. Such effects have been observed in various diseases, e.g. osteogenesis imperfecta [1] or fluorosis [2]. We present new results obtained on a set of samples exhibiting various mineral pathological disorders including osteoporosis, primitive hyperparathyroidism and fluorosis obtained using synchrotron quantitative SAXS imaging (qsSAXS). We show that different pathologies exhibit characteristic structural signature arising from the mineral structure and that the observed spatial fluctuations are correlated with histology [3]. We discuss those results to highlight the relevant length scales at which the imaging/analysis should be conducted and the impact of the histological dependency on macroscopic based statistics (Fig 1).

References
3) A. Gourrier et al, in preparation

Figure 1: Overlay of qsSAXS image (collagen structure, green) and qsSAXS (nanoparticle size, red) showing a histological dependence. Scale bar: 0.5 mm.
Osteocyte lacuna segmentation from ultra-high resolution desktop micro-CT images: Low precision reveals limitation of state of the art

Duncan C Betts1, Elliott Goff1, Michele Casanova1, Zhihu Li1, Patrik Christen1, Ralph Müller1
dbets@ethz.ch

1Institute for Biomechanics, ETH Zurich, Zurich, Switzerland

Imaging osteocyte lacuna in 3D is difficult; their volume is a few hundred µm³ and they are surrounded by a dense matrix. A resolution of approximately 1 µm is required to resolve them, but this still requires high quality images. Since 2009, several studies have used desktop micro-CT systems to image lacuna, segmenting them using global thresholds and size-based component labelling. However, no validation regarding the error in classification of lacuna has been performed. We established a ground truth by manually labelling osteocytes within sub-volumes. This was compared to two segmentation strategies: threshold and watershed. Sub-volumes of approximately 0.021mm³ were extracted from micro-CT images totalling 14 from 2 human iliac crest biopsies and 16 for mouse vertebrae. The images had a nominal voxel size of 1.2µm, and were scanned on a µCT50 (Scanco Medical, Bruttisellen, Switzerland), at energies of 70kVp for the mice vertebrae and 55, 70 and 90kVp for the human biopsies. Each sub-volume was counted by three independent observers, and the 3D position of each lacuna marked. Inter-observer error was defined as the coefficient of variation of the three observers. The two segmentation methods were then compared to the median counter to determine the sensitivity/true positive (TPR) and precision/false discovery (FDR) rates.

The inter-observer error in lacuna count was less than 13% for both groups. Compared to the median count, the total number of detected lacuna showed no statistical difference for watershed with the human samples and thresholding with the mouse vertebrae, see figure 1. While watershed consistently had a higher sensitivity compared to thresholding, this is at the expense of poor precision, with a false discovery rate up to 29% compared to thresholding’s 19%. In conclusion, state-of-the-art lacuna segmentation methods have poor precision, improved algorithms are needed and our data provides a much-needed platform to benchmark these on.

Prevalence of trabecular microcalli in human vertebrae increases with alendronate treatment

Annika vom Scheidt1, Michael Amling1, Klaus Puschel2, Björn Busse1
avin-scheidt@uke.de
1Department of Osteology and Biomechanics, University Medical Center Hamburg-Eppendorf, Germany
2Department of Legal Medicine, University Medical Center Hamburg-Eppendorf, Germany

Despite the widespread use of anti-resorptive bisphosphonates in osteoporosis therapy, the drugs’ site-specific mode of action and related fracture risk reductions are not fully understood. Especially in vertebrae, bisphosphonates reduce fracture risk very efficiently, but effects on microdamage repair are unclear. Specifically, bisphosphonates’ influence on microcalli in trabecular bone - an important feature of bone strength maintenance - hasn’t been investigated. Therefore, the aim of this study was to quantify microcalli in human vertebrae from osteoporotic and bisphosphonate-treated individuals employing micro-computed tomography. Bone cylinders (3x9mm, length=20mm) from the anterior part of L3 vertebrae from osteoporotic (n=8, age=82±6y) and bisphosphonate-treated women (n=6, age=82±8y, alendronate treatment=4±2y) were scanned with micro-CT (resolution=3.5µm). Each 3D dataset was visually inspected for microcalli. Detected microcalli were classified according to morphology and position. Microcalli were termed woven bone microcalli, if they were globular, and remodeled microcalli, if they were hollow and had a smooth surface or an elongated shape. Here, (i) woven bone microcalli at plates, (ii) woven bone microcalli at rods, (iii) remodeled microcalli at plates, and (iv) remodeled microcalli at rods were analyzed. Our data showed that bisphosphonate-treated bone presents more woven bone microcalli at trabecular rods compared to osteoporotic bone (T-test, p<0.047, cf. Figure 1), independent of bone volume fraction. The amount of woven bone microcalli at plates and the amount of remodeled microcalli at plates and rods was similar in both groups. Under alendronate treatment, microcalli accumulate in vertebral trabecular bone possibly due to reduced remodeling or promoted microdamage repair. Consequently, an elevated microcallus density in the trabecular network may lead to increases in bone mass and thus reinforcement of the microstructure. These changes may contribute to bisphosphonates’ efficacy in vertebral fracture prevention.
Three-dimensional imaging of crack path and osteonal microstructure in human cortical bone on three paired anatomical locations
Rémy Gauthier, Max Langer, Hélène Follet, Cécile Olivier, Frédéric Rongiéras, David Mitton, Françoise Peyrin
1 Univ Lyon, Université Claude Bernard Lyon 1, IFSTTAR, LBM, UMR_T9405, Lyon, France
2 Univ Lyon, Université Claude Bernard Lyon 1, Creatis, CNRS UMR 5220, Inserm U1206, INSA Lyon, Lyon, France
3 Univ Lyon, Université Claude Bernard Lyon 1, INSERM, LYS IMR 1033, Lyon, France
4 Service Chirurgie Orthopédique et Traumatologie – Hôpital Desgenettes, Lyon, France

The comprehension of crack propagation mechanisms in human cortical bone is of great importance for the improvement of fracture risk prediction. It is known that crack advance can be slowed down by toughening mechanisms, such as micro-damage formation near the crack tip. These mechanisms are thought to be related to bone microstructure. Recent results showed that under low loading rate, the radius diaphysis resisted better to crack propagation than the femoral diaphysis or neck (Gauthier et al., JMBBM, submitted). X-Ray CT imaging at the microscopic scale (µCT) is a standard method for the assessment of cortical bone architecture but the assessment of micro-damage requires sub-microscopic spatial resolution. The aim of the current study is to investigate the microstructure and micro-damages of paired anatomical locations subjected to toughness experiments. We assessed the microstructure of human cortical bone of 8 paired radius diaphysis, femoral diaphysis and necks (female, 50 - 91 yd) using Synchrotron Radiation SRµCT in absorption and phase modes (voxel size 0.7 µm). Image acquisition was performed on two volumes of interest in each sample: the first one corresponds to a region where no mechanical stress was applied, to investigate structural differences between the locations; the second one, to a damaged region where three-point bending toughness tests were performed under a quasi-static strain rate, to evaluate structural changes, as micro-damages formation, due to crack propagation. Phase µCT allows the enhancement of the visibility of osteons, that might play a role in crack propagation mechanisms as illustrated on the figure. After acquisition, we designed an imaging processing workflow to extract quantitative information on bone structural elements, such as Haversian canals, osteons or lacunae. Cracks and micro-damages were also segmented and quantified to investigate their relationships with human cortical bone toughness.

3D digital anatomic angioarchitecture of the mouse spinal cord: A synchrotron radiation micro-CT study
Hongbin Lu1, Yong Cao1, Nishuangfei Fei1, Jianzhong Hu1
1 Department of Sports Medicine, Research Center of Sports Medicine, Xiangya Hospital, Central South University, Changsha, China
2 Department of Spine Surgery, Research Center of Sports Medicine, Xiangya Hospital, Central South University, Changsha, China

Comprehensive analysis of 3D angioarchitecture within the intact mouse spinal cord remains technically challenging due to its sophisticated anatomical properties. In this study, we aim to present a framework for ultra-high resolution digitalized mapping of the normal mouse spinal cord angioarchitecture and to determine the physiological parameters using synchrotron radiation micro-CT (SRµCT). Animal experiments were performed according to a protocol approved by the Animal Care Committee of Central South University. Male C57BL/6 mice (n = 8) were used in this ex vivo study. After a proportional mixture of contrast agents (Microfil MV-122) perfusion, the intact spinal cord covered the cervical spinal from the upper of the 1th cervical vertebra to the 5th lumbar vertebra were harvested and cut into proper lengths within three distinct regions: Cervical 3-Slevel, Thoracic 10-12 level, Lumbar 3-Slevel spinal cord and examined using SRµCT. This method enabled the replication of the complicated microvasculature network of the normal mouse spinal cord at the ultrahigh resolution level, allowing for the precise quantitative analysis of the vascular morphological difference among cervical, thoracic, and lumbar spinal cord in a 3D manner. Apart from a series of delicate 3D digital anatomical maps of the mouse spinal cord angioarchitecture ranging from the cervical and thoracic to the lumbar spinal cord were presented. The 3D reconstruction data of SRµCT made virtual micro-endoscopy and 3D printing of the spinal cord microvasculature network possible and provided deep insight into the nature and role of spinal cord intricate angioarchitecture. Our data proposed a new approach to outline systematic visual and quantitative evaluations on the 3D arrangement of entire hierarchical microvascular images of the normal mouse spinal cord at ultrahigh resolution. The technique may have great potential and become useful for future research on the poorly understood nature and function of the neurovascular interaction, particularly to investigate their pathology changes in various models of neurovascular disease.
In-vivo tracking of individual cortical bone remodeling events in a rabbit model

Arash Panahifar1, Kimberly Harrison1, David M.L. Cooper1
1Department of Anatomy and Cell Biology, College of Medicine, University of Saskatchewan, Saskatoon, Canada

Introduction

There is very little known about the spatio-temporal ‘behavior’ of remodeling events in cortical bone and their role in bone deterioration and fragility. Due to the lack of sufficient resolution and the associated high radiation dose needed, in-vivo tracking of individual cortical pores has not been possible. We overcome these limitations through synchrotron-based phase contrast imaging of a rabbit model.

Methods

The distal tibia of skeletally mature female rabbits were scanned in-vivo using in-line phase contrast micro Computed Tomography (micro-CT) at 12.8µm pixel size, 60cm target-to-detector distance, and 40keV X-ray energy at the BM17-ID beam line of the Canadian Light Source. The animals were recovered and the same region was re-scanned two weeks later, but this time ex-vivo. The two data sets were reconstructed and cross sections were automatically registered in 3D (Amira software).

Results

The scans lasted 40-60 seconds with 20y radiation dose. The phase contrast is developed from refractive index variations at the interface of bone tissue and pores, therefore the quality of image is significantly enhanced without an increase in radiation dose. The cortical porosities were successfully detected. Once registered, individual remodeling-related resorption spaces were identified and their progression measured as the distance between the matching cutting cone tips in scan 1 and 2 (Figure A).

Conclusion

Synchrotron-based phase contrast micro-CT improves the detection of cortical pores significantly at equivalent radiation dose to conventional micro-CT and holds the potential to provide novel spatial and temporal information about the role of cortical bone remodeling in diseases such as osteoporosis.
Prevalence of type 2 diabetes mellitus (T2DM) in juveniles is increasing; however, the effect on skeletal development is unknown. Diabetes-induced impeded mechanical optimisation during growth could lead to fragility and arthropathic complications. The objective of this study was to quantify skeletal shape abnormalities in the Zucker Diabetic Fatty (ZDF) rat, an early-onset T2DM model, using active shape models (ASMs) with the hypothesis that onset during growth induces mechanically inferior shapes.

The femora of ZDF diabetic and non-diabetic rats (23 weeks, N=5/group) were µCT scanned and ASMs created after aligning and scaling to a template. Principal component analysis (PCA) revealed the primary modes of shape variation and the degree to which each individual shape deviated from the mean along each mode (normalised shape parameter). Accordingly, user-defined landmarks determined the distance between femoral head and greater trochanter, femoral neck-shaft angle and transversepyndary width. The medial-lateral (ML) and anterior-posterior (AP) cross-sectional diameters at the mid-shaft and distal 1/3 length were also determined. T-tests assessed group differences and were considered significant at p<0.05. The femur shape was described by 7 modes of variation, with the shape parameters significantly different between groups for the first mode (Fig 1). This mode described variation in head-trochanter distance, as well as ML and AP diameters. Correspondingly, the diabetic animals showed relatively smaller head-trochanter distance (-14.1%), reduced ML diameter (mid-shaft: -2.1%, distal: -5.5%) and increased AP diameter (distal: +6.9%). The femoral shape was altered in early-onset T2DM diabetic rats, independent of size. Smaller head-trochanter distance and less elliptical cross-sections are indicative of immature shapes and impeded bone adaptation during development, supporting the hypothesis. Future intervention studies could determine the potential for restoring normal bone growth.

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Visualization and pathological characteristics of cartilage and subchondral bone change in lumbar facet joint OVX mouse model using PPCT imaging

There is little information regarding the morphology change of cartilage and subchondral bone in OVX-induced lumbar facet joint (LFJ) osteoarthritis. The purpose of this study was to 3D visualize and pathological characteristics of cartilage and subchondral bone change in OVX-induced LFJ osteoarthritis mouse model using propagation-based phase-contrast computed tomography (PPCT) combining with histopathological method. The mice were subdivided randomly into two groups of bilaterally OVX animals and control animals. All animals in OVX and control groups were killed 8 week postoperatively. For a detailed qualitative and quantitative 3D evaluation, structural alterations of facet joint cartilage surface and subchondral bone architecture were evaluated by PPCT. The image quality were evaluated and compared with histology. PPCT imaging provides 3D visualization of altered cartilage with simultaneous high detail of the subchondral bone abnormalities. Quantitative analysis demonstrated that the cartilage volume, surface area and thickness were decreased in OVX groups both in the inferior articular process (IAP) and superior articular process (SAP) compared to the control group at the same ages. Meanwhile, these morphological change were accompanied by obvious destruction of the subchondral bone surface and trabecular bone in the OVX group. The delineation of 3D pathological changes in PPCT imaging is similar to histopathological finding with Safranin O staining. In additional, increased CGRP ingrowth in subchondral bone were observed and confirmed by WB in OVX group compared with control group. These results indicated that PPCT may has great potential for in simultaneously analysis of the LFJ by providing 3D morphological change about cartilage and the subchondral bone, and their relationship in OA conditions. Degenerative FC possessed greatly increased nerve ingrowth in subchondral bone may play an important role in the progression of OVX-induced LFJ OA and caused LBP.
### Assessment of bone marrow metabolism by FG PET allows early detection of experimental osteolytic bone metastasis

**Stephan Ellmann**, Lisa Seyler, Jochen Evers, Henrik Heinem, Michael Uder, Tobias Bäuerle
tobias.baeuerle@uk-erlangen.de
University Medical Center Erlangen, Department of Radiology, Erlangen, Germany

**Introduction**

Early detection of skeletal metastases is crucial for staging and treatment of osteotropic primary tumors. While skeletal scintigraphy is the standard technique for early assessment of osteoblastic metastasis, small osteolytic lesions are rather diagnosed using MRI and CT. This study aimed to evaluate bone marrow metabolism by FDG PET in experimental osteolytic metastasis for early detection of these lesions as compared to MRI and CT.

**Materials and Methods**

For induction of osteolytic metastasis in the hind leg, a total of n=12 rats underwent injection of MDA-MB-231 breast cancer cells into the right superficial epigastric artery. MRI, CT and PET imaging was performed before (day 0) as well as on days 10, 20 and 30 after tumor cell inoculation. Multiparametric MRI including T1, T2, T2* and diffusion weighted imaging was performed at 7T (Clin Scan, Bruker), while 18F-FDG PET and CT were assessed on a hybrid scanner (Inveon, Siemens). The bone marrow metabolism of FDG was determined by the SUV ratio between the affected (tumor cell inoculation) and contralateral (control) bone marrow in the respective hind leg.

**Results**

Morphologic images from MRI and CT displayed bone marrow tumors and osteolytic lesions, respectively, at days 20 and 30 after surgery. Significant changes in the SUV ratio within the bone marrow of the hind legs, however, were detectable as early as at day 10 after tumor cell inoculation (Figure). MRI mapping techniques (T1, T2, T2*) and diffusion weighted imaging did not result in significant changes within the bone marrow of the hind leg before bone metastases were visible. As shown in the attached Figure, an increased bone marrow metabolism is detected in the proximal tibia of the hind leg at day 10, while osteolytic lesions occurred at day 20 and 30 after tumor cell inoculation.

**Conclusion**

Increased bone marrow metabolism as determined by FDG PET is an early indicator of osteolytic breast cancer bone metastases.

### Dual energy synchrotron X-ray imaging of bone-seeking tracer elements

**Arash Panahifar**, Nazanin Samadi, L Dean Chapman, David M L Cooper
d.a.panahifar@usask.ca
1 Department of Anatomy and Cell Biology, University of Saskatchewan, Saskatoon, Canada
2 Department of Physics & Engineering Physics, University of Saskatchewan, Saskatoon, Canada
3 Canadian Light Source, Saskatoon, Canada

**Introduction**

Proper formation and remodeling of bone are critical aspects of bone health which can be disrupted in pathologies including osteoporosis, osteoarthritis, and bone cancer. Functional imaging is an invaluable tool in understanding such disease, but is limited to use of radioisotopes and suffers from low resolution. We utilized synchrotron-based X-ray techniques to acquire combined high-resolution functional and structural images.

**Methods**

Healthy male rats of 1 or 8 month-old (i.e., developing skeleton vs. skeletally mature) were dosed orally for 4 weeks with 18F barium chloride (3mCi, or 4mCi). Tracer distribution in bone was evaluated in 2D and 3D by X-ray dual energy K-edge Subtraction (KES) (130μm) and Spectral KES (SKES) (52-100μm) techniques at the BioMedical Imaging and Therapy (BMIT) beamline at the Canadian Light Source. KES requires scanning the sample twice at few eV’ above and below the K-edge energy of the tracer, whereas the SKES provides an energy spectrum around the K-edge, thus eliminating the second scan. The synchrotron monochromatic source offers precise tunability of X-ray energy. The results were validated against Electron Probe Micro Analysis, X-ray fluorescence, and mass-spectrometry.
IL-20R1, IL-22R1 and bone quality: New therapeutic targets against bone fragility and osteoporosis

Julia Tiebus1, Gianluca Iori2, Johannes Schneider2, Kay Raum2, Robert Sabat1

1 Molecular Immunopathology, Department of Dermatology, Charing Cross Hospital, London, UK
2 Berlin Brandenburg Center for Regenerative Medicine

Bone remodelling is a permanent process driven by a complex network of local factors, hormones, cytokines and growth factors. Among these, a role in bone metabolism of the interleukin (IL)-10 cytokine family members, IL-20 and IL-22, has been proposed based on studies revealing their involvement in osteoporosis and rheumatoid arthritis (Hsu et al., 2011; Zhang et al., 2011; Hsu et al., 2006). In this study, 100-MHz scanning acoustic microscopy (SAM), microcomputed tomography (µCT) and three-point bending tests were used to assess acoustic impedance Z, morphological characteristics and biomechanical properties of mouse bone tissue in control (WT), IL-20 receptor 1 knocked-out (IL-20R1-/-) and IL-22R1-/- mice. In comparison to WT animals, IL-20R1-/- mice showed a moderate thinning of the cortical bone and a significant reduction in acoustic impedance values Z at tissue level. In contrast, the impedance values Z in IL-22R1-/- mice were greater than in IL-20R1-/-, but could not reach the WT levels. Interestingly, IL-22R1-/- animals demonstrated a clear thickening of the cortical bone compared to WT mice. At the whole-bone level, ultimate load and stiffness were reduced in transgenic animals compared to WT controls. Taken together, these data suggest a critical role of IL-20 and IL-22 in bone structure and elastic tissue properties.


Material science meets biology: Study of the 3D structural and mechanical environment of cells regulating modeling in bones without osteocytes

Lior Ofer1, Elazar Zelzer4, Paul Zaslansky3, Ron Shahar1

1 lior.ofei1@mail.huji.ac.il 2 Koret School of Veterinary Medicine, The Hebrew University of Jerusalem, Rehovot, Israel
3 Department of Molecular Genetics, Weizmann Institute of Science, Rehovot, Israel
4 Department for Restorative and Preventive Dentistry, Charité - Universitätsmedizin, Berlin, Germany

Bone is a stiff material that is subjected to cyclic loading for entire life spans, during which loading magnitude and direction can change dramatically. In order to avoid failure, bone material has the ability to remove accumulated damage (remodelling), and adapt its external geometry to better withstand changing loading patterns (modeling). Both processes are carried out by the coordinated activity of osteoblasts and osteoclasts, under the regulation of osteocytes, which are 90% of bone cells. Considering the pivotal role assigned to osteocytes and their ubiquitous distribution, it is surprising that bones of neoteleost (modern) fish completely lack them. Despite their absence, we have recently shown that anosteocytic bones are capable to remodel and model. This raises questions regarding the effectiveness of these processes and the necessity of bone-embedded cells in remodeling regulation. In order to gain insight into the regulation of the anosteocytic modeling process, as well as to evaluate its mechanical effectiveness, we compared the structural, mechanical and biological consequences of controlled loading of bones with and without osteocytes. Our integrated approach combines 3D data from interdisciplinary and varied methodologies. These include synchrotron nano-tomography, advanced microscopy (scanning electron microscopy, confocal microscopy), mechanical testing (nanoindentation), finite element modeling, histology and molecular methods (in-situ hybridization). This approach allows us to study the structural and mechanical environment of the cells regulating modeling, follow new material formation and resorption in response to loading and find its spatial relationship to molecular signals. Our findings so far suggest an intriguing and novel form of modeling-control in fish bones, which differs from that of other vertebrate groups and might explain the evolutionary shift toward anosteocytic skeleton in fish.
### Background

Human epidermal growth factor receptor (EGFR) expression level correlates with the ability of breast adenocarcinoma (BAC) to metastasize. Thus, EGFR-specific imaging in BAC is essential for visualizing overexpression as a signature of highly aggressive BAC and for identifying candidates for anti-EGFR therapy. Here, we present a signal amplification strategy to assess EGFR expression in BAC bone metastasis using MRI and PET.

### Methods

We used a well-characterized rat model of BAC targeted metastasis of MDA-MB-231-luc-D3H2LN to femur/tibia bones resulting from the injection of tumor cells via superficial epigastric artery. Tumor progression was monitored by using bioluminescence and T2w SE MRI. In 20-30d post tumor cell injection, we performed an IV injection of a mixture of humanized monoclonal antibody Fab(2) fragments (Cetuximab) linked to deglycosylated horseradish peroxidase (HRP) and glucose oxidase (GOx), i.e. enzymes with complementing activities. Second, we administered low-molecular weight molecules (SHT-DOTAGAd, 0.15 mmol Gd/kg or SHT-DOTAGlyMe68Gala, 20MBq (0.1 mmol)/kg). The latter small molecules act as reducing substrates of enzyme-complemented reaction yielding the products that are retained if both anti-EGFR Fab(2) conjugates co-accumulated in vivo.

### Results

We analyzed the differential MR signal decay in vivo using dynamic T1w signal acquisition. The patterns of signal decay following the administration of SHT-DOTAGAd substrate revealed differences in the time course of substrate elimination from the tissue which was dependent on the specificity of the initial mAb: we observed a bi-exponential signal decay in osteolytic and non-osteolytic tumor only if MDA-MB-231 tumor-bearing animals were preinjected with a pair EGFR-targeted mAb conjugates (Figure). PET imaging also demonstrated the increase of imaging signal in animals injected with EGFR-targeted conjugates. The endpoint MR in vivo imaging after an injection of enzyme-linked Fab(2) conjugates showed detailed images of tumors, which correlated with immunohistochemical detection of EGFR expression.

### Conclusions

Enzyme-mediated amplification of imaging signal using MR and PET is a promising strategy for performing receptor-specific imaging in BAC bone metastasis.

### Acknowledgement

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### Receptor-specific imaging in experimental breast cancer bone metastasis by MRI and PET using a signal amplification strategy

Alexei Bogdanov1, Gupta, Suresh2, Aurora Rodriguez-Rodriguez1, Peter Caravan3, Zheng Shaokuan4, Tobias Bauerle5,6
6 tobias.bauerle@uk-erlangen.de
1 University of Massachusetts Medical School, Radiology - Worcester, US
2 Martins Center for Biomedical Imaging, Massachusetts General Hospital, Radiology - Charlestown, US
3 Advanced MRI Center, University of Massachusetts Medical School, Radiology - Worcester, US
4 University Medical Center, Department of Radiology, Erlangen, Germany

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### BMD and structural analysis of CT-images of OA knees comparing subchondral bone under meniscus and not under meniscus

Frederike Sannmann1, Christine Chappard2, Jean-Denis Laredo3, Klaus Engelke4,5
4,5 Service de radiologie hôpital Lariboisière, 2 rue Ambroise Paré Paris, France
1 Institute of Medical Physics, University of Erlangen-Nürnberg, Erlangen, Germany
2 B2OA UMR 7052 CNRS Paris Diderot University, 10 avenue de Verdun Paris, France

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### Acknowledgement

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### Background

A recent micro-CT study in normal human cadaveric knees has shown that subchondral bone structure of the tibial plateau was thinner and BV/TV, Tb.N, Tb.Th were lower compared to locations not covered by the meniscus (LnCM).

### Objective

Here we investigated whether patients with OA also showed location dependent differences of bone mineral density (BMD) and trabecular structure.

### Methods

Clinical whole body CT scans using a high resolution protocol of 20 OA patients (Kellgren-Lawrence scores 2-3) were analyzed using MIAF-Knee. Subchondral bone was divided into three volumes of interests (VOIs) that differed in distance from the subchondral bone plate (Figure). In this study only the VOI closest to the joint in the tibia was used. It was further divided into medial and lateral parts, each of which was separated into sub VOIs located underneath and not underneath the meniscus (Figure). For each of the resulting four VOIs BMD, and anisotropy and inhomogeneity characterizing the subchondral bone structure were measured. Anisotropy measures the degree of directionality of voxels with similar gray values in a VOI; global inhomogeneity is a measure of the standard deviation of gray values.

### Results

In the table average results for the total medial and lateral VOIs are listed. Δ(LnCM-LCM) is the difference between locations covered and not covered by the meniscus.

### Conclusion

Results in the OA patients confirmed the micro-CT results in the normal knee cadaver. BMD underneath the meniscus is significantly lower (P<0.05) compared to locations not covered by the meniscus. At the same time the subchondral bone structure below the meniscus is characterized higher anisotropy and lower inhomogeneity.

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### Notes

The table average results for the total medial and lateral VOIs are listed. Δ(LnCM-LCM) is the difference between locations covered and not covered by the meniscus.

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### Notes

MIAF-Knee shawing VOIs in Femur and Tibia. LCM is shown with yellow contours, LCM with red contours in the Tibia.
**Abstract**

**BMD-calibrated measurements of local porosity in human femoral cortical bone**

Gianluca Iori1, Vantte Kilappa2, Frans Heer1, Caroline Wyers1, Peter Varga1, Johannes Schneider1, Joop van den Bergh3, Kay Raum1

1 Berlin-Brandenburg Center for Regenerative Therapies, Charité - Universitätsmedizin Berlin, Germany
2 Mango Solutions, Chippenham, UK
3 Department of Internal Medicine, Subdivision of Rheumatology, Maastricht University Medical Center and NUTRIM, Maastricht, The Netherlands

**Methods**

Both knees of N=35 participants with unilateral ACL reconstructions 6-years earlier were imaged with high resolution peripheral quantitative computed tomography (XtremeCT2). Per knee, 6cm (1008 slices) were collected at 61μm isotropic voxel size. Bone mineral density (BMD) and microarchitecture was assessed in the subchondral region of both the medial and lateral weight-bearing surfaces (Figure 1) at three depths (shallow: 0-2.5mm, mid: 2.5-5mm, and deep: 5-7.5mm).

**Results**

BMD decreased with depth for both femur and tibia and for both medial and lateral weight-bearing regions (Table 1). The local BMD-Ct.Po correlation was evaluated at length scales from 60 μm to 1.2 mm; a calibration rule was obtained for the local BMD-based Ct.Po estimation. On a validation sample set (n=17) we compared BMD-based Ct.Po predictions with ground-truth values measured by SAM. BMD explained up to the 74% of the local Ct.Po variability over 756 x 756 μm² regions. At this length scale, R² and RMSE of the local Ct.Po prediction were 0.79 and 4.47%, respectively. Ct.Po predictions obtained for entire femoral cross sections gave R²=0.62 and RMSE=2.91. Compared to other HR-pQCT-based approaches (1,3), these were affected by a smaller bias (Mean Difference = 1.40). If confirmed for different QCT scanners, this approach may lead to reliable estimates of Ct.Po at skeletal sites where HR-pQCT is not available.

**Conclusions**

The differences within and between knees identified in this cross-sectional analysis highlight the importance of investigating the etiology of PTOA. We have recently started a longitudinal study to investigate the etiology of PTOA.

**References**

Optimising the quantification of bone microstructure in the human calcaneus using HR-pQCT

Louis M. Metcalf, Anna A. Fogden, Rhea H. Patel, Margaret A. Paggiosi, Graham J. Kemp, Eugene V. McCloskey

1 MRC-Arthritis UK Centre for Integrated research into Musculoskeletal Ageing (CIMA), Department of Oncology and Metabolism, University of Sheffield, UK
2 The Mellanby Centre for Bone Research, Academic Unit of Bone Metabolism, Department of Oncology and Metabolism, University of Sheffield, UK
3 MRC-Arthritis UK Centre for Integrated research into Musculoskeletal Ageing (CIMA), Magnetic Resonance and Image Analysis Research Centre (MARFARC), University of Liverpool, Liverpool, UK

High-resolution peripheral quantitative computed tomography (HR-pQCT) quantifies volumetric bone mineral density (vBMD) and bone microstructure at peripheral sites in vivo. We previously piloted a procedure to scan the human calcaneus using HR-pQCT ex vivo. In the present study, we aimed to optimise scan settings and perform a regional quantitative assessment of calcaneal HR-pQCT scans in vivo.

Ten participants (mean age 61±5 years) had unilateral calcaneal scans using HR-pQCT at a voxel size 82 μm. The foot was positioned in the lower leg cast and 110-slice scans were collected through the superior and inferior regions of the calcaneus at 100ms and 200ms integration times (100t and 200t); the 100t and 200t scans were rigidly registered and the common volumes of the scans were evaluated. vBMD and trabecular microstructure were quantified and presented as mean percentage (95% CI) differences between the two integration times and the two regions. Between 100t and 200t scans there were no differences in vBMD (all <1%). The 200t scans yielded lower trabecular number (superior: -17% [-20, -14%], p<0.001; inferior: -26% [-34, 21%], p<0.001) and greater apparent trabecular thickness (superior: +22% [17, 27%], p<0.001; inferior: +39% [27, 53%], p<0.001) compared to the 100t scans of the identical bone volumes. At either integration time, the superior region showed greater trabecular vBMD than the inferior region (e.g. 200t scan, +40% [34, 48%], p<0.001), reflecting in part a higher number (+14% [4, 24%], p=0.034) of thicker (+31% [26, 36%], p<0.001) trabeculae.

We have developed a procedure for in vivo quantitative assessment of calcaneal vBMD and trabecular microstructure using HR-pQCT. Future work will determine measurement precision and compare the measurements with BMD at other skeletal sites in patients with and without fracture.

Three-dimensional mapping of the joint space for knee osteoarthritis based on high-resolution computed tomography: A multiscale analysis

Houda Mezlini-Gharsallah, Rabaa Youssef, Jean denis Laredo, Christine Chappard

1 B2OA UMR 7052 CNRS Paris Diderot University, Paris, France
2 ECA Linklab La Mansa Tunis, Tunisia
3 Radiology department Hospital Lariboisière, Paris, France

We propose a new method to assess the three-dimensional (3D) local variation of the joint space (JS) at the medial knee compartment using high-resolution peripheral computed tomography images performed on specimens. The results were compared with local cartilage thickness measurements.

We imaged left knee specimens from 16 males and 25 females (mean age of 81.9 years ±10.1) with HR-pQCT; voxel size =82 μm (XtremeCT Scanco®). A semi-automated method was developed to segment the 3D JS between femur and tibia to obtain a distance map based on a combination of thresholding and active contour methods. From this map, the following JS parameters were measured: volume (JS_vol), minimum (JS_min), maximum (JS_max), mean (JS_mean), Standard Deviation (JS_SD), median (JS_median), asymmetry (JS_asym) and entropy (JS_ent).

After opening the knees, the histopathological Outerbridge (Gr 1 to Gr 4) was performed. Then cartilage and bone cores were extracted from the tibial plateau in three positions: center (uncovered by meniscus), peripheral covered by meniscus, and posterior (partially covered by meniscus). The cores were imaged with a Skyscan 1172® (voxel size of 10 μm) and cartilage thickness was measured based on the sphere method.

Values for JS_min, JS_asym, JS_ent, Gr1, and Gr2 were statistically different from Gr3-4 (P<0.002). The JS_asym was correlated with cartilage thickness measured in the three different positions (-0.49P<0.01). At the posterior site, JS_min, JS-mean, JS_median and JS_ent were correlated with cartilage thickness (-0.34P=0.03) and JS_ent at the peripheral site (r=0.35, P=0.03).

Parameters extracted from a 3D map of the medial JS obtained from HR-pQCT images indicate local variations of the JS. These parameters are related to local measurements of cartilage thickness especially in the posterior part of the tibial plateau and could be useful to identify early OA.
A real-size FDTD simulation of ultrasound propagation inside human radius
Yoshiki Nagatani1, Jiao Mana2, Mami Matsukawa3, Koki Takano1, Ko Chiba1
nagatani@ultrasonics.jp
1 Department of Electronics, Kobe City College of Technology, Japan
2 Oyo Electric Co., Ltd., Japan
3 Faculty of Science and Engineering, Doshisha University, Japan
Simulation studies of the ultrasonic wave propagation inside human bones have been investigated by many researchers in order to improve the accuracy of osteoporosis diagnosis. However, due to the limitation of the image resolution and the computational resource, real-size simulations of the ultrasonic diagnosis system have not been performed.
In this paper, three-dimensional elastic FDTD (finite-difference time-domain) simulations of the high resolution human radius with a real-size diagnosis equipment used in practical use (LID-100, Oyo Electric) is performed. The geometry data was derived by the HR-pQCT (high resolution peripheral quantitative CT) system (XtremeCT II, SCANCO medical). The spatial resolution was 60 μm, where the cancellous structure was clearly represented. For the accurate simulation of the pulse ultrasound at 1 MHz, the resolution was raised to 40 μm. The bone density of the model was varied by changing the binarizing threshold of the images. Two concave transducers were immersed in water facing each other at interval of 100 mm. The size of the simulation field was 770x2540x500 pixels (30.8x101.6x20.0 mm³).
Using the setup, the effects of bone density, the elasticity (wave speed) of the bone, and the angle of the incident wave were investigated. As a result, the amplitude of the primarily arriving wave, which propagates inside cortical part rather than cancellous bone, was so small that the wave moderately affects the secondary wave. The speed of the primary wave depended on the elasticity, whereas the secondary wave, which propagates inside cancellous bone, was strongly affected by the bone density. The result tells us that the pulse ultrasound can reflect the condition of the cancellous bone of the human radius in addition to the cortical part in vivo measurement. These interesting behavior should be carefully checked in the future work.

Bone repair and ultrasound stimulation: A multiscale computational study
Cécile Baron1, Carine Guivier-Curien2, Vu-Hieu Nguyen3, Salah Naili3
cecile.baron@univ-amu.fr
1 Aix-Marseille University, CNRS, ISM UMR 7287, 13009 Marseille, France;
2 APHM, Hôpital Sainte-Marguerite, Institute for Locomotion, 13009, Marseille;
3 Université Paris Est, MSME UMR 8208 CNRS, Créteil, France
Bone is a complex biological tissue which remodels all along healing. Bone remodeling is the result of bone cells activation due to mechanical stresses. The osteocytes are thought to be the principal mechanosensory cells of bone. They are immersed in the lacuno-canalicular network (LCN) filled with interstitial fluid (IF). There is theoretical and experimental evidence that osteocytes are stimulated via fluid shear stress induced drag forces acting on osteocyte cell processes within canaliculi. Low Intensity Pulsed Ultrasound (LIPUS) is a current clinical treatment to speed up or consolidate bone healing. But debate is still open to know how LIPUS mechanically stimulates bone regeneration. The aim of this preliminary study is to numerically investigate LIPUS stimulation from a tissue-scale model to a cellular-scale model. Two numerical models were developed with the commercial software Comsol Multiphysics. The first tissue-scale model (ModBone) simulates the interaction of the ultrasound (US) stimulation with healing cortical bone. It considers an anisotropic poroelastic media to evaluate the mechanical effects induced into the IF of the LCN. The second model is the cellular-scale model (ModOst) including a fluid model of one osteocyte process surrounded by the IF inside a canaliculus embedded in the extracellular matrix. The IF pressure gradient induced by US stimulation in ModBone is applied as a boundary condition for the fluid in ModOst. The IF shear stress magnitude applied on osteocyte process is calculated and compared with shear stress levels cell activation recorded in literature. The shear stress induced drag forces applied on the osteocyte process are evaluated. This preliminary study gains an insight into the mechanotransduction process induced by the interaction of low intensity pulsed ultrasound with the lacuno-canalicular network of cortical bone.
Simulations of ultrasound propagation through the skull are used for transcranial focusing and predicting intracranial fields for therapeutic applications. Numerical models require maps of acoustic properties, usually drawn from medical images with limited resolution and corresponding loss of microstructure detail. Here, clinical CT images of two post-mortem human skulls were obtained, alongside co-registered micro-CT images of bone samples from the skulls. These were used as inputs to a k-space pseudospectral time domain (PSTD) model to determine the influence of bone microstructure on transcranial transmission of 1 MHz ultrasound. Acoustic properties were assigned to the micro-CT data based on a bone tissue segmentation, and progressively homogenised to mimic the effect of imaging resolution. Maps were derived from clinical CT data by interpolating between the segmentation values. Results demonstrated that loss of microstructure can lead to an increase in simulated pressure transmission of up to 79% and in time of flight up to 1 μs (one acoustic period), as well as changes in the shape of the transcranial field. Use of a nearest neighbour algorithm for downsampling at clinical CT resolutions gave up to 32% lower error in transmission when compared to linear interpolation. Simulations using clinical CT data showed good agreement with micro-CT data homogenised at the same resolution. Transmission loss could be corrected for by increasing the simulated absorption value to account for scattering losses, and is sensitive to how the boundaries of the bone are defined.

The differentiation between conditions of healthy thin and porous bone is a challenging task for densitometry and fracture risk assessment. Ultrasonic testing based on guided waves can help, however, the variation of soft tissues confounds results. The aim was to demonstrate discrimination between thin and porous bone conditions in the presence of varied soft layer by testing of phantoms and comparative mathematical modelling of ultrasound propagation. Phantoms were wedge-type plates made of acrylic glass covered by natural animal meat tissues. Thickness gradients in the phantoms were similar to those in the human proximal tibia. Concentration of pores penetrating the cortex from the inner to outer surface gradually varied. Ultrasonic testing was stepwise axial profiling at 100 and 500 kHz. Mathematical modeling of acoustic waves’ propagation was held using ACELAN finite element package. Bone fragments were simulated by axisymmetric composite structures, where healthy and osteoporosis conditions differed by the thickness and material properties. The soft tissues were modeled by an elastic medium with a low Young modulus. The ultrasonic action was simulated by application of oscillating mechanical stress, and the measured response was the radial displacement of the surface. Cases of three thicknesses of the external soft tissues were considered.

Examples of ultrasonic profiles in phantoms mimicking norm and osteoporosis (OP) [left] and examples of mathematically simulated ultrasonic signals at 100 kHz related to the same conditions (right) in the presence of 5 mm thick soft layer. (Dx - arrival of fast symmetric and Ao - peak of slow antisymmetric Lamb waves).
Abstracts IBDW/ESUCB 2017

Simulation study on axial ultrasound propagation in cortical bone model – effects of shape and heterogeneity
Koki Takano¹, Yoshiki Nagatani¹, Mami Matsukawa²
¹ Doshisha University
² Kobe City College of Technology

Axial ultrasound propagation in the heterogeneous cortical bone was studied. First, longitudinal wave velocity distribution in the long bone cortical bone was experimentally measured with spatial resolution of 1 mm. By the bilinear interpolation and the piecewise cubic Hermite interpolation, a 3D longitudinal wave velocity model was created with resolution of 40 mm. Assuming the uniaxial anisotropy, distributions of all elastic moduli of the model (model A) were estimated. For reference, a 3D anisotropic homogeneous model (model B) was also obtained. The complicated shape of the models follows the initial cortical bone. Average thickness of these models was 2.7 mm. The elastic finite-difference time-domain method was used to simulate ultrasound propagation in the model. A single sinusoidal wave at 1 MHz has propagated in the models immersed in water. An emitter and a receiver array (11 elements) were configured with distances ranging from 2.2 to 42.2 mm. From the arrival time difference of first arriving signals (FAS) at the receivers, FAS wave velocities were estimated. As the wave propagates, the FAS velocities in models A and B decreased similarly (Fig. 1). In an anisotropic rectangular model (model C) with no changes of thickness and shape, the velocities were constant. This decrease seems to come from the surface shape of the models. In the models A and B, the distance between the surface and the receiver changed: 5.2 mm near the receiver 1 and 6.0 mm near the receiver 11. The changes of distance (less than 10%) possibly affect the velocity decreases because the velocities were estimated assuming constant distance. Of course, in addition to the effect of distance, other factors such as heterogeneity and wavefront changes need to be considered.

Introduction
Dual-energy X-ray absorptiometry’s (DXA) ability to resolve only two superimposed materials results in exact solutions for soft tissue mass over bone but necessitates significant spatial approximation to estimate soft tissue composition over bone. To improve the accuracy of soft tissue composition measurement, we propose a novel combination of 3D optical whole body imaging with DXA for true pixel-by-pixel 3-compartment densitometry.

Methods
A prototype device has been developed by integrating three 3D optical cameras (Kinect, Microsoft, Redmond, WA) above and below a custom optically-transparent tabletop installed on a Hologic Discovery/W (Hologic, Marlborough, MA). Depth images from the cameras are assembled to estimate X-ray path lengths corresponding to each DXA pixel. Material separation was demonstrated using multiple scans on a 6-cm step phantom of materials biologically equivalent to fat (blue wax), water (plastic water), and protein (Delrin). For calibration, 45 thickness combinations were used. A recruitment of 30 participants is underway.

Results
The device is shown in Figure 1, top. Using the calibration, we created deconvolved material images of the phantom fat, water, and protein compartments. (Figure 1, bottom). Individual optical images of the step phantom had thickness errors (SD) of approximately 2.3 mm at each step. Evaluation of multiple optical images showed that collection of 20 images reduces error below 0.5 mm. In vivo measurement agreement between Ultra DXA and standard DXA will be demonstrated using collected patient data. Additionally, full 4-compartment imaging will be presented.

Discussion
We have demonstrated the capability of Ultra DXA to solve for 3 materials simultaneously with high precision and accuracy. If successful, this device could offer a new tool for rapid, accessible, high fidelity body composition assessment including protein and water separation, which may be valuable for monitoring of conditions such as sarcopenia.

WW, CH, HW, TK, and KW are employees and/or stockholders of Hologic, Inc. JS has received research grant funding from Hologic, Inc. and GE Healthcare and serves as an advisor for BodySpec (Absolute Health & Performance LLC)

Integrating dual energy X-Ray and 3D surface imaging for enhanced multicompartment tissue composition assessment: The Ultra DXA project
Bennett K. Ng¹, Wei Wang², Chao Huang², Howard Weiss³, Thomas L. Kelly³, Kevin E. Wilson², John A. Shepherd⁴
¹ University of California, Berkeley and University of California, San Francisco
² Graduate Program in Bioengineering
³ Hologic, Inc.
⁴ Department of Radiology and Biomedical Imaging, University of California, San Francisco

Detection of Age-Related Changes in the Complex Nature of Bone Microarchitecture
Winston W. Womening, Wei Wang, Chao Huang, Howard Weiss, Thomas L. Kelly, Kevin E. Wilson, John A. Shepherd
Hologic, Inc.

Abstracts IBDW/ESUCB 2017

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Koki Takano¹, Yoshiki Nagatani¹, Mami Matsukawa²
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Bennett K. Ng¹, Wei Wang², Chao Huang², Howard Weiss³, Thomas L. Kelly³, Kevin E. Wilson², John A. Shepherd⁴
¹ University of California, Berkeley and University of California, San Francisco
² Graduate Program in Bioengineering
³ Hologic, Inc.
⁴ Department of Radiology and Biomedical Imaging, University of California, San Francisco

Detection of Age-Related Changes in the Complex Nature of Bone Microarchitecture
Winston W. Womening, Wei Wang, Chao Huang, Howard Weiss, Thomas L. Kelly, Kevin E. Wilson, John A. Shepherd
Hologic, Inc.
Predicting body composition from forearm and lateral distal femur hologic bone densitometry scans
Bo Fan,1 Bennett Ng,1,2 Natasha Din,1 Leila Kazemi1, Babette Zemel3, Amir Fasha Mahmoudzadeh1, John Shepherd7
7 Department of Radiology & Biomedical Imaging, University of California San Francisco
2 Bioengineering program University of California Berkeley
3 Children’s Hospital of Philadelphia
4 Cincinnati Children’s Hospital Medical Center

Background
Quantitation of body composition with regional DXA scans is desirable for infants and small children for whom whole body (WB) DXA scans are impractical due to motion and poor prediction from age and BMI.

Objective
To develop an accurate method to predict total body %FAT using regional DXA scans

Methods
Forearm (FA), lateral distal femur (LDF) and WB DXA scans (Hologic systems) of healthy young children enrolled in Bone Mineral Accretion in Young Children Study were evaluated. FA and LDF scans were acquired with a 3T MR system (MAGNETOM Skyra, Siemens Healthcare). The protocol included: T1w TSE, high-speed T2-corrected multi-echo MRS, and three versions of a GRE VIBE Dixon sequence (2pt Dixon prototype, standard 6pt and 6pt Dixon prototype). To compare the results among FA and LDF scans, the Dixon maps were positioned on the FA and LDF maps and a correlation analysis was performed.

Results & Discussion
T1w TSE results in high-resolution, high-contrast images, which can be used for fascia segmentation and IMAT separation. Parametric proton density fat (PDFF) and water fraction (PDWF) maps obtained from Dixon sequences can be used for IMAT quantification. The low PDFF correlation of 0.99 and 0.42 (old and young) between the 2pt and 6pt Dixon sequences can be explained by non-opposed and non-in-plane TEs. Correlations between 6pt Dixon sequences and MRS were 0.96 and 0.93, however PDFF was on average 1.4 and 1.9 times higher in MRS. This is probably due to the fact that MRS was validated in liver tissue, while an overestimation of PDFF in low-fat tissue like muscle is known. Standard and advanced 6pt Dixon prototype sequences gave identical PDFF results but in the standard sequence a fat-water swap occurred in 25% of all subjects.

Conclusion
T1w TSE sequences provide excellent contrast and are sequences of choice to measure muscle and IMAT volume. Unlike MRS, MRI provides a representative analysis of muscle composition, but quantitative imaging of PDFF remains challenging and appropriate sequences have to be chosen carefully.

Table 1: Regression analysis of comparing regional, WB sub-regional and WB total %FAT associations.

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Random forest based segmentation of hand muscle in MRI
Andreas Friedberger, Camille Figueiredo, Oleg Museyko, Alexandra Gimmi, Isabelle d’Oliveira, Tobias Bäuerle, Jürgen Rech, Oliver Chaudry, Michael Uder, Georg Schett, Klaus Engelke
1 Institute of Medical Physics, University of Erlangen-Nuremberg, Erlangen, Germany
2 Department of Medicine III, University Erlangen-Nuremberg, Erlangen, Germany
3 Institute of Medical Physics, University of Erlangen-Nuremberg, Erlangen, Germany
4 Pathological Institute, University Hospital of Erlangen-Nuremberg, Erlangen, Germany

Abstract
A new random forest based segmentation with excellent reanalysis precision for hand muscle in MR images has been developed. Visual registration quality between T1 and Dixon fat fraction images was excellent but accuracy still has to be quantified.

Methods
56 sarcopenic (80±5 yrs) and 23 healthy (28±4 yrs) males were examined. MRI acquisition was performed using a 3T scanner (MAGNETOM Skyra; Siemens; 18-channel body surface coil). T1wTSE and 6pt TSE Dixon sequences were measured at the mid-thigh (length 10 cm, voxel size 0.5x0.5x3.0 mm³, 34 slices). Dixon imaging provides separate fat and water images.

T1wTSE images were segmented slice by slice starting with a fuzzy c-mean clustering, differentiating muscle, adipose tissue, bone, and background. The outer contour was refined by thresholding low intensity voxels. Then a level set algorithm was applied to obtain a closed, tightly fitting 3D surface around the muscle tissue. Results were manually improved if necessary. Segmented masks were affine registered to the Dixon fat fraction (FF) images (quotient of the fat signal to the sum of the fat and water signals).

Results
The figure shows T1wTSE and FF images of a young, healthy and an older sarcopenic male demonstrating fat infiltration at higher age. Segmentation results were obtained in the T1wTSE images but are displayed on FF images. Volumes of subcutaneous adipose tissue and within the muscle segmentation were quantified. So far 6 patients were successfully segmented, the average processing time was 483 s.

Conclusion
A muscle segmentation, which in combination with Dixon imaging directly provides FF has been successfully developed, analysis of larger datasets is currently ongoing.

Results
Analysis of 76 hand MRI scans took 2 min per scan. In majority slight user interactions were necessary, especially for deleting segmented forearm muscles. Inter- (intraoperator) precision errors were 5.0cm³ or 0.19% (3.4cm³ or 0.13%) for hand and 1.5cm³ or 0.23% (0.35cm³ or 0.05%) for muscle volume.

Conclusions
A new random forest based segmentation with excellent reanalysis precision for hand muscle in MRI scans has been developed. Visual registration quality between T1 and Dixon fat fraction images was excellent but accuracy still has to be quantified.

Background
Sarcopenia is characterized by a progressive loss of skeletal muscle mass, substituted by adipose tissue. Dual energy x-ray absorptiometry can differentiate overall lean and fat mass. However, a local muscle analysis requires 3D imaging, like magnetic resonance imaging (MRI). The aim was to develop a 3D method to segment the thigh muscle in T1 weighted turbo spin echo (T1wTSE) images and measure the fat content in corresponding 6pt Dixon fat images.

Methods
56 sarcopenic (180±5 yrs) and 23 healthy (28±4 yrs) males were examined. MRI acquisition was performed using a 3T scanner (MAGNETOM Skyra; Siemens; 18-channel body surface coil). T1wTSE and 6pt TSE Dixon sequences were measured at the mid-thigh (length 10 cm, voxel size 0.5x0.5x3.0 mm³, 34 slices). Dixon imaging provides separate fat and water images.

T1wTSE images were segmented slice by slice starting with a fuzzy c-mean clustering, differentiating muscle, adipose tissue, bone, and background. The outer contour was refined by thresholding low intensity voxels. Then a level set algorithm was applied to obtain a closed, tightly fitting 3D surface around the muscle tissue. Results were manually improved if necessary. Segmented masks were affine registered to the Dixon fat fraction (FF) images (quotient of the fat signal to the sum of the fat and water signals).

Results
The figure shows T1wTSE and FF images of a young, healthy and an older sarcopenic male demonstrating fat infiltration at higher age. Segmentation results were obtained in the T1wTSE images but are displayed on FF images. Volumes of subcutaneous adipose tissue and within the muscle segmentation were quantified. So far 6 patients were successfully segmented, the average processing time was 483 s.

Conclusion
A muscle segmentation, which in combination with Dixon imaging directly provides FF has been successfully developed, analysis of larger datasets is currently ongoing.

Objective
Development of an accurate method for hand muscle segmentation in MR images to quantify volume and fat.

Methods
T1 weighted MR scans of 30 RA patients were used to develop a random forest (RF) based method for hand muscle segmentation. Pixel classification features were mean grey values and standard deviations of the pixel vicinity with radii 1 to 3. Additionally, gradient magnitude and 4 Gabor filters (GF) with angles 0°, 45°, 90° and 135° were used. Feature extraction was applied to normalized grey value images. Best RF and GF parameters were found by 4-fold cross validation. Island extraction and simple morphological operations refined the RF segmentation. The procedure is fully automated but allows for manual corrections. Multimodal rigid registration of muscle segmentation masks to MR Dixon fat fraction images was used for fat quantification. Reanalysis precision was determined in 14 scans. Three operators analyzed each image once and one operator each image three times.
The relationship between ultrasonic backscatter propagation properties and cancellous bone microstructural variations
Xingxing Chou,1 Feng Xu,1 Ying Li,1 Chengcheng Liu,1 Dean Ta2
1 Department of Electronic Engineering, Fudan University, Shanghai, China
2 Department of Acoustics, Tongji University, No. 1239 Siping Road, Shanghai 200092, China

The microstructure of cancellous bone changes variedly according to its position within a bone and bearing direction. To investigate the relationship between the ultrasonic backscatter propagation properties and cancellous bone microstructural variations, three erosion procedures were performed to simulate various changes in the cancellous bone microstructure with increasing porosity. The finite difference time domain (FDTD) method was used to simulate the backscatter signal in cancellous bone when the ultrasound incident direction perpendicular and parallel to the major trabecular orientation. Numerical models were reconstructed using 3-D X-ray microcomputed tomographic (μ-CT) images taken from a bovine cancellous bone, and their microstructures were changed with three erosion procedures. In one procedure, the erosion was randomly distributed in every direction of the trabecula surface, but in the other two procedures, the erosion was distributed parallel and perpendicular to the major trabecular orientation. The propagation properties of the apparent backscatter coefficient (ABC) variability due to the trabecular microstructure were derived as functions of the porosity. The regressions between the ABC and the porosity showed significant negative correlations for the three erosion procedures when perpendicular and parallel to the major trabecular orientation (R=0.90–0.99, p<0.01). The simulations showed the ABC for the same porosity was varied by three erosion procedures. The results verified the ABC was sensitive to the weight of the trabecular microstructural variations parallel and perpendicular to the major trabecular orientation. This paper investigated the variability in the ABC induced by the cancellous bone microstructure, and the results suggested that the effect of the trabecular microstructure varied variations should be sufficiently considered when using ABC in cancellous bone assessment.

Keywords
ultrasound backscatter, cancellous bone, trabecular microstructure; backscatter coefficient

This work was supported by the NSFC (11525416, 11504057 and 11604054).

Contrast resolution enhancement in ultrasonic computed tomography of bones by way of a wavelet-based coded excitation method
Philippe Lasaygues1, Khaled Metwally1, Cecile Baron1, Samantha Fernandez2, Laure Boissier1
1 Aix-Marseille Univ, CNRS, Centrale Marseille, LMA, Marseille, France
2 Aix-Marseille Univ, CNRS, ISM, Marseille, France

Ultrasonic Computed Tomography (USCT) is an imaging modality of biological soft tissues. The difficulties, that occur with bones, are bound with the higher acoustical impedance difference, which strongly alters the propagation of the ultrasonic waves, and generally induces low Contrast-to-Noise Ratio (CNR). A solution can be find in optimal smoothing of physical effects using low frequency schemes (<3MHz). However, the resolution of the signal and of the reconstructed image is bound to decrease, and it is necessary to find new methods of recording and processing these signals, and to develop more efficient algorithms. Loosveldt and Lasaygues (Ultrasonics, 2011) developed a method, called the ‘Wavelet-Coded Excitation’ (WCE) method, based on a multi-scale decomposition procedure of the signals enabling to process all the information available in terms of frequency and time. The aim of this work is to investigate the feasibility of the WCE method as a means of CNR enhancement of the cross-sectional USCT imaging of long bones. Experiments were conducted on a Sawbones™ composite paired-bone phantom (tibia-fibula), and on an ex-vivo chicken drumstick. The ultrasonic sinograms were obtained using a multiplexed 2D-ring antenna and 8 MHz-transducers. The appropriate transmitted incident wave between both transducers of the antenna has to match the wavelets’ mathematical properties, and a solution is proposed based on a “zone-by-zone” simulated annealing algorithms. USCT images were compared with X-ray CT scan, and the quality of reconstructions was analyzed using the CNR criterion. For the phantom, the CNR is increasing by 42.5% using WCE method. For the chicken drumstick, after performing WCE method, the CNR is increasing by 11%. Even though the discrepancies were shown, this feasibility study for wavelet-coded excitation method combined with Ultrasonic Computed Tomography present interesting performances for bone imaging.
Studying the effect of porosity and pore size in cortical bone on ultrasonic parameters

Omid Yousefian1, Yasamin Karbalaeisadegh1, Gianluca Iori1, Kay Raum2, Marie Muller3
1 Mechanical and Aerospace Engineering, North Carolina State University, Raleigh, NC, USA
2 Acoustic Microscopy and Ultrasound Spectroscopy, Berlin-Brandenburg Center for Regenerative Therapies, Berlin, Germany
3 Mechanical and Aerospace Engineering, North Carolina State University, Raleigh, NC, USA

In cortical bone, osteoporosis impacts both pore size and porosity. Significant research has been conducted towards the development of ultrasonic techniques for the assessment of osteoporosis. However, the independent effect of pore size and porosity on ultrasonic parameters remains unclear. Here, we address the effect of pore size and porosity on ultrasound attenuation, phase velocity and scattering using the Nakagami model. The Nakagami-model parameter \( m \) and \( \Omega \) were calculated with the backscatter signal of interest (SOI). The scattering mean free path was measured using the Nakagami model. The Nakagami-model parameter \( m \) and \( \Omega \) was significantly correlated with BMD (R=0.58, p<0.01) and trabecular structure (R=0.70, p<0.01). The results revealed that as the bone density increased, the envelope of the backscatter signal changed from pre-Rayleigh to Rayleigh and even Rician distributions. This study suggested that the statistical analysis have great potential for the ultrasonic backscatter measurement of cancellous bone.

Keywords: ultrasonic backscatter, cancellous bone evaluation, statistical analysis, Nakagami distribution.

Omid Yousefian1, Yasamin Karbalaeisadegh1, Gianluca Iori2, Kay Raum2, Marie Muller3
1 Mechanical and Aerospace Engineering, North Carolina State University, Raleigh, NC, USA
2 Mechanical and Aerospace Engineering, North Carolina State University, Raleigh, NC, USA
3 Mechanical and Aerospace Engineering, North Carolina State University, Raleigh, NC, USA

Ultrasonic backscatter characterization of cancellous bone using Nakagami model

Chengcheng Liu1, Boyi Li2, Ying Li1, Feng Xu1, Dean Te2, Weiqi Wang1
1 Institute of Acoustics, Tongji University, No. 1239 Siping Road, Shanghai, China
2 Department of Electronic Engineering, Fudan University, Shanghai, China

Ultrasonic backscatter is a non-invasive tool for cancellous bone evaluation. The backscatter signal directly reflects the microstructure of trabecular bone. The goal of this study is to investigate the feasibility of using the Nakagami model parameter \( m \) and \( \Omega \) for cancellous bone characterization in human cadaveric cancellous bone. A 2-D finite difference time domain approach was used to simulate the propagation of elastic waves in numerical models of axial cross-section of cancellous bone. The Nakagami-model parameter \( m \) and \( \Omega \) was significantly correlated with BMD (R=0.58, p<0.01) and trabecular structure (R=0.70, p<0.01). The results revealed that as the bone density increased, the envelope of the backscatter signal changed from pre-Rayleigh to Rayleigh and even Rician distributions. This study suggested that the statistical analysis have great potential for the ultrasonic backscatter measurement of cancellous bone.

Keywords: ultrasonic backscatter, cancellous bone evaluation, statistical analysis, Nakagami distribution.

This work was supported by the NSFC (11504057, 11525416 and 11327405), Science and technology support program of Shanghai (13441901900)
A Multiscale analysis of tibial subchondral bone micro-architecture based on cone beam computed tomography
Gaëlle Mitton1, Hamid Bouchadour2, Eliza Budyn3, Klaus Engelke1, Jean Denis Lavede4, Christine Chappard4
1 B2OA UMR 7052 CNRS-Paris Diderot University, Paris, France
2 LMT UMR 8535 CNRS- ENS Cachan, Cachan, France
3 Institute of Medical Physics, University of Erlangen-Nürnberg, Germany
4 Radiology Department Hospital Lantosvielle, Paris, France

The best resolution to assess three dimensional (3D) micro-architecture changes of the subchondral bone induced by osteoarthritis is not known. We imaged 13 left knee specimens from 6 males and 7 females (mean age of 82.2 years ±8.4) with a Xview computed tomograph NSI* at 75 and 300 μm (bin 4*4 of projections) as voxel size. The medial compartments were also imaged at 30μm with the same device. A visual site matching was performed between 30, 75, and 300 μm scans. All images were binarized based on the Otsu method and the following direct 3D parameters were measured: bone proportion (BV/TV,%), specific surface (BS/BV,1/mm), trabecular thickness (Tb.Th,mm), trabecular spacing (Tb.Sp,mm), trabecular number (Tb.N,1/mm), structure model index (SMI), connectivity density (Conn.Den) and degree of anisotropy (DA).

For all parameters, the differences were significant (p<0.001) between 30-75μm versus 300μm, but also between 75μm versus 300μm for BV/TV, Tb.N and Tb.Sp. For Conn.Den, the difference was significant between 30 versus 75 and 300 μm. BV/TV, BS/BV, Tb.Th and SMI were significantly correlated between 30 and 75μm and between 75 and 300μm. Tb.Th only between 30 and 75 μm and DA only between 75 and 300μm. There were no significant correlations in Tb.Sp and Conn.Bone micro-architectural parameters were highly dependent on voxel size, the differences between 75μm and 300μm was particular significant for Tb.N and in a lesser extent for Tb.Th. The partial volume effect could explain the differences between 75 and 300μm and precise site matching partly explained differences between 75 and 30μm. Tb.Th and DA were highly dependent on the acquisition conditions. These results must be confirmed on clinical CT scanners.

In conclusion, the resolution of 75μm that can be potentially obtained with HR-pQCT devices is probably the best resolution to assess bone micro-architecture.

<table>
<thead>
<tr>
<th>30μm</th>
<th>75μm</th>
<th>300μm</th>
<th>ANOVA (p/Post-Hoc test)</th>
<th>Determination Coeff. (R²) 30 vs 75 and 75 vs 300</th>
</tr>
</thead>
<tbody>
<tr>
<td>BV/TV (%)</td>
<td>20.0±6.0</td>
<td>25.0±6.3</td>
<td>45.6±4.8</td>
<td>&lt;0.001/30-75 vs 300</td>
</tr>
<tr>
<td>BS/BV (1/mm)</td>
<td>19.0±6.6</td>
<td>11.4±1.6</td>
<td>3.1±3.3</td>
<td>&lt;0.001/30 vs 75 vs 300</td>
</tr>
<tr>
<td>Tb.Th (mm)</td>
<td>0.20±0.03</td>
<td>0.30±0.03</td>
<td>1.2±0.2</td>
<td>&lt;0.001/30-75 vs 300</td>
</tr>
<tr>
<td>Tb.N (1/mm)</td>
<td>1.0±0.2</td>
<td>0.8±0.15</td>
<td>0.4±0.1</td>
<td>ns</td>
</tr>
<tr>
<td>Tb.Sp (mm)</td>
<td>0.67±0.12</td>
<td>0.84±0.11</td>
<td>1.6±0.2</td>
<td>&lt;0.001/30 vs 75 vs 300</td>
</tr>
<tr>
<td>Conn.Den</td>
<td>19.0±7.2</td>
<td>2.6±0.5</td>
<td>0.02±0.03</td>
<td>0.008/30 vs 75 vs 300</td>
</tr>
<tr>
<td>SMI</td>
<td>1.4±0.8</td>
<td>1.1±0.5</td>
<td>0.3±0.5</td>
<td>&lt;0.001/30 vs 75 vs 300</td>
</tr>
<tr>
<td>DA</td>
<td>2.0±0.2</td>
<td>2.4±0.1</td>
<td>2.0±0.2</td>
<td>&lt;0.001/30 vs 75 vs 300</td>
</tr>
</tbody>
</table>

* p<0.05; ** p<0.01
Quantitative comparison of different micro CT based trabecular bone image analysis software tools

Dieter Pahr1, Lukas Steiner

1 pahr@ilsb.tuwien.ac.at
2 Institute of Lightweight Design and Structural Biomechanics, TU Wien
3 Department of Anatomy and Biomechanics, Karl Landsteiner University of Health Sciences, Krems

Introduction

Trabecular bone geometry is usually measured by using micro CT imaging. Morphometrical parameters like bone density (BV/TV), degree of anisotropy (DA), trabecular thickness (TbTh), trabecular spacing (TbSp), and bone surface (BS) are obtained from such images to quantify the bone’s quality [1]. Different software tools are available, however, the level of agreement or differences of such image analysis tools was not quantified yet.

Methods

We used BoneJ (www.bonej.org), Scanco IPL (www.scanco.ch), and medtool (www.dr-pahr.at) to analyze a set of 437 micro CT datasets from different software tools. Standard statistical methods and Bland-Altman-plots are used for the comparisons.

Results

The figure shows Bland-Altman plots of selected results. The mean relative changes were highest when comparing BoneJ to Scanco measures, in particular 16.4% for TbSp and 98.8% for DA. BoneJ/medtool results for DA showed a difference of 95.3%. Similar quantities for TbTh and TbSp are obtained for BoneJ/medtool. Scanco and medtool showed only 4.7% of difference for DA but 18.9% for TbTh and 16.4% for TbSp. Smooth BS changes were around 11% (medtool/BoneJ) and 8.1% (Medtool/Scanco).

Discussion

The work shows that micro CT based morphological bone parameters obtained by different software programs cannot be compared directly. Depending on the specific implementation they differ considerably. DA Measures are most critical, whereas BS, TbTh, and TbSp shows differences up to 20%. In future a standardization is necessary or at least comparison of such measures from different software tools should be avoided.

References

1. Hildebrand et al., J Bone Miner Res, 1999
2. Gross et al., Biomechanics and Modeling, 2013
Adolescent Idiopathic Scoliosis (AIS) is associated with low bone mass. This study aimed at evaluating if Ca+Vit-D supplementation could improve bone strength and prevent curve progression in AIS.

**Materials and Methods**

This was a randomized double-blinded placebo-controlled trial on 330 AIS girls (11-14 years old, femoral neck aBMD Z-scores <0 and Cobb angle >15°) randomized to Group1 (placebo), Group2 (600mg Calcium+400IU Vit-D3/day) and Group3 (600mg Calcium+800IU Vit-D3/day). Treatment duration was 2-yr. At baseline and 24-month, Finite Element Analysis (FEA) on HR-pQCT parameters, serum and urinary calcium, ultrasound spectroscopy, and bone microstructure was recorded by synchrotron radiation micro-computed tomography (voxel size=6.5µm). Subvolumes (2.5x3.5x3.5mm3) from the reconstructed volumes of each specimen were used to quantify the microstructural parameters by CT Analyzer V1.16 (SkyScan, Kontich, Belgium). The effective stiffness coefficients (Cijff) of the subvolumes were calculated using Fast Fourier Transform (FFT)-based homogenization (voxel size=15µm) with fixed transverse isotropic bone matrix stiffness and isotropic material (water) in pores.

The variation of vascular porosity of cortical bone is a major determinant of the variation of mesoscopic (millimeter-scale) stiffness. Therefore, porosity was regarded as void volume fraction in former studies and the role of pore network microarchitecture has been little investigated. This work aims to investigate the relationships between microstructure and mesoscopic stiffness of cortical bone.

**Introduction**

Bone microstructure was recorded by synchrotron radiation micro-computed tomography (voxel size=6.5µm). Subvolumes (2.5x3.5x3.5mm3) from the reconstructed volumes of each specimen were used to quantify the microstructural parameters by CT Analyzer V1.16 (SkyScan, Kontich, Belgium). The effective stiffness coefficients (Cijff) of the subvolumes were calculated using Fast Fourier Transform (FFT)-based homogenization (voxel size=15µm) with fixed transverse isotropic bone matrix stiffness and isotropic material (water) in pores.

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Osteoporotic fracture in elderly Chinese men and women: A comparison of vertebral-cortex-fracture based and vertebral-deformity based methods
Min Deng, James Griffith, Jason Leung, Anthony Kwok, Timothy Kwak, Ping Chung Leung
vivi@ort.cuhk.edu.hk
The Chinese University of Hong Kong

Background
The best method to define osteoporotic vertebral fracture (VF) remains to be established. Vertebral-deformity (VD) based method has been in used, but vertebral-cortex-fracture (VCF) based method may offer better sensitivity and specificity for mild VF.

Objective
This study evaluated VCF based method for osteoporotic VF evaluation in elderly Chinese population with reference to VD based method and bone mineral density (BMD) measurement.

Methods
Mr. OS (Hong Kong) and Ms. OS (Hong Kong) represent the first large-scale cohort studies on bone health in elderly Chinese men and women. Based on quantitative measurement, the severity of VCF method detected fractures was classified into grade-1, grade-2, and grade-3 according to Genant's VD criteria. The radiographs of 1,954 elderly Chinese men (mean: 72.3 years) and 1,953 elderly Chinese women (mean: 72.5 years) were evaluated.

Results
According to VCF, grade-1, 2-3 VFs prevalence was 1.89%, 1.74% and 2.25% in men, and 3.33%, 3.07%, and 5.53% in women. In men and women, 13.7% (35/233) and 34.9% (48/139) of vertebrae with VD grade-1 deformity were VCF(+, with fracture) respectively. In men and women, 89.7% (33/35) and 66.7% (48/72) of vertebrae with VCF grade-1 fracture had VD grade-1 deformity. For grade-1 change, VD (-, negative without fracture) & VCF (+, positive with vertebral cortex line fracture) subjects tend to have a lower BMD than the VDX+&VCF(-) subjects. In subjects with VD grade-2 deformity, those were also VCF(+, positive) tended to have a lower BMD than those were VCF(-). In all grades, VDX(+&VCF(-)) subjects tended to have highest BMD, while VD(-)&VCF(-) subjects tended to have lowest BMD. The location of osteoporotic fracture distribution is shown in Fig 1.

Conclusion
VCF method may be more sensitive to VF associated mild lower BMD than VD method.

Persistent Low Bone Mass (LBM) at Maturity in Adolescent Idiopathic Scoliosis (AIS) Patients – A 4-year Longitudinal Follow-up Study
Wai Ping Fiona Yu1, Vivian Wong Yin Hung1, Benjamin Hon Kee Yip1, Ling Qin1, Tsz Ping Lam2, Jack Chun Yu Cheng2
vivi@ort.cuhk.edu.hk
1 Bone Quality and Health Centre, Department of Orthopaedics and Traumatology, The Chinese University of Hong Kong
2 Division of Family Medicine and Primary Care, Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong

AIS is 3D deformity of spine which mainly affecting girls during puberty. Cross-sectional studies have shown that about 30% AIS girls had LBM at femoral neck. The aim of this longitudinal study was to investigate whether BMD will persist at the time of skeletal maturity in AIS girls. 508 pre-matured AIS Chinese girls, aged 11-15, were recruited. Bilateral femoral neck BMD was measured by DXA at baseline and at skeletal maturity. Z-score BMD of hip (zBMD)<-1 was defined as LBM. Correlation of zBMD between initial measurement and at maturity was performed. Logistic regression results showed patients with LBM at baseline can significantly predict the BMD status at maturity with an odd ratio of 1.99 (95%CI 1.61-2.46) times more likely than re-gression. Persistent throughout the puberty period in AIS girls and potentially to have lower peak bone mass in adulthood. Early detection and treatment of KBM in AIS girls may help to reduce the risk of osteoporosis related problems in their later life.

<table>
<thead>
<tr>
<th>Normal BMD at maturity</th>
<th>LBM at maturity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.796</td>
<td>0.204</td>
</tr>
<tr>
<td>0.237</td>
<td>0.763</td>
</tr>
</tbody>
</table>

Table 1. Transition probability for 4 years follow-up time
Thoracolumbar intervertebral disc area morphometry in elderly Chinese: radiographic quantifications at baseline and year-4 follow-up

Jun-Qing Wang, Zoltán Káplár, Jason Leung, James F. Griffith, Ping Chung Leung, Yi-Xiang Wang
griffith@cuhk.edu.hk
The Chinese University of Hong Kong

Objective
To develop a quantitative index for lumbar disc space narrowing (DSN) evaluation in elderly subjects, and to quantify the areal loss of thoracic and lumbar disc space over four years in elderly females and males.

Methods
With the database of MrOS (Hong Kong) and MsOS (Hong Kong) and those who attended the year-4 follow-up (n = 1519 for men and n = 1546 for women), data of 491 women and 592 men were randomly selected. For each spine, the anterior, middle, and posterior heights, anteroposterior diameter and structure area of discs (T4T5 to L4L5) were measured on lateral radiographs. Disc Area Index for Lumbar Spine (DAIL) was developed and compared with semi-quantitative expert DSN grading (DAIL=disc area/(upper vertebral anteroposterior diameter)^2+(lower vertebral anteroposterior diameter)^2)/2).

Results
DAIL had good sensitivity and specificity for detecting DSN and specifying its grade (Fig 1). Thoracic discs showed an increase in anterior wedge index over the 4 years which could potentially contribute to kyphosis...
Cortical bone is an anisotropic material with hierarchical structure whose elastic properties are described at different length scales. At millimeter-scale, the whole set of stiffness tensor can be conveniently measured by resonant ultrasound spectroscopy (RUS). At microscopic-scale, micro-indentation test and scanning acoustic microscopy are usually used to quantify the elastic properties. However, the last two methods do not provide the entire stiffness tensor of bone matrix (microscopic-scale). To overcome this difficulty, we introduce a new approach to retrieving the elastic tensor of the matrix based on a numerical optimization procedure using Fast Fourier Transform (FFT)-based homogenization for the forward computation. From the mid-diaphysis of 28 human femurs, 55 cubic cortical bone specimens (3x4x5mm3) were harvested and the mesoscopic stiffness coefficients (Cijkl) were measured by RUS. Pore network was recorded by synchrotron radiation micro-computed tomography (voxel size=6.5µm). A sub volume (2.5x3.5x4.5mm3) from the reconstructed volume of each specimen was used to calculate the effective stiffness coefficients (Cijkl) using FFT-based homogenization (voxel size=15µm) for trial values of the bone matrix stiffness (Cij assuming transverse isotropy) and assuming the presence of water in pores. The specimen-specific matrix stiffness Cij was found by inverse homogenization, i.e., by minimizing the root-mean-square error (RMSE) between Cijkl and Cijkl (Table 1). The RMSE between Cijkl and Cijkl is between 0.36% and 0.40% (mean±std). Significant correlations were found between C44m, C33exp, C13exp and C44exp (0.3266m, C11exp, C13exp, C44exp and C66exp (0.47ijm remain to be validated by in independent measurements.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value (GPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C11m</td>
<td>21.77±30.87</td>
</tr>
<tr>
<td>C22m</td>
<td>31.43±38.70</td>
</tr>
<tr>
<td>C33m</td>
<td>12.07±20.53</td>
</tr>
<tr>
<td>C44m</td>
<td>6.09±7.38</td>
</tr>
<tr>
<td>C66m</td>
<td>4.11±6.31</td>
</tr>
</tbody>
</table>

Table 1: The bone matrix elastic coefficients retrieved from the numerical procedure.
Osteoporotic vertebral fractures mostly occur under non-traumatic loading conditions due to the destruction of the trabecular architecture. Little is known about the effects of osteoporosis on tissue mechanical properties that are important since they provide rigidity and resistance to the fracture, particularly regarding atraumatic vertebral fractures. The aim of this study was to use scanning acoustic microscopy (SAM) to evaluate weather tissue mechanical properties of vertebral trabecular tissue are compromised in patients with atraumatic vertebral fractures. Percutaneous transpedicular biopsies were obtained from fractured vertebrae (FxFr, N=71) and from non-fractured vertebrae (Fx, N=33) of the same patients and from non-fractured controls (Ko, N=68). 169 half-cylindric specimens were embedded in PMMA. The resulting cast was cut in 3.5 mm thick slices. The cross-sectional area in each slice was 1.2 x cm². Confocal reflection amplitude was measured by scanning a 100-MHz focusing transducer over the specimen. Specimen dimensions were defined by the anatomical shape of femoral diaphysis: radial (axis 1), transverse (axis 2) and axial (axis 3). The confocal reflectivity was measured by a confocal microscope. The specimen was scanned with a 30 µm step size. Three-point bending tests were conducted at two strain rates 10⁻¹ s⁻¹ and 10⁻¹ s⁻¹ to measure the mechanical properties of bone. This study aims at investigating the relationship between different aspects of bone quality and understanding how bone quality may affect stiffness at the mm-scale and toughness. The transverse isotropic stiffness tensor was measured by resonant ultrasound spectroscopy (RUS) and the vascular porosity was estimated from synchrotron radiation microcomputed tomography (SR-μCT) imaging. A cross-section at the mid-diaphysis was sectioned from the left femur of 27 human cadavers. Then, 54 parallelepiped-shape samples (size 3x4x5 mm³) were prepared for RUS measurements and SR-μCT imaging (voxel size 6.5 µm). Another set of adjacent 54 samples (size 3x4x25 mm³) was harvested for mechanical testing and the remaining material was used for cross-links and collagen quantification. These last samples were divided into two samples (1x2x25 mm³) then notched (1 mm length) in their middle in the transverse direction. Three-point bending tests were conducted at two strain rates 10⁻¹ s⁻¹ and 10⁻¹ s⁻¹ to measure bone toughness (elastic modulus and dynamic KicDyn). Specimen dimensions are defined by the anatomical shape of femoral diaphysis: radial (axis 1), circumferential (axis 2) and axial direction (axis 3). Immature and mature collagen crosslinks were separated by reversed-phase HPLC method and quantified using fluorescence and mass spectrometry detection. The bone-quality markers analysed here seem to differently affect toughness and stiffness. Indeed, markers that showed a effect in toughness did not in stiffness. Porosity was significantly correlated with stiffness but not with toughness. Enzymatic immature cross-links significantly correlated with stiffness coefficients, while only the non-enzymatic cross-link pentosidine significantly affected toughness. Existing correlations between elastic parameters and toughness are shown in Table 1. Knowing the effects of these markers in the mechanical properties of bone may provide a more precise estimate for the fracture risk.

**Table 1: Spearman correlations of toughness with Young’s moduli (E₁, E₂) and Poisson’s ratios (ν₁₂, ν₁₃, ν₂₃).**

<table>
<thead>
<tr>
<th>E₁</th>
<th>E₂</th>
<th>ν₁₂</th>
<th>ν₁₃</th>
<th>ν₂₃</th>
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<tr>
<td><strong>KicDyn</strong></td>
<td><strong>KicDyn</strong></td>
<td><strong>ν₁₂</strong></td>
<td><strong>ν₁₃</strong></td>
<td><strong>ν₂₃</strong></td>
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<tr>
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</tr>
<tr>
<td><strong>ν₁₃</strong></td>
<td>NS</td>
<td>NS</td>
<td><strong>ν₁₂</strong></td>
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<td><strong>ν₂₃</strong></td>
<td>NS</td>
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</tbody>
</table>

**Notes:**

* *p<0.05; **p<0.001; NS: non significant*
Trabecular tissue Young's modulus assessed from resonant ultrasound spectroscopy

Hassiba Daoui1,2, Xiran Cai1, Fouad Boubenider2, Pascal Laugier1, Quentin Grimal1

1 Sorbonne Universités, UPMC Univ Paris 06, INSERM UMR-S 1146, CNRS UMR 7371, Laboratoire d’Imagerie Biomédicale, Paris, France
2 Université des sciences et de technologie Houari Boumediene, faculté de physique, laboratoire de physique des matériaux, équipe ondes et acoustique, Alger, Algeria

The material properties of the trabeculae at the tissue-level, together with the microstructure and bone volume fraction determine the apparent mechanical properties of trabecular bone at the scale of several millimeters.

We present a novel method to measure trabecular tissue elastic modulus Et using resonant ultrasound spectroscopy (RUS). The first resonant frequency of a cuboid sample is measured by a custom-made setup of RUS (Figure 1) and used to back-calculate Et based on a micro-finite element simulation. The forward model predicting the frequency to be matched with the experimental frequency consists in: (1) using an arbitrary test value of Et, calculating with micro-finite elements the stiffness tensor using the direct-mechanics method (six mechanical loadings enabling the complete identification of the apparent elasticity) based on the computed tomography images of the specimen, (2) calculating with the Rayleigh-Ritz method the eigenfrequency of the first vibrational mode of the sample using the previously determined stiffness tensor. Finally, Et is back-calculated using the measured frequency through a linear interpolation of the simulated data Et vs. frequency.

The method was applied to four bovine bone specimens. Average (standard deviation) of Et were 13.12(1.06) GPa. We found that a measurement of a single resonant frequency of the specimen enables an estimation of tissue Young's modulus in line with data published previously. RUS is a relatively low-cost technique that is non-destructive and efficient to measure large series of bone samples. RUS could be an alternative to quasi-static mechanical testing of specimens for elasticity measurements. The technique proposed in this study could contribute to a better documentation of bone tissue elastic properties of trabecular bone. Tissue elastic properties are important parameters of micro-finite element analysis for clinical assessment of bone strength.

Figure 1: The custom-made setup of RUS used to measure the first resonant frequency of the cuboid trabecular samples.
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