2nd Joint Meeting

OF THE

Bone Research Society

AND THE

British Orthopaedic Research Society

23-25 June 2008

MANCHESTER, UK

Final Programme and Abstracts

Organisers:

Judith Adams

Carol Evans

Terry O'Neill

Peter Selby

University of Manchester

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Judith Adams
Carol Evans
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Peter Selby

www.brsoc.org.uk
www.borsoc.org.uk

Contents

Bone Research Society

The Society (formerly known as the Bone and Tooth Society) is the oldest and largest scientific society in Europe that is dedicated to further research into clinical and basic science problems related to mineralised tissues. The meeting attracts a wide audience from throughout the UK and, increasingly, from continental Europe and further afield. The presentations are traditionally a balance between clinical and laboratory-based studies. The participation of young scientists and clinicians is actively encouraged.

Committee 2008

President: Jonathan Reeve (Cambridge)
President Elect: Cyrus Cooper (Southampton)
Secretary: Colin Farquharson (Edinburgh, UK)
Treasurer: Jonathan Tobias (Bristol)

Kay Colston (London)
Mark Cooper (Birmingham)
Miep Helfrich (Aberdeen)
Richard Keen (London)
David Marsh (London)
Eugene McCloskey (Sheffield)
Andy Pitsillides (London

Student Representatives:
Claire Clarkin (London)
Nick Harvey (Southampton)

Membership Enquiries

Portland Customer Services
Tel: +44 (0)1206 796351
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Email: brs@portland-services.com

NEXT YEAR'S BRS MEETING

15-16 June 2009
London
Jointly with the British Society for Matrix Biology

BONE RESEARCH SOCIETY

www.brsoc.org.uk

British Orthopaedic Research Society

The British Orthopaedic Research Society (BORS) is a multidisciplinary association founded in 1961 and devoted to pursuing research relevant to orthopaedic and musculoskeletal surgery. The research interests of its membership (currently over 700) are varied and include:

- Biological Science
- Biomechanics
- Osteo-articular Pathology
- Biotribology
- Molecular Biology
- Bioengineering
- Medical Imaging
- Patient Management

Committee 2008

President: Brigitte Scammell (Nottingham)
Secretary: Roger Bayston (Nottingham)
Treasurer: Trudy Roach (Southampton)
Mark Birch (Newcastle upon Tyne)
Gordon Blunn (London)
David Marsh (London)
Hamish Simpson (Edinburgh)
Xuebin Yang (Leeds)

Membership Enquiries

Tel: +(0)0115 8231115
Fax: +(0)0115 8231118
Email: Oas-admin@nottingham.ac.uk

NEXT YEAR'S BORS MEETING

22-23 June 2009
Newcastle upon Tyne

Arcana ossium quis explorat B.O.R.S.

www.borsoc.org.uk

Awards, Sponsors and Other Supporters

New Investigator Awards

The following awards were made by the Bone Research Society Committee according to marks given to blinded abstracts during the independent review process:

D Heath (Sheffield): OC24: Inhibiting Dickkopf-1 (Dkk-1) prevents the development of osteolytic bone disease in multiple myeloma

P Mahon (Southampton): OC19: Maternal vitamin D insufficiency and fetal bone development

A Moustafa (London): OC02: Loading-related reduction in osteocyte sclerostin expression in vivo is associated with bone formation in trabecular and cortical bone

I Orriss (London): OC09: MicroCT analysis of P2Y1 and P2Y2 receptor knockout mice demonstrates significant changes in bone phenotype

The Bone Research Society will make further awards during the meeting as follows (2 in each category, clinical and non-clinical):

Best Oral

Best Oral Poster

Best Poster

The British Orthopaedic Research Society will make awards during the meeting as follows:

Best Oral

Best Oral Poster

Best Poster

Best Clinical Paper

Gold Sponsors:

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Programme Overview

Monday 23 June

08.30

09.00

09.30

10.00

10.30

11.00 **Registration**
COFFEE & POSTER HANGING

11.30 **SYMPOSIUM:**
Current concepts in musculoskeletal research
Room C16

12.00

12.30 **LUNCH**
Foyer

13.00

13.30 **BRS-BORS**
Clinical Afternoon
Room C16

14.00

14.30

15.00

15.30 **TEA**

16.00 **CLINICAL CASES**
Room C16

16.30

17.00 **TEA and Poster Viewing**
Foyer

17.30 **WELCOME**

KEYNOTE LECTURE
Room C16

18.00

18.30 **SATELLITE SYMPOSIUM:**
Advances in RANK/RANKL/OPG Pathway Research
Room C16

19.00

19.30

20.00

20.30 **Civic Reception**
Manchester Town Hall

21.00

NEW INVESTIGATORS' SESSION: Shaping your future in skeletal biology
Room D7

Tuesday 24 June

08.30

09.00 **SYMPOSIUM: New aspects of bone repair and ortho-pharmacology**
Room C16

09.30

10.00 **ORAL COMMUNICATIONS (BRS/BORS)**
Room C16

10.30

11.00

11.30 **COFFEE**
Attended Posters (odds)
Foyer

12.00

12.30 **ORAL COMMUNICATIONS (BRS)**
Room C16

13.00

13.30 **LUNCH & POSTERS**
Foyer

14.00

14.30 **SYMPOSIUM:**
Mechanobiology
Room C16

15.00

15.30

16.00 **TEA**
Attended Posters (evens)
Foyer

16.30

17.00 **ORAL COMMUNICATIONS (BORS)**
Room C16

17.30

18.00

18.30

19.00

19.30

20.00

20.30 **Conference Dinner and Party**
Barnes Wallis Building,
University of Manchester

21.00

ORAL COMMUNICATIONS (BORS)
Room C2

ORAL COMMUNICATIONS (BRS)
Room C2

Wednesday 25 June

08.30		
09.00	**SYMPOSIUM: Imaging bone structure: From bench to bedside** Room C16	
09.30		
10.00		
10.30	**COFFEE** **Attended Posters (Odds 10:00-10:30; Evens 10:30-11:00)** Foyer	
11.00		
11.30	**JOINT BORS/BRS ORAL POSTERS** Room C16	
12.00		
12.30	**ORAL POSTERS (BRS)** Room C16	**BORS AGM** Room C2
13.00	**LUNCH & POSTERS** Foyer	
13.30		
14.00	**ORAL POSTERS (BORS)** Room C16	**BRS AGM** Room C2
14.30	**BORS SYMPOSIUM: What is new in osteoarthritis and cartilage?** Room C16	**BRS SYMPOSIUM: New concepts in vitamin D** Room C2
15.00		
15.30	**ORAL COMMUNICATIONS (joint BRS/BORS)** Room C16	
16.00		
16.30	**AWARDS** Room C16	
17.00		
17.30		
18.00		
18.30		
19.00		
19.30		
20.00		
20.30		
21.00		

Programme
Monday 23 June

10:30 -11:00

Registration

Coffee and poster hanging

11:00-12:30

SYMPOSIUM
Current concepts in musculoskeletal research

Chairs:
Jonathan Reeve (Cambridge, UK)
Brigitte Scammell (Nottingham, UK)

11:00 WHAT ARE THE FUTURE DEVELOPMENT NEEDS IN TRAUMA AND ORTHOPAEDICS?
Brigitte Scammell (Nottingham, UK)

11:25 IMPLANT-RELATED INFECTION. WHERE DO WE GO FROM HERE?
Roger Bayston (Nottingham, UK)

11:50 NICE, FRAX AND OSTEOPOROSIS
Jon Tobias (Bristol, UK)

12:10 DISCUSSION
NICE: WHAT ROLE FOR BRS/BORS?

12:30-13:30

Lunch

13:30-16:30 **ROOM C16**

BRS-BORS CLINICAL AFTERNOON

Chairmen:
David Marsh (London, UK)
Peter Selby (Manchester, UK)

13:30 IS01 THE NATIONAL HIP FRACTURE DATABASE
Rob Wakeman (Basildon, UK)

14:00 IS02 WHAT IS A VERTEBRAL FRACTURE? EFFECTS OF STUDY DESIGN MEASUREMENT IMPRECISION ON STUDY OUTCOMES
Mark Lunt (Manchester, UK)

14:20 IS03 VERTEBROPLASTY/KYPHOPLASTY: WHEN TO INTERVENE
Rick Whitehouse (Manchester, UK)

14:40 IS04 BONE AS AN ENDOCRINE "GLAND": PHOSPHATE AND OTHER TARGETS
William Fraser (Liverpool, UK)

15:10-15:30

Tea

PARALLEL SESSION

15:30-16:30 **ROOM C16**

CLINICAL CASES

Chairmen:
William Fraser (Liverpool, UK)
Rick Whitehouse (Manchester, UK)

15:30 CC1 SOFT TISSUE CALCIFICATION IN THE HAND- A BENIGN ENTITY?
KS Rankin, WA Hadden, GG McLeod*
Department of Orthopaedic Surgery, Perth Royal Infirmary, UK

15:45 CC2 AN OMINOUS RADIOLOGICAL SIGN OF IMPENDING ALENDRONATE-RELATED FEMORAL SUBTROCHANTERIC INSUFFICIENCY FRACTURES - AN INDICATION FOR PROPHYLACTIC OPERATIVE FIXATION?
S Das De, T Setiobudi, S Das De*
Department of Orthopaedic Surgery, National University Hospital, Singapore

16:00 CC3 NOT ALL REFERRALS FROM MAXILLOFACIAL SURGEONS ARE OSTEONECROSIS OF THE JAW
JS Bubbear[1], R Green[2], RW Keen[1]*
[1]Metabolic Unit, Royal National Orthopaedic Hospital, Stanmore, UK; [2]Department of Radiology, Royal National Orthopaedic Hospital, Stanmore, UK

16:15 CC4 A TEN YEAR RETROSPECTIVE STUDY INTO THE MORTALITY AND MORBIDITY BENEFITS ACHIEVED BY PROPHYLACTIC STABILISATION OF SKELETAL METASTASES
SR Davies[1], C Dent[1], P Barrett-Lee[2]*
[1]Department of Orthopaedics, University Hospital of Wales, Cardiff, UK; [2]Department of Oncology, Valindra Hospital, Cardiff, UK

PARALLEL SESSION

15:30-16:30 ROOM D7

NEW INVESTIGATORS' SESSION: Shaping your future in skeletal biology

Chairmen:
Claire Clarkin (London, UK)
Nick Harvey (Southampton, UK)

15:30	WELCOME AND INTRODUCTION
15:35	BARBARA MAWER VISITING FELLOWSHIP *Claire Clarkin (London, UK)*
15:40	PATHWAYS TO TENURE *Alan Silman (Manchester, UK)*
15:50	WHAT MAKES A SUCCESSFUL FELLOWSHIP APPLICATION? *Chris Buckley (Birmingham, UK)*
16:00	LIFE AS AN ARC CLINICAL FELLOW *Ken Poole (Cambridge, UK)*
16:10	EXAMPLE OF CAREER VIA ACADEMIC ROUTE MINUS FELLOWSHIP *Alison Gartland (Sheffield, UK)*
16:20	OPEN DISCUSSION
16:30	CLOSE

16:30-17:15

Tea/posters

17:15-17:20 ROOM C16

Welcome

Chairmen:
Jonathan Reeve (Cambridge, UK)
Brigitte Scammell (Nottingham, UK)

Alan North
Vice-President and Dean
Faculty of Life Sciences & Faculty of Medical and Human Sciences

17:20-18:00 ROOM C16

KEYNOTE LECTURE: Moving beyond the bone and joint decade: rejuvenating the research agenda

Alan Silman (Manchester, UK)

18:00-19:15 ROOM C16

SATELLITE SYMPOSIUM Advances in RANK/RANKL/OPG Pathway Research

Supported by Amgen

Chairmen:
Graham Russell (Oxford, UK)
Eugene McCloskey (Sheffield, UK)

18:00	LESSONS LEARNED FROM RANK LIGAND INHIBITION IN HURANKL KNOCK-IN MICE AND IN OVARIECTOMISED MONKEYS *Serge Ferrari (Geneva, Switzerland)*
18:20	CLINICAL EXPERIENCE WITH RANK LIGAND INHIBITION: OSTEOPOROSIS AND RHEUMATOID ARTHRITIS *David Reid (Aberdeen, UK)*
18:40	TUMOUR-INDUCED BONE DESTRUCTION *Janet Brown (Leeds, UK)*
19:00	QUESTIONS AND ANSWERS

20:00-21:00 Manchester Town Hall

Civic Reception

Programme
Tuesday 24 June

08:30-09:30 **ROOM C16**

SYMPOSIUM
New aspects of bone repair and ortho-pharmacology

Chairmen:
Jonathan Reeve (Cambridge, UK)
Brigitte Scammell (Nottingham, UK)

08:30 IS05 MECHANO-BIOLOGY OF FRACTURE HEALING
Georg Duda (Berlin, Germany)

09:00 IS06 ENHANCING BONE REPAIR WITH PHARMACOTHERAPY
David Marsh (London, UK)

09:30-11:00 **ROOM C16**

ORAL COMMUNICATIONS (BRS/BORS)

Chairmen:
Jonathan Reeve (Cambridge, UK)
Brigitte Scammell (Nottingham, UK)

09:30 OC01 INFLAMMATORY CYTOKINES CAUSE LOSS OF DNA METHYLATION TOGETHER WITH INDUCTION OF ABNORMAL GENE EXPRESSION IN HEALTHY HUMAN ARTICULAR CHODROCYTES

K Hashimoto[1,2], S Kokubun[2], E Itoi[2], HI Roach[2]*

[1]Bone & Joint Research Group, Institute of Developmental Sciences, University of Southampton, UK; [2]Dept of Orthopaedic Surgery, Tohoku University School of Medicine, Sendai, Japan

09:42 OC02 LOADING-RELATED REDUCTION IN OSTEOCYTE SCLEROSTIN EXPRESSION IN VIVO IS ASSOCIATED WITH BONE FORMATION IN TRABECULAR AND CORTICAL BONE

AM Moustafa, G Zaman, L Saxon, LE Lanyon, J Price*

Department of Veterinary Basic Sciences, The Royal Veterinary College, Royal College Street, London NW1 0TU, UK

09:54 OC03 A BIOACTIVE SCAFFOLD FOR BONE REGENERATIVE MEDICINE

DMC Sharp, A Martin, N Khan, H Simpson, BS Noble*

Musculoskeletal Tissue Engineering Collaboration (MTEC), MRC Centre for Regenerative Medicine, University of Edinburgh Medical School, UK

10:06 OC04 PREDICTION OF INCIDENT HIP FRACTURE RISK BY FEMUR GEOMETRY VARIABLES MEASURED BY HIP STRUCTURAL ANALYSIS IN THE STUDY OF OSTEOPOROTIC FRACTURES

S Kaptoge[1], TJ Beck[2], J Reeve[1], KL Stone[3], TA Hillier[4], JA Cauley[5], SR Cummings[6]*

[1]Departments of Medicine and Public Health and Primary Care, University of Cambridge, Cambridge, UK; [2]Department of Radiology, The Johns Hopkins University School of Medicine, Baltimore MD, USA; [3]California Pacific Medical Centre Research Institute, San Francisco CA, USA; [4]Kaiser Permanente Centre for Health Research Northwest and Hawaii, Portland Oregon, USA; [5]Department of Epidemiology, University of Pittsburgh, Pittsburgh PA, USA; [6]California Pacific Medical Centre, Research Institute, and Department of Epidemiology and Biostatistics, University of California, San Francisco CA, USA

10:18 OC05 VARIATION IN THE INTERLEUKIN-1 RECEPTOR ANTAGONIST GENE PROTECTS AGAINST OSTEOLYSIS AFTER TOTAL HIP ARTHROPLASTY: A CLINICAL AND GENE EXPRESSION STUDY

A Gordon[1], E Kiss-Toth[2], E Greenfield[3], R Eastell[1], JM Wilkinson[1]*

[1]Academic Department of Bone Metabolism, University of Sheffield, Sheffield, UK; [2]Department of Genomic Medicine, University of Sheffield, Sheffield, UK; [3]Department of Orthopaedics, Case Western Reserve University, Cleveland, USA

10:30 OC06 EFFECTS OF ACUTE HYPOXIA ON OSTEOCLAST ACTIVITY: A BALANCE BETWEEN ENHANCED RESORPTION AND INCREASED APOPTOSIS

HJ Knowles[1], NA Athanasou[2]*

[1]Botnar Research Centre, University of Oxford, UK; [2]Department of Pathology, Nuffield Department of Orthopsedic Surgery, University of Oxford, UK

10:42 OC07 ISOLATION OF SENESCENT MULTIPOTENT STROMAL CELLS FROM HUMAN FRACTURE NON-UNIONS

S Bajada[1], JB Richardson[2], WEB Johnson[1]*

[1]Centre for Spinal Studies, Keele University at the RJAH Orthopaedic Hospital, Oswestry, UK; [2]Institute of Orthopaedics, RJAH Orthopaedic Hospital, Oswestry, UK

11:00-12:00

Coffee

ATTENDED POSTERS (ODDS)

PARALLEL SESSION

12:00-13:00 **ROOM C16**

ORAL COMMUNICATIONS - BRS

Chairmen:
Colin Farquharson (Edinburgh, UK)
Harri Sievänen (Tampere, Finland)

12:00 OC08 PRIMARY OSTEOBLASTS AND BONE MATRIX OF BONES WITH DIFFERENT FUNCTIONS HAVE DISTINCT CHARACTERISTICS

SCF Rawlinson[1], G Zaman[2], IJ McKay[1], M Ghuman[1], FJ Hughes[1], VJ Kingsmill[1]*

[1]Adult Oral Health, Barts and The London School of Medicine and Dentistry, UK; [2]Bone Unit, The Royal Veterinary College, UK

12:12 OC09 MICROCT ANALYSIS OF P2Y1 AND P2Y2 RECEPTOR KNOCKOUT MICE DEMONSTRATES SIGNIFICANT CHANGES IN BONE PHENOTYPE

IR Orriss[1], HR Evans[2], A Gartland[2], TR Arnett[1]*

[1]Department of Anatomy and Developmental Biology, University College London, London, UK; [2]Academic Unit of Bone Biology, University of Sheffield, Sheffield, UK

12:24 OC10 RANKL-INDEPENDENT OSTEOCLASTOGENESIS IN PAGET'S DISEASE

F Jones, H Knowles, J Wass, N Athanasou*

Nuffield Department of Orthopaedic Surgery, University of Oxford, Oxford, UK

12:36 OC11 UROCORTIN STRONGLY SUPPRESSES BONE RESORPTION IN IN-VITRO-DERIVED MURINE OSTEOCLASTS

CE Combs, K Fuller, TJ Chambers, KM Lawrence*

St George's, University of London, Cramner Terrace, London, SW17 0RE, UK

12:48 OC12 TSG-6 REGULATES BONE REMODELLING THROUGH INHIBITION OF OSTEOBLASTOGENESIS AND OSTEOCLAST ACTIVATION

DJ Mahoney[1,2], K Mikecz[3], T Ali[2,4], G Mabilleau[1], D Benayahu[5], A Plaas[6], CM Milner[2,4], AJ Day[2,4], A Sabokbar[1]*

[1]Botnar Research Centre, Nuffield Department Orthopaedic Surgery, University of Oxford, OX3 7LD, UK; [2]MRC Immunochemistry Unit, Department of Biochemistry, University of Oxford, OX1 3QU, UK; [3]Department of Orthopaedic Surgery, Rush University Medical Centre, Chicago IL 60612, USA; [4]Faculty of Life Sciences, Michael Smith Building, University of Manchester, M13 9PT, UK; [5]Department of Cell and Developmental Biology, Sackler School of Medicine, Tel Aviv University, Tel Aviv 69978, Israel; [6]Department of Biochemistry, Rush University Medical Centre, Chicago IL 60612, USA

PARALLEL SESSION

12:00-13:00 **ROOM C2**

ORAL COMMUNICATIONS - BORS

Chairmen:
Hamish Simpson (Edinburgh, UK)
Xuebin Yang (Leeds, UK)

12:00 OC13 EXPRESSION OF THE CELL TO CELL ADHESION MOLECULE, ALCAM, IN BREAST CANCER PATIENTS AND THE POTENTIAL LINK WITH SKELETAL METASTASIS

SR Davies[1], C Dent[1], G Watkins[2], J King[3], K Mokbel[4], RE Mansel[2], WG Jiang[2]*

[1] Department of Orthopaedics, University Hopsital of Wales, Cardiff, UK; [2]Metastasis and Angiogenesis Research Group, Department of Surgery, Cardiff University School of Medicine, Cardiff, UK; [3]University of South Alabama, Centre for Lung Biology, 3330 MSB, Mobile, Alabama 36688-0002, USA; [4]Department of Surgery, St. George Hospital, London, UK

12:12 OC14 ROLE OF EPIGENETIC MODIFIERS IN BONE MARROW STROMAL CELL DIFFERENTIATION

AT El-Serafi, ROC Oreffo, HI Roach*

Bone and Joint Research Group, DOHaD division, School of Medicine, University of Southampton, UK

12:24 OC15 CHONDROCYTE SURVIVAL IN ARTICULAR CARTILAGE EXPLANTS - THE INFLUENCE OF SUBCHONDRAL BONE

AK Amin[1,2], JS Huntley[1], AHRW Simpson[1], AC Hall[2]*

[1]Department of Orthopaedic and Trauma Surgery, University of Edinburgh, UK; [2]Centre for Integrative Physiology, School of Biomedical Sciences, University of Edinburgh, UK

12:36 OC16 ABNORMAL IN SITU HUMAN CHONDROCYTE MORPHOLOGY IS ASSOCIATED WITH INCREASED LEVELS OF IL-1BETA BUT NOT MMP-13

DH Murray[1], PG Bush[1], IJ Brenkel[2], AC Hall[1]*

[1]Centre for Integrative Physiology, University of Edinburgh, UK; [2]Department of Orthopaedics, Queen Margaret Hospital, Dunfermline, UK

12:48 OC17 HEAT SHOCK PROTEIN AND APOPTOSIS IN SUPRASPINATUS TENDINOPATHY

NL Millar[1,2], AQ Wei[1], 'TJ Molloy[1], F Bonar[1], GAC Murrell[1],*

[1]Orthopaedic Research Institute, St. George Hospital Campus, University of New South Wales, Sydney, Australia; [2]West of Scotland Orthopaedic Training Programme, Glasgow, UK

13:00-14:00

Lunch and posters

14:00-15:30 **ROOM C16**

SYMPOSIUM
Mechanobiology

Chairmen:
David Marsh (London, UK)
Jonathan Tobias (Bristol, UK)

14:00 IS07 IMPACT OF PHYSICAL ACTIVITY ON THE SKELETON
Harri Sievänen (Tampere, Finland)

14:30 IS08 LOW PROTEIN INTAKE AND BONE RESPONSES TO MECHANICAL LOADING
Patrick Ammann (Geneva, Switzerland)

15:00 IS09 PRIMING OF SKELETAL MECHANOBIOLOGICAL MEMORY
Andy Pitsillides (London, UK)

15:30-16:30

Tea

ATTENDED POSTERS (EVENS)

PARALLEL SESSION

16:30-18:06 **ROOM C2**

ORAL COMMUNICATIONS - BRS

Chairmen:
Cyrus Cooper (Southampton, UK)
Terry O'Neill (Manchester, UK)

16:30 OC18 GENETIC VARIATION IN THE AROMATASE GENE INFLUENCES HEEL ULTRASOUND PARAMETERS: RESULTS FROM THE EUROPEAN MALE AGEING STUDY (EMAS)
KL Limer[1], SR Pye[1], W Thomson[1], S Boonen[2], H Borghs[2], D Vanderschueren[2], IT Huhtaniemi[3], JE Adams[4], KA Ward[4], G Bartfai[5], F Casanueva[6], JD Finn[7], G Forti[8], A Giwercman[9], TS Han[10], K Kula[11], MEJ Lean[10], N Pendleton[12], M Punab[13], AJ Silman[1], FCW Wu[7], TW O'Neill[1] and the EMAS Study Group*
[1]ARC Epidemiology Unit, The University of Manchester, UK; [2]Katholieke Universiteit Leuven, Belgium; [3]Imperial College London, UK; [4]Department of Imaging Science and Biomedical Engineering, The University of Manchester, UK; [5]University of Szeged, Hungary; [6]University of Santiago de Compostela, Spain; [7]Department of Endocrinology, The University of Manchester, UK; [8]University of Florence, Italy; [9]Lund University, Sweden; [10]University of Glasgow, Scotland; [11]University of Lodz, Poland; [12]Clinical Gerontology, The University of Manchester, UK; [13]University of Tartu, Estonia

16:42 OC19 MATERNAL VITAMIN D INSUFFICIENCY AND FETAL BONE DEVELOPMENT
PA Mahon[1], NC Harvey[1], SR Crozier[1], HM Inskip[1], SM Robinson[1], NK Arden[1], R Swaminathan[2], C Cooper[1], KM Godfrey[1]*
[1]MRC Epidemiology Resource Centre, University of Southampton, UK; [2]Department of Chemical Pathology, St Thomas' Hospital, London, UK

16:54 OC20 PARENTAL HEIGHT AND CHILDHOOD MILK INTAKE AT 4 YEARS ARE ASSOCIATED WITH CATCH UP BONE MINERAL ACCRUAL IN EARLY CHILDHOOD
NC Harvey, MK Javaid, ZA Cole, SM Robinson, SR Crozier, HM Inskip, KM Godfrey, EM Dennison, C Cooper*
MRC ERC, University of Southampton, Southampton, UK

17:06 OC21 COMPARISON OF DXA AND QUS FOR PREDICTION OF FRACTURE RISK AMONG OLDER MEN AND WOMEN: THE EPIC-NORFOLK COHORT STUDY
A Moayyeri[1], S Kaptoge[1], RN Luben[1], S Bingham[2], NJ Wareham[3], J Reeve[1], KT Khaw[1]*
[1]Department of Public Health and Primary Care, University of Cambridge, UK; [2]MRC Dunn Human Nutrition Unit; [3]MRC Epidemiology Unit, Cambridge, UK

17:18 OC22 USE OF DXA-BASED STRUCTURAL ENGINEERING MODELS OF THE PROXIMAL FEMUR TO PREDICT HIP FRACTURE
L Yang[1], N Peel[2], J Clowes[3], EV McCloskey[1], R Eastell[1]*
[1]Academic Unit of Bone Metabolism, University of Sheffield, UK; [2]Metabolic Bone Centre, Northern General Hospital, Sheffield, UK; [3]Mayo Clinic, Rochester, USA

17:30 OC23 OSTEOPROTEGRIN AS A PROGNOSTIC INDICATOR FOR BONE METASTASIS IN DUCTAL BREAST CANCER
SR Davies[1], RE Mansel[2], WG Jiang[2]*
[1]Department of Orthopaedics, University Hospital of Wales, Cardiff, UK; [2]Metastasis and Angiogenesis Research Group, Department of Surgery, Cardiff University School of Medicine, Cardiff, UK

17:42 OC24 INHIBITING DICKKOPF-1 (DKK-1) PREVENTS THE DEVELOPMENT OF OSTEOLYTIC BONE DISEASE IN MULTIPLE MYELOMA
DJ Heath[1], AD Chantry[1], C Buckle[1], L Coulton[1], JD Shaughnessy Jr[2], H Evans[1], DR Stover[3], K Vanderkerken[4], PI Croucher[1]*
[1]Academic Unit of Bone Biology, University of Sheffield, UK; [2]Myeloma Institute for Research and Therapy, University of Arkansas for Medical Sciences, USA; [3]Novartis Institutes for Biomedical Research Incorporated, Cambridge, USA; [4]Department of Haematology and Immunology, Vrije Universiteit Brussel, Belgium

17:54 OC25 A RANDOMISED DOUBLE BLIND PLACEBO CONTROLLED TRIAL TO DETERMINE THE MAGNITUDE OF CHANGE IN BONE MINERAL DENSITY IN RESPONSE TO LASOFOXIFENE

SJ Glover[1], A Rogers[1], R Eastell[1]*

Academic Unit of Bone Metabolism, University of Sheffield, Sheffield, UK

PARALLEL SESSION

16:30-18:06 **ROOM C16**

ORAL COMMUNICATIONS - BORS

Chairmen:
Gordon Blunn (Stanmore, UK)
Andrew McCaskie (Newcastle upon Tyne, UK)

16:30 OC26 THE METAPHYSEAL-DIAPHYSEAL INDEX SCORE, A NOVEL METHOD OF PREVENTING INTRA-OPERATIVE PERIPROSTHETIC FRACTURE IN MODERN UNCEMENTED HEMIARTHROPLASTY

R Chana[1], R Mansouri[2], C Jack[1], MR Edwards[1] R Singh[3], F Khan[2]*

[1]Trauma and Orthopaedics, South East Thames Region, London, UK; [2]Trauma & Orthopaedics, Queen Elizabeth Hospital, London, UK; [3]Trauma & Orthopaedics, Lewisham Hospital, London, UK

16:42 OC27 ANALYSIS OF EX VIVO RESURFACING HIP PROSTHESES AND COMPARISON WITH CLINICAL DATA

TJ Joyce[1], D Langton[2], S Jameson[2], AVF Nargol[2]*

[1]Centre for Rehabilitation and Engineering Studies, School of Mechanical and Systems Engineering, Newcastle University, Newcastle upon Tyne, NE1 7RU, UK; [2]Joint Replacement Unit, University Hospital of North Tees, Hardwick, Stockton-on-Tees, TS19 8PE, UK

16:54 OC28 EFFECTS OF METAL IONS ON OSTEOBLAST ACTIVITY

G Mabilleau, HS Gill, A Sabokbar*

Botnar Research Centre, Nuffield Department of Orthopaedic Surgery, University of Oxford, OX3 7LD, UK

17:06 OC29 CEMENT MANTLE THICKNESS DETERMINES CEMENT PENETRATION AND STEM SUBSIDENCE IN IMPACTION GRAFTING

M Ganapathi[1], JH Kuiper[1,2], S Griffin[1], E Saweeres[1], N Graham[1]*

[1]The Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry, UK; [2]Institute for Science and Technology in Medicine, Keele University, UK

17:18 OC30 MENISECTOMY ELEVATES FRICTION AND WEAR OF ARTICULAR CARTILAGE IN THE KNEE JOINT

L McCann, E Ingham, Z Jin, J Fisher*

Institute of Medical and Biological Engineering, University of Leeds, UK

17:30 OC31 VERIFICATION OF A NOVEL SPINE WEAR SIMULATOR

RE Vicars[1], J Fisher['1], N Heyes[2], R Birrell[2], RM Hall[1]*

[1]Institute of Medical and Biological Engineering, School of Mechanical Engineering, University of Leeds, UK; [2]Simulation Solutions Ltd, Manchester, UK

17:42 OC32 SURROGATE-BONE VERTEBRAL MODELS ARE NOT APPROPRIATE FOR USE IN THE MECHANICAL ASSESSMENT OF VERTEBROPLASTY

RJ Oakland[1], N Kapur[1], J Timothy[2], T Buckland[3], RM Hall[1]*

[1]School of Mechanical Engineering, University of Leeds, UK; [2]Neurosurgery, Leeds Teaching Hospitals Trust, UK; [3]Apatech Ltd, Hertfordshire, UK

17:54 OC33 NEW TECHNIQUE OF BONE ALLOGRAFT STERILIZATION USING SUPERCRITICAL CARBON DIOXIDE MAINTAINS BONE MECHANICAL PROPERTIES: A SIGNIFICANT ADVANCE IN POTENTIAL FOR USE OF BONE ALLOGRAFT IN TRAUMA AND ORTHOPAEDIC SURGERY

LC Biant[1], R Mammucari[2], J Pham[3], WR Walsh[4], NR Foster[2], SM Bell[3]*

[1]The Royal National Orthopaedic Hospital, Stanmore, UK; [2]Department of Chemical Engineering, University of New South Wales, Sydney, Australia; [3]Department of Microbiology, Prince of Wales Hospital, Sydney, Australia; [4]Orthopaedic Research Laboratories, University of New South Wales, Sydney, Australia

20:00-midnight

Conference Dinner and Party

BARNES WALLIS BUILDING,
UNIVERSITY OF MANCHESTER

Programme
Wednesday 25 June

09:00-10:00 **ROOM C16**

SYMPOSIUM
Imaging Bone Structure: From bench to bedside

Chairmen:
Eugene McCloskey (Sheffield, UK)
James Richardson (Oswestry, UK)

09:00 IS10 BONE STRENGTH ASSESSMENT FROM MORPHOMETRY AND STRUCTURE
Judith Adams (Manchester, UK)

09:30 IS11 FINITE ELEMENT ANALYSIS (FEA) IN THE ASSESSMENT OF BONE STRENGTH
Sandra Shefelbine (London, UK)

10:00-11:00

Coffee

ATTENDED POSTERS (Odds 10:00-10:30; Evens 10:30-11:00)

11:00-12:00 **ROOM C16**

JOINT BORS/BRS ORAL POSTERS

Chairmen:
Roger Bayston (Nottingham, UK)
Mark Cooper (Birmingham, UK)

11:00 OP1 AGEING EFFECTS ON FEMORAL NECK TRABECULAR BONE: ROLE IN HIP FRACTURE
CD Thomas[1], PM Mayhew[2], JG Clement[1], N Loveridge[2], CJ Burgoyne[2], J Reeve[2]*
[1]Dental Science, Melbourne University, Australia; [2]Medicine & Engineering, Cambridge University, UK

11:05 OP2 FRICTION AS A POTENTIAL CAUSE OF PARATENONITIS
PR Landham, L Nokes, C Byrne, D Dowson, C Dent, P Theobald*
Institute of Medical Engineering & Medical Physics, Cardiff University, Cardiff, UK

11:10 OP3 AN OSTEOGENIC SCAFFOLD CARRIER FOR THE DELIVERY OF HUMAN MARROW STROMAL CELLS TO A MURINE CALVARIAL DEFECT
AJ Martin, JL Tremoleda, P Vadillo, N Khan, V Mann, BS Noble*
Musculoskeletal Tissue Engineering Collaboration, MRC Centre for Regenerative Medicine, University of Edinburgh Medical School, Edinburgh, UK

11:15 OP4 DEVELOPMENT OF A COMBINATION VACCINE AGAINST STAPHYLOCOCCAL IMPLANT-RELATED INFECTION
E Edis, BE Scammell, R Bayston*
Division of Orthopaedic and Accident Surgery, University of Nottingham, UK

11:20 OP5 TEMPORAL EXPRESSION OF PHOSPHO1 DURING CHICK LIMB BUD MESENCHYMAL CELL DIFFERENTIATION AND MINERALISATION
VE MacRae[1], MG Davey[1], S Narisawa[2], MC Yadav[2], J L Millan[2], C Farquharson[1]*
[1]Bone Biology Group, Roslin Institute, UK; [2]Burnham Institute for Medical Research, USA

11:25 OP6 CHONDROPROTECTIVE STRATEGIES: INCREASING THE OSMOLARITY OF JOINT IRRIGATING SOLUTIONS
AK Amin[1,2], JS Huntley[1], AHRW Simpson[1], AC Hall[2]*
[1]Department of Orthopaedic and Trauma Surgery, University of Edinburgh, UK; [2]Centre for Integrative Physiology, School of Biomedical Sciences, University of Edinburgh, UK

11:30 OP7 EVIDENCE FOR ADENOSINE RECEPTOR REGULATION OF OSTEOGENESIS VERSUS ADIPOGENESIS IN MESENCHYMAL STEM CELLS
B Gharibi[1,2], C Elford[1], BM Lewis[2], J Ham[2], BAJ Evans[1]*
[1]Department of Child Health, School of Medicine, Cardiff University, Heath Park, Cardiff CF14 4XN, UK; [2]Centre for Endocrinology and Diabetes Sciences, School of Medicine, Cardiff University, Heath Park, Cardiff CF14 4XN, UK

11:35 OP8 FROG GLUE ENHANCES ROTATOR CUFF REPAIR EX VIVO
NL Millar[1,2], TA Bradley[1], NA Walsh[1], IR Appleyard[1] MJ Tyler[1], GAC Murrell[1]*
[1]Orthopaedic Research Institute, St. George Hospital Campus, University of New South Wales, Sydney, Australia; [2]West of Scotland Orthopaedic Training Programme, Glasgow, UK

11:40 OP9 GLUTAMATE TRANSPORTER INHIBITORS INFLUENCE OSTEOBLAST GENE EXPRESSION
K Brakspear[1], P Parsons[2], DJ Mason[1]*
[1]School of Biosciences, Cardiff University, Cardiff, CF10 3US, UK; [2]Smith and Nephew Research Centre, York Science Park, York, YO10 5DF, UK

11:45 OP10 COMPARATIVE STUDY ON THE POTENTIAL USE OF DIFFERENT HUMAN CELL TYPES IN CARTILAGE TISSUE ENGINEERING
S Saha[1], J Kirkham[1], D Wood[1], S Curran[2], XB Yang[1]*
[1]Department of Oral Biology, University of Leeds, Leeds LS2 9LU,UK; [2]Smith & Nephew Research Centre, York Science Park, Heslington, York YO10 5DF, UK

11:50 OP11 HYPOXIA FACILITATES BONE INVASION BY INCREASING BREAST CANCER CELL EXPRESSION OF MATRIX METALLOPROTEINASE-1

KS Rankin, CH Gerrand, RL Lakey, AP Sprowson, AW McCaskie, MA Birch*
Musculoskeletal Research Group, University of Newcastle upon Tyne, UK

11:55 OP12 THE CARTILAGE MATRIX BIOLOGY OF ANTEROMEDIAL OSTEOARTHRITIS OF THE KNEE

SM McDonnell[1], R Rout[1], AP Hollander[2], IM Clark[3], DW Murray[1], HS Gill[1], PA Hulley[1], AJ Price[1]*
[1]Nuffield Department of Orthopaedic Surgery, University of Oxford, UK; [2]Academic Department of Rheumatology, University of Bristol, UK; [3]University of East Anglia, Norwich, UK

PARALLEL SESSION

12:00-12:30 **ROOM C16**

BRS ORAL POSTERS

Chairmen:
Nick Harvey (Southampton, UK)
Andy Pitsillides (London, UK)

12:00 BRS-OP1 SULFORAPHANE - A NEW THERAPY FOR MUTLIPLE MYELOMA?

RM Locklin[1], PA Hulley[1], RGG Russell[1], CM Edwards[2]*
[1]Institute of Musculoskeletal Sciences, Botnar Research Centre, Nuffield Department of Orthopaedic Surgery, University of Oxford, Oxford, UK; [2]Department of Cancer Biology, Vanderbilt University Medical Center, Nashville, Tennessee, USA

12:05 BRS-OP2 ETHNIC DIFFERENCES IN FIBROBLAST GROWTH FACTOR 23 AND PHOSPHATE EXCRETION IN RESPONSE TO PHOSPHATE LOADING

L Du[1], L Yan[1], I Schoenmakers[1], B Zhou[2], LM Jarjou[3], S Nigdikar[1], GR Goldberg[1,3], A Prentice[1,3]*
[1]MRC Human Nutrition Research, Elsie Widdowson Laboratory, Fulbourn Road, Cambridge, UK; [2]Department of Preventive Medicine, Shenyang Medical College, Shenyang, PR China; [3]MRC Keneba, The Gambia

12:10 BRS-OP3 A RANDOMIZED CONTROL TRIAL OF ONCE WEEKLY RISEDRONATE FOR PREVENTION OF BONE LOSS OBSERVED IN A SINGLE FLARE-UP OF INFLAMMATORY BOWEL DISEASE

MH Kriel[1], CSJ Probert[1], TJ Creed[2], M Lockett[3], AJ Bell[4], D Linehan[5], JH Tobias[1]*
[1]Department of Clinical Sciences at South Bristol, University of Bristol, UK; [2]Department of Gastroenterology, Bristol Royal Infirmary, Bristol, UK; [3]Department of Medicine, Frenchay Hospital, Bristol, UK; [4]Department of Medicine, Weston-Super-Mare General Hospital, Weston-Super-Mare, UK['5]Department of Medicine, Royal United Hospital, Bath, UK

12:15 BRS-OP4 BACKGROUND UVB EXPOSURE IN PREGANCY AND SKELETAL DEVELOPMENT IN CHILDHOOD

**AE Sayers[1], BJ Boucher[2], JH Tobias[1]*
[1]Academic Rhuematology, University of Bristol, UK; [2] Diabetes & Metabolic Medicine, Royal London Hospital, UK

12:20 BRS-OP5 ORAL CALCIUM SUPPLEMENTATION REVERSES THE BIOCHEMICAL PICTURE OF PARATHYROID HORMONE RESISTANCE IN UNDERPRIVILEGED INDIAN TODDLERS

M Z Mughal[1], A Khadilka[2], N Hanumante[3], M Sayyad[4], N Sanwalka[5], V Khadilkar[2], M Vaidya[6], A Joshi[3]*
[1]Saint Mary's Hospital for Women & Children, Manchester, UK; [2]Hirabai Cowasji Jehangir Medical Research Institute, Pune, India; [3]Poona Medical Foundation Research Center, Pune, India; [4]Abeda Inamdar Senior College, Pune, India; [5]Pune University, Pune, India; [6]Cummins College of Engineering, Pune, India

12:25 BRS-OP6 A RANDOMIZED CONTROLLED TRIAL OF THE EFFECTS OF VITAMIN D SUPPLEMENTATION UPON MUSCLE POWER IN ADOLESCENT GIRLS

*KA Ward*P[1], G Das[2], J Berry[1], SA Roberts[1], JE Adams[1], MZ Mughal[3]*
[1]University of Manchester, UK; [2]Central Manchester Primary Care Trust, UK; [3]Central Manchester & Manchester Children's University Hospitals NHS Trust, UK

PARALLEL SESSION

12:00-12:30 **ROOM C2**

BORS AGM

12:30-13:30

Lunch and posters

PARALLEL SESSION

13:30-14:00 **ROOM C16**

BORS ORAL POSTERS

Chairmen:
Roger Bayston (Nottingham, UK)
Mark Birch (Newcastle, UK)

13:30 BORS-OP1 IS THERE A BENEFIT FROM IMMEDIATE BROTH CULTURE OF INTRA-OPERATIVE MUSCULOSKELETAL SPECIMENS?
S Ahmad, AHRW Simpson*
[1]Department of Trauma and Orthopaedics, Royal Infirmary of Edinburgh and University of Edinburgh, UK

13:35 BORS-OP2 IN VITRO WEAR TESTS OF ORTHOPAEDIC BIOPOLYMERS WITH A VISCO-SUPPLEMENT ADDED TO THE LUBRICANT
TJ Joyce, YH Huang*
School of Mechanical and Systems Engineering, Newcastle University, Newcastle upon Tyne, UK

13:40 BORS-OP3 FUNCTIONAL OUTCOME FOLLOWING HIP RESURFACING: THE IMPORTANCE OF COMPONENT SIZE AND ACETABULAR ORIENTATION
SS Jameson, DJ Langton, AVF Nargol*
Joint Replacement Unit, University Hospital of North Tees, Hardwick, Stockton-on-Tees, UK

BORS-OP4 WITHDRAWN

13:45 BORS-OP5 INDICATIONS FOR TOTAL KNEE ARTHROPLASTY IN THE VALGUS KNEE - IS THE SIGNIFICANCE OF INSTABILITY TRULY UNDERSTOOD?
A Prasthofer, L Unitt, A Sambatakakis*
Department of Orthopaedics, Solihull Hospital, Solihull, UK

13:50 BORS-OP6 DOUBLE BUNDLE ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION USING THE CALAXO OSTEOCONDUCTIVE INTERFERENCE SCREW
A Getgood, M Kent, I McNamara, A Dickinson, H Elmadbouh, T Bhullar*
Edith Cavell Hospital, Peterborough, UK

PARALLEL SESSION

13:30-14:00 ROOM C2

BRS AGM

PARALLEL SESSION

14:00-15:00 ROOM C16

BORS SYMPOSIUM
What is new in osteoarthritis and cartilage?

Chairmen:
Bruce Caterson (Cardiff, UK)
Trudy Roach (Southampton, UK)

14:00 IS12 WHERE ARE WE NOW WITH CARTILAGE AND MENISCAL TRANSPLANTATION?
James Richardson (Oswestry, UK)

14:30 IS13 WHAT DO WE KNOW ABOUT THE PATHOAETIOLOGY OF OSTEOARTHRITIS?
Thomas Aigner (Leipzig, Germany)

PARALLEL SESSION

14:00-15:00 ROOM C2

BRS SYMPOSIUM
New concepts in Vitamin D

Chairmen:
Richard Keen (London, UK)
Zulf Mughal (Manchester, UK)

14:00 IS14 VITAMIN D AND BONE: ENDOCRINOLOGY AND AUTO/PARACRINOLOGY
Hans van Leeuwen (Rotterdam, Netherlands)

14:30 IS15 NON-SKELETAL EFFECTS OF VITAMIN D
Kay Colston (London, UK)

15:10-16:10 **ROOM C16**

ORAL COMMUNICATIONS (joint BRS/BORS)

Chairmen:
Miep Helfrich (Aberdeen, UK)
Brigitte Scammell (Nottingham, UK)

15:10 OC34 POLYURETHANE MICROARRAYS: A NOVEL PLATFORM FOR SELECTION OF SKELETAL OSTEOPROGENITORS FROM HUMAN BONE MARROW
RS Tare[1], F Khan[2], G Tourniaire[2], SM Morgan[1], M Bradley[2], ROC Oreffo[1]*
[1]Bone and Joint Research Group, Centre for Human Development, Stem Cells and Regeneration, Institute of Developmental Sciences, University of Southampton, Southampton SO16 6YD, UK; [2]School of Chemistry, University of Edinburgh, Edinburgh EH9 3JJ, UK

15:22 OC35 CHONDROITIN SULPHATE SULPHATION MOTIFS AS SPECIFIC COMPONENTS OF THE STEM/PROGENITOR CELL NICHE IN MUSCULOSKELETAL TISSUES

B Caterson, AJ Hayes, D Tudor, MA Nowell, CE Hughes*

School of Biosciences, Cardiff University, UK

15:34 OC36 BREAKING AN EGGSHELL: AGE-RELATED THINNING OF THE FEMORAL NECK CORTEX IN-VIVO (THE 100 WOMEN STUDY)

KES Poole[1], CM Rose[1], PM Mayhew[1], JK Brown[2], P Bearcroft[3], N Loveridge[1], J Reeve[1]*

[1]Department of Medicine, University of Cambridge, UK; [2]Mindways Software Inc., Austin, USA; [3]Department of Radiology, University of Cambridge, UK

15:46 OC37 THE EPITOPE PROFILE AND ADIPOGENIC DIFFERENTIATION OF INFRAPATELLAR FAT PAD DERIVED STEM CELLS AND POTENTIAL CLINICAL APPLICATIONS

WS Khan[1], S Anand[2], S Tew[1], DS Johnson[2], JG Andrew[1], TE Hardingham[1]*

[1]UK Centre for Tissue Engineering and Wellcome Trust Centre for Cell Matrix Research, University of Manchester, M13 9PT, UK; [2]Stockport NHS Foundation Trust, Stepping Hill Hospital, Poplar Grove, Stockport, SK2 7JE, UK

15:58 OC38 TIMING OF FIRST INFUSION OF ZOLEDRONIC ACID 5 MG AFTER RECENT HIP FRACTURE AFFECTS ANTIFRACTURE EFFICACY AND REDUCTION OF MORTALITY

M Stone[1], EF Eriksen[2], KW Lyles[3], CS Colon-Emeric[3], CF Pieper[3], JS Magaziner[4], JD Adachi[5], L Hyldstrup[6], L Nordsletten[7], S Boonen[8], P Mesenbrink[9], DM Reid[10], J Wass[11], E Dennison[12], GD Summers[13], A McLellan[14]*

[1]Llandough Hospital, Cardiff, UK; [2]Novartis Pharma AG, Basel, Switzerland; [3]Duke University Medical Center, VAMC, Durham, NC, US; [4]Univ Maryland, Baltimore, MD, US; [5]McMaster University, Hamilton, ON, Canada; [6]Hvidovre Hospital, Hvidovre, Finland; [7]Ulleval University Hospital, Oslo, Norway; [8]Katholieke Universiteit Leuven, Leuven, Belgium; [9]Novartis Pharmaceuticals Corp, East Hanover, NJ, US; [10]University of Aberdeen, Aberdeen, UK; [11]Nuffield Orthopaedic Centre, Oxford, UK; [12]Southampton General Hospital, Southampton, UK; [13]Derbyshire Royal Infirmary, Derbyshire, UK; [14]Western Infirmary, Glasgow, UK

16:10-16:25 **ROOM C16**

Awards

Chairmen:
Cyrus Cooper (Southampton, UK)
Brigitte Scammell (Nottingham, UK)

16:25

END OF MEETING

Posters

Oral Posters - Joint sessions

OP1 AGEING EFFECTS ON FEMORAL NECK TRABECULAR BONE: ROLE IN HIP FRACTURE
CD Thomas[1], PM Mayhew[2], JG Clement[1], N Loveridge[2], C J Burgoyne[2], J Reeve[2]*
[1]Dental Science, Melbourne University, Australia;[2]Medicine & Engineering, Cambridge University, UK

OP2 FRICTION AS A POTENTIAL CAUSE OF PARATENONITIS
PR Landham, L Nokes, C Byrne, D Dowson, C Dent, P Theobald*
Institute of Medical Engineering & Medical Physics, Cardiff University, Cardiff, UK

OP3 AN OSTEOGENIC SCAFFOLD CARRIER FOR THE DELIVERY OF HUMAN MARROW STROMAL CELLS TO A MURINE CALVARIAL DEFECT
AJ Martin, JL Tremoleda, P Vadillo, N Khan, V Mann, BS Noble*
Musculoskeletal Tissue Engineering Collaboration, MRC Centre for Regenerative Medicine, University of Edinburgh Medical School, Edinburgh, UK

OP4 DEVELOPMENT OF A COMBINATION VACCINE AGAINST STAPHYLOCOCCAL IMPLANT-RELATED INFECTION
E Edis, BE Scammell, R Bayston*
Division of Orthopaedic and Accident Surgery, University of Nottingham, UK

OP5 TEMPORAL EXPRESSION OF PHOSPHO1 DURING CHICK LIMB BUD MESENCHYMAL CELL DIFFERENTIATION AND MINERALISATION
VE MacRae[1], MG Davey[1], S Narisawa[2], MC Yadav[2], J L Millan[2], C Farquharson[1]*
[1]Bone Biology Group, Roslin Institute, UK;[2]Burnham Institute for Medical Research, USA

OP6 CHONDROPROTECTIVE STRATEGIES: INCREASING THE OSMOLARITY OF JOINT IRRIGATING SOLUTIONS
AK Amin[1,2], JS Huntley[1], AHRW Simpson[1], AC Hall[2]*
[1]Department of Orthopaedic and Trauma Surgery, University of Edinburgh, UK;[2]Centre for Integrative Physiology, School of Biomedical Sciences, University of Edinburgh, UK

OP7 EVIDENCE FOR ADENOSINE RECEPTOR REGULATION OF OSTEOGENESIS VERSUS ADIPOGENESIS IN MESENCHYMAL STEM CELLS
B Gharibi[1,2], C Elford[1], BM Lewis[2], J Ham[2], BAJ Evans[1]*
[1]Department of Child Health, School of Medicine, Cardiff University, Heath Park, Cardiff CF 14 4XN, UK;[2]Centre for Endocrinology and Diabetes Sciences, School of Medicine, Cardiff University, Heath Park, Cardiff CF 14 4XN, UK

OP8 FROG GLUE ENHANCES ROTATOR CUFF REPAIR EX VIVO
NL Millar[1,2], TA Bradley[1], NA Walsh[1], IR Appleyard[1] MJ Tyler[1], GAC Murrell[1]*
[1]Orthopaedic Research Institute, St. George Hospital Campus, University of New South Wales, Sydney, Australia;['2]West of Scotland Orthopaedic Training Programme, Glasgow, UK

OP9 GLUTAMATE TRANSPORTER INHIBITORS INFLUENCE OSTEOBLAST GENE EXPRESSION
K Brakspear[1], P Parsons[2], DJ Mason[1]*
[1]School of Biosciences, Cardiff University, Cardiff, CF10 3US, UK;[2]Smith and Nephew Research Centre, York Science Park, York, YO10 5DF, UK

OP10 COMPARATIVE STUDY ON THE POTENTIAL USE OF DIFFERENT HUMAN CELL TYPES IN CARTILAGE TISSUE ENGINEERING
S Saha[1], J Kirkham[1], D Wood[1], S Curran[2], XB Yang[1]*
[1]Department of Oral Biology, University of Leeds, Leeds LS2 9LU,UK;[2]Smith & Nephew Research Centre, York Science Park, Heslington, York YO10 5DF,UK

OP11 HYPOXIA FACILITATES BONE INVASION BY INCREASING BREAST CANCER CELL EXPRESSION OF MATRIX METALLOPROTEINASE-1
KS Rankin, CH Gerrand, RL Lakey, AP Sprowson, AW McCaskie, MA Birch*
Musculoskeletal Research Group, University of Newcastle upon Tyne, UK

OP12 THE CARTILAGE MATRIX BIOLOGY OF ANTEROMEDIAL OSTEOARTHRITIS OF THE KNEE
S M McDonnell[1], R Rout[1], A P Hollander[2], I M Clark[3], R Davidson[3], T Simms[2], D W Murray[1], H S Gill[1], P A Hulley[1], A J Price[1]*
[1]Nuffield Department of Orthopaedic Surgery, University of Oxford, UK;[2]Academic Department of Rheumatology, University of Bristol, UK;[3]University of East Anglia, Norwich, UK

Oral Posters - BORS

BORS-OP1 IS THERE A BENEFIT FROM IMMEDIATE BROTH CULTURE OF INTRA-OPERATIVE MUSCULOSKELETAL SPECIMENS?
S Ahmad, AHRW Simpson*
[1]Department of Trauma and Orthopaedics, Royal Infirmary of Edinburgh and University of Edinburgh, UK

BORS-OP2 IN VITRO WEAR TESTS OF ORTHOPAEDIC BIOPOLYMERS WITH A VISCO-SUPPLEMENT ADDED TO THE LUBRICANT
TJ Joyce, YH Huang*
School of Mechanical and Systems Engineering, Newcastle University, Newcastle upon Tyne, UK

BORS-OP3 FUNCTIONAL OUTCOME FOLLOWING HIP RESURFACING: THE IMPORTANCE OF COMPONENT SIZE AND ACETABULAR ORIENTATION
SS Jameson, DJ Langton, AVF Nargol*
Joint Replacement Unit, University Hospital of North Tees, Hardwick, Stockton-on-Tees, UK

BORS-OP4 *Withdrawn*

BORS-OP5 INDICATIONS FOR TOTAL KNEE ARTHROPLASTY IN THE VALGUS KNEE- IS THE SIGNIFICANCE OF INSTABILITY TRULY UNDERSTOOD?
A Prasthofer, L Unitt, A Sambatakakis*
Department of Orthopaedics, Solihull Hospital, Solihull, UK

BORS-OP6 DOUBLE BUNDLE ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION USING THE CALAXO OSTEOCONDUCTIVE INTERFERENCE SCREW
A Getgood, M Kent, I McNamara, A Dickinson, H Elmadbouh, T Bhullar*
Edith Cavell Hospital, Peterborough, UK

Posters - BORS

BORS-P01 A KINEMATIC ASSESSMENT OF NORMAL ELBOW MOVEMENT IN ACTIVITIES OF MODERN DAY LIVING
A Sinha[1], J Moorehead[2], V Bhalaik[1], P Brownson[1]*
[1]Department of Orthopaedics, Royal Liverpool and Broadgreen University Hospital, Liverpool, UK;[2]Department of Orthopaedics, University Hospital Aintree, Liverpool, UK

BORS-P02 A MURINE MODEL OF INTERNAL PLATE FIXATION
T Savaridas, AY Muir, MS Gaston, BS Noble, AHRW Simpson*
Musculoskeletal Tissue Engineering Collaboration, The University of Edinburgh, UK

BORS-P03 A NEW WAY TO DRILL ACL TUNNELS
A Karim[1], J Thomas[1], NP Thomas[2], G Puddu[1], AA Amis[1]*
[1]Imperial College London, UK['2]North Hampshire Hospital, UK

BORS-P04 A PILOT STUDY OF THE MECHANICAL BEHAVIOUR OF SPINAL METASTASES PRE- AND POST-VERTEBROPLASTY
RJ Oakland[1], NR Furtado[1], J Timothy[2], RM Hall[1]*
[1]School of Mechanical Engineering, University of Leeds, UK;[2]Neurosurgery, Leeds Teaching Hospitals Trust, UK

BORS-P05 A PRELIMINARY CADAVERIC STUDY INVESTIGATING THE BIOMECHANICAL EFFECTIVENESS OF PROPHYLACTIC VERTEBRAL AUGMENTATION ADJACENT TO VERTEBROPLASTY UNDER CYCLIC LOADING
RJ Oakland[1], NR Furtado[1], RK Wilcox[1], J Timothy[2], RM Hall[1]*
[1]School of Mechanical Engineering, University of Leeds, UK;[2]Neurosurgery, Leeds Teaching Hospitals Trust, UK

BORS-P06 A ROLE FOR MEMBRANE TRANSPORT PROTEINS IN GROWTH PLATE CHONDROCYTE HYPERTROPHY; AN IMMUNOHISTOCHEMICAL STUDY
PG Bush, AC Hall*
Centre for Integrative Physiology, University of Edinburgh, UK

BORS-P07 ANTHROPOMETRIC MEASUREMENTS OF KNEE JOINT IN INDIAN POPULATION: CO-RELATION WITH CURRENT KNEE ARTHROPLASTY SYSTEMS
VB Bagaria[1], NS Harshavardhana[2], VR Sapre[1], AS Chadda[1]*
[1]NIIDAN Orthopaedic Centre, Nagpur, INDIA;[2]Queen's Medical Centre, Nottingham, UK

BORS-P08 ARTHROPLASTY FOR POST TRAUMATIC OSTEOARTHRITIS OF THE INDEX FINGER METACARPOPHALANGEAL JOINT IN YOUNG INDIVIDUAL
J Velpula, V Gupta, M Madhu, D Cohen, L Sanz, A Abraham, A Muhamad, M Waseem*
Macclesfield District General Hospital, Macclesfield, UK

BORS-P09 AUDIT AND RE-AUDIT OF THE USE OF BONE PROTECTION TREATMENT IN ELDERLY PATIENTS WHO ATTENDED WITH FALLS IN HULL ROYAL INFIRMARY
MM Lynn,VM Konala, RK Bachuwar, MH Khan*
Department of Medicine for Elderly, Hull Royal Infirmary, East Yorkshire, UK

BORS-P10 *Withdrawn*

BORS-P11 BIOMECHANICAL EVALUATION OF CEMENT-IN-CEMENT INTERFACE IN HIP REVISION SURGERY
G Rudol[1], R Wilcox[2], E Tsiridis[3]*
[1]Academic Department of Trauma and Orthopaedics, School of Medicine, University of Leeds, Leeds, UK;[2]Institute of Medical and Biological Engineering, University of Leeds, Leeds, UK;[3]School of Mechanical Engineering, University of Leeds, Leeds, UK

BORS-P12 BONE AND JOINT CIRCULATION REVISITED
*MC Beverly**
Ealing Hospital, Middx UB1 3HW, UK

BORS-P13 BONE MORPHOGENETIC PROTEINS 1 TO 7 IN HUMAN BREAST CARCINOMAS EXPRESSION PATTERN AND CLINICAL AND PROGNOSTIC RELEVANCE
SR Davies[1], G Watkins[2], A Douglas-Jones[2], RE Mansel[2], WG Jiang[2]*
[1]Department of Orthopaedics, University Hospital of Wales, Cardiff, UK;[2]Metastasis and Angiogenesis Research Group, Department of Surgery, University Hospital of Wales,Cardiff, UK

BORS-P14 CHONDROCYTE DEATH IN MECHANICALLY INJURED ARTICULAR CARTILAGE - THE INFLUENCE OF EXTRACELLULAR CALCIUM
AK Amin[1,2], JS Huntley[1], PG Bush[2], AHRW Simpson[1], AC Hall[2]*
[1]Department of Orthopaedic and Trauma Surgery, University of Edinburgh, UK;[2]Centre for Integrative Physiology, School of Biomedical Sciences, University of Edinburgh, UK

BORS-P15 CHROMIUM, COBALT AND TITANIUM METALLOSIS FOLLOWING A FAILING NOTTINGHAM SHOULDER REPLACEMENT
WS Khan[1], M Agarwal[2], AG Cox[3], J Denton[1], EM Holt[2]*
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BORS-P16 COMPARISON BETWEEN CLOSED WOUND DRAINAGE AND NO DRAINAGE IN TOTAL KNEE ARTHROPLASTY
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BORS-P17 CORELATION OF PERIOPERATIVE FRACTURES OF THE FEMUR & TIBIA IN COMPUTER ASSISTED TOTAL KNEE ARTHROPLASTY WITH RIGID BODY TRAJECTORY
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BORS-P18 *Withdrawn*

BORS-P19 DETERMINING HUMAN SKELETAL MUSCLE VOLUME USING 3D FREEHAND ULTRASOUND
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BORS-P20 *Withdrawn*

BORS-P21 DOES ECHOCARDIOGRAPHIC CARDIAC FUNCTION CORRELATE WITH FRACTURED NECK OF FEMUR OUTCOME?
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BORS-P22 DOES THE RATE OF DEFORMATION AFFECT THE MECHANICAL RESPONSE OF DURA MATER?
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BORS-P23 *Withdrawn*

BORS-P24 ELEMENTAL ANALYSIS OF PERIPROSTHETIC TISSUES BY LA-ICP-MS AND ICP-MS
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BORS-P25 ENHANCED OSTEOBLASTIC DIFFERENTIATION BY STROMAL CELL-DERIVED FACTOR-1 IN HUMAN MESENCHYMAL STEM CELLS
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BORS-P26 ENHANCING THE WOUND COVERAGE DURING BONE TRANSPORT FOR INFECTED NON UNION OF TIBIA: REPORT OF A SIMPLE TECHNIQUE
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BORS-P27 FACTORS AFFECTING PULLOUT STRENGTH OF CANNULATED CANCELLOUS BONE SCREWS
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BORS-P28 *Withdrawn*

BORS-P29 FEMORAL CANAL PREPARATION AND INTRAMEDULLARY PRESSURE - BROACH DESIGN CONSIDERATIONS
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BORS-P30 FEMORAL SUBTROCHANTERIC FRACTURE AND LONG-TERM BISPHOSPHONATE THERAPY: IS THERE AN ASSOCIATION?
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BORS-P31 FLUID SHEAR STRESSES IN FLEXCELL(TM) DEVICE
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BORS-P32 HEALING OF A SEGMENTAL BONE DEFECT USING TRUFIT SCAFFOLD - RHBMP-2 CONSTRUCTS
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BORS-P33 *Withdrawn*

BORS-P34 INFLUENCE OF BONE QUALITY IN THE STABILITY OF IMPLANT FIXATION
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BORS-P35 INTERVERTEBRAL DISC DEFECT FOLLOWING COLLAGENASE ENZYME INJECTION: AN EXPERIMENTAL STUDY IN BOVINE COCCYGEAL INTERVERTEBRAL DISC
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BORS-P36 LEARNING FROM THE DEAR ANTLER MODEL: USING LAMININ-5 TO SEAL SKIN TO TRANSCUTANEOUS ORTHOPAEDIC IMPLANTS
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BORS-P37 LEWINNEK'S SAFE ZONE AND INCIDENCE OF DISLOCATION AFTER COMPUTER-ASSISTED POSITIONING OF THE ACETABULAR CUP FOR TOTAL HIP ARTHROPLASTY BASED ON JOINT KINEMATICS
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BORS-P38 MENISCAL SUTURE WITH ACL RECONSTRUCTION: LONG TERM OUTCOME
A Karim, JRD Murray, H Pandit, F Wandless, NP Thomas*
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BORS-P39 MICRO-CT VOLUME MEASUREMENT FOR WEAR SIMULATION
RE Vicars, J Fisher, RM Hall*
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BORS-P40 MICROMECHANICAL CHARACTERISATION OF SOFT TISSUE: NEW TEXTURE METHOD AND PRELIMINARY RESULTS
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BORS-P41 MODULAR ENDOPROSTHETIC RECONSTRUCTION FOR INFECTED RE-REVISION PROSTHESIS : INITIAL EXPERIENCE
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BORS-P42 NEW METHOD OF SCOLIOSIS DEFORMITY ASSESSMENT: ISIS 2 SYSTEM
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BORS-P43 OSTEOARTHRITIS HISTOPATHOLOGY SCORING SYSTEMS
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BORS-P44 OUR ORTHOGERIATRIC PATHWAY SO FAR FOR FRACTURED NECK OF FEMUR PATIENTS
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BORS-P45 PEDOBAROGRAPHIC ASSESSMENT FOLLOWING RUPTURE OF THE TENDO ACHILLIS
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BORS-P46 PHYSIOLOGICAL FREE BOUNDARY CONDITION MUSCULO-SKELETAL MODELLING OF THE PELVIS AND FEMUR
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BORS-P47 PLATELET RICH CONCENTRATE AND BONE FORMATION: INTERACTION OF PLATELET RICH CONCENTRATE WITH BONE GRAFT MATERIALS
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BORS-P48 PROTECTION OF THE BONE WITH A SKELETALLY-ATTACHED PROSTHESIS FOR TRANSFEMORAL AMPUTATION
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BORS-P49 QUANTITATIVE DENSITY INFORMATION WITH COMPUTED RADIOGRAPHY
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BORS-P50 RAPID PROTOTYPING TECHNOLOGY (RPT) FOR SPINAL DEFORMITY: A CASE REPORT
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BORS-P51 RECONSTRUCTION OF POSTERO-LATERAL INSTABILITY OF THE ELBOW WITH FCR GRAFT -A PROSPECTIVE STUDY
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BORS-P52 REDUCING EXPOSURE TO METAL IONS FOLLOWING HIP RESURFACING: THE IMPORTANCE OF ACETABULAR ORIENTATION
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BORS-P53 REFINEMENT OF THE CLINICAL INDICATIONS FOR DYNAMIC NEUTRALISATION SYSTEM FOR THE SPINE FOR THE TREATMENT OF BACKPAIN
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BORS-P54 RESULTS OF METAL ON METAL HIP ARTHROPLASTY IN PATIENTS YOUNGER THAN 40 YEARS
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BORS-P55 ROLE OF TRIPOLAR HIP WITH CONSTRAINED ACETABULAR INSERT IN REVISION ARTHROPLASTY: EARLY RESULTS
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BORS-P56 SEPTIC ARTHRITIS OF NATIVE HIP JOINTS: GIRDLESTONE AND BEYOND
BJF Dean, PC Matthews, K Medagoda, BL Atkins, AR Berendt, I Byren*
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BORS-P57 STAPHYLOCOCCAL BINDING TO BONE: FURTHER UNDERSTANDING OF THE BONE SIALOPROTEIN - BINDING PROTEIN AND SDR PROTEINS
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BORS-P58 STATISTICAL ANALYSIS OF PELVIC GEOMETRY
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BORS-P59 SUBCHONDRAL BONE OSTEOBLASTS CAN INDUCE CHONDROCYTE MINERALIZATION DURING OSTEOARTHRITIS AND THIS PROCESS IS RELEVANT TO CARTILAGE DEGRADATION
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BORS-P60 THE COMPRESSIVE PROPERTIES AND FRACTURE TOUGHNESS OF PMMA CEMENT REINFORCED WITH GLASS FLAKE
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BORS-P61 THE CORRECTION OF THE INTERMETATARSAL ANGLE FOLLOWING FUSION OF THE FIRST METATARSOPHALANGEAL JOINT : WHAT CAN WE EXPECT?
SKV Pydah, EM Toh, A Sinha, SP Sirikonda, CR Walker*
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BORS-P62 THE EFFECT UPON STANDING LOAD DISTRIBUTIONS WITH LEG LENGTH DISCREPANCY
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BORS-P63 THE EFFECTS OF CISPLATIN AND DOXORUBICIN ON ADULT AND IMMATURE RAT SKELETON
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BORS-P64 THE IMPACT OF BONE FRAGMENT DIMENSIONS ON A VERTEBRAL TRAUMA
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BORS-P65 THE M2 DASH- MANCHESTER-MODIFIED DISABILITIES OF ARM SHOULDER AND HAND SCORE
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BORS-P66 THE STABILITY OF A PIN IMPLANT IN AN OVARECTOMISED RAT MODEL
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BORS-P67 UPPER GI-TRACT ENDOSCOPY RESULTS IN PATIENTS WITH ABDOMINAL SIDE EFFECTS ACCOMPANYING BISPHISPHONATE AND STRONTIUMM RANELATE THERAPY
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BORS-P68 USE OF NAVIGATION SYSTEM FOR INTRA-OPERATIVE EVALUATION OF ACCURATE PLACEMENT OF BONE TUNNELS IN RECONSTRUCTION OF THE ANTERIOR CRUCIATE LIGAMENT
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BORS-P69 VERTEBRAL FRACTURE ASSESSMENT (USING DXA) IS A PRECISE METHOD OF MEASURING INTERVERTEBRAL DISC HEIGHT
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BRS-OP1 SULFORAPHANE - A NEW THERAPY FOR MUTLIPLE MYELOMA?
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BRS-OP2 ETHNIC DIFFERENCES IN FIBROBLAST GROWTH FACTOR 23 AND PHOSPHATE EXCRETION IN RESPONSE TO PHOSPHATE LOADING
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BRS-OP3 A RANDOMIZED CONTROL TRIAL OF ONCE WEEKLY RISEDRONATE FOR PREVENTION OF BONE LOSS OBSERVED IN A SINGLE FLARE-UP OF INFLAMMATORY BOWEL DISEASE
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BRS-OP4 *Withdrawn*

BRS-OP5 ORAL CALCIUM SUPPLEMENTATION REVERSES THE BIOCHEMICAL PICTURE OF PARATHYROID HORMONE RESISTANCE IN UNDERPRIVILEGED INDIAN TODDLERS
M Z Mughal[1], A Khadilka[2], N Hanumante[3], M Sayyad[4], N Sanwalka[5], V Khadilkar[2], M Vaidya[6], A Joshi[3]*
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BRS-OP6 A RANDOMIZED CONTROLLED TRIAL OF THE EFFECTS OF VITAMIN D SUPPLEMENTATION UPON MUSCLE POWER IN ADOLESCENT GIRLS
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BRS-P01 3D FINITE ELEMENT ANALYSIS OF X-RAY IMAGES FOR BONE STRENGTH ASSESSMENT
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BRS-P02 A COMPUTATIONAL MODEL RELATING 2D CELL SPREADING TO 3D SCAFFOLD COLONIZATION FOR SKELETAL TISSUE REGENERATION
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BRS-P03 A LONGITUDINAL STUDY OF CHANGES IN BONE MASS IN WOMEN WITH INFLAMMATORY ARTHRITIS USING DIGITAL X-RAY RADIOGRAMMETRY : RESULTS FROM THE NORFOLK ARTHRITIS REGISTER (NOAR)
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BRS-P04 A NOVEL IN VITRO MODEL OF OSTEOARTHRITIS FACILITATES IMPROVED UNDERSTANDING OF HUMAN ARTICULAR CHONDROCYTE BEHAVIOUR
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BRS-P05 A RETROSPECTIVE AUDIT OF THE USE OF PAMIDRONATE FOR FIBROUS DYSPLASIA
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BRS-P06 ASSAY PERFORMANCE AND SAMPLE EVALUATION FOR RAT/MOUSE PINP ENZYMEIMMUNOASSAY
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BRS-P07 ASSOCIATION BETWEEN RISK FACTORS FOR CARDIOVASCULAR DISEASE (CVD)AND BONE MINERAL DENSITY (BMD) IN POST-MENOPAUSAL OSTEOPOROSIS
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BRS-P08 ATP RELEASE FROM OSTEOBLASTS IS INCREASED IN RESPONSE TO MECHANICAL LOADING BY DIFFERENT AMOUNTS WHEN GROWN IN STANDARD MONOLAYER AND NOVEL 3D SCAFFOLDS

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BRS-P09 AUTOMATED SYSTEM FOR MEASUREMENT OF CONDUCTIVITY AND ITS USE AS AN ALTERNATIVE TO CREATININE FOR CORRECTION OF URINARY N-TELOPEPTIDE LEVELS

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BRS-P10 AUTOPHAGY IN OSTEOCLASTS: A POSSIBLE ROLE IN THE PATHOGENESIS OF PAGET'S DISEASE OF BONE

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BRS-P11 BONE MARROW DERIVED MESENCHYMAL STEM CELLS EXPRESS PERICYTE MARKERS IN CULTURE AND SHOW ENHANCED CHONDROGENESIS IN HYPOXIC CONDITIONS

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BRS-P12 BONE MARROW LEVELS OF 25 HYDROXY VITAMIN D ARE NOT DEPRESSED IN CASES OF HIP FRACTURE COMPARED TO CONTROLS

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BRS-P13 BONE SUBSTITUTES: ARE THEY USEFUL AS AN ADJUNCT FOR FRACTURE HEALING

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BRS-P14 BONE TISSUE STRUCTURE AND FUNCTIONING IN POSTMENOPAUSAL WOMEN ENGAGED IN VARIOUS PHYSICAL EXERCISES

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BRS-P15 CAN FALL RISK BE INCORPORATED INTO FRACTURE RISK ASSESSMENT ALGORITHMS?: A PILOT STUDY OF RESPONSIVENESS TO BISPHOSPHONATES

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BRS-P16 CELL MODIFICATION IN 3D: OSTEOGENIC STIMULATION OF HBMSC AFTER HYDROXYAPATITE COATING IN THE ABSENCE OF CHEMICAL CUES

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BRS-P17 CERAMIDE: A NOVEL MEDIATOR OF OSTEOBLAST CELL DEATH

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BRS-P18 CHARACTERISATION OF AN ANTIGEN SPECIFIC TO THE GOLGI APPARATUS OF BONE CELLS

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BRS-P19 CHARACTERISATION, OSTEOGENIC POTENTIAL AND CLINICAL PERFORMANCE OF A SOUTH CHINA SEA CORALLINE HYDROXYAPATITE/CALCIUM CARBONATE

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BRS-P20 COMPUTER AIDED DIAGNOSIS OF OSTEOPOROTIC VERTEBRAL FRACTURE USING APPEARANCE MODELS AND AN AUTOMATIC SEGMENTATION

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BRS-P21 CREATION OF A 3D SHAPE FOR THE PROXIMAL FEMUR FROM A SINGLE 2D RADIOGRAPHIC IMAGE

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BRS-P22 DETERMINANTS OF SERUM FIBROBLAST GROWTH FACTOR-23 (FGF-23) IN CHRONIC KIDNEY DISEASE

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BRS-P23 DIFFERENTIAL EFFECTS OF GLUCOCORTICOIDS ON FIBROBLASTS: MECHANISMS UNDERLYING THE ADVERSE EFFECTS OF THERAPEUTIC STEROIDS

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BRS-P24 DIFFERENTIATION FATES OF HUMAN MESENCHYMAL STEM CELLS IN IMMUNOCOMPROMISED MICE

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BRS-P25 E11 AND RHOA SIGNALLING DURING OSTEOCYTOGENESIS

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BRS-P26 FEMORAL NECK CUT HEIGHT IN THOMPSON HEMIARTHOPLASTY SURGERY

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BRS-P27 FGF-SIGNALLING AS A REGULATOR OF THE TRANSFORMED STATE OF OSTEOSARCOMA CELLS

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BRS-P28 HIGHLY CONTROLLED SURFACE PRESENTATION OF PROTEIN SIGNALLING MOTIFS TO REGULATE BONE FORMATION

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BRS-P29 HUMAN FETAL PROGENITOR CELL RESPONSE TO OSTEOGENIC GROWTH FACTORS AND SERUM-FREE MEDIUM: A CELLULAR MODEL FOR SKELETAL DIFFERENTIATION

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BRS-P30 HYPOXIA INDUCED DEATH PATHWAYS IN HUMAN TENOCYTES

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BRS-P31 IMPLANTATION OF CELL MICRO-PELLETS DERIVED FROM HUMAN EMBRYONIC AND ADULT STROMAL STEM CELLS INTO AN ARTICULAR CHONDRAL DEFECT IN THE RAT KNEE JOINT

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BRS-P32 IN VITRO BONE GROWTH RESPONDS TO TISSUE-LEVEL MECHANICAL STRAIN IN THREE-DIMENSIONAL POLYMER SCAFFOLDS

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BRS-P33 INFLUENCE OF 25-HYDROXYVITAMIN D ON BONE HEALTH: RESULTS FROM THE EUROPEAN MALE AGEING STUDY (EMAS)

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BRS-P34 KERATIN 18 IS UPREGULATED IN CELLS FROM PAGETIC LESIONS AND AFFECTS GENE EXPRESSION IN HUMAN OSTEOBLASTS

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Posters

BRS-P35 LOVASTATIN MODULATES CHONDROCYTE CELL CYCLE AND MATRIX OUTPUT
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BRS-P36 MUTATIONS IN RANK ASSOCIATED WITH PAGETIC DISEASES CAUSE LACK OF SIGNAL PEPTIDE CLEAVAGE AND FORMATION OF ORGANISED SMOOTH ER WHEN OVEREXPRESSED IN OSTEOCLASTS
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BRS-P37 OSTEOBLAST MATURITY DICTATES RESPONSE TO VASCULAR ENDOTHELIAL GROWTH FACTOR
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BRS-P38 OSTEOBLAST-LIKE CELLS WITH THE LRP5 GAIN OF FUNCTION MUTATION SHOW GENDER-RELATED DIFFERENCES IN BASAL PROLIFERATION BUT NO ENHANCED RESPONSE TO MECHANICAL STRAIN
B Javaheri, A Sunters, G Zaman, RFL Suswillo, LE Lanyon, J Price*
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BRS-P39 OSTEOCALCIN AS A PROGNOSTIC INDICATOR FOR BONE METASTASIS IN DUCTAL BREAST CANCER
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BRS-P40 OSTEOCYTES HAVE MORE CAVEOLAE THAN OSTEOBLASTS
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BRS-P41 OSTEOCYTES REPAIR PLASMA MEMBRANE DISRUPTION FOLLOWING PHYSICAL INJURY IN VITRO
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BRS-P42 PERSISTENCE OF FUNCTIONAL HUMAN OSTEOGENIC STEM CELLS FOLLOWING IN VIVO IMPLANTATION IN A RAT CALVARIAL LESION
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BRS-P43 PLATELET-DERIVED GROWTH FACTOR STIMULATES OSTEOPROTEGERIN PRODUCTION IN OSTEOBLASTIC CELLS
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BRS-P44 PODOSOME BELTS CORRELATE WITH RESORPTIVE ACTIVITY BY OSTEOCLASTS ON PLASTIC
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BRS-P45 PRIMARY HUMAN OSTEOBLASTS CONTAIN A GREATER NUMBER OF K2P CHANNELS THAN OSTEOSARCOMA CELL LINES
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BRS-P46 PROTEOMIC IDENTIFICATION OF PRENYLATED RAB/SMALL GTPASE PROTEINS IN HUMAN OSTEOCLASTS
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BRS-P47 STIFF WRISTS DO BADLY - WHAT DETERMINES RATE OF RECOVERY OF GRIP STRENGTH AFTER DISTAL RADIAL FRACTURE?
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BRS-P48 STRUCTURAL-FUNCTIONAL BONE STATE OF THE POSTMENOPAUSAL WOMEN WITH VERTEBRAL FRACTURES
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BRS-P49 TEMPORAL RELEASE OF ENCAPSULATED OSTEOGENIC AND ANGIOGENIC FACTORS FROM BIODEGRADABLE POLYMER SCAFFOLDS ENHANCE HUMAN BONE MARROW STROMAL CELL BONE REGENERATION
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BRS-P50 THE EFFECT OF TRAINING STATUS ON THE METABOLIC RESPONSE OF BONE TO EXHAUSTIVE RUNNING EXERCISE
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BRS-P51 THE EFFECTS OF RECOMBINANT HUMAN GROWTH HORMONE (RHGH) AND INSULIN-LIKE GROWTH FACTOR-I (RHIGF-I) ON HUMAN OSTEOCLASTS

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BRS-P52 *Withdrawn*

BRS-P53 THE MOLECULAR RESPONSE OF HUMAN BONE TO MECHANICAL STIMULATION

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BRS-P54 THE POTENTIAL INHIBITORY ROLE OF SUPRESSOR OF CYTOKINE SIGNALLING-2 IN CHONDROCYTE GH/IGF-1 SIGNALLING VIA THE JAK/STAT PATHWAY

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BRS-P55 THE RELATIONSHIP BETWEEN MUSCLE STRENGTH MEASUREMENTS AND BONE IN YOUNG ADULT MALES

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BRS-P56 THRESHOLDS FOR THE MEASUREMENT OF CORTICAL THICKNESS IN-VIVO USING COMPUTED TOMOGRAPHY (THE 100 WOMEN STUDY)

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BRS-P57 ULTRASTRUCTURAL EXAMINTAION OF COLLAGEN FROM ALKAPTONURIC TISSUE PROVIDES CLUES TO PATHOGENESIS OF OCHRONOSIS

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Abstracts

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IS01
THE NATIONAL HIP FRACTURE DATABASE

Robert Wakeman

The National Hip Fracture Database (NHFD) is a Joint Initiative of the British Geriatrics Society and the British Orthopaedic Association. Hip fracture has long been recognized as a tracer for the care of frail elderly patients needing urgent surgical intervention. Regional audits, Department of Health Performance Indicators and the Royal College of Physicians Falls and Bone Health Audit all show wide variations in practice and outcomes. The purpose of the NHFD is to provide a means of data collection and benchmarking that will encourage individual health care providers to identify their weaknesses and will provide them with indicators of possible changes in their delivery of care that may improve treatment. The minimum dataset has been developed with a view to encouraging maximum participation. Fields include demographic details and the NHS / CHI number which allows for linkage to the Office of National Statistics data on mortality. Hospital pathways are examined from the time it takes to get a bed to the proportion of patients admitted from home who are discharged home within 30 days. Outcomes are measured at 30, 120 and 365 days. The database is web based, which allows for real-time upload of individual patient data and immediate comparison with national data. The introduction of bespoke fields allows for customization of data collection, permitting local and regional audit projects. There is also the possibility of using the website to collect data for Randomized Controlled Trials.

Currently, twenty five hospitals are contributing data with seventy seven organizations from around England, Wales, Northern Ireland and the Isle of Man, registered for participation. Over ten thousand hip fractures have been uploaded, allowing for the development of case mix adjusted outcomes.

Participation is open to all hip fracture units in the United Kingdom and the website can be browsed using a demonstration password at, www.nhfd.co.uk.

IS02
WHAT IS A VERTEBRAL FRACTURE? EFFECTS OF STUDY DESIGN MEASUREMENT IMPRECISION ON STUDY OUTCOMES

Mark Lunt

Arthritis Research Campaign Epidemiology Unit, Manchester, UK

There are a number of methods of detecting vertebral fractures based on measurements of vertebral heights that are widely used in epidemiological studies and clinical trials. They have the advantage of objectivity and reproducibility over the subjective evaluation of a radiograph. However, such methods will never achieve perfect sensitivity and specificity. In this talk, I will look at the sources and consequences of misclassification by these methods.

Most current methods depend on comparing measured heights to expected heights, and assuming that if a height is very much smaller than expected, there is a fracture. However, the method used to calculate the expected height needs to be insensitive both to missing data (it is not uncommon for individual vertebra to be unmeasurable on an otherwise useable radiograph) and to fractures in the vicinity of the height being considered leading to reductions in the heights from which the expected height is calculated. Different methods of addressing these problems will be described and evaluated, and possible routes for improvements suggested.

Vertebral morphometry may be used with either a single radiograph, to identify prevalent deformities, or with two radiographs taken over a period of time to identify incident fractures that occurred between the two films. Having two films means that there are now two sources of information to calculate the expected heights on the second film: different methods use different ways to combine these sources of information. The advantages and disadvantages of current methods will be explored.

A vital component of the error in vertebral morphometry is the precision to which the heights are measured. Greater imprecision will lead to greater misclassification rates, which can bias the estimated prevalence of fracture and the association of risk factors with fracture outcomes. In many contexts, the relative costs of false positives and false negatives are difficult to quantify. However, in the context of an epidemiological study, the costs can be quantified in terms of a reduction in the power of the study and bias in the estimates of the relative risks for the predictors of fracture. The optimal method may depend on the population being studied:

IS03
VERTEBROPLASTY/KYPHOPLASTY: WHEN TO INTERVENE

Richard Whitehouse

Osteoporotic vertebral fractures are common. Many are painless. Those that come to medical attention are characterised by sudden onset of pain, which usually resolves within 6-8 weeks of onset. Most can be managed with simple analgesia but a small proportion require opiates and/or hospitalisation. Some fractures are persistently painful and do not resolve within 6-8 weeks. Treatment of these latter fractures can be problematic. Surgery is rarely contemplated - the patients are often elderly with co-morbidities and their bone is not strong enough to take surgical instrumentation. Custom made spinal braces are expensive and rarely acceptable to the patient.

Vertebroplasty is the percutaneous injection of bone cement into the fractured vertebra, under image guidance. This technique provides permanent pain relief from osteoporotic vertebral fracture in about 80-90% of appropriately selected patients. Kyphoplasty is a more recently developed procedure, whereby high pressure balloons are introduced into the fractured vertebra and inflated to elevate the fracture, reduce the kyphosis and produce a cavity within the vertebra.

The balloons are then deflated and removed and the cavity filled with bone cement. Whilst still a percutaneous procedure, performed under image guidance, kyphoplasty is a more time consuming procedure, which may require a general anaesthetic. It is more expensive and technically more demanding than vertebroplasty. The advantages claimed for kyphoplasty over vertebroplasty include a lower complication rate, greater restoration of vertebral body height and greater reduction in kyphosis than for vertebroplasty. These latter benefits may reduce respiratory compromise and also reduce subsequent axial vertebral loading and future fracture risk. There are few publications comparing kyphoplasty and vertebroplasty but data supporting the advantages of kyphoplasty are accumulating.

Whilst the pain relief from these procedures is similar at any time since fracture, the benefits of kyphoplasty in restoring height and reducing kyphosis are most apparent in recent fractures (less than 6 weeks old), with consequent implications for workload and costs.

My presentation will illustrate the techniques of vertebroplasty and kyphoplasty, the imaging used to assess patients for the procedures and some of the equipment used for the procedures.

IS04
BONE AS AN ENDOCRINE "GLAND": PHOSPHATE AND OTHER TARGETS

William D Fraser

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To be defined as endocrine a "gland" or cell must produce biologically active substances which are secreted into the body. The active substances then exert regulatory functions typically in cells other than those in which they are produced and can act locally or more typically, as in the case of hormones, by travelling through the circulation to act at a distance from the cell producing the active substance. A further important component of an endocrine system is the presence on the target cell of a unique receptor where the active

molecule can bind and trigger an intracellular response. Lastly having initiated the response a further classical component of an endocrine system is that the resulting activity of the cellular interaction alters the environment such that feedback of the change occurs and interacts with endocrine cell resulting in regulation of secretion of the active substance. In recent years new molecules involved in the regulation of phosphate have been discovered and their mechanisms of action studied which suggests that the overall process could be described as endocrine with bone cells the source of the active molecules.

Regulation of phosphate is a complex process involving the kidney, intestine and skeleton. Serum phosphate in adults is maintained between 0.7-1.4 mmol/L. Throughout 24 hours serum phosphate demonstrates a diurnal variation with a significant increase after the evening meal to a peak in the early hours of the morning falling to a nadir early morning. 1,25 dihydroxy vitamin D can promote phosphate and calcium absorption via the intestine and can increase phosphate mobilization from the bone by stimulating osteoclastic resorption of bone mineral containing hydroxyapetite as the storage form of phosphate. Parathyroid Hormone (PTH) can have effects on phosphate via the kidney by increasing the expression of the type IIa sodium-phosphate co-transporter (NPT2a) in the proximal tubule and down regulating NPT2a by decreasing the time the transporter remains in the apical membrane of the tubule. PTH action at the tubule promotes phosphaturia and will lower circulating phosphate indirectly. PTH can act via the osteoclast to stimulate both bone resorption and bone formation depending on the fluctuation in PTH and so can either release or deposit phosphate in bone depending on the PTH signal. However it is clear that the variations observed in PTH and 1,25 dihydroxyvitamin D in health and disease do not fully explain the changes in phosphate homeostasis and so the existence of a “phosphotonin(s)” has been suspected for some time.

One molecule that has emerged as an important regulatory phosphotonin is Fibroblast Growth Factor 23 (FGF 23). FGF23 has been shown to decrease serum phosphate by acting via specific receptors on kidney and intestinal cells to suppress proximal tubular phosphate reabsorption and intestinal phosphate absorption. The production of FGF23 has been identified in bone cells, particularly osteocytes, and FGF23 acts on the kidney through a specific receptor system which is composed of Klotho and subtypes of FGF receptors. Excess actions of FGF23 cause several hypophosphatemic diseases characterized by impaired renal phosphate reabsorption and rickets/osteomalacia. In contrast, deficient actions of FGF23 result in hyperphosphatemic tumoral calcinosis with enhanced renal phosphate reabsorption. The O-glycosylation of FGF23 via UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 3 GALNT 3 is an important regulator of the biological actions of FGF23. In humans phosphate infusion significantly increases and carbohydrate ingestion decreases serum phosphate, respectively, however, FGF23 does not alter in response to these acute changes. Long term/chronic increased ingestion of phosphate increases FGF23 and alterations in phosphate regulated by PTH and growth hormone (GH) result in changes in FGF23 concentrations. Administration of 1,25 dihydroxy vitamin D has also been shown to decrease circulating FGF23 in certain disease states but increase FGF23 in others .

It would appear therefore, that part of the mechanism evolved to regulate phosphate metabolism involves bone as an endocrine gland with bone cells involved in production of the active molecule, FGF23, with its actions at a distant site via specific receptors and an evolving complex feedback process.

IS05
MECHANO-BIOLOGY OF FRACTURE HEALING

Georg N Duda

Julius Wolff Institut and Center for Musculoskeletal Surgery, Charité, Berlin

Starting from the importance of muscles and mechanical forces on bone healing it can be shown that a certain amount of mechanical stimulation is helpful to healing, while too much could result in a delay to the healing processes. Such basic understanding of mechanical stimulation may help to activate the endogenous healing processes and employ them even in cases where healing would not occur naturally. Our work aims to understand the body's own processes and, where necessary, to stimulate them, so as to reproduce natural regeneration of the musculoskeletal system by identifying and targeting the most effective approaches over a number of different scales (cell, tissue, organ, extremity). We have demonstrated that the early phases of bone regeneration are especially sensitive to mechanical stimulation. In particular, the processes of angiogenesis and inflammation, as well as the beginning of endochondral ossification, can be guided through mechanical stimulation. Within the framework of our research network, it is aimed to demonstrate the biological signalling cascade and to this knowledge to stimulate healing, particularly in mechanically critical situations. The optimisation of implants or surgical technique can additionally provide an alternative to biological stimulation for supporting the natural processes of healing or reducing delaying influences. The challenge in providing such solutions must lie not only in the hands and experience of the surgeon, but also in the application of successful research.

IS06
ENHANCING FRACTURE REPAIR WITH PHARMACOTHERAPY

David Marsh

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There are two main clinical drivers behind the search for drugs that enhance fracture healing. The first is assurance of healing - avoiding nonunion in fractures at risk. Secondary treatment comes at a high price for both the patient and the health service. The second is acceleration of healing - getting fractures, which will heal anyway, to do so faster. This has benefits in promoting rehabilitation in its widest sense. Different groups of patients, from the elderly fragility fracture to the younger high energy injury, stand to gain in different degrees from these goals. But in all, it is important to be confident that the enhancing treatment will not induce complications of its own.

The normally very reliable biology of fracture healing is modulated by old age, osteoporosis and the drugs used to treat it, as well as soft tissue injury in high energy injuries. These suggest several targets for pharmacotherapy in the patients mainly at risk:

- Stimulation of the periosteal healing response, both its Intensity and duration
- Angiogenesis as the partner of osteogenesis in repair
- Systemic release and local capture of MSCs, in addition to their local induction
- Prevention of resorption around implants and disuse osteoporosis
- Modulation of inflammatory response, particularly in high energy injury

Enhancing drugs may be delivered to the fracture site to have their effect locally; the scope for this would be increased by the availability of injectable formulations. A systemically-delivered agent would have advantages, particularly if it could serve two purposes, in treating generalized osteoporosis as well as stimulating healing of an incident fracture. So far the evidence base for drugs that deliver assurance and acceleration of fracture healing is slim, with many trials too small to be convincing. However the BESTT trial, despite some methodological misgivings, does suggest that BMP-2 produces both goals in high energy long bone fractures.

So far we have considered therapy of fresh fractures, where cost-effectiveness depends on identification of patients at risk. However, patients with delayed union or established nonunion have already declared themselves to have an expensive problem and an effective treatment here would be very valuable. But the biology of nonunion is very different from that of the fresh fracture and evidence from one situation cannot be assumed to apply to the other. Again, evidence is sparse, with most reported studies devoid of meaningful controls. However the evidence for efficacy in nonunion of BMP-7 is reasonable and has been enough to convince the European regulatory authorities, if not the FDA. But convincing data about cost-utility is still lacking.

There are many candidate fracture-enhancing drugs in the pipeline and the need is great for the building of the requisite research networks. With enough energy and funding, the next few years could see exciting progress.

IS07

IMPACT OF PHYSICAL ACTIVITY ON THE SKELETON

Harri Sievänen

Bone Research Group, UKK Institute, Tampere, Finland

Bone tissue has capacity to respond to a variety of mechanical and physiological needs over the whole life span. Primarily human musculoskeleton forms a locomotive apparatus that adapts to habitual functional loading. Muscle activity imposes stresses on the bones while consequent, minuscule load-induced deformations initiate cellular processes that eventually lead to tissue-level adaptation of the bone. Obviously any substantial organ-level strengthening is a long process requiring several years. As regards the overall adaptability, bones have considerable potential (ad ~50% or more) to increase their structural rigidity and strength.

Clinical knowledge on true effects of different physical loadings on bone rigidity is yet quite scarce - largely because of methodological limitations. There is abundant evidence for positive effects of exercise on DXA-measured bone mineral density (BMD) or bone mass, but these effects have generally remained small - some percents on average. However, it is the structure, rather than the bulk, that principally determines the whole bone mechanical competence.

Studies on athletes provide useful “natural experiments” to unravel associations of specific, long-term physical activity on bone structure, and some general principles can be inferred. High impacts and impacts from atypical directions are most effective for strengthening the bone. Cortical wall of the loaded bone is thicker, particularly if subjected to high impacts. At the epiphyseal sites, cross-sections of loaded bones are not necessarily larger, but this may be the case at the forearm, particularly so if the exercise has been started before puberty. Cross-sections of the loaded diaphyses are larger, particularly if subjected to large bending loads. Cross-sectional geometry (~shape) reflects also the predominant loading direction. Trabecular apparent density (~trabecular architecture) of the loaded bone is higher, being close to 'ceiling' particularly if subjected to high impacts. Responses in upper and lower extremities are different, the former having more potential - apparently due to lack of regular weight-bearing loading. Also, the responses can differ between the sexes because of inherent stiffening effect of estrogen on female bone. Altogether, the phenotype of 'athletic' bone is generally strong, which apparently accounts for the protection against fragility fractures in later life, as indicated by epidemiological data.

IS08

LOW PROTEIN INTAKE AND BONE RESPONSES TO MECHANICAL LOADING

Patrick Ammann

Division of Bone Diseases, Department of Rehabilitation and Geriatrics, University Hospital Geneva

Despite its inert appearance, bone is a living tissue which is able to adapt to mechanical loading by modifying both its geometry, or size, and its intricate microarchitecture. This implicates the formation of new bone which requires optimal production of anabolic growth factors. Previous studies have highlighted the importance of IGF-I in this process of adaptation. Reduced protein intake results in a depressed somatotrop axis with a decrease in the production and action of GH and IGF-I, all of which lead to sizeable reductions in bone formation. Such a situation could preclude a corrective adaptation of the skeleton to mechanical loading.

Following ovariectomy, the decrease in trabecular bone volume at the level of the femoral neck is associated with a compensatory increment of the neck diameter. This corresponds to an adaptation of the proximal femoral architecture to maintain similar bone strength in order to provide optimal loading capacity. This is associated with a rise in circulating plasma IGF-I. Under an isocaloric low protein diet, (which is known to prevent the increase in circulating IGF-I), all of the compensatory mechanisms described above failed to transpire. This observation clearly underlines the importance of optimal nutrition in these physiological compensatory processes.

During mastication, it was demonstrated that the regular application of a load every 0.5-1.5 second, via the teeth, on bone is able to influence both the geometry and microarchitecture of the mandible. A soft diet (which prevents loading of the mandible) leads to an alteration of these parameters. Thus under a low protein hard diet, similar modifications of these parameters were observed, probably due to the impossibility of the mandible to adapt to mechanical loading. Finally major decreases in bone strength and bone mass were observed at the level of the proximal tibia following ovariectomy and isocaloric low protein intake. In the same rats, ovariectomy negatively affected the microarchitecture of the mandible and protein malnutrition further impairmed these parameters. This is explained by the fact that mechanical loading partially compensates for the bone loss seen following ovariectomy and this process of mechanical loading is not possible under protein malnutrition.

These different animal models highlight the importance of optimal protein intake to maintain the possible modification of microarchitecture and geometry in response to mechanical loading.

IS09

PRIMING OF SKELETAL MECHANOBIOLOGICAL MEMORY

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It is acknowledged that a dynamic adaptive relationship exists between skeletal tissue structure and the prevailing mechanical environment. As such, the structure and mass of both cartilaginous and bone tissues, whose primary function is to provide support for locomotor activities, is considered to be exquisitely sensitive to modified load-bearing. Further, it is commonly asserted that these structural characteristics are also established during development, at least partly, by similar adaptive mechanisms. A role for such adaptation in developmental attainment of appropriate structure is, however, relatively unsubstantiated. This review will examine the role of movement in the embryonic development of functional articular cartilage joint surfaces and in bone formation. Data supportive of critical periods, during which particular tissues in the developing skeleton become receptive to the impact of movement, will also be discussed. Furthermore, results from novel model systems for manipulating embryonic mobility in ovo and for applying controlled mechanical stimuli to joint and bone in vivo will be presented to describe the cell-signalling events that underpin some of these mechano-dependent events in the developing, growing and ageing skeletal system. Together, these findings support the intriguing possibility that mechanomodulatory influences may be harnessed to accelerate, control or engineer formation and repair of skeletal or joint tissues.

IS10

BONE STRENGTH ASSESSMENT FROM MORPHOMETRY AND STRUCTURE

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'Areal' bone mineral density (BMD_a), as measured by two dimensional (2D) dual energy X-ray absorptiometry (DXA), accounts for approximately 60-70% of bone strength; the remaining 30-40% is depended on geometry, material properties; architecture and trabecular structure of bone. There are now methods available to explore these other properties of bone, but as they are technically challenging and not widely available they remain as research tools at present.

More can be extracted from DXA than are routinely used in clinical practice (hip axis length HAL; hip strength analysis HAS). Quantitative computed tomography (QCT) has advantages over DXA in that it provides volumetric BMD separately of cortical and trabecular bone, and although routinely applied centrally (lumbar spine) and to peripheral sites (radius and tibia), application to the hip is now feasible and precision has been improved with multi-detector (MDCT), spiral volumetric body CT scanners. From QCT can derived biomechanical parameters of bending and torsional strength (moment of inertia and stress/strain index). Trabeculae measure between 50-200 microns; it has now become feasible to image trabecular structure using either conventional body MDCT (spatial resolution [SR] 200 microns; radiation dose limits application to central body sites) or high resolution micro CT (SR 40 microns) in peripheral skeletal sites or bone samples. High resolution magnetic resonance imaging (MRI) in peripheral sites (SR 150 microns) and in specimens (small bore MRI scanners SR 50 microns) is also now possible, but requires high field MRI scanners (1.5 Tesla) and specific receiver coils. From these images can be applied histomorphometry

and finite element analysis (FEA) to extract more detailed information of bone structure and strength. Although technically challenging these more advanced quantitative methods are now being introduced into therapeutic trials and other studies, but there role in clinical diagnosis and management of patients with bone disorders is still to be determined.

IS11
FINITE ELEMENT ANALYSIS (FEA) IN THE ASSESSMENT OF BONE STRENGTH

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Accurate assessment of bone strength is critical for predicting fracture risk and evaluating treatment efficacy. In diseases such as osteoporosis in which the bone is compromised, evaluating bone strength can provide clinicians with an understanding of the mechanical integrity of the bone. The current gold standard for assessing bone quality is measuring bone mineral content using imaging techniques (DEXA or CT). The mechanical strength of the bone, however, is determined not only by its mineral content, but also by its structure. A finite element model of a bone takes into account the geometry, material properties, and loading conditions, from which the mechanical stress and strain can be determined. This talk will introduce how finite elements analysis has been used to assess bone strength including how the geometry is constructed, how material properties are assigned, and what loading conditions are used. There are many measures of strength: yield strength (the stress at which the material permanently deforms), ultimate strength (the stress at which the materials fails), and fatigue strength (the maximum stress that can be sustained for a given number of cycles). Finite element models can be used to estimate these values but are limited by assumptions that are required in defining the geometry, material properties or loading conditions of the model. Finite element models can also predict failure loads and location of failure using a number of different material failure criteria at the whole bone level or at the micro-level of the trabecular structure. In order to demonstrate accuracy, a finite element model must be validated, normally with experimental results. Though huge advances have been made in creating accurate finite element models of bone, much work still needs to be done before they can be used in a clinical setting.

IS12
WHERE ARE WE NOW WITH CARTILAGE AND MENISCAL TRANSPLANTATION?

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There has been great progress in 2007 with the publication of several relevant papers on cartilage transplantation.

The long term results of ACI seem good at 10 years, and the Aberdeen health economics group published that even a 10 to 20% improvement in outcome following ACI would justify the cost of ACI.

Gunner Knutsen found that those with poor histology following either microfracture or autologous chondrocyte implantation (ACI) did have poor outcomes. Tigenix ran a very high standard PRCT and found that at 1 year ACI produced significantly better histology than Microfracture in patients with chondral defects.

So there is an argument for the first time that ACI is predicted to give better results than microfracture.

Many new methods of performing ACI are being promoted, but there is no comparative evidence within the types of ACI.

Cartilage transplantation has no randomised trials under way as yet. The provision of donor grafts was greatly delayed by centralisation until recently, but the Liverpool tissue bank is now organized and learning about the need to package grafts well. There is a great debate on how best to size the meniscus. Probably many other factors need to be considered to select the right patients and obtain the best results. Angus Strover advocates that only male sourced menisci should go into male patients, for instance. The hunt is on for a tissue engineered meniscus.

Options for generating a biological joint replacement in a laboratory have difficulties of avoiding infection. Myjoint is a European-funded project to grow the new joint in the patient, but in a separate anatomical site from the one it is destined to replace. Only cells can form the parts of a joint, so the different cell engineering treatments in orthopaedics are helping to provide the necessary experience for this and similar developments.

IS13
WHAT DO WE KNOW ABOUT THE PATHOAETIOLOGY OF OSTEOARTHRITIS?

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Osteoarthritis has, for a long time, been regarded as a pathological condition resulting from the degeneration or destruction of articular cartilage tissue that covers and protects our moving joints. This is certainly an oversimplified view which ignores the involvement of other structural joint constituents in the disease process such as the synovial membrane and bone.

Still, the extracellular matrix of articular cartilage is the primary target of osteoarthritic cartilage degradation and in fact many aspects of the disease and its pathogenesis are related to its matrix. However, also the cartilage cells, the chondrocytes, play a pivotal role within the disease process as they are mainly responsible for the anabolic-catabolic balance which is essential for matrix maintenance and tissue function. Thus, besides severe changes within the extracellular matrix, the cells also display abnormalities during osteoarthritic cartilage degeneration. These changes include activation of anabolic and catabolic activities and alterations in cell number through processes like proliferation and (apoptotic) cell death. All these processes appear to occur in different sites and times during the disease process and significantly contribute to the initiation and progression of the disease. In addition and maybe even more problematic for preserving tissue homeostasis are un-structured reaction patterns typically seen in osteoarthritic chondrocytes. This may lead to impairment of the cells' attempts to halt and/or reverse the disease process and, as such, may represent the point of no return for disease progression. Evidence suggests that the aging of cells plays an important role in the pathogenesis of osteoarthritis. Thus, anti-aging strategies might well complement present pathogenetic concepts related to processes of anabolism, catabolism, apoptosis, and inflammation that are all known to be important for osteoarthritis. Unclear remains the role of genetic factors, which obviously play a role for the joint as for all other tissues. But this might be more related to joint development as well as many other factors rather than cartilage (patho)physiology itself.

IS14
VITAMIN D AND BONE: ENDOCRINOLOGY AND AUTO/PARACRINOLOGY

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Vitamin D is one of the major factors involved in calcium homeostasis via actions on intestine, kidney, parathyroid gland, and bone. The biologically most active vitamin D molecule is 1α,25-dihydroxyvitamin D3 (1α,25-(OH)2D3). In bone, 1α,25-(OH)2D3 is important for mineralization, either indirectly via control of calcium absorption in intestine and reabsorption in the kidney, but also via direct action on osteoblasts. 1α,25-(OH)2D3 is formed from the parental vitamin D molecule by sequential hydroxylations in the liver (25-hydroxylation) and kidney (1α-hydroxylation): 25-hydroxyvitamin D3 (25-(OH)D3) formed in the liver is transported to the kidney bound to the vitamin D binding protein (DBP) and is then metabolized to 1α,25-(OH)2D3 by the renal cytochrome P450 enzyme 25-hydroxyvitamin D3-1α-hydroxylase..However, 1α-hydroxylase expression and activity is not restricted to the kidney. The first evidence for extra-renal 1α-hydroxylase was based on studies of patients with sarcoidosis in whom conversion from 25-(OH)D3 to 1α,25-(OH)2D3 was demonstrated in affected lymph nodes and pulmonary alveolar macrophages. More recently, it was reported that 1α-hydroxylase expression was increased in pathological parathyroid glands, and also up-regulated in various other malignant conditions. Prostate cells also express 1α-hydroxylase, but here the activity of the enzyme is decreased in the cancer cells. 1α-Hydroxylase expression has also been demonstrated in a variety of normal extra-renal tissues like skin, lymph nodes, colon, pancreas, adrenal medulla, dendritic

cell, endothelial cells, brain, hypothalamus, placenta, and recently also in bone. Bone cells contain all the components, 1α-hydroxylase, megalin, cubulin, vitamin D receptor, 24-hydroxylase, necessary for vitamin D to fulfill an autocrine/paracrine action. In a more general perspective, the data on vitamin D contribute to the currently emerging concept of steroid hormone production within its target tissues. This implicates a transition from a hormone acting at a distant site of synthesis, to a local factor acting in an auto/paracrine manner.

IS15
NON-SKELETAL EFFECTS OF VITAMIN D

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In addition to its important role in the maintenance of the skeleton, there is mounting evidence that vitamin D has effects on other body systems and that adequate supplies of vitamin D are required for optimal health. The main source of vitamin D is considered to be cutaneous synthesis with exposure to sunlight but some is obtained from dietary sources. Vitamin D deficiency leads to failure of normal bone mineralization. However, a low vitamin D status has also been implicated in a range of diseases including cardiovascular disease, tuberculosis, multiple sclerosis and diabetes. Some epidemiological studies have indicated that vitamin D deficiency and decreased exposure to solar UVB radiation are associated with risk for several forms of cancer. The active metabolite of vitamin D and its synthetic analogues have been shown to have potent anti-proliferative effects in a variety of cancer cell types, including breast cancer cells. Normal and neoplastic breast tissues contain the vitamin D receptor and gene ablation studies have implicated the receptor in normal breast development. There is now evidence that breast cells contain the 1alpha hydroxylase enzyme required for generation of 1,25-dihydroxyvitamin D from circulating 25- hydroxyvitamin D. Studies in both the UK and USA have reported that low circulating concentrations of 25-hydroxyvitamin D are associated with a higher risk for breast cancer. Local synthesis of 1,25-dihydroxyvitamin D in breast tissue may contribute to maintenance of normal cell function, which could be impaired in vitamin D deficiency. Efforts to improve vitamin D status could have significant protective effects against a variety of chronic diseases including breast and certain other cancers.

ORAL COMMUNICATIONS

OC01
INFLAMMATORY CYTOKINES CAUSE LOSS OF DNA METHYLATION TOGETHER WITH INDUCTION OF ABNORMAL GENE EXPRESSION IN HEALTHY HUMAN ARTICULAR CHONDROCYTES

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Epigenetic DNA de-methylation at specific CpG promoter sites is associated with abnormal synthesis of matrix-degrading enzymes in human osteoarthritis (Arthritis Rheum 52:3110-24), but the mechanisms that trigger or cause loss of DNA methylation are not known. Since inflammatory cytokines are known to induce abnormal gene expression in cultured chondrocytes, we wanted to know whether this induction also involved loss of DNA methylation. If so, the abnormal gene expression would be permanent and transmitted to daughter cells rather than a simple up-regulation. To test this hypothesis, we selected IL-1b as the abnormally expressed gene. Healthy chondrocytes, harvested from human femoral head cartilage following a fracture, were divided into five groups: non-culture; control culture; culture with the de-methylating agent 5-aza-deoxycytidine (5-aza-dC); culture with the inflammatory cytokine IL-1b; or with TNF-α/oncostatin M. Total RNA and genomic DNA were extracted at confluency, relative mRNA expression of IL-1b was quantified by SybrGreen-based real-time PCR, and a method for quantifying the percent of cells with DNA methylation at a specific CpG site was developed (Epigenetics 2: 86-95).

The methylation status of 16 CpG sites in the promoter of IL-1b was determined by the bisulfite modification method. The two CpG sites important for the epigenetic regulation of IL-1b were at -247bp and -290bp, the latter was selected to quantify DNA methylation. 5-aza-dC halved DNA methylation, which resulted in 4-8 fold increases in IL-1b expression; showing that DNA de-methylation per se increases gene expression. However, far greater effects were seen with the inflammatory cytokines. IL-1b increased its own expression 50-100 fold, whereas TNF-α/OSM increased IL-1b expression 500-1000 fold. DNA methylation varied inversely, IL-1b reducing methylation to ~15% and TNF-α/OSM abolishing DNA methylation almost completely.

This is the first demonstration that inflammatory cytokines have the capacity to cause loss of DNA methylation. We also confirmed previous work that IL-1b induces its own expression in healthy chondrocytes, thus setting up a dangerous positive feed-back mechanism. If true in vivo, both the auto-induction and the heritable expression of IL-1b by a growing number of chondrocytes could explain the unrelenting progression of osteoarthritis.

OC02
LOADING-RELATED REDUCTION IN OSTEOCYTE SCLEROSTIN EXPRESSION IN VIVO IS ASSOCIATED WITH BONE FORMATION IN TRABECULAR AND CORTICAL BONE

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Sclerostin is a glycoprotein produced by osteocytes which has been reported to be suppressed in cortical bone by mechanical loading '1'. We investigated the effect of in vivo loading on sclerostin expression in osteocytes in both trabecular and cortical bone.

The right ulna and tibia of 17 week old female C57Bl/6 mice were subjected to non-invasive axial cyclic loading on two consecutive days (peak strains of 2800 and 2000 microstrain, respectively; 40 single loading cycles, each followed by a 10 sec rest). Mice were sacrificed 24h after the last loading session. Cortical bone was sectioned and immunostained for sclerostin at sites where we had previously established by micro-CT that these loads stimulated new bone formation. Sclerostin expression was also studied in the secondary spongiosa of the proximal tibia which showed load related new bone formation and in the primary spongiosa which did not.

In the ulna, the number of sclerostin positive stained osteocytes was reduced by loading in cortices subject to both compression (control; 54±3% and loaded; 15±4%, P<0.001) and tension (control; 55±3%

and loaded; 21±6%, P<0.001). The number of sclerostin positive osteocytes was also reduced by loading in cortices of the tibia (control medial cortex; 60±7% and loaded; 23±4%, P<0.001; control lateral cortex; 56±9% and loaded; 16±1%, P<0.001). In the secondary spongiosa, the number of sclerostin positive osteocytes was reduced by loading (control; 73±2% and loaded; 44±1%, P<0.01). In contrast, in the primary spongiosa there was no such reduction (control; 78±5% and loaded; 74±6%).

In summary, loading sufficient to stimulate new bone formation suppresses sclerostin expression by osteocytes in regions of cortex exposed to tensile and compressive strain. Loading-related reduction in osteocyte sclerostin expression also occurs in trabecular bone, but only in the regions where loading is followed by new bone formation.

1. Robling et al., JBC Epub Dec 17 2007

OC03

A BIOACTIVE SCAFFOLD FOR BONE REGENERATIVE MEDICINE

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Approximately 5 - 10% of all bone fractures are associated with impaired healing. It is thought that regenerative medicine has the potential to improve on existing treatments for non-union fractures, and the European market for such treatments is projected to reach £2.2 billion in 2010. The use of scaffolds for the delivery of both growth factors and human Marrow Stromal Cells (hMSCs) is thought to be a promising approach. It may be desirable to promote proliferation and chemotaxis of hMSCs at the defect site shortly after implantation, and differentiation in the longer term. This is likely to require a dual delivery system, capable of releasing multiple drugs with different release profiles. Our aim has been to develop a polymer scaffold capable of releasing bioactive molecules that are able to direct the differentiation of primary hMSCs down the osteoblastic lineage. We have examined two mutually compatible drug delivery systems: collagen coating for short term release, and polymer encapsulation for longer term release.

Polymer scaffolds were manufactured and coated with Type I Collagen containing BMP-7. hMSCs from three different patient sources were exposed to the scaffolds for 14 days. The cells were then histochemically stained for Alkaline Phosphatase (ALP) and photographed. The areas of ALP staining were then normalised against the total cell count.

Normalised ALP expression was increased compared to the controls for three different patients ('110 ± 39% SE, n=6, p=0.005', '540 ± 270% SE, n=6, p=0.001', and '32 ± 17% SE, n=6'). Scaffolds were also manufactured either with 1,25 Vitamin D3 (another active compound) in a coating of Collagen, or encapsulated using proprietary methodologies. It was found that both treatments significantly increased normalised Alkaline Phosphatase expression within the 14d experimental period demonstrating release of the active 1,25 Vitamin D3 ('88 ± 37% SE, n=6, p=0.012' and '100 ± 32% SE, n=6, p=0.012' respectively).

Our findings suggest that, subject to future testing and development, such bioactive scaffolds could form the basis for a dual drug delivery system, suitable for applications in bone regenerative medicine.

OC04

PREDICTION OF INCIDENT HIP FRACTURE RISK BY FEMUR GEOMETRY VARIABLES MEASURED BY HIP STRUCTURAL ANALYSIS IN THE STUDY OF OSTEOPOROTIC FRACTURES

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The role of bone tissue's geometric distribution in hip fracture risk requires full evaluation in large population-based datasets. We tested whether section modulus, a geometric index of bending strength, predicted hip fracture better than bone mineral density (BMD).

Among 7,474 women from the Study of Osteoporotic Fractures with hip DXA scans at baseline there were 635 incident hip fractures recorded over 13 years. Hip structural analysis software was used to derive variables from the DXA scans at the narrow neck (NN), intertrochanter (IT), and Shaft (S) regions. Associations of derived structural variables with hip fracture were assessed using Cox proportional hazard modelling. Hip fracture prediction was assessed using the C-index concordance statistic.

Incident hip fracture cases had larger neck-shaft angles, larger subperiosteal and estimated endosteal diameters, greater distances from lateral cortical margin to centre of mass (lateral distance), and higher estimated buckling ratios (P<0.0001 for each). Areal BMD, cross sectional area, cross-sectional moment of inertia, section modulus, estimated cortical thickness, and centroid position were all lower in hip fracture cases (P<0.044). In hip fracture prediction using NN region parameters, estimated cortical thickness, areal BMD, and estimated buckling ratio were equivalent (C-index = 0.72 95% CI (0.70, 0.74), but section modulus performed less well (C-index = 0.61 (0.58, 0.63), p<0.0001 for difference). In multivariable models combining HSA variables and age, effects of bone dimensions i.e. lateral distance, subperiosteal diameter, and estimated endosteal width were interchangeable whereas age and neck-shaft angle were independent predictors. Several parsimonious multivariable models that were prognostically equivalent for the NN region were obtained combining a measure of width, a measure of mass, age, and neck-shaft angle (BMD is a ratio of mass to width in the NN region), C-index = 0.77 (0.75, 0.79). Trochanteric fractures were best predicted by analysis of the IT region.

Since section modulus failed to predict hip fracture risk as well as areal BMD, the thinner cortices and wider bones among those who fractured may imply that simple failure in bending is not the usual event in fracture. Fracture might require initiation, e.g. by localized crushing or buckling of the lateral cortex.

OC05

VARIATION IN THE INTERLEUKIN-1 RECEPTOR ANTAGONIST GENE PROTECTS AGAINST OSTEOLYSIS AFTER TOTAL HIP ARTHROPLASTY: A CLINICAL AND GENE EXPRESSION STUDY

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Total hip arthroplasty (THA) wear debris induced macrophage expression of pro-inflammatory cytokines has been associated with osteolysis both in vitro and in animal and human subjects. Interleukin-1 receptor antagonist (IL-1RA) is an anti-inflammatory cytokine which may limit bone destruction. Polymorphisms (SNPs) within the IL-1RN gene are associated with differences in susceptibility to infectious and inflammatory conditions and disorders of bone remodelling. This study investigated the association between the IL-1RA+2018T/C SNP (rs419598) and osteolysis after THA, and with mRNA and protein expression in an in-vitro wear debris-macrophage stimulation assay.

611 North European Caucasians who had received a cemented THA for primary osteoarthritis were genotyped for the IL-1RN+2018 SNP using Taqman methods. 62 subjects with a Charnley THA were selected from the genotyping population. Control subjects had no radiographic osteolysis and the osteolysis group had previously undergone revision surgery for aseptic loosening. Peripheral blood mononuclear cells were extracted and stimulated with endotoxin-stripped titanium particles (TiCL, endotoxin level 0 Eu/ml) and endotoxin-stripped particles with adherent LPS added back (TiAB, endotoxin level 140 Eu/ml); non-stimulated and LPS-stimulated cells were used as negative and positive controls. Cell lysate IL-1RA mRNA levels were assessed by rqRT-PCT following a 3-hour stimulation. Cell supernatant IL-1RA protein levels were assayed after 24 hours stimulation using a multiplex method.

The IL-1RN+2018C allele was underrepresented in patients with osteolysis after THA versus control THA subjects (chi-squared test 5.96, P=0.015). After correction for other risk factors for osteolysis, the adjusted odds ratio for osteolysis associated with carriage of the IL-1RN+2018C SNP was 0.69 (0.48 to 0.99, p=0.048). IL-1RA mRNA expression increased linearly with IL-1RN+2018C allele copy number in gene-dose dependent manner (ANOVA p=0.013). The IL-

1RA+2018C allele did not significantly affect IL-1RA protein expression (ANOVA p>0.05), however a similar trend towards increased levels with increased C allele copy number was observed.

Carriage of the IL-1RA+2018C allele is associated with both a decreased risk of osteolysis after THA and increased IL-1RA mRNA expression in-vitro. The mechanism for this functional effect remains unclear, however these findings support the importance of the IL-1RA in osteolysis and aseptic loosening.

OC06

EFFECTS OF ACUTE HYPOXIA ON OSTEOCLAST ACTIVITY: A BALANCE BETWEEN ENHANCED RESORPTION AND INCREASED APOPTOSIS

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Osteoclasts are the primary mediators of pathological bone resorption in diseases including cancer metastasis to bone and rheumatoid arthritis. In both conditions micro-environmental hypoxia is associated with disease progression. Hypoxia has been described to enhance monocyte-osteoclast differentiation in feline and murine cultures while inhibiting the activity of mature osteoclasts from disaggregated rat bone. We describe the first investigation into effects of acute hypoxia on human osteoclasts in culture.

Mature osteoclasts were obtained either by differentiation of peripheral blood mononuclear cells (PBMC) with M-CSF (25 ng/ml) + RANKL (50 ng/ml) for 17 days or by curettage of fresh samples of Giant Cell Tumour of Bone. 24 h exposure of mature osteoclasts to 2-5% O2 produced a 2-3 fold increase in resorption over that achieved at 8-21% O2, while incubation at 0.1% O2 completely inhibited osteoclast activity. The increased resorption at 2-5% O2 was associated with a 36-40% increase in TRAP enzyme activity, as assayed by conversion of pNPP to p-nitrophenol, and a 15% increase in Cathepsin K activity, assayed by degradation of the Cathepsin K-specific substrate Z-Gly-Pro-Arg-MCA.

At the same time, 24 h exposure of mature osteoclasts to 2% O2 resulted in reduced expression of TRAP mRNA and a 75-80% reduction in the number of TRAP- and VNR-positive multi-nucleated cells compared with incubation at 5-21% O2. This was associated with increased osteoclast apoptosis as assayed by percentage population uptake of trypan blue and DAPI staining. Based on trypan blue results, 24 h exposure to 2% O2 rendered 21% of osteoclasts non-viable and almost 100% by 72 h compared with <6% in normoxic control populations. 24 h at 0.1% O2 resulted in 97% osteoclast apoptosis

These results suggest that within the normal bone microenvironment of 7-9% O2 osteoclast resorptive activity is comparable with that observed under standard tissue culture conditions. However in diseased bone, where the pO2 may fall to <2% O2, a delicate balance between hypoxia-mediated osteoclast apoptosis and hypoxia-induced osteoclast activation mediates pathological bone resorption.

OC07

ISOLATION OF SENESCENT MULTIPOTENT STROMAL CELLS FROM HUMAN FRACTURE NON-UNIONS

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Non-union is poorly understood. It is unknown if multipotent cells are present in non-union tissue or whether the activity of such cells is dysfunctional. Clinically, this is important as it may predict the success of novel therapies such as BMP treatments and cell-transplantation. This study aimed to study the characteristics of cell types present in human fracture non-union tissue, in comparison with bone marrow stromal cells (BMSC) from the patient and other healthy patients.

Non-union tissue was harvested (n=8) from long bones. Cells were isolated enzymatically and cultured in monolayer. BMSC were isolated by density gradient centrifugation of iliac crest biopsies. Their phenotype was assessed by FACS analysis for CD34, 45 and 105 markers. Their comparative growth kinetics was examined, as was their osteogenic and adipogenic capacity following extended culture in defined medium. Cell differentiation status was evaluated using alkaline phosphatase, von Kossa and oil-red O staining. Cell senescence was assessed via cell morphology, senescence associated Beta-galactosidase (SA-Beta)-Gal) activity.

Non-union cells grew in monolayer, but showed different morphologies; many non-union cells contained stress filaments (typical of senescent cells) or were of stellate appearance. In addition, significantly more non-union cells were positive for SA-Beta-Gal activity compared to BMSC (P=0.0006). Growth kinetics showed longer doubling times for cells isolated from non-union tissue when compared to BMSC isolated from the patient. Long term culture of non-union cells showed early growth arrest at passages 3-8. FACS analysis showed isolated cells to be CD34/45 negative and CD105 positive. Both non-union cells and BMSC differentiated along osteogenic and adipogenic lineages to varying extents.

Our novel results show that cells from non-union tissue exhibit senescence in culture. Hence, cell senescence is potentially involved in the aetiopathogenesis of non-unions. Whether or not this senescence has arisen through cell division (during failed repair attempts) or via abnormal biomechanical loading warrants further study. The influence of senescent cells on the healing process also requires investigation. Clearly these cells are able to differentiate into osteoblasts in vitro but may have an aberrant influence on union in vivo.

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OC08

PRIMARY OSTEOBLASTS AND BONE MATRIX OF BONES WITH DIFFERENT FUNCTIONS HAVE DISTINCT CHARACTERISTICS

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Primary ossification can be categorized developmentally as either intramembranous or endochondral. The dual lineage of skeletal elements, derived from either cranial neural crest (in the case of certain dermal bones of the skull) or mesoderm (almost the entire post-cranial skeleton), may account for the varied site-specific skeletal phenotypes apparent in the adult. Mechano-responsive weight-bearing limb bones are susceptible to age-related, post-menopausal and disuse osteoporoses, whilst such bone loss does not occur normally in the protective calvarial bones that constitute the skull vault. This attribute may be reflective of the quality of the matrix produced by the respective resident osteoblasts.

Consequently, we have studied the calvarial and limb bone matrices from male rats (110+/-5 grams). There are compositional (glycosaminoglycan concentration, as determined by the intensity of measured alcian blue staining, parietal: 54.3 ± 1.4; ulna: 74.3 ± 3.1 M.I.E.x100, mean ± SEM, p<0.002) and organizational (osteocyte number, parietal: 612 ± 19; ulna: 773 ± 40 osteocytes per mm2, mean ± SEM, p<0.01) differences between skull and limb bones. Examination of the resident cells of calvarial and limb bone by gene array and real time-RT-PCR identifies the idiosyncratic basal gene expression profiles. Notably, there is an increased basal level of expression of genes in the calcium signalling, axonal guidance, actin cytoskeleton, integrin and the Wnt/beta-catenin signalling pathways in calvarial bone. Primary osteoblasts derived from parietals and ulnae confirm that, even in cell culture, particular differences are maintained. This suggests that osteoblasts from distinct functional sites behave in a pre-programmed, lineage-derived fashion.

Analogous to the functional variants of muscle type (skeletal, smooth and cardiac), we propose that the biochemical and biophysical properties of the weight-bearing and protective classes of cortical bone are discrete, and based on their initial derivation. Recognizing these real differences in the skeleton means that induction of the intrinsic osteo-regulatory mechanism peculiar to resident osteoblasts of calvariae (and subsequent osteoporosis-resistant bone matrix formation) in limb bone osteoblasts may offer a novel therapeutic mechanism to prevent the osteoporoses to which weight-bearing bones are susceptible.

OC09

MICROCT ANALYSIS OF P2Y1 AND P2Y2 RECEPTOR KNOCKOUT MICE DEMONSTRATES SIGNIFICANT CHANGES IN BONE PHENOTYPE

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Extracellular nucleotides, signalling through P2 receptors, play a significant role in bone biology modulating both osteoblast and osteoclast function. Eight P2Y receptor subtypes, including P2Y1 and P2Y2, have been detected on bone cells. In vitro activation of the P2Y1 receptor by ATP and ADP stimulates osteoclast formation and activity, whilst ATP and UTP, signalling via the P2Y2 receptor, inhibit bone mineralisation. In this study we have investigated the effects of P2Y1 and P2Y2 receptor deletion on bone using 2-month old knockout mice. Both P2Y1R-/- and P2Y2R-/- mice had no overt phenotype and exhibited no gross abnormalities. DEXA analysis (Lunar PIXImus) showed no differences in lean tissue or fat content. P2Y1R-/- mice displayed 5-14% decreases in total, hind limb and spinal bone mineral density (BMD) and bone mineral content (BMC); although total BMC and BMD were unchanged in P2Y2R-/- mice, a 9-17% increase in the BMC of the hind limbs was observed. A more detailed analysis of trabecular bone using MicroCT (SkyScan 1172) showed significant decreases in the trabecular bone volume (BV/TV) of the P2Y1R-/- tibia (23%, $p<0.05$) and femur (35%, $p<0.01$). Quantification of trabecular number showed a reduction of 25% in the tibia ($p<0.01$) and 32% in the femur ($p<0.0001$). In the P2Y2R-/- mice, BV/TV was increased by 43% ($p<0.01$) in the femur and 21% in the tibia. Increases in femoral trabecular thickness (17%, $p<0.01$) and trabecular number (33%, $p<0.05$) were also observed. Significant changes in the structural model index and trabecular pattern factor were also noted in the P2Y1R-/- and P2Y2R-/- mice. The differences in the trabecular architecture of the P2Y1R-/- mice were somewhat unexpected given that P2Y1 receptor activation stimulates bone resorption in vitro; consequently, the effects of receptor deletion may predominantly affect osteoblast function. The increased trabecular bone parameters in the P2Y2R-/- mice are consistent with the in vitro effects on mineralisation; thus, deletion of the P2Y2 receptor could potentially limit the negative actions of extracellular nucleotides on bone. These data provide further evidence for the important role of purinergic receptors in modulating bone remodelling in vivo.

OC10

RANKL-INDEPENDENT OSTEOCLASTOGENESIS IN PAGET'S DISEASE

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Paget's disease is a focal disorder of bone remodeling characterized by large, numerous, and overactive osteoclasts. Osteoclasts are known to form from circulating mononuclear phagocyte precursors in the presence of M-CSF, a survival and proliferation factor, and RANKL, a key growth factor. It is thought that pagetic osteoclasts are exposed to high levels of M-CSF and are hypersensitive to RANKL, which would promote excessive osteoclast differentiation and activation. There are a number of growth factors and cytokines, however, that have been found to be able to substitute for either M-CSF or RANKL, including several members of the TNF superfamily, for example TNFalpha and LIGHT. We have found that another member of the TNF superfamily, APRIL, can also act as a RANKL substitute. Peripheral blood mononuclear cells (PBMCs) cultured with M-CSF (25ng/ml) and APRIL (25ng/ml) induced the formation of large numbers of TRAP+ and VNR+ multinucleated cells capable of resorbing bone. This APRIL-induced osteoclastogenesis was found to be independent of RANKL. To study the role APRIL and other substitutes have on pathological bone resorption in Paget's disease we cultured these growth factors with PBMCs extracted from Paget's disease patients. Our results showed that LIGHT induced the greatest amount of resorption (60% relative to M-CSF + RANKL (50ng/ml)) and this appeared to vary based on patients' treatment levels. This amount of resorption is 30% greater than the amount that LIGHT can induce with PBMCs from 'normal' patients. An ELISA indicated that the concentration of LIGHT in patients' serum was not elevated as compared to age/sex matched controls, which combined with our resorption results suggests these pagetic osteoclast precursors are hypersensitive to LIGHT. This could be due either to an increased expression of receptors or a promotion of downstream signalling pathways. However, an ELISA for APRIL and VEGF found that the concentration of these growth factors was significantly elevated above the controls and patients undergoing treatment, which suggests these factors may also have a key role in the pathological resorption characteristic of Paget's disease. Further analysis of the growth factor profile of Paget's disease patients may provide further insight into the pathogenesis of this disease.

OC11

UROCORTIN STRONGLY SUPPRESSES BONE RESORPTION IN IN-VITRO-DERIVED MURINE OSTEOCLASTS

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Urocortin (Ucn) is a 40 amino acid peptide, related to the hypothalmic corticotrophin releasing factor (CRF) family which now also includes Ucn 2 and 3. It is widely distributed in the CNS, digestive, cardiovascular, reproductive, immune and endocrine systems where it has diverse functions, including cardioprotection, control of appetite and modulation of inflammation. Of particular interest, Ucn has been shown to be increased in the synovial fluid of patients with rheumatoid arthritis, and Ucn reduces inflammation and bone erosion in a mouse model of the disease. However, nothing is known on the role

We therefore looked at the effect of Ucn on osteoclast generation and function. Ucn suppressed the generation of osteoclast-like cells (Ocl) in cultures of murine non-adherent bone marrow cells incubated for 5 days in M-CSF and RANKL. We then tested the effect of Ucn on osteoclast function. To do this, in vitro derived Ocl were sedimented onto bone slices, and incubated with/without Ucn. We found strong suppression of bone resorption. To confirm that this was a distinct effect on osteoclastic function rather than formation, we tested the effect of Ucn on actin ring formation. Ucn similarly potently suppressed the formation of actin rings in osteoclasts, in a dose-dependent manner, with 50% inhibition of actin ring formation occurring at 5x10-9M, and almost complete inhibition at 10-7M.

In all other tissues Ucn exerts its effect by activating either CRFR1 or R2 which are either coupled to Gs or Gq, consequently elevating cAMP or generating IP3/diacylglycerol. We assessed expression of Ucn and its receptors in bone cells using semi-quantitative RT-PCR. We found that although osteoclasts, macrophages and osteoblasts do not express any of the known CRF receptor subtypes, osteoclasts and macrophages both express Ucn itself. The absence of known receptor types was supported by experiments in which we found that a receptor-antagonist did not block the effects of Ucn on Ocl function. Furthermore, selective PKA/PKC inhibitors did not suppress the anti-resorptive effect of Ucn.

Therefore, Ucn potently inhibits osteoclasts via a mechanism independent of known CRF receptors, through a novel mechanism that is under current investigation.

OC12

TSG-6 REGULATES BONE REMODELLING THROUGH INHIBITION OF OSTEOBLASTOGENESIS AND OSTEOCLAST ACTIVATION

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TSG-6 (Tumour-Necrosis-Factor Stimulated Gene-6), a non-constitutively expressed protein consisting of contiguous Link and CUB modules, is secreted by a wide variety of cell types and has been shown to protect against joint damage in animal models of arthritis '1,2'. To date, various protein and glycosaminoglycan ligands have been identified, most interacting with the Link domain '3'. Here we have investigated the role of TSG-6 in bone metabolism by determining its effects on RANKL-induced osteoclast activity and BMP-mediated osteoblast differentiation and by comparing the histomorphometric parameters of WT and TSG-6 null mice.<BR.Using ELISA and BIAcore assays, we have shown that TSG-6 binds to sRANKL and to BMPs-2, 4,

5, 6, 7, 13 and 14, which are known to promote osteoclastogenesis and osteoblastogenesis, respectively. TSG-6 had no effect on RANKL-induced osteoclast formation but reduced bone resorption in a dose-dependent manner, suggesting that it might inhibit osteoclast activation by direct association with RANKL. Furthermore, TSG-6 inhibited the BMP-2-induced alkaline-phosphatase activity of osteoblastic cell lines. Full-length TSG-6 was found to inhibit osteoclast activation and osteoblast differentiation to a greater extent than either the isolated Link and CUB domain. Consistent with this, the dissociation constants determined here suggest that sRANKL and BMP-2 both interact at composite binding surfaces involving the Link and CUB modules of TSG-6. Micro-computerised tomography of non-arthritic TSG-6-/- mice revealed a significantly greater bone density than wild type, indicating a role for TSG-6 in bone homeostasis. In support of this, immunohistochemistry of WT mouse knee joints showed staining for TSG-6 that was strongest within epiphyseal and metaphyseal bone marrow, and at the margins of bone marrow and trabecular bone.

We therefore hypothesise dual functions for TSG-6 in bone remodelling; one protective, where it inhibits RANKL-induced bone erosion in inflammatory diseases such as arthritis, and the other homeostatic, where its interactions with BMP-2 and RANKL help to balance mineralization by osteoblasts and resorption by osteoclasts. As such TSG-6 has a potential role for the development of treatment stratergies in bone disease.

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OC13

EXPRESSION OF THE CELL TO CELL ADHESION MOLECULE, ALCAM, IN BREAST CANCER PATIENTS AND THE POTENTIAL LINK WITH SKELETAL METASTASIS

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Activated leukocyte cell adhesion molecule (ALCAM) has been shown to be involved in cell migration and in both homotypic/homophilic adhesion and heterotypic/heterophilic adhesion. It has been shown that a decreased level of ALCAM expression in human breast cancer tissue correlated with a significantly poor prognosis.

Aim: Previous studies have looked at nodal and general metastasis; in this analysis using an expanded tumour cohort, we, for the first time, specifically identified patients who went on to develop skeletal metastasis.

Primary breast cancer tissues (n=234) and non-neoplastic mammary tissue (n=34) were collected and patients were routinely followed up clinically after surgery. The immunohistochemical distribution and location of ALCAM was assessed in the normal breast tissue and carcinoma and the level of ALCAM transcripts in the frozen tissue was determined using real-time quantitative PCR. The results were analysed against the clinical data looking principally at the levels in patients with skeletal metastasis but also in relation to the nodal involvement, ER status, Nottingham Prognostic Index and survival.

The immunohistochemical staining intensity shows that the cytoplasmic staining in normal breast tissue is significantly stronger than that in breast cancer tissue (p=0.023) and also the breast cancer tissue from patients who went onto develop skeletal metastasis (p=0.048). The ALCAM transcript levels were the lowest in patient with skeletal metastasis (p=0.0048) compared to those who were disease free. Significantly lower transcript levels were also found the patients who developed local recurrence (p=0.040), and who died from breast cancer (p= 0.0075). Other indicators of poor prognosis show a significant difference: patients with moderate and poor NPI prognosis lower levels than those with a good prognosis (p=0.05, p=0.0089 respectively); and lower in patients with a positive ER status than those ER negative patients (p=0.043).

This study has for the first time shown that the patient who went on to develop skeletal metastasis tended to have the lowest levels of ALCAM transcript in their breast cancers. This fact could be used to provide patient with a more accurate prognosis and identify those who may benefit enhanced monitoring and early medical and orthopaedic treatment.

OC14

ROLE OF EPIGENETIC MODIFIERS IN BONE MARROW STROMAL CELL DIFFERENTIATION

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Regenerative medicine provides the hope for many intractable diseases as a treatment option and the area is currently the subject of intense investigation in academia and industry. Human bone marrow stromal cells (HBMSCs) possess the ability to differentiate into a variety of cell types of the stromal lineage including cells of the osteogenic and chondrogenic lineages. However, the process of in vitro differentiation is usually inefficient, difficult to reproduce in many cases and, to date, unable to produce homogenous cell populations, which is critical for tissue engineering. Epigenetic regulation of gene expression is recognized as a key mechanism governing cell determination, commitment, and differentiation as well as maintenance of those states. The main components of epigenetic control are DNA methylation and histone acetylation. During development, the epigenetic status changes as cells differentiate along specific lineages. We reasoned that epigenetic modifiers might direct the differentiation pathway of HBMSCs towards either osteogenic or chondrogenic lineage. HBMSCs were serum-starved for 24 hours to synchronise the cell cycle, then treated on three consecutive days either with the DNA demethylating agent 5-Aza-deoxycytidine (5-Aza-dC) 1?M, or the histone deacetylase inhibitor Trichostatin A (TSA) 100 nM or a combination of both. After confluency, the cells were grown in pellet culture for 21 days to facilitate formation of an extracellular matrix. 5-Aza-dC increased the amount of osteoid in the pellet by at least 5 fold compared with controls as assessed by histochemistry, whereas TSA enhanced formation of a cartilage matrix. The differentiation was further enhanced by culturing the pellets in osteogenic or chondrogenic media. These studies suggest that loss of DNA methylation stimulates osteogenic differentiation, whereas inhibition of histone deacetylation favours chondrogenesis. Epigenetic changes thus play an important role in HBMSCs differentiation and offer new approaches in skeletal tissue engineering programs. The challenge will be to define the crucial genes in which loss of DNA methylation has taken place or how changes in histone acetylation (and other histone modifications) affect lineage differentiation.

OC15

CHONDROCYTE SURVIVAL IN ARTICULAR CARTILAGE EXPLANTS - THE INFLUENCE OF SUBCHONDRAL BONE

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Articular cartilage is attached to subchondral bone but little is known regarding bone-cartilage interactions important for chondrocyte survival. In this study, bovine articular cartilage has been evaluated in vitro to determine if the presence of subchondral bone influences chondrocyte survival. We hypothesised that (1) Excision of subchondral bone from articular cartilage would increase in situ chondrocyte death in explant culture and, (2) Chondrocyte death could be abrogated by co-culturing articular cartilage with the excised subchondral bone.

Articular cartilage explants (n=132) harvested from the metacarpophalangeal joints of three-year old cows (N=12) were placed into three groups: (1) subchondral bone excised from articular cartilage (Group A) (2) subchondral bone left attached to articular cartilage (Group B) (3) subchondral bone excised, but co-cultured with articular cartilage (Group C). Explants were cultured in serum-free media over 7 days with or without media changes to assess the effect of potential soluble mediators. Using confocal laser scanning microscopy to image in situ chondrocytes, fluorescent probes to determine cell viability and biochemical assays to detect alterations in the culture media, differences in the chondrocyte responses (cell density, spatial distribution, percentage cell death) and culture medium composition between Groups A, B and C were quantified over time (2.5 hours versus 7 days).

There was no significant change in cell density for Groups A, B and C over 7 days (t-test, p>0.05). With excision of subchondral bone from

articular cartilage (Group A), there was a marked increase in chondrocyte death over 7 days primarily within the superficial zone involving an extensive area of the articular surface ($p<0.05$). There was no significant increase in chondrocyte death over the same time period for Groups B and C ($p>0.05$). Corresponding increases in the protein content of the culture media for Groups B and C but not for Group A, suggested that the release of soluble factors from subchondral bone may have influenced chondrocyte survival in the superficial zone.

Subchondral bone interacts with articular cartilage in vitro and promotes chondrocyte survival in the superficial zone. These data support the concept of a functional bone-cartilage system in vivo.

OC16

ABNORMAL IN SITU HUMAN CHONDROCYTE MORPHOLOGY IS ASSOCIATED WITH INCREASED LEVELS OF IL-1BETA BUT NOT MMP-13

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Chondrocytes are responsible for the mechanical resilience of cartilage by controlling the synthesis/degradation of the extracellular matrix. In osteoarthritis (OA), increased activity of cytokines/degradative enzymes (e.g. IL-1beta, MMP-13) play a key role leading to matrix breakdown/cartilage loss. Studying early events in OA might identify targets for limiting the deleterious changes to cartilage stability. Human chondrocyte shape in situ is normally elipsoidal/spheroidal however abnormal forms within otherwise macroscopically normal cartilage are present. Changes to cell shape can alter ECM metabolism and thus these abnormal forms might be an early event in OA. We have investigated whether levels of IL-1beta and MMP-13 are altered in human chondrocytes of abnormal morphology.

Tibial plateau cartilage was obtained from patients undergoing knee arthroplasty and only areas graded 0 or 0-1 studied. The shape of fluorescently-labelled in situ chondrocytes was classified by confocal scanning laser microscopy with cartilage depth, and cells characterised as normal (no cytoplasmic processes) or abnormal (one/more cytoplasmic process). Within grade 0 cartilage about 40% of the cells demonstrated abnormal morphology with a reduced proportion in deep zones. Fluorescence immunohistochemistry of antibodies for IL-1beta or MMP-13 was studied in the same cells and quantified. There was an increase in IL-1beta fluorescence with abnormal chondrocytes within the superficial ($p=0.033$; 21 joints >190 cells) and deep zones ($p=0.001$; 8 joints >100 cells). There were no differences between MMP-13 labelling of normal compared to abnormal chondrocytes within either the superficial or deep zones.

Our results suggest that in relatively non-degenerate cartilage, a proportion of the chondrocyte population demonstrated abnormal morphology and that these cells have elevated levels of IL-1beta but not MMP-13. However, we do not know if chondrocyte shape alters cytokine levels, or vice versa. Additionally, the role of cartilage age is unclear, as although the cartilage samples were relatively normal they were obtained from aged individuals. Nevertheless these results show changes to chondrocyte morphology and increased levels of IL-1beta, and thus presumably matrix catabolism - in relatively normal human articular cartilage, raising the possibility that this is an early event in cartilage degeneration.

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OC17

HEAT SHOCK PROTEIN AND APOPTOSIS IN SUPRASPINATUS TENDINOPATHY

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Excessive apoptosis has been found in torn supraspinatus tendon1 and mechanically loaded tendon cells2. Following oxidative and other forms of stress, one family of proteins that is often unregulated are Heat Shock Proteins (HSPs). The purpose of this study was to determine if HSPs were unregulated in human and rat models of tendinopathy and to determine if this was associated with increased expression of regulators of apoptosis (cFLIP, Caspases 3&8).

A running rat supraspinatus tendinopathy overuse model 3 was used with custom microarrays consisting of 5760 rat oligonucleotides in duplicate. Seventeen torn supraspinatus tendon and matched intact subscapularis tendon samples were collected from patients undergoing arthroscopic shoulder surgery. Control samples of subscapularis tendon were collected from ten patients undergoing arthroscopic stabilisation surgery and evaluated using semiquantative RT-PCR and immunohistochemistry.

Rat Microarray: Upregulation of HSP 27 (x3.4) &70 (x2.5) and cFLIP (x2.2) receptor was noted in degenerative rat supraspinatus tendon subjected to daily treadmill running for 14 days compared to tendons of animals subject to cage activity only. Histological analysis: All torn human supraspinatus tendons exhibited changes consistent with marked tendinopathy. Matched subscapularis tendon showed appearances of moderate-advanced degenerative change. Apoptosis mRNA expression: The expression levels of caspase 3 & 8 and HSPs 27 & 70 were significantly higher in the torn edges of supraspinatus when compared to matched subscapularis tendon and control tendon ($p<0.01$). cFLIP showed significantly greater ($p<0.001$) expression in matched subscapularis compared to supraspinatus and control tendon. Immunohistochemical analysis: cFLIP, Caspase 3 & 8 and HSP 27 and 70 was confirmed in all samples of torn supraspinatus tendon. Significantly increased immunoactivity of Caspase 3&8 and HSP 27 & 70 were found in torn supraspinatus ($p<0.001$) compared to matched and normal subscapularis. The proteins were localized to tendon cells.

The finding of significantly increased levels of Heat Shock Proteins in human and rat models of tendinopathy with the co-expression of other regulators of apoptosis suggests that Heat Shock Proteins play a role in the cascade of stress activated-programmed cell death and degeneration in tendinopathy.

OC18

GENETIC VARIATION IN THE AROMATASE GENE INFLUENCES HEEL ULTRASOUND PARAMETERS: RESULTS FROM THE EUROPEAN MALE AGEING STUDY

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Genes related to oestradiol metabolism, such as the aromatase gene (CYP19A1), are attractive candidates for a role in bone homeostasis. Previous studies have demonstrated that individuals with loss-of-function mutations in CYP19A1 have Osteopenia. CYP19A1 is in a region of linkage to bone mineral density (BMD); however, genetic association studies have produced conflicting results. We used data from the European Male Aging Study (EMAS) to investigate if polymorphisms in CYP19A1 were associated with heel qualitative ultrasound (QUS) parameters; speed of sound (SOS) and broad band ultrasound attenuation (BUA) in men.

Men aged 40-79 years were recruited from population registers in 8 European centres for participation in EMAS and invited for a blood sample and heel QUS (Hologic, SAHARA). Fourteen polymorphisms spanning CYP19A1 were genotyped; 13 SNPs using the Sequenom MassArray platform and 1 indel using fluorescently-labelled PCR, an ABIPRISM 3100 genetic analyser and Genescan software (ABI). Oestradiol (E2) and testosterone (T) levels were measured using electrochemiluminescence immunoassays (Elecys E170, Roche). The relationships between QUS parameters (BUA & SOS) and CYP19A1 polymorphisms were assessed using linear regression, generating corrected standard errors to account for heteroscedasticity due to recruitment centre, with results expressed as beta-coefficients (beta) and 95% confidence intervals (CI). Adjustments were made for age and centre.

2693 men, mean±SD age 60.1±11.1 years were included. Their mean±SD BUA was 80.0±18.9 dB/MHz and SOS 1550.2±34.1 m/s. Significant associations were observed between QUS parameters and

multiple SNPs in a linkage disequilibrium block spanning intron 1 to the 3'UTR. The strongest association was found at the TCT indel in intron 4. Individuals carrying the deletion allele had a lower BUA: heterozygotes (beta=-1.96(-3.43, -0.49) p=0.009), homozygotes (beta=-3.32(-5.59, -1.05) p=0.004) when compared to individuals without the deletion allele. Similar associations were found with SOS: heterozygotes (beta=-3.68(-6.31, -1.04) p=0.006), homozygotes (beta=-7.13(-11.22, -3.04) p=0.001). The associations remained significant after further adjustment for height, weight, T and E2 levels. Heel BMD, derived from BUA and SOS, also showed significant association with polymorphisms in CYP19A1.

Our data confirm evidence of association between polymorphisms in CYP19A1 and bone health in a population sample of European men.

OC19

MATERNAL VITAMIN D INSUFFICIENCY AND FETAL BONE DEVELOPMENT

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Epidemiological studies suggest that maternal vitamin D status during pregnancy has a long-term influence on the bone health of the offspring. Using three-dimensional ultrasound (3DUS), we have previously demonstrated a subgroup of fetuses which show splaying of the distal femoral metaphysis. This is similar to the skeletal changes seen with childhood rickets and therefore in this study we explored the relationship between maternal vitamin D status and offspring distal femoral metaphyseal splaying in utero.

Participants were recruited from the Southampton Womens' Survey, an ongoing longitudinal study of women aged 20-34 years in Southampton, UK, characterised in detail before and during pregnancy. We used a KretzGE Voluson 730 3DUS system to acquire thigh volumes of 424 fetuses at both 19 and 34 weeks gestation. Measurements were taken on stored images of the femoral distal cross-sectional area (CSA), using a method developed for this study. 25-hydroxyvitamin D concentrations were measured in maternal blood serum samples taken at 34 weeks gestation (Diasorin RIA).

Maternal 25(OH)-vitamin D blood values ranged from 8 to 180 nmol/L (median 61 nmol/L). These were log transformed for statistical analysis and correlated with the fetal femur distal CSA measurements. Lower maternal vitamin D concentrations were associated with greater fetal femur distal CSA at 19 weeks gestation ($r = -0.15$, $p = 0.003$) and at 34 weeks gestation ($r = -0.11$, $p = 0.03$). We derived the ratio of distal CSA/femur length as a measure of femur shape: lower maternal vitamin D levels were associated with a higher CSA/femur length ratio at 19, but not at 34 weeks gestation ($r = -0.17$, $p<0.001$ and $r = -0.09$, $p = 0.07$, respectively).

Lower maternal vitamin D status in pregnancy was associated with widening of the distal metaphysis of the fetal femur, as early as the 19th week of gestation. This finding raises the possibility that improving maternal vitamin D status could improve the bone health of the offspring.

OC20

PARENTAL HEIGHT AND CHILDHOOD MILK INTAKE AT 4 YEARS ARE ASSOCIATED WITH CATCH UP BONE MINERAL ACCRUAL IN EARLY CHILDHOOD

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Peak bone mass is a major determinant of osteoporosis risk in later life and is strongly influenced by patterns of post-natal growth. These patterns, in turn may be influenced by skeletal mineralization at birth and subsequent catch up or down. In this study we explored the parental and childhood determinants of skeletal growth relative to peers in 4-year old children.

Children were recruited from offspring in the Southampton Womens Survey (SWS), a longitudinal study of women aged 20-34 years, who were characterised in detail before and during pregnancy. The children underwent assessment of diet, lifestyle and health by questionnaire, anthropometry and DXA measurement of whole body bone mass (Hologic Discovery using paediatric software). 254 children (130 boys) had also undergone DXA assessment within 16 days of birth. Within group Z-scores for bone area(BA), bone mineral content(BMC), areal bone mineral density(aBMD) and estimated volumetric BMD(vBMD) were generated at both timepoints and change defined by 4 year Z-score minus birth Z-score, adjusted for the baseline measurement. Catch up or down was defined as a change of +/- 0.67 SD or more from birth to 4 years. Correlation and logistic regression methods were used.

There were strongly statistically significant relationships between indices of bone mass at birth and at 4 years old except for vBMD (BA: $r=0.32, p<0.0001$; BMC: $r=0.38, p<0.0001$; aBMD: $r=0.15, p=0.002$; vBMD: $r=-0.04, p=0.546$). After adjusting for neonatal BMC, 52 (20.5%) children showed catch up and 59 (23.2%) showed catch down for BMC. The predictors of increased chance of catch up vs down for BA and BMC included maternal height (BMC: OR=1.07; 95%CI:1.00-1.14, p=0.049), paternal height (BMC: OR=1.16; 95%CI:1.05-1.28, p=0.004) and childhood milk intake at 4 years (BMC: OR=7.6; 95%CI:1.4-39.9, p=0.02). The relationships with change in aBMD were weaker and there were no significant predictors of change in vBMD. All associations remained robust after adjusting for gestational age.

Parental height and childhood milk intake predicted chance of alteration of the skeletal growth trajectory in early childhood, after adjusting for birth size. These data are consistent with an interaction between genetic and environmental factors in determining the trajectory of skeletal mineral accrual in early childhood.

OC21

COMPARISON OF DXA AND QUS FOR PREDICTION OF FRACTURE RISK AMONG OLDER MEN AND WOMEN: THE EPIC-NORFOLK COHORT STUDY

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The role of quantitative ultrasound (QUS) for management of osteoporosis is debated. Although QUS is known to be correlated with bone mineral density (BMD), the predictive power of QUS for fractures in comparison to dual-energy X-ray absorptiometry (DXA), the current reference standard for diagnosis of osteoporosis, is unclear. We examined this in a sample of men and women in the European Prospective Investigation into Cancer (EPIC)-Norfolk who had both heel QUS and hip DXA between 1995 and 1997 and were followed for any incident fracture up to March 2007. From 1,454 participants (701 men) aged 65-76 years at baseline, 79 suffered a fracture over 15,567 person-years of follow-up (10.3±1.4 years). In a sex-stratified multivariate Cox proportional-hazard model including age, height, weight, past history of fracture, smoking, alcohol intake and DXA total hip BMD, 1 SD decrease in BMD was associated with a hazard ratio (HR) for fracture of 2.28 (95% CI 1.75-2.98). In multivariate model with heel broadband ultrasound attenuation (BUA) in place of BMD, HR for 1 SD decrease in BUA was 2.02 (95% CI 1.54-2.65). While the global measures of model fit (including Bayesian and Akaike's information criteria, LR chi-square, D-statistic, Nagelkerke's and Cox-Snell R-square) were slightly supporting the model with DXA measure, measures of discrimination (area under ROC curve 0.685 vs 0.679) and calibration (Hosmer-Lemeshow statistic 0.82 vs 0.45) showed relative superiority of the model with BUA. Using the alternate Cox models with DXA and BUA, we calculated exact 10-year absolute risk of fracture for all participants and categorized them in groups of <5%, 5% to <15%, and >=15%. Comparison of groupings based on DXA vs BUA models showed a total reclassification of 24.9% of participants with the predicted risks using BUA model closer to the observed risks (especially among the 52.2% reclassified highest-risk group). The power of QUS for prediction of fractures among the elderly appears comparable to that of DXA. Given the ease and low cost of ultrasound, further studies or meta-analyses are required to clarify whether QUS with clinical risk factors would be cost-effective for primary care case-finding in the non-availability of DXA.

OC22

USE OF DXA-BASED STRUCTURAL ENGINEERING MODELS OF THE PROXIMAL FEMUR TO PREDICT HIP FRACTURE

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Several DXA-based structural engineering models of the proximal femur have been developed to estimate stress due to sideway falls. Their usefulness in predicting hip fracture has not yet been established and we therefore evaluated these models.

The hip DXA scans of 51 postmenopausal women with hip fracture and 153 age, height and weight matched controls were re-analyzed using a special version of Hologic software that produced a pixel-by-pixel BMC map. Based on the maps, stress analysis using curved-beam, curved composite beam and finite element models were performed. An index of fracture risk (IFR) was defined as the stress divided by the yield stress at each pixel and the maximum and averaged IFR in the femoral neck (FN), trochanter (TR) and total hip (TH) were calculated. Student test, conditional logistic regression and receiver operating characteristics (ROC) analysis were conducted. The analysis was performed regarding hip fracture as a homogeneous condition and repeated separately for FN and TR fractures.

All IFR parameters in the trochanter and total hip and a variable number of IFR parameters in the femoral neck were significantly ($p<0.05$) larger in the case than in the control groups. The odds ratio of increased fracture risk associated with one SD increase in those parameters ranged from 1.4 (95% CI 1.1-1.9) to 4.2 (95% CI 2.3-7.5). IFR parameters and BMD were highly negatively correlated (coefficients ranged from -0.57 to -0.72) and they did not complement each other in fracture prediction. The averaged IFR derived from the finite element model had a significantly ($p<0.05$) larger area under the ROC curve (AUC) and higher specificity at 80% sensitivity than TH BMD in discriminating either hip fracture as a whole (AUC 0.817 v. 0.771, Specificity 71 v. 58) or FN fracture (AUC 0.805 v. 0.742, Specificity 66 v. 53).

All structural engineering models of the proximal femur are useful in predicting hip fracture but only the finite element models can produce parameters that discriminate hip fracture significantly better than total hip BMD.

OC23

OSTEOPROTEGRIN AS A PROGNOSTIC INDICATOR FOR BONE METASTASIS IN DUCTAL BREAST CANCER

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Osteoprotegrin is a soluble decoy receptor which binds to receptor activator of NF-kappaB ligand (RANKL) inhibiting its interactions with RANK and so preventing osteoclast formation. It is down regulated within the bone microenvironment in the presence of metastatic caners partly as a result of parathyroid hormone-related protein (PTHrP) expression.

Aim: To investigate whether osteoprotegrin transcript levels can be used to predict the occurrence of bone metastases in the largest group of breast cancers, the ductal carcinomas.

Primary ductal breast cancer tissues (n =90) and non-neoplastic mammary tissue (n = 32) were collected and patients were routinely followed up clinically after surgery. The immunohistochemical distribution and location of osteoprotegrin was assessed in the normal breast tissue and carcinoma and the level of osteoprotegrin transcripts in the frozen tissue was determined using real-time quantitative PCR. The results were analysed against the clinical data looking principally at the levels in patients with different prognostic out comes, metastasis, local recurrence, skeletal metastasis and death but also in relation to indicators of poor prognosis: the nodal involvement, ER status and the Nottingham Prognostic Index.

The osteoprotegrin transcript levels were significantly lower in patients who developed metastases or who passed away as a result of the breast cancer. Compared to patients who were disease free at follow-up the transcript levels in patients with metastases ($p=0.047$) or who died ($p=0.050$) were significantly lower. Patients who had bone and generalized metastases also had a significantly lower osteoprotegrin transcript level ($p=0.049$) compared to normal subjects. Indicators of poor prognosis such as nodal involvement, ER status and Nottingham Prognostic Index did not show a significant difference, however, patients who were disease free and had a positive ER status (an indicator of poorer prognosis) did have a significantly lower transcript level ($p=0.038$).

In ductal carcinoma decreased levels of osteoprotegrin transcript correlated with a poor prognosis. The data suggests that osteoprotegrin expression is of clinical significance with patient with low transcript levels suffering from a cancer with a more aggressive phenotype making them more susceptible to skeletal metastases and death.

OC24

INHIBITING DICKKOPF-1 (DKK-1) PREVENTS THE DEVELOPMENT OF OSTEOLYTIC BONE DISEASE IN MULTIPLE MYELOMA

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Multiple myeloma (MM) is associated with the development of osteolytic bone disease caused by increased osteoclastic bone resorption and impaired osteoblastic bone formation. Dickkopf-1 (Dkk-1), a soluble inhibitor of Wnt signaling and osteoblastogenesis, is elevated in the serum of patients with MM and correlates with the presence of osteolytic bone disease. In this study, we investigated the effect of inhibiting Dkk-1, on the development of osteolytic bone lesions in the 5T2MM murine model of MM. We demonstrated using immunohistochemistry, that in common with some primary human myeloma cells, Dkk-1 is expressed by murine 5T2MM myeloma cells. Injection of 5T2MM cells into C57BL/KaLwRij mice resulted in the development of osteolytic bone lesions, mediated by increased osteoclast numbers and a decrease in osteoblast numbers and bone formation. Mice bearing 5T2MM cells were treated with an anti-Dkk-1 antibody (10mg/Kg, i.v. twice weekly) from the time of paraprotein detection (8 weeks). Anti-Dkk-1 treatment prevented 5T2MM induced suppression of osteoblast numbers ($p<0.001$) and the surface occupied by osteoblasts ($p<0.001$) when compared to vehicle treated mice. Treatment increased the mineralising bone surface by 28 percent and the rate of bone formation by 25 percent, although not significantly; however, there was no change in mineral apposition rate. Inhibiting Dkk-1 had no effect on osteoclast numbers or the bone surface occupied by osteoclasts. Importantly, microCT analysis demonstrated that anti-Dkk-1 treatment significantly protected against 5T2MM induced trabecular bone loss ($p<0.05$) and prevented the development of osteolytic bone lesions ($p<0.05$). Treatment had no significant effect on serum paraprotein concentrations. These data suggest that inhibiting Dkk-1 prevents the suppression of bone formation and in doing so is effective in preventing the development of osteolytic bone disease in myeloma, offering an effective therapeutic approach to treating this important aspect of multiple myeloma.

OC25

A RANDOMISED DOUBLE BLIND PLACEBO CONTROLLED TRIAL TO DETERMINE THE MAGNITUDE OF CHANGE IN BONE MINERAL DENSITY IN RESPONSE TO LASOFOXIFENE

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Lasofoxifene is a novel selective estrogen receptor modulator (SERM) currently being developed for the treatment of postmenopausal osteoporosis. The aim of this study was to determine the effects of lasofoxifene on bone mineral density (BMD) at the lumbar spine (LS), total hip (TH) and distal forearm (DF).

This was a 2-year prospective, randomized, double-blind, placebo controlled study. Fifty-two postmenopausal osteopenic women, ages 55 to 77 (mean 63.7) years were recruited from a single centre (Sheffield, UK), 43 of whom completed the 2 years. Subjects were randomized to receive either lasofoxifene (0.25 mg/day) or placebo, in a 1:1 ratio. All women received calcium (1000mg/d) and vitamin D (400 IU/d) for a lead-in period of 6 weeks and for the duration of the study. Duplicate measurements of BMD at the LS and TH were made by dual-energy x-ray absorptiometry (DXA, Hologic QDR 4500

Acclaim) and at the DF (DTX 200, Osteometer) at baseline, one and two years in all subjects.

There were no significant differences in mean baseline BMI or BMD between the treatment groups. Percentage change in mean LS BMD, from baseline, was significantly (p<0.001) greater in the lasofoxifene group compared to placebo at 1 year (2.41% and -0.89% respectively) and 2 years (3.33% and 0.24% respectively). An increase in TH BMD was apparent after 2 years in the lasofoxifene (2.20%) group compared to placebo (0.00%) (P<0.01). There was no significant difference in the change in DF BMD in women treated with placebo or lasofoxifene at either 1 or 2 years.

We conclude that the use of lasofoxifene therapy leads to significant increases in LS BMD after one year of therapy, whereas a change in TH BMD was not apparent until 2 years of therapy. In this group of postmenopausal women, no significant change in BMD at the DF was observed through 2 years of treatment.

OC26

THE METAPHYSEAL-DIAPHYSEAL INDEX SCORE, A NOVEL METHOD OF PREVENTING INTRA-OPERATIVE PERIPROSTHETIC FRACTURE IN MODERN UNCEMENTED HEMIARTHROPLASTY

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Introduction: The JRI Furlong HAC LOL hemiarthroplasty stem has shown increased periprosthetic fracture rates compared to previous literature(15.2% vs 7.4%). This study will seek to identify a measurable radiographic index, the Metaphyseal-Diaphyseal Index (MDI) score to determine whether intra-operative fracture in osteoporotic bone can be predicted to influence the type of prosthesis used (cemented or uncemented).

Methodology: Over 5 years prospectively, a cohort of 560 consecutive patients undergoing hemiarthroplasty (cemented and uncemented) were evaluated. Clinical outcomes and radiographic analysis was performed. The Vancouver Classification was used to classify periprosthetic fracture. The MDI score was calculated using radiographs from the uncemented group. As a control (gold standard), Yeung et al's CBR score was also calculated. From this, a receiver operating characteristic (ROC) curve was formulated for both scores and area under the curve (AUC) compared. Intra and inter-observer correlations were determined. Cost analysis was also worked out for adverse outcomes.

Results: 407 uncemented and 153 cemented stems were implanted. 62 periprosthetic fractures occurred in the uncemented group (15.2%), 9 occurred in the cemented group (5.9%), p<0.001. The revision rate for sustaining a periprosthetic fracture (uncemented group) was 17.7%, p<0.001. MDI's AUC was 0.985 compared to CBR's 0.948, p<0.001. The MDI score cut-off to predict fracture was 21, sensitivity 98.3%, specificity 99.8%, positive predictive value 90.5% and negative predictive value 98%. ANCOVA analysis ruled out any other confounding factors as being significant. The intra and inter-observer Pearson correlation scores were r=0.99, p<0.001. The total extra cost due to the intra-operative fractures was ú40,140.

Discussion: The MDI score has been shown to be a potentially useful, cost effective way of preventing this serious complication from occurring. We recommend that any femur scoring 21 or less on the MDI score be considered for cemented hemiarthroplasty. Level of evidence: Level 2 Diagnostic Study: Investigating a diagnostic test against gold standard.

OC27

ANALYSIS OF EX VIVO RESURFACING HIP PROSTHESES AND COMPARISON WITH CLINICAL DATA

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Resurfacing metal-on-metal hip arthroplasty is currently showing promising clinical results. However there are concerns related to such implants, including the elevated levels of metal ions typically seen in patients. Valuable data can be obtained from explanted prostheses but due to their recent introduction few retrieval studies on resurfacing hip prostheses have been published.

Five ASR hip resurfacing prostheses were revised due to pain. From two patients, head and cup were available for independent explant analysis. In the other three cases only femoral components were available. All were removed from female patients and all were revised to ceramic-on-ceramic hip prostheses. Post-operative radiographic measurements of cup inclination and anteversion were obtained using the EBRA software. The surface roughness values of the articulating surfaces of the explants were measured using a non-contacting profilometer. A co-ordinate measuring machine was used to measure the diameter of the head and the cup and thus the diametral clearance. The same measurements were then taken from a new unused ASR prosthesis and compared. Using elastohydrodynamic theory the minimum effective film thickness of the implant was calculated. In turn this allowed the lubrication regime to be determined.

The average roughness values of the head and the cup of one implant were found to be 0.135microns and 0.058microns respectively, with a diametral clearance of 110microns. These results indicated that, at the time of removal, the prosthesis would have operated in the boundary lubrication regime. Other explants showed evidence of localised contact between the head and the rim of the acetabular cup, and these showed articulating surfaces with typical roughness values of between 0.025microns and 0.050microns. The new ASR had head and cup surface roughness values of 0.010microns and 0.012microns respectively and a diametral clearance of 87microns, implying that a new implant would operate under fluid film lubrication. All cups five were implanted with inclination angles over 45 degrees and anteversion over 25 degrees.

These results suggest that components with high inclination and anteversion angles display greater than expected wear and may operate in boundary rather than fluid film lubrication which may eventually lead to early failure.

OC28

EFFECTS OF METAL IONS ON OSTEOBLAST ACTIVITY

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Metal-on-metal (MoM) bearing technology, made of cobalt-chromium (Co-Cr) alloys, is being used in anticipation of extending the durability of hip replacements. Increasingly, concern has been expressed that long term exposure to Co2+ and Cr3+ could cause DNA damage and immune dysfunction; specifically a reduction in the circulating number of CD8+ cytotoxic cells. More recently, we reported that Co2+ and Cr3+ affected the differentiation of osteoclast precursors into bone-resorbing osteoclasts. Despite these observations the effects of metal ions on osteoblast activity have been poorly investigated. The aim of the current study was to elucidate the effects of various metal ions on osteoblast activity in vitro.

Cells of the human osteosarcoma cell line SaOS-2 were cultured in the presence of 0, 1, 10 and 100 µM Co2+ and Cr3+. The morphology, viability, cytokine release (TNFalpha, IL-1beta, IL-6, LIGHT, MIP-1alpha and VEGF) and alkaline phosphatase activity were investigated after 24h and 48h in contact with metal ions. Finally the capacity of SaOS-2 to produce and mineralize a new bone matrix was assessed by the Alizarin red method. All experiments were repeated at least 5 times and the differences between each were determined using non-parametric Mann-Whitney test.

Compared to untreated cultures, although the morphology looked normal after 48h, the viability indicated that Co2+ and Cr3+ ions at high concentrations induced some significant and irreversible damages to the osteoblast cells. Interestingly, any of the cytokines investigated were released in contact with metal ions after 24h or 48h. The alkaline phosphatase activity was significantly increased by low concentrations of Co2+ and decreased by high concentrations of Cr3+ after 24h and 48h. Moreover, the degree of mineralization of a new bone matrix in vitro was significantly reduced when the SaOS-2 cells were exposed to high concentrations of Cr3+, but significantly increased when they were exposed to Co2+.

Our results indicated that irreversible damages are caused to the cells as soon as 24h with high concentrations of metal ions. For osteoblasts cells, Co2+ appeared to be less toxic than Cr3+ at high concentrations.

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OC29

CEMENT MANTLE THICKNESS DETERMINES CEMENT PENETRATION AND STEM SUBSIDENCE IN IMPACTION GRAFTING

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The adequacy of cement mantles around some impaction-grafting systems has been criticised yet good clinical results have been reported. This study investigates this contradiction by asking (1) Does cement mantle thickness affect cement penetration depth? (2) Does cement mantle thickness affect early mechanical stability?

Twelve artificial femora were prepared to simulate cavitary defects. Porcine cancellous bone was morselized. The defect was reconstructed by impaction grafting, using a size 0, 1 or 2 tamp. Bone cement was injected, and a size 0, 1 or 2 Exeter stem inserted. By using all nine tamp/prosthesis combinations, 0-4 mm thick cement mantles were produced. Femora were positioned in a testing machine and loaded with 2500 cycles of 2500 N. Prosthesis subsidence and retroversion were measured. Each femur was sliced transversely and the sections digitised. Solid cement mantle thickness and cement penetration depth were measured using image analysis. Correlation analysis was used to find if tamp/stem mismatch (nominal mantle thickness) influenced actual solid mantle thickness and cement penetration. We then analysed if tamp size, stem size, solid mantle thickness or cement penetration determined stem subsidence and retroversion.

Cement mantles were produced with an average thickness of 1.7-2.2 mm, with largest variations proximally (1.5-2.8 mm). Average cement penetration was 0.3-2.0 mm, with largest variations proximally (0.4-3.5 mm). Thicker solid mantles gave less penetration ($r=-0.62$). Stem subsidence ranged from 0.4-2.5 mm and correlated significantly with tamp size ($r=0.59$, $p<.05$). Better correlations were found with solid mantle thickness ($r=0.90$, $p<0.05$) and cement penetration depth ($r=-0.81$). Stem retroversion ranged from 0.1-2.0 degrees and correlated with stem size ($r=-0.53$) but not with tamp size.

Tamp/stem mismatch determined the thickness of the solid cement mantle around impaction-grafted stems, and thinner mantles were associated with deeper cement penetration. Thinner mantles and deeper penetration were associated with reduced stem subsidence. Stem retroversion was associated with stem size only, and larger for thinner stems. Thinner cement mantles will therefore be associated with deeper penetration and reduced stem subsidence upon loading. This association may explain the good long-term results of impaction-grafted Exeter stems, despite deficient solid cement mantles.

OC30

MENISCECTOMY ELEVATES FRICTION AND WEAR OF ARTICULAR CARTILAGE IN THE KNEE JOINT

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Total meniscectomy has been shown to induce osteoarthritic changes in the underlying articular cartilage(AC) and bone in the natural knee (Fairbank 1948; McDermott 2006). This indicates the meniscus plays an important protective role, providing joint congruity and distributing contact forces, hence reducing contact stress. However, no friction and wear studies have been performed on meniscectomy. The aim of this study was to study the tribological response of the medial compartmental natural knee with and without the intact meniscus, under physiological dynamic loading and motion. The effect of normal and reduced loading was investigated.

Eighteen month old bovine medial compartmental knees were used. A pendulum friction simulator (Simulation Solutions, UK) was used to apply a dynamic axial loads with peak loads of 1000N (normal) and 260N (reduced). Flexion-extension of amplitude 23degrees was applied and the experiments ran for 3600 cycles at 1Hz. Lubricant was 25% bovine serum in saline. A 9.4 Tesla MRI (Bruker) scanner and Analyze software (Mayo Clinic, US) were used to calculate wear volumes. A surface profilometer (Talysurf, Taylor-Hobson, UK) was used to measure the surface roughness of the specimen before and after the test.

Coefficient of friction was found to increase with increased loading, with and without meniscus. With meniscus intact, no wear was found on AC and contact stresses were 4.9MPa and 2.8MPa, for normal and reduced loading respectively. On removal of meniscus, friction was higher at both loading conditions and surface fibrillation found on some of the AC surfaces. Contact stresses rose to 17.2MPa and 8.6MPa for normal and reduced loading.

This study has shown for the first time, the direct elevation of the coefficient of friction, immediate surface fibrillation and biomechanical wear of AC upon removal of the meniscus. On removal of meniscus, peak stresses rose and surface damage occurred on AC surfaces. The removal of the meniscus means forces act across smaller areas and contact stresses are increased. Wear is increased due to the subsequent increase in direct solid-solid contact and loss of fluid support due to the unique biphasic nature of AC. This further supports retaining meniscus whenever possible in knee joint surgery.

OC31

VERIFICATION OF A NOVEL SPINE WEAR SIMULATOR

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Total disc replacement is an alternative to spinal fusion in treating degenerative disc disease, whilst preserving motion and reducing the risk of subsequent DDD at adjacent levels. Current designs have evolved from technology used in total hip replacements with metal-metal or metal-PE bearing surfaces. These articulating systems may be prone to wear and it is essential the medical engineering community assess their performance using appropriate simulators

Utilising previous Leeds simulation design experience, current knowledge on spinal kinetics and prevailing Standards for spinal testing, a comprehensive set of requirements was generated from which a simulator design was produced. The Leeds Spine wear simulator, developed in conjunction with Simulation Solutions Ltd, incorporates five active degrees of freedom: axial compression, axial rotation, flexion-extension, lateral bending and anterior-posterior displacement. The fifth DOF, unique to the Leeds simulator, is anticipated to be particularly important for the study of mobile bearing devices such as the Charité. Loads and motions are applied by electro-mechanical actuators, providing accurate and precise control without the low band width suffered from pneumatics or contamination from hydraulic systems. This validation study determines the accuracy and precision of the simulator with regards to the degrees of freedom required by the newly published standard ISO 18192-1. Here, loads and motions have to be within ±5% of the maximum value and ±0.5degrees, respectively. The simulator's response to demand input signals was determined for load and motion using independent measuring devices; a digital inclinometer for motions and load cell for force.

The load calibration was found to be within ±1% of the maximum load within the specified load range of 600-2000N. Flexion-extension, lateral bending and axial rotation were found to be within ±0.5, ±0.3 and ±0.5 degrees respectively, within and beyond the operating ranges specified by ISO.

The Leeds spine wear simulator is the first orthopaedic wear simulator to include electro-mechanical actuators for all active DOF, and the first spinal wear simulator to include a minimum of 5 active DOF. This novel simulator meets the demanding tolerances required by ISO for testing of total disc replacements. Validation of the simulator is currently being undertaken to determine its suitability against explanted devices and debris located within tissues.

OC32

SURROGATE-BONE VERTEBRAL MODELS ARE NOT APPROPRIATE FOR USE IN THE MECHANICAL ASSESSMENT OF VERTEBROPLASTY

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Numerous in vitro studies have utilised bone models for the assessment of orthopaedic medical devices and interventions. The drivers for this usage are the low cost, reduced health concerns and lower inter-specimen variability when compared to animal or human cadaveric tissues. Given this widespread exploitation of these models the push for their use in the assessment of spinal augmentation applications would appear strong. The aim of the research was to

investigate the use of surrogate-bone vertebral models in the mechanical assessment of vertebroplasty.

Nine surrogate-bone whole vertebral models with an open-cell trabeculae configuration were acquired. Initial µCT scans were performed and a bone marrow substitute with appropriate rheological properties was injected into the trabeculae. Quasi-static loading was performed to determine the initial fracture strength in a manner previously used with human cadaveric vertebrae. Following fracture, vertebroplasty was undertaken in which there was a nominal 20% volume fill. Following augmentation the VBs were imaged using uCT and then subjected to an axial load using the same protocol.

The surrogate models had a substantially thicker cortex than that of human osteoporotic vertebrae. During compression, the surrogate-bone models did not exhibit the characteristic 'toe-region' observed in the load-deformation profile of cadaveric vertebrae. The mean initial and post-augmentation failure strength of the surrogate vertebrae were 1.35kN ± 0.15kN and 1.90kN ± 0.68kN, respectively. This equates to a statistically significant post-vertebroplasty increase by a factor of 1.38. In comparison with human osteoporotic bone, no significant difference was noted in the relative increase in fracture strength between the artificial and human VB following augmentation.

Despite the apparent equivalence of the strength and stiffness of the artificial vertebrae compared to that of the cadaveric specimens, there are significant differences in both pre- and post augmentation behaviour. In particular, the load-deformation curve shows significant differences in shape particularly at the toe end and in post failure behaviour. There are also issues surrounding where the marrow and cement flows during the injection process thus affecting the final distribution of the cement.

OC33

NEW TECHNIQUE OF BONE ALLOGRAFT STERILIZATION USING SUPERCRITICAL CARBON DIOXIDE MAINTAINS BONE MECHANICAL PROPERTIES: A SIGNIFICANT ADVANCE IN POTENTIAL FOR USE OF BONE ALLOGRAFT IN TRAUMA AND ORTHOPAEDIC SURGERY

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Bone allograft use in trauma and orthopaedic surgery is limited by the potential for cross infection due to inadequate acceptable decontamination methods. Current methods for allograft decontamination either put the recipient at risk of potentially pathogenic organisms or markedly reduce the mechanical strength and biological properties of bone. This study developed a technique of sterilization of donor bone which also maintains its mechanical properties.

Whole mature rat femurs were studied, as analogous to strut allograft. Bones were inoculated by vortexing in a solution of pathogens likely to cause cross infection in the human bone graft situation. Inoculated bones were subjected to supercritical carbon dioxide at 250 bar pressure at 35 degrees celsius for different experimental time periods until a set of conditions for sterilization was achieved. Decontamination was assessed by vortexing the treated bone in culture broth and plating this on suitable culture medium for 24 hours. The broth was also subcultured. Controls were untreated-, gamma irradiated- and dehydrated bone. Mechanical testing of the bones by precision three-point bending to failure was performed and the dimensions and cross-section digitally assessed so values could be expressed in terms of stress.

Mechanical testing revealed bone treated with supercritical carbon dioxide was consistently significantly stronger than that subjected to gamma irradiation and bones having no treatment (due to the minor dehydrating effect of the carbon dioxide).Terminal sterilization of bone is achieved using supercritical carbon dioxide and this method maintains the mechanical properties.

The new technique greatly enhances potential for bone allograft in orthopaedic surgery.

OC34

POLYURETHANE MICROARRAYS: A NOVEL PLATFORM FOR SELECTION OF SKELETAL OSTEOPROGENITORS FROM HUMAN BONE MARROW

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Bone marrow stromal cells represent a heterogeneous population, which includes reticular endothelial cells, fibroblasts, adipocytes and osteoprogenitors. One of the approaches for isolation of osteoprogenitors from human bone marrow mononuclear cell (hBMMC) populations involves immunoselection of these progenitors using the STRO-1 monoclonal antibody. Traditional methods like magnetically-activated cell sorting (MACS) and FACS, for enrichment of immunolabelled cells, require expensive instrumentation and skilled personnel, thereby presenting the need for alternative strategies. The present study aimed to develop a simple strategy for the isolation of skeletal osteoprogenitors from human bone marrow, by screening a library of novel polyurethanes (PUs) for their abilities to selectively bind to the human bone marrow STRO-1+ osteoprogenitor population.

Complete arrays comprising of 120 well-characterised PUs, contact printed in a microarray format on glass slides coated with a thin layer of agarose, were incubated overnight with STRO-1+ cells, which had been previously isolated by MACS. Analysis using a fluorescent microscope, which allowed automated capture of images for each polymer spot, and the Pathfinder software, identified 31 PUs that were capable of binding to STRO-1+ cells. 4 PUs (labelled 16, 17, 61 and 71), out of the 31 PUs, exhibited high affinity for binding to STRO-1+ cells as more than 30 STRO-1+ cells were observed bound to these polymer spots. When focused arrays comprising of the 31 PUs were incubated overnight with hBMMC samples, in which the osteoprogenitors were immunolabelled with the STRO-1 antibody bound to a FITC-tagged secondary antibody, the 4 high-affinity PUs were able to selectively immobilise the STRO-1+ osteoprogenitors from hBMMC populations. Focused arrays were then incubated with the human MG63 osteogenic cell line (known to express the STRO-1 antigen) as well as human fetal cells, derived from cartilaginous femora, containing a small proportion of cells which express the STRO-1 antigen. PU-16, 17, 61 and 71 failed to exhibit any affinity for binding to the MG63 cells or STRO-1+ cells from the human fetal cell population, thereby demonstrating their selectivity for STRO-1+ osteoprogenitors from hBMMC populations. This novel platform therefore serves as a simple alternative tool for the selective isolation of skeletal osteoprogenitors from hBMMC populations.

OC35

CHONDROITIN SULPHATE SULPHATION MOTIFS AS SPECIFIC COMPONENTS OF THE STEM/PROGENITOR CELL NICHE IN MUSCULOSKELETAL TISSUES

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In the mid-1980s we produced and characterised several monoclonal antibodies 'mAbs 3-B-3(-); 4-C-3, 6-C-3 & 7-D-4) that recognised unique native sulphation motifs in chondroitin sulphate (CS) glycosaminoglycan (GAG) chains on connective tissue proteoglycans (PGs). These antibodies were shown to specifically locate CS-PGs in the peri-cellular regions surrounding putative sites where haemopoietic stem cells were undergoing lymphopoiesis in the Bursa of Fabricius of embryonic chicks. In later studies, we also observed immunostaining for some of these mAbs '3-B-3(-) & 7-D-4' in chondrocyte clusters present in tissue sections from late-stage osteoarthritic cartilage from canine and human patients. In a recent study 'Hayes et al (2008), J. Histochem Cytochem. 56: 125-128' we have used these anti-CS sulphation motif mAbs to specifically identify stem/chondroprogenitor cells in the surface/superficial zone of hyaline articular cartilage. Furthermore, we used these mAbs in FACS analyses to sort and isolate chondroprogenitor cells for potential pluripotent cell enrichment in tissue engineering/tissue regeneration technologies. We have also used several of these mAbs to identify stem/progenitor cells in different anatomical and

functional regions of the tendon; i.e. where the tendon wraps around bone in compressed regions where the cells exhibit a more chondrogenic phenotype and also in the outer zones of the tendon surrounding pericytes where vascularisation occurs. In the developing intervertebral some of these mAbs specifically recognise stem/progenitor cells at the interzone between the outer and inner anulus an also the boundary of the nucleus with the inner annulus, these results indicating their use for stem/progenitor cell identification and isolation in other musculoskeletal tissues. Interestingly, these mAbs also immunostained the pericellular environment (stem cell niche) in the crypts of the gut and the limbus of the eye where stem cells reside. Collectively, this data strongly suggests that these mAbs recognising CS sulphation motifs can be used as biomarkers to identify stem cell niches in numerous tissues of the body and that they can be used for stem/progenitor cell isolation for use in tissue engineering/regeneration procedures. This work was supported by BBSRC and ARC funding.

OC36

BREAKING AN EGGSHELL: AGE-RELATED THINNING OF THE FEMORAL NECK CORTEX IN-VIVO (THE 100 WOMEN STUDY)

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We previously identified cortical thinning of the femoral neck as a probable cause of hip fracture using high resolution pQCT of cadaveric femurs and histology. Ageing thinned the supero-posterior (SP) cortex (which can become egg-shell thin in old age) while thinning of the inferior cortex was an additional feature in hip fracture cases. These regions are subjected to a high applied force during sideways falling and their structural failure can result in intracapsular hip fracture. The 100 Women Study is a cross-sectional study investigating cortical thickness (C.Th) in life from 20-90 years using multislice CT.

100 healthy women were recruited by decade from age 20 to 90 (IQR 38-72). Participants consented to an extension of a routine clinical pelvic CT scan (Siemens 64) to include both hips (1mm slice thickness, 0.59 mm voxel size). The starting position for cross sections was a 1mm thick mid-femoral neck slice at an eccentricity of 1.4, since this location along the neck axis was highly reproducible and unaffected by age (mean 51%, SE 0.016%). 5 parallel 1mm slices were evaluated towards the midline. Age effects on regional C.Th were evaluated using linear regression in anatomical quadrants using a fixed threshold of 450mg/cm3 and Mindways Software (BIT-2). Existing measurements of post-mortem femurs using pQCT and clinical CT were used to validate BIT-2.

In the superoposterior quadrant, there was a marked decline in C.Th with advancing age, from an estimated 1.95mm aged 25 to 0.4mm aged 85 (C.Th = 2.6 - 0.026*Age, r2= 0.51, p<0.0001). However, age had no effect on infero-anterior regional cortical thickness (p=0.79). Age explained 51%, 31%, and 28% of the variance in SP, SA, and IP C.Th respectively (p<0.0001). The effective dose (IMPACT software) for the hip scans alone was 1.8mSV for a 60kg woman.

Femoral neck C.Th can be estimated in vivo. Regional superoposterior cortical thinning as a consequence of ageing supports a biomechanical explanation for the exponentially increased hip fracture susceptibility in elderly fallers. These in vivo CT methods are ideally suited to application in longitudinal studies of ageing, hip fracture risk, and novel anabolic agents.

OC37

THE EPITOPE PROFILE AND ADIPOGENIC DIFFERENTIATION OF INFRAPATELLAR FAT PAD DERIVED STEM CELLS AND POTENTIAL CLINICAL APPLICATIONS

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There is an ever-increasing clinical need for the regeneration and replacement of tissue to replace soft tissue lost due to trauma, disease and cosmetic surgery. A potential alternative to the current treatment modalities is the use of tissue engineering applications using mesenchymal stem cells that have been identified in many tissue including the infrapatellar fat pad. In this study, stem cells isolated from the infrapatellar fat pad were characterised to ascertain their origin, and allowed to undergo adipogenic differentiation to confirm multilineage differentiation potential.

The infrapatellar fat pad was obtained from total knee replacement for osteoarthritis. Cells were isolated and expanded in monolayer culture. Cells at passage 2 stained strongly for CD13, CD29, CD44, CD90 and CD105 (mesenchymal stem cell markers). The cells stained poorly for LNGFR and STRO1 (markers for freshly isolated bone marrow derived stem cells), and sparsely for 3G5 (pericyte marker). Staining for CD34 (haematopoetic marker) and CD56 (neural and myogenic lineage marker) was negative. {BR}For adipogenic differentiation, cells were cultured in adipogenic inducing medium consisting of basic medium with 10ug/ml insulin, 1uM dexamthasone, 100uM indomethacin and 500uM 3-isobutyl-1-methyl xanthine. By day 16, many cells had lipid vacuoles occupying most of the cytoplasm. On gene expression analyses, the cells cultured under adipogenic conditions had almost a 1,000 fold increase in expression of peroxisome proliferator-activated receptor gamma-2 (PPAR gamma-2) and 1,000,000 fold increase in expression of lipoprotein lipase (LPL). Oil red O staining confirmed the adipogenic nature of the observed vacuoles and showed failure of staining in control cells.

Our results show that the human infrapatellar fat pad is a viable potential autogeneic source for mesenchymal stem cells capable of adipogenic differentiation as well as previously documented ostegenic and chondrogenic differentiation. This cell source has potential use in tissue engineering applications.

OC38

TIMING OF FIRST INFUSION OF ZOLEDRONIC ACID 5 MG AFTER RECENT HIP FRACTURE AFFECTS ANTIFRACTURE EFFICACY AND REDUCTION OF MORTALITY

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Zoledronic acid (ZOL) 5 mg given IV within 90 days of a low trauma hip fracture reduces the risk of new osteoporotic fractures and death. However, the impact of timing of the first infusion on fractures and mortality requires further exploration.

Prespecified secondary analysis (% change in total hip and femoral neck BMD) and post-hoc analysis (fracture reduction and mortality) of the HORIZON Recurrent Fracture Trial; a randomized, double-blind, placebo controlled trial of ZOL 5 mg in 2127 men and women with low-trauma hip fracture. ANOVA and Cox proportional hazards regression, respectively, were used to evaluate % change in BMD and incidence of clinical fractures and death adjusting for the timing of first infusion.

Median time of first infusion after hip fracture repair was 46 days (range 1 to 123 days). Increases in total hip BMD for ZOL 5 mg vs placebo at 24 months ranged from 3.43% to 8.40% and statistically significant increases relative to placebo were observed when the dose was later than 2 weeks after hip fracture repair. Clinical fractures and mortality exhibited reduction for first infusions administered as early as 2 weeks after surgical repair. The risk reduction (RR) for vertebral fractures (67% RR vs 15% RR) and hip fractures (61% RR vs 36% RR increase) were significantly greater when the first dose of ZOL 5 mg was dosed >6 weeks vs <6 weeks after hip fracture repair (both P<0.01), but the number of fracture events was small. ZOL 5 mg had no adverse effects on fracture healing, regardless of the timing of infusion. The most common AEs with ZOL were transient post-dose symptoms.

This post-hoc analysis suggests that first infusions of zoledronic acid given as early as 2 weeks after hip fracture repair reduce clinical fractures and mortality.

ORAL POSTERS

OP1

AGEING EFFECTS ON FEMORAL NECK TRABECULAR BONE: ROLE IN HIP FRACTURE

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Hip fracture risk rises 100-1000 fold by age 80 and this is only partly explained by declining bone mineral density (BMD). Mayhew et al (2005) showed that a potentially independent cause of fragility is local cortical thinning predisposing to local crushing or elastic instability (buckling) of the compressed supero-lateral cortex in a fall. Trabecular buttressing would protect the hip against cortical buckling but not crushing. We have quantified the effect of ageing on subcortical trabecular bone in the femoral neck and assessed its contribution to cortical resistance to local buckling.

In this extended and revised analysis, we measured with computed tomography the distribution of bone in the mid-femoral neck of 35 female and 42 male proximal femurs from cases of sudden death aged 20-95. As a threshold for elastic instability, we calculated the critical stress sigma from the geometric properties and density of the cortical zone most highly loaded in a sideways fall. Using traditional engineering principles for measuring a so-called elastic foundations effect on stability, we estimated the amount by which sigma was increased by adjacent trabecular bone.

With normal ageing, trabecular bone density declined asymmetrically, being fastest in the superior half. The most rapid loss occurred postero-laterally where compression is greatest, amounting to a 42% reduction in women (34% in men) over 5 decades. Generally, we found that trabecular bone density and cortical bone thickness declined at similar relative rates in each cortical sector when the femoral neck cross section was divided radially into octants. Trabecular bone was calculated to increase the elastic stability of the vulnerable supero-posterior cortex by 50% above that provided by the cortical bone in the absence of trabeculae.

The capacity of the femur to absorb energy in a sideways fall becomes compromised with normal ageing, since both cortical thickness and trabecular bone decline by about half, where the hip is most vulnerable, about twice as rapidly as femoral neck BMD. If elastic instability (not cortical crushing) initiates fracture, interventions increasing trabecular bone have considerable potential to reduce fracture risk. This is because the gradient relating increasing sigma with increasing trabecular bone density is steep.

OP2

FRICTION AS A POTENTIAL CAUSE OF PARATENONITIS

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Paratenonitis describes inflammation of the paratenon and commonly presents as an overuse injury. The paratenon is the connective tissue sheath that surrounds tendons - including tendo Achilles, and serves to minimise friction with the outer layer of the tendon, the epitenon. Whilst this conjunction allows the tendon to glide smoothly on muscular contraction, the presentation of paratenonitis typically follows periods of frequent, repetitive musculo-skeletal movements; hence, paratenonitis commonly afflicts the elite and, albeit to a lesser extent, amateur athlete. The extent to which friction at the epitenon-paratenon juncture contributes to this tendinopathy remains unclear, and this study is therefore concerned with the coefficient of friction and the lubrication regime.

By using a specially designed and validated apparatus, the in vivo paratenon-epitenon conjunction was approximated using bovine flexor tendon paratenon and a glass disc; this is being an equivalent experimental set-up to that used in other studies exploring soft tissue contacts. Bovine synovial fluid was used to lubricate the conjunction at 37 deg C, and the frictional characteristics were analysed over a range of sliding speeds and loads.

The coefficient of friction was found to generally lie between 0.1 - 0.01. This range suggests that a system of mixed lubrication applies - where the synovial fluid is causing partial separation of the two surfaces. However, when the data is plotted in the form of a Stribeck curve, the trend suggests that boundary lubrication prevails - where lubrication is determined by surface-bound proteins.

The coefficient of friction at the epitenon-paratenon interface appears to be approximately one order of magnitude greater than that typically reported within the healthy synovial joint. Additionally, the synovial joint is thought to exhibit some fluid film lubrication (i.e. total surface separation), whereas the epitenon-paratenon lubrication regime appears to vary only between the inferior mixed and boundary systems - depending on the specific biomechanical conditions. This data would suggest that the coefficient of friction at the epitenon-paratenon interface is relatively high and thus is potentially significant in the incidence of paratenonitis. Such a hypothesis could be of particular interest to sports-medicine and orthopaedic specialists.

OP3

AN OSTEOGENIC SCAFFOLD CARRIER FOR THE DELIVERY OF HUMAN MARROW STROMAL CELLS TO A MURINE CALVARIAL DEFECT

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The use of autologous marrow stromal cells (MSCs) for bone repair appears to offer a therapy that may be ready for clinical trial in the near future. However, it is suspected that a scaffold carrier will be required to maintain viable, functional MSCs at the lesion. We present here the development of an osteogenic scaffold carrier for human MSCs that has successfully initiated repair in a murine calvarial defect.

Polycaprolactone scaffolds with interconnected porosity were constructed in-house using a proprietary extraction technique. Scaffolds were subsequently modified via an accelerated coating process to produce an apatite-like mineral on the scaffold surface. Human MSCs isolated from femoral bone were statically seeded onto the scaffolds at a density of 100,000 cells/scaffold. Cell/scaffold constructs were treated with osteogenic supplements for 4 days and then implanted into critically-sized calvarial defects in NOD-scid mice for a period of 10 weeks. Additional constructs were maintained in either unsupplemented or osteogenic media for 21 days in vitro to assess the osteogenic potential of the scaffolds.

In vitro testing confirmed the ability of cells to survive on the scaffold for up to 21 days; all of the cells in the scaffolds stained positive for lactate dehydrogenase activity. In osteogenic media, alkaline phosphatase (ALP), a marker of osteogenic differentiation, was detected in 79.8+/-7.8 % of the cells on the scaffolds after 21 days, and the scaffolds were full of Type I collagen. Mineralised extracellular matrix was also deposited in the scaffolds, and histological sections demonstrated that the seeded cells were intimately associated with the newly-formed mineral. No ALP or new mineral was detected in the scaffolds in the control media after 21 days.

Histological analysis demonstrated the successful integration of the scaffolds within the host and substantial amounts of bone repair in the defect. The scaffold was filled with live tissue after 10 weeks, and live osteocytes were embedded in new bone deposits within the scaffold. The demonstration of the positive effects of cell / scaffold constructs in this model of inadequate repair point to the likely future development of cell assisted repair strategies for use in the clinic.

OP4

DEVELOPMENT OF A COMBINATION VACCINE AGAINST STAPHYLOCOCCAL IMPLANT-RELATED INFECTION

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Prosthetic joint infection (PJI) is an increasing problem and management commonly involves prosthesis removal with serious consequences. Biofilm-forming staphylococci are the most common causative organisms with Staphylococcus aureus being most virulent and methicillin-resistant Staphylococcus aureus (MRSA) more than doubling the infection mortality rate. Bacterial adhesion is an essential primary event in biofilm formation and infection establishment. The development of a novel combination vaccine programme to prevent staphylococcal PJI by directing antibody

against factors involved in adhesion and biofilm formation, and investigation of S. aureus binding-domains as potential vaccine components for adhesion inhibition is described.

Selected target antigens included the S. aureus fibronectin-binding protein (FnBP) and iron-regulated surface determinant (IsdA), which have been shown to be important for infection establishment and predominantly bind to host fibronectin and fibrinogen respectively. Escherichia coli clones harbouring recombinant S. aureus binding-domain DNA sequences were used for expression and purification of antigen domains. In vitro antibody evaluation determined whether immune inhibition of bacteria - ligand binding can significantly impact on attachment to plasma-conditioned biomaterial (in presence of other bacterial ligands).

Adhesion of homologous and heterologous (MRSA PJI isolate) S. aureus to plasma-conditioned steel was significantly reduced (approximately 50 percent average reduction, p <0.0001) when pre-exposed to anti-rFnBP-A antiserum (with pre-immune serum control) that was 50-fold more dilute than the actual titre from immunisation. Inhibition was related to ligand presence but not staphylococcal Protein A, and reduced adhesion was not observed with the mutant strain, indicating specific inhibitory antibody involvement, and demonstrating for the first time the potential of rFnBP-A for prevention of S. aureus PJI. Adhesion-inhibitory activity was also observed with a purified IgG-fraction of rIsdA antiserum but this activity appeared to be masked by non-IsdA - related interactions when non-IgG - purified antiserum was assessed.

OP5

TEMPORAL EXPRESSION OF PHOSPHO1 DURING CHICK LIMB BUD MESENCHYMAL CELL DIFFERENTIATION AND MINERALISATION

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PHOSPHO1 is a phosphatase implicated in the initiation of inorganic phosphate generation for matrix mineralisation. This study has established the temporal expression of PHOSPHO1 during chondrogenesis and endochondral ossification within the developing chick limb bud. This model permits the monitoring of PHOSPHO1 expression during mesenchymal cell differentiation into mineral producing chondrocytes. Micromasses were prepared from stage 24 limb bud mesenchymal cells and cultured for 0, 3, 7 and 10d. Alcian blue (proteoglycan synthesis) and alizarin red (mineral formation) staining was negligible at 0d, with a marked increase in staining intensity at 7-10d, confirming mesenchymal cell differentiation into chondrocytes with subsequent mineralisation. mRNA and protein expression of PHOSPHO1, tissue non-specific alkaline phosphatase (TNAP) and collagen II was determined. Phospho1 expression was observed at all time points, with a notable increase by 7d. Interestingly, Phospho1 expression decreased between 7d and 10d. This agrees with previous studies suggesting that PHOSPHO1 is involved in the initialisation of mineral formation. Furthermore, exposure of micromass cultures to lansoprazole (7d; 100uM), an inhibitor of PHOSPHO1 activity, reduced alizarin red staining (21%; P<0.05). TNAP was expressed at 0-3d, with a marked decrease at 7-10d. A comparable pattern has previously been reported for TNAP activity in chick limb bud cultures. Collagen II was absent at 0d and was upregulated at 3d onwards. Further studies using chick limb tissue at E3.5, E5.5, E6.5 and E10.5 were undertaken. Increased PHOSPHO1 protein expression was seen at E6.5 and E10.5. These data were complemented by increased Phospho1 mRNA expression in E6.5 and E10.5 compared to E3.5 and E5.5. TNAP protein expression was noted at all developmental stages, with no obvious differences in expression levels. Collagen II expression was present from E5.5 onwards. Using whole-mount in-situ hybridisation, Phospho1 mRNA expression was observed in chick metatarsi (E6.5) around the mid-shaft of the bone. Immunohistochemical staining of tibia sections (E6.5) revealed that PHOSPHO1 staining was localised to the osteoid and associated periosteal osteoblasts within the mid-diaphyseal region. Some chondrocytes within the rudiment also stained positively. These studies concur with our hypothesis that PHOSPHO1 has a pivotal role in the first phase of the mineralisation process.

OP6

CHONDROPROTECTIVE STRATEGIES: INCREASING THE OSMOLARITY OF JOINT IRRIGATING SOLUTIONS

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0.9% Saline and Hartmann's are commonly used joint irrigating solutions during articular surgery. The objective of the study was to determine whether the osmolarity of these solutions affects chondrocyte death in mechanically injured articular cartilage.

The osmolarity of 0.9% Saline (285 mOsm) and Hartmann's (255 mOsm) solutions was varied from 100-600 mOsm by the addition of distilled water or sucrose. Osteochondral explants (rectangular blocks, n=72) harvested from the metacarpophalangeal joints of six different three-year old cows were exposed to prepared solutions of different osmolarity for 2 minutes to allow in situ chondrocytes (cells embedded within their native extracellular matrix) to respond to the altered osmotic environment. Explants were then mechanically injured through the full thickness of articular cartilage with a fresh scalpel and incubated in the same solution for 2.5 hours. Using confocal laser scanning microscopy (CLSM) and fluorescent probes to determine cell viability, percentage cell death (PCD, 100 x number of dead cells/ number of dead and live cells) was quantified within the full thickness of mechanically injured articular cartilage as a function of solution osmolarity.

Cell death was localised to the superficial zone (first 100 microns from the articular surface) of injured cartilage for explants exposed to the control 0.9% Saline (285 mOsm) and Hartmann's (255 mOsm) solutions, with relative sparing of the middle and deep zones (analysis of variance (ANOVA), p<0.05). Compared to the control explants exposed to 0.9% Saline, PCD in the superficial zone was greatest for the low osmolarity (100 mOsm) saline solution and least for the high osmolarity (600 mOsm) saline solution (ANOVA, p=0.04). PCD in the superficial zone significantly decreased for explants exposed to 600 mOsm solutions of 0.9% Saline and Hartmann's, compared to their respective control solutions (p<0.05 for paired comparisons). There was no significant difference in the PCD between 600 mOsm solutions of 0.9% Saline and Hartmann's (p=0.5).

Increasing the osmolarity of 0.9% Saline and Hartmann's solutions is chondroprotective in a surgically relevant model of mechanical cartilage injury. These experiments have important clinical relevance for the design of irrigation solutions during arthroscopic and open articular surgery.

OP7

EVIDENCE FOR ADENOSINE RECEPTOR REGULATION OF OSTEOGENESIS VERSUS ADIPOGENESIS IN MESENCHYMAL STEM CELLS

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Selection of adipogenesis over osteogenesis is known to be associated with several conditions (e.g. ageing, glucocorticoid treatment, immobilization) that lead to bone loss. Both adipocytes and osteoblasts are derived from marrow mesenchymal stem cells (MSCs). Our previous data showed that MSCs express adenosine receptors (ARs), and that adenosine stimulates mineralization of MSC derived osteoblasts. We present further evidence that the adenosine signalling pathway regulates MSC differentiation.

Osteoblastic differentiation of MSCs was induced by dexamethasone and ascorbate-2-phosphate, whilst mineralization was induced by including 2mM beta-glycerophosphate. Cellular responses to AR agonists/antagonists i.e. cAMP accumulation, proliferation, differentiation and mineralization was determined by radioimmunoassay, MTS, alkaline phosphatase (ALP) activity and alizarin red staining respectively. Adipogenesis was induced using a medium that included a PPAR gamma agonist (thiazolidinedione). We also induced adipogenesis in 7F2 cells (osteoblasts) using ascorbate-2-phosphate, indomethacin and dexamethasone. Adipogenesis was assessed by oil red O staining, as well as FACS analysis following Nile red staining.

AR agonists stimulated cAMP accumulation during osteoblastic differentiation of MSCs and the rank order of potency was NECA (universal AR agonist)>adenosine>CGS21680 (A2a AR agonist); at 100microM agonist, the respective increases were 100, 20 and 3.5 fold (P<0.001). Similarly AR agonists also increased ALP by up to 70% (P<0.001) after 2, 5 and 7 days of differentiation. The A2b AR antagonist, MRS1706 reversed the stimulatory effects of NECA on ALP activity (P<0.001) whereas the A1 AR antagonist PSB36 was ineffective (P<0.385). Adenosine (100microM) and NECA (10microM) also increased (by up to 300%, P<0.003) mineralization of MSCs after 10 days of incubation. Using our differentiation medium around 12% of our MSC population differentiated to adipocytes after 10 days. In 7F2 cells this increased to 45%. Interestingly, cAMP production following NECA stimulation was significantly reduced in adipocyte differentiated cultures when compared to undifferentiated cells. Furthermore, 10microM NECA or CCPA (A1 AR agonist) significantly increased adipogenesis.

These studies suggest that adenosine may be a significant signalling molecule in regulating differentiation of MSCs, and transdifferentiation of osteoblasts and adipocytes. Targeting adenosine signal pathways may therefore be important for preventing or treating conditions where there is insufficient bone formation and excessive marrow adipogenesis.

OP8

FROG GLUE ENHANCES ROTATOR CUFF REPAIR EX VIVO

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Rotator cuff tendons are typically reattached to the proximal humerus using either transosseous sutures or suture anchors. Their primary mode of failure is at the tendon bone interface 1. Surgical adhesives are used to bond cartilage, tendons and bone, and to close wounds. In an attempt to increase the tendon-bone interface we investigated the addition of a novel adhesive secreted from a species of Australian frog (Notaden bennetti) 2 to different methods of rotator cuff repair.

Forty two fresh frozen sheep infraspinatus tendons were repaired using 3 different techniques: transosseous sutures; two Mitek RC Quickanchors with 1 suture per anchor and two Opus Magnum anchors with 1 suture per anchor all using a mattress stitch configuration. In each group 7 shoulders were repaired with the addition of a small amount of frog glue to the infraspinatus footprint while 7 were used as control with no adhesive. Mechanical testing was performed using a mechanical tensile testing machine.

The strongest construct in the control groups was the Mitek suture anchors (mean 86±5 N) followed by the Opus suture anchor (69±6N) and transosseous repair (50±6N). This proved significant (p<0.05) between both metallic anchors and the transosseous repair.{BR}The addition of frog glue resulted in a significant increase in load to failure and total energy required until failure in all repair techniques (p<0.01). There was a 2 fold increase in load to failure of both the Opus Magnum (143±8N) and Mitek RC Fastin (165N±20 N) anchors while the transosseous repair (86± 8 N) had a 1.7 fold increase in its load to failure.

This data suggests that: (1) suture anchor fixation is a stronger construct requiring a larger amount of total force to fail than transosseous repair using a one suture repair technique, that (2) the addition of an adhesive to the tendon-bone interface significantly enhances both ultimate load and total energy required to failure in all repair types. The unique properties of this frog glue (strong, flexible, sets in water and biocompatibility) may ultimately lead to the production of a useful adjunct for rotator cuff repair in humans.

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OP9

GLUTAMATE TRANSPORTER INHIBITORS INFLUENCE OSTEOBLAST GENE EXPRESSION

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Mechanical loading plays a key role in the physiology of bone, allowing bone to functionally adapt to its environment. A screen for genes associated with mechanical load-induced osteogenic signalling identified the glutamate transporter GLAST-1, implicating the excitatory amino acid glutamate in the mechanoresponse. Since then, bone cells have been shown to express functional components from each stage of the glutamate signalling pathway. Five high affinity Na+-dependant excitatory amino acid transporters (EAATs) terminate glutamatergic signalling. EAAT1 (GLAST-1) is expressed by osteocytes and bone-forming osteoblasts in vivo, and is responsible for a variety of cellular functions that may influence osteogenesis including glutamate uptake, glutamate release, glutamate-gated ion channel activity and the activation of intracellular signalling pathways. RT-PCR revealed mRNA expression of EAATs 1-3 and both splice variants of EAAT1 (EAAT1a and EAAT1exon9skip) in MG-63 osteoblasts.

We inhibited glutamate transport in MG-63 osteosarcoma cells using small molecule inhibitors of EAATs 1-5 (L-trans-Pyrrolidine-2,4-dicarboxylic acid (t-PDC) and DL-threo-b-benzyloxyaspartic acid (TBOA)) . These inhibitors(0-1mM) were not toxic and had no effect on proliferation over 24hrs in the presence and absence of exogenous glutamate (0.5mM),but did influence gene expression determined by quantitative RT-PCR.

EAAT1 and EAAT3 mRNA expression increased with TBOA treatment 3-fold and 5-fold respectively. EAAT1a was expressed at very low levels although there was an apparent repression of this variant by both inhibitors. Interestingly, the EAAT1exon9skip variant is relatively abundant (10-20% that of full-length EAAT1) despite its proposed dominant negative role over glutamate uptake. Osteocalcin and osteonectin expression were significantly upregulated upon EAAT inhibition by t-PDC in the presence of glutamate and also by TBOA alone; whereas no changes in expression were detected upon treatment with glutamate alone.

Changes in gene expression were significant upon normalisation to total RNA but not upon normalisation to GAPDH expression and are currently being confirmed using alternative reference genes and in other osteoblast cell lines. This data confirms previously published data that mechanically regulated glutamate transporters may be important in regulating bone homeostasis.

OP10

COMPARATIVE STUDY ON THE POTENTIAL USE OF DIFFERENT HUMAN CELL TYPES IN CARTILAGE TISSUE ENGINEERING

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Articular cartilage has limited regenerative potential. Regeneration via autografts or cell therapy is clinically efficacious but the extent of regenerative success depends upon use of an appropriate cell source. The aim of this study was to compare the proliferative and chondrogenic potentials of three human cell types (human bone marrow stromal cells - HBMSCs, neonatal and adult chondrocytes) commonly used in cartilage tissue engineering.

HBMSCs, neonatal and adult chondrocytes (passage 2) were cultured in basal and chondrogenic media. At 2, 4 and 6 days, the cells were analysed for morphology and doubling time. Alkaline phosphatase specific activity (ALPSA) was quantified for each group at 2, 4 and 6 weeks. Chondrogenic potential of each cell type was assessed via a pellet culture model. Cryosections were stained with Alcian blue/ Sirius Red.

HBMSCs showed either elongated or polymorphic phenotypes, with a doubling time of 40 h. Neonatal chondrocytes showed a uniform spindle shape and had the shortest doubling time (16 h). Adult chondrocytes, were also spindle shaped, though slightly larger than the neonatal cells, with a longer doubling time of 22 h. Expression of ALPSA in basal media was of the order HBMSCs > adult chondrocytes >, neonatal chondrocytes. In chondrogenic culture, this order changed to adult chondrocytes > HBMSCs > neonatal chondrocytes.

In 3D pellet cultures, all three cell types stained positive for Alcian Blue and showed the presence of chondrocyte-like cells enclosed in lacunae.

This comparative study suggests that neonatal chondrocytes are the most proliferative with lowest ALP expression. However, in terms of clinical applications, HBMSCs may be better for cartilage regeneration given their lower ALP expression under chondrogenic conditions when compared with adult chondrocytes under the same conditions. The study has provided information to inform clinical cell therapy for cartilage regeneration.

OP11

HYPOXIA FACILITATES BONE INVASION BY INCREASING BREAST CANCER CELL EXPRESSION OF MATRIX METALLOPROTEINASE-1

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The mechanisms by which breast cancer metastasises to bone are poorly understood. The hypoxic environment of bone has been postulated as a mediator of breast cancer cell invasion into bone.

A novel in vitro model of the bone microenvironment was created by culturing aggressive MDA-MB-231 breast cancer cells at 1% oxygen on a porous polymer (poly '2-hydroxyethyl methacrylate') mixed with collagen to simulate bone microarchitecture. Cell to cell and cell to extracellular matrix interactions were assessed by fluorescence microscopy. Integrin binding to the ECM was assessed by measurement of the phosphorylation of focal adhesion kinase (FAK) using Western blot. Transcription of matrix metalloproteinase-1 (MMP-1) was assessed by real time polymerase chain reaction. Expression of MMP-1 and vascular endothelial growth factor (VEGF) was measured by enzyme linked immunosorbant assay (ELISA). Expression of hypoxia inducible factor (HIF) was measured by Western blot. All experiments were repeated at 3 times. Statistical assessment was by one way ANOVA with Bonferonni post hoc.

This model allowed cell to cell and cell to extracellular matrix interactions to be controlled. Hypoxia increased breast cancer cell invasion into the simulated bone microarchitecture. This increased invasion correlated with increased transcription and expression of MMP-1 and increased expression of HIF and VEGF. In addition, the rapidly invading cells increased their phosphorylation of FAK.

Our work has shown that when the HIF and VEGF pathways are activated, breast cancer cells increase expression of MMP-1 and are therefore able to destroy the bony microarchitecture at an increased rate. In addition, this destruction is related to the cell to ECM binding events as indicated by the increased phosphorylation of FAK.

This novel model of the bone microenvironment has opened up new avenues of investigation into the mechanisms of breast cancer bony metastases. Further work to identify the exact mechanisms by which the hypoxia pathways activate the expression of MMP-1 will allow novel therapeutic targets to be identified.

OP12

THE CARTILAGE MATRIX BIOLOGY OF ANTEROMEDIAL OSTEOARTHRITIS OF THE KNEE

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Anteromedial Osteoarthritis of the Knee (AMOA) is a distinct phenotype of OA. Within this pattern of disease, the anterior third of the medial tibial plateau exhibits full thickness cartilage loss. The middle third has damaged partial thickness cartilage, and the posterior third has retained cartilage, which is seen on macroscopic visual assessment to be normal. This study investigates the molecular features of progressive severities of cartilage damage within this phenotype.

Ten medial tibial plateau specimens were collected from patients undergoing unicompartmental knee replacements. The cartilage within the area of macroscopic damage was divided into equal thirds: T1(most damaged), to T3 (least damaged). The area of macroscopically undamaged cartilage was taken as a 4th sample, N. The specimens were prepared for histological (Safranin-O) and immunohistochemical analysis (Type I and II Collagen, proliferation and apoptosis). Immunoassays were undertaken for Collagens I and II and GAG content. Real time PCR compared gene expression between areas T and N.

There was a decrease in OARSI grade across the four areas, with progressively less fibrillation between areas T1, T2 and T3. Area N had a grade of 0 (normal). The GAG immunoassay showed decreased levels with increasing severity of cartilage damage ($p<0.0001$). Proliferation and apoptosis, as expected, were increased in the more damaged areas. There was no significant difference in the Collagen II content or gene expression between areas. The Collagen I immunohistochemistry showed increased staining within chondrocyte pericellular areas in the undamaged region (N) and immunoassays showed that the Collagen I content of this macroscopically and histologically normal cartilage, was significantly higher than the damaged areas ($p<0.0001$). Furthermore, real time PCR showed a significant increase in Collagen I expression in the macroscopically normal areas compared to the damaged areas ($p=0.04$).

We conclude that in this phenotype the Collagen I increase, in areas of macroscopically and histologically normal cartilage, may represent very early changes of the cartilage matrix within the osteoarthritic disease process. This may be able to be used as an assay of early disease and as a therapeutic target for disease modification or treatment.

ORAL POSTERS - BORS

BORS-OP1

IS THERE A BENEFIT FROM IMMEDIATE BROTH CULTURE OF INTRA-OPERATIVE MUSCULOSKELETAL SPECIMENS?

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The diagnosis of musculoskeletal infection is an ongoing problem. Multiple specimens and histology peri-operatively have been used to increase the accuracy of the diagnosis. However, to determine antibiotic resistance profiling it is essential to grow bacteria from the patient. The aim of this prospective study was to evaluate whether there is an increase in the rate of isolation of micro-organisms from musculoskeletal tissue samples sent directly in broth culture or whether there is an over-diagnosis due to false positive contaminants.

Samples were taken from patients undergoing planned orthopaedic surgery (some with and some without suspected infection). Each specimen was harvested with separate instruments. The specimens were placed into universal containers without broth according to our standard protocol and also into containers with broth. These samples were cultured and the results analysed for any difference in culture growth. A total of 72 specimens were taken in the operating theatre (36 in broth, 36 without broth). The results of culture were compared to a diagnosis of infection from clinical and histological data.

Overall there were 24 true positive samples in the study (sensitivity of 66.7%) and 32 true negative samples (specificity of 88.9%). The isolation of bacteria from the culture of samples sent in broth had a sensitivity of 77.8% and a specificity of 83.3%. Whereas, the sensitivity and specificity of musculoskeletal specimens sent without broth were 55.6% and 94.4%, respectively.

The results of the study show that there is an increase in the rate of isolation of micro-organisms from musculoskeletal tissue samples sent directly in broth culture, compared to specimens sent without broth. However, the broth samples resulted in a higher rate of false positives. This study concludes that placing musculoskeletal specimens directly in broth in the operating theatre for culture improves the rate of microbiological diagnosis. However, a larger study with more patients would be of use to confirm this.

BORS-OP2

IN VITRO WEAR TESTS OF ORTHOPAEDIC BIOPOLYMERS WITH A VISCO-SUPPLEMENT ADDED TO THE LUBRICANT

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Injections of hyaluronic acid solutions, often known as visco-supplements, into the joints of patients suffering from osteoarthritis are an accepted therapy. In most replacement joints, wear of the biomaterials used in them is a critical concern. For in vitro wear tests of such materials the recommended lubricant is one based on bovine serum. However, unlike synovial fluid, bovine serum does not contain hyaluronic acid. The aim of the work reported here was to take a clinically used hyaluronic acid solution, Ostenil, and to investigate its influence on the wear of two orthopaedic biopolymers

Ultra high molecular weight polyethylene (UHMWPE) and poly tetra fluoro ethylene (PTFE) were tested in turn using a four-station, multi-directional, pin-on-plate wear test rig which had previously been shown to reproduce clinical wear factors for UHMWPE, PTFE and polyacetal. For each biopolymer three lubricants were employed: 33% bovine serum (2 stations); 33% bovine serum + Ostenil (1 station); and distilled water + Ostenil (1 station). Polymeric test pins were subject to a load of 40N and articulated against polished stainless steel plates. Wear factors were determined by dividing the volume lost by the product of the load and the sliding distance (units x 10-6mm3/Nm).

The UHMWPE wear tests ran to 66.3km sliding distance. The addition of Ostenil to dilute bovine serum resulted in a wear factor of 1.4 x 10-6mm3/Nm for UHMWPE. The wear factor was 1.6 x 10-6mm3/Nm when dilute bovine serum alone was used as the lubricant. This shows good agreement with a wear factor of 2.1 x 10-6mm3/Nm reported for failed UHMWPE acetabular cups. PTFE provides an accelerated wear test with clinical validity. In the presence of 33% bovine serum a mean wear factor for PTFE of 40 x 10-6mm3/Nm was measured. The wear factor was 59 x 10-6mm3/Nm for dilute bovine serum plus Ostenil. For explanted PTFE acetabular cups a wear factor of 37 x 10-6mm3/Nm has been calculated. For both polymers wear was least when the lubricant was distilled water plus Ostenil. However a transfer film was found and such films are not clinically valid.

BORS-OP3

FUNCTIONAL OUTCOME FOLLOWING HIP RESURFACING: THE IMPORTANCE OF COMPONENT SIZE AND ACETABULAR ORIENTATION

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Optimal cup orientation for metal-on-metal hip resurfacing has yet to be established. Guidance is based on hip replacement data and in vitro studies. We sought to determine the influence of component size and positioning on early clinical outcome.

This study comprises a consecutive series of 200 hip resurfacings. All had Harris Hip Scores (HHS) at one-year review. Acetabular inclination angles were measured on pre-operative radiographs, and cup inclination / anteversion angles on 3-month post-operative films using EBRA. Restoration of anatomy was defined as placement of the cup within +/-5 degrees of pre-operative inclination. The difference between pre-operative acetabular and post-operative cup inclination was termed cup-angle difference (CAD).

HHS inversely correlated with CAD (P=0.023) and anteversion (P=0.003), and directly correlated with femoral head size (P<0.001). In patients with restoration of inclination anatomy mean HHS at one year was significantly higher at 98.7 compared with cups placed outside the normal anatomy restoration limits (93.8, P=0.003). Patients with anteversion >20 degrees had a significantly lower HHS (P=0.010) compared with cups anteverted <20 degrees. 96% of patients with HHS <90 had malaligned cups (inclination over 45 degrees, anteversion over 20 degrees).

Restoring pre-operative cup inclination, anteverting the cup <20 degrees and using large femoral heads improves early clinical outcome following MonM hip resurfacing. We recommend accurate pre-operative planning and meticulous attention to intra-operative cup positioning with these results in mind.

BORS-OP4

WITHDRAWN

BORS-OP5

INDICATIONS FOR TOTAL KNEE ARTHROPLASTY IN THE VALGUS KNEE- IS THE SIGNIFICANCE OF INSTABILITY TRULY UNDERSTOOD?

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Soft tissue balance is known to be an important factor for the success of Total Knee Arthroplasty (TKA). This is of particular relevance in the surgical management of a valgus knee which has both bony and soft tissue abnormalities which need addressing. The correction of instability, particularly in severely valgus knees is essential to post operative outcome as instability is often a component of pre-operative functional disability. Traditional surgical techniques involve soft tissue releases and bony cuts to achieve the correct balance. Evaluation of balance is currently based on subjective intra-operative clinical assessment, or the feel of the knee. More recently, an instrument to objectively measure soft tissue balance following bony cuts has been developed. Soft tissue releases using this instrument may be extensive.

502 patients aged 45-90 years underwent 522 Kinemax TKAs, performed by seven surgeons in five centres between October 1999 and December 2002. Soft tissue releases were recorded and objective soft tissue balance recorded using a balancer device. Independent observers assessed patients using 3 outcome measures for a minimum of 12 months. Pre-operative alignment was divided into 6 groups according to the degree of varus or valgus deformity (mild, moderate, severe varus or valgus).

There is a significant difference in the improvement of the knee scores between the severely valgus knees and all varus knees (ANOVA p=0.000). Significant differences were found between pre-operative pain scores, knee scores and medio-lateral stability between severely varus and severely valgus knees (ANOVA p=0.029, p=0.000 & p=0.000 respectively).

Knees with severe valgus deformities have significantly worse pre operative scores and show greater improvement with equivocal post-operative outcome, when compared to those with severe varus deformity. In addition to pain relief, is the correction of instability the key to this improvement in this group of patients?

BORS-OP6

DOUBLE BUNDLE ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION USING THE CALAXO OSTEOCONDUCTIVE INTERFERENCE SCREW

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The purpose of this study was to describe our experience of the Calaxo Osteoconductive interference screw (Smith & Nephew) when used for both femoral and tibial graft fixation in Double Bundle ACL reconstruction.

Since May 2006, all patients with an ACL deficient knee were reconstructed using the Double Bundle technique. All were followed prospectively and outcome data collected. Evidence of fixation failure was established subjectively by clinical examination (Lachman, Anterior Draw, Pivot Shift) and objectively via KT-1000 arthrometer. Following ethical approval, post-operative CT scans (immediate and 1 year) were performed on our first 10 patients allowing assessment of tunnel dimensions/fill.

Thirty two patients (29 male, 3 female) with a mean age of 30 (range 18-46) were included. At last follow-up, no evidence of graft/fixation failure was found; KT-1000 mean side-side difference 1.4mm (range -3 to +6). All patients had a positive pivot shift preoperatively which was abolished postoperatively. One patient had a postoperative infection with no other complications reported. Radiologically the screws did not show complete resorption but areas of new bone were identified.

We have shown satisfactory results with use of the Calaxo screw when used in Double Bundle Reconstruction. We have not had any cases of the adverse local soft tissue reaction, which has led to this screw being withdrawn from clinical use. Even when using a total of four screws in each knee. A previous study published by Seibold (2007) has shown tunnel widening and communication when suspensory fixation is used in Double Bundle reconstruction. This has the potential risk of leading to fracture between the tunnels. This has not been seen with the Calaxo screw which may be a result of the biological action of the screw which should ultimately lead to a reduction in these risks.

ORAL POSTERS - BRS

BRS-OP1

SULFORAPHANE - A NEW THERAPY FOR MUTLIPLE MYELOMA?

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Multiple myeloma involves the clonal expansion of malignant plasma cells within the bone marrow cavity where they interact with haematopoietic and osteoblastic cells. These interactions provide critical support for the survival and growth of myeloma cells, and the development of myeloma bone disease. Tumour necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) induces myeloma cell apoptosis in vitro and has specific anti-tumour activity in vivo. However osteoprotegerin (OPG), expressed by osteoblasts and bone marrow stromal cells, functions as a soluble decoy receptor for TRAIL and protects myeloma cells against TRAIL-induced apoptosis. Thus the close association between myeloma cells and bone marrow cells inhibits the anti-myeloma effects of TRAIL. Sulforaphane (SFN), an isothiocyanate produced by cruciferous vegetables, especially broccoli, has potent anticancer effects and is effective against a variety of tumour types. In this study we investigated the effects of SFN on myeloma cells and other bone marrow cells, alone or in combination with the apoptotic agent TRAIL and the TRAIL agonist antibody anti-DR5. SFN alone strongly inhibited growth of myeloma cells (cell counts and Alamar blue assay) from 3.5microM and induced apoptosis (nick translation) from 7microM. In contrast SFN had no noticeable effect on PBMCs and did not affect growth or differentiation of primary osteoblasts or marrow stromal cells. Treatment of myeloma cells with SFN in combination with an effective dose of TRAIL had little additional effect, and SFN did not alter the cell surface expression of TRAIL receptors. However combining low-dose SFN with lower doses of TRAIL synergistically increased apoptosis. More markedly, SFN increased the effectiveness of anti-DR5 treatment at both normal and low doses and reduced the time to apoptosis. The effect of SFN on myeloma cells, unlike TRAIL, was not reduced by the addition of OPG or of osteoblast-conditioned medium. In triple-combination with TRAIL and OPG, SFN enhanced the residual effect of TRAIL.

These results suggest that SFN could provide a novel therapeutic approach to multiple myeloma and in particular, combined therapy with other apoptotic agents could sensitize myeloma cells and help offset the protective effect of OPG while reducing effects on other bone marrow cells.

BRS-OP2

ETHNIC DIFFERENCES IN FIBROBLAST GROWTH FACTOR 23 AND PHOSPHATE EXCRETION IN RESPONSE TO PHOSPHATE LOADING

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Fibroblast growth factor 23 (FGF23) is an important regulator of phosphate (P) metabolism by enhancing renal P excretion. This study investigated changes in FGF23 in response to P-loading in healthy adults aged 60-75 y in UK, China and The Gambia. Subjects (15 males, 15 females per country) received 2g phosphorus for 5 days (1g in the morning and 1g in the afternoon, Phosphate-Sandoz). Fasting early morning blood and urine samples were collected at baseline and day 5, before and 2h after P-loading and analysed for plasma P (pP) and C-terminal FGF23 (pFGF23, Immutopics), and urinary P (uP) and creatinine (Cr).

At baseline, in British, Chinese and Gambian subjects respectively, mean pP was 0.98 (SD 0.15), 1.09 (0.16) and 1.09 (0.14) mmol/l (group effect P=0.009; British < Chinese and Gambian); uP/Cr was 1.94 (0.63), 1.81 (0.58) and 1.60 (0.51) [no significant (NS) group effect]; and pFGF23 [geometric mean (95% CI)] was 35.9 (29.5, 43.6), 36.9 (31.0, 44.1) and 52.4 (35.8, 76.9) RU/ml (NS). There was a significant increase in pP and uP/Cr at 2h, with no significant

difference between groups for pP. The % increase in uP/Cr was significantly greater in Chinese than in British and Gambian subjects [for example: 62.5 (SE5.0)%, 41.4 (3.4)% and 29.9 (5.8)% respectively on day 5] (1). There was no significant change in pFGF23 at 2h in any group. By day 5, % changes in fasting samples in British, Chinese and Gambian subjects respectively were: pP +6.7 (SE1.6, P<0.01), -0.7 (1.8, NS) and +10.8 (2.0, P<0.01) (group effect P=0.0002; Chinese < British and Gambian); uP/Cr +84.7 (4.0, P<0.01), +81.9 (5.7, P<0.01) and +126.9 (5.5, P<0.01) (group effect P<0.0001; British and Chinese < Gambian); pFGF23 +24.7 (3.6, P<0.001), +16.1 (2.9, P<0.001) and +38.7 (5.7, P<0.001) (group effect P=0.001; Chinese < Gambian).

P-loading induced a significant increase in fasting pFGF23 at day 5 but not at 2h after P-loading in all groups. pFGF23 can not explain the increase and ethnic differences in uP/Cr at 2h but may explain the ethnic differences in fasting uP/Cr and pP at day 5.

(1) Yan L et al. Osteoporosis Int 2007; 18:S277-278.

BRS-OP3

A RANDOMIZED CONTROL TRIAL OF ONCE WEEKLY RISEDRONATE FOR PREVENTION OF BONE LOSS OBSERVED IN A SINGLE FLARE-UP OF INFLAMMATORY BOWEL DISEASE

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Inflammatory bowel disease (IBD) is associated with an increased risk of fracture, presumably reflecting the accumulative effect of multiple disease flare-ups, and concomitant glucocortocioid (GC) therapy, on the skeleton. Strikingly, in patients receiving GC therapy for a flare-up of Crohn's disease (CD), in the absence of calcium and vitamin D supplementation or any other bone protective therapy, 4% bone loss at Ward's Triangle (WT) was observed in our previous study after only 8 weeks. Here, we report a randomized control trial to examine whether equivalent bone loss occurs in patients with a flare-up in IBD administered calcium and vitamin D supplements with or without bisphosphonates. Participants underwent a baseline DXA scan of the lumbar spine (LS, L2-4) and both hips within one week of commencing GC therapy for a relapse in either CD or ulcerative colitis (UC). All participants received calcium and vitamin D supplements and were randomized to receive placebo or risdedronate 35mg once weekly for 8 weeks and then a repeat DXA was performed. A total of 78 patients completed the study (mean age 42.5, 57.7% male); 39 received placebo (16 CD and 23 UC), and 39 risedronate (17 CD and 22 UC). Both groups were comparable for age, disease duration and baseline bone mineral density (BMD). At the LS, no change occurred in the placebo group (0.05 +/- 0.5, P = 0.9), whereas there was a gain in BMD in the risedronate group (0.95 +/- 0.45, P = 0.04) (mean% +/- SEM by paired Student's t-test). At the total hip, a small decrease in BMD occurred in both placebo and risedronate groups (0.5 +/- 0.2, P = 0.04; 0.5 +/- 0.3, P = 0.048, placebo and risedronate respectively). At WT, substantial bone loss was observed in the placebo group (1.8 +/- 0.4, P = 0.001), whereas no change was seen in the risedronate group (0.8 +/- 0.4, P = 0.09) (P = 0.05 for between-group comparison). We conclude that despite calcium and vitamin D supplementation, IBD patients sustain rapid bone loss during a single flare-up treated with GC, particularly at WT, which is ameliorated by risedronate.

BRS-OP4

BACKGROUND UVB EXPOSURE IN PREGANCY AND SKELETAL DEVELOPMENT IN CHILDHOOD

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In a previous small prospective study, maternal vitamin D levels were found to be associated with bone mineral content (BMC) of the child at age nine, suggesting a possible role of maternal vitamin D status in programming of skeletal development (Javaid et al, 2006, Lancet 367). We investigated whether an equivalent association exists in the considerably larger Avon Longitudinal Study of Parents and Children (ALSPAC), using erythemal UV (eUV) derived from meteorological monitoring data during the third trimester of pregnancy as a proxy measure of background UVB exposure, and hence a surrogate for maternal vitamin D status. This followed a preliminary study in 346 expectant mothers from ALSPAC, in which we confirmed a strong association between eUV and serum 25-hydroxy-vitaminD, both measured in the last trimester of pregnancy (p=0.0075x10-27, r2=0.3127).

First, we investigated associations between birth length, birth weight and eUV, controlling for gestational age. There was a strong positive association between eUV and crown heel length (p=0.00004 , N=10569), such that those in the lowest 5% of UV exposure (low winter) were 0.26cm shorter than those with the highest 5 % (high summer). In contrast, there was no association between eUV and birth weight. Subsequently, we examined the relationship between eUV and skeletal parameters as measured at age 9.9 years. Whereas eUV showed little relation to height, positive associations were observed with total body less head BMC, bone mineral density, and bone area (BA), derived from total body DXA scans (analyses adjusted for height, weight, age at scan, and gestational age; p<0.02, N=7336). For example, BMC and BA were 6.9g and 4.9cm2 higher respectively, in mothers with eUV levels in the highest 5% (high summer) versus lowest 5% (low winter).

Maternal vitamin D status, as reflected by eUV, appears to have a major influence on longitudinal growth in utero, but this effect is no longer apparent in later childhood. In contrast, associations were observed between maternal eUV and overall skeletal size and BMC, as assessed in nine-year-old children.

BRS-OP5

ORAL CALCIUM SUPPLEMENTATION REVERSES THE BIOCHEMICAL PICTURE OF PARATHYROID HORMONE RESISTANCE IN UNDERPRIVILEGED INDIAN TODDLERS

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Underprivileged toddlers in Pune, India, accustomed to low dietary calcium intake (<400 mg/day) but who were vitamin D replete 'serum 25(OH)D 126±63 nmol/l)' had low serum ionized calcium 'iCa 1.03 ±0.05 mmol/l; (1.12 to 1.23)' and raised serum inorganic phosphorous 'P 1.9±0.18 mmol/l; (1.2 to 1.8)' concentrations in the face of elevated serum parathyroid hormone 'PTH 7.6 ± 5.7 pmol/l; (1.1 to 6.4)' concentration. We speculated that dietary calcium (Ca) deficiency might lead to end organ resistance to PTH, thus resulting in mild hypocalcaemia and hyperphosphataemia.

Fifty-one subjects (25 male; 2.4±0.8 yrs) from an urban slum in Pune were randomised to of 500mg of oral Ca supplement or placebo, daily, for 8 weeks. All subjects received 20 mg of oral elemental iron, daily, as 90% had serum ferritin concentration <12 micrograms/l.

The mean serum PTH fell in the Ca supplemented (p=0.001) but not in the placebo (p=0.303) group. There was a significant increase in serum iCa concentration and a decrease in P concentration in toddlers randomised to receiving a daily Ca supplements, suggesting that low dietary Ca intake contributed to transient end organ resistance to PTH. Further studies are needed to confirm these findings and to elucidate mechanism by dietary Ca deficiency causes an end organ resistance to PTH.

BRS-OP6

A RANDOMIZED CONTROLLED TRIAL OF THE EFFECTS OF VITAMIN D SUPPLEMENTATION UPON MUSCLE POWER IN ADOLESCENT GIRLS

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Myopathy is the major clinical symptom of hypovitaminosis D. As part of a double blind, randomised controlled trial of vitamin D supplementation we measured muscle power and force at baseline and follow-up. At baseline muscle power was positively related to

25hydroxy vitamin D status (25(OH)D). We hypothesised that after 12 months vitamin D supplementation muscle power would increase more in the supplemented group than in the placebo group.

Seventy three of the original 99 girls screened for the trial had 25(OH)D levels of less than 15ng/ml. All girls recruited to the trial had baseline muscle measurements using jumping mechanography (Novotec Medical). Muscle measurements were repeated after 12 months vitamin D supplementation (4 doses 150 000IU Ergocalciferol). A single two legged jump was performed. Maximum power was recorded from 2LJ with greatest height. Sixty-eight girls (94%) completed the trial and 64 of these had follow-up measurements; reasons for loss to follow up are leaving school (n=3) and starting treatment for clinical symptoms of 25(OH)D deficiency. Differences between groups were tested using analysis of covariance adjusting for baseline weight, log baseline 25(OH)D and baseline measurement. Exploratory analyses of whether vitamin D level affected response to supplementation was performed after splitting baseline 25(OH)D level into tertiles (< 5.5ng/ml, 5.51 to 6.95 ng/ml, >6.95 ng/ml); ANOVA tested difference between groups.

At follow up 25(OH)D status was 22.4ng/ml (SD 3.6, range 13.8 to 29.2) in the active group and 6.3 ng/ml (SD 2.6, range 2.4 to 13.2) in controls. There were no significant differences between the vitamin D treated group and controls for any of the parameters studied. Muscle power increased in the supplementation group with lowest baseline 25(OH)D levels (p = 0.057). After 12 months supplementation with vitamin D there were no overall differences in muscle power between the treated group and controls despite improvements in the active groups 25(OH)D status. However, there was improvement in power in girls taking supplementation in the lowest tertile of baseline 25(OH)D.

CLINICAL CASES

CC1

SOFT TISSUE CALCIFICATION IN THE HAND- A BENIGN ENTITY?

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Spontaneous amorphous calcification in the soft tissues of the hand is a rare, but recognised phenomenon. Case reports in the literature claim that this condition is self limiting, with patients eventually becoming asymptomatic. We present a case of aggressive soft tissue spontaneous amorphous calcification of the hand at the metacarpo-phalangeal joint requiring surgical intervention

A 31 year old female secretary presented with a 48 hour history of increasing pain at the middle finger metacarpo-phalangeal joint. Examination revealed erythema and tenderness around the joint. Radiographs revealed an area of opacification adjacent to the middle finger metacarpal head. A diagnosis of acute soft tissue calcification was made. The area was injected with local anaesthetic and steroid to moderate relief. Symptoms were persistent at 2 weeks and MRI was performed. This showed a soft tissue mass adjacent to the metacarpal head with accompanying significant erosion into the bone. Due to the persistence of symptoms and the aggressive features on the MRI, excision biopsy was arranged.

A poorly defined calcified mass infiltrating the synovium and capsule and eroding the adjacent metacarpal head was excised from the dorso-radial aspect of the joint.

The tissue showed patchy fibrocartilagenous metaplasia with deposition of numerous round/oval tiny calcified bodies. The histological pattern was not typical of either tumoral calcinosis or tophaeous pseudogout. The histopathological diagnosis was idiopathic calcinosis.

At 2 months, this patient continues to have mild pain and slight functional impairment.

Spontaneous amorphous soft tissue calcification in the hand is an uncommon phenomenon. Some reports have described this as a variant of calcium pyrophosphate deposition disease with a benign, self limiting course. Our case shows that this type of calcification in the hand is not necessarily benign. An excision biopsy was mandatory in this case to exclude an invasive tumour as a cause for the bony erosion. We believe that any patient presenting with this condition should be closely monitored and if symptoms persist, further investigation is mandatory, ideally with MRI. Surgery plays a role in confirming the diagnosis and excluding potentially progressive tumours such as rare soft tissue sarcomas.

CC2

AN OMINOUS RADIOLOGICAL SIGN OF IMPENDING ALENDRONATE-RELATED FEMORAL SUBTROCHANTERIC INSUFFICIENCY FRACTURES - AN INDICATION FOR PROPHYLACTIC OPERATIVE FIXATION?

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Recent reports suggest that long-term alendronate therapy may result in an unusual pattern of femoral subtrochanteric fracture. We aimed to determine if the presence of a specific radiographic feature in patients on alendronate could be used to predict an impending insufficiency fracture and thereby prevent its occurrence through further investigations and prophylactic fixation in high-risk patients.

Sixty-two subtrochanteric fractures treated surgically from 2001 to 2007 were reviewed and radiographs of 25 low-energy fractures were independently evaluated. Incidence of alendronate therapy, clinical data, and other investigations like bone mineral density (BMD) scans were recorded.

Seventeen fractures (68%) were associated with alendronate therapy. Hypertrophy of the lateral cortex of the femur with splaying of the fracture ends was noted in 70.1% of patients on alendronate; initial radiographs were not available in 17.6% and 11.8% had stress fractures identified by bone scan. None of the fractures in the non-alendronate group had this pattern. The fracture configuration in the alendronate group suggested that an ellipsoid thickening in the lateral cortex had been present prior to fracture. Indeed, 6 patients on alendronate (35.3%) had pre-existing radiographs as early as 3

years prior to fracture and all had this feature. Four of them had bone scans, which confirmed a stress fracture. Hip pain was often associated with this radiographic sign but may not be specific as patients were already on follow-up for other musculoskeletal conditions. BMD scans were not predictive of an impending fracture as they were mostly in the osteopaenic range. Only 50% with proven stress fractures had prophylactic fixation, while the remainder sustained overt fractures.

Alendronate-related subtrochanteric fractures are associated with a specific pre-existing radiographic abnormality. We recommend that all patients on long-term alendronate - particularly those with hip pain or a previous subtrochanteric fracture - be routinely followed-up with plain radiographs of the pelvis. If an ellipsoid feature is noted in the subtrochanteric region, further investigations like bone scan or MRI should be sought. Patients with evidence of stress fracture should be strongly considered for prophylactic operative fixation. We believe this is a cost-effective strategy to prevent subtrochanteric insufficiency fractures in patients on alendronate.

CC3

NOT ALL REFERRALS FROM MAXILLOFACIAL SURGEONS ARE OSTEONECROSIS OF THE JAW

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A 67 yr old Asian lady was referred by the maxillofacial surgeons with a history of bone resorption at the right mandibular ramus resulting in total loss of the coronoid process and extreme notching of the lower border with in 50% loss of height in the angle region. Biopsy of the temporalis insertion into the coronoid process had shown an ethesopathy with mild inflammation, degeneration and fibrosis. Review of this biopsy at our hospital had shown heavy resorption with little inflammatory reaction and no granulomas. The patient was referred for an opinion regarding whether this was idiopathic bone resorption or represented an arthropathy or connective tissue disease. On examination, she had features of digital clubbing in the right index finger. There was no synovitis of any joint. Skin was normal. Routine blood tests showed normal full blood count, renal and liver function. ESR was initially elevated at 45mm/hr (although this has come down to 19mm/hr) with a normal CRP (<5 mg/L). 25-OH vitamin D was 42 and her PTH mildly elevated (8.4) with a normal serum calcium. She is anti-nuclear antibody negative, but has a positive extractable nuclear antigen (anti-Ro). Serum angiotensin converting enzyme levels were normal. Radiological investigations showed multiple areas of acro-osteolysis and marginal joint erosions affecting the hands, lateral left and right clavicles, left neck of humerus, feet, 11th rib, and left ulnar. MRI of the hands showed joint based synovitis as well as the erosive changes that had been previously identified. Our radiology colleagues have advised us that her imaging finding would be consistent with a diagnosis of multicentric reticulohisticytosis. This is a rare condition with fewer than 200 reported cases in the literature. It is characterised by a destructive arthiritis and skin lesions. Our patient does not have the skin lesions, but this has been reported in the literature. We are currently pursuing a biopsy of the erosions in the hands to look for histiocytes.

CC4

A TEN YEAR RETROSPECTIVE STUDY INTO THE MORTALITY AND MORBIDITY BENEFITS ACHIEVED BY PROPHYLACTIC STABILISATION OF SKELETAL METASTASES

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Skeletal metastases are an increasing sequaelae for patients with a wide range of neoplastic lesions owing to the increasing incidences of cancer. The diagnosis of a skeletal metastasis is, however, at present a terminal diagnosis representing uncontrolled tumour dissemination. The metastatic destruction of the bone reduces its load bearing capabilities progressing to the principle orthopaedic complication, that of complete loss of cortical integrity.

Aim: We examine the population suffering a complication of skeletal metastasis in terms of their mortality and morbidity. We compare patients who underwent surgical stabilization as a result of a fracture through a metastatic lesion against those who underwent prophylactic stabilization.

This is a retrospective study of all patients within the Cardiff centre who underwent an operation for a metastatic bone lesion over a 10 year period (n=140). The patients were identified using pathological records created when samples were sent at the time of the operations. The patients were all followed up for a minimum of 24 months. The demographics of the patients were collected and a detailed analysis of the primary tumour, the surgical procedure, the mobility, and survival of the patients was undertaken. The patients data was then cross referenced with the database at the regional cancer centre and the post operative radiotherapy treatment regimen were collected.

Patients who underwent prophylactic surgical stabilization had a significant survival advantage compared to those stabilized following a fracture ($p=0.002$). The morbidity postoperatively, defined by the patients functional mobility, also shows the benefits of prophylactic stabilization with significantly improved mobility when compared to the mobility following fracture stabilization ($p=0.033$). It has also been shown that there is a significant postoperative survival benefit for those patients who were able to regain mobility ($p<0.01$).

Our results show a significant survival benefit of prophylactic fixation rather than fixation following fracture which is in line with previous studies We have also, for the first time in a large number study, shown that there is a survival benefit for patients who are able to mobilize following surgery and if prophylactic stabilization was undertaken patients were significantly more mobile postoperatively.

POSTERS - BORS

BORS-P01

A KINEMATIC ASSESSMENT OF NORMAL ELBOW MOVEMENT IN ACTIVITIES OF MODERN DAY LIVING

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The range of functional elbow movement has previously been studied by Morrey et al in 1981. This data has been used to provide objective basis for determination of disability impairment and to determine the optimum position for elbow splinting or arthrodesis and to assist in design of elbow prosthesis. It is now approaching thirty years since this study was carried out and many of the activities described are no longer representative of our lives in the 21st century.

The aim of this study was to evaluate the functional range of elbow movement as applied to a predetermined list of activities of daily living considered relevant to modern day life.

Twenty normal volunteers were studied. Ten men and ten women. The range of elbow motion required for specific activities was recorded by means of Polhemus Fastrak magnetic tracking measurement system. There were two sets of activities. The first set was similar to those used by Morrey et al and represented activities of daily living concerned with personal hygiene e.g. the ability to touch back of head, top of the head etc The second set of activities was adapted to represent common activities in 21st century e.g. using a phone, reading a newspaper, using a computer keyboard and mouse and driving (steering and changing gears).

This study suggests that the activities of daily living related to personal hygiene required elbow flexion from a maximum of 146.57 degrees (average flexion to touch neck) to a minimum of 1.33 degrees (average flexion to touch toes). The modern day activities were accomplished using arcs of motion of varying magnitude. The use of phone required an average arc of flexion of 107.67 degrees (range 78.93 - 139.77) while driving required an average arc of 32.69 degrees (range 8.62 - 96.03) of flexion and supination arc of 52.30 degrees (range 12.80 - 120.12). Use of a computer required an average flexion of 40.61degrees (keyboard) and 34.33 degrees (mouse).

This data compliments the work previously carried out by Morrey. It defines the functional range of movement for common activities of daily living.

BORS-P02

A MURINE MODEL OF INTERNAL PLATE FIXATION

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Fracture fixation aims to maintain reduction of closely apposed bone fragments and restrict mobility at the fracture site while limiting further disruption to vascular supply at the fracture site to aid fracture repair. Plate fixation allows precise anatomical realignment of bony fragments under direct vision and accelerates functional recovery. There are no described models of internal plate fixation in small animals.

8 adult male Sprague-Dawley rats were assessed following fracture with plain radiography and histology. A transverse osteotomy was created using a circular saw of 0.1mm thickness and plate fixation following anatomical reduction under direct vision was obtained with a custom made 4-hole stainless steel plate (16mm x 4mm x 1mm) with 1.25mm diameter holes (Physics Workshop, The University of Edinburgh, UK) and four 1.2mm x 5mm screws (PTS Ltd, East Grinstead, UK). The tibia was approached via an antero-medial incision. The plate was applied to the medial surface of the tibia following compression at the fracture site. The fascia and skin were closed with 3-0 vicryl.

Plain radiographs revealed no visible callus. Histology revealed healing via enchondral ossification. Four-point bending strength of the fractured limb is compared to that of the contra-lateral limb to assess the mechanical integrity of fracture healing.

This is a simple, reproducible, and cost-effective model in an adult rat which could be used to assess the effect of systemically or locally applied substances on internal plate fixation where anatomical reduction is obtained and confirmed under direct vision intra-operatively as is the case in clinical practice. This model has been refined to obtain compression at the fracture site while maintaining rigid fixation to obtain primary fracture healing. A novel model of internal plate fixation in a rat tibia has been developed.

BORS-P03

A NEW WAY TO DRILL ACL TUNNELS

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To compare the tunnel positioning, direction and tunnel mouth geometry of femoral ACL tunnels created using arthroscopic conventional anterograde and Retroscrew retrograde drilling techniques in human cadaver specimens; and to compare the tunnel mouth geometry of tibial and femoral tunnels drilled in dissected porcine specimens and human synthetic bone.

Sixteen cadaver specimens were divided into 2 groups: an Anterograde drilling Group A and retrograde drilling Retroscrew Group R. All tunnels were drilled by 2 expert knee surgeons; the knees were then dissected. Mouldings of the tunnel mouths were made using PMMA, then cannulated machined Nylon rods with the same diameter as the tunnel, containing a central 1mm diameter Kirschner wire, were inserted into the tunnels and AP and lateral plain X-rays were taken. For the laboratory controlled drilling experiments, 6 fresh pig femurs and blocks of synthetic bone were divided into 3 drilling groups: anterograde tibia, anterograde femur and retrograde femur. A total of 58 holes were drilled under laboratory conditions. The resulting tunnel moulds, drilled holes and X-rays were analysed to determine tunnel uniformity, tunnel entry points and tunnel positions.

Tunnel mouth diameters were significantly larger in the anterograde drilling groups (p values <0.001, paired t tests). In the cadaver specimens, tunnel entry position in relation to the ACL footprint was different between the groups, and there was a significant difference in the angulation of the femoral tunnels (the retrograde tunnels being more transverse), but no difference in the number of ACL attachment hits, or in the uniformity or angulation of the tibial tunnels.

The use of the Retroscrew device or an in to out technique in anterograde drilling, results in a more uniformly drilled ACL tunnel. This may result in a better graft fit within the tunnels, reduce synovial fluid ingress and increase the rate of osteointegration. There was no difference in the ACL footprint hit rate between the two drilling techniques. However, there was significant variation in the drill entry points and angulation of the femoral tunnels drilled by each of our expert surgeons in order to reach the ACL attachment.

BORS-P04

A PILOT STUDY OF THE MECHANICAL BEHAVIOUR OF SPINAL METASTASES PRE- AND POST-VERTEBROPLASTY

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The most common site for bone metastases (BM) and lesions arising from multiple myeloma (MM) is the spine with severe osteolytic infiltrations leading to fracture and bone pain. Despite these deleterious events, very little is known about the mechanical behaviour of either the infiltrated or post-fracture augmented vertebrae. The purpose of this pilot study was to investigate (i) the mechanical behaviour of vertebrae with lesion involvement and (ii) the biomechanical effectiveness of vertebroplasty incorporating coblation.

Two cadaveric spines were acquired from which 12 vertebrae were acquired with bladder metastases and 13 with MM lesions. Load-deformation behaviour was determined using a previously developed protocol from which fracture strength data were acquired. Fractured vertebrae were then assigned to two groups: group 1 - lesion material removed by coblation prior to vertebroplasty; group 2 - no coblation prior to vertebroplasty. All vertebrae were fractured post-augmentation under the same loading protocol. At each stage microCT assessments were conducted to investigate lesion morphology and cement volume/distribution.

MM vertebrae were characterised by many small lesions, generalised bone degradation and multiple compromise of the cortical wall. In contrast, large focal lesions were present in the BM vertebrae in

which the cortical wall generally remained intact. The initial failure strength of the MM vertebrae were significantly lower than BM vertebrae (L=2200N vs 950N, P<0.001). A significant improvement in relative fracture strength was found post augmentation for both lesion-types (1.42 ± 0.51, P=0.0006). Coblation provided a marginally significant increase in the same parameter post-augmentation (P=0.08) and, qualitatively, improved the ease of injection.

Bladder BM and MM vertebral lesions showed significant differences in both trabecular morphology and bone quality that leads to clinically relevant variations in the fracture behaviour of the vertebrae. Vertebroplasty appears to improve the post-fracture strength of the vertebrae by a similar amount to that observed in osteoporosis. However, variations in morphology and levels of bone degradation between different pathologies would suggest that the vertebroplasty intervention should be optimised in terms of both cement properties and delivery to maximise this structural enhancement.

BORS-P05

A PRELIMINARY CADAVERIC STUDY INVESTIGATING THE BIOMECHANICAL EFFECTIVENESS OF PROPHYLACTIC VERTEBRAL AUGMENTATION ADJACENT TO VERTEBROPLASTY UNDER CYCLIC LOADING

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Although the short term outcomes of percutaneous vertebroplasty for the management of painful osteoporotic vertebral compression fracture (VCF) have been promising, there are significant concerns surrounding the longer-term effects of the treatment. In particular, there may be an associated increased risk of fracture in the vertebrae adjacent to the augmentation site. The objectives of this preliminary study were to investigate the segmental effects of vertebroplasty with prophylactic reinforcement of the adjacent vertebra under cyclic loads. The effects of reducing the elastic modulus of the cement were also assessed.

Nine T12-L2 human vertebral segments were prepared and a VCF was generated in the superior vertebrae. Vertebroplasty was performed on the fractured T12 vertebra. Subsequently, the adjacent intact L1 vertebra was prophylactically augmented with cement of differing elastic moduli (100-12.5% of the base cement). Following elastic quasi-static compression tests before and after augmentation, specimens were subject to incrementally increasing dynamic loads in proportion to patient body weight (BW) to assess fatigue properties of the construct. Quantitative CT assessments were conducted at several stages to assess the vertebral condition and quantify the gross dimensions of the segment.

No significant difference in construct stiffness was found pre- or post-augmentation (t=1.4, P=0.19). Displacement plots during dynamic loading showed little evidence of fracture under normal physiological loads (1-2.5 x BW). A third of specimens continued to endure increasing load demands with no fracture following testing. In six specimens, however, greater loads induced eleven fractures: seven in augmented vertebrae (2 x T12, 5 x L1) and four in the adjacent L2 vertebra. Altering the cement modulus had no effect on segmental compromise.

In this preliminary investigation, prophylactic augmentation adjacent to vertebroplasty showed little evidence of inducing fractures under normal physiological loads associated with moderate physical activity, although loads representing more strenuous activities did generate adjacent and peri-augmentation compromise. The frequency or location of the induced fracture within the vertebral segment did not appear to be related to the elastic modulus of the cement in the adjacent vertebra.

BORS-P06

A ROLE FOR MEMBRANE TRANSPORT PROTEINS IN GROWTH PLATE CHONDROCYTE HYPERTROPHY; AN IMMUNOHISTOCHEMICAL STUDY

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Growth plate chondrocyte volume increase is essential for bone lengthening. The mechanisms involved are unclear, but could comprise swelling ((1); increase in water content) or hypertrophy ((2); an increase in both water and protein proportionally) mediated processes. Both require the up-regulation of cytoplasmic membrane transporters to increase intracellular osmolytes (swelling) or amino acids for protein production (hypertrophy). In order to elucidate the mechanism(s) responsible, this study set out to identify the presence of transport proteins, known to be involved in swelling and hypertrophy mediated cell volume increase, in the mammalian growth plate. Immunohistochemistry was used to determine relative transporter populations, and to measure tissue distribution and cellular localisation appropriate for cell volume increase.

Growth plates from proximal tibia of 7 day rat pups were dissected and fixed in 4% paraformaldehyde. Tissue sections were prepared using standard immuno-histochemical procedures. 1o antibodies for NKCC, system A amino acid transport (SNAT2), and the astrocyte glutamate transporter (GLAST) were used. Fluorescently tagged 2o antibodies were visualised using confocal laser scanning microscopy and analysed in an unbiased quantitative manner.

Amino acid transporters SNAT2 and GLAST exhibited little staining in the proliferative zone (PZ), but did appear on the cytoplasmic membrane of hypertrophic zone (HZ) cells. NKCC showed some cytoplasmic fluorescence in the PZ, which significantly translocated to the cytoplasmic membrane in the HZ. Cellular mRNA for these transporters are preferentially expressed in growth plate HZ over PZ (3). We show here that all transporters are also preferentially expressed in the HZ, and that their localisation to the plasma membrane is consistent with cell volume increase. SNAT2 and GLAST, through tertiary transport mechanisms, can create a milieu of amino acids suitable for protein synthesis (4), hence a hypertrophic volume increase mechanism; however NKCC is a powerful system for cell volume increase by swelling in many other cell types (5).

Our data suggest that both swelling and hypertrophic mechanisms are involved in the increase of cell volume, and hence bone lengthening.

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BORS-P07

ANTHROPOMETRIC MEASUREMENTS OF KNEE JOINT IN INDIAN POPULATION: CO-RELATION WITH CURRENT KNEE ARTHROPLASTY SYSTEMS

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There is no data concerning morphological dimensions of distal femur, proximal tibia and patella in Indian population. The objective was to analyse the anthropometric data in Indian knees and to co-relate them with existing knee arthroplasty systems.

MRI scans of 25 patients (15 males & 10 females) who underwent bilateral knee scans for ligamental injuries were collected. Patients with arthritis, bone loss, varus/valgus deformity of >15 degrees and those with immature skeleton were excluded. The mean age was 32 yrs (18-53 yrs). Three surgeons independently measured medio-lateral(ML), antero-posterior(AP) dimensions & aspect ratio(AR) of distal femur, proximal tibia and unresected patellar thickness(PT) on three occasions one week apart to account for intra & inter-observer variability. The resultant data of 50 knees was analysed using SPSS v14.0 and compared with five prosthesis knee systems (PFC sigma, NexGen, Scorpio, IB-II & Gender specific knee).

The mean ML & AP for proximal tibia was 73.3±5.3 & 47.8±4.3 mm. The mean ML & AP (lateral condyle) for distal femur was 74.3±5.9 & 65.4±5.0 mm. The mean PT was 24.7 & 21.8 mm in males & females respectively. The ML & AP showed a statistically significant positive correlation with the height of the person (ML r=0.55; AP r=0.50 & p=0.01). The tibial and femoral AR showed higher ratio for smaller knees & smaller ratio for larger knees i.e. decline in AR for increasing AP dimension. None of the prosthesis designs mimicked this deccrease in AR and NexGen prosthesis infact showed an increase in AR. Gender differences in the morphological data were shown by variable tibial AR.

Most of the available TKR prosthesis designs differ from actual knee morphometry of Indian population. These data provides the basis for designing optimal prosthesis for people of Indian/Asian origin in UK and overseas.

BORS-P08

ARTHROPLASTY FOR POST TRAUMATIC OSTEOARTHRITIS OF THE INDEX FINGER METACARPOPHALANGEAL JOINT IN YOUNG INDIVIDUAL

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Intra-articular fractures of the head of the index finger metacarpal are at risk of developing traumatic osteoarthritis. The use of MCPJ Arthroplasty in post traumatic arthritis is not routinely performed especially in young individual

We present a case initially managed by external fixation resulting in a non functioning stiff finger, which did not respond to tenolysis or arthrolysis, but improved significantly with a MCPJ arthroplasty.

Case Report:- A 26-year old man sustained closed isolated intra articular fracture of metacarpal head of index finger. Initially patient underwent closed reduction and external fixation with supplementary K wires the external fixator was removed after two months once the fracture had united. Eight months following surgery the index finger was stiff and had radiological signs of osteoarthritis. At this stage extensor tendon tenolysis and MCPJ arthrolysis was performed, with Adcongel application. Only 10 degrees of flexion was gained at the MCPJ following the second surgery. Two years following the injury a piro carbon (name of implant) MCPJ arthroplasty was performed. A dorsal approach was made with a local impaction bone grafting technique. 18 months after the joint replacement, the patient had full pain free range of movement in the hand with good grip strength, and had returned back to work. Pre and post arthroplasty DASH scores were 18.33 and 11.66 respectively. Patient satisfaction score (VAS) was 9/10.{BR} Post traumatic MCP joint arthritis in young individuals can be treated with arthroplasty. Our 18 months follow up shows excellent function, with high patient satisfaction and back to the work.

BORS-P09

AUDIT AND RE-AUDIT OF THE USE OF BONE PROTECTION TREATMENT IN ELDERLY PATIENTS WHO ATTENDED WITH FALLS IN HULL ROYAL INFIRMARY

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Introduction: Falls with bone fractures are common in elderly patients. An audit of the use of bone protection treatment in elderly patients who attended the Hull Royal Infirmary with falls was done in 2003. Following this, departmental audit presentation was done twice between 2004 and 2007 and recommendations on the importance of bone protection treatment in elderly patients were disseminated. A repeat audit was performed in early 2008.

Methods: It is a cross-sectional study. We reviewed case-notes of patients who were currently in-patients in hospital between 01/01/2008 and 14/02/2008. The same questionnaire adapted from the Royal College of Physicians and Bone and Tooth Society of Great Britain guideline(July 2000)was used for both audits. Medical notes were checked for the risk factors for the osteoporosis and use of bone protection treatment in these patients.

Results:	2008	2003
1. Total number of the patients	40	29
2. Mean age of patients	88	87
3. Total number of the patients who got the DXA scan	4/40 (10%)	2/29 (6.9%)
4. Proportion of the patients on the bone protection treatment	28/40 (70%)	12/29 (41.3%)
5. Proportion of the patients with bone fractures who were not on the bone protection treatment	5/40 (12.5%)	8/29 (27.6%)
6. Proportion of the patients with DXA positive results received proper bone protection treatment	4/4 (100%)	2/2 (100%)
7. None of the patients has hip protector	0/40 (0%)	0/29 (0%)

Conclusion: There was a moderate improvement in the proportion of the patients receiving bone proportion treatment. There was also a significant improvement in the proportion of the patients with bone fractures who received the treatment.

BORS-P10

WITHDRAWN

BORS-P11

BIOMECHANICAL EVALUATION OF CEMENT-IN-CEMENT INTERFACE IN HIP REVISION SURGERY

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When the primary cement mantle surrounding the femoral stem of the hip arthroplasty is stable, in-cement revision appeals as a valid option. We investigated whether mechanical roughening of the primary surface offers extra stability in the presence of fluid.

We analysed surface finish (Talysurf) of the Exeter femoral stem cement-metal interface before and after reaming with a standard hand reamer. Cylindrical blocks of polymethylmethacrylate cement (Simplex, Stryker) represented primary cement mantles. In the control their flat surface was cast against polished Exeter stem. In the surface alteration groups standardised machine cutting was used to represent either the effect of a hand reamer or the surface finish with Ra 10 folds higher - as calibrated by data on surface analysis. Such a surface was left dry or stained with 0.1 ml/cm2, 0.01ml/cm2 or 0.001ml/cm2 of bone marrow equivalent prior to the application of the secondary cement. Shearing strength (Autograph AGS, Shimadzu, Japan) was compared between the variants using ANOVA.

In the control group (smooth surface) shearing strength of the interface was dropping proportionally to the volume of fluid used. Roughening, especially at the Ra of 5um or higher provided protective effect on the shearing strength of the cement-in-cement interface in the presence of relatively large volume of fluids.

In cement revision seems to be a valid option when the original mantle is stable. Strength of cement-in-cement interface may be increased by roughening of the primary mantle surface and small fluid amounts of variable consistency, inevitably present in clinical practice, will not adversely affect the shearing strength of the construct.

BORS-P12

BONE AND JOINT CIRCULATION REVISITED

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Intraosseous pressure (IOP) in cancellous bone was measured experimentally and was found to vary considerably even when using a standardised technique. This has previously caused frustration with the technique for many years. However, superimposed on the variability in IOP there was a reliable underlying wave form with two distinct patterns. The patterns closely correspond to the arterial pulse wave and to the respiratory wave. Systemic drug administration, physical joint and limb position changes, and joint loading also predictably affect the underlying IOP. Proximal arterial and venous occlusion have a direct and repeatable effect on IOP. When applied logically, combinations of these tests give useful information about cancellous subchondral bone circulation at the needle tip in vivo.

Triple simultaneous recordings in separate areas of cancellous bone appear to show that each bone behaves as a compartmentalised perfused sponge in a semiclosed system. The Ficat saline stress test was used. The method is shown to damage local bone microcirculation. It does not appear to have a logical place in the functional exploration of bone or in assessing subchondral perfusion and vascularity. Aspiration may be more appropriate. There appears to be a subchondral microvascular 'bone blood pump'. There is clinical, experimental and pathological evidence to support this fresh interpretation of bone physiology.

By applying these simple techniques in a controlled way a useful understanding of compartment syndromes and bone microcirculation, physiology and perfusion can be gained. IOP studies have been of limited value in the past but based on this interpretation can be of real value in understanding bone physiology and pathology.

BORS-P13

BONE MORPHOGENETIC PROTEINS 1 TO 7 IN HUMAN BREAST CARCINOMAS EXPRESSION PATTERN AND CLINICAL AND PROGNOSTIC RELEVANCE

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Bone morphological proteins (BMPs) have a diverse role and they act in a time, concentration and cell type specific manner. They have been shown to regulate cellular motility and the cells ability to invade and recently BMP molecules have been shown to have an impact on the biological behaviour of breast cancer cells. In this study we looked, for the first time, at the expression of a panel of BMPs in breast carcinomas

Fresh frozen primary breast cancer tissues (n =120) and non-neoplastic mammary tissue (n = 32) were used. The distribution and location of BMPs was assessed using immunohistochemical methods and the levels of BMPs (BMP-1, -2, -3, -4, -5, -6, and -7) were determined using quantitative RT-PCR. The results were analysed against the clinical, pathological and follow-up (10 years) data.

BMP-2 and BMP-7 had a contrast pattern of expression in normal and tumour tissues, in that BMP-2 transcript level was lower and BMP-7 was higher in breast tumours than normal tissues. BMP-2 transcript was also significantly lower in tumours from patients with a moderate and poor prognosis than from those with a good prognosis (p=0.04). Also both BMP-2 and BMP-7 showed a significant difference between node positive and node negative tumours (p=0.033 and p=0.031 respectively). BMPs 1, 3, 4, 5 and 6 showed an inconsistent variation in transcript levels within the cancer subgroups with no statistically significant results.

This study has demonstrated the differential expression pattern of BMP molecules in breast cancer and reveals a potential prognostic value of BMP-2 and BMP-7 for the patients. The findings may also suggest that these BMPs may be potential therapeutic targets.

BORS-P14

CHONDROCYTE DEATH IN MECHANICALLY INJURED ARTICULAR CARTILAGE - THE INFLUENCE OF EXTRACELLULAR CALCIUM

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Calcium signalling has been recognised as an important regulator in mechanisms of chondrocyte death associated with mechanical articular cartilage injury. The objective of the study was to determine whether calcium present in the extracellular media affects chondrocyte death following mechanical injury. The primary hypothesis was that exposure of articular cartilage to calcium-free media decreases in situ chondrocyte death following sharp mechanical injury (within hours). The secondary hypothesis was that subsequent culture of injured articular cartilage in calcium-rich media increases in situ chondrocyte death (within days).

Osteochondral strips were harvested from the metacarpophalangeal joints of six different cows within 12 hours of slaughter. The osteochondral strips were pre-incubated (37C) in calcium-free (0 mM, controls) and calcium-rich (2-20 mM) culture media for 12 hours to allow tissue equilibration with the media prior to experimental mechanical injury. The osteochondral strips were then mechanically injured through the full thickness of articular cartilage with a fresh scalpel to obtain rectangular osteochondral explants (n=60). The rectangular explants (with scalpel injured cartilage edges) were incubated further in calcium-free and calcium-rich media over 7 days. Using confocal laser scanning microscopy and fluorescent probes to determine cell viability, in situ chondrocyte death was quantified within the full thickness of mechanically injured articular cartilage as a function of medium calcium concentration (0-20 mM) and time (2.5 hours and 7 days).

Exposure of articular cartilage to calcium-free media (0 mM) significantly reduced superficial zone chondrocyte death after mechanical injury compared with exposure to calcium-rich media (2-20 mM, ANOVA at 2.5 hour, p=0.002). In calcium-rich media, although the extent of chondrocyte death increased with increasing medium calcium concentration, cell death remained localised to the superficial zone of articular cartilage over 7 days (ANOVA, p<0.05). However, in calcium-free media, there was an increase in chondrocyte death within deeper zones of articular cartilage over 7 days.

Extracellular calcium significantly affects chondrocyte death in mechanically injured articular cartilage. These data have important clinical implications for the design of calcium-containing joint irrigating solutions used during articular surgery.

BORS-P15

CHROMIUM, COBALT AND TITANIUM METALLOSIS FOLLOWING A FAILING NOTTINGHAM SHOULDER REPLACEMENT

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We report the case of a patient who developed extensive metallosis following an uncemented Nottingham Shoulder Replacement (Biomet, UK) requiring a revision. Extensive metallosis of a shoulder joint replacement resulting in pain and failure has not previously been described in the literature.

A fifty-five year old patient underwent an uncemented Nottingham Shoulder Replacement for destructive rheumatoid arthritis. The patient complained of continuous pain in the shoulder and underwent an exploration. At operation the patient had blackening of not only intraarticular but also extraarticular tissues and the subchondral bone. On histological analyses of samples taken during surgery, it was evident that there was a profound metallosis with a macrophage response with some giant cell formation. Single line Microprobe Laser Ablation-Inductively Coupled Plasma-Mass Spectrometer system (LA-ICP-MS) scans through the surface of the histology block of periprosthetic tissue area identified the intracellular particles as containing the elements chromium, cobalt and molybdenum in the same relative concentration as the main humeral head prosthetic component. Occasional large extracellular particles of 200 micron size were identified as titanium with an identical elemental signature as the osteo-intigration layer on the prosthetic humeral componant. Urinalysis showed significant levels of essential trace elements cobalt and chromium, and non-essential trace elements titanium and aluminium when compared to normal controls

The pain continued despite a humeral head exchange and a decision was made to proceed to a revised cemented Bio-modular total shoulder replacement (Biomet, UK). Macroscopic analyses of the titanium porous coating of the removed stem showed that the coating had started to flake and come apart at the peripheries. LA-ICP-MS analysis of the particles embedded in the UHMWPE glenoid component had the same elemental composition as those in the humoral shaft osteo-intigration layer and the large particles in the periprosthetic tissues. Macroscopic analyses of the retrieved humeral head showed numerous radial scratches on the surface of the head consistent with abrasive wear.

This is the first case of metallosis where titanium has been used with a harder material and the authors believe the metallosis was caused by surface hardening of titanium, and these titanium particles embedded in the UHMWP surface were responsible for the wear, acting like sandpaper. This would explain why the metallosis continued despite an exchange of the humeral head.

BORS-P16

COMPARISON BETWEEN CLOSED WOUND DRAINAGE AND NO DRAINAGE IN TOTAL KNEE ARTHROPLASTY

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The use of drains in total knee arthroplasty remains controversial. The drains do not affect the patients' hospital stay, blood loss or the patients' satisfaction in any way. On the contrary the drains tend to cost the National Health Service dearly.

This prospective, non-randomised study was designed to evaluate the role of drains in routine total knee arthroplasty. Our study involved a single surgeon and a single prosthetic knee implant. Tourniquet was

used which was released after applying the dressing. We analysed the following parameters û age, sex of the patient, length of stay and haemoglobin drop. We investigated 100 patients undergoing knee arthroplasties out of which 50 patients had drains inserted and 50 had no drains inserted. The group having no drains inserted had an average age of 70 years with a range of 54-88 years and a male to female ratio of 3:4. The average length of stay in hospital was 5 days and the average haemoglobin drop was 22gm/ml. The group having drains inserted had an average age of 69 years with range of 54-87 years and a male female ratio of 1:2. The average length of stay in hospital was 5 days and average haemoglobin drop was 30 gm/ml.

Thus on conclusion we found that patients without any drains placed had a comparable length of hospital stay and a lesser drop in haemoglobin as compared to the group of patients where drains were used. There were no wound complications in this group either. The cost-effectiveness of not using drains supported by better patient satisfaction and easier dressing post-operatively on the ward outweighs against argument in the favour of placing drains.

BORS-P17

CORELATION OF PERIOPERATIVE FRACTURES OF THE FEMUR & TIBIA IN COMPUTER ASSISTED TOTAL KNEE ARTHROPLASTY WITH RIGID BODY TRAJECTORY

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Background: There are reports of adverse events such as periprosthetic fracture following TKA, which may be secondary to additional rigid body fixation '1' and other numerous etiologic factors '2,3'. This study presents three patients who developed periprosthetic fracture above the femoral component in two cases and below the tibial component in one case. We analysed the autopsy findings to review the fracture of the distal femur occurring after total knee arthroplasty in order to identify risk factors related to rigid body fixation site on the distal femur. We prospectively reviewed the effect of rigid body fixation site on the femur and tibia on the subsequent occurrence of a periprosthetic fracture of the distal aspect of the femur and proximal aspect of tibia after computer assisted primary total knee arthroplasty in such patients.

Materials & Method: Three periprosthetic fractures occurred between 2003 and 2007 among 316 navigated total knee arthroplasties performed during this period. The circumstances of these fractures were noted in comparison with other prosthetic implants specifically to address the influence of rigid body fixation site as a stress riser. Two fractures of the distal femur and one fracture of the proximal tibia occurred in patients who had had a total knee arthroplasty during the same time period.

Result: Rigid body trajectories were analysed in 316 knees in our series. During an average follow-up period of 1.1 years, only two supracondylar femoral fractures and one proximal tibial fracture occurred. In all cases fracture initiated below the screw hole. The rigid body fixation site was not appear to be sufficient to be the only cause of fracture as fracture line was not initiated from the fixation site as found during the autopsy.

Discussion: This study shows that fracture of the distal femur and proximal tibia occurs in certain preferential circumstances. The rigid body fixation site may not be responsible for initiating such a fracture. Nevertheless, it may an element frequently associated with such a fracture.

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BORS-P18

WITHDRAWN

BORS-P19

DETERMINING HUMAN SKELETAL MUSCLE VOLUME USING 3D FREEHAND ULTRASOUND

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Measurements of change in skeletal muscle volume can indicate response to treatment in cancer patients and also the rate of rehabilitation in the case of joint replacement. Currently, Magnetic Resonance (MR) is the favoured method for muscle volume measurements however it is resource intensive and waiting times for non urgent cases are long. 3D Ultrasound provides a non invasive method of obtaining accurate muscle volume measurements and is acquired using a standard clinical ultrasound machine and an external optical tracking devices to monitoring the position of the transducer during scanning. 3D Ultrasound is much quicker and easier to access than MR and it is also less intimidating to children, the elderly and the very ill. We have shown for the first time that 3D Freehand Ultrasound can be used to accurately determine human skeletal muscle volume in vivo. Volume measurements of the rectus femoris quadricep muscle were obtained using 3D Freehand Ultrasound from four healthy volunteers and were validated against volume measurements derived using MR. Muscle volume measurements obtained using 3D Ultrasound were within 8% of the corresponding values from MR. The mean difference was 0.22cm3 with a standard deviation of 0.44cm3.

BORS-P20

WITHDRAWN

BORS-P21

DOES ECHOCARDIOGRAPHIC CARDIAC FUNCTION CORRELATE WITH FRACTURED NECK OF FEMUR OUTCOME?

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Retrospective study: Patients with #NOF that underwent echocardiography were identified. Patients were divided in to two groups based on left ventricular function. Group 1 - good to mild LV dysfunction. Group 2 - moderate to severe LV dysfunction. Outcome was measure by using: Average time taken for surgery, Duration of stay in the hospital, Mortality, Any change in the mobility and social history

75 patients were analysed. Group1: Avg age 82, M: F=8:39, Avg waiting for surgery - 8 days, Avg stay - 37 days, Mortality - 22 %, Mobility: 28 % no change, 31 % down grade by one degree. 60 % no change in discharge destination. Group2: Avg age 84, M: F=6:22, Avg waiting for surgery -13 days, Avg stay - 45 days, Mortality - 54 %, Mobility: 90 % down grade by more than two grades, 25 % no change discharge destination.

Outcome was better in patients with good to mild L.V dysfunction with mortality rate being higher in those with moderate to severe L.V dysfunction. Average waiting time for surgery and duration of stay was significantly higher in severe L.V dysfunction group. Mobility was more downgraded in moderate to severe L.V dysfunction group. While 75 % had change in their place of final destination for this group, 40 % had similar change in good to mild L.V dysfunction group.

We feel that this information helps us to quantify and qualify the risk of not surviving the inpatient episode and is valuable to patients and their families. The risks surrounding surgery are often difficult to breech with families as the doctors view is often seen as pessimistic. This will also help us to give information with respect to mobility and place of residence, which can be used to plan care packages with families.

BORS-P22

DOES THE RATE OF DEFORMATION AFFECT THE MECHANICAL RESPONSE OF DURA MATER?

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The dura mater, which encloses and protects the sensitive spinal cord, may undergo high-rate deformations during a vertebral trauma. These elevated rates may induce a different response in the dura mater compared to a physiological situation due to its viscoelastic nature. The objective of this work was to determine whether a variation in the rate of deformation had a measurable effect on the mechanical response of dura mater.

Bovine specimens from both the axial and the transverse direction were tested in uniaxial traction to failure. Tests were performed at three different strain rates, with a difference between the lowest and the highest rate of a factor 100. The tests were recorded with a video to enable the calculation of the actual strain in the material.

Stress-strain curves showed that the dura mater presented the typical J-shaped behaviour of viscoelastic soft tissue under tension. The first part of the curve, where the collagen fibres become disentangled and aligned with the loading direction, was shorter for the specimens in the transverse than in the axial direction. The maximum stress and strain were also lower in the transverse direction than the axial direction. These results are supported by previous studies that suggest that the collagen fibres in the dura mater are directed mainly along the body axis. Further, an Ogden model was applied to the data and differences were found in the material parameters between the two specimen directions. However, no difference was found in these parameters for the different strain rates.

In conclusion, the resistance of the dura alone appears not to change notably by a 100-fold change in rate of deformation. Although this would suggest that the rate of deformation is not important during a high-rate trauma, e.g. a burst fracture, this study does not take into account the important interactions between the dura and the cerebrospinal fluid, which may have a rate-determined effect.

BORS-P23

WITHDRAWN

BORS-P24

ELEMENTAL ANALYSIS OF PERIPROSTHETIC TISSUES BY LA-ICP-MS AND ICP-MS

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The elemental composition of tissues surrounding implanted metal containing prostheses is important in the recognition of prosthetic failure pathways. From a clinical aspect and patient safety it is necessary to assess the local and body burden of potentially toxic elements.

Two complimentary techniques, Laser Ablation Inductively Coupled Plasma Mass Spectroscopy (LA-ICP-MS) and Inductively Coupled Plasma Mass Spectroscopy (ICP-MS) are available for spatial and bulk analysis of surgically removed tissues respectively and give multi-elemental sensitivity typically at the PPB range. At the revision of a spinal fusion on a 40 year old patient it was noted that tissues adjacent to the metalwork were discoloured. Microscopic examination of the histology sections showed focal accumulation of particulate material. Using an image of the histology section as a guide LA-ICP-MS analysis data was obtained through the accumulation areas on the surface of the histology block. Total elemental tissue levels were measured by ICP-MS. Removed screws and plates were analysed and used as elemental reference controls. LA-ICP-MS showed the co-localisation of Co, Cr, Ni, V and Mn and Zn. There were also deposits of Fe not associated with other elements. Bulk analysis by ICP-MS confirmed the presence of the target metals.

The two techniques allow the analyst to acquire two sets of information. LA-ICP-MS gives spatial but semi-quantitative information whereas ICP-MS gives quantitative bulk information but not the biologically important 'where is it and what's it doing' information. As more potentially toxic metals are used in surgery and they are implanted for a longer period it is important that the release and accumulation of these elements is monitored

BORS-P25

ENHANCED OSTEOBLASTIC DIFFERENTIATION BY STROMAL CELL-DERIVED FACTOR-1 IN HUMAN MESENCHYMAL STEM CELLS

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It has been reported that stromal cell-derived factor-1 (SDF-1) and its receptor CXC chemokine receptor 4 (CXCR4) play roles in stem cell homing and are related to short-term and long-term engraftments of stem cells. Transduced bone marrow stromal stem cell lines, secreting high SDF-1 levels, displayed an enhanced ability to form ectopic bone in vivo. Furthermore, blocking SDF-1/CXCR4 signaling strongly inhibited bone morphogenic protein 2 (BMP2)-induced osteogenic differentiation of ST2 bone marrow stromal cells. The purpose of this study is to investigate whether SDF-1 will affect the osteogenic differentiation in human mesenchymal stem cells. Human mesenchymal stem cells (hMSCs) were obtained from the iliac crest of healthy donors. hMSCs were treated with osteoinductive medium or recombinant SDF-1 or osteoinductive medium plus recombinant SDF-1. Osteogenic differentiation of the treated hMSCs was assessed by observation of the morphological changes, alkaline phosphatase (ALP) activity and the calcium deposition. The proliferation of the hMSCs was also estimated during the treatment. Cell morphological changes and significantly up-regulated ALP activities were only observed in the osteoinductive medium group and osteoinductive medium plus SDF-1 group. However, SDF-1 shows a significant effect in early osteogenic differentiation when the SDF-1 was added into the osteoinductive medium. Cell proliferation was also significantly up-regulated in these two groups. These results may indicate an enhanced role of SDF-1 in osteogenic differentiation. Both osteoinductive groups showed increased cell proliferation and whether these cells are transient amplified cells requires further investigation.

BORS-P26

ENHANCING THE WOUND COVERAGE DURING BONE TRANSPORT FOR INFECTED NON UNION OF TIBIA: REPORT OF A SIMPLE TECHNIQUE

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Successful treatment of infected non union in long bone fractures has always been a challenge to many orthopaedic surgeons. Segmental excision of the infected bone followed by bone transportation is one of the common modalities of treatment in such difficult cases. Apart from the challenge due to the resultant large bone defect, often the surrounding unhealthy skin and soft tissues further hinder adequate coverage of the bone. Plastic surgical procedures are often unsuccessful to cover the resultant bone and soft tissue defects in such infected cases.

We would like to report the method of treatment we have undertaken in treating a 53 year old patient with infected non union of distal shaft of tibia with an osteomyelitic segment of seven centimetres. After segmental bone excision and soft tissue debridement, a seven centimetre long wound with bone gap resulted. This was reduced to four centimetres after acute limb shortening and application of Taylor Spatial frame. After two subsequent debridements, a continuous vacuum therapy was applied to the resultant wound. A piggy back circular frame was applied to the tibia and a proximal corticotomy was performed two weeks after the first operation. Bone transport was commenced three weeks after the first operation and the vacuum therapy was continued during this period.

After six weeks of bone transportation and vacuum therapy, we noted that there was not only a remarkable growth of granulation tissue that filled the soft tissue defect, but also satisfactory signs of bony union across the docking site. The wound was subsequently covered with split skin graft.

We would like to emphasise the benefits of a simple method such as vacuum therapy in enhancing cover of the large soft tissue defects during bone transportation in infected non union cases, before resorting to complex plastic surgical procedures.

BORS-P27

FACTORS AFFECTING PULLOUT STRENGTH OF CANNULATED CANCELLOUS BONE SCREWS

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Cannulated cancellous bone screws are employed in several aspects of trauma surgery. Self-drilling/self-tapping screws have been designed to ease insertion and reduce operating times. We investigated the effects of host factors such as osteoporotic bone and surgical factors such as over-drilling the guide-wire or placing screws beyond the far cortex on screw pullout strength of cannulated screws in normal and validated osteoporotic bone models.

Screw 1 was 6.5mm titanium, self-drilling/self-tapping screw (Synthes). Screw 2 was 6.5mm stainless steel, self-drilling/self-tapping screw (Synthes). Screw 3 was 6.5mm titanium, self-drilling/self-tapping screw (Depuy). Screw 4 was 7.0mm stainless steel, self tapping screw (Depuy). Normal bone was simulated with 20pcf. solid rigid polyurethane foam blocks and osteoporotic bone was simulated with 10pcf. blocks. The far cortex was simulated with 3mm short-fiber-filled epoxy sheet. Screws were inserted as per manufacturers' instructions and were pulled out using a tensile testing machine.

In normal bone Screw 3 had a pullout strength of 2681 +/- 244N, significantly higher than other screws tested ($p<0.01$). All screws demonstrated significantly lower pullout strength in osteoporotic bone ($p<0.01$). Screw 3 performed best in osteoporotic bone with mean pullout strength of 678 +/- 23N($p<0.05$). Over-drilling the guide-wire (against manufacturers' advice) significantly reduced pullout strength by almost 33%($p<0.01$). Inserting screws beyond the far cortex significantly increased the pullout strength of all screws by as much as 80%($p<0.01$).

Cannulated cancellous screws have significantly reduced hold in osteoporotic bone with pullout strength approximately 75% that in normal bone. The Depuy 6.5mm titanium, self-drilling/self-tapping screw, performed best in both normal and osteoporotic bone models. Self-drilling/self-tapping screws were designed to be inserted without over-drilling. Insertion against the manufacturers' guidelines significantly reduces their pullout strength. The hold can be significantly increased by insertion beyond the far cortex. This has implications particularly in managing tibial plateau fractures.

BORS-P28

WITHDRAWN

BORS-P29

FEMORAL CANAL PREPARATION AND INTRAMEDULLARY PRESSURE - BROACH DESIGN CONSIDERATIONS

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Serious complications can ensue with total hip replacement including cardiac stress due to marrow embolization '1-2'. Although the associated mortality rate is low, the incidence of embolic events intra operatively remains high with up to 20% embolism occurring during femoral preparation and 50% during stem insertion and reduction '2'. An important factor in avoiding pulmonary embolism is to ensure that fat and bone marrow are not driven into the venous system as a result of femoral bone manipulation. Current total hip replacement techniques involve broaching of the medullary canal with incremental size rasps. The design of such broaches can be improved to allow for removal of excess fat and bone marrow.

Three new rasp design variants were investigated. Variant 1 was a standard toothed rasp, design variant 2 was the same as variant 1 with a hollowed body while variant 3 was a novel slotted design. These were tested in a foam model to assess the design efficiency using rasp penetration per impact data. The designs were then tested in 5 cadaveric femurs to investigate the effectiveness of the rasp in removing excess fat and bone marrow, as well as potential bone particles collection for possible bone grafting '3'.

Design variant 3 was shown to offer a 40% improvement in cutting efficiency compared to the standard teeth design. The hollow features of rasp variant 2 allowed for removal of fat and bone marrow as the rasp was pulled out of the canal. The slotted design (variant 3) presented the additional advantage of bone chip collection.

Simple features can be designed into femoral rasps to reduce intramedullary pressure during femoral canal preparation. This should be carefully considered during instrumentation development. Hollow rasps have the potential of reducing the risk of embolism by removing excess fat and bone marrow, while slotted design have the additional advance of bone debris collection for potential grafting and reduced risk of femoral fractures.<BR.}References: 1. Gandhi et al, J Arthrop 2006, 2. Hagio et al, J Arthrop 2003, 3. Kold et al, J Arthrop 2006

BORS-P30

FEMORAL SUBTROCHANTERIC FRACTURE AND LONG-TERM BISPHOSPHONATE THERAPY: IS THERE AN ASSOCIATION?

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Recent evidence suggests that long-term bisphosphonate therapy may lead to insufficiency fractures at the subtrochanteric femur. The aim of this study is to demonstrate an association between bisphosphonate use and a specific pattern of low-energy subtrochanteric fracture. The fracture pattern we noted was simple, transverse or oblique, with cortical hypertrophy of the lateral aspect of the femur.

Fifty-one subtrochanteric fractures admitted to a tertiary institution from January 2001 to December 2007 were reviewed and 20 patients with low-energy fractures were identified. Clinical data, incidence and duration of bisphosphonate use and outcome were recorded. Plain radiographs were blindly reviewed by three physicians of varying seniority, and they predicted, based on fracture pattern alone, whether the patient was on bisphosphonates.

There were 19 females and 1 male; all were Chinese and 1 patient had bilateral fractures. The average age was 63.1 (range 44 - 88) and 12 patients (60 %) were on alendronate for a mean duration of 4.5 years. Patients on alendronate were younger and from a higher socioeconomic group, and the medication had often been prescribed by general practitioners despite bone mineral densities in the osteopaenic range. A typical fracture pattern was noted in 91.7% of patients on alendronate but was not seen in the non-alendronate group; conversely, we were able to correctly ascertain whether patients were taking alendronate with a mean accuracy of 85.7% based on radiographs alone. Five patients on alendronate therapy had delayed union after surgical fixation; 3 of them had associated implant breakage and all required reoperation and bone grafting.

Femoral subtrochanteric fracture in patients on long-term alendronate has a pathognomonic radiographic configuration. Evidence indicates that the use of bisphosphonates is beneficial in patients with established osteoporosis. However, our study suggests that in patients with osteopaenia, anti-resorptive agents like alendronate may cause over-suppression of bone turnover (OSBT), which may have a deleterious effect rather than a protective one. It is important to recognise this association, as OSBT may lead to higher rates of non-union or delayed union after surgery, and we recommend that such fractures be treated using intra-medullary devices and primary bone grafting.

BORS-P31

FLUID SHEAR STRESSES IN FLEXCELL(TM) DEVICE

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To advance the study of mechanotransduction, the ability to apply well-defined mechanical stimuli to cells is essential. Commercial systems provide controlled biaxial substrate strains for cells cultured on a silicone membrane. This strain is accompanied by fluid shear stress to which cells are highly sensitive but is yet to be quantified in current systems. The aim of this study was to quantify fluid shear stress at the membrane surface in BioFlex wells (Flexcell, Intern. Corp., Hillsborough, NC) using Computational Fluid Dynamics (CFD) varying the strain magnitude and frequency, and also the viscosity of

the culture medium. Parallel culture studies assessed the biological significance of these simulations.

An axisymmetric CFD model with grid resolutions from 50,000 to 100,000 elements, deformable mesh and neo-Hookean hyperelasticity to represent off-post membrane deformation, was constructed in CFD-ACE+ (ESI Group, Paris, France). On-post membrane displacement during operation was defined from previous measurements. A range of values of frequency (0.1 - 2 Hz), strain (1 - 10%) and medium viscosity (1 - 1500 mPas) were investigated in the simulation and in the BioFlex seeded with MC3T3-E1 cells, with carboxymethylcellulose (CMC) to control medium viscosity. mRNA expression of Fos and Ptgs2 was measured by quantitative PCR.

Preliminary results indicate fluid wall shear stresses vary smoothly along the surface of the on-post membrane, with larger stresses in the region of membrane vertical displacement. At 1 Hz with 5% strain and viscosity of 1mPa s, flow in the BioFlex well was laminar. Fluid shear stresses varied between 0 and 4mPa on-post and up to 40mPa off-post. Initial results with 0.1wt% and 0.2wt% CMC medium (approximate viscosities 20 mPas and 31 mPas) showed no detectable changes in Fos and Ptgs2 mRNA-expression from standard medium.

Studies of osteoblasts reported dose-dependent responses to in vitro fluid shear stresses from 10mPa, although recent work found higher stresses are required for transduction. With membrane stretch and fluid wall shear stress characterised and corresponding levels of gene upregulation, indications of the relative importance of these stimuli will be obtained. This deepened insight into mechanotransduction is essential for new stimuli-driven therapies for musculoskeletal regeneration.

BORS-P32

HEALING OF A SEGMENTAL BONE DEFECT USING TRUFIT SCAFFOLD - rhBMP-2 CONSTRUCTS

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The use of bioactive biomaterials for fracture repair or bone regeneration has rapidly gained importance in recent years. This study optimized a femoral segmental bone defect model in athymic (nude) mice to assess the efficacy of a combination of Trufit scaffold and rhBMP-2 for promotion of bone defect repair.

Eight male athymic MF1 mice (Harlan Labs: 7 week-old) were used in this study. All surgical procedures were subject to ethical and Home Office approval. Mice were anaesthetised and the right femur exposed from a lateral approach. A 2 mm section of bone was removed from the mid-shaft of the femur with a high speed microdrill and saline irrigation. The bone defect was repaired using prefabricated (2 mm long, 1.7 mm diameter) Trufit scaffold (Smith & Nephew) absorbed with (n=4) or without (n=4) rhBMP2 (0.125 micro gram / micro litre). Once secure alignment was achieved, fixation was applied using an intramedullary pin (25G hypodermic needle). The time taken for each mouse to walk normally was recorded. Animals were culled after 6 weeks and the defect assessed using conventional X-ray imaging.

Images showed no significant bone density loss in the operated limb compared to the control side. Fracture non-union was evident when Trufit alone was used. In contrast, Trufit - rhBMP2 treated defects revealed bone-bridging in three of the animals, while the defect gap was much reduced in the fourth.

In conclusion, this study showed that a combination of Trufit scaffold and rhBMP-2 can successfully repair segmental bone defects, indicating its potential use in bone tissue engineering for clinical therapy.

BORS-P33

WITHDRAWN

BORS-P34

INFLUENCE OF BONE QUALITY IN THE STABILITY OF IMPLANT FIXATION

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Orthopaedic implants have been successfully used in the treatment of long bone fractures. The stability of fracture fixation influences the rate of fracture healing and hence the purchase strength of the implant is important. The quality of bone may influence the stability of fracture fixation and hence influence rate of bone healing. We aimed to study the influence of the bone quality, i.e. osteoporotic and normal healthy bone, on the strength of fracture fixation when using intramedullary nails.

A composite model made from a stainless steel Intrameduulary Nail (IMN) (12mmx1mm), with similar dimensions to clinically used IMN systems, was connected to a load cell (Instron machine) and axial forces upto 1.4 kN (2xbody weight) applied to reproduce the forces experienced during weight bearing. The distal end of the intramedullary nail was secured using a variety of bone cylinders of dimensions 50mmx5mm, 75mmx5mm and 100mmx5mm to represent the proximal femoral diaphysis, diaphyseo-metaphyseal junction and distal femoral metaphysis. Two types of bone materials were tested representing both osteoporotic and normal healthy bones. These bone cylinders were of comparable dimensions to the average femur. The distal end of the IMN was attached to the centre of the cylinder with a dedicated single rod (5mm diameter) to represent the cross screw.

There was 4 times decrease in implant hold in the metaphyses when compared to the diaphyses in both type of bones. The quality of bone influenced the strength of fixation of the implant. The pull out force and axial stability provided by osteoporotic bone, to the implant, was found to be 3 times less compared to normal bone in the diaphyses. However there was no significant difference between the two type of bones in the metaphyses.

In clinical practice, patients with osteoporotic bones, the purchase strength of the screw will not be adequate enough to provide support to the implants in diaphyses. There is an overall decrease in the screw fixation strength when used in metaphyseal end of the femur. Early weight bearing, when using extreme distal fixation, may potentially delay or result in non-union of the bone.

BORS-P35

INTERVERTEBRAL DISC DEFECT FOLLOWING COLLAGENASE ENZYME INJECTION: AN EXPERIMENTAL STUDY IN BOVINE COCCYGEAL INTERVERTEBRAL DISC

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The current report describes a study in bovine intervertebral disc in which the effects of intradiscal injection of collagenase enzyme were evaluated with respect to volume of defect created in the disc and histological changes.

Objectives: To establish a model of DD that would achieve optimal reduction in the NP mimicking human DDD and examine histological changes.

Bovine IVD were subjected to chemonucleolysis using collagenase enzyme injected into the CC1-CC2 and CC2-CC3 discs. Discs were injected with collagenase (C7926, Sigma Blend F 2006.) enzyme (0.3 ml -150 gm/ml through the end plate allowing digestion to proceed for 12 -15 hrs at 37 degree Celsius in an incubator. In total ten specimen blocks prepared from five bovine tails were used. Disc volumes were measured prior to the instillation then defects created were also measured. Four sections from each disc were stained with H&E. The stained sections were viewed under a bright field microscope.

The collagenase treated IVD demonstrates clear loss of the distinct boundary between the NP and AF, and replacement of the nucleus by digested debris. These changes lead to the creation of a well defined space in the NP. A reduction in IVD space of average 8% was achieved. Histological examination was performed. The sections were stained for routine histology with H&E. In order to examine the size and extent of the defect caused by digestion and distinguish

microscopic alteration of the IVD. All sections showed clear damage to the NP, whereas, the effect of the enzyme on the AF varied. There was no effect of collagenase enzyme on the VEP and vertebral body. The NP is for the most part depopulated of chondrocytic cells by collagenase treatment, whereas the annulae and VEP retained their cellularity. Poorly opposed lamellae, fragmentation of lamellae and disorganized fibrous material replacing central lamellae are among the alterations in the AF.

An effective reduction in disc volume can be achieved experimentally with an appropriate dose of collagenase enzyme and can establish a space big enough for further experimental injection such as stem cells and biomatrix injections.

BORS-P36

LEARNING FROM THE DEAR ANTLER MODEL: USING LAMININ-5 TO SEAL SKIN TO TRANSCUTANEOUS ORTHOPAEDIC IMPLANTS

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Intraosseous transcutaneous amputation prostheses (ITAP) could overcome many of the complications of current stump-socket prosthesis design by attaching the prosthesis directly to the skeleton (Prendegrass-2006). High rates of infection have prevented previous attempts to create this (Prendegrass-2006). A tight epithelial seal at the transcutaneous interface is crucial to preventing infection. Laminin-5 (Ln-5) is an adhesion protein found in the epithelial basement membrane, playing an important role in keratinocyte attachment (Litegens-2006). The aim of this study was to use Ln-5 to increase keratinocyte adhesion to the biomaterials used in ITAP and to augment this by covalently bonding Ln-5 onto these biomaterials.

Smooth (Control), Silanised without Ln-5 (Si), silanised with Ln-5 (SiLn) and adsorbed Ln-5 (AdLn) 10mm Ti6AL4V discs were prepared. 185ng of Ln-5 and 10000 keratincytes were added per disc. n=6 assays were performed after 24 and 48 hours. Cell attachment was assessed by immunolocalisation of vinculin in focal contacts and co-localisation of BP180/Plectin in hemidesmosomes (HD). Cell area was measured using image analysis. Average roughness (Ra) (Taylor-Hobson Talysuf-10) and surface wettability (Adobe Photoshop-10) measures were also determined. All data were analysed using non-parametric tests.

Cells on AdLn were larger (median 1835 micrometers squared 95 per cent CI 1577-2355) with more vinculin (median 27 CI 26.9-29.0) and hemidesmosomes markers per cell (median 11.75 CI 11.52-13.27) compared with all other substrates ($p<0.05$). Si resulted in small cells (median 853.46 CI 724.98-947.14) with few adhesion plaques (Median 10.16 CI 9.09-12.18)Vinculin and Median 2.5 CI 0.53-4.59-BP180/Plectin) compared with all other groups ($p<0.05$). SiLn resulted in more vinculin plaques (Median 19.16 CI 16.89-20.05) compared with Si (Median 10.16 CI 9.03-12.18) ($p<0.05$) but no significant differences were seen in BP180/Plectin. AdLn resulted in more vinculin (Median 27 CI 26.9-29.0) and higher BP180/Plectin counts (Median 11.75 CI 9.72-13.27) compared to silanized Laminin (Median 19.16 CI 16.83-20.05 and Median 5.95 CI 4.17-8.49) ($p<0.05$).{BR}Si and SiLn surfaces were more hydrophobic than Control and AdLn ($P<0.05$). Ra-values were highest for SiLn ($p<0.05$) with no significant difference between the other sub-groups.

AdLn improves keratinocyte binding to ITAP biomaterials but covalent bonding does not augment this improvement.

BORS-P37

LEWINNEK'S SAFE ZONE AND INCIDENCE OF DISLOCATION AFTER COMPUTER-ASSISTED POSITIONING OF THE ACETABULAR CUP FOR TOTAL HIP ARTHROPLASTY BASED ON JOINT KINEMATICS

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Acetabular component orientation during total hip arthroplasty affects dislocation; hip arthroplasty navigation systems have been introduced to avoid the errors reported after acetabular component orientation using a manual technique '1'. Orthopilot navigation systems for computer-assisted total hip arthroplasty (THA) may be used to address component malposition. The purpose of this study was to analyze Lewinnek's safe zone and incidence of dislocation in the preliminary cases to report the incidence of dislocation encountered in the clinical practice.

38 primary THA were implanted with the orthopilot system (26 women, 12 men, mean age 68 +/- 7.8 years, age range 54-83 years) for degenerative hip disease. One optoelectronic rigid body was fixed percutaneously on the pelvis after cutaneous palpation for bony landmarks. The acetabulum was prepared first followed by the femur using reamers and broaches of increasing size. The acetabular cup was positioned only with the navigation system in the pilot cases.

An average inclination of 42.0 degrees (range: 38 degrees -50 degrees; SD+/-2.8 degrees) and an average anteversion of 16.4 degrees (range: 12 degrees -20 degrees; SD+/-5.0 degrees) were obtained in the computer-assisted study group. One patient fell three weeks after implantation causing posterior dislocation; there was recurrence and revised. Another had a hematoma and dislocation was reduced on 4th post-operative day, when the patient was fully mobilized. The third patient had a dislocation on the 2nd post-operative day at the time mobilization.

Dislocation may occur with computer assisted cup position, as there is no ideal position for the cup, which can be used for all patients. The study cases were inside the safety zone recommended by Lewinnek. The accuracy of placing the acetabular component within a predefined safe zone using computer guidance was achieved with respect to the anterior pelvic plane. Factors other than acetabular component orientation may also contributed to the incidence of dislocation '1'. However, we believe that inaccurate landmark registration and simplified palpation was a potential source of error. As epicutaneous palpation of anatomic landmarks is necessary to determine the pelvic coordinate system, soft tissue distribution may affect anteversion accuracy of the palpation procedure in orthopilot acetabular cup navigation.

1. Minoda Y, Kadowaki T, Kim M. Acetabular component orientation in 834 total hip arthroplasties using a manual technique. Clin Orthop Relat Res. 2006 Apr;445:186-91 2. Tannast M, Langlotz F, Kubiak-Langer M, Langlotz U, Siebenrock KA. Accuracy and potential pitfalls of fluoroscopy-guided acetabular cup placement. Comput Aided Surg. 2005 Sep-Nov;10(5-6):329-36.

BORS-P38

MENISCAL SUTURE WITH ACL RECONSTRUCTION: LONG TERM OUTCOME

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In the context of ACL reconstruction there is debate regarding meniscal preservation or meniscectomy, particularly when the absence of a functioning meniscus is well known to predispose to degenerative change within the knee.

44 patients with non-complex, non-degenerative meniscal tears were identified from a prospectively collected ACL database. All zones of tear and chronic tears were included. 9 patients were excluded because of previous meniscal/cruciate surgery or because of varied techniques of meniscal repair. The remaining 35 all underwent vertical mattress suture meniscal repair at the time of ACLR. Follow up was by IKDC subjective scores, clinical examination and cruciometry. Survival of meniscal repair was calculated by life table analysis, defined by failure of repair, requiring subsequent meniscectomy.

The mean subjective follow up was at 10 years (7-14 years) in 24/35 patients (69% follow up). The mean IKDC scores were 70.5 (meniscectomy) 84.2 (meniscal repair) and 88.2 (native menisci). Survival analysis revealed a best case of 89 % 10 year survival and at worst a 49% survival.

There was a significant improvement in mean IKDC scores for meniscal repair versus meniscectomy and between patients with normal native menisci and meniscal repair undergoing ACLR. Long-term survival of meniscal repair with ACLR (between 49% and 89% at 10 years) makes repair of the meniscus (including white-white and chronic tears) the treatment of choice to maximise patient subjective outcome.

BORS-P39

MICRO-CT VOLUME MEASUREMENT FOR WEAR SIMULATION

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The wear of total disc replacements is a concern given the history of long-term failure due to wear in other articulating joint replacements. In-vitro simulations are used to predict the wear behaviour, using gravimetric measurements to quantify the debris released. Volumetric measurement techniques allow visualisation of the wear patterns as well as measurement of the overall changes in geometry which is a combination of creep and wear. These measurements allow a more meaningful comparison to explants. The purpose of this study is to compare the repeatability of a MicroCT scanning technique to gravimetric measurements and analyse its suitability for wear measurement in a TDR simulator study.

Prior to measurement, the specimen was washed with isopropanol and stored in a controlled environment for 48 hours. Gravimetric measurements of a Charité disc were repeated five times. MicroCT scans were taken using the Scanco MicroCT80, with a resolution of 1024 pixels, energy of 70kVp/114microA and an integration time of 300s. The scans were analysed using a binary code, so that voxel intensities are attributed to polyethylene or air, from which total volume of the specimen was calculated. The effect of specimen positioning, increased integration time and increased scan resolution were studied.

The mean and standard deviation of both measurement techniques were calculated and compared. Gravimetric measurements found the mass of the disc to be 2331481±6micrograms, equivalent to 2506.970±0.007mm'3 (density=930kg/m'3). MicroCT measurement found the total volume of the disc to be a mean of 2444±3mm'3, with repositioning of the specimen yielding no significant difference. Increasing the integration time of the scan led to no significant improvement in error, and increasing the resolution of the scan increased error due to noise.

Current TDR simulator studies have produced typical wear rates of <200micrograms/MC, equivalent to <0.22 mm'3/MC. The MicroCT technique described here cannot detect this magnitude of wear, and so although this technique has been successfully used for explanted TDR, further advancements are required in order to achieve dimensional volumetric wear measurements for in-vitro studies. Additionally, further consideration is needed to identify contribution of volume changes due to creep in both explanted and in-vitro tested TDR.

BORS-P40

MICROMECHANICAL CHARACTERISATION OF SOFT TISSUE: NEW TEXTURE METHOD AND PRELIMINARY RESULTS

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The influence of mechanical conditions on musculoskeletal degeneration and regeneration processes is well known. A mechanobiological approach is therefore key to successful regenerative therapies, and such an approach requires extensive knowledge of mechanical properties at all levels of structural hierarchy. Digital Image Correlation (DIC) provides a non-contact optical method for estimating full field Lagrangian strains on surfaces, and in conjunction with stereomicroscopy offers a powerful new tool for studying the mechanical behavior of tissues at many scales, given suitable optical texture. The goal of this study is to demonstrate the operation of DIC using a novel and widely applicable method for obtaining optical texture, with exemplary data from tendon material.

A stereomicroscope (SMZ1000, Nikon, UK) equipped with twin 1 MPixel cameras (GC1380, Prosilica, Canada) provided a maximum resolution of 0.4µm / pixel. A Biodynamics testing machine (Bose Electroforce, US) with twin symmetric actuators each with 0.2 µm displacement resolution was mounted underneath the stereomicroscope. Specimens were tested at 37 (+/-1) degrees C immersed in phosphate buffered saline containing 1.6wt% polyethylene glycol to account for blood protein oncotic pressure. An inset microscope cover slip provided distortion-free imaging. Optical texture was obtained using a Venturi particle delivery device (Particle Therapeutics, UK) to embed 3 micrometer gold particles in the tissue. DIC software (LaVision, Germany), previously calibrated to the stereomicroscope, was used to determine local displacement and strain. Mouse tail tendon fascicles were used to demonstrate the operation of the system.

Cryo-sections through the tendon material demonstrated penetration of the gold particles up to 50 micrometers into the tissue surface. Particles were stable with rinsing of specimens. Preliminary results clearly show non-homogeneous strain distributions in the tissue surface, with local sliding giving shear strains of up to 3 times applied strains. Imaging accuracy in measuring displacement was estimated at +/- 2 micrometers.

A novel method for obtaining optical texture in DIC has been demonstrated and preliminary results in mouse tail tendon show the potential for its application in the micromechanical characterization of a wide variety of soft tissues. This will be key in the endeavour of designing stimuli-driven regenerative therapies.

BORS-P41

MODULAR ENDOPROSTHETIC RECONSTRUCTION FOR INFECTED RE-REVISION PROSTHESIS : INITIAL EXPERIENCE

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Background: Post re-revision arthroplasty infection is a global problem.Variable rates are quoted in literature. Limited treatment options available depending on surgeons preference and available resources. Endoprosthetic reconstruction is one such option to be considered as a salvage procedure in tackling this unique and difficult problem.

Analyse preliminary results post endoprosthetic reconstruction for infected re-revision prostheses.

Retrospective analysis with case note and radiograph review of ten patients with infected re-revision knee implants and osteolysis operated between 2004 and 2008 (8 - Distal femur & 2 - Total femur Replacement). Mobility was wheelchair aided due to pain, global instability & persistent infection inspite of recurrent washouts and antibiotic therapy. Due to associated comorbidities, bone loss and nature of infection, a two stage procedure was considered inappropriate.

Mean age and follow up were 74.2 years and 30.5 months respectively. Average post operative mobilisation was with frame at 5 days, 2 sticks at 2 weeks. They were concomitantly treated with prolonged course of antibiotics (mean : 3 months intravenous and 3.5 months oral) as per guidelines from infectious disease department. 2 patients required intervention by plastic surgeons at same setting. Xray at 6, 12 & 24 months showed no changes from immediate post-op. CRP,ESR and WBC count were within normal limits at the end of antibiotic therapy. One patient required prolonged pain relief with poor mobility due to instability in the opposite knee. Finally due to associated comorbid factors this patient died at six months.

Salvage endoprosthetic reconstruction has been useful to treat this cohort of infected re-revision. It reduced morbidity by early mobilisation and avoiding a second major operation, as in two stage revision. Multidisciplinary support from plastic surgeons and specialist microbiologists is required. It has provided effective pain relief, stability and improved mobility in our initial experience.

BORS-P42

NEW METHOD OF SCOLIOSIS DEFORMITY ASSESSMENT: ISIS 2 SYSTEM

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Scoliosis deformity has, traditionally, been assessed using radiographic angle measurements. The aim of this study was to confirm that ISIS 2 3D back shape measurements are valid and confident method of diagnosing and follow up of patients with scoliosis.

Three-dimensional back measurements were performed in our ISIS 2 Laboratory. Equipment included camera/projector stand, patient

stand with reference plane and a PC. Represented in clinical reports were height map, contour plot, transverse section plot, coronal plot, sagittal sections and bilateral asymmetry maps.

520 ISIS 2 scans on 242 patients were performed from February 2006 to December 2007. 58 patients were male (median age 16 years, SD 3.71, min 7, max 25) and 184 female (median age 14.5 years, SD 3.23, min 5, max 45). Average number of scans per patient was 2.01 with the range of 1-10 scans. Most common curve was right sided thoracic curve. Median back length was 421 mm (CI 404.96-415.1). Pelvic rotation median value was 1(CI 0.24-0.84). Median flexion/extension measured 3(CI 3.27-3,94). Imbalance values were: median 4mm, CI 0.98-3.88, min -55mm, max 53mm. Median upper lateral asymmetry was -12(with CI -12.90 to -8.98, min -78, max 46. For lower lateral asymmetry median value was 5(CI 3.00-7.82,). Maximum skin angle was from 0- 40, with median value of 7and CI 7.57-8.57. Median value for minimum skin angle was -5(CI -6.90 to -5.91, min-36, max 0). Median kyphosis angle was 33(CI 32.84-35.28, min 0, max 79). Median lordosis angle was 25 (CI 24.17-16.95, min -41, max 65). For left volumetric asymmetry parameter median value was 4 (CI 7.69-10.27, min 0, max 9), while for the right volumetric asymmetry parameter median value was 11 (CI 14.09-16.66, min 0, max 90). In 111 patients we were able to compare ISIS 2 scoliosis measurements with radiographic measurements. No statistically significant difference was found between two measurements ($p>0.05$).

ISIS 2 scoliosis measurements are non-invasive, low-cost three-dimensional topographic back measurements which can be confidently used in scoliosis diagnosis and monitoring of curve progression.

BORS-P43

OSTEOARTHRITIS HISTOPATHOLOGY SCORING SYSTEMS

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The Osteoarthritis (OA) Research Society International (OARSI) histological grading system for OA was reported in 2006 to improve on the 'gold standard' Mankin histopathology grading system developed in 1971. The aim of this study was to compare the two grading systems.

Six human tibial plateaus retrieved at knee replacement surgery were processed into blocks which were sectioned and stained with Safranin O and fast green. The sections were graded 3 times by 3 observers using each grading system. The inter- and intra-observer correlation and the reliability (Cronbach's alpha value) were calculated using SPSS 14.0.

Statistically Cronbach's alpha values for both OARSI and Mankin systems were high (>0.7) when comparing 1), grades between the 3 observers and 2), grades done by the same observer at different times. The inter-observer correlation for the OARSI system was higher and thus more reproducible between different observers. The Mankin system however showed better internal consistency as shown by a higher intra-observer correlation.

In conclusion, neither system was statistically more reliable than the other. However, the OARSI system is more comprehensive, as the Mankin system does not take into account important OA histopathology, such as exposure of subchondral bone through the erosion of articular cartilage, nor the presences or absence of osteophytes. Although the Mankin system is easier to learn and apply, we propose that the OARSI system attributes a numerical value more representative of the extent of OA histopathology.

BORS-P44

OUR ORTHOGERIATRIC PATHWAY SO FAR FOR FRACTURED NECK OF FEMUR PATIENTS

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Neck of Femur Fractures (NOFFs)in elderly patients are mainly a symtom of their general geriatric condition and not their primary pathology. The special skills available on an orthopaedic ward are required by these patients only over the first 2-3 days. The majority of the competences these patients need are not available on site and have to be obtained through visiting external input, e.g. in regular geriatric rounds per week. This unavoidably brings inconveniences and delays for the patients and puts them at risk of missing important issues. Patients with NOFFs with their primarily medical problems also block trauma beds during their 'geriatric' phase of treatment when they need no orthopaedic input. Therefore 4 years ago we proposed the creation of an orthogeriatric pathway with the patients on a geriatric ward visited by the orthopaedic team who performs the surgery. In April 2007 a decision was taken to review the outcomes of these patients and redesign our previous Integraded Care Pathway. The new orthogeriatric service pathway was launched in September 2007.

The easiest parameter summing up all the decisive validation criteria is the length of stay (LoS) until fitness for return home (with support of community services where required) or for transfer to a nursing home or rehabilitation division is obtained. In the first 3 months after launching this pathway in our hospital a reduction of the average LoS by 7 days down to 18 days (median 16 days) has been obtained on 78 patients compared with the corresponding patient selection of the previous audited 3 months with an average LoS of 25 days.

We are now working on logistical details where there is room for improvement. Continuous auditing will go on and will show whether this improvement can be maintained or even pushed further.

BORS-P45

PEDOBAROGRAPHIC ASSESSMENT FOLLOWING RUPTURE OF THE TENDO ACHILLIS

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A key factor delaying rehabilitation after a tendo Achillis (TA) rupture is gait abnormality. The objective of this study was to quantify changes in planter pressures after a rupture of the TA in four groups of patients: 1)15 controls subjects, mean 40 years, with no history of lower limb abnormality, 2)14 patients, mean 48 years, treated in a non-weight-bearing plaster cast, 12 patients, mean age 45 years, treated with immediate weight-bearing in a rigid orthosis, 4)14 patients, mean age 51 years, treated with immediate weight-bearing in a flexible orthosis.

Mean and maximum peak planter pressures within the forefoot and heel were measured using in-shoe pressure pads two weeks after removal of the cast/orthosis; five gait cycles were recorded. The terminal stance and pre-swing phases were also measured as a proportion of the total stance phase of the gait cycle. One-way ANOVA was used to compare the difference in means between the groups.

The normal control group had less then 2 percent difference between the limbs on all of the measured parameters. The patients in the plaster cast and rigid orthotic groups had significant deficits ($p = 0.04$ and <0.001 compared to control) in mean peak forefoot pressures, implying weakness in the triceps surae. However, the patients in the flexible orthosis group had only an 11 percent deficit ($p = 0.25$ compared to control). All of the patients treated for a TA rupture had increased heel pressures but only the rigid orthotic group had cadence abnormalities ($p = <0.001$). This may be the result of abnormal motor patterns secondary to mobilising in the rigid orthosis.

This study highlights the gait abnormalities associated with triceps surae weakness following rupture of the TA. Accelerated rehabilitation using weight-bearing orthotics may alleviate some of these problems, but new designs for flexible orthotics may be required for maximum benefit.

BORS-P46

PHYSIOLOGICAL FREE BOUNDARY CONDITION MUSCULO-SKELETAL MODELLING OF THE PELVIS AND FEMUR

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Free boundary condition modelling is a numerical method in which musculo-skeletal constructs such as the pelvis and the femur are modelled with the explicit inclusion of muscular and ligamentous structures in preference to the implementation of fixed boundary conditions acting on the cortex, which has been shown to be a poor representation of the in-vivo situation. The technique as applied to the pelvis has been shown to be a useful tool in terms of informing surgeons of the biomechanical risks associated with different

approaches to hip joint arthroplasty, with the antero-lateral approach in particular being shown to present a particular risk of limp, confirmed by gait analysis, although not captured by standard survey techniques.

This study investigates the use of the technique as applied to the femur, as well as indicating the important parameters and considerations to be taken into account in potentially extending the technique to model other orthopaedic structures such as the spine. The developed model of the femur clearly demonstrates the role of the muscles in reducing the strains found on the medial and lateral aspects of the femoral shaft for single leg stance, as well as the anterior and posterior aspects for a single leg squat, at a knee flexion angle of 30 degrees. Through changing the muscle parameters and geometric parameters the modelling approach can be used to assess the likely effects on the femur of muscle damage through injury, ageing or surgery, as well as having the potential to inform the likely outcome of corrective surgery such as that used in some cerebral palsy patients.

The perceived advantage of the free boundary condition approach to physiological finite element modelling of orthopaedic structures is that it provides a one-step transparent process. This is as opposed to the two-step process used in fixed boundary condition force balanced models which require the use of an inverse dynamic optimisation model to resolve the muscle forces prior to performing finite element analysis, and are subject to inaccuracies associated with assuming non-deformable skeletal structures in the implementation of the inverse dynamic optimisation method.

BORS-P47

PLATELET RICH CONCENTRATE AND BONE FORMATION: INTERACTION OF PLATELET RICH CONCENTRATE WITH BONE GRAFT MATERIALS

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Platelet rich concentrate (PRC) is in routine use for orthopaedic and dental surgery. For the treatment of bone defects PRC is commonly combined with bone graft substitutes (BGSs) with the aim of enhancing bone healing. The main hypothesis under investigation is that the effect of PRC on bone formation can be modulated by the BGS. To test this hypothesis, we sought to determine the effect of combining PRC with various bone graft materials on the proliferation, differentiation and bone nodule formation in-vitro of human bone marrow stromal cells (hBMSCs).

PRC was produced from the blood of ten healthy volunteers using CAPTION (S&N). hBMSCs were prepared from trabecular bone marrow recovered from femoral heads. Cells were isolated following standard protocols. Demineralised bone matrix (DBM) was prepared from trabecular bone harvested from femoral heads. Allograft was prepared as for DBM without the demineralisation phase. The beta-tricalcium phosphate (beta-TCP) used was GenOS (S&N). All tests were carried out in osteopermissive media.

Combination of PRC with either DBM or beta-TCP resulted in an increase in proliferation of hBMSCs over the BGS alone at both 3 and 5 days exposure in culture; this was not the case with allograft where addition of PRC had no significant effect. At the same time points, the combination of PRC with DBM or beta-TCP resulted in reduced alkaline phosphatase activity in comparison to the BGSs alone. As before no effect was seen when PRC was combined with allograft. After 23 days, the addition of PRC to all three BGSs resulted in a significantly increased mineralisation response from hBMSCs compared to the BGSs alone.

The results presented here suggest that PRC is effective at enhancing bone formation when combined with a number of BGSs. However, the effectiveness of PRC to enhance bone formation was significantly modulated by the nature of the BGS. The implication from this work is that it is important to optimise the PRC /BGS combination in order to gain maximum benefit in clinical use.

BORS-P48

PROTECTION OF THE BONE WITH A SKELETALLY-ATTACHED PROSTHESIS FOR TRANSFEMORAL AMPUTATION

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ITAP (Intraosseous Transcutaneous Amputation Prosthesis) is a prosthesis suspension system which uses a bone implant to anchor the amputation prosthesis to the skeleton. It is a solution for amputees who encounter pressure sores or abrasion of the skin from rubbing against a socket and may aid attachment for amputees with short residual limbs. A component for the prosthesis has been designed to protect the femur from potentially damaging loads applied to the implant. With this 'fail-safe' device installed the amputee can walk normally but during an episode of high loading, such as a fall, the femur is protected from fracture by activation of the fail-safe mechanism in bending and torsion. The aims of this study were to determine the required settings for the fail-safe mechanism for different bone and implant geometries and for varying interface conditions between the bone and the implant.

Finite element analysis (FEA) was used to investigate the transmission of loads to the bone from the intramedullary stem. Typical bending, torsional and axial loading was applied. A tubular FEA model was used as an approximation of the femur shaft with a cylindrical implant to systematically investigate the effects of varying geometry and interface conditions. The resulting stresses in the bone were compared with the strength of cortical bone and the strength of the bone-implant interface to identify the maximum permissible loads.

As an example of the results, a bone with a diameter that is smaller by 2 millimetres requires a torque setting decreased by 30 percent in order to prevent shear fracture. With 30 percent less area of bone integration the bending moment setting must be reduced by 12 percent. The addition of a collar at the resected end of the bone reduces the risk of bone resorption at the outer edge because it prevents stress shielding.

From the FEA results the critical loading conditions and levels have been identified for varying geometries and bone integration. Recommendations for the fail-safe activation setting parameters have been determined taking in to account the length and size of the residual bone.

BORS-P49

QUANTITATIVE DENSITY INFORMATION WITH COMPUTED RADIOGRAPHY

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Use of an aluminium (Al) step wedge to provide calibration between X-ray optical density and aluminium equivalent thickness has been widely reported by researchers. However, due to non-standardised methods, it is still not used routinely in clinical assessment. The advent of computed radiography (CR) offers new opportunities to improve step-wedge calibration, taking advantage of the wider dynamic range and direct digitisation of X-ray images.

An Al step wedge of ten 5mm thick steps was X-rayed using a Fuji CR system. Images of the step wedge and a knee phantom were taken at various energy and Fuji processing settings. Automatic detection of the steps, performed in Matlab using Canny edge detection and the Hough transform, was used to assess optimum settings for the CR system and to analyse methods of relating grey level to Al thickness. Dose values and background variation due to the anode Heel effect were evaluated by acquiring an 'empty field' X-ray at different energy settings and with varying copper filtering thicknesses. The effects of beam hardening and contributions of soft tissue and bone thickness were considered using a custom-made phantom modelling soft tissue thicknesses.

Experimental results indicate that the dimensions of the step wedge provide an accurate calibration between grey level and Al thickness. Fitting a straight line to the log of the net grey level values provided an excellent model of the data (R-squared = 0.99). A straight line relationship is also obtained between the log of the dose and grey level (R-squared=0.99). However, it is vital to ensure that no

automatic histogram-analysis affects these relationships. 1.5mm copper filtration at clinical settings (66kV, 6.3mAs) was used to assess and correct for the Heel effect in the anode-cathode direction using a 1D model, allowing position-independent grey level measurements. Correcting for bone thickness, soft tissue and beam hardening further improves measurement accuracy.

A thorough assessment of the entire X-ray process is necessary to achieve accurate and comparable density information using a step wedge with digital X-rays. This technique has the potential to provide density and fracture healing information for clinicians without altering the diagnostic quality of X-ray images.

BORS-P50

RAPID PROTOTYPING TECHNOLOGY (RPT) FOR SPINAL DEFORMITY: A CASE REPORT

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The production of a copy of a bony deformity with complex geometry is one of the important applications of the integration between two modern computer based technologies i.e. rapid prototyping (RP) and reverse engineering (RE). RP is the application of engineering principle wherein a real physical 3D model is generated using computer software generated display images based on CT/MRI scans. They serve as important learning tools for understanding anatomy and rehearsing complex surgeries which have steep learning curve.

Congenital scoliosis presents with the challenge of complex reconstruction in an immature axial skeleton. X-rays & CT/MRI scans used routinely for evaluation and planning on occasions provide inadequate information on the precise three-dimensional extent of bony defects. A physical real model manufactured from 3D CT virtual image addresses the above limitations and can offer surgeons better understanding of complex anatomical detail providing an intuitive physical relationship between patient and the model.

We hereby present a case report about use of anatomical modelling in management of congenital scoliosis in a two & half year old child with a T10 hemivertebra. Rapid prototyping was used for the construction of an anatomical 1:1 ratio model which helped to understand complex anatomy and plan hemivertebra resection during anterior surgery. It facilitated 360 degrees visualisation of pedicles and planning entry points, trajectories & lengths for pedicle screw insertion. The model also facilitated contouring of implants prior to posterior instrumentation. Pre-operative surgical rehearsal was carried out before the actual surgery on the patient. A near anatomical coronal alignment and sagittal balance of the spinal column was restored post-operatively.

RP medical models act as important treatment planning and surgical rehearsal tools. They also serve as additional tool in surgeon's armoury against possible medico-legal action / litigation and validate surgical decision making for complex deformity corrections. The merging of computational analysis & modelling, designing and fabrication will serve as an important means in optimising outcomes of such complex congenital multi-planar paediatric spinal deformities.

BORS-P51

RECONSTRUCTION OF POSTERO-LATERAL INSTABILITY OF THE ELBOW WITH FCR GRAFT -A PROSPECTIVE STUDY

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We are presenting early results repair of postero lateral instability of elbow using flexor carpi radialis as an auto graft.

Posterolaterl instability is caused by insufficiency of the lateral collateral ligament complex.Various methods and techniques have been described in the literature. One of which is reconstruction. A variety of grafts can be used for reconstruction ranging from auto graft to synthetic graft. Literature review has shown good results with auto graft. Palmaris longus, Tendo Achilles, Plantaris, Extensor carpi ulnars and Semitedinous are some of the described auto-grats used. In our study we have used flexor carpi radialis auto graft for reconstruction.

Surgical Technique: Flexor carpi radialis was harvested percutaneoulsy on the same side. Standard lateral incision was made over the elbow a triangular tunnel was made on the lateral aspect of the distal humerus to create a yoke stitch and an ulanr tunnel was made in the crista supinator tubercle. The flexor carpi radialis graft was passed between these tunnels.

In our study we managed 14 patients with clinically postero lateral instability of the elbow, all are due to trauma. All patients were investigated with MRI scan. We have managed with the above technique. Post of special irom brace was give, allowing limited mobilization between 60-90 degrees, for six weeks. Lateral protective mobilization for next 6 weeks. Regular follow up at 2/52, 6 /52, 12/52, 6 months and 12 months. Average follow up was 9 months.

All patients are back to there occupation, vas 9/10, high patients satisfaction, mean post operative mayo score was 90. Our early results are encouraging, fcr auto graft will give good reconstruction, high patients satisfaction, back to there occupation.

BORS-P52

REDUCING EXPOSURE TO METAL IONS FOLLOWING HIP RESURFACING: THE IMPORTANCE OF ACETABULAR ORIENTATION

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Metal ion concentrations following metal on metal hip resurfacing arthroplasty remain a concern. Variables associated with increased metal ion concentrations need to be established. This study provides metal ion data from a consecutive cohort of the first 76 patients implanted with a fourth generation hip resurfacing prosthesis.

All patients agreed to post-operative blood metal ion sampling at a minimum of one year. The whole blood chromium (Cr) and cobalt (Co) levels were measured by inductively coupled plasma-mass spectrometry. Post-operative radiographic measurements of cup inclination and anteversion were obtained using the EBRA software.

Mean whole blood Cr and Co concentrations in patients receiving the smallest femoral implants (51mm or smaller) were greater than in the patients implanted with the largest prostheses (53mm or larger) by a factor of 3 and 9 respectively. Ion concentrations in the small femoral group were significantly related to acetabular inclination ($R=0.439$, $P<0.001$ for Cr, $R=0.372$, $P=0.004$ for Co) and anteversion ($R=0.330$, $P=0.010$ for Cr, $R=0.338$, $P=0.008$ for Co). There was no significant relationship in the large implant group. Mean Cr and Co concentrations in patients with accurately orientated cups (inclination over 45 degrees, anteversion under 20 degrees) were 3.7 microg/l and 1.8 mircog/l respectively, compared to 9.1 microg/l and 17.5 microg/l in malaligned cups (inclination over 45 degrees, anteversion over 20 degrees).

Reduced surface contact area caused by cup malalignment may increase contact stresses resulting in high wear if fluid film lubrication is inadequate. Inadequate fluid film lubrication has previously been reported with smaller heads in vitro. High blood ion levels (and therefore the systemic exposure of an individual to metal ions) may reflect high wear rates of the metal bearing surfaces. Accurate acetabular component positioning is essential in order to reduce systemic metal ion exposure following hip resurfacing with smaller implants.

BORS-P53

REFINEMENT OF THE CLINICAL INDICATIONS FOR DYNAMIC NEUTRALISATION SYSTEM FOR THE SPINE FOR THE TREATMENT OF BACKPAIN

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In this study we report the clinical outcome following Dynamic Neutralisation System for the Spine. Our objectives are to revalidate the most suitable clinical indication(s) of Dynesys in patients with backpain.

A prospective cohort study on consecutive 374 patients who had Dynesys for backpain from Septmber 2000 to present. Average age of patients was 57 years and male to female ratio were (40%:60%).

Preoperative assessment involved ODI, SF36, VAS for leg and backpain and the diagnosis was confirmed with physical examination, x rays, spinal probe and lumbar spine MRI. Regular follow up was arranged at 2 weeks, 3, 6 and 12 months then on annual intervals. In our cohort, clinical indications were: Degenerative Disc Disease(DDD) 271patients, Spondylolisthesis 55 patients, Adjacent segment disease(ASD) 30 patients, Spinal canal stenosis 18 patients. Paired t-test was used for comparison between preoperative and postoperative scores and p-value was used to show the significance.

Overall outcome assessment revealed significant improvement in ODI, SF36 and VAS in comparison with preoperative status (p-value < 0.05). Improvement was greatest in DDD group and average for ASD. Patients with stenosis performed better when the procedure involved adjunct decompression. Similarly, results of decompression and fusion were better than Dynesys alone in patients with spondylolisthesis.

1. Dynesys was successfully controlled symptoms of DDD in the intermediate term. 2. Dynesys can be used as surgical treatment for symptomatic ASD. 3. Dynesys alone in the treatment of spondylolysthesis resulted in a 45% re-operation rate, and we believe it should not be recommended as an indication. 4. Dynesys alone is not recommended as a treatment for symptomatic spinal stenosis.

BORS-P54

RESULTS OF METAL ON METAL HIP ARTHROPLASTY IN PATIENTS YOUNGER THAN 40 YEARS

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The results of conventional total hip arthroplasty (THA) with metal-on-polyethylene articulations have been disappointing in very young patients. Osteolysis remains a cause of concern with polyethylene wear rates of 0.07mm to 0.2 mm per year. The first generation of metal-on-metal prostheses introduced by McKee and Watson Farrar were not successful due to design deficiency. The second generation metal-on-metal designs have shown a decreased wear rate of 0.001 mm per annum and hoped to achieve improved wear characteristics with a decreased rate of osteolysis and loosening.

The purpose of this study was to retrospectively analyse the second-generation metal-on-metal Hip articulation in younger patients, based on clinical and radiological criteria.

Fifty five metal-on-metal THA were performed on 44 patients younger than 40 years of age. Thirty-four patients (45 hips) were available for complete radiological and clinical analysis with a mean age of 31 years and a mean follow up of 7.7 years. Out of the 10 patients excluded, 7 were lost to follow up and 3 died (1 due to breast carcinoma and the others following pulmonary emboli). The mean pre-operative Harris Hip Score of 48 improved to 99 at the time of final follow up and the Oxford hip score improved from pre-operative mean of 48 to 21 at the latest follow up. 42 hips (93.33%) had an excellent outcome with 3 hips requiring a femoral component revision. Radiologically 4% acetabular components and 8% femoral components showed non-progressive radiolucency at a mean follow up of 7.7 years. One hip had a femoral stem subsidence of 4 mm.

The extremely low failure rate on resumption of high level occupational and leisure activities gives early evidence of suitability of metal-on-metal articulation for the very young patient. Metal ion generation and its concentration in the body fluids still remains a theoretical cause for concern regarding mutagenicity and cancer. In our series we have not encountered any adverse effects secondary to metal ion generation or metallosis. We would however, support further prospective follow up and epidemiological studies in these patients who belong to the active reproductive age group.

BORS-P55

ROLE OF TRIPOLAR HIP WITH CONSTRAINED ACETABULAR INSERT IN REVISION ARTHROPLASTY: EARLY RESULTS

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Tripolar hip with constrained acetabular insert is used to enhance hip stability in recurrent dislocators and endoprosthetic reconstruction. A locking mechanism connects the constraining component with the articulating component to capture the prosthetic femoral head in place.Soft tissue insufficiency is a common finding in this group of patients.

To assess functional and radiological outcomes post tripolar hip with constrained acetabular cup.

Retrospective case note and radiograph review of eleven patients with tripolar constrained acetabular acetabular insert. Mean age & follow up were 75 & 2 years respectively. Surgery completed between 2005 and 2008.Eight patients had recurrent dislocations and revision surgeries, one patient had iatrogenic tear of hip musculature during hemiarthroplasty, which was revised at same time to tripolar and two patients underwent total femur replacement for infected re-revision as a terminal procedure. Pre operative mobility was mostly restricted to wheelchair.

Mean post operative mobility in the first cohort of eight patients was with frame on day two, two sticks at day five and one stick at four weeks. The patient with iatrogenic injury had a slow course due to associated comorbidity and chest infection. She mobilised with two sticks at four weeks and one stick at three months. In the two patients with total femur replacement mobility was slow as expected,with frame at one week, two sticks at four weeks and one stick at three months. Radiographs showed no evidence of progressive osteolysis or loosening.

There was good functional recovery with no evidence of clinical or radiological deterioration. There has been a significant improvement in mobility and stability. Tripolar Hip has provided good initial results with no dislocations or failure of acetabular shell or failure of constrained liner. Poor hip musculature is one of the indicators for this surgery.

BORS-P56

SEPTIC ARTHRITIS OF NATIVE HIP JOINTS: GIRDLESTONE AND BEYOND

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In the 1940s, Gathorne Robert Girdlestone, an orthopaedic surgeon in Oxford, pioneered the excision of the femoral head in cases of pyogenic arthritis of the hip. Modern management stresses antibiotic therapy with or without arthrotomy. Following a number of tertiary referrals characterised by prolonged morbidity that was successfully resolved by excision arthroplasty, we set out to evaluate the clinical characteristics, and our own management of native hip joint septic arthritis, in a secondary referral population sixty years after Girdlestone's seminal paper.

We performed a retrospective review of all first presentations of native hip septic arthritis to our multidisciplinary unit between January 1995 and December 2006. We excluded patients with prosthetic joint infections, and tertiary referrals.

Patient Demographics: We identified 27 cases, 15 male and 12 female, median age 52 years (range 1-89). Bacteriology: Gram positive organisms predominated, including 11 cases of Staph. aureus and 3 of Strep. pneumoniae (fig. 3). 10 cases were culture negative, but had septic arthritis confirmed by other investigations. Management: Nineteen patients (70%) had aspiration or washout of the joint within 24 hours of presentation. Seven (25%) underwent excision arthroplasty, of whom six went on to have a total hip replacement. The mean symptom duration of the excision arthoplasty group was significantly greater than the mean of the whole group, at 345 days compared to 94 days. Median length of hospital stay was 20 days. The mean duration of intravenous antibiotic therapy was 4.2 weeks, with ceftriaxone used as the sole agent in 16 cases (57%).

Patients with a shorter symptom duration were prioritised for rapid surgical intervention. Clinical outcome was documented in 26 cases at out-patient follow-up, with 16 (57%) asymptomatic and 8 (29%) reporting minimal symptoms. One patient died of complications pertaining to systemic sepsis.

Septic arthritis of native hip joints poses challenges even in the 21st century. In this series of patients, Girdlestone's procedure was required in nearly one quarter of cases in whom delayed presentation had led to joint destruction. With multidisciplinary management, functional outcome of acute or chronic infection is generally good.

BORS-P57

STAPHYLOCOCCAL BINDING TO BONE: FURTHER UNDERSTANDING OF THE BONE SIALOPROTEIN - BINDING PROTEIN AND SDR PROTEINS

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The bone sialoprotein - binding protein (Bbp) expressed by Staphylococcus aureus is a member of the staphylococcal serine-aspartate repeat (Sdr) family of proteins, which also includes clumping factors (ClfA, ClfB) and the Sdr proteins that have been identified in both S. aureus (SdrC, SdrD, SdrE) and S. epidermidis (SdrF, SdrG, SdrH). There is evidence to suggest that Bbp, SdrD, and SdrE play important roles in establishing bone infection, and Bbp is known to bind host bone sialoprotein (BSP), but the ligands for the other Sdr proteins are currently unknown. Further understanding of the molecular interaction between Bbp and BSP is required with a view to further understanding and elucidation of the Sdr protein ligands. All of the proteins within the Sdr family are structurally similar, each possessing an A-domain, shown to be the ligand-binding domain of the Clf proteins, and an R-domain (serine-aspartate repeat region involved in peptide display). Bbp and the Sdr proteins differ from the Clf proteins by the presence of three to five B-motifs whose function is unknown. We investigated the hypothesis that like other Sdr family proteins the binding domain for host BSP may be localised to the A domain of S. aureus Bbp.{BR}Oligonucleotide primers were designed for polymerase chain reaction (PCR) amplification of the bbp A-domain from S. aureus O-24 (osteomyelitis isolate) genomic DNA. Recombinant DNA techniques were used to produce an Escherichia coli clone harbouring the recombinant bbp-A sequence, followed by subsequent expression and purification of recombinant protein, and analysis of functional ligand binding by enzyme-linked immunosorbant assay (ELISA).

Recombinant protein expression was challenging and required the production of several E. coli clones and two expression vector systems. Investigational research highlighted problems with the currently published bbp gene sequence. After accounting for the sequence problems, an E. coli clone was produced that was shown to express 6-histidine - tagged rBbp-A. ELISA analysis showed that the purified domain was not functional. The data presented here, in addition to previous research on the B-motifs of Bbp suggest that the B-motifs are required for functional conformation of the ligand-binding domain.

BORS-P58

STATISTICAL ANALYSIS OF PELVIC GEOMETRY

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Whilst it is accepted that variances in pelvic geometry, such as acetabular depth, affect the biomechanics of the hip, less is known about the relative influences of the different geometric factors. Knowledge of the relationship between high stresses in the acetabulum and geometrical differences in the pelvis could inform new orthopaedic implant designs and aid surgeons' pre-operative planning.

In order to gain knowledge of inter-patient geometric variation, 14 full three dimensional pelvis datasets have been statistically analysed. This study describes the pelvis in terms of its major varying dimensions and indicates the level of variance over the sample group. Algorithms have been developed to fit a sphere and a plane to each acetabulum and calculate the thickness of the supporting pelvis behind the acetabulum. Measurements of size, angle and surface imperfections are derived from the algorithms. Each pelvis was analysed statically under a single load case using a finite element model with a mesh size of approximately 200,000 tetrahedral elements. Homogeneous isotropic material properties for cortical and trabecular bone were used in order to isolate the effects of changing the geometry.

Abduction of the acetabulum, thickness of the pelvis behind the acetabulum and surface imperfections were all found to have a high influence on stress distribution. Quantification of these relative effects has enabled stress patterns to be predicted over different geometries to a high degree of accuracy. The ability to derive these stress patterns based on CT data, increasingly gathered for navigational purposes, is seen to be a useful surgical tool, which could be used to inform minor corrective surgery in preference to full hip arthroplasty.

Further work will look at the movement of the acetabulum and the development of a similar method for predicting acetabular displacement based on geometric and material property differences. This is seen to be useful in a assessing the behaviour and inter-patient variability of the natural acetabulum, as well as having application in assessing existing and new acetabular cup designs.

BORS-P59

SUBCHONDRAL BONE OSTEOBLASTS CAN INDUCE CHONDROCYTE MINERALIZATION DURING OSTEOARTHRITIS AND THIS PROCESS IS RELEVANT TO CARTILAGE DEGRADATION

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In our study, site specific localization of mineralization markers were detected in the OA cartilage indicating pathological mineralization of articular cartilage is a characteristic feature of osteoarthritis (OA); however, the underline mechanism and its relevance with cartilage degeneration are not clear. The involvement of subchondral bone changes in OA has been reported previously with the characterization of abnormal subchondral bone mineral density (BMD) and enhanced production of bone turnover markers. Corroborating with other study results, we also found that osteoblasts derived from OA subchondral bone showed significant increase in the mRNA levels of tested mineralization markers. Interestingly, osteoblasts from OA subchondral bone could significantly decrease cartilage matrix expression; whereas, increased the mineralization by chondrocytes. Moreover, osteogenic differentiation factors like CBFA1, ALP, and type X collagen (Col-X) were upregulated in chondrocytes co-cultured with OA osteoblasts compared to the chondrocytes co-cultured with normal osteoblasts. Furthermore, chondrocyte mineralization was followed by an enhanced mRNA and protein levels of MMP-2, MMP-9 and MMP-13, all of which were detrimental to cartilage integrity in vivo. The data reported here suggests that the upregulation of subchondral bone-mineralization, typical of OA progression, causes cartilage mineralization, and that the mineralization of chondrocytes induce increased MMP levels with a subsequent degradation of the articular cartilage.

BORS-P60

THE COMPRESSIVE PROPERTIES AND FRACTURE TOUGHNESS OF PMMA CEMENT REINFORCED WITH GLASS FLAKE

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Whilst bone cements are the cornerstone for many orthopaedic applications, their less than ideal properties for some applications may contribute to long-term failure in these procedures. The aim of the research outlined here was to investigate the use of glass flakes in the modification of the mechanical properties of PMMA cements.

PMMA cement was modified using both milled and micronised glass flakes in 1, 2, 5 and 10 percent proportions by weight. The cement was hand mixed using a standardised protocol and injected into moulds for subsequent mechanical testing. Ultimate strength and elastic modulus were investigated using compression experiments whilst the fracture toughness was obtained from the double torsion test. SEM was used to investigate the fracture surfaces post-testing.

The addition of the glass flakes significantly reduced the modulus in the cement with the lowest values occurring for the 1 percent cohort. A similar trend was observed for ultimate strength. ANOVA demonstrated the statistically significant effect of flake type on both strength and modulus. As the proportion of milled additive increased the fracture toughness also rose to a value double that observed in the control specimens. After this the fracture toughness leveled off. The micronised glass flakes had a similar effect although the increase was not as great as for milled material. The difference in effect from the two materials was shown to be a statistically significant. The effect of milled glass flakes was more noticeable than that of the micronised ones. The flakes seem to reinforce the material under

tensile condition (represented by the fracture toughness) and act to prevent crack propagation. However, a less significant effect was found in the compressive behaviour, maybe due to porosities created during flakes addition or the lack of coupling between the flake and the surrounding PMMA matrix such that they act as flaws themselves. Further investigations are needed to elucidate other mechanical properties as well as the biological responses to this modified material before trials can begin to assess its clinical utility.

BORS-P61

THE CORRECTION OF THE INTERMETATARSAL ANGLE FOLLOWING FUSION OF THE FIRST METATARSOPHALANGEAL JOINT : WHAT CAN WE EXPECT?

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Introduction: Standard arthrodesis of the first metatarsophalageal joint (MTPJ) is often carried out for degenerative disease in the presence of a hallux valgus without a first metatarsal corrective osteotomy. Despite this there is an improvement in the intermetatarsal angle (IMA) as well as the position of the tibial sesamoid. We attempt to quantify the amount of correction in this study.

A cohort of 42 (49 feet) consecutive patients (13 males, 29 females) treated from May 2006 to Dec 2007 were reviewed. The mean age was 60.27 years (39 to 82 years). All patients underwent a standard primary fusion of the first MTPJ with a low profile plate and compression screw. There was no attempt to free the sesamoids, perform a lateral release or medial reefing of the medial capsule. We measured the hallux valgus angle (HVA), IMA as well as the position of the tibial sesamoid pre and postoperatively using a digital radiology imaging system.

The mean improvement in IMA was 3.81 degrees (p=0.000, 95% CI 2.99-4.62) with a mean correction of 2.53degrees (p=0.00, 95% CI 1.78-3.28), 7.07degrees (p=0.00, 95% CI 5.5-8.63) and 5.94degrees (p=0.00, 95% CI 3.95-7.93) in the mild, moderate and severe groups respectively. The tibial sesamoid position also tends to improve by one station (spearman correlation 0.839, p=0.000) post operatively.

There is an improvement in the IMA when the first MTPJ is fused. This improvement is proportional to the severity of the initial HVA and IMA. There is also an improvement in the resting position of the tibial sesamoid. We conclude that with a mobile first metatarsal medial cuneiform joint, the IMA corrects spontaneously when the first MTPJ is arthrodesed negating the need for a separate corrective osteotomy of the first metatarsal.

BORS-P62

THE EFFECT UPON STANDING LOAD DISTRIBUTIONS WITH LEG LENGTH DISCREPANCY

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Leg length discrepancy (LLD) is a well recognized complication of total hip arthroplasty. Large LLDs can cause abnormal weight bearing, leading to increased wear, aseptic loosening of the replacement hip and pain. Some patients with only minor LLD complain of major difficulties. The aim of this project was to investigate the effect of leg length discrepancy on static limb loading.

A pedobarograph was used to measure the limb loading of 20 normal volunteers aged 19 to 60. Each volunteer was asked to stand on the pedobarograph with both feet. A 2 second recording was taken to establish their body weight. Readings were then taken of the left foot on the pedobarograph and with the right foot off. The height of the right foot was varied to replicate LLD. Three readings were taken in each of the following positions: feet level, right foot 3.5cm lower and right foot 3.5cm higher.

With both feet at the same level, the left limb took 54% of the load. When the Right foot was lower, (simulating a long left leg), the left leg took 40% of the load. A paired t-test comparison with the level load showed a significant difference with $P < 0.001$. When the Right foot was higher, (simulating a long right leg), the left leg took 61% of the load. A paired t-test comparison with the level load showed a significant difference with $P = 0.002$.

Our results have shown that weight distribution increased in the shorter limb when LLD was simulated. This uneven distribution is likely to lead to early fatigue when standing and may explain why some patients with LLD post hip arthroplasty have poorer outcomes.

BORS-P63

THE EFFECTS OF CISPLATIN AND DOXORUBICIN ON ADULT AND IMMATURE RAT SKELETON

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We investigated the effects of chemotherapy drugs on the skeleton. Cisplatin and doxorubicin, the two most commonly used chemotherapy agents for malignant bone tumours, were given to adult and immature Wistar rats according to a currently used clinical protocol by European Osteosarcoma Intergroup. After three episodes of combined cisplatin and doxorubicin treatment given over five weeks, the rats were sacrificed and their femora were retrieved for mechanical and histological analysis. The results of mechanical testing revealed that the ultimate bending and torsion strength of the femoral shaft was significantly reduced after chemotherapy treatment in both adult and immature rats. The bending strength was significantly reduced from 277.2 ± 22.7 N in the control group to 222.0 ± 51.2 N in the chemotherapy group ($p = 0.018$) and the torsion strength significantly reduced from10.4 + 2.5 N in the control group to 7.4 + 2.2 N in the chemotherapy group ($p = 0.026$) in adult rats. In immature rats, although the differences were significant they were not as great. There was marked reduction in the ultimate shear strength of the distal femoral physes in the immature rats. Histological analysis of the distal femoral growth plates in the immature rats also revealed morphologic change with a significant reduction in cell numbers in both proliferative and hypertrophic chondrocytes in the chemotherapy group. Furthermore, in our rat bone defect model, where a 1mm femoral defect was stabilised by external fixator, cisplatin and doxorubicin significantly reduced the rate of bone regeneration leading to lower bone density after 3 and 5 weeks. The results suggested that chemotherapy weakens the bone, leads to a weaker junction of the growth plate, and effects growth plate morphology as well as reducing bone regeneration. Therefore, special attention has to be paid to the patients undergoing chemotherapy to prevent injury because of the lower tolerance of the bones and the growth plates to the external forces.

BORS-P64

THE IMPACT OF BONE FRAGMENT DIMENSIONS ON A VERTEBRAL TRAUMA

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Vertebral traumas, such as burst fractures, may cause a bone fragment to impinge on the spinal cord at a high velocity and thereby generate a neurological deficit. Despite such serious outcomes, the understanding of the impact between the bone and the cord complex is still limited. The objective of this work is to evaluate the effect of the bone fragment impact area on the deformation of the spinal cord.

Three simulated bone fragments with different impact areas were propelled onto bovine specimens using a transverse impact rig. Specimens included spinal cord, the surrounding cerebrospinal fluid (saline solution in this study) and the encasing dura mater. Tests were recorded with a high-speed video camera and image processing was used to track the trajectory of the fragment into the cord. Maximum deformation of the cord, duration of deformation as well as a coefficient of restitution were calculated.

The results showed that a decrease in impact area gave a significantly higher cord deformation. When the impacts were made on the unprotected cord, the durations tended to increase and the coefficient of restitution decrease with a decrease in impact area, probably due to the higher pressure created by a smaller fragment, leading to an easier penetration into the cord.

Previous studies have found that a greater temporary cord deformation has a negative effect on the final neurological deficit. A higher injury energy may produce smaller bone fragments with smaller impact areas causing a higher deformation, which would confirm clinical results showing a positive correlation between injury

energy and degree of neurological deficit. A higher injury energy may also produce higher fragment velocities, and the combination of a smaller impact area with a higher velocity may thus outweigh the effect of the smaller mass of a generally smaller fragment. In conclusion, a smaller impact area has a greater impact on a spinal cord trauma.

BORS-P65

THE M2 DASH- MANCHESTER-MODIFIED DISABILITIES OF ARM SHOULDER AND HAND SCORE

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The Disability of the Arm, Shoulder and Hand (DASH) questionnaire was originally designed, and has been validated, as a measure of disability in patients with disorders of the upper limb. The aim of this study was two-fold; firstly, to investigate the construct validity of the DASH score in patients following injuries to the upper and lower limbs, and to confirm that DASH score does not measure disability solely attributed to the upper limb. Secondly, to create a modified DASH questionnaire (M2 DASH) with fewer questions that can discriminate clearly between disabilities due to problems at the upper limb, and is more specific to the upper limb.

Patients were asked to fill in the DASH questionnaire in a fracture clinic following ethical approval. This included upper limb injuries (79), lower limb injuries (61) and control subjects (52). The median DASH scores for the three groups were 57, 16 and 1 respectively. The DASH scores varied significantly between the three groups (Kruskal-Wallis: $p<0.001$); the scores for the upper limb group were higher than the lower limb group (Mann-Whitney: $p<0.001$), and the scores for the lower limb group was higher than the control group (Mann-Whitney: $p<0.001$). The M2 DASH questionnaire was developed using questions specific to the upper limb and included questions 1-4, 6, 13-17, 21-23 and 26-30. The median M2 DASH scores for the three groups were 50, 7 and 0 respectively. The revised questionnaire score was then calculated for the upper limb group and a correlation study showed good correlation between the two questionnaires.

Our study shows that the original DASH questionnaire is not specific for the upper limb. This has important implications in measuring response in injuries and disease that involve both upper and lower limbs. We have devised a revised questionnaire that we suggest is referred to as M2 DASH questionnaire to allow identification as different from the original DASH questionnaire. The M2 DASH questionnaire has the advantage of being more specific for the upper limb than the DASH questionnaire, and it correlates well with the original DASH questionnaire when looking at isolated upper limb injuries.

BORS-P66

THE STABILITY OF A PIN IMPLANT IN AN OVARECTOMISED RAT MODEL

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This study used a rat pin model to enable evaluation of the stability of an implant in compromised or weakened bone. Ovarectomised rats have been previously used to investigate the response of postmenopausal bones response to drug therapies. This study investigated the stability of a tibial pin implant whose surface articulates with the femoral surface in induced osteopenic bone.

12 female Sprague Dawley rats, 6 intact and 6 ovarectomised (mean body weight: 249g and 348g respectively) (Charles Rivers, Margate) received a stainless steel pin tibial implant which had been plasma sprayed with hydroxyapatite (Plasma Biotal Ltd.) and were sacrificed after 7 weeks. All procedures had received ethical approval and were carried out in accordance with the regulations as laid down in the Animals (Scientific Procedures) Act 1986. Briefly, the right hind limb was prepared and a lateral patellar approach made allowing medial dislocation of the patellar tendon. A hole was drilled centrally in the tibia and counterbored, into which a pin was press fit allowing articulation with the femur. After the animal was sacrificed at 7 weeks, the right and left hind legs were dissected, fixed, dehydrated and defatted before being embedded in resin. Longitudinal sections were cut, ground and polished (Accutom and Rotopol, Struers). One section from each specimen was stained for Tartrate Resistant Acid Phosphatase (TRAP) to identify osteoclasts, and another was stained using Paragon (3 mins at 85oC) for general histological analysis. Sections were examined under light microscopy (Dialux 20, Leica). Images were grabbed from around the implant and at the growth plate using dedicated software (Bioquant).

Macroscopic examination revealed the pins in both groups to be stable. The ovarectomised group supported and stabilised the pin despite the presence of osteopenia.

The ovarectomised rat pin model is a valid model of problems relevant to postmenopausal bone loss. The weakened bone was able to support a tibial pin implant, and allowed for a more relevant in vivo model of the response to an implant of postmenopausal bone.

BORS-P67

UPPER GI-TRACT ENDOSCOPY RESULTS IN PATIENTS WITH ABDOMINAL SIDE EFFECTS ACCOMPANYING BISPHISPHONATE AND STRONTIUMM RANELATE THERAPY

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Bisphosphonates are effective treatment for osteoporosis but have been associated with gastrointestinal (GI) mucosal injury. Gastrointestinal disorders referred after strontium ranelate (SR) therapy are nausea and diarrhea; however, the mechanism underlying these symptoms have not yet been elucidated. The aim of the study was to compare the endoscopic and histological changes in upper GI tract after Alendronate (AL) and SR in patients with nausea, dysphagia and abdominal pain, which lasted at least 1 month and led to discontinuation of the therapy.

21 postmenopausal women receiving 70 mg/w AL (n = 12) or 2 g/d SR (n = 9) for a minimum of 12 weeks (mean 23 weeks) without a history of upper GI tract disease before antiresorptive therapy was studied. None of them used antisecretory drugs or NSAID's. All subjects underwent endoscopy (+ urease test) and evaluator-blinded assessment of the esophageal, gastric (corpus and pylorus), and duodenal mucosa. Inflammation, immune activity, glandular atrophy and intestinal metaplasia findings were scored as either normal, mild, moderate, or marked, according to the Sydney system and using visual analog scales.

Eesophagitis, esophagal ulcers or errosions were not observed. In both groups, the results of pathologic analysis of biopsy specimens were described as normal. Similarly, gastroduodenal ulcers or errosions were not observed and the results of pathologic analysis of duodenum biopsy specimens were described as normal. Superficial gastritis occurrence in the strontium ranelate group was 4 cases and and in the alendronate group 5 cases, mean gastric endoscopy and pathology scores for both groups were similar ($P > 0.05$). Overall incidence of HP infection was similar in both groups (3 vs 3) without coincidence with mucosal changes.

Our study demonstrated that there is no difference in upper GI tract side effects after bisphosphonate and strontium ralenate therapy, and that as such they may be associated with the presence of superficial gastritis.

BORS-P68

USE OF NAVIGATION SYSTEM FOR INTRA-OPERATIVE EVALUATION OF ACCURATE PLACEMENT OF BONE TUNNELS IN RECONSTRUCTION OF THE ANTERIOR CRUCIATE LIGAMENT

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70 % of ACL reconstructions are also carried out by orthopedic surgeons, who perform limited number of procedures in a year with or without arthroscopy '1'. Computer-assisted navigation systems should allow assessment topographic anatomy with correct anatomical placement of the tunnels '2'. In this study, we describe our experience of using the orthopilot software for navigation of the ACL graft implant during our learning curve. The preciseness of the tibial tunnel placement was evaluated, and the advantages of this

navigation system for open technique ACL reconstruction are discussed after 2 years of clinical follow up.

49 consecutive ACL reconstruction procedures orthopilot navigation system were performed and evaluated regarding the positioning of the tibial tunnel against Blumensaat's line using XR and the route of the graft by magnetic resonance imaging (MRI).

Kinematic navigation enables us to measure anteroposterior and rotational knee stability, isometry, impingement and the angles of bone tunnel placement. At the 2 year follow-up, maximally extended lateral knee X-p revealed that the anterior edge of the tibial tunnel and Blumensaat's line were almost aligned and that roof impingement was avoided; the T2-weighted MR images showed that the graft was placed close to and parallel to the intercondylar roof in all the knees. The ratio of the distance between Blumensaat's line and the anterior edge of the tibial tunnel at the level of the tibial plateau to the anteroposterior width in fully extended true lateral radiographs was 2.3% +/- 2.4%.

The computer-assisted navigation system improves accuracy and decreases dispersion of the tibial tunnel placement against Blumensaat's line in single-bundle ACL reconstruction. Computer assisted surgery allows the reconstruction procedure more reliable, eliminating the problem of skeletal variation among patients. We did not require performing any secondary procedure such as notchplasty and finding no evidence of graft laxity at 2 years follow up.

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BORS-P69

VERTEBRAL FRACTURE ASSESSMENT (USING DXA) IS A PRECISE METHOD OF MEASURING INTERVERTEBRAL DISC HEIGHT

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Degenerative disc disease is a significant cause of low back pain and measurement of intervertebral disc height provides an indication of the health and status of the intervertebral disc. Vertebral fracture assessment (VFA) using dual X-ray absorptiometry is a low ionising-radiation dose method of assessing the presence of vertebral fractures. The fan-beam technology eliminates the cranial-caudal distortion which occurs in projection radiography. Furthermore, the vertebral column is acquired in one continuous digital image thereby minimising motion / positioning artefacts. Vertebral and disc morphometry can then be assessed from these images through the application of markers placed on key points on the image. Frobin et al in 1997 '1' described a ratio for the evaluation of intervertebral disc height namely the ventral disc height divided by the mean depth of the cranial vertebral body (VD/CD) which corrects for variations in stature. The aim of this study was to investigate whether this ratio, VD/CV, can be precisely measured from VFA images acquired using a Hologic Delphi (Bedford, MA). VD/CV was calculated from the VFA images ten times on ten subjects to calculate the short-term precision of this method. The RMS SD and RMS CV% were calculated from these data, with a confidence of 90 degrees of freedom.

The short term precision for each measured disc level (RMS SD, RMS CV%) was as follows: T12/L1: 0.013, 4.877%; L1/L2: 0.014, 4.43%; L2/L3: 0.012, 3.31%, L3/L4: 0.013, 3.59%; L4/L5: 0.009, 2.66%.

These results demonstrate that VD/CD can be precisely measured from VFA scans using the method described by Frobin et al. The results demonstrate a smaller degree of error that that reported by Frobin from his measurements made using projection radiographs. This might be an effect of the divergent beam on the projection radiographs. In conclusion, VFA represents a precise and low dose method for investigating vertebral disc height. One limitation of this method is that the subjects are scanned supine rather than in the preferred erect position. Further research is required to investigate the effect of posture and position on disc height.

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POSTERS - BRS

BRS-P01

3D FINITE ELEMENT ANALYSIS OF X-RAY IMAGES FOR BONE STRENGTH ASSESSMENT

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Finite element analysis (FEA) is a computer simulation technique that can predict the deformation of a 3D structure such as a bone when a load is applied, providing a measure of stiffness (N/mm). Finite element analysis of X-ray images (FEXI) is an FEA technique developed to analyse a conventional 2D DXA-derived BMD image of a bone such as the proximal femur.

18 excised human femora had previously been CT scanned and mechanically tested to failure in a stance loading configuration. 2D BMD equivalent images were derived from the CT scan data for implementation within the FEXI analysis. 3D-FEXI utilized a shape template to generate 3D shapes for FEA from the BMD images. For stance loading, the shaft axis of the proximal femur was orientated at an angle of 70 degrees to the ground without anteversion. A support platen was applied to the base of the shaft portion and restrained in all directions. A load platen was applied to the top of the femoral head and only allowed to move in the vertical direction. A vertical load of 1kN was applied to the loading platen and its vertical displacement recorded. Dividing the applied load by the resultant platen displacement yielded the stiffness of the bone (N/mm). For the 3D FE analysis, each voxel was considered to be a discrete finite element and the material properties of the elements were derived from the volumetric density and the corresponding Young's modulus calculated using published data. 3D-FEXI analysis for the stance loading condition and BMD measurements were performed based on BMD projections generated from the CT scans and compared to failure loads obtained from mechanical testing of the bones.

The ability of BMD and 3D-FEXI to predict the failure load of the same proximal femurs was compared, providing coefficients of determination R'2% of 54.5% and 80.4% respectively.

This ex vivo study demonstrates that 3D-FEXI derived from conventional 2D BMD images has the potential to significantly increase the accuracy of failure load determination of the proximal femur compared with that currently achieved with BMD.

BRS-P02

A COMPUTATIONAL MODEL RELATING 2D CELL SPREADING TO 3D SCAFFOLD COLONIZATION FOR SKELETAL TISSUE REGENERATION

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Insufficient cell ingrowth is a key problem encountered in tissue reconstruction in large 3D constructs and impacts, significantly, on the clinical application of porous biomaterials for bone reconstruction. To address this issue, migration and proliferation of an interacting cell population can be studied in vitro using wound healing type assays and theoretical models. To date, limited experimental observations impede a precise assessment of such models and insight into the underlying mechanisms affecting cell-scaffold colonisation. Thus the objective of the current study was to use applied mathematical modelling to derive intrinsic parameters from experimental laboratory studies, to characterise cell population spreading in 2D, and evaluate the applicability of these methods to predict 3D scaffold colonization by human skeletal populations.

Image analysis was applied to a circle migration assay to quantify migration as well as proliferation of skeletal cell types including human osteosarcoma cells (MG63) and Human Bone Marrow Stromal Cells (HBMSCs) 'Sengers, 2007'. To represent cell population behaviour, both the standard Fisher equation, as well as a sharp front model were evaluated. The high spatial and temporal detail with which the cell distributions were mapped enabled a precise evaluation of the correspondence between experimental results and theoretical model predictions in 2D. This analysis revealed that the standard Fisher equation is appropriate for describing the migration

behaviour of the HBMSC population, whereas for the MG63 cells a sharp front model is more appropriate.

Based on the parameters estimated from these 2D studies, a computational (Finite Element) model was developed to predict the progression of cell colonization on the surface of 3D scaffolds. To provide experimental validation, measurements of HBMSC population migration on human trabecular bone slices were compared with dedicated micro CT-based Finite Element models. The observed results confirmed the ability of the model to represent the experimentally observed pattern of cell population spreading. Furthermore, by incorporating the micro architecture the model is able to relate the global scaffold colonization rate to the local cell population migration velocity. This type of mathematical model will prove useful in understanding and predicting cell ingrowth and improving strategies for the control of skeletal tissue regeneration

BRS-P03

A LONGITUDINAL STUDY OF CHANGES IN BONE MASS IN WOMEN WITH INFLAMMATORY ARTHRITIS USING DIGITAL X-RAY RADIOGRAMMETRY : RESULTS FROM THE NORFOLK ARTHRITIS REGISTER (NOAR)

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Digital x-ray radiogrammetry (DXR) is an alternative to DXA of the hand or wrist in assessment of bone health in patients with inflammatory polyarthritis (IP). It has been shown to correlate well with DXA. There are though few data looking at changes in bone mass based on assessment of serial radiographs and how these relate to disease related factors. The aim of this investigation was to characterise changes in bone mass assessed using DXR in women with IP and to examine the influence of disease related factors on any observed change in bone mass.

Women aged 16 years and over with recent onset IP were recruited to the Norfolk Arthritis Register (NOAR) between 1990 and 1998 and followed annually. At baseline, subjects completed the health assessment questionnaire (HAQ) and their joints were examined by a metrologist for the presence of swelling and tenderness. Radiographs of the hand were performed in a subgroup of subjects at the first and subsequent annual visits. Height and weight was measured in the fifth year following the baseline survey. The hand radiographs were assessed using DXR (Pronosco X-Posure) which gives measurements of bone mineral density (BMD) in the second to fourth metacarpals. Linear mixed models were used to investigate whether disease related factors predicted change in BMD. Results are expressed as beta coefficients and 95% confidence intervals (CI), with adjustments made for age, height and weight.

238 women, mean age 54.9 years (SD =13.9) were included in the analysis. The mean time between serial radiographs was 4.4 years. The median number of swollen joints was 11 (6-18). Mean HAQ score 1.1 (SD=0.7), mean BMD as assessed by DXR for the first radiograph was 0.523 g/cm2 and declined by -0.024 g/cm2 (SE=0.003), representing a 1.0% decline per year. After adjusting for age, height and weight, increasing HAQ score (unit change) was associated with a decrease in BMD (beta coefficient=-0.012; 95%CI -0.021, -0.002). Increasing disease activity as measured by the swollen joint count was associated with a decrease in BMD (beta=-0.009; 95%CI -0.017, -0.001).

DXR is a sensitive method of detecting change in bone mass in women with IP and sensitive also to changes in disease activity.

BRS-P04

A NOVEL IN VITRO MODEL OF OSTEOARTHRITIS FACILITATES IMPROVED UNDERSTANDING OF HUMAN ARTICULAR CHONDROCYTE BEHAVIOUR

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Human articular chondrocytes (HACs) derived from explants following hip and knee arthroplasty are widely used to investigate the molecular mechanisms of osteoarthritis. The main problem with these cells is their early loss of phenotype from chondrocytic to fibroblastic. Studies have shown that hypoxia has an important role in maintaining HAC phenotype. In addition, the culture of HACs on different surfaces and scaffolds that more closely simulate the in vivo extracellular matrix environment has an important effect on cell behaviour. Our objective was to improve the simulation of the microenvironment in which HACs are cultured in order to enhance the in vitro investigation of osteoarthritis.

We fabricated a novel and reliable porous polymer (poly '2-hydroxyethyl methacrylate') surface which allowed close control of the cell to cell and cell to extracellular matrix (ECM) interactions. In addition, we cultured the cells in profound hypoxic conditions (1% oxygen). We used real time polymerase chain reaction (PCR) to quantify the expression collagen 2 as a marker of chondrocyte activity. Enzyme linked immunosorbant assay (ELISA) was utilised to measure expression of matrix metalloproteinase-1 (MMP-1). All experiments were repeated at least 4 times. Statistical assessment was by one way ANOVA with Bonferonni post hoc.

Cells cultured on the porous polymer surface and in 1% oxygen had significantly higher transcripts of collagen 2, indicating increased chondrocytic behaviour. These cells also showed increased expression of MMP-1 which increased their ability to degrade the ECM.

Discussion: Increased expression of collagen 2 by the HACs in our model was not surprising, however the increased expression of MMP-1 is a novel finding in this setting. Assessment MMP-13 by ELISA showed no significant increases in our model. This suggests that pathways activating MMP-1 are important in the progression of osteoarthritis.

This study indicates that the current widely used model of HAC culture in normoxia and in monolayer needs refinement in order to more closely simulate the in vivo microenvironment. This will allow enhanced understanding of the molecular mechanisms of osteoarthritis and thus the discovery of novel potential therapeutic targets.

BRS-P05

A RETROSPECTIVE AUDIT OF THE USE OF PAMIDRONATE FOR FIBROUS DYSPLASIA

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Fibrous dysplasia (FD) is a relatively uncommon condition presenting with combinations of focal bone abnormalities, cutaneous hyperpigmentation and endocrinopathy. It is caused by a post-zygotic mutation in a G-protein coupled receptor (GNAS1) leading to constitutive activation of several hormone signaling pathways. Severely affected patients present in childhood with extensive bone lesions + endocrine disorder e.g. premature puberty (McCune-Albright syndrome) but less severely affected individuals can present later with painful bone lesions or fracture. The use of intravenous bisphosphonates (e.g. pamidronate) has been proposed for the treatment of bone lesions to reduce pain, deformity and risk of fracture. As part of the development of a new service we retrospectively examined the safety and effectiveness of bisphosphonate treatment in patients diagnosed with FD at our orthopaedic hospital (the largest elective joint replacement centre in Europe with a major bone tumour unit). A questionnaire designed to capture both quantitative and qualitative date (number of treatments, pain scores, QOL) was distributed to adults with FD who had received IV pamidronate (n=13). 11 patients replied. Responses were correlated with data recorded in the notes. Most patients (n=10) had FD restricted to a small number of bones. The only endocrine disorder was hypophosphataemia (n=1). The primary finding was that reported pain scores after pamidronate were significantly lower than before treatment (7.8+/-1.5 vs 2.9+/-3.0 (mean+SD) on scale of 1-10 with 10 worst pain; $p<0.001$). Given the low numbers it was impossible to assess any effect on the appearance of FD lesions or risk of complications. The commonest adverse effect was flu-like symptoms after the first dose (n=6) but one patient with FD of the sphenoid developed transient periorbital swelling and visual disturbance. Although the retrospective nature of the study and lack of a control group limit the conclusions that can be made IV pamidronate appears effective in improving symptoms in most patients with FD. Further examination of the effectiveness of bisphosphonates in FD would require a multicentre controlled trial.

BRS-P06

ASSAY PERFORMANCE AND SAMPLE EVALUATION FOR RAT/MOUSE PINP ENZYMEIMMUNOASSAY

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PINP (procollagen type I amino-terminal peptide) is a biomarker for collagen synthesis and bone formation. The quantitative measurement of PINP has, until recently, only been possible in human samples. IDS developed a rodent PINP assay necessitating the characterization of samples and assay performance. This competitive EIA uses rabbit anti-rat/mouse PINP coated onto microtitre wells. Calibrators, controls and samples (5µL) are added with biotinylated PINP, followed by enzyme-labeled avidin, and substrate (TMB). The colour intensity of the stopped reaction is inversely proportional to the PINP concentration. The EIA was validated for intra-assay and inter-assay precision, cross reactivity, linearity and spike recovery.

The IDS Rat/Mouse PINP EIA displays excellent intra- and inter-assay precision (<8% and <10%, respectively). No cross reactivity was detected for human PINP or PIIINP or rat PIIINP. PINP diluted in a linear fashion (observed/expected of 93.8%) and had excellent spike recovery of 96.7%. Sample stability was determined using pooled mouse sera in aliquots stored at -80C; freeze/thaw cycle effects were also studied. Three matched samples (serum, EDTA or heparinized plasma from the same animal) were analyzed to determine sample type influence. Eight to 49 week old mice were also sampled to study the age-related pattern of PINP release.

Mouse PINP did not decrease in frozen samples stored for 3 months, nor was there a deleterious effect due to two freeze/thaw cycles. No significant difference was seen in PINP levels due to sample type (18.3±3.0ng/mL serum, 17.0±3.5ng/mL EDTA plasma or 19.1±4.3ng/mL heparinised plasma, n=18). Mouse PINP levels decreased with age: 86.0±20.3ng/mL ng/mL at 8 wks, 43.5±4.0ng/mL at 20 weeks, and 21.4±0.8 ng/mL at 27.5 weeks and 21.1±7.2ng/mL at 49 weeks. These results demonstrate that mice and PINP measurement will be useful for bone biological studies since mice possess the same temporal PINP pattern as humans.

BRS-P07

ASSOCIATION BETWEEN RISK FACTORS FOR CARDIOVASCULAR DISEASE (CVD)AND BONE MINERAL DENSITY (BMD) IN POST-MENOPAUSAL OSTEOPOROSIS

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Accumulating evidence suggests an association between CVD and osteoporosis. Similar pathophysiological mechanisms link osteoporosis and atherosclerosis including lipid abnormalities. However data regarding the relationship between BMD and hyperlipidaemia remain conflicting. The aim was to investigate the association between BMD and serum lipids (total cholesterol (TC), LDL-C, HDL-C, triglycerides (TG)) in a group of post-menopausal women attending an osteoporosis clinic. We recruited 99 women; age mean 'SD' 71 '9.25' years. Demographic data and lifestyle factors such as level of exercise, smoker, were obtained. BMD was determined at the lumbar spine (LS), femoral neck (FN) and total hip (TH). Lipid profiles were included in the general biochemical protocol for patients attending the clinic. Univariate and multiple linear regression analyses were carried out. A significant correlation was seen between LS BMD and TC (r= 0.3, p=0.0065) and LDL-C (r= 0.25, p=0.02). After adjustment for confounders such as age, BMI, lifestyle factors, vitamin D status, renal function, BMD at the LS was still significantly negatively correlated with LDL-C (p = 0.036). TH BMD was negatively related to HDL-C (r=0.26, p=0.02). However following correction for confounders, the results failed to reach significance (p=0.07).Subjects with TC > 5.5 mmol/L had lower LS BMD ('Z' score -1.1'1.0' v/s -0.54 '1.08', p= 0.02). A significant association was observed between 25 (OH) vitamin D and TC (p=0.036).

This study supports the involvement of lipids in osteoporosis. Measurement of lipid profile may be useful in the biochemical evaluation/screening of patients attending the osteoporosis clinic.

BRS-P08

ATP RELEASE FROM OSTEOBLASTS IS INCREASED IN RESPONSE TO MECHANICAL LOADING BY DIFFERENT AMOUNTS WHEN GROWN IN STANDARD MONOLAYER AND NOVEL 3D SCAFFOLDS

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Osteoblasts release ATP via a non-lytic mechanism into the extracellular microenvironment where it is detected by neighbouring osteoblasts expressing purinergic (P2) receptors, modulating a wide range of osteoblast functions. Previous studies have demonstrated that ATP is constitutively released from osteoblasts in vitro and increases in response to mechanical loading. The aim of this study was to determine whether the amount of ATP released from osteoblasts subjected to mechanical loading differs when cells are cultured in different dimensions. SaOS2 and Te85 osteoblastic cell lines were grown as monolayer cultures in 24 well plates and exposed to mechanical loading in the form of medium displacement. ATP released into the bulk phase was measured using the luciferin/luciferase assay. After loading, plates were fixed, stained and imaged to exclude the possibility that ATP release was due to cell death. Three dimensional (3D) cultures of SaOS2 and Te85 cells were grown in polyurethane (PU) scaffolds for one week and then cyclically loaded in a modified Electroforce 3200 powered BOSE biochamber at 5% strain for between 20 and 32 minutes. Medium samples were taken at regular intervals and flash frozen in liquid nitrogen prior to analysis for ATP and lactate dehydrogenase (LDH) as a marker of cell death. Scaffolds were fixed and a detailed histological analysis of cell number and distribution performed. Loading of monolayer cultures resulted in a significant increase of ATP release from SaOS2 (5 fold) and Te85 (20 fold) cells. Cyclic loading of scaffolds for 30 minutes resulted in a two fold increase in ATP release. Subsequent experiments demonstrated ATP release is induced by loading bouts as short as 2 minutes. Histological analysis of 3D scaffolds demonstrated a significant increase in cell number between the first and second week after seeding, whereas scaffolds loaded one week after seeding showed no such increase. No cell death was detected in any of the cultures, confirming active ATP release. Determining the molecular mechanisms behind this difference in ATP release will provide further insight into the understanding of ATP signalling in osteoblasts in response to loading.

BRS-P09

AUTOMATED SYSTEM FOR MEASUREMENT OF CONDUCTIVITY AND ITS USE AS AN ALTERNATIVE TO CREATININE FOR CORRECTION OF URINARY N-TELOPEPTIDE LEVELS

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Urinary N-telopeptide measurements (uNTx) can provide valuable clinical information on bone resorption, such as providing a rapid assessment as to whether patients are responding to bisphosphonates and other therapies. There are several assays available to accurately measure uNTx. However, urinary levels are significantly influenced by urine concentration so uNTx measurements are normally corrected by dividing by the creatinine concentration. Creatinine is an imperfect molecule for concentration correction because its excretion is known to be affected by a number of variables such as muscularity, age, physical activity, diet and urine flow. We have previously found that conductivity could be a good alternative to creatinine for correction of uNTx levels. To gain more clinical evidence for conductivity correction, an automated method has been developed to handle a larger number of samples.

The method comprises of a Biodot pump dispenser and X/Y/Z robotic arm with auto-sampler, in conjunction with a flow-through micro-conductivity cell and reader. The automated method showed excellent correlation R2= 0.945, y = 0.969 + 0.69, with the standard method of conductivity measurement (WTW-330i handheld conductivity meter).

When these automated measurements of conductivity were applied to correct uNTx concentration they were found to give a good correlation with creatinine corrected uNTx levels. Therefore,

conductivity may be a viable alternative to creatinine for concentration correction of uNTx, and this system will allow the rapid and accurate, automated measurement of multiple samples.

BRS-P10

AUTOPHAGY IN OSTEOCLASTS: A POSSIBLE ROLE IN THE PATHOGENESIS OF PAGET'S DISEASE OF BONE

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Paget's Disease of Bone (PDB) is a common, typically late-onset condition characterised by focal areas of increased bone turnover. Within Pagetic lesions osteoclast number, activity and multinuclearity are all increased. Hyperactivation of osteoblasts also occurs, but newly synthesised bone is architecturally disorganised and prone to fracture. Mutations in the gene encoding Sequestosome-1/p62 (SQSTM1) have been identified as a cause of PDB. SQSTM1 is required both for the formation and degradation of ubiquitin-containing aggregates by autophagy. All PDB-causing mutations examined to date affect the ability of SQSTM1 to bind ubiquitin. Previous work in our lab has identified a novel interaction between SQSTM1 and Autophagy Linked FYVE protein (ALFY) in human osteoclast-like cells (hOCL), and has also shown that ALFY localisation is abnormal in HEK293 cells transfected with mutant SQSTM1. ALFY has been proposed to target cytosolic protein aggregates for autophagic degradation. In this study, we have examined the intracellular localisation of SQSTM1 and ALFY in hOCL that have been starved of amino acids to induce autophagy.

hOCL were generated on glass coverslips from human peripheral blood mononuclear cells cultured with M-CSF and RANKL. Upon formation of multinucleated hOCL, the cells were starved in HBSS for up to two hours and fixed. Subsequently, immunohistochemistry with confocal microscopy was used to study the intracellular localisation of SQSTM1 and ALFY.

In unstarved multinuclear hOCL and mononuclear precursors, SQSTM1 was localised throughout the nucleus and ALFY was located predominately at the nuclear membrane. Upon starvation, SQSTM1 and ALFY levels increased and both relocalised from the nucleus to the cytoplasm. After two hours, formation of aggregates containing ALFY and SQSTM1 was observed in multinucleated cells, but not in mononuclear cells on the same coverslip. These results support a role for the interaction between SQSTM1 and ALFY in osteoclast physiology, and suggest that hOCLs are more sensitive to the induction of autophagy than their precursors.

This novel finding suggests a role for autophagy in the pathogenesis of PDB. It may also provide a possible explanation for the tissue-specific effects of mutations in SQSTM1 observed in individuals affected with PDB.

BRS-P11

BONE MARROW DERIVED MESENCHYMAL STEM CELLS EXPRESS PERICYTE MARKERS IN CULTURE AND SHOW ENHANCED CHONDROGENESIS IN HYPOXIC CONDITIONS

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Bone marrow derived mesenchymal stem cells are a potential source of cells for the repair of articular cartilage defects. Hypoxia has been shown to improve chondrogenesis in adult stem cells. In this study we characterised bone marrow derived stem cells and investigated the effects of hypoxia on gene expression changes and chondrogenesis.

Adherent colony forming cells were isolated and cultured from the stromal component of bone marrow. The cells at passage 2 were characterised for stem cell surface epitopes, and then cultured as cell aggregates in chondrogenic medium under normoxic (20% oxygen) or hypoxic (5% oxygen) conditions for 14 days. Gene expression analysis, glycosoaminoglycan and DNA assays, and immunohistochemical staining were determined to assess chondrogenesis.

Bone marrow derived adherent colony forming cells stained strongly for markers of adult mesenchymal stem cells including CD44, CD90 and CD105, and they were negative for the haematopoietic cell marker CD34 and for the neural and myogenic cell marker CD56. Interestingly, a high number of cells were also positive for the pericyte marker 3G5. Cell aggregates showed a chondrogenic response and in lowered oxygen there was increased matrix accumulation of proteoglycan, but less cell proliferation, which resulted in 3.2-fold more glycosoaminoglycan per DNA after 14 days of culture. In hypoxia there was increased expression of key transcription factor SOX6, and the expression of collagens II and XI, and aggrecan was also increased.

Pericytes are a candidate stem cell in many tissue and our results show that bone marrow derived mesenchymal stem cells express the pericyte marker 3G5. The response to chondrogenic culture in these cells was enhanced by lowered oxygen tension, which up-regulated SOX6 and increased the synthesis and assembly of matrix during chondrogenesis. This has important implications for tissue engineering applications of bone marrow derived stem cells.

BRS-P12

BONE MARROW LEVELS OF 25 HYDROXY VITAMIN D ARE NOT DEPRESSED IN CASES OF HIP FRACTURE COMPARED TO CONTROLS

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Femoral neck fractures in the elderly are associated with increased cortical remodelling and endosteal resorption, leading to regional increases in porosity and reduced cortical thickness. Vitamin D metabolites play a central role in the maintance of normal serum calcium levels and may though interactions with parathyroid hormone (PTH) exert an important influence on bone structure.

To investigate whether the excess remodelling of cortical bone in UK hip fracture subjects might be largely driven by vitamin D deficiency we have measured by radioimmunoassay the levels of 25 hydroxy vitamin D (25 (OH) D) in bone marrow samples extracted from the proximal femurs of 16 female subjects who had suffered fracture (mean age 82.1 yrs, se 1.9) and 9 sex matched post mortem controls (mean age 83.8, se 2.5).

25 (OH) D concentrations were significantly greater in the fracture cases (median 3.7, IQR 2.5-3.9ng/g) than in the control group (median 1.5, IQR 0.9-2.3ng/g; P 0.0007, non-parametric Wilcoxon/Kruskal-Wallis test). It was not possible to collect analyzable blood samples from post mortem controls, so we analysed vitamin D metabolites in the femoral neck bone marrow, using a previously validated approach to extraction. That marrow vitamin D levels were higher in the hip fracture cases was unexpected. While it is not known how closely marrow vitamin D levels parallel those in the blood, it is generally agreed that vitamin D stores are largely found in body fat, including the marrow.

It was suggested in the 1970s that bone loss and hip fracture risk in the UK was driven by vitamin D deficiency. Our results suggest that the alterations in femoral neck bone microstructure and remodelling in hip fracture cannot be assigned to the single cause of relative deficiency of vitamin D. Vitamin D deficiency or insufficiency may increase remodelling and loss of bone tissue. However in hip fracture there are likely to be additional factors making hip fracture cases more vulnerable than controls to fracture in a fall.

BRS-P13

BONE SUBSTITUTES: ARE THEY USEFUL AS AN ADJUNCT FOR FRACTURE HEALING

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Artificial bone graft substitutes are widely available. They can be osteo-conductive, osteo-inductive or a combination of the two.

We performed a retrospective study to compare the effect of two different bone graft substitutes in fracture healing. We also assessed cost effectiveness and any outcome differences in the osteo-conductive and osteo-inductive materials.

In total we have treated 29 cases with bone graft substitute. The cohort included 11 males and 18 female patients. The average age was 59. Primary bone grafting was used in 24 patients and secondary bone grafting was used in 5 patients. 20 patients received osteo-inductive bone substitute and 9 patients received osteo-conductive bone substitute. We followed up the patients clinically and radiologically.

In all cases fracture union was achieved both clinically and radiologically. The average time taken for radiological union was 5.5 months. The union time is almost the same in both groups.No secondary procedures were required in our study group.

With our study we found that artificial bone grafts are equally good in treating appropriate fractures. It is more cost effective by reducing the hospital stay, morbidity to the patients and the operative time. Both forms of artificial graft were useful and effective in achieving fracture healing.

BRS-P14

BONE TISSUE STRUCTURE AND FUNCTIONING IN POSTMENOPAUSAL WOMEN ENGAGED IN VARIOUS PHYSICAL EXERCISES

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Influence of physical exercises on bone tissue structure and functioning in postmenopausal women. 52 women of postmenopausal age were divided into five groups: 1) attending yoga class no less than 5 years, n=8; 2) jogging no less than 5 years, n=12; 3) former gymnastic champions with nearly 10-20-year sporting life, n=10; 4) unengaged in any sports (control, n=13); and 5) postmenopausal women (14.0±2.2 years, n=10) at around 65 years of age, suffering from osteoporosis and doing physical exercises with loads (1 kg weight). The women of the last group participated in this study during 6 months. All women were standardized by age, body weight and post menopause duration.

Bone tissue measurements of speed of sound (SOS), broadband ultrasound attenuation (BUA), Stiffness index (STF) and Z (SD) were performed by ultrasonic densitometry ('Achilles+').

The SOS parameter values were (1526±12.8; 1529±5.1; 1534±9.3; 1520±8.4) in groups 1, 2, 3 and 4, respectively, and had no significant differences among study groups. The BUA value was higher in gr. 3 (113.7±3.1) in comparison with gr. 4 (106±1.4; $p<0.05$). Its value did not have significant differences in gr. 1 and gr. 2 (106.5±3.4 and 110.4±2.8) compared to control group value (106±1.4). The STF values in gr. 1, gr. 2 and gr. 3 made respectively 78.3±5.6; 81.7±3.1 and 85.2±4.5 and did not differ significantly from the control (76.1±3.1). The parameter Z (SD) registered in gr. 3 group versus gr. 4 had the following meanings: 0.96±0.2 and 0.02±0.2 ($p>0.05$). Performance of physical exercises with loads against the background of calcium drugs intake by post-menopausal women led to the increase of SOS parameter after 6 months of exercising in comparison with its basal value (1497.3±5.7 and 1501.3±6.0, $p>0.05$), while the values of BUA parameter remained almost unchanged (66.3±1.9 and 71.7±4.2). The Stf parameter was 66.3±1.9 and 71.7±4.2; Z (SD) changed from -0.8±0.1 to -0.6±0.1 ($p<0.05$).

Sports at young age and performance of physical exercises with loads lead to the increase of bone tissue indices at the post-menopausal age, as has been proved by ultrasonic densitometry data.

BRS-P15

CAN FALL RISK BE INCORPORATED INTO FRACTURE RISK ASSESSMENT ALGORITHMS?: A PILOT STUDY OF RESPONSIVENESS TO BISPHOSPHONATES

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Recent tools developed for the prediction of fracture risk, including the FRAX(TM) tool produced by the WHO, have largely excluded falls as a risk variable due to the uncertain efficacy of bone-active agents such as bisphosphonates to reduce fracture risk in such patients. We examined the interaction between reported falls history and a surrogate marker of falls risk, the sit-to-stand test1, in a prospective, placebo-controlled, randomized trial of the bisphosphonate, clodronate, over 3 years.

5212 women aged 75 years or more and unselected for osteoporosis were recruited to the study. At entry, they were asked to report if they had sustained more than one fall in the previous month and also underwent physical assessments including their ability to rise from a chair (the sit-to-stand test; classified as not possible, with difficulty or without difficulty).

Multiple falls were reported by only 4% of women at entry who were older ($p=0.0025$) than women without multiple falls but had similar prevalences of prior fractures, glucocorticoid use, rheumatoid arthritis, maternal hip fracture and smoking with no differences in BMI or femoral neck BMD. Inability or difficulty in rising from a standard chair, observed in 31% of the women, was associated with increased reports of multiple falls (RR 2.66, 95%CI 1.96-3.61). An unsuccessful chair test was also associated with older age ($p<0.001$), a higher prevalence of prior fractures ($p=0.014$), more frequent glucocorticoid exposure ($p<0.001$) and self-reported rheumatoid arthritis ($p<0.001$). Importantly, however, inability or difficulty in rising from a chair was associated with a higher BMI ($p<0.001$) and femoral neck BMD ($p=0.016$). Oral clodronate 800mg daily was associated with a 24% reduction in osteoporotic fracture incidence (HR 0.76, 95%CI 0.63-0.93). The efficacy of clodronate was similar in women with an unsuccessful chair test to those with no difficulty in rising (HR 0.79 vs. 0.74 respectively, p-value for interaction with treatment >0.30).

We conclude an indicator of the risk of falls does not significantly impact on the efficacy of clodronate in reducing the incidence of fracture. If confirmed in other studies with other agents, falls risk indicators could be incorporated into risk assessment tools designed to target skeletal therapies.

1Nevitt et al. Risk factors for recurrent nonsyncopal falls. A prospective study. JAMA 1989,261,2663-8

BRS-P16

CELL MODIFICATION IN 3D: OSTEOGENIC STIMULATION OF HBMSC AFTER HYDROXYAPATITE COATING IN THE ABSENCE OF CHEMICAL CUES

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Bone loss remains a considerable unmet challenge and proposed treatments for osseous defects remains limited and long-term outcomes, at present, unclear. Thus, there is a clinical need to develop alternative strategies to augment bone formation for therapeutic application. One possible strategy would be to combine bionanotechnology and skeletal cell biology to examine if modifications of human bone marrow stromal cells (HBMSC) with surface coatings of suitably functionalised nanoparticles can result in osteogenic induction in the absence of chemical cues. We have investigated such an approach using HBMSC progenitor cell/hydroxyapatite conjugates and demonstrated the potential to form osteoid tissue in vitro and in vivo.

Aqueous colloidal suspensions of amino acid functionalised hydroxyapatite (HAp) nanoparticles were prepared (HAp/alanine and HAp/arginine), with and without the inclusion of arginine-glycine-aspartic acid (RGD) peptide, and added to a HBMSC suspension (20 microlitres per million cells, ~ 7 x 108 particles per cell). Cells were cultured in monolayer for up to 21 days or in a 3D pellet culture system both in vitro and in vivo for 21 days.

Transmission electron microscopy analysis indicated both surface coatings and cell uptake of HAp nanoparticles within 24 hours of treatment. A high proportion of metabolically active cells were present in monolayer culture after 7 days and biochemical analysis indicated significantly increased alkaline phosphatase (ALP) activity in HAp/A or HAp/R coated cells in comparison with uncoated cells. Additionally, HBMSC coated with HAp/A/RGD and HAp/R/RGD demonstrated a further increase in ALP activity at RGD-peptide concentrations of 0.5mg/ml and 0.75mg/ml respectively. Significantly, areas of osteoid formation were observed in three-dimensional pellets after 21 days, both in vitro and following sub cutaneous implantation in immunocompromised mice. Immunocytochemistry revealed extensive formation of areas of fibrous collagen, which was demonstrated as mineralised by TEM

and SEM microscopy, within both peripheral and central regions only within the 3D constructs of pre-coated cells.

These studies outline the potential of hydroxyapatite nanocoat approaches to promote osteogenic cell differentiation and 3D construct formation in the absence of chemical cues demonstrating the future potential for skeletal regeneration applications as well as new models to examine skeletal cell differentiation and function.

BRS-P17

CERAMIDE: A NOVEL MEDIATOR OF OSTEOBLAST CELL DEATH

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It is well-established that disturbances in osteoblast programmed cell death (PCD) may underlie the pathogenesis of metabolic bone diseases such as osteoporosis. Ceramide, the precursor to all complex sphingolipids, is a critical bioactive secondary messenger that has been demonstrated to play a role in PCD in a number of tissues. However, whether ceramide plays a role in PCD in bone has not yet been studied. To address this, we first studied the effect of ceramide on the viability of MC3T3-E1 cells and primary murine osteoblasts. Using the MTT assay we have demonstrated that exogenous C2-ceramide, but not its inactive precursor dihydroceramide, reduces MC3T3-E1 osteoblast viability in a dose-dependent manner, with 10 µM and 150 µM C2-ceramide reducing cell viability by 14% and up to 71%, respectively. Primary osteoblasts displayed a 5-fold increased sensitivity to low doses of C2-ceramide. Further analysis using the caspase inhibitor DEVD-CHO, together with Annexin V and TUNEL staining, demonstrated that this reduction in viability was due to induction of caspase-dependent apoptotic cell death. Furthermore, transmission electron microscopy analysis indicated that the PCD induced by ceramide in osteoblasts showed nuclear fragmentation characteristic of apoptosis, as well as the presence of autophagosomes typical of autophagic cell death. Western blot analysis demonstrated that the activation of the MAPKs ERK and p38, but not JNK, were involved in ceramide-induced osteoblast PCD.

We have also demonstrated that synthesis of endogenous ceramide is required for TNF-_ induced cell death in osteoblasts. Pretreatment with chloropromazine (an acid sphingomyelinase inhibitor) and Fuminosine B1 (an inhibitor of de novo ceramide synthesis) showed full rescue of the TNF-_ reduced osteoblast viability as detected by MTT assay. However, pretreatment with sphingolactone 24 (a neutral sphingomyelinase inhibitor) showed only partial rescue of the reduction in viability, suggesting that the level of endogenous ceramide is an important mediator of osteoblast PCD.

Taken together, this work has highlighted a novel role for ceramide in inducing caspase-dependent osteoblast PCD. Therefore, ceramide could be utilised as a therapeutic tool for bone diseases such as osteopetrosis and osteosarcoma. Furthermore, targeting of the endogenous ceramide pathway could potentially provide novel treatments for osteoporosis.

BRS-P18

CHARACTERISATION OF AN ANTIGEN SPECIFIC TO THE GOLGI APPARATUS OF BONE CELLS

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Screening of a panel of monoclonal antibodies has identified an antigen which is highly expressed in osteoclasts and at a lower level in osteoblasts. We used osteosarcoma cells to study the antigen as they have reliable expression and proliferate rapidly.

Live imaging was carried out using fluorescently labelled antibody. Cells were seeded on glass petri dishes at 30% confluence. Chariot, (Vector Laboratories), was used to mediate uptake of antibody into the cells. Cells were monitored over a seven day period, until confluence, by confocal microscopy. Antibody against collagen VI and chariot vector alone were used as controls. Co-localisation studies were performed on cells fixed in 4% paraformaldehyde. Markers against the golgi, endoplasmic reticulum, mitochondria, the endocytic pathway and the nucleus were applied to the cells as recommended by the supplier, (Molecular probes). Data was analysed using Image J software. Cells were lysed and fractionated into cytosol, organelles, nucleus and cytoskeleton. Immunoprecipitation was performed using protein G labelled Dynabeads, (Invitrogen). Antibody was bound to the beads before incubation with cell lysate. Gels were then stained with Simply blue safe stain, (Invitrogen), and used for Western blotting. For Western blotting proteins were transferred to nitrocellulose membrane at 30V for one hour. Membranes were then blocked with skimmed milk powder prior to indirect antibody labelling and development with ECL detection reagent, (GE Healthcare).

The antibody was taken up into the cells within 30 minutes of incubation with antibody. It appears to reside in perinuclear vesicles from this point through to confluence. At confluence 70% of cells appear to contain the antibody. Cells appear healthy and proliferate normally. Control antibody shows differences in expression.

Co-localisation studies show that the antigen co-localises with the golgi apparatus and not the endoplasmic reticulum, mitochondria, the endocytic pathway or the nucleus. Fractionation of cells shows the antigen to be specific to the organelles. Western blotting of immunoprecipitate reveals a band of approximately 90kDa, which cannot be seen by coomassie staining. Imaging and cell fractionation show the antigen to be located in the organelles, specifically the golgi. Scaling-up of the immunoprecipitation procedure should allow for identification of the antigen.

BRS-P19

CHARACTERISATION, OSTEOGENIC POTENTIAL AND CLINICAL PERFORMANCE OF A SOUTH CHINA SEA CORALLINE HYDROXYAPATITE/CALCIUM CARBONATE

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Coralline hydroxyapatite (CHA) is prepared by hydrothermic conversion from the calcium carbonate exoskeleton of sea coral. CHA has been shown to be effective as a bone graft substitute. However, complete convertion of calcium carbonate into hydroxyapatite may result in slow bioresorption following implantation. We have recently developed a partially converted coralline hydroxyapatite/calcium carbonate (CHACC). The aims of this study were (1) to characterise the material properties of CHACC by using powder X-ray diffraction (XRD), Fourier transform infra-red (FTIR), energy dispersive X-ray spectroscopy (EDX), thermo-gravimetric analyze (TGA) and scanning electron microscopy (SEM), (2) to examine the effects of CHACC on osteogenic cell proliferation and differentiation by using human mesenchymal stem cells (hMSCs) in vitro and by implanting hMSC in vivo together with CHACC and a bisphosphonate, risedronate, into CB17 scid beige mice and (3) to study clinical performance of CHACC as a bone substitute in sixteen patients with bone tumours. The results show that CHACC is a mixture of hydroxyapatite and calcium carbonate with the latter as the main component. Hydroxyapatite forms a thick (30 um) coating that envelopes the surface of main porous calcium carbonate material. CHACC supported hMSC proliferation and osteogenic differentiation in vitro, and bone formation in vivo in CB17 scid beige mice. All clinical cases showed normal wound healing with no infection or other complications being observed. X-ray examination showed that after implantation visible callus formation was observed at one month, the density of implanted CHACC decreased from three months accompanied by bone density increase in the gaps between CHACC. Clinical bone healing was achieved at 4 months and the majority of the CHACC was degraded at 18-24 months. In conclusion, CHACC appears to be an excellent bone graft material showing biointegration with host tissues, high osteoconductivity and good biodegradability and appears an attractive alternative to autogenous grafts.

This study is a part of a PhD project of Tongji Medical College of Huazhong University of Science & Technology, China.

BRS-P20

COMPUTER AIDED DIAGNOSIS OF OSTEOPOROTIC VERTEBRAL FRACTURE USING APPEARANCE MODELS AND AN AUTOMATIC SEGMENTATION

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Osteoporosis is a progressive skeletal disease leading to increased susceptibility to fractures. Vertebral fractures are the most common, occur in younger patients, and so may provide early diagnosis. Current quantitative morphometric methods of vertebral fracture detection lack specificity. We use detailed shape and texture information to develop quantitative classifiers. These methods require accurate segmentation of vertebrae, which we obtain (semi)automatically using Active Appearance Models.

The vertebrae in a training set of 360 lateral dual energy X-ray absorptiometry (DXA) scans were manually segmented. Hence detailed shape and image texture of vertebrae were statistically modelled using Appearance Models, producing an appearance parameter set for each vertebra. The vertebrae were given a gold standard classification using a consensus reading by two radiologists using the Algorithmically Based Qualitative (ABQ) method. Linear discriminants were trained on the vertebral appearance parameters (given the manual segmentation) as in '1'. Appearance model parameters were adjusted from values in '1' to optimise classifier performance via bootstrap experiments. Classifier performance was next evaluated using automatic segmentations. Active Appearance Models using overlapping groups of 5 vertebrae were derived from the same training set, and used to obtain automatic vertebral segmentations via a leave-8-out train/test loop. Final leave-1-out classifier tests were performed to derive classifier ROC curves, given the automatic segmentations as input. These were compared to a morphometric algorithm, with height ratio thresholds derived from the sample distributions of the normal vertebrae.

Given the manual segmentation, the appearance classifier gives a false positive rate (FPR) of 5% at 95% sensitivity; compared to an 18% FPR with height morphometry. With automatic segmentations the appearance classifier sensitivity is 86% at 5% FPR, whereas the morphometric sensitivity is 75%.

Specificity at high sensitivity is enhanced by using an appearance-based classifier, which uses detailed shape and image texture to better distinguish between mild fractures and some kinds of non-fracture shape deformities. Reasonable sensitivity can be achieved using an automatic segmentation, but occasional segmentation failures would require manual correction.

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BRS-P21

CREATION OF A 3D SHAPE FOR THE PROXIMAL FEMUR FROM A SINGLE 2D RADIOGRAPHIC IMAGE

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This paper describes the development and initial validation of a technique to generate a 3D proximal femur shape based upon a single projection 2D radiographic image.

CT scans of 42 excised human femora were utilised to facilitate and assess the validity of the approach. These were equally split into Training, from which the 3D shape template was created, and Test cohorts. A ray casting technique was applied to the CT scan data for each proximal femur to create 2D mappings of BMD as well as offset and depth from a reference plane. The BMD of each pixel within the BMD mapping was calculated with reference to the calibrated volumetric density data. Generalized Procrustes Analysis and Thin Plate Splines were employed to create an average 3D shape template that was subsequently warped to suit the size and shape of individual 2D images in the Test set. This approach assumes a proportional change in bone depth corresponding to a proportional change in overall size of the bone.

Utilising the 2D similarity measure defined as the Euclidean distance between landmarks, the 2D profile of the reconstructed shape was found to be a 99.75% match to the input radiograph. 2D error maps for depth and offset, computed as the per-vertex average of distances in 3D space between the predicted and original shapes, resulted in a mean depth error of 1.7mm compared to an average bone depth of 34mm, and a mean offset error of 1.3mm. The errors in depth prediction were found to be directly proportional to a change in the ratio of bone length and breadth to bone depth. Also, most of the offset and depth errors were edge artifacts, being consistent across all Test cases.

This study has demonstrated the potential for creation of the 3D shape for the proximal femur from a single 2D radiographic image. This technique may have a number of potential applications including derivation of volumetric density from areal BMD and 3D finite element analysis for prediction of the mechanical integrity of the proximal femur.

BRS-P22

DETERMINANTS OF SERUM FIBROBLAST GROWTH FACTOR-23 (FGF-23) IN CHRONIC KIDNEY DISEASE

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Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD)is a clinical syndrome that develops as a systemic disorder of mineral and bone metabolism in CKD. It is manifested by abnormalities in bone and mineral metabolism and /or extra-skeletal calcification. The involvement of parathyroid hormone (PTH) in CKD-MBD is well - recognised. The recently identified phosphaturic factor ; fibroblast-growth factor-23 (FGF-23) has been found to be elevated in patients with CKD, although the driving stimulus for the increase in FGF-23 remains unclear. It is postulated that FGF-23 may play a central role in the regulation of phosphate and therefore bone metabolism in these patients. The aim of this study was to investigate (1) the factors which influence serum FGF-23 in a population with CKD and (2) the association between markers of mineral metabolism including FGF-23 and BMD. We studied 129 ambulant patients (53 females and 76 males) attending the renal unit with a mean (SD) age of 53(14) years.Thirty five patients had an eGFR of >60 ml/min; CKD 2 'mean(SD) 79(14) ', 54 patients an eGFR between 30-60 ml/min; CKD3 'mean(SD) 46(9)' and 40 patients had an eGFR of <30 ml/min; CKD4 'mean(SD) 21(5)ml/min.BMD was measured at the lumbar spine (LS), femoral neck (FN), forearm (FA) and total hip (TH). Laboratory analyses including measurement of PTH, FGF-23, 25 (OH) vitamin D were undertaken. Univariate analyses and multiple linear regression models were used. Non-parametric data were log-transformed. Significant differences were observed in circulating FGF-23 (RU/ml)between patients with CKD 3 and CKD 2 (CKD3 73.1 (73), CKD2 55.7(56) p <0.05), CKD4 and CKD 2 (CKD 4 129 (203), CKD 2 55.7 (56) p <0.01). Univariate analysis showed a weak positive correlation between FGF-23 and PTH (r= 0.16, p= 0.07). Age (p=0.015), gender (p=0.032), eGFR (p=0.016) and CRP (p<0.00001) were significant independent predictors of FGF-23. A significant correlation between BMD at the hip and PTH was seen (p=0.023). FGF-23 did not correlate with BMD. Our study support the findings of increases in FGF-23 in early CKD. However FGF-23, in contrast to PTH does not influence BMD. The association of FGF-23 and CRP, an inflammatory marker merits further investigation.

BRS-P23

DIFFERENTIAL EFFECTS OF GLUCOCORTICOIDS ON FIBROBLASTS: MECHANISMS UNDERLYING THE ADVERSE EFFECTS OF THERAPEUTIC STEROIDS

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Therapeutic glucocorticoids have dramatic effects on tissues that arise from mesenchymal stem cell precursors. Glucocorticoids have been reported to decrease or increase proliferation in cultured primary osteoblasts. Tissue fibroblasts are closely related to osteoblasts but sensitivity of these cells to glucocorticoids has been less well studied. Synovial fibroblasts (SFs) are a major target of glucocorticoids in inflammatory arthritis whereas dermal fibroblasts (DFs) may be adversely affected in the same patient. It is unknown whether these

clinical differences are due to similar or distinct effects of glucocorticoids on fibroblast function.

We therefore examined the effects of glucocorticoids on proliferation, differentiation and apoptosis in matched primary cultures of synovial and dermal fibroblasts generated from synovium and skin obtained from patients undergoing joint replacement surgery (n=4). Treatment with either 100nM dexamethasone (DEX) or cortisol inhibited proliferation of DFs in both tritiated thymidine and FACS cell-cycle assays (e.g. 48+12% (mean+SD) decrease by tritiated thymidine; $p<0.01$). By contrast, proliferation of SFs was stimulated by glucocorticoids in both assays (29+13% increased cell number; $p<0.01$). Glucocorticoids substantially inhibited the expression of inflammatory genes (e.g. COX-2) in SFs but had little effect in DFs (mRNA expression decreased by 52% for SFs ($p<0.01$), but only 10% for DFs (NS)). Glucocorticoids decreased expression of type 1 collagen to a similar degree (59% with SFs ($p<0.01$), 54% with DFs). There was no difference in sensitivity to apoptosis as determined by MTT assay.

Fibroblasts from different tissues respond differently to glucocorticoid excess. The reduction in inflammatory gene expression in SFs is likely to be important in the beneficial effects of glucocorticoids in inflammatory arthritis whereas the reduced proliferation of DFs and decreased collagen formation are likely to account for the poor healing of skin in Cushing's. Whether skin or synovial fibroblasts reflect changes occurring in osteoblasts remains to be determined.

BRS-P24

DIFFERENTIATION FATES OF HUMAN MESENCHYMAL STEM CELLS IN IMMUNOCOMPROMISED MICE

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Human mesenchymal stem cells (hMSCs) were genetically-marked by using retroviral vectors encoding enhanced green fluorescent protein (eGFP). These cells were placed into a variety of tissue sites, including direct implantation into the tibialis anterior muscle (TAM) of immunocompromised mice (NOD/SCID and C.B-17 SCID/beige) and the cell fates and developmental potentials investigated. Some hMSCs survived for up to 12 weeks and the cell morphologies exhibited were seen to be dependent upon the residential site. Administration of hMSCs intravenously showed specific accumulation solely in the lungs and were rarely detectable elsewhere. Following implantation of hMSCs into the TAM in close proximity to bone tissue, reactive host callus formation as well as ectopic human bone formation were both seen to increase significantly compared with controls. eGFP and human RUNX2, alkaline phosphatase, osteocalcin, collagen type I and osteopontin mRNA expressions were seen in mice implanted with the labelled hMSCs but not in controls. Active clearance of the reactive callus and the ectopic bone was observed by osteoclast-like cells. It is concluded that the eGFP-marked hMSCs survive and differentiate morphologically into a variety of apparent mesenchymal phenotypes in vivo. Further studies are necessary to determine the full capacity and extent of the differentiation potentials of human marrow MSCs in this experimental system. However, whilst these cells are shown here to participate extensively in bone formation and turnover, any strategy to promote enhanced, prolonged osteogenesis is likely to require continuous supply of local bone-forming signals. In addition, the observed rapid clearance of formed osteogenic tissue necessitates modulation and restriction of host osteoclast/macrophage responses.

BRS-P25

E11 AND RHOA SIGNALLING DURING OSTEOCYTOGENESIS

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E11 is a transmembrane glycoprotein that we (and others) have shown to be one of the earliest markers expressed during osteocytogenesis. A link has been established between E11 expression and the activation of the small GTPase RhoA in several cell types (Martin-Villar et al. J Cell Sci. 2006) with the activation of RhoA resulting in increased cellular invasion into the extracellular matrix and thereby demonstrating a mechanism by which osteoblasts may become embedded in the osteoid.

We utilised the MLO-A5 (late osteoblast/early osteocyte) cell line to study the temporal expression patterns of RhoA and two other small GTPases Rac1 and Cdc42, as well as the RhoA effector protein ROCK, over a 15-day culture period. Expression was examined by RT-PCR and western blotting and the activity of RhoA was analysed using the GLISA assay, which is specific for GTP-bound RhoA. Expression of E11 and the matrix metalloproteinases MT1-MMP and MMP2 was measured by western blotting and quantitative RT-PCR.

RhoA, Rac1 and Cdc42 mRNA and protein expression was seen in the MLO-A5 cells by day 3 of culture and through to day 15. The active form (GTP-bound) of RhoA was shown to increase over time in culture, up to 2.5 fold by day 9. The expression of E11, MT1-MMP and MMP2 followed a similar pattern, increasing until day 9 before reaching a plateau. Messenger RNA from both isoforms of ROCK (I and II) was also present in the MLO-A5 cells.

Our findings show that activation of the RhoA signalling pathway is a feature of the differentiation of MLO-A5 cells and that there is a correlation between E11 expression and RhoA activation during this process. RhoA has also been linked to activation of both MT1-MMP and MMP2 and the expression pattern of these markers could suggest a signalling cascade involving E11-induced RhoA activation and subsequent activation of MT1-MMP and MMP2. This may be mediated by the RhoA downsteam effector protein ROCK, which is also expressed by these cells.

BRS-P26

FEMORAL NECK CUT HEIGHT IN THOMPSON HEMIARTHOPLASTY SURGERY

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Since the 1950's, the Thompson Hemiarthroplasty has been widely used in the UK for the treatment of displaced intracapsular neck of femur fractures (Lloyd, 2006). The prosthesis has a long neck and broad collar, and its successful implantation relies on making an accurate femoral neck cut, which ideally should be at the level of the intertrochanteric line (ITL). A margin of error allowing the cut to be up to 5mm above this is permissible, due to post-operative calcar resorption (Thompson, 1954). If the neck is too long, the literature predicts increased risk of femoral shaft fracture (Kwok, 1982), poor abductor function (Thompson, 1954), risk of dislocation (Pajarinen, 2002), and increased acetabular erosion (D'Arcy, 1976).We aimed to determine the range of neck cut heights (NCH) within a 3 month period at our Hospital, investigate any adverse outcomes and compare our results with national and international standards.

We retrospectively analysed our operative records for a 3 month period (March-May 2007) and identified 38 patients who had undergone Thompson Hemiarthoplasty. Data collected included Surgeon Grade, neck cut height (NCH) and any relevant complications recorded in the patient notes.

Of 33 patients analysed, 19 (58%) had unacceptable NCH's, of which 9 (27%) were greater than 10mm above the ITL. One patient sustained a dislocation and the hip was revised subsequently - NCH for this patient = 12.4mm ($p=0.14$). Another had a fall post-operatively whilst an in-patient and fractured the contralateral hip (NCH = 1mm). There were no intra-operative fractures, and due to the short length of follow-up, no acetabular erosion was recorded. Abductor function was not assessed. In hospital mortality was 13%.

The in-hospital mortality is comparable to national standards. Of note, although not statistically significant, the one patient who sustained a dislocation had a long neck cut. However, we have analysed 3 months of data in a large teaching hospital, and found that neck cuts are unacceptable in >50% of the operations audited. We recommend that guidelines are drafted and distributed to surgeons who routinely perform the Thompson Hemiarthoplasty to remind them of the importance of NCH in preventing complications.

BRS-P27

FGF-SIGNALLING AS A REGULATOR OF THE TRANSFORMED STATE OF OSTEOSARCOMA CELLS

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Signalling through the Fibroblast Growth Factor Receptor (FGFR) family is essential for normal skeletal development. Recently,

deregulated FGFR signalling has been described as an important factor in the development of cancers including breast and prostate. However, whether there is a similar role for FGF signalling in the development of skeletal malignancies has not been studied. Our analysis of a transgenic mouse model of osteosarcoma (OS) caused by overexpression of the c-Fos proto-oncogene demonstrated high levels of expression of both FGFR1 and FGFR3 protein in transformed osteoblasts in tumours from these mice. Furthermore, high levels of FGFR1 protein expression were seen at sites of tumour initiation, suggesting that signalling through this receptor may play a role at early stages of tumour formation. These results in mice led us to investigate the role of FGF signalling in the pathogenesis of human OS. Tissue microarray analysis demonstrated that approximately 70% of primary biopsies express high levels of FGFR1 and FGFR3. This number increased to 85% for FGFR1 in matched biopsies taken after chemotherapy, implicating signalling via FGFR1 as a possible mechanism of osteoblast survival in OS, implicating signalling via FGFR1 as a possible mechanism of osteoblast survival in OS.

Enhanced proliferative capacity and the ability to grow in anchorage-independent conditions are key features of malignant cells. We therefore studied the roles of FGF signalling in these processes in human OS cell lines. Activation of FGF signalling by bFGF had a mitogenic effect in two different human OS cell lines (MG-63 and U2OS). Furthermore, exogenous bFGF enhanced the capacity of U2OS cells to grow in anchorage-independent conditions. Reduction of FGF signalling using the chemical inhibitor, SU5402, had the opposing effects, with 10uM SU5402 inhibiting the anchorage-independent growth of both U2OS and MG-63 cells. Similarly, colony formation of OS cells derived from c-Fos transgenic tumours was inhibited by SU5402. Therefore, these data demonstrate that FGF signalling is important for the transformed state of both human and murine OS cells.

These results suggest a novel role for FGF signaling in the pathogenesis of OS and may present a new therapeutic target for their treatment.

BRS-P28

HIGHLY CONTROLLED SURFACE PRESENTATION OF PROTEIN SIGNALLING MOTIFS TO REGULATE BONE FORMATION

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Immobilised ligands have a profound affect on cell activity. In this study a protein engineering approach produced monolayer protein scaffold surfaces that maintain structure, orientation and hence bioactivity. Active motifs from bone morphogenetic protein (BMP)-2 and osteopontin (OPN) were inserted into a TolAIII protein vector; that was modified to contain a cysteine residue, which would chemiadsorb to gold in a similar way to a thiol molecule. The scaffold protein allows the active sequences to be displayed in a way that is orientated. Scaffold proteins were self-assembled onto gold surfaces from aqueous solution and monolayer binding confirmed by Surface Plasma Resonance (BIAcore). OPN-Tol dose-dependently supported the adhesion and spreading through vinculin adhesion sites of primary rat osteoblasts. Biological activity of the BMP motif was verified by adding the recombinant protein as part of the scaffold to cells transfected with a SMAD responsive-reporter construct demonstrating SMAD activation . This shows that the BMP2 motif in the scaffold protein has the potential to reproduce at least some aspects of BMP signalling. After growing cells on TolA-BMP2 and Tol-OPN surfaces for 28 days bone-like nodules were seen on BMP2 surfaces (11.6 ±4.2% total area) and this covered a significantly higher area of the surface than the TolAIII control(0.0195 ± 0.03%). The nodules were stained with Alizarin red, which showed more structured nodules on the BMP2 surfaces. Tol-BMP2 patterned by soft lithography, influenced the osteoblast monolayer to form discrete bone nodules only in Tol-BMP2 regions. Furthermore, exposure to Tol-BMP2 surfaces for 24 hours with subsequent replating on bare gold induced significant levels of mineralised matrix compared to bare gold or Tol alone. Recyling the 24 hour cell-exposed surfaces and plating on fresh cells demonstrated continued osteoblast differentiation indicating that the Tol-BMP2 had not been removed from the surface. Thus immobilising the proteins on the surface has not affected the properties of the proteins and the protein motifs have maintained their functionality. This technology effectively immobilises bioactive protein motifs on a surface for analysis of cell behaviour in vitro and provide the basis for future tissue engineering constructs.

BRS-P29

HUMAN FETAL PROGENITOR CELL RESPONSE TO OSTEOGENIC GROWTH FACTORS AND SERUM-FREE MEDIUM: A CELLULAR MODEL FOR SKELETAL DIFFERENTIATION

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Skeletal injuries present a significant socio-economic burden in an increasingly aged population. We have previously shown cell populations derived from human fetal femur tissue are capable of multi-potential differentiation and de novo bone formation and may provide a platform for tissue regeneration strategies. The aim of these studies was to determine if fetal femur-derived skeletal populations could provide a unique comparative model system for skeletal differentiation. Cells were isolated from human fetal femur tissue at 8-11 weeks post conception and primary cultures established in basal conditions (alpha-MEM/10% fetal calf serum) prior to application of osteogenic factors or chemically defined (serum-free) media (CDM). Expanded fetal populations demonstrated an average population doubling time of 21.5 +/- 1.0 hours, and displayed a normal karyotype over 20 population doublings. Widespread expression of the IgM antibody 7D4, targeted to the proteoglycan Versican, was observed by immunocytochemistry of fetal femur sections and flow cytometry analysis of day 12 basal cultures. The presence of skeletal progenitors (3-11%) was indicated using STRO-1 and comparable expression (4-11%) observed with 7D4. Subsequent culture in osteogenic conditions (ascorbate / dexamethasone) enhanced alkaline phosphatase (ALP) activity in a dose-dependent manner. However, addition of established osteogenic factors BMP-2, Pleiotrophin, Simvastatin or Vitamin D3 resulted in significantly reduced ALP activity in comparison to control cultures. Maintenance in a chemically defined medium generated a unique undifferentiated cell population, with comparable cell numbers to cultures grown in the presence of serum, however, cells exhibited significantly reduced ALP activity indicating dedifferentiation. Application of ascorbate/dexamethasone to CDM cultures resulted in increased ALP activity, however rescue of phenotype could only be achieved in the presence of serum. Ongoing studies including microarray analysis are focused on elucidating the mechanisms underlying the differential fetal progenitor cell response. These results indicate the potential of such a fetal model for phenotype rescue studies, screening assays and examination of skeletal differentiation in comparison to standard adult human bone marrow stromal cultures.

BRS-P30

HYPOXIA INDUCED DEATH PATHWAYS IN HUMAN TENOCYTES

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Degenerative tendon conditions are very common, painful and disabling. As a tissue tendon is poorly understood and this currently limits effective treatment. We have undertaken a detailed cellular and molecular study of biopsies across a spectrum of rotator cuff tears and find a disturbing loss of tenocytes, correlating with degenerating matrix and vasculature. Specifically, we find upregulation of the hypoxia-induced death gene BNIP3 in parallel with increasing apoptosis. Tendons are relatively avascular, are not generally considered to be at special risk from hypoxia and consequently little is known about tenocyte responses to reduced oxygen. We have therefore examined this in vitro using healthy primary human hamstring tenocytes within three passages of isolation. Hypoxia (0.1% oxygen) significantly induced tenocyte apoptosis after 24h, assessed by DAPI staining. Western blotting analysis further revealed that hypoxia inducible factor-1 alpha (HIF-1alpha) was rapidly induced from undetectable basal levels within 1h of exposure to hypoxic conditions. HIF-1alpha dramatically increased and reached a maximum level between 1h and 8h. Hypoxia also induced a sustained upregulation of BNIP3 and its

homolog Nix between 8h and 24h in tenocytes. In addition, the pro-apoptotic protein Bad was upregulated by 4h-16h of hypoxia. In contrast, hypoxia failed to induce changes in other pro-apoptotic proteins including Puma, Bim, Bak and Bax in tenocytes, although these pro-apoptotic proteins are reported to be upregulated by hypoxia in other cell types. Pro-apoptotic protein Noxa was below detectable level in human tenocytes following hypoxia treatment. Anti-apoptotic proteins Bcl2 and Bcl-xL were expressed in tenocytes and remained unchanged by hypoxia. These data indicate that tenocytes are sensitive to hypoxia and respond by activating classical HIF-1alpha-driven pathways. Furthermore, the specific pattern of upregulated death genes does not overlap completely with those in other tissues and at least one death gene, BNIP3, has now been detected in biopsies from degenerative rotator cuff, indicating a possible contribution to disease pathogenesis.

BRS-P31

IMPLANTATION OF CELL MICRO-PELLETS DERIVED FROM HUMAN EMBRYONIC AND ADULT STROMAL STEM CELLS INTO AN ARTICULAR CHONDRAL DEFECT IN THE RAT KNEE JOINT

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Cartilage injuries remain a common clinical problem. The intrinsic capacity for cartilage to repair is limited, resulting in poor functional repair. A regenerative approach focussing on cell-based therapy is a promising means to efficiently repair cartilage. We investigated the survival and engraftment of cells derived from human embryonic stem cells (hESC) or adult bone marrow stromal cells (hMSC) and their ability to promote regeneration after implantation into a chondral defect in the rat knee. hMSC cells were isolated from femoral bone harvested from patients undergoing orthopaedic surgery under informed consent. The H7-hES cell line was expanded in feeder free conditions using established techniques. hMSCs and Embryoid body-derived H7-hESCs were cultured for 14 days in a high-cell density system to induce chondrogenic differentiation and implanted into a chondral knee defect in both adult WT and nude male rats. Pre-labelling with the fluorescent probe CM-Dil (20 microM; Molecular Probes) allowed tracking of implanted cells. Empty defects served as controls. At 21 days post-implantation samples were collected and histologically assessed for repair and for persistence of implanted human cells.

Labelled hESC and hMSC-derived cells could be detected in both nude and WT rats within the defect area. Histological analysis revealed that the repair tissue within the defect containing implanted adult and embryonic-derived cells consisted of a more cartilaginous tissue type than if the defect was left empty. A histological scoring system modified from Wakitani score (J Bone Joint Surg, 1994) was used to assess the efficacy of the repair, including cell morphology, matrix-staining, architecture of the implanted defect, surface regularity, formation of the tidemark and integration with the adjacent host cartilage and the underlying subchondral bone integrity. Preliminary observations suggest that the implantation of human stem cells improves the overall histological grading of the repair of the chondral defect in knees of WT animals compared to controls (8.6 ± 2.1 and 18.3 ± 1.4 respectively). Further characterisation of the regenerate tissue within the lesion is ongoing. These findings describe the survival and engraftment of chondrogenic differentiated cells derived from hESCs after implantation, supporting their potential future use as therapies for cartilage repair.

BRS-P32

IN VITRO BONE GROWTH RESPONDS TO TISSUE-LEVEL MECHANICAL STRAIN IN THREE-DIMENSIONAL POLYMER SCAFFOLDS

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This study tests the hypothesis that differences in local mechanical strains within a cyclically compressed scaffold predict differences in local mineralization.

Twelve cylindrical PLLA scaffolds (Ø9_4 mm, porosity 90%) were scanned with a micro-CT scanner (resolution 15 µm). The voxel data was used to calculate local strains due to compression inside each scaffold, using micro-Finite Element (micro-FE) analysis. Osteoblastic cells grown from rat tibia bone chips were cultured until second passage. Six scaffolds (B1) were seeded with 2.5 million cells and six (B2) with 5 million cells. Seeded scaffolds were kept for two (B1) or three (B2) weeks in static conditions after which they were cyclically compressed (1 Hz, 1.5% strain) one hour per day, for a period of one week. After culturing, each scaffold was re-scanned to determine the distribution of mineralized nodules. The micro-FE data was used to determine the largest principal strain at the pore surface at the site of each mineralized nodule. To compare between strains at mineralized and non-mineralized sites within single scaffolds, we also determined the largest principal strain at the pore surface at 200 non-mineralized sites.

Compression gave a highly non-homogeneous distribution of local strains at pore surfaces, with compressive/tensile and high/low magnitude strains in close proximity. After culture, the average number of mineralized nodules per scaffold was 36±18SD (B1) and 59±24SD (B2). The average value of the absolute largest principal strains at mineralized sites was 2-4 times larger than that at sites without a nodule for each individual scaffold (0.021 vs. 0.007%; $p<0.001$, Wilcoxon signed-rank test).

When comparing strain magnitude between sites in the scaffolds that did and did not form mineralized nodules, average strains were 2-4 times larger at sites that formed a nodule. This suggests that bone cells in a 3-D environment are sensitive to the absolute magnitude of the local surface strain. The range of average surface strains at sites where a nodule formed (<0.1%) is comparable to strain levels that induce formation of mineralized nodules on deformable 2-D membranes with similar cells and culture conditions.

BRS-P33

INFLUENCE OF 25-HYDROXYVITAMIN D ON BONE HEALTH: RESULTS FROM THE EUROPEAN MALE AGEING STUDY (EMAS)

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Vitamin D is an important factor in maintaining bone health. The aim of this study was to determine the influence of vitamin D on measures of bone health in middle aged and elderly European men.

Men aged between 40 and 79 years were recruited from population registers in 8 European centres for participation in a prospective study of male ageing: the European Male Ageing Study (EMAS). Subjects were invited by letter to attend for an interviewer-administered questionnaire, quantitative ultrasound (QUS) of the calcaneus (Hologic - SAHARA) and a fasting blood sample from which 25-hydroxyvitamin D3 levels were assayed. The questionnaire included the Physical Activity Scale for the Elderly (PASE). In two of the recruitment centres, the men attended also for dual energy X-ray absorptiometry (DXA) of the hip and spine (Hologic QDR 4500 Discovery). Height and weight were measured in all subjects. The relationships between the QUS parameters (broadband ultrasound attenuation 'BUA' and speed of sound 'SOS'), DXA measurements (BMD of the femoral neck, total hip and lumbar spine) and 25-OHD were assessed using linear regression with adjustments made for age, height, weight, PASE score and centre.{BR}3259 men, mean age 60.0 years (standard deviation 'SD'=11.0) were included in the analysis. Their mean BUA was 80.2 dB/MHz (SD=19.0) and SOS 1550.7 m/s (SD=34.1). 768 subjects had DXA measurements. Mean BMD at the femoral neck was 0.806 g/cm2 (SD=0.127), total hip 1.013 g/cm2 (SD=0.145) and lumbar spine 1.054 g/cm2 (SD=0.176). Mean 25-OHD was 25.0 ng/ml (SD=12.7). After adjusting for age, height, weight, PASE score and centre, higher levels of 25-OHD were associated with higher BUA (beta coefficient per 10 ng/ml change in vitamin D =0.735; 95% confidence interval 'CI' 0.188, 1.282) and SOS (beta coeff per 10 ng/ml change=1.781; 95% CI 0.791, 2.771).

Similarly, higher 25-OHD levels were associated with increased BMD at the femoral neck (beta coeff per 10 ng/ml change =0.010; 95% CI 0.004, 0.017), total hip (beta coeff per 10 ng/ml change =0.013; 95% CI 0.005, 0.020) and lumbar spine (beta coeff per 10 ng/ml change =0.012; 95% CI 0.002, 0.021).

In this population survey of middle aged and elderly European men, higher levels of 25-OHD were associated with increased bone mass and bone ultrasound parameters.

BRS-P34

KERATIN 18 IS UPREGULATED IN CELLS FROM PAGETIC LESIONS AND AFFECTS GENE EXPRESSION IN HUMAN OSTEOBLASTS

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Paget's disease is characterised by focal regions of accelerated bone turnover. The osteoclasts within the pagetic lesion are larger than normal osteoclasts and contain a higher number of nuclei. Given the tight coupling between osteoclasts and osteoblasts and the important role that osteoblasts play in the regulation of osteoclast activity, we investigated the possibility that pagetic osteoblasts also play a role in the development of the disease. We have collected RNA from osteoblasts and bone marrow grown from pagetic and control, non-pagetic bone. Microarray analysis identified a number of genes that were differentially regulated in the pagetic osteoblasts, suggesting that the osteoblasts within the pagetic lesion differ from those in normal bone. The intermediate filament keratin 18 was one of the most highly upregulated genes in osteoblasts from pagetic lesions (6.8-fold increase compared to non-pagetic controls, p=0.04). Real time RT-PCR in 14 pagetic and 28 non-pagetic osteoblast samples, and in 14 pagetic and 21 non-pagetic bone marrow samples confirmed that keratin 18 was upregulated more than 3-fold in pagetic osteoblasts and bone marrow. In order to investigate the effects of over-expression of keratin 18 in osteoblasts, we have transduced primary human osteoblasts with an adenoviral vector expressing keratin 18 and compared these to cells transduced with a control vector. Real-time RT-PCR analysis showed that over-expression of keratin 18 altered the level of expression of several genes. These changes included increased expression of bone morphogenic protein 6 and the chemokine MCP1. In the SaOS2 human osteosarcoma cell line, over-expression of keratin 18 induced the expression of MCP1 and interleukin 6. Interestingly, MCP1 and interleukin 6 were also upregulated in the pagetic osteoblasts tested on the microarrays. These results suggest that keratin 18 plays a role in osteoblast biology, and over-expression of this gene can reproduce some of the features of pagetic osteoblasts.

BRS-P35

LOVASTATIN MODULATES CHONDROCYTE CELL CYCLE AND MATRIX OUTPUT

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Upon differentiation chondrocytes begin to produce large amounts of sulphated glycosaminoglycans (sGAG) and collagen II. Recent studies have implicated cytoskeletal remodelling in control of this process. Inhibition of the small GTPase Rho and its downstream effector Rho kinase (ROCK) have been found to promote chondrogenesis. The prenylation of Rho by geranylgeranyl transferase I causes sequestering to membrane surfaces, allowing interaction with other signalling molecules. Statins inhibit protein prenylation and thus Rho signalling. We therefore set out to examine whether the statins could affect chondrocyte differentiation.

The ATDC5 cell line, which recapitulates chondrogenesis in vitro, was seeded into plasticware coated with 2% agarose allowing the formation of three dimensional micromasses. These were cultured for two weeks in the presence or absence of chondrogenic medium (containing insulin and ascorbic acid) and with varying concentrations of lovastatin. Cells were seeded as 100,000 and one million cells per micromass and were either treated directly or grown in differentiation medium for 1 week before statin treatment commenced. Upon harvesting, sGAG content was determined by dimethylmethylene blue assay and corrected for DNA content. Significance was determined using one way ANOVA with Dunnett post hoc testing. Safranin O, PCNA, TUNEL, actin-phalloidin, Sox 9, Collagen I and Collagen II staining were performed.

The chondrogenic medium alone caused a rapid increase in micromass size which was more pronounced in the smaller pellets. This was partly due to an increase in cell proliferation. Additionally, per cell sGAG concentration increased. Lovastatin inhibited prenylation of the Rho family member Rap 1a at doses from 0.1 to 1 micromolar in these pellet cultures as confirmed by Western blot and also induced changes in the arrangement of the actin cytoskeleton. Treatment with lovastatin caused a dose-dependent decrease in cell proliferation. Combination treatment of ATDC5s, either directly or following a differentiation period, with chondrogenic medium and lovastatin caused a three-fold dose-dependent-increase in per cell sGAG concentration, greater than that caused by chondrogenic medium alone ($p<0.01$).

Statins induce remodelling of the actin cytoskeleton in chondrocytes and inhibit cell proliferation. Per cell matrix output is increased, suggesting enhanced chondrocyte differentiation.

BRS-P36

MUTATIONS IN RANK ASSOCIATED WITH PAGETIC DISEASES CAUSE LACK OF SIGNAL PEPTIDE CLEAVAGE AND FORMATION OF ORGANISED SMOOTH ER WHEN OVEREXPRESSED IN OSTEOCLASTS

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Early onset Paget's disease of bone (ePDB), Familial Expansile Osteolysis (FEO) and Expansile Skeletal Hyperphosphatasia (ESH) result from heterozygous insertion mutations in the signal peptide region of RANK. They are characterised by focal areas of increased bone resorption due to hyperactive osteoclasts. We have previously shown that these mutant RANK proteins do not localise to the plasma membrane, but accumulate within organised smooth endoplasmic reticulum (OSER) when overexpressed in HEK-293 cells. The aim of this study was to determine the localisation of mutant RANK when overexpressed in osteoclasts and to investigate whether this mislocalisation could be due to lack of signal peptide cleavage.

Mutant RANK proteins were overexpressed in human osteoclasts by adenoviral transduction. Immunostaining and confocal microscopic analysis demonstrated that FEO-RANK did not localise to the plasma membrane, but accumulated within circular structures in the cytosol. Transmission electron microscopy of transduced osteoclasts confirmed that these structures represent OSER within osteoclasts overexpressing FEO-RANK, but not WT-RANK. To investigate whether the presence of FEO, ePDB or ESH mutations results in lack of signal peptide membrane cleavage of the RANK protein, two in vitro translation assays were used. The size of translated proteins produced in the Xenopus egg extract translation system (XEE; post-translational modification can take place) were compared to the size of those translated in a rabbit reticulocyte lysate (RRL; no post-translational modification can take place). The size of WT-RANK was larger when translated in the RRL system, suggesting that signal peptide cleavage occurred as expected in the XEE system. By contrast, there was no difference in the sizes of FEO-, ePDB- and ESH-RANK between the RRL and XEE systems, demonstrating that no signal peptide cleavage had taken place.

Overexpression of disease-associated RANK proteins in human osteoclasts induces OSER formation. Since overexpression of ER-resident membrane proteins results in the formation of OSER, it appears that the lack of signal peptide cleavage effectively converts RANK into an ER-resident protein, preventing localisation to the plasma membrane. Further study is required to determine why this might lead to a hyperactive osteoclast phenotype.

BRS-P37

OSTEOBLAST MATURITY DICTATES RESPONSE TO VASCULAR ENDOTHELIAL GROWTH FACTOR

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Vascular endothelial growth factor (VEGF) has a multifaceted role in bone remodelling influencing early osteoblastogenesis, promoting angiogenesis to aid bone repair and chemo-attraction of several cell types needed for bone formation. Consequently, VEGF is a good candidate for therapeutic strategies in bone healing and tissue engineering. The aim of this study was to characterise osteoblast responsiveness to VEGF during osteogenesis.

Isolated rat calvarial osteoblasts were treated with recombinant VEGF165. Cellular responses to VEGF including proliferation, differentiation and extracellular matrix mineralization were assessed using an MTT assay, by measuring Alkaline Phosphatase activity and Von Kossa staining respectively. Short term responses to VEGF treatment were also investigated by Western blotting with antibodies against phospho-p44/42 and phospho-Akt. RT-PCR with primers for VEGFA, B, C, D, VEGF Receptors 1, 2, 3 and Osterix, Runx2, Alkaline Phosphatase, Osteocalcin, Osteopontin, and BMP2 were used for transcript profiling while Taq-Man PCR was used to quantify transcription levels.

Treatment of osteoblasts with VEGF (1ng/ml - 10ng/ml) under osteogenic conditions for 14 days did not influence alkaline phosphatase activity. Treatments of osteoblasts with VEGF (1ng/ml - 10ng/ml) for up to 28 days significantly increased mineral deposition and enhanced bone nodule formation compared to controls (ANOVA, P=0.042). To characterise how VEGF influenced bone formation, its activity was assessed on immature bone cells. In proliferation assays VEGF had no effect on early osteoblasts though some evidence of signal transduction was observed with Akt activation. To further clarify if VEGF responsiveness in our culture system was differentiation dependent, experiments were performed to analyse VEGF-related transcripts at 0, 7, 14, 21 and 28 days. RT-PCR identified transcripts for VEGF isoforms and receptors with apparent changes in mRNA abundance over time. VEGFR3 transcripts declined as osteoblast maturation progressed while VEGFR2 mRNA levels were upregulated. VEGFR1 mRNA levels remained unchanged. Furthermore, transcripts for Osteocalcin and both differentiation factors Runx2 and Osterix were upregulated at 24h-48h when osteoblasts matured for 21 days were treated with VEGF whilst immature cells were unresponsive, as supported by recent quantitative-PCR data.

We hypothesise that osteoblast maturity dictates the ability to respond to VEGF and this is driven by differential VEGF receptor expression.

BRS-P38

OSTEOBLAST-LIKE CELLS WITH THE LRP5 GAIN OF FUNCTION MUTATION SHOW GENDER-RELATED DIFFERENCES IN BASAL PROLIFERATION BUT NO ENHANCED RESPONSE TO MECHANICAL STRAIN

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The G171V gain of function mutation in the Wnt co-receptor Lrp5 (Lrp5+) is associated with high bone mass and a greater responsiveness to loading '1' in females than in males '2'. We investigated this gender-related difference in bone cells in vitro.

Primary osteoblast-like cells were isolated from long bones of 19-week-old Lrp5+ mice and their WT littermates. These cells were grown and fixed on days 2, 4, 6 and 8 after seeding. The effects of strain were assessed by cell counting 48h after subjecting cultures to a single period of different peak dynamic strains (1Hz, 600cycles) by 4-point bending of the plastic strips on which they were seeded

Both male and female Lrp5+ cells proliferated more rapidly than male and female WT cells respectively (MLrp5+vs MWT $p<0.001$; MLrp5+vs FWT $p<0.001$; FLrp5+vs MWT $p<0.001$; FLrp5+vs FWT $p<0.001$). Female Lrp5+ cells proliferated significantly faster than males Lrp5+ cells ($p<0.001$). There was no gender-related difference in WT cells. Peak strains of 3400 microstrain stimulated a significant increase in cell number in female WT (16.7%, $p<0.05$) and Lrp5+ cells (24.3%, $p<0.001$). There was no difference in strain responsiveness between female WT and Lrp5+ cells (FWT 16.7%, FLrp5+ 24.3%). Lower strains elicited no proliferative response in cells from either sex or genotype.

These data demonstrate that the Lrp5+ mutation is associated with significant differences in basal proliferation rate of primary osteoblast-like cells of both sexes. Proliferation is significantly higher in females than males. Strain stimulates proliferation in both WT and Lrp5+ cells but there is no difference in these responses. These data do not support the high bone mass of the Lrp5+ mutation being due to inherent higher sensitivity of osteoblast-like cells to mechanical strain.

1.Akhter et al., (2004) Bone, 35: 162-169, 2.Saxon et al., (2007) JBMR, 22, Suppl 1: S523

BRS-P39

OSTEOCALCIN AS A PROGNOSTIC INDICATOR FOR BONE METASTASIS IN DUCTAL BREAST CANCER

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Osteocalcin is a noncollagenous protein found in bone and dentin. It is synthesized in bone by osteoblasts and clinical studies have shown that the circulating level reflect the rate of bone formation which is increased in patients with skeletal metastases. Osteocalcin transcript levels have not previously been investigated to determine a relationship their levels and prognosis.

To investigate whether osteocalcin transcript levels can be used to predict the occurrence of bone metastases in the largest group of breast cancers, the ductal carcinomas.

Primary ductal breast cancer tissues (n =90) and non-neoplastic mammary tissue (n = 32) were collected and patients were routinely followed up clinically after surgery. The immunohistochemical distribution and location of osteocalcin was assessed in the normal breast tissue and carcinoma and the level of osteocalcin transcripts in the frozen tissue was determined using real-time quantitative PCR. The results were analysed against the clinical data looking principally at the levels in patients with different prognostic out comes, metastasis, local recurrence, skeletal metastasis and death but also in relation to indicators of poor prognosis: the nodal involvement, ER status and the Nottingham Prognostic Index.

The osteocalcin transcript levels were significantly lower in all the patients who demonstrated some evidence of recurrence or metastasis. Compared to patients who were disease free at follow-up the transcript levels in patients with metastases ($p=0.050$), local recurrence ($p=0.050$) and skeletal metastases ($p=0.050$) were all significantly lower. In patients who had died from breast cancer at follow-up also had a lower level of transcripts ($p=0.081$). Indicators of poor prognosis such as nodal involvement, ER status and Nottingham Prognostic Index did not show a significant difference.

In ductal carcinoma decreased levels of osteocalcin correlated with a poor prognosis. The data suggests that osteocalcin expression is of clinical significance with patient with low levels suffering from a cancer with a more aggressive phenotype making them more susceptible to local recurrence, general metastasis and most relevantly skeletal metastases.

BRS-P40

OSTEOCYTES HAVE MORE CAVEOLAE THAN OSTEOBLASTS

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Caveolae are invaginations of the cell membrane. Their core structural proteins, caveolins, interact with cell signaling molecules, including endothelial nitric oxide synthase (eNOS). Caveolin-1 is known to keep eNOS in an inactive state within the caveolae, where it may be activated following exposure of the cell to mechanical force such as fluid shear stress. NO production is considered a crucial early response in mechanically stimulated endothelium and bone. eNOS null mice have a reduced bone mass due to an osteoblast defect, whereas caveolin-1 null mice show increased bone stiffness and size because of accelerated osteoblast maturation. The relationship between caveolae and eNOS is not yet understood in osteoblastic cells. Our aim was to examine caveolae numbers in osteoblastic and osteocytic cells.

Primary osteoblasts (pOB) and osteocytes (pOCY) were obtained from C57Bl6 wildtype mice calvaria, pOB from similar eNOS null tissue, and compared with the murine cell-lines MC3T3 osteoblasts and MLOY4 osteocytes. Cells were examined using transmission electron microscopy (TEM) either confluent or non-confluent (60-70%). Caveolae are expressed as median number per mm cell boundary. Caveolins 1 and 2 were estimated using immunofluoresecence and western blotting.

TEM showed that MLO-Y4 and pOCY had a significantly higher number of caveolae (93/mm) than osteoblasts (20/mm), P=<0.001. There was no difference between the number of caveolae in the apical and basal side of the cells (P=0.30). Confluent cells showed more clusters of caveolae than non-confluent cells (P=<0.001). eNOS null pOB had a significantly higher number of caveolae (48/mm) than C57Bl6,P=0.011, yet similar to numbers found in MC3T3s (47/mm). MLOY4s contained the same amount of caveolin-1, but more caveolin-2 than osteoblasts, as normalized per cell number. Immunofluorescence staining confirmed caveolin-1 on plasma membranes in all cells and demonstrated an intracellular accumulation of caveolin-2 in MLOY4s and pOCYs.

Caveolae are clearly evident in all osteoblastic cells, and confluent cells have more of them. Why eNOS null osteoblasts have more caveolae than wildtype is intriguing and the functional implications need further study. Importantly, we consistently find that osteocytes have significantly higher numbers of caveolae than osteoblasts. We propose this may have implications for their mechanosensory properties.

BRS-P41

OSTEOCYTES REPAIR PLASMA MEMBRANE DISRUPTION FOLLOWING PHYSICAL INJURY IN VITRO

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Microdamage in bone contributes to fractures and acts as a stimulus for bone remodeling. The cause of osteocyte death near the microdamage site is unknown but it is hypothesized that it may be the physical damage of the osteocyte itself. In light of a number of studies suggesting that the rapid repair of plasma membrane disruption is possible and essential to cell survival here we have tested the ability of osteocytes to survive damage and estimated the rapidity of the repair in response to hormone treatment prior to injury.

We have developed a cell-wounding model using the osteocyte-like cell line MLOY4. Propidium iodide (PI) uptake was used to estimate cell wounding and repair over time. The cells were incubated in the presence or absence of either rhPTH (50nM) rhGH (100ng/ml) or 17 beta oestradiol (100nM) for one hour after which time they where injured using a sharp blade and PI was added at 0 seconds - 2 minutes, 5 minutes, 30 minutes and 24 hours post injury to identify the cells that failed to reseal over time. Lack of cell membrane repair was expressed as a percentage of total cells on the cut using 4', 6-diamidino-2-phenylindole (DAPI +ve) that remained leaky to PI (PI +ve). It was found that large numbers of osteocytes were capable of re-sealing their plasma membrane and surviving following mechanical injury. At 0 seconds - 2 minutes 18.5% ± 0.93 (SEM) of the cells had been damaged however repair was increased over time with only 3% ± 0.32 (SEM) cells still damaged after 24 hours. Pre treatment with either rhPTH, rhGH or 17 beta oestradiol significantly accelerated repair such that the PI +ve cells reduced to less than or equal to 9 % ± 0.14 (SEM) at 0 seconds - 2 minutes and 0.86% ± 0.089 (SEM) by 24 hours. While the exact mechanism of repair is currently under investigation it will be interesting to determine whether the saving effect is distinct to each compound. These findings may provide a new understanding of how osteocytes sense and respond to injury and the potential of therapeutical compounds to maintain osteocyte viability in disease and old age.

BRS-P42

PERSISTENCE OF FUNCTIONAL HUMAN OSTEOGENIC STEM CELLS FOLLOWING IN VIVO IMPLANTATION IN A RAT CALVARIAL LESION

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The development of cell-based therapies using human stem cells requires extensive, preclinical examination in appropriate animal models to yield information on their efficacy.

Either human embryonic stem cell (hESCs)- or human bone marrow stromal cell (hMSCs)-derived osteoprogenitor cells, mixed with human demineralised bone (DBM) were implanted in a critical sized calvarial defect in immunocompetent (Sprague-Dawley; WT) and immunodeficient (RNU-'Foxn1'/'rnu'; nude) rats to investigate their engraftment and cellular response in the regenerate two weeks post-implantation.

Human cells were detected only in nude rats by FISH (Fluorescent in situ hybridization for human DNA) analysis two weeks post-implantation. Both hMSCs and hESCs engendered a significant increase in bone formation compared to DBM alone in these animals as visualised by Von Kossa staining. No differences in bone formation were detected in any treatment groups in WT animals. RT-PCR analysis for human specific osteocalcin revealed the presence of this gene in cells isolated from within the lesion in nude animals implanted with cells, indicating the maintenance of an osteoblastic phenotype. Using in situ nick translation, significantly lower numbers of apoptotic cells were detected at the lesion site in nude compared to WT animals (P=0.015 & P=0.009 for hMSC & hESC respectively). This difference was not observed when DBM alone was implanted (P=0.1). Interestingly, in WT animals, the presence of human cells within the defect area appeared to increase the degree of apoptosis. All animal groups showed a good angiogenic response at the defect site (presence of endothelial marker vWF) 14 days post-implantation.

These data suggest that the differences in the apoptotic response between nude and WT rats may impact on their osteogenic response and be related to the characteristics of their immune systems. Here we provide evidence that osteoprogenitor cells derived through directed differentiation from hESCs or hMSCs can survive, maintain an osteoblastic phenotype and enhance bone regeneration in a calvarial defect. However our data also suggest that xenoreactivity and its influence on engraftment of implanted human cells in animal lesions are important considerations in the use of animal models in the development of cell based therapies.

BRS-P43

PLATELET-DERIVED GROWTH FACTOR STIMULATES OSTEOPROTEGERIN PRODUCTION IN OSTEOBLASTIC CELLS

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Osteoprotegerin (OPG) is a major regulator of osteoclastogenesis, bone resorption and vascular calcification. Identifying growth factors that influence the production of OPG increases our understanding of bone metabolism and could lead to improved treatments for conditions such as osteoporosis and hypercalcaemia of malignancy. Platelet-derived growth factor (PDGF) is a potent mitogen and chemo attractant and has previously been described as a factor released from osteoclasts responsible for inhibiting osteoblastogenesis.

PDGF has also been reported to stimulate the production of OPG in vascular smooth muscle cells in a model of atherosclerosis. To our knowledge, no further investigations concerning OPG regulation by PDGF have been published to date. While studying the regulation of OPG production in osteoblastic cells in vitro we observed that PDGF stimulated OPG production in two human osteosarcoma cell lines (MG63, Saos-2) and one mouse pre-osteoblastic cell line (MC3T3-E1) by 152%, 197% and 113% respectively over 24 hours. OPG was measured in culture medium by ELISA. Using signalling inhibitors we demonstrate that PDGF signals through ERK and not via p38, NFkappaB, or JNK. When MC3T3-E1 cells were incubated for 7 days

in osteoblast differentiation medium containing ascorbic acid, dexamethasone and beta-glycerophosphate, the OPG response to PDGF was attenuated. A more differentiated human osteoblastic cell, hFOB, did not show an increase in OPG in response to PDGF. Our results highlight how the differentiation status of osteoblastic cell lines affects the ability of PDGF to stimulate OPG production.

These findings suggest a role for PDGF in countering the resorptive effects of inflammatory cytokines produced during fracture healing by stimulating the production of OPG.

BRS-P44

PODOSOME BELTS CORRELATE WITH RESORPTIVE ACTIVITY BY OSTEOCLASTS ON PLASTIC

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Osteoclasts resorb bone by adhering to the bone surface and forming a peripheral sealing zone (actin ring), within the confines of which the cell secretes protons and hydrolytic enzymes. Resorptive activity is likely to be undertaken only by osteoclasts that are on a bone surface. The question arises, what are the characteristics of the substrate that induce resorptive activity in osteoclasts?

When osteoclasts are incubated on plastic or glass substrates they can form belts of podosomes that resemble the actin rings formed by osteoclasts during bone resorption. However, the relationship between podosome belts and actin rings is controversial. We therefore decided to analyse this relationship by comparing makers of resorptive behaviour in osteoclasts expressing actin rings and podosome belts. In the presence of RANKL, osteoclasts form actin rings spontaneously on bone, and form podosome belts on vitronectin- or collagen-coated plastic. We have previously found that secretion of tartrate-resistant acid phosphatase (TRAP) by osteoclasts on bone correlates with bone resorption. Therefore, we tested the correlation between podosome belts, actin rings and TRAP release by osteoclasts on plastic and bone. To do this, osteoclasts were generated from non-adherent bone marrow cells by incubation in RANKL and M-CSF for 5 days. The osteoclasts were then lifted into suspension and sedimented onto slices of devitalised bovine bone, or onto plastic coverslips previously coated with vitronectin, collagen or fibronectin.

Both vitronectin and collagen stimulated TRAP release from osteoclasts on plastic. TRAP release was up to ten times greater with than without vitronectin, and was over three times greater than on bone. TRAP release on collagen was biphasic, rising to twice the level induced by bone before falling at higher densities. The proportion of osteoclasts exhibiting podosome belts on plastic correlated with TRAP release for both vitronectin- and collagen-coated plastic. In contrast, osteoclasts on coverslips coated with fibronectin neither released TRAP nor formed podosome belts.

These results suggest that vitronectin- and collagen-coating of plastic induces resorptive behaviour in osteoclasts, and that, despite the difference in appearance, podosome belts, like actin rings, signify actively resorbing cells.

BRS-P45

PRIMARY HUMAN OSTEOBLASTS CONTAIN A GREATER NUMBER OF K2P CHANNELS THAN OSTEOSARCOMA CELL LINES

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Twin pore domain potassium (K2P) channels are widely expressed throughout the body, and have a variety of roles including setting the resting membrane potential, responses to hypoxia and pH changes, and in mechanotransduction. Recently, one member of the K2P family, TREK-1, has been reported to be present in human osteoblasts. However, the presence and role of other K2P channels in bone cells remains unknown.

Primers were designed to target all functional K2P channels. Preliminary studies in rat osteoblasts and UMR-106 cells identified mRNA encoding for TASK-1, TRAAK and TWIK-2. Screening moved onto the human cell lines TE-85, MG-63 and SaOS-2 which represent increasing stages of differentiation according to their expression of osteoblastic markers. The data from human-derived MG-63 and SaOS-2 cells was similar to that earlier described in the rat. TE-85 cells express TASK-2, TWIK-1 & TREK-1 channels in addition to the others. Primary human osteoblasts contained all of the K2P channels covered so far, and also the 'H+' sensitive channels TASK-3 & -5.

The TE-85 cell line represents a model of less-differentiated osteoblasts. The large number of channels observed in this cell line could point to a role for K2P channels in early osteoblast function and differentiation. Primary human osteoblasts in culture may require K2P channels more mature osteoblast functions. TASK-1 has been shown to be highly sensitive to small fluctuations in physiological pH. The TRAAK channel produces an outwardly rectifying current in response to unsaturated fatty acids and stretch. TWIK-2 is a weak outward rectifier thought to be important in setting membrane potential. Possible roles for these channels in bone include involvement in pH-sensitive and mechanosensitive bone remodelling.

Further work aimed at clarifying the significance of the RT-PCR results using immunocytochemistry and Real-Time PCR is on-going. We have already confirmed the expression of several channels using commercially available antibodies. Real-Time PCR will enable us to directly compare the level of expression between cell lines, and permit functional studies to measure transcriptional changes in response to modulators of bone formation.

BRS-P46

PROTEOMIC IDENTIFICATION OF PRENYLATED RAB/SMALL GTPASE PROTEINS IN HUMAN OSTEOCLASTS

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Rabs are a large family (>70 members) of small GTPases that play a crucial role in the regulation of intracellular vesicular trafficking. The correct subcellular localisation, and therefore function, of these proteins is dependent on prenylation, which involves the attachment of isoprenoid groups to C-terminal cysteine residues. We have found that anti-resorptive phosphonocarboxylate drugs specifically inhibit Rab prenylation, highlighting the critical role of these GTPases for osteoclast function. However, the expression profile and role of specific Rab GTPases in osteoclasts remains poorly understood. We have therefore employed a proteomic approach to identify the Rab GTPases that are highly expressed in osteoclasts.

PBMCs were isolated from whole blood of healthy volunteers and osteoclasts generated by culturing with M-CSF and RANKL. Osteoclasts were then lysed in buffer containing triton X114, which enabled enrichment of the Rab GTPases following fractionation into aqueous and detergent-rich phases, into which the prenylated Rab proteins partition. Enriched proteins were then separated by 2D SDS-PAGE and prenylated Rabs identified by overlaying with an identical gel from lysates of cells in which Rabs had been metabolically labelled using '14C'mevalonate. Selected spots were trypsin-digested and proteins identified by peptide analysis using MALDI-ToF. In addition, proteins enriched as above were separated by 1D SDS-PAGE, then spots corresponding to the molecular weight of Rabs (21-28kDa) were picked for analysis by LC-MS/MS.

Using these approaches we have identified 19 Rabs in human osteoclasts (all 19 by LC-MS/MS, but only 8 using MALDI-TOF), as well as Rap1, a prenylated GTPase that we previously showed to be highly expressed in osteoclasts. The Rabs identified include several that have been previously described in osteoclasts, including Rab7, Rab3D, Rab6 and Rab11 but also several that have not previously been described in osteoclasts, including Rab18, for which there is no known role in any cell type. Using western blotting and immunostaining, we have confirmed that Rab18 is expressed in vesicular structures in osteoclasts, and we are now analysing the function of Rab18 in osteoclasts using adenoviral delivery of a dominant-negative form and knockdown of expression using siRNA.

BRS-P47

STIFF WRISTS DO BADLY - WHAT DETERMINES RATE OF RECOVERY OF GRIP STRENGTH AFTER DISTAL RADIAL FRACTURE?

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Grip strength is adversely affected by distal radial fracture, but the factors affecting the rate at which patients recover grip are unclear. A

cohort of 34 patients with displaced distal radial fractures (severe enough to require initial fixation with intrafocal (Kapandji) wiring) were followed for six months after fracture. All patients had an acceptable position on x-ray at six weeks after fracture. Patients were treated in plaster until wires were removed at 5 weeks and were assessed at 6, 12 and 26 weeks for ranges of wrist movement, grip strength, and pain (VAS). We found progressive recovery with time but, compared with the opposite wrist, grip recovery was still incomplete at 6 months. Rate of recovery of grip and ROM were not related to either the preoperative or final dorsal or radial angle. There was a striking correlation between arc of flexion/extension at 6 weeks and proportion of grip (fracture side/ normal side) strength returned at 6, 12 and 26 weeks (Spearman r= 0.81, 0.75 and 0.54, all p<0.001). The grip at 12 and 26 weeks was more closely correlated with flexion/extension at 6 weeks than the contemporaneous arc of flexion/extension. Pain on activity at 6 weeks was related to grip at 6, 12 and 26 weeks, but to range of flexion/extension only at 6 weeks. The relationship between reported pain and current grip decreased with time. Flexion/extension arc was a stronger predictor of grip than pain at all time points. The finding that flexion/extension at 6 weeks is strongly predictive of grip at 3 and 6 months suggests either that articular damage due to the fracture or stiffness due to the cast may determine the rate of recovery of grip. Both might be improved by early mobilisation of the wrist without plaster after fixation.

BRS-P48

STRUCTURAL-FUNCTIONAL BONE STATE OF THE POSTMENOPAUSAL WOMEN WITH VERTEBRAL FRACTURES

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Vertebral fractures (VF) are the most common osteoporotic fracture, and were usually associated with falls and other low-energy trauma. Women with low bone mineral density and prevalent vertebral fractures have a greater risk of new incident vertebral fractures.This research was aimed at studying the structural-functional bone tissue state among women in postmenopausal period with VF.

The total of 71 postmenopausal women 50-74 years old having VF in their anamnesis (I group) were examined by ultrasound bone densitometer ('Achilles+'). The control group included postmenopausal women without any osteoporotic fractures in their anamnesis (II group), being standardized by age, BMI, etc. The speed of sound (SOS, m/s), broadband ultrasound attenuation (BUA, dB/MHz) and a calculated 'Stiffness' index (SI, %), T and Z-range were measured

The main risk factors for the osteoporotic VF turned out to be a menarche after 15 years, an early and late menopause. All indexes of ultrasound densitometry in postmenopausal women with VF were significant lower compared the data of healthy patients during all postmenopausal period. 'Stiffness' index was 65.7±5.5 % in I group and 83.5±1.7 in II group, p<0.05 (duration of postmenopausal period 1-9 years), 64.8±3.3 % in I group and 76.8±1.3 % in II group, p<0.05 (duration of postmenopausal period 11-19 years) and 60.3±4.0 % in I group and 76.2±2.0 % in II group, p<0.05 (duration of postmenopausal period more than 20 years). The ultrasound parameters were veritably lower among of all postmenopausal women with VF than among all control group (SOS: 1525,5+-2,0 and 1498,0+-4,0 m/s, p < 0,05; BUA: 107,3+-0,7 and 99,5+-1,4 dB/MG, p < 0,05; SI: 78,6+-0,9 and 65,9+-1,9 %, p < 0,05).

Ultrasound densitometry is an effective screening method to reveal the women of risk group having future osteoporotic vertebral fracture in postmenopausal period.

BRS-P49

TEMPORAL RELEASE OF ENCAPSULATED OSTEOGENIC AND ANGIOGENIC FACTORS FROM BIODEGRADABLE POLYMER SCAFFOLDS ENHANCE HUMAN BONE MARROW STROMAL CELL BONE REGENERATION

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The regenerative process of bone tissue involves complex and coordinated signal cascades. In the clinical settings where the bone defect is too large for natural repair, a replacement material is required to enhance the osteogenic healing process. Angiogenic factors such as vascular endothelial growth factor (VEGF) and osteogenic factors such as bone morphogenic protein-2 (BMP-2) are known to play a prominent role in bone formation and bone healing. Orchestrating the presentation of these factors and different kinetic release profiles by the encapsulation of these scaffolds within intelligent scaffold structures will enhance the coordinated capacity of the regeneration of critical sized bone defects. The aim of this study was to determine if the delivery of VEGF165 and rhBMP-2 from a biodegradable alginate/Poly D,L-lactic acid (PLA) composite with the addition of human bone marrow stromal cells (HBMSC) could enhance the bone regenerative capability in a mouse-femur segmental defect.

VEGF165 encapsulated within alginate and rhBMP-2 were both encapsulated within a PLA polymer, using supercritical CO{sub}2{/sub} technology, forming a complex monolith scaffold of alginate (VEGF) within PLA (BMP-2) (alginate-VEGF/PLA-BMP-2). These scaffolds were seeded with or without HBMSC and implanted into a mouse (MF1nu/nu) femur segmental defect (5mm) for four weeks (n=4 mice per group). The femur-defect samples were analysed for bone regeneration using micro-computer tomography.

The alginate-VEGF/PLA-BMP-2 + HBMSC group showed significant bone regeneration in the femur-segmental defect compared to the alginate/PLA and alginate-VEGF/PLA-BMP-2 groups by indices of increased Bone Volume (BV mm{super}3{/super}), trabecular number (Tb.N/mm) and reduced trabecular separation (Tb.Sp (mm)) in the defect region. BV±S.D: alginate/PLA = 6.63±1.06; alginate-VEGF/PLA-BMP-2 = 9.92±1.78; alginate-VEGF/PLA-BMP-2 + HBMSC = 17.79±1.85 (P<0.001). Tb.N/mm: alginate/PLA = 1.81±0.33; alginate-VEGF/PLA-BMP-2 = 2.59±0.53; alginate-VEGF/PLA-BMP-2 + HBMSC = 5.32±0.61 (P<0.001). Tb.Sp(mm): alginate/PLA = 0.45±0.07; alginate-VEGF/PLA-BMP-2 = 0.32±0.072; alginate-VEGF/PLA-BMP-2 + HBMSC = 0.12±0.014 (P<0.01).

In conclusion, these studies demonstrate the ability to deliver, temporally, a combination of HBMSC, angiogenic and osteogenic growth factors released from biodegradable scaffold composites to sites of bone defects in a regulated manner, can enhance the regeneration of large bone defects. Such cell based and tissue engineering strategies offer innovative approaches in orthopaedics and the wider tissue reparative arena.

BRS-P50

THE EFFECT OF TRAINING STATUS ON THE METABOLIC RESPONSE OF BONE TO EXHAUSTIVE RUNNING EXERCISE

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This study examined the role of aerobic fitness in the metabolic response of bone to exercise to help understand the role of training status in the pathogenesis of stress fractures during military training.

Eleven recreationally-active (RA; mean(1SD) maximal rate of oxygen uptake (VO2max): 55(7) ml/min/kg), 10 endurance-trained (ET; VO2max: 68(6) ml/min/kg) and 10 control (CON; VO2max: 53(4) ml/min/kg) male subjects completed one 8-day trial. On days 1-3 and 5-8, subjects rested and consumed a controlled diet. On day 4, RA and ET completed intermittent, exhaustive treadmill running (EE) at 65-70% VO2max. Fasting blood was obtained before (BASE), during, at 0.5, 1, 1.5 and 2 h after exercise, and on 4 follow-up days (R1-R4). CON rested throughout, providing blood samples at BASE

and R1-R4. Markers of bone resorption (Beta-CTX) and formation (P1NP, Bone-ALP), PTH, ACa and OPG were measured.

All variables were unchanged in CON. Beta-CTX was higher than BASE on all follow-up days in RA and ET ($p<0.05$). P1NP increased in ET from BASE to R1-R3 ($p<0.05$), but was unchanged in RA. Bone-ALP was unchanged in both groups. OPG increased from BASE at every time-point up to 2 h of recovery in RA and ET ($p<0.05$) and remained higher up to R4 in RA ($p<0.05$). ACa and PTH increased ($p<0.001$) during exercise in RA and ET. ACa was higher ($p<0.05$) in ET than in RA immediately following EE and up to 1 h of recovery. PTH decreased from BASE ($p<0.05$) at 1 and 1.5 h of recovery in RA and at 1, 1.5 and 2 h in ET.

EE was associated with increased bone resorption. Increased OPG may indicate the activation of bone resorption or be a direct effect of exercise. Changes in P1NP suggest increased bone resorption was accompanied by an increase in bone formation in ET, but not in RA, although there were no significant differences between groups. The increase in PTH cannot be explained by reduced ACa but may be related to changes in circulating phosphate or glucose concentrations.

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BRS-P51

THE EFFECTS OF RECOMBINANT HUMAN GROWTH HORMONE (rhGH) AND INSULIN-LIKE GROWTH FACTOR-I (rhIGF-I) ON HUMAN OSTEOCLASTS

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Growth hormone deficiency (GHD) is associated with reduced bone turnover, decreased bone mineral density and increased risk of osteoporotic fractures. The extent to which these are direct or indirect effects of GH action is not understood. We have assessed the effects of GH and IGF-I on osteoclastogenesis and osteoclast function.

Blood was collected from 24 GHD (12 females) patients (age-range 7-75 yrs) before and after 6 weeks of GH therapy, and from 24 age- and gender-matched controls. Osteoclasts were generated from mononuclear cells using M-CSF and RANKL. In other in vitro studies, cells from adult volunteers were treated with M-CSF and RANKL, and with/without rhGH (100-400 ng/ml), rhIGF-I (10-100 ng/ml) or anti-IGF-1 (4 µg/ml). Osteoclast function was measured by staining pits on ivory discs and image analysis. Results are expressed as % resorption (mean ± SD).

Cells from prepubertal GHD patients 6 weeks post-GH therapy demonstrated an increase in resorption compared to results with cells pre-GH treatment (pre-GH 4.9±5.6 %; post-GH 11.7±6.9 %). Both of these values were significantly ($p<0.01$) lower than prepubertal controls. In adult (<55 years) GHD patients, however, we observed a significant ($p<0.01$) decrease of resorption after therapy (post-GH 19.8±11.4 %; pre-GH 27.2±11.4 %). Both these values were significantly ($p<0.01$ and 0.001 respectively) higher than adult controls (15.1±14.2 %). By contrast, our in vitro studies with adult controls showed that rhGH and rhIGF-1 significantly and dose-dependently increased osteoclast resorption (e.g. 0 v 400 ng/ml GH; 9.2±8.6 % v 20.1±9.3 %; $p<0.001$; 0 v 100 ng/ml IGF-1; 9.2±9.1 % v 21.2±5.1 % $p<0.001$). In the presence of anti-IGF-I the stimulatory effect of GH on resorption was significantly (<0.05) decreased. Furthermore we have observed that anti-IGF-1 alone, but in the presence of M-CSF and RANKL, decreased resorption.

In GHD the effect of GH on osteoclast function is probably age-dependent. We speculate that in children it stimulates resorption to enable bone modeling and linear growth whereas in adults bone resorption is decreased. Furthermore, the stimulatory effect of GH on osteoclasts is probably mediated by IGF-I. IGF-1 might also play a role in normal osteoclast formation and function.

BRS-P52

WITHDRAWN

BRS-P53

THE MOLECULAR RESPONSE OF HUMAN BONE TO MECHANICAL STIMULATION

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Bone is the ultimate 'smart' engineering material being capable of altering its internal architecture in response to mechanical stimulation (exercise). While it is now accepted that the osteocyte acts as the mechanosenor in bone directing the activity of cells of both the osteoblast and osteoclast lineage in a targeted manner, the molecular signaling of this response remains to be elucidated. Here using a 3D bioreactor system (Zetos TM) in conjunction with microarray gene expression profiling we have studied the molecular response of human trabecular bone to mechanical stimulation.

Trabecular bone samples were obtained from six individuals undergoing elective arthroplasty. Affymetrix Human Genome U133 Plus 2.0 arrays were used to compare the genome wide expression of 38,500 genes in response to exercise in samples maintained within the bioreactor chambers for 3 days, subjected to either daily loading regime for 5 minutes using maximum of 3000 µstrain in a jumping waveform repeated at 1 Hz or control no load. Differential gene expression was calculated using Rank Products (RP) analysis (1). In a pair wise comparison of Load vs Control samples 260 genes were found to have significantly (p less than or equal to 0.0001) higher expression and 121 genes significantly (p less than or equal to 0.0001) lower expression at a false detection rate (FDR) of <5. The top changed groups included members of the structural constituents of bone and ossification (BGLAP, MGP, COL1A1, DMP1 and BMP5) as well as prostaglandin synthesis (PTGS) and Wnt signalling family proteins. qRT-PCR has been used to both confirm the microarray data and to initiate studies into the physiological relevance of novel mechano-responsive genes identified. The data will provide functional information which could feed into existing studies concerned with identification of genetic polymorphism disease related markers as well as identification of potential new therapeutic targets to combat age related bone loss.

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BRS-P54

THE POTENTIAL INHIBITORY ROLE OF SUPRESSOR OF CYTOKINE SIGNALLING-2 IN CHONDROCYTE GH/IGF-1 SIGNALLING VIA THE JAK/STAT PATHWAY

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Suppressor of Cytokine Signalling-2 (SOCS2) tightly controls postnatal growth through the regulation of GH and IGF-1 signalling. SOCS2 null mice grow significantly larger than wild-type mice, with significantly longer bones. The precise mechanisms by which SOCS2 inhibits GH/IGF-1 signalling are unclear.

The actions of SOCS2 on GH and IGF-1 signalling in growth plate chondrocytes have yet to be reported. The primary aim of this study was to investigate STAT signalling in chondrocytes in response to GH and IGF-1. We also investigated the temporal expression of SOCS2 in response to GH and IGF-1 to examine which pathways are likely to regulate SOCS2.

RT-PCR studies showed that the IGF-1 and GH receptors are both expressed by murine primary chondrocytes and the ATDC5 chondrogenic cell line. STAT signalling in chondrocytes was investigated by Western Blotting and quantified using densitometry. Phosphorylation of STAT1, STAT3 and STAT5 increased in ATDC5 (3, 1.5 and 4 fold respectively) and primary cells (9, 2 and 6 fold respectively) in response to GH (500ng/ml). No response to IGF-1 (50ng/ml) was noted. In all cases total STAT1, 3 and 5 was unchanged. The greatest responses seen were by STAT1 and 5, with only modest differences in STAT3 noted. The lack of STAT signalling in response to IGF-1 was not unexpected as the IGF-1 receptor does not contain specific tyrosine-based motifs recognized by STATs.

The temporal expression of SOCS2 protein in response to GH (500ng/ml) and IGF-1 (50ng/ml) was also investigated in primary chondrocytes, at various time intervals (8hrs, 24hrs, 48hrs and 72hrs). SOCS2 expression increased in response to GH, an effect that increased with time to peak after 48 hours. SOCS2 expression did not increase in response to IGF-1. These data together confirm that GH signalling stimulates SOCS2 production, which is likely to act as a negative feedback loop to regulate STAT activation and GH signalling in chondrocytes.

Studies using chondrocytes from SOCS2 null mice will further allow us to investigate the precise role of SOCS2 in GH signalling. It is possible that SOCS2 may be a potential therapeutic target for enhancing GH signalling in children with short stature.

BRS-P55

THE RELATIONSHIP BETWEEN MUSCLE STRENGTH MEASUREMENTS AND BONE IN YOUNG ADULT MALES

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With the exception of traumatic events it is generally accepted that muscles have a major role in skeletal development and maintenance. Grip strength is commonly used as an indicator of muscle force in the upper limb. The attachments of the long forearm flexors and extensors (producing grip) are distant from the bone commonly measured (the radius). The muscles which produce supination and pronation are more directly attached to the radius. The purpose of the study was to identify if there is a comparable relationship between grip, supination and pronation strength and bone parameters in the upper limbs of young males (YM).

European Caucasian YM aged 18-24 years were recruited (n=100). Peripheral quantitative computed tomography (pQCT) measurements were taken at the 4 and 50% non-dominant radius. Grip strength (Kg) was measured using a JAMAR dynamometer. A novel method was developed using a Nicolas hand-held dynamometer to measure supination and pronation strength (Kg). Dependent variables at the 50% radius included: total bone area of radius and ulna (TBARU mm2), radius area (RA mm2) muscle cross sectional area (MCSA mm2), cortical bone mineral content (BMC mg/mm), cortical density (CD mg/cm3), cortical area (CA mm2), cortical thickness (CT mm), moment of inertia (AMI mm4), stress strain index (SSI mm3) and medullary area (MA mm2). At the 4% radius included: total bone area (TBA mm2) trabecular density (TrabBMD mg/cm3) and total density (TotBMD mg/cm3).

The influence of muscle parameters upon bone outcomes was tested using ANCOVA adjusting for height and weight. At the 50% radius there were significant relationships between TBARU, MCSA, RA, BMC,CA, CT, AMI and SSI for grip strength ($p<0.05$) and: TBARU, MCSA, RA, CD and MA for supination strength ($p<0.05$). At the 4% site there were significant relationships between TBA and grip and supination strength ($p<0.05$). No parameters reached significance for pronation strength at either site.

Supination muscle strength measurements are a valuable predictor of bone parameters in YM. Results suggest that supination might be a more sensitive measure than grip for the assessment of the muscle bone relationship.

BRS-P56

THRESHOLDS FOR THE MEASUREMENT OF CORTICAL THICKNESS IN-VIVO USING COMPUTED TOMOGRAPHY (THE 100 WOMEN STUDY)

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We previously identified cortical thinning of the femoral neck as a probable cause of hip fracture using high resolution pQCT of cadaveric femurs. Ageing thins the supero-posterior (SP) cortex while hip fracture cases demonstrate additional thinning of the inferior cortex. In an interim analysis of The 100 Women Study (a cross-sectional study investigating cortical thickness, C.Th, in life from 20-90 years using multislice CT and Mindways software, BIT-2) SP C.Th declined with age at the same rate as seen in our pQCT cadaveric study. Conversely, in-vivo CT appeared to overestimate C.Th inferiorly using a cortical-cancellous delineation threshold of 350mg/cm3. We hypothesized that this threshold misclassified cancellous bone inferiorly leading to inaccurate delineation of the endocortical boundary (particularly in the young/higher cancellous BMD).

We analysed BIT-2 CT measurements of 8 PVA-filled Simax tubes (of varying known thicknesses) in the Siemens CT scanner. Subsequently we compared BIT-2 measured C.Th (using a variety of thresholds) with high resolution pQCT C.Th (Gaussian of Laplace method, 0.275mm resolution, Scanco 1000) of the same 22 post-mortem cadaveric femurs from the Melbourne Femur Collection (using a water bath to simulate soft-tissue in the Siemens CT scanner at 1mm slice thickness and 0.59mm voxel size).

With Simax tubes, there was good correlation (r2 0.97, $p<0.0001$) at thicknesses as low as 1 mm indicating that Siemens CT and BIT-2 could accurately measure thin cortices. In cadaveric femurs, BIT-2 C.Th was higher than pQCT thicknesses. The difference was dependent on age and individual quadrants and greatest in the IA region and in the young (with delineation of the endosteal boundary the primary cause). Analysing the Siemens CT data at various thresholds (200, 350, 450, and 500mg/cm3) demonstrated that the differences declined with increasing threshold and were closest to zero at 450 in the SP region (0.006±0.11; mean ± SEM) and at 500 (0.29±0.09) in the IA region.

BIT-2 software accurately determined the thickness of thin cortices in-vivo. A cortical threshold of 450mg/cm3 resulted in the best average delineation of the endosteal boundary supero-posteriorly, but cortical-cancellous delineation using clinical CT might be improved by a region-specific threshold.

BRS-P57

ULTRASTRUCTURAL EXAMINTAION OF COLLAGEN FROM ALKAPTONURIC TISSUE PROVIDES CLUES TO PATHOGENESIS OF OCHRONOSIS

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Alkaptonuria is a rare disorder of tyrosine metabolism that was first identified as a genetic disease by Garrod 100 years ago. It is characterised by the build up of homogentisic acid (HGA) in body tissues. The build up of HGA, due to lack of homogentisate dioxygenase, in tissues results in deposition of a melanin like pigment (termed ochronosis). Ochronosis is severely damaging to connective tissue, especially cartilages situated in the load bearing joints.

We have previously noted variation between the amounts of deposition within tissues and also between individuals. Understanding the exact location of deposition may help to understand the mechanism of binding or to highlight other factors which contribute to ochronosis. The present study aims to identify the exact location of ochronotic pigment in bone and cartilage, using both light and electron microscopy.

Alkaptonuric articular surfaces show marked ochronotic pigmentation, often covering all visible surfaces. Light microscopy of bone and cartilage identify the deposition of the ochronotic pigment in the extracellular matrix; bound to collagen fibres. Examination at ultrastructural level using T.E.M confirms the location and highlights a distinctive binding pattern of ochronotic pigment to the surface of collagen fibres when seen in longitudinal section. In regions of deposition, the collagen appears degenerated and structurally compromised. The pigment appears shard like, bridging across the cross-banding. Pigment is abundant in some regions yet nanometres away the collagen appears normal; unpigmented and uncompromised in structure. When viewed in transverse section, the deposition can be seen on the surface of the collagen, and also protruding into the body of the fibre. There is evidence suggesting internalisation of the pigment in the collagen fibre body, suggesting initial deposition during collagen assembly. In an in vitro model, we observed that collagen assembly is affected by the presence of high levels of HGA in the culture environment. The naked collagen appears to facilitate the binding of HGA at levels far greater than that observed in vivo. Fibrils appear encrusted in pigment and structurally bear little resemblance to the highly uniform patterns seen in vivo, or in vitro cultures without HGA.

Abstracts

Speaker Profiles

Judith Adams

Judith Adams is Consultant Radiologist, Manchester Royal Infirmary and Honorary Professor of Diagnostic Radiology, Imaging Science & Biomedical Engineering (ISBE) at the University of Manchester, UK. She is a musculo-skeletal radiologist with a particular interest in metabolic bone disease (especially osteoporosis) and quantitative assessment of the skeleton. Her publications include 155 scientific papers, 20 reviews and 23 chapters and she has collaborated in £3M research grants in past 8 years. Professor Adams has served as Dean (Vice President) of the Royal College Radiologists, Chairman of the Osteoporosis Group of the European Society of Skeletal Radiology (ESSR) and of the National Osteoporosis Society (NOS) Bone Densitometry Forum.

Thomas Aigner

Following studies in philosophy and theology in Munich Dr Aigner went on to study medicine at the Friedrich-Alexander-University in Erlangen-Nürnberg, Germany, spending a year in Birmingham in 1991/92. Dr Aigner was Head of the Osteoarticular and Arthritis Research Group (Department of Pathology) in Erlangen from 1996-2006 and in March 2006 he became Deputy Director of the Institute of Pathology at the University of Leipzig. He became Professor of Pathology in November 2007. His research interests are in cell biology of the (aging) skeleton, functional genomics of osteoarthritis, tissue engineering, matrix biochemistry and pathology, and neoplasias of the skeleton.

Patrick Ammann

Patrick Ammann is an internist with a subspecialty focus on metabolic bone diseases, osteoporosis and disorders of mineral metabolism. He is presently Head of the preclinical investigation group of osteoporosis and bone metabolism at the Division of Bone Diseases in the Department of Rehabilitation and Geriatrics of the Geneva Hospitals, Switzerland. He is involved in both basic and clinical research investigating skeletal development, pathophysiology of osteoporosis, effect of nutrition and antiosteoporotic treatments on bone mechanical properties and their determinants (including intrinsic bone tissue quality). A special focus on mandibular osteoporosis and implant osseointegration are other recent interests. He is also in charge of a rehabilitation unit for patients with osteoporotic fractures. He has received numerous awards, both international and national, for his contribution to the understanding of metabolic bone disease pathophysiology.

Kay Colston

After gaining a PhD in the Endocrine Unit at Royal Postgraduate Medical School, London, Dr Colston undertook postdoctoral studies at Stanford University Medical Center, California, working on characterization and tissue distribution of vitamin D receptors. She is now Reader in Clinical Biochemistry and Metabolism at St George's University of London. Current research interests include anti-tumour effects of vitamin D and studies on cancer-induced bone disease.

Georg Duda

Prof Dr Georg N Duda is director of the Julius Wolff Institute and member of the Centre for Musculoskeletal Surgery at the Charité-Universitätsmedizin Berlin, Germany. His research interest is mainly focused on biomechanical aspects of musculoskeletal healing and regeneration, and the development of new methods to document healing progress. In particular, the effect of physical effects on the endogenous regeneration pathway is evaluated using biomechanical, histological and molecular biological methods.

Born and raised in Berlin, Professor Duda graduated from the Technical University, Berlin in 1991. He began his career at the biomechanics laboratory of the Mayo Clinic, USA, received his PhD from the Technical University of Hamburg-Harburg, continued at the John-Hopkins-University, USA and the Institute of Orthopaedic Research and Biomechanics in Ulm. In 1997, he returned to Berlin and established a network on musculoskeletal healing:

Basic research is performed in the clinical research group “Bone Healing” (DFG KFO 102) and the collaborative research centre “Musculoskeletal Regeneration” (DFG SFB 760). Translational research is focussed in the BMBF funded “Berlin-Brandenburg Centre for Regenerative Therapies (BCRT)”. These centres are complemented by a PhD graduate school (DFG GSC 203).

Bill Fraser

Professor Bill Fraser was born and educated in Glasgow, graduating from Glasgow University with BSc (Hons) MBChB and MD (Hons). He trained in Glasgow's teaching hospitals before spending time as a consultant/travelling fellow in Canada.

In 1991 he was appointed Senior Lecturer in Chemical Pathology and Head of the Metabolic Bone Disease Unit at the Royal Liverpool University Hospital, promoted to Reader in 1998, Professor in 2001, and Head of the Unit of Clinical Chemistry in 2008. He supervises a very active research group

investigating the diagnosis and treatment of metabolic bone disease including osteoporosis and Paget's Disease of bone.

Bill Fraser is on the Editorial Board of several journals, a Director of the Supra Regional Assay Service for bone metabolism and calcium homeostasis, and a Medical Advisor to the National Osteoporosis Society. He was the recipient of the ACB Foundation Award for 2006.

Mark Lunt

After completing an MSc in Medical Statistics, Mark began his academic career as a statistician with the European Prospective Osteoporosis Study (EPOS), based at the Institute of Health in Cambridge, in 1992, where he worked on the epidemiology of low bone density and vertebral fracture. In 1999, he moved to the Arthritis Research Campaign Epidemiology Unit in Manchester. Here he continued his work on osteoporosis and vertebral deformity, but also developed new interests in the epidemiology of rheumatic disease. He completed a PhD with the Open University in 2003, entitled "Statistical methods of detecting vertebral fractures". Most recently, his primary focus has been on methods of making causal inferences from observational data: to this end, the academic year 2006-2007 was spent on sabbatical with the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital and Harvard University, Boston.

David Marsh

David Marsh is Professor of Clinical Orthopaedics, UCL Institute of Orthopaedics and Musculoskeletal Science at the Royal National Orthopaedic Hospital in Stanmore. After studying medical sciences at Cambridge University he was awarded his MB BCh in 1975 and FRCS in 1980. In 1990 he was awarded his MD from the University of Cambridge. After working as Wellcome Research Fellow at the Physiological Laboratory at the University of Cambridge he became Lecturer in Orthopaedics at the University of Manchester. He then spent several years as Professor of Trauma and Orthopaedics at Queens University in Belfast before moving to Stanmore in 2005. His research interests focus on the biology of fracture healing and distraction osteogenesis; tissue engineering of bone; treatment of osteoporosis and fragility fractures; clinical trials of fracture treatment; and measurement of outcome in fractures and limb reconstruction.

Andrew Pitsillides

Andrew Pitsillides graduated with a BSC (Hons) degree in Applied Biology in 1984, before studying for a PhD whilst at the Kennedy Institute of Rheumatology (1988). His work at the Kennedy included studies on cell biochemistry and function in various joint tissues, including human synovium, cartilage and animal models of inflammation. He later worked in the Rheumatology unit, UCL Medical School, where he pursued the mechanisms regulating extracellular matrix glycosaminoglycan synthesis, which he extended to include cell: matrix cross-talk in his studies focused on embryonic joint cavity formation. His move to the Royal Veterinary College in 1993 and a lectureship in 1994 coincided with the extension of his studies to include the role of mechanical influences in these early events, essential for the development of the skeletal system and in the control of adult bone remodelling. Much of this work in bone focused on defining novel roles for soluble autocoids, including nitric oxide, in communicating the mechanomodulatory osteogenic/anti-resorptive effects of load-bearing and centred on the contribution of the osteocyte to spatial control of these events. He was appointed Reader in 2006 and his group's work has recently focused on defining the cell-signalling events that underpin the close relationship between cells and their matrix and changes in load-induced responses in the developing, growing and ageing skeletal system. His description of novel model systems for manipulating embryonic mobility in ovo and for applying controlled mechanical stimuli to joint and bone tissues in vivo offer powerful new tools for exploring the means by which local mechanical events are converted to signals that can fashion changes in cell matrix synthesis and behaviour.

James Richardson

From early on I was keen to specialise in Orthopaedics and have been fortunate to work in a range of hospitals in the UK and abroad. Aberdeen was where I graduated in Medicine in 1977 and then I began working in Orthopaedics. I have worked at Elgin, Inverness, Oxford, Glasgow and Leicester as well as training here at Oswestry during my specialist registrar training. I returned to Oswestry in 1994 to take up the post of Professor of Orthopaedics and specialising in lower limb surgery. In Oxford I researched fracture healing and my MD Thesis was on the same. I have a monthly specialist clinic for patients with problem fractures and non-unions and provide Lautenbach procedure for infected cases. I am now running a trial in mesenchymal stem cell therapy for non-union of fractures in the long bone (tib/fib and femur). Oswestry is the only hospital offering this service in the UK and we have now treated over 10 patients. With the expertise of our scientists and the help of a local charity, the Institute

of Orthopaedics, a cartilage cell service producing chondrocytes has been running for a number of years and well over 200 patients have been treated for local chondral defects using autologous chondrocyte cell implantation (ACI).

Sandra Shefelbine

Dr Sandra J Shefelbine is a lecturer at Imperial College London in the Department of Bioengineering. She has a BSE in Mechanical Engineering from Princeton University, an MPhil in Engineering Design from Cambridge, and a PhD from Stanford University in Mechanical Engineering. She was a National Science Foundation International Post-doctoral Research Fellow at the Institute for Orthopaedic Research in Ulm, Germany, followed by a post-doctoral fellowship in the Department of Radiology at University of California in San Francisco. Her research in mechanobiology examines how the mechanical environment affects the musculoskeletal system during growth, fracture healing, and aging.

Harri Sievänen

Dr Harri Sievänen, ScD, is senior scientist and head of the Bone Research Group, UKK Institute, Tampere, Finland. He also holds posts of Adjunct Professor in Biomedical Engineering at the Tampere University Medical School and Adjunct Professor in Biomechanics at the Department of Biomedical Engineering of the Tampere University of Technology. His research interests are in various aspects of clinical and experimental bone research, including physical activity and exercise, whole body vibration training, and imaging methods for analysing and modelling the bone structure. During his 20 year scientific career, he has authored or co-authored more than 160 peer-reviewed scientific articles and supervised more than 10 doctoral studies.

Alan Silman

Professor Silman is the first Medical Director of the UK Arthritis Research Campaign (ARC) having been appointed in January 2007. Prior to this from 1988 he was Director of the ARC's Epidemiology Unit based at Manchester University and Professor of Rheumatic Disease Epidemiology at the same institution. He is also a consultant rheumatologist at the Manchester Royal Infirmary with a subspecialty interest in the management of Behcet's disease.

Professor Silman has had an extensive research career and has published widely in the fields of the epidemiology and genetic epidemiology of rheumatoid arthritis (RA), outcome studies in RA, epidemiological studies of osteoporotic fracture and of both regional and widespread musculoskeletal pain disorders. He has also has had major research interests in scleroderma and Behcet's disease. More recently he has been involved in assessment of drug safety and was the initiator and joint principle investigator of the British Society of Rheumatology Biologics Register.

He has published over 500 peer reviewed papers. He was the joint author of Epidemiology of the Rheumatic Diseases and is one of the five editors of the international textbook Rheumatology (5th Edition, Elsevier). He is on the editorial board of several international rheumatology journals.

Currently he is also a member of the Executive of the European League Against Rheumatism (EULAR) and Chairman of their Standing Committee on Epidemiology. In the UK, amongst other responsibilities he is a member of the Pharmacovigilence Expert Advisory Group of the Medicinal and Health Products Regulatory Agency and chairs the Ministry of Defence Oversight Committee on research of the health of servicemen in the current Iraq war. He is chairman of the epidemiology sub-panel for the 2008 Research Assessment Exercise. He has served on a number of research boards of the major UK research funders such as the Medical Research Council and Wellcome Trust.

Hans van Leeuwen

Hans (JPTM) van Leeuwen is Professor of Calcium and Bone Metabolism and Head of the Bone and Calcium Research group, The Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands. His main research targets are: a) mesenchymal stem cell and osteoclast differentiation and identification of regulatory mechanisms herein by systems biological approaches; b) extracellular matrix formation and mineralization; c) mechanism of action of steroid hormones and interaction with non-steroid hormone signaling mechanisms; d) transcellular calcium transport processes in mineralization and bone resorption; e) genetic risk factors for skeletal disorders.

Rob Wakeman

I was appointed as a Consultant Orthopaedic Surgeon to Basildon University Hospital in 1994. I developed an interest in hip fracture audit through participation in the Royal College of Surgeons audit of 1995 -7 and, in 2003, I started concurrent audit on all hip fracture patients aged fifty and over who were treated at Basildon. In 2006 I was appointed to the NHS Institute's Developing Quality and Value team, looking at the hip fracture pathway. I have been involved with the NHFD since 2004, and have been employed as one of the part time Clinical Leads since 2007.

Richard Whitehouse

Dr Richard Whitehouse has been a consultant musculoskeletal radiologist at Manchester Royal Infirmary since 1991, prior to which he worked as a research fellow in computed tomography at Manchester Medical School, where he also investigated various techniques of bone mineral density measurement. His MD thesis was on dual energy quantitative computed tomography. He is a member of the International Skeletal Society and the British and European societies of Skeletal Radiology. He has been performing vertebroplasty for eight years and recently introduced kyphoplasty to the interventional musculoskeletal procedures he performs.

Exhibitor Profiles

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IDS is a leader in the field of Vitamin D analysis, offering both manual and automated 25(OH) Vitamin D methods, an award-winning 1,25-Dihydroxy Vitamin D RIA system, and now announces OCTEIA 1,25(OH)2 Vitamin D, an EIA employing the proven immunocapsule sample preparation.

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To learn more about Medtronic Sofamor Danek's MySpineTools.com or to get more information on our spinal technologies, please talk to us at the meeting or visit our website www.medtronic.com.

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Qados are the distributors of the Faxitron X ray imaging cabinets in the UK. These cabinets are widely used for imaging bone both during research or during routine work in the Histopathology Departments. Digital imaging options are also available from Qados, for example the EZ240 X ray scanner from NTB.

Qados also represents Cisbio International in the UK, Cisbio produce Quadramet which is for bone pain palliation after breast, prostrate or bladder cancer treatment. If you would like to look at the complete Qados portfolio please visit www.qados.co.uk.

Roche/GSK

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Roche aims to improve people's health and quality of life with innovative products and services for the early detection, prevention, diagnosis and treatment of disease. Part of one of the world's leading healthcare groups, Roche in the UK employs nearly 2,000 people in pharmaceuticals and diagnostics. Globally Roche is the leader in diagnostics, and a major supplier of medicines for the treatment of cancer, transplantation, virology, bone and rheumatology, obesity and renal anaemia. Find out more at www.rocheuk.com

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For further information on Shire, please visit the Company's website: www.shire.com

Technoclone

Technoclone Ltd is a specialist in the field of bone, cartilage and mineral metabolism immunoassays and is the exclusive distributor in the UK and Ireland of both the Metra® range of Bone Marker assay kits from Quidel and Cartilage assays kits from Ibex Diagnostics.

The Metra® range of ELISA assays includes a highly specific Bone Alkaline Phosphatase (BAP) assay, serum Osteocalcin, Collagen Type –1 C-Terminal propeptide (CICP), DPD and Total DPD, PYD, alpha-1 Helical Peptide and YKL-40, as well as a chromogenic Creatinine assay and other research reagents.

Details of new kits from Quidel will be available at the BRS meeting including

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- Metra® TRAP 5b ELISA
- Metra® Osteoprotegerin ELISA

Ibex Diagnostics specialises in cartilage assay kits including

- C2C ELISA for cartilage degradation (serum & urine)
- CPII & CS-846 ELISA's for cartilage formation (serum & urine)

Technoclone also markets an extensive range of autoimmune assays in multiplex and ELISA format, Complement assays and research reagents and multiplex human cytokine assays.

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Notes

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